Tetrabutylammonium Tribromide in Organic Synthesis
&
N-Acylation in Aqueous Medium

Submitted By

Sarala Naik

Department of Chemistry

Indian Institute of Technology Guwahati

North Guwahati, Guwahati-781039

May 2006

Dedicated to My Parents

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the guidance of Professor Bhisma K. Patel.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Sarala Naik

May, 2006.
IIT Guwahati

Sarala Naik

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Sarala Naik has been working under my supervision since July, 2003 as a regular registered Ph. D. student. I am forwarding her thesis entitled "Tetrabutylammonium Tribromide in Organic Synthesis and *N*-Acylation in Aqueous Medium" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

May, 2006.
IIT Guwahati

25/5/06
Prof. Bhisma K. Patel
Supervisor

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

COURSE CERTIFICATE

This is to certify that Sarala Naik has satisfactorily completed all the courses required for the Ph.D degree program. These courses include

CH 630	A Molecular Approach to Physical Chemistry
CH 603	Supramolecules: Concepts and Applications
CH611	Bioinorganic Chemistry
CH627	New Reagents in Organic Chemistry

Sarala Naik has successfully completed her Ph.D qualifying examination in May 2004.

Prof. A. T. Khan 25/5/06
Head
Department of Chemistry
I. I. T. Guwahati

Dr. Anil K. Saikia
Secretary
Departmental Post Graduate Committee
I. I. T. Guwahati

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

Ph.D. GRADE CARD

Roll No.: 03612208 Department: Chemistry

Name: Sarala Naik Semester: July-Nov, 2003

Course	Course Name	Credit	Grade
CH 603	Supra Molecules: Concept and Applications	6	AB
CH 630	A Molecular Approach to Physical Chemistry	6	BB
CH 611	Bioinorganic Chemistry	6	BB
CH 627	New Reagents in Organic Synthesis	6	AB

Semester Performance Index: (S. P. I): 8.50

Cumulative Performance Index: (C. P. I): 8.50

Date: May , 2006

Assistant Registrar
(Academic)

Acknowledgements

I express my sincere gratitude to my supervisor, Prof. Bhisma K. Patel for his able guidance, timely suggestions and advice during my tenure as a research scholar under his supervision. His healthy remarks always kept me motivated and inspired me to do better. I have imbibed his sense of punctuality and systematic planning. I am also thankful to him for the pleasant work atmosphere provided during the complete research period.

I am deeply indebted to Prof. Mihir Kanti Chaudhuri for his advice, suggestions and helps in all spheres of my life. I am grateful to him for his patented reagent on which I have worked throughout my research tenure.

I express my sincere thanks to Prof. Abu T. Khan who apart from evaluating different stages of my research work being the chairman of my doctoral committee has also helped me whenever I have needed his help and suggestions.

I am thankful to the members of my doctoral committee Dr. V. Manivannan and Dr. M. Jawed for reviewing my work during comprehensive, research proposal and synopsis seminar.

I am obliged to the former head of the Department of Chemistry, Prof. J. B. Baruah for his cooperation at different stages from the pioneering stage of the Ph. D program. I am also thankful to all faculty members, staffs, and technical assistants, scientific officer who has offered help directly or indirectly at different stages during my research work. I am thankful to Dept of Chemistry for offering me the state of the art facilities.

I would like to acknowledge Council of Scientific and Industrial Research, New Delhi for the financial support provided in the form of Senior Research Fellowship for the complete tenure of my Ph.D.

I am thankful to Dr. Ram Kinkor Roy, BITS Pilani, for the theoretical calculations provided by him, which I required to explain some of the experimental results in my thesis.

I am thankful to Ghasiram Patel, Dr. Neeta Bohidar and Prof. R. K. Behera, who have taught me at different stages in school, college and university by virtue of which I am at this stage.

I appreciate my senior, Gopinathda's help and guidance which he has offered to me from the beginning of my research life to date. I am also thankful to my junior Veerababu for his selfless efforts he put in helping me whenever required in and beyond the research work. Thanks to my lab mates Gitalee, Siva, Kishoreda for providing a nice and pleasant atmosphere in the lab and also thanks to Gopalda, Tridibda,

Deepa didi, Lopa, Priti, Debashishda for being nice seniors and friends from the very beginning of my stay over here.

My special thanks to Sudipa didi and Himani for their valuable friendship, encouragement and support they have provided in each sweet and bitter moments during my stay over here. I am also thankful to my friends Amrita, Sasmita and Tulika for their friendship and help at different stages.

I am also thankful to Hrusikesh, Sanjeeb, Sibani, Sujata, Subhalaxmi, Muni, Aparna, Tulsi, and Jyotsna whose friendship I will owe forever.

My sisters Sarada, Gayatri, Dharitri, and brothers Ramesh, Umesh, Durga, Dinesh will always be acknowledged for their love, affection and care. I am grateful to my grandma and grand father for taking pain all through their life to bring me up. I am also thankful to my mama, piusi and mami for their moral support.

My parents are my source of inspiration who have struggled a lot to fulfill each and every requirements of me and I would be very happy if I can fulfill a part of my father's expectation. I am grateful to my parents for their affection and inspiration.

My heartfelt thanks to my husband, Sanjit for his love, affection, support and for being so understanding over these years. I am also very much thankful to him for his co- operation and patience in all spheres.

Classification of Compounds

The products or compounds prepared have been listed in the present work section of chapter 1 and chapter 2 of the thesis with the following names

1,3-Dithiolane	a
1,3-Dithiane	b
1,3-Dioxolane	c
1,3-Dioxane	d
1,3-Oxathiolane	e
Tetrahydropyranyl ethers	f
Acetates	g
Propionates	h
Isobutyrates	i
Pivalates	j
Benzoates	k
NHBoc	l
Succinamic Acid	m
Maleamic Acid	n
Phthalamic Acid	o

Abstract

The contents of this thesis have been divided into two chapters summarising the results based on the experimental works performed during the complete course of the research. Each chapter constitutes four sections, sections A-D describing introduction, present work, experimental work and spectral data respectively. Tetrabutylammonium tribromide (TBATB) in organic synthesis is the theme of chapter 1 in which various synthetically useful organic functional group transformations such as thioacetalisation, transthioacetalisation of carbonyl compounds, tetrahydropyranylation and depyranylation, acylation of alcohols and direct condensation of carboxylic acids with alcohols achieved utilising the *in situ* acidity of TBATB has been described. With the endeavour to understand the chemoselectivity in thioacetalisation, a brief theoretical study has also been performed and described in chapter 1. The second chapter of this dissertation elucidates the results pertaining to *N*-acylation of amines in water serving as the reaction medium.

CHAPTER 1

Tetrabutylammonium Tribromide in Organic Synthesis

Section 1A: Introduction

Organicammonium tribromides are the alternative source of bromine. These are crystalline stable solids and hence easy to maintain desired stoichiometry and also easy to store, transport and handle. Among the various tribromides we have chosen the tribromide, TBATB (tetrabutylammonium tribromide), for our study, whose precursor TBAB is less expensive compared to other organicammonium bromides.

After a comprehensive perusal of literature relating to the preparation as well as synthetic applications of TBATB we arrived at the following conclusions.

- TBATB has been prepared in an environmentally benign way using V_2O_5-H_2O_2 and its usefulness as a brominating and oxidising agent has been explored extensively in the last few decades.
- This reagent is an efficient generator of anhydrous HBr in alcohols and many other organic solvents. Its acidity can be tuned to a wide range of pH ranging from acidic to near neutral. This aspect is yet to be explored in organic syntheses.

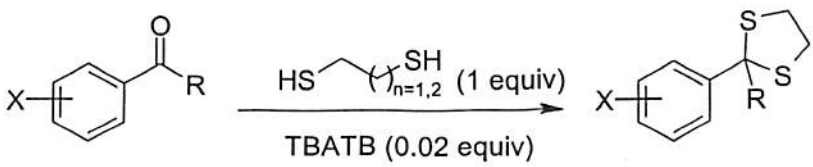
- The various organic transformations which occur exploiting its mild acidity are quite useful especially when compatibility of various functional groups under a specific reaction condition is an important subject.

  We have explored TBATB as a milder *in-situ* source of HBr for various organic functional group transformations, which is summarised below.

Section 1B: Present Work

1B.1. Chemoselective Thioacetalisation of Carbonyl Compounds Catalysed by Tetrabutylammonium Tribromide (TBATB)

This section focuses in part the utilisation of the *in-situ* acidity of the reagent TBATB for the chemoselective thioacetalisation of aldehydes over ketones, chemoselective thioacetalisation of one aldehyde over the other. The other section describes the brief theoretical study to explain the reason governing the chemoselectivity in aldehydes with electron releasing and electron withdrawing substituents. In addition this section also describes the scope of the reagent TBATB in thioketalisation of ketones, transthioacetalisation of acetals / ketals.The experimental procedure for thioacetalisation / thioketalisation is remarkably simple and do not require the use of dry solvents and inert atmosphere or reflux conditions. To a stirred solution of carbonyl compound and 1,2-ethanedithiol or 1,3-propanedithiol in THF was added a catalytic quantity of TBATB (0.02 equiv) and the mixture was left stirred at room temperature, Scheme 1B.1.



R = H; X = H, Me, OMe, OH, NO_2, Cl, $N(CH_3)_2$, OAc, OBz, OBn, Oallyl

R = CH_3; X = H and R = C_6H_5 ; X = H

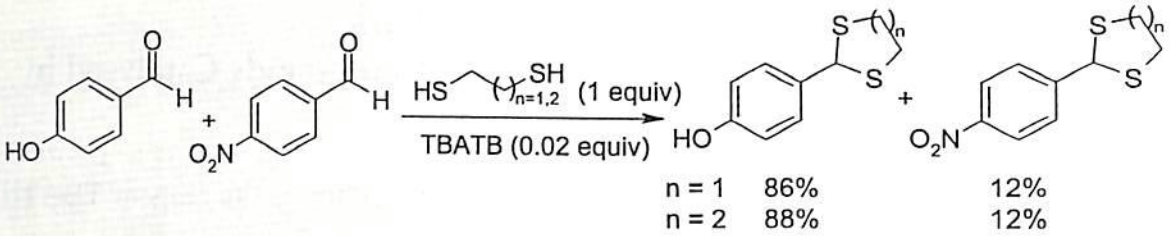
Scheme 1B.1. Thioacetalisation of Aldehydes / Ketones

The versatility of the process has been proved with a wide range of aldehydes and ketones with various stereo-electronic factors. A variety of functional groups such as O-acetyl, *O*-benzoyl, *O*-benzyl, *O*-allyl and double bonds were found to be quite stable during the reactions, as depicted in Scheme 1B.1.

Chemoselectivity

Various competitive reactions were performed between different aldehydes, ketones as well as aldehydes with different bisnucleophiles to understand the factors responsible for the selectivity. Is it the

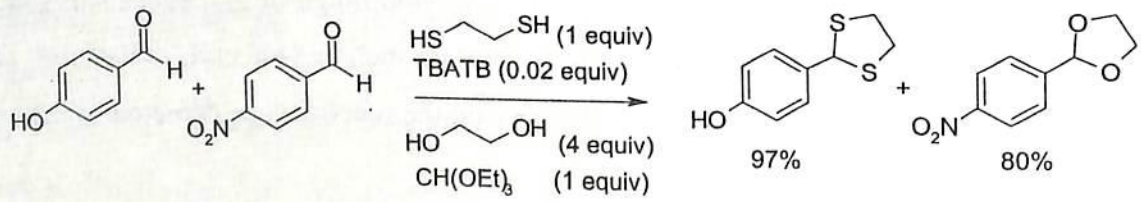
intrinsic reactivity of the substrates or catalyst or reaction conditions that govern the selectivity? When an equimolar mixture of *p*-hydroxybenzaldehyde and *p*-nitrobenzaldehyde was reacted with an equimolar amount of 1,2-ethanedithiol and TBATB (0.02 equiv) in THF, *p*-hydroxybenzaldehyde was thioacetalised in good yield where as *p*-nitrobenzaldehyde gave poor yield, which is shown in the Scheme 1B.2.



Scheme 1B.2. Chemoselective Thioacetalisation of Aldehydes

This selectivity obtained in thioacetalisation is in sharp contrast to the selectivity obtained in the previous work pertaining to acetalisation, where a substrate containing an electron-withdrawing group such as *p*-nitrobenzaldehyde reacts preferentially over a substrate containing an electron-donating group, *p*-hydroxybenzaldehyde. It was argued that due to lower electron density (**0.218**) around the carbonyl carbon of *p*-nitrobenzaldehyde compared to *p*-hydroxybenzaldehyde (**0.228**), the former is more susceptible to nucleophilic attack by alcohols for acetalisation.

When an equimolar mixture of *p*-hydroxybenzaldehyde and *p*-nitrobenzaldehyde was reacted with an equimolar mixture of 1,2-ethanedithiol, 1,2-ethanediol and triethylorthoformate, TBATB (0.01 equiv) in THF, *p*-hydroxybenzaldehyde was completely thioacetalised where as *p*-nitrobenzaldehyde was acetalised to 35% and the rest being starting material. It may be mentioned here that for the complete acetalisation of *p*-nitrobenzaldehyde, 4 equivalents of the diol is necessary. When the above competitive reaction was performed with 1,2-ethanediol (4 equiv) and 1,2-ethanedithiol (1 equiv) a complete chemoselective thioacetalisation of *p*-hydroxybenzaldehyde (97%) and acetalisation of *p*-nitrobenzaldehyde (80%) was observed as shown below in Scheme 1B.3.



Scheme 1B.3. Chemoselective Acetalisation and Thioacetalisation

Thus, in aldehydic substrates containing both electron-donating and electron-withdrawing group, for the selective protection at the electron rich aldehydic carbonyl site, thioacetalisation process is

preferred and for the protection at the electron-deficient aldehydic carbonyl acetalisation is desirable. Unfortunately, the same logic of electron density could not account for the selectivity obtained in thioacetalisation reaction inspite of similarity in their reaction mechanism with acetalisation reactions. It is also noteworthy that here the selectivity is independent of the catalysts ($BF_3.Et_2O$, NBS, I_2 and HBr), solvents ($CHCl_3$, Et_2O, toluene and CH_3CN) and the reaction temperature (80°C, 30°C and -10°C). Not surprisingly the reactions were found to be slower at lower temperature (-10°C).

IB.1.1. Theoretical Interpretation on Chemoselectivities in Acetalisation and Thioacetalisation and Oxathioacetalisation

This section represents a combined study (experimental as well as theoretical) of the chemoselectivities involved in the acetalisation, thioacetalisation, oxathioacetalisation of *p*-nitrobenzaldehyde and *p*-hydroxybenzaldehyde with an objective to investigate the dependence of cyclic *O,O*; *S,S* and *S,O* acetal formation with the variation of substitution on the phenyl ring of benzaldehyde.

A theoretical investigation have concluded that the global electrophilicity (w) of benzaldehyde and its different substituents is the sole factor in governing the chemoselectivity in acetalisation, although steric factors also cause minor variation in the yield in some cases.

Global Reactivity Descriptor

From a qualitative proposition the global electrophilicity descriptor is defined as follows:

$$w = \mu^2 / 2\eta$$

Here, w is considered to be the electrophilic power of the concerned chemical species and bears the conceptual similarity to power of classical electricity (i.e. Power = V^2/R), where V and R represent the potential difference and resistance respectively). In the above, μ is the 'chemical potential' and η is 'global chemical hardness' of the concerned chemical species.

Physical Significance

The more is the difference of the global electrophilicity value between electrophile and nucleophile the better is the yield because lower is the w value stronger is the nucleophile.

Local Reactivity Descriptors

Parallel to the development of global reactivity descriptor some local reactivity descriptors were also proposed because of their potential use in predicting local (or site) reactivity (selectivity) of a chemical species. The condensed local softness values are represented by s_k^+, and s_k^- of atom 'k' towards nucleophilic, electrophilic attack respectively.

Physical Significance

In a molecule the atom 'k', for which s_k^+ value is highest, is the most preferred atom to be attacked by a nucleophile. Similarly, highest values of s_k^- for any atom 'k' indicate it to be the most preferable atom for electrophilic attack. The local reactivity descriptors as well as global electrophilicity values were calculated using MPA/6-31G (D, P) method using Gaussian program and HPA/dnp methods using DMOL program. The HPA method is more reliable than MPA in explaining the chemoselectivity.

Explanation to Selectivity Based on the Values Calculated by HPA/dnp Method

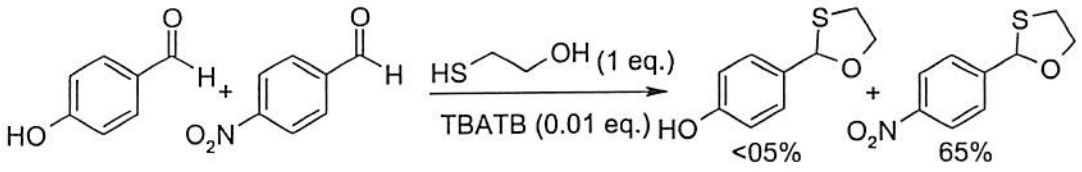
Because of large size and negligible negative charge (-0.0530) (in HPA / dnp method) sulphur atoms in 1,2-ethanedithiol behave as soft bases. So, the interaction of carbonyl carbon (having comparatively lower positive charge on it) in *p*-hydroxybenzaldehyde with sulphur atom in 1,2-ethanedithiol is mainly orbital controlled soft-soft in nature. Because of higher positive charge this type of soft-soft interaction will not be effective with *p*-nitrobenzaldehyde. Thus the major product expected is cyclic *S,S* acetal of *p*-hydroxybenzaldehyde.

The higher positive charge on the carbonyl carbon of *p*-nitrobenzaldehyde than on the carbonyl carbon of *p*-hydroxybenzaldehyde, which is also due to the electron withdrawing nature of $-NO_2$ group and high negative charge on oxygen of 1,2-ethanediol makes the charge controlled hard-hard interaction very effective. The hard-hard interaction between carbonyl carbon of *p*-hydroxybenzaldehyde and oxygen of 1,2-ethane diol is not that effective because of lower positive charge on carbonyl carbon in the former. Also the difference of global electrophilicity between *p*-nitrobenzaldehyde and 1,2-ethanediol is significantly higher than between *p*-hydroxybenzaldehyde and 1,2-ethanediol. These two factors favour the *O,O* acetal formation of *p*-nitrobenzaldehyde.

Because of the competitive reaction condition *p*-nitrobenzaldehyde forms *O,O* acetal with 1,2-ethane diol and *p*-hydroxybenzaldehyde forms *S,S* acetal with 1,2-ethanedithiol. The reason is that the highest global electrophilicity of *p*-nitrobenzaldehyde plus higher positive charge of carbonyl carbon favours it to react with the lowest electrophile (*i.e.* strongest nucleophilic) 1,2-ethanediol (which has also higher negative charge on oxygen atoms) in a charge controlled hard-hard way. Similarly, *p*-hydroxybenzaldehyde reacts with 1,2-ethanedithiol in an orbital controlled soft-soft pathway.

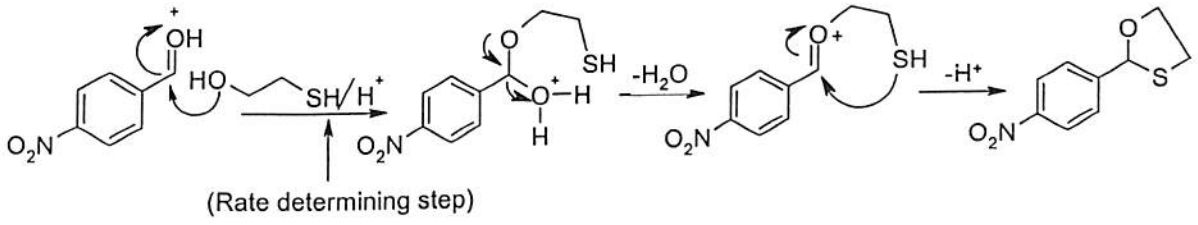
When an equimolar mixture of *p*-hydroxybenzaldehyde and *p*-nitrobenzaldehyde was reacted with an equimolar amount of mercaptoethanol and TBATB (0.01 equiv) in THF, *p*-nitrobenzaldehyde

was oxathioacetalised in good yield where as *p*-hydroxybenzaldehyde gave poor yield, which is shown in the Scheme 1B.4.



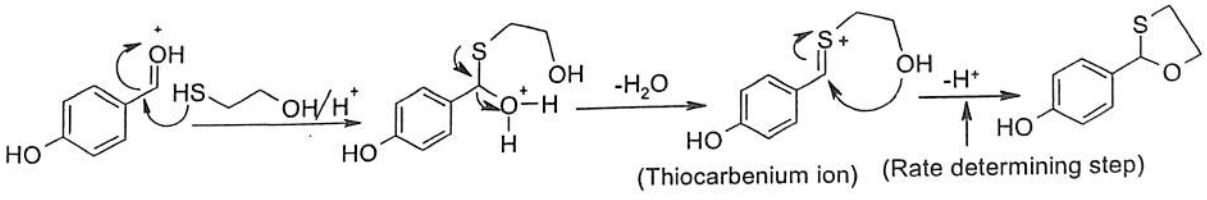
Scheme1B.4. Chemoselective Oxathioacetalisation

Higher positive charge on carbonyl carbon of *p*-nitrobenzaldehyde and higher negative charge on mercaptoethanol $HS(CH_2)_2OH$ favours oxathioacetal formation for *p*-nitrobenzaldehyde. As per explanations in the previous schemes it is expected that the initial attack by oxygen atom in mercaptoethanol to the deactivated carbonyl group of *p*-nitrobenzaldehyde will take place in the first step which is charge controlled. This is then followed by an intramolecular nucleophilic attack by the sulphur atom on the oxycarbenium ion as shown in Scheme 1B.5.



Scheme1B.5. Proposed Mechanism for Oxathioacetalisation

Here as both the first and third steps are energetically favourable, the yield of *S,O*-oxathioacetal of *p*-nitrobenzaldehyde is higher. The probable reaction mechanism shown above is consistent with the product distribution in Scheme 1B.4. It has also been experimentally found that *O,O* acetals can easily be converted to *S,S* and *S,O* acetals (because third step is energetically more favourable in case of transthioacetalisation process. On the other hand sulphur atom is attacking first to the carbonyl carbon of the *p*-hydroxybenzaldehyde followed by an intra-molecular attack of oxygen atom of mercaptoethanol as shown in Scheme1B.6.



Scheme1B.6. Proposed Mechanism for Oxathioacetalisation

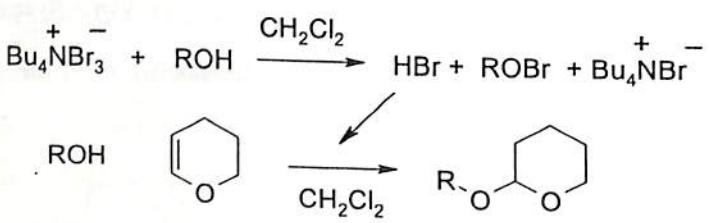
It has been concluded from the theoretical investigation that atomic charges, global electrophilicity descriptor (*w*) and hard-soft acid base concept are used to explain the chemoselectivity

in acetalisation, thioacetalisation and oxathioacetalisation. Although *w* values can explain the yields, charge and local softness values of the interacting sites explain the plausible reaction mechanism. The type of attack on the most electrophilic atom *i.e.* carbonyl carbon of the aldehyde by the most nucleophilic atoms oxygen atom of diol and sulphur atom of dithiol helps to understand whether the attack is charge-controlled or orbital-controlled. Although in general, both the steric and electronic factors contribute to the stability of the transition state, the contribution of steric factor is negligible here as in both the substrates *p*-hydroxybenzaldehyde and *p*-nitrobenzaldehyde, substituted groups are in para position. Hence it seems to be physically meaningful to assume that electronic factors are the sole contributors to the stability of transition states thus control the reactivity that influences the yields of the reactions studied here.

1B.2. Tetrabutylammonium Tribromide TBATB-Promoted Tetrahydro- pyranylation and Depyranylation of Alcohols

Tetrahydropyranylation is normally achieved with a mild acidic reagent in an aprotic solvent such as CH_2Cl_2, THF, acetone etc.; and deprotection also with an acidic reagent but in a polar or protic solvent such as methanol, ethanol, isopropanol, acetonitrile, etc.

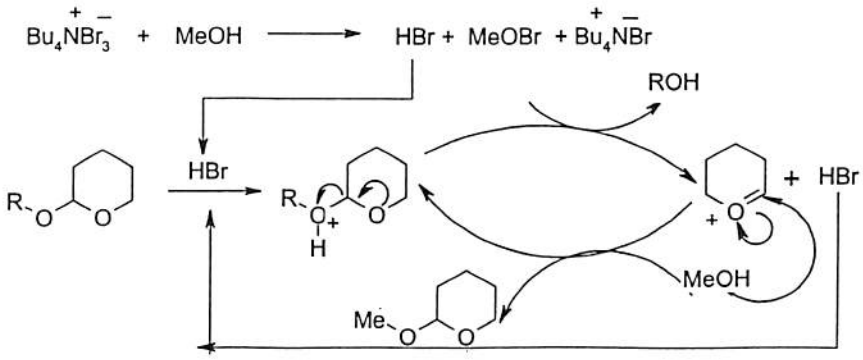
Tetrahydropyranylation of alcohols was performed using TBATB (0.025 equiv.) as a promoter in the presence of 3,4-dihydro-2*H*-pyran (1.1equiv) in CH_2Cl_2 at room temperature. Tetrahydropyranylation did not occur when the blank runs were performed in the absence of TBATB. Despite the use of an aprotic solvent CH_2Cl_2 during pyranylation, the occurrence of this reaction may be attributed to the *in situ* formation of HBr by the interaction of alcohol with TBATB, as shown in Scheme 1B.7.



Scheme 1B.7. Tetrahydropyranylation of Alcohols

Depyranylation was performed using TBATB by changing the solvent to methanol instead of CH_2Cl_2. In addition to generating HBr, methanol also facilitates the reaction by a transacetalisation process. Gas chromatographic co-injection analysis unequivocally established the formation of 2-

methoxytetrahydropyran as a transacetalisation product and in turn the mechanism. The proposed reaction mechanism is shown below in Scheme 1B.8.



Scheme 1B.8. Depyranylation of Tetrahydropyranyl Ethers

The general applicability of the methodology was confirmed by the tetrahydropyranylation of a wide spectrum of hydroxyl compounds ranging from primary, secondary, tertiary, benzyl alcohols in good yields with TBATB as a promoter. The tolerance of various protecting groups has been examined by reacting substrates bearing substituents such as nitro, alkene, alkyne, esters, OBn, Boc, isopropylidene, OTs etc.

This methodology provides a useful alternative for the preparation as well as cleavage of tetrahydropyranyl ethers to the corresponding alcohols. The main advantages of our methodology are mild reaction conditions, high efficiencies, quick and clean, economic viability of the reagent, industrial applicability and tolerance to a wide range of functionalities. We believe that this will be a useful addition to modern synthetic methodologies. The possibility of deprotection using the same catalyst with slight change in experimental protocol makes this method an attractive strategy, offering advantages over other methods, which use different catalysts.

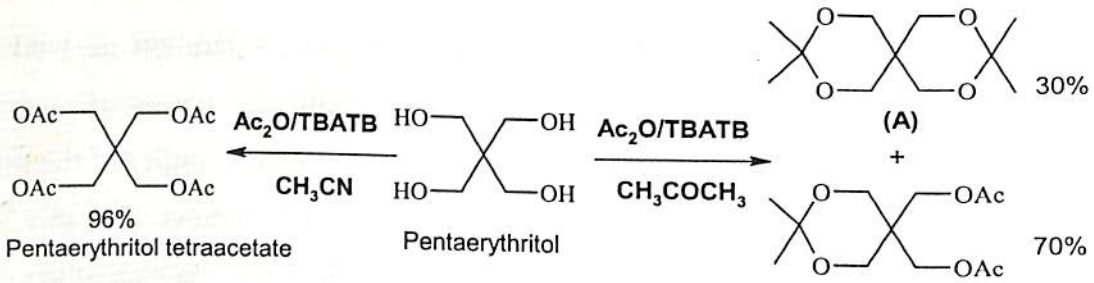
1B.3. Tetrabutylammonium Tribromide (TBATB) as an Efficient Reagent for Acylation of Alcohols, Amines and Thiols

Earlier we have reported that the acidity of the reaction medium employing tribromides can be tuned by changing the polarity of the solvent. So taking this into account; the acylation of alcohols, amines and thiols were performed using acetic anhydride in different solvents such as toluene, methylene chloride, chloroform and acetone. When 3-phenyl propanol was reacted with acetic anhydride in the presence of TBATB in above solvents separately, it was observed that the reaction proceeded much faster in acetone compared to other solvents. This may be due to the reaction of acetone with

TBATB to form bromoacetone and thereby generating anhydrous HBr *in situ*, which catalyses the reaction. This result prompted us to use acetone as the reaction medium.

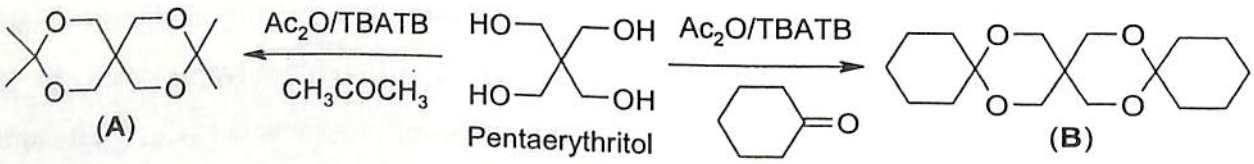
The acetylation of a wide range of structurally varied aliphatic, benzylic, allylic alcohols, amines, phenols and thiol highlight the fact that the method is capable of generalisation. The acetylation methodology was also successfully applied to a representative variety of functionalised alcohols. Due to the mild reaction conditions a number of functional groups remain intact, in spite of being capable of reacting with tribromides. In terms of compatibility and selectivity this method is superior to many of the reported methods. Solvent and steric factors in substrates as well as anhydrides play a significant role during the formation of acylates. The acetylation of diol was achieved with 2.5 equivalents of acetic anhydride.

When pentaerythritol, a substrate with four symmetrical hydroxyl groups was subjected to react under the present reaction condition with 5 equivalents of acetic anhydride two products were obtained in the ratio (3:7). However, the desired tetra acetylated product was obtained by changing the solvent to acetonitrile, Scheme 1B.9.



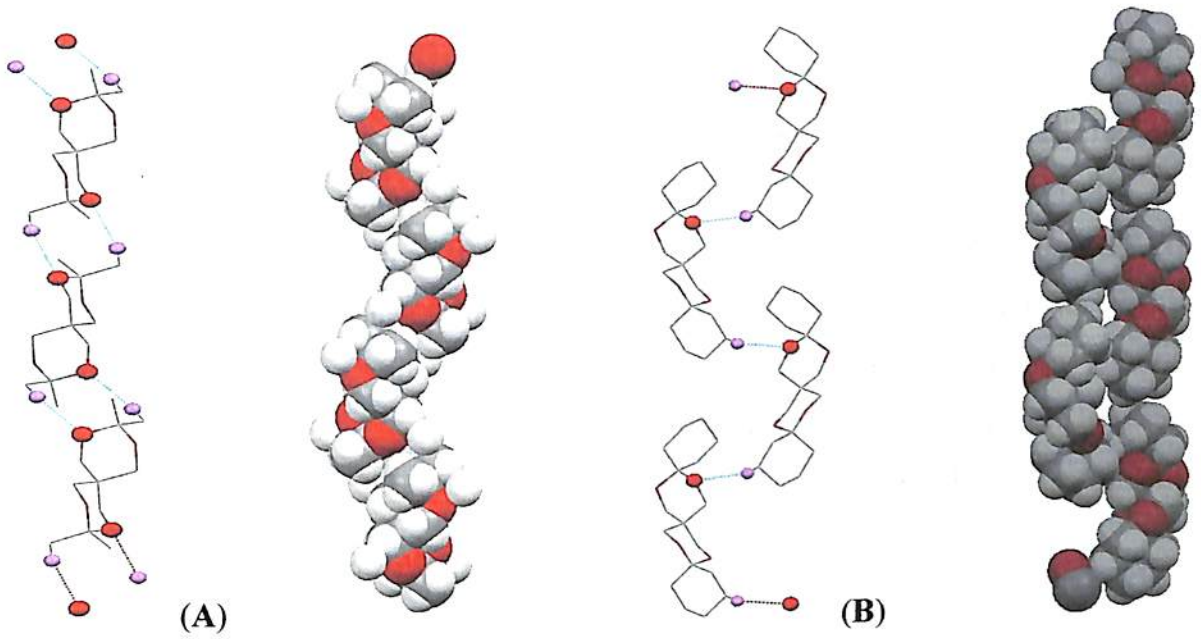
Scheme 1B.9. Acetylation and Isopropylidation of Pentaerythritol

After being intrigued by the above results, when the reaction was performed with cyclohexanone, similar results were obtained. The two crystalline compounds so obtained are 3,3,9,9-tetramethyl-2,4,8,10-tetraoxa-spiro[5.5]undecane, (A) and 7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]-heneicosane (B) respectively, Scheme 1B.10.



Scheme 1B.10. Isopropylidation and Cyclohexylidation of Pentaerythritol

The two bis acetals derived from pentaerythritol with acetone and cyclohexanone were of interest. These crystalline compounds gave the following structure.



Scheme 1B.11. View Illustrating Intramolecular Hydrogen-Bonded Interactions Between Adjacent Molecules Within the Helix. Carbon-Bound Hydrogen Atoms have been Omitted for Clarity. (A) 3,3,9,9-Tetramethyl-2,4,8,10-tetraoxa-spiro[5.5]undecane and (B) 7,11,18,21-Tetraoxatrispiro [5.2.2.5.2.2] heneicosane.

The weaker CH….O interaction mediates the unprecedented helical assembly of sterically encumbered bis acetals. These molecules contain a high degree of encoded molecular recognition functionality. One of the oxygen atom from one side form complementary weak CH….O interactions with the adjacent molecule. Additionally, due to steric crowding of cyclohexyl and dimethyl groups the molecule is forced in to a twisted conformation. Combinations of these molecular features would translate into a helical supramolecular array held together by intermolecular C-H….O interaction as shown in Scheme 1B.10.

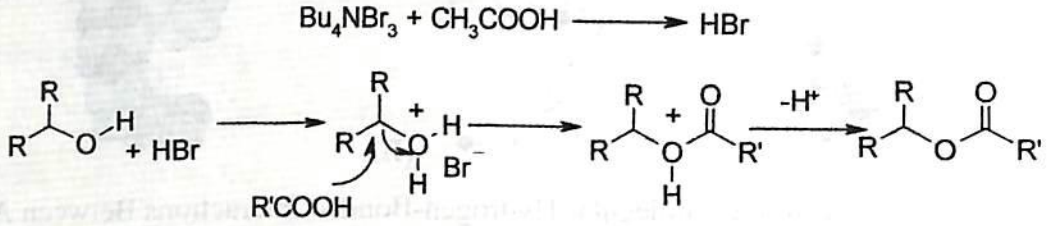
1B.4. Tetrabutylammonium tribromide Mediated Condensation of Carboxylic Acids with Alcohols

Direct condensation of alcohols with carboxylic acid is preferred to acylation using anhydrides or acid chlorides. But the direct condensation of carboxylic acids with alcohols is generally avoided because the equilibrium between the substrates and the products require the elimination of water from the reaction mixture using dehydrant or azeotropically to shift the equilibrium in favour of product.

To investigate the direct condensation of carboxylic acids with alcohols in presence of TBATB, 3-phenyl propanol was treated with glacial acetic acid (5 mL) in the presence of TBATB (0.5 mmol)

was carried out at elevated temperature. Surprisingly, even without the removal of water, esterificatior was very satisfactory; hence no special precaution was required for the removal of water from the reaction mixture.

In a control reaction when decanol was treated with TBATB (0.1 mmol) no alcohol brominatior was observed at all. TBATB is known to release anhydrous HBr in an alcoholic medium and othe organic solvent. The pH of the neat acetic acid recorded was 0.8, which drop to a value of -0.9 or addition of TBATB under the identical reaction condition. The HBr with pKa (-9) is sufficiently acidi as compared to protonated carboxylic acid pKa (-7) and protonated alcohol pKa (-2). Thus, alcoho would preferentially protonated over carboxylic acid. The nucleophilic attack of carboxylate on th oxonium species will yield acylated product as shown in Scheme 1B.12.



Scheme 1B.12. Mechanism of Acylation with Acetic Acid

TBATB is found to be an excellent source of anhydrous HBr, which catalyses the direc condensation of acid with alcohol. The operation is quite simple, because chemical dehydrating agent such as anhydrides, silyl additives or special apparatus such as Soxhlet-thimble, Dean-Stark apparatus i not necessary. Reaction under a solvent free condition, shorter reaction time accompanied by good yiel and operational simplicity are some of the interesting features of this procedure.

The other two sections *viz.* Section 1C and 1D describes the general experimental procedures an spectral data of this chapter.

CHAPTER 2
N-Acylation of Amines in Aqueous Medium
Section 2A: Introduction

Chemical products and processes have contributed fundamentally in shaping the world, as w know it today. With the aid of modern instruments and techniques, organic synthesis has continuousl generated products which are synthetically useful. Further development is required in terms o environmentally friendly processes and products, which is socially desirable and also can b economically affordable. Most organic solvents are flammable, explosive, toxic and carcinogenic. Th removal of organic solvents and use of environmentally friendly solvents in chemical synthesis is a

important aspect in the drive towards benign chemical technologies. Being the solvent of life, water is necessarily a non-toxic solvent and environmentally friendly solvent.

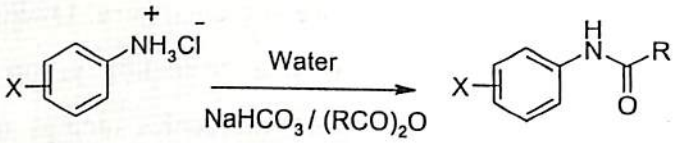
Water is a solvent of academic interest as well as human and economic interest because it minimises environmental impact, increases operational safety and provides a low cost and reusable reaction medium for pursuing reaction chemistry. Furthermore it is also the most abundant, cheap, non-toxic, safe and non-hazardous solvent hence can serve as an alternative solvent for organic reactions. The possibility of using water as the solvent for organic reactions with surprising and unanticipated results has been addressed in the literature. But the lower solubility of organic apolar substrates (reactants) in water, incompatibility of the intermediates with water and the competition between the desired reaction and hydrolysis restricts its use in organic synthesis. In general, apolar organic compounds can be solubilised in water by addition of organic cosolvents, amphiphiles such as hydrotrope or surfactant and by ionic derivatisation with control of pH, use of buffer or hydrophilic auxiliaries.

Acylation of amines is a fundamental process in organic chemistry. Owing to the nucleophilic and basic character of amines they must be blocked with a protecting group during a multi-step synthesis, e.g. in the synthesis of a diverse array of biological molecules such as amino acids, peptides, glycopeptides, aminoglycosides, β-lactams, nucleosides, sphingosines and alkaloids. Acylation of amines can be carried out using acyl transfer reagents, acetic acid and acylating reagents. Most of the acyl / acetyl transfer reagents are expensive and are obtained by acylation / acetylation with acylating / acetylating agents making them unsuitable for large-scale reactions. Acylating reagents such as acyl halides and acid anhydrides are usually employed in the presence of either acidic or basic catalysts. Thus, desirable features for these reactions would be a neutral medium, innocuous by-products, mild reaction conditions and greater tolerance towards other nucleophilic centers.

2B.1. N-Acylation of Amines in the Form of Amine Hydrochlorides in Water Using a Variety of Acyclic and Cyclic Anhydrides

Water is the non-toxic, cheap and the most abundant solvent, which is an interesting solvent for organic reactions serving as an alternative reaction medium. But the lower solubility of apolar substrates in water limits its use. In general, apolar organic compounds can be solubilised by addition of amphiphiles such as surfactant and on the other side amines in particular can be solubilised in water in the form of amine hydrochlorides.

Aliphatic and aromatic amines are basic in nature and can easily be protonated by mineral acids. To test our hypothesis and to optimise the reaction conditions, aniline was converted to water-soluble anilinium hydrochloride using aqueous HCl. The protonated ammonium species is non-nucleophilic due to non-availability of the lone pair of electrons on the nitrogen atom. Thus, when acetic anhydride was added to an aqueous solution of amine hydrochloride no acetylation occurred. However, upon addition of basic salts such as $NaHCO_3$ to the above medium, free amines were liberated which reacted immediately with acetic anhydride precipitating the acetylated product with the evolution of carbon dioxide. The reaction worked best when the final pH of the medium is *ca.* 5.5 approximately one pKa unit higher compared to that of acetic acid (pKa 4.8). Protonation of amine in an acidic medium has been confirmed by a hypochromic shifts of (π-π^*) and (n-π^*) by titrating a dilute solution of aniline with a dilute solution of HCl using UV spectrophotometer. A hyperchromic shift of these transitions upon addition of a dilute solution of sodium bicarbonate confirms the regeneration of free amines. The general scheme for the acylation is given below in Scheme 2B.1



X = H, CH_3, OCH_3, OH, NH_2, F

R = CH_3, CH_3CH_2, C_6H_5, CH_2CH_2COOH, CH=CHCOOH, C_6H_5COOH

Scheme 2B.1. *N*-Acylation of Amines

It has been observed that during the acetylation of aryl amines in an organic reaction medium electron-donating groups in the aromatic ring facilitate the reaction where as electron-withdrawing groups slow down the reaction. No such effect was observed by the present methodology and all the substrates reacted with equal ease. However, aryl amines gave better yields as compared to alkyl amines.

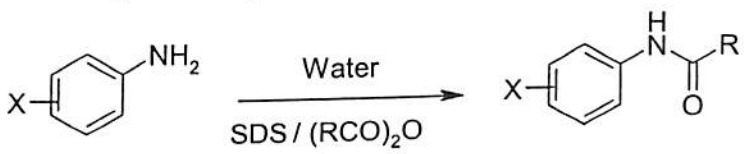
2B.2. N-Acylation of Amines Using Various Acyclic and Cyclic Anhydrides Using the Surfactant SDS for Dissolution of Amines in Water

The use of mineral acid (HCl) or base ($NaHCO_3$) makes the above method less attractive. Considering the environmental aspects, we looked for a greener alternative, devoid of any acidic or basic reagents. In one of our ongoing projects we noticed the solubility of several aromatic and aliphatic amines in an aqueous medium in the presence of sodium dodecyl sulfate (SDS). The SDS concentration (2.31×10^{-4} M) required for the dissolution of several aromatic amines is much lower than the critical

micelle concentration (8.3 x 10^{-3} M) of SDS, thus ruling out the possibility of micelle formation for the dissolution of amines. Initially, we speculated that the dissolution of the hydrogen donor amino group might be due to interaction with the hydrogen acceptor sulfonic acid group of SDS. But when the sodium salt of methane sulfonic acid was used instead of SDS, the amine did not dissolve at all; hence the possibility of the above type of interaction is ruled out. Other surfactants such as triton-X 100 and hexadodecyl ammonium bromide and phase transfer reagents such as tetrabutylammonium bromide can be used instead of SDS, thereby supporting the presence of hydrophobic-type interactions. Hydrophobic interactions are important non-covalent driving forces for inter- and intramolecular binding and assembly processes in aqueous chemistry.

In the earlier method the protonated ammonium ion obtained by the dissolution of amines in an acidic medium is non-nucleophilic, requiring a base to regenerate the nucleophilic amine for acylation. However, when SDS is used for its dissolution it retains its nucleophilic character.

Thus, when acetic anhydride was added to a SDS solution of an amine, acetylated products were obtained in moderate to good yields. It was gratifying to observe that the product precipitates from the reaction mixture in most of these cases. Increasing the ionic strength of the medium by adding sodium chloride to the reaction medium enhanced the amount of precipitation. To our utter surprise no base was required and the pH of the medium recorded at the end of the reaction was ca.7 when acetic anhydride was used as acetylating agent. The general is given below in Scheme 2B.2.



X = H, CH_3, OCH_3, OH, NH_2, F

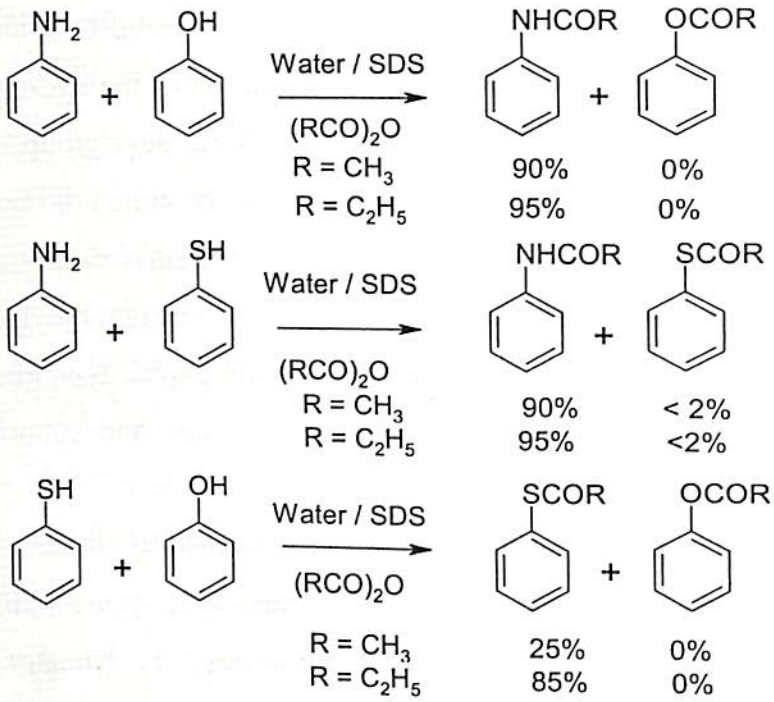
R = CH_3, CH_3CH_2, $CH(CH_3)_2$, $OC(CH_3)_3$, C_6H_5,

CH_2CH_2COOH, CH=CHCOOH, C_6H_5COOH

Scheme 2B.2. *N*-Acylation of Amines

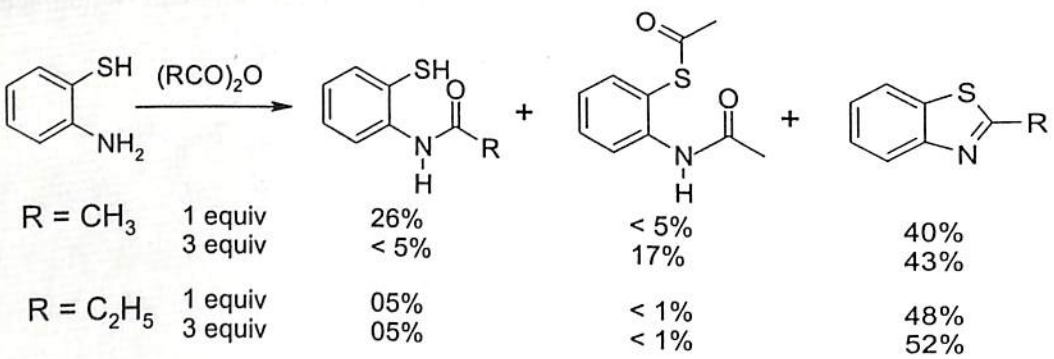
Chemoselectivity

Taking advantage of the differential reactivity of the nucleophiles amines, thiol and phenol under the present condition, we performed intermolecular chemoselective acetylation and benzoylation of aniline over thiophenol and phenol.

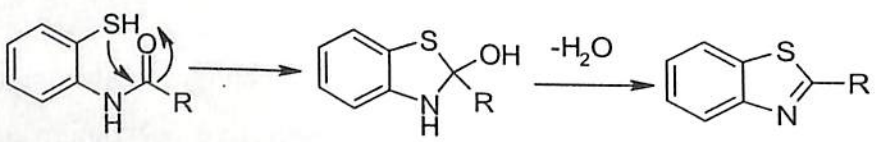


Scheme 2B.3. Intermolecular Chemoselectivity of Amines

The acetylation of 2-aminothiophenol produced the corresponding acetamide; the thiophenolic moiety remaining untouched with one equivalent of the reagent showing the intramolecular chemoselectivity, Scheme 2B.4.

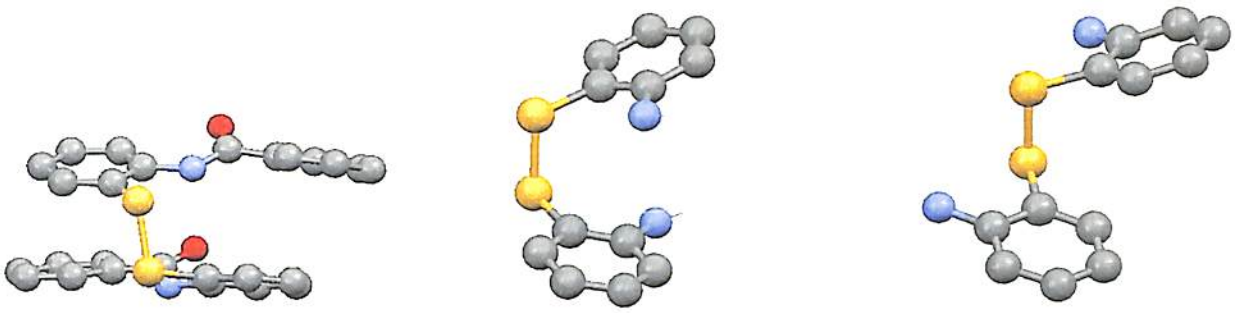


Scheme 2B.4. Intramolecular Chemoselectivity of 2-Aminothiophenol



Scheme 2B.5. Proposed Mechanism for the Formation of Products in Scheme 2B.4

A molecular clip motif has been induced due to weak π-π interactions in bis(2-benzoylaminophenyl)disulphide. Although the bent structure due to dihedral angle of 86.17° for S-S bond is itself embedded in its precursor bis(2-aminophenyl) disulphide (B), we speculate that the clip motif is achieved only by the introduction of additional phenyl groups during benzoylation, Figure 1.



(A) (A) (B)

Figure 1. (A) Bis(2-benzoylaminophenyl)disulphide and Bis(2-aminophenyl) disulphide(B)

In conclusion, this method represents a tremendous opportunity for the practice of green chemistry. The reactions are in general very clean giving good to moderate yields with excellent selectivity and no side products have been isolated. The method is environmentally friendly with respect to by-products. In addition chromatographic purification of the acylated product is not required. The simplicity, low cost of this procedure competes as a better practical alternative to the existing methods for the selective acylation of primary amines in the presence of phenols.

The other two sections *viz*. Section 2C and 2D describes the general experimental procedures and spectral data of this chapter.

Chapter 1

TetrabutylammoniumTribromide in Organic Synthesis

1A. Introduction

Increasing knowledge of the properties of molecules has led the way for synthesis of new compounds either by exploiting their advantages or by replacing their disadvantages with suitable alternatives. Bromine and its halogen brethren have become a necessary part of our complex world. Synthetic chemists are allured to bromine due to the versatile applications of bromoorganics in the synthesis of large number of natural products as well as in the manufacture of pharmaceuticals, intermediates for agrochemicals and other specialty chemicals. The commercial importance of bromoorganics is further evident from the availability of numerous industrially valuable products such as pesticides, insecticides, herbicides, fire retardants and other new materials, which carry bromo functionality. But the viciously corrosive red fuming liquid emits choking fumes, which is detrimental to human health. Added to this, the necessity for safe and responsible handling of this corrosive chemical has also been a cause of irrational fear. Intrigued by the potential hazards associated with molecular bromine and bearing in mind its indispensable role as well in human life, a safer alternative, organicammonium tribromide was developed.

1A.1. Brief Account on Different Organicammonium Tribromides

Organicammonium tribromides are the storehouse of bromine. These crystalline stable solids are convenient source of bromine owing to the ease in maintenance of the desired stoichiometry and the ease in storage, transportation and handling. Several organicammonium tribromides have been reported in the literature, which includes tetramethylammonium tribromide (TMATB), tetrabutylammonium tribromide (TBATB), tetraethylammonium tribromide (TEATB), cetyltrimethylammonium tribromide (CTMATB), pyridine hydrobromide perbromide (PHPB), phenyltrimethylammonium tribromide (PTATB), 1,8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide ($DBUHBr_3$), pentylpyridinium tribromide (PPTB), 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide. In addition to these tribromides, a ditribromide reagent such as 1,2-dipyridiniumditribromide-ethane (DPTBE) or 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) has also been reported.

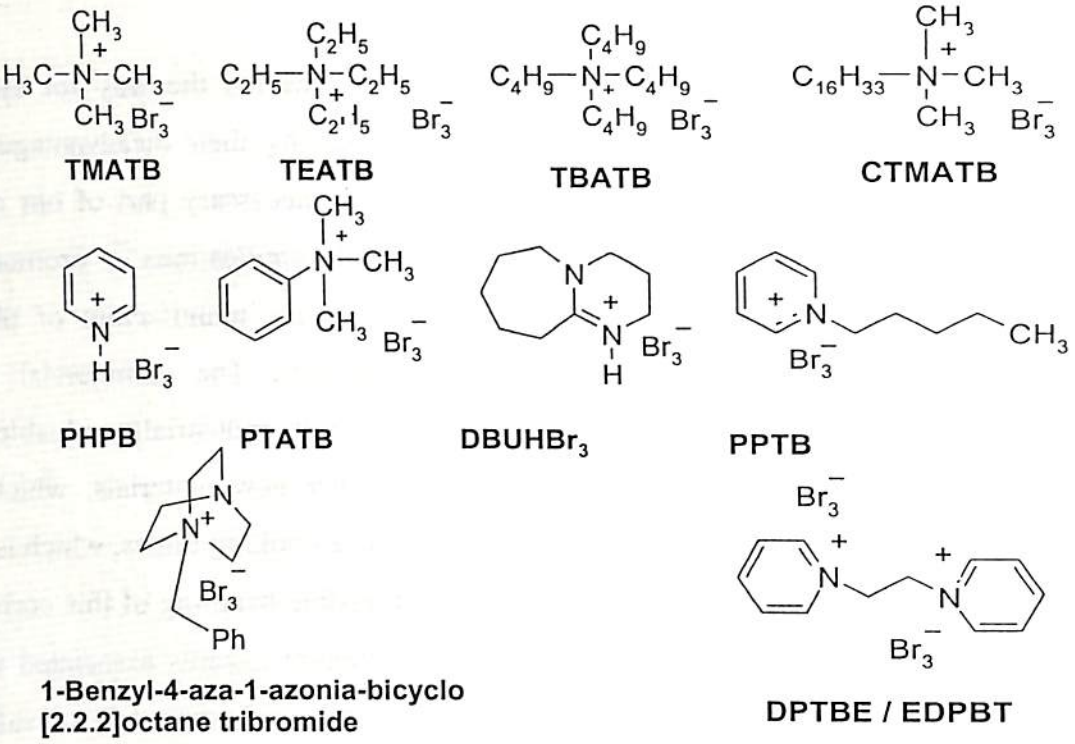
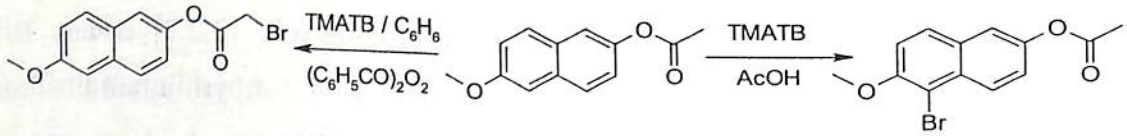


Figure 1.1

A summary of the work regarding their preparation as well as applications as reported in literature has been presented below. Chattway and Höfle were the first to report the preparation of tetramethylammonium tribromide (TMATB).[1] It was obtained by treating tetramethylammonium bromide with bromine in acetic acid. The product TMATB was found to contain 50.9% of active bromine. Its brominating property was studied by Avramoff and coworkers. TMATB furnished the sole nuclear bromination product, 2-acetyl-5-bromo-6-methoxynaphthalene when reacted with 2-acetyl-6-methoxy-naphthalene in acetic acid but gave α-brominated product with change in reaction conditions. Scheme 1A.1.[2]

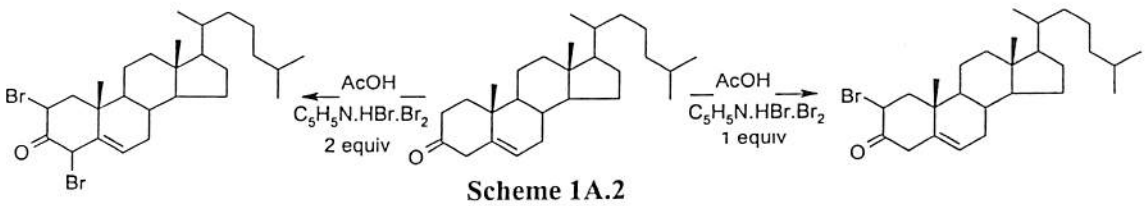


Scheme 1A.1

Djerassi and Scholz introduced pyridine hydrobromide perbromide ($C_5H_5N.HBr.Br_2$ or PHPB) in later years. It was prepared using equimolar amounts of bromine, pyridine and HBr (48% aq. solution).

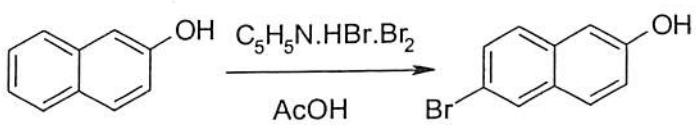
The red prismatic crystals of PHPB with a melting point of 134°C were crystallised from acetic acid with 45% available bromine.[3] This is a selective brominating agent used for α-bromination of ketones.

The monobrominated product, 2-bromo cholestanone and the dibromo derivative, 2, 4-dibromo cholestanone were obtained exclusively when used in 1 and 2 equivalents respectively with cholestanone, Scheme 1A.2.



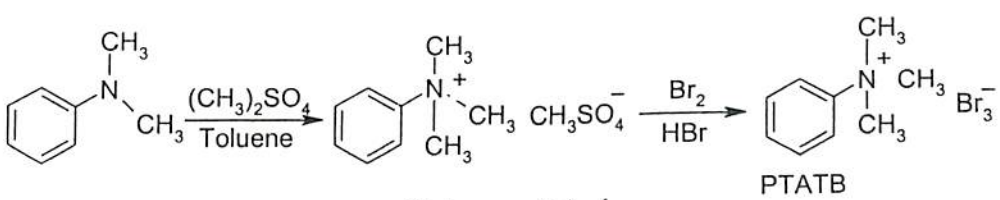
Scheme 1A.2

Merker *et al.* have further shown the efficacy of this reagent as a suitable substitute for bromine in performing bromination of various aromatic substrates, Scheme 1A.3.[4]



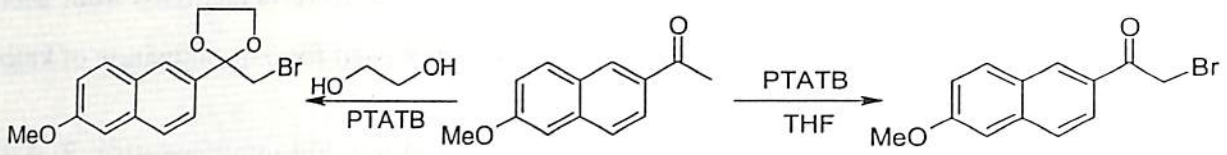
Scheme 1A.3

Phenyltrimethylammonium tribromide (PTATB) was prepared by adding 1.2 mole of Br_2 to one mole of phenyltrimethylammonium sulfomethylate in 48% HBr solution, Scheme 1A.4.[5] The crude orange-yellow precipitate that was recrystallised from acetic acid was found to contain 42.5% active bromine.



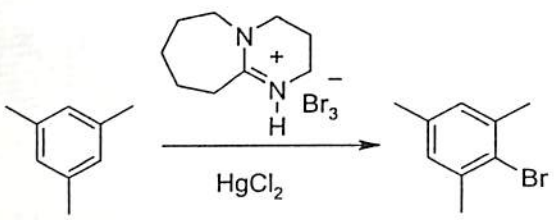
Scheme 1A.4

This reagent was found to be more stable compared to pyridinium hydrobromide perbromide (PHPB). PTATB is an excellent source of bromine when dissolved in THF and its reactivity is different from molecular bromine. It is found to be much less electrophilic and is less reactive towards aromatic rings and double bonds as compared to molecular bromine.[6] It is useful for selective α-bromination of ketones and ketals, Scheme 1A.5.[7]



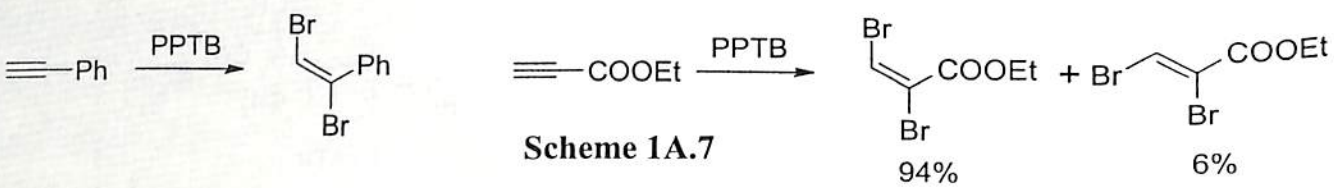
Scheme 1A.5

Synthesis of 1, 8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide ($DBUHBr_3$) in quantitative yield using an equimolar amount of bromine on DBU HBr in acetic acid, has been shown by Muathen.[8] This crystalline compound shows a greater stability over pyridine hydrobromide perbromide, which is reported to have three different bromine compositions with three different melting points.[9] Activated aromatics and heteroaromatics such as aniline, thiophene were brominated smoothly with good yield in aqueous DMF whereas a fairly reactive aromatic system such as mesitylene was brominated in presence of an equimolar amount of $HgCl_2$.



Scheme 1A.6

Owing to the high solubility of the protonated DBU in aqueous medium, $DBUHBr_3$ can be recovered and regenerated from the reaction medium after isolation of brominated products by treatment of the aqueous medium with HBr and $NaBrO_3$.

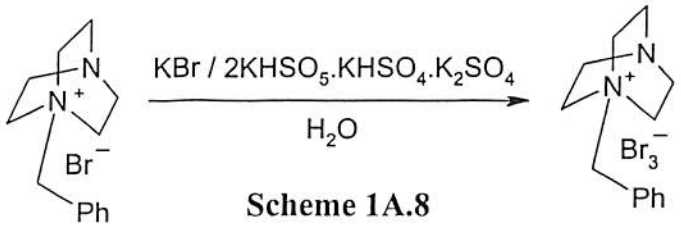


Scheme 1A.7

Salazar *et al.* have reported the synthesis of a room temperature ionic liquid tribromide, pentylpyridinium tribromide (PPTB), upon addition of an equimolar amount of bromine to a solid crushed pentylpyridinium bromide. This served as a vapour pressure free bromine analogue for bromination of ketones, aromatics, alkenes and alkynes. Dibromination of phenylacetylene afforded one sole isomer in excellent yield where as ethylpropiolate led to a mixture of *cis-trans* isomers, Scheme 1A.7.[10]

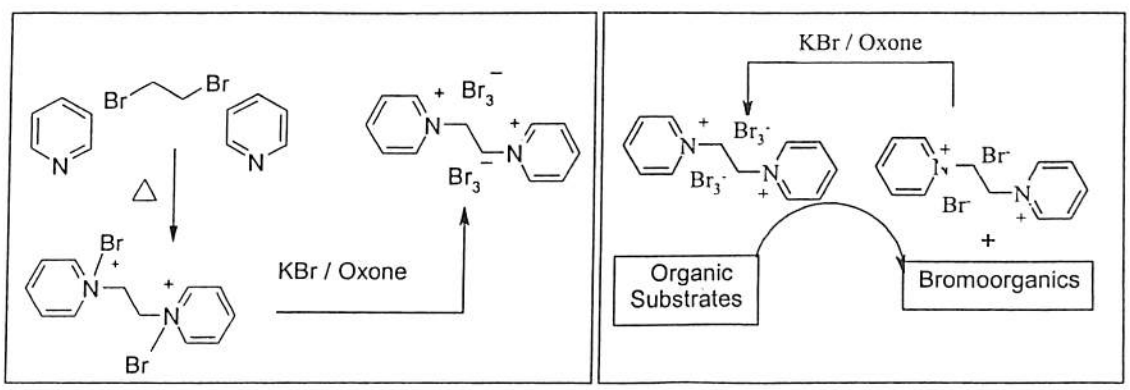
Synthesis of 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide by the addition of an aqueous solution of Oxone® to a solution of 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane bromide and

KBr, has been shown by Hajipour *et al*, Scheme 1A.8. [11] This is a reactive but selective brominating agent for the bromination of aniline derivatives in small amount of methanol in the presence of $CaCO_3$.



Scheme 1A.8

Recently our group has reported the synthesis of a new ditribromide reagent, 1,2-dipyridiniumditribromide-ethane (DPTBE) or 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). It was prepared by refluxing pyridine (2 equiv) with dibromoethane (1 equiv). The resultant 1,2-dipyridiniumdibromide-ethane (DPDBE) or 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) when treated with KBr (4.5 equiv) followed by oxidation of bromide to bromine using an aqueous solution of Oxone® (2 equiv) resulted in an orange precipitate of DPTBE or EDPBT. The active bromine content per molecule of DPTBE or EDPBT is 48%, which is higher compared to that of some of the other known tribromides. This reagent is superior to many of the tribromides in terms of selectivity, and recyclability.[12]



Scheme 1A.9

1A.1.1. Literature Reports on use of Tetrabutylammonium Tribromide in Organic Synthesis

The preparation of tetrabutylammonium tribromide (TBATB) by employing molecular bromine and tetrebutylammonium bromide was first reported by Buckles *et al.*[13] It has an active bromine content of 33%. It was found that the stereospecificity of addition of bromine to *cis*-stilbene decreases with

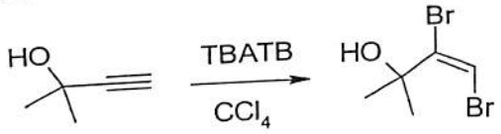
increase in polarity of solvent giving more and more meso-α,α'-dibromobenzyl in place of the *dl*-isomer whereas with a tribromide restoration of stereospecificity in more polar solvents was observed giving the *dl*-dibromide.[14]

Berthelot *et al.* have made an extensive study on the bromination of different substrates with TBATB. Phenols and amines have been brominated with TBATB to give the corresponding *p*-bromo product in $CHCl_3$. A mechanism involving electrophilic substitution by the tribromide has been suggested to account for the monobromination at the para position of phenols and amines in aprotic and non-basic solvents by tetrabutylammonium tribromide.[15]

R = NH_2, OH

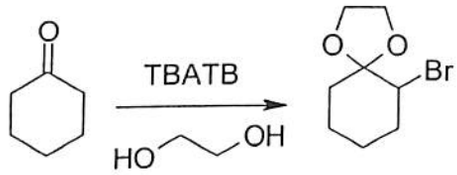
Scheme 1A.10

Stereoselective bromination of alkynes by TBATB has also been reported. Unlike the other reported methods using bromine, TBATB in CCl_4 gives the (E) isomer exclusively, Scheme 1A.11.[16]



Scheme 1A.11

TBATB has been shown to be a convenient reagent for α-bromination of ketone, but when reacted in the presence of ethylene glycol simultaneous keto protection was observed.[17]



Scheme 1A.12

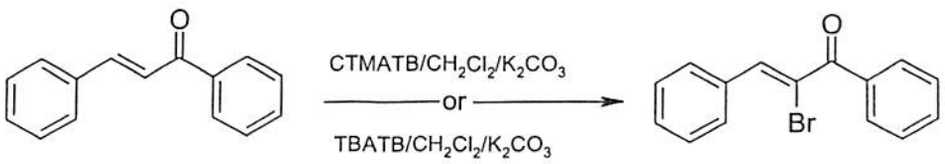
Berthelot *et al.* later reported bromination of styrene and ketone using TBATB to yield respectively dibromo styrene ($PhCHBrCH_2Br$) and α-bromo ketone.[18]In the later years Kajigaeshi *et al* reported the synthesis of TBATB without using molecular bromine. Bromine was generated *in situ* using $NaBrO_3$ and HBr.[19]The efficacy of the methodology was employed for α-bromination of various ketones.

Bellucci *et al.* have reported the diastereoselective bromination of allyl glucosides using tetrabutylammonium tribromide. Both (*R*) and (*S*)-2,3-dibromo-l-propanol with enantiomeric excess (ee

upto 60% have been obtained by diastereoselective addition of Br_2 to allyl glucosides and galactosides having only one unprotected hydroxyl group at C-2 or C-6 using tetrabutylammonium tribromide, followed by hydrolysis. The absolute configuration is shown to depend on the position of free hydroxyl and at the anomeric centre.[20]

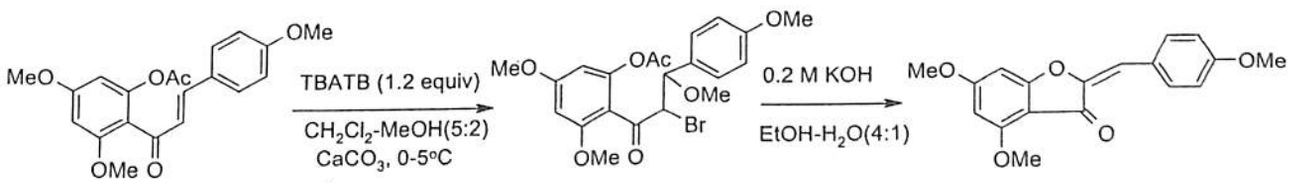
In the recent years, Chaudhuri *et al.* have developed an environmentally benign route for the preparation of TBATB using peroxovanadium (V)-mediated biomimetic oxidation of bromide circumventing the use of Br_2 or HBr.[21] TBATB was obtained readily from the reaction of TBAB with H_2O_2 and V_2O_5. The stable, orange crystalline TBATB obtained in this way is air and moisture tolerant, easy to handle, store and maintain the desired stoichiometry. The *in situ* generated tribromide has been used for bromination of various organic substrates.[22]

Khan *et al.* have reported a convenient and useful method of preparation for various acyclic and cyclic α-bromoenones from the corresponding enones using organicammonium tribromides *vis*. TBATB and CTMATB. The dibromoderivative of enone undergoes elimination in the presence of K_2CO_3 giving α-bromoenones, Scheme 1A.13.[23]



Scheme 1A.13

An environmentally benign synthesis of aurones and flavones from 2'-acetoxychalcones using tetrabutylammonium tribromide has been reported by Khan *et al.*, Scheme 1A.14.[24]The bromination step is the decisive step which directs the formation of flavone and aurone. The formation of the cyclised product aurone is attributed to Br being a better leaving group than OMe and hence favouring the cyclisation exclusively at the α-position.

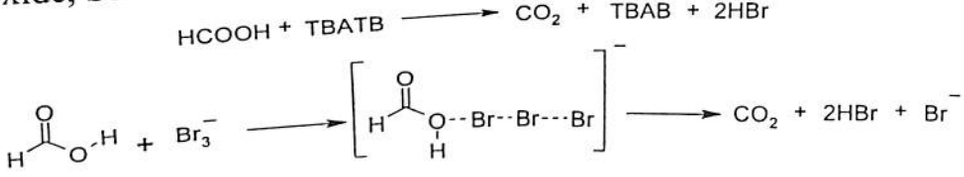


Scheme 1A.14

The use of TBATB as a brominating agent has been addressed broadly in the above section. In addition to being used as an efficient brominating agent, TBATB is widely used as an oxidising agent. A literature review of its use as an oxidising agent is presented below.

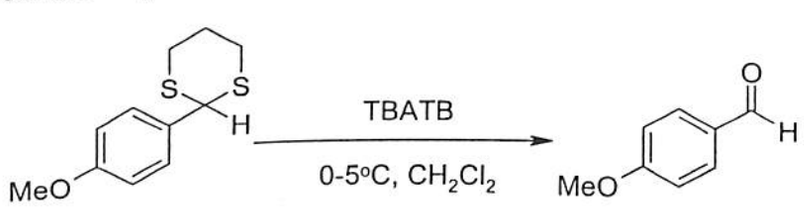
The tribromide ion of TBATB has been exploited as the reactive oxidising species for the oxidation of aliphatic alcohols, substituted benzyl alcohols, secondary alcohols, vicinal and nonvicinal diols by Sharma and Banerjee. They have also carried out a correlation analysis of reactivity in oxidation of different substituted benzyl alcohols by TBATB. The rate of reaction increases with increase in the polarity of the solvent. The reaction is susceptible to both polar and steric effects of the substituents. A mechanism involving transfer of hydride ion from the substrate to tribromide in the rate determining step has been proposed.[25] An extensive study on the kinetics and mechanism of oxidation of aliphatic aldehydes, α-hydroxy acids, α-amino acids, formic and oxalic acids, lower oxyacids of phosphorous has also been performed by the same group.[26]

The oxidation of organic acids such as formic acid and oxalic acid by TBATB leads to the formation of carbon dioxide, Scheme 1A.15.



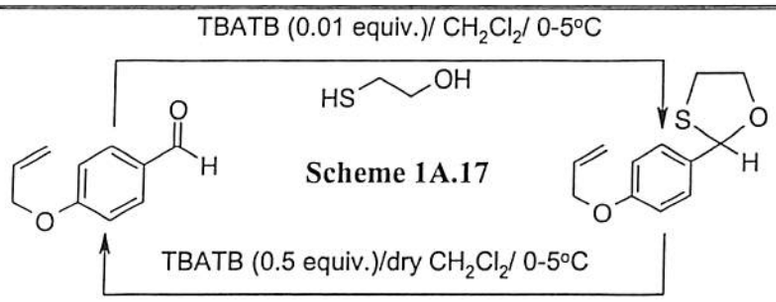
Scheme 1A.15

Chouhan and Sharma have reported the oxidation of DL-methionine by TBATB to corresponding sulfoxides and also studied the oxidation of various thioacids viz. thioglycollic, thiolactic, thiomalic acids by TBATB in acetic acid.[27] Oxidative regeneration of carbonyl compounds from dithioacetals has been described by Khan *et al.* using tetrabutylammonium tribromide, Scheme 1A.16.[28]



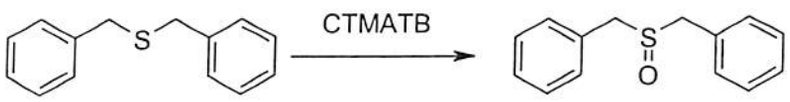
Scheme 1A.16

Sharma *et al.* reported the oxidative regeneration of carbonyl compounds from oximes.[29] useful and convenient synthetic protocol for interconversion of carbonyl compounds to th corresponding 1,3-oxathiolanes and vice versa employing organic ammonium tribromide (OATB) w also reported, Scheme 1A.17.[30]



Scheme 1A.17

Synthesis of CTMATB, and TEATB and the application of CTMATB to selective oxidation of sulfides to sulfoxides have also been addressed in the literature showing CTMATB as an oxidising agent.[31]

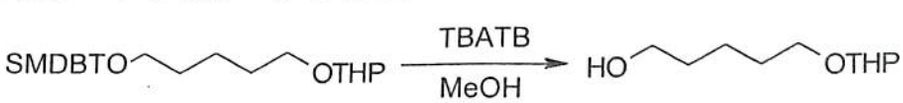


Scheme 1A.18

The tribromide, TBATB has been extensively utilised for the bromination of organic substrates and reports exemplifying it as an oxidising agent have also been described in the literature. Its precursor TBAB is less expensive compared to other organicammonium bromides, and it is prepared in an environmentally benign route using V_2O_5- H_2O_2. This makes TBATB a synthetically useful reagent. Hence its applications to various other aspects of organic synthesis were found to be of interest.

Prompted by the report of Kajigneshi *et al.* about the generation of HBr and MeOBr from benzyltrimethylammonium tribromide in methanol[32] it was speculated that TBATB would react similarly with alcohol.

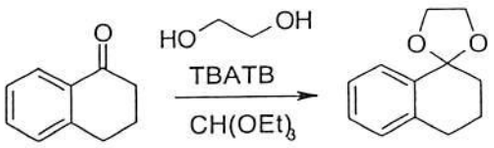
In the previous years, our group has exploited TBATB-MeOH as an efficient chemoselective reagent for the cleavage of *tert*-butyldimethylsilyl (TBDMS) ether, Scheme 1A.19.[33] The solvent dependent study of the cleavage of TBDMS ethers with TBATB highlighted the possibility of tuning the acidity of TBATB in various solvents. Its acidity can be tuned from highly acidic pH to near neutral pH in various organic solvents. It has been inferred that TBATB can readily differentiate THP over TBDMS and TBDMS over TBDPS. The apparent order of stability obtained is phenolic TBDMS > 1° OTBDPS > 2° OTBDMS > 2° OTHP > 1° OTHP > 1° OTBDMS > 1° ODMTr.



Scheme 1A.19

Our group has also explored the role of tetrabutylammonium tribromide as an efficient generator of HBr in the chemoselectice acetalisation of carbonyl compounds, Scheme 1A.20.[34] Acyclic and cyclic

acetals of various carbonyl compounds were obtained with 0.01 equiv. of TBATB. No α-brominated product was observed for substrtates amenable to α-bromination.



Scheme 1A.20

After a comprehensive perusal of literature relating to the preparation as well as synthetic applications of TBATB we arrived at the following conclusions.

- TBATB can be prepared in an environmentally benign way.
- Its usefulness as a brominating and oxidising agent has been explored widely in the last few decades.
- This reagent is an efficient generator of anhydrous HBr in alcohols and many other organic solvents. Its acidity can be tuned to a wide range of pH ranging from acidic to near neutral.
- The various organic transformations which occur exploiting its mild acidity are quite useful especially when compatibility of various functional groups under a specific reaction condition is an important subject.

1A.2. Protecting Groups

Organic chemistry was originally the study of compounds connected with life owing to its wide coverage commencing from essential constituents of living matter such as carbohydrates, proteins, fats, nucleic acids, enzymes, and hormones to essential requirements of human life such as food, fuel, shelter and clothing, the principal component of each of which is organic. Now organic synthesis has reached to a level where the continuous generation of organic processes and products of synthetic utility has made it indispensable to the sustenance of human life.

Organic synthesis is an engineering on atomic scales, which takes into account various delicate operations to be performed. A synthetic plan to achieve a complex target is a matrix of several independent and parallel strategies involving several factors such as fragment synthesis, fragment linkage, stereochemistry, functional group interconversion and protecting groups.[35] The analysis of a complex target molecule retro synthetically simplifies a synthetic procedure by virtue of the formation of synthons, which are accessible either commercially or with the aid of laboratory procedures. However, the sequential steps take into account the compatibility of the functional groups under the

reaction conditions employed. Functional group compatibility is the basis for the conception of protecting group, which play a pivotal role in a multi-step organic synthesis. Though the introduction of protecting groups lengthens the synthetic route by two steps supplementing their removal under milder conditions but it cannot be circumvented. Owing to their usefulness, they have become an obligatory feature in organic synthesis. The protection-deprotection sequence is probably the most recurrent functional group interconversion in multistep organic synthesis.

1A.2.1. Carbonyl Protecting Groups

The electrophilic nature of the carbonyl group is a dominant feature in its extensive chemistry. Due to the electropositive nature of the carbonyl carbon, it is susceptible to nucleophilic attack, Scheme 1A.21.

Scheme 1A.21

Thus, protection of a carbonyl group from nucleophilic attack until its electrophilic nature is exploited is one of the most challenging problems of organic synthesis. Nevertheless, carbonyl-protecting groups also play an important role during multistep syntheses in organic, medicinal, carbohydrate, and drug design chemistry. A very small but useful catalog of protecting groups for carbonyl functionality of aldehydes and ketones includes acetals, thioacetals, oxathioacetals and 1,1-diacetates (Figure 1.2).

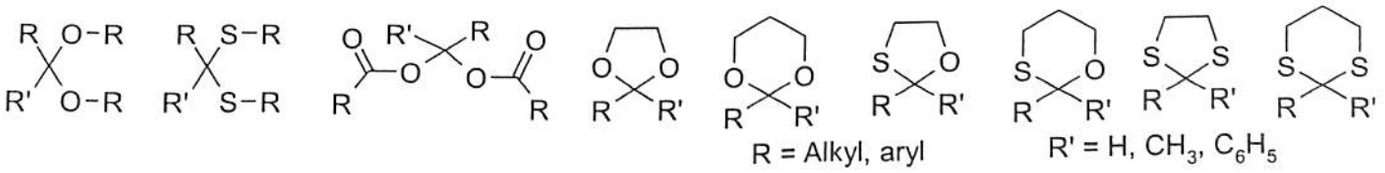


Figure 1.2

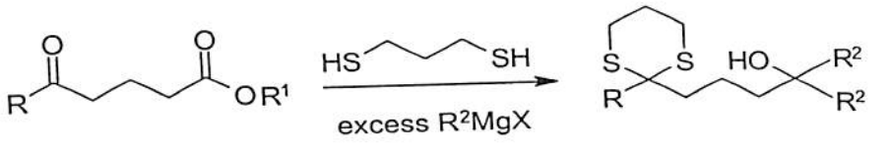
1A.2.1.1. Dithioacetals

1A.2.1.1. (a) Significance of Dithioacetals as Protecting Group

Dithioacetals such as 1,3-dithiolanes and 1,3-dithianes are the most widely used carbonyl protecting groups owing to their stability towards various reagents such as nucleophilic, basic, mild oxidising, catalytic and hydride reducing agents during a multi-step synthesis. They are easy to prepare as compared to *O,O*-acetals and are more stable towards chromatographic purification as well as acids

and bases. Further the use of the less obnoxious dithiols compared to acyclic thiols makes cyclic dithioacetals a suitable protecting group during a multi-step synthesis. The following section describes the significance of dithioacetals as a carbonyl protecting group.

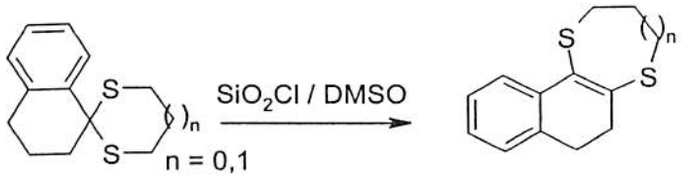
To carry out the reaction at the less electrophilic carbonyl carbon of the ester moiety, protection of the more reactive carbonyl group is necessary, which can be achieved as shown below, Scheme 1A.22.



Scheme 1A.22

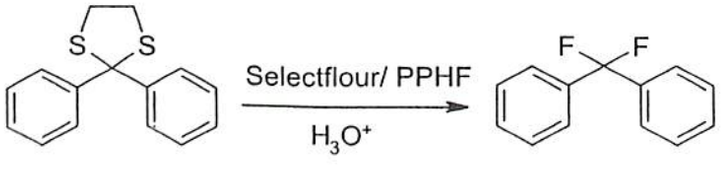
The protection of carbonyl group as a dithioacetal has been used for the synthesis of various natural and non-natural products.[36]

The ring expansion annelation of 1,3-dithiolanes and 1,3-dithianes has been used for the construction of larger rings containing sulfur atoms such as 1,4-dithiepins and 1,4-dithiins in dry CH_2Cl_2 in presence of SiO_2Cl / DMSO, Scheme 1A.23.[37]



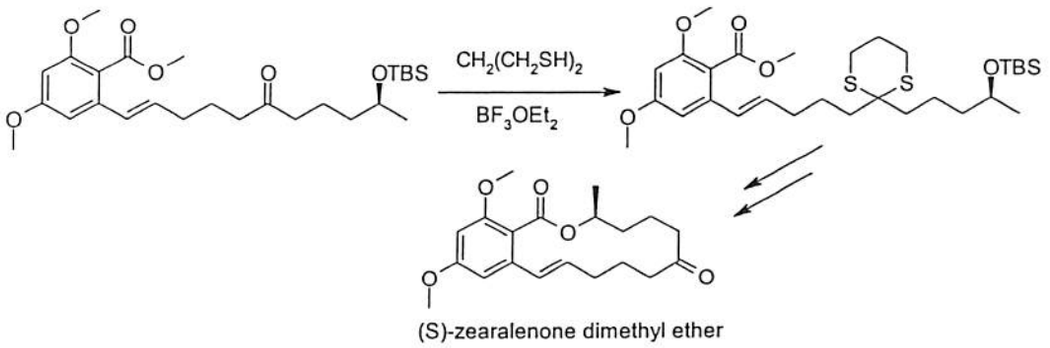
Scheme 1A.23

2,2-diphenyl-1,3-dithiolane of diaryl ketones has been used for synthesis of *gem*-difluoro compounds using selectflour® and pyridinium polyhydrogen fluoride, Scheme 1A.25.[38] The *gem*-difluoro compounds have found a wide range of biological applications.[39]



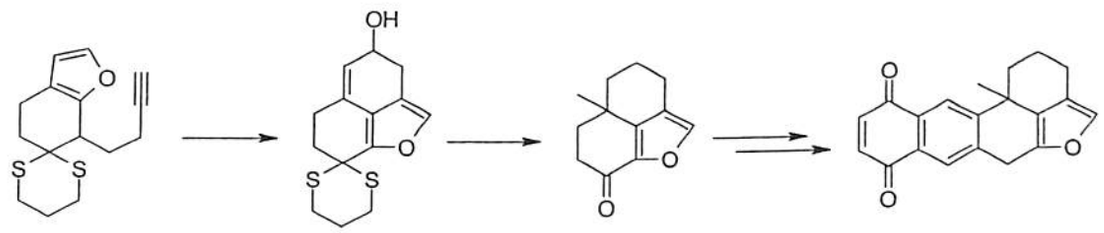
Scheme 1A.24

Protection of carbonyl group in the starting material is necessary before macrolactonisation in the synthesis of (S)-zearalenone dimethyl ether, a macrolide with anabolic and uterotropic activity, Scheme 1A.25.[40]



Scheme 1A.25

Kanematsu *et al.* have synthesised the natural fused furan xestoquinone by protecting the carbonyl group as dithiane, which is a powerful cardiotonic constituent isolated from marine sponge, Scheme 1A.26.[41]



Scheme 1A.26

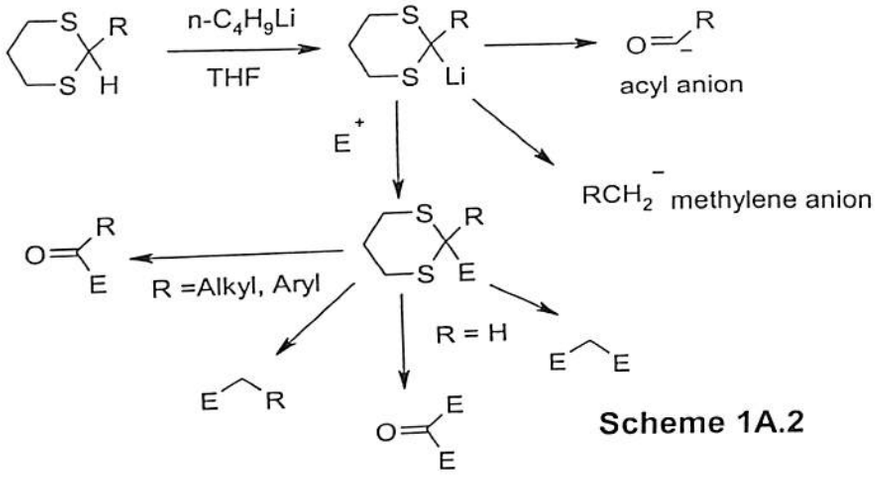
Dithioacetals are most often used inspite of the difficulties associated with their removal because of their inherent stability towards acidic conditions as compared to the corresponding *O,O*-acetals and *O,S*-acetals.

1A.2.1.1. (b) Synthetic Applications of 1, 3-Dithianes as Acyl Anion Equivalents

In addition to serving as a protecting group for carbonyl functionality of aldehydes and ketones, the synthetic applications of dithioacetals can be attributed as the main reason for its versatile chemistry. Dithioacetals in general and 1,3-dithianes in particular has attracted the attention of synthetic chemists due to the role of 1,3-dithianes as precursors for synthetic acyl anion equivalents, masked methylene functions for carbon-carbon bond forming reactions.[42,35]

Functionalisation of the masked carbonyl group allows different transformations, Scheme 1A.27. Some of these approaches have been used extensively for the total synthesis of complex

polyfunctionalised natural products.[43] The lithiated 1, 3-dithianes generated from the 1, 3-dithianes and butyl lithium are the most successful sulphur-stabilised acyl anion equivalents and are used as masked nucleophilic acylating agents.[44] This allows the normal reactivity of acyl carbon atom to be reversed. The temporary reversal of reactivity of a functional group is described by the term umpolung, which was first coined by Seebach.[45]



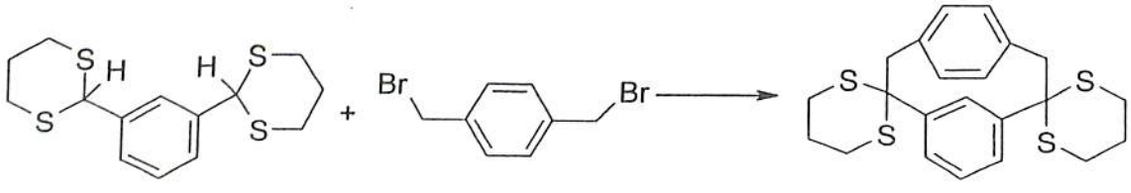
Scheme 1A.2

Various applications of the lithiated 1,3-dithianes are summarised below. Synthesis of 1,2- and 1,3-dicarbonyl compounds from dithianes, asymmetric synthesis based on 1,3-oxathianes, synthesis of oxo polyene macrolide antibiotics exploiting the dithiane chemistry has also been described in the literature.[46]

Aldehydes can be converted to ketones with increase in carbon number by alkylation of dithiane followed by hydrolysis with Hg^{2+} / H_3O^+ Scheme 1A.28.[47]

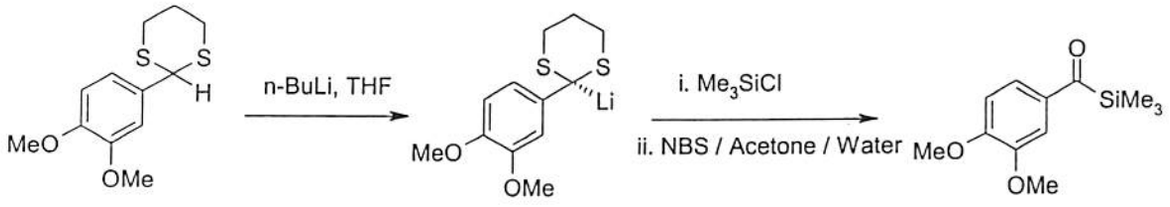
Scheme 1A.28

Cycloalkylation of the lithiated carbanion occurs with aryl halides as electrophile, Scheme 1A.29.[48]



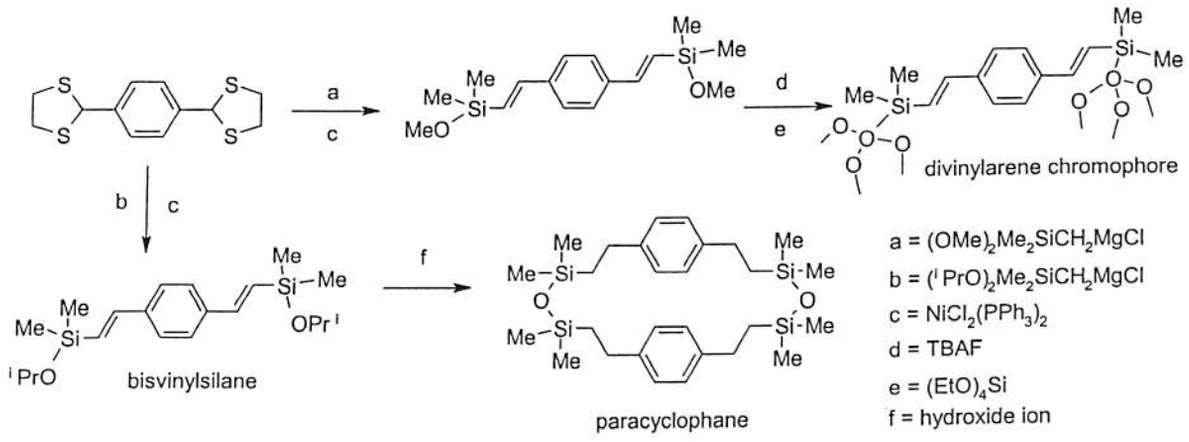
Scheme 1A.29

Acylsilanes can be obtained from cyclic 1,3-dithianes as shown in Scheme 1A.30.[49a] Acylsilanes are frequently applied in Reformatsky reactions,[49b] and intermolecular cyclisation.[49c]

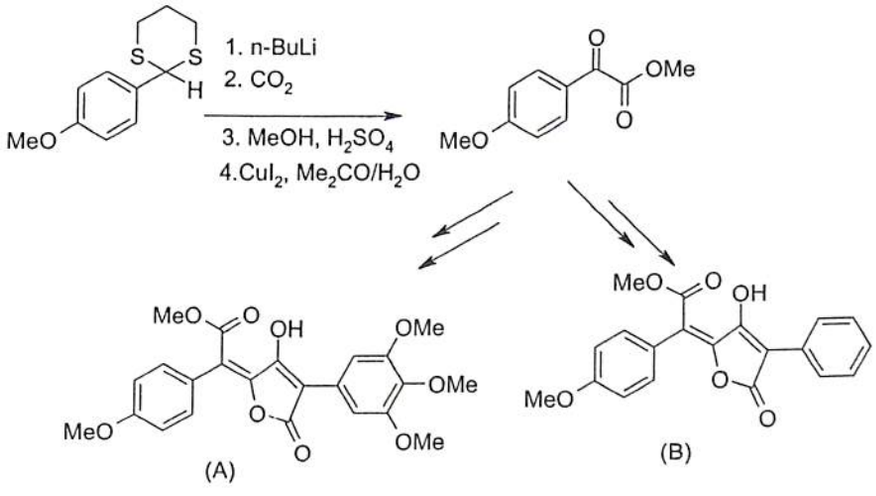


Scheme 1A.30

The silylolefination of dithioacetals is yet another important transformation, which is useful for the synthesis of vinyl silanes, Scheme 1A.31.[50] Vinylsilanes are utilised for the synthesis of paracyclophane and sol gel having divinylarene chromophore, Scheme 1A.31.



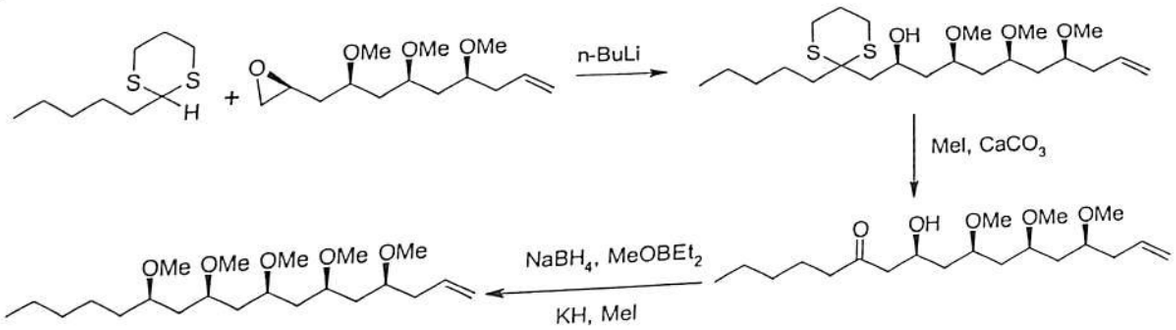
Scheme 1A.31



Scheme 1A.32

The methyl benzoylformate derivative obtained from the dithiane[51] (Scheme 1A.32) has been used for the synthesis of permethylated gomphidic acid (A) and *O*-methylisopinastric acid (B) which have long since been recognised as the pigments responsible for the striking yellow and orange colour of lichens.

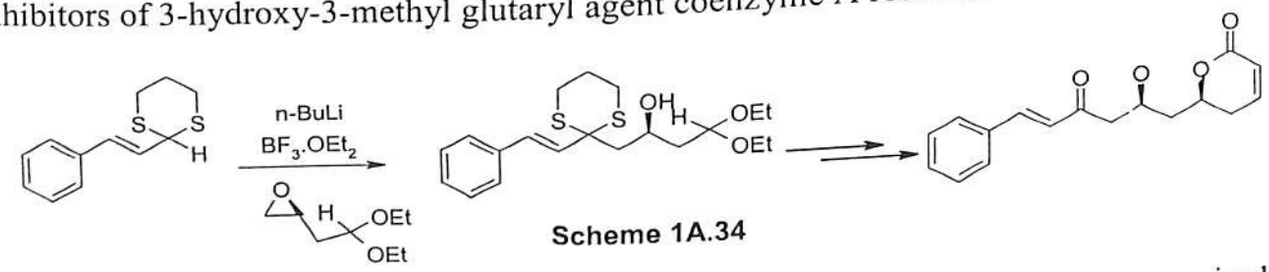
When epoxides react with 2-lithio-1,3-dithiane derivatives enantiomerically pure masked β-hydroxy carbonyl compounds are obtained in a single step, this strategy which has extensively been used in the synthesis of natural products, is summarised below.



