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.

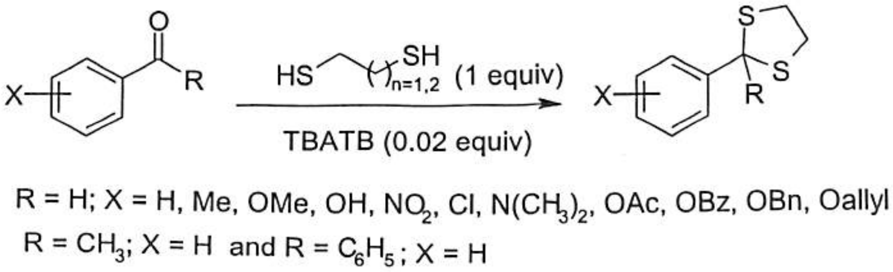
- The various organic transformations which occur exploiting its mild acidity are quite useful especially when compatibility of various functional groups under a specific reaction condition is an important subject.

  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

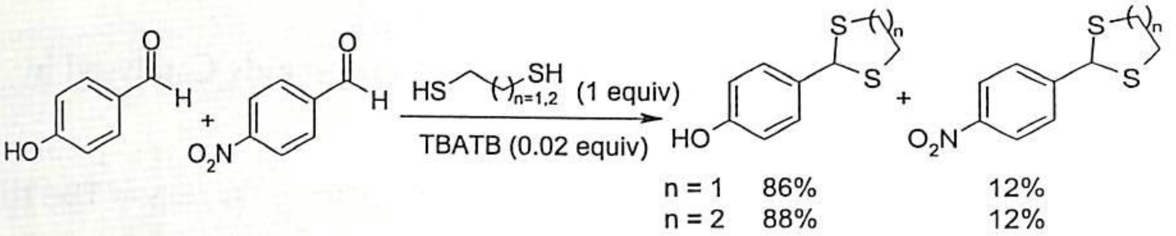
R = CH_3; X = H and R = C_6H_5; X = H

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

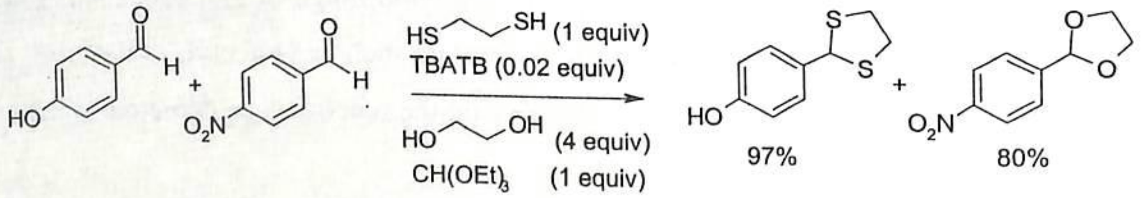
Various competitive reactions were performed between different aldehydes, ketones as well as aldehydes with different bisnucleophiles to understand the factors responsible for the selectivity. Is it the intrinsic reactivity of the substrates or catalyst or reaction conditions that govern the selectivity? 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.

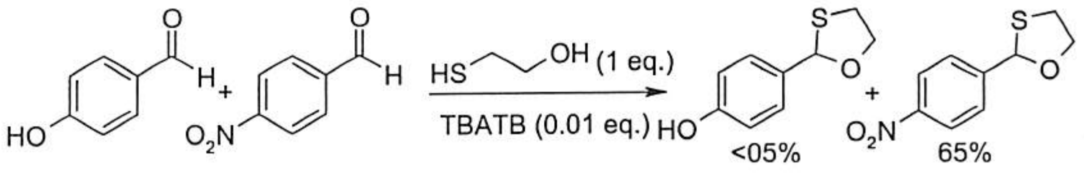
Explanation to Selectivity Based on the Values Calculated by HPA/ dnp Method

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.