Scheme 1A.33

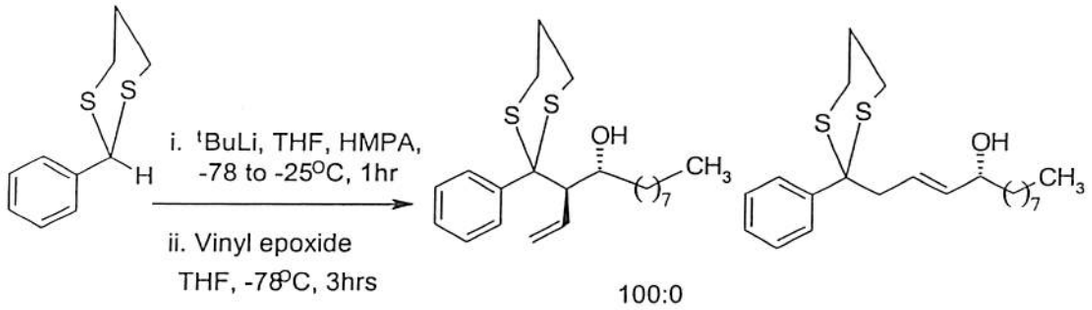
Isotactic 4,6,8,10,12-penta methoxy 1-alkene isolated from tolytoxin-producing blue-green algae has been synthesised by Mori *et al.* from 2-pentyl-1,3-dithiane and its absolute stereochemistry has been determined, Scheme 1A.33.[52]

Jiang and Chen synthesised (*5S, 7S*)-Kurzilactone applying the cinnamaldehyde dithiane as the starting material, Scheme 1A.34.[53] Kurzilactone shows remarkable cytotoxicity against KB cells and has a close structural relationship with the pharmacologically important statin family, which are highly potent inhibitors of 3-hydroxy-3-methyl glutaryl agent coenzyme A reductase.



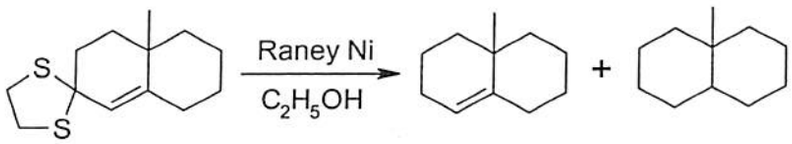
Scheme 1A.34

Smith *et al.* have reported highly chemoselective addition of lithiated dithiane to vinyl epoxides by exploiting the steric nature of the dithiane. The exclusive S_N2 addition product has been reported to be formed when 2-lithio-2-phenyl-1,3-dithiane was reacted with vinyl epoxide containing two nucleofugal sites, which is a clear indication of the selective attack at the activated allylic position and not at the alkene terminal, Scheme 1A.35.[54]



Scheme 1A.35

Dithioacetals can be used as intermediates for the conversion of carbonyl functions to parent hydrocarbons by reductive desulphurisation.[55] Hydrogenolytic desulphurisation employing Raney nickel in boiling ethanol has been proved to be a useful tool in structural and small scale synthetic transformational work. Dithioacetals derived from aldehydes, ketones, monocyclic ketones, polycyclic ketones can be desulphurised with Raney nickel, Scheme 1A.36.[56]



Scheme 1A.36

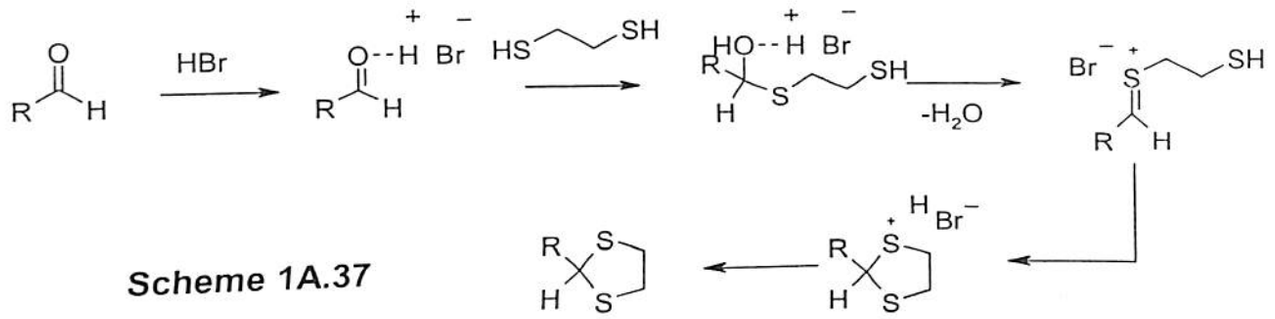
Hydrazine with or without alkali has been found to desulphurise cyclic or acyclic dithioketals in diethylene glycol. The use of alkali reduces the effective temperature of reaction considerably. The sulphur was reduced completely to sulphide, no mercaptan being generated in the reaction. The reaction temperature is lower than those required in Wolff-Kishner reduction.[57]

1A.2.2.1. (c) Methods of Preparation of Dithioacetals

In view of the usefulness of dithioacetals as a protecting group as well as the versatile applications of 1,3-dithianes in organic synthesis as described above, several procedures have been reported over the years in the literature for masking aldehydes and ketones as dithioacetals. Dithioacetals are obtained by protic or Lewis acid-catalysed condensation of carbonyl compounds with dithiols or by a transthioacetalisation of cyclic and acylic acetals. Most of the protic and Lewis acids work on the general principle of activating the carbonyl group towards nucleophilic attack by dithiol.

Various protic acids, Lewis acids, other miscellaneous reagents used to date for thioacetalisation are HCl,[58] PTSA,[59] $BF_3.OEt_2$,[60] $(CH_3)_3SiCl$,[61] $ZnCl_2$,[62] anhydrous $AlCl_3$,[63] $TiCl_4$,[64] $SiCl_4$,[65] $InCl_3$,[66] $LaCl_3$,[67] WCl_6,[68] $NiCl_2$,[69] $InBr_3$,[70] I_2,[71a,b] Zn or $Mg(OTf)_2$,[72] $In(OTf)_3$,[73] $Y(OTf)_3$,[74] 5M $LiClO_4$,[75] LiBr,[76] $LiBF_4$,[77] $MoO_2(acac)_2$,[78] NBS,[79] aq.HBr.[80]

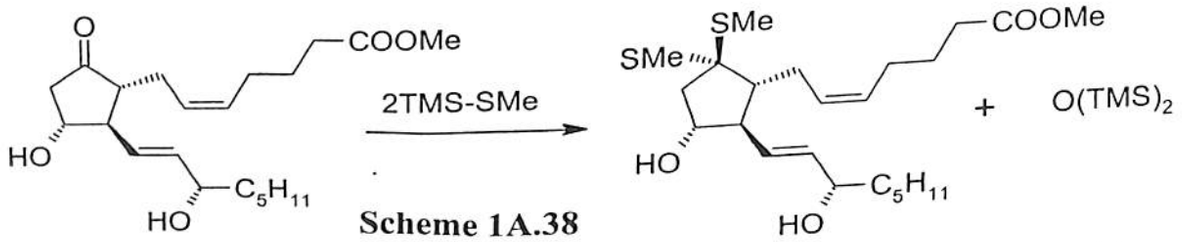
NBS has been speculated to generate HBr by the reaction with dithiol,[79] which further activates the carbonyl group for further reaction with dithiol to produce hemithioacetal-type intermediate, which loses water molecule to afford dithiol protected aldehyde, Scheme 1A.37.



Scheme 1A.37

Different Lewis acids supported on silicagel are advantageous as compared to their unsupported counterpart due to their higher activity and easy removal from the reaction medium after completion o the reaction. Catalysis by silicagel treated with thionyl chloride,[81] anhydrous $FeCl_3$ dispersed on silic gel,[82] anhydrous $CoBr_2$,[83] SiO_2-$Cu(OTf)_2$,[84] $TaCl_5$-silica gel,[85] Iodine supported on natural phosphate, silica supported sodium hydrogen sulfate $NaHSO_4.SiO_2$,[87] P_2O_5/SiO_2[88] are also reported. Soli superacid,[89]zeolite[90] have also been reported. Zeolites can potentially replace conventional corrosiv liquid acids due to the presence of high and tunable acidity.

In addition, other reagents such as methylthiotrimethylsilane (TMS-SMe), has also been reporte long back in the literature to achieve acyclic thioacetals. This reagent without any acid catalysis unde neutral condition converts aldehydes and ketones to the corresponding acyclic thioacetal, Schem 1A.38.[91]

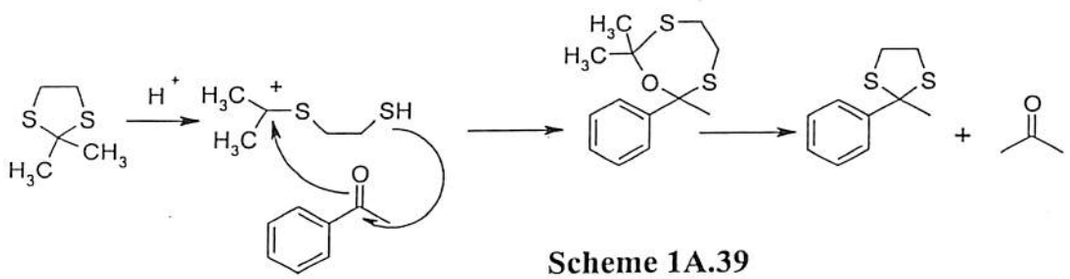


Scheme 1A.38

Few other reagents include bis (diisobutylaluminium)-1,2-ethanedithiolate,[92] polyphosphori acid trimethylsilyl esters[93] and 2-chloro-1,3,2-dithioborolane.[94] The 2-chloro-1,3,2-dithioborane is a ver reactive thioacetalising agent but the corresponding 2-phenyl-1,3,2-dithioborolane is a mild agent wit steric selectivity.

In addition to these afore mentioned reagents, 2,2-dimethyl-2-sila-1,3-dithiane / $BF_3.Et_2O$,[95] 2,2 dimethyl-1,3-dithiolane[96] has been developed for this purpose. The formation of 1,3-dithiolane can be

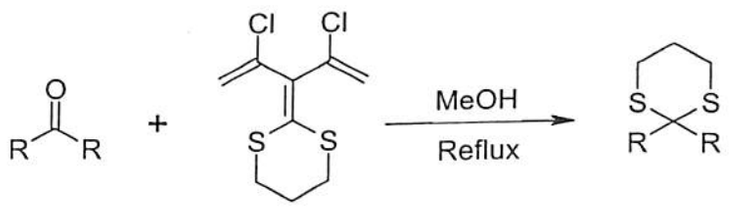
achieved by an exchange reaction from 2, 2-dimethyl-1, 3-dithiolane catalysed by solid acidic catalyst, Amberlyst 15 under microwave irradiation, Scheme 1A.39.[96]



Scheme 1A.39

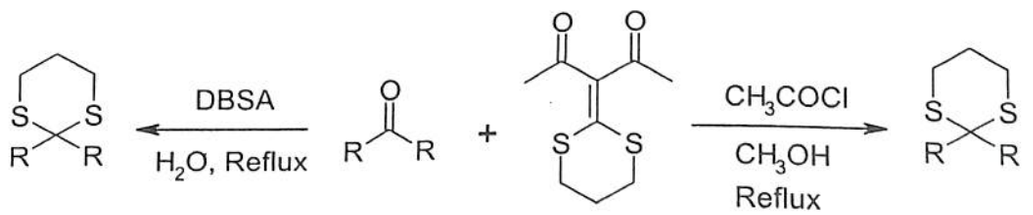
Thioacetalisation of carbonyl compounds has also been achieved using a surfactant-type Brønsted acid in an aqueous medium.[97]

Recently, odourless and nonthiolic alternatives have also been reported to achieve thioacetalisation. Reagent 2-[2-Chloro-1-(1-chlorovinyl)allylidenel-1,3-dithiane[98] is a 1,3-propanedithiol equivalent, which is a stable, nonthiolic and odourless ketene dithioacetal. Thioacetalisation with this reagent is carried out in dry, solvents such as MeOH, EtOH, THF, CH_2Cl_2, *t*-BuOH, *i*-PrOH under reflux condition, Scheme 1A.40. This reaction takes place at elevated temperature. The change in pH indicates that the reaction proceeds with the release of acid. This is a chemoselective reagent for protection of aldehydes over ketones.



Scheme 1A.40

Methyl 2-(1,3-dithian-2-ylidene)-3-oxobutanoate is also another thioacetalisation reagent.[99] The reagent 3-(1,3-Dithian-2-ylidene)pentane-2,4-dione has emerged as another odourless thioacetalisation reagent. It has also been used in water as a thioacetalisation reagent, Scheme 1A.41.[100]



Scheme 1A.41

1A.2.2. Hydroxyl Protecting Groups

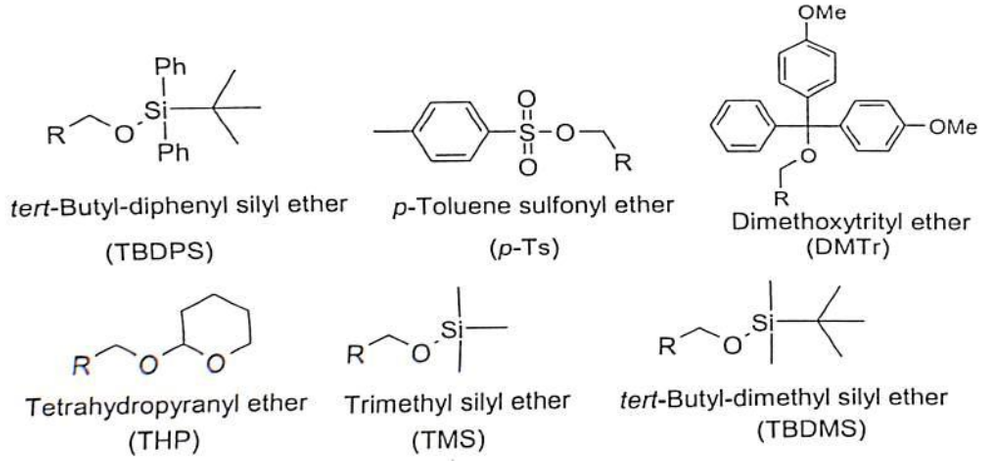


Figure 1.3

Hydroxy protecting groups have gained significant interest because of their fundamenta importance and the crucial role they play in multistep organic synthesis. The hydroxyl group must b protected during oxidation, acylation, halogenation with hydrogen halides or phosphorous base reagents. Protection and deprotection of hydroxy groups in polyols as well as multifunctiona compounds represents a fundamental tool in the synthesis of elaborated target compounds i carbohydrate, amino acid and nucleoside / nucleotide chemistry and several biologically activ molecules. The utility of various protecting groups for the protection of hydroxyl function has bee enhanced by the availability of a myriad and diverse array of methods for their introduction an removal. Among the various protecting groups for alcohols the most frequently employed are ethe which includes tetrahydropyranyl (THP), *tert*-butyldimethylsilyl (TBDMS), trimethylsilyl (TMS), *ter* butyldiphenylsilyl (TBDPS), 4,4'-dimethoxytrityl (DMTr), methoxymethyl (MOM), tosyl (Ts) ether Figure 1.3.

1A.2.2.1. Tetrahydropyranyl Ethers

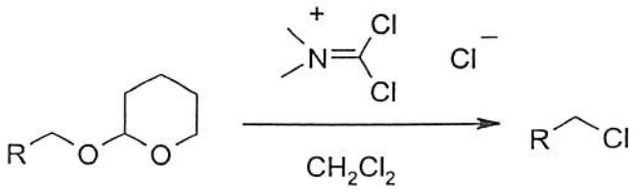
1A.2.2.1. (a) Significance of Tetrahydropyranyl Ethers as Protecting Group

Tetrahydropyranyl ethers (THP ethers) were one of the first generally useful protecting grou for alcohols to be adopted.[101] The easy installation as well as facile and selective removal of these eth renders them attractive in complex organic synthesis. In addition tetrahydropyran derivatives are le expensive, and stable under a variety of reaction conditions such as strongly basic media, met hydrides, Grignard reagents, acylating agents, oxididative and alkylating agents.[35,42]

The only drawback is the formation of an additional stereocentre that may lead to diastereomeric mixtures if the alcohol already possesses a stereogenic centre. This complicates the NMR spectra and hence makes its interpretation difficult. In spite of this detraction it is the most extensively and frequently used protecting group for alcohols.[35,42]

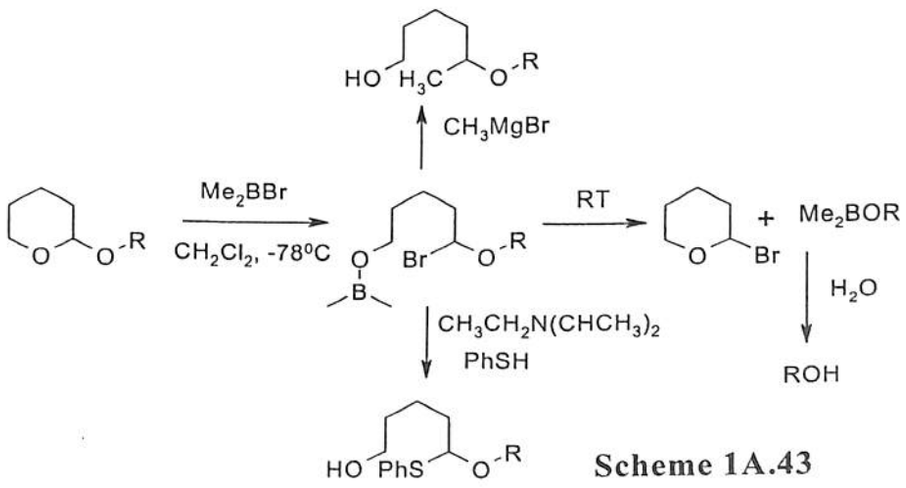
1A.2.2.1. (b) Applications of THP Ethers in Organic Synthesis

In addition to serving as a protecting group THP ethers are also useful intermediates for further functional group transformations such as THP to acetates, alkyl halides etc. These ethers are resistant to various reaction conditions as mentioned above but are not stable under strongly acidic media. The conversion of THP ethers to acetates serves as an important transformation.[102] The conversion of THP protecting group to alkyl halides has also been achieved, Scheme 1A.42.[103] The conversion of THP ethers to alkyl halides is of significant interest in organic synthesis.



Scheme 1A.42

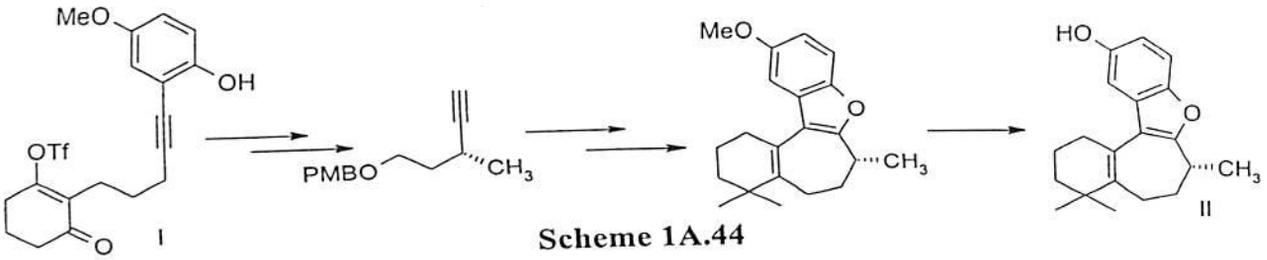
The carbon-oxygen bond of the pyran ring of THP ether has been reported to cleave in presence of Me_2BBr to generate α-bromo ether intermediates.



Scheme 1A.43

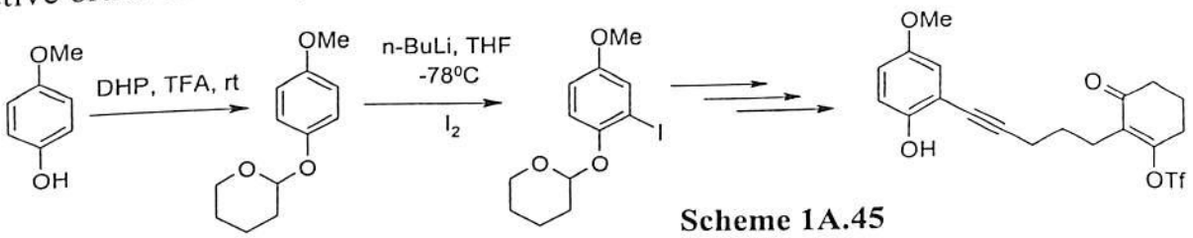
The α-brmo ether intermediates have been exploited synthetically to generate stable ring opened products by trapping with various nucleophiles such as thiols, alcohols, cyanide, hydride reagents, alkyl lithium, Grignard reagent, cuprate reagents, Scheme 1A.43.[104]

THP ether as a protecting group has a strong tendency to direct regioselective ortho-lithiation This has been highlighted in the total synthesis of the marine terpenoid natural product (-)-frondosin B (II),[105] Scheme 1A.44 which has potential HIV-inhibitory properties.[106]

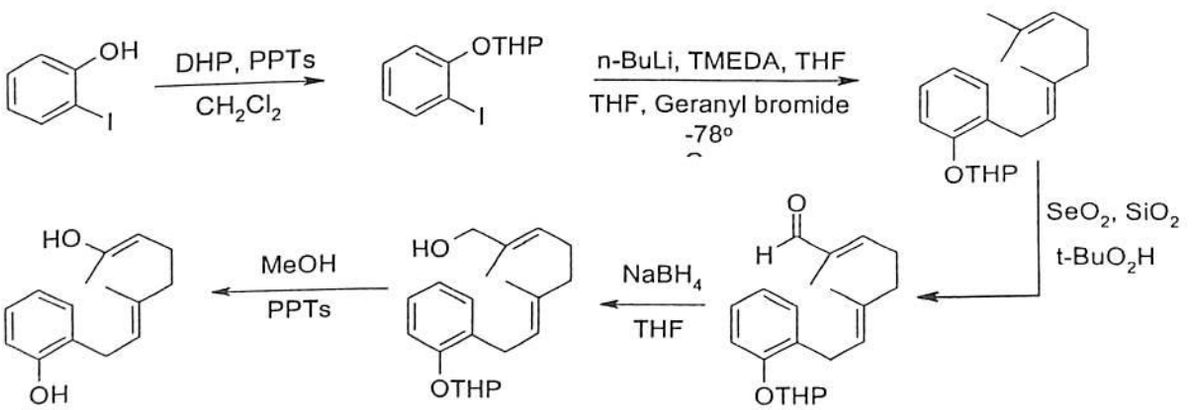


Scheme 1A.44

The synthesis of compound I in the above scheme which is the starting material for the targe compound (-)-frondosin B, II requires a careful choice of protecting group for the phenolic hydrox group. Tetrahydropyranyl ether as a protecting group has a strong tendency to direct regioselectiv ortho-lithiation, which facilitates the synthesis of the compound I from *p*-methoxy phenol, Schem 1A.45. Here it may be noted that the use of MOM protecting group instead of THP, did not affect th desired selective ortho-lithiation, rather it resulted in a 1:1 mixture of regioisomeric products.



Scheme 1A.45

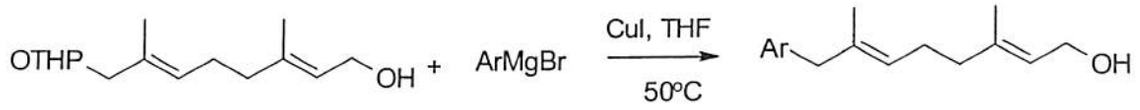


Scheme 1A.46

The THP protecting group also influences the selective oxidation of allylic methyl groups geraniol derivatives in addition to the regioselective ortholithiation, which has been depicted in t preparation of cyclic isoprenoid residues (Scheme 1A.46). It has been suggested that the biosynthe origin of phenolic isoprenoids involve the C-alkylation of phenol by an active isoprenoid allylic deriva

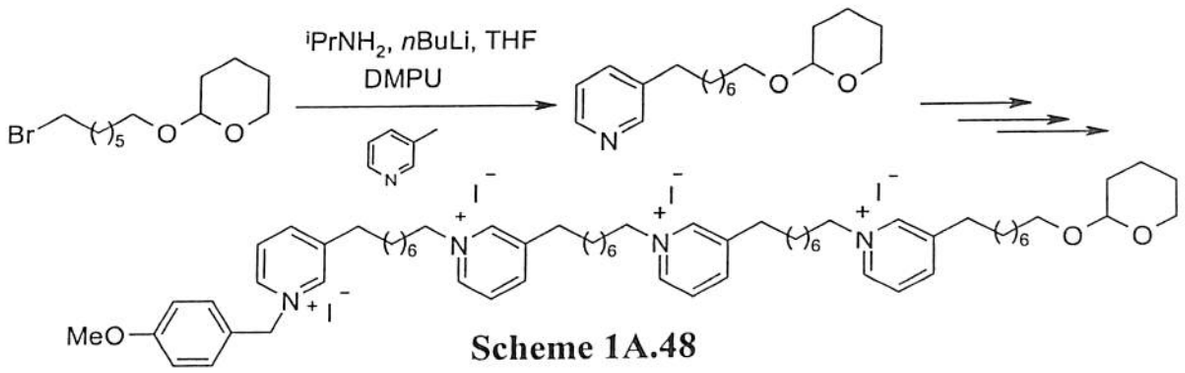
ive. Synthesis of geranylphenol derivatives using 2-lithiophenols and geranyl substrates has been reported by Paz and Rodrigues. [107]

Allylic THP protecting groups are more stable than allyl halides and can serve as protecting group as well as reactive centers in Cu(I) mediated Grignard reaction. This was shown in the preparation of aromatic farnesol analogues via Cu(I) mediated Grignard coupling of THP ethers, Scheme 1A.47.[108] While the basis of the special reactivity of the THP group is not completely clear, a simple comparison of parallel reactions showed that the THP derivative of geraniol undergoes this displacement at least 10-fold faster than the corresponding methyl or phenyl ethers. Farnesyl pyrophophate analogues are useful chemotherapeutic agents.[109]



Scheme 1A.47

The synthesis of linear oligomers related to polymeric alkylpyridinium metabolites uses THP protecting group, Scheme 1A.48.[110]



Scheme 1A.48

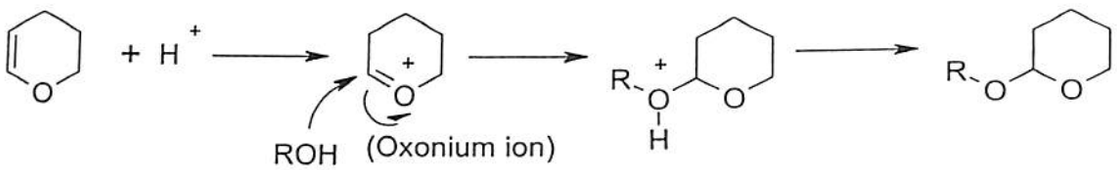
Pyridinium compounds often exhibit antibacterial activity, and this feature is exploited in the fields of pharmaceutical industry and medicine. Substituted pyridinium derivatives, for example, can be attached to different surfaces and used for removing bacteria from water, or can be incorporated in dental resins, thus offering protection from infections by oral streptococci.

1A.2.2.1. (c) Literatre Methods of Tetrahydropyranylation and Depyranylation

A wide variety of catalysts, homogeneous as well as heterogeneous has been described for the tetrahydropyranylation and detetrahydropyranylation of alcohols and phenols. Various protic acids, Lewis acids, transition metal catalysts, heterogeneous catalysts and other miscellaneous catalysts have

been reported towards this end. Generally, tetrahydropyranylation can be achieved in an aprotic solvent and depyranylation in a polar or protic solvent with a mild acidic catalyst.

The reaction proceeds by protonation of the enol ether carbon of dihydopyran to generate a highly electrophilic oxonium ion which is then attacked by the alcohol to give the corresponding tetrahydropyranylated derivative, Scheme 1A.49.

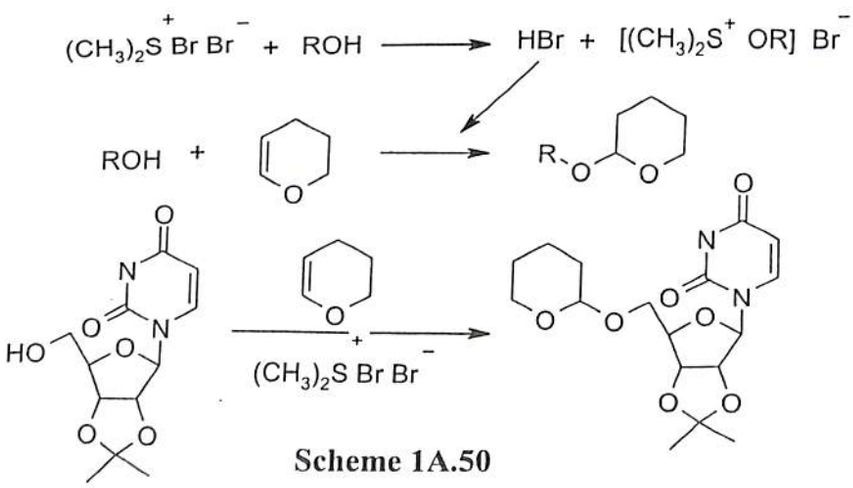


Scheme 1A.49

In the directory of various Lewis and protic acids those were used in the early 1970 includes $BF_3.OEt_2$,[111] HCl,[112] PTSA,[113] PPTs.[114] p-Toluene sulphonic acid (PTSA) is a very strong acid giving eliminated product along with the desired product with tertiary alcohol whereas PPTs being milder than PTSA gave no elimination product. TPP.HBr was also used in the later years for tetrahydropyranylation.[115]

Yadav *et al.* achieved tetrahydropyranylation using equimolar amounts of alcohol, dihydropyran and NH_4Cl in THF at reflux conditions with the pH being 5.93. NH_4Cl.[116]

ATPB and PPTs are comparable catalysts for protection of acid labile substrates but ATPB is preferred as it is less hygroscopic than PPTs. There are two functionalities responsible for the catalytic activities of ATPB, the acidic proton present α to the carbonyl group and the phosphonium center.[117]



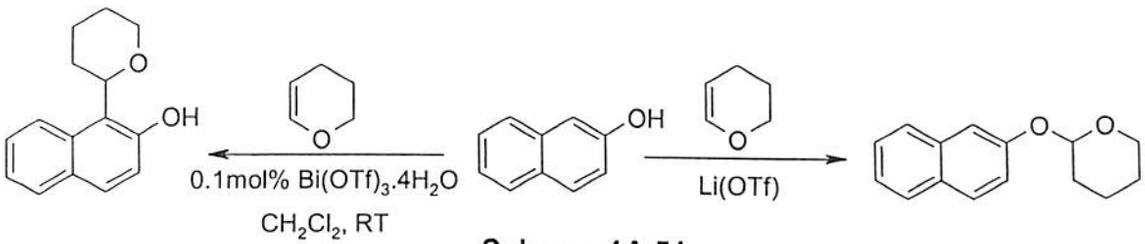
Scheme 1A.50

Khan *et al.* have carried out the solvent free tetrahydropyranylation of various alcohols using bromodimethylsulfonium bromide, $(CH_3)_2S^+Br\ Br$, which is reported to generate HBr on reaction with

alcohol, Scheme 1A.50. The acid sensitive isopropylidene group remained intact and bromination of the double or triple bonds didnot occur.[118]

I_2 is speculated to generate HI *in situ* by interaction with alcohol. Yadav and coworkers as well as Deka *et al.* have exploited the *in situ* acidity of I_2 for tetrahydropyranylation of alcohols.[119]

Triflates[120] such as $Sc(OTf)_3$,[120a] $In(OTf)_3$,[120b] LiOTf,[120c] $Bi(OTf)_3$[120d] have also been used successfully for carrying out tetrahydropyranylation. The potential of $Li(OTf)_3$ as a neutral catalyst for tetrahydropyranylation has been exploited, Scheme 1A.51.



Scheme 1A.51

Solvent free tetrahydropyranylation with high substrate to catalyst ratio makes $AlCl_3.6H_2O$ as an efficient and practical alternative.[121] The reaction also proceeds well for tertiary and bulky alcohols.

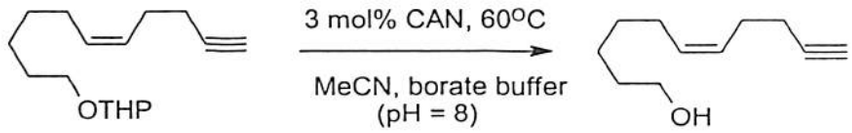
Afonso and Branco have shown the tetrahydropyranylation of alcohols in the ionic liquids [bmim][BF_4], [bmim][PF_6] with PPTs and TPP.HBr.[122]

Various transition metal catalysts such as [$Ru(CH_3)_3$-(triphos)]$(OTf)_2$,[123] heteropolyacids,[124] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[125] CAN[126] have also been used for the tetrahydropyranylation of alcohols and phenols. Heteropolyacids exhibit weak super acidic properties and are used where reaction requires electrophilic catalysis. $K_5CoW_{12}O_{40}\cdot 3H_2O$ is an excellent and effective catalyst for tetrahydropyranylation and depyranylation of parent alcohols.

Other reagents such as trimethyliodosilane (TMSI),[127] organotin phosphate condensates,[128] bis [trimethylsilyl] sulphate[$(H_3C)_3SiO]_2SO_2$[129] has also been reported to achieve this transformation.

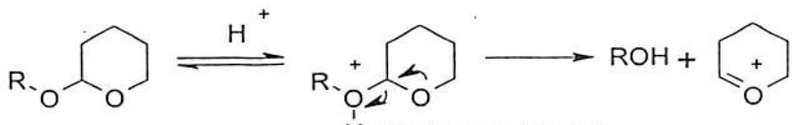
Heterogeneous catalysis has gained importance with respect to its extensive applications achieving selective reactions, lowering waste production and rendering the synthetic processes more attractive from both economical and environmental standpoint. Acid-base heterogeneous catalysis is based on the physicochemical properties of zeolites, clays and metal oxides.[130] Various heterogeneous catalysts used for tetrahydropyranylation are Amberlyst H-15,[131] ion-exchange resins,[132] Nafion,[133] Montmorillonite K10 clay,[134] acid zeolites,[135] envirocat EPZG®,[136] hydrated zirconia (ZrO_2),[137] acetonyltriphenyl phosphonium bromide supported on polystyrene,[117] SO_3H-SiO_2,[138] solid acid $H_6P_2W_{18}O_{62}.24H_2O$,[139] $Al_2O_3/ZnCl_2$.[140]

Few other catalysts, which commonly perform both the reactions effectively includes ATPB,[117b] I_2-microwave,[119c] CAN,[126b] Montmorillonite K-10 clay,[134c] $ZrCl_4$,[141] LiBr.[142] Owing to the neutral conditions employed, unmasking of highly acid sensitive substrates proceeds without any decomposition or rearrangement with CAN, Scheme 1A.52.[126b]



Scheme 1A.52

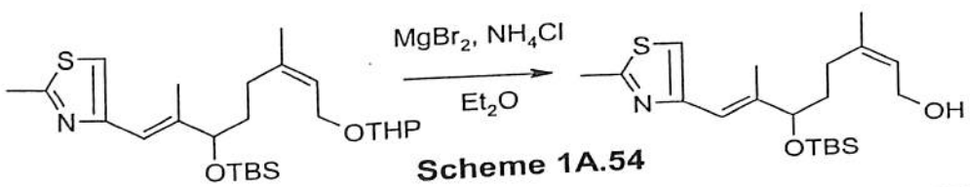
Removal of THP ethers generally employs aqueous reaction media acidified with mineral acids or non-aqueous media acidified with organic acids. The general scheme of deprotection under acid catalysed condition is given in the Scheme 1A.53.



Scheme 1A.53

There are also few reports achieving detertahydropyranylation using reagents such as $BF_3.Et_2O$-C_2H_5SH,[143] LiCl in H_2O-DMSO.[144] Detetrahydropyranylation has also been performed with various other reagents such as TsOH / MeOH,[145] distannoxane,[146] triphenylphosphine dibromide,[147] *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (TBTU).[148]

The selective removal of allylic THP ether in epothilone B intermediate has been achieved using magnesium bromide and ammonium chloride in ether without affecting the acid-sensitive allylic TBS ether, Scheme 1A.54.[149]



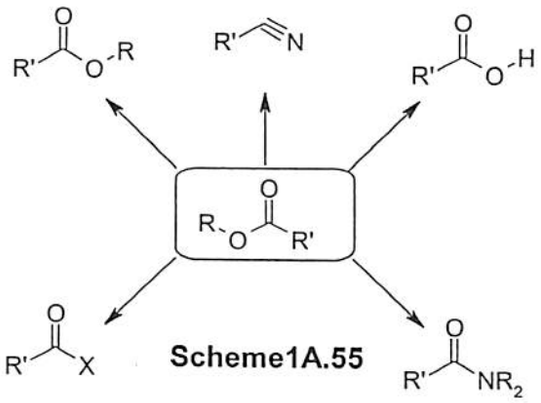
Scheme 1A.54

The deprotection of tetrahydropyranyl (THP) and 4,4'-dimethoxytrityl (DMT) ethers in presence of TBS ether has been achieved using iodine in methanol.[150] Lee *et al.* reported one hydrolysing method for the cleavage of tetrahydropyranyl ethers under reflux condition at 65°C using CBr_4-MeOH.[151]

Heravi *et al* reported the efficient and environmentally friendly oxidative deprotection of THP ethers with montmorillonite supported Fe(III) nitrate and clay under microwave irradiation in solvent free condition.[152] The oxidative deprotection of THP ethers to carbonyl compounds with $K_2Cr_2O_7/AlCl_3$ has been achieved under solid phase condition.[153]

1A.2.2.2. Esters

1A.2.2.2. (a) Significance of Esters



Scheme1A.55

The esters, amides and thioesters serve as key intermediate and / or protecting group in synthetic chemistry and biology.[154] Esters are also used for further organic functional group transformations, Scheme 1A.55.

In addition to its importance in organic synthesis, the ester units have also found important industrial applications as a building block for transformations such as polymerisation (ring opening of lactones), polycondensation or macrolactonisation reactions.

1A.2.2.2. (b) Applications of Esters

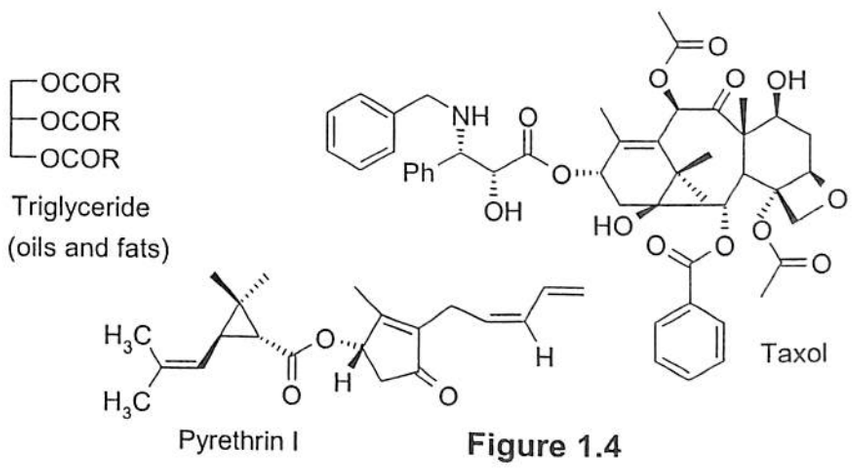
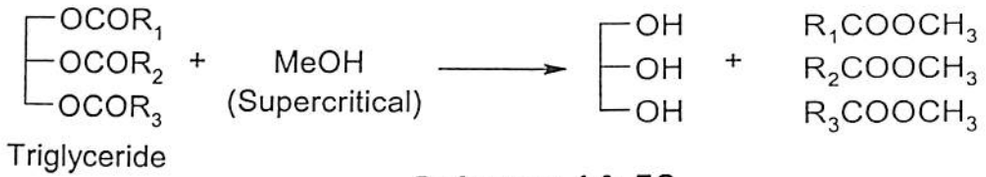


Figure 1.4

Esters have numerous other applications ranging from natural product syntheses to industrial scale production of bulk chemicals, fine chemicals, drugs, plasticisers, perfumes, food preservatives, cosmetics, pharmaceuticals, solvents and chiral auxiliaries. Most of the natural products that are of biological importance and synthetic interest consist of highly oxygenated carbon skeletons. These are frequently used for derivatisation and characterisation of alcohols. Organic esters exist in simple form such as triglycerides in the form of fats and oils to complex form as in pyrethrin, a potent insecticide

(Figure 1.4). Pyrethroid esters are natural insecticides which are expensive to extract from natural sources and hence synthetic pyrethroids esters have been developed. The synthesis of taxol and its analogues exemplifies how profoundly esterification contributes to this field.[155]

The transformation of rapeseed oil, which consists of fatty acid esters of glycerin (triglyceride), into the methyl esters, Scheme 1A.56 is of practical importance since these lighter esters are useful as biodiesel fuel.[155]



Scheme 1A.56

The phosphoester lecithin is used for the emulsification of milk products and reduction of viscosity in chocolates. Perfumes, cosmetics, soaps, toothpastes, mouthwashes, medical products, bath products, air fresheners, chewing gums, beverages, alcohols, food products, deodrants, paints, adhesives, rubbers, plastics, leather, printing inks, textile uses various flavouring agents are invariably esters. Various fragrances in apple, apricot, banana, lemon, and peach are due to the presence of geranylacetate. Benzyl acetate is used as anesthetics, printing inks and lacquers. Benzyl benzoate is used as floral fragrance such as tuberose and as solvent, medecinal agents and plasticiser, Figure 1.5.[155]

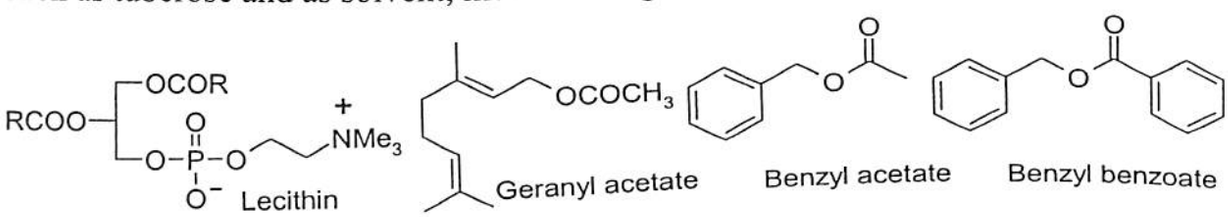


Figure 1.5

Polyesters are used in textile fibers, films, bottles, resins, plastics. The polyester fiber polyethylene terephthalate (PET) is the condensation polymer between ethylene glycol and terephthalic acid and is used as plastic in electronic devices, bumpers etc. Polytrimethylene terephthalate (PTT) and polybutylene terephthalate (PBT) are the polyesters used as fibers which have shape-stability, softness, good elasticity and are easy to dye, Figure 1.6.[155]

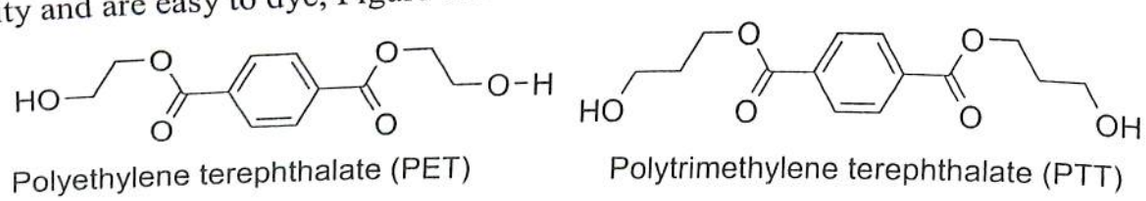
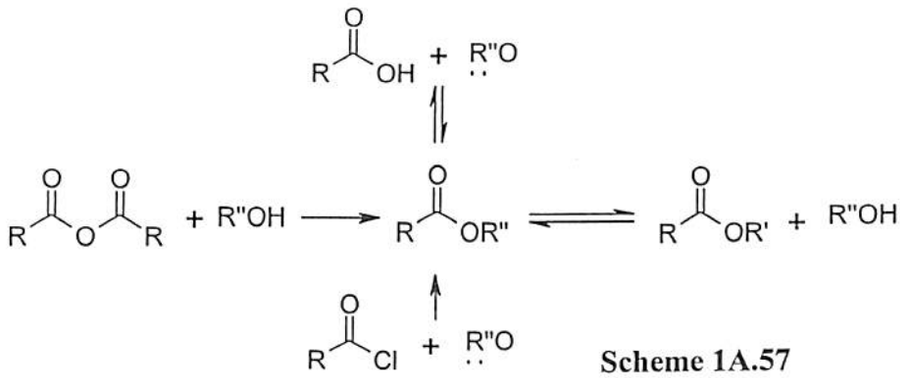


Figure 1.6

1A.2.2.2. (c) Methods of Preparation of Esters

The widespread applications of esters have led several procedures in the literature for esterification of alcohols. The common route to ester synthesis from alcohols involves acyl transfer from an acylating agent such as an acyl chloride, acid anhydride or an ester. It can also be synthesised from carboxylic acids and alcohols or by a transesterification method from an ester and alcohol, Scheme1A.57.



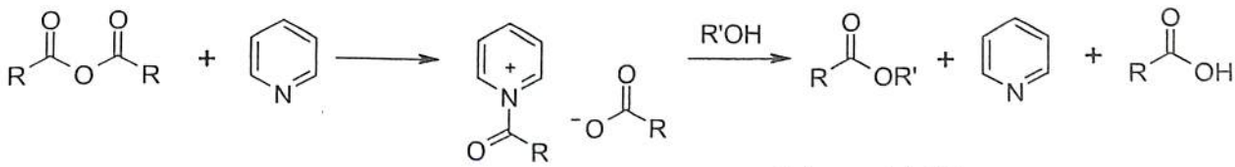
Scheme 1A.57

(c1) Reaction with Acid Anhydrides

The acylation of alcohols is generally achieved with acid anhydrides as the acyl source because of their ready availability and stability. It has been achieved in the presence of various base activators and acid catalysts.[156]

(i) Base Activators

Traditionally, bases such as triethyl amine, pyridine, 4-(dimethylamino)pyridine (DMAP), 4-(1-pyrrolidino) pyridine (PPY) have been employed as catalyst or stoichiometric reagents for acetylation, which promotes the reaction.[157] The use of these bases both in stoichiometric or catalytic amounts is effective. Excess triethylamine or pyridine should be added to trap the acid formed in the reaction mixture. It is postulated that *N*-acylpyridinium carboxylates are key intermediates, undergoing nucleophilic attack by alcohols (Scheme 1A.58).[155]

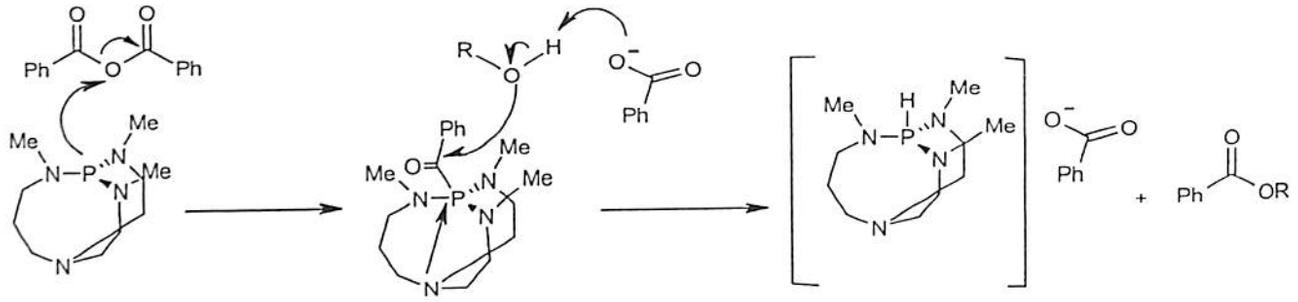


N-acylpyridinium carboxylate **Scheme 1A.58**

Tributylphosphine (Bu_3P) is a weak base with comparable activity to DMAP employed for acetylation. The advantages of Bu_3P over DMAP are it is cheap, less toxic, not easily deactivated by the

carboxylic acids generated in reactions using acid anhydride and can be used under nearly neutral condition.[155, 158]

Verkade *et al.* have explored the non-ionic superbase $P(MeNCH_2CH_2)_3N$ as a catalyst for acylation with acid anhydrides for hindered and acid-sensitive alcohols.[159] The mechanism is given below in Scheme 1A.59.



Scheme 1A.59

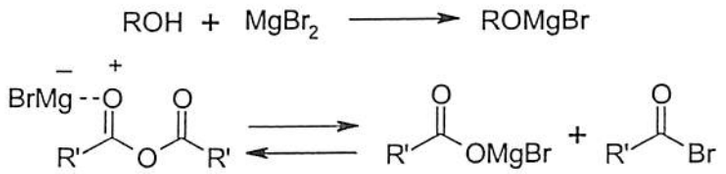
(ii) Acid Catalysts

Because of the toxicity, flamability and unpleasant odour of the above mentioned bases, they are less attractive. Acylation under an acid catalysed condition has also been reported.[160] Protic acids such as sulfonic acids, sulphuric acids and perchloric acids are employed but last few decades have witnessed a dramatic progress in the utilisation of Lewis acid catalysts in the acid anhydride procedure.

Metal triflates have been used as efficient catalysts for the acylation. Various metal triflates used as effective Lewis acids for acylation are trimethylsilyl triflate,[161] $Sn(OTf)_2$,[162] $TiCl(OTf)_3$,[163] $Eu(OTf)_3$,[164] $La(OTf)_3$,[165] $In(OTf)_3$,[166] LiOTf,[167] $Sc(OTf)_3$,[168] $Bi(OTf)_3$,[169] $Cu(OTf)_2$,[170] $Yb(OTf)_3$,[171] $Ce(OTf)_3$,[172] $Gd(OTf)_3$,[173] $VO(OTf)_2$.[174] It has been reported that triflic acid liberated *in situ* through ligand exchange reaction, might be the actual catalytic species during metal triflate-catalysed acetylation.[166] Recently an oxomolybdenum species[175] has also been used for acylation of various protic nucleophiles.

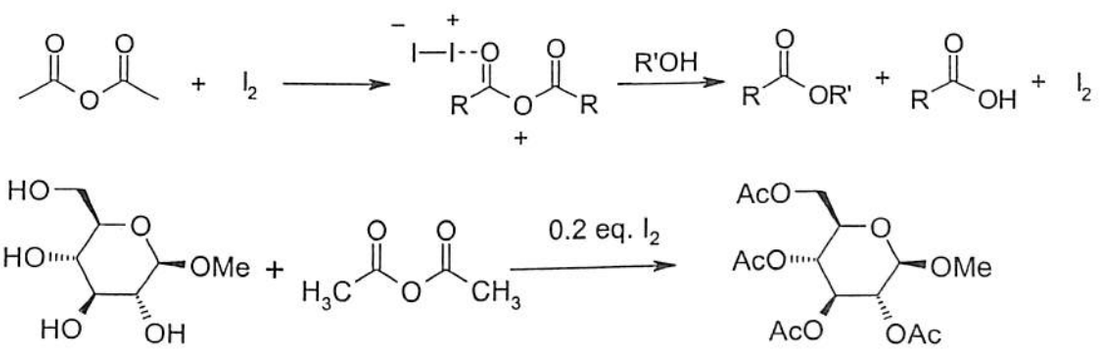
Metal salts derived from protic acids weaker than triflic acid have been employed as more useful catalysts for acetylation of acid-sensitive substrates.[176] Metal halides that have been used for acylation are $ZnCl_2$,[176a] $CoCl_2$,[176b] $TaCl_5$,[176c] $RuCl_3$,[176d] $InCl_3$,[176e] $ZrCl_4$.[176f] Zirconium (IV) has a high charge-to-size ratio (Z^2/r) 22.22 e^2m^{-10} compared to most of the other metal ions employed as acetylation catalyst hence zirconium derivatives were speculated to be a better activator of Ac_2O due to stronger coordination between Zr^{4+} and Ac_2O.

The addition of tertiary amine to a combination of $MgBr_2$ and anhydride enhances the rate of benzoylation and pivaloylation of alcohols.[177] This is attributed to the dual activation arising from magnesium alkoxide formation and the formation of $MgBr_2$-anhydride complex which may fragment into acyl bromide and magnesium carboxylate, Scheme 1A.60.



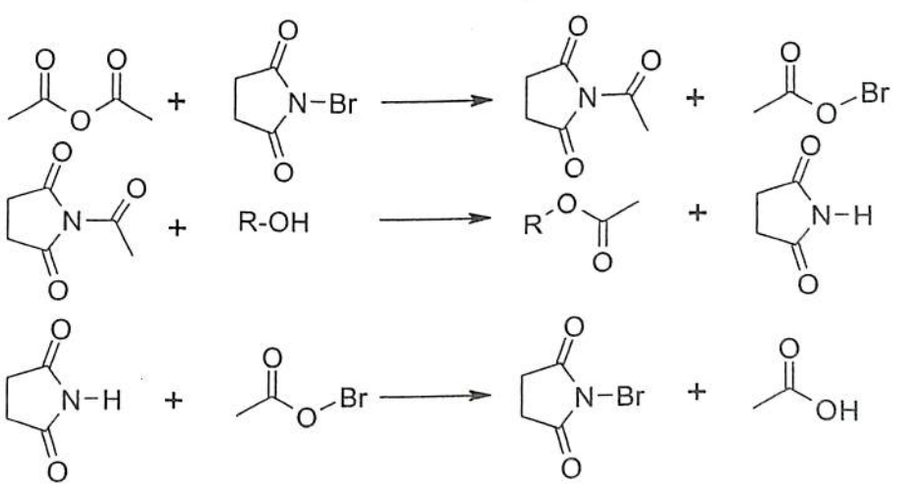
Scheme 1A.60

It has ben reported that iodine acts as a Lewis acid and mediates the acetylation of sugars and other alcohols by activating the carbonyl group of the anhydride[178] as shown in Scheme 1A.61.



Scheme 1A.61

Karimi *et al* have utilised NBS[179] as the catalyst for acylation, NBS reacts with anhydride to form N-acetyl succinimide which in turn reacts with alcohol to give the desired product, Scheme 1A.62.



Scheme 1A.62

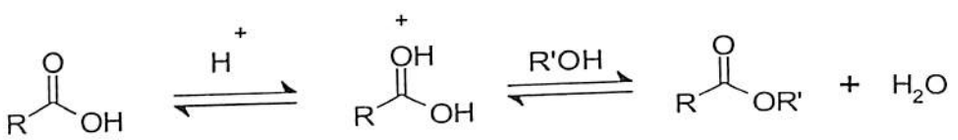
The *in situ* HBr generation in reaction medium from the reaction between acetonyltriphenylphosphonium bromide (ATPB) and alcohol catalyses the acetylation of alcohols as stated by Khan *et al.*[180]

Metal perchlorates[181] such as $TiCl_4/AgClO_4$,[181a] $LiClO_4$,[181b] $Mg(ClO_4)_2$,[181c] $BiOClO_4$[181d] has also been found to be effective in acetylating alcohols with anhydrides. Singh *et al* have reported the scopes and limitations of Lewis acid catalysed acylation.[182]

Various heterogeneous catalysts used for this purpose include $HClO_4$-SiO_2,[183] Scandium trifluoromethanesulphonimide,[184] $Sc(NTf_2)_3$,[185] Nafion-H,[186] Yttria-Zirconia,[187] heteropoly acid,[188] $MeSO_3H/Al_2O_3$,[189] solid surface-Al_2O_3,[190] distannoxane.[175]

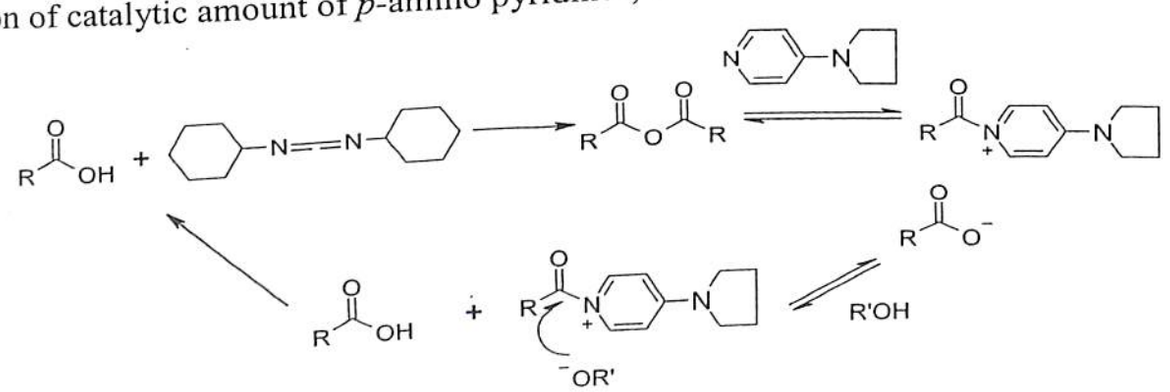
(c2) Esterification of Carboxylic Acids

The direct condensation of carboxylic acids with alcohols is another means of esterification. Various Brönsted acid catalysts such as HCl, HBr, H_2SO_4, H_3PO_4, HBF_4 are employed which catalyses the acetylation by the following mechanism, Scheme 1A.63.



Scheme 1A.63

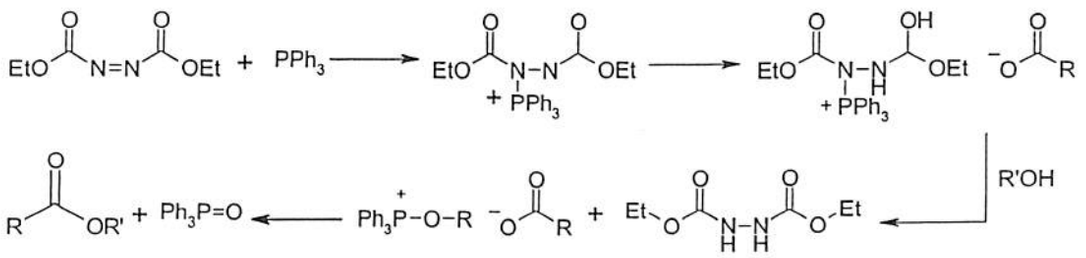
The conversion of alcohols to corresponding esters with carboxylic acids has also been achieved by the use of stoichiometric amount of DCC (dicyclohexylcarbodiimide) is one of the oldest method. The formation of *N*-acylurea as one of the side product in the above method has been overcome by addition of catalytic amount of *p*-amino pyridines, Scheme 1A.64.



Scheme 1A.64

The carboxylic acid is first converted by DCC into an anhydride, which then forms an acylpyridinium species. Nucleophilic attack on the acyl group by carboxylate R'O (alkoxide ion) produces ester concomitantly with regeneration of *p*-amino pyridines, together with a half quantity of RCOOH, which is again subjected to the reaction with DCC as shown above in Scheme 1A.64.[155]

Mitsunobu reaction is another popular technique of esterification using alcohols and carboxylic acids. The reaction proceeds under neutral condition at or below room temperatute employing more than stoichiometric amount of reagent. The mechanism involves the addition of DEAD (diethyl azodicarboxylate) and PPh_3 at the initial step forming a zwitterion. This zwitterion reacts with carboxylic acid to afford a phosphonium carboxylate which on reaction with alcohol directly generates a key intermediate, alkoxyphosphonium salt which further undergoes nucleophilic attack by the carboxylate ion to furnish the desired ester, Scheme 1A.65.[155]

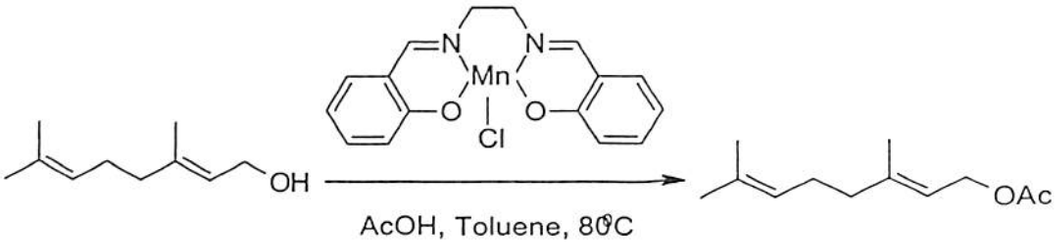


Scheme 1A.65

Various Lewis acids and other reagents and procedures for direct condensation of alcohols with carboxylic acids include R_2SnO,[191] diorgano tin chloride.[192] Stoichiometric condensation of alcohols and acids uses various chemical and physical means for the removal of water formed from the reaction mixture. Silyl dehydrating additives are used for $TiCl(OTf)_3$[163] mediated condensation where as for $TiCl_2(ClO_4)_2$[193] and $Sc(OTf)_3$[168a] catalysed condensation anhydride is essential for the removal of water. Water formed during the condensation catalysed by Hf(IV) and Zr(IV) salts has been reported to be removed azeotropically using Soxhlet thimble and calcium hydride or 4Å molecular sieves.[194] Besides these, several other reagents and procedures accounting for this transformation includes $La(OTf)_3$,[164] $Ce(OTf)_3$,[195] diphenylammoniumtriflate (DPAT),[196] and $K_5CoW_{12}O_{40}.3H_2O$.[197] Primary carboxylic acids on being heated with benzene in presence of catalytic quantity of tris(methoxyphenyl)bismuthanes, are selectively activated to couple with equimolar amounts of alcohols to produce the esters in satisfactory yield.[198]

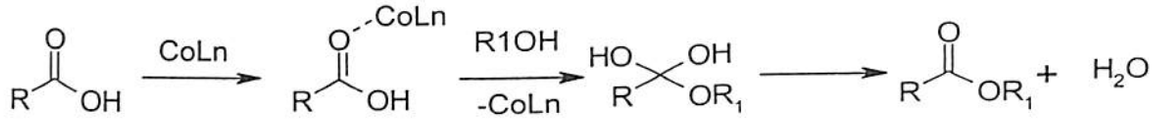
Choudary *et al.* have reported acylation of alcohols with carboxylic acids with high atom economy in presence of natural and Na^+-exchanged form of montmorillonite and noted that choice of

cation has a large effect on the efficiency of the reaction. montmorillonites clay.[199] Mn(III) salen complex has also been used by the same group as a recyclable catalyst for this purpose. [200]



Scheme 1A.66

Recently the direct condensation of carboxylic acids with alcohols has also been achieved with pillared clays,[201] CAN,[202] KF,[203] and $CoCl_2.6H_2O$.[204] The $CoCl_2$ catalysed acylation with acetic acid is shown to proceed by a Lewis acid catalysed pathway as shown below, Scheme 1A.67.



Scheme 1A.67

IA. 3. References

1. Chattaway, F. D.; Hoyle, G. *J .Chem. Soc.* **1923**, 654.
2. Avramoff, M.; Weiss, J.; Schaechter, O. *J. Org. Chem.* **1963**, *28*, 3256.
3. (a) Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 417. (b) Fieser, L. F. Fieser, M. *Reagents for Organic Synthesis*. New York: Wiley, 1967, 967.
4. Vona, J. A.; Merker, P. C. *J. Org. Chem.* **1949**, *14*, 1048.
5. *Org. Synth. Coll.vol.*6, 175.
6. Marquet, A.; Jacques, J. *Bull. Soc. Chim. Fr.* **1965**, 511.
7. (a) Marquet, A.; Jacques, J. *Bull. Soc. Chim. Fr.* **1962**, 90. (b) Johnson, W. S.; Dolf Bass, J.; Williamson, K. L. *Tetrahedron* **1963**, *19*, 861.
8. Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740.
9. Paquet, L. A., Ed. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 6, pp 4738 and 4370.
10. Salazar, J.; Dorta, R. *Synlett* **2004**, *7*, 1318.
11. Hajipour, A. R.; Imanieh, H.; Pourmousavi, S. A. *Synth. Commun.* **2004**, *34*, 4597.
12. Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267.
13. Buckles, R. E.; Popov, A. I.; Zeleny, W. F.; Smith, R. J. *J. Am. Chem. Soc.* **1951**, *73*, 4525.
14. (a) Buckles, R. E.; Bader, J. M.; Thurmaier, R. J. *J. Org. Chem.* **1962**, *27*, 4523. (b) Buckles, R. E.; Miller, J. L.; Thurmaier, R. J. *J. Org. Chem.* **1967**, *32*, 888.
15. (a) Berthelot, J.; Guette, C.; Ouchefoune, M.; Desbene, P. L.; Basselier, J. J. *J. Chem. Res.* (S) **1986**, *10*, 381. (b) Berthelot, J.; Guette, C.; Essayegh, M. Desbene, P. L.; Basselier, J. J. *Synth. Commun.* **1986**, *16*, 1641. (c) Berthelot, J.; Guette, C.; Desbene, P. L.; Basselier, J. J.; Chaquin, P.; Masure, D. *Can. J. Chem.* **1989**, *67*, 2061.
16. Berthelot, J.; Fournier, M. *Can. J. Chem.* **1986**, *64*, 603.
17. Fournier, F.; Fournier, M.; Berthelot, J. *Bull. Soc. Chim. Belg.* **1984**, *93*, 157.

18. Berthelot, J.; Fournier, M. *J. Chem. Ed.* **1986**, *63*, 1011.
19. Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Shizuo, F. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1159.
20. Bellucci, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron: Asymmetry* **1995**, *6*, 221.
21. Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163. (b) Chaudhuri, M. K.; Bora, U.; Dehury, S. K.; Dey, D.; Dhar, S. S.; Kharmawophlang, W.; Choudary, B. M.; Mennepalli, L. K. Patent no. US2004126308.
22. Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247.
23. Bose, G.; Barua, P. M. B.; Chaudhuri, M. K.; Kalita, D. Khan, A. T. *Chem. Lett.* **2001**, *4*, 290.
24. Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907.
25. (a) Baghmar, M.; Sharma, P. K. *Proc. Indian Aca. Sci, Chem. Sci.* **2001**, *113*, 139. (b) Kumar, A.; Sharma, P. K.; Banerji, K. K. *J. Phy. Org. Chem.* **2002**, *15*, 721. (c) Gosain, J.; Sharma, P. K. *J. Indian Chem. Soc.* **2002**, *79*, 815. (d) Gosain, J.; Sharma, P.K. *Proc. Indian Aca. Sci, Chem. Sci.* **2003**, *115*, 135.
26. (a) Baghmar, M.; Sharma, P. K. *Int. J. Chem. Kinet.* **2001**, *33*, 390. (b) Baghmar, M.; Sharma, P. K. *Indian J. Chem., Sect. A* **2001**, *40A*, 311. (c) Shukla, R.; Sharma, P. K.; Banerji, K. K. *J. Chem. Sci.* **2004**, *116*, 101. (d) Gosain, J.; Sharma, P. K. *Indian J. Chem., Sect. A* **2002**, *41A*, 321. (e) Sharma, P. K. *Indian J. Chem., Sect. A* **2002**, *41A*, 1612.
27. Chouhan, V. S.; Sharma, V. *Int. J. Chem. Sci.* **2003**, *4*, 341. (b) Chouhan, V. K.; Sharma, V. *J. Indian Chem. Soc.* **2005**, *82*, 302.
28. Mondal, E.; Bose, G.; Khan, A.T. *Synlett* **2001**, *6*, 785.
29. Kumar, A.; Choudhary, K.; Sharma, P. K.; Banerji, K. K. *Indian J. Chem., Sect. A* **2001**, *40A*, 252.
30. Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett.* **2002**, *43*, 2843.
31. Bora, U.; Chaudhuri, M. K.; Dey, D.; Dhar, S. S. *Pure Appl. Chem.* **2001**, *73*, 93. (b) Kar, G.; Saikia, A. K.; Bora, U.; Dehury, S. K.; Chaudhuri, M. K. *Tetrahedron Lett.* **2003**, *44*, 4503.
32. Kajigneshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Chem. Lett.* **1987**, 627.
33. Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177.
34. Gopinath, R.; Haque, Sk. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842.
35. Kocieñski, P. J. *Protecting Groups*, Georg Thieme Verlag Stuttgart, New York, **1994**.
36. Metzner, P.; Thuillier, A. *Sulphur Reagents in Organic Synthesis*, Academic Press, New York, 1994, pp 76.
37. Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *J. Org. Chem.* **2002**, *67*, 2572.
38. Reddy, V. P.; Ramesh, A.; Perambuduru, M. K.; Welz-Biermann, U.; Buchholz, H.; Prakash, G. K. S. *Chem. Commun.* **2005**, 654.
39. Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619.
40. Solladié, G.; Rubio, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1990**, *1*, 187. (b) Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreño, M. C.; García Ruano, J. L. *J. Org. Chem.* **1991**, *56*, 2317.
41. Kanematsu, K.; Soejima, S.; Wang, G.; *Tetrahedron Lett.* **1991**, *32*, 4761.
42. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed, Wiley & Sons, New York, **1999**.
43. Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron*, **2003**, *59*, 6147.
44. Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.
45. Gröbel, B, -T.; Seebach, D. *Synthesis* **1977**, 357 and references therein.
46. (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077. (b) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (c) Eliel, E. L.; Morris-Natsche, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937. (d) Utimoto, K.; Nakamura, A.; Molsubara, S. *J. Am. Chem. Soc.* **1990**, *112*, 8189. (e) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.
47. Weil, R.; Collignon, N. *Bull. Soc. Chim. Fr.* **1974**, 253.
48. Boekelheide, V.; Anderson, P. H.; Hylton, T. A. *J. Am. Chem. Soc.* **1974**, *96*, 1558. (b) Vogtle, F.; Neumann, P. *Synthesis* **1973**, 85.

49. (a) Patrocinio, A. F.; Moran, P. J. S. *J. Organomet. Chem.* **2000**, *603*, 220. (b) Horiuchi, Y.; Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1995**, *36*, 5353. (c) Chuang, T. H.; Fang, J. M.; Jiaang, W. T.; Tsai, Y. M. *J. Org. Chem.* **1996**, *61*, 1794.
50. Luh, T. -Y. *J. Organomet. Chem.* **2002**, *653*, 209.
51. Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 84.
52. Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631.
53. Jiang, B.; Chen, Z. *Tetrahedron Asymmetry* **2001**, *12*, 2835.
54. Smith, A. B. III; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 14516.
55. Olsen, R. K.; Currier Jr., J. O. *The Chemistry of the Thiol Group ed.* Patai, S. John Wiley & Sons, New York, **1974**, part 2, pp.519.
56. Hauptmann, H.; Walter, W. F. *Chem. Rev.* **1962**, *62*, 347.
57. Georgian, V.; Harrisson, R.; Gubisch, N. *J. Am. Chem. Soc.* **1959**, *81*, 5834.
58. Ralls, J. W.; Dobson, R. M.; Reigel, B. *J. Am. Chem. Soc.* **1949**, *75*, 3320.
59. Djerassi, C.; Gorman, M. *J. Am. Chem. Soc.* **1953**, *75*, 3704. (b) Truce, W. E.; Roberts, F. E. *J. Org. Chem.* **1963**, *28*, 961.
60. Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945. (b) Marshall, J. A.; Anderson, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858. (c) Nakata, T.; Nagao, S.; Mori, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461.
61. Ong, B. S.; Chan, T. H. *Synth. Commun.* **1977**, *7*, 283.
62. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.
63. Ong, B. S. *Tetrahedron Lett.* **1980**, *21*, 4225.
64. Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, 24, 1289.
65. Ku, B.; Oh, D.Y. *Synth Commun.* **1989**, 19, 433.
66. Muthusamy, S.; Arulananda Babu, S.; Gunanathan, C. *Tetrahedron Lett.* **2001**, *42*, 359.
67. Garlaschelli, L.; Vidari, G. *Tetrahedron Lett.* **1990**, *31*, 5815.
68. Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett*, **1998**, 739.
69. Khan, A.T.; Mondal, E.; Sahu, P.R.; Islam, S. *Tetrahedron Lett.* **2003**, *44*, 919.
70. Ceschi, M. A.; Felix, L. de. A.; Peppe, C. *Tetrahedron Lett.* **2000**, *41*, 9695.
71. (a) Samajdar, S.; Basu, M. K.; Becker, F. F.; Banik, B. *Tetrahedron Lett.* **2001**, *42*, 4425. (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527.
72. Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.
73. Muthusamy, S.; Babu, S. A.; Gunanathan, C. *Tetrahedron* **2000**, *58*, 7897.
74. De, S.K. *Tetrahedron Lett.* **2004**, *45*, 2339.
75. Saraswathy, V. G.; Geetha, V.; Sankaranan, S. *J. Org. Chem.* **1994**, *39*, 4665.
76. Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58.
77. (a) Jadav, J. S.; Reddy, B. S.; Pandey, S. K. *Synlett* **2001**, 238. (b) Kazahaya, K.; Tsuji, S.; Sato, T. *Synlett* **2004**, *9*, 1640.
78. Rana, K. K.; Guin, C.; Jana, S.; Roy, S. C. *Tetrahedron Lett.* **2003**, *44*, 8597.
79. Kamal, A.; Chouhan, G. *Synlett* **2002**, 474.
80. Shinde, P. D.; Borate, H. B.; Wakharkar, R. D. *Arkivoc* **2004** (*xiv*) 110.
81. Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427.
82. Patney, H. K. *Tetrahedron Lett.* **1991**, *32*, 2259.
83. Patney, H. K *Tetrahedron Lett.* **1994**, *35*, 5717.
84. Patney, H. K.; Margan, S. *Tetrahedron Lett.* **1996**, *37*, 4621.
85. Chandrasekhar, S.; Takhi, M.; Reddy, Y. R.; Mohapatra, S.; Rao, C. R.; Reddy, V. K. *Tetrahedron* **1997**, *53*, 14997.
86. Zahouily, M.; Mezdar, A.; Rakik, J.; Elmakssoudi, A.; Rayadh, A.; Sebti, S. *J. Mol. Catal. A: Chemical* **2005**, *233*, 43.
87. Das, B.; Ramu, R.; Reddy, M. R.; Mahender, G. *Synthesis* **2005**, *2*, 250.
88. Hajipour, A.; Zarei, A.; Khazdooz, L.; Zhamatkesh, S.; Ruoho, A. *Phosphorous, Sulphur and Silicon and the Related Elements* **2006**, *181*, 387.

89. Olah, G. A.; Narang, S. C.; Meidar, D.; Salem, G. F. *Synthesis* **1981**, 282.
90. (a) Lalitha, A.; Pitchumani, K.; Srinivasan, C. *Green Chem.* **1999**, 173. (b) Deka, N.; Sarma, J. C. *Chem. Lett.* **2001**, 794.
91. Evans, D. A.; Grimm, K. G.; Truesdale, L. K. *J. Am. Chem. Soc.* **1975**, *97*, 3229.
92. Satho, T.; Uwaya, S.; Yamakawa, K. *Chem. Lett.* **1983**, 667.
93. Kakimoto, M.; Seri, T.; Imai, Y. *Synthesis* **1987**, 164.
94. Morton, D. R.; Hobbs, S. J. *J. Org. Chem.* **1979**, *44*, 656.
95. Soderquist, J. A.; Miranda E. I. *Tetrahedron Lett.* **1986**, *27*, 6305.
96. Perio, B.; Hamelin, J. *Green Chem.* **2000**, *2*, 252.
97. Kobayashi, S.; Iimura, S.; Manabe, K. *Chem. Lett.* **2002**, 10.
98. (a) Liu, Q.; Che, G.; Yu, H.; Liu, Y.; Zhang, J.; Zhang, Q.; Dong, D. *J. Org.Chem.* **2003**, *68*, 9148. (b) Yu, H.; Liu, Q.; Yin, Y.; Fang, Q.; Zhang, J.; Dong, D. *Synlett* **2004**, *6*, 999.
99. Sun, R.; Liu, Q.; Yu, H.-F.; Zhao, Y.-L.; Liu, J.; Ouyang, Y.; Dong, D.-W. *Chinese J. Chem.* **2005**, *23*, 1060.
100. Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4535.
101. Parham, W. E.; Anderson, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 4187.
102. Reddy, C. S.; Smitha, G. Chandrasekhar, S. *Tetrahedron Lett.* **2003**, *44*, 4693.
103. Schlama, T.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 3517.
104. Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure Appl. Chem.* **1988**, *60*, 1705.
105. Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675.
106. Hallock, Y. F.; Cardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153.
107. Paz, J. L.; Rodrigues, J. A. R. *J. Braz. Chem. Soc.* **2003**, *14*, 975.
108. Mechelke, M. F.; Wiemer, D. F. *Tetrahedron Lett.* **1998**, *39*, 783.
109. Bos, J. L. *Cancer Res.* **1989**, *49*, 4682. (b) Chang, E. H.; Furth, M. E.; Scolnik, E. M.; Lowy, D. R. *Nature* **1982**, *297*, 479.
110. Mancini, I.; Sicurelli, A.; Guella, G.; Turk, T.; Maček, P.; Sepčić, K. *Org. Biomol. Chem.* **2004**, *2*, 1368.
111. Alper, H.; Dinkes, L. *Synthesis* **1972**, 81.
112. Bernady, K. F.; Brawner, M.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438.
113. Boom, V. J. H.; Herschied, J. D. M.; Reese, C. B. *Synthesis* **1973**, 169.
114. Myasita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
115. Bolitt, V.; Mioskowski, C.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4583.
116. Yadav, J. S.; Srinivas, D.; Reddy, G. S. *Synth. Commun.* **1998**, *28*, 1399.
117. (a) Hon, Y.-S.; Lee, C.-F.; Chen, R.-J.; Szu, P.-H. *Tetrahedron* **2001**, *57*, 5991. (b) Hon, Y.-S.; Lee, C.-F. *Tetrahedron Lett.* **1999**, *40*, 2389.
118. Khan, A. T.; Mondal, E.; Borah, B. M.; Ghosh, S. *Eur. J. Org. Chem.* **2003**, 4113.
119. (a) Kumar, H. M. S.; Reddy, B. V. S.; Reddy, E. J.; Yadav, J. S. *Chem. Lett.* **1999**, 857. (b) Deka, N.; Sarma, J. C. *J. Org. Chem.* **2001**, *66*, 1947. (c) Deka, N.; Sharma, J. C. *Synth. Commun.* **2000**, *30*, 4435.
120. (a) Oriyama, T.; Watahiki, T.; Kobayashi, Y.; Hirano, H.; Suzuki, T. *Synth. Commun.* **2001**, *31*, 2305. (b) Mineno, T. *Tetrahedron Lett.* **2002**, *43*, 7975. (c) Karimi, B.; Maleki, J. *Tetrahedron Lett.* **2002**, *43*, 5353. (d) Stephens, J. R.; Butler, P. L.; Clow, C. H.; Oswald, M. C.; Smith, R. C.; Mohan, R. S. *Eur. J. Org. Chem.* **2003**, 3827.
121. Namboodiri, V. V.; Varma, R. S. *Tetrahedron Lett.* **2002**, *43*, 1143.
122. Branco, L. C.; Afonso, C. A. M. *Tetrahedron* **2001**, *57*, 4405.
123. Ma, S.;Venanzi, L. M. *Tetrahedron Lett.* **1993**, *34*, 5269.
124. Molnar, A.; Beregszaszi, T. *Tetrahedron Lett.* **1996**, 37, 8597.
125. Habibi, M. H.; Tangestaninejad, S.; Baltork, I. M.; Mirkhani V.; Yadollahi, B. *Tetrahedron Lett.* **2001**, *42*, 2851.
126. Pachamuthu, K.; Vankar, Y. D. *J. Org. Chem.* **2001**, *66*, 7511. (b) Marko, I. E.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, Y.; Wiaux, M. *Tetrahedron Lett.* **1999**, *40*, 5613.
127. Olah, G. A.; Husain, A.; Singh, B. P. *Synthesis* **1985**, 703.

128. Otera, J.; Niibo, Y.; Chikada, S.; Nozaki, H. *Synthesis* **1988**, 328.
129. Morizawa, Y.; Mori, I.; Hiyama, T.; Nozaki, H. *Synthesis* **1983**, 899.
130. Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199.
131. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.
132. Menger, F. M.; Chu, C. H. *J. Org. Chem.* **1981**, *46*, 5044
133. Olah, G. A.; Husain, A.; Singh, B. P. *Synthesis* **1983**, 892.
134. (a) Hoyer, S.; Laszlo, P.; Orlović, M.; Polla, E. *Synthesis* **1986**, 655. (b) Campele, J. M.; Garcia, A.; Lafont, F.; Luna, D.; Marinas, J. M. *Synth. Commun.* **1994**, *24*, 1345. (c) Taniguchi, T.; Kadoka, K.; ElAzab, A.S.; Ogasawara, K. *Synlett* **1999**, 1247.
135. Kumar, P.; Dinesh, C. U.; Reddy, R. S.; Pandey, B. *Synthesis* **1993**, 1069.
136. Bandgar, B. P.; Jagtap, S. R.; Aghade, B. B.; Wadgaonkar, P. P. *Synth.Commun.* **1995**, *25*, 2211.
137. Gajare, A. S.; Sabde, D. P.; Shingare, M. S.; Wakharkar, R. D. *Synth.Commun.* **2002**, *32*, 1549.
138. Shimizu, K.; Hayashi, E.; Hatamachi, T.; Kodama, T.; Kitayama, Y. *Tetrahedron Lett.* **2004**, *45*, 5135.
139. Romanelli, G. P.; Baronetti, G.; Thomas, H. J.; Autino, J. C. *Tetrahedron Lett.* **2002**, *43*, 7589.
140. Ranu, B. C.; Saha, M. *J. Org. Chem.* **1994**, *59*, 8269.
141. Rezai, N.; Meybodi, F. A.; Salahi, P. *Synth. Commun.* **2000**, *30*, 1799.
142. Reddy, M. A.; Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Synth. Commun.* **2000**, *30*, 4323.
143. Nambiar, K. P.; Mitra, A. *Tetrahedron Lett.* **1994**, *35*, 3033.
144. Maiti, G.; Roy, S. C. *J. Org. Chem.* **1996**, *61*, 6038.
145. Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.
146. Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 5743.
147. Wagner, A.; Heitz, M.-P.; Mioskovski, C. *J. Chem. Soc. Chem. Commun.* **1989**, 1619.
148. Ramasamy, K. S.; Averett, D. *Synlett* **1999**, 6, 709.
149. Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439.
150. Ramasamy, K. S.; Bandaru, R.; Averett, D. *Synth. Commun.* **1999**, *29*, 2881.
151. Lee, A. S.-Y.; Su, F.-Y.; Liao, Y.-C. *Tetrahedron Lett.* **1999**, *40*, 1323.
152. Heravi, M. M.; Ajami, D.; Mojtahedi, M. M.; Ghassemzadeh, M. *Tetrahedron Lett.* **1999**, *40*, 561.
153. Baltrok, I. M.; Sadeghi, M. M.; Adibi, A. -H. *Molecules* **2001**, *6*, 900.
154. (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart J. F. *Angew Chem., Int. Ed.* **2002**, *41*, 898. (b) Karan, C.; Miller, B. L. *Drug Discovery Today* **2000**, *5*, 67.
155. Otera, J. *Esterification. Methods, Reactions and Applications,* Wiley-VCH: Weinheim **2003**.
156. Larock, R. C. *Comprehensive Organic Transformations*, VCH: New York, **1989**; pp. 980.
157. (a) Schlubach, H. H.; Repenning, K. *Angew Chem.*, **1959**, *71*, 193. (b) Steglich, W.; Höfle, G. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 569. (d) Scriven, E. F.V. *Chem. Soc. Rev.* **1983**, *12*, 129. (e) Berry, D. J.; Digiovanna, C. V.; Metrick, S. S.; Murugan, R. *Arkivoc* **2001** (ii) 944. (f) Orita, A.; Sakamato, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899. (g) Orita, A.; Ito, T.; Yasui, Y.; Otera, J. *Synlett* **1999**, 1927.
158. (a) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286. (b) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (c) Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093.
159. D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.
160. Cope, A. C.; Herrick, E. C. *Organic Syntheses, Collect. Vol. 4,* Wiley: New York: **1963**; pp.304.
161. (a) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *Chem. Commun.* **1996**, 2625. (b) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342.
162. Mukaiyama, T.; Shiina, I.; Miyashra, M. *Chem. Lett.* **1992**, 625.
163. Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem Lett.* **1995**, 141.
164. Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351.
165. Damen, E. W. P.; Braamer, L.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 6081.
166. Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743.
167. Karimi, B.; Maleki, J. *J. Org. Chem.* **2003**, *68*, 4951.

168. (a) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413. (b) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. (c) Zhou, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559. (d) Jarowicki, K.; Kocienski, P. *Org. Synth.* **1997**, 454.
169. (a) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877. (b) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, 66, 8926. (c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T.; Rao, K. R. *Tetrahedron Lett.* **2004**, *45*, 6037. (d) Carrigan, M. D.; Freiberg, D. A.; Smith, R. C.; Zerth, H. M.; Mohan, R. S. *Synthesis* **2001**, 2091. (e) Baltork, I. M.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851. (f) Peterson, K. E.; Smith, R. C.; Mohan, R. S. *Tetrahedron Lett.* **2003**, *44*, 7723. (g) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373. (h) Gaspard-Iloughmane, H.; Roux, C. L. *Eur. J. Org. Chem.* **2004**, 2517.
170. Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611.
171. Clarke, P. A.; Kayaleh, N. E.; Smith, M. A.; Baker, J. R.; Bird, S. J.; Chan, C. *J. Org. Chem.* **2002**, *67*, 5226.
172. Dalpozzo, R.; Nino, A. D.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* **2003**, *44*, 5621.
173. Alleti, R.; Perambuduru, M.; Samantha, S.; Reddy, V. P. *J. Mol. Cat. A: Chemical*, **2005**, *226*, 57.
174. Chen, C. –T.; Kuo, J.-H.; Li, C.-H.; Barhate, N. B.; Hon, S.-W.; Li, T.-W.; Chao, S.-D.; Liu, C.-C.; Li, Y.-C.; Chang, I.-H.; Lin, J.-S.; Liu, C. -J.; Chou, Y.-C. *Org. Lett.* **2001**, *3*, 3729.
175. Chen, C. –T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C. –H.; Liu, C. –Y. *J. Org. Chem.* **2005**, *70*, 1188.
176. (a) Backer, R. H.; Bordwell, F. G. *Org. Synth.* **1955**, *3*, 141. (b) Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001. (c) Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263. (d) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2919. (e) Chakraborti, A. K; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 6749. (f) Chakraborti, A. K; Gulhane, R *Synlett* **2004**, 627.
177. Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702.
178. Phukan, P. *Tetrahedron Lett.* **2004**, *450*, 4785.
179. Karimi, B.; Seradj, H. *Synlett* **2001**, 519.
180. Khan, A. T.; Chaudhury, L. H. Ghosh, S. *Eur. J. Org. Chem.* **2005**, 2782.
181. (a) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516. (b) Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* **2001**, 1584; Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2002**, *43*, 6331. (c) Chakraborti, A. K.; Sharma, L.; Gulhane, R. S. *Tetrahedron* **2003**, *59*, 7661; Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Synlett* **2003**, 39. (d) Chakraborti, A. K.; Gulhane, R.; Shivani. *Synlett* **2003**, 1805.
182. Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369.
183. Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896.
184. Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265.
185. Kumareswaran, R.; Pachamuthu, K.; Vankar, Y. D. *Synlett* **2000**, 1652.
186. Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dongare, M. K. *Synlett* **2001**, 206.
187. Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F.; Amani, K. *Chem.Commun.* **2003**, 764.
188. Sharghi, H.; Sarvari, M. H. *Tetrahedron* **2003**, *59*, 3627.
189. (a) Yadav, V. K.; Babu, K. G. *J. Org. Chem.* **2004**, *69*, 577. (b) Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047.
190. Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420.
191. Steliou, K.; S.-Nowosielska, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578.
192. Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
193. (a) Otton, J.; Ratton, S.; Vasney, V. A.; Markova, G. D.; Nametov, K. M.; Bakhmutov, V. I.; Komarova, L. I.; Vinogradova, S. V.; Korshak, V. V. *J. Polym. Chem.* **1988**, *26*, 2199. (b) Shiina, I.; Mukaiyama, T.; Miyoshi, S.; Miyashita, M. *Chem. Lett.* **1994**, 515.

194. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (b) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Synlett* **2001**, 1117. (c) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179.
195. Iranpoor, N.; Shekarriz, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 455.
196. Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249.
197. Habibi, M. H.; Tangestaninejad, S.; Mirkhani, V.; Yadollahi, B. *Tetrahedron* **2001**, *57*, 8333.
198. Ogawa, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. *J. Chem. Soc. Perkin Trans.1* **1994**, 3473.
199. Choudary, B. M.; Bhaskar, V.; Kantam, M. L.; Rao, K. K.; Raghavan, K. V. *Green Chemistry* **2000**, 67.
200. Choudary, B. M.; Kantam, M. L.; Bharathi, B; Reddy, C. V. *J. Mol. Catal. A: Chem.* **2001**, *168*, 69.
201. Akçay, M. *Appl. Catal. A: Gen.* **2004**, *269*, 157.
202. Kuttan, A.; Nowshudin, S.; Rao, M. N. A. *Tetrahedron Lett.* **2004**, *45*, 2663. (b) Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.-J.; Wu, Y.-C. *Tetrahedron Lett.* **2003**, *44*, 331. (c) Goswami, P.; Chowdhury, P. *New J. Chem.*, **2000**, *24*, 955.
203. Bosco, J. W. J.; Raju, B. R.; Saikia, A. K. *Synth. Commun.* **2004**, *34*, 2849.
204. Velusamy, S.; Borpuzari, S.; Punniyamurthy, T. *Tetrahedron*, **2005**, *61*, 2011.

1B. Present Work

1B.1. Chemoselective Thioacetalisation of Carbonyl Compounds Catalysed by Tetrabutylammonium Tribromide (TBATB)

Acetals, oxathioacetals and thioacetals are the most widely used groups for masking a carbonyl compound. During a multi-step synthetic process the acetal and thioacetal protected carbonyl groups are resistant to attack by various reagents such as nucleophilic, basic, oxidising, catalytic, and hydride reducing agents.[1] Thioacetals are most often used as protecting group in spite of the difficulties associated with their removal because of their greater stability towards acidic conditions as compared to corresponding *O,O*-acetals and *S,O* acetals. In addition to serving as a protecting group for carbonyl compounds, thioacetals are widely used as precursors for acyl anion equivalents and masked methylene functions in carbon-carbon bond forming reactions. Some of these approaches have been used extensively for the synthesis of several natural products, which has been discussed in the introduction chapter, section **1A.2.1.1 (a and b)**. More over *S,S*-acetals can also be used as intermediates for the conversion of the carbonyl functions to the parent hydrocarbons by reductive desulphurisation.

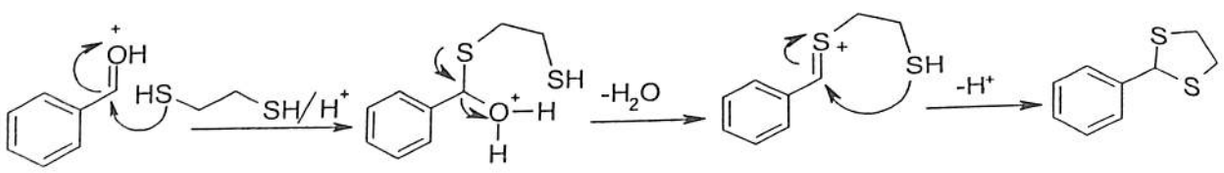
Dithioacetals has been achieved by protic or Lewis acid-catalysed condensation of carbonyl compounds with dithiols or by a transthioacetalisation of cyclic and acylic acetals. Recent reports on odourless 1,3-dithiane equivalents used for thioacetalisation are also available. A comprehensive list of various protic acids, Lewis acids, miscellaneous reagents and supported reagents used for thioacetalisation have been described in section **1A.2.1.1 (c)** in the introduction chapter.

The drawbacks associated with some of the procedures reported in the literature include formation of side products such as hemithioacetal, vinyl sulfides from enolisable carbonyl compounds. Other problems associated are difficulties in work-up, isolation, requirement of inert atmosphere, harsh reaction conditions, expensive and stoichiometric reagents, anhydrous conditions, failure to protect deactivated and hindered substrates. Sometime strong acidity of reagents results in incompatibility with other protecting groups whereas in some cases neutrality of the medium obstructs the completion of the reaction. Molecules bearing multiple carbonyl groups are frequently encountered and in those cases, the carbonyl group being modified must be differentiated from the other carbonyls and from acetals and ketals, which can also be considered as members of carbonyl family. One of the problems associated is poor selectivity when applied to a mixture of aldehyde and ketone.

Recently, several methods are reported for the chemoselective thioacetalisation between aldehydes and ketones. However, there are only few methods known for the chemoselective thioacetalisation between ketones and between aldehydes but, none of the reported methods describe the chemoselective thioacetalisation of a carbonyl compound with different dithiols. Chemoselective transthioacetalisation between different acetals has not been reported at all. Thus, selective thioacetalisation of carbonyl compounds are of great synthetic value. However, the development in this area demands a synthetic methodology satisfying all the above-mentioned criteria and also not only chemoselectivities between aldehydes and ketones but also between different aldehydes and different ketones. It is also important to understand what governs the selectivity, is it the intrinsic reactivity of the substrates or catalyst or reaction conditions?

Tetrabutylammonium tribromide (TBATB), the stable orange crystalline solid has emerged as an efficient reagent for various organic transformations as desribed in the section **1A.1.1** in the introduction chapter. When used in stoichiometric amount this reagent is reported to unmask thioacetal.[2] However using a catalytic quantity (0.02 equiv) it acts as a promoter for thioacetalisation of aldehydes and thioketalisation of ketones.

The experimental procedure for thioacetalisation / thioketalisation is remarkably simple and do not require the use of dry solvents and inert atmosphere or reflux conditions. To a stirred solution of carbonyl compound and 1,2-ethanedithiol or 1,3-propanedithiol in THF was added a catalytic quantity of TBATB (0.02 equiv) and the mixture was left stirred at room temperature. The role of TBATB is not clear but it is most likely that it reacts with dithiol similar to alcohols as reported by our group[3] to generate HBr, which may activate the carbonyl group by protonation at the carbonyl oxygen for further reaction, Scheme 1B.1.



Scheme 1B.1 Proposed Mechanism for Thioacetalisation

In a control experiment, when benzaldehyde was treated with a catalytic quantity of 48% HBr (0.02 equiv) instead of TBATB and 1,2-ethanedithiol, benzaldehyde 1,3-dithiolane was obtained in good yield (95%). The versatility of the process has been proved with a wide range of aldehydes and ketones with various stereo-electronic factors. Under these conditions, a wide range of aldehydes and ketones

containing electron-donating, electron-withdrawing, conjugated and hindered groups could all be transformed to the corresponding 1,3-dithiolanes and 1,3-dithianes in good yields, which has been summarised in Table1.1.

Table 1.1. Thioacetalisation[a] of Carbonyl Compounds

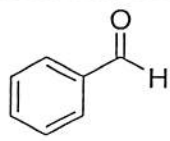
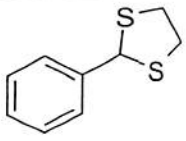
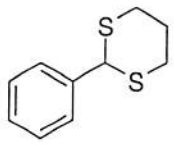
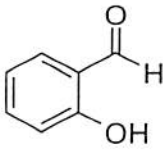
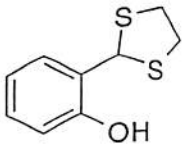
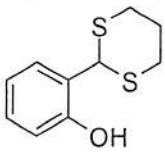
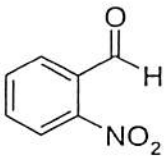
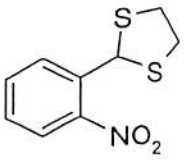
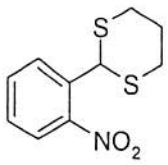
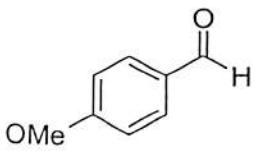
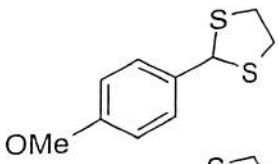
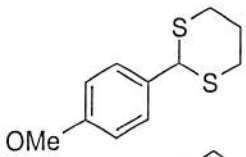
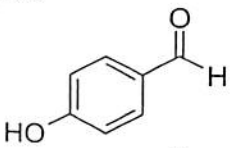
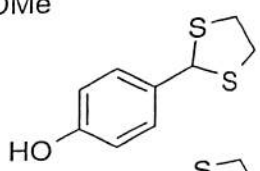
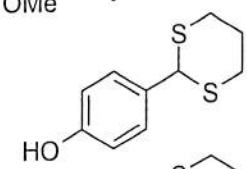
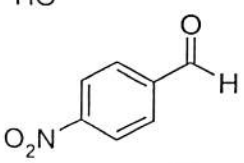
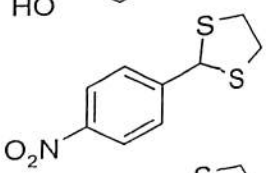
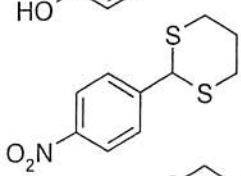
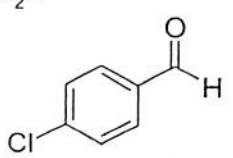
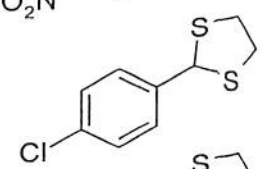
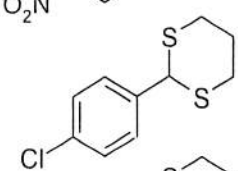
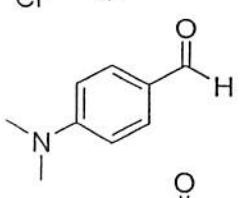
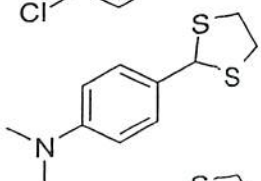
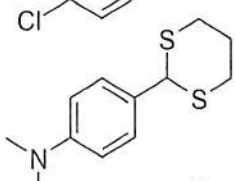
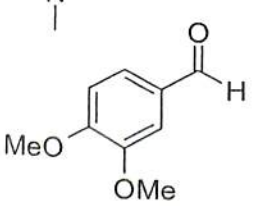
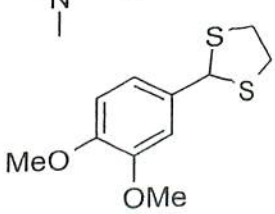
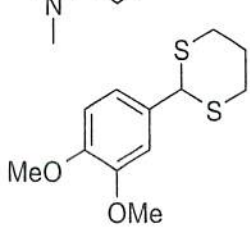
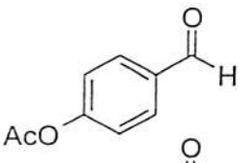
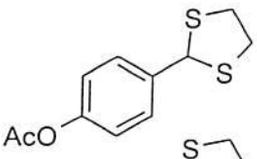
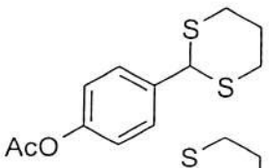
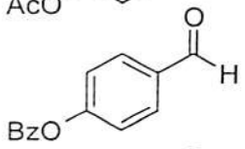
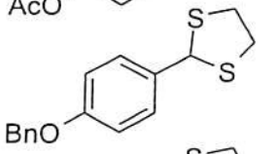
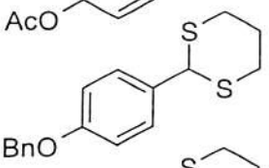
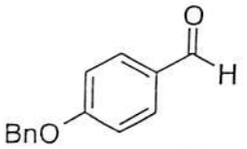
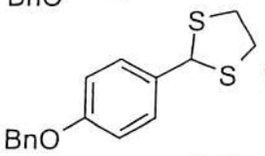
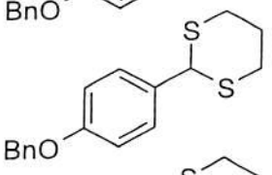
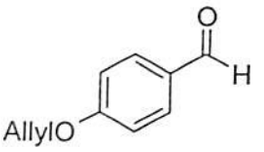
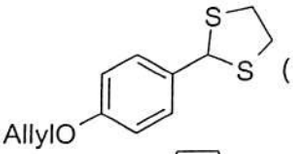
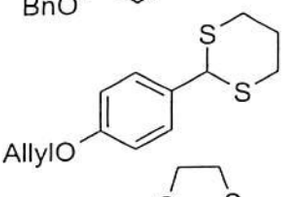
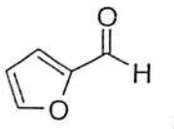
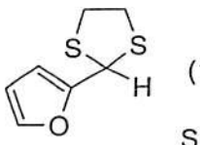
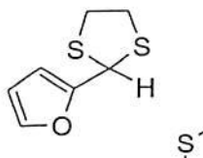
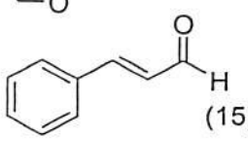
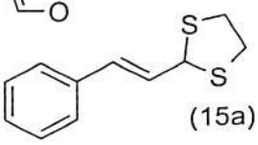
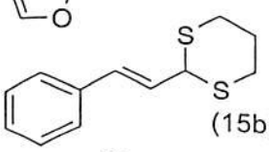
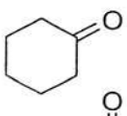
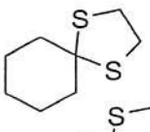
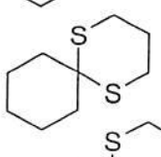
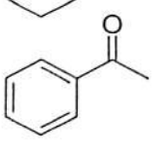
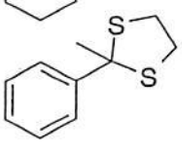
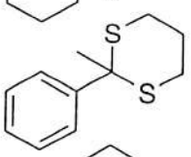
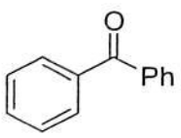
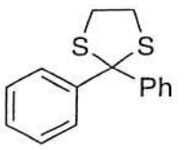
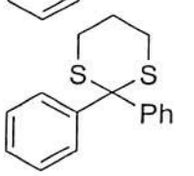
Substrate	Time/h	X_1	Yield[b,c](%)	X_2	Yield[b,c](%)
 (1)	0.08	 (1a)	96	 (1b)	96
 (2)	0.50	 (2a)	95	 (2b)	95
 (3)	1.50	 (3a)	45	 (3b)	30
 (4)	0.08	 (4a)	87	 (4b)	84
 (5)	0.50	 (5a)	97	 (5b)	94
 (6)	1.50	 (6a)	70	 (6b)	70
 (7)	1.00	 (7a)	80[d]	 (7b)	79[d]
 (8)	1.00	 (8a)	81[d]	 (8b)	75[d]
 (9)	1.00	 (9a)	90	 (9b)	80

Table Contd....

Table 1.1. Thioacetalisation[a] of Carbonyl Compounds

Substrate		Time/h	X_1	Yield[b,c](%)	X_2	Yield[b,c](%)
	(10)	1.00	 (10a)	70	 (10b)	70
	(11)	1.00	 (11a)	72	 (11b)	68
	(12)	1.00	 (12a)	85	 (12b)	83
	(13)	1.00	 (13a)	77	 (13b)	70
	(14)	1.00	 (14a)	70	 (14b)	80
	(15)	0.2	 (15a)	88	 (15b)	81
	(16)	0.50[e]	 (16a)	75	 (16b)	75
	(17)	1.00[e]	 (17a)	90	 (17b)	85
	(18)	3.00[e]	 (18a)	79[d]	 (18b)	82[d]

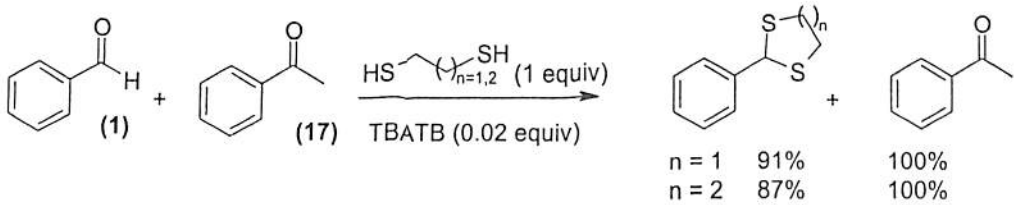
X_1=1,3dithiolane; X_2 =1,3-dithiane. [a]Reactions were monitored by TLC / GC. [b]Confirmed by comparision with IR and ^{1}H NMR of the authentic sample. [c]Isolated yields. [d]Based on the recovery of starting material. [e]0.1equiv of TBATB was used.

As can be seen from Table 1.1, most of the substrates gave excellent yields of the corresponding dithioacetals. Aldehydes containing electron-donating groups such as *o*-hydroxybenzaldehyde **2** and *p*-hydroxybenzaldehyde **5** gave excellent yields of the corresponding products. However, aldehydes containing electron-withdrawing substituents such as *o*-nitrobenzaldehyde **3** and *p*-nitrobenzaldehyde **6** gave poor yields of the corresponding dithioacetals. Aldehydes with substituents such as *p*-chloro

benzaldehyde **7**, *N,N*-dimethylamino benzaldehyde **8**, 3,4-dimethoxy benzaldehyde **9** when reacted with dithiol and TBATB under the present optimised condition gave satisfactory yield. A variety of functional groups such as *O*-acetyl **10**, *O*-benzoyl **11**, *O*-benzyl **12** were found to be quite stable during the reactions. The compatibility of the methodology was demonstrated by the regioselective thioacetalisation of unsaturated aldehydes in good yields as shown in the case of aldehydes **13** and **15**. Furfuraldehyde **14** reacted to give 80% yield of the thioacetalised product. Importantly, no other side products, *viz.* bromination were observed. Aliphatic **16**, aromatic **17** and hindered aromatic ketones **18** reacted slowly under the given condition giving poor yields. However, a better yield was obtained by using (0.1 equiv) of the reagent.

This difference in reactivity of the aldehydes and the ketones suggested that the method can be useful for the selective protection of aldehydes. However, various reagents and procedures has been reported in literature for chemoselective thioacetalisation of aldehydes over ketones which includes the use of $InBr_3$,[4] $InCl_3$,[5a] $In(OTf)_3$,[6] I_2,[7] $ZnCl_2$,[8] LiBr,[9] $LiBF_4$,[10] 5M $LiClO_4$,[11] silicagel treated with thionyl chloride,[12] NBS,[13] $NiCl_2$,[14] $Sc(OTf)_3$,[15] trichlorocyanuric acid,[16] 2-stanna-1,3 dithiane and 1,3-dithiolane catalysed by organotin triflates.[17]

When dithiol (1 equiv) was added to an equimolar mixture of an aldehyde **1** and a ketone **17** it was observed that in this mixture, the aldehyde formed the dithiolane and dithiane whilst the ketone was almost completely recovered, Scheme 1B.2.

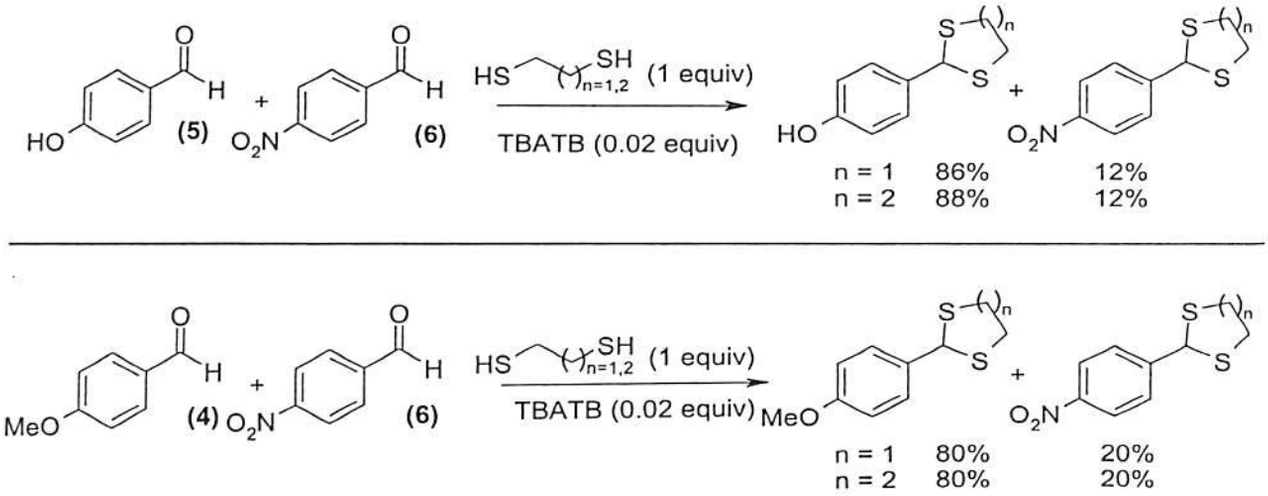


Scheme 1B.2 Chemoselective Thioacetalisation of Aldehyde over Ketone

Similar chemoselectivity was observed in the thioacetalisation of benzaldehyde **1** over acetophenone **17** with other catalysts such as I_2,[7] NBS,[13] $BF_3.Et_2O$,[18] and with HBr. [19]The selectivity remained unaltered even when the reaction was performed at different temperatures (-10°C and 80°C) and with different solvents ($CHCl_3$, Et_2O, toluene and CH_3CN) using TBATB as the catalyst. **Thus in this case the selectivity is due to the intrinsic reactivity of the substrates and is independent of the catalyst, solvent and reaction temperature.** This is because of the higher ground state energy and

lower transition state for aldehydes as compared to the higher ground state stabilisation and higher activation energy for ketones as explained for acetalisation reactions.[3]

Realising the sharp contrast in the reactivity of *p*-hydroxybenzaldehyde **5** over *p*-nitrobenzaldehyde **6** in terms of reaction time and yield in Table 1.1, we decided to make selective thioacetalisation as our objective. Thus, in a competitive reaction between *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6** it was observed that the formerwas thioacetalised. In an analogous reaction between *p*-methoxybenzaldehyde **4** and *p*-nitrobenzaldehyde **6** the former was thioacetalised preferentially, Scheme 1B.3.



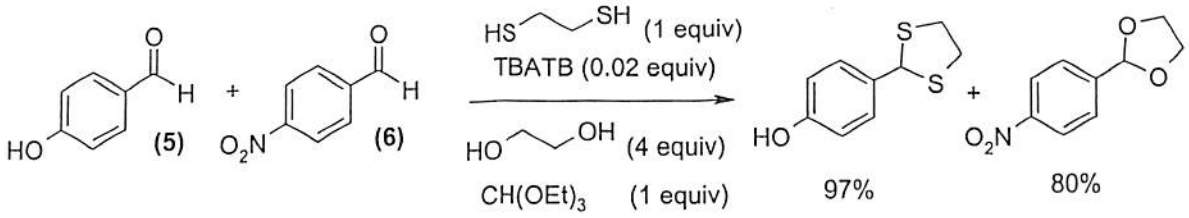
Scheme 1B.3 Chemoselective Thioacetalisation of Aldehydes

This selectivity obtained in thioacetalisation is in sharp contrast to the selectivity obtained in the previous work pertaining to acetalisation, where a substrate containing an electron-withdrawing group such as *p*-nitrobenzaldehyde **6** reacts preferentially over a substrate containing an electron-donating group, *p*-hydroxybenzaldehyde **5**. It was argued that due to lower electron density 0.218 around the carbonyl carbon of *p*-nitrobenzaldehyde **6** compared to 0.228 of *p*-hydroxybenzaldehyde **5**, the former is more susceptible to nucleophilic attack by diols for acetalisation.[3] Here again the selectivity is independent of the catalysts ($BF_3.Et_2O$, NBS, I_2 and HBr), solvents ($CHCl_3$, Et_2O, toluene and CH_3CN) and the reaction temperature (-10°C and 80°C). Not surprisingly the reactions were found to be slower at lower temperature (-10°C).

Unfortunately, the same logic could not be extended for the thioacetalisation reactions in spite of similarity in their reaction mechanism with acetalisation reactions. One plausible explanation would be the stabilisation of filled sulphur orbitals towards thiocarbenium ion predominates over the effects due to electron-donating and electron-withdrawing groups present in the aromatic ring. A second explanation

could be due to a higher molecular orbital coefficient at the carbonyl carbon of *p*-hydroxybenzaldehyde **5**, the sulphur nucleophile with its larger orbital overlaps efficiently satisfying the Bürgi-Dunitz trajectory of 107° for a favourable nucleophilic attack.

Thus, in aldehydic substrates containing both electron-donating and electron-withdrawing group, for the selective protection at the electron rich aldehydic carbonyl site, thioacetalisation process is preferred and for the protection at the electron-deficient aldehydic carbonyl acetalisation is desirable. This assumption of ours is evident from the following competitive experiment, Scheme 1B.4.



Scheme 1B.4 Chemoselective Acetalisation and Thioacetalisation

When an equimolar mixture of *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6** was reacted with an equimolar mixture of 1,2-ethanedithiol, 1,2-ethanediol and triethylorthoformate, TBATB (0.01 equiv) in THF, *p*-hydroxybenzaldehyde **5** was completely thioacetalised where as *p*-nitrobenzaldehyde **6** was acetalised to 35% and the rest being starting material. It may be mentioned here that for the complete acetalisation of *p*-nitrobenzaldehyde, 4 equivalents of the diol is necessary.[3] When the above competitive reaction was performed with 1,2-ethanediol (4 equiv.) and 1,2-ethanedithiol (1 equiv.) a complete chemoselective thioacetalisation of *p*-hydroxybenzaldehyde (97%) and acetalisation of *p*-nitrobenzaldehyde (80%) was observed and the rest being starting materials as shown above in Scheme 1B.4.

From the above schemes it has been observed that the variation in yields depends on the type of substituents in the aromatic ring in acetalisation and thioacetalisation reaction. Hence it was concluded that the selectivity obtained is due to the intrinsic reactivity of the substrates and is independent of the reaction condition (catalyst, solvent, and temperature).

1B.1.1. Theoretical Interpretation on Chemoselectivities in Acetalisation and Thioacetalisation and Oxathioacetalisation

This section of the chapter represents a combined study (experimental as well as theoretical) of the chemoselectivities involved in the acetalisation, thioacetalisation, oxathioacetalisation of *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6**. The main objective is to investigate the dependence of cyclic *O,O*; *S,S* and *S,O* acetal formation with the variation of substitution on the phenyl ring of benzaldehyde.

A theoretical investigation[20] have concluded that the global electrophilicity (w)[21] of benzaldehyde and its different substituents is the sole factor in governing the chemoselectivity in acetalisation, although steric factors also cause minor variation in the yield in some cases. Thus based on the theoretical investigation the selectivity obtained in the above schemes can be explained on the basis of difference of w values between aldehydes and the nucleophiles.

Global Reactivity Descriptor

From a qualitative suggestion by Maynard *et al.*[22] Parr and co-workers[21] have proposed a global electrophilicity descriptor as follows

$$w = \mu^2 / 2\eta$$

Here, w is considered to be the electrophilic power of the concerned chemical species and bears the conceptual similarity to power of classical electricity (i.e, Power = V^2/R of classical electricity, where V and R represent the potential difference and resistance respectively). In the right hand side of the above equation, μ is the 'chemical potential' and η is 'global chemical hardness' of the concerned chemical species.

Physical Significance

The more is the difference of the global electrophilicity value between electrophile and nucleophile the better is the yield because lower is the w-value stronger is the nucleophile.

Local Reactivity Descriptors

Parallel to the development of global reactivity descriptor some local reactivity descriptors were also proposed because of their potential use in predicting local (or site) reactivity (selectivity) of a

chemical species. The condensed local softness values are representated by, s_k^+ and s_k^- of atom 'k' towards nucleophilic, electrophilic, and radical attack on it, respectively.[23]

Physical Significance

In a molecule the atom 'k', for which s_k^+ value is highest, is the most preferred atom to be attacked by a nucleophile. Similarly, highest values of s_k^- and s_k^0 for any atom 'k' indicate it to be the most preferable atom for electrophilic and radical attack.

In our present study of chemoslectivity in thioacetalisation in this section, we have chosen the aldehyde with electron-releasing substituent *i.e. p*-hydroxybenzaldehyde and with electron-withdrawing substituent *i.e., p*-nitrobenzaldehyde. These two aldehydes have more than one comparatively strong reactive sites (phenyl ring carbon atoms). Thus, the electron-withdrawing or electron-releasing effects by the substituted groups are somewhat stabilised by the intervening phenyl ring carbon atoms, before these effects are felt by the carbonyl carbon. Under such circumstances it looks more physical to compare the values of w than the s_k^+ values of carbonyl carbon to explain the yield of acetalisation. The generated values of w can explain qualitatively the preferential electrophilic addition and hence the yield of acetalisation obtained. Though both steric and electronic factors affect the yield, only electronic factors can be taken care of by w.[20]

Table 1.2. MPA and HPA based Charges ^{q}k, $^{s}k^{+}$, and $^{s}k^{-}$ values of the atoms (underlined) which are relevant in the present study. The $^{s}k^{+}$ and $^{s}k^{-}$ values are in atomic units.

	MPA/6-31G(D,P)			HPA/dnp		
Carbonyl System	q_k	s_k^+	s_k^-	q_k	s_k^+	s_k^-
p-$NO_2C_6H_4\underline{C}HO$	0.5276	0.2696	0.1780	0.1192	0.2934	0.2099
p-$OHC_6H_4\underline{C}HO$	0.5099	0.7988	0.1653	0.1024	0.3242	0.2233
$CH_2\underline{S}H\text{-}CH_2\underline{S}H$	0.0459	0.9043	0.9432	-0.0530	0.6512	0.9077
$CH_2\underline{O}H\text{-}CH_2\underline{O}H$	-0.3121	0.6130	0.4728	-0.2315	0.2144	0.4798
$CH_2\underline{O}H\text{-}CH_2SH$	-0.2974	0.0904	0.0878	-0.2308	0.1749	0.4408
$CH_2OH\text{-}CH_2\underline{S}H$	0.0171	1.5737	1.6644	-0.0480	0.7467	0.9261

HPA: Hirshfield Population Analysis; MPA: Mulliken Population Analysis

The charge values were evaluated by Hirshfield population analysis (HPA)[24] using DMOL[20] program and by Mulliken population analysis (MPA)[25] using Gaussian program. For systems having more than one reactive sites of comparable strength, local reactivity descriptors cannot be used as reliable indicators of global reactivity trends.[26]

Several case studies have rigorously shown the conceptual advantages of HPA over MPA.[27] The global and local descriptors calculated by HPA/dnp method in the present study are considered here as more useful.

Table 1.3. MPA and HPA based global electrophilicity (i.e., w) values of the chemical systems relevant for comparison of competitive acetalisation in the present study. The values are in atomic units.

	MPA/6-31G(D,P)	HPA/dnp
Chemical Systems	w	w
p-$NO_2C_6H_4CHO$	0.0808	0.1212
p-OHC_6H_4CHO	0.0347	0.0698
CH_2SH-CH_2SH	0.0206	0.0417
CH_2OH-CH_2OH	0.0149	0.0381
CH_2OH-CH_2SH	0.0143	0.0379

Because of large size and negligible negative charge (-0.0530) (in HPA / dnp method) sulphur atoms in 1,2-ethanedithiol behave as soft bases. So, the interaction of carbonyl carbon (having comparatively lower positive charge on it) in *p*-hydroxybenzaldehyde **5** with sulphur atom in 1,2-ethanedithiol is mainly orbital controlled soft-soft in nature. Because of higher positive charge this type of soft-soft interaction will not be effective with *p*-nitrobenzaldehyde **6**. Thus the major product is expected cyclic *S, S* acetal of *p*-hydroxybenzaldehyde **5** in Scheme 1B.3, as described in page 60.

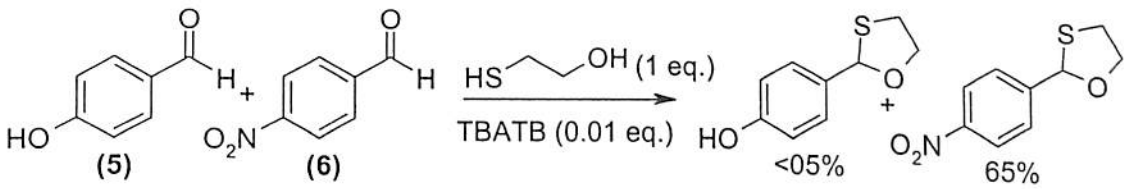
On the other hand, the higher positive charge on the carbonyl carbon of *p*-nitrobenzaldehyde **6** (0.1192) than on the carbonyl carbon of *p*-hydroxybenzaldehyde **5** (0.1024) calculated by HPA/dnp method, which is also due to the electron withdrawing nature of $-NO_2$ group and high negative charge on oxygen of 1,2-ethanediol makes the charge controlled hard-hard interaction very effective. The hard-hard interaction between carbonyl carbon of *p*-hydroxybenzaldehyde **5** and oxygen of 1,2-ethane diol is not that effective because of lower positive charge on carbonyl carbon in the former (this will be particularly true when a competitor like *p*-nitrobenzaldehyde **6** is already present in the reaction medium). Also the difference of global electrophilicity between *p*-nitrobenzaldehyde **6** and 1,2-ethane-

diol is 0.0831, which is significantly higher than between *p*-hydroxybenzaldehyde **5** and 1,2-ethanediol (0.0317). These two factors favour the *O,O* acetal formation of *p*-nitrobenzaldehyde **6**. Although the s_k^+ value of carbonyl carbon in *p*-hydroxybenzaldehyde **5** is little higher in HPA/dnp method it seems not to have influenced the yield.

Because of the competitive reaction condition *p*-nitrobenzaldehyde **6** forms *O,O* acetal with 1,2-ethane diol and *p*-hydroxybenzaldehyde **5** forms *S,S* acetal with 1,2-ethanedithiol as shown in the scheme 1B.4, page 61. The reason is that the highest global electrophilicity of *p*-nitrobenzaldehyde **6** (0.1212) plus higher positive charge of carbonyl carbon (0.1192) favours it to react with the lowest electrophile (*i.e.*, strongest nucleophilic) 1,2-ethanediol (which has also higher negative charge on oxygen atoms, -0.2315) in a charge controlled hard-hard way. Similarly, *p*-hydroxybenzaldehyde **5** reacts with 1, 2-ethanedithiol in an orbital controlled soft-soft pathway.

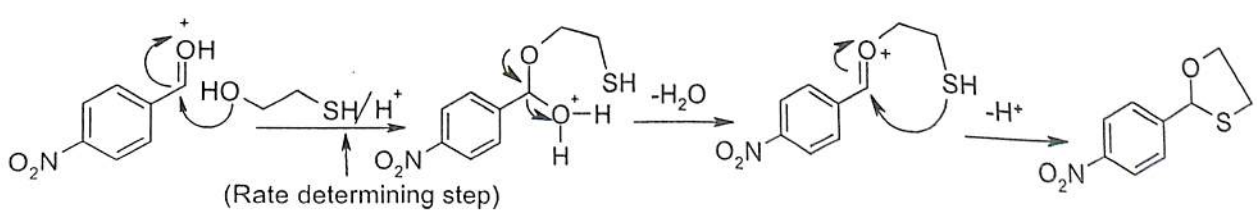
After finding an explanation for the chemoselectivity obtained in acetalisation and thioacetalisation with the aid of the theoretical investigation, we further extended this to oxathioacetalisation, Scheme 1B.5.

Higher positive charge on carbonyl carbon of *p*-nitrobenzaldehyde **6** and higher negative charge on mercaptoethanol $HS(CH_2)_2OH$ favours oxathioacetal formation for *p*-nitrobenzaldehyde **6**.



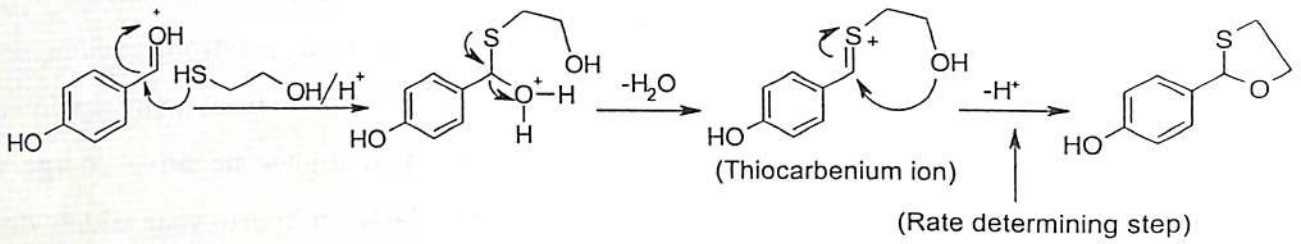
Scheme 1B.5 Chemoselective Oxathioacetalisation

As per explanations in the previous schemes it is expected that the initial attack by oxygen atom in mercaptoethanol to the deactivated carbonyl group of *p*-nitrobenzaldehyde **6** will take place in the first step which is charge controlled. This is then followed by an intramolecular nucleophilic attack by the sulphur atom on the oxycarbenium ion as shown in Scheme 1B.6.



Scheme 1B.6 Proposed Mechanism for Oxathioacetalisation

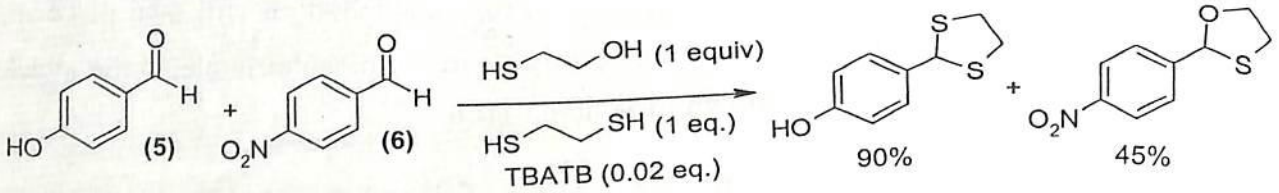
Here in the above scheme (Scheme 1B.6), as both the first and third steps are energetically favourable, the yield of *S,O*-oxathiocetal of *p*-nitrobenzaldehyde **6** is higher. The probable reaction mechanism shown above is also consistent with the product distribution in Scheme 1B.4, page no. 61. Also, it has been experimentally found that *O,O* acetals can easily be converted to *S,S* and *S,O*-acetals. On the other hand sulphur atom is attacking first to the carbonyl carbon of the *p*-hydroxybenzaldehyde **5** followed by an intra-molecular attack of oxygen atom of mercaptoethanol as shown in Scheme 1B.7.



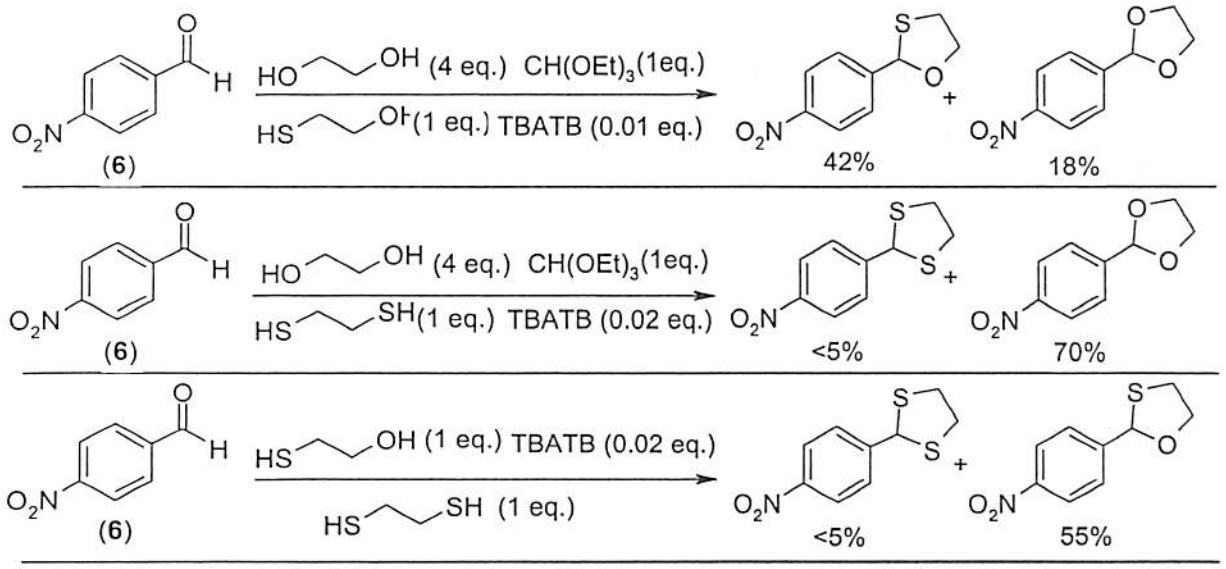
Scheme 1B.7 Proposed Mechanism for Oxathioacetalisation

In the above mechanism given in Scheme 1B.7, the first step is energetically favourable and is assumed to be predominantly orbital-controlled as has been observed in Schemes 1B.3 and 1B.4. (page, 60 and 61) But the third step *i.e.,* the attack of oxygen of mercaptoethanol to an electron rich thiocarbenium moiety is not favourable and we believe it to be the rate-determining step. Now, because the rate-determining step in case of oxathioacetal *i,e., S,O* acetal formation of *p*-nitrobenzaldehyde **6** (the first step in Scheme 1B.6) is energetically more favourable to that of the rate determining step in case of *p*-hydroxybenzaldehyde **5** (third step in Scheme 1B.7), the yield of *S,O* acetal formation in case of the former is higher than that of the later, Scheme 1B.5.

From the earlier schemes we have found from that *p*-hydroxybenzaldehyde **5** is favouring thioacetal formation and *p*-nitrobenzaldehyde **6** is favoring acetal and oxathioacetal formation. To confirm it again the following experiment has been performed, Scheme 1B.8.



Scheme 1B.8 Chemoselective Oxathioacetalisation and Thioacetalisation



Scheme 1B.9 Chemoselective Oxathioacetalisation and Acetalisation of *p*-Nitrobenzaldehyde

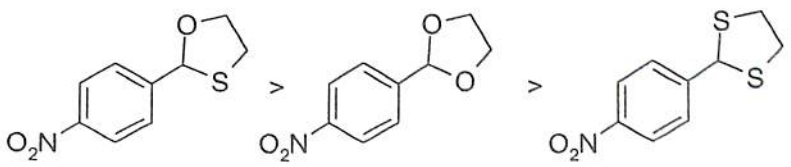
The carbonyl carbon of *p*-nitrobenzaldehyde **6** will be attacked first by the oxygen atom of the mercaptoethanol in a predominantly charge controlled pathway, Scheme 1B.6.

Instead of explaining the yields of the reactions individually a general approach seems to be more convincing. The trends of the yields of *O*,*O*, *S*,*O* and *S*,*S* acetals for 4-nitrobenzaldehyde **6** as shown above, could be explained on the basis of two considerations.

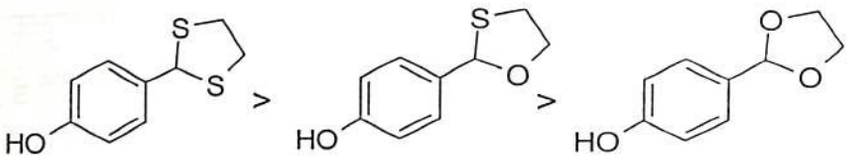
(i) The attack on carbonyl carbon of *p*-nitrobenzaldehyde **6** by oxygen atom of 1,2-ethanediol nucleophile is mainly charge controlled because of the high positive charge on carbonyl carbon of *p*-nitrobenzaldehyde **6** and higher negative charges on oxygen of 1,2-ethanediol. As sulphur atom of 1,2-ethanedithiol has negligible negative charge on it, the attack on carbonyl carbon by sulphur atom is much less effective either as charge-controlled or as orbital controlled.

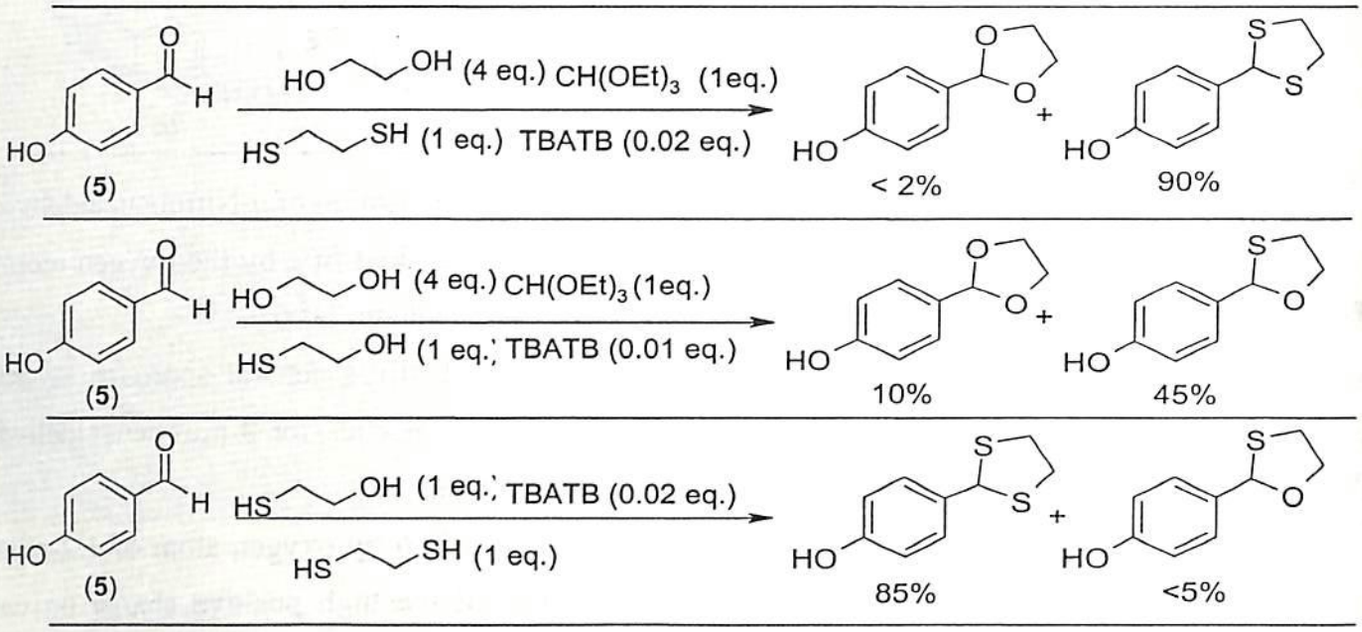
(ii) It also depends on the difference of global electrophilicity (w) between *p*-nitrobenzaldehyde **6** and the nucleophiles. The more is the difference the better is the yield because lower is the w value, stronger is the nucleophile.

Thus, in this present study the yield of formation of different cyclic acetals from *p*-nitrobenzaldehyde **6** follow the trend as below:



The trends of the yields of *O,O*; *S,O* and *S,S* acetals for *p*-hydroxybenzaldehyde **5** obtined is as follows which could be confirmed from the experiments, Scheme 1B.10.





Scheme 1B.10 Chemoselective Thioacetalisation and Oxathioacetalisation of *p*-Hydroxybenzaldehyde

As discussed in Schemes 1B.3 and 1B.4, the formation of *S,S* acetal is preferred over *O,O* acetal because of favourable orbital controlled reaction between *p*-hydroxybenzaldehyde **5** and 1,2-ethanedithiol, which is not the case when the nucleophile is 1,2-ethanediol. Similarly, formation of *S,O* acetal is preferred over *O,O* acetal because of the favourable orbital controlled attack of sulphur atom on the carbonyl carbon of *p*-hydroxybenzaldehyde **5**, Scheme 1B.7. Again the yield of *S,S* acetal is much higher than that of *S,O* acetal because the third step of mechanism shown in Scheme 1B.7 will be energetically more favourable in case of 1,2-ethanedithiol as sulphur atom is a better electron donor (to the thiocarbenium ion) than oxygen atom.

The yields of different acetals obtained from *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6** could be explained theoretically by a multitude of factors together. These are,

(i) Global electrophilicity difference between the electrophiles *i.e.*, *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6** and the nucleophiles *i.e.*, 1,2-ethanediol, 1,2-ethanedithiol and mercaptoethanol.

(ii) Type of attack on the most electrophilic atom *i,e.*, carbonyl carbon by the most nucleophilic atoms *i.e.*, oxygen or sulphur atom. This helps to understand whether the attack is charge controlled or orbital controlled.

(iii) Energetics at different stages of the reaction.

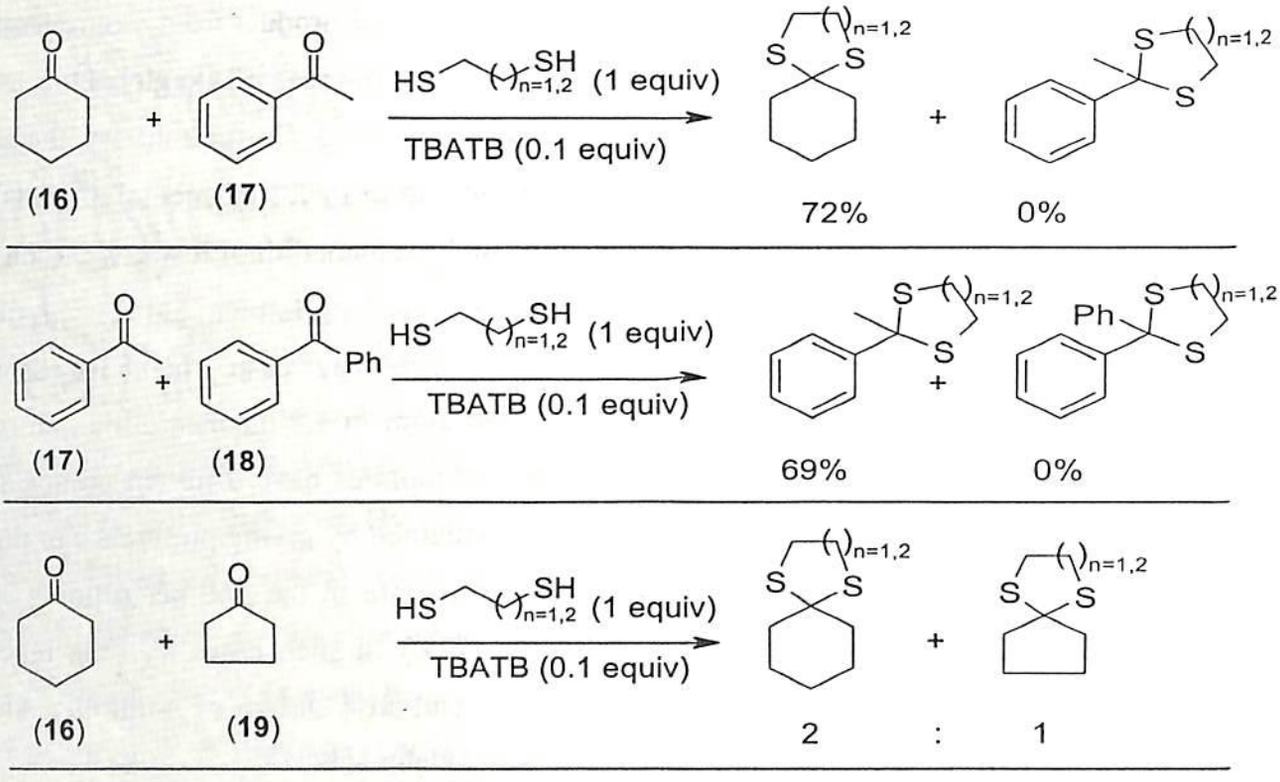
Unambiguous preference of *p*-nitrobenzaldehyde **6** for 1,2-ethanediol and that of *p*-hydroxybenzaldehyde **5** for 1,2-ethanedithiol clearly shows that only global electrophilicity *w* difference between the electrophiles and the nucleophiles is not sufficient to explain the observed yields. Had it been so, it would have been expected to get higher yield of *S,S* acetal product from *p*-nitrobenzaldehyde **6** than that from *p*-hydroxybenzaldehyde **5**, owing to the higher difference of the global electrophilicity values between *p*-nitrobenzaldehyde **6** and 1,2-ethanedithiol, Table 1.3. On the contrary, the reaction in Scheme 1B.5 clearly suggests the higher preference of oxygen atom in 1,2-ethanediol towards carbonyl carbon in *p*-nitrobenzaldehyde **6** and that of sulphur atom in 1,2-ethanedithiol towards carbonyl carbon in *p*-hydroxybenzaldehyde **5**. These evidences led us to invoke the long known, old concept of charge - controlled attack in the former and orbital - controlled attack in the later case. The above assumption is also justified because of the high negative charge on oxygen atom in 1,2-ethanediol but almost neutral sulphur atom in 1,2-ethanedithiol. In reactions where the nucleophiles have different groups at the two ends *i.e.*, in mercaptoethanol, the observed yields could be explained by giving preference to that type of attack which leads to energetically more favourable transition state in the rate determining step (e.g., reactions in Schemes 1B.5 and last reactions in Schemes 1B.9.) In such cases also the reactions are assumed to be initiated by the attack of oxygen atom to the carbonyl carbon of *p*-nitrobenzaldehyde **6** and by sulphur atom to the carbonyl carbon of *p*-hydroxybenzaldehyde **5**.

We would like to emphasise here that an energetic study, which includes the evaluation of activation energy in the rate - determining step, is not warranted for in the present case. This is because activation energy provides an account of the stability of the transition state (with respect to the reactants), which can be considered as the 'effect' of the phenomena involved in the process of chemical reaction. We are here to find out the 'cause', rather than the 'effect' (as the reaction yields obtained in the experimental study serve that purpose), which influences the stability of the transition state. While, in general, both the steric and electronic factors contribute to the stability of the transition state, the contrib-

ution of the former is negligible in the present study as in both the substrates *p*-nitrobenzaldehyde **6** and *p*-hydroxybenzaldehyde **5** the substituted groups (*-NO₂*, *-OH* and *-CHO*) are in para position. Thus, it seems to be physically meaningful to assume that electronic factors are the sole contributors to the stability of the transition state (and thus control the reactivity) which influences the yields of the reactions studied here. This is exactly what is considered in the present study.

Chemoselective Thioketalisation of Ketones

There have been reports of selective thioketalisation of aliphatic ketones over aromatic ketones. However, there are only few methods known for the chemoselective thioketalisation between ketones employing $InBr_3$,[4] $In(OTf)_3$,[6] 5M $LiClO_4$,[11] $ZnCl_2$,[8] I_2[7] $Sc(OTf)_3$,[15] organotin triflates.[17]

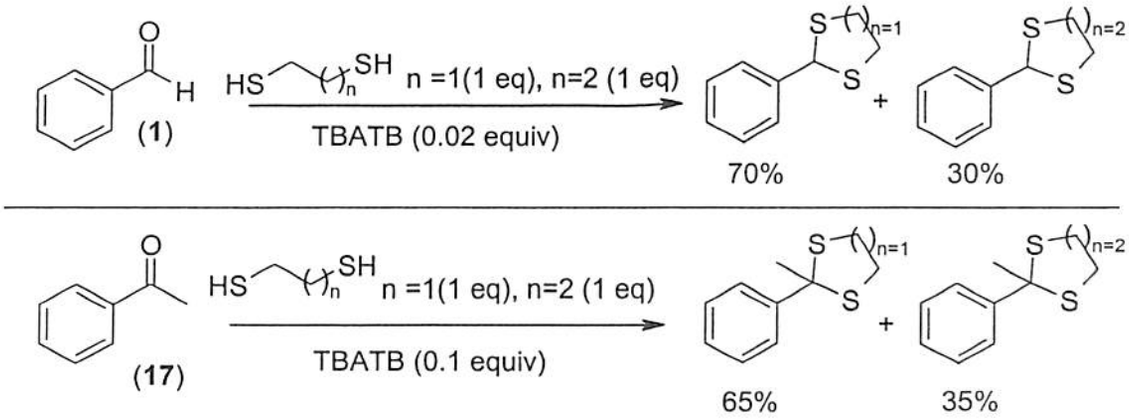


Scheme 1B.11 Chemoselective Thioketalisation

By employing our methodology aliphatic cyclic ketone could be preferentially thioketalised over aromatic ketones as demonstrated for cyclohexanone **16** and acetophenone **18**. Further, it was observed that the less hindered aromatic ketone acetophenone **18** could be selectively thioketalised in the presence of a hindered aromatic ketone, benzophenone **19** employing the present protocol, Scheme 1B.11. This method was then used for the selective protection of a six membered aliphatic ketone **16** as a thioketal in the presence of a five membered aliphatic ketone **17**, Scheme 1B.11. Thus this methodology will be

useful for selective protection of a six membered aliphatic ketone in the presence of a five membered aliphatic ketone.

Earlier our group have also reported a competitive reaction between 1,2-ethane diol and 1,3-propane diol for the same carbonyl compound and has found good degrees of selectivities.[3] The apparent order of acetal formation of different carbonyl group is: aldehyde-1,3-dioxanes > aldehyde-1,3-dioxolanes > ketone-1,3-dioxolanes > ketone-1,3-dioxanes.[3] This prompted us to investigate whether any preferential formation of a particular thioacetal or thioketal exists for a carbonyl group when reacted with an equimolar mixture of dithiols. When benzaldehyde **1** was reacted in the presence of both 1,2-ethanedithiol and 1,3-propanedithiol in equimolar amounts, the ratio of 1,3-dithiolane over 1,3-dithiane was found to be 7:3. When the same competitive reaction was performed with acetophenone **18**, similar selectivity was observed as shown in Scheme 1B.12.



Scheme1B.12. Chemoselective Thioacetalisation/ Thioketalisation

Thus, 1,3-dithiolane formation is preferred both for aldehydes and ketones compared to 1,3-dithiane. However, during acetalisation process the preferences obtained were different, aldehyde preferring 1,3-dioxanes and ketones 1,3-dioxolanes.[3]

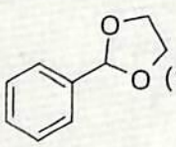
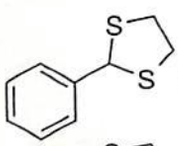
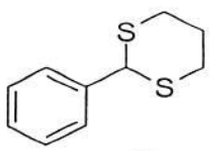
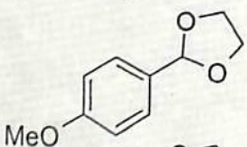
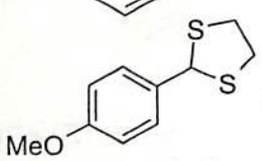
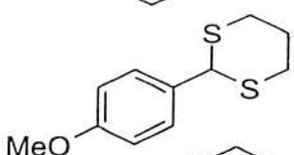
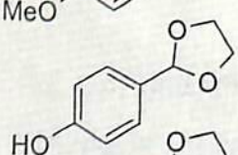
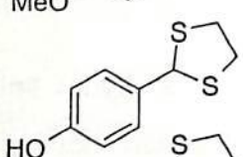
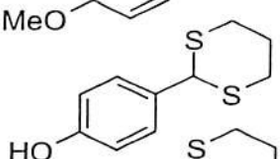
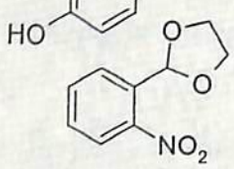
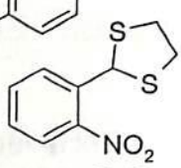
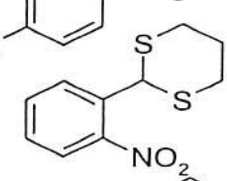
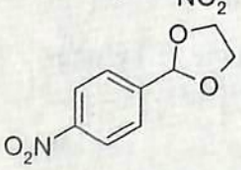
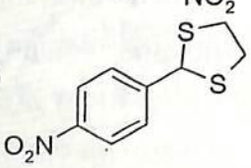
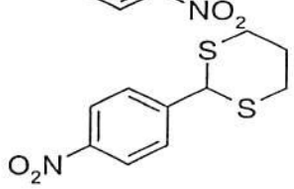
Thus from the present study the apparent order of thioacetal and thioketal formation of different carbonyl group is: aldehyde-1,3-dithiolane > aldehyde-1,3-dithiane > ketone-1,3-dithiolane > ketone-1,3- dithiane.

1B.1.2. Transthioacetalisation

The protection followed by deprotection and subsequent reprotection with a different protecting group is a usual practice in a multi-step synthesis as demanded by their stability under the reaction conditions in subsequent steps. Thus, a direct method for this transformation avoiding the intermediate

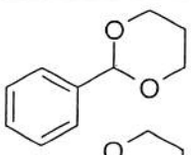
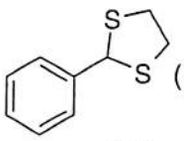
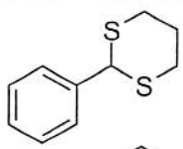
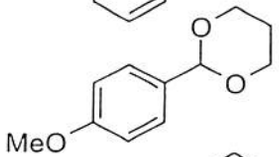
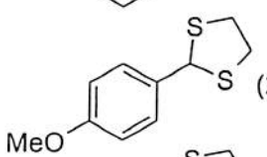
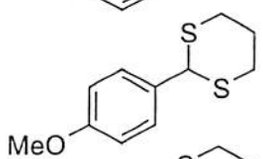
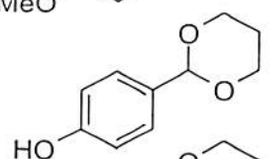
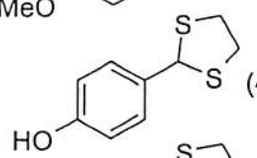
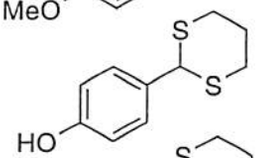
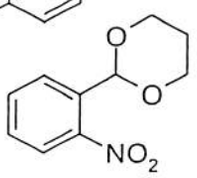
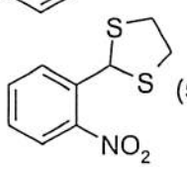
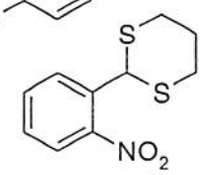
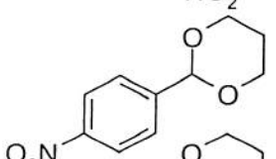
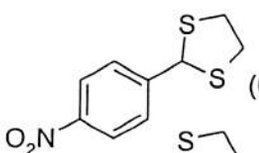
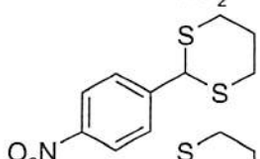
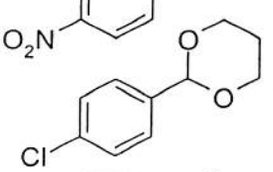
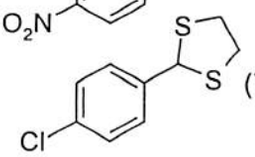
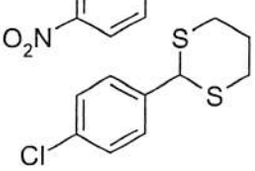
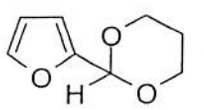
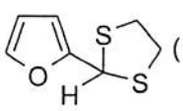
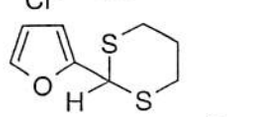
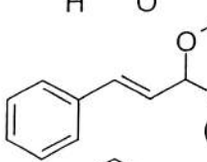
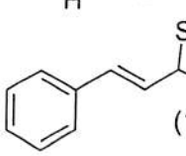
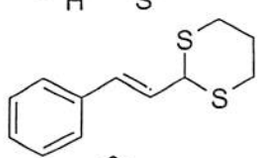
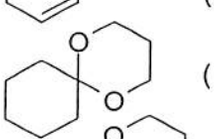
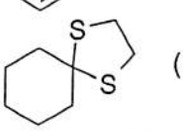
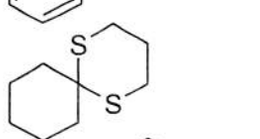
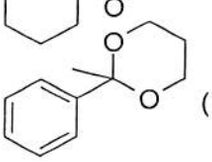
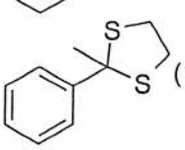
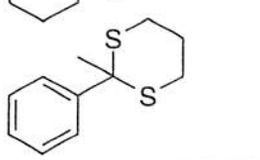
step of going back to the parent functionality is gaining more importance in order to improve the overall synthetic efficiency. Transthioacetalisation of acetal is a useful transformation for the preparation of *S,S*-acetals and in comparison with thioacetalisation of carbonyl compounds, it is faster and cleaner. The reactions are faster because the reactive intermediate oxocarbenium is rapidly generated by the protonation of one of the oxygen atoms of the acetal, which leaves by an anchimeric assistance from the other oxygen attached to the same carbon where as the thioacetalisation of the carbonyls are initiated by coordination to a protic acid. Catalysts such as 5M $LiClO_4$,[11] WCl_6,[28] I_2,[7] trichloroisocyanuric acid,[16] are known to be active both towards thioacetalisation and transthioacetalisation process. Number of other acidic reagents such as $MgBr_2$,[29] $TeCl_4$,[30] $ZrCl_4$,[31] $SiO_2/SOCl_2$[12] and neutral kaolin clay[32] have also been reported for this purpose. Very recently it has been achieved using ionic liquids under a solvent free conditions[33] and using $InCl_3$.[5b,c] None of the reported methods describe chemoselective transthioacetalisation between acetals and ketals and between different acetals.

Table 1.4 Transthioacetalisation of 1,3-Dioxolane in Presence of TBATB

Substrate	Time/h	X_1	Yield[b,c](%)	X_2	Yield[b,c](%)
 (1c)	0.08	 (1a)	99	 (1b)	98
 (2c)	0.08	 (2a)	98	 (2b)	94
 (4c)	0.08	 (4a)	97	 (4b)	99
 (5c)	0.75	 (5a)	82	 (5b)	89
 (6c)	0.33	 (6a)	84	 (6b)	85

X_1= 1,3-dithiolane, X_2 = 1,3-dithiane. [a] Reactions were monitored by TLC/GC. [b]Confirmed by comparision with IR and ^1H NMR of the authentic sample. [c] % Isolated yield.

Table 1.5 Transthioacetalisation of 1,3-Dioxane in Presence of TBATB

Substrate	Time/h	X_1	Yield[b,c](%)	X_2	Yield[b,c](%)
 (1d)	0.08	 (1a)	93	 (1b)	94
 (2d)	0.08	 (2a)	95	 (2b)	94
 (4d)	0.08	 (4a)	97	 (4b)	97
 (5d)	0.75	 (5a)	82	 (5b)	89
 (6d)	0.33	 (6a)	85	 (6b)	84
 (7d)	0.08	 (7a)	93	 (7b)	94
 (14d)	0.08	 (14a)	98	 (14b)	99
 (15d	0.08	 (15a)	83	 (15b)	90
 (16d)	0.08	 (16a)	89	 (16b)	92
 (17d)	0.08	 (17a)	91	 (17b)	89

X_1= 1,3-dithiolane, X_2 = 1,3-dithiane. [a] Reactions were monitored by TLC/GC. [b]Confirmed by comparision with IR and ^1H NMR of the authentic sample. [c] %Isolated yield.

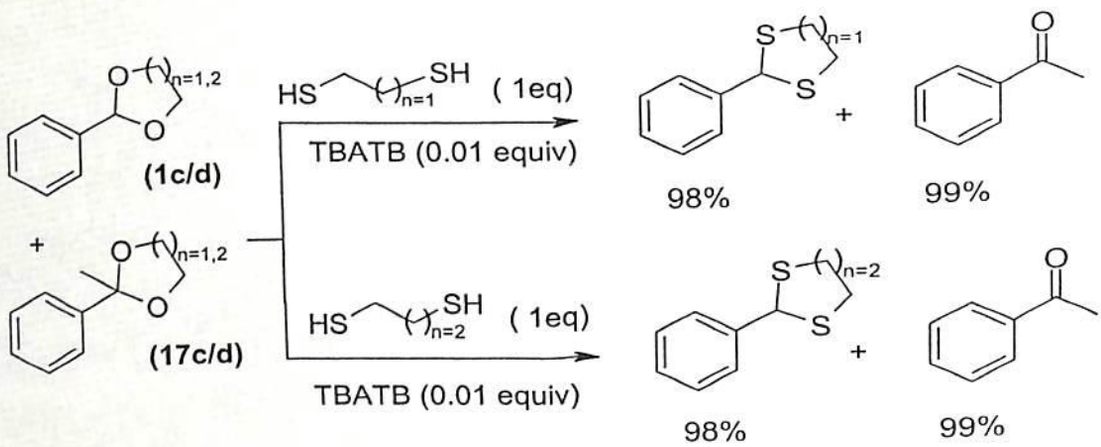
In this context we have explored TBATB as the catalyst for the chemoselective transthioacetalisation. A lower quantity of TBATB (0.01 equiv) was used as compared to direct thioace-

talisation from the corresponding carbonyls. In a typical reaction, to cyclic 1,3-dioxolane or 1,3-dioxane (1 equiv) and 1,2-ethanedithiol or 1,3-propanedithiol (1 equiv) in acetonitrile was added a catalytic amount of TBATB (0.01 equiv) and stirred at room temperature for certain period of time. The result is summarised in Table 1.4.

All the reactions were complete in less than 5 minutes giving excellent yield of products. A wide range of structurally varied cyclic *O,O*-acetals underwent transthioacetalisation either with 1,2-ethanedithiol or 1,3-propanedithiol to furnish the corresponding *S,S*-acetals in nearly quantitative yields. During the process no parent carbonyl compound could be detected by gas chromatographic analysis of the reaction mixture.

It is worth to mention that direct thioacetalisation of aromatic aldehydes containing electron-withdrawing group such as *o*-nitrobenzaldehyde **5** and *p*-nitrobenzaldehyde **6** gave poor yields, whereas transthioacetalisation of acetals **5c** and **6c** gave excellent yields of the corresponding thioacetals.

Substrates containing double bonds remained unscathed by this process. Aromatic acetals and ketals smoothly underwent transthioacetalisation and transthioketalisation as shown above in Table 1.4. Similarly 1,3-dioxane also underwent transthioacetalisation to yield the corresponding1,3-dithiolane and 1,3-dithiane with 1,2-ethanedithiol and 1,3-propane dithiol respectively as shown above in Table 1.5.

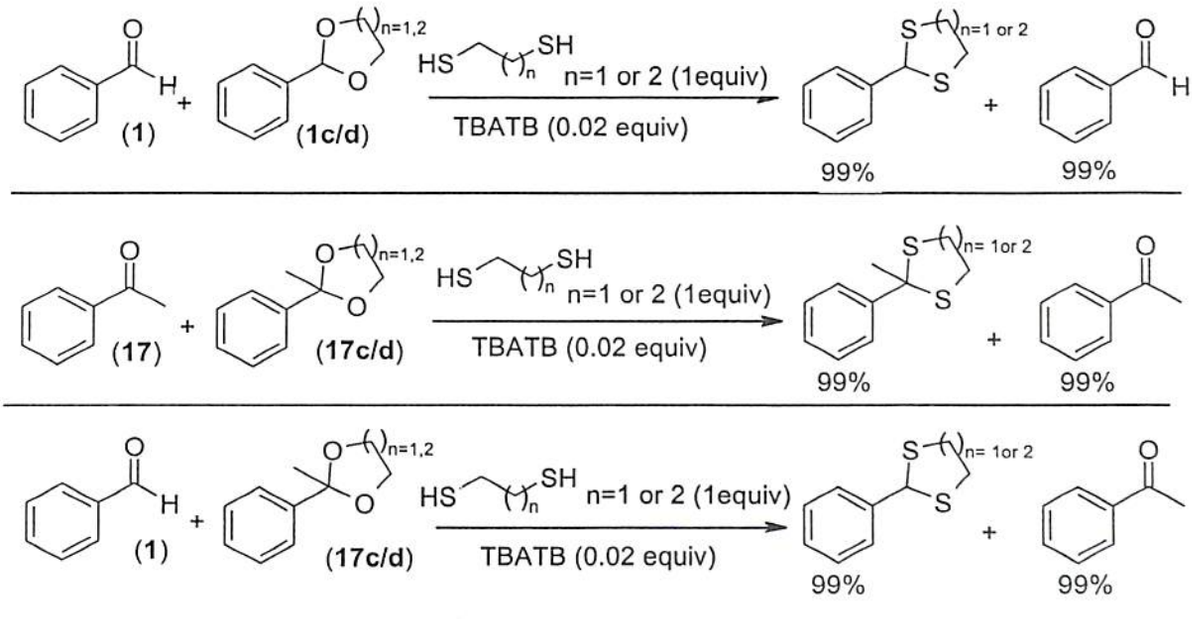


Scheme 1B.13. Chemoselective Transthioacetalisation and Deketalisation

When an equimolar mixture of an acetal **1c** or **1d** (1 equiv) and a ketal **17c** or **17d** (1 equiv) was allowed to react with either 1,2-ethanedithiol or 1,3-propanedithiol (1 equiv) and a catalytic amount of TBATB (0.01 equiv) in acetonitrile at ambient temperature, a nearly quantitative yield of the thioacetal was obtained with a trace amount of ketal (< 2%) and during the process the acetophenone ketal was deprotected to acetophenone **17** as shown above in Scheme 1B.13.

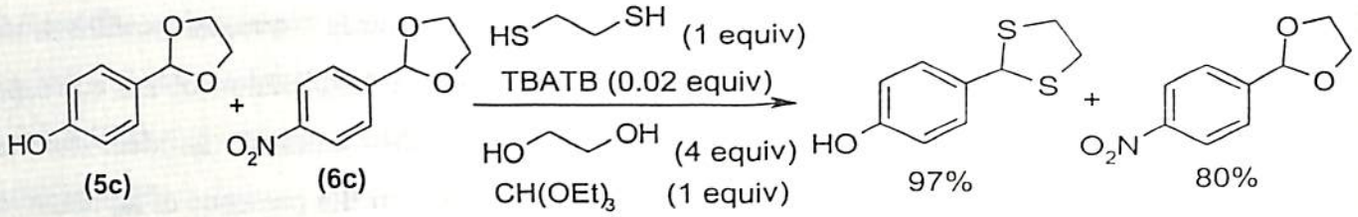
Acetals and ketals are much more reactive towards transthioacetalisation and transthioketalisation compared to the direct thioacetalisation and thioketalisation of the corresponding carbonyl compounds. Chemoselective catalytic activity of the catalyst is demonstrated by transthioacetalisation and transthioketalisation of an acetal or a ketal in the presence of an aldehyde or a ketone.

In a competitive reaction, cyclic acetals of benzaldehyde **1c** or **1d** and acetophenone **17c** or **17d** were preferentially protected in the presence of benzaldehyde **1** and acetophenone **17** respectively in quantitative yields, Scheme 1B.14. However, in an attempt to carryout chemoselective transthioketalisation of ketals **17c** or **17d** over aldehyde **1** failed in spite of the higher reactivity of the ketals towards transthioketalisation and during the process the ketal **17c** or **17d** was deprotected to ketone **17** and aldehyde was thioacetalised as shown above in Scheme 1B.14.



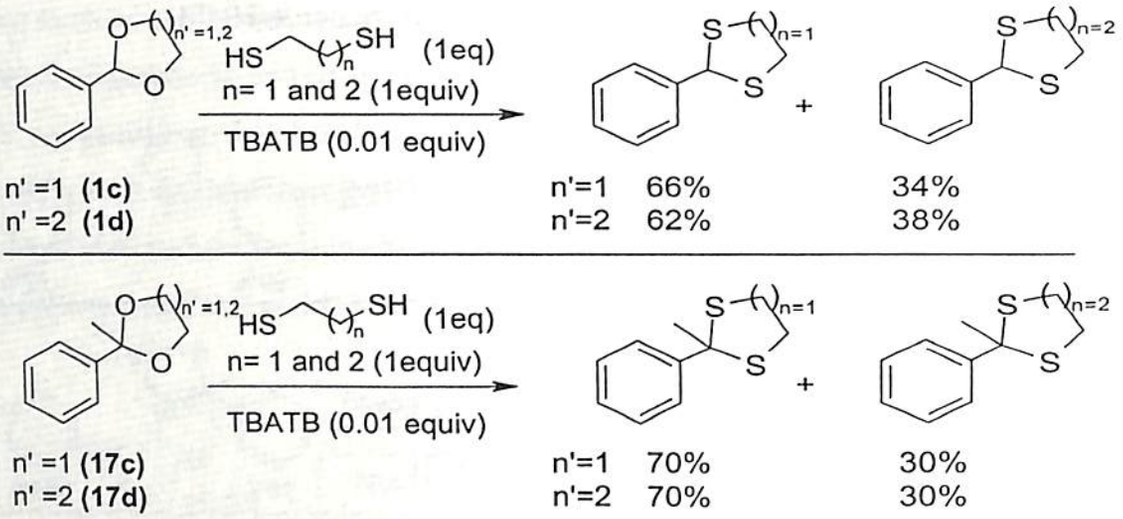
Scheme 1B.14. Chemoselective Transthioacetalisation and Transthioketalisation

The preferential transthioacetalisation of an acetal containing an electron-donating substituent **5c** and **6c** over an acetal containing an electron-withdrawing group **6c** is demonstrated in Scheme 1B.15.



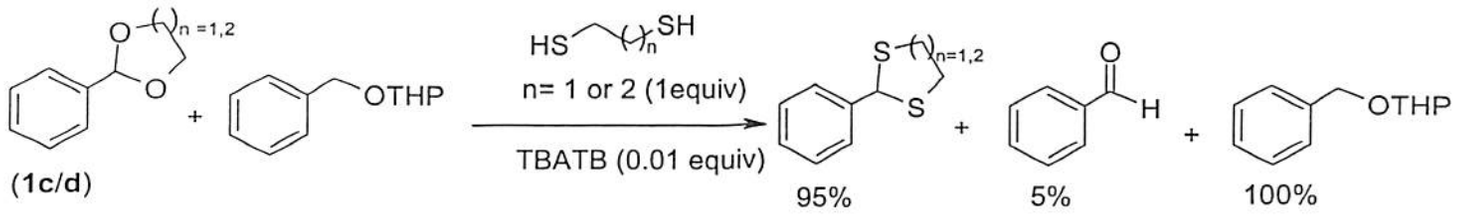
Scheme 1B.15. Chemoselective Transthioacetalisation

This observation is consistent with preferential thioacetalisation of *p*-hydroxybenzaldehyde **5** over *p*-nitrobenzaldehyde **6** (Scheme 1B.3). In an analogous competitive reaction, 1,3-dioxolane of *p*-methoxybenzaldehyde **2a** has been preferentially transthioacetalised in the presence of 1,3-dioxolane of *p*-nitrobenzaldehyde **6a**. It has been found that acetal of *p*-nitrobenzaldehyde is much more stable compared to acetal of *p*-hydorxybenzaldehyde.[34]



Scheme1B.16 Transthioacetalisation and Transthioketalisation

When aldehyde-1,3-dioxolane **1c** or aldehyde-1,3-dioxane **1d** were reacted with an equimolar mixture of 1,2-ethanedithiol or 1,3-propanedithiol, acetal preferentially form 1,3-dithiolane, an observation consistent with the preferential formation of 1,3-dithiolane in a competitive reaction directly from an aldehyde, Scheme 1B.12. In a similar competitive reaction with ketals **17c** or **17d** a higher percentage of 1,3-dithiolane was obtained (Scheme 1.16). Further the chemoselectivity of the method was demonstrated by competitive reaction between a symmetrical acetal **1c** and an unsymmetrical acetal such as THP ether of benzyl alcohol. The former was preferentially thioacetalised over the later, Scheme 1B.17. It is not surprising since unsymmetrical acetal such as THP ethers are much more stable under acidic conditions as compared to the symmetrical acetals.[34]



Scheme1B.17 Chemoselective Transthioacetalisation of Symmetrical Acetals

In conclusion, various aldehydes and ketones were protected as their thioacetals and thioketals under mild reaction conditions in the presence of catalytic amount of TBATB. By using this method a particular carbonyl group can be selectively blocked in the presence of another such as between aldehydes and ketones, between two aldehydes and two ketones. A combined (experimental as well as theoretical) study revealed the factors governing the chemoselectivity obtained in aldehydes containing electron releasing and electron withdrawing groups in various acetalisation reactions. Transthioacetalisation of *O,O*-acetals and *O,O*-ketals were also achieved using this catalyst. In comparison with the existing methods using many acidic catalysts, this method is very general, simple, high-yielding, environmentally friendly and oxygen and moisture tolerant. In terms of selectivity and efficiency this procedure is superior to many of the reported methods where oxidants as well as strong acids are used. Due to the mild reaction conditions, a number of functional groups, albeit being capable of reacting with TBATB remains intact.

1B.1.2. References

1. (*a*) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, **1999**. (*b*) Kocieñski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, **1994**. (*c*) Meskens, F. A. J. *Synthesis,* **1981**, 501. (*d*) Schelhaas, M.; Waldmann, H. *Angew.Chem. Int. Ed. Engl.* **1996**, *35*, 2056.
2. Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, *6*, 785.
3. Gopinath, R.; Haque, Sk. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842.
4. Ceschi, M. A.; Felix, L. de. A.; Peppe, C. *Tetrahedron Lett.* **2000**, *41,* 9695.
5. (a) Muthusamy, S.; Arulananda Babu, S.; Gunanathan, C. *Tetrahedron Lett.* **2001**, *42*, 359. (b) Ranu, B. C.; Das, A.; Samanta, S. *Synlett* **2002**, 727. (c) Kamal, A.; Chouhan, A. *Tetrahedron Lett.* **2003**, *44*, 3337.
6. Muthusamy, S.; Babu, S. A.; Gunanathan, C. *Tetrahedron* **2000**, *58*, 7897.
7. (a) Samajdar, S.; Basu, M. K.; Becker, F. F.; Banik, B. *Tetrahedron Lett.* **2001**, *42*, 4425. (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527.
8. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.
9. Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58.
10. Jadav, J. S.; Reddy, B. S.; Pandey, S. K. *Synlett.* **2001**, 238. (b) Kazahaya, K.; Tsuji, S.; Sato, T. *Synlett* **2004**, 1640.
11. Saraswathy, V. G.; Geetha, V.; Sankaranan, S. *J. Org. Chem.* **1994**, *39*, 4665.
12. Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427.
13. Kamal, A.; Chouhan, G. *Synlett*, **2002**, 474.

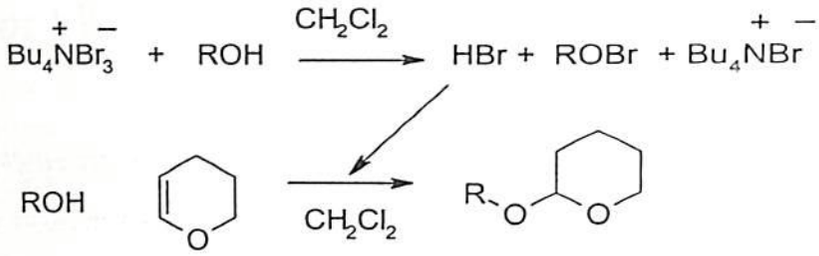
14. Khan, A. T.; Mondal, E.; Sahu, P. R.; Islam, S. *Tetrahedron Lett.* **2003**, *44*, 919.
15. Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2002**, *43*, 1347.
16. Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Synlett* **2001**, 1641.
17. Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1993**, *58*, 4971.
18. (a) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945. (b) Marshall, J. A.; Anderson, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858. (c) Nakata, T.; Nagao, S.; Mori, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461.
19. Shinde, P.D.; Borate, H.B.; Wakharkar, R.D. *Arkivoc* **2004**, (*xiv*) 110.
20. Roy, R. K.; Usha, V.; Patel, B. K.; Hirao, K. *J. Computational Chem.* **2006**, *27*, 773.
21. Parr, R.G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
22. Maynard, A. T.; Huang, M.; Rice, W. G.; Covel, D. G. *Proc. Natl. Acad. Sci.U.S.A* **1998**, *95*, 11578.
23. (a) Ghosh, S. K.; Berkowitz, M. *J. Chem. Phys.* **1985**, *83*, 2976. (b) Yang, W; Parr, R. G. *Proc. Natl. Acad. Sci. USA.* **1985**, *82*, 6723.
24. Hirshfield, F. L. *Theor. Chim. Acta* **1977**, *44*, 129.
25. Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.
26. Roy, R. K.; Usha, V.; Pauloviè, J.; Hirao, K. *J. Phys. Chem.* **2005**, *109*, 4601.
27. (a) Roy, R. K.; Pal, S.; *J. Chem. Phys.* **1999**, *110,* 8236. (b) Roy, R. K.; Hirao, K.; Pal, S.; *J. Chem. Phys.* **2000**, *113,* 1372. (c) Roy, R. K.; Tajima, N.; Hirao, K. *J. Phys. Chem.* **2001**, *105,* 211. (d) Roy, R. K. *J. Phys. Chem. A* **2001**, *107,* 397. (e) Roy, R. K. *J. Phys. Chem. A* **2001**, *107,* 10428.
28. Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett*, **1998**, 739.
29. Park, J. H.; Kim, S. *Chem. Lett.* **1989**, 629.
30. Tani, H.; Masumoto, K.; Inamasu, T. *Tetrahedron Lett.* **1991**, *32*, 2039.
31. Rezai, N.; Meybodi, F. A.; Salahi, P. *Synth. Commun.* **2000**, *30*, 1799.
32. Jnaneshwar, G. K.; Barhate, N. B.; Sudalai, A.; Deshpande, V. H.; Wakharkar, R. D.; Gajare, A. S.; Shingare, M. S.; Sukumar, R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 965.
33. Ranu, B. C.; Das, A.; Samanta, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1520.
34. Gopinath, R.; Paital, A. R.; Patel, B. K. *Tetrahedron Lett.* **2002**, *43*, 5123.

1B.2. Tetrabutylammonium Tribromide TBATB- Catalysed Tetrahydro-pyranylation and Depyranylation of Alcohols

THP ethers are one of the most widely used protecting groups employed during a multi step organic synthesis because of low cost and stability towards various reaction conditions such as strong bases, Grignard reagents, hydrides, redox reagents, alkylating, acylating agents and catalytic hydrogenation and easy removal under mild acidic conditions. Protection is normally achieved with a mild acidic reagent in an aprotic solvent such as CH_2Cl_2, THF, acetone etc.; and deprotection also with an acidic reagent but in a polar or protic solvent such as methanol, ethanol, isopropanol, acetonitrile, etc. Numerous methods have been reported for tetrahydropyranylation[1-3] and detetrahydropyranylation.[1,2,4] Commonly used catalysts are potassium dodecatangestocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$),[5] $ZrCl_4$,[6] I_2-microwave irradiation,[7] LiBr,[8] acetonyltriphenylphosphonium bromide,[9] I_2,[10] NH_4Cl,[11] heteropolyacids,[12] which catalyse both these transformations effectively by merely changing the solvent system. In addition to these reagents many more reagents and procedures have also been devised which have been described extensively in the introduction chapter in **section 1A.2.2.1(c) page no. 25.** However, some of these procedures suffer due to the use of expensive and toxic reagents, high temperature, longer reaction times and incompatibility with other acid-sensitive functional groups. Therefore, there is a need to develop an alternative method for the protection as well as deprotection of alcohols under mild reaction conditions.

Tetrabutylammonium tribromide (TBATB) has been used for the cleavage of *tert*-butyldimethylsilyl ethers,[13] cleavage of dithioacetals[14] and few other transformations as described in the introduction chapter. In this section we have reported a mild and efficient method for the tetrahydropyranylation of alcohols using tetrabutylammonium tribromide (0.025 equiv) as a catalyst in the presence of 3,4-dihydro-2*H*-pyran (1.1 equiv) in methylene chloride at room temperature, whereas the detetrahydropyranylation could be readily achieved using the same reagent in methanol at room temperature.

Tetrahydropyranylation did not occur when the blank runs were performed in the absence of TBATB. Despite the use of an aprotic solvent during pyranylation, the occurrence of this reaction may be attributed to the *in situ* formation of HBr by the interaction of alcohol with TBATB, as shown in Scheme 1B.18.



Scheme 1B.18. Tetrahydropyranylation of Alcohols

The general applicability of this methodology can be seen from the wide spectrum of hydroxyl compounds ranging from primary aliphatic **20**, **22-23**, **49,** benzylic **24-27**, hindered primary alcohol **31** and secondary alcohols (**33-35**, **38**) are protected as THP ethers in high yields with TBATB as the promoter, Table 1.6.

Table 1.6. Tetrahydropyranylation[a] of Alcohols in the Presence of TBATB

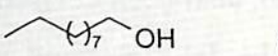
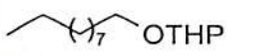
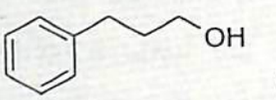
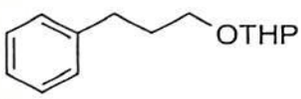
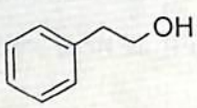
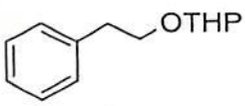
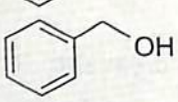
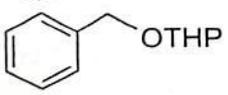
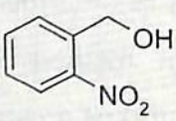
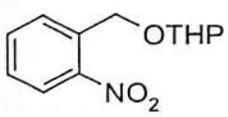
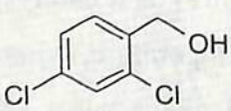
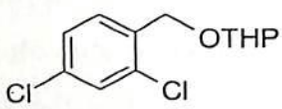
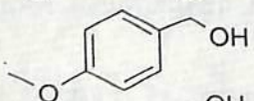
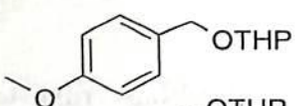
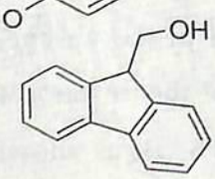
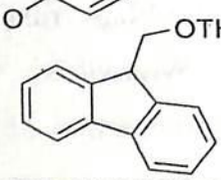
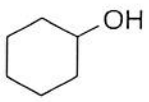
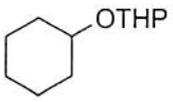
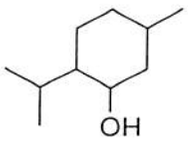
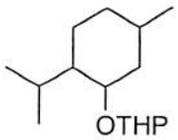
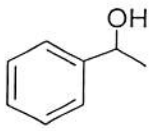
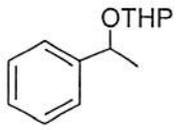
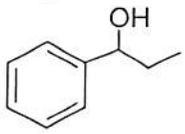
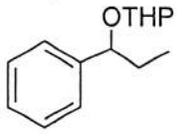
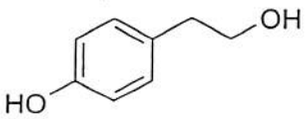
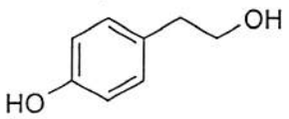
Substrate		Product		Time/h	Yield[b,c](%)
	(20)		(20f)	0.50	87
	(22)		(22f)	0.50	89
	(23)		(23f)	0.75	88
	(24)		(24f)	1.00	85
	(25)		(25f)	2.00	79
	(26)		(26f)	1.00	85
	(27)		(27f)	1.00	79
	(31)		(31f)	1.00	78

Table Contd.....

Table 1.6. Tetrahydropyranylation[a] of Alcohols in the Presence of TBATB

Substrate		Product		Time/h	Yield[b,c](%)
	(33)		(33f)	1.00	75
	(34)		(34f)	1.00	74
	(35)		(35f)	0.50	80
	(38)		(38f)	0.41	85
	(49)		(49f)	1.00	85

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparision with IR and ^{1}H NMR. [c]Isolated yield

Table1.7. Tetrahydropyranylation[a] of Functionalised Alcohols

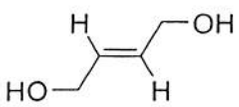
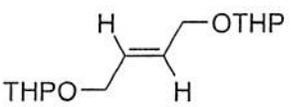
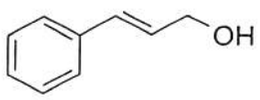
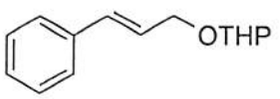
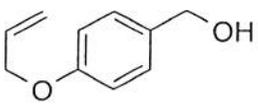
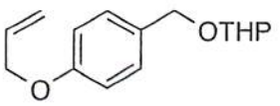
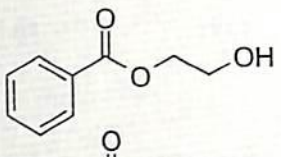
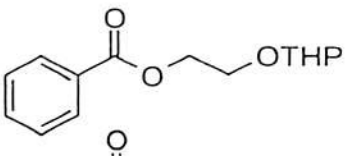
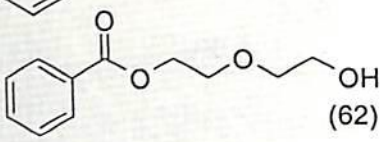
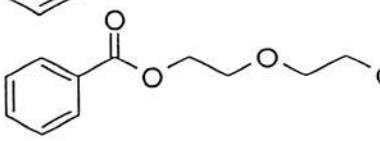
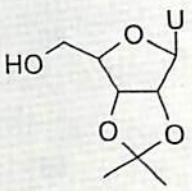
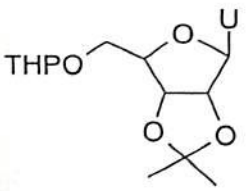
Substrate		Product		Time/h	Yield[b,c](%)
	(52)		(52f)	1.50	80
	(53)		(53f)	0.5[d]	95
	(54)		(54f)	0.33[d]	91
	(55)		(55f)	2.00	65
	(56)		(56f)	2.00	63

Table Contd...

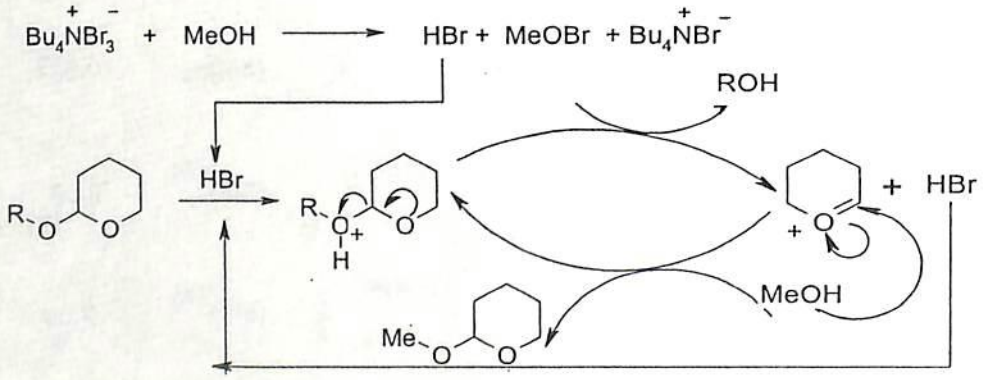
Table1.7. Tetrahydropyranylation[a] of Functionalised Alcohols

Substrate	Product	Time/h	Yield[b,c](%)
 (61)	 (61f)	1.00	71
 (62)	 (62f)	1.00	76
 (64)	 (64f)	0.41	88

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparision with IR and ^{1}H NMR. [c]Isolated yield [d]Double amounts of THP were used.

The tolerance of various protecting groups under the reaction conditions has been examined by reacting substrates bearing substituents such as OTs (**52**), alkene (**53, 55-56**), alkyne (**54**), esters (**61-62**), isopropylidine (**64**) etc. under the optimised condition of protection and is summarised in Table 1.7 given below.

It has been shown that organicammonium tribromide such as benzyltrimethylammonium tribromides generate HBr and MeOBr in methanol.[15] Taking cues from this and our earlier observations[13,14] the following mechanism has been proposed for the deprotection, as shown in Scheme 1B.19.



Scheme 1B.19. Proposed Mechanism of Depyranylation of THP Ethers

Gas chromatographic co-injection analysis unequivocally established the formation of 2-methoxytetrahydropyran as a transacetalisation product and in turn the mechanism. 2-Methoxytetrahydropyran was prepared by reacting methanol with 3,4-dihydro-2*H*-pyran in the presence of I_2.[10] Other alcoholic solvents such as ethanol and isopropanol can also be used for the deprotection.

Table 1.8. Depyranylation[a] of THP ethers of Different Alcohols

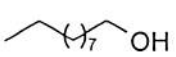
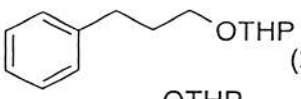
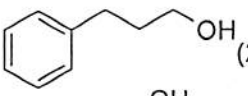
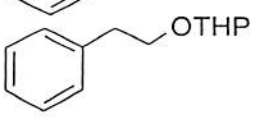
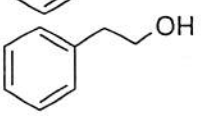
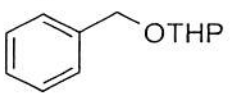
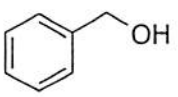
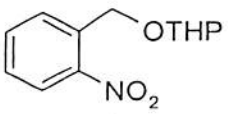
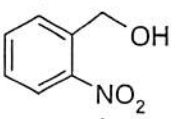
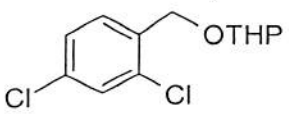
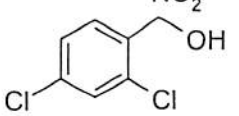
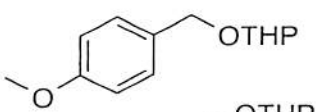
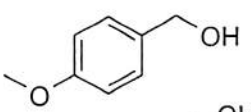
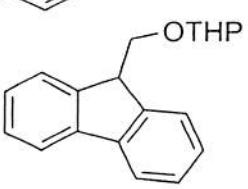
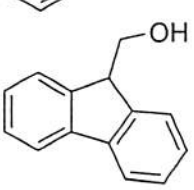
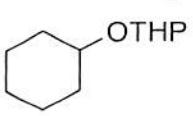
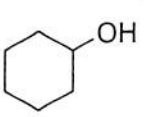
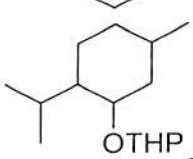
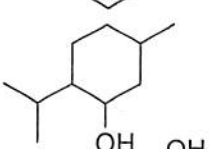
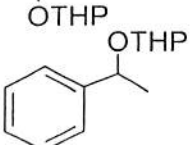
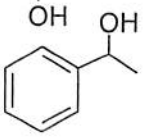
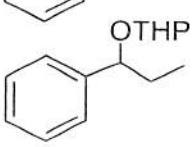
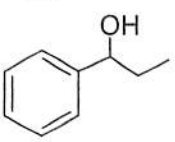
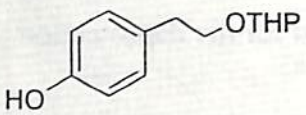
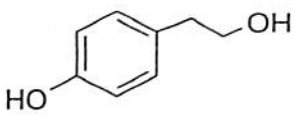
Substrate	Product	Time/h	Yield[b,c](%)
 (20f	 (20)	0.08	95
 (22f	 (22)	0.50	94
 (23f	 (23)	0.75	95
 (24f	 (24)	0.16	95
 (25f	 (25)	0.50	95
 (26f	 (26)	0.50	95
 (27f	 (27)	0.50	93
 (31f	 (31)	2.00	90
 (33f	 (33)	0.08	92[d]
 (34f	 (34)	0.08	92
 (35f	 (35f)	1.00	95
 (38f	 (38f)	1.00	97

Table Contd.....

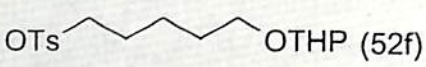
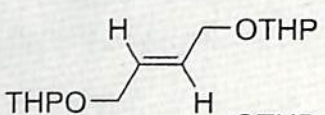
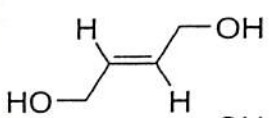
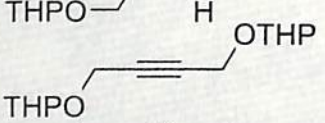
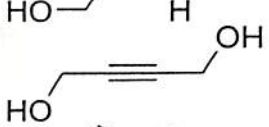
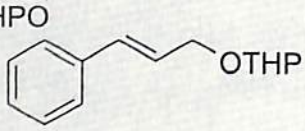
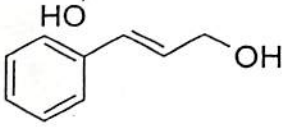
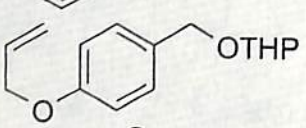
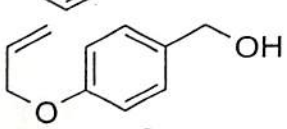
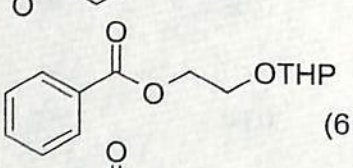
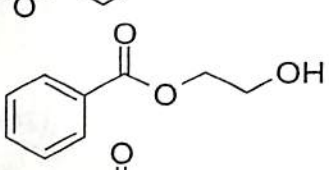
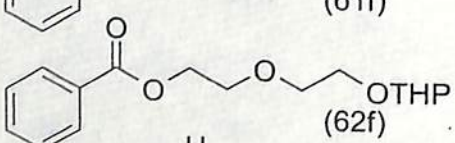
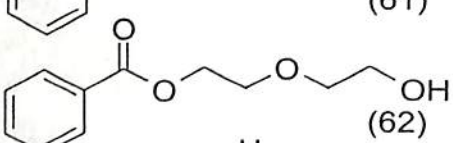
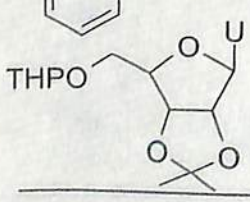
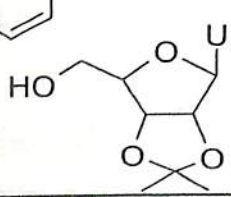
Table 1.8. Depyranylation[a] of THP ethers of Different Alcohols

Substrate	Product	Time/h	Yield[b,c](%)
 (49f)	 (49f)	1.00	98

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparision with IR and ^{1}H NMR. [c]Isolated yield [d]Determined by GC.

The THP ethers obtained from the tetrahydropyranylation under the optimised condition were subjected to depyranylation with 0.1 equivalent of TBATB in methanol.Thus, the tetrahydropyranyl ethers of a wide range of alcohols *vis.* primary, secondary, benzylic, were depyranylated in good yields in shorter reaction time with 0.1 equiv of TBATB in MeOH. The results have been summarised and presented above in Table 1.8.

Table 1.9. Depyranylation[a] of THP Ethers of Functionalised Alcohols

Substrate	Product	Time/h	Yield[b,c](%)
 (52f)	 (52)	0.50	93
 (53f)	 (53)	0.16	95
 (54f)	 (54)	0.33	92
 (55f)	 (55)	0.16	98
 (56f)	 (56)	0.25	95
 (61f)	 (61)	0.16	97
 (62f)	 (62)	0.16	92
 (64f)	 (64)	1.5	75

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparision with IR and ^{1}H NMR. [c]Isolated yield .

In conclusion, this methodology provides a useful alternative for the preparation as well as cleavage of tetrahydropyranyl ethers to the corresponding alcohols. The main advantages of our methodology are mild reaction conditions, high efficiencies, quick and clean, economic viability of the reagent, industrial applicability and tolerance to a wide range of functionalities. We believe that this will be a useful addition to modern synthetic methodologies. The possibility of deprotection using the same catalyst with slight change in experimental protocol makes this method an attractive strategy, offering advantages over other methods, which use different catalysts.

1B.2.1 References

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; (b) Kocien´ski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 1994.
2. Jarowicki, K.; Kocien´ ski, P. *J. Chem. Soc., Perkin Trans.* 1 **2000**, 2495.
3. (a) Deka, N.; Sarma, J. C. *J. Org. Chem.* **2001**, *66*, 1947; (b)Ionic liquids Branco, L. C. *Tetrahedron* **2001**, *57*, 4405; (c) Babu, B. S.; Balasubramanian, K. K. *Synlett* **1999**, *8*, 1261; (d) Nishiguchi, T.; Hayakawa, S.; Hirasaka, Y.; Saitoh, M. *Tetrahedron Lett.* **2000**, *41*, 9843; (e) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Costantino, U. *Tetrahedron Lett.* **1998**, *28*, 8159; (f) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, *39*, 9287.
4. (a) Davis, K. J.; Bhalerao, U. T.; Rao, B. V. *Synth. Commun.* **2000**, 30, 2301; (b) Marko´ , I. S.; Ates, A.; Augustyns, B.; Gautier, A.; Quesnel, Y.; Turet, L.; Wiaux, M. *Tetrahedron Lett.* **1999**, 40, 5613; (c) Ramasamy, K. S.; Averett, D. *Synlett* **1999**, 6, 709; (d) Lee, A. S.-Y.; Su, F.-Y.; Liao, Y.-C. *Tetrahedron Lett.* **1999**, 40, 1323; (e) Ramasamy, K. S.; Bandaru, R.; Averett, D. *Synth. Commun.* **1999**, 29, 2881.
5. Habibi, M. H.; Tangestaninejad, S.; Baltork, I. M.; Mirkhani, V.; Yadollahi, B. *Tetrahedron Lett.* **2001**, 42, 2851.
6. Rezai, N.; Meybodi, F. A.; Salahi, P. *Synth. Commun.* **2000**, 30, 1799.
7. Deka, N.; Sarma, J. C. *Synth. Commun.* **2000**, 30, 4435.
8. Reddy, M. A.; Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Synth. Commun.* **2000**, 30, 4323.
9. Hon, Y.-S.; Lee, C.-F. *Tetrahedron Lett.* **1999**, 40, 2389.
10. Kumar, H. M. S.; Reddy, B. V. S.; Reddy, E. J.; Yadav, J. S. *Chem. Lett.* **1999**, 857.
11. Jadav, J. S.; Srinivas, D.; Reddy, G. S. *Synth. Commun.* **1998**, 28, 1399.
12. Molnar, A.; Beregszaszi, T. *Tetrahedron Lett.* **1996**, 37, 8597.
13. Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177.
14. Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785.
15. Kajigaeshi, S.; Kakinami, T.; Hirakawa, T. *Chem. Lett.* **1987**, 627.