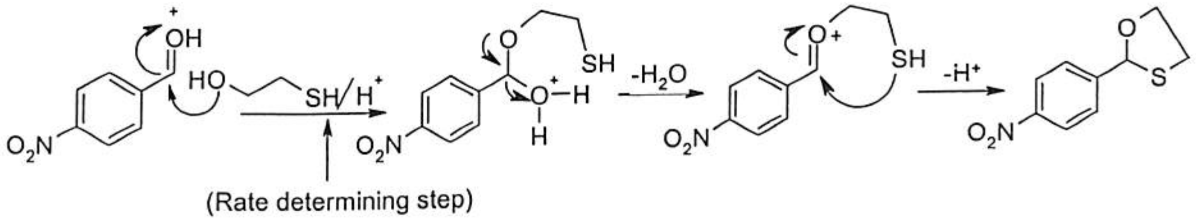
Because of the competitive reaction condition *p*-nitrobenzaldehyde forms *O,O* acetal with 1,2-ethane diol and *p*-hydroxybenzaldehyde forms *S,S* acetal with 1,2-ethanedithiol. The reason is that the highest global electrophilicity of *p*-nitrobenzaldehyde plus higher positive charge of carbonyl carbon 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.



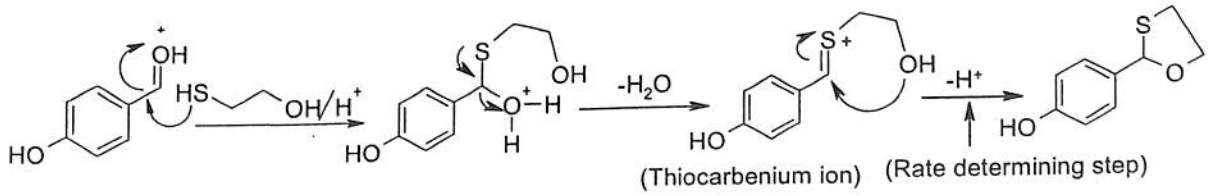
Scheme1B.4. Chemoselective Oxathioacetalisation

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.



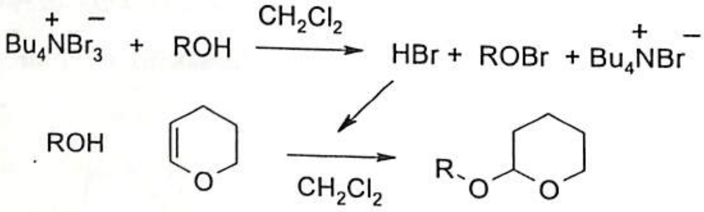
Scheme1B.6. Proposed Mechanism for Oxathioacetalisation

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.

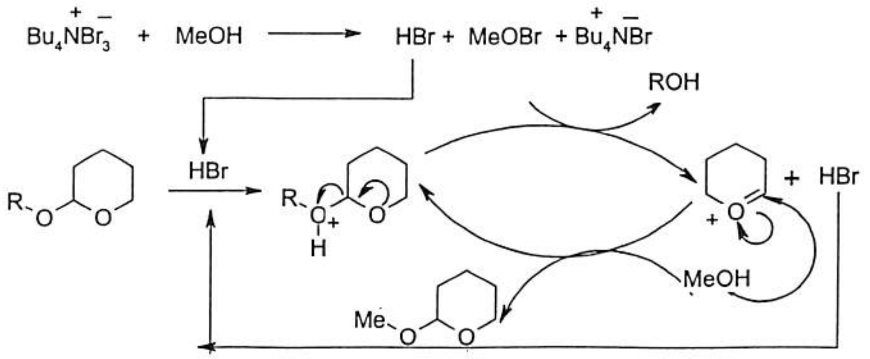
Tetrahydropyranylation of alcohols was performed using TBATB (0.025 equiv.) as a promoter in the presence of 3,4-dihydro-2*H*-pyran (1.1equiv) in CH_2Cl_2 at room temperature. Tetrahydropyranylation did not occur when the blank runs were performed in the absence of TBATB. Despite the use of an aprotic 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.