1B.3. Tetrabutylammonium Tribromide (TBATB) as an Efficient Reagent for Acylation of Alcohols, Amines and Thiols

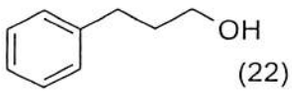
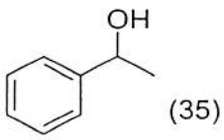
Acylation of protic nucleophiles such as alcohols, amines, and thiols is an important and commonly used reaction in organic chemistry. The resulting esters, amides and thioesters serve as important functional components and / or intermediates in synthetic chemistry and biology.[1-3] In these reactions, acid chlorides, anhydrides or acyl transfer reagents are often used as the acyl sources in the presence of basic or acidic catalysts. In general acid anhydrides are employed as the acyl sources because of their ready availability and stability. Traditionally, bases such as triethylamine, pyridine, 4-(dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) and tributylphosphine (Bu_3P) were employed, which has been described in the introduction chapter, **section.1A.2.2.2(c1), page 31**.Because of their toxicity, flammability and unpleasant odours these bases are less attractive. Acylation under acid catalysed conditions has been reported with several reagents.[4-5] Metal triflates and perchlorates have been used for the purpose owing to their acidic nature. Metal halides are also used to achieve acylation of alcohols in good yields. Various metal triflates, perchlorates and halides used are listed in the introduction chapter in **section.1A.2.2.2(c1), page 32**. Other reagents / catalysts employed are TMSCl,[6] $HClO_4$-SiO_2,[7] $Sc(NTf_2)_3$,[8] Nafion-H,[9] Yttria-Zirconia,[10] distannoxane[11] heteropoly acid,[12] $MeSO_3H/Al_2O_3$,[13] solid surface-Al_2O_3,[14] and oxomolybdenum species.[15]

Although metal triflates, perchlorates and other acid catalysts are effective for the acylation reaction, the preparation of metal triflates often require direct mixing of metal oxides with excess of hot triflic acid. The incomplete removal of triflic acid during the preparation of metal triflates limits the overall efficiency of the process. It has also been reported that triflic acid liberated *in situ* through a ligand exchange reaction, might be the actual catalytic species during metal triflate-catalysed acetylation.[16] Triflic acid being a strong protic acid having a large negative H_0 value (–14.1)[17] results in side reactions with acid-sensitive substrates. The strong Lewis acid character of triflates demand the necessity of carrying out the acetylation of acid sensitive substrates at lower temperature and in the presence of large excess of Ac_2O to avoid side reactions such as dehydration and rearrangement. Some triflates are moisture sensitive and hence reaction should be performed under dry condition. The potential hazards associated with the manufacture and use of perchlorates owing to their explosive nature has prevented their extensive applications to industrial processes especially when large amounts of these perchlorates are involved.[18] Other problems associated with some of the existing methods are difficulties in work-up and isolation, the need for an inert atmosphere, harsh reaction conditions,

expensive reagents, special attention to be taken for preparation of reagents, low yields, longer reaction times, dry solvents and incompatibility with other protecting groups. In this context search for achieving general nucleophilic acyl substitution of anydrides in a catalytic, mild fashion with integrity of existing acid and base sensitive functionalities remains in great demand. Though a plethora of reagents and procedures for acylation have been documented in the literature, need to find an efficient and mild acylation reaction still remains.

In this section, we reveal a new, mild procedure for preparation of various esters, amides and thioesters with a variety of aliphatic and aromatic anhydrides in the presence of catalytic quantity of TBATB, which acts as a source of anhydrous HBr in acetone.

Table1.10. Solvent Dependent Acetylation of 3-Phenylpropanol **22** and 1-Phenyl ethanol **35**

Substrate	Solvent	Time/h	Yield[a]
 (22)	Toluene	1.5	88
	CH_2Cl_2	1.0	91
	CH_3CN	0.58	93
	CH_3COCH_3	0.08	95
 (35)	Toluene	2.0	80
	CH_2Cl_2	1.25	86
	CH_3CN	0.83	92
	CH_3COCH_3	0.25	93

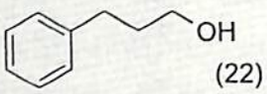
[a]GC yield

Initially 3-phenyl propanol **22** (5 mmol) was taken as the model substrate for acetylation and was reacted with acetic anhydride (6.25 mmol) in a donor solvent such as acetonitrile (10 mL) in the presence of catalytic quantity of TBATB (0.5 mmol). Progress of the reaction was monitored using thin layer chromatography, which showed complete conversion of the alcohol to its acetate within 0.58h. Earlier we have mentioned in the introduction chapter that the acidity of the reaction medium employing tribromides can be tuned by changing the polarity of the solvent. So using this fact; the reaction was performed in different solvents such as toluene, methylene chloride, chloroform and acetone. When 3-phenyl propanol **22** was reacted with acetic anhydride in the presence of TBATB in above solvents separately, it was observed that the reaction proceeded much faster in acetone compared to other

solvents. This could be due to the reaction of acetone with TBATB forming bromoacetone and thereby generating anhydrous HBr *in situ*, which catalyses the reaction. In a control experiment treatment of the reaction mixture with a catalytic quantity of bromine and aq. HBr instead of TBATB in acetone yielded 95% and 88% of acylated product respectively within 0.16h. The summary of the solvent dependent study is shown in Table 1.10. This result prompted us to use acetone as the reaction medium.

The reagent and the methodology are superior with respect to other conventional reagents as it results in a highly efficient acetylation of 3-phenyl propanol **22,** Table 1.11.

Table1.11. Acetylation of 3-phenylpropanol

Substrate	Reagents used	Time/h	Yield[a]
 (22)	$ZnCl_2$	24	30
	$CoCl_2$	24	35
	$MgBr_2$	24	40
	$RuCl_3$	24	70
	NBS	8.0	92
	$Cu(OTf)_2$	24	55
	$LiClO_4$	24	60
	$HClO_4$-SiO_2	24	30
	TBATB	0.25	98

[a]GC yield

Summary of the acetylation using 0.1 equiv of different reagents employing acetone as the solvent is shown in Table 1.11. It may be noted that the yields reported in this table are much lower than those has been reported in the literature, a possible reason could be the use of different amounts of catalyst, acetic anhydride and solvent system.

Table1.12. Acetylation[a] of Alcohols with Ac_2O Catalysed by TBATB

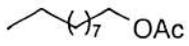
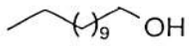
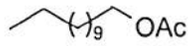
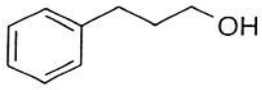
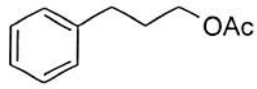
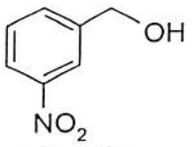
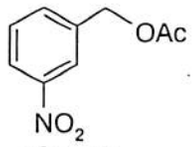
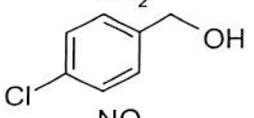
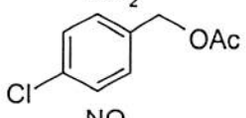
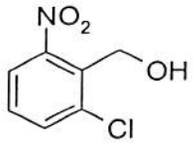
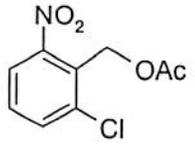
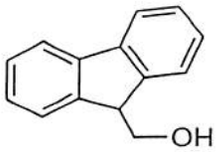
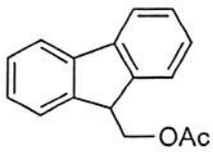
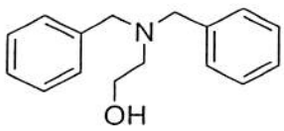
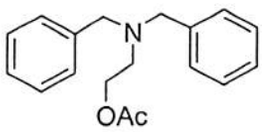
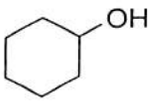
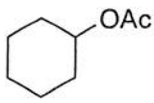
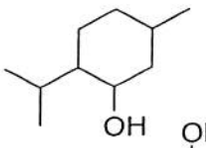
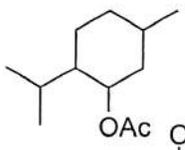
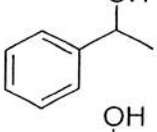
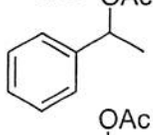
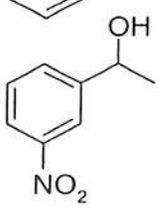
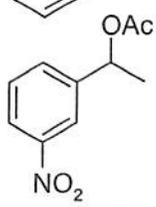
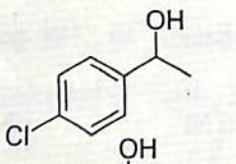
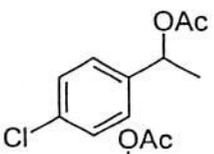
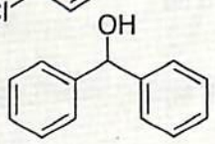
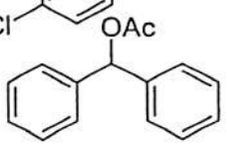
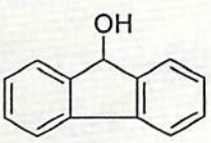
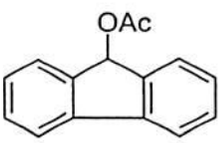
Substrate		Product		Time/h	Yield[b,c] (%)
	(20)		(20g)	0.80	92
	(21)		(21g)	0.80	93
	(22)		(22g)	0.80	95
	(26)		(26g)	0.25	90
	(28)		(28g)	0.16	92
	(30)		(30g)	24	80
	(31)		(31g)	0.16	95
	(32)		(32g)	0.16	90
	(33)		(33g)	0.16	85
	(34)		(34g)	0.16	87
	(35)		(35g)	0.25	92
	(36)		(36g)	0.58	84

Table Contd.....

Table1.12. Acetylation[a] of Alcohols with Ac_2O Catalysed by TBATB

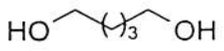
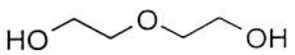
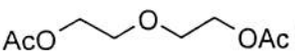
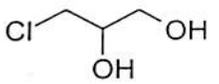
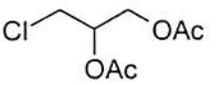
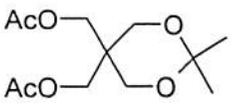
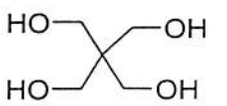
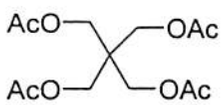
Substrate		Product		Time/h	Yield[b,c] (%)
	(37)		(37g)	0.58	89
	(39)		(39g)	0.50	89
	(40)		(40g)	5.00	79[d]

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparision with IR and ^1H NMR. [c]Isolated yield. [d]Reflux condition.

Under the present optimised reaction condition, diverse arrays of alcohols were converted to their respective acetates as can be seen in Table 1.12. Aliphatic primary alcohols **20-22** were transformed to their corresponding acetates in excellent yields in a short time. Benzylic alcohols with deactivated substituents in the aromatic ring such as 3-nitrobenzyl alcohol **26** and 4-chlorobenzyl alcohol **28** were also acetylated efficiently. By employing this reagent we carried out acetylation of hindered primary deactivated alcohol, 2-chloro-6-nitro benzyl alcohol **30** in excellent yield but with a longer reaction time 24h. However, other hindered alcohols **31-32** underwent acetylation smoothly giving product in excellent yield. Secondary alicyclic alcohol such as cyclohexanol **33** was converted to its acetate in good yield. It was gratifying to observe that menthol **34** was completely converted to menthyl acetate **34a** with 1.25 equiv of Ac_2O within 0.16h, an earlier work has reported that it was acetylated in 1.5 h at 0°C with 5 equiv of Ac_2O in the presence of 1 mol% of $Bi(OTf)_3$.[19] Benzylic secondary alcohols such as **35, 37-39** underwent acetylation smoothly but with a slightly longer reaction time as compared to their primary analogues. However, the scope of acetylation is somewhat limited for hindered aromatic secondary alcohol 9-fluorenyl alcohol **40**, which took 5h for complete conversion under reflux. The results obtained have been summarised in Table 1.12.

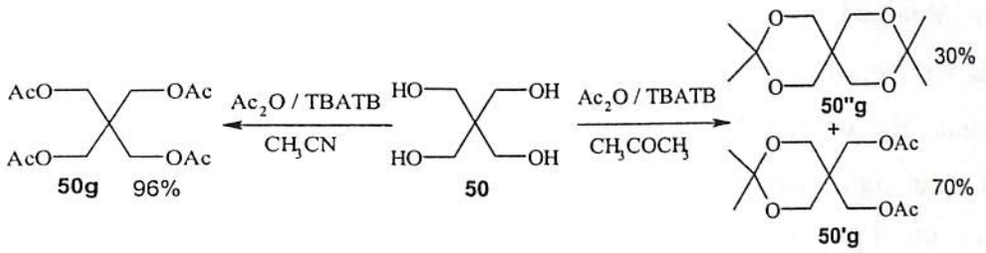
Primary aliphatic diols such as 1,5-pentane diol (**42**), diethylene glycol (**44**), 2,2-dimethyl 1,3-propane diol (**45**) and 3-chloro-1,2-propane diol **47** were diacetylated completely with 2.5 equiv of acetic anhydride. Results have been summarised in Table 1.13.

Table1.13. Acetylation[a] of Diols with Ac_2O Catalysed by TBATB in Acetone

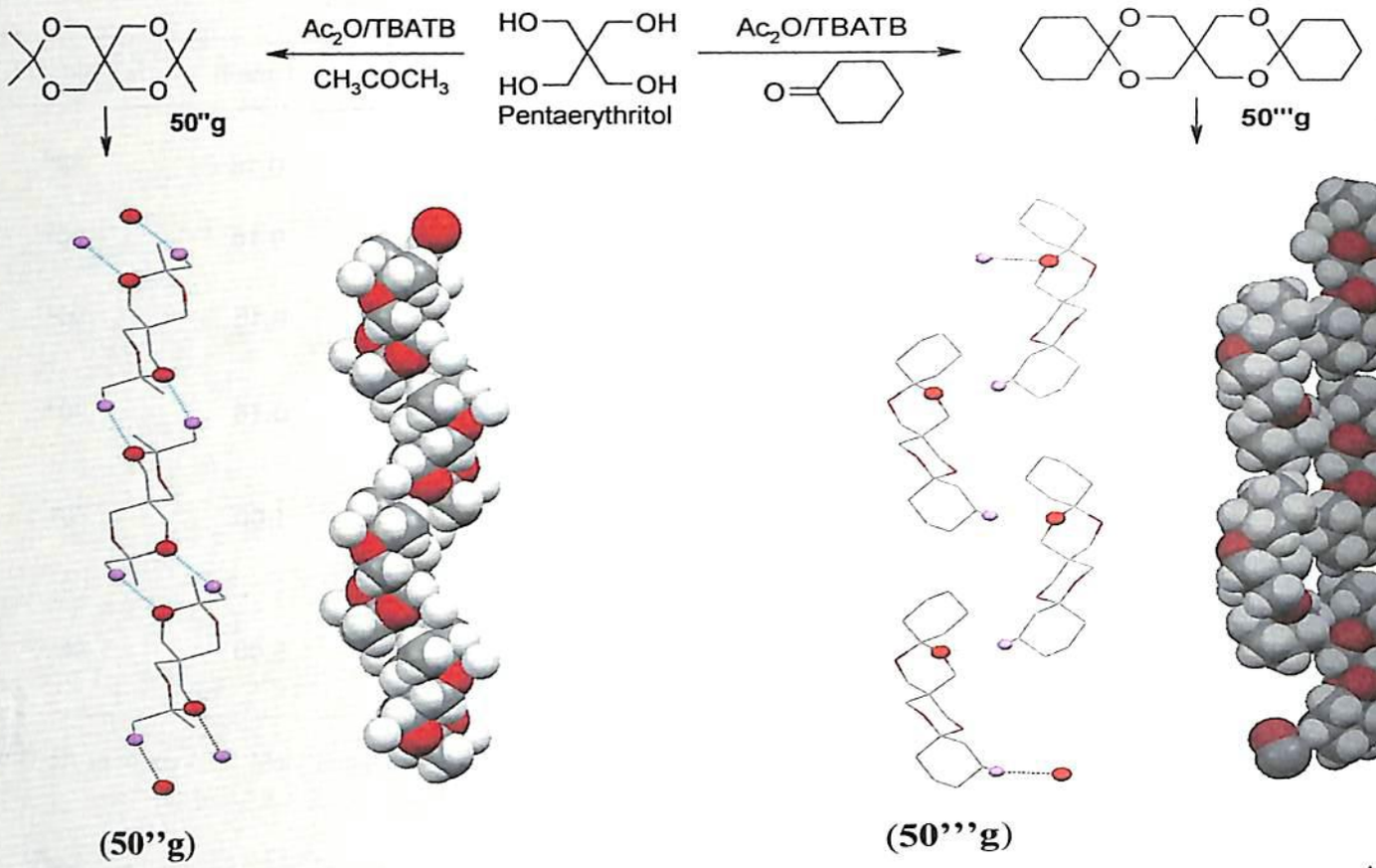
Substrate		Product		Time/h	Yield[b,c] (%)
	(42)		(42g)	0.16	89[d]
	(44)		(44g)	0.16	90[d]
	(45)		(45g)	0.16	90[d]
	(47)		(47g)	0.16	90[d]
	(50)		(50'g)	1.00	70[e]
	(50)		(50g)	5.00	96[f]

[a]Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^1H NMR. [c]Isolated yield. [d]2.5 equiv of Ac_2O were used. [e]5 equiv of Ac_2O were used in acetone. [f]5 equiv of Ac_2O were used in acetonitrile.

When pentaerythritol **50**, a substrate containing four symmetrical hydroxyl groups, was reacted with acetic anhydride (5 equiv) it gave a diisopropylidine derivative **50"g** along with the isopropylidine diacetate **50'g** in the ratio (30:70). It is worth noting that a change of solvent from acetone to acetonitrile resulted in the formation of pentaerythritol tetraacetate **50g** as the sole product in nearly quantitative yield (96%), Scheme 1B.20.



Scheme 1B.20 Acetylation and Isopropylidination of Pentaerythritol

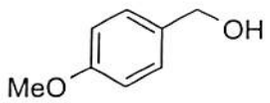
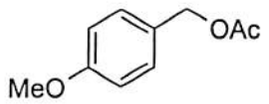
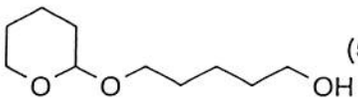
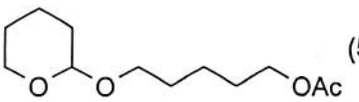
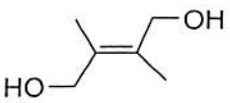
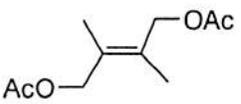
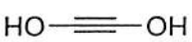
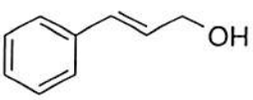
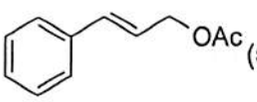
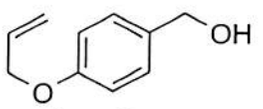
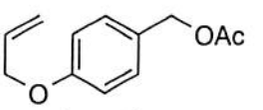
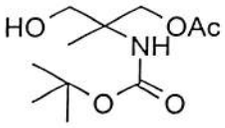
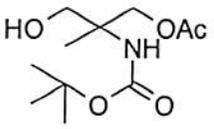
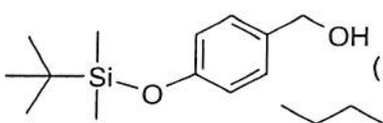
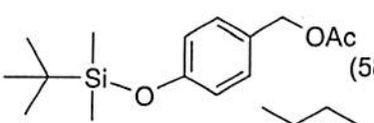
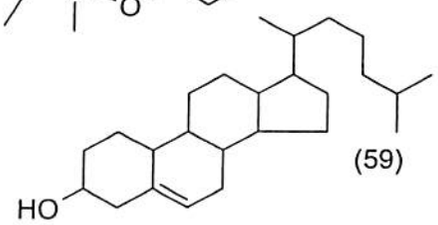
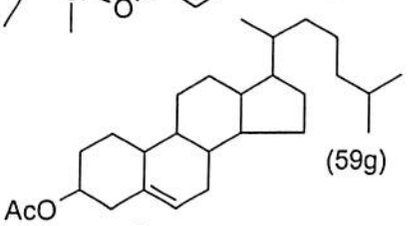
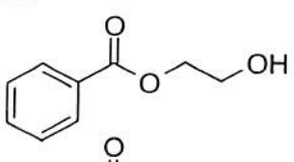
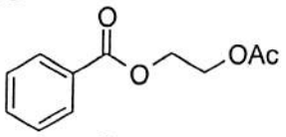
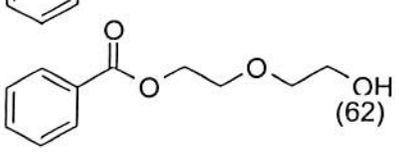
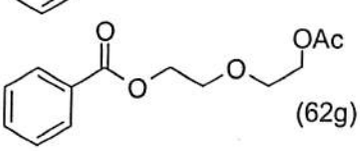


Scheme 1B.21. View Illustrating Intramolecular Hydrogen-Bonded Interactions Between Adjacent Molecules Within the Helix. Carbon-Bound Hydrogen Atoms have been Omitted for Clarity. **(50"g)** 3,3,9,9-Tetramethyl-2,4,8,10-tetraoxa-spiro[5.5]undecane and **(50"'g)** 7,11,18,21-Tetraoxatrispiro [5.2.2.5.2.2] heneicosane.

These crystalline compounds gave the structure as shown in Scheme 1B.21. The two bis acetal derived from pentaerythritol with acetone and cyclohexanone were of interest. The two crystallin compounds so obtained are 3,3,9,9-tetramethyl-2,4,8,10-tetraoxa-spiro[5.5]undecane **(50"g)** an 7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]heneicosane **(50"'g)** respectively. The weaker CH....(interaction mediate the unprecedented helical assembly of sterically encumbered bis acetals. Thes molecules contain a high degree of encoded molecular recognition functionality. One of the oxyge atom from one side form complimentary weak CH....O interactions with the adjacent molecul Additionally, due to steric crowding of cyclohexyl and dimethyl groups the molecule is forced in to twisted conformation. Combinations of these molecular features would translate into a helic supramolecular array held together by intermolecular C-H....O interaction as shown in Scheme 1B.2 The detailed description is elucidated in the next section **1B.3.1**.

Further scope of this present acetylation methodology was also successfully applied to representative variety of functionalised alcohols, Table 1.14.

Table1.14. Acetylation[a] of Functionalised Alcohols with Ac_2O Catalysed by TBATB

Substrate	Product	Time/h	Yield[b,c] (%)
 (27)	 (27g)	0.16	92
 (51)	 (51g)	0.16	87
 (53)	 (53g)	1.00	84[c]
 (54)	 (54g)	1.25	86[c]
 (55)	 (55g)	0.08	89
 (56)	 (56g)	0.33	90
 (57)	 (57g)	1.05	70
 (58)	 (58g)	1.00	85
 (59)	 (59g)	8.00	90
 (61)	 (61g)	0.08	92
 (62)	 (62g)	0.66	94

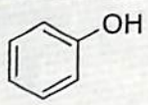
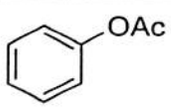
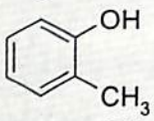
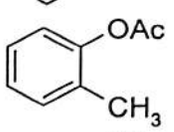
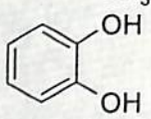
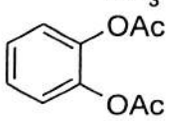
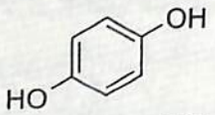
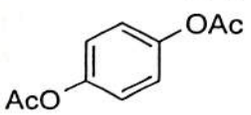
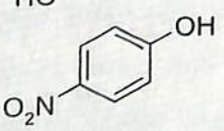
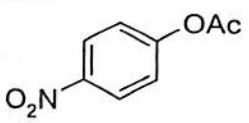
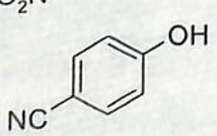
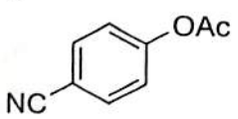
[a]Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^{1}H NMR. [c]Isolated yield.

The substrates bearing acid sensitive groups such as OMe **27**, THP **51** remained intact under the described reaction condition. Diacylated product was obtained without affecting the multiple bonds in substrates, but-2-ene-1,4-diol **53** and but-2-yne-1,4-diol **54** with acetic anhydride (2.5 equiv). The

present method is also effective for acylation of α,β-unsaturated alcohol such as cinnamyl **55**. Conversion of 4-allyloxy benzyl alcohol **56** to its acetate also occurred smoothly without affecting the double bond, Table 1.14.

A substrate containing two hydroxyls and a NHBoc functionality **57** gave monoacylated product without affecting the NHBoc group when reacted with 1.2 equiv of acetic anhydride. Cholesterol **59** took comparatively longer reaction time for the transformation. Moreover, substrates bearing acid sensitive groups such as OMe **27**, THP **51**, NHBoc **57**, and TBS ether **58**, and base sensitive groups such as benzoate **61-62** remained intact under the described reaction condition revealing the functional group compatibility. The pKas of HBr, $HClO_4$ and triflic acid respectively are –9, -10, and –13 showing that triflic and perchloric acids have stronger acidic character compared to HBr. It may be noted that strong Lewis acid character of metal triflates makes them unsuitable for acid-sensitive substrates. In scandium triflate catalysed acetylation, rearranged products of allylic alcohols have been observed.[20d] Results obtained for differential functionalised alcohols have been summarised in Table 1.14.

Table1.15. Acetylation[a] of Phenols with Ac_2O Catalysed by TBATB

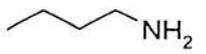
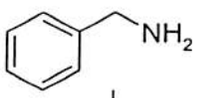
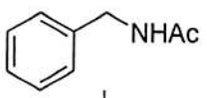
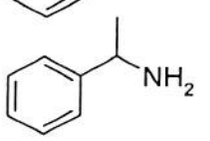
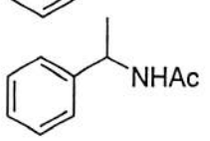
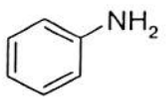
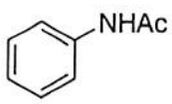
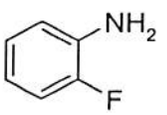
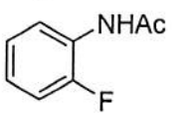
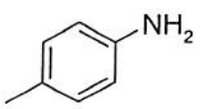
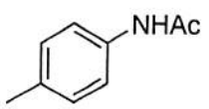
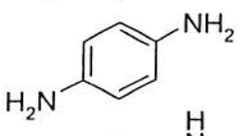
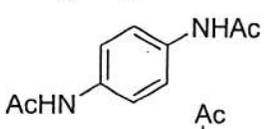
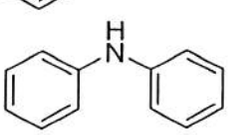
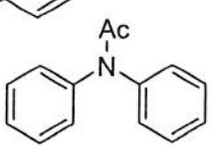
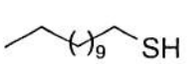
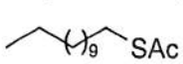
Substrate		Product		Time/h	Yield[b,c] (%)
	(65)		(65g)	5.0	80
	(66)		(66g)	3.0	82
	(67)		(67g)	5.0	78
	(68)		(68g)	5.0	85
	(69)		(69g)	24.0	25
	(70)		(70g)	24.0	15

[a] Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^{1}H NMR. [c]Isolated yield.

The acetylation of a wide range of structurally varied aliphatic, benzylic, allylic alcohols and phenols highlight the fact that the method is capable of generalisation. However, phenols were sluggish under the present reaction condition and took comparatively longer reaction time for completion (Table 1.15). This result was attributed to the differential nucleophilicities of phenols and aliphatic alcohols under the reaction condition.

It is noteworthy to quote that phenols are less nucleophilic than aliphatic alcohols under acidic condition but more nucleophilic under basic condition.[20b] Phenols containing electron-donating groups in the aromatic ring **66-68** were acetylated with ease in comparision to those with electron-withdrawing groups **69-70**, Table 1.15.

Table1.16. Acetylation[a] of Amines and Thiol with Ac_2O Catalysed by TBATB

Substrate		Product		Time/h	Yield[b,c] (%)
	(73)		(73g)	0.08	80
	(74)		(74g)	0.08	89
	(76)		(76g)	0.08	85
	(78)		(78g)	0.08	95
	(79)		(79g)	0.08	90
	(84)		(84g)	0.08	92
	(86)		(86g)	0.08	92
	(93)		(93g)	16	75
	(94)		(94g)	1.0	70[d]

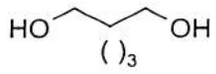
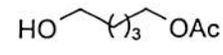
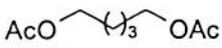
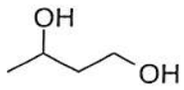
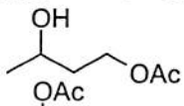
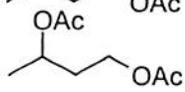
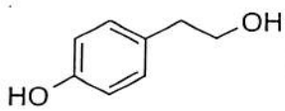
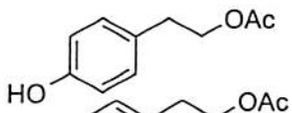
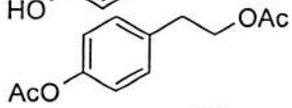
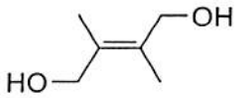
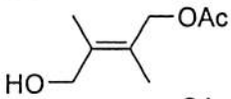
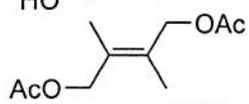
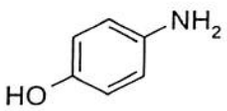
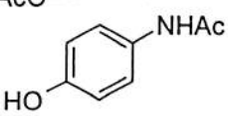
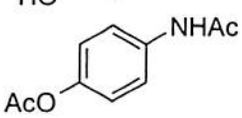
[a] Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^{1}H NMR. [c]Isolated yield. [d]CH_3CN was used as the solvent.

Numerous procedures have been reported in literature for acylation of amines.[1,22,23] Some of the catalysts that are capable of acylating alcohols, phenols, thiols and amines are $RuCl_3$,[5e] $InCl_3$,[5f] $BiOClO_4$[21] heteropoly acid,[12] solid surface-Al_2O_3,[14] oxomolybdenum species,[15] $V(O)(OTf)_2$.[24]

The versatility of the described procedure can be observed from its successful application to *N*- and *S*-acylation of structurally different amines and thiols. Primary aliphatic amines **73, 74, 76** and anilines with various electron releasing and withdrawing substituents **78, 79, 84, 86** were converted to their corresponding amides in short time, whereas secondary amine **93** took hours for completion. This result is not surprising since *N*-acylation of primary amines has been carried out without the use of any acidic or basic catalyst.[25] Thioacetal and hemithioacetal were obtained as side products when acylation of dodecanethiol **94** was carried out in acetone. However, the corresponding thioacetate was obtained by changing the solvent to acetonitrile. The results have been summarised above in Table 1.16.

The marginal difference in acylation rate between primary and secondary alcohols, particularly for diols containing both types of hydroxyl yields substantial amount of diacylate.[26a] Selective monoacylation of symmetrical as well as unsymmetrical diols with various reagents using symmetrical anhydrides have been reported.[11, 12,13,14,19c, 26,27,28,29]

Table1.17. Selective Monoacetylation[a] of Diols with Ac_2O Catalysed by TBATB

Substrate		Product		Time/h	Yield[b,c] (%)
	(42)		(42'g)	0.08	65
			(42g)		25
	(46)		(46'g)	0.16	80
			(46g)		15
	(49)		(49g)	0.16	85
			(49'g)		00
	(52)		(52'g)	0.50	75
			(52g)		20
	(88)		(88g)	0.08	90
			(88'g)		00

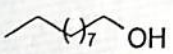
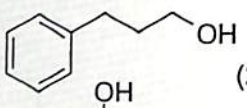
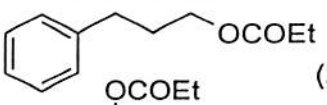
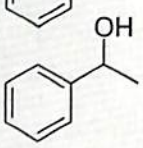
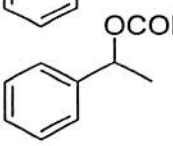
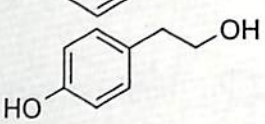
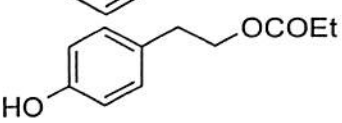
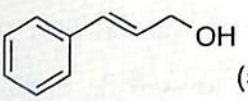
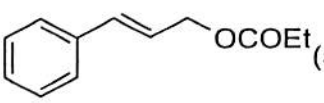
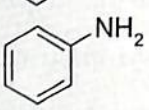
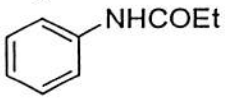
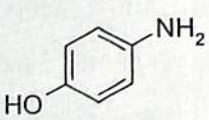
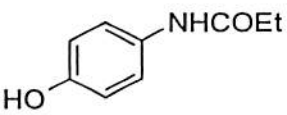
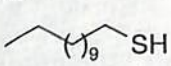
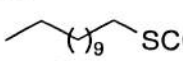
[a] Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^{1}H NMR. [c]Isolated yield.

High selectivity was obtained for unsymmetrical aliphatic diol possessing both primary and secondary hydroxyl groups such as 1,3-butane diol **46**. The primary hydroxyl group was selectively acetylated prior to secondary one with lot wise addition of 1.2 equiv of acetic anhydride in the presence of 0.1 equiv of TBATB in acetone. However, lower selectivity was observed for symmetrical primary diols **42** and **53** even with lot wise addition of the anhydride. The ratios of mono and diacetylated product obtained for substrates pentane-1,5-diol **42** and but-2-ene-1,4-diol **53** were respectively 65:25 and 75:20. The poor reactivity of phenols with acetic anhydride in presence of TBATB raised a genuine possibility of selective acylation of aliphatic alcohols over phenols. For substrate **49** containing both primary and phenolic hydroxyl group, selective monoacetylation occurred at the aliphatic hydroxyl giving exclusively monoacetylated product **49a**. Substrate *p*-aminophenol **89** produced the corresponding acetamide; without affecting the phenolic group. Selective *N*-acetylation is of significant

interest for the preparation of the antipyretic and analgesic drug paracetamol **89a.** Results obtained have been summarised below in Table 1.17.

There are few reports of pivaloylation, benzoylation and acylation using other anhydride and alcohols.[15,19,20,30] It is worth noting that none of the procedures reported in the literature has focused on the acylation of alcohols, amines, and thiols with isobutyric anhydride. In order to extend the scope of the methodology, acylation of alcohols, amines, and thiols with other anhydrides was carried out under the identical condition as described using acetic anhydride. A variety of aliphatic and aromatic alcohols **20**, **22**, **35**, **49**, **55**, amine **78**, and thiol **94** could be propionylated using propionic anhydride to their corresponding propionates **20h**, **22h**, **35h**, **49h**, **55h**, **78h**, and **94h**. Chemoselective propionylation of primary alcohol over phenol, and amine over phenol could be observed as demonstrated for substrates **49** and **89** respectively as shown in Table 1.18.

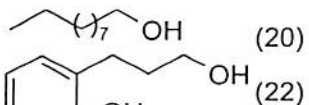
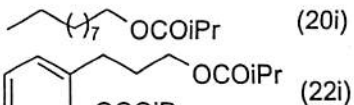
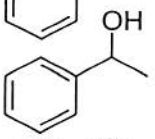
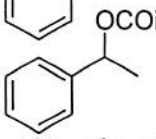
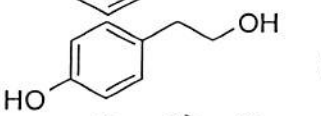
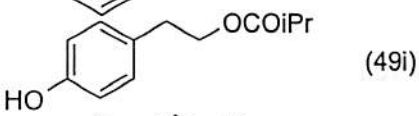
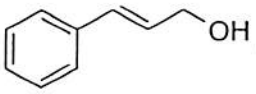
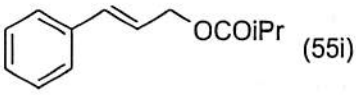
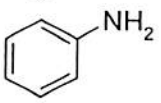
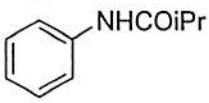
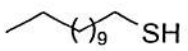
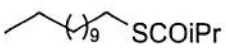
Table 1.18. Propionylation of Alcohols, Amine and Thiol with $(EtCO)_2O$ Catalysed by TBATB

Substrate		Product		Time/h	Yield[b,c] (%)
	(20)		(20h)	0.25	88
	(22)		(22h)	0.25	94
	(35)		(35h)	0.5	90
	(49)		(49h)	0.16	82
	(55)		(55h)	0.25	93
	(78)		(78h)	0.8	95
	(89)		(89h)	0.16	96
	(94)		(94h)	1.0	72[d]

[a] Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^1H NMR. [c]Isolated yield. [d]CH_3CN was used as the solvent.

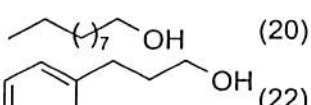
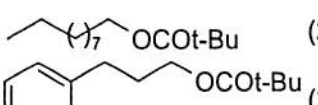
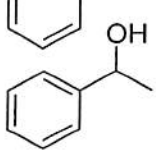
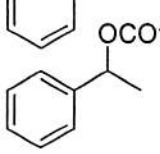
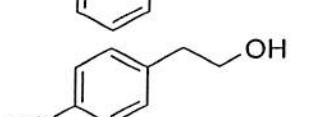
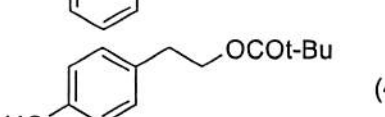
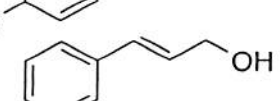
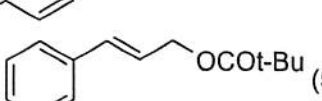
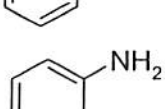
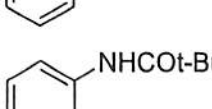
Other anhydride such as isobutyric reacted successfully with various alcohols such as **20**, **22**, **35**, **49**, **55** amine **78**, and thiol **94** to yield the corresponding isobutyrates **20i**, **22i**, **35i**, **49i**, **55i**, **78i** and **94i** as shown in Table 1.19.

Table 1.19. Isobutyrylation[a] of Alcohols, Amine and Thiol with $(iPrCO)_2O$ Catalysed by TBATB

Substrate		Product		Time/h	Yield[b,c] (%)
	(20)		(20i)	0.33	89
	(22)		(22i)	0.33	92
	(35)		(35i)	0.5	88
	(49)		(49i)	0.16	95
	(55)		(55i)	0.25	80
	(78)		(78i)	0.08	94
	(94)		(94i)	1.0	78[d]

[a] Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^1H NMR. [c]Isolated yield. [d]CH_3CN was used as the solvent.

Table 1.20. Pivaloylation of Alcohols, Amine and Thiol with $(t\text{-}BuCO)_2O$ Catalysed by TBATB

Substrate		Product		Time/h	Yield[b,c] (%)
	(20)		(20j)	1.0	86
	(22)		(22j)	1.0	90
	(35)		(35j)	1.5	80
	(49)		(49j)	1.33	82
	(55)		(55j)	1.5	89
	(78)		(78j)	0.25	88

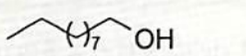
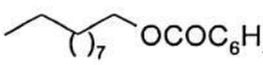
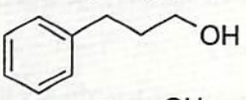
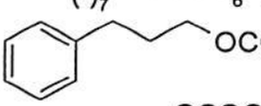
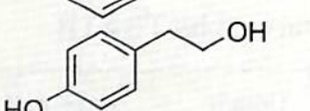
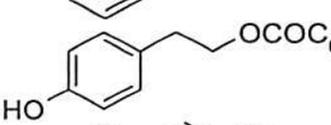
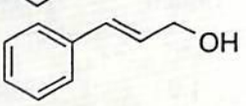
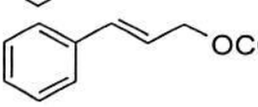
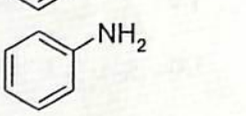
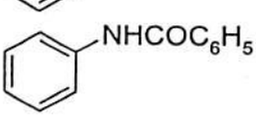
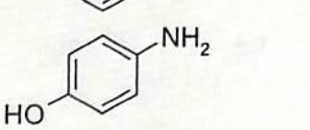
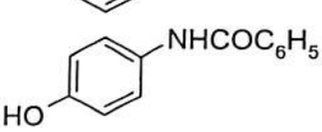
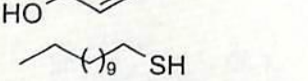
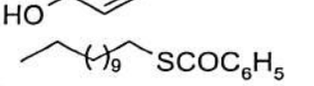
[a]Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^1H NMR. [c]Isolated yield.

It is needless to mention that chemoselective isobutyrylation and pivaloylation of primary alcohol over phenol was observed as demonstrated for substrate **49**, Table 1.19 and 1.20. Similarly the

pivalates **20j, 22j, 35j, 49j, 55j, 78j** were obtained in good yields from their corresponding alcohols and amine under the present condition with pivalic anhydride in the presence of catalytic amount of TBATB, Table 1.20.

Benzoic anhydride, an aromatic anhydride reacted with various alcohols such as **20, 22, 49** and **55** giving corresponding benzoates **20k, 22k, 49k, 55k** respectively. Similar to other anhydrides, benzoic anhydride also reacted with the amines **78** and **89** and thiol **94** to give **78k, 89k,** and **94k** respectively. The reaction of benzoic anhydride with various alcohols, amine and thiol is summarised in Table 1.21. In general, the more hindered the anhydride; the slower is the acylation rate. Notably, under the present reaction condition there is not much difference in the acylation rates of alcohols, amines and thiols with acetic, propionic and isobutyric anhydride but the reaction is slower for pivalic and benzoic anhydride. This observation is consistent with the observations made by others.[19a,b]

Table 1.21. Benzoylation[a] of Alcohols, Amine and Thiol with $(C_6H_5CO)_2O$ Catalysed by TBATB

Substrate		Product		Time/h	Yield[b,c] (%)
	(20)		(20k)	5.0	75
	(22)		(22k)	2.5	87
	(49)		(49k)	2.0	80
	(55)		(55k)	5.0	85
	(78)		(78k)	0.25	93
	(89)		(89k)	0.25	92
	(94)		(94k)	5.0	68[d]

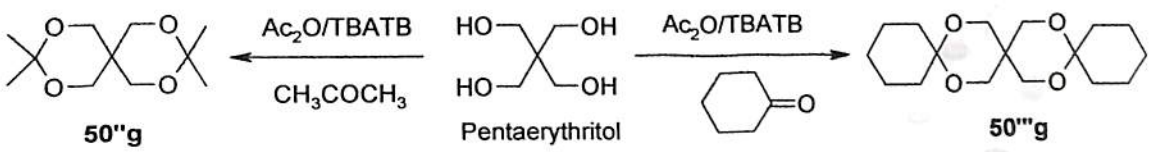
[a]Reactions were monitored by TLC. [b]Confirmed by comparision with IR, ^{1}H NMR. [c]Isolated yield. [d]CH_3CN was used as the solvent.

The reagent TBATB serves as an excellent source of anhydrous HBr in acetone, which catalyses structurally diverse alcohols, amines, thiols, and phenols with different anhydrides. No bromination was observed for substrates susceptible to bromination due to consumption of active bromine in TBATB by acetone giving bromoacetone and HBr. Solvent and steric factors in substrates as well as anhydrides play a significant role during the formation of acylates. Chemoselective acylation of symmetrical diols, primary hydroxyl over secondary and phenolic, and amines over phenols has been achieved. Compared

to the existing methods, which uses various acidic and basic catalysts, this method is very general, simple, gives high yield, has shorter reaction time, and is environmental friendly. In terms of compatibility and selectivity this method is superior to many of the reported methods. Due to the mild reaction conditions a number of functional groups remain intact, in spite of being capable of reacting with tribromides.

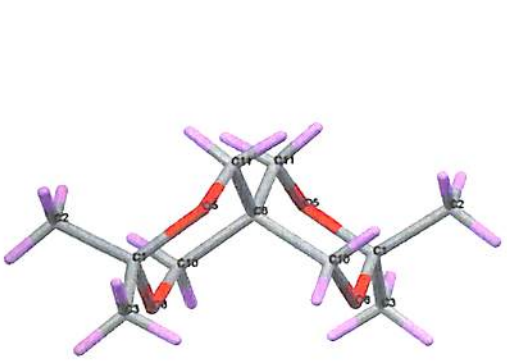
1B.3.1. Hydrogen Bonded Super Helical Structure of Diisopropylidene and Dihexylidene Dderivative of Pentaerythreitol

In this section we have described the crystal structure of of two bis acetals **50''g** and **16''g**. The reaction of pentaerythritol with acetone and cyclohexanone in the presence of tetrabutylammonium tribromide, TBATB yields 3,3,9,9-tetramethyl-2,4,8,10-tetraoxa-spiro[5.5]undecane **50''g** and 7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]heneicosane **16''g** respectively as shown in Scheme 1B.21 inearlier section and Scheme 1B.22 given below.

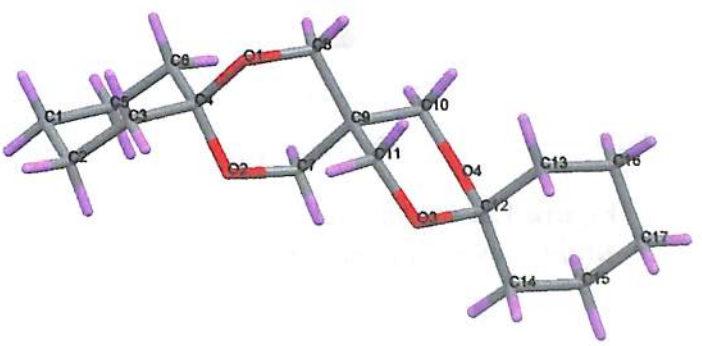


Scheme 1B.21

Single crystals were obtained by crystallising the compounds in ethyl acetate: hexane (1:1). Compound **50''g** has one spiro centre where as compound **50'''g** has three such centres. Asymmetric unit of both **50''g** and **50'''g** has four units each. The prospective view of **50''g** and **50'''g** along with atom labelling scheme is shown in Figure 1.7.



50''g

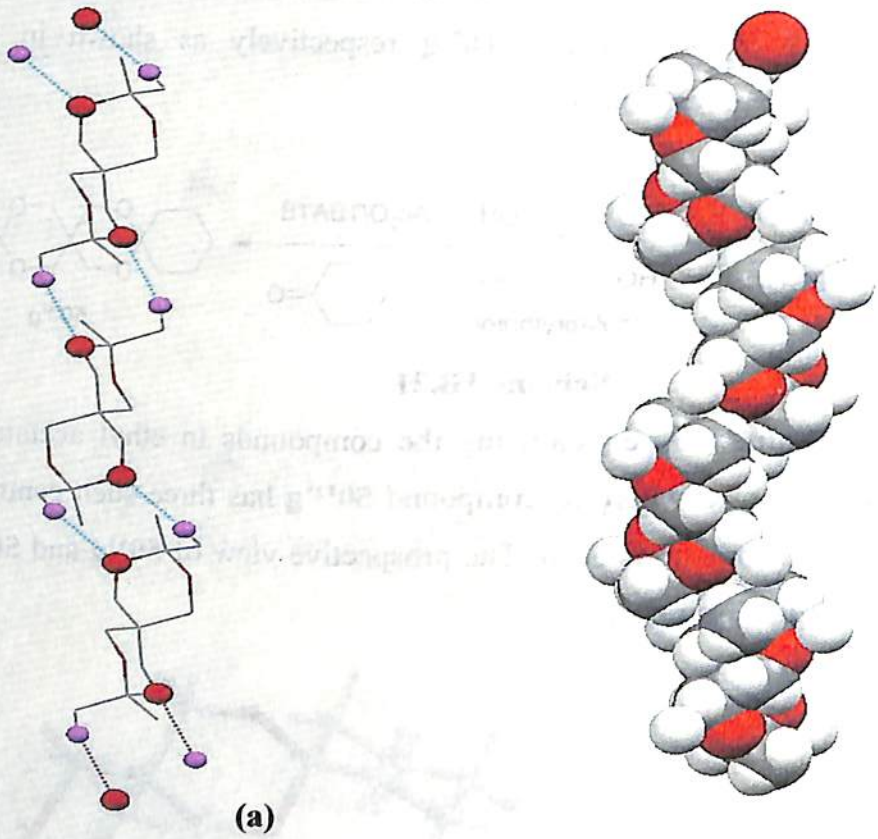


50'''g

Figure 1.7. Prospective View of **50''g** and **50'''g** Showing the Atom Labeling Schemes.

The weaker CH....O interaction mediate the unprecedented helical assembly of sterically encumbered bis acetals. These molecules contain a high degree of encoded molecular recognition functionality. One of the oxygen atom from one side form complimentary weak CH....O interections with the adjacent molecule. Additionally, due to steric crowding of dimethyl group and cyclohexyl in **50''g** and **50'''g** respectively, the molecule is forced in to a twisted conformation. Combination of these molecular features would translate into a helical supramolecular array held together by intermolecular C-H....O interaction.

Compound **50''g** crystal packs into supramolecular hydrogen bonded helices that extend indefinitely through the crystal lattice Figure 1.8 (a).



(a) **(b)**

Figure 1.8. *(a)* View Illustrating Intramolecular Hydrogen-Bonded Interactions Between Adjacent Molecules within the Helix. Hydrogen Atoms Other than Hydrogen Bonded has been Omitted for Clarity. (b) Space Filling Model with Hydrogen Atom.

It is this extended net work of strong and directional C-H.....O intermolecular hydrogen bonds (2.719 Å in length) that drive the formation of the helix. The path of the helix can easily be traced by following the hydrogen bonds counterclockwise around the two-fold screw axis of the helix. Two unit

of the 3,3,9,9-tetramethyl-2,4,8,10-tetraoxa-spiro[5.5]undecane **50''g** combined to make up a single turn of the helix generating a large helical pitch of 16.8Å.

Table 1.22. Crystal Data and Structure Refinement for **(50''g)**

Identification code	sn02	
Empirical formula	$C_{11}\ H_{20}\ O_4$	
Formula weight	216.27	
Temperature	273(2) K	
Wavelength	71.073 pm	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 8.3368(6) Å	α= 90°.
	b = 9.4794(9) Å	β= 92.072(5)°.
	c = 14.8905(12) Å	γ = 90°.
Volume	1.17599(17) nm^3	
Z	4	
Density (calculated)	1.222 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	472	
Crystal size	0.50 x 0.28x 0.23 mm^3	
Theta range for data collection	2.74 to 28.32°.	
Index ranges	-11<=h<=10, -12<=k<=12, -19<=l<=19	
Reflections collected	5014	
Independent reflections	1433 [R(int) = 0.0126]	
Completeness to theta = 28.32°	97.2 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1433 / 0 / 71	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0452, wR2 = 0.1436	
R indices (all data)	R1 = 0.0513, wR2 = 0.1546	
Largest diff. peak and hole	0.250 and -0.217 $e.Å^{-3}$	

The central spiro unit of compound **50'''g** is exactly identical to that of **50''g**. Due to the large steric factor due to the cyclohexyl system, the crystal packs into supramolecular hydrogen bonded helices that extend indefinitely through the crystal lattice, Figure 1.9.

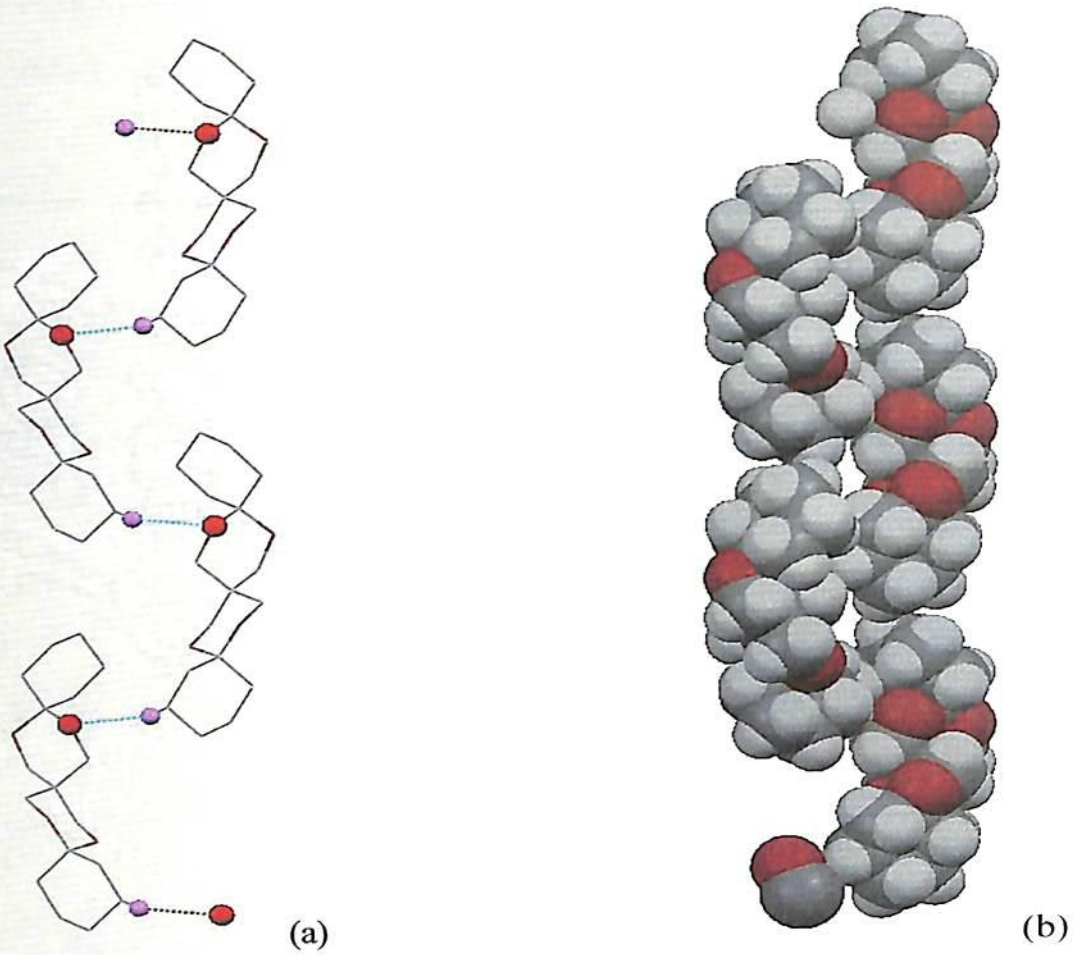


Figure 1.9. (a) View Illustrating Intramolecular Hydrogen-Bonded Interactions Between Adjacent Molecules within the Helix. Hydrogen Atoms Other than Hydrogen Bonded has been Omitted for clarity. (b) Space Filling Model With Hydrogen Atom.

But unlike **50''g** there is only one intermolecular CH...O interection (2.709 Å in length) that drive the formation of the helix. The path of the helix can be can easily be traced by following the zig zag hydrogen bonding pattern. The helical pitch of 13.92Å is less than that of **50''g** due to the formation of a DNA type double helical structure.

Table 1.23. Crystal Data and Structure Refinement for (**50'''g**).

Identification code	bkp007
Empirical formula	C_{17} H_{28} O_4
Formula weight	296.39
Temperature	273(2) K
Wavelength	71.073 pm
Crystal system	Monoclinic
Space group	P2(1)

Table 1.23 Contd.

Table 1.23. Crystal Data and Structure Refinement for (**50'''g**).

Unit cell dimensions	a = 11.1274(5) Å	α= 90°.
	b = 13.9251(6) Å	β= 118.108(3)°.
	c = 11.6790(6) Å	γ = 90°.
Volume	1.59623(13) nm^3	
Z	4	
Density (calculated)	1.233 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	648	
Crystal size	0.48 x 0.26 x 0.13 mm^3	
Theta range for data collection	2.09 to 29.59°.	
Index ranges	-15<=h<=15, -19<=k<=19, -16<=l<=13	
Reflections collected	13534	
Independent reflections	7947 [R(int) = 0.0149]	
Completeness to theta = 29.59°	93.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7947 / 1 / 380	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.1085	
R indices (all data)	R1 = 0.0534, wR2 = 0.1173	
Absolute structure parameter	0.5(6)	
Extinction coefficient	0.0032(10)	
Largest diff. peak and hole	0.269 and -0.199 $e.Å^{-3}$	

At the molecular level, the crystal contains a single enantiomer of the ketone. This local chirality translate in the crystal into the formation of only left-handed helices at the supra molecular level. Thus there might be an auto-resolution process that is effective during crystallisation where by the preassembled helices communicate with the neighbouring helics during the packing of crystal lattice. Because of their implications in the origin of homochirality such chiral resolution process are of significant interest.[31]

Description of Crystal Structure

Data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART [32] software and refined with SAINT[33] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarisation effects. Absorption corrections were applied with the

program SADABS.[34] The structure was solved by direct methods implemented in SHELX-97[34] program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. All the colorless crystals were isolated in rectangular shape from ethyl acetate and hexane mixture (8:2) at room temperature.

All non-H atoms were refined by full-matrix least squares in anisotropic, all H atoms in isotropic approximation, against F^2 of all reflections. All C and O atoms including any heteroatoms were refined in anisotropic approximation. The isotropic parameters and the positions of the hydrogen attached to polar atoms such as O and N were refined in the final structure models. The crystallographic tables include the crystal parameterrs and the refinement factors.

1B.3.2. References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.
2. (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart J. F. *Angew Chem., Int. Ed.* 2002, *41*, 898. (b) Karan, C.; Miller, B. L. *Drug Discovery Today* 2000, *5*, 67.
3. Larock, R. C. In *Comprehensive Organic Transformations*, VCH: New York, 1989; p. 980.
4. Cope, A. C.; Herrick, E. C. *Organic Syntheses, Collect. Vol. 4,* Wiley: New York: 1963; p.304.
5. (a) Backer, R. H.; Bordwell, F. G. *Org. Synth.* **1955**, *3*, 141. (b) Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001. (c) Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263. (d) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702. (e) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 2919. (f) Chakraborti, A. K; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 6749. (g) Chakraborti, A. K; Gulhane, R *Synlett* **2004**, 627. (h) Phukan, P. *Tetrahedron Lett.* **2004**, *450*, 4785. (i) Karimi, B.; Seradj, H. *Synlett* 2001, 519. (j) Khan, A. T.; Chaudhury, L. H. Ghosh, S. Eur. *J. Org. Chem.* **2005**, 2782. (k) Sarvari, H.; Hashem, M; S.; *Tetrahedron* **2005**, *61*, 10903.
6. Kumareswaran, R.; Gupta, A.; Vankar, Y. D. *Synth. Commun.* **1997,** *27*, 277.
7. Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003,** 1896.
8. Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265.
9. Kumareswaran, R.; Pachamuthu, K.; Vankar, Y. D. *Synlett* **2000**, 1652.
10. Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dongare, M. K. *Synlett* **2001**, 206.
11. (a) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998,** *63*, 2420. (b) Orita, A.; Sakamato, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999,** *55*, 2899. (c) Orita, A.; Ito, T.; Yasui, Y.; Otera, J. *Synlett* **1999**, 1927.
12. Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F.; Amani, K. *Chem.Commun.* **2003,** 764.
13. Sharghi, H.; Sarvari, M. H. *Tetrahedron* **2003,** *59*, 3627.
14. (a) Yadav, V. K.; Babu, K. G. *J. Org. Chem.* **2004,** *69*, 577. (b) Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047.
15. Chen, C. –T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C. –H.; Liu, C. –Y. *J. Org. Chem.* **2005**, *70,* 1188.
16. Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743.
17. Olah, G. A.; Prakash, G. K. S. *Super Acids*; Wiley: New York, 1985.
18. Long, J. *Chemical health and Safety* 2002, 9, 12.

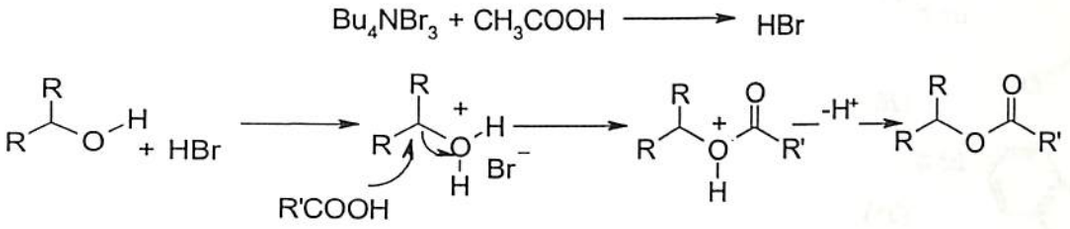
19. (a) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877. (b) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, 66, 8926.(c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T.; Rao, K. R. *Tetrahedron Lett.* **2004**, *45*, 6037. (d) Carrigan, M. D.; Freiberg, D. A.; Smith, R. C.; Zerth, H. M.; Mohan, R. S. *Synthesis* 2001, 2091. (e) Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851. (f) Peterson, K. E.; Smith, R. C.; Mohan, R. S. *Tetrahedron Lett.* **2003**, *44*, 7723. (g) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373. (h) Gaspard-Iloughmane, H.; Roux, C. L. *Eur. J. Org. Chem.* **2004**, 2517.
20. (a) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413. (b) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. (c) Zhou, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559. (d) Jarowicki, K.; Kocienski, P. *Org. Synth.* **1997**, 454.
21. Chen, C. –T.; Kuo, J. -H.; Li, C. –H.; Barhate, N. B.; Hon, S. –W.; Li, T. –W.; Chao, S. –D.; Liu, C. –C.; Li, Y. –C.; Chang, I-H.;Lin, J. –S.; Liu, C. –J.; Chou, Y-C. *Org. Lett.* **2001**, *3*, 3729.
22. (a) Humphrey, C. E.; Easson, M. A. M.; Tierney, J. P.; Turner, N. J. *Org. Lett.* **2003**, *5*, 849. (b) Atkinson, R. S.; Barker, E.; Sutcliffe, M. J. *Chem. Commun.* **1996**, 1051. (c) Ahmed, S.; Iqbal, J. *J. Chem. Soc. Chem. Commun.* **1987**, 114. (d) D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963. (e) Katritzky, A. R.; He, H. -Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
23. Li, J– S.; Li, A. –X. *J. Chem. Soc. Perkin Trans I,* **1998**, 1913.
24. Chakraborti, A. K.; Gulhane, R.; Shivani. *Synlett* **2003**, 1805.
25. (a) Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *Eur. J. Org. Chem.* **2004,** 1254. (b) Ranu, B. C.; Dey, S. S.; Hajra, A. *Green Chemistry*, **2003**, *5*, 44.
26. (a) Framis, V.; Camps, F.; Clapés, P. *Tetrahedron Lett.* **2004**, *45*, 5031. (b) Clarke, P. A. *Tetrahedron Lett.* **2002**, *43*, 4761. (c) Nishiguchi, T.; Kawamine, K.; Ohtsuka, T. *J. Org. Chem.* **1992**, *57*, 312. (d) Breton, G. W. *J. Org. Chem.* 1997, *62*, 8952. (e) Srinivas, K. V. N. S.; Mahender, I.; Das, B. *Synlett* 2003, 2419.
27. Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369.
28. Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351.
29. Clarke, P. A.; Kayaleh, N. E.; Smith, M. A.; Baker, J. R.; Bird, S. J.; Chan, C. *J. Org. Chem.* **2002**, *67*, 5226.
30. (a) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342. (b) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *Chem. Commun.* **1996**, 2625.
31. (a) Norsten, T. B.; McDonald, R.; Branda, N. R. *Chem. Commun.* **1999**, 719. (b) Suárez, M.; Branda, N.; Lehn, J.-M.; Decian, A.; Fischer, J. *Helv. Chim. Acta.* **1998**, 81. (c) Jacques, J.; Collet, A.; Wilen, S. H. Enantomers, Racemates and Resolution, Wiley Interscience, New York, 1981. (d) Koshima, H.; Hayashi, E.; Matsuura, T.; Tanaka, K.; Toda, F.; Kato, M.; Kiguchi, M. *Tetrahedron Lett* **1997**, *38*, 5009. (e) Leiserowitz, L.; Weinstein, M.; *Acta Crystallogr., Sect. B.* **1975**, *31*, 1463.
32. SMART V 4.043 Software for the CCD Detector System; Siemens Analytical Instruments Division: Madison, WI, 1995.
33. SAINT V 4.035 Software for the CCD Detector System; Siemens Analytical Instruments Division: Madison, WI, 1995.
34. Sheldrick, G. M. SHELXL-97, *Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen (Germany), 1997.

1B.4 Tetrabutylammonium Tribromide Mediated Condensation of Carboxylic Acids with Alcohols

Acylations using acid anhydrides work well, but the conversion is inherently wasteful since half of every acid anhydride molecule is lost as carboxylic acid utilising only one acyl group for acylation. On the other hand acyl chlorides are equally efficient acylating agents but their use is restricted owing to their moisture sensitive, corrosive and lacrymating properties. The use of large amount of acylating reagents and activators should be avoided in order to promote Green chemistry and atom efficiency. To fulfill these requirements direct condensation of alcohols with carboxylic acids is the ultimate choice. But the direct condensation of carboxylic acids with alcohols is generally avoided because the equilibrium between the substrates and the products require the elimination of water from the reaction mixture using dehydrant or azeotropically to shift the equilibrium in favour of product. This has been achieved conventionally by condensing carboxylic acid and alcohol with one being in large excess to drive the reaction in forward direction. The reagents and procedures for direct condensation include $B(OH)_3$,[1] R_2SnO,[2] diorgano tin chloride.[3] Stoichiometric condensation of alcohols and acids using $TiCl(OTf)_3$[4c] involve silyl dehydrating additives where as for $TiCl_2(ClO_4)2$[4a,b] and $Sc(OTf)_3$[4d] mediated condensation, anhydride is essential for the removal of water. Water formed during the condensation catalysed by Hf(IV) and Zr(IV) salts has been reported to be removed azeotropically using Soxhlet thimble and calcium hydride or 4Å molecular sieves.[5] Besides these, several other reagents and procedures accounting for this transformation includes $La(OTf)_3$,[6a] $Ce(OTf)_3$,[6b] diphenylammoniumtriflate (DPAT),[6c] triaryl bismuthanes,[7] $K_5CoW_{12}O_{40}.3H_2O$[8] montmorillonites clay,[9] Mn(III) salen complex,[10] pillared clays,[11] CAN,[12] KF[13] and $CoCl_2.6H_2O$.[14] Though some of the reported methods are quite useful for this conversion, some of these methods require expensive dehydrating agents like 4-nitrobenzoic anhydride, silyl additives, CaH_2 and special equipment such as Soxhlet thimble. Some of the reagents are toxic and some of these are expensive. Therefore, there is still a need to search for other suitable alternatives circumventing the above mentioned problems. TBATB in an organic medium being an *in-situ* source of anhydrous HBr manifests itself as a milder alternative to conventional protic and Lewis acids. In continuation to the applications of TBATB for various organic transformations, we have reported here the acylation of alcohols using various carboxylic acids under a solvent free condition.

To investigate this reaction 3-phenyl propanol **22** (5 mmol) was treated with glacial acetic acid (5 mL) in the presence of TBATB (0.5 mmol) at room temperature and progress of the reaction was monitored by thin layer chromatography. Only 40% conversion was achieved even after 24 h. However,

shorter reaction time 0.25 h and better yield (95%) was achieved by performing the reaction at refluxed temperature. Surprisingly, even without the removal of water, esterification was very satisfactory; hence no special precaution was required for the removal of water from the reaction mixture. In a control reaction when decanol **20** (1 mmol) was treated with TBATB (0.1 mmol) no alcohol bromination was observed at all. TBATB is known to release anhydrous HBr in an alcoholic medium and other organic solvent. The pH of the neat acetic acid recorded was 0.8, which drop to a value of -0.9 on addition of TBATB under the identical reaction condition. The HBr with pKa (-9) is sufficiently acidic as compared to protonated carboxylic acid pKa (-7) and protonated alcohol pKa (-2).[15] Thus, alcohol would preferentially be protonated over carboxylic acid. The nucleophilic attack of carboxylate ion on the oxonium species will yield acylated product as shown in Scheme 1B.21.



Scheme 1B.21

By employing this reagent a wide variety of aliphatic, aromatic primary, secondary benzylic alcohols containing electron releasing and electron withdrawing groups could be acetylated to produce the corresponding esters in good to excellent yields. Under the present optimised reaction condition, aliphatic alcohols **20-22** were transformed to corresponding acetates in excellent yields. Benzylic alcohol **26** with electron withdrawing substituent, and electron donating substituent **27** could also be acetylated in shorter time. Acetylation of hindered primary alcohols **31-32** could be achieved in good yields under the present reaction condition. However, symmetrical diols such as pentane-1,5-diol **42,** diethylene glycol **45,** and 2,2-dimethyl-1,3-butane diol **46** were diacetylated completely under the present reaction condition. Hindered secondary alcohols **34, 35, 37,** and **39** were converted to their corresponding acetates in moderate yield. Small percentage of brominated product (< 5%) was observed as side product for substrate containing double bond such as cinnamyl alcohol **55** and p-O-allyl alcohol **56**. More over, acid sensitive groups such as OMe **27**, allyloxy group **56** as well as base sensitive benzoate group **60-61** remained intact under the described reaction condition revealing the functional group compatibility of this method, Table 1.22.

Table1.22. Acylation[a] of Alcohols with Acetic acid in the Presence of TBATB.

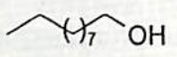
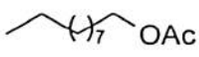
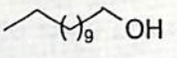
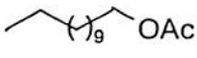
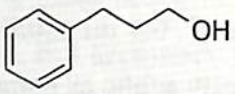
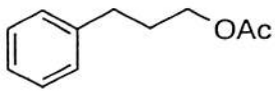
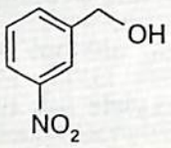
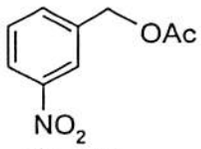
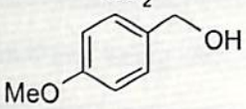
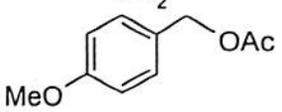
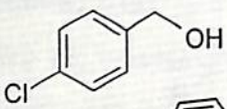
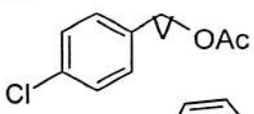
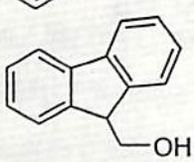
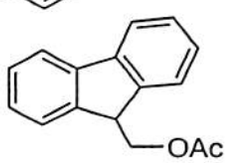
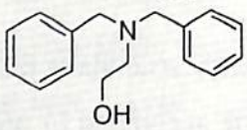
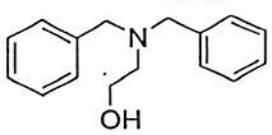
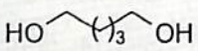
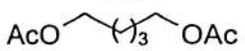
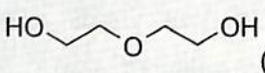
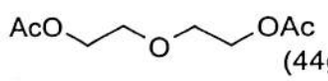
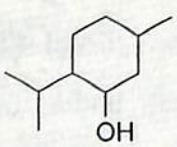
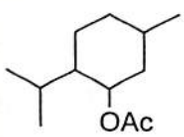
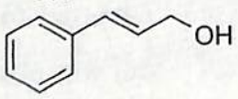
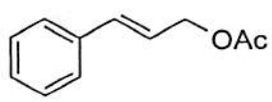
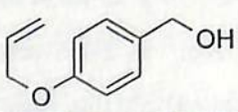
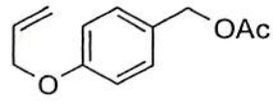
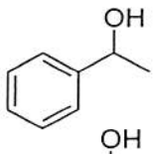
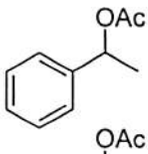
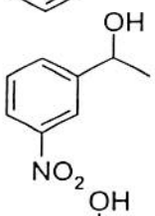
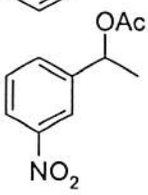
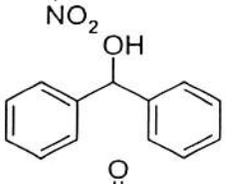
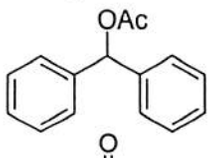
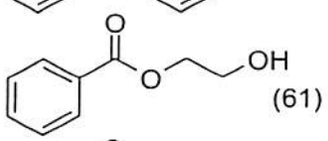
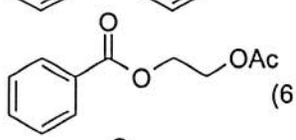
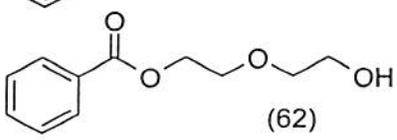
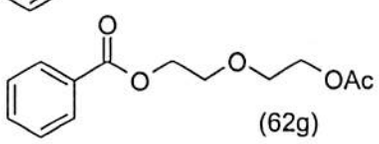
Substrate		Product		Time/h	Yield[b,c] (%)
	(20)		(20g)	0.25	92
	(21)		(21g)	0.25	93
	(22)		(22g)	0.25	95
	(26)		(26g)	0.5	90
	(27)		(27g)	0.16	92
	(28)		(28g)	0.16	92
	(31)		(31g)	0.66	95
	(32)		(32g)	0.16	92
	(42)		(42g)	0.16	89
	(44)		(44g)	0.16	90
	(45)		(45g)	0.16	90
	(34)		(34g)	0.75	87
	(55)		(55g)	0.33	82
	(56)		(56g)	0.50	92

Table Contd...

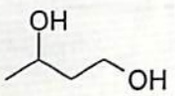
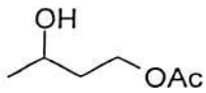
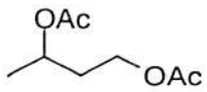
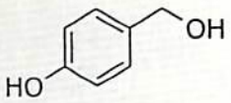
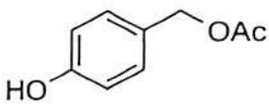
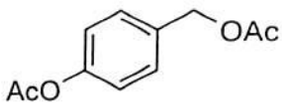
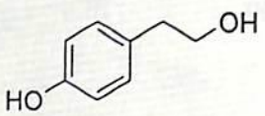
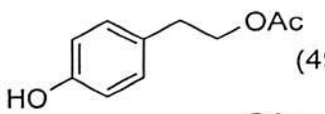
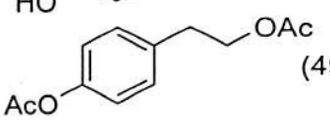
Table1.22. Acylation[a] of Alcohols with Acetic Acid in the Presence of TBATB

Substrate	Product	Time/h	Yield[b,c] (%)
 (35)	 (35g)	0.66	80
 (36)	 (36g)	0.92	80
 (39)	 (39g)	1.00	78
 (61)	 (61g)	0.50	92
 (62)	 (62g)	0.66	94

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparision with IR and ^{1}H NMR. [c]Isolated yield.

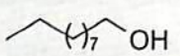
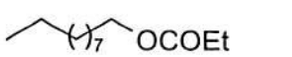
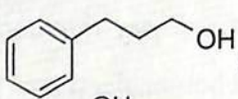
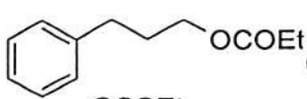
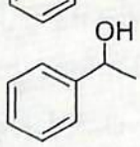
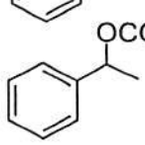
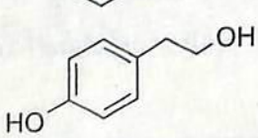
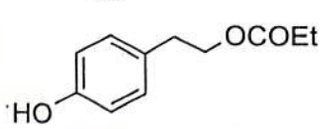
The differential reactivity of substrates containing primary and secondary alcoholic group prompted us to perform chemoselective acylation amongst these group. When 1,3-butane diol, **46** was subjected to react under the described condition with acetic acid, the ratio of primary monoacetylated and diacetylated products obtained were 42:45 respectively, showing poor chemoselectivity between primary and secondary alcohol, Table 1.23. However, as could be seen from Table 1.23, for substrate 4-(2-hydroxy-ethyl)-phenol, **49** the primary aliphatic hydroxy group was exclusively acetylated in the presence of phenolic hydroxy group. Benzylic alcoholic group was chemoselectively acetylated over phenolic group under the present condition for substrate **48** in Table 1.23.

Table 1.23. Acetylation[a] of Diols with Acetic acid in the Presence of TBATB.

Substrate	Product	Time/h	Yield[b,c] (%)
 (46)	 (46'g)	0.33	42
	 (46g)		45
 (48)	 (48g)	0.50	83
	 (48'g)		00
 (49)	 (49g)	0.66	87
	 (49'g)		00

[a]The reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR, ^{1}HNMR of the authentic sample. [c]Isolated yield

Table 1.24. Acylation[a] of Alcohols with EtCOOH in the Presence of TBATB.

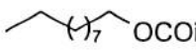
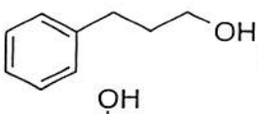
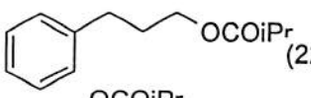
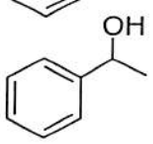
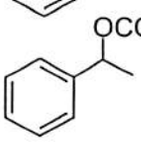
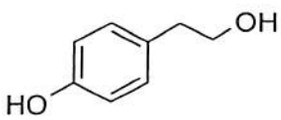
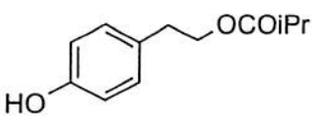
Substrate	Product	Time/h	Yield[b,c](%)
 (20)	 (20h)	0.25	90
 (22)	 (22h)	0.33	95
 (35)	 (35h)	0.50	80
 (49)	 (49h)	0.42	87

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR ^{1}HNMR of the authentic sample.[c]Isolated yield.

The scope of the condensation reaction was extended for propionylation, isobutyralation and pivaloylation. When various alcohols were reacted in presence of TBATB (10 mol%) with propionic,

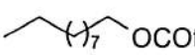
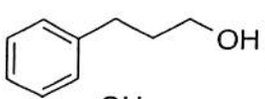
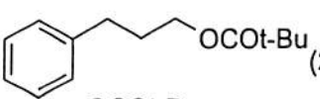
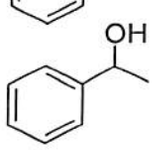
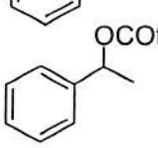
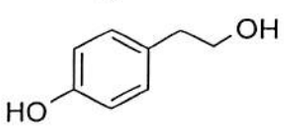
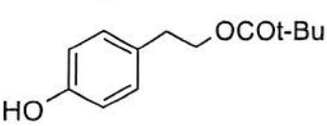
isobutyric and pivalic acid respectively furnished corresponding propionates, isobutyrates and pivalates as given below in Table 1.24-Table 1.26 respectively in good to high yields.

Table 1.25. Acylation[a] of Alcohols with iPrCOOH in the Presence of TBATB.

Substrate	Product	Time/h	Yield[b,c](%)
 (20)	 (20i)	0.33	88
 (22)	 (22i)	0.33	80
 (35)	 (35i)	0.75	79
 (49)	 (49i)	0.58	86

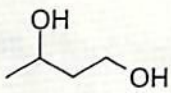
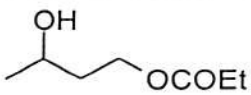
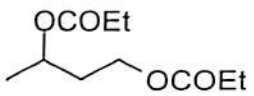
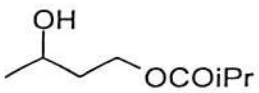
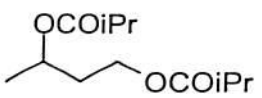
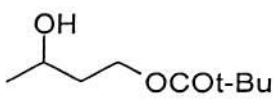
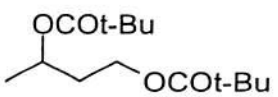
[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR ^{1}HNMR of the authentic sample.[c]Isolated yield.

Table 1.26. Acylation[a] of Alcohols with (*t*-BuCOOH) in the Presence of TBATB.

Substrate	Product	Time/h	Yield[b,c](%)
 (20)	 (20i)	0.75	83
 (22)	 (22i)	0.75	86
 (35)	 (35i)	1.00	76
 (49)	 (49i)	0.92	82

[a]Reactions were monitored by TLC,.GC. [b]Confirmed by comparison with IR ^{1}HNMR of the authentic sample.[c]Isolated yield.

Table 1.27. Acylation[a] of Butane-1,3-diol with Various Acids in the Presence of TBATB.

Substrate	Carboxylic Acid	Product		Time/h	Yield[b,c](%)
 (46)	EtCOOH		(46'h)	0.50	30
			(46h)		60
	iPrCOOH		(46'i)	0.42	60
			(46i)		30
	t-BuCOOH		(46'j)	1.5	70
			(46j)		15

[a]The reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR, ^{1}HNMR of the authentic sample. [c]Isolated yield

As could be observed from above tables, for a given alcohol the rate of acylation increases with increase in the bulkiness of the carboxylic acid. Taking cue from the above observation, study on the effect of steric bulkiness of the acids on the selectivity in acylation was thought to be quite useful.

When butane-1,3-diol, **46** was reacted with various acids, the ratio of mono and di products observed is summarised in Table 1.27. As could be seen from Table 1.27, a better chemoselective acylation of primary alcohol was observed for primary alcohol with increase in bulkiness of acid group during a specified reaction time.

In conclusion, TBATB is found to be an excellent source of anhydrous HBr which catalyses the direct condensation of acid with alcohol. The reagent TBATB is air stable, low toxic and easy to handle. The operation is quite simple, because chemical dehydrating agents such as anhydrides, silyl additives or special apparatus such as Soxhlet-thimble, Dean-Stark apparatus is not necessary. Reaction under a solvent free condition, shorter reaction time accompanied by good yield and operational simplicity are some of the interesting features of this procedure.

1B.4.1. References

1. Otera, J. *Esterification. Methods, Reaetions and Applications,* Wiley-VCH: Weinheim **2003**.
2. Steliou, K.; S.-Nowosielska, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578.
3. Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
4. (a) Otton, J.; Ratton, S.; Vasney, V. A.; Markova, G. D.; Nametov, K. M.; Bakhmutov, V. I.; Komarova, L. I.; Vinogradova, S. V.; Korshak, V. V. *J. Polym. Chem.* **1988,** *26*, 2199. (b) Shiina, I.; Mukaiyama, T.; Miyoshi, S.; Miyashita, M. *Chem. Lett.* **1994**, 515. (c) Mukaiyama, T.; Shiina, I. *Chem. Lett.* **1995**, 141. (d) 11. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*. 4413.
5. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (b) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Synlett* **2001**, 1117. (c) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179.
6. (a) Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351. (b) Iranpoor, N.; Shekarriz, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 455. (c) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249.
7. Ogawa, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. *J. Chem. Soc. Perkin Trans.1*, **1994**, 3473.
8. Habibi, M. H.; Tangestaninejad, S.; Mirkhani, V.; Yadollahi, B. *Tetrahedron* **2001,** *57*, 8333.
9. Choudary, B. M.; Bhaskar, V.; Kantam, M. L.; Rao, K. K.; Raghavan, K. V. *Green Chemistry* **2000**, 67.
10. Choudary, B. M.; Kantam, M. L.; Bharathi, B; Reddy, C. V. *J. Mol. Cat. A: Chem.* **2001**, *168*, 69.
11. Akçay, M. *Appl. Catal. A: Gen.* **2004**, *269*, 157.
12. (a) Kuttan, A.; Nowshudin, S.; Rao, M. N. A. *Tetrahedron Lett.* **2004**, *45*, 2663. (b) Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.-J.; Wu, Y.-C. *Tetrahedron Lett.* **2003**, *44*, 331.
13. Bosco, J. W. J.; Raju, B. R.; Saikia, A. K. *Synth. Commun.* **2004**, *34*, 2849.
14. Velusamy, S.; Borpuzari, S.; Punniyamurthy, T. *Tetrahedron*, **2005**, *61*, 2011.
15. March, J. Advanced Organic Chemistry; Wiley Interscience: New York, **1992**.

1C. Experimental Section

1C.1. General Remarks

All the solvents and reagents employed were of reagent grade (AR grade) and used as purchased without further purifications, unless otherwise stated, and were obtained from E. Merck, Sigma-Aldrich, SRL, Qualigens. Organic extracts were dried over anhy. Na_2SO_4. Sovents were removed in arotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by Thin Layer Chromatography (TLC) on silica gel GF_{254} (0.25mm). Gas liquid chromatography was performed using HP 6890 series II instrument with HP-1, a cross linked methyl silicon gum capillary column (30m x 0.32mm x 0.25μm) fitted with FID, and quantification was done using HP integrator.

1C.2. Characterisation of Organic Substrates

Fourier transform-infrared (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or KBr pelets. Melting points were recorded with a Büchi B-540 melting point apparatus. Fast atom bombardment (FAB) mass was recorded using a JEOL SX-120/DA-6000 instrument using argon (60KV, 10mA) as the FAB gas. Elemental analyses were carried out in automatic C, H, and N analyzer on 2400 Perkin Elmer Series II/CNO. Nuclear Magnetic Resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetra methyl silane as the internal standard for ^{1}H NMR (300 and 400 MHz) and $CDCl_3$ or DMSO-d_6 solvents as internal standard for ^{13}C NMR (75 and 100 MHz). GC-MS were recorded using a capillary column (30 X 0.25 mm X 0.25 mμ) in EI mode.

1C.3. General Experimental Procedures

1C.3.1. General Procedure for Preparation of 1,3-Dithiolanes and 1,3-Dithianes of Aldehydes and Ketones: (Scheme 1B.1)

To a solution of aldehyde (5 mmol) in THF (5 mL) and 1,2-ethanedithiol or 1,3-propanedithiol (5.5 mmol) was added tetrabutylammonium tribromide (0.1 mmol). The homogeneous reaction was left at room temperature and the progress of the reaction mixture was monitored by TLC and GC. After completion of the reaction, the reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) and the product was extracted with ethyl acetate (2 × 25 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. Further purification was achieved by a flash column

chromatography and products were identified by comparison of their NMR, IR, GC, and GC co-injection with authentic samples prepared by known methods.

1C.3.2. Chemoselective Thioacetalisation of Aldehydes in the Presence of Ketones: (Scheme 1B.2)

To the mixture of benzaldehyde **1** (1 mmol), acetophenone **17** (1 mmol) and 1,2-ethanedithiol or 1,3-propanedithiol (1 mmol) in THF was added tetrabutylammonium tribromide (0.02 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.3. Chemoselective Thioacetalisation of *p*-Hydroxybenzaldehyde 5 in the Presence of *p*-Nitrobenzaldehyde 6: (Scheme 1B.3)

To the mixture of *p*-hydroxybenzaldehyde **5** (1 mmol), *p*-nitrobenzaldehyde **6** (1 mmol) and 1,2-ethanedithiol or 1,3-propanedithiol (1 mmol) in THF (2 mL) was added tetrabutylammonium tribromide (0.02 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.4. Chemoselective Acetalisation of *p*-Nitrobenzaldehyde 6 and Thioacetalisation of *p*-Hydroxybenzaldehyde 5: (Scheme 1B.4)

To an equimolar (1 mmol each) mixture of *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6** in THF (2 mL) was added 1,2-ethanedithiol (1 mmol) and 1,2-ethanediol (4 mmol) followed by triethylorthoformate (1 mmol) and TBATB (0.02 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.5. Chemoselective Oxathioacetalisation of *p*-Nitrobenzaldehyde 6 in the Presence of *p*-Hydroxybenzaldehyde 5: (Scheme 1B.5)

Similar to chemoselective thioacetalisation of *p*-hydroxybenzaldehyde in the presence of *p*-nitrobenzaldehyde except TBATB (0.01 mmol) was used instead of 0.02 mmol and 2-mercaptoethanol was used in stead of 1,2-ethanedithiol.

1C.3.6. Chemoselective Oxathioacetalisation of *p*-Nitrobenzaldehyde and Thioacetalisation of *p*-Hydroxybenzaldehyde: (Scheme 1B.8)

To an equimolar mixture (1 mmol each) of *p*-hydroxybenzaldehyde **5** and *p*-nitrobenzaldehyde **6** in THF (2 mL) was added an equimolar mixture of 2-mercaptoethanol and 1,2-ethanedithiol (1 mmol

each) in THF (1 mL) followed by tetrabutylammonium tribromide (0.02 mmol). The heterogeneous reaction was left stirring at room temperature and the progress of the reaction was monitored by TLC and GC. After completion of the reaction, the reaction mixture was poured into $NaHCO_3$ solution (2 mL) and the products were extracted with ethyl acetate (2 × 10 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. The percentages of products formed were first determined by gas liquid chromatography followed by isolating the products by column chromatography using ethyl acetate hexane as eluents.

1C.3.7. Chemoselective Oxathioacetalisation over Acetalisation of *p*-Nitrobenzaldehyde 6: (Scheme 1B.9)

To the solution of *p*-nitrobenzaldehyde (1 mmol) in THF (2 mL) was added a solution of 1,2-ethanediol (4 mmol), 2-mercaptoethanol (1 mmol) in THF (1 mL) followed by triethylorthoformate (1 mmol) and tetrabutylammonium tribromide (0.01 mmol). The homogeneous reaction was left at room temperature and the progress of the reaction was monitored by TLC and GC. After completion of the reaction, the reaction mixture was poured into saturated $NaHCO_3$ solution (2 mL) and the products were extracted with ethyl acetate (2 × 10 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. The percentages of products formed were first determined by gas liquid chromatography followed by isolating the products by column chromatography using ethyl acetate hexane as eluents.

1C.3.8. Chemoselective Acetalisation over Thioacetalisation of *p*-Nitrobenzaldehyde: (Scheme 1B.9)

Similar to chemoselective oxathioacetalisation over acetalisation of *p*-nitrobenzaldehyde except 1,2-ethanedithiol was used instead of 2-mercaptoethanol.

1C.3.9. Chemoselective Oxathioacetalisation over Thioacetalisation of *p*-Nitrobenzaldehyde: (Scheme 1B.9)

Similar to chemoselective acetalisation over thioacetalisation of *p*-nitrobenzaldehyde (experiment 9) except no triethylorthoformate was used and 2-mercaptoethanol (1 mmol) was used instead of 1,2-ethanediol (4 mmol).

1C.3.10. Chemoselective Thioacetalisation over Acetalisation of *p*-Hydroxybenzaldehyde: (Scheme 1B.10)

Procedure similar to that of Scheme 1B.9, except *p*-hydroxybenzaldehyde was used instead of *p*-nitrobenzaldehyde.

1C.3.11. Chemoselective Oxathioacetalisation over Acetalisation of *p*-Hydroxybenzaldehyde: (Scheme 1B.10)

Procedure similar to that of Scheme 1B.9, except *p*-hydroxybenzaldehyde was used instead of *p*-nitrobenzaldehyde.

1C.3.12. Chemoselective Thioacetalisation over Oxathioacetalisation of *p*-Hydroxybenzaldehyde: (Scheme 1B.10)

Procedure similar to that of experiment 10, except *p*-hydroxybenzaldehyde was used instead of *p*-nitrobenzaldehyde.

1C.3.13. Chemoselective Ketalisation of Different Ketones: (Scheme 1B.11)

To an equimolar (1 mmol each) mixture of two ketones and 1,2-ethanedithiol or 1,3-propanedithiol (1 mmol) in THF (2 mL) was added tetrabutylammonium tribromide (0.1 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.14. Chemoselective Thioacetalisation and Thioketalisation of Aldehydes and Ketones with Dithiols: (Scheme 1B.12)

To an equimolar mixture of 1,2-ethanedithiol and 1,3-propanedithiol (1 mmol each) in THF (2 mL) was added an aldehyde or a ketone (1 mmol) followed by TBATB (0.02 mmol for aldehyde and 0.1 mmol for ketone). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.15. Chemoselective Transthioacetalisation of Acetals (1,3-Dioxolane or 1,3-Dioxane) in the Presence of Ketals (1,3-Dioxolane or 1,3-Dioxane): (Scheme 1B.13)

To the mixture of acetal (1 mmol), ketal (1 mmol) and 1,2-ethanedithiol or 1,3-propanedithiol (1 mmol) in acetonitrile (2 mL) was added tetrabutylammonium tribromide (0.01 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.16. Chemoselective Transthioacetalisation of Acetal (1,3-Dioxolane or 1,3-Dioxane) in the Presence of Aldehyde and Transthioketalisation of Ketal (1,3-Dioxolane or 1,3-Dioxane) in the Presence of Ketone: (Scheme 1B.14)

To the mixture of acetal or ketal (1 mmol) and its corresponding carbonyl compound (1 mmol) and 1,2-ethanedithiol or 1,3-propanedithiol (1 mmol) in acetonitrile (2 mL) was added tetrabutylammonium tribromide (0.01 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.17. Chemoselective Transthioacetalisation and Transthioketalisation of Acetals (1,3-Dioxolane or 1,3-Dioxane) and Ketals (1,3-Dioxolane or 1,3-Dioxane) with Dithiols: (Scheme 1B.16)

To an equimolar mixture of acetal or ketal (1 mmol) 1,2-ethanedithiol and 1,3-propanedithiol (1 mmol each) in acetonitrile (2 mL) was added tetrabutylammonium tribromide (0.01 mmol). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.18. Chemoselective Transthioacetalisation of Symmetrical Acetal in the Presence of an Unsymmetrical Acetal (THP Ether): (Scheme 1B.17)

To an equimolar mixture of benzaldehyde acetal (1,3-dioxolane or 1,3-dioxane), tetrahydropyranyl ether of benzylalcohol and 1,2-ethanedithiol or 1,3-propanedithiol (1 mmol) in acetonitrile (2 mL) was added tetrabutylammonium tribromide (0.01 eq). The homogeneous reaction was left at room temperature. The percentages of products formed at different times were determined by gas liquid chromatography.

1C.3.19. General Procedure for Tetrahydropyranylation of Alcohols: (Scheme 1B.18)

To a solution of alcohol (5mmol) in dichloromethane (10mL) was added 3,4-dihydro-2H-pyran (5.5 mmol) and tetrabutylammonium tribromide (TBATB) (0.125mmol) and the resulting solution was left at room temperature. The progress of the reaction was monitored by GC/TLC. On completion, a saturated solution of sodium bicarbonate (10mL) was added and the product was extracted with dichloromethane (2 x 25 mL). The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4. The solvent was removed to give crude THP ether. GC retention time was identical

with that of authentic sample. IR, ^{1}H NMR and ^{13}C NMR data were in good agreement with the spectral data described.

1C.3.20. General Procedure for Depyranylation of THP ethers of Alcohols: (Scheme IB.19)

To a solution of THP ether (5mmol) in methanol (10mL) was added TBATB (0.50mmol) and the resulting solution was left at room temperature. The progress of the reaction was monitored by GC/TLC. On completion of the reaction, methanol was removed under vacuum and product was purified through a short column of silica gel to obtain pure alcohol. GC retention time was idetical with that of authentic sample. IR, ^{1}H NMR and ^{13}C NMR data were in good agreement with the spectral data described.

1C.3.21. General Procedure for Reaction of Alcohols, Amines, and Phenols with Acetic, Propionic, Isobutyric, and Pivalic Anhydride:

Reagent TBATB (0.5 mmol) was added to a stirred solution of acetone (10 mL) followed by alcohol or amine or phenol (5 mmol) and acetic anhydride (6.25 mmol). The progress of reaction was monitored by TLC. After completion of the reaction, solvent was evaporated in a rotary evaporator and admixed with ethyl acetate (25 mL). Organic layer was washed successively with water (2 x 5 mL) followed by saturated $NaHCO_3$ solution (5 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and solvent was concentrated in a rotary evaporator. The compound was purified by passing it over a short column of silica gel, using a mixture of hexane and ethyl acetate as eluent

1C.3.22. General Procedure for Benzoylation of Alcohols, Amines and Phenols with Benzoic Anhydride:

Similar to the acetylation with acetic anhydride except 5 mmol of benzoic anhydride was used per 5 mmol of the substrate.

1C.3.23. General Procedure for Reaction of Thiol with Acetic, Propionic, and Isobutyric anhydride:

Similar to the reaction of alcohols with anhydrides, but acetonitrile was used instead of acetone as the reaction medium.

1C.3.24. General Procedure for Benzoylation of Thiols with Benzoic Anhydride:

Similar to the acetylation with acetic anhydride but 5 mmol of benzoic anhydride was used per 5 mmol of the substrate in acetonitrile.

1C.3.25. General Procedure for the Selective Monoacetylation of Diols:

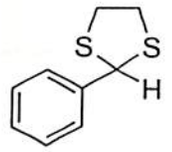
Similar to the acetylation of alcohols with acetic anhydride except 6 mmol of acetic anhydride was used per 5 mmol of the substrate with lot wise addition of anhydride over a period of 0.5h. The products were purified over a column of silica gel, using a mixture of hexane and ethyl acetate as eluent.

1C.3.26. General Procedure for Acetylation of Alcohols with TBATB in Acetic Acid, Propionic acid, Isobutyric acid and Pivalic acid:

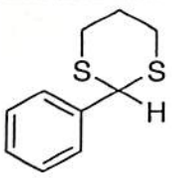
To a solution of alcohol (5 mmol) in acetic acid (5 mL) was added tetrabutylammonium tribromide TBATB (0.5 mmol). The reaction mixture was refluxed and the progress of the reaction was monitored by TLC and GC. After completion of the reaction, the reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and the product was extracted with ethyl acetate (2 × 15 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. Further purification was achieved by column chromatography and products were identified by comparison of their NMR, IR, GC, and GC co-injection with authentic samples prepared by known methods.

1C.4. Spectral Data

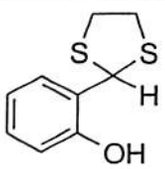
1C.4.1. (Dithiolanes (a) and Dithianes (b))



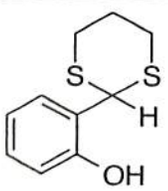
2-Phenyl-[1,3]dithiolane (1a): IR (Neat): 3051,2924, 1664, 1209, 906, 691. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.34 (m, 2H, -SC*H*$_2$-), 3.50 (m, 2H, -SC*H*$_2$-), 5.64 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 7.30 (m, 3H, Ar*H*), 7.47 (m, 2H, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.4, 56.1, 127.0, 128.3, 128.8, 138.4.



2-Phenyl-[1,3]dithiane (1b): IR (KBr): 3037, 2940, 2894, 2827, 1593, 1491, 1429, 1281, 1183, 1066, 912, 728, 697 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.91 (m, 1H, -SCH_2-C*H*$_2$-CH_2S-), 2.17 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.80-3.20 (m, 4H, 2 x -SC*H*$_2$-), 5.16 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 7.31 (m, 3H, Ar*H*), 7.46 (m, 2H, Ar*H*). ^{13}C NMR (50MHz, $CDCl_3$): δ 24.9, 31.9, 51.3, 127.6, 128.3, 128.6, 139.0.

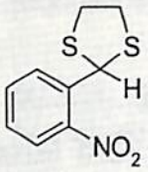


2-Hydroxyphenyl-1,3-dithiolane (2a): IR (KBr): 3385, 2929, 1602, 1490, 1454, 1351, 1275, 1228, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (m, 2H, -SC*H*$_2$), 3.50 (m, 2H, -SC*H*$_2$), 5.82 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 6.85 (m, 2H, Ar*H*), 7.20 (d, 1H, ArH), 7.32 (d, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.7, 54.0, 117.2, 120.3, 121.8, 129.7, 129.9, 154.9.

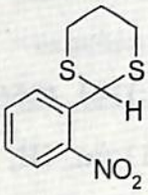


2-Hydroxyphenyl-1,3-dithiane (2b): IR (KBr): 3319, 2950, 2900, 1596, 1501, 1450, 1350, 1276, 1204, 861 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.20 (m, 1H, -SCH_2-

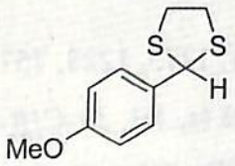
CH(*H*)-CH_2S-), 2.92 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.07 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 5.40 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2$S-), 6.33 (s, 1H, -O*H*), 6.88 (m, 2H, Ar*H*), 7.25 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 32.0, 47.6, 117.6, 121.2, 124.1, 129.6, 130.5, 154.7.



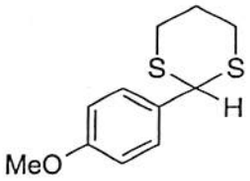
2-Nitrophenyl-1,3-dithiolane (3a): IR (KBr): 2991, 2935, 1600, 1526, 1347, 1280, 860, 799, 720 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.92 (m, 2H, -SC*H*$_2$$CH_2$S-), 3.12 (m, 2H, -$SCH_2$C*H*$_2$S-), 5.88 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 7.43 (m, 1H, Ar*H*), 7.61(m, 1H, Ar*H*), 7.87 (m, 2H, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 39.7, 50.4, 124.4, 128.3, 130.2, 133.1, 136.9, 148.1.



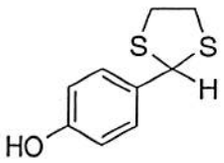
2-Nitrophenyl-1,3-dithiane (3b): IR (KBr): 2930, 2909, 1527, 1352, 1280, 1173, 784, 723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.20 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.93 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.13 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 5.89 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2$S-) 7.44 (m, 1H, Ar*H*), 7.62 (m, 1H, Ar*H*), 7.88 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 29.7, 32.3, 46.0, 124.8, 129.1, 130.8, 133.5.



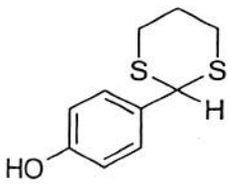
4-Methoxyphenyl-1,3-dithiolane (4a): IR (KBr): 2955, 2938, 2831, 1609, 1510, 1470, 1429, 1254, 1177, 1034, 840, 762 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.32 (m, 2H, -SC*H*$_2$), 3.46 (m, 2H, -SC*H*$_2$), 3.79 (s, 3H, Ar-OC*H*$_3$), 5.63 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 6.83 (d, 2H, J = 8.8 Hz, Ar*H*), 7.45 (d, 2H, J = 8.8 Hz, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.3, 55.3, 56.1, 113.8, 129.2, 132.0, 159.3.



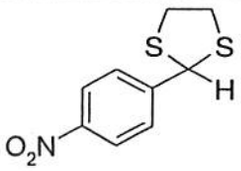
4-Methoxyphenyl-1,3-dithiane (4b): IR (KBr): 2925, 2895, 1600, 1500, 1439, 1250, 1050 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.59-1.86 (m, 2H, -SCH_2-C$\underline{H_2}$-CH_2S-), 2.72-2.89 (m, 4H, 2 x -SC$\underline{H_2}$-), 3.66 (s, 3H, -OC$\underline{H_3}$), 4.99 (s, 1H, Ar-C$\underline{H}$(-$SCH_2CH_2CH_2S$-), 6.72 (d, 2H, Ar$\underline{H}$), 7.24 (d, 2H, Ar$\underline{H}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 31.2, 49.7, 54.3, 113.0, 127.9, 130.3, 158.5.



2-(4-Hydroxy-phenyl-[1,3]dithiolane (5a): IR (KBr): 3396, 2919, 1603, 1506, 1455, 1362, 1250, 1214, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.24-3.49 (m, 4H, 2 x -SC$\underline{H_2}$), 5.63 (s, 1H, Ar-C$\underline{H}$(-SCH_2CH_2S-), 6.75 (d, 2H, J = 8.4 Hz, Ar$\underline{H}$), 7.34 (d, 2H, J = 8.4 Hz, Ar$\underline{H}$), 7.54 (s, 1H, -O$\underline{H}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.9, 54.6, 114.1, 128.2, 130.4, 155.8.

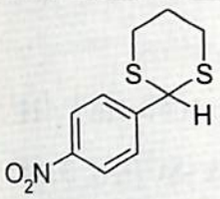


2-(4-Hydroxy-phenyl-[1,3]dithiane (5b): IR (KBr): 3355, 3328, 2929, 2890, 1609, 1510, 1266, 1211, 1176, 766, 764 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.93 (m, 1H, -SCH_2-CH(<u>H</u>)-CH_2S-), 2.16 (m, 1H, -SCH_2-CH(<u>H</u>)-CH_2S-), 2.89 (m, 2H, -SCH_2-CH_2-C$\underline{H_2}$S-), 3.05 (m, 2H, -SC$\underline{H_2}$-CH_2-CH_2S-), 4.80 (s, 1H, -O$\underline{H}$), 5.12 (s, 1H, Ar-C$\underline{H}$(-$SCH_2CH_2CH_2S$-), 6.78 (m, 2H, Ar$\underline{H}$), 7.34 (m, 2H, Ar$\underline{H}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0, 32.2, 50.7, 115.6, 129.2, 131.4, 155.6.

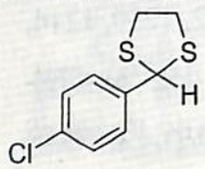


2-(4-Nitro-phenyl-[1,3]dithiolane (6a): IR (KBr): 3073, 2930, 1600, 1520, 1352, 1112, 870, 728 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.37-3.57 (m, 4H, 2 x -SC$\underline{H_2}$-), 5.65 (s, 1H, Ar-C$\underline{H}$(-SCH_2CH_2S-), 7.67

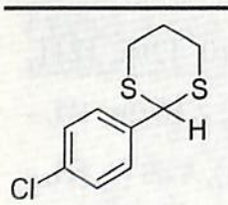
(d, 2H, J = 8.7 Hz, Ar*H*), 8.15 (d, 2H, J = 8.7 Hz, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.9, 55.3, 124.1, 129.2, 147.8, 149.1.



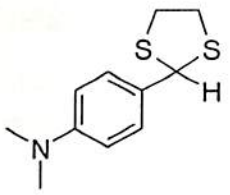
2-(4-Nitro-phenyl-[1,3]dithiane (6b): IR (KBr): 3078, 2960, 2914, 2848, 1608, 1526, 1424, 1352, 1276, 1111, 865, 732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.23 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.95 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.08 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 5.23 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 7.66 (d, 2H, ArH), 8.21 (d, 2H, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.7, 31.7, 50.3, 123.9, 128.9, 146.1, 147.6.



2-(4-Chloro-phenyl)-[1,3] dithiolane (7a): IR (KBr): 2976, 2925, 1670, 1588, 1481, 1404, 1209, 1091 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.42 (m, 4H, 2 x -SCH_2-), 5.59 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 7.27 (d, 2H, J = 8.8 Hz, Ar*H*), 7.44 (d, 2H, J = 8.8 Hz, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.2, 55.3, 128.4, 129.2, 133.5, 134.9.

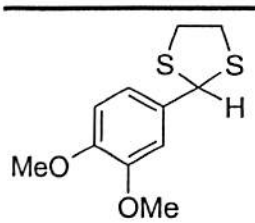


4-Chlorophenyl-1,3-dithiane (7b): IR (KBr): 3048, 2929, 2894, 1598, 1490, 1280, 1178, 1080, 830, 763 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.01 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.50 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.99 (m, 4H, -SC*H*$_2$-CH_2-CH_2S-), 5.13 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 7.38 (m, 4H, Ar*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 31.9, 50.5, 128.9, 129.2, 134.1, 137.6.

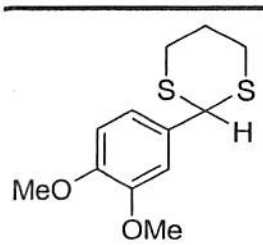


4-(N,N'-dimethyl)phenyl-1,3-dithiolane (8a): IR (KBr): 2930, 2904, 1609, 1532, 1358, 1173, 830, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.99 (s, 6H, -N(C<u>*H*</u>$_3)_2$), 3.33 (m, 2H, -SC<u>*H*</u>$_2$-CH_2S-), 3.51 (m, 2H, -SCH_2-C<u>*H*</u>$_2$S-), 5.65 (s, 1H, Ar-C<u>*H*</u>(-SCH_2CH_2S-), 6.66 (d, 2H, *J* = 9.0 Hz, Ar<u>*H*</u>), 7.39 (d, 2H, *J* = 9.0 Hz, Ar<u>*H*</u>). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.1, 40.6, 56.5, 112.3, 128.8.

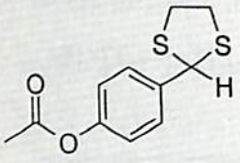
4-(N, N'-dimethyl)phenyl-1,3-dithiane (8b): IR (KBr): 2909, 2797, 1609, 1527, 1358, 1168, 774 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.91 (m, 1H, -SCH_2-CH(<u>*H*</u>)-CH_2S-), 2.16 (m, 1H, -SCH_2-CH(<u>*H*</u>)-CH_2S-), 2.80-3.10 (m, 10H, -SCH_2-CH_2-C<u>*H*</u>$_2$S- and –$N(CH_3)_2$), 5.11 (s, 1H, Ar-C<u>*H*</u>(-$SCH_2CH_2CH_2$S-), 6.67 (d, 2H, *J* = 9.0 Hz, Ar<u>*H*</u>), 7.33 (d, 2H, *J* = 9.0 Hz, Ar<u>*H*</u>). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 32.3, 40.5, 50.9, 112.3, 128.5.



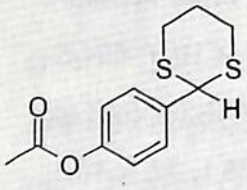
3,4-Dimethoxyphenyl-1,3-dithiolane (9a): ^1H NMR (200 MHz, $CDCl_3$): δ 3.38 (m, 4H, 2 x -SCH_2-), 3.76 (s, 3H, Ar(OC<u>*H*</u>$_3$), 3.81 (s, 3H, Ar(OC<u>*H*</u>$_3$), 5.50 (s, 1H, Ar-C<u>*H*</u>(-SCH_2CH_2S-), 6.85 (m, 3H, Ar<u>*H*</u>). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.1, 55.9, 110.7, 110.8, 120.2, 131.9, 148.8.



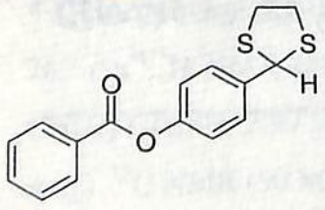
3,4-Dimethoxyphenyl-1,3-dithiane (9b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.16 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.90 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.05 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 3.86 (s, 3H, Ar(OC*H*$_3$)), 3.89 (s, 3H, Ar(OC*H*$_3$)), 5.13 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 6.82 (d, 1H, J = 8.4 Hz, Ar*H*), 7.02 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 32.1, 51.1, 55.8, 110.7, 111.0, 119.9, 131.6, 148.9.



4-Acetoxyphenyl-1,3-dithiolane (10a): IR (KBr): 2925, 1762, 1614, 1511, 1374, 1204, 1009, 912 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, -$COCH_3$), 3.34 (m, 2H, -SC*H*$_2$$CH_2S$-), 3.47 (m, 2H, -$SCH_2$C*H*$_2$S-), 5.62 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 7.02 (d, 2H, J = 8.4 Hz, Ar*H*), 7.52 (d, 2H, J = 8.4 Hz, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 40.1, 55.6, 121.5, 129.0, 137.8, 150.2, 169.3.

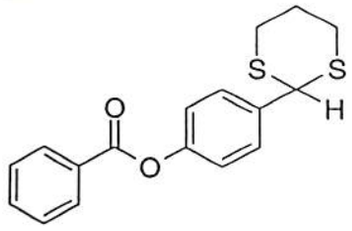


4-Acetoxyphenyl-1,3-dithiane (10b): IR (KBr): 2950, 2904, 2827, 1756, 1603, 1511, 1424, 1372, 1239, 1019, 922, 768 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.15 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.27 (s, 3H, -COC*H*$_3$), 2.88 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.04 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 5.15 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 7.05 (d, 2H, J = 8.4 Hz, Ar*H*), 7.47 (d, 2H, J = 8.4 Hz, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 24.9, 31.9, 50.6, 121.7, 128.9, 136.6, 154.4, 169.2.

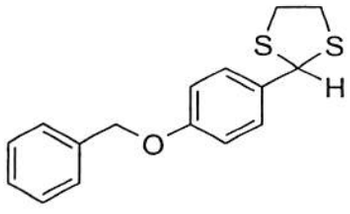


4-Benzoylphenyl-1,3-dithiolane (11a): M.p 102°C. IR (KBr): 1736, 1603, 1506, 1270, 1200, 1173, 1068, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (m, 2H, -SC*H*$_2$$CH_2S$-), 3.50 (m, 2H, -$SCH_2CH_2S$-), 5.66 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 7.16 (d, 2H, Ar*H*), 7.53 (m, 5H, Ar*H*), 8.19 (d, 2H, Ar*H*). ^{13}C

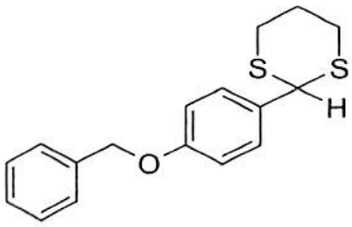
NMR (75 MHz, $CDCl_3$): δ 40.2, 55.7, 121.6, 122.5, 128.5, 129.1, 130.1, 133.6, 137.8, 151.2, 165.0. Anal. Calcd for $C_{16}H_{14}O_2S_2$: C, 63.54; H, 4.67. Found: C, 63.60; H, 4.71.



4-Benzoylphenyl-1,3-dithiane (11b): IR (KBr): 3068, 2955, 2894, 1731, 1593, 1506, 1424, 1265, 1204, 1168, 1071, 1020, 886, 769, 707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.93 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.16 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.90 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.06 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 5.19 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 7.19 (d, 2H, Ar*H*), 7.41 (m, 1H, Ar*H*), 7.51 (m, 3H, Ar*H*), 7.64 (m, 1H, Ar*H*), 8.18 (d, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 32.0, 50.6, 121.9, 122.5, 128.5, 129.0, 130.1, 133.6, 136.7, 150.7, 164.9.

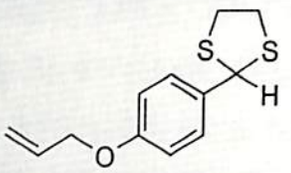


4-Benzyloxyphenyl-1,3-dithiolane (12a): M.p 92°C. IR (KBr): 2916, 1609, 1512, 1251, 1251, 1173, 1013 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.28 (m, 2H, -SC*H*$_2$$CH_2S$-), 3.46 (m, 2H, -$SCH_2$C*H*$_2$S-), 5.02 (s, 2H, -C*H*$_2$Ph), 5.61 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 6.89 (d, 2H, J = 8.4 Hz, Ar*H*), 7.35 (m, 7H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.1, 56.0, 70.0, 114.7, 127.3, 127.9, 128.5, 129.1, 132.1, 136.8, 158.5. Anal. Calcd for $C_{16}H_{16}OS_2$: C, 66.63; H, 5.59 %. Found: C, 66.68; H, 5.57.

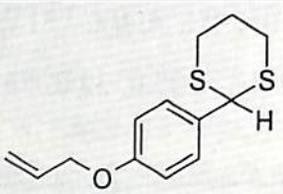


4-Benzyloxyphenyl-1,3-dithiane (12b): IR (KBr): 2945, 2889, 1609, 1511, 1393, 1245, 1189, 1009, 748. ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.14 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.88 (m, 2H, -SCH_2-CH_2-C*H*$_2$S-), 3.03 (m, 2H, -SC*H*$_2$-CH_2-CH_2S-), 5.03 (s, 2H, -C*H*$_2$Ar), 5.12

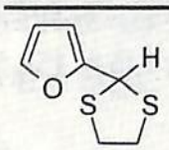
(s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 6.92 (d, 2H, *J* = 8.5 Hz, Ar*H*), 7.37 (m, 7H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 32.1, 50.7, 70.0, 114.9, 127.4, 127.9, 128.5, 128.9, 131.5, 136.8, 158.7.



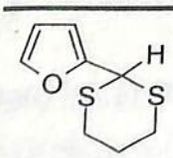
4-O-allylphenyl-1,3-dithiolane (13a): ^1H NMR (400 MHz, $CDCl_3$): δ 3.34 (m, 2H, -SCH_2CH_2S-), 3.50 (m, 2H, -SCH_2CH_2S-), 4.52 (m, 2H, -$OCH_2CH{=}CH_2$), 5.30 (m, 2H, -$OCH_2CH{=}CH_2$), 5.62 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 6.03 (m, 1H, -$OCH_2CH{=}CH_2$), 6.87 (m, 2H, Ar*H*), 7.42 (m, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.1, 55.9, 68.8, 114.6, 117.7, 129.0, 129.4, 131.9, 133.1, 158.3.



4-O-allylphenyl-1,3-dithiane (13b): IR (KBr): 2914, 1603, 1506, 1429, 1245, 1183, 1015, 779 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.95 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.16 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.91 (m, 2H, -SCH_2-CH_2-CH_2S-), 3.05 (m, 2H, -SCH_2-CH_2-CH_2S-), 4.53 (m, 2H, -$OCH_2CH{=}CH_2$), 5.12 (s, 1H, Ar-C*H*(-$SCH_2CH_2CH_2S$-), 5.29 (m, 1H, -CH=CH(*H*)), 5.40 (m, 1H, -CH=C*H*(H)), 6.04 (m, 1H, -$OCH_2CH{=}CH_2$), 6.87 (d, 2H, Ar*H*), 7.38 (d, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 32.1, 50.7, 68.8, 114.8, 117.7, 128.9, 130.0, 131.4, 133.1, 158.6.

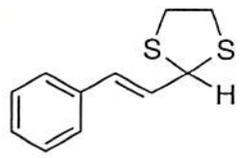


2-Furyl-1,3-dithiolane (14a): ^1H NMR (300 MHz, $CDCl_3$): δ 3.30 (m, 2H, -SCH_2CH_2S-), 3.44 (m, 2H, -SCH_2CH_2S-), 5.62 (s, 1H, Ar-C*H*(-SCH_2CH_2S-), 6.28 (m, 2H, Ar*H*), 7.36 (s, 1H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.1, 47.4, 107.0, 110.3, 142.5, 154.2.

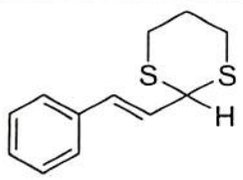


2-Furyl-1,3-dithiane (14b): IR (KBr): 2904, 1496, 1424, 1276, 1163, 1015, 943, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.12 (m, 1H, -SCH_2-CH(*H*)-CH_2S-), 2.94

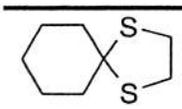
(m, 4H, -SCH_2-CH_2-C$\underline{H}_2$S-), 5.22 (s, 1H, Ar-C$\underline{H}$(-$SCH_2CH_2CH_2$S-), 6.34 (m, 1H, Ar$\underline{H}$), 6.40 (m, 1H, Ar$\underline{H}$), 7.36 (s, 1H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 30.0, 41.8, 107.6, 110.4, 142.0, 151.5.



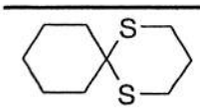
Cinnamyl-1,3-dithiolane (15a): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.27 (m, 4H), 5.12 (d, 1H, Ar-C$\underline{H}$(-SCH_2CH_2S-), 6.00 (dd, 1H), 6.52 (d, 1H), 7.26 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.8, 52.0, 126.8, 128.0, 128.7, 129.4, 130.1, 136.2.



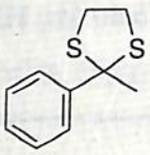
Cinnamyl-1,3-dithiane (15b): IR (KBr): 3027, 2919, 2853, 1614, 1542, 1486, 1424, 1271, 1173, 1040, 963, 764, 697. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.88 (m, 1H, -SCH_2-CH($\underline{H}$)-CH_2S-), 2.11 (m, 1H, -SCH_2-CH($\underline{H}$)-CH_2S-), 2.88 (m, 4H, -SCH_2-CH_2-C$\underline{H}_2$S-), 4.80 (d, 1H, Ar-C$\underline{H}$(-$SCH_2CH_2CH_2$S-), 6.25 (dd, 1H), 6.74 (d, 1H), 7.39 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.1, 30.1, 47.6, 125.9, 126.6, 128.0, 128.5, 133.3, 136.0.



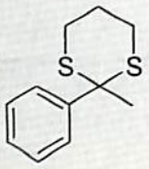
1,4-Dithia-spiro[4,5] -decane (16a): IR (Neat): 2930, 2853, 1440, 1271, 1132, 1030 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (m, 2H), 1.62 (m, 4H), 2.00 (m, 4H), 3.28 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0, 26.2, 38.3, 42.9, 69.2.



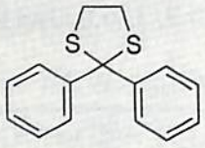
1,5-Dithia-spiro[5,5]-undecane (16b): IR (Neat): 2930, 2853, 1440, 1265, 1127, 1015, 907, 861, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (m, 2H), 1.62 (m, 4H, -SCH_2-CH_2-C$\underline{H}_2$S-), 2.03 (m, 6H), 2.85 (m, 4H, -SC$\underline{H}_2$-CH_2-CH_2S-). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 25.7, 25.8, 26.0, 37.8, 50.2.



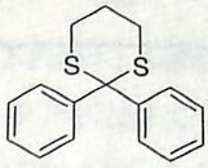
2-Methylphenyl-1,3-dithiolane (17a): IR (Neat): 2971, 2935, 1598, 1491, 1445, 1276, 1071, 1030, 774, 702 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.40 (m, 4H), 7.21 (m, 1H, Ar*H*), 7.30 (m, 2H, Ar*H*), 7.74 (d, 2H, *J* = 7.5 Hz, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8, 40.2, 68.5, 126.7, 127.0, 127.9, 145.8.



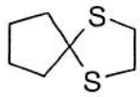
2-Methylphenyl-1,3-dithiane (17b): IR (Neat): 3063, 2909, 2832, 1603, 1496, 1440, 1388, 1286, 1189, 1071, 764, 702 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (s, 3H, Ar(C)C*H*$_3$), 1.93 (m, 2H, -$SCH_2CH_2CH_2S$-), 2.69 (m, 4H, -SCH_2-CH_2-CH_2S-), 7.25 (m, 1H, Ar*H*), 7.37 (m, 2H, Ar*H*), 7.93 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 27.9, 32.7, 53.8, 126.9, 127.6, 128.4, 143.7.



2,2-Diphenyl-1,3-dithiolane (18a): IR (KBr): 2930, 2846, 1598, 1485, 1450, 1419, 1276, 1086, 748, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.39 (s, 4H, -$S(CH_2)_2S$-), 7.27 (m, 6H, Ar*H*), 7.59 (m, 4H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.1, 127.2, 127.9, 128.2, 144.6.

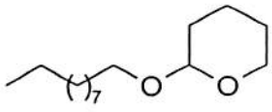


2,2-Diphenyl-1,3-dithiane (18b): IR (KBr): 3063, 2955, 2899, 2832, 1598, 1496, 1445, 1286, 1158, 1009, 861, 753, 699. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (m, 2H, -SCH_2-CH_2-CH_2S-), 2.75 (m, 4H, -SCH_2-CH_2-CH_2S-), 7.31 (m, 6H, Ar*H*), 7.67 (m, 4H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 29.3, 127.5, 128.3, 129.3, 142.4.

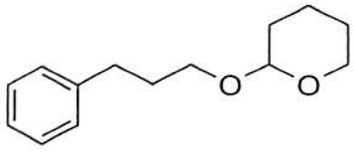


1,4-Dithia-spiro[4,4] -nonane (19a): IR (Neat): 2960, 2924, 2878, 1449, 1275, 1168, 1101, 978, 851, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.74-1.77 (m, 4H, $-CH_2-$), 2.07-2.14 (m, 4H, $-CH_2-$), 3.30 (s, 4H, 2 x $-SCH_2-$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.48, 39.37, 43.92, 70.86.

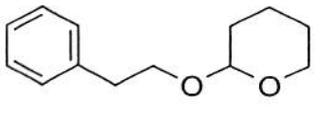
1C.4.2. Tetrahydropyranyl Ethers (f)



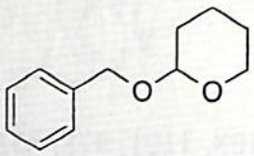
2-Butoxy-tetrahydro-pyran (20f): IR (Neat): 2919, 2854, 1469, 1354, 1218, 1127, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, $-CH_2C\underline{H}_3$), 1.20-1.40 (brs, 14H, $-CH_2CH_2$), 1.50-1.69 (m, 6H), 1.7 (m, 1H), 1.80 (m, 1H), 3.35 (m, 1H), 3.50 (m, 1H), 3.75 (m, 1H), 3.85 (m, 1H), 4.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 20.1, 23.1, 25.9, 26.6, 29.7, 29.9, 29.98, 30.0, 30.2, 31.1, 32.3, 62.6, 68.0, 99.0.



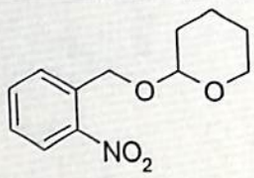
2-(3-Phenyl-propoxy)-tetrahydro-pyran (22f): ^1H NMR (400 MHz, $CDCl_3$): δ 1.48-1.96 (m, 8H), 2.69 (m, 2H), 3.35-3.49 (m, 2H), 3.72-3.85 (m, 2H), 4.56 (m, 1H), 7.23 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 25.4, 30.6, 31.2, 32.4, 62.1, 66.7, 98.7, 125.6, 128.1, 128.3, 141.9.



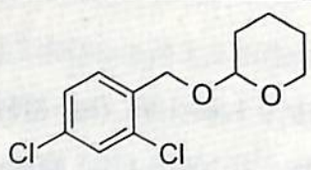
2-Phenethyloxy-tetrahydro-pyran (23f): IR (Neat): 2938, 2869, 1728, 1605, 1498, 1450, 1354, 1269, 1200, 1141, 1120, 1066, 1034, 970, 906, 869, 816, 752, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35-2.00 (brm, 6H), 2.91 (m, 2H), 3.45 (m, 1H), 3.61 (m, 1H), 3.64 (m, 1H), 3.96 (m, 1H), 4.59 (m, 1H), 7.25 (m, 5H).



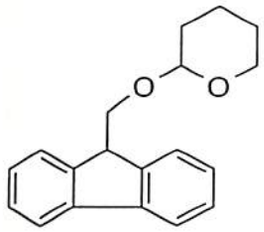
2-Benzyloxy-tetrahydro-pyran (24f): IR (Neat): 2945, 2868, 1460, 1352, 1265, 1203, 1122 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ1.48-1.90 (m, 6H, -O-CH_2-($C\underline{H}_2$)$_3$-CH-)-O-), 3.52 (m, 1H), 3.89 (m, 1H,), 4.42 (d, 1H, J = 11.6 Hz), 4.70 (m, 1H, -O$C\underline{H}$(CH_2)$_3$$CH_2$-O), 4.80 (d, 1H, J = 12.0 Hz) 7.25 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (100 M Hz, $CDCl_3$): δ 19.8, 25.9, 31.0, 62.4, 69.1, 97.9, 127.7, 128.0, 128.5, 138.5.



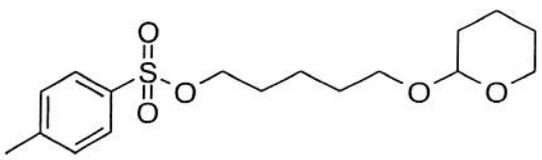
2-(2-Nitro-benzyloxy)-tetrahydro-pyran (25f): ^1H NMR (400 MHz, $CDCl_3$): δ 1.43-1.99 (m, 6H), 3.52 (m, 1H), 3.89 (m, 1H), 4.75 (m, 1H), 4.89 (d, 1H, J = 15.6 Hz), 5.15 (d, 1H, J = 14.8 Hz), 7.40 (t, 1H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.2 Hz), 7.80 (d, 1H, J = 7.6 Hz), 8.05 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.7, 30.8, 62.6, 66.1, 98.9, 124.7, 128.0, 128.9, 133.6, 135.2, 147.4. Peaks appearing due to minor contamination of other enantiomers (20.1, 25.8, 31.6, 63.1, 94.7). Anal. calcd for $C_{12}H_{15}NO_4$: C, 60.75; H 6.37; N 5.90. Found C, 61.04, H, 6.31, N, 5.82.



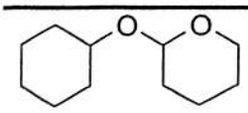
2-(2,4-Dichloro-benzyloxy)-tetrahydro-pyran (29f): IR (Neat): 2942, 2862, 1591, 1468, 1382, 1350, 1200, 1129, 1073, 1034, 972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48-2.0 (m, 6H), 3.55 (m, 1H), 3.88 (m, 1H), 4.50 (d, 1H, J = 13.2 Hz), 4.79 (m, 2H), 4.80 (d, 1H, J = 13.2 Hz), 7.23 (m, 1H), 7.35 (d, 1H, J = 1.6 Hz), 7.44 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.8, 30.8, 62.5, 66.0, 98.6, 127.1, 129.1, 129.8, 133.5, 133.6, 135.0.



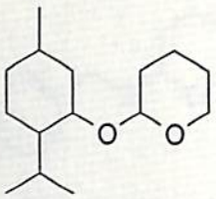
2-(9H-Fluoren-9-ylmethoxy)-tetrahydro-pyran (31f): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50-2.0 (brm, 6H), 3.45 (m, 1H), 3.54 (t, 1H, *J*= 8.8 Hz), 3.83 (m, 1H), 4.05 (t, 1H, *J* = 8.0 Hz), 4.18 (t, 1H, *J* = 8.0 Hz), 4.67 (t, 1H, *J* = 3.2 Hz), 7.26 (d, 2H, *J* = 7.6 Hz), 7.34 (t, 2H, *J* = 7.2 Hz), 7.63 (d, 2H, *J* = 7.6 Hz), 7.72 (d, 2H, *J*=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$); δ 18.0, 24.1, 29.2, 46.4, 60.5, 68.6, 97.4, 118.17, 118.18, 123.6, 123.7, 125.2, 125.2, 125.7, 139.5, 143.0, 143.5.



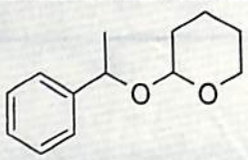
Toluene-4-sulfonic acid 5-(tetrahydro-pyran-2-yloxy)-pentyl ester (52f): IR (Neat): 2945, 2868, 1603, 1465, 1362, 1183, 1132, 1081, 1050, 968, 963 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40-1.70 (m, 12H), 2.45 (s, 3H), 3.32-3.35 (m, 1H), 3.49-3.50 (m, 1H), 3.68-3.70 (m, 1H), 3.80-3.89 (m, 1H), 4.03 (t, 2H, *J* = 6.8 Hz), 4.53-4.54 (m, 1H), 7.34 (d, 2H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 21.7, 22.3, 25.5, 28.8, 29.1, 30.8, 62.4, 67.1, 70.5, 98.8, 127.7, 129.6, 133.0, 144.5.



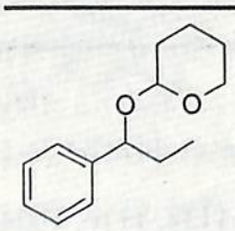
2-Cyclohexyloxy-tetrahydro-pyran(33f): IR (Neat): 2934, 2867, 1454, 1362, 1203, 1132, 1116, 1024, 1004 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07-1.36 (m, 5H), 1.46-1.52 (m, 5H), 1.58-1.86 (m, 6H), 3.38-3.44 (m, 1H), 3.49-3.56 (m, 1H), 3.79-3.88 (m, 1H), 4.64 (dd, 1H, *J* = 4.6 Hz, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 24.1, 24.4, 25.5, 25.7, 31.2, 31.7, 33.7, 62.7, 74.3, 96.5.



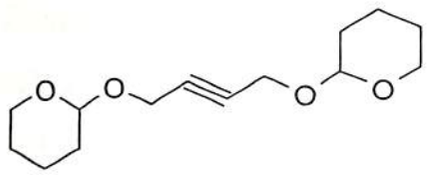
2-(2-Isopropyl-5-methyl-cyclohexyloxy)-tetrahydro-pyran (34f): ^{1}H NMR (400 MHz, $CDCl_3$): Obtained as a mixture of diastereomers. ^{13}C NMR (100 MHz, $CDCl_3$) (Peaks appearing due to both diastereomers): δ 16.0, 16.7, 20.1, 20.7, 21.6, 21.7, 22.7, 22.8, 23.4, 23.7, 25.6, 25.9, 26.00, 26.04, 31.6, 31.7, 31.8, 32.2, 34.8, 34.9, 40.5, 43.9, 48.5, 49.2, 62.7, 63.3, 74.4, 80.2, 94.6, 101.5. Anal. calcd for $C_{15}H_{28}O_2$: C, 74.95; H 11.74. Found C, 74.58, H, 12.02.



2-(1-Phenyl-ethoxy)-tetrahydro-pyran (35f): IR(KBr): 2945, 2873, 1455, 1383, 1214, 1122, 1030, 984, 702cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40-1.98 (m, 9H), 3.50 (m, 1H), 3.98 (m, 1H), 4.40 (m, 1H), 4.90 (m, 1H), 7.30 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 24.8, 25.98, 31.2, 63.0, 73.5, 96.3, 126.6, 127.1, 128.3, 143.8. Peaks appearing due to minor contamination or other diastereomers (19.7, 22.4, 25.95, 31.3, 62.2, 73.3, 96.4, 126.1, 127.5, 128.5, 143.9). Anal. calcd for $C_{13}H_{18}O_2$ C, 75.69; H 8.80. Found C, 75.78, H, 8.92.

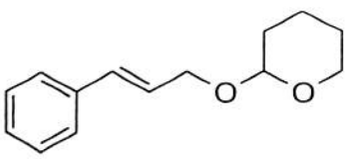


2-(1-Phenyl-propoxy)-tetrahydro-pyran (38f): IR (Neat): 3042, 2938, 2874, 1614, 1501, 1456, 1383, 1204, 1121, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): Obtained as a mixture of diastereomers δ 0.93 (t, 3H, J = 7.6 Hz), 1.41-1.88 (m, 8H), 3.48 (m, 1H), 3.95 (m, 1H), 4.40 (t, 1H, J = 4 Hz), 4.59 (t, 1H, J = 6 Hz), 7.2-7.4 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 20.0, 26.0, 31.2, 31.6, 62.7, 78.8, 95.5, 126.7, 127.2, 128.2, 142.5, Peaks appearing due to contamination of other diastereomers (10.2, 19.6, 25.9, 30.1, 31.1, 62.2, 80.1, 98.1, 127.0, 127.5, 128.4, 143.5). Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H 9.15. Found C, 76.59, H, 9.04.

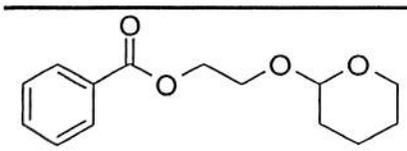


THP Ether of But-2-yne -1,4-diol (54f)

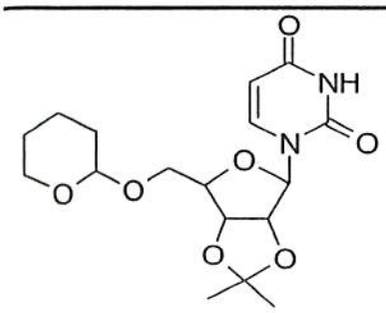
IR (Neat): 2940, 2873, 1445, 1399, 1352, 1271, 1209, 1127, 1025, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.46-1.79 (m, 12H), 3.43-3.48 (m, 2H), 3.73-3.79 (m, 2H), 4.24 (d, 4H, J = 15.3 Hz), 4.74 (t, 2H, J = 3.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 25.2, 30.1, 54.2, 61.8, 81.8, 96.7 .



2-(3-Phenyl-allyloxy)-tetrahydro-pyran (55f): IR (Neat): 3037, 2943, 2863, 1609, 1501, 1447, 1352, 1204, 1126, 1027, 969 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50-1.86 (m, 6H), 3.50 (m, 1H), 3.90 (m, 1H), 4.15 (m, 1H), 4.38 (m, 1H), 4.69 (m, 1H), 6.30 (m, 1H), 6.60 (d, 1H, J = 16 Hz), 7.15-7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 25.9, 31.0, 62.5, 67.9, 98.1, 126.2, 126.7, 127.8, 128.7, 132.5, 136.9.

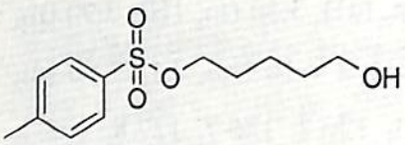


1-Phenyl-3-(tetrahydro-pyran-2-yloxy)-propan-1-one (61f): ^1H NMR (400 MHz, $CDCl_3$): δ 1.45-1.90 (brm, 6H), 3.51 (m, 1H), 3.80 (m, 1H), 3.88 (m, 1H), 4.05 (m, 1H), 4.51 (m, 2H), 4.71 (m, 1H), 7.44 (m, 2H), 7.55 (m, 1H), 8.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 25.8, 30.8, 62.3, 64.5, 65.5, 99.0, 128.5, 129.8, 130.3, 133.0, 166.6.

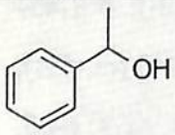


1-[2,2-Dimethyl-6-(tetrahydro-pyran-2-yloxymethyl)-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-1H-pyrimidine-2,4-dione (64f): IR (Neat): 3235, 3109, 2966, 2935, 2817, 1788, 1690, 1481, 1409, 1271, 1209, 1107, 1055, 989 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ 1.33 (s, 3H), 1.34 (s, 3 H), 1.49 (s, 3H), 1.51 (s, 3H), 1.47-1.90 (m, 12H), 3.49-3.57 (m, 4H), 3.65 (dd, 1H, J = 2.4 Hz, J = 11.2 Hz), 3.78-3.83 (m, 2H), 3.94 (dd, 1H, J = 3.2 Hz, J = 11.2 Hz), 4.01-4.05 (m, 2H), 4.37-4.42 (m, 1H), 4.57-4.59 (m, 1H), 4.73-4.74 (m, 1H), 4.81-4.82 (m, 1H), 4.87-4.88 (m, 1H), 4.89-4.95 (m, 1H), 5.64 (d, 1H, J = 8.0 Hz), 5.66 (d, 1H, J = 8.0 Hz), 5.88 (d, 1H, J = 2.4 Hz), 5.90 (d, 1H, J = 2.4 Hz), 7.61 (d, 1H, J = 8.0 Hz), 7.65 (d, 1H, J = 8.0 Hz), 8.58 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0,20.8, 25.5, 25.58, 25.6, 25.78, 25.8, 27.6, 30.8, 32.4, 63.0, 63.1, 64.2, 67.5, 67.8, 80.9, 81.2, 85.4, 85.7, 85.9, 92.9, 94.8, 99.2, 99.8, 102.0, 102.3, 114.2, 114.4, 140.8, 141.5, 150.5, 163.8.

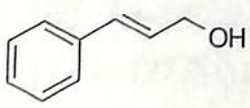
1C.4.3. Alcohols



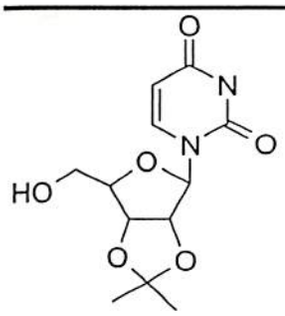
Toluene-4-sulphonic acid 5-hydroxy- pentyl ester (52): IR (Neat): 3401, 1598, 1475, 1373, 1189, 1071, 963 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.37-1.40 (m, 2H), 1.50-1.53 (m, 2H), 1.65-1.69 (m, 2H), 2.45 (s, 3H), 3.60 (t, 2H, J = 6.4 Hz), 3.91 (brs, 1H), 4.02 (t, 2H, J = 6.4 Hz), 7.34 (d, 2H, J = 7.6 Hz), 7.78 (d, 2H, J = 8.4 Hz).



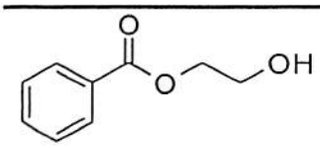
1-Phenyl ethanol (35): IR (Neat): 3396, 3042, 2981, 2940, 1609, 1501, 1460, 1373, 1301, 1204, 1081, 1025, 907, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (d, 3H, J = 6.0 Hz) 1.97 (s, 1H), 4.89 (q, 1H, J = 6.0 Hz), 7.24-7.35 (m, 5H).



Cinnamyl alcohol (55): IR (Neat): 3356, 3026, 2923, 2849, 1654, 1599, 1496, 1452, 1093, 1014, 970 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 1H), 4.25 (d, 2H, J = 7.1 Hz), 6.30 (m, 1H), 6.54 (d, 1H, J = 15.9 Hz), 7.24 (m, 5H. ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.69, 126.44, 127.67, 128.46, 128.57, 131.12, 136.63 .

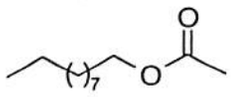


2',3'-Isopropylidene Uridine (64): IR (KBr): 3313, 3236, 1705, 1675, 1475, 1398, 1275, 1244, 1219, 1163, 1127, 1081, 860, 804, 768, 722 cm^{-1}. ^1H NMR (400MHz, DMSO-d_6): δ 1.38 (s, 3H), 1.60 (s, 3H), 3.83 (m, 1H), 3.95 (m, 1H), 4.31 (m, 1H), 5.07 (m, 1H), 5.58 (d, 1H), 5.75 (d, 1H), 7.39(d, 1H).

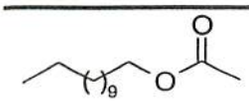


Benzoic acid 2-hydroxy-ethyl-ester (61): IR (KBr): 3418, 2953, 2882, 1718, 1601, 1452, 1373, 1316, 1277, 1177, 1123, 1070, 906, 711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 1H), 3.97 (t, 2H), 4.49 (t, 2H), 7.52 (m, 3H), 8.09 (m, 2H).

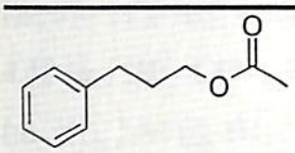
1C.4.4. Acetates (g)



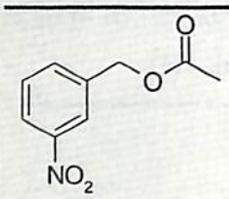
Acetic acid decyl ester (20g): IR (Neat): 2924, 2858, 1746, 1465, 1362, 1244, 1045, 743 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 0.88 (t, 3H, -$CH_2C\underline{H}_3$, J = 7.2 Hz)), 1.26 (m, 14H), 1.60 (m, 2H), 2.04 (s, 3H), 4.05 (t, 2H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 22.3, 24.1, 27.3, 29.9, 30.6, 30.7, 30.9, 33.3, 65.9, 172.2.



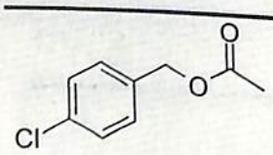
Acetic acid dodecyl ester (21g): IR (Neat): 2929, 2863, 1746, 1470, 1362, 1239, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $-CH_2C\underline{H}_3$, J = 6.9 Hz), 1.26 (m, 18H, $-OCH_2CH_2(C\underline{H}_2)_9-$), 1.62 (m, 2H, $-OCH_2C\underline{H}_2(CH_2)_9-$), 2.04 (s, 3H, $-COC\underline{H}_3$), 4.05 (t, 2H, $-OC\underline{H}_2CH_2(CH_2)_9-$, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.0, 22.7, 25.9, 28.6, 29.2, 29.3, 29.50, 29.54, 29.6, 31.9, 64.7, 171.3.



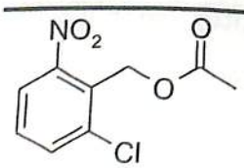
Acetic acid 3-phenyl-propyl ester (22g): IR (Neat): 3067, 3032, 2960, 2863, 1741, 1460, 1370, 1244, 1040, 748, 707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.95 (quint, 2H, $-CH_2C\underline{H}_2CH_2-$), 2.04 (s, 3H, $-COC\underline{H}_3$), 2.68 (t, 2H, $-C\underline{H}_2Ph$, J = 7.5 Hz), 4.08 (t, 2H, $-C\underline{H}_2O-J$ = 6.6 Hz), 7.19 (m, 3H, Ar$\underline{H}$), 7.30 (m, 2H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 30.1, 32.1, 63.8, 125.9, 128.3, 128.4, 141.1, 171.1.



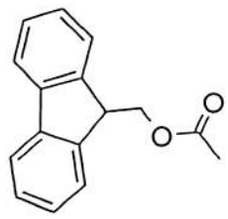
Acetic acid 3-nitro-benzyl ester (26g): IR (Neat): 3088, 2950, 2873, 1746, 1536, 1355, 1229, 1090, 1040, 815, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, $-COC\underline{H}_3$), 5.21 (s, 2H, $-OC\underline{H}_2Ph$), 7.56 (t, 1H, J = 7.9 Hz, Ar$\underline{H}$), 7.70 (d, 1H, Ar$\underline{H}$, J = 7.5 Hz), 8.23 (m, 2H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 64.7, 122.7, 123.0, 129.5, 133.8, 138.0, 148.2, 170.5.



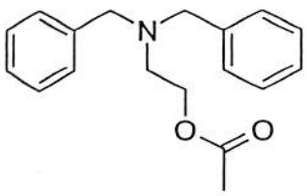
Acetic acid 4-chloro-benzyl ester (28g): IR (Neat): 3037, 2950, 2893, 1736, 1495, 1383, 1229, 1096, 1045, 1024, 815, 605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H, $-COC\underline{H}_3$), 5.06 (s, 2H, $-OC\underline{H}_2Ph$), 7.31 (m, 4H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 65.4, 128.7, 129.6, 134.1, 134.4, 170.7.



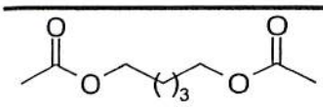
Acetic acid 2-chloro-6-nitro-benzyl ester (30g): IR (KBr): 3109, 3073, 2925, 2858, 1736, 1541, 1454, 1352, 1250, 1055, 942, 819, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, -COC$\underline{H}_3$), 5.26 (s, 2H, -OC$\underline{H}_2$Ph), 7.56 (d, 1H, Ar$\underline{H}$, J = 8.8 Hz), 8.13 (dd, 1H, Ar$\underline{H}$, J_1= 8.4 Hz, J_2 = 2.8 Hz), 8.29 (d, 1H, Ar$\underline{H}$, J = 2.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 62.8, 124.1, 124.2, 130.6, 135.9, 139.9, 146.8, 170.4.



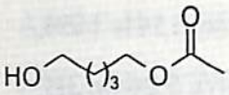
Acetic acid 9H-fluorene-9-ylmethyl ester (31g): IR (KBr): 3050, 2953, 2899, 1731, 1449, 1383, 1244, 1040, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H, -COC$\underline{H}_3$), 4.17 (t, 1H, -OCH$_2$C$\underline{H}$-, J = 7.2 Hz), 4.32 (d, 2H, -OC$\underline{H}_2$CH-, J = 7.2 Hz), 7.32 (m, 4H, Ar$\underline{H}$), 7.56 (d, 2H, Ar$\underline{H}$, J = 7.5 Hz), 7.72 (d, 2H, Ar$\underline{H}$, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 46.6, 66.3, 119.9, 124.9, 127.0, 127.7, 141.2, 143.7, 170.8.



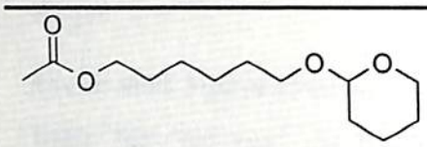
Acetic acid 2-dibenzylamino-ethyl ester (32g): IR (KBr): 2935, 2807, 1737, 1504, 1455, 1396, 1263, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H, -COC$\underline{H}_3$), 2.71 (t, 2H, -NC$\underline{H}_2$CH$_2$O-, J = 6.0 Hz), 3.64 (s, 4H, -N(C$\underline{H}_2$)$_2$Ph), 4.15 (t, 2H, -NCH$_2$C$\underline{H}_2$O-, J = 6 Hz), 7.20-7.38 (m, 10H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.0, 59.0, 62.8, 127.2, 128.4, 128.9, 139.5, 171.0.



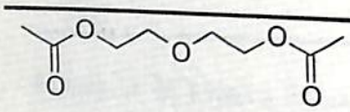
Acetic acid 5-acetoxy-pentyl ester (42g): IR (Neat): 2955, 2875, 1741, 1460, 1372, 1244, 1045, 612 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 1.44 (m, 2H, -CH$_2$C$\underline{H}_2$CH$_2$-), 1.66 (m, 4H, -OCH$_2$C$\underline{H}_2$CH$_2$-), 2.05 (s, 6H, -COC$\underline{H}_3$), 4.07 (t, 4H, -C$\underline{H}_2$OCOCH$_3$, J = 6.6 Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 22.3, 28.1, 64.1, 171.0.



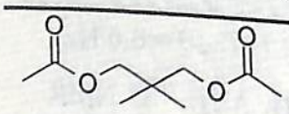
Acetic acid 5-hydroxy-pentyl ester (42'g): IR (Neat): 3421, 2945, 1741, 1460, 1368, 1245, 1062, 1040 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 2H, HO-$CH_2C\underline{H_2}$-), 1.61 (m, 4H, HO-$CH_2CH_2(C\underline{H_2})_2$-), 2.02 (s, 3H, -COC$\underline{H_3}$), 2.16 (brs, 1H, -O$\underline{H}$), 3.60 (t, 2H, HO-C$\underline{H_2}CH_2$-, J = 6.6 Hz), 4.01 (t, 2H, -C$\underline{H_2}$OCOCH_3, J = 6.6 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 22.1, 28.3, 32.2, 62.5, 64.4, 171.3.



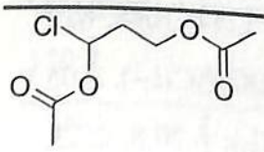
Acetic acid 6-(tetrahydro-pyran-2-yloxy)-hexyl ester (51g): IR (KBr): 2940, 2863, 1747, 1460, 1363, 1245, 1132, 1030, 984, 881 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 3H), 1.50-1.85 (m, 12H), 2.04 (s, 3H, -COC$\underline{H_3}$), 3.39 (m, 1H), 3.51 (m, 1H), 3.73 (m, 1H), 4.05 (t, 2H, J = 6.4 Hz), 4.57 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 21.4, 25.9, 26.0, 26.2, 26.3, 26.5, 28.8, 28.9, 30.0, 30.1, 31.2, 62.6, 62.7, 64.7, 64.8, 67.7, 67.8, 99.0, 99.1. 171.3. (additional peaks are due to diastereomeric peak).



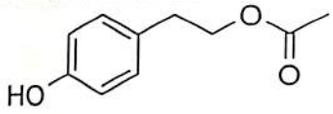
Acetic acid 2-(2-acetoxy-ethoxy)-ethyl ester (44g): IR (KBr): 2960, 2883, 1741, 1460, 1380, 1244, 1142, 1060, 968, 860, 609 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.09 (s, 6H), 3.70 (t, 4H, J = 4.8 Hz), 4.23 (t, 4H, J = 4.8 Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 63.3, 68.9, 170.8.



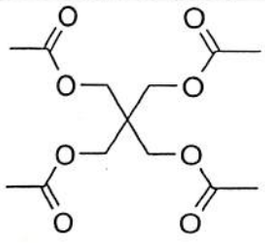
Acetic acid 3-acetoxy-2,2-dimethyl-propyl ester (45g): IR (KBr): 2975, 2899, 1741, 1480, 1383, 1245, 1050, 938 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 6H, -CH(C$\underline{H_3}$)$_2$), 2.03 (s, 6H, -COC$\underline{H_3}$), 3.85 (s, 4H, -(OC$\underline{H_2}$)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.7, 34.4, 69.1, 171.0.



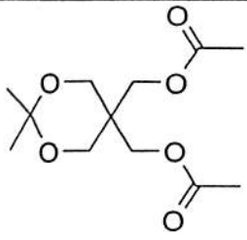
Acetic acid 3-acetoxy 3-chloro-propyl ester (47g): IR (KBr): 2966, 1741, 1650, 1383, 1235, 1050, 764, 610 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.11 (s, 3H), 3.66 (m, 2H), 4.23 (m, 1H), 4.34 (m, 1H), 5.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.2, 42.5, 62.7, 70.7, 170.0, 170.5.



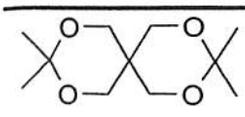
Acetic acid 2-(4-hydroxy-phenyl)-ethyl ester (49g): IR (KBr): 3395, 3027, 2960, 1726, 1623, 1521, 1460, 1367, 1260, 1045, 840 cm^{-1}.^1H NMR (400MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.83 (t, 2H, J = 6.8Hz), 4.22 (t, 2H, J =6.8 Hz), 6.78 (m, 2H, Ar*H*), 7.02 (m, 2H, Ar*H*), 7.34 (brs, 1H).



Tetraacetate of pentaerythritol (Acetic acid 3-acetoxy-2,2-bis-acetoxy methyl-propyl ester) (50g): IR (KBr): 2981, 2909, 1742, 1481, 1383, 1245, 1045, 917 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 12H, -COC*H*$_3$), 4.12 (s, 8H, (-OC*H*$_2$)$_4$).^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 41.9, 62.6, 170.5.

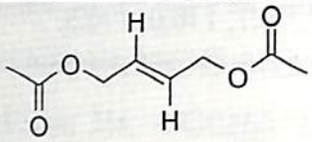


Acetic acid 5-acetoxymethyl-2, 2-dimethyl-[1,3]dioxan-5-ylmethyl ester (50'g): IR (KBr): 2991, 2955, 2889, 1747, 1460, 1385, 1240, 1096, 1053, 927, 840 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 6H), 2.06 (s, 6H, -COC*H*$_3$), 3.74 (s, 4H,-C*H*$_2$OCH(CH$_3$)$_2$), 4.10 (s, 4H, -C*H*$_2$OCOCH$_3$).^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 23.9, 37.4, 62.2, 63.5, 98.8, 170.8.

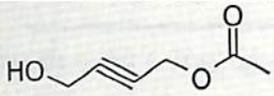


Diisopropylidine of pentaerythritol or 3,3,9,9-Tetramethyl-2,4,8,10-tetraoxaspiro[5.5]undecane (50''g) IR (KBr): 2996, 2945, 2873, 1455, 1388, 1265, 1199, 1096, 1061, 940, 846 cm^{-1}. ^1H NMR (400

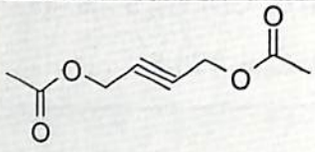
MHz, $CDCl_3$): δ 1.40 (s, 12H, -OC(C<u>H</u>$_3$)$_2$), 3.72 (s, 8H, -OC<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 33.0, 64.4, 98.8.



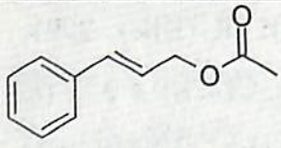
Acetic acid 4-acetoxy-but-2-enyl ester (43g): IR (KBr): 3047, 2950, 1751, 1444, 1372, 1239, 1040, 983 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 6H, -COC<u>H</u>$_3$), 4.61 (m, 4H, -C<u>H</u>$_2$OCO-), 5.69 (m, 2H, -OCH$_2$C<u>H</u>=C<u>H</u>CH$_2$O-). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 59.8, 127.9, 170.6.



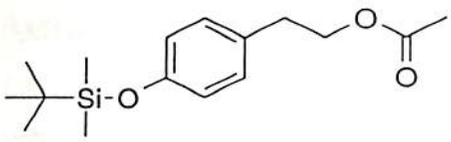
Acetic acid 4-hydroxy-but-2-enyl ester (53'g): IR (KBr): 3437, 2940, 2873, 1742, 1445, 1380, 1250, 1030 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H, -COC<u>H</u>$_3$), 2.57 (brs, 1H, -OH), 4.19 (d, 1H, -CC<u>H</u>(H)OH, J = 6.56 Hz), 4.61 (d, 1H, -CCH(<u>H</u>)OH, J = 7.08 Hz), 5.56 (m, 1H, -C<u>H</u>(H)OCOCH$_3$), 5.79 (m, 1H,- CH(<u>H</u>)OCOCH$_3$).^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 58.2, 60.1, 125.3, 133.3, 171.2.



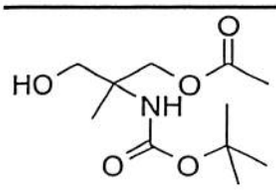
Acetic acid 4-acetoxy-but-2-ynyl ester (54g): IR (KBr): 2939, 1751, 1444, 1383, 1219, 1157, 1034, 970, 922, 830, 609 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6H, -COC<u>H</u>$_3$), 4.71 (s, 4H, -C<u>H</u>$_2$OCOCH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 52.4, 80.9, 170.2.



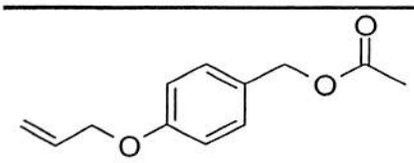
Acetic acid 3-phenyl-allyl ester (55g): IR (KBr): 3032, 2950, 1741, 1500, 1455, 1370, 1234, 1029, 978, 750, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H, -COC<u>H</u>$_3$), 4.72 (m, 2H, -C<u>H</u>$_2$OCOCH$_3$), 6.27 (m, 1H, PhC<u>H</u>=CH-), 6.63 (d, 1H, -OCH$_2$C<u>H</u>=CH- J = 16.0 Hz), 7.20-7.40 (m, 5H, Ar<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 65.4, 123.4, 126.8, 128.3, 128.8, 134.3, 136.4, 170.8.



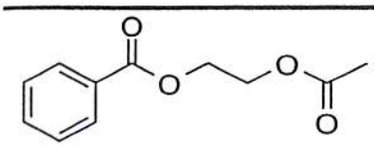
Acetic acid 2-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-ethyl ester (58g): IR (KBr): 2960, 2868, 1751, 1613, 1521, 1470, 1367, 1270, 1045, 922, 840, 788, 701 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H, -Si($C\underline{H}_3$)$_2$-), 1.0 (s, 9H, -Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 2.08 (s, 3H, -COC$\underline{H}_3$), 2.86 (t, 2H, -OCH$_2$C$\underline{H}_2$-, J = 7.2 Hz), 4.29 (t, 2H, -OC$\underline{H}_2$CH$_2$-, J = 7.2 Hz), 6.80 (d, 2H, Ar$\underline{H}$, J = 8.4 Hz), 7.10 (d, 2H, Ar$\underline{H}$, J = 8.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ -3.9, 18.6, 21.3, 26.1, 34.7, 65.4, 120.2, 129.9, 130.5, 154.4, 171.0.



Acetic acid 2-tert-butoxycarbonylamino-3-hydroxy-2-methyl-propyl ester (57g): IR (KBr): 3416, 2981, 2940, 1747, 1716, 1511, 1370, 1245, 1168, 1050, 871 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H, -CHC$\underline{H}_3$), 1.43 (s, 9H, -OC($C\underline{H}_3$)$_3$), 2.10 (s, 3H, -COC$\underline{H}_3$), 3.61 (q, 2H, J = 11.2 Hz), 4.21 (m, 2H), 3.57 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 21.3, 28.7, 56.5, 66.6, 67.2, 80.4, 155.8, 171.3.

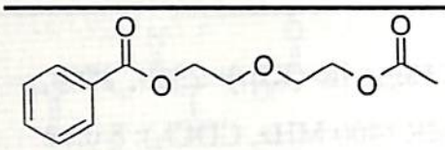


Acetic acid 4-allyloxy-benzyl ester (56g): IR (KBr): 3083, 2960, 2868, 1743, 1620, 1516, 1460, 1424, 1370, 1239, 1040, 830 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H, -COC$\underline{H}_3$), 4.52 (d, 2H, -OC$\underline{H}_2$CH=CH$_2$, J = 5.1 Hz), 5.03 (s, 2H, -OC$\underline{H}_2$Ph,), 5.28 (dd, 1H, -CH=C$\underline{H}$(H), J_1 = 10.5 Hz, J_2 = 1.2 Hz), 5.40 (dd, 1H, -CH=CH($\underline{H}$), J_1 = 17.2 Hz, J_2 = 1.2 Hz), 6.03 (m, 1H, -C$\underline{H}$=CH(H),), 6.89 (d, 2H, Ar$\underline{H}$, J = 8.7 Hz), 7.28 (d, 2H, Ar$\underline{H}$, J = 8.7 Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 66.0, 68.7, 114.7, 117.7, 128.1, 130.0, 133.0, 158.6, 170.9.

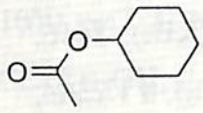


Benzoic acid 2-acetoxy-ethyl ester (61g): IR (KBr): 3078, 3032, 2945, 2878, 1746, 1618, 1516, 1465, 1383, 1234, 1183, 1034, 937, 830 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, -COC$\underline{H}_3$), 4.39 (m,

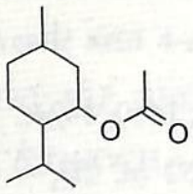
2H), 4.48 (m, 2H), 7.41 (m, 2H, Ar*H*), 7.54 (m, 1H, Ar*H*), 8.01 (m, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 62.1, 62.6, 128.3, 129.6, 132.2, 133.1, 166.3, 170.8.



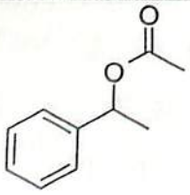
Benzoic acid 2-(2-acetoxy-ethoxy)-ethyl ester (62g): IR (KBr): 3075, 2960, 2884, 1737, 1603, 1455, 1378, 1286, 1240, 1117, 1066, 963, 851, 728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 3H, -COC*H*$_3$), 3.65 (m, 2H), 3.74 (m, 2H), 4.14 (m, 2H), 4.39 (m, 2H), 7.34 (m, 2H, Ar*H*), 7.46 (m, 1H, Ar*H*), 7.96 (m, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 63.2, 63.7, 68.83, 68.84, 128.1, 129.4, 129.8, 132.8, 166.2, 170.7.



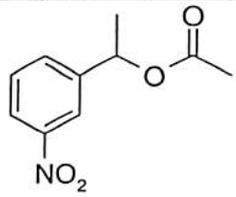
Acetic acid cyclohexyl ester (33g): IR (KBr): 2939, 2873, 1741, 1454, 1367, 1250, 1050, 1024 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.22-1.42 (m, 6H), 1.55 (m, 1H), 1.72-1.96 (m, 4H), 2.03 (s, 3H).^{13} C NMR (75 MHz, $CDCl_3$): δ 20.6, 23.8, 25.3, 31.6, 72.7, 170.7.



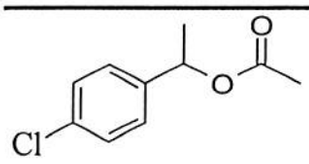
Acetic acid 2-isopropyl-5-methyl-cyclohexyl ester (34g): IR (KBr): 2955, 2873, 1741, 1460, 1375, 1244, 1029, 988, 906 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.76 (d, 3H, J = 6.9 Hz), 0.88-1.08 (m, 9H), 1.31-1.50 (m, 2H), 1.66 (m, 2H), 1.86 (m, 1H), 1.98 (m, 1H), 2.03 (s, 3H), 4.67 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 20.7, 21.3, 22.0, 23.4, 26.2, 31.3, 34.2, 40.9, 46.9, 74.1, 170.7.



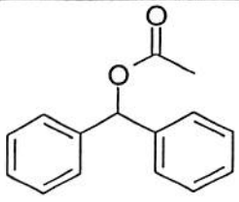
Acetic acid-1-phenyl-ethyl ester (35g): IR (KBr): 3040, 2980, 2934, 1750, 1458, 1375, 1244, 1070, 1034, 955, 768, 702 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 1.53 (d, 3H, J = 6.6 Hz), 2.07 (s, 3H), 5.87 (q, 1H, J = 6.6) 7.34 (m, 5H, Ar*H*). ^{13} C NMR (75 MHz, $CDCl_3$): δ 21.3, 22.2, 72.3, 126.0, 127.8, 128.4, 141.6, 170.3.



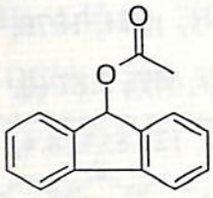
Acetic acid 1-(3-nitro-phenyl)-ethyl ester (36g): IR (KBr): 3083, 2986, 2934, 1741, 1536, 1449, 1357, 1244, 1070, 1040, 815, 743, 686 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.58 (d, 3H, -OCHC*H*$_3$), J = 6.9 Hz), 2.12 (s, 3H, -COC*H*$_3$), 5.94 (q, 1H, J = 6.9 Hz, -OC*H*CH_3), 7.54 (t, 1H, Ar*H*, J = 7.8 Hz), 7.68 (d, 1H, Ar*H*, J = 7.8 Hz), 8.14 (d, 1H, Ar*H*, J = 8.1 Hz), 8.22 (s, 1H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 22.1, 71.1, 120.9, 122.7, 129.5, 132.2, 143.8, 148.3, 170.0.



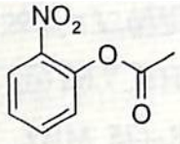
Acetic acid 1-(4-chloro-phenyl)-ethyl ester (37g): IR (KBr): 2986, 2939, 1741, 1500, 1375, 1239, 1071, 1020, 950, 830, 543 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (d, 3H, -OCHC*H*$_3$, J = 6.6 Hz), 2.06 (s, 3H, -COC*H*$_3$), 5.83 (q, 1H, -OC*H*CH_3, J = 6.6 Hz), 7.30 (m, 4H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 22.1, 71.5, 127.5, 128.6, 133.5, 140.2, 170.2.



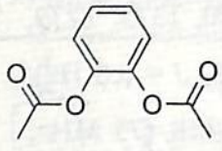
Acetic acid benzhydryl ester (39g): IR (KBr): 3070, 3037, 2991, 2945, 2888, 1730, 1700, 1603, 1465, 1383, 1224, 1170, 1060, 891, 762, 702 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 2.07 (s, 3H), 6.80 (s, 1H), 7.25 (m, 10H, Ar*H*).^{13}C NMR (100MHz, $CDCl_3$): δ 21.2, 127.0, 127.8, 128.4, 140.1, 169.9.



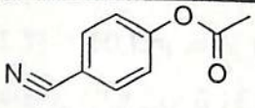
Acetic acid 9H-fluoren-9-yl ester (40g):IR (KBr): 3057, 2929, 1731, 1613, 1449, 1378, 1321, 1234, 1034, 932, 855, 758, 548 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, -COC$\underline{H}_3$), 6.74 (s, 1H, -OC$\underline{H}$-), 7.24 (t, 2H, Ar$\underline{H}$, *J* = 7.5 Hz), 7.35 (t, 2H, Ar$\underline{H}$, *J* = 7.3 Hz), 7.50 (d, 2H, Ar$\underline{H}$, *J* = 7.5 Hz), 7.60 (d, 2H, Ar$\underline{H}$, *J* = 7.5 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 75.0, 119.9, 125.8, 127.7, 129.4, 140.9, 141.9, 171.7.



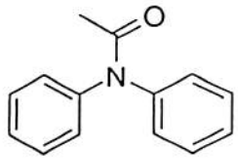
Acetic acid 2-nitrophenyl ester (66g): IR (KBr): 1777, 1608, 1531, 1480, 1352, 1193, 1015, 917, 705 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.38 (s, 3H), 7.24 (m, 1H, Ar$\underline{H}$), 7.40 (m, 1H, Ar$\underline{H}$), 7.66 (m, 1H, Ar$\underline{H}$), 8.09 (m, 1H, Ar$\underline{H}$).^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 125.2, 125.8, 126.6, 134.7, 141.7, 144.1, 168.6.



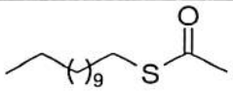
Acetic acid 2-acetoxy phenyl ester (67g): IR (KBr): 1767, 1500, 1444, 1380, 1255, 1214, 1180, 1105, 1024, 925, 835, 775, 605 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.27 (s, 6H), 7.14-7.26 (m, 4H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 123.3, 126.5, 142.0, 168.2.



Acetic acid 4-cyano-phenyl ester (69g): IR (KBr): 2233, 1775, 1603, 1506, 1376, 1200, 1168, 1014, 915, 855, 553 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, -COC$\underline{H}_3$), 7.23 (d, 2H, Ar$\underline{H}$, *J* = 6.9 Hz), 7.68 (d, 2H, Ar$\underline{H}$, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 109.5, 118.1, 122.6, 133.5, 153.8, 168.4.

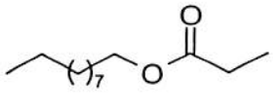


N,N-Diphenyl-acetamide (93g): IR (KBr): 3472, 3067, 1716, 1675, 1598, 1495, 1383, 1306, 1080, 1040, 760, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H, -COC$\underline{H}_3$), 7.28 (m, 10H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8, 126.4, 127.7, 128.3, 129.1, 129.6, 133.0, 170.5.

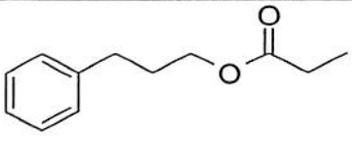


Thioacetic acid S-dodecyl ester (94g): IR (KBr): 2924, 2852, 1700, 1465, 1362, 1137, 963, 732, 630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, -$SCH_2(CH_2)_{10}C\underline{H}_3$, J = 7.2 Hz), 1.25 (brm, 18H, -$SCH_2CH_2(C\underline{H}_2)_9C\underline{H}_3$), 1.56 (m, 2H, -$SCH_2C\underline{H}_2(C\underline{H}_2)_9C\underline{H}_3$), 2.32 (s, 3H, -COC$\underline{H}_3$), 2.86 (t, 2H, -$SC\underline{H}_2CH_2(CH_2)_9C\underline{H}_3$ J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 23.1, 29.2, 29.6, 29.7, 29.9, 30.0, 30.05, 31.0, 32.3, 195.9.

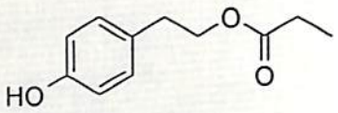
1C.4.5. Propionates (h):



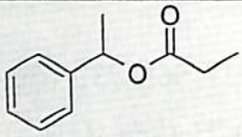
Propionic acid decyl ester (20h): IR (KBr): 2929, 2858, 1741, 1470, 1352, 1188, 1086, 809 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, 3H, -$OCH_2(CH_2)_8C\underline{H}_3$, J = 6.8 Hz), 1.07 (t, 3H, -$COCH_2C\underline{H}_3$, J = 7.6 Hz), 1.19 (brm, 14H, -$CH_2(C\underline{H}_2)_7CH_3$), 1.53 (m, 2H, -$OCH_2C\underline{H}_2$-, J = 6.8 Hz), 2.26 (q, 2H, -$COC\underline{H}_2CH_3$, J = 7.6 Hz), 3.99 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 6.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 9.1, 14.0, 22.6, 25.8, 27.1, 27.6, 28.6, 29.20, 29.24, 29.5, 31.8, 64.4, 174.6.



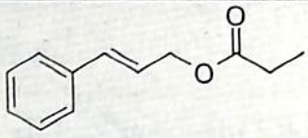
Propionic acid 3-phenyl-propyl ester (22h): IR (KBr): 3027, 2960, 1747, 1460, 1358, 1194, 1086, 1025, 748, 707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 3H, -$COCH_2C\underline{H}_3$, J = 7.6 Hz), 1.95 (m, 2H, -$OCH_2C\underline{H}_2CH_2Ph$), 2.33 (q, 2H, -$COC\underline{H}_2CH_3$, J = 7.6 Hz), 2.68 (t, 2H, -$OCH_2CH_2C\underline{H}_2Ph$, J = 8 Hz), 4.09 (t, 2H, -$OC\underline{H}_2CH_2CH_2Ph$, J = 6.4Hz), 7.18 (m, 3H, Ar$\underline{H}$), 7.27 (m, 2H, Ar$\underline{H}$).^{13}C NMR (100 MHz, $CDCl_3$): δ 9.6, 28.0, 30.7, 32.6, 63.9, 126.2, 128.59, 128.62, 141.4, 174.5.



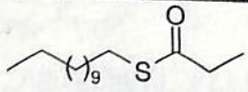
Propionic acid 2-(4-hydroxy-phenyl)-ethyl ester (49h): IR (KBr): 3406, 2986, 2945, 1716, 1614, 1516, 1470, 1352, 1219, 1086, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, 3H, -$COCH_2CH_3$, J = 7.6 Hz), 2.32 (q, 2H, -$COCH_2CH_3$, J = 7.6 Hz), 2.85 (t, 2H, -OCH_2CH_2Ph, J = 7.2 Hz), 4.24 (t, 2H, -OCH_2CH_2Ph, J = 7.2 Hz), 6.77 (m, 2H), 7.05 (d, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.6, 28.1, 34.6, 65.8, 115.7, 129.5, 130.2, 154.8, 175.6.



Propionic acid 1-phenyl-ethyl ester (35h): IR (KBr): 3037, 2991, 2939, 1742, 1460, 1367, 1189, 1075, 763, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, 3H, -$COCH_2CH_3$, J = 7.6 Hz), 1.52 (d, 3H, $ArCHCH_3$, J = 6.4 Hz), 2.34 (m, 2H, -$COCH_2CH_3$), 5.88 (q, 1H, $ArCHCH_3$, J = 6.4 Hz), 7.33 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.6, 22.7, 28.3, 72.4, 126.2, 127.9, 128.6, 142.0, 173.8.

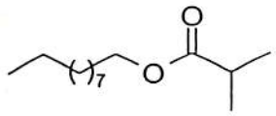


Propionic acid 3-phenyl-allyl ester (55h): IR (KBr): 3027, 2986, 2945, 1741, 1465, 1362, 1183, 1075, 973, 742, 696 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, 3H, -$COCH_2CH_3$, J = 7.2 Hz), 2.37 (q, 2H, -$COCH_2CH_3$, J = 7.6 Hz), 4.72 (dd, 2H, -OCH_2CH, J_1 = 6.8 Hz, J_2 = 1.2 Hz), 6.28 (m, 1H, -OCH_2CH=CH-), 6.64 (d, 1H, -OCH_2CH=CH-, J = 15.6 Hz), 7.24 (m, 1H, ArH), 7.30 (m, 2H, ArH), 7.36 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.6, 28.0, 65.3, 123.5, 126.8, 128.2, 128.8, 134.2, 136.4, 174.3.

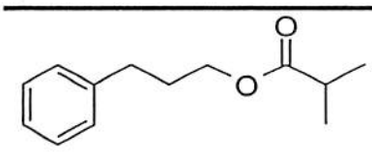


Thiopropionic acid S-dodecyl ester (94h): IR (KBr): 2935, 2863, 1701, 1470, 1107, 1030, 943 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, -CH_2CH_3, J = 7.0 Hz), 1.17 (t, 3H, -$COCH_2CH_3$, J = 7.6Hz), 1.25 (brs, 18H, $CH_3(CH_2)_9CH_2CH_2S$-), 1.58 (m, 2H, $CH_3(CH_2)_9CH_2CH_2S$-), 2.56 (q, 2H, -$COCH_2CH_3$, J = 7.6 Hz), 2.86 (t, 2H, $CH_3(CH_2)_9CH_2CH_2S$-, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 14.6, 23.1, 29.2, 29.3, 29.5, 29.8, 29.9, 30.0, 30.02, 30.05, 32.3, 37.8.

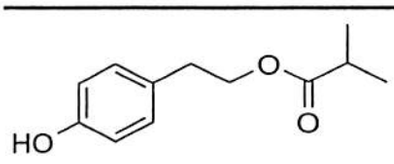
1C.4.6. Isobutyrates (i):



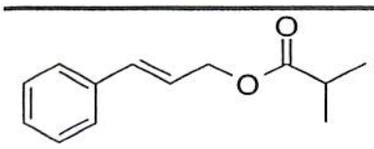
Isobutyric acid decyl ester (20i): IR (KBr): 2934, 2858, 1736, 1470, 1393, 1342, 1265, 1198, 1163, 1122, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, $-CH_2CH_2C\underline{H}_3$, J = 7.2 Hz), 1.16 (d, 6H, $-COCH(C\underline{H}_3)_2$, J = 6.8 Hz), 1.26 (brm, 14 H, $CH_3(C\underline{H}_2)_7CH_2$-), 1.62 (m, 2H, $-OCH_2C\underline{H}_2$-,), 2.53 (septet, 1H, $-COC\underline{H}(CH_3)_2$, J = 7.2 Hz), 4.05 (t, 2H, $-OC\underline{H}_2CH_2$-, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 19.4, 23.1, 26.3, 27.5, 29.0, 29.6, 29.7, 29.9, 32.3, 34.4, 64.7, 177.2.



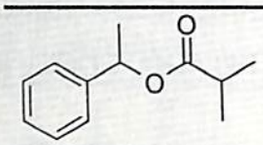
Isobutyric acid 3-phenyl-propyl ester (22i): IR (KBr): 3035, 2976, 1731, 1603, 1460, 1388, 1337, 1260, 1199, 1153, 1086, 1025, 743, 702 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, 6H, $-COCH(C\underline{H}_3)_2$, J = 7.2 Hz), 1.96 (m, 2H, $-OCH_2C\underline{H}_2CH_2Ph$), 2.54 (septet, 1H, $-COC\underline{H}(CH_3)_2$, J = 6.4 Hz), 2.68 (t, 2H, $-OCH_2C\underline{H}_2CH_2Ph$, J = 8.4 Hz), 4.08 (t, 2H, $-OCH_2C\underline{H}_2CH_2Ph$, J = 6.4 Hz), 7.14-7.30 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 30.7, 32.6, 34.5, 63.9, 126.2, 128.60, 128.63, 141.4, 177.2.



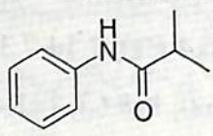
Isobutyric acid 2-(4-hydroxy-phenyl)-ethyl ester (49i): IR (KBr): 1342, 2981, 2878, 1742, 1711, 1624, 1516, 1475, 1352, 1271, 1163, 994, 830, 558 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, 6H, $-COCH(C\underline{H}_3)_2$, J = 7.2 Hz), 2.53 (septet, 1H, $-COC\underline{H}(CH_3)_2$, J = 7.2 Hz), 2.85 (t, 2H, $-OCH_2C\underline{H}_2Ph$, J = 7.2 Hz), 4.24 (t, 2H, $-OC\underline{H}_2CH_2Ph$, J = 7.2 Hz), 6.76 (d, 2H, Ar$\underline{H}$, J = 8.4 Hz), 7.06 (d, 2H, Ar$\underline{H}$, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 34.6, 65.7, 115.6, 129.5, 130.2, 154.8, 178.1.



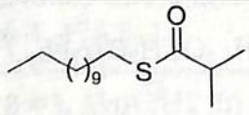
Isobutyric acid 3-phenyl-allyl-ester (55i): IR (KBr): 3032, 2976, 2934, 2878, 1737, 1401, 1271, 1199, 1168, 974, 753, 697 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, 6H, -COCH($C\underline{H}_3$)$_2$, J = 7.2 Hz), 2.60 (m, 1H, -COC$\underline{H}$(CH_3)$_2$,), 4.73 (dd, 2H, -OC$\underline{H}_2$CH, J_1 = 6.4 Hz, J_2 = 1.6 Hz), 6.29 (m, 1H, -$OCH_2C\underline{H}$=CH-), 6.65 (d, 1H, -OCH_2CH=C$\underline{H}$-, J = 16 Hz), 7.25 (m, 1H, Ar$\underline{H}$), 7.33 (m, 2H, Ar$\underline{H}$), 7.39 (m, 2H, Ar$\underline{H}$).^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 34.5, 65.2, 123.6, 126.8, 128.2, 128.8, 134.1, 136.4, 177.0.



Isobutyric acid 1-phenyl-ethyl ester (35i): IR (KBr): 3032, 2981, 2940, 2848, 1742, 1460, 1388, 1260, 1209, 1158, 1071, 769, 707 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (m, 6H, -COCH($C\underline{H}_3$)$_2$,), 1.51 (d, 3H, ArCHC$\underline{H}_3$, J = 6.8 Hz), 2.56 (septet, 1H, -COC$\underline{H}$(CH_3)$_2$, J = 6.8 Hz), 5.87 (q, 1H, ArC$\underline{H}CH_3$, J = 6.8 Hz), 7.32 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 22.7, 34.6, 72.2, 126.1, 127.9, 128.5, 142.2, 176.3.

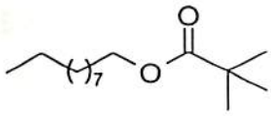


N-Phenyl-isobutyramide (78i): IR (KBr): 3302, 3268, 3206, 3145, 2976, 2935, 2873, 1670, 1608, 1547, 1506, 1450, 1393, 1312, 1250, 1214, 1107, 948, 764 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, -COCH ($C\underline{H}_3$)$_2$, J = 6.8 Hz), 2.51 (m, 1H, -COC$\underline{H}$(CH_3)$_2$), 7.10 (t, 1H, Ar$\underline{H}$, J = 7.2 Hz), 7.30 (t, 2H, Ar$\underline{H}$, J = 7.6 Hz), 7.52 (d, 2H, Ar$\underline{H}$, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 36.9, 120.2, 124.3, 129.1, 138.3, 175.7.



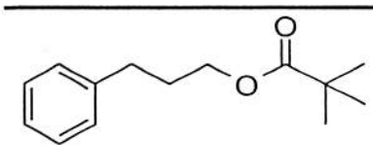
Thioisobutyric acid S-dedecyl ester (94i): IR (KBr): 2930, 2858, 1700, 1470, 1388, 1096, 984, 866, 712 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, -$CH_2C\underline{H}_3$, J = 6.8 Hz), 1.18 (d, 6H, -COCH($C\underline{H}_3$)$_2$, J = 7.2Hz), 1.26 (brs, 18H, $CH_3(C\underline{H}_2)_9CH_2CH_2$S-), 1.55 (m, 2H, $CH_3(CH_2)_9C\underline{H}_2CH_2$S-), 2.72 (septet, 1H, -COC$\underline{H}$(CH_3)$_2$, J = 7.2 Hz), 2.84 (t, 2H, $CH_3(CH_2)_9CH_2C\underline{H}_2$S-, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 19.8, 23.1, 28.9, 29.3, 29.5, 29.8, 29.9, 30.0, 30.1, 32.3, 43.5, 204.3.

1C.4.7. Pivalates (j)



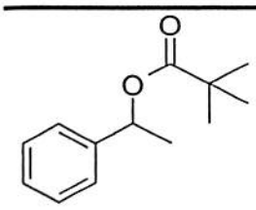
2,2-Dimethyl-propionic acid decyl ester (20j):

IR (KBr): 2935, 2863, 1737, 1465, 1372, 1291, 1163, 1045 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, -$CH_2CH_2C\underline{H}_3$, J = 7.2 Hz), 1.19 (s, 9H, -$COC(C\underline{H}_3)_3$), 1.26 (brm, 14H, $CH_3(C\underline{H}_2)_7CH_2$-), 1.60 (m, 2H, -$OCH_2C\underline{H}_2$-,), 4.04 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 23.1, 26.3, 27.6, 29.0, 29.6, 29.7, 29.9, 32.3, 39.1, 64.8, 178.6.

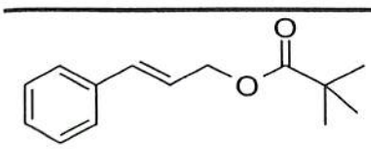


2,2-Dimethyl-propionic acid 3-phenyl-propyl ester (22j):

IR (KBr): 3070, 3032, 2971, 2873, 1737, 1486, 1460, 1286, 1153, 1040, 750, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H, -$COC(C\underline{H}_3)_3$), 1.94 (m, 2H, -$OCH_2C\underline{H}_2CH_2Ph$), 2.68 (t, 2H, -$OCH_2C\underline{H}_2CH_2Ph$, J = 8 Hz), 4.06 (t, 2H, -$OCH_2C\underline{H}_2CH_2Ph$, J = 6.4 Hz), 7.14-7.29 (m, 5H, Ar$\underline{H}$,). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 30.7, 32.6, 39.2, 63.9, 126.2, 128.60, 128.63, 141.4, 178.6.

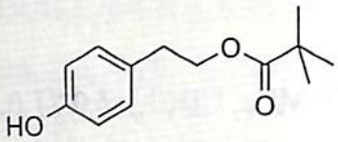


2,2-Dimethyl-propionic acid 1-phenyl-ethyl ester (35j): IR (KBr): 3039, 2986, 2878, 1731, 1460, 1373, 1286, 1163, 1066, 769, 707 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H, -$COC(C\underline{H}_3)_3$), 1.50 (d, 3H, $ArCHC\underline{H}_3$, J = 6.8 Hz), 5.84 (q, 1H, $ArC\underline{H}CH_3$, J = 6. 4 Hz), 7.32 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 27.6, 39.1, 72.3, 125.9, 127.8, 128.6, 142.3, 177.7.



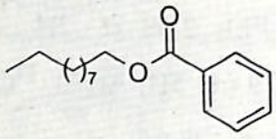
2,2-Dimethyl-propionic acid 3-phenyl-allyl ester (55j): IR (KBr): 3027, 2971, 2873, 1731, 1455, 1372, 1276, 1153, 968, 753, 702 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ δ 1.23 (s, 9H, -$COC(C\underline{H}_3)_3$), 4.71

(d, 2H, -OC$\underline{H}_2$CH, J = 6.0 Hz), 6.29 (m, 1H, -OCH$_2$C$\underline{H}$=CH-), 6.63 (d, 1H, -OCH$_2$CH=C$\underline{H}$-, J = 15.6 Hz), 7.21-7.40 (m, 5H, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ δ 27.7, 39.2, 65.3, 123.8, 126.8, 128.2, 128.8, 133.8, 136.5, 178.4.

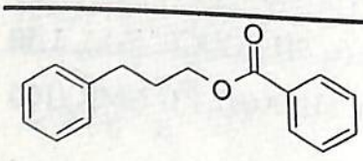


2,2-Dimethyl-propionic acid 2-(4-hydroxy-phenyl)-ethyl ester (49j): IR (KBr): 3411, 2976, 1731, 1706, 1624, 1521, 1455, 1363, 1301, 1168, 1045, 830 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H, -COC(C$\underline{H}_3$)$_3$), 2.86 (t, 2H, -OCH$_2$C$\underline{H}_2$Ph, J = 7.0), 4.22 (t, 2H, -OC$\underline{H}_2$CH$_2$Ph, J = 7.0 Hz), 6.76 (d, 2H, Ar$\underline{H}$, J = 8.4 Hz), 7.07 (d, 2H, Ar$\underline{H}$, J = 8.8Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 34.6, 39.1, 65.4, 65.5, 115.5, 130.1, 130.2, 154.5.

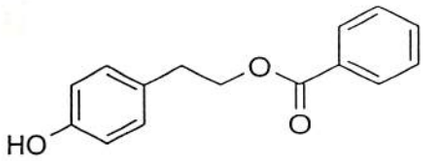
1C.4.8. Benzoates (k)



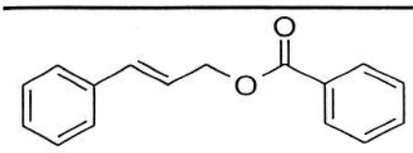
Benzoic acid decyl ester (20k): IR (KBr): 2935, 2858, 1726, 1603, 1470, 1388, 1285, 1178, 1116, 717 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, -CH$_2$CH$_2$C$\underline{H}_3$, J = 7.2 Hz), 1.27-1.44 (m, 14H, CH$_3$(C$\underline{H}_2$)$_7$CH$_2$-), 1.76 (m, 2H, -OCH$_2$C$\underline{H}_2$-), 4.31 (t, 2H, -OC$\underline{H}_2$CH$_2$-, J = 6.8 Hz), 7.43 (m, 2H, Ar$\underline{H}$), 7.54 (m, 1H, Ar$\underline{H}$), 8.04 (d, 2H, Ar$\underline{H}$, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 23.1, 26.5, 29.2, 29.7, 29.9, 32.3, 65.4, 128.5, 129.7, 130.7, 132.9, 166.7.



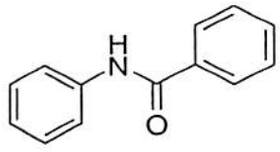
Benzoic acid 3-phenyl-propyl ester (22k): IR (KBr): 3432, 3080, 3032, 2945, 1721, 1609, 1465, 1388, 1276, 1112, 712 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (m, 2H, -OCH$_2$C$\underline{H}_2$CH$_2$Ph), 2.78 (t, 2H, -OCH$_2$CH$_2$C$\underline{H}_2$Ph, J = 8 Hz), 4.33 (t, 2H, -OC$\underline{H}_2$CH$_2$CH$_2$Ph, J = 6 Hz), 7.15-7.31 (m, 6H, Ar$\underline{H}$), 7.43 (m, 2H, Ar$\underline{H}$), 7.54 (m, 1H, Ar$\underline{H}$), 8.02 (d, 1H, Ar$\underline{H}$, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.8, 32.8, 64.7, 126.3, 128.69, 128.72, 128.79, 128.85, 129.8, 133.1, 141.4, 166.7.



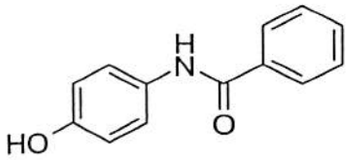
Benzoic acid 2-(4-hydroxy-phenyl)-ethyl ester (49k): IR (KBr): 3324, 2950, 2879, 1731, 1603, 1516, 1455, 1383, 1209, 1112, 1061, 880, 825, 717, 564, 523 $cm.^{-1}$ ^1H NMR (400 MHz, $CDCl_3$): δ 3.00 (t, 2H, -$OCH_2C\underline{H}_2Ph$, J = 6.8 Hz), 4.48 (t, 2H, -$OC\underline{H}_2CH_2Ph$, J = 6.8 Hz), 5.00 (brs, 1H, Ar$O\underline{H}$), 6.78 (d, 2H, Ar$\underline{H}$, J = 8.0 Hz), 7.14 (d, 2H, Ar$\underline{H}$, J = 8.0 Hz), 7.42 (t, 2H, Ar$\underline{H}$, J = 7.6 Hz), 7.55 (m, 1H, Ar$\underline{H}$), 8.00 (d, 2H, Ar$\underline{H}$, J = 7.6 Hz). ^{13}C NMR (100 MHz $CDCl_3$): δ 34.7, 66.2, 115.6, 128.6, 129.8, 129.9, 130.2, 130.3, 133.2, 154.6, 166.9.



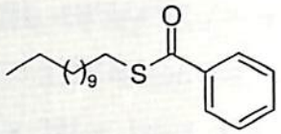
Benzoic acid 3-phenyl-allyl ester (55k): IR (KBr): 3062, 3032, 2935, 2858, 1598, 1501, 1460, 1388, 1281, 1116, 963, 712 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 4.98 (dd, 2H, J_1= 6.8Hz, J_2 = 1.2 Hz), 6.42 (m, 1H), 6.74 (d, 1H, J = 16.0 Hz), 7.23-7.57 (m, 8H), 8.08 (m, 2H).



N-Phenyl-benzamide (77k): IR (KBr): 3350, 3048, 1660, 1605, 1532, 1440, 1327 cm^{-1}. ^1H NMR (300MHz, DMSO-d6): δ 7.12 (m, 1H), 7.34 (m, 2H), 7.55 (m, 3H), 7.83 (d, 2H), 7.98 (d, 2H), 10.23 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ 120.4, 123.5, 127.6, 128.0, 128.3, 131.2, 135.1, 139.1, 165.6.



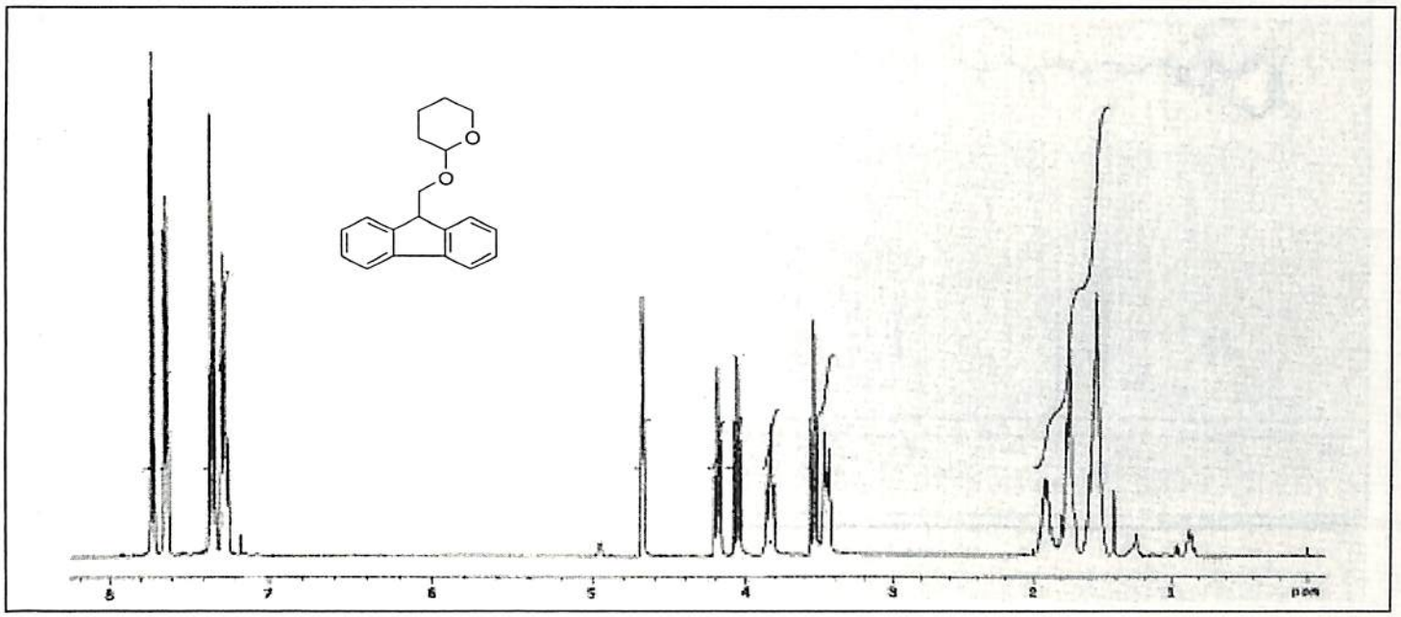
N- (4-Hydroxy-phenyl)-benzamide (88k): IR (KBr): 3334, 1650, 1545, 1511, 1440, 1325, 1235, 825, 707 cm^{-1}. ^1H NMR (400MHz, DMSO-d6): δ 6.75 (m, 2H, Ar$\underline{H}$), 7.38-7.61(m, 6H, Ar$\underline{H}$), 7.93 (m, 2H, Ar$\underline{H}$), 10.04 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ 115.0, 122.3, 127.6, 127.7, 128.3, 131.31, 135.2, 153.9, 165.0.