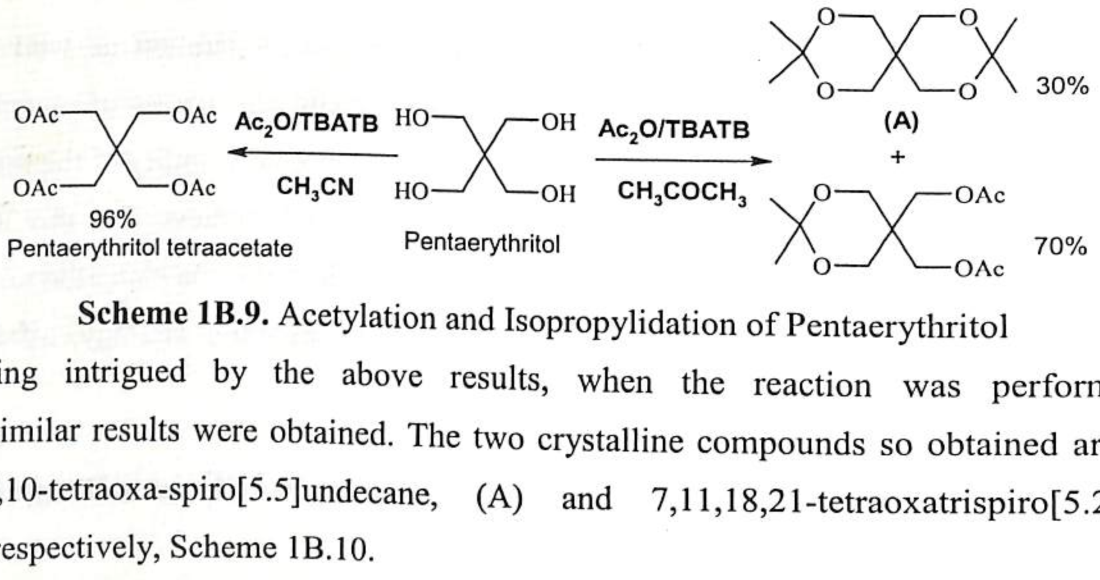
1B.3. Tetrabutylammonium Tribromide (TBATB) as an Efficient Reagent for Acylation of Alcohols, Amines and Thiols

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.

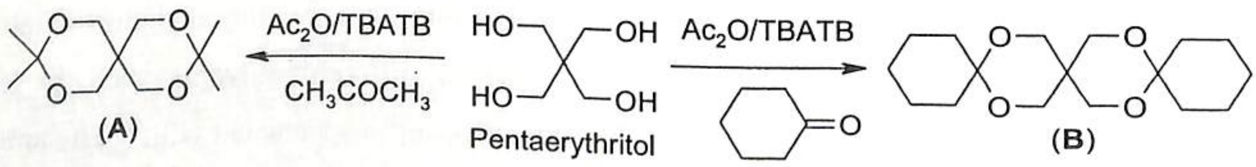
The acetylation of a wide range of structurally varied aliphatic, benzylic, allylic alcohols, amines, phenols and thiol highlight the fact that the method is capable of generalisation. The acetylation methodology was also successfully applied to a representative variety of functionalised alcohols. Due 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.



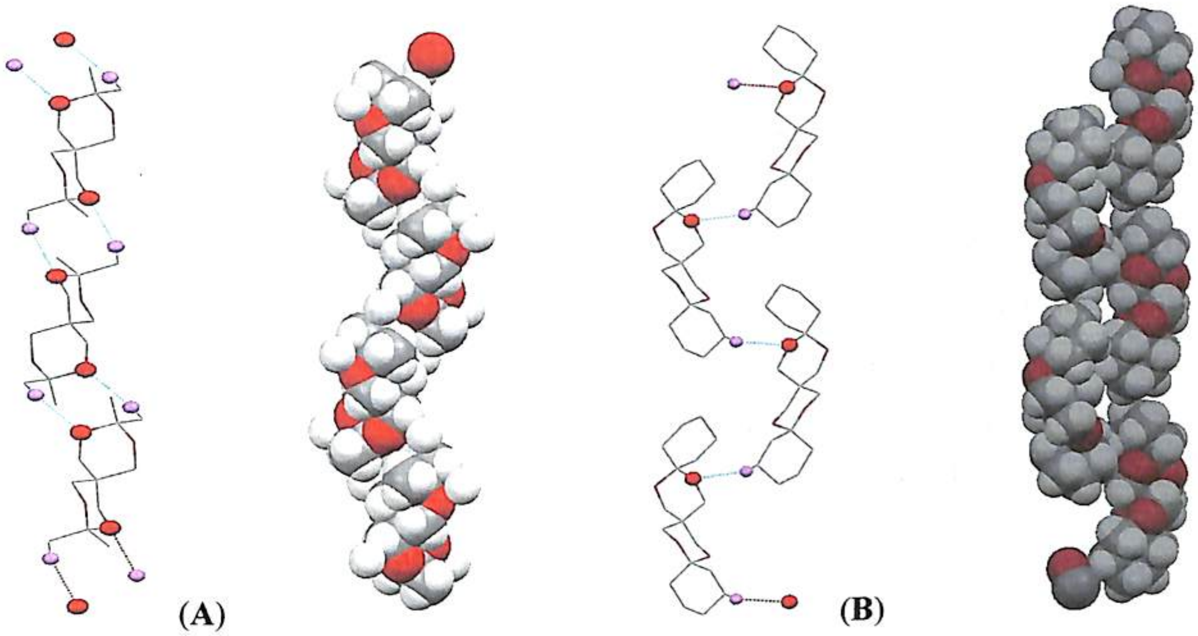
Scheme 1B.9. Acetylation and Isopropylidation of Pentaerythritol

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.

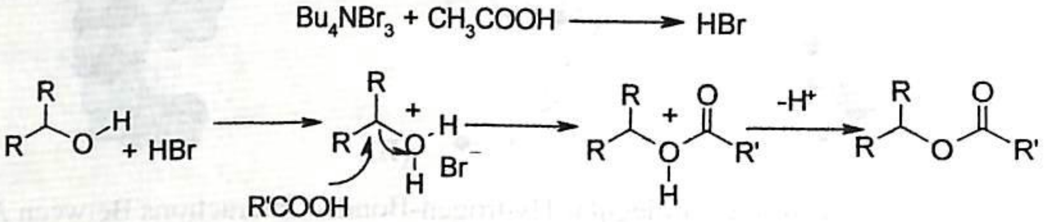
The weaker CH….O interaction mediates the unprecedented helical assembly of sterically encumbered bis acetals. These molecules contain a high degree of encoded molecular recognition functionality. One of the oxygen atom from one side form complementary weak CH….O interactions with the adjacent molecule. 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, esterificatio was very satisfactory; hence no special precaution was required for the removal of water from th reaction mixture.

In a control reaction when decanol was treated with TBATB (0.1 mmol) no alcohol brominatio 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 o 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 c 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.

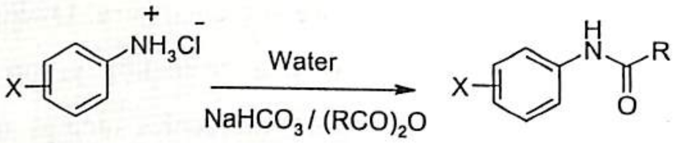
Water is a solvent of academic interest as well as human and economic interest because it minimises environmental impact, increases operational safety and provides a low cost and reusable reaction medium for pursuing reaction chemistry. Furthermore it is also the most abundant, cheap, non-toxic, safe 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

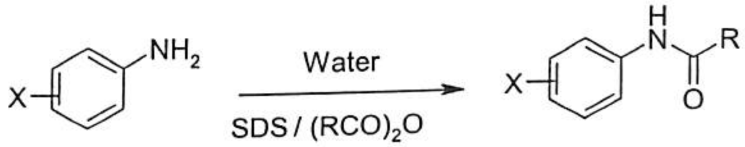
It has been observed that during the acetylation of aryl amines in an organic reaction medium electron-donating groups in the aromatic ring facilitate the reaction where as electron-withdrawing groups slow down the reaction. No such effect was observed by the present methodology and all the substrates 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.