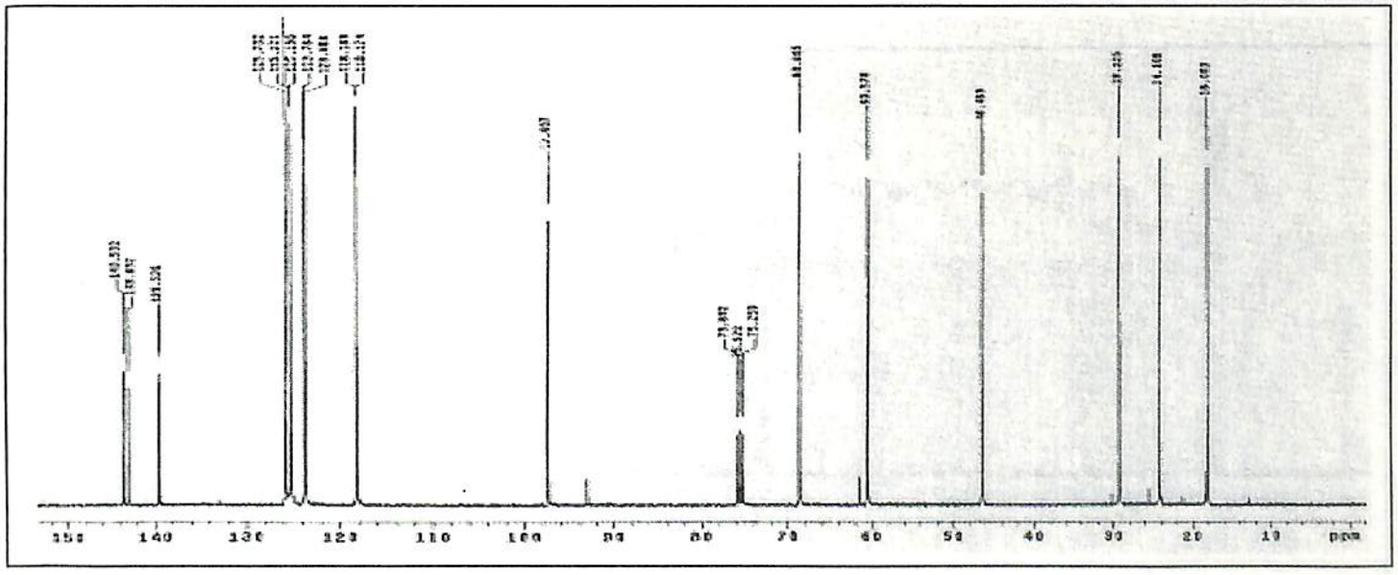
Thiobenzoic acid S-dodecyl ester (94k): IR (KBr): 2930, 2858, 1670, 1593, 1465, 1209, 912, 780, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, $-CH_2CH_3$, J = 7.2 Hz), 1.26 (s, 18H, $CH_3(CH_2)_9CH_2CH_2S$-, 1.67 (m, 2H, $CH_3(CH_2)_9CH_2CH_2S$-), 3.06 (t, 2H, m, 2H, $CH_3(CH_2)_9CH_2CH_2S$-, J = 7.6 Hz), 7.44 (t, 2H, Ar*H*, J = 7.6 Hz), 7.54 (t, 1H, Ar*H*, J = 8.0 Hz), 7.96 (d, 2H, Ar*H*, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 29.0, 29.2, 29.3, 29.4, 29.60, 29.66, 29.72, 32.0, 127.0, 128.4, 133.0, 137.1, 191.8.

1D. Spectra

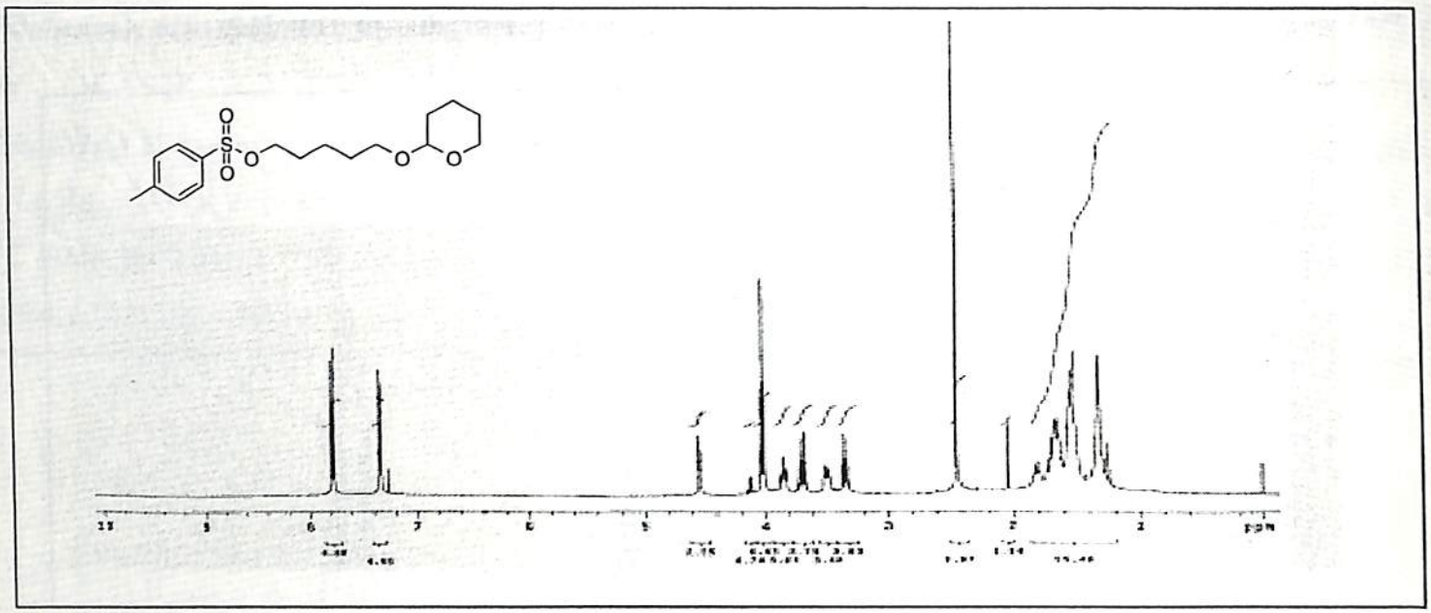
^{1}H NMR (400 MHz, $CDCl_3$):**2-(9H-Fluoren-9-ylmethoxy)-tetrahydro-pyran (31f)**



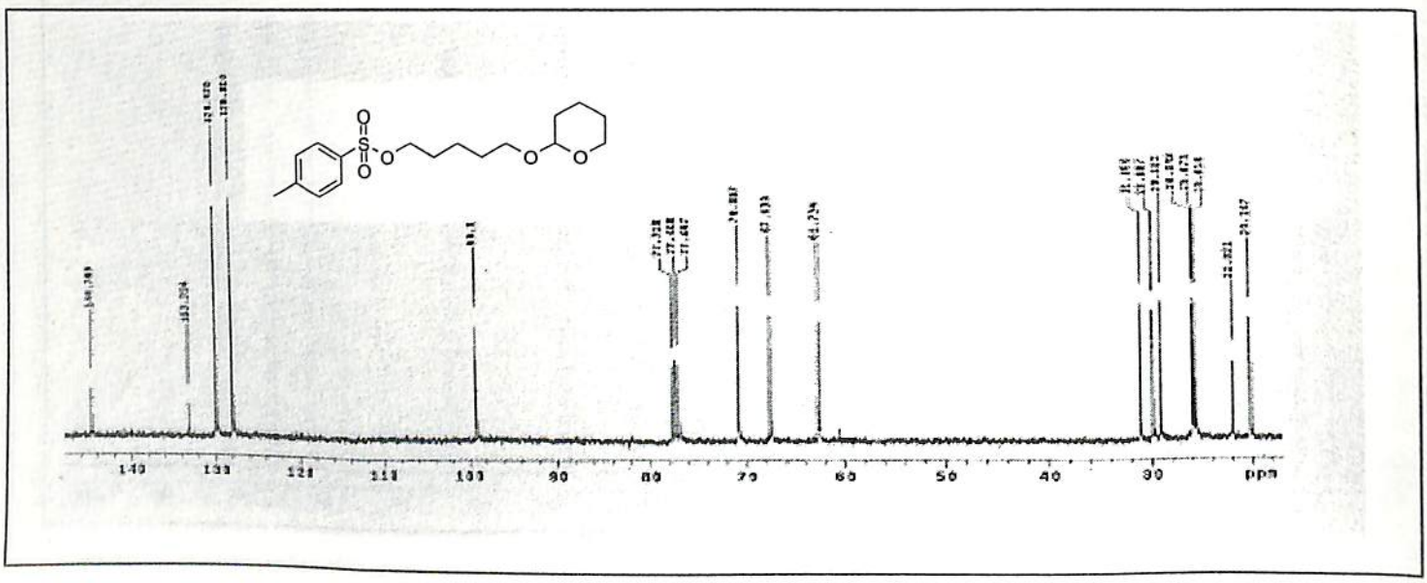
^{13}C NMR (100 MHz, $CDCl_3$): **2-(9H-Fluoren-9-ylmethoxy)-tetrahydro-pyran (31f)**



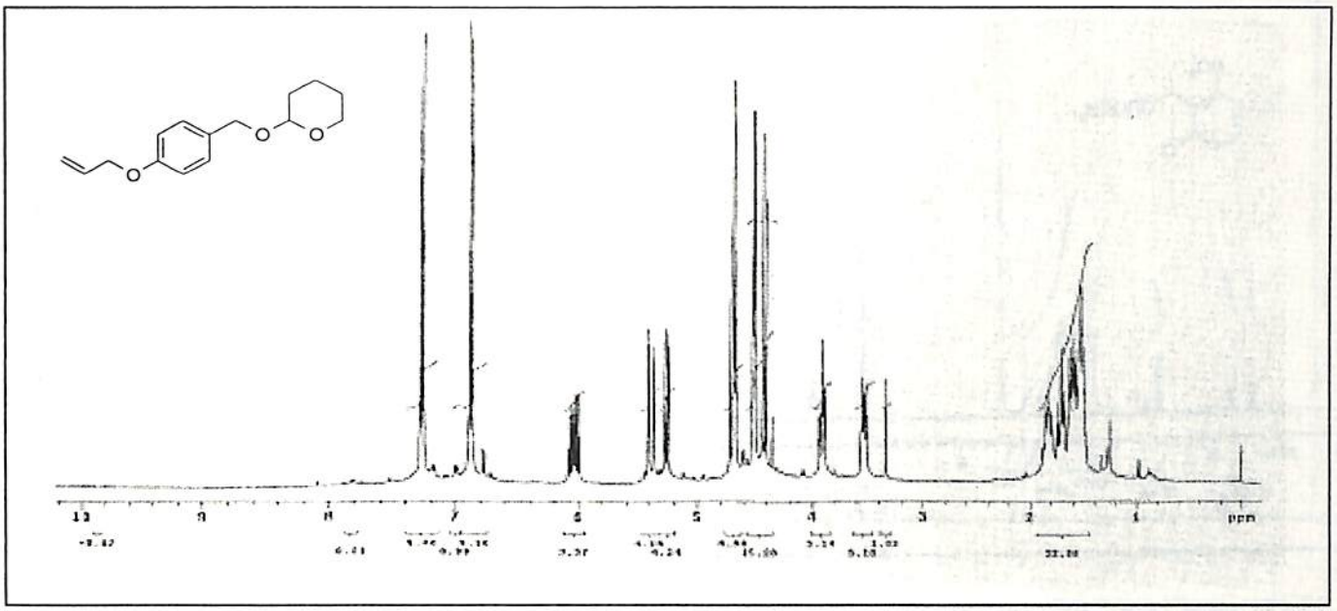
^{1}H NMR (400 MHz, $CDCl_3$): **Toluene-4-sulfonic acid 5-(tetrahydro-pyran-2-yloxy)-pentyl ester (52f)**:



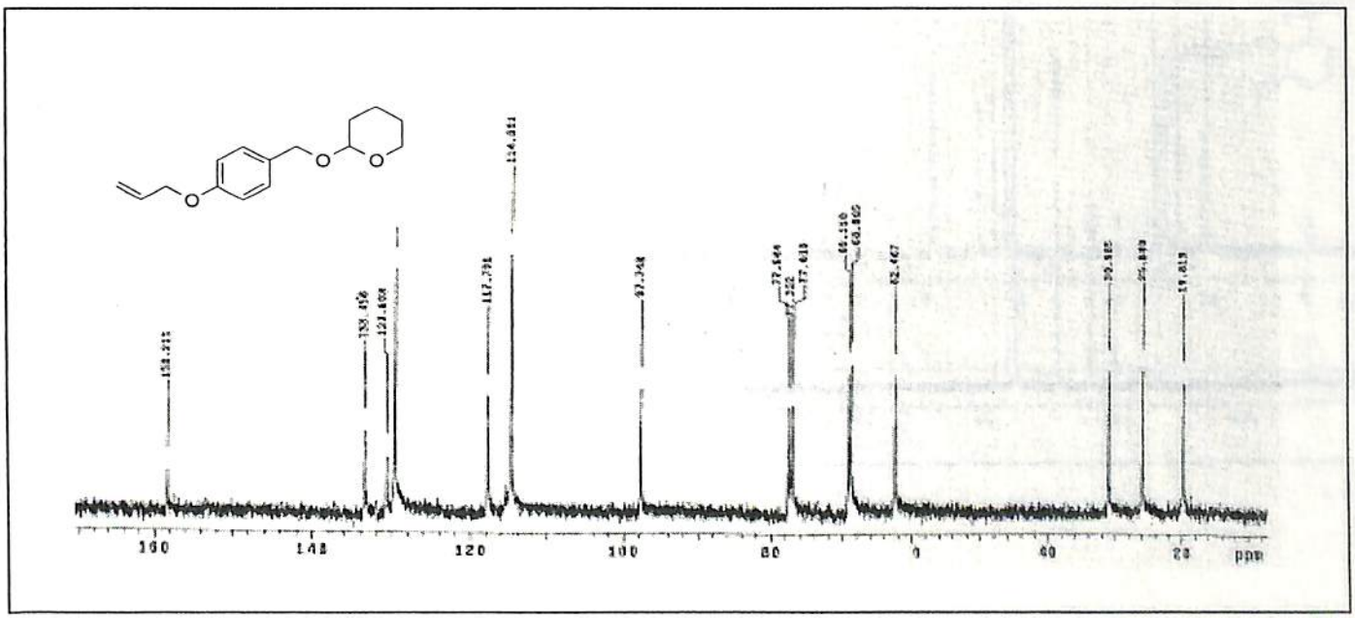
^{13}C NMR (100 MHz, $CDCl_3$): **Toluene-4-sulfonic acid 5-(tetrahydro-pyran-2-yloxy)-pentyl ester (52f)**



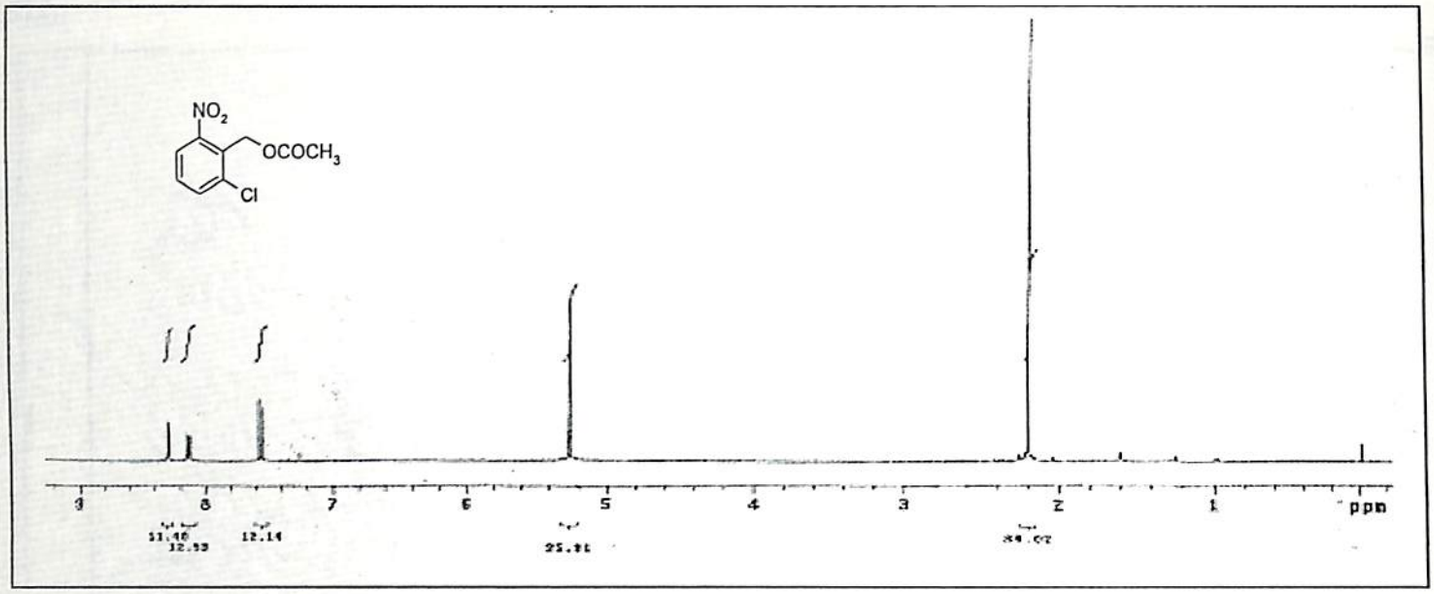
^{1}H NMR (400 MHz, $CDCl_3$): **2-(4-Allyloxy-benzyloxy)-tetrahydro-pyran (53f)**



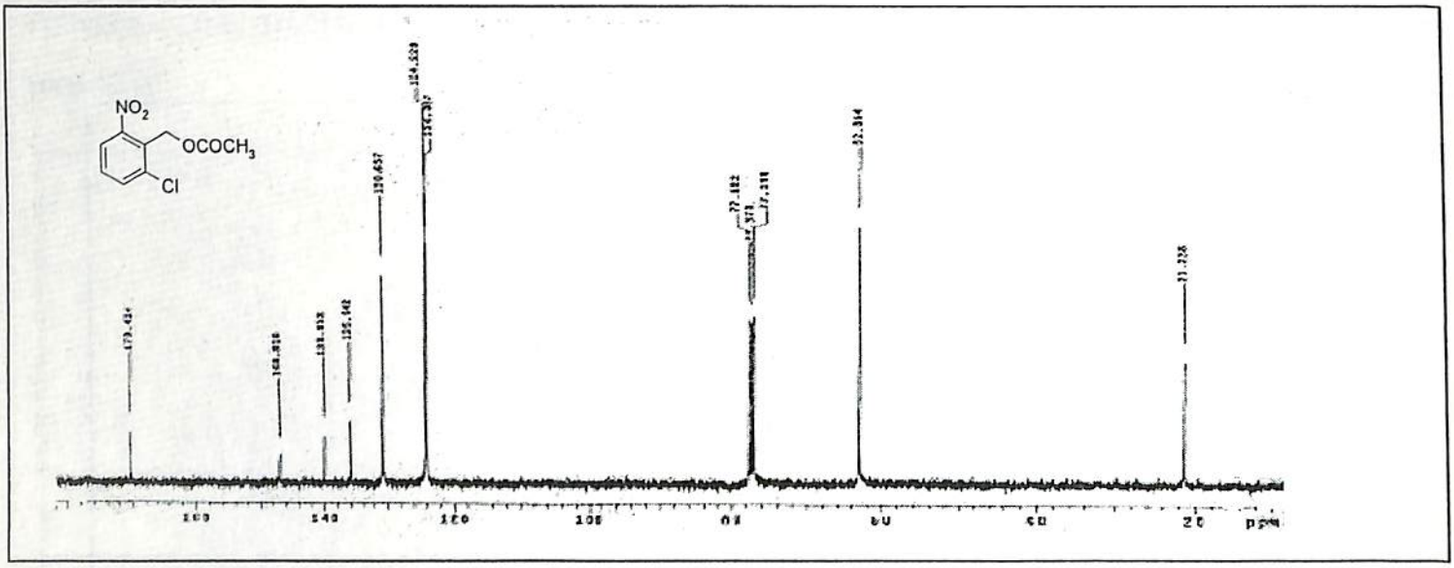
^{13}C NMR (100 MHz, $CDCl_3$): **2-(4-Allyloxy-benzyloxy)-tetrahydro-pyran (53f)**



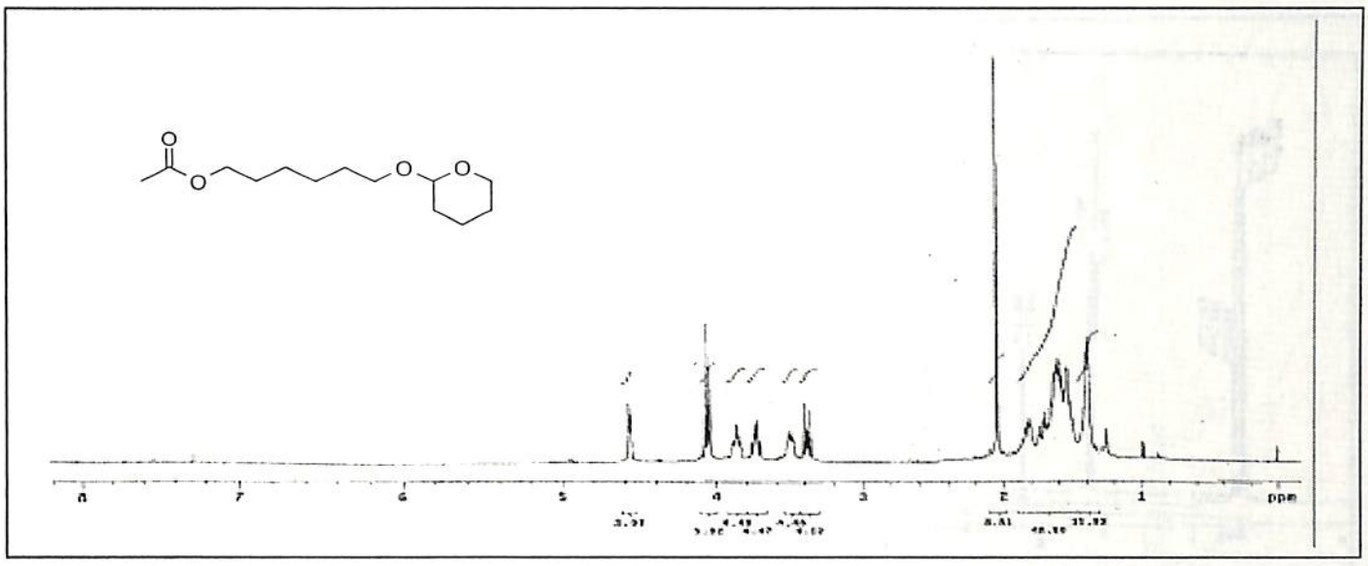
^{1}H NMR (400MHz, $CDCl_3$): **Acetic acid 2-chloro-6-nitro-benzyl ester (30g):**



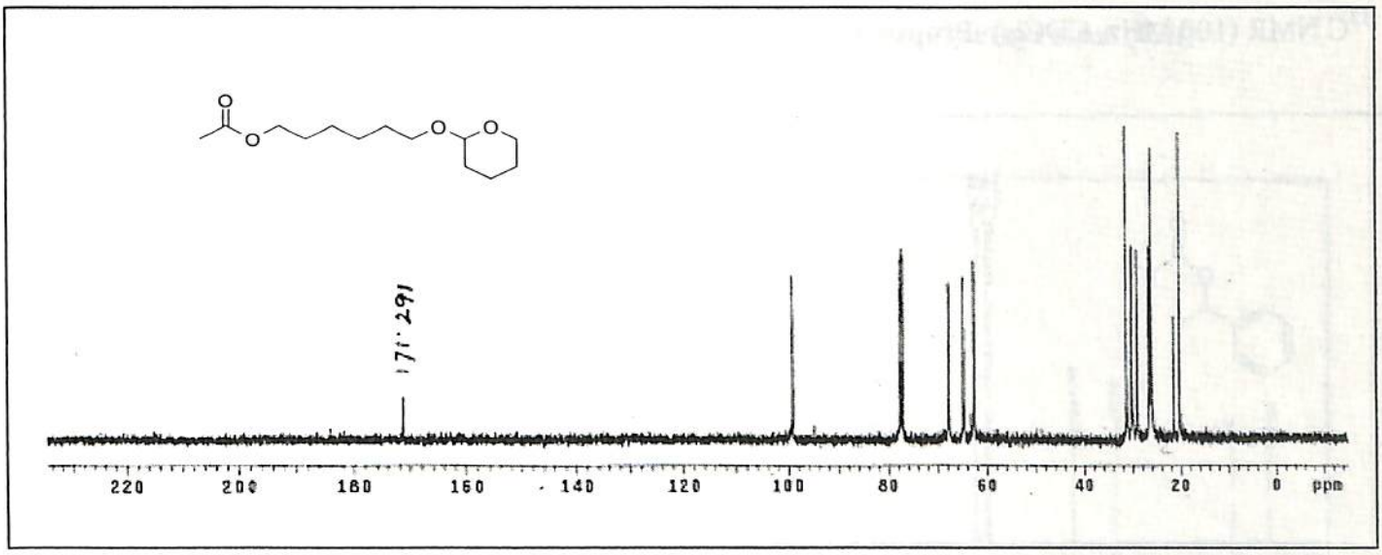
^{13}C NMR (100MHz, $CDCl_3$): **Acetic acid 2-chloro-6-nitro-benzyl ester (30g)**



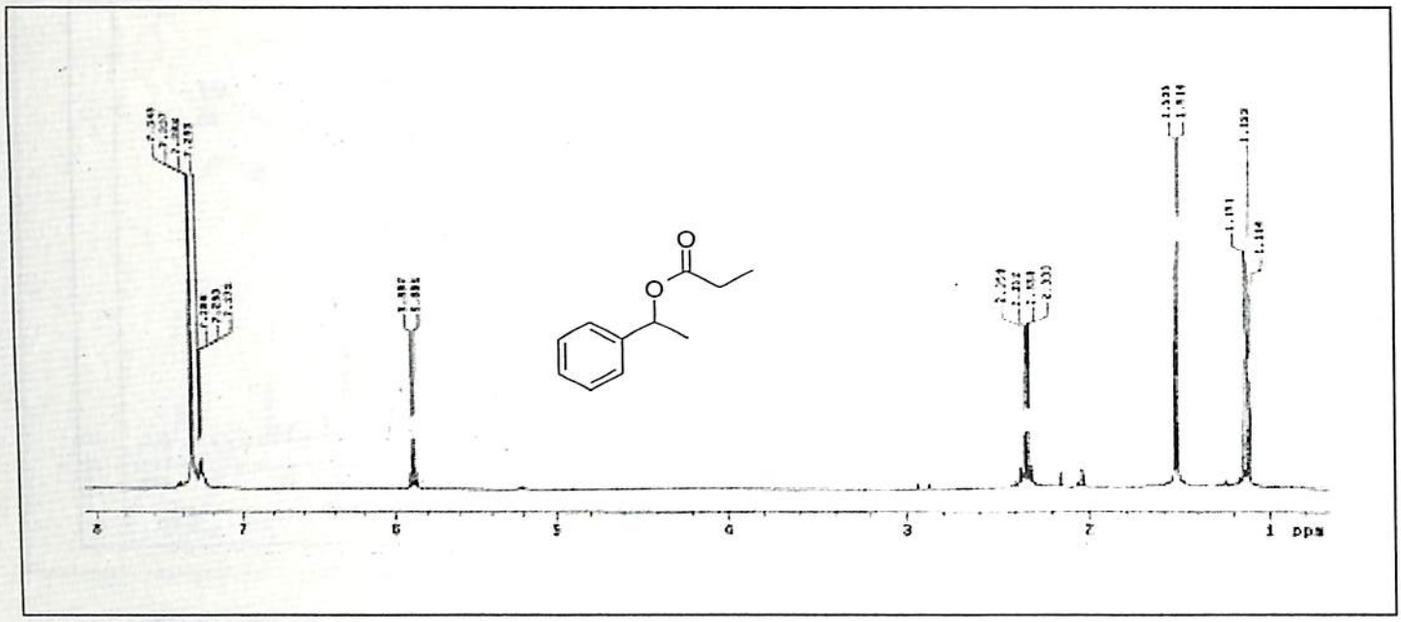
^{1}H NMR (400 MHz, $CDCl_3$): **Acetic acid 6-(tetrahydro-pyran-2-yloxy)-hexyl ester (51g)**



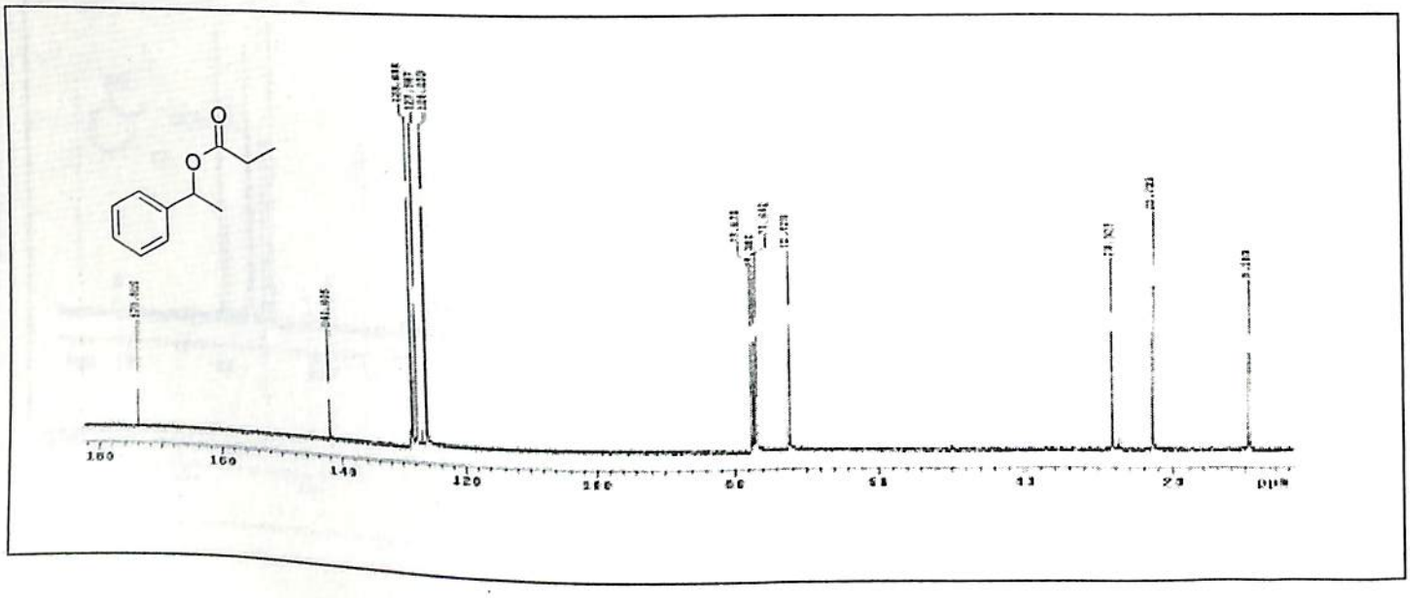
^{13}C NMR (100 MHz, $CDCl_3$): **Acetic acid 6-(tetrahydro-pyran-2-yloxy)-hexyl ester (51g)**



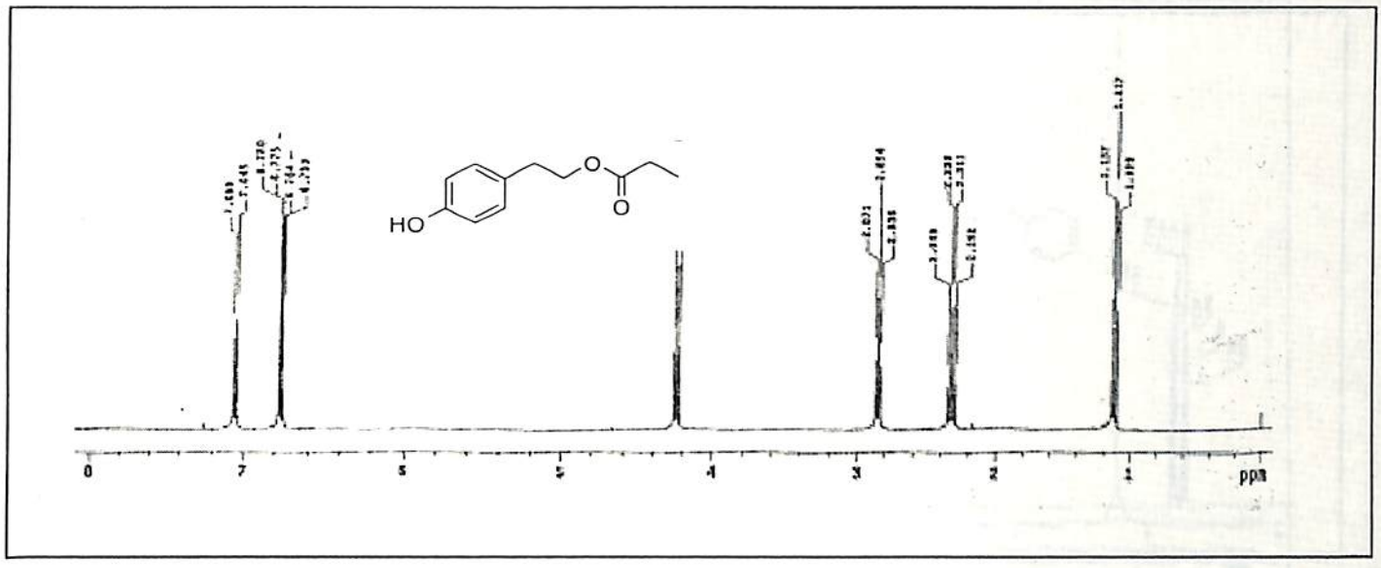
^{1}H NMR (400 MHz, $CDCl_3$): **Propionic acid 1-phenyl-ethyl ester (35h)**



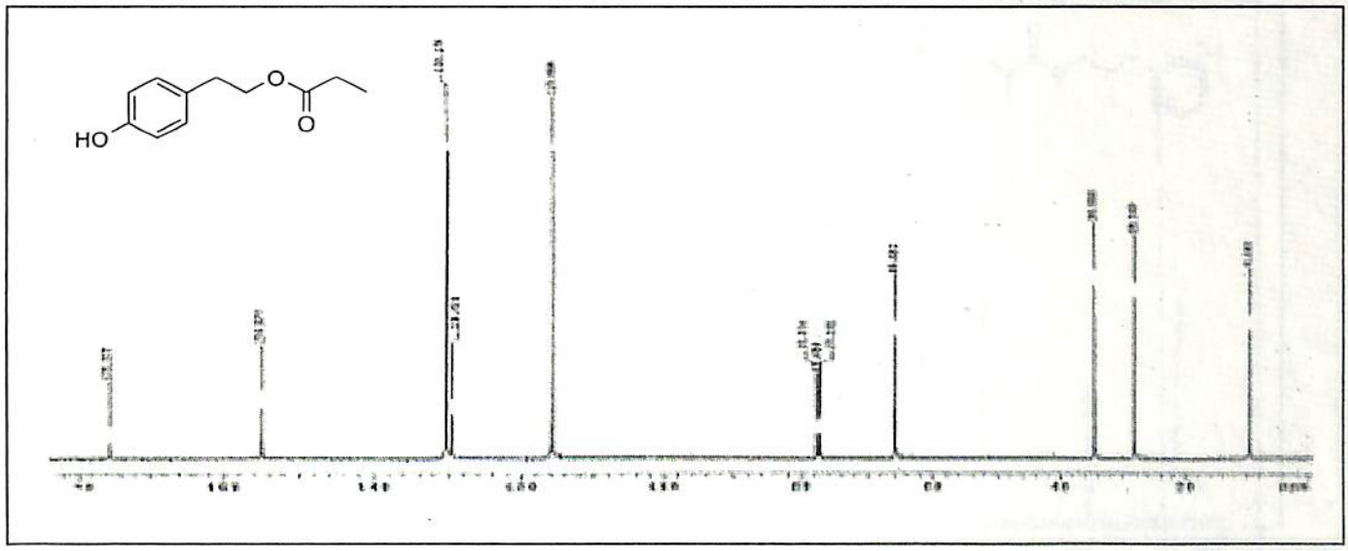
^{13}C NMR (100 MHz, $CDCl_3$): **Propionic acid 1-phenyl-ethyl ester**



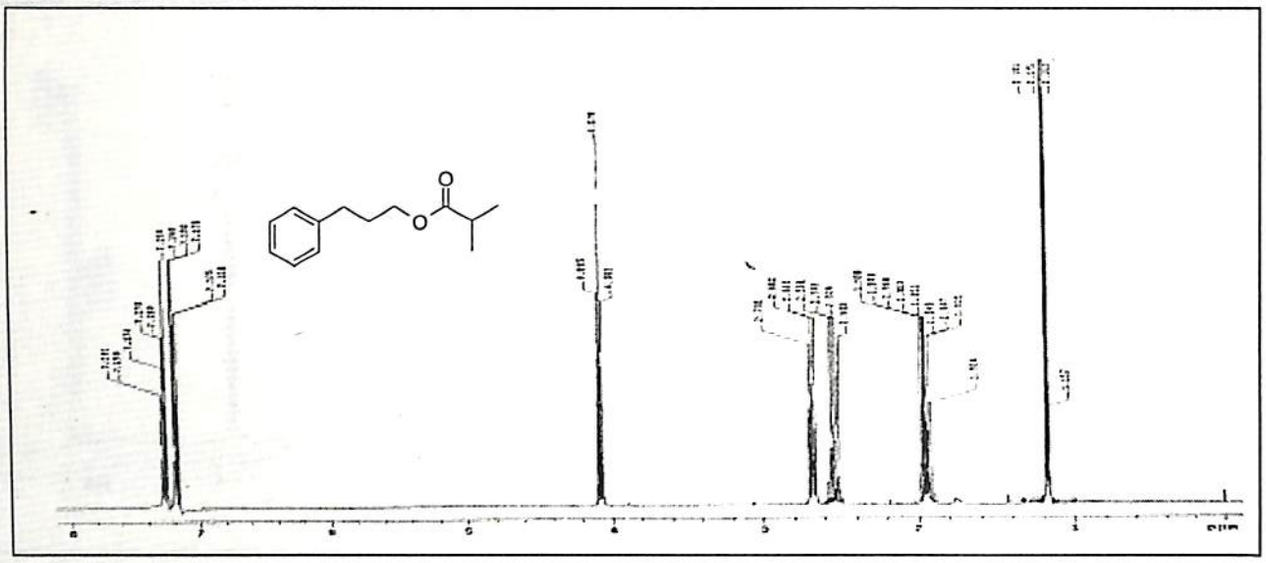
^{1}H NMR (400 MHz, $CDCl_3$): **Propionic acid 2-(4-hydroxy-phenyl)-ethyl ester (49h)**



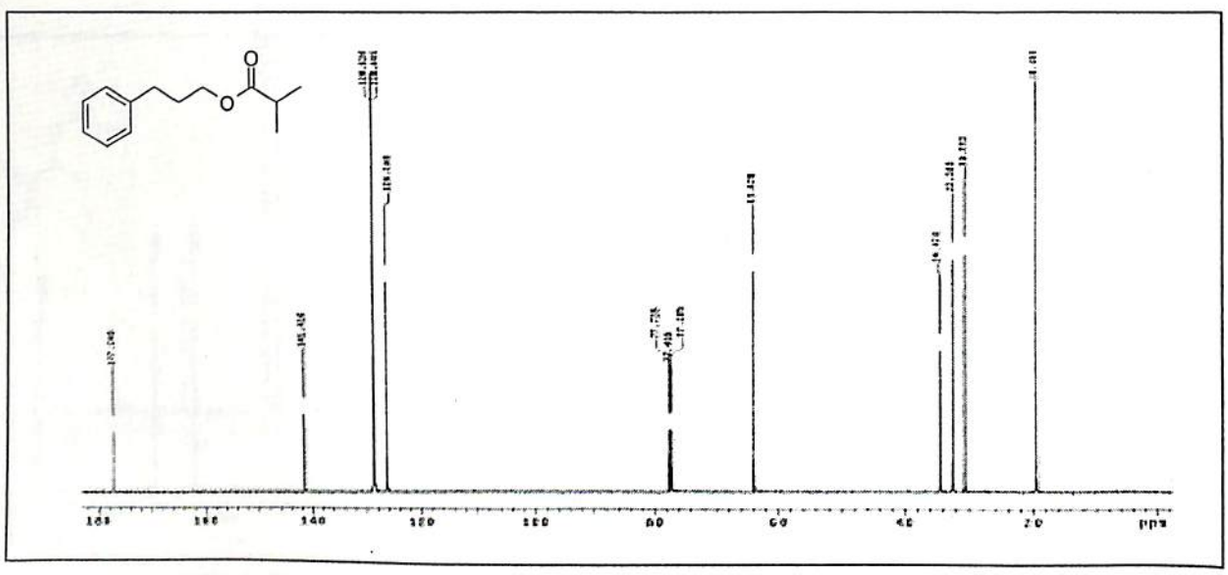
^{13}C NMR (100 MHz, $CDCl_3$): **Propionic acid 2-(4-hydroxy-phenyl)-ethyl ester (49h)**



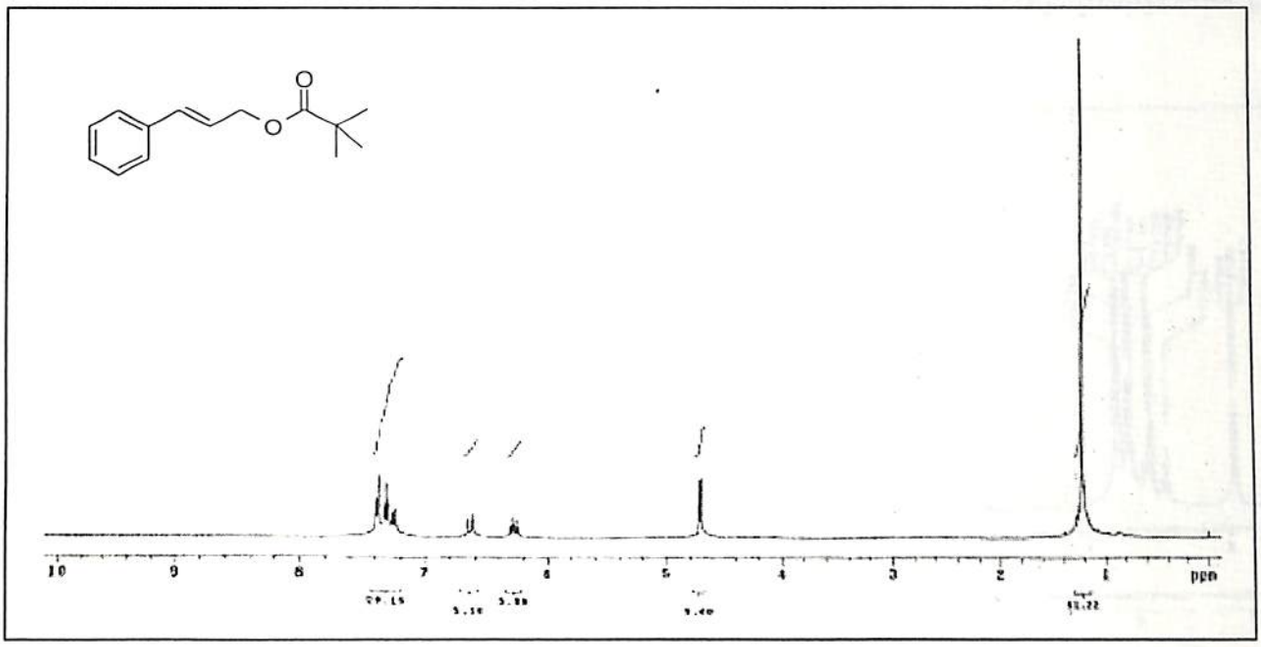
^{1}H NMR (400 MHz, $CDCl_3$): **Isobutyric acid 3-phenyl-propyl ester (22i)**



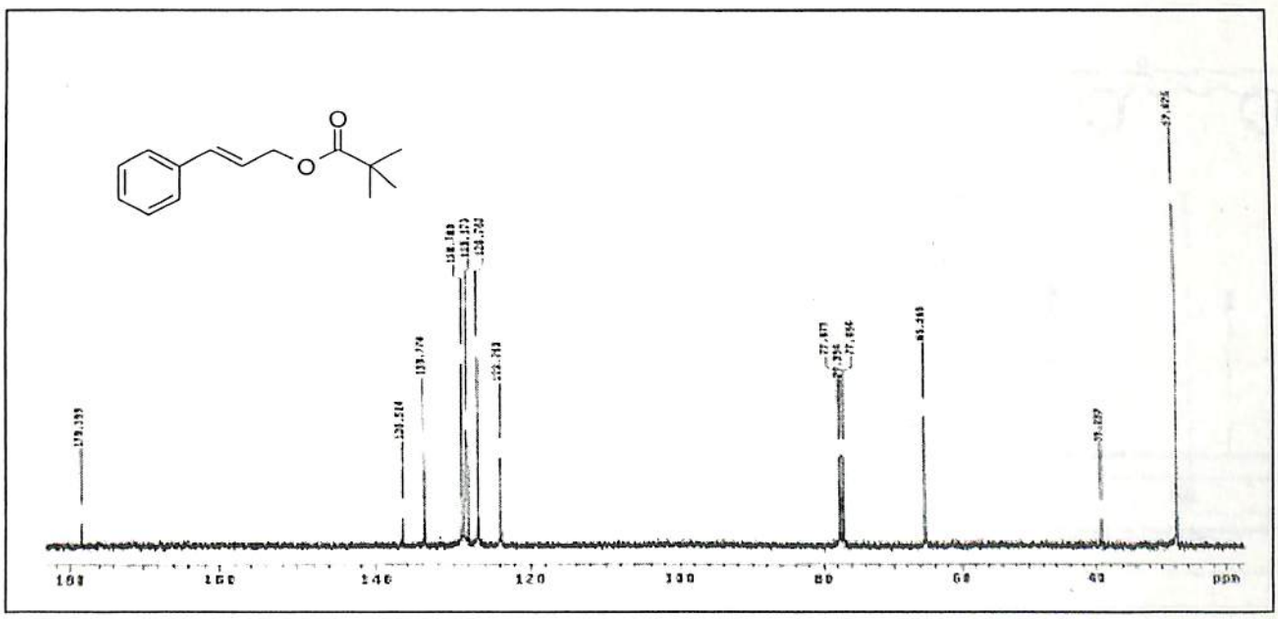
^{13}C NMR (100 MHz, $CDCl_3$): **Isobutyric acid 3-phenyl-propyl ester (22i)**



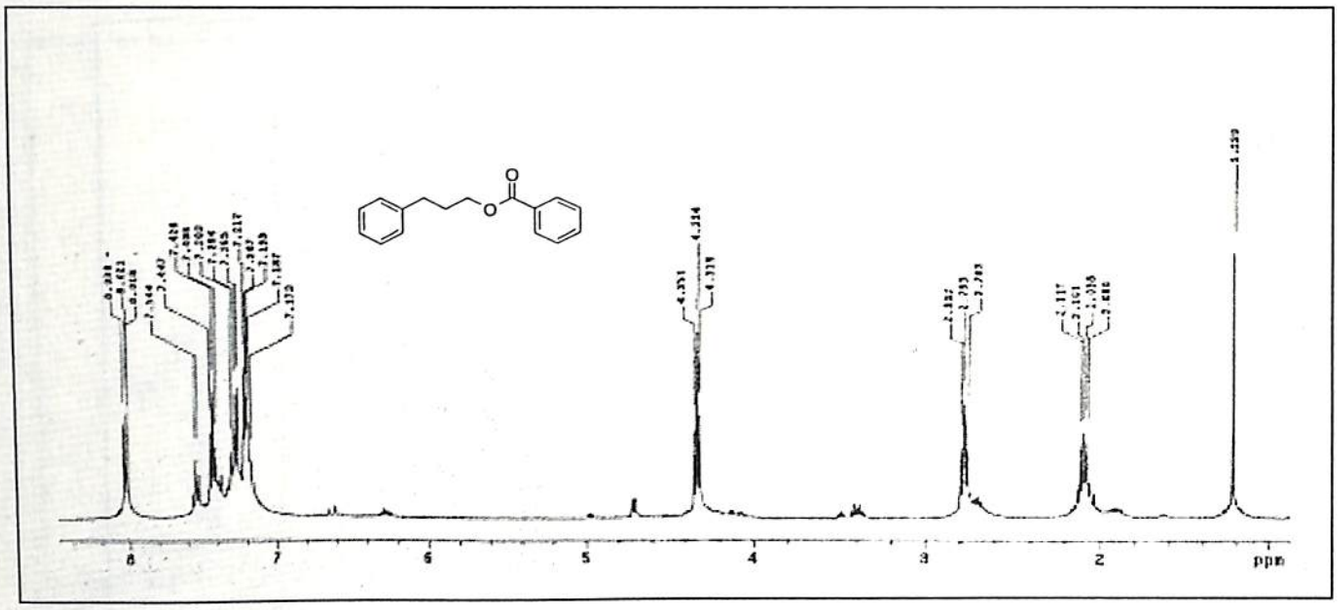
^{1}H NMR (400 MHz, $CDCl_3$): **2,2-Dimethyl-propionic acid 3-phenyl-allyl ester (55j)**



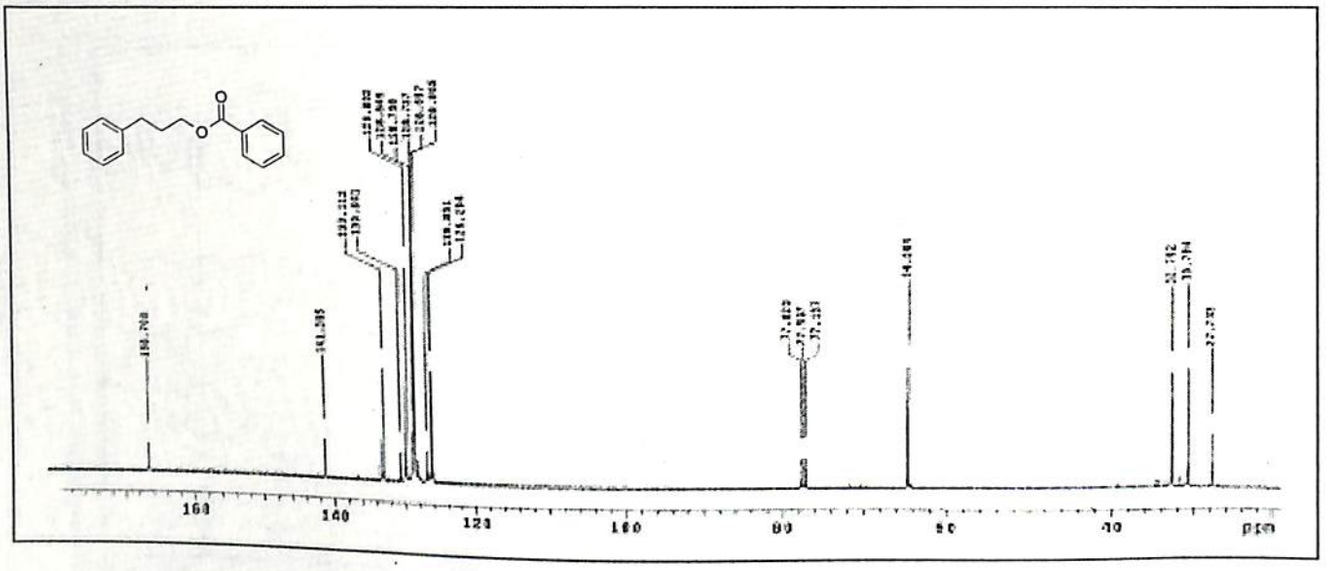
^{13}C NMR (100 MHz, $CDCl_3$): **2,2-Dimethyl-propionic acid 3-phenyl-allyl ester (55j)**



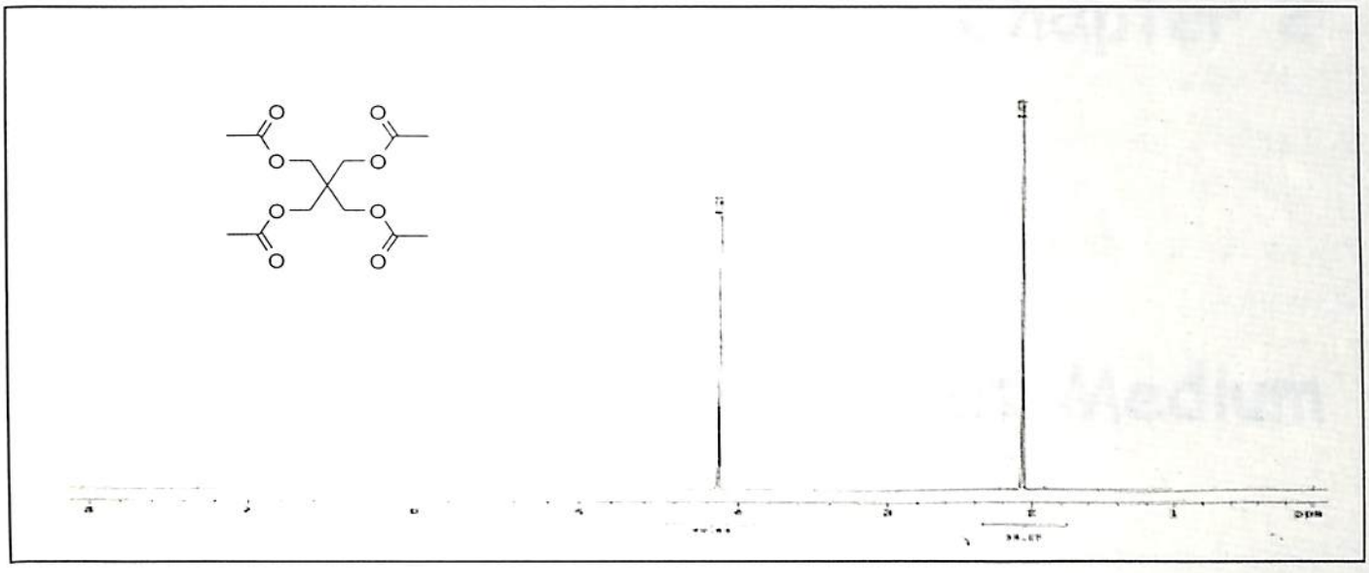
^{1}H NMR (400 MHz, $CDCl_3$): **Benzoic acid 3-phenyl-propyl ester (22k)**



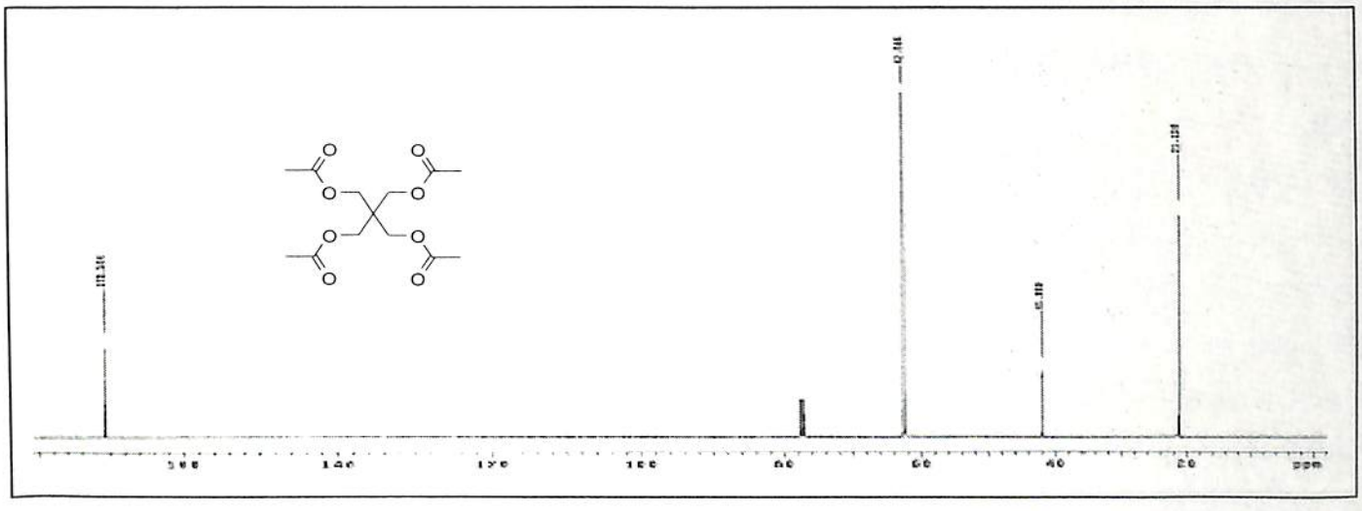
^{13}C NMR (100 MHz, $CDCl_3$): **Benzoic acid 3-phenyl-propyl ester (22k)**



^{1}H NMR (400 MHz, $CDCl_3$): **Acetic acid 3-acetoxy-2,2-bis-acetoxy methyl-propyl ester (50g)**:



^{13}C NMR (100 MHz, $CDCl_3$): **Acetic acid 3-acetoxy-2,2-bis-acetoxy methyl-propyl ester (50g)**



Chapter 2

N-Acylation in Aqueous Medium

2A. Introduction

Chemical products and processes have contributed fundamentally in shaping the world, as we know it today. Implementation of modern instruments and techniques in organic synthesis has continuously assisted the generation of many synthetically useful products. Further development is required in terms of environmentally friendly processes and products, which is socially desirable and also can be economically affordable. Several methods exist for performing environmentally friendly chemistry. The use of environmentally friendly solvents in organic reaction is one of them. Most of the organic solvents are flammable, explosive, toxic or carcinogenic. Hence the exclusion of organic solvents in chemical synthesis is an important step to accomplish benign chemical technologies. On the other hand many of the target molecules such as carbohydrates, peptides and nucleotides are readily soluble in water. Being the solvent of life, water is necessarily a non-toxic solvent.

2A.1. Water: The Unique Solvent

Water minimises environmental impact, increases operational safety and can provide a low cost reaction medium for pursuing reaction chemistry. Furthermore it is the most abundant, cheap, non-toxic, safe and non-hazardous solvent hence can serve as an alternative solvent for organic reactions. But the lower solubility of organic apolar substrates (reactants), incompatibility of the intermediates in water and the competition between the desired reaction and hydrolysis restricts its use in organic synthesis. On the other hand, after Breslow's discovery of a positive effect on the reaction rates and selectivities of the Diels-Alder reaction, special attention has been focused on the origin of the aqueous acceleration. Breslow has demonstrated that the hydrophobic effect accelerates Diels-Alder reaction and gives high endo-exo selectivity.[1] Despite the solubility problems of organic substrates in water after the seminal contribution of Breslow, new additions are continuously being made to the catalog of organic reactions that can be performed effectively with water as the solvent. In general, apolar organic compounds can be solubilised in water by addition of organic cosolvents, amphiphiles such as surfactant and by ionic derivatisation with control of pH. The possibility of using water as the solvent for organic reactions with surprising and unanticipated results has been addressed in the literature.[2] Several books and reviews have been devoted towards the use of water in organic reactions. A series of most of the fundamentally useful reactions such as aldol reactions, allylations, aminohydroxylations, cycloadditions, cyclopropanations, epoxidations, dihydroxylations, and hydrogenations, oxidation, organometallic

reactions has been performed with similar or improved rates, yields and selectivity in aqueous media compared to the corresponding reactions in organic media.[3]

In addition, the experimental procedures using water as the reaction medium are simplified owing to easy isolation of products accompanied by recycling of water-soluble catalysts and reagents by phase separation.

2A.2. Amino Protecting Groups

Owing to the nucleophilic and basic character of amines they must be blocked with a protecting group during a multi-step synthesis, *e.g.* in the synthesis of a diverse array of biological molecules such as amino acids, peptides, glycopeptides, aminoglycosides, β-lactams, nucleosides, sphingosines and alkaloids. Few from the catalog of amino protecting groups are given below, Figure 2.1.

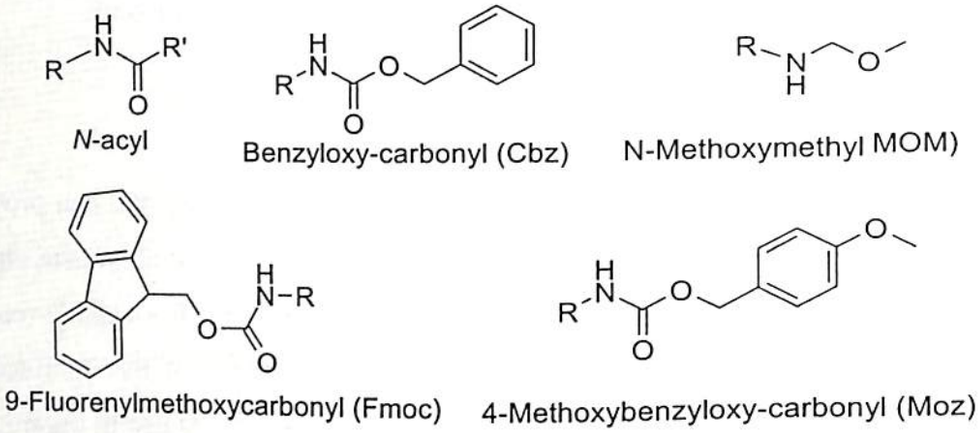


Figure 2.1

In the directory of amino protecting groups, few which are frequently used takes into account *N*-acyl, 2-nitrobenzyl, *N*-methoxymethyl (MOM), 9-fluorenylmethoxycarbonyl (Fmoc), 4-methoxybenzyloxy-carbonyl (Moz), benzyloxy carbonyl (Cbz), allylic and benzylic protecting groups as shown in the above scheme. In addition Schiff's bases are used as the amine protecting group where electron withdrawing protecting groups are avoided.[4]

2A.2.1. *N*-Acyl Protecting Groups

2A.2.1.1. (a) Significance of *N*-Acyl Protecting Groups

N-acyl derivatives are well known and most widely used protecting groups for the amines. It is often used as a protecting group in organic synthesis as it provides an efficient and inexpensive means for protecting an amino functionality in a multi-step synthetic process.[5] *N*-acylation is also an important

reaction in combinatorial peptide synthesis.[6]The amide functionality is an important unit in various naturally occurring as well as synthetic organic molecules. Despite the harsh hydrolytic conditions required for their deprotection they are useful in many applications.[4] Various *N*-acyl protecting groups are summarised below, Figure 2.2.

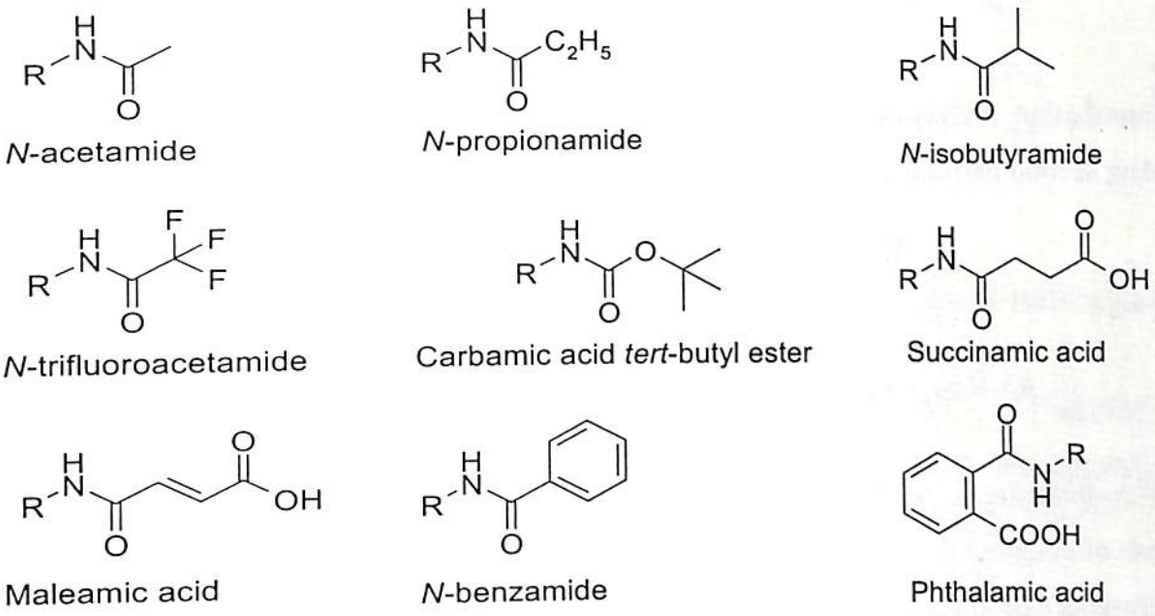
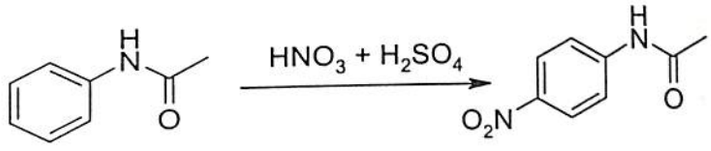


Figure 2.2

Among the various *N*-acyl amino protecting groups, *N*-acetyl in particular is of great synthetic utility in organic synthesis as this protecting group restricts the activating influence of the amino group towards electrophilic ring substitution reactions, Scheme 2.1.[7]

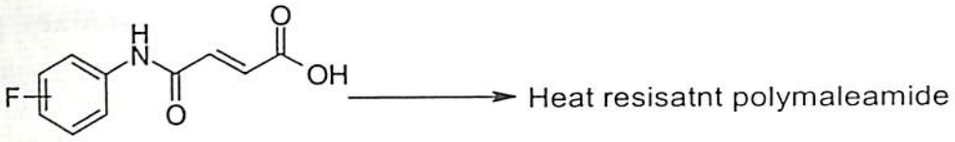


Scheme 2.1

The isobutyryl and benzoyl amides have been used for purine base protection during solid phase peptide nucleic acid (PNA) on controlled pore glass (CPG) solid support.[8] Among the various other amine-protecting groups, the *t*-butoxycarbonyl (Boc) group has been frequently used in organic synthesis for its easy removal under acidic conditions.[9] The *N*-Boc protected amino acids are also used for the backbone protection of peptide nucleic acid.[8]

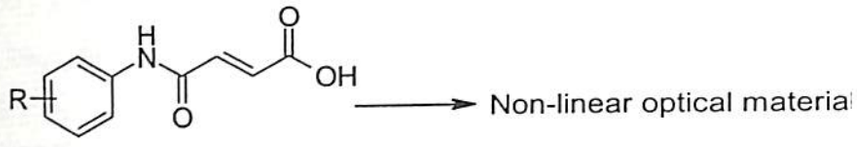
N-aryl maleamic acids and succinamic acids are formed by the reaction of amines with maleic anhydride and succinic anhydride respectively. These are important classes of compounds having

fungicidal, insecticidal and herbicidal properties. The *N*-fluorophenylmaleamic acids are useful as intermediates for heat resistant polymaleamides, Scheme 2.2.[10]



Scheme 2.2

The fluoro, alkyl, alkoxy or nitro substituted phenyl maleamic acids behave as non-linear optical material showing second harmonic generation, Scheme 2.3.[11]



R = Halo, Alkyl, Alkoxy, Nitro

Scheme 2.3

The *N*-arylphthalamic acid formed by the reaction of amine with phthalic anhydride is an interesting class of compound due to its negative geotropic effect in germinating roots. There has also been recent resurgence of interest in *N*-phenyl phthalimide derivatives and its analogues because of their potential in a number of areas such as aminopeptidase inhibition,[12a] anticonvulsant activity, [12b] and promotion of tumour necrosis factor alpha (TNF alpha) production.[12c]

The pharmacological activity of *N*-phenylphthalimide and ortho fluoro substituted phthalimide and the corresponding phthalamic acid has been tested in Swiss white male mice. The former have been reported to influence lipid metabolism reducing the plasma cholesterol, triglyceride levels where as the later significantly increases cholesterol, triglycerides and the animal's body weight.[13]

2A.2.1. 2. Literature Reports on *N*-Acylation in Organic Medium

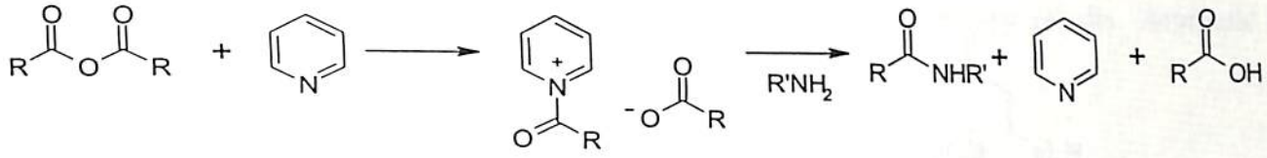
The common route to the synthesis of amide involves the treatment of activated derivatives of carboxylic acids such as acyl halides, acid anhydrides or esters with amines.

(A) *N*-Acetylation of Amines

(A1) Acid Chlorides or Anhydrides in Presence of Basic and Acidic Catalysts

The acetylation of amines can be achieved with acetylating agents such as acid halides or acid anhydrides as the acyl source in the presence of basic[14] and acidic[15] catalysts which are summarised below.

Bases such as pyridine,[14a] 4-(dimethylamino)pyridine (DMAP),[14b] tributyl phosphine (Bu_3P),[14c] $MgBr_2$-Et_3N,[14d] aminophosphine superbase $(PMeNCH_2CH_2N)_3$[14e] have been employed as catalyst or stoichiometric reagents for acetylation, which promotes the reaction. The use of these bases both in stoichiometric or catalytic amounts is effective. Excess triethylamine or pyridine is added to trap the acid formed in the reaction mixture.



Scheme 2.4

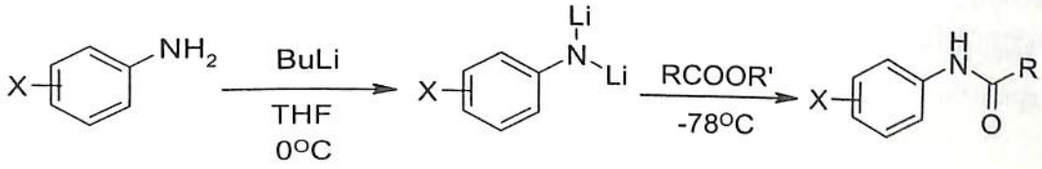
In the reaction with anhydride and pyridine *N*-acylpyridinium carboxylates are key intermediates, undergoing nucleophilic attack by amines as shown in Scheme 2.4.

Various acidic catalysts used for acetylation of amines include $CoCl_2$,[15a] TMSOTf,[15b] $Sc(OTf)_3$,[15c] $Cu(OTf)_2$,[15d] $In(OTf)_3$,[15e] vanadyl triflate,[15f] Mn(III)-salen complex,[15i] Montmorillonite K-10,[15j] Montmorillonite K-10 and KSF,[15k] Yttria-zirconia based Lewis acid,[15l] Zeolite H-FER.[15m]

(A2) Aminolysis of Esters

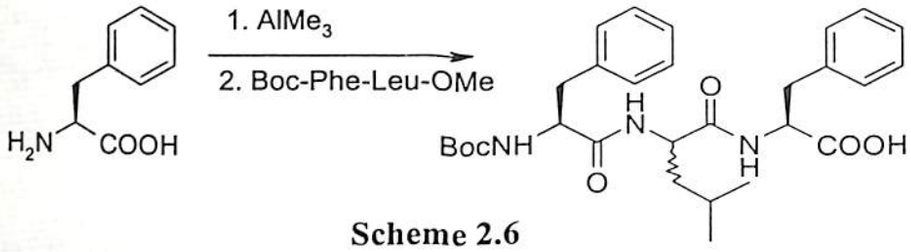
The direct transformation of carboxylic esters to amides or aminolysis is a potentially important synthetic operation. It is generally a sluggish reaction which is only amenable to esters having good leaving groups such as nitrophenyl, thiophenyl, vinyl, hydroxylamines and *N*-hydroxyimides.[16] To enable the use of alkyl esters for aminolysis, numerous acidic and basic catalysts have been investigated in the literature.

Aminolysis of esters lacking sensitive functionality have been achieved using strong basic catalysts such as $NaNH_2$,[17a] NaH,[17b] CH_3ONa,[17c] $RMgX$[17d] and BuLi[17e]. Despite the ease of preparation and versatility, lithium amides have not found much application as an aminolysis agent because of the poor nucleophilicity, particularly in the case of aromatic amides.[18] In contrast to monolithium amides, dilithium amides exhibit high reactivity and enable the facile aminolysis of esters under very mild conditions, Scheme 2.5.[19]



Scheme 2.5

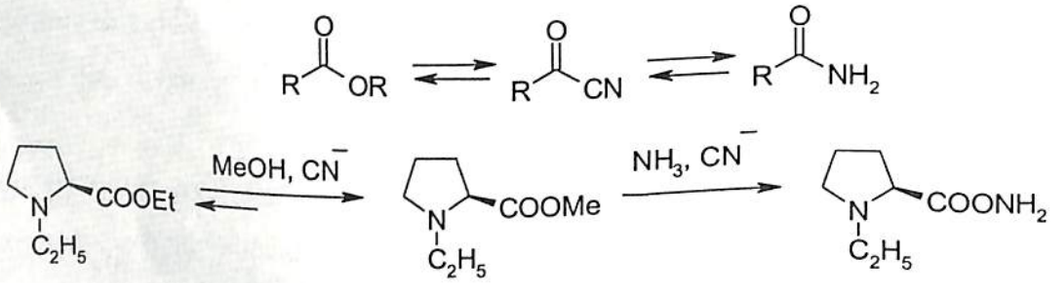
The Lewis acid mediated *N*-acylation developed by Weinreb *et al.* relies upon the high nucleophilicity of dimethylaluminium amides.[20] This methodology has been widely used in the synthesis of peptides. The modified Weinreb's method for synthesis of oligonucleotides involved the treatment of *N*-protected amino acids with trimethylaluminium followed by addition of *N*-protected amino acid esters (Scheme 2.6).



Scheme 2.6

Carboxylic esters have also been transformed into carboxamides by a one pot procedure involving saponification prior to coupling in the presence of bis(*o*-nitrophenyl)phenylphosphonate and tetrabutylammonium salts by Mukaiyama and Watanabe.[21]

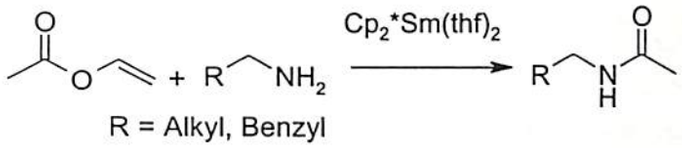
The role of acyl cyanide as mild acylating agents for various heteronucleophiles and carbon nucleophiles have been reported. In addition the inherent favourable properties of acyl cyanides in peptide synthesis have also already been explored. Taking cue from these reports it has been inferred that cyanide group might serve as a strong nucleophile with low basicity to provide the reactive acyl cyanide intermediate in the aminolysis of esters, Scheme 2.7.[22]



Scheme 2.7

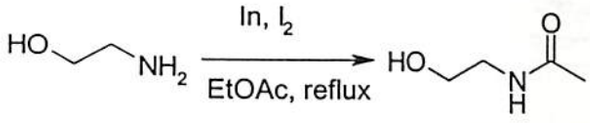
(A3) Transesterification

Vinyl and isopropenyl acetate serves as acetylating agent for the acetylation of alcohols and amines in presence of $Cp_2Sm(thf)_2$, Scheme 2.8.[23] The Sm(III) complex derived from $Cp_2Sm(thf)_2$ and vinyl acetate is the active species.



Scheme 2.8

Ranu *et al.* have reported the indium triiodide-catalysed transesterification process, Scheme 2.9.[24] Aliphatic and benzyl amines and primary alcohols give satisfactory results. Aromatic amines remain unreacted under this condition.



Scheme 2.9

The reactions involving acyl halides, anhydrides, esters have advantages and drawbacks, recently described by Katritzky.[25]

(A4)Acyl Transfer Reagents

This is based on the principle; first acyl group is transferred to a bulky nucleophile. The bulky acyl transfer reagent so generated then reacts with the subsequent nucleophile. A variety of such reagents have been developed for the acylation of amino group listed in Figure 2.3. These are highly selective acetylating agents for primary amines in the presence of secondary amines and, in particular, for the less sterically hindered of two different secondary amines. Due to steric bulkiness around the acyl carbonyl group in the acyl transfer reagent, *N*-acylation occurs at the less hindered amino group compared to the bulkier amino group. Products with high chemo selectivity are obtained with these reagents compared to acid chlorides and anhydrides. Various reagents with bulky leaving groups which act as acyl transfer reagents for acylation of amines are *N*-acetyl-*N*-acyl-3-amino-quinazolinones,[26a] ortho substituted *N, N*-diacetyl anilines,[26b] *N*-acyl-5,7-dinitroindolines,[26c]2-acyl pyridazin-3-one,[26d] *N*-acyl-2-methylamino-2-thiazoline,[26e] *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl) methanesulfonamides,[26g] chiral 2-acetyl amino-2'-diacetylamino-1,1'-binaphthyl.[26f] Polymer bound 4-acyloxy pyrimidines have also been utilised as solid surface reagents for acylation of amines under microwave irradiation.[26f] Solid supported cyclohexane-1,3-dione (CHD) has been used as capture and release reagent for synthesis of amides.[26i]

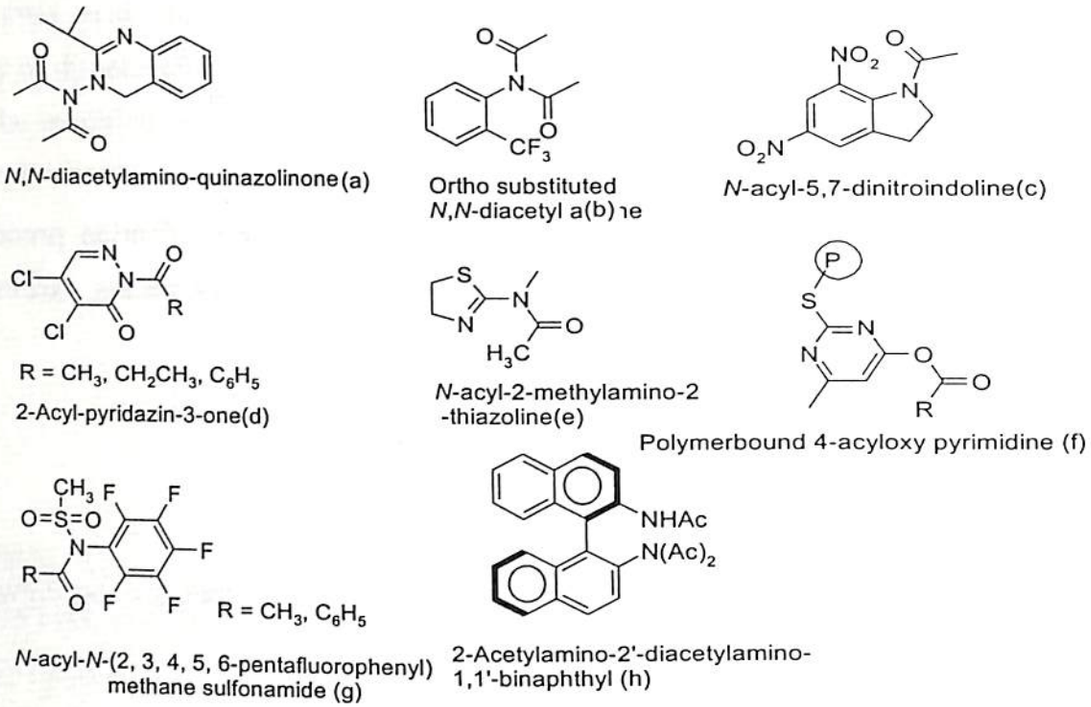
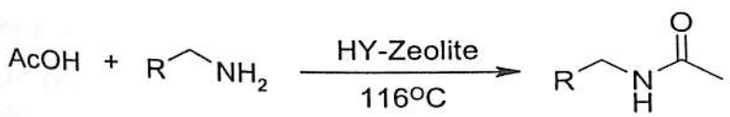


Figure 2.3

(A5) Direct Condensation of Carboxylic Acids with Amines

The expensive synthesis of acyl transfer reagents should be avoided and hence considerable interest has been focused on the formation of amides by the direct combination of carboxylic acids and amines. Formation of carboxamides from carboxylic acids and amines implies the activation of carboxyl group in the process.[27] The activation of carboxyl group involves its conversion to activated ester.

The *in situ* activation of carboxyl group have been achieved by the use of coupling reagents[28] such as carbodiimides,[28a] $Sn(N(TMS)_2)_2$,[28b] PPh_3 and NBS.[28c] The coupling reagents are not suitable for sterically hindered and low reactive substrates and are also expensive.



Scheme 2.10

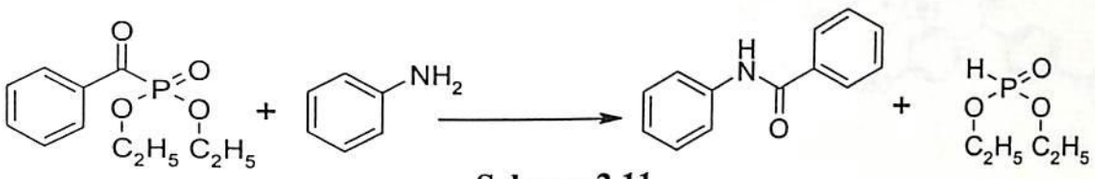
Raghavan *et al.* have shown the liquid phase acylation of amines with acetic acid over HY zeolite, Scheme 2.10.[29] The possible mechanism for this reaction as explained is the protonation of carbonyl group at the Bronsted acid sites of HY zeolite and reaction of the resulting acylium ion with amine to yield the amide.

The preparation of amide with equimolar quantity of carboxylic acids and amines in presence of Me_2NSO_2Cl and *N*,*N*-dimethylamine has also been reported.[30]

Pyrolytic preparation of amides in absence of any catalyst or solvent is one of the existing methods being employed.[31]This involve harsh conditions with respect to reaction temperature and time.

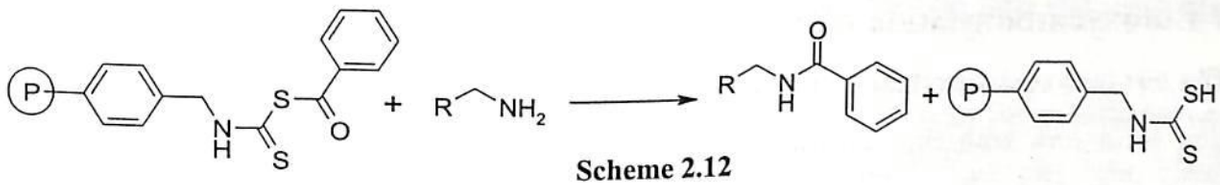
(B) *N*-Benzoylation of Amines

N-benzoylated products are normally obtained from benzoic acid, benzoyl halides, benzoic anhydride, esters of benzoic acid, and benzoyl transfer reagents under different experimental conditions. There has been report utilising polymeric benzoic anhydride to benzoylate amines.[32] Benzoylation of amines has also been achieved with dialkyl benzoyl sulfonates, Scheme 2.11.[33]



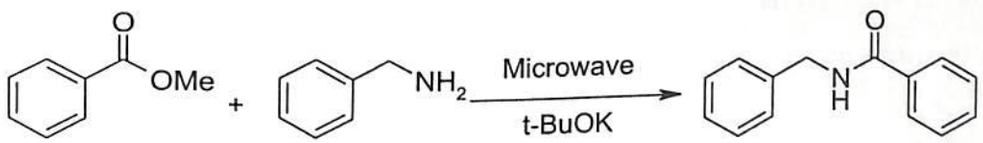
Scheme 2.11

Polymer bound mixed carboxylic dithiocarbamic anhydrides have been used as acylating reagents, Scheme 2.12.[34]



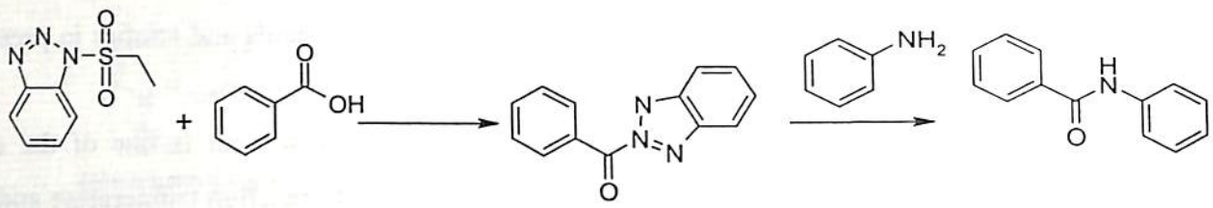
Scheme 2.12

Another procedure by Varma *et al.* entails the addition of *t*-BuOK to a mixture of amine and ester under solvent free condition and microwave irradiation to achieve benzoylation of amines, Scheme 2.13.[35]



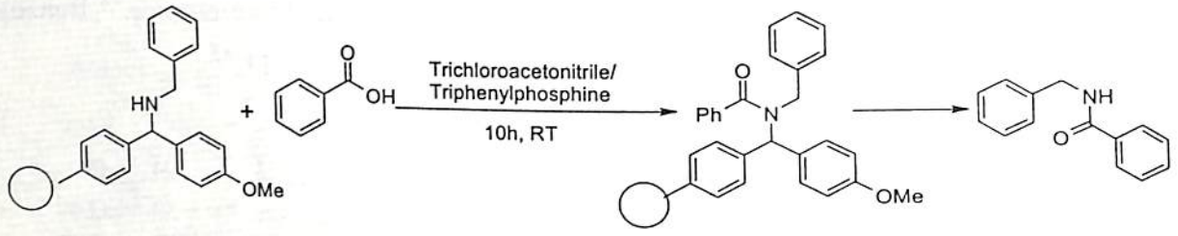
Scheme 2.13

Carboxylic acids are converted in a one-pot reaction into *N*-acylbenzotriazoles. This active ester on treatment with ammonia, primary and secondary amine to yield the corresponding primary, secondary and tertiary amide respectively, Scheme 2.14.[25]



Scheme 2.14

The coupling agent trichloroacetonitrile and triphenyl phosphine converts benzoic acid to benzoyl chloride mildly and rapidly under acid free condition *in situ* and the desired benzoylated product is obtained in good yield, Scheme 2.15.[36]



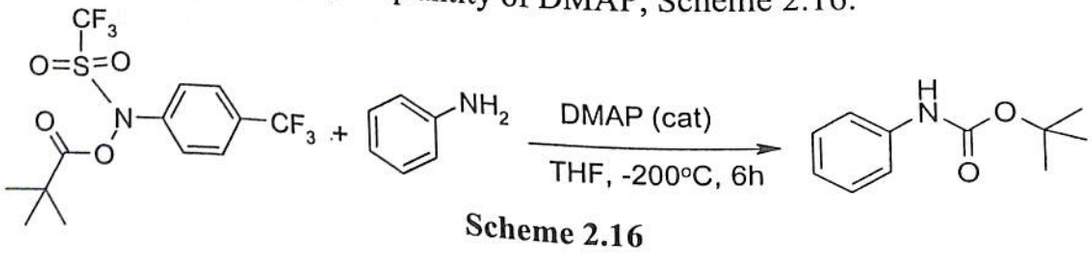
Scheme 2.15

Solvent free preparation of amides from carboxylic acids and amines under microwave irradiation has also emerged as an alternative to pyrolytic condensation to amide.[37]

(C) *tert*-Butoxycarbonylation of Amines

The *tert*-butoxycarbonylation of amines to procure NHBoc derivatives of amine can be achieved by reaction of amines with Boc anhydride, Boc azide or with *tert*-butyl-α-methylvinyl carbonate as amino protecting reagents.[38]

It has also been achieved by employing *N-tert*-butoxycarbonyltrifluoromethyl-sulfonyl-4-trifluoromethylanilide as a chemoselective alkoxycarbonylation reagent.[39] This reagent in absence of DMAP gives only 31% of NHBoc product of aniline after 24 h, however a better yield (93%) was achieved in 6h in the presence of catalytic quantity of DMAP, Scheme 2.16.

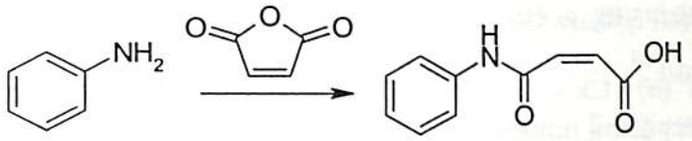


Scheme 2.16

(D) Synthesis of Maleamic and Succinamic Acids

The (arylcarbamoyl) propenoic acids or maleamic acid and propanoic acid or succinamic acid are potential pesticides prepared by the condensation of amine with maleic anhydride or succinic anhydride respectively.[40] Equimolar mixture of amine and anhydrides in ether at room temperature gave the corresponding succinamic, maleamic acids.[41]

The (*Z*)-malcamic acids has been reported to be prepared by reacting amine with maleic anhydride in presence of Montmorillonite clay K-10 and KSF,[15k] $PdCl_2$,[42] and Al_2O_3.[43] The direct condensation of amine with maleic anhydride in the absence of any acidic or basic catalyst has been achieved in acetonitrile,[44] and chloroform[45] as the reaction medium, Scheme 2.17.

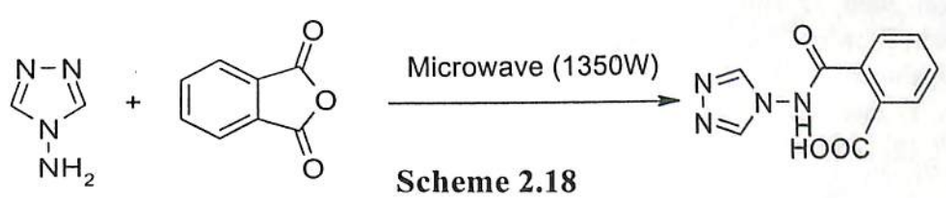


Scheme 2.17

(E) Synthesis of *N*-Arylphthalamic Acids

The synthesis of *N*-arylphthalamic acids involves the ring opening reaction of phthalic anhydride with amines by using coneventional heating.[46] This involves longer reaction time and more laboratory work.

Synthesis of anilinic acids from phthalic anhydride and their in vitro insecticidal screening as protectants of maize against Sitophilus zeamais have also been reported.[47] It has also been achieved by microwave heating which is based on the principle that two solid reagents with low melting points or a solid and a liquid reagent are able to melt rapidly giving a polar liquid, which is more prone to microwave absorption. When equimolar amount of the amine and anhydride is subjected to microwave irradiation in a domestic microwave oven operating at 1350 watt and 2450 MHz for 1-3 min, the corresponding *N*-arylphthalamic acid is obtained, Scheme 2.18. The ring opening occurs through the nucleophilic attack of the amine nitrogen atom on carbonyl carbon.[48]



Scheme 2.18

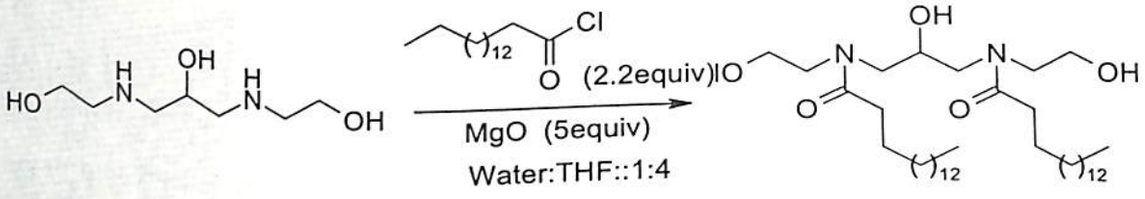
2A.2.1.3. Literature Reports on *N*-Acylation in Aqueous Medium

A great deal of interest has been surfaced in the last decades in performing various organic reactions in water after Breslow's seminal contribution entailing the hydrophobic effect responsible for high endo-exo selectivity in Diels-Alder reaction. There are only a handful of reports on acylation of amines in aqueous medium. It has been carried out in an aqueous medium using amine, hydrochloric acid, a concentrated solution of sodium acetate and acetic anhydride.[49]

The acetylation of various amino acids with acetic anhydride in the presence of sodium hydroxide solution in water has been described by DeWitt and Ingersoll.[50]

Richardson and McLauchlan have prepared *N*-acetyl derivative of 3-amino-3,6-dideoxy L-glucose and L-galactose using acetic anhydride in an aqueous medium.[51] Few other reports are also available towards this end.[52]

Lee *et al.* have reported recently the chemoselective *N*-acylation of amino alcohols promoted by MgO in aqueous organic medium,[53] Scheme 2.19.



Scheme 2.19

The laboratory scale preparation of *N*-arylphthalamic acids has been reported by addition of aromatic amines to aqueous slurry of finely ground phthalic anhydride at elevated temperatures.[54] Hydrolysis of the anhydride is negligible in the process and the avoidance of organic solvents makes the process quite economical.

2A.3. References

1. Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
2. (a) Li, C.J.; Chang, T.H. *Organic Reactions in Aqueous Media* John Wiley & Sons; New York, 1997. (b) Grieco, P. A.; Ed.; *Organic Synthesis in Water*, Blackie Academy & Professional; London, 1998. (c) *Pure Appl.Chem.* **2000**, 72, entire issue.
3. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (c) Herrmann, W. A.; Kohlpaintner, C.W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524. (d) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. (e) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (f) Kobayashi, S. *Synlett* **1994**, 689. (g) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (h) Shu, K.; Kei, M. *Acc. Chem. Res.* **2002**, *35*, 209. (i) Okuhara, T. *Chem. Rev.***2002**, *102*, 3641. (j) Pae, A. N.; Cho, Y. S. *Current Organic Chemistry* **2002**, *6*, 715. (k) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533. Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chemistry* **2001**, 3, 229. (l) Aplander, K.; Hidestal, O.; Katebzadeh, K.; Lindstörm, U. F. *Green Chemistry* **2006**, *8*, 22. (m) Ding, R.; Katebzadeh, K.; Roman,

L.; Bergquist, K.-E.; Lindstörm, U. M. *J. Org. Chem.* **2006**, *71*, 352. (n) Lindstörm, U. M.; Andersson, F. *Angewandte Chemie*, *Int. Ed.* **2006**, *45*, 548.
4. Spivey, A. C.; Leese, D. *Annu. Rep. Prog. Chem., Sect. B*, **2002**, *98*, 41.
5. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, **1999**. (b) Kocieñski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, **1994.**
6. Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Arkivoc* **2004** (*i*), 12.
7. *Vogel's Text Book of Practical Organic Chemistry*, Fifth Edition, p.906.
8. Kofoed, T.; Hansen, H.F.; Orum, H.; Koch, T. *J. Peptide Sci* **2001**, *7*, 402.
9. Subhas Bose, D.; Lakshminarayan, V. *Synthesis* **1999**, 1, 66.
10. Goto, Y.; Koinuma, Y.; Nakayama, M. *Jpn Kokai Tokkyo Koho* **1990**, 4.
11. Miyata, S.; Sato, H.; Hayashi, A.; Iizuka, H. *Jpn. Kokai Tokkyo Koho* **1990**, 6.
12. (a) Shimazawa, R.; Takayama, H.; Fujimoto, Y.; Komoda, M.; Dodo, K.; Yamasaki, R.; Shirai, R.; Koiso, Y.; Miyata, K.; Kato, F.; Kato, M.; Miyachi, H.; Hashimoto, Y. *J. Enzyme Inhib.* **1999**, *14*, 259. (b) Bailleux, V.; Vallee, L.; Nuyts, J. P.; Vamecq, J. *Chem. Pharm. Bull.* **1994**, *42*, 1817. (c) Shibata, Y.; Sasaki, K.; Hashimoto, Y.; Iwasaki, S. *Chem. Pharm. Bull.* **1996**, *44*,156.
13. Sena, V. L. M.; Srivastava, R. M.; Oliveira, S. P.; Lima, V. L. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2671.
14. (a) Olson, V.R.; Feldman, H.B. *J. Am. Chem. Soc.* **1937**, *59*, 2003. (b) Hofle, G.; Steglich, V.; Vorbruggen, H. *Angew Chem., Int. Ed. Engl.* **1978**, *17*, 569. (c) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (d) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702. (e) D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963. (f) Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, 57, 7047. (g) Paul, S.; Nanda, P.; Gupta, R.; Laupy, A. *Tetrahedron Lett.* **2002**, *43*, 4261.
15. (a) Ahmed, S.; Iqbal, J. *J. Chem. Soc., Chem. Commun.***1987**, 114. (b) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342. (c) Zhao, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559. (d) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611. (e) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743. (f) Chen, C.-T.; Kuo, J.-H.; Li, C.-H.; Barhate, N. B.; Hon, S.-W.; Li, T.-W.; Chao, S.-D.; Liu, C.-C.; Li, Y.-C.; Chang, I.-H.; Lin, J.-S.; Liu, C.-J.; Chou, Y.-C. *Org. Lett.* **2001**, *3*, 3729. (i) Choudary, B. M.; Kantam, M. L.; Bharati, B.; Reddy, V. C. R. *J. Mol Cat. A.* **2001**, *168*, 69. (j) Li, A-X.; Li, T-S.; Ding, T-H. *Chem. Commun.* **1997**, 1389. (k) Li, T.-S.; Li, A.-X. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913. (l) Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dangare, M. K. *Synlett* **2001**, 206. (m) Chavan, S. P.; Anand, R.; Pasupathy, K.; Rao, B. S. *Green Chemistry* **2001**, 320.
16. Beckwith, A. L. J. *In The Chemistry of Amides*; Zabicky, J. Ed.; Wiley-Interscience: New York, 1970; 96.
17. (a) Huebner, C. F.; Lucas, R.; MacPhillamy, H. B.; Troxell, H. A. *J. Am. Chem. Soc.* **1955**, *77*, 469. (b) Singh, B. *Tetrahedron Lett.* **1971**, 321. (c) De Fevand, R. J.; Strickler, P. D. *J. Org. Chem.* **1963**, *28*, 2915. (d) Bassett, H. L.; Thomas, C. R. *J. Chem. Soc.* **1954**, 1188. (e) Yang, K.-W.; Cannon, J. G.; Rose, J. G. *Tetrahedron Lett.* **1970**, 1791.
18. Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 5745.
19. Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett* **1999**, 729.
20. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
21. Watanabe, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 285.
22. Hogberg, T.; Strom, P.; Ebner, M.; Ramsby, S. *J. Org. Chem.* **1987**, *52*, 2033.
23. Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, *61*, 3088.
24. Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2223.
25. Katritzky, A. R.; He, H. -Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
26. (a) Atkinson, R. S.; Barker, E.; Sutcliffe, M. J. *Chem. Commun.* **1996**, 1051. (b) Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 3751. (g) Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843. (c) Helgen, C.; Bochet, C. G. *Synlett* **2001**, 1968 (d) Kang, Y.-J.; Chung, H.-A.; Kim, J.-J.; Yoon, Y.-J. *Synthesis* **2002**, 733. (e) Kim, T.H.; Yang, G.-Y *Tetrahedron Lett.* **2002**, *43*, 9553. (h) Kondo, K.; Kurosaki, T.; Murakami, Y. *Synlett*

1998, 725. (f) Petricci, E.; Botta, M.; Corelli, F.; Mugnaini, C. *Tetrahedron Lett.* **2002**, *43*, 6507. (i) Humphrey, C. E.; M. Easson, A.M.; Tierney, J. P.; Turner, N. J. *Org. Lett.* **2003**, *5*, 849.

27. Benz, G.; In *Comprehensive Organic Synthesis* Trost, B.M., Fleming, I. Eds.; Pergamon: Oxford, 1991; vol. 6, p.381.
28. Sheehan, J.C.; Hess, G.P. *J. Am. Chem. Soc.* **1995**, *77*, 1067; Lawrence, R.H.; Biller, S.A.; Fryszman, O.M.; Poss, M.A. *Synthesis* **1997**, 553. (b) Burnell-Curty, C.; Roskamp, E. J. *Tetrahedron Lett.* **1993**, *34*, 5193. (c) Froyen, P. *Synth. Commun.* **1995**, *25*, 959. Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323.; Vago, I.; Greiner, I. *Tetrahedron Lett.* **2002**, *43*, 6039.
29. Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Green Chemistry* **2000**, *2*, 104.
30. Wakasugi, K. Nakamura, A.; Tanabe, Y. *Tetrahedron Lett.* **2001**, *42*, 7427.
31. Jursic, B.S.; Zdravkovski, Z. *Synth. Commun.* **1993**, *23*, 2761.
32. Shambhu, M. B.; Digenis, G.A *Tetrahedron Lett.* **1973**, *18*, 1627.
33. Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980**, *45*, 4162.
34. Haridasan, V. K.; Ajayaghosh, A.; Pillai, V. N. R. *J. Org. Chem.* **1987**, *52*, 2662.
35. Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40*, 6177.
36. Girard, C.; Tranchant, I.; Niore, P.-A.; Herscovici, J. *Synlett* **2000**, 1577.
37. Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155.
38. Kita, Y.; Haruta, J.-i.; Yasuda, H.; Fukunaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697.
39. Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc., Perkin Trans.* 1, **1999**, 2233.
40. Omuaru, V. O. T. *Indian J. Chem.* **1998**, *37B*, 814.
41. (a) Gholap, A. D.; Patel, V. M.; Patil, R. C.; Balasubramaniyan, P.; Balasubramaniyan, V. *Indian J. Chem. Edn.* **1980**, *7*, 26. (b) Patel, V. M.; Balasubramaniyan, V. *Indian J. Chem., Sect. B* **1977**, *15B*, 1142.
42. Paraskewas, S.; Lapatsanis, L. *Synthesis* **1979**, 457.
43. Ravinder, V.; Rani, P. U.; Balaswamy, G. *Indian J. Heterocyclic Chem.* **2004**, *14*, 73.
44. Sun, W. S.; Park, Y. S.; Yoo, J.; Park, K. D.; Kim, S. H.; Kim, J. -H.; Park, H. -J. *J. Med. Chem.* **2003**, *46*, 5619.
45. Garanados, A. M.; Rossi, R. H. de *J. Org. Chem.* **2001**, *66*, 1548.
46. Khajavi, M.S.; Nikpour, F.; Hajihadi, M.; *J. Chem. Res. (S)* **1996**, 96.
47. Omuaru, Victor O. T.; Boisa, N.; Obuzor, G.U. *Indian J. Chem., Sect. B* **1998**, *37B* (*7*), 704.
48. Sena, V. L. M.; Srivastava, R. M.; Oliveira, S. P.; Lima, V. L. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2671.
49. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry* ., 5th ed.; Longman: Singapore, **1989**.
50. Dewitt, H. D.; Indersoll, A. W.; *J. Am. Chem. Soc.* **1951**, *73*, 3359.
51. Richardson, A. C.; McLauchlan, K. A. *J. Chem. Soc.* **1962**, 2499.
52. (a) Roseman, S.; Ludowieg, J. *J. Am. Chem. Soc.* **1954**, *76*, 301. (b) Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* **1992**, *22*, 2703. (c) Sakakibara, T.; Watabe, Y.; Yamada, M.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 247.
53. Kim, D.-H.; Rho, H.-S.; You, J. W.; Lee, J. C. *Tetrahedron Lett.* **2002**, *43*, 277.
54. Besan, J.; Kovacs, M.; Nadasy, M. *Hungarian Journal of Industrial Chemistry* **1979**, *7*, 77.

Section 2B: Present Work

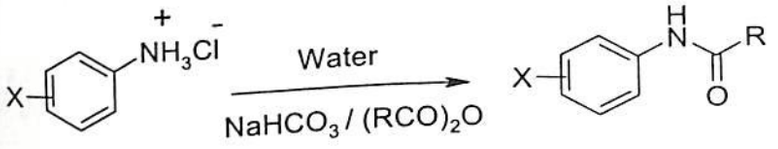
2B.1. Mild and Eco-friendly Chemoselective Acylation of Amines in Aqueous Medium

The acylation of amines is a fundamental process and is often used in organic synthesis as it provides an efficient and inexpensive means for protecting an amino functionality in a multi-step synthetic process. Owing to the nucleophilic and basic character of amines they must be blocked with a protecting group during a multi-step synthesis, *e.g.* in the synthesis of a diverse array of biological molecules such as amino acids, peptides, glycopeptides, aminoglycosides, β-lactams, nucleosides, sphingosines and alkaloids. *N*-acyl derivatives are well-known protecting groups for the amines.[1] Acylation of amines is sometimes carried out using acyl transfer reagents[2] such as *N*-acetyl-*N*-acyl-3-amino-quinazolinones, 2-acyl pyridazin-3-one, *N*-acyl-2-methylamino-2-thiazoline,*N*-acyl-5,7-dinitroindolines, chiral 2-acetyl amino-2'-diacetylamino-1,1'-binaphthyl, ortho substituted *N,N*-diacetyl anilines, *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl)methanesulfonamides, and at the other times with acetic acid,[3] but acylating reagents such as acyl chlorides and acid anhydrides are usually employed in presence of either acidic[4] or basic catalysts.[5] These reactions have advantages and drawbacks, recently described by Katritzky.[6] Most of the acetyl transfer reagents are expensive and are obtained by acetylation with acetylating agents making them unsuitable for large scale reactions. The reaction of carboxylic acids with amines is of less preparative value.[7]Some of these reagents and catalysts lead to waste as well as some reactions involving organic solvents is often toxic and polluting, hence unacceptable in the present days. The eco friendly practical pathways are limited due to number of reasons.

A crucial factor for green chemical processes in solution involves the choice of cheap, safe and non-toxic solvents. Water being abundant in nature is the obvious choice. Water is not just a ''green'' solvent, but also has special effects on reactions arising from intra- and inter-molecular non-covalent interactions leading to novel solvation and assembly processes. Since Breslow's discovery of a positive effect on the reaction rates and selectivities of the Diels Alder reaction, which is otherwise known to be in sensitive to solvent effects, special attention has been focused on the origin of the aqueous acceleration.[8] Despite the solubility problems of organic substrates in water, after this seminal

contribution there has been an upsurge in interest in using water as the solvent, not only to enhance the reaction rates but also to perform organic reactions that would otherwise be impossible. Several books and reviews have been devoted to such uses.[9] Thus; development of an efficient and convenient synthetic methodology in water is an important area of research. Considering the importance of acylation as well as environmental factors acylation of amines in an aqueous medium has been described in this chapter, which fulfils many of the above requirements. Acetylation of aromatic amines has been carried out in aqueous media but with a limited number of substrates.[10] The same has been achieved using amine, hydrochloric acid, concentrated solution of sodium acetate (5 M) and acetic anhydride.[11]

We thought to add sodium bicarbonate, which is cheaper than sodium acetate to an aqueous solution of amine hydrochloride, which will liberate free amine and react with acetic anhydride and convert the liberated acetic acid to sodium acetate in the medium. Aliphatic and aromatic amines are basic in nature and can easily be protonated by mineral acids. To test our hypothesis and to optimise the reaction conditions, aniline **78** was converted to water-soluble anilinium hydrochloride using aqueous HCl. The protonated ammonium species is non-nucleophilic due to non-availability of the lone pair of electrons on the nitrogen atom. Thus, when acetic anhydride was added to an aqueous solution of amine hydrochloride no acetylation occurred. However, upon addition of basic salts, such as $NaHCO_3$ to the above medium, free amines were liberated, which reacted immediately with acetic anhydride, precipitating the acetylated product with the evolution of carbon dioxide, Scheme 2B.1. The reaction works best when the final pH of the medium is *ca.* 5.5, approximately one pKa unit higher compared to that of acetic acid (pKa 4.8).



X = H, CH_3, OCH_3, OH, NH_2, F

R = CH_3, C_2H_5, C_6H_5, CH_2CH_2COOH, CH=CHCOOH, C_6H_4COOH

Scheme 2B.1. *N*-Acylation of Amines in the Form of Amine Hydrochlorides

Protonation of amine in an acidic medium has been confirmed by hypochromic shifts at 226 nm and 276 nm for ($\pi - \pi^*$) and (n- π^*) respectively, by titrating a dilute solution of 2-fluoroaniline **79** with

a dilute solution of HCl using UV spectrophotometer. A hyperchromic shift of these transitions upon addition of a dilute solution of sodium bicarbonate confirms the regeneration of free amines. This methodology was successfully applied to several amines, which underwent acetylation very smoothly in good yields

Table 2.1. *N*-Acetylation[a] of Amines with Acetic Anhydride

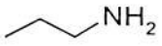
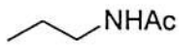
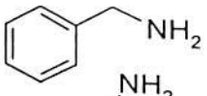
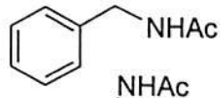
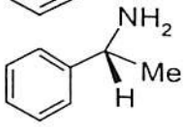
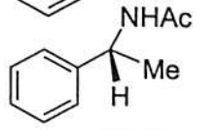
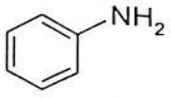
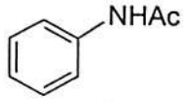
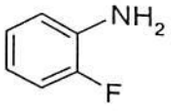
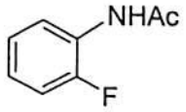
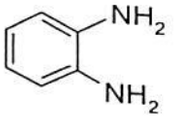
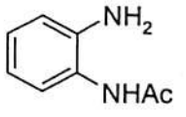
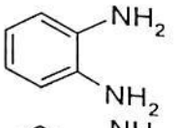
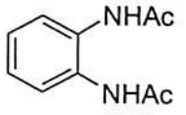
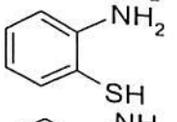
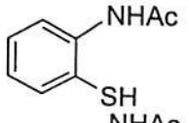
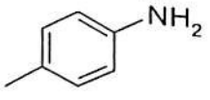
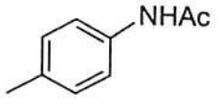
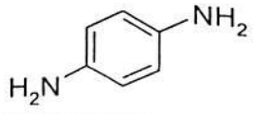
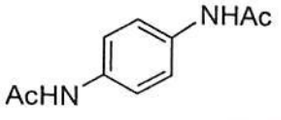
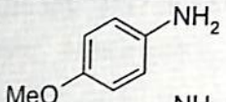
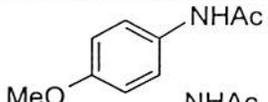
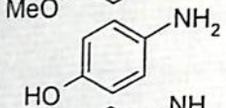
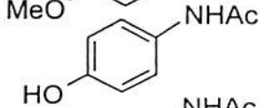
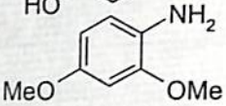
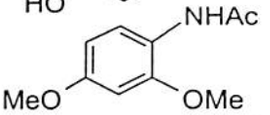
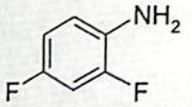
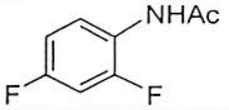
Substrate		Product		Yield[b] (%)
	(72)		(72g)	63
	(73)		(73g)	71
	(74)		(74g)	94
	(76)		(76g)	79
	(78)		(78g)	93
	(79)		(79g)	94
	(81)		(81g')	93[c]
	(81)		(81g)	85[d]
	(82)		(82g)	26[e]
	(84)		(84g)	97
	(86)		(86g)	93[d]

Table Contd.....

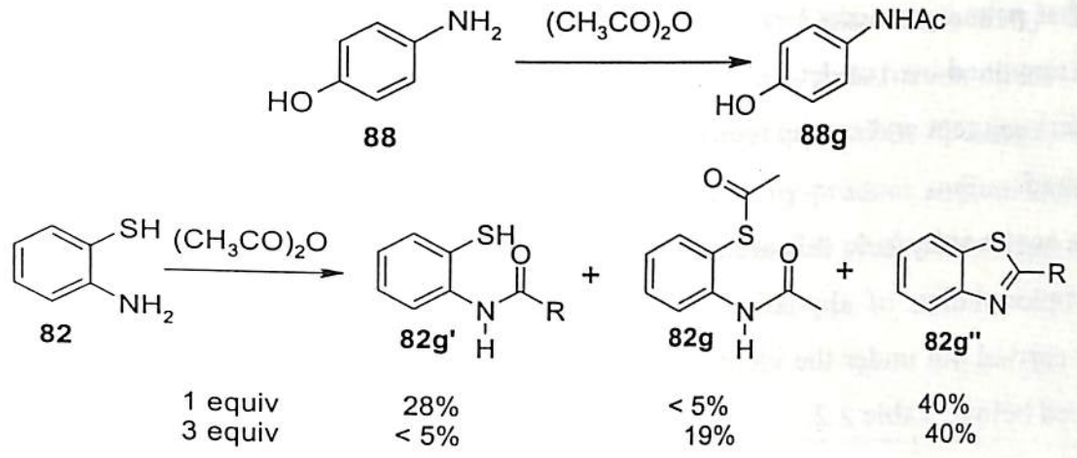
Table 2.1. *N*-Acetylation[a] of Amines with Acetic Anhydride

Substrate	Product	Yield[b](%)
 (87)	 (87g)	95
 (88)	 (88g)	95
 (91)	 (92g)	87
 (92)	 (92g)	85

[a]Confirmed by comparison with IR, ^1H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]Based on the recovery of starting material. [d]3 equivalents of Ac_2O were used. [e]Rest of the products being diacetylated product **82g** and 2-methyl-benzothiazole **82g''**.

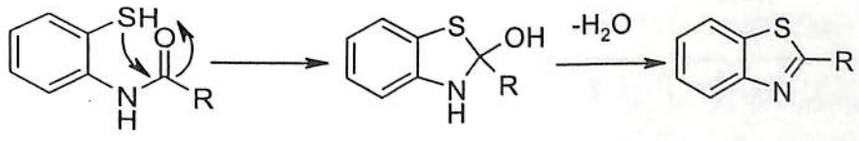
The optimised acetylation reaction was performed by adding 1.5 equivalent of acetic anhydride to the substrate amine hydrochloride (pH *ca.*1.6) dissolved in water followed by addition of $NaHCO_3$ in one lot to obtain a final pH *ca.* 5.5. Under the optimised reaction conditions aliphatic **72-74** and various aromatic amines gave good yields of product. Chiral amine **76** can be easily acetylated with complete retention of optical activity. Aromatic primary amines of varying electronic and steric factors were examined. Aniline **78**, aniline with electron-donating substituents such as NH_2 (**81**, **86**), SH (**82**), CH_3 (**84**), OMe (**87**, **91**) OH (**88**) in ortho and /or para position in the aromatic ring and with electron-withdrawing substituent such as F (**79**, **92**) gave equally satisfactory yield, (Table 2.1). It is interesting to note that in most of these cases the product precipitates in less than 5 minutes. It has been observed that acetylation of aryl amines when performed in an organic reaction medium, substrate containing electron-donating groups in the aromatic ring facilitate the reaction, whereas electron-withdrawing groups slow down the reaction. No such effect was observed by the present methodology and all the substrates react with equal rates. However, aryl amines gave better yield as compared to alkyl amines. The results have been summarised above in Table 2.1.

As can be seen from the above table, the acetylation of 2-aminothiophenol **82** and 4-aminophenol **88** produced the corresponding acetamides; the phenolic and thiophenolic moiety remained untouched with one equivalent of the reagent. The selective acetylation of 4-aminophenol **88** is of significant interest for the preparation of antipyretic and analgesic drugs paracetamol **88g**. Taking advantage of the differential reactivity between nucleophiles, we were able to carry out intramolecular chemoselective acetylation of amines over phenols and thiols, Scheme 2B.2.



Scheme 2B.2. Intermolecular and Intrameolecular Chemoselectivity of Amines

The reaction of 2-aminothiophenol **82** with one equivalent of acetic anhydride forms an interesting heterocyclic product 2-methylbenzothiazole **82g''** (*ca.*40%) along with a trace amount of diacetylated product **82g** (<5 %) and monoacetylated product **82g'** (>28%) and. However treatment of 3 equivalents of acetic anhydride with 2-aminothiophenol **82** results in the formation of diacetylated product **82g** (19%), monoacetylated product **82g'** (<5%) and 2-methylbenzothiazole **82g''** (40%), Scheme 2B.2. The formation of 2-methyl-benzothiazole **82g''** is via acetylation of amine followed by a nucleophilic attack of thiophenolic group on the carbonyl carbon of the amide and subsequent water elimination. Formation of 2-methyl-benzothiazole **82g''** confirmed the chemoselective acetylation of amines over thiols, Scheme 2B.3.

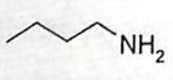
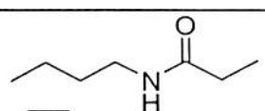
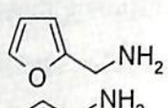
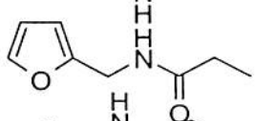
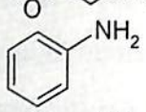
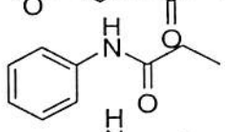
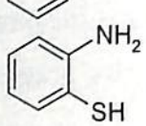
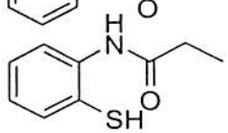
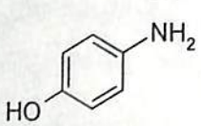
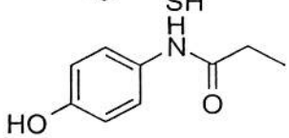


Scheme 2B.3

The monoacetylation of 1,2-phenylenediamine **81** demonstrates the efficacy of the method. However, no chemoselectivity was observed for symmetrical diamine1,4-phenylene diamine **86** even with one equivalent of the acetic anhydride. In most of these cases the acetylated product precipitated out from the aqueous reaction medium and in few cases it was extracted with ethyl acetate to yield the pure product, except in the case of substrates **72** and **73,** in which the product required extraction and in the case of substrates **81** and **82** the products required extraction as well as chromatographic separation. It was found that primary amines underwent smooth acetylation where as secondary amines such as diphenylamine remained inert under the present experimental conditions. The by-product sodium acetate is a useful buffering agent and can be recovered from the aqueous effluent by concentrating the aqueous medium, if desired.

Besides acetic anhydride this method is also amenable to acyclic, cyclic, aliphatic and aromatic anhydrides. Propionylation of aliphatic **73, 75,** and aromatic amine **78, 82, and 88** using propionic anhydride was carried out under the identical conditions as described for acetic anhydride. Results have been summarised below, Table 2.2.

Table 2.2 *N*-Propionylation[a] of Amines with Propionic Anhydride

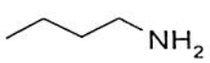
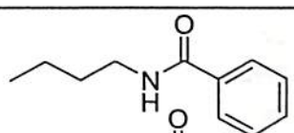
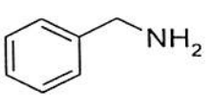
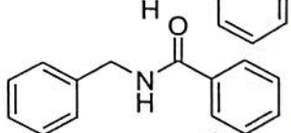
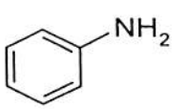
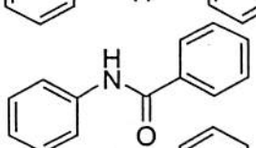
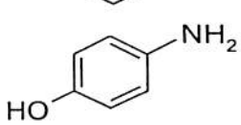
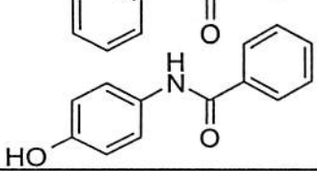
Substrate		Product		Yield[b] (%)
	(73)		(73h)	83
	(75)		(75h)	95
	(78)		(78h)	93
	(82)		(82h)	08[c]
	(88)		(88h)	96

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields.[c]Rest of the products being 2-ethyl-benzothiazole.

As can be seen from the table, substrate 2-aminothiophenol **82** gave heterocyclic product 2-ethylbenzothiazole **82h''** as the exclusive product and *N*-(2-mercapto-phenyl)-propionamide **82h'** as the minor product there by supporting the chemoselective propionylation of amines over thiols. Here again amino functionality has been chemoselectively propionylated in the presence of phenols and thiols as demonstrated for 4-aminophenol **88** and 2-aminothiophenol **82** respectively.

Benzoylation of aliphatic amine **73**, benzylamine **74**, aromatic amine **78** and chemoselective benzoylation of 4-aminophenol **88** further proves the efficacy and chemoselectivity of the present aqueous methodology. In this case benzoic anhydride (1 equiv) was added to an amine hydrochloride solution followed by solid sodium bicarbonate. The product precipitated in to lumps, which can be recrystallised either from acetonitrile or from ethyl acetate. The by-product sodium benzoate can be recovered from the aqueous medium if desired. Results pertaining to this study have been summarised in Table 2.3.

Table 2.3 *N*-Benzoylation[a] of Amines with Benzoic Anhydride

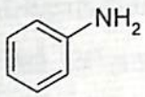
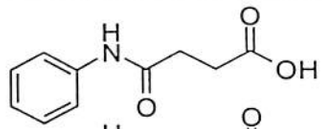
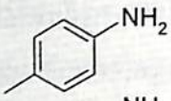
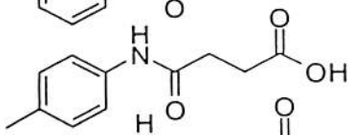
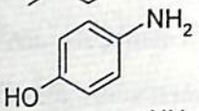
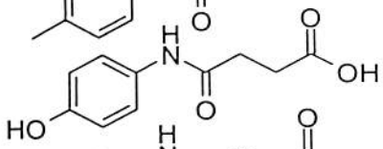
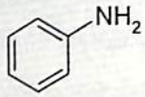
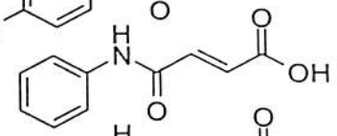
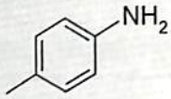
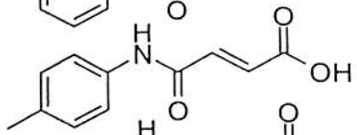
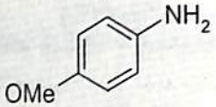
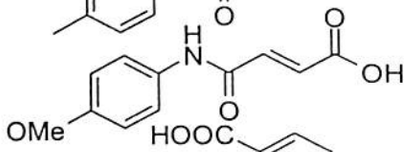
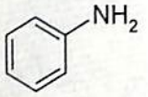
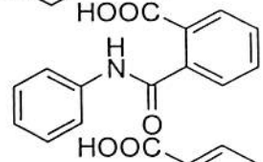
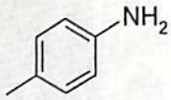
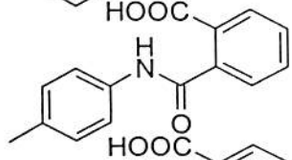
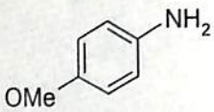
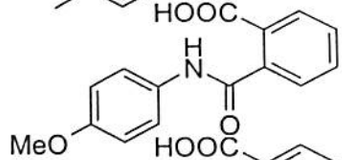
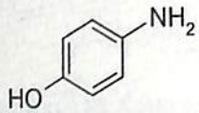
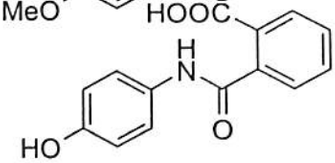
Substrate		Product		Yield[b](%)
	(73)		(73k)	85
	(74)		(74k)	88
	(78)		(78k)	91
	(88)		(88k)	93

[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields.

The novel aspect of the present methodology was applied to cyclic anhydrides such as succinic and maleic anhydride. In this case 1.2 equivalent of the anhydride was used per equivalent of amine. Aniline **78** as well as aniline with various substituents in the aromatic ring such as CH_3 (**84**), OMe (**87**)

and OH (**88**) reacted with equal ease with succinic, maleic and phthalic anhydride to yield the corresponding acylates, Table 2.4

Table 2.4 Acylation[a] of Amines with Succinic, Maleic and Phthalic Anhydride

Substrate		Product		Yield[b] (%)
	(78)		(78m)	79
	(84)		(84m)	82
	(88)		(88m)	86
	(78)		(78n)	78
	(84)		(84n)	83
	(87)		(87n)	85
	(78)		(78o)	86
	(84)		(84o)	84
	(87)		(87o)	81
	(88)		(88o)	88

[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields.

The reaction took place readily with simultaneous precipitation of solid product. Finally the methodology was tested with an aromatic cyclic anhydride, phthalic anhydride. Finely powdered phthalic anhydride 1 equivalent was added to the amine hydrochloride solution followed by solid sodium bicarbonate. This has been tested with a number of aromatic amines and the result is summarised in Table 2.4.

In conclusion, this method represents a tremendous opportunity for the practice of green chemistry. The notable advantages of the method are: (i) operational simplicity, (ii) moderate to good yields, (iii) no chromatographic separation, (iv) excellent selectivity for aryl amines over phenols and thiols and (v) general applicability. The method is environmentally friendly with respect to by-products and effluent are innocuous. The by-product sodium acetate and benzoate are useful buffering agents. We believe this will present a better and more practical alternative to the existing methodologies for selective acylation of primary amines and thus will find useful application in the synthesis of complex natural products where selective protection of hydroxy, thio and amino group is required.

2B.1.1. References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*, Georg Thieme Verlag: New York, 1994.
2. (a) Atkinson, R. S.; Barker, E.; Sutcliffe, M. J. *Chem. Commun.* **1996**, 1051. (b) Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 3751. (c) Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843. (d) Kang, Y.-J.; Chung, H.-A.; Kim, J.-J.; Yoon, Y.-J. *Synthesis* **2002**, 733. (e) Helgen, C.; Bochet, C. G. *Synlett* **2001**, 1968 (f) Kim, T.H.; Yang, G.-Y *Tetrahedron Lett.* **2002**, *43*, 9553. (g) Kondo, K.; Kurosaki, T.; Murakami, Y. *Synlett* **1998**, 725.
3. (a) Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Green Chemistry* **2000**, *2*, 104. (b) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2223. (c) Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, *61*, 3088. (d) Balaji, B. S.; Sasidharan, M.; Kumar, R.; Chanda, B. *Chem. Commun.* **1996**, 707. (e) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 9063.
4. Chen, C.-T.; Kuo, J.-H.; Li, C.-H.; Barhate, N. B.; Hon, S.-W.; Li, T.-W.; Chao, S.-D.; Liu, C.-C.; Li, Y.-C.; Chang, I.-H.; Lin, J.-S.; Liu, C.-J.; Chou, Y.-C. *Org. Lett.* **2001**, *3*, 3729. (b) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342. (c) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611. (d) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743. (e) Zhao, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559. (f) Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215. (g) Li, T.-S.; Li, A.-X. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913. (h) Chavan, S. P.; Anand, R.; Pasupathy, K.; Rao, B. S. *Green Chemistry* **2001**, 320. (6i) Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dangare, M. K. *Synlett* **2001**, 206. (j) Sabitha, G.; Reddy, B. V.

S.; Srividya, R.; Yadav, J.S. *Synth. Commun.* **1999**, *29*, 2311. (k) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877. (l) Choudary, B. M.; Kantam, M. L.; Bharati, B.; Reddy, V. C. R. *J. Mol Cat. A.* **2001**, *168*, 69. (m) Li, A-X.; Li, T-S.; Ding, T-H. *Chem. Commun.* **1997**, 1389. (n) Ahmed, S.; Iqbal, J. *J. Chem. Soc., Chem. Commun.***1987**, 114.

5. (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (b) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702. (c) D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963. (d) Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047. (e) Paul, S.; Nanda, P.; Gupta, R.; Laupy, A. *Tetrahedron Lett.* **2002**, *43*, 4261.
6. Katritzky, A. R.; He, H. -Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
7. March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 416.
8. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
9. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (c) Herrmann, W. A.; Kohlpaintner, C.W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524. (d) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. (e) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (f) Kobayashi, S. *Synlett* **1994**, 689. (g) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (h) Shu, K.; Kei, M. *Acc.Chem. Res.* **2002**, *35*, 209. (i) Okuhara, T. *Chem. Rev.* **2002**, *102*, 3641. (j) Pae, A. N.; Cho, Y. S. *Current OrganicChemistry* **2002**, *6*, 715.
10. (a) DeWitt, H. D.; Indersoll, A.W. *J. Am. Chem. Soc.* **1951**, *73*, 3359. (b) Roseman, S.; Ludowieg, J. *J. Am. Chem. Soc.* **1954**, *76*, 301. (c) Richardson, A. C.; McLauchlan, K. A. *J. Chem. Soc.* **1962**, 2499. (d) Kim, D. -H.; Rho, H. -S.; You, J. W.; Lee, J. C. *Tetrahedron Lett.* **2002**, *43*, 277. (e) Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* **1992**, *22*, 2703. (f) Sakakibara, T.; Watabe, Y.; Yamada, M.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 247.
11. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry.* 5th ed.; Longman: Singapore, **1989**.

2B.2. Chemoselective Acylation of Amines in Aqueous Medium

All the known aqueous acylation methods use acids, bases or combinations of both. One of the reasons for using an acid in an aqueous medium is to convert the amine into a water-soluble ammonium salt and the base is to neutralise the acid liberated from the anhydride. The use of mineral acids or bases makes the above method less attractive. Considering the environmental aspects, we looked for a greener alternative, devoid of any acidic or basic reagents.

In one of our ongoing projects we noticed the solubility of several aromatic and aliphatic amines in an aqueous medium in the presence of sodium dodecyl sulfate (SDS). The SDS concentration (2.31×10^{-4} M) required for the dissolution of several aromatic amines is much lower than the critical micelle concentration (8.3×10^{-3} M) of SDS, thus ruling out the possibility of micelle formation for the dissolution of amines. Initially, we speculated that the dissolution of the hydrogen donor amino group might be due to interaction with the hydrogen acceptor sulphonic acid group of SDS. But when the sodium salt of methane sulphonic acid was used instead of SDS, the amine did not dissolve at all; hence the possibility of the above type of interaction is ruled out. Other surfactants such as triton-X 100 and hexadodecyl ammonium bromide and phase transfer reagents such as tetrabutylammonium bromide can be used instead of SDS, thereby supporting the presence of hydrophobic-type interactions.

In our earlier method described in Section 2B.1.1, the protonated ammonium ion obtained by the dissolution of amines in an acidic medium is nonnucleophilic, requiring a base to regenerate the nucleophilic amine for acylation. However, when SDS is used for its dissolution it retains its nucleophilic character. This was further confirmed by UV spectral analysis. No change in UV absorption was observed at 226 nm and 276 nm when SDS was added to a dilute solution of 2-fluoroaniline **79**. Thus, when acetic anhydride was added to an SDS solution of an amine, acetylated products were obtained in moderate to good yields as shown in Table 2.5. It was gratifying to observe that the product precipitates from the reaction mixture in most of these cases. Increasing the ionic strength of the medium by adding sodium chloride to the reaction medium enhanced the amount of precipitation. To our utter surprise no base was required and the pH of the medium recorded at the end of the reaction was *ca.*7. Several examples illustrating this novel procedure for acetylation are presented in Table 2.5.

The optimised acetylation reactions were performed by adding acetic anhydride (7.5 mmol) to the substrate amine (5 mmol) dissolved in water (20 mL) with sodium dodecyl sulfate (20 mg). The method works well for aliphatic amines **71** and **73** when the anhydride was added in portions but gave

poor yields when it was added in one lot. Benzyl amine **74** and furfurylamine **75** gave the corresponding acetamide in good yields. Chiral amines **76** and **77** can be easily acetylated with complete retention of optical activity. Primary aryl amines **78-84, 86-89, 91, 92** with varying steric and electronic factors, were examined and all gave excellent yields of the corresponding acetamides. In most of these cases the products precipitated in less than 5 min. Thus unlike differential reactivities of amines with electron-donating and electron-withdrawing groups towards acetylation in organic medium, present aqueous method show similar reactivity. In most cases, the acetylated product precipitates from the aqueous reaction medium but in a few cases it was extracted with ethyl acetate to yield the pure product. However, in the case of substrates **81** and **82**, the products required chromatographic separation. It was found that primary amines underwent smooth acetylation whereas secondary amines and tertiary amines remained inert under the present experimental conditions. The results have been summarised in Table 2.5.

Table 2.5. Acetylation[a] of Amines with Acetic Anhydride

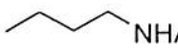
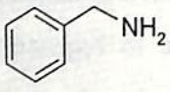
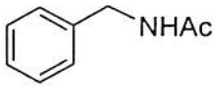
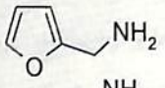
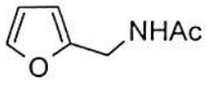
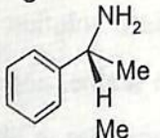
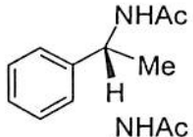
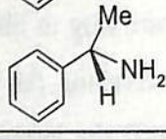
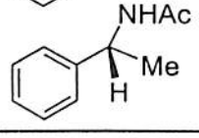
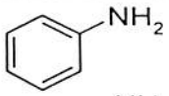
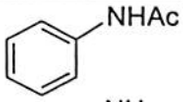
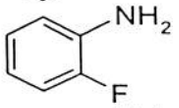
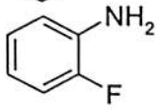
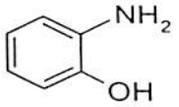
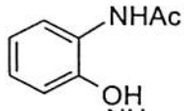
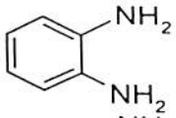
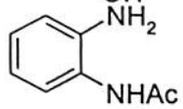
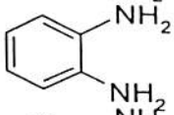
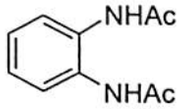
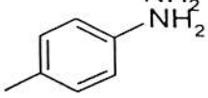
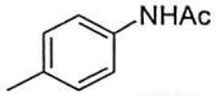
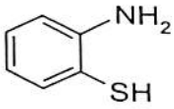
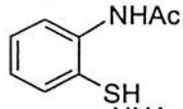
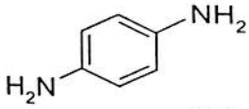
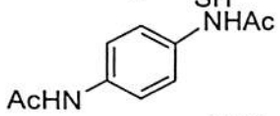
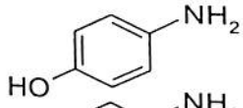
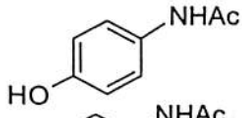
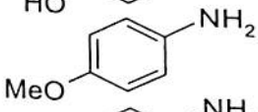
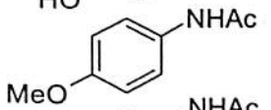
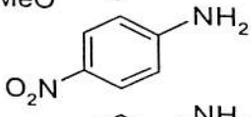
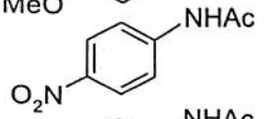
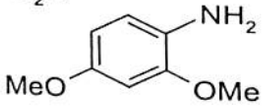
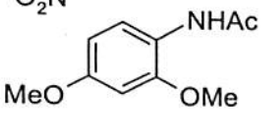
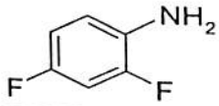
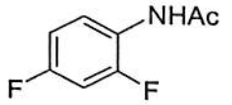
Substrate		Product		Yield[b] (%)
	(72)		(72g)	74
	(73)		(73g)	71
	(74)		(74g)	85
	(75)		(75g)	95
	(76)		(76g)	76
	(77)		(77g)	78

Table Contd.....

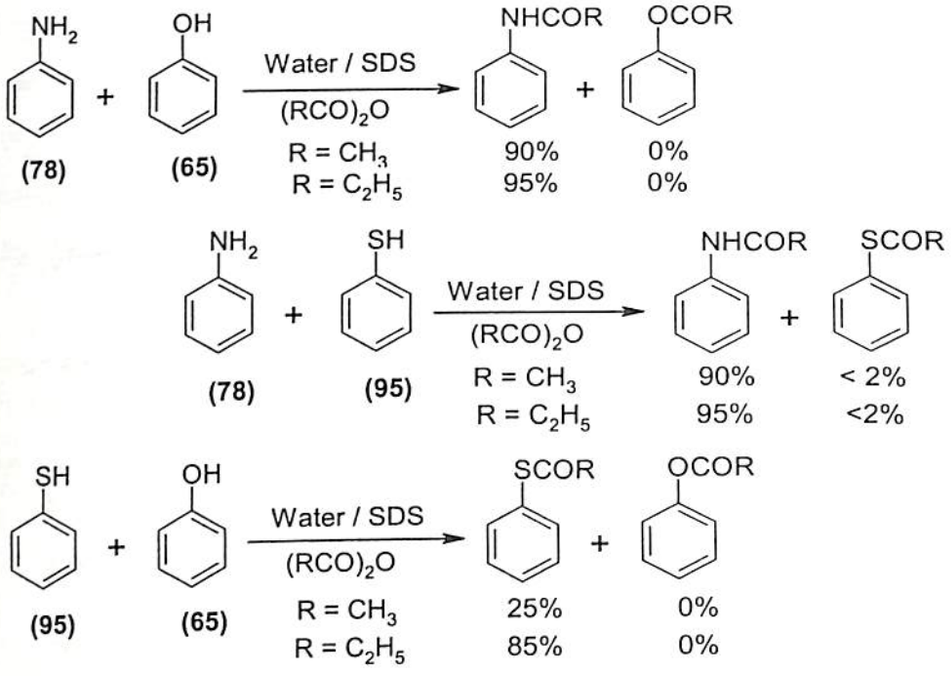
Table 2.5. Acetylation[a] of Amines with Acetic Anhydride

Substrate		Product		Yield[b](%)
	(78)		(78g)	83
	(79)		(79g)	81
	(80)		(80g)	84
	(81)		(81g')	91[c]
	(81)		(81g)	91[d]
	(84)		(84g)	83
	(82)		(82g')	28[e]
	(86)		(86g)	94[d]
	(86)		(86g)	99
	(87)		(87g)	83
	(89)		(89g)	86[f]
	(91)		(91g)	87
	(92)		(92g)	77

[a] Confirmed by comparison with IR, ^1H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]Based on the recovery of starting material. [d]3 equivalents of Ac_2O were used. [e]Rest of the products being 82g'and 82g.'' [f]The reaction was performed in 1:1 mixture of acetonitrile-water.

Taking advantage of the differential reactivity between various nucleophiles such as NH_2, OH, SH, which are susceptible to acetylation, we were able to carry out intermolecular chemoselective acetylation of amines over phenol and thiol. Thus, in a competitive acetylation reaction with an

equimolar mixture of aniline **78** and phenol **65** by this procedure, aniline was acetylated selectively leaving the phenol unaffected. In an analogous reaction between aniline **78** and thiophenol **95**, the thiophenol remained untouched. However, in a competitive reaction between phenol **65** and a thiophenol **95**, the thiophenol was selectively acetylated over phenol, Scheme 2B.4. This observation is in sharp contrast to selective acetylation of phenol over thiophenol in an organic medium.[1] Thus an exactly opposite selectivity was observed in an aqueous medium.

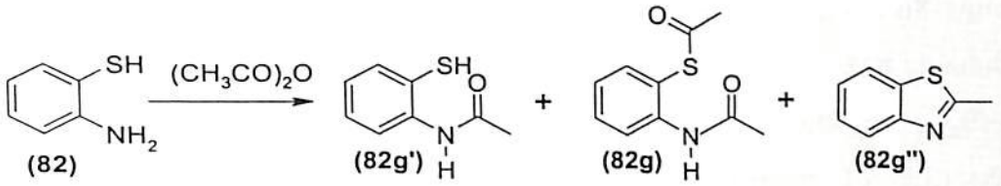


Scheme 2B.4 Intermoleclar Chemoselective Acetylation of Amines

Similar chemoselectivity was also observed for intramolecular reactions. Thus, acetylation of 2-aminophenol **80**, 2-aminothiophenol **82,** and 4-aminophenol **88** produced the corresponding acetamides; the phenolic and thiophenolic moieties remaining unaffected with one equivalent of the reagent. Chemoselectivity in symmetrical diamines were also studied under the identical conditions and was obsereved that the substrate1,2-phenylenediamine **81** gave exclusively the monoacetylated product **81g'** with one equivalent of acetic anhydride. However, similar chemoselectivity could not be achieved for substrate 1,4-phenylenediamine **86**, which gave exclusively the diacetylated product even with only one equivalent of the acetylating agent.

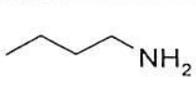
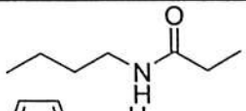
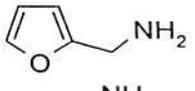
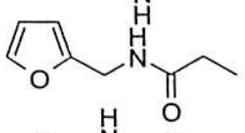
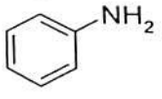
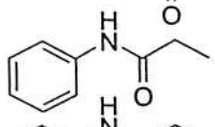
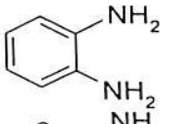
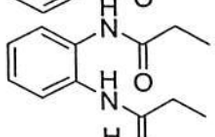
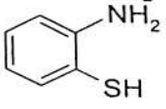
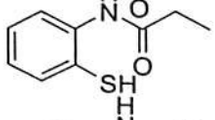
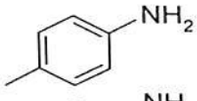
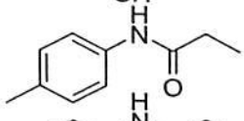
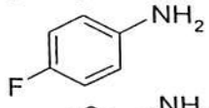
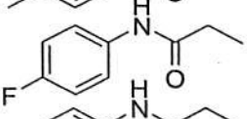
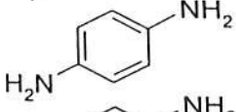
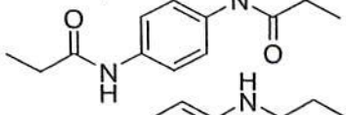
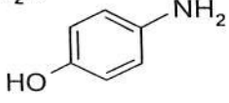
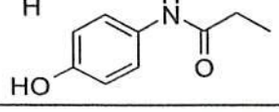
It is worth quoting that the chemoselectivity obtained in this acetylation procedure is identical in all respect to that described in the earlier section, 2B.1.1. An interesting heterocyclic product, 2-methyl-benzothiazole **82g''**, was obtained in 40% isolated yield, the rest being *N*-(2-mercapto-phenyl)acetamide

82g' and *S*-[2-(acetyl amino)-phenyl] thioacetic acid ester **82g**, when 2-aminothiophenol **82** was acetylated as shown in Scheme 2B.5. The formation of 2-methyl-benzothiazole **82g''** further demonstrates the chemo selective acetylation of amines over thiols. It may be mentioned here that the compound 2-methylbenzothiazole **82g''** is used in the synthesis of polycarbocyanine and thiocyanine dyes, as well as for (arylfuryl) benzothiazoles.



Scheme 2B.5 Chemoselective Acetylation of Amines

Table 2.6. Propionylation[a] of Amines with Propionic Anhydride

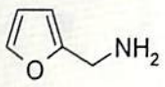
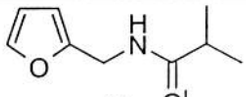
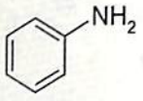
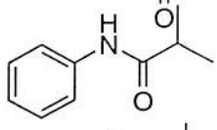
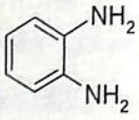
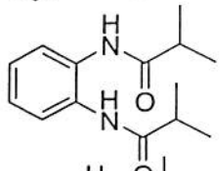
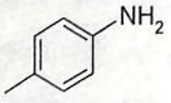
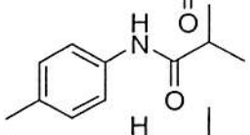
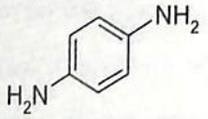
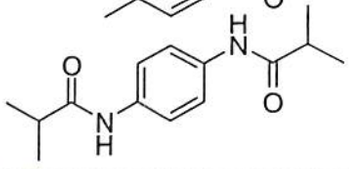
Substrate		Product		Yield[b] (%)
	(73)		(73h)	81
	(75)		(75h)	95
	(78)		(78h)	87
	(81)		(81h)	88[c]
	(82)		(82h')	05[d]
	(84)		(84h)	84
	(85)		(85h)	84
	(86)		(86h)	94[c]
	(88)		(88h)	97

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]3 equivalents of propionic anhydride were used. [c]Rest of the products being 82h and 82h.''

In order to extend the scope of the method further, the acylation of amines with propionic anhydride was carried out under identical conditions. Thus a variety of amines could be efficiently propionylated in good yields as shown in Table 2.6. Amines have been chemoselectively propionylated over phenols and thiols as demonstrated for 4-aminophenol **88** and 2-aminothiol **82** respectively. No chemoselectivity could be achieved with the symmetrical diamines 1,2-phenylenediamine **81** and 1,4-phenylenediamine **86** even with one equivalent of the anhydride. Substrate 2-aminothiol **82** gave 2-(ethyl)-benzothiazole **82h''** as the major product and *N*-(2-mercaptophenyl) propionamide **82h'** as the minor product suggesting chemo selective propionylation of amines over thiols.

The versatility of the present methodology is evident from its application to various other aliphatic, acyclic, cyclic, and aromatic anhydrides. When furfuryl amine **75**, aniline **78**, *p*-toluidine **84,** symmetrical diamines 1,2-phenylenediamine **81** and 1,4-phenylenediamine **86** were subjected to react with isobutyric anhydride under the similar reaction conditions, corresponding *N*-isobutyrates **75i, 78i, 81i, 84i, 86i** were formed in good yields as summarised below in Table 2.7.

Table 2.7. Isobutyrylation[a] of Amines with Isobutyric Anhydride

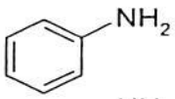
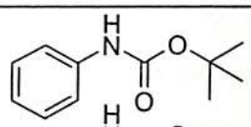
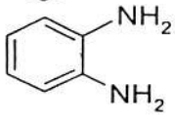
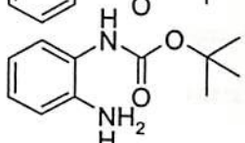
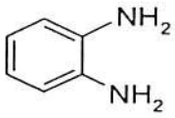
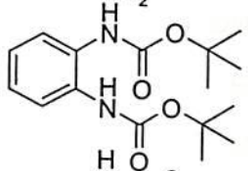
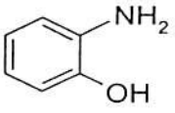
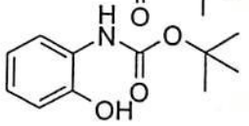
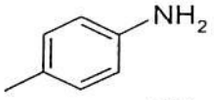
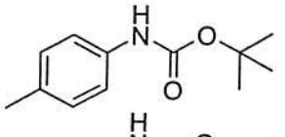
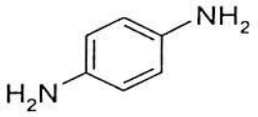
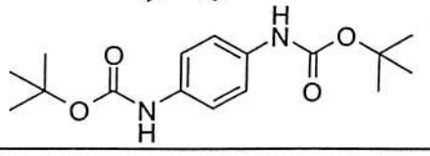
Substrate	Product	Yield[b] (%)
 (75)	 (75i)	95
 (78)	 (78i)	78
 (81)	 (81i)	76[c]
 (84)	 (84i)	79
 (86)	 (86i)	89[c]

[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]3 equivalents of isobutyric anhydride were used.

Boc anhydride is a low melting solid which is used for the acylation of amino functionality giving the *t*-butoxy carbonyl (Boc) derivatives. Present methodology was applied for synthesis of

various NHBoc derivatives of aniline **78**, 1,2-phenylene diamine **81**, 2-aminophenol **83**, *p*-toluidine **84**, and 1,4-phenylene diamine **86**. For substrate **81**, a mixture of mono and di product was formed with 1 equivalent of Boc anhydride which was purified by column chromatography, no such selectivity was observed for 1,4-phenylene diamine **86.** However, for both diamines, di products were obtained with 3 equivalents of the anhydride, Table 2.8.

Table 2.8. *tert*-Butoxycarbonylation[a] of Amines with Boc Anhydride

Substrate	Product	Yield[b] (%)
 (78)	 (78I)	95
 (81)	 (81I)	17[c]
 (81)	 (81I)	75[d]
 (83)	 (83I)	75
 (84)	 (84I)	78
 (86)	 (86I)	94[d]

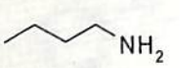
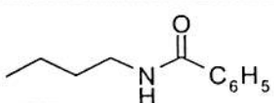
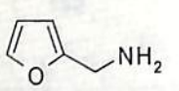
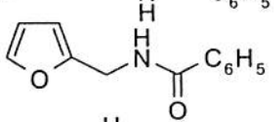
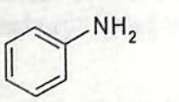
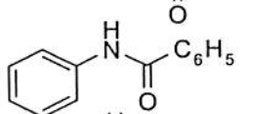
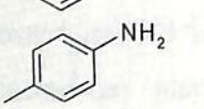
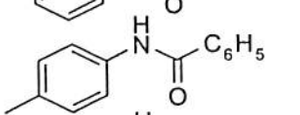
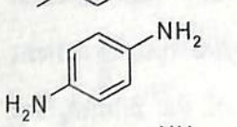
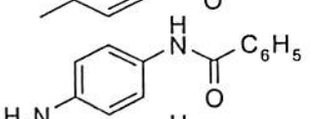
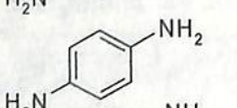
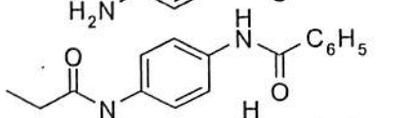
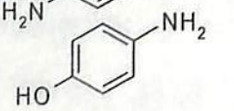
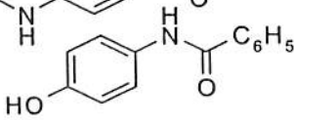
[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]Rest being diproduct and starting material with 1equivalent of Boc anhydride. [d]3 equivalents of Boc anhydride were used.

N-Benzoylated products are normally obtained from benzoic acid, benzoyl halides, benzoic anhydride, esters of benzoic acid, and benzoyl transfer reagents under different experimental conditions.[2] Employing the present aqueous method, various amines could be benzoylated in excellent yields. Although benzoic anhydride can be directly added to an aqueous solution of the amine, the reaction times are normally longer and some benzoic anhydride remained unreacted, giving lower yields and an impure product. However, better yields and pure product could be obtained by adding an acetonitrile (2 mL) solution of benzoic anhydride (5 mmol) to an aqueous solution of amine (5 mmol) dissolved in water and SDS. The reaction was usually completed within 5 min. Removal of acetonitrile under reduced pressure led to precipitation of the benzoylated product along with benzoic acid. The

precipitated benzoic acid was converted into water-soluble sodium benzoate by adding solid sodium hydrogen carbonate until effervescence ceases. The benzoylated product was filtered off to yield the pure compound. Sodium benzoate can be quantitatively recovered from the aqueous filtrate on concentration if required. The success of the method has been tested with aliphatic **73**, benzylic **74** and furfurylic **75** amines. Aryl amines such as **78** and **84** gave the corresponding benzamides in quantitative yields, results have been summarised in Table 2.7. Excellent intermolecular chemo selective benzoylation of amines over phenols and thiols, and thiols over phenol, has already been demonstrated in Scheme 2B.4 further supporting the preferential *S*-acylation over *O*-acylation in an aqueous medium.

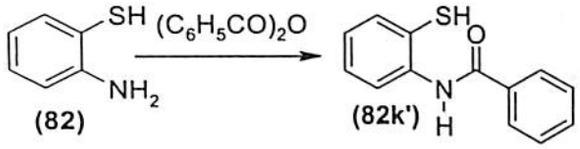
No chemoselectivity of the symmetrical diamine 1,4-phenylenediamine **86** was achieved when acetic and propionic anhydrides were used. However, excellent chemoselectivity could be achieved in the benzoylation of a symmetrical diamine in aqueous medium as shown for substrate **86**. This is probably because the monobenzoylated product **86h'** is highly hydrophobic and therefore precipitates from the aqueous medium before it can undergo dibenzoylation if one equivalent of benzoic anhydride is used. However, the dibenzoylated product could be obtained in quantitative yields with two equivalents of benzoic anhydride.

Table 2.9. Benzoylation[a] of Amines with Benzoic Anhydride

Substrate		Product		Yield[b]
	(73)		(73k)	88
	(75)		(75k)	92
	(78)		(78k)	96
	(84)		(84k)	97
	(86)		(86k)	91
	(86)		(86k)	98[c]
	(88)		(88k)	98

[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]2 equivalents of benzoic anhydride were used.

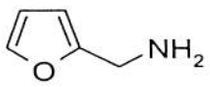
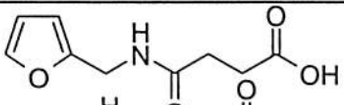
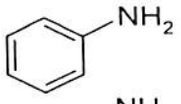
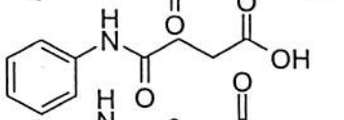
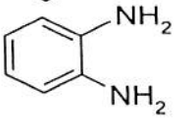
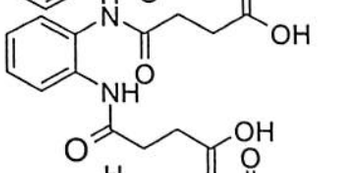
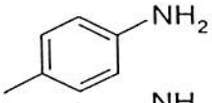
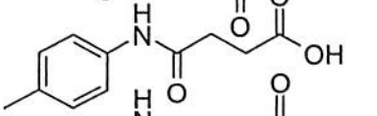
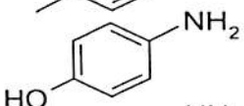
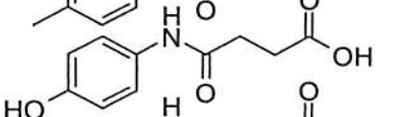
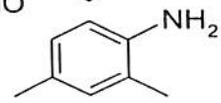
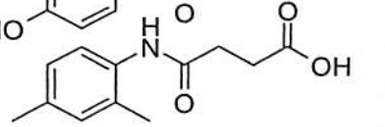
Again an intramolecular chemoselective benzoylation of amine has been shown with 2-aminothiol **82** and 4-aminophenol **88**.



Scheme 2B.6 Chemoselective Benzoylation of Amines

When the same reaction was repeated after an interval of one month it was observed that a different product **82k''** was obtained along with the expected *N*-(2-mercapto-phenyl)-benzamide **82k'.** The product **82k''**crystallised as yellow shiny crystals in ethanol. The shiny crystals when subjected to X-Ray diffraction studies revealed the structure as bis(2-benzoylaminophenyl)disulphide **82k''.** Analysis pertaining to the formation of this product is included in the last section of this chapter, in section 2B.1.2.1.

Table 2.10. Acylation[a] of Amines with Succinic Anhydride

Substrate		Product		Yield[b] (%)
	(75)		(75m)	75
	(78)		(78m)	82
	(81)		(81m)	83[c]
	(84)		(84m)	81
	(88)		(88m)	87
	(90)		(90m)	84

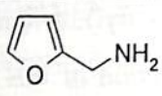
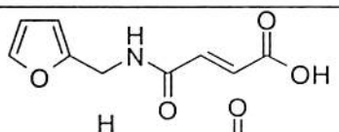
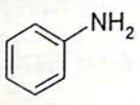
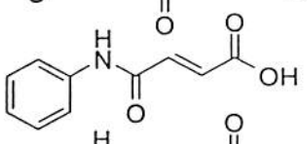
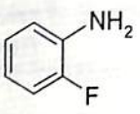
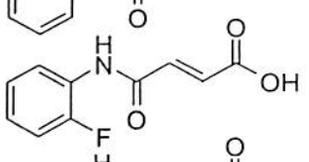
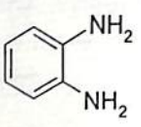
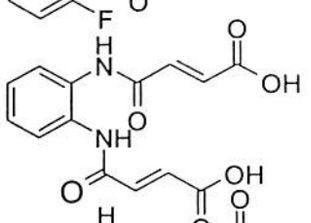
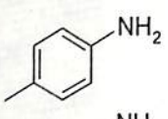
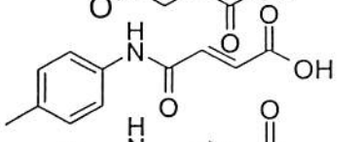
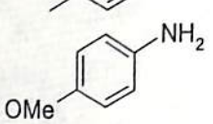
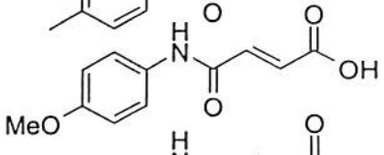
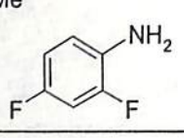
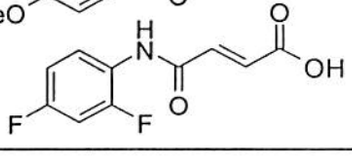
[a]Confirmed by comparison with IR, ^1H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]3 equivalents of succinic anhydride were used.

The (arylcarbamoyl) propenoic acids or maleamic acid and propanoic acid or succinamic acid have been prepared by the condensation of amine with maleic anhydride or succinic anhydride using a

variety of conditions.[3] The novel aspect of the present method was further applied to cyclic anhydrides such as succinic anhydride and maleic anhydride.

In the case of succinic anhydride, 1.2 equivalents of the anhydride was added in portions over a period of ten minutes to an aqueous solution of amine (1 equiv). The reaction took place readily with concurrent precipitation of the white solid product. This has been tested with a number of aromatic amines and the results are summarised in Table 2.10. Here again chemoselective succcinylation of amine has been achieved over phenols as shown for 4-amino phenol **88**.

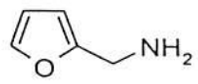
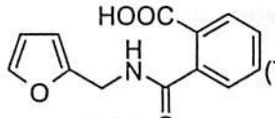
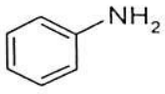
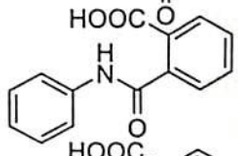
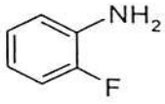
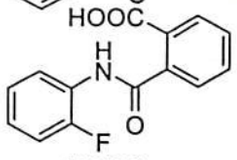
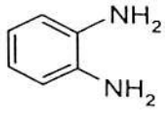
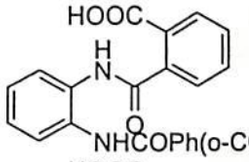
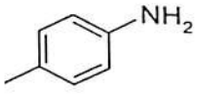
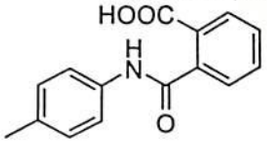
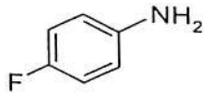
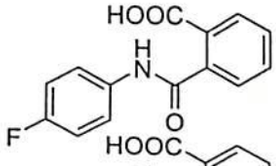
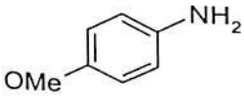
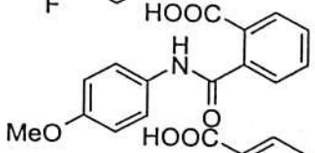
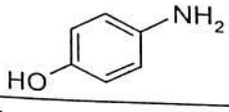
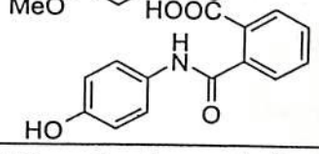
Table 2.11. Acylation[a] of Amines with Maleic Anhydride

Substrate	Product	Yield[b] (%)
 (75)	 (75n)	70
 (78)	 (78n)	84
 (79)	 (79n)	78
 (81)	 (81n)	79[c]
 (84)	 (84n)	84
 (87)	 (87n)	84
 (92)	 (92n)	79

[a] Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]2.4 equivalents of maleic anhydride were used.

Amines also react successfully with maleic anhydride giving good yields of the desired products under similar conditions (Table 2.11). All the amines tested could be converted into the corresponding aryl maleamic acid in good yields. These reactions were performed analogously to the reaction using succinic anhydride. It is worth mentioning that maleamic and succinamic acids are important classes of compounds having fungicidal, insecticidal and herbicidal properties.

Table 2.12. Acylation[a] of Amines with Phthalic Anhydride

Substrate		Product		Yield[b](%)
	(75)		(75o)	78
	(78)		(78o)	87
	(79)		(79o)	65
	(81)		(81o)	65[c]
	(84)		(84o)	85
	(85)		(85o)	93
	(87)		(87o)	89
	(88)		(88o)	91

[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]2.equivalents of phthalic anhydride were used.

Substituted *N*-arylphthalamic acids have been synthesised by the reaction of phthalic anhydride and arylamines under different conditions.[4] There has been a recent resurgence of interest in *N*-phenylphthalimide derivatives and their analogues because of their potential biological activity, such as amino peptidase inhibition,[5a] anticonvulsant activity,[5b] and promotion of tumor necrosis factor alpha (TNF alpha) production.[5c]

Again, owing to the insolubility of phthalic anhydride in water, an acetonitrile (5 mL) solution of phthalic anhydride (5 mmol) was added to an aqueous solution of amine (5 mmol). Arylphthalamic acid precipitated on evaporation of acetonitrile. The product was filtered and recrystallised from acetonitrile

to yield the crystalline compound in excellent yields. The reaction of phthalic anhydride with various amines is summarised in Table 2.12. It may be noted here that cyclic anhydrides react considerably more slowly than acyclic anhydrides when the reaction is catalysed by montmorillonite K-10 in an organic solvent. As demonstrated here, both acyclic and cyclic anhydrides react with different amines with equal ease when the reaction was performed in an aqueous medium.

Table 2.12. Acylation[a] of Amines with Phthalic Anhydride

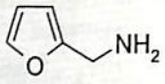
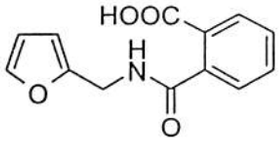
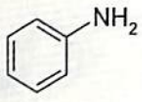
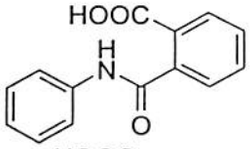
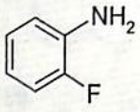
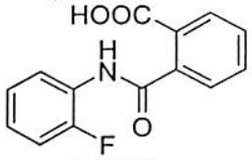
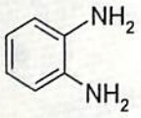
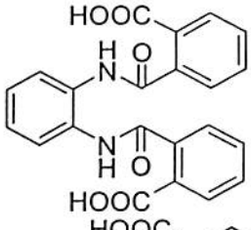
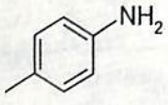
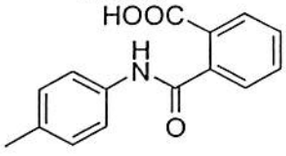
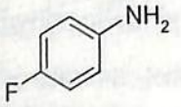
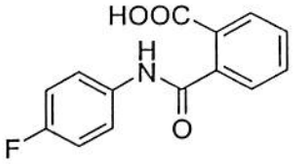
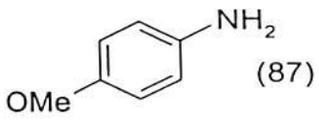
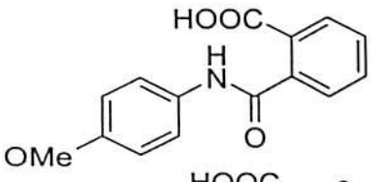
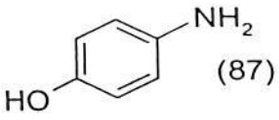
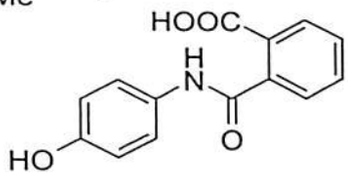
Substrate	Product	Yield[b]
 (75)	 (75o)	78
 (78)	 (78o)	87
 (79)	 (79o)	65
 (81)	 (81o)	65[c]
 (84)	 (84o)	85
 (85)	 (85o)	93

Table Contd...

Table 2.12. Acylation[a] of Amines with Phthalic Anhydride

Substrate	Product	Yield[b]
 (87)	 (87o)	89
 (87)	 (87o)	91

[a]Confirmed by comparison with IR, ^{1}H and ^{13}C NMR of the authentic sample. [b]Isolated yields. [c]2 equivalents of phthalic anhydride was used.

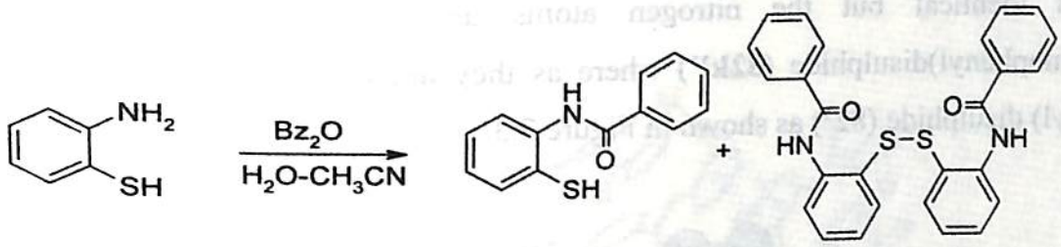
In conclusion, this method represents a tremendous opportunity for the practice of green chemistry. The reactions are, in general, very clean giving good to moderate yields with excellent selectivity, and no side products have been isolated. Amines were efficiently acylated by both cyclic and acyclic anhydrides by dissolving them in an aqueous medium with the help of a surfactant, sodium dodecyl sulfate (SDS). Cyclic and acyclic anhydrides reacted with equal ease with an amine, and amines with various stereo-electronic factors reacted at the same rates with an anhydride. Chemo selective acylation of amines in the presence of phenols and thiols and of thiols in the presence of phenols has been achieved. In addition, chromatographic purification of the acylated product is not required. The method is environmentally friendly with respect to by-products. Although procedures exist for acylation of amines, the simplicity and low cost of our procedure allow it to compete as a better practical alternative to the existing methods for selective acylation of primary amines in the presence of phenols and thiols and particularly of thiols in the presence of phenols. The reverse order of chemoselectivity, thiol over phenol will find useful application in the synthesis of complex natural products where selective protection of thio and amino groups is required in the presence of thiol. No acidic or basic reagents are used during the reaction. No chromatographic separation is required for isolation of the acylated products. Reactions in a neutral aqueous medium, easy isolation of products, and innocuous by-products make the present method a green chemical process.

2B.2.1. References

1. Li, T.-S.; Li, A.-X. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913.
2. (a) Rordý´guez, J-G.; Martý´n-Villamil, R.; Ramos, S. *New. J. Chem.* **1998**, 865. Kikukawa, K. (b) Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, *46*, 4413. (c) Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40*, 6177. (d) Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett* **1999**, 729. (e) Sim, T. B.; Yoon, N. M. *Synlett* **1994**, 827. (f) Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155. (g) Li, P.; Xu, J.-C. *Tetrahedron* **2000**, *56*, 4437. (h) Goswami, B. N.; Borthakur, N.; Ghosh, A.C. *J. Chem. Res. Synop.* **1998**, 268.
3. (a) Li, T.-S.; Li, A.-X. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913. (b) Omuaru, V. O. T. *Indian J. Chem.* **1998**, *37B*, 814. (c) Gholap, A. D.; Patel, V. M.; Patil, R. C.; Balasubramaniyan, P.; Balasubramaniyan, V. *Indian J. Chem. Edn.* **1980**, *7*, 26. (d) Patel, V. M.; Balasubramaniyan, V. *Indian J. Chem.* **1977**, *15B*, 1142.
4. (a) Sena, V. L. M.; Srivastava, R. M.; Oliveira, S. P.; Lima, V. L. M. *Biorg. Med. Chem. Lett.* **1998**, *8*, 2671. (b) Perry, C. J.; Parveen, Z. *J. Chem. Soc., Perkin Trans. 2* **2001**, 512. (c) Omuara, V. O. T.; Boisa, N.; Obuzor, G. U. *Indian J. Chem.* **1998**, *37B*, 704.
5. (a) Shimazawa, R.; Takayama, H.; Fujimoto, Y.; Komoda, M.; Dodo, K.; Yamasaki, R.; Shirai, R.; Koiso, Y.; Miyata, K.; Kato, F.; Kato, M.; Miyachi, H.; Hashimoto, Y. *J. Enzyme Inhib.* **1999**, *14*, 259. (b) Bailleux, V.; Vallee, L.; Nuyts, J. P.; Vamecq, J. *Chem. Pharm. Bull.* **1994**, *42*, 1817. (c) Shibata, Y.; Sasaki, K.; Hashimoto, Y.; Iwasaki, S. *Chem. Pharm. Bull.* **1996**, *44*, 156.

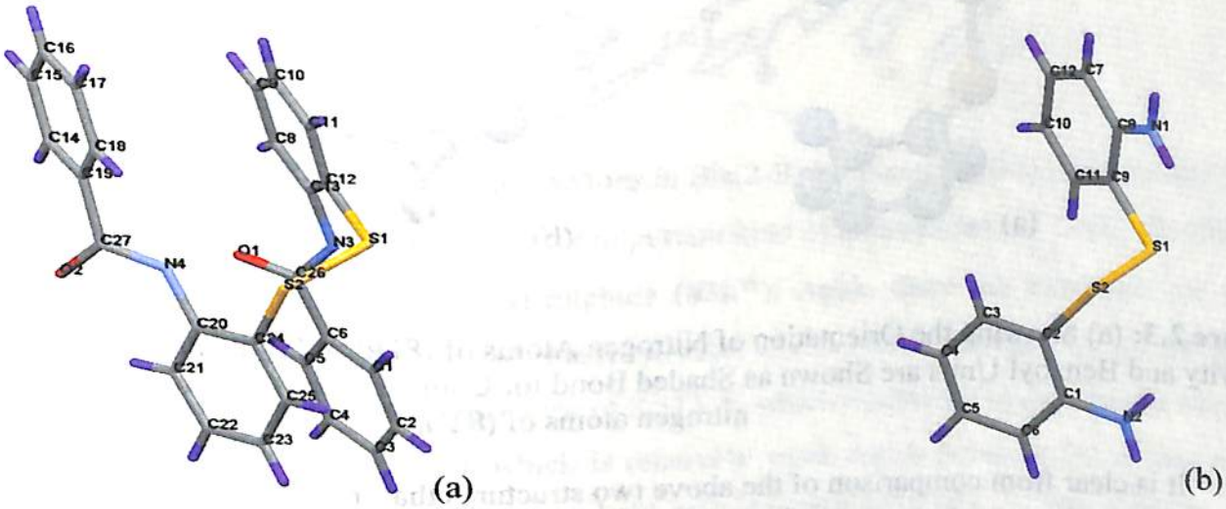
2B.3. Study on the Clip Motif from Bis (2-Benzoylaminophenyl) Disulphide

During the course of aqueous benzoylation of 2-aminothiophenol **82** one would have expected *N*-(2-mercapto-phenyl)-benzamide **82k'** as the sole product, but in addition to this another product was also obtained in good yield. X-Ray crystallography analysis of the second product revealed the structure as bis(2-benzoylaminophenyl)disulphide **82k''**, Scheme 2B.7. Formation of bis(2-benzoylaminophenyl)disulphide **82k''** may be in part due to the oxidation of 2-aminothiophenol **82** to corresponding disulphide **82'** followed by benzoylation and may be in part due to the oxidation of *N*-(2-mercapto-phenyl)-benzamide **82k'** to bis(2-benzoylaminophenyl)disulphide, **82k''**.



(82) **(82k')** **(82k'')**

Scheme 2B.7



(a) (b)

Figure 2.2. (a) Prospective View of (82k'') Showing the Clip Motif and Atom Labeling Schemes. (b) Prospective View of (82') Showing Atom Labeling Schemes.

The crystal suitable for X-ray diffraction studies were grown by the slow evaporation of a solution of bis(2-benzoylaminophenyl)disulphide (**82k''**) in ethanol. It was found that (**82k''**) crystallises in P1 space group. The asymmetric unit consists of two molecules per unit. The crystal structure reveals an unprecedented and a novel clip type of motif as shown in Figure 2.2.

This lead to the question what is the driving force for this type of clip motif? Is it in built due to the dihedral angle around S-S bond or is induced by a noncovalent π-π- stacking interactions between aromatic units. In order to find out the forces leading to clip motif the crystal structure of the parent disulphide, bis(2-aminophenyl) disulphide (**82'**) was also determined. The crystal suitable for X-ray diffraction studies were grown by the slow evaporation of a solution of bis(2-aminophenyl) disulphide (**82'**). It was found that (**82'**) crystallises in Pbca space group. The asymmetric unit consists of eight molecules per unit. At the first glance it looked like as if the clip motif is inbuilt in nature. However, a careful examination of the structure revealed that although the dihedral angle around the S-S bond (86.17°) is identical but the nitrogen atoms are pointing towards each other in bis(2-benzoylaminophenyl)disulphide (**82k''**) where as they are away from each other in the case bis(2-aminophenyl) disulphide (**82'**) as shown in Figure 2.3.

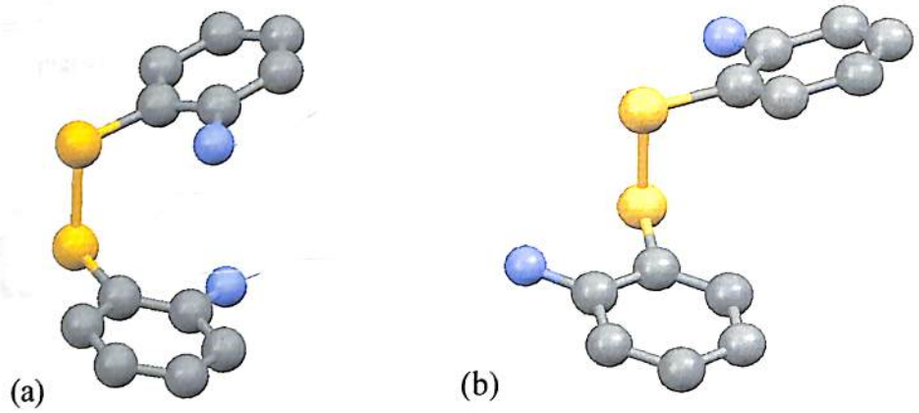


Figure 2.3: (a) Showing the Orientation of Nitrogen Atoms of (**82k''**), Hydrogen Atoms are Omitted for Clarity and Benzoyl Units are Shown as Shaded Bond for Comparision. (b) Showing the Orientation of nitrogen atoms of (**82'**).

It is clear from comparison of the above two structures that the clip motif is not inbuilt rather it is induced by a weak non covalent π–π interaction between one of the 2-aminothiophenyl and benzoyl ring as shown in Figure 2.4

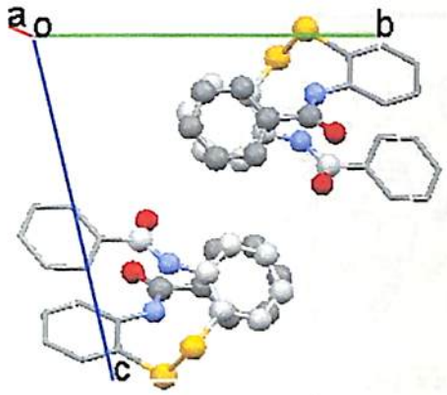


Figure 2.4: Showing π–π Interaction Between Two Aromatic Rings.

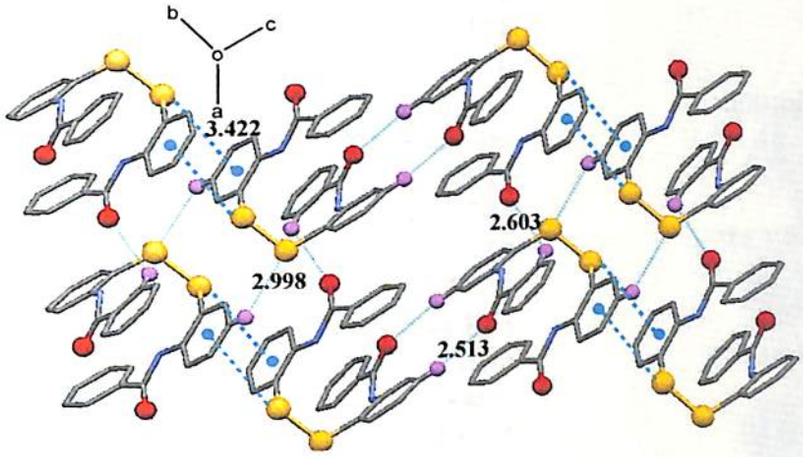


Figure 2.5: Showing Different Kind of Interactions in Bis(2-Benzoylaminophenyl)Disulphide (**82k''**).

In addition to π–π interaction three other important kind of interactions *viz.* C-H…O, CH…S and S–π exists in bis(2-benzoylaminophenyl)disulphide (**82k''**). Again there are two types of C-H…O interactions. One is a strong complementary intermolecular CH…O bond between O1 of one molecule and CH9 of adjacent molecule held at a distance of 2.513 Å, which contribute to the zig-zag tape kind of structure. The other C-H…O interaction which is relatively weak and is between O2 of one molecule and CH1 of the adjacent molecule, which are held at a distance of 2.603 Å. The CH…S distance between S1 and CH23 is 2.998 Å. The other sulphur atom (S2) contribute to the supramolecular architecture by having two complementary S-π interaction between sulphur atom (S2) and phenyl ring of the adjacent molecule (3.422 Å). All these interaction are shown in Figure 2.5.

Table 2.15. Crystal Data and Structure Refinement for Bis(2-Benzoylaminophenyl) Disulphide (**82k''**).

Identification code	Clip	
Empirical formula	$C_{13}H_{12}NOS$	
Formula weight	230.30	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9680(2) Å	α= 76.6730(10)°.
	b = 11.5541(3) Å	β= 81.4310(10)°.
	c = 12.3157(3) Å	γ = 87.1600(10)°.
Volume	1090.84(5) $Å^3$	
Z	4	
Density (calculated)	1.402 Mg/m^3	
Absorption coefficient	0.272 mm^{-1}	
F(000)	484	
Crystal size	0.35 x 0.28 x 0.19mm^3	
Theta range for data collection	1.72 to 28.37°.	
Index ranges	-8<=h<=10, -15<=k<=14, -14<=l<=16	
Reflections collected	12295	
Independent reflections	4831 [R(int) = 0.0213]	
Completeness to theta = 28.37°	88.3 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4831 / 0 / 290	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0618, wR2 = 0.1966	
R indices (all data)	R1 = 0.0703, wR2 = 0.2084	
Extinction coefficient	0.000(3)	
Largest diff. peak and hole	0.594 and -0.253 $e.Å^{-3}$	

Several weak noncovalent interactions contribute to the supramolecular architecture of bis(2-aminophenyl) disulphide (**82'**) these interactions are NH….S, NH….π and NH….N. Figure 2.6 shows the atom numbering scheme. The NH…S interaction is between N2H1B of one molecule with S1 of the adjacent molecule which is held at a distance of 2.755 Å. This interaction can be clearly seen in Figure 2.6 (a). The other hydrogen atom attached to N2 *i.e* N2H1A form a NH…H type of interaction with the N1 of adjacent molecule and the N2H1A…N1 distance is 2.477Å. This interaction can be clearly seen in Figure 2.6 (a). The other nitrogen atom N1 in addition to participating in NH…N type of interaction also makes NH….π type of contact with the adjacent phenyl ring which is at a distance of 2.847 Å as shown in Figure 2.6 (b).

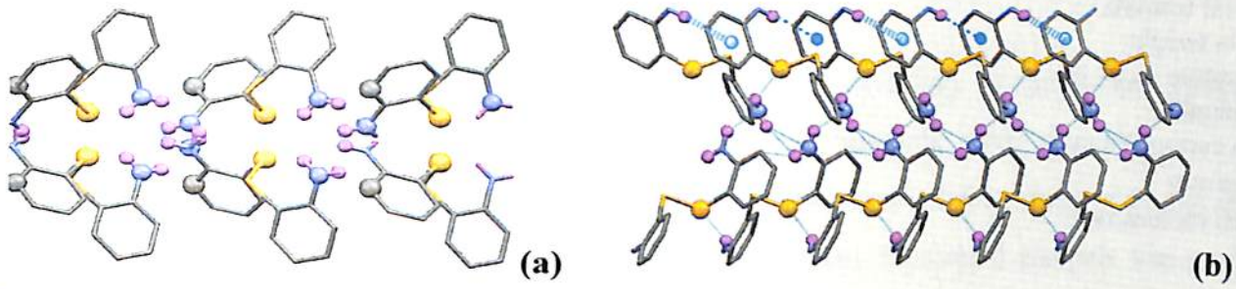


Figure 2.6: Showing Different Type of Interactions in (**82''**). (a) View along a-Axis, (b) View Along c-Axis. Other Hydrogens are Omitted for Clarity Except the Interacting Hydrogen.

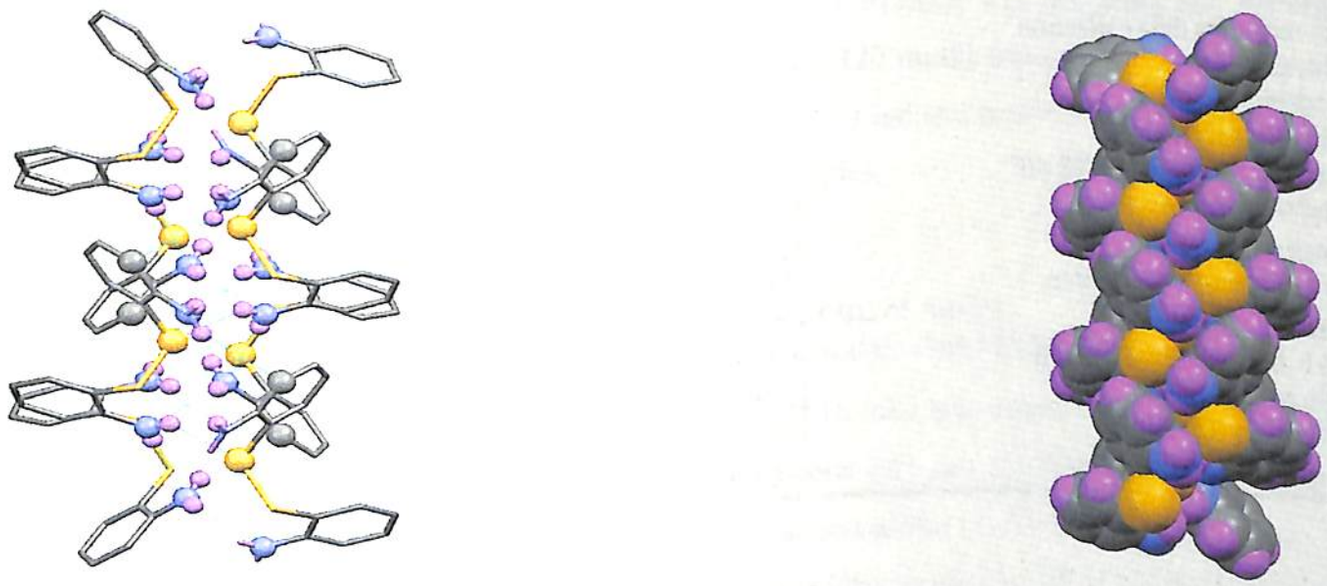


Figure 2.7: Showing Different Types of Interactions Inside the Helix (a) Other Hydrogens are Omitted for Clarity Except the Interacting Hydrogen (b) A Space Filled View.

Another interesting feature of this molecule is that all the interactions between different polar groups is inside and the relatively hydrophobic phenyl rings are outside forming a typical DNA type of super helix with a pitch of 8.233 Å, (Figure 2.7).

In conclusion although several reports describe generation of different clip motifs but non hav reported clip derived by controlling the S-S dihedral angle and aromatic π–π interactions.

Table 2.16. Crystal Data and Structure Refinement for Bis(2-aminophenyl) disulphide (**82'**)

Identification code	sn1	
Empirical formula	$C_{12}H_{12}N_2S_2$	
Formula weight	248.36	
Temperature	273(2) K	
Wavelength	71.073 pm	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 823.26(4) pm	α= 90°.
	b = 1318.28(6) pm	β= 90°.
	c = 2282.03(13) pm	γ = 90°.
Volume	2.4767(2) nm^3	
Z	8	
Density (calculated)	1.332 Mg/m^3	
Absorption coefficient	0.403 mm^{-1}	
F(000)	1040	
Crystal size	0.48 x 0.32 x 0.20 mm^3	
Theta range for data collection	1.78 to 28.46°.	
Index ranges	-10<=h<=10, -17<=k<=17, -29<=l<=30	
Reflections collected	28018	
Independent reflections	3018 [R(int) = 0.0435]	
Completeness to theta = 28.46°	96.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3018 / 0 / 146	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0583, wR2 = 0.1587	
R indices (all data)	R1 = 0.0740, wR2 = 0.1746	
Extinction coefficient	0.0000(12)	
Largest diff. peak and hole	0.592 and -0.508 $e.Å^{-3}$	

Section 2C. Experimental Section

2C.1. General Remarks

All the reagents were commercial grade and purified according to established procedures. Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica-gel 60 F254 (0.25 mm). Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Electronic spectra of solutions were recorded in Hitachi U-2001 UV-Vis spectrophotometer at 298K. Melting points were recorded with a Büchi B-540 melting point apparatus. NMR spectra were recorded in $CDCl_3$ or $[D_6]$ DMSO with tetramethylsilane as the internal standard for ^1H (200, 300 and 400 MHz) or $CDCl_3$ or $[D_6]$ DMSO solvent as the internal standard for ^{13}C (50, 75 and 100 MHz). For few substrates extraction was necessary and the organic solution was concentrated and passed through silica gel (60-120 mesh) using EtOAc/hexane to afford the analytically pure compound. All the compounds were identified and confirmed by IR and NMR (^1H and ^{13}C) spectroscopy and by comparison with authentic samples.

2C.2. General Experimental Procedures:

2C.2.1. General Procedure for Reaction of Amines in the Form of Amine Hydrochloride with Acetic, Propionic, Succinic and Maleic Anhydride: (Scheme 2B.1.)

To a stirred suspension of amine (1 mmol) in water (5 mL) was added 6N HCl (in the volume range of 240-400 μL) until the solution became homogeneous (pH ca.1.5). The resulting homogenous solution was cooled in an ice bath. To this was added an anhydride (1-1.5 mmol) followed by solid sodium bicarbonate (185-300 mg) until there was no further effervescence or pH of the mixture becomes ca 5.5. The precipitated product was filtered, washed with water (2 × 1 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases, where product did not precipitate out the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated in a rotary evaporator under reduced pressure to yield the pure product which were identified by comparison of their NMR, IR, GC and GC co-injection with authentic samples prepared by known methods.

2C.2.2. General Procedure for Reaction of Amines in the Form of Amine Hydrochloride with Benzoic and Phthalic Anhydride: (Scheme 2B.1.)

To a stirred suspension of amine (1 mmol) in water (5 mL) was added 6N HCl (in the volume range of 240-400 μL) until the solution became homogeneous (pH ca.1.5). The resulting homogenous solution was cooled in an ice bath. To this was added benzoic or phthalic anhydride (1mmol) dissolved in acetonitrile (1mL) followed by solid sodium bicarbonate (185-300 mg) until there was no further effervescence or pH of the mixture becomes ca 5.5. The product precipitates into lumps after removal of acetonitrile in a rotary evaporator. It was filtered, washed with water (2 × 1 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases, where product did not precipitate out the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The organic extract was dried over anhydrous Na_2SO_4 and the solvent was evaporated in a rotary evaporator under reduced pressure to yield the pure product which were identified by comparison of their NMR, IR, GC and GC co-injection with authentic samples prepared by known methods.

2C.2.3. General Procedure for Reaction of Amines with Acetic, Propionic, Isobutyric, Boc, Succinic and Maleic Anhydride (SDS Method)

Sodium dodecyl sulphate (SDS, ca.20 mg) was added to a stirred heterogeneous suspension of amine (5 mmol) in water (20 mL) until a homogeneous solution was formed, (in case of turbidity, the mixture was warmed to obtain a clear solution). The anhydride (7.5 mmol for acetic and propionic anhydride and 6 mmol for succinic and maleic anhydride) was added to this over a period of 5 min. The acetylated product precipitated within 5-10 min. The precipitated product was filtered, washed with water (2-1 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases where the product did not precipitate, the reaction mixture was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were dried with anhydrous Na2SO4 and the solvent was removed in a rotary evaporator under reduced pressure to yield the pure product, which was identified by its NMR and IR spectra and GC pattern, and by GC co-injection with authentic samples prepared by known methods.

2C.2.4. General Procedure for Reaction of Amines with Benzoic and Phthalic Anhydride

Sodium dodecyl sulphate (SDS, ca. 20 mg) was added to a stirred heterogeneous suspension of amine (5 mmol) in water. (20 mL) until a homogeneous solution was formed, (in case of turbidity, the mixture was warmed to obtain a clear solution). Benzoic or phthalic anhydride (5 mmol) dissolved in

acetonitrile (5 mL) was added to this in one lot. After stirring for 5 min the acetonitrile was evaporated and the product precipitated from the aqueous layer. To the aqueous solution containing precipitate, solid sodium hydrogen carbonate was added pinch-wise until the effervescence ceased and the pH was near neutral. The remaining precipitated product was filtered, washed with water (2 x 1 mL), dried by pressing between folds of filter paper and finally dried in a vacuum desiccator. In cases where the product did not precipitate, the reaction mixture was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed in a rotary evaporator under reduced pressure to yield the pure product, which was identified by its NMR and IR spectra and GC pattern, and by GC co-injection with authentic samples prepared by known methods. Good crystals of the compound can be obtained either from acetonitrile or from ethyl acetate.

2C.2.5. Intermolecular Chemoselective Acylation of Aniline and Phenol: (Scheme 2B.4)

Sodium dodecyl sulphate (SDS, ca. 4 mg) was added to a stirred suspension of aniline (1 mmol) and phenol (1 mmol) in water (6 mL). To this was added acetic anhydride (1 mmol). After stirring for 10 min the reaction mixture was extracted with ethyl acetate (2 x 10 mL).The percentage of products formed was determined by gas liquid chromatography using a crossed-linked methyl silicon gum capillary column (30 m x 0.32 mm x 0.25 μm) fitted with FID.

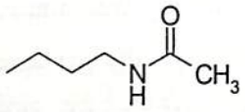
2C.2.6. Chemoselective Acylation of Aniline and Thiophenol: (Scheme 2B.4)

Sodium dodecyl sulphate (SDS, ca. 4 m) was added to a stirred suspension of aniline (1 mmol) and thiophenol (1 mmol) in water (6 mL). To this heterogeneous mixture acetic anhydride (1 mmol) was added. After stirring for 10 min the reaction mixture was extracted with ethyl acetate (2 x10mL). The percentage of products formed was determined by gas liquid chromatography using a crossed-linked methyl silicon gum capillary column (30 m x 0.32 mm x 0.25 μm) fitted with FID.

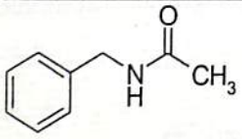
2C.2.7. Chemoselective Acylation of Thiophenol and Phenol: (Scheme 2B.4)

Sodium dodecyl sulphate (SDS, ca. 4 mg) was added to a stirred suspension of aniline (1 mmol) and thiophenol (1 mmol) in water (6 mL). To this heterogeneous mixture acetic anhydride (1 mmol) was added. After stirring for 10 min the reaction mixture was extracted with ethyl acetate (2 x 10 mL). The percentage of products formed was determined by gas-liquid chromatography using a crossed-linked methyl silicon gum capillary column (30 m x 0.32 mm x 0.25 μm) fitted with FID.

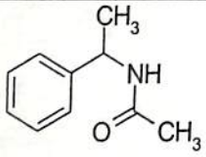
2C.3. Spectral Data



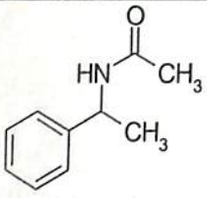
N-Butyl-acetamide (73g): IR (KBr): 3315, 3284, 3094, 2962, 2930, 2868, 1660, 1555, 1438, 1368, 1291, 731, 603 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, 3H, $-CH_2C\underline{H}_3$), 1.42 (m, 4H, $(-C\underline{H}_2)_2CH_3$), 1.97 (s, 3H, $-COC\underline{H}_3$), (3.22 m, 2H, $-C\underline{H}_2NH-$), 6.5 (brs, 1H, -N*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 20.4, 23.3, 31.8, 39.7, 170.9.



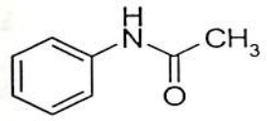
N-Benzyl-acetamide (74g): IR (KBr): 3303, 3066, 3037, 1654, 1560, 1545, 1500, 1461, 1382, 1283, 740, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 3H, $-COC\underline{H}_3$), 4.43 (d, 2H, J = 5.8 Hz, $-C\underline{H}_2Ph$), 5.79 (brs, 1H, -N*H*), 7.32 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 43.7, 127.5, 127.8, 128.7, 138.2, 169.8.