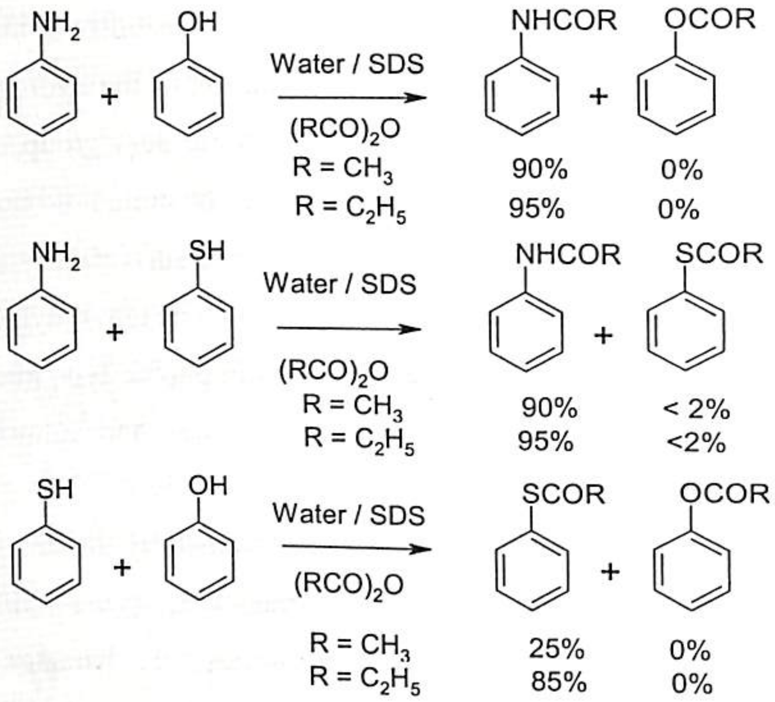
X = H, CH_3, OCH_3, OH, NH_2, F

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

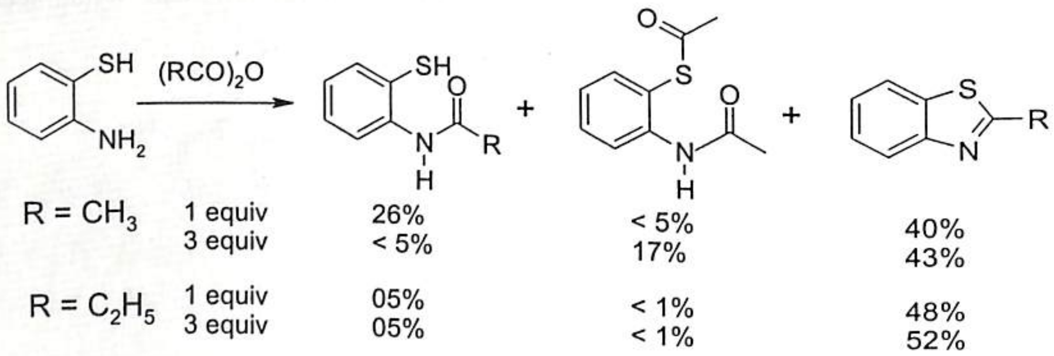
Chemoselectivity

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.

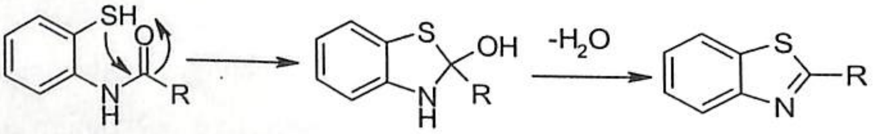


Scheme 2B.3. Intermolecular Chemoselectivity of Amines

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.

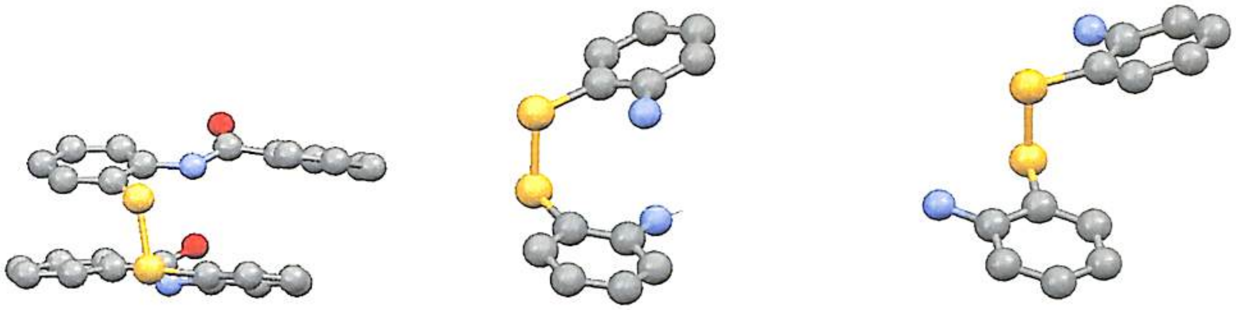


Scheme 2B.4. Intramolecular Chemoselectivity of 2-Aminothiophenol



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.