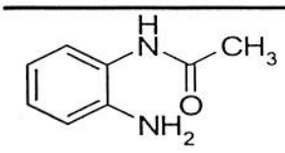
(*R*)-N-Phenyl-ethyl-acetamide (76g): IR (KBr): 3432, 3292, 3149, 3071, 2974, 1642, 1553, 1448, 1382, 1281, 757 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 1.30 (d, 3H, J = 7.0 Hz, $-CHC\underline{H}_3$), 1.82 (s, 3H, $-COC\underline{H}_3$), 4.87 (m, 1H, $-C\underline{H}CH_3$), 7.23 (m, 5H, Ar*H*), 8.4 (brs, 1H, -N*H*). ^{13}C NMR (50 MHz, DMSO-d_6): δ 22.8, 22.9, 48.1, 126.3, 126.9, 128.6, 145.1, 168.8.



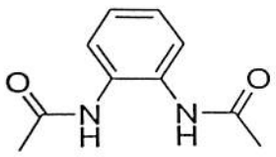
(*S*)-N-Phenyl-ethyl-acetamide (77g): IR (KBr): 3269, 3067, 2974, 2932, 1638, 1557, 1452, 1382, 1281, 1215, 691 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 1.35 (d, 3H, J = 7.0 Hz, $-CHC\underline{H}_3$), 1.86 (s, 3H, $-COC\underline{H}_3$), 4.90 (m, 1H, $-C\underline{H}CH_3$), 7.28 (m, 5H, Ar*H*), 8.4 (brs, 1H, -N*H*). ^{13}C NMR (50 MHz, DMSO-d_6): δ 22.8, 23.0, 48.1, 126.3, 126.9, 128.5, 145.2, 168.6.



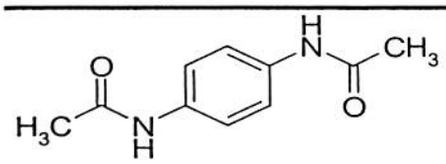
N-Phenyl-acetamide (78g): IR (KBr): 3303, 3262, 3210, 3149, 1664, 1602, 1560, 1505, 1438, 1372, 1326, 1264, 1044, 1018, 757, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, -COC<u>H_3</u>), 7.02 (m, 1H, Ar<u>H</u>), 7.29 (m, 2H, Ar<u>H</u>), 7.60 (m, 2H, Ar<u>H</u>), 10.0 (s, 1H, -N<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 118.9, 122.8, 128.5, 139.2, 168.1.



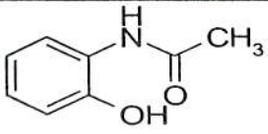
N-(2-Amino-phenyl)-acetamide (81'g): IR (KBr): 3461, 3369, 3282, 3047, 1647, 1589, 1541, 1503, 1459, 1375, 1305, 1260, 1218, 968, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H, -COC<u>H_3</u>), 3.65 (brs, 2H, -N<u>H_2</u>), 6.75 (m, 2H, Ar<u>H</u>), 7.01 (m, 2H, Ar<u>H</u>), 7.64 (brs, 1H, -N<u>H</u>). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.9, 118.4, 119.8, 126.0, 127.7, 129.42, 141.4, 169.7.



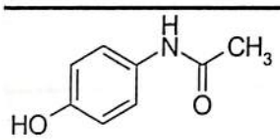
N-(2-Acetylamino-phenyl)-acetamide (81g): IR (KBr): 3236, 3129, 3021, 1669, 1608, 1536, 1460, 1367, 1316, 1034, 960, 768, 722, 600 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.07 (s, 6H, -COC<u>H_3</u>), 7.11 (m, 2H, Ar<u>H</u>), 7.52 (m, 2H, Ar<u>H</u>), 9.37 (s, 2H, -N<u>H</u>). ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.6, 124.5, 124.7, 130.4, 168.6.



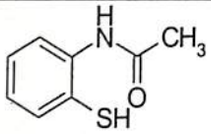
N-(4-Acetylamino-phenyl)-acetamide (86g):IR (KBr): 3303, 3170, 3083, 2858, 1669, 1572, 1521, 1403, 1372, 1321, 1255, 1014, 840, 756, 599, 522 cm^{-1}.^1H NMR (300 MHz, DMSO-d_6): δ 2.06 (s, 6H, -COC<u>H_3</u>), 7.10 (m, 2H, Ar<u>H</u>), 7.53 (m, 2H, Ar<u>H</u>), 9.43 (s, 2H, -N<u>H</u>).^{13}C NMR (75 MHz, DMSO-d_6): δ 23.7, 124.8, 130.5, 168.8.



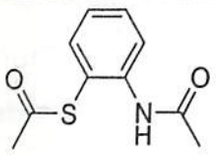
N-(2-Hydroxy-phenyl)-acetamide (80g): IR (KBr): 3406, 3088, 3050, 2976, 2879, 2745, 2622, 1669, 1600, 1547, 1460, 1383, 1330, 1290, 1250, 1204, 1100, 1040, 770, 671 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.19 (s, 3H, -COC*H*$_3$), 6.79 (t, 1H, *J*=8.0Hz, Ar*H*), 6.88 (d, 1H, *J*=7.6Hz, Ar*H*), 6.97 (t, 1H, *J*=7.6Hz, Ar*H*), 7.53 (d, 1H, *J*=8.0Hz Ar*H*,), 9.20 (brs, 1H, -N*H*), 9.52 (brs, 1H, -O*H*)^{13}C NMR (50 MHz, $CDCl_3$): δ 24.3, 117.2, 119.7, 122.4, 125.5, 126.8, 148.2, 169.9.



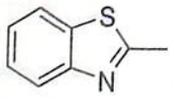
N-(4-Hydroxy-phenyl)-acetamide (88g): IR (KBr): 3334, 3160, 2924, 1660, 1613, 1567, 1511, 1444, 1378, 1326, 1260, 1111, 1010, 968, 840, 808, 685 cm^{-1}.^{1}H NMR (300 MHz, DMSO-d_6): δ 1.99 (s, 3H, -COC*H*$_3$), 6.67 (d, 2H, Ar*H*), 7.37 (d, 2H, Ar*H*), 9.19 (brs, 1H, -N*H*), 9.67 (brs, 1H, -O*H*).^{13}C NMR (75 MHz, DMSO-d_6): δ 22.8, 115.0, 121.3, 131.2, 153.1, 167.6.



N-(2-Mercapto-phenyl)-acetamide (82'g): IR (KBr): 3380, 3268, 2926, 1669, 1585, 1527, 1471, 1435, 1374, 1298, 1037, 760 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 1H, -S*H*), 1.98 (s, 3H, -COC*H*$_3$), 7.02 (m, 1H, Ar*H*), 7.40 (m, 2H, Ar*H*) 7.93 (brs, 1H, -N*H*), 8.31 (m, 1H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 121.7, 123.5, 124.40, 124.8, 132.5, 136.7, 140.2, 168.9.

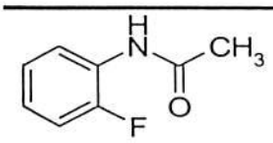


Thioacetic acid S-(2-acetylamino-phenyl) ester (82g): IR (KBr): 3340, 3063, 2920, 1695, 1580, 1519, 1437, 1375, 1294, 1141, 1120, 948, 757, 665, 624 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.14 (s, 3H, -NHCOC*H*$_3$), 2.42 (s, 3H, -SCOC*H*$_3$), 7.13 (m, 1H, Ar*H*), 7.42(m, 2H, Ar*H*), 7.69 (brs, 1H), 8.25 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0, 30.7, 117.7, 122.8, 125.20, 131.9, 136.5, 140.0, 168.7, 193.8.

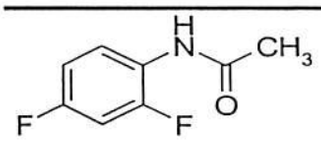


2-Methyl benzothiazole (82''g) IR (KBr): 3063, 2928, 2848, 1600, 1532, 1460, 1434, 1380, 1320, 1270, 1245, 1180, 1163, 1060, 1015, 871, 764, 733, 641 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (s,

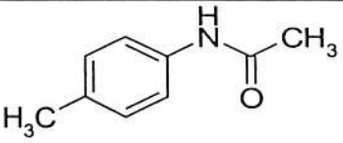
3H, -COC<u>*H*</u>$_3$,), 7.32 (t, 1H, *J* = 9.0Hz, Ar<u>*H*</u>), 7.43 (t, 1H, *J* = 9.0Hz, Ar<u>*H*</u>), 7.79 (d, 1H, *J*=8.4Hz, Ar<u>*H*</u>), 7.94 (d, 1H, *J* = 8.4Hz, Ar<u>*H*</u>).^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 121.3, 122.3, 124.6, 125.8, 135.6, 153.3, 166.9.



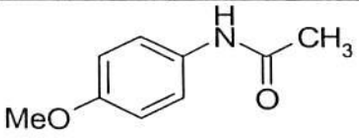
N-(2-Fluoro-phenyl)-acetamide (79g): IR (KBr): 3250, 3122, 3063, 2924, 2850, 1669, 1615, 1545, 1491, 1456, 1370, 1320, 1254, 1196, 1102, 966, 757 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.2 (s, 3H, -COC<u>*H*</u>$_3$), 7.02 (m, 1H, Ar<u>*H*</u>), 7.28 (s, 1H, Ar<u>*H*</u>), 7.3 (s, 1H, -N<u>*H*</u>), 7.42 (s, 1H, Ar<u>*H*</u>), 8.2 (m, 1H, Ar<u>*H*</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 114.6, 114.9, 122.2, 124.35, 124.38, 124.43, 126.2, 126.3, 150.9, 154.1, 168.6.



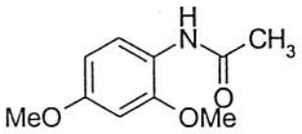
N-(2,4-difluoro-phenyl)-acetamide (92g): IR (KBr): 3272, 3211, 3144, 3061, 1669, 1629, 1557, 1507, 1434, 1383, 1265, 1142, 1101, 958, 855 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, -COC<u>*H*</u>$_3$), 6.86 (m, 2H, Ar<u>*H*</u>), 7.27 (brs, 1H, -N<u>*H*</u>), 8.22 (m, 1H, Ar<u>*H*</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 103.2, 103.5, 103.5, 103.7, 111.1, 111.14, 111.32, 111.35, 122.5, 122.9, 123.0, 153.5, 157.4, 159.8, 168.3.



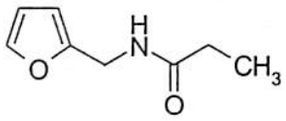
N-p-Tolyl-acetamide (84g): IR (KBr): 3285, 3188, 3122, 3063, 2924, 1665, 1615, 1549, 1506, 1456, 1320, 1269, 822, 757 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, -COC<u>*H*</u>$_3$), 2.29 (s, 3H, ArC<u>*H*</u>$_3$), 7.09 (d, 2H, Ar<u>*H*</u>), 7.35 (d, 2H, Ar<u>*H*</u>), 7.37 (brs, 1H, -N<u>*H*</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 24.3, 120.2, 129.4, 133.8, 135.4, 168.8.



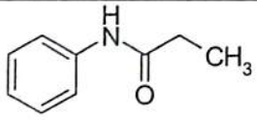
N-(4-Methoxy-phenyl)-acetamide (87g): IR (KBr): 3249, 3125, 3070, 3008, 2962, 2837, 1660, 1607, 1564, 1465, 1324, 1246, 770 cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13 (s, 3H, -COC<u>*H*</u>$_3$), 3.77 (s, 3H, ArOC<u>*H*</u>$_3$), 6.84 (d, 2H, Ar<u>*H*</u>), 7.39 (d, 2H, Ar<u>*H*</u>), 7.45 (s, 1H, -N<u>*H*</u>).^{13}C NMR (50 MHz, $CDCl_3$): δ 24.64, 55.87, 114.54, 122.38, 131.45, 156.87, 168.72.



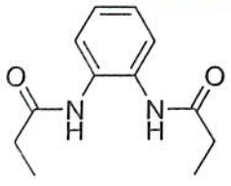
N-(2,4-Dimethoxy-phenyl)-acetamide (91g):IR (KBr): 3284, 3245, 3004, 2965, 2942, 2841, 1660, 1614, 1538, 1504, 1470, 1416, 1280, 1212, 1161, 1025, 837 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H, -COC$\underline{H}_3$), 3.77 (s, 3H, -OC$\underline{H}_3$), 3.82 (s, 3H, -OC$\underline{H}_3$), 6.44 (m, 2H, Ar$\underline{H}$), 7.52 (brs, 1H, -N$\underline{H}$), 8.18 (d, 1H, *J* = 9.5 Hz, Ar$\underline{H}$).^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 55.5, 55.6, 98.5, 103.6, 120.7, 121.2, 149.1, 156.3, 167.8.



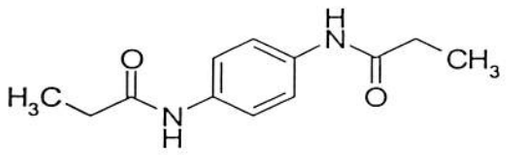
N-Furan-2-ylmethyl propionamide (75h) : ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 1.12 (t, 3H, *J*=7.6Hz, -CH_2C$\underline{H}_3$), 2.21 (q, 2H, *J* = 7.6Hz, -C$\underline{H}_2$$CH_3$), 4.34 (d, 2H, *J* = 5.6Hz, -C$\underline{H}_2$NH-), 6.19 (m, 1H, Ar$\underline{H}$), 6.30 (m, 1H, Ar$\underline{H}$), 7.34 (s, 1H, -NH), 7.60 (s, 1H, Ar$\underline{H}$). ^{13}C NMR (50 MHz, DMSO+$CDCl_3$): δ 10.08, 29.24, 36.28, 106.86, 110.33, 141.60, 152.00, 174.11.



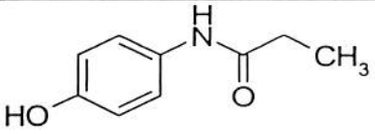
N-Phenyl-propionamide (78h): IR (KBr): 3252, 3191, 3155, 3083, 2971, 2930, 1665, 1603, 1552, 1501, 1440, 1373, 1310, 1258, 1204, 748 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, 3H, -CH_2C$\underline{H}_3$, *J* = 8.0Hz), 2.32 (q, 2H, -C$\underline{H}_2$$CH_3$, *J* = 8.0Hz), 7.03 (m, 1H, Ar$\underline{H}$), 7.24 (m, 2H, Ar$\underline{H}$) 7.48 (m, 2H, Ar$\underline{H}$), 7.70 (s, 1H, -N$\underline{H}$).^{13}C NMR (100 MHz, $CDCl_3$): δ 9.66, 30.57, 119.90, 124.05, 128.83, 138.01, 172.40.



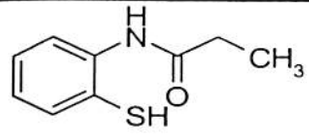
N-(2-Propionylamino-phenyl)-propionamide (81h): IR (KBr): 3288, 1660, 1600, 1542, 1511, 1455, 1368, 1301, 1230, 1205, 1081, 753, 707 cm^{-1}.^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (t, 6H, -CH_2C$\underline{H}_3$), 2.27 (q, 4H, -C$\underline{H}_2$$CH_3$), 7.11 (m, 2H, Ar$\underline{H}$), 7.24 (m, 2H, Ar$\underline{H}$), 8.51 (s, 2H, -N$\underline{H}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 9.70, 29.99, 125.55, 125.84, 130.61, 173.67.Elemental Analysis ($C_{12}H_{16}N_2O_2$): Calcd C 65.45 H 7.27 N 12.72; Expt C 64.97 H 7.45 N 13.24.



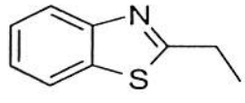
N-(4-Propionylamino-phenyl)-propionamide (86h): IR (KBr): 3268, 3160, 3078, 2971, 2930, 1665, 1578, 1516, 1410, 1383, 1306, 1245, 1080, 1015, 922, 840, 774 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6): δ 1.05 (t, 6H, -CH_2CH_3), 2.26 (q, 4H, -CH_2CH_3), 7.47 (s, 4H, Ar*H*), 9.76 (s, 2H, -N*H*). ^{13}C NMR (100 MHz, DMSO-d6): δ 9.75, 29.34, 119.36, 134.59, 171.64.



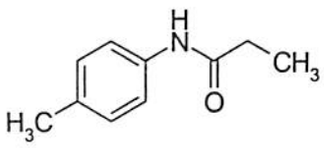
N-(4-Hydroxy-phenyl)-propionamide (88h): IR (KBr): 3319, 3200, 3000, 1650, 1615, 1520, 1440, 1405, 1210, 1050, 850 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6): δ 1.04 (t, 3H, -CH_2CH_3), 2.26 (q, 2H, -CH_2CH_3), 7.47 (s, 4H, Ar*H*), 9.76 (s, 2H, -N*H*, -O*H*). ^{13}C NMR (100 MHz, DMSO-d6): δ 9.8, 18.6, 114.9, 120.8, 131.1, 153.0, 171.2.



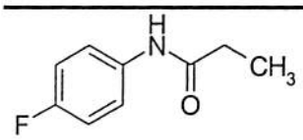
N-(2-Mercapto-phenyl)-propionamide (82'h): IR (KBr): 3283, 3252, 2976, 1660, 1585, 1532, 1440, 1378, 1286, 1209, 1081, 927, 748, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, 3H, -CH_2CH_3), 2.14 (q, 2H, -CH_2CH_3), 6.96 (t, 1H, Ar*H*), 7.36 (m, 3H, Ar*H*), 7.95 (s, 1H, -N*H*), 8.33 (d, 1H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.5, 30.6, 120.8, 124.1, 132.0, 136.3, 139.8, 171.9.



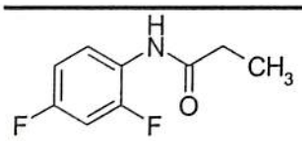
2-Ethyl-benzothiazole (82''h): IR (KBr): 3063, 2976, 2940, 1530, 1440, 1317, 1150, 1100, 1020, 910, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (t, 3H, -CH_2CH_3), 3.15 (q, 2H, -CH_2CH_3), 7.25 (t, 1H, Ar*H*), 7.35 (t, 1H, Ar*H*), 7.75 (d, 1H, Ar*H*), 7.88 (d, 1H, Ar*H*).^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 27.65, 121.45, 122.34, 124.61, 125.87, 134.90, 152.99, 173.72.



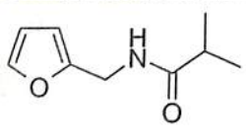
N-p-Tolyl-propionamide (84h): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, 3H, J = 7.6Hz, -$CH_2C\underline{H}_3$), 2.28 (s, 3H, Ar$C\underline{H}_3$, 2.35 (q, 2H, J = 7.6Hz, -$C\underline{H}_2CH_3$), 7.05 (d, 2H, J = 8.0Hz, Ar$\underline{H}$), 7.46 (d, 2H, J = 8.0Hz, Ar$\underline{H}$), 9.25 (brs, 1H, -N$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.39, 21.27, 30.59, 120.13, 129.30, 132.89, 136.69, 172.83.



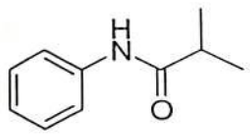
N- (4-Fluoro-phenyl)-propionamide (85h): IR (KBr): 3298, 3263, 3206, 3160, 3100, 2981, 1665, 1614, 1557, 1507, 1409, 1306, 1214, 1076, 1015, 835, 774 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 3H, -$CH_2C\underline{H}_3$, J = 8.0Hz), 2.28 (q, 2H, -$C\underline{H}_2CH_3$, J = 8.0Hz), 6.89 (m, 2H, Ar$\underline{H}$), 7.37 (m, 3H, Ar$\underline{H}$ and -N$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.63, 30.48, 115.39, 115.61, 121.66, 121.74, 133.93, 158.02, 160.43, 172.16.



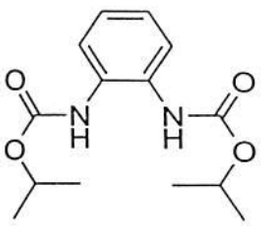
N-(2,4-Difluoro-phenyl)-propionamide (92h): IR (KBr): 3283, 2925, 2853, 1675, 1542, 1501, 1428, 1209, 1102, 968, 848, 820, 725 cm^{-1}.^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05 (t, 3H, -$CH_2C\underline{H}_3$, J = 9.0Hz), 2.34 (q, 2H, -$C\underline{H}_2CH_3$, J = 9.0Hz), 7.02 (m, 1H, Ar$\underline{H}$), 7.25 (m, 1H, Ar$\underline{H}$), 7.75 (m, 1H, Ar$\underline{H}$), 9.61 (s, 1H, -N$\underline{H}$).^{13}C NMR (75 MHz, DMSO-d_6): δ 9.6, 31.3, 103.7, 104.0, 104.4, 110.8, 111.1, 122.9, 125.8, 125.9, 156.9, 160.0, 160.1, 172.4.



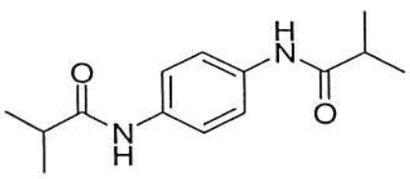
N-Furan-2-ylmethyl-isobutyramide (75i): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, 6H, -$CH(C\underline{H}_3)_2$, J = 6.4Hz), 2.39 (m, 1H, -$C\underline{H}(CH_3)_2$), 4.41 (m, 2H, -$C\underline{H}_2$Ar), 5.90 (brs, 1H, -N$\underline{H}$), 6.20 (m, 1H, Ar$\underline{H}$), 6.31(m, 1H, Ar$\underline{H}$), 7.38 (m, 1H, Ar$\underline{H}$).^{13}C NMR (100 MHz, $CDCl_3$): δ 19.97, 35.93, 36.84, 107.52, 110.66, 142.27, 151.58, 176.84.



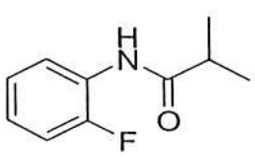
N-Phenyl-isobutyramide (78i): IR (KBr): 3304, 3268, 3206, 3145, 2976, 2935, 2873, 1670, 1608, 1547, 1506, 1450, 1393, 1312, 1250, 1214, 1107, 948, 764, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, -CH($C\underline{H}_3$)$_2$, J = 6.8Hz), 2.51 (m, 1H, $C\underline{H}(CH_3)_2$), 7.10 (t, 1H, J = 7.2Hz, Ar$\underline{H}$), 7.30 (t, 2H, J = 7.6Hz, Ar$\underline{H}$), 7.52 (d, 2H, J = 8.0Hz, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.06, 36.95, 120.20, 124.32, 129.08, 138.29, 175.74.



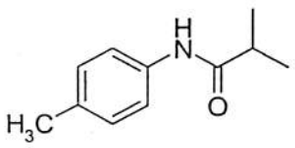
N-(2-Isobutyrylamino-phenyl)-isobutyramide (81i): IR (KBr): 3227, 2980, 1653, 1545, 1465, 1383, 1296, 1219, 1102, 948, 764, 702, 677 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, 12H, -CH($C\underline{H}_3$)$_2$, J = 6.4Hz), 2.49 (m, 2H, $C\underline{H}(CH_3)_2$), 7.13 (m, 2H, Ar$\underline{H}$), 7.26 (m, 2H, Ar$\underline{H}$), 8.38 (brs, 2H, -N$\underline{H}$).^{13}C NMR (100 MHz, $CDCl_3$): δ 20.02, 36.40, 125.94, 126.19, 130.97, 176.93.



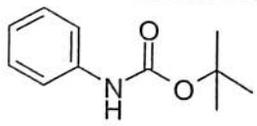
N-(4-Isobutyrylamino-phenyl)-isobutyramide (86i): IR (KBr): 3288, 3145, 3053, 2971, 1660, 1552, 1470, 1404, 1296, 1240, 1102, 955, 830, 702 cm^{-1}.^1H NMR (400 MHz, DMSO): δ 1.14 (d, 12H, -CH($C\underline{H}_3$)$_2$, J=6.4Hz), 2.56 (m, 2H, $C\underline{H}(CH_3)_2$), 7.51 (s, 4H, Ar$\underline{H}$), 9.55 (brs, 2H, -N$\underline{H}$). ^{13}C NMR (100 MHz, DMSO): δ 24.99, 40.55, 124.91, 139.87, 180.33.



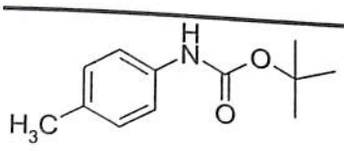
N-(2-Fluoro-phenyl)-isobutyramide (79i): IR (KBr): 3278, 3058, 2979, 2930, 2884, 1670, 1614, 1537, 1455, 1383, 1310, 1265, 1210, 1107, 948, 856, 760, 697 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, 6H, -CH($C\underline{H}_3$)$_2$, *J*=6.8Hz), 2.57 (m, 1H, $C\underline{H}(CH_3)_2$), 7.07 (m, 3H, Ar$\underline{H}$), 7.46 (brs, 1H, -N$\underline{H}$), 8.31 (t, 1H, *J*=8.0Hz, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.96, 37.02, 114.82, 115.01, 122.20, 124.36, 124.43, 124.64, 124.67, 126.57, 126.67, 151.49, 153.90, 175.58.



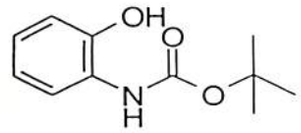
N-p-Tolyl-isobutyramide (84i): IR (KBr): 3278, 3196, 3124, 3053, 2976, 2930, 2879, 1665, 1608, 1537, 1470, 1414, 1310, 1255, 1209, 1107, 820, 717 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, 6H, -CH($C\underline{H}_3$)$_2$, *J*=6.4Hz), 2.30 (s, 3H, Ar$C\underline{H}_3$), 2.49 (m, 1H, $C\underline{H}(CH_3)_2$), 7.09 (d, 2H, *J*=8.4Hz, Ar$\underline{H}$), 7.40 (d, 2H, *J*=8.4Hz, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.08, 21.27, 36.85, 120.31, 129.53, 133.82, 135.76, 175.61.Elemental analysis (C_{11} H_{15}NO): Calcd C 74.57 H 8.47 N 7.90; Expt C 72.99 H 8.66 N 9.04.



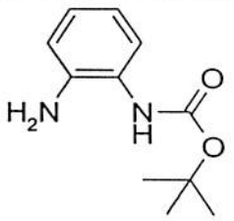
Phenyl-carbamic acid tert-butyl ester (78l):IR (KBr): 3319, 2925, 2863, 1700, 1609, 1542, 1450, 1373, 1322, 1255, 1168, 1061, 1020, 835, 753, 702 cm^{-1}.^{1}H NMR (400 MHz, DMSO+$CDCl_3$): δ 1.52 (s, 9H, -OC($C\underline{H}_3$)$_3$), 6.98 (t, 1H, *J* = 7.2Hz, Ar$\underline{H}$), 7.25 (t, 2H, *J* = 8.0Hz, Ar$\underline{H}$), 7.40 (d, 2H, *J* = 8.0Hz, Ar$\underline{H}$), 7.55 (brs, 1H). ^{13}C NMR (100 MHz, DMSO+$CDCl_3$): δ 27.73, 28.76, 118.72, 122.75, 128.89, 138.95, 153.15.



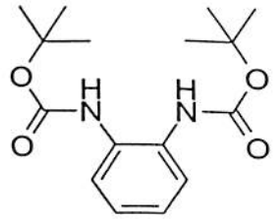
p-Tolyl-carbamic acid tert-butyl ester (84l): IR (KBr): 3355, 2986, 2930, 2761, 1706, 1614, 1527, 1409, 1320, 1250, 1168, 1058, 915, 835, 779, 671, 513 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 9H, -OC($C\underline{H}_3$)$_3$), 2.28 (s, 3H, Ar$C\underline{H}_3$), 6.48 (brs, 1H, -N$\underline{H}$), 7.06 (d, 2H, *J* = 8.8Hz, Ar$\underline{H}$), 7.22 (d, 2H, *J* = 7.6Hz, Ar$\underline{H}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.18, 28.08, 118.93, 129.63, 132.69, 135.92, 153.0.



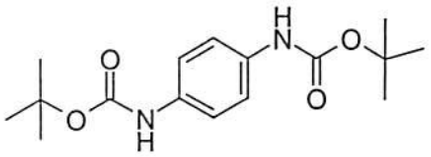
(2-Hydroxy-phenyl)-carbamic acid tert-butyl ester (80l): IR (KBr): 3426, 3298, 2986, 2710, 2582, 1701, 1615, 1527, 1470, 1352, 1281, 1235, 1163, 1050, 905, 851, 748, 620 cm^{-1}. ^1H NMR (400 MHz, DMSO+$CDCl_3$): δ 1.50 (s, 9H, -OC(C<u>*H*</u>$_3$)$_3$), 6.52-6.87 (brm, 4H, Ar<u>*H*</u>), 7.34 (brs, 1H), 7.79 (d, 1H, *J* = 8.0Hz, Ar<u>*H*</u>), 9.30 (brs, 1H).^{13}C NMR (100 MHz, DMSO+$CDCl_3$): δ 28.8, 80.6, 115.7, 119.4, 120.1, 123.3, 127.1, 146.1, 153.6.



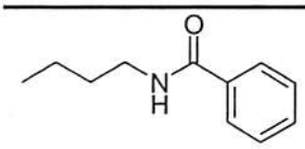
(2-Amino-phenyl)-carbamic acid tert-butyl ester (81'l):IR (KBr): 3416, 3360, 3010, 2986, 2935, 1685, 1603, 1511, 1460, 1380, 1303, 1265, 1163, 1064, 856, 748, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 9H, -OC(C<u>*H*</u>$_3$)$_3$), 3.59 (brs, 2H), 6.24 (brs, 1H), 6.77 (m, 2H, Ar<u>*H*</u>), 6.99 (m, 1H, Ar<u>*H*</u>), 7.25 (d, 1H, *J*=7.2Hz, Ar<u>*H*</u>).^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 80.8, 117.8, 119.7, 124.9, 126.3, 140.1, 154.0.



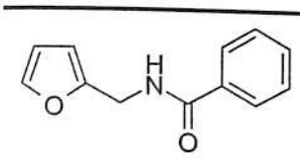
(2-tert-Butoxycarbonylamino-phenyl)-carbamic acid tert-butyl ester (81l):IR (KBr): 3380, 3268, 3119, 2981, 2935, 1696, 1605, 1537, 1460, 1399, 1245, 1163, 1061, 912, 760, 646 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 18H, -OC(C<u>*H*</u>$_3$)$_3$), 6.74 (brs, 2H), 7.11 (m, 2H, Ar<u>*H*</u>), 7.46 (brs, 2H, Ar<u>*H*</u>).^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 81.0, 124.4, 125.4, 154.06.



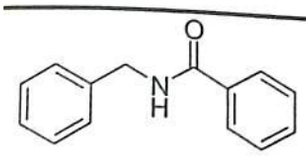
(4-tert-Butoxycarbonylamino-phenyl)-carbamic acid tert-butyl ester (86l): IR (KBr): 3365, 2986, 2945, 1701, 1614, 1542, 1409, 1312, 1235, 1163, 1065, 907, 825, 774, 649 cm^{-1}.^{1}H NMR (400 MHz, DMSO + $CDCl_3$): δ 1.49 (s, 18H, -OC(C*H*$_3$)$_3$), 7.31 (s, 4H, Ar*H*), 8.74 (s, 2H, -N*H*).^{13}C NMR (100 MHz, DMSO+$CDCl_3$): δ 28.9, 119.3, 134.4, 153.5.



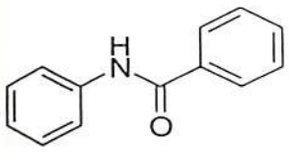
N-Butyl-benzamide (73k): IR (KBr): 3068, 2966, 2940, 1655, 1526, 1500, 1426, 1302, 1220, 1050, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.32 (m, 2H), 1.55 (m, 2H), 3.39 (q, 2H), 6.69 (brs, 1H), 7.31-7.80 (brm, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.62, 20.0, 31.48, 39.79, 126.84, 128.58, 129.93, 131.17, 167.87.



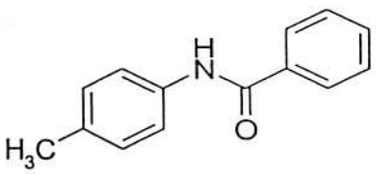
N-Furan-2-ylmethyl-benzamide (75k): IR (KBr): 3073, 2848, 2561, 1696, 1639, 1552, 1429 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (d, 2H, J = 5.6 Hz), 6.27 (m, 2H), 6.89 (brs, 1H), 7.31-7.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.90, 107.59, 110.39, 126.98, 128.41, 129.99, 131.53, 142.12, 151.02, 167.55.



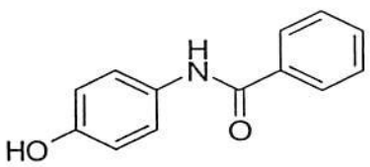
N-Benzyl-benzamide (74k): ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (d, 2H, PhC*H*$_2$NH-), 6.43 (brs, 1H, -N*H*), 7.24-7.50 (m, 8H), 7.76 (d, 2H, J=8.0Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 44.08, 126.82, 127.38, 127.68, 128.37, 128.56, 131.33, 138.01, 167.15.



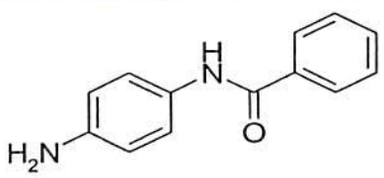
N-Phenyl-benzamide (78k): ^{1}H NMR (300 MHz, DMSO-d6): δ 7.12 (m, 1H), 7.34 (m, 2H), 7.55 (m, 3H), 7.83 (d, 2H), 7.98 (d, 2H), 10.23 (s, 1H).^{13}C NMR (75 MHz, DMSO-d6): δ 120.39, 123.47, 127.56, 128.02, 128.30, 131.16, 135.07, 139.07, 165.65.



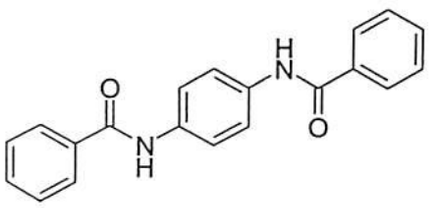
N-p-Tolyl-benzamide (84k): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 7.12 (d, 2H, J = 8.0 Hz), 7.39-7.61 (m, 6H), 7.83 (d, 2H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.84, 120.43, 127.02, 128.40, 129.46, 130.11, 131.64, 133.67, 135.25, 171.96.



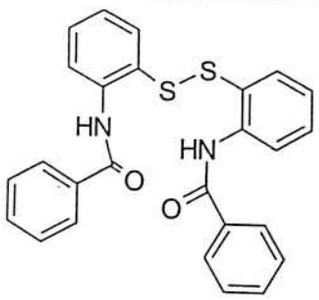
N- (4-Hydroxy-phenyl)-benzamide (88k): ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.75 (m, 2H), 7.38-7.61(m, 6H), 7.93 (m, 2H), 10.04 (s, 1H).^{13}C NMR (100 MHz, DMSO-d6): δ 115.05, 122.35, 127.56, 127.74, 128.34, 131.31, 135.23, 153.86, 165.03.



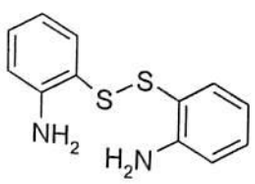
N-(4-Amino-phenyl)-benzamide (86'k): ^{1}H NMR (400 MHz, DMSO-d6):δ 6.54 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H J =8.4 Hz), 7.48-7.96 (m, 5H), 9.85 (s, 1H), 10.22 (s, 2H).^{13}C NMR (100 MHz, DMSO-d6): δ 113.68, 120.64, 122.23, 127.58, 128.54, 131.46, 134.95, 145.16, 165.30.



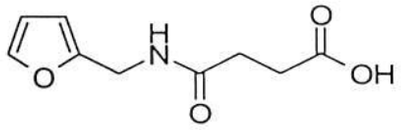
N-(4-Benzoylamino-phenyl)-benzamide (86k): IR (KBr): 3339, 1650, 1542, 1399, 1317, 830, 712, 671 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.35-7.98 (m, 14H), 10.44 (s, 2H).^{13}C NMR (100 MHz, DMSO-d_6): δ 120.71, 127.65, 128.60, 129.30, 132.90, 135.09, 167.38.



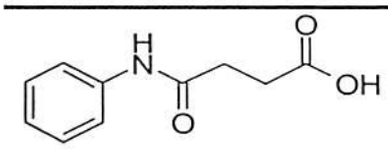
Bis (2-Benzoylaminophenyl) Disulphide (82k''): IR (KBr): 3375, 3324, 3058, 1680, 1578, 1521, 1434, 1306, 764, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.94 (m, 2H), 7.30 (m, 2H), 7.41-7.48 (m, 4H), 7.55 (m, 2H), 7.55 (m, 2H), 7.69 (m, 4H), 8.48 (d, 2H), 8.92 (brs, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 120.4, 123.4, 124.2, 126.8, 128.7, 131.8, 132.2, 134.1, 136.4, 139.7, 164.7.



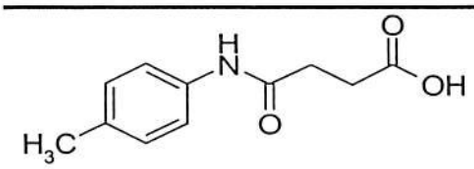
Bis(2-aminophenyl) disulphide (82'): IR (KBr): 3385, 3304, 3170, 3068, 1629, 1465, 1440, 1312, 1255, 1158, 861, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.30 (brs, 4H), 6.55 (t, 2H, J = 8.0Hz), 6.67 (d, 2H, J= 8.0Hz), 7.12 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 115.0, 117.9, 118.4, 131.3, 136.5, 148.3.



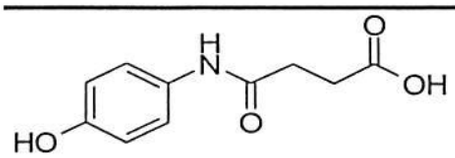
N-Furan-2ylmethyl-succinamic acid (75m):IR (KBr): 3298, 3068, 2934, 1721, 1705, 1649, 1552, 1420, 1254, 1183, 1085, 1014, 750, 715 cm^{-1}.^{1}H NMR (300 MHz, DMSO-d6): δ 2.33 (m, 2H), 2.44 (m, 2H), 4.22 (d, 2H, J = 5.4 Hz), 6.20 (s, 1H), 6.35 (s, 1H), 7.52 (s, 1H), 8.30 (m, 1H), 12.29 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d6): δ 29.2, 30.0, 35.7, 106.9, 110.6, 142.1, 152.5, 171.2, 174.0.



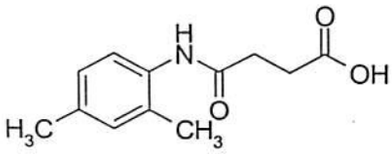
N-Phenyl-succinamic acid (78m): IR (KBr): 3324, 3062, 2939, 1705, 1669, 1608, 1552, 1505, 1424, 1336, 1229, 1193, 911, 745 cm^{-1}.^{1}H NMR (300 MHz, DMSO-d6): δ 2.56 (m, 4H), 7.02 (m, 1H), 7.28 (m, 2H), 7.59 (m, 2H), 9.95 (s, 1H), 12.15 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d6): δ 28.9, 31.1, 119.0, 123.0, 128.7, 139.3, 170.2, 173.9.



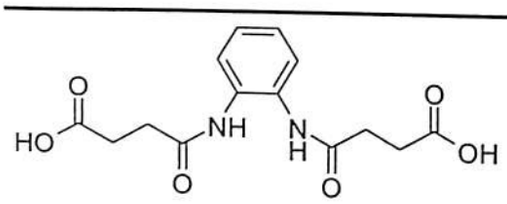
N-p-Tolyl-succinamic acid (84m): IR (KBr): 3318, 3057, 2934, 1705, 1664, 1603, 1541, 1439, 1331, 1234, 906 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6): δ 2.19 (s, 3H), 2.49 (s, 4H), 7.04 (d, 2H, J = 8.4Hz), 7.42 (d, 2H, J = 8.4Hz), 9.82 (s, 1H), 12.08 (brs, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ 20.44, 28.84, 30.71, 118.92, 129.06, 131.77, 136.84, 169.83, 173.91.



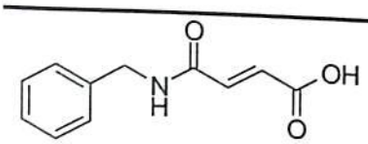
N- (4-Hydroxy-phenyl)-succinamic acid (88m): IR (KBr): 3339, 3307, 1694, 1659, 1555, 1513, 1231, 927 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d6): δ 2.56 (s, 4H), 6.74 (d, 2H, J = 8.7 Hz), 6.90 (m, 1H), 7.20 (m, 1H), 7.41 (d, 2H, J = 8.4 Hz), 9.74 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d6): δ 29.2, 31.1, 116.1, 121.1, 131.2, 153.3, 169.8, 174.2.



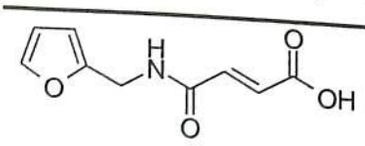
N- (2,4-Dimethyl-phenyl)-succinamic acid (90m): IR (KBr): 3288, 2919, 1701, 1650, 1527, 1434, 1199, 1035, 917 cm^{-1}. ^1H NMR (300 MHz, DMSO-d6): δ 2.13 (s, 3H), 2.23 (s, 3H), 2.54 (m, 4H), 6.92 (d, 1H, J = 8.1 Hz), 6.99 (s, 1H), 7.21 (d, 1H, J = 8.1 Hz), 9.20 (s, 1H), 12.0 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d6): δ 17.7, 20.5, 29.0, 30.5, 125.1, 126.3, 130.7, 131.7, 133.8, 134.0, 170.0, 173.9.



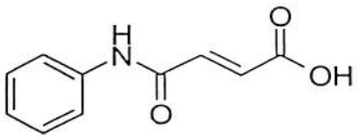
N-[2-(3-Carboxy-propionylamino)- phenyl]-succinamic acid (81m): IR (KBr): 3529, 3428, 3375, 3329, 2934, 1710, 1674, 1603, 1521, 1481, 1456, 1357, 1254, 1208, 1167, 947, 846, 758, 656, 559 cm^{-1}. ^1H NMR (400 MHz, DMSO-d6): δ 2.50 (m, 8H), 7.08 (s, 2H), 7.49 (s, 1H), 9.21 (s, 2H), 12.14 (brs, 2H). ^{13}C NMR (100 MHz, DMSO-d6): δ 29.06, 30.86, 124.60, 124.80, 130.44, 170.65, 174.07.



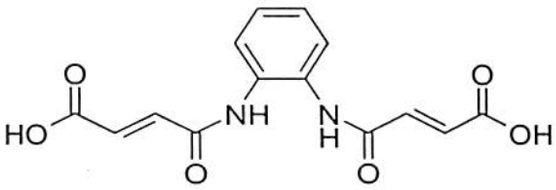
3-Benzylcarbamoyl-acrylic acid (74n): ^1H NMR (400 MHz, DMSO-d6): δ 4.45 (s, 2H, -C$\underline{H}_2$Ar), 6.26 (d, 1H, COC$\underline{H}$=CHCOOH, J=16.0 Hz), 6.44 (d, 1H, -COCH=C$\underline{H}$COOH, J=12.0 Hz), 7.24-7.39 (m, 5H, Ar$\underline{H}$), 9.49 (s, 1H, -N$\underline{H}$), 14.5 (s, 1H, -COO$\underline{H}$).^{13}C NMR (100 MHz, DMSO-d6): δ 42.40, 126.95, 127.39, 128.20, 131.25, 132.13, 164.95, 165.58.



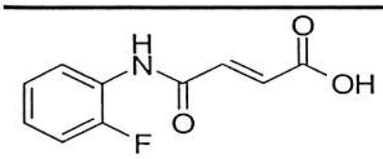
3-[(Furan-2-ylmethyl)-carbamoyl]-acrylic acid (75n): ^1H NMR (400 MHz, CD_3CN): δ 4.51 (d, 2H, -C$\underline{H}_2$Ar), 6.26-6.46 (m, 3H), 7.48 (s, 1H), 8.15 (s, 1H). ^{13}C NMR (100 MHz, CD_3CN): δ 36.24, 107.95, 110.28, 130.80, 135.37, 142.47, 149.56, 164.43, 166.03. Elemental analysis ($C_9H_9NO_4$): Calcd C 55.38 H 4.61 N 7.17 Expt C 53.58 H 4.91 N 6.97.



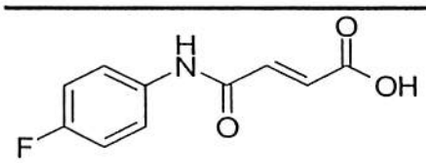
3-Phenylcarbamoyl-acrylic acid (78n): IR (KBr): 3431, 3283, 3108, 3073, 1705, 1634, 1547, 1454, 1332, 855 cm^{-1}. ^1H NMR (300 MHz, DMSO-d6): δ 6.34 (m, 1H, -COC*H*=CHCOOH), 6.51 (m, 1H, -COCH=C*H*COOH), 7.10 (m, 1H, Ar*H*), 7.34 (m, 2H, Ar*H*), 7.64 (m, 2H, Ar*H*), 10.50 (s, 1H, -N*H*), 13.25 (brs, 1H, -O*H*).^{13}C NMR (75 MHz, DMSO-d6): δ 119.6, 123.9, 128.8, 130.6, 131.7, 138.5, 163.3, 166.8.



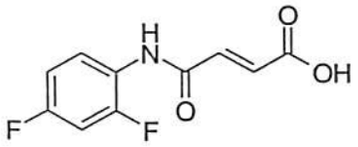
3-[2-(3-Carboxy-acryloylamino)-phenylcarbamoyl]-acrylic acid (81n): ^1H NMR (400 MHz, DMSO-d6): δ 6.26 (d, 1H, -COC*H*=CHCOOH, *J*=12.0 Hz), 6.63 (d, 1H, -COCH=C*H*COOH, *J*=16.0 Hz), 7.22 (m, 2H, Ar*H*), 7.69(m, 2H, Ar*H*), 10.08 (s, 1H, -N*H*).



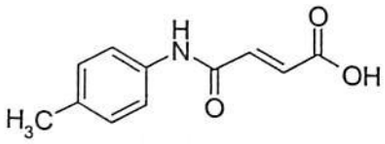
3-(2-Fluoro-phenylcarbamoyl)-acrylic acid (79n): ^1H NMR (400 MHz, DMSO-d6): δ 6.35 (d, 1H, -COC*H*=CHCOOH, *J*=12.0 Hz), 6.72 (d, 1H, -COCH=C*H*COOH, *J* = 16.0 Hz), 7.10-7.19 (m, 3H, Ar*H*), 8.15 (s, 1H, -N*H*), 11.0 (brs, 1H, -O*H*).^{13}C NMR (100 MHz, DMSO-d6): δ 115.58, 115.77, 124.21, 124.58, 124.61, 125.19, 125.29, 126.56, 126.63, 131.85, 133.06, 133.17, 134.03, 152.78, 155.23, 164.43, 166.38.



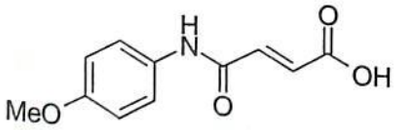
3-(4-Fluoro-phenylcarbamoyl)-acrylic acid (85n): ^1H NMR (400 MHz, DMSO-d6): δ 6.29 (d, 1H, -COC*H*=CHCOOH, *J*=12.0 Hz), 6.45 (d, 1H, -COCH=C*H*COOH, *J*=12.0 Hz), 7.17 (t, 2H, Ar*H*, J=8.0 Hz), 7.63 (q, 2H, Ar*H*.) ^{13} C NMR (100 MHz, DMSO-d6): δ 121.96, 130.94, 132.41, 135.61, 157.81, 160.17, 163.83, 167.49.



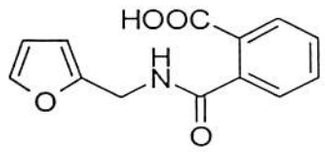
3-(2,4-Difluoro-phenylcarbamoyl)-acrylic acid (92n): ^{1}H NMR (300 MHz, DMSO-d6): δ 6.32 (d, 1H, -COC*H*=CHCOOH, *J* =12.0 Hz), 6.51(d, 1H, -COCH=C*H*COOH, *J* =12.0 Hz), 7.07 (t, 1H, Ar*H*, *J* = 9.0 Hz), 7.29 (t, 1H, Ar*H*, *J* = 9.0 Hz), 7.83 (q, 1H, Ar*H*), 10.24 (s, 1H, -N*H*). ^{13} C NMR (75 MHz, DMSO-d6): δ 104.0, 104.3, 104.7, 111.2, 111.5, 122.1, 122.2, 125.8, 125.9, 130.9, 131.0, 152.5, 152.6, 155.8, 155.9, 157.2, 157.4, 160.5, 160.6, 163.6, 167.2.



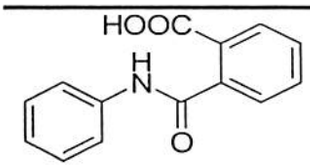
3-p-Tolylcarbamoyl-acrylic acid (84n): ^{1}H NMR (300 MHz, DMSO-d6): δ 2.26 (s, 3H, ArC*H*$_3$), 6.30 (d, 1H, -COC*H*=CHCOOH, *J* = 12.0 Hz), 6.48 (d, 1H, -COCH=C*H*COOH, *J* = 12.0 Hz), 7.14 (d, 2H, ArH, *J* = 6.0Hz), 7.52 (d, 2H, ArH, *J* = 9.0Hz), 10.39 (s, 1H, -NH), 13.32 (brs, 1H, -O*H*).^{13}C NMR (75 MHz, DMSO-d6): δ 20.5, 119.6, 129.3, 130.8, 131.7, 133.1, 136.0, 163.1, 166.9.



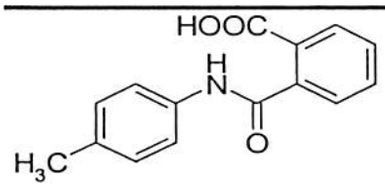
3-(4-Methoxy- phenylcarbamoyl)-acrylic acid (87n): ^{1}H NMR (300 MHz, DMSO-d6): δ 3.70 (s, 3H, -OC*H*$_3$), 6.30 (d, 1H, -COC*H*=CHCOOH, *J* =12.0 Hz), 6.47 (d, 1H, -COCH=C*H*COOH, *J* =12.0 Hz), 6.90 (d, 2H, ArH, *J*= 9.0Hz) 7.55 (d, 2H, ArH, *J*= 9.0Hz), 10.42 (s, 1H, -NH), 13.52 (brs, 1H, -O*H*). ^{13}C NMR (75 MHz, DMSO-d6): δ 55.3, 114.1, 121.8, 131.2, 131.5, 131.9, 156.0, 163.0, 166.8.



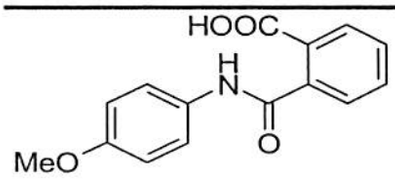
N-Furan-2ylmethyl-phthalamic acid (75o): ^{1}H NMR (400 MHz, CD_3CN): δ 4.52 (d, 2H), 6.36 (m, 1H), 6.41 (m, 1H), 7.34-7.61 (brm, 5H), 7.91 (m, 1H). ^{13}C NMR (100 MHz, CD_3CN): δ 36.52, 107.20, 110.49, 127.86, 129.90, 129.97, 130.26, 131.86, 137.36, 142.21, 151.82, 167.35, 169.47.



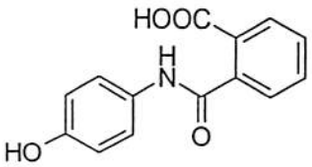
N-Phenyl-phthalamic acid (78o): IR (KBr): 3431, 2679, 2561, 1696, 1424, 1296, 943, 712 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.08 (t, 1H), 7.33 (t, 2H), 7.49-7.74 (brm, 5H), 7.95 (d, 1H), 10.34 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 119.7, 123.4, 127.5, 128.7, 129.0, 129.6, 130.1, 131.8, 139.0, 139.6, 167.6;



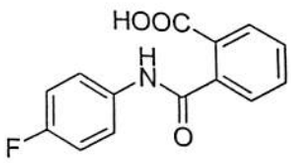
N-p-Tolyl-phthalamic acid (84o): IR (KBr): 3315, 1725, 1635 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.26 (s, 3H), 7.13 (d, 2H), 7.50-7.67 (m, 5H), 7.87 (d, 1H), 10.25 (s, 1H), 13.02 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.68, 119.14, 127.31, 128.50, 128.83, 129.02, 129.56, 131.14, 131.73, 136.56, 138.41, 166.48, 166.86.



N-(4-Methoxy-phenyl)-phthalamic acid (87o): IR (KBr): 3285, 1708, 1694, 1659 cm^{-1} ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H), 6.92 (d, 2H), 7.55-7.67 (m, 5H), 7.87 (d, 1H), 10.32 (s, 1H). 13.10 (s, 1H).^{13}C NMR (75 MHz, DMSO-d_6): δ 55.22, 113.46, 120.78, 127.39, 128.88, 129.10, 129.74, 131.19, 132.35, 138.51, 154.81, 166.36, 167.02.



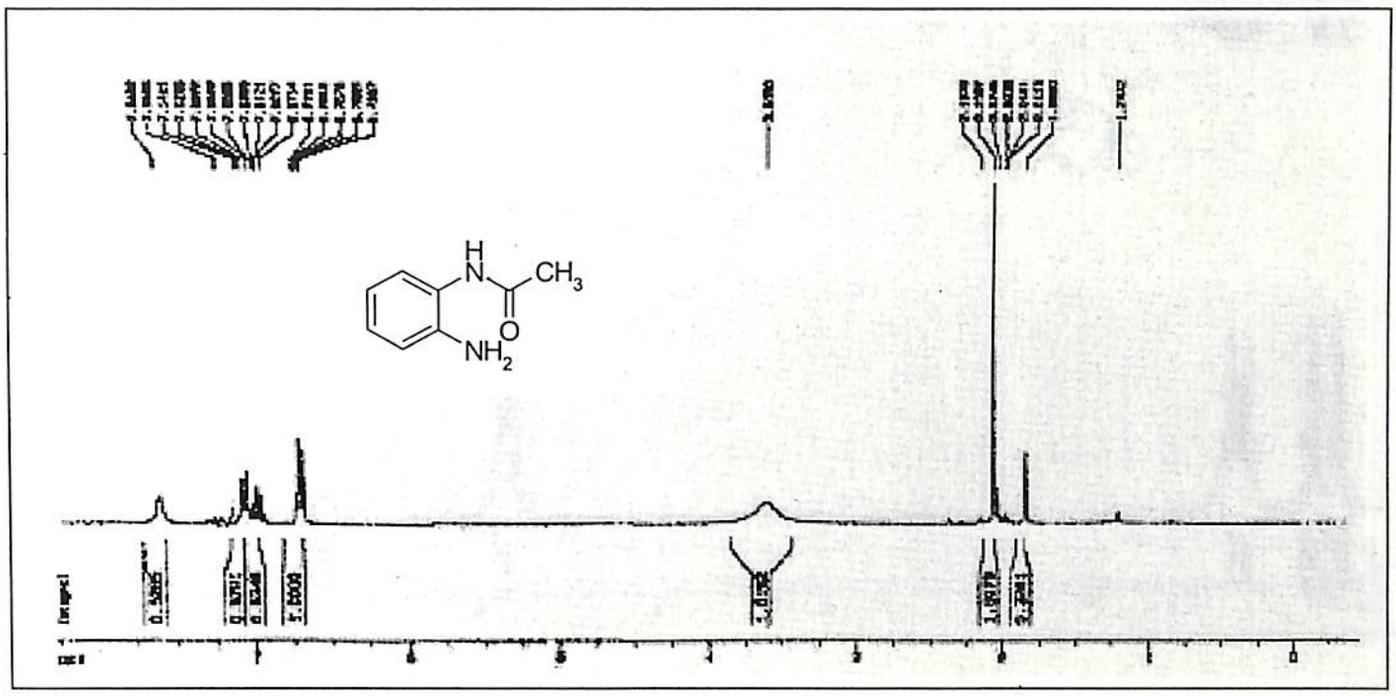
N-(4-Hydroxy-phenyl)-phthalamic acid (88o): IR (KBr): 3287, 1714, 1653 cm^{-1}.^{1}H NMR (300 MHz, DMSO-d6): δ 6.72 (d, 2H), 7.44-7.66 (m, 5H), 7.84 (d, 1H), 9.20 (brs, 1H), 10.07 (s, 1H), 13.14 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d6): δ 114.49, 120.79, 127.24, 128.64, 128.86, 129.69, 130.69, 130.93, 138.37, 152.70, 165.91, 166.88.



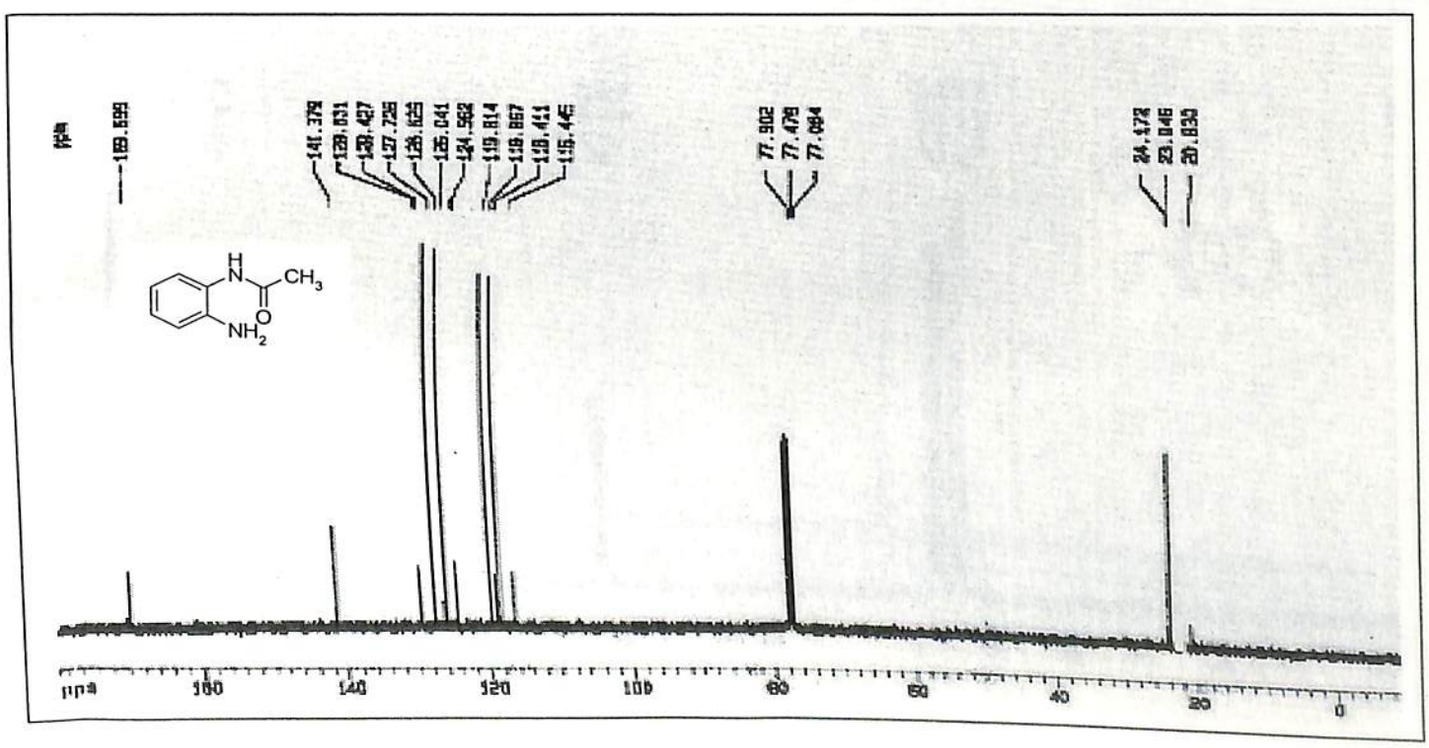
N- (4-Fluoro-phenyl)-phthalamic acid (85o): ^{1}H NMR (300 MHz, DMSO-d6): δ 7.13-8.00 (brm, 8H), 10.39 (s, 1H), 13.11 (brs, 1H). ^{13}C NMR (75 MHz, DMSO-d6): δ 115.0, 115.3, 115.6, 115.9, 121.2, 121.3, 123.4, 127.8, 128.2, 128.7, 128.9, 129.4, 129.6, 129.7, 130.0, 130.7, 131.0, 131.4, 131.6, 131.7, 132.0, 134.7, 136.0, 138.8, 156.5, 159.7, 167.0, 167.3, 167.4, 168.0.

2D.spectra

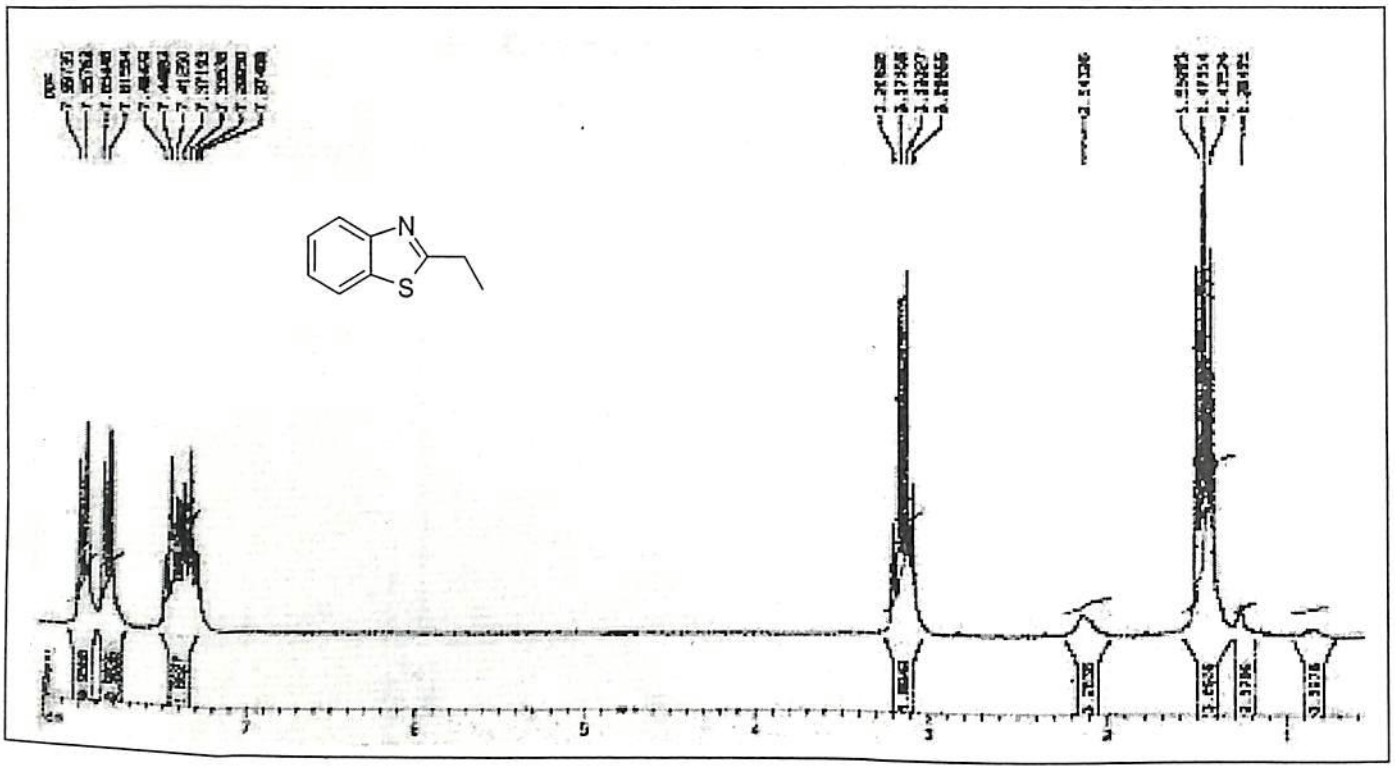
^{1}H NMR (300 MHz, $CDCl_3$):**N-(2-Amino-phenyl)-acetamide (81'g)**



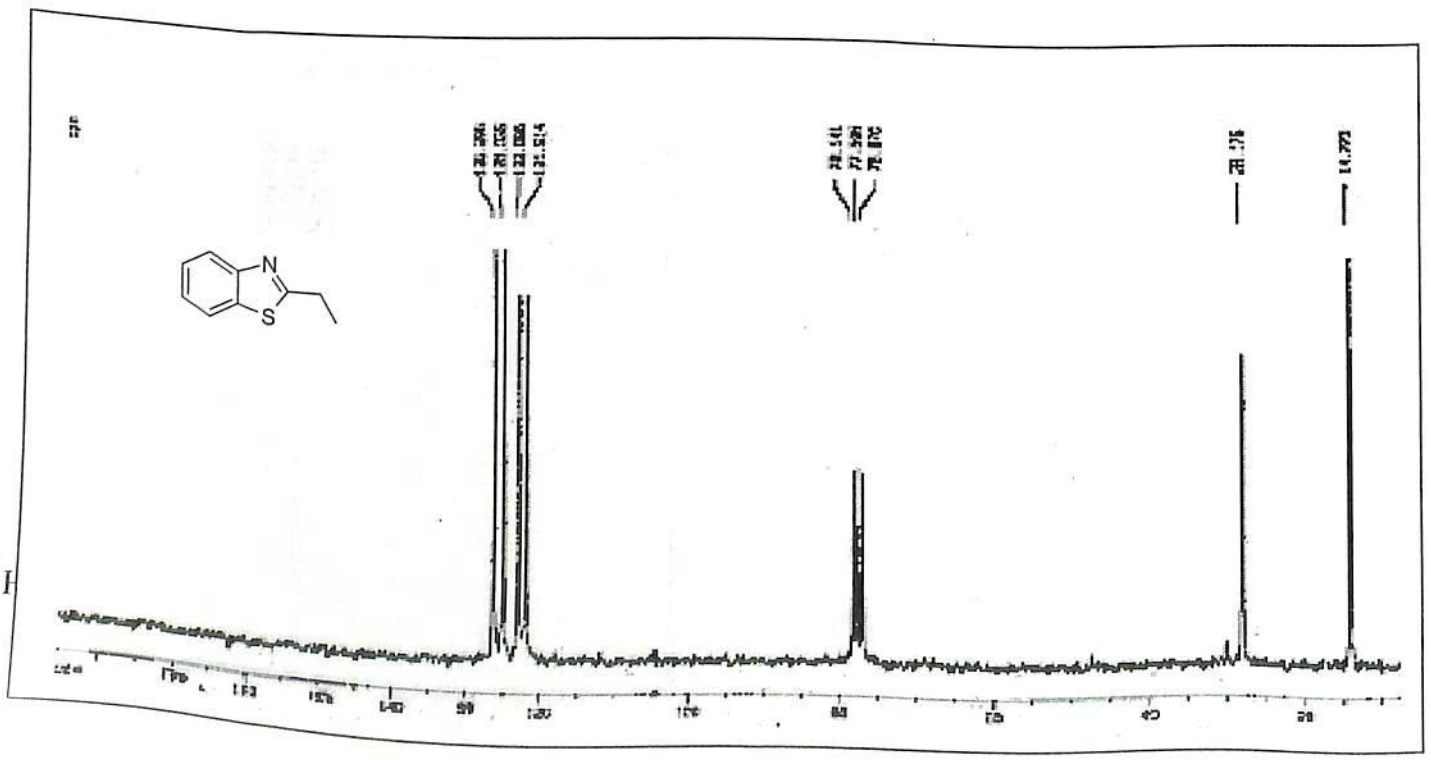
^{13}C NMR (75 MHz, $CDCl_3$) : **N-(2-Amino-phenyl)-acetamide (81'g)**



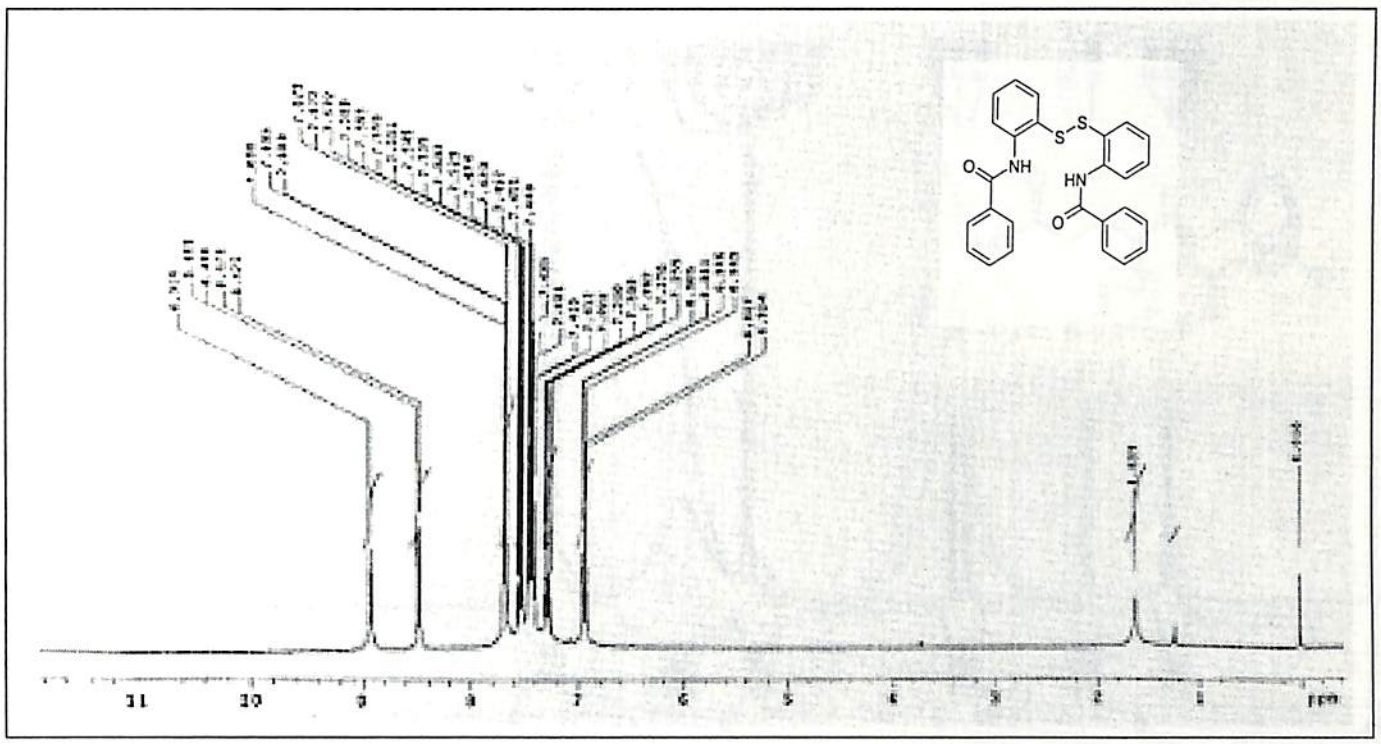
^{1}H NMR (300 MHz, $CDCl_3$): **2-Ethyl-benzothiazole (82''h)**



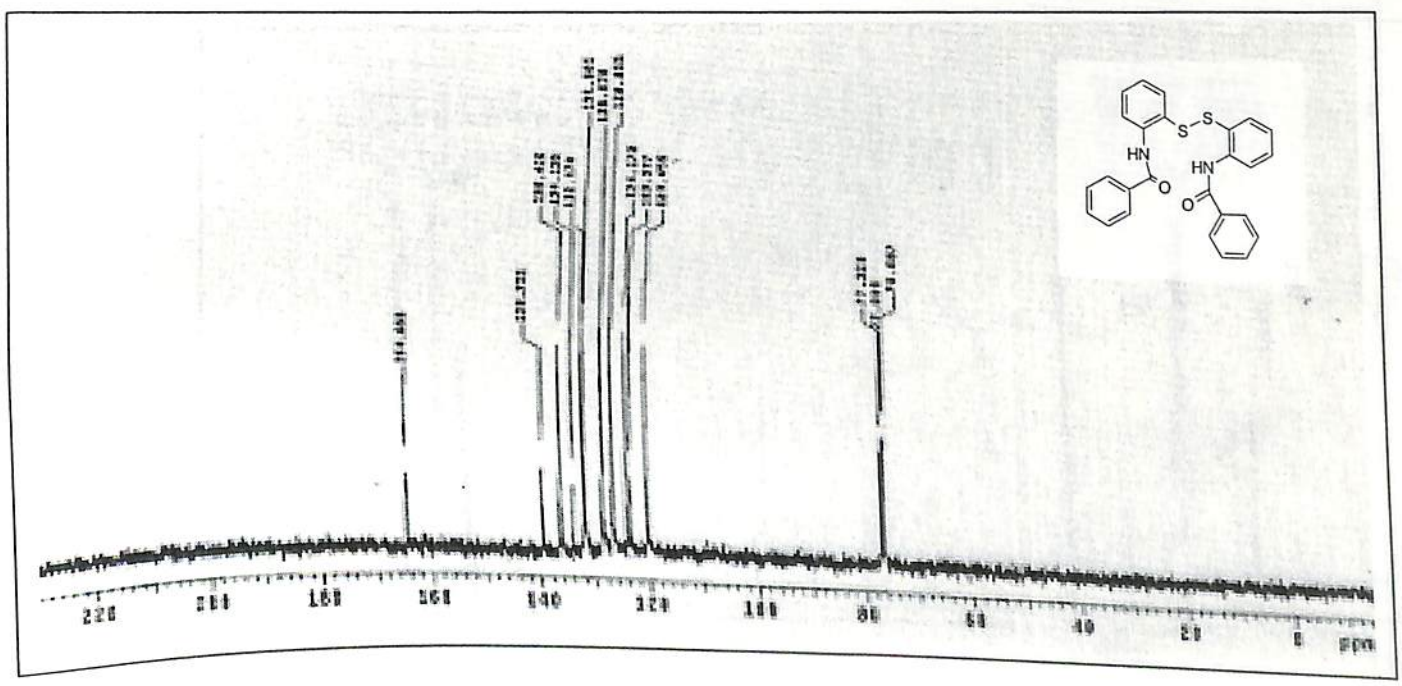
^{13}C NMR (75 MHz, $CDCl_3$): **2-Ethyl-benzothiazole (82''h)**



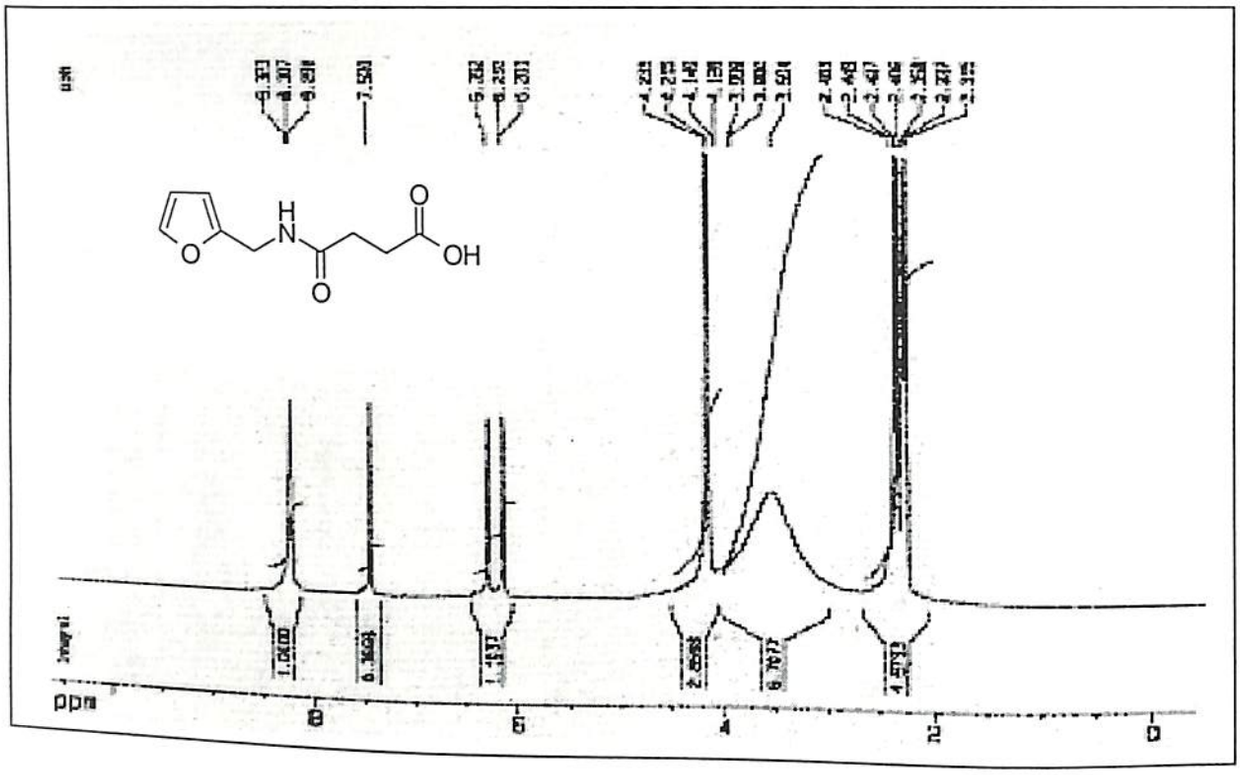
^{1}H NMR (400 MHz, $CDCl_3$): **Bis (2-benzoyl aminophenyl) disulphide (82k'')**



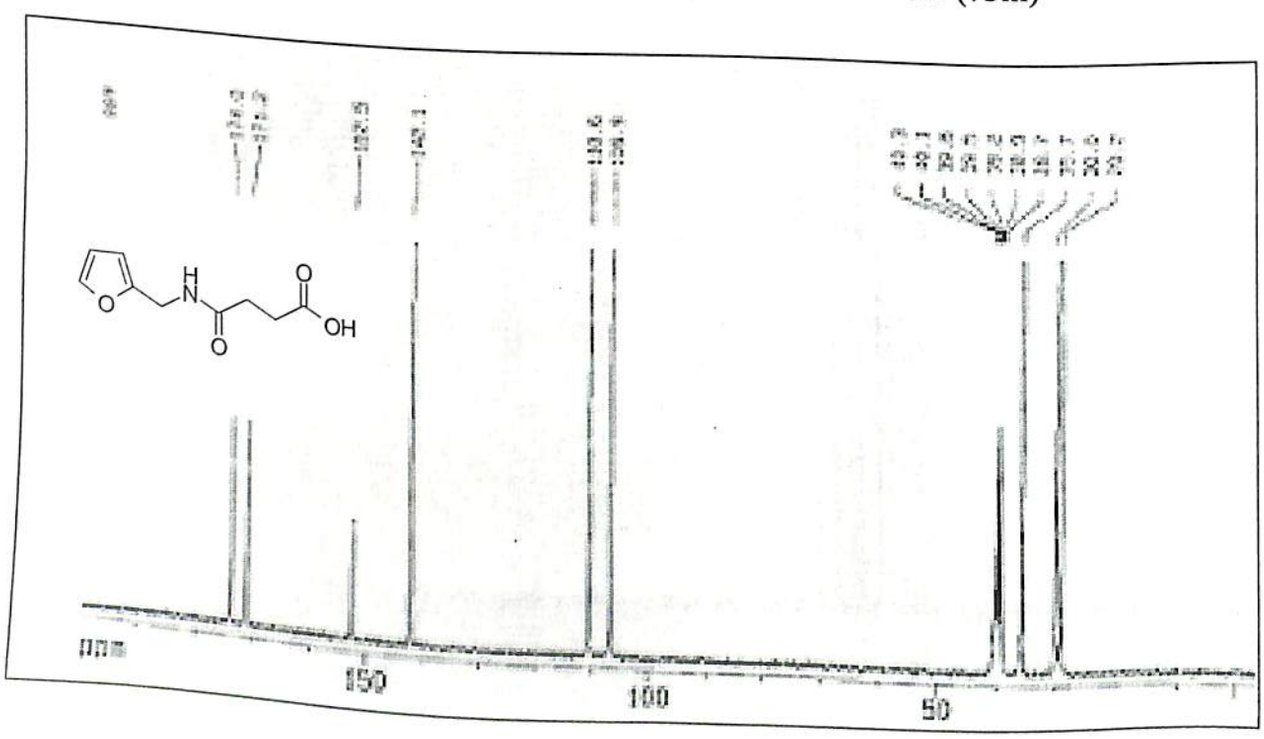
^{13}C NMR (100 MHz, $CDCl_3$): **Bis (2-benzoyl aminophenyl) disulphide (82k'')**



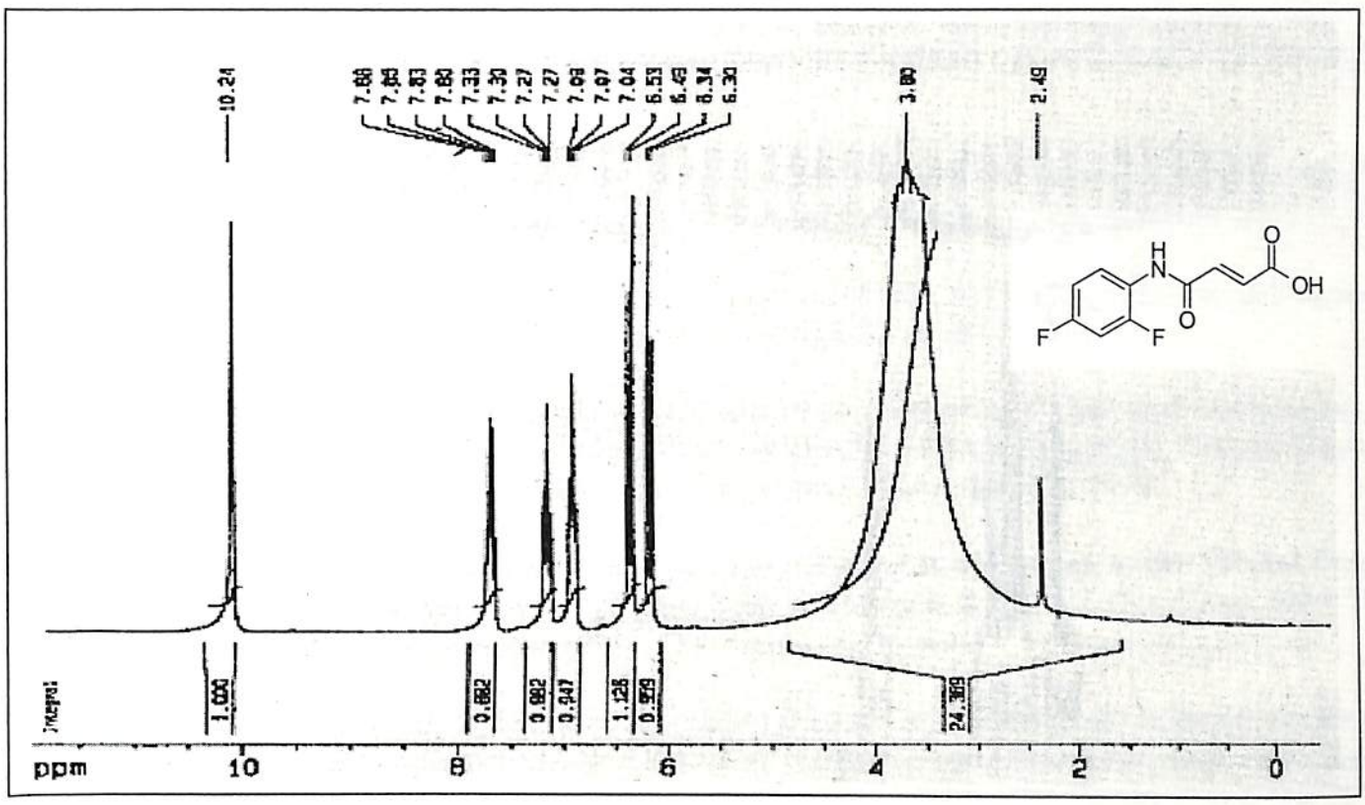
^{1}H NMR (300 MHz, DMSO-d_6): **N-Furan-2ylmethyl-succinamic acid (75m)**



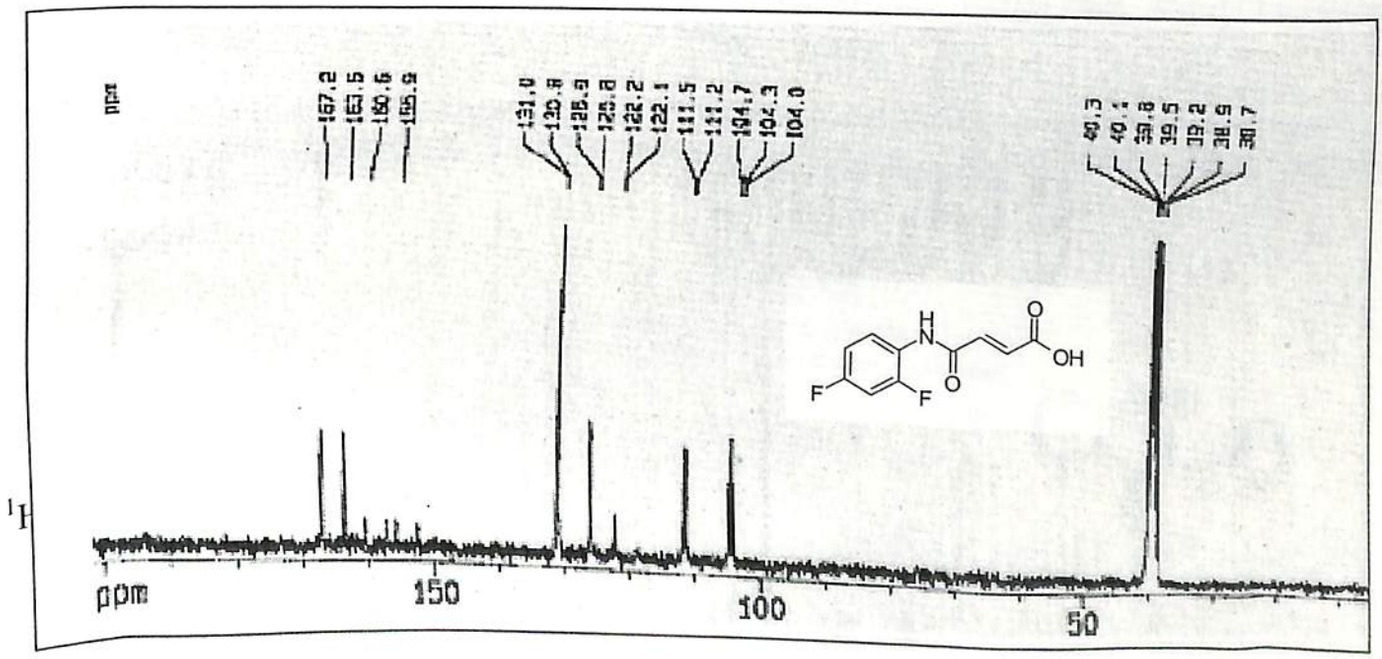
^{13}C NMR (75 MHz, DMSO-d_6): **N-Furan-2ylmethyl-succinamic acid (75m)**



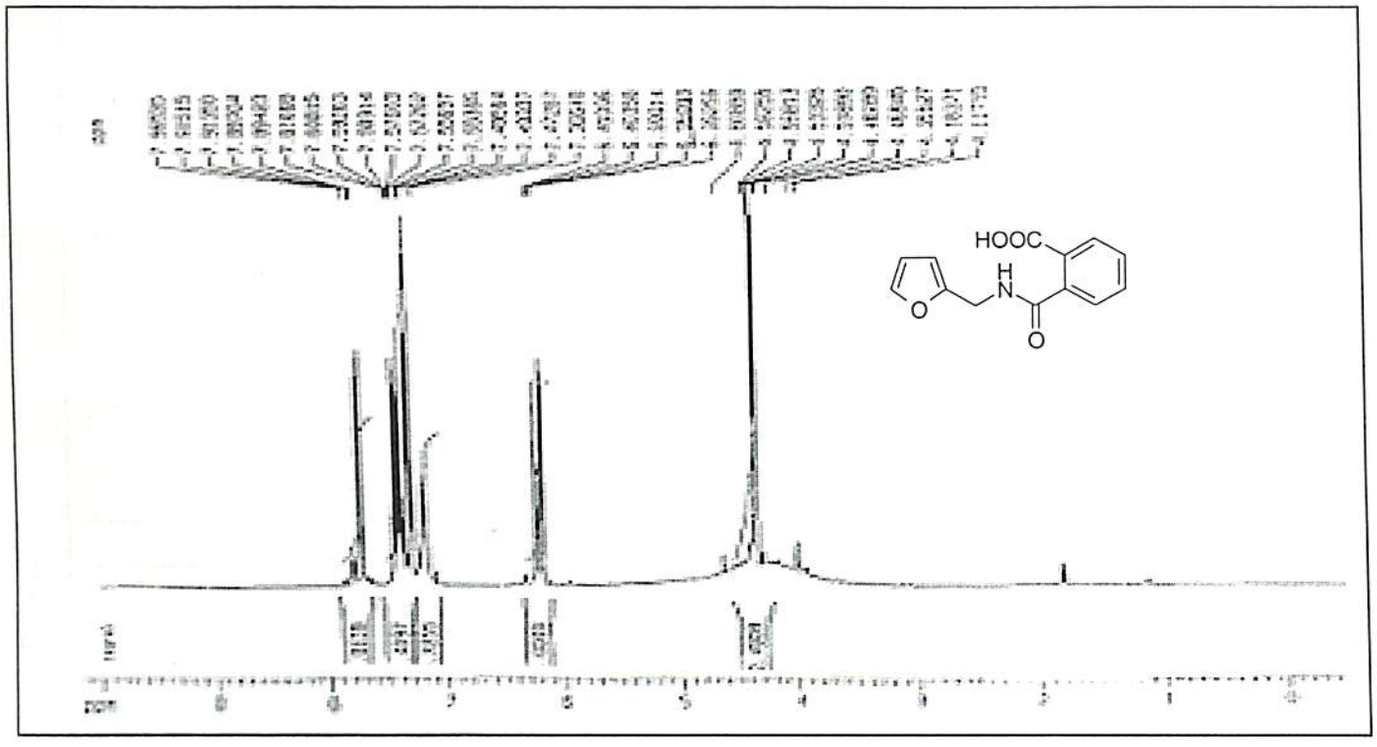
^{1}H NMR (300 MHz, DMSO-d6): **3-(2,4-Difluoro-phenylcarbamoyl)-acrylic acid (92n)**



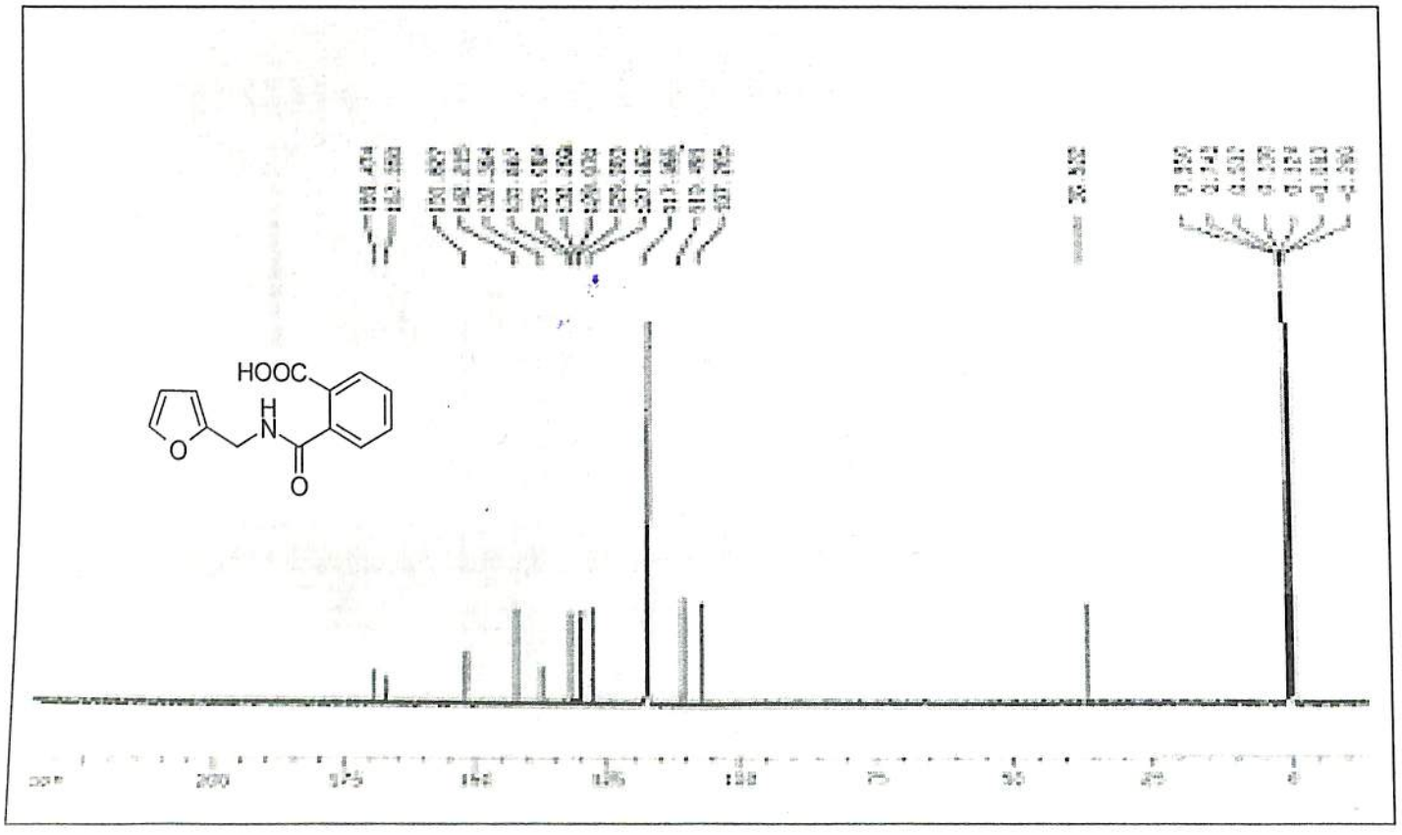
^{13}C NMR (75 MHz, DMSO-d6): **3-(2,4-Difluoro-phenylcarbamoyl)-acrylic acid (92n)**



^{1}H NMR (300 MHz, CD_3CN): **N-Furan-2ylmethyl-phthalamic acid (75o)**



^{13}C NMR (75 MHz, CD_3CN): **N-Furan-2ylmethyl-phthalamic acid (75o)**



Research Publications

1. **Tetrabutylammonium tribromide (TBATB)-Promoted Tetrahydropyranylation and Depyranylation of Alcohols.** Sarala Naik, Rangam Gopinath and Bhisma K. Patel *Tetrahedron Lett.* **2001**, *42*, 7679.

2. **Mild and Eco-friendly Chemoselective Acylation of Amines in Aqueous Medium.** Sarala Naik, Gitalee Bhattacharjya, Veerababurao Kavala and Bhisma K. Patel. *Arkivoc* **2004** (i), 55.

3. **Chemoselective Acylation of Amines in Aqueous Media.** Sarala Naik, Gitalee Bhattacharjya, Bandana Talukdar and Bhisma K. Patel *Eur. J. Org. Chem.* **2004**, 1254.

4. **Chemoselective Thioacetalisation and Transthioacetalisation of Carbonyl Compounds Catalysed by Tetrabutylammonium Tribromide (TBATB).** Sarala Naik, Rangam Gopinath, Mausumi Goswami and Bhisma K.Patel *Org. Biomol. Chem.* **2004**, 2, 1670.

5. **A New Recyclable Ditribromide Reagent for Efficient Bromination under Solvent Free Condition.** Veerababurao Kavala, Sarala Naik and Bhisma K. Patel *J. Org. Chem.* **2005**, 70, 4267.

6. **Tetrabutylammonium tribromide Mediated Direct Condensation of Carboxylic acids with Alcohols.** Sarala Naik, Kavala Veerababurao, Rangam Gopinath and Bhisma K.Patel. *Arkivoc* **2006** (i), 119.

7. **Chemoselectivities in Acetalisation, Thioacetalisation, Oxathioacetalisation and Azathioacetalisation**. Ram Kinkar Roy, Priyanka Bagaria, Sarala Naik, Kavala Veerababurao and Bhisma K. Patel *J. Phys. Chem. A* **2006**, *110*, 2181.

8. **1,1'-(Ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) as a recyclabe catalyst for Acylation.** Sarala Naik, Kavala Veerababurao, Rangam Gopinath and Bhisma K. Patel. *Arkivoc* **2006** (xi), 21.