NEWER SYNTHETIC METHODOLOGIES FOR TETRAHYDROPYRANYLATION/DEPYRANYLATION, TRANSITION METAL-FREE OXIDATION AND THIA-MICHAEL REACTIONS

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by
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to the
DEPARTMENT OF CHEMISTRY
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May, 2006

Dedicated to my

Late Grandfather

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CERTIFICATE-I

This is to certify that Mr. Subrata Ghosh has satisfactorily completed all the courses required for the Ph. D degree programme.

These courses include:

CH 603	Supra Molecules: Concept and Applications
CH 627	New Reagents in Organic Synthesis
CH 630	A Molecular Approach to Physical Chemistry
CH 632	Advance Group Theory

Mr. Subrata Ghosh successfully completed his Ph. D. qualifying examination on December 31, 2003.

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This is to certify that Mr. Subrata Ghosh has been working in my research group since July 22, 2002 as a regular registered Ph. D. student. I am forwarding his thesis entitled "NEWER SYNTHETIC METHODOLOGIES FOR TETRAHYDROPYRANYLATION/ DEPYRANYLATION, TRANSI-TION METAL-FREE OXIDATION AND THIA-MICHAEL REACTIONS" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

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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 Abu T. Khan.

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.

Guwahati
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CH 603	Supra Molecules: Concept and Applications	6	BB
CH 627	New Reagents in Organic Synthesis	6	AB
CH 630	A Molecular Approach to Physical Chemistry	6	BB
CH 632	Advance Group Theory	6	BB

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Subrata Ghosh

SUMMARY

This dissertation describes the successful efforts on the development of newer synthetic methodologies for tetrahydropyranylation/depyranylation, transition metal-free oxidation and thia-Michael reactions.

The thesis contains mainly three chapters. Each chapter is subdivided into two parts viz. **Part I** and **Part II**.

Part I describes a review of literature of the present work and its significance. Similarly, **Part II** gives an account of the work carried out by the candidate.

Chapter I, Part I elaborates the importance of tetrahydropyranyl ethers in organic synthesis and their preparations from the corresponding hydroxyl compounds as well as their cleavage into the parent hydroxyl compounds. In addition, it also highlights reasons for choosing the research problem for investigation.

Part II of the first chapter consists of three sections such as **Section A**, **Section B** and **Section C,** respectively. Each section describes the new synthetic protocol for tetrahydropyranylation of various hydroxyl compounds and their depyranylation by employing new reagents, which act as either pre-catalyst or catalyst.

Section A contains a description of new synthetic protocol for chemoselective tetrahydropyranylation/depyranylation of alcohols and phenols using bromodimethylsulfonium bromide (BDMS) as an efficient and useful pre-catalyst.

By applying this methodology, various aliphatic primary alcohols (**46-48**) and secondary alcohols **49-52** and **14** were smoothly converted into the corresponding tetrahydropyranyl ethers **75-81** and **15**, respectively in good to high yields. The primary hydroxyl group can be protected chemoselectively in presence of phenolic hydroxyl group as well as mono protection of diols is also possible (**82** and **83**). A large number of alcohols containing other protecting groups such as acetyl (**55**), benzoyl (**56**), trityl (**57**), TBDPS ether (**58**), allyl (**59-62**) were converted to the desired THP ethers **84-91** respectively under this reaction conditions without affecting other protecting groups. Moreover, various phenolic compounds **64-66** were transformed very easily to the corresponding THP ethers **93-95** in good yields. Interestingly, carbohydrate as well as nucleosidic compounds **69-74** can also be protected to the THP ethers **98-103** by using our protocol. All the protected compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, by elemental analyses and all were in full agreement with the expected products. Similarly, deprotection can be achieved by employing our protocol. When a series of THP ethers mentioned in Table 2

on page 16 gave the corresponding parent hydroxyl compounds in good yields. It is noteworthy to mention that no bromination takes place during experimental conditions.

Section B describes the potentiality of cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) as a mild and efficient heterogeneous catalyst for tetrahydropyranylation /depyranylation of alcohols and phenols.

In the present scenario, the heterogeneous catalysts find extensive application in organic synthesis due to several advantages over homogeneous catalysts such as high catalytic activity and selectivity, readily available, simple work-up procedure, minimum corrosion and formation of less byproduct etc. Though BDMS is a highly efficient pre-catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols, but the main disadvantage is that the reagent has to be prepared prior to use. We perceived that catalytic amounts of cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) can be used as a heterogenous catalyst for tetrhydropyranylation/depyranylation of alcohols and phenols in acetonitrile. A series of alcohols and phenols were converted into the corresponding THP ethers by employing the protocol. However, the method suffers from one serious drawback; for example, it is not applicable for sulfur containing compounds. Therefore, we were interested to look for another method, which will be more versatile and more effective.

Section C elaborates a highly efficient synthetic protocol for tetrahydropyranylation /depyranylation of alcohols and phenols. In recent years, bismuth compounds have been gaining interest in various organic transformations. We conceived that bismuth(III) nitrate pentahydrate, which is commercially and readily available at a very low cost as well as relatively nontoxic, might be a useful catalyst for tetrahydropyranylation/depyranylation. By using this catalyst, various alcohols, phenols, carbohydrates and nucleosides were successfully converted to the corresponding THP ethers in good yields. Interestingly, by employing this procedure, benzylidene protected compound (**132**) can also be transformed to the corresponding THP ether (**147**) and a primary hydroxyl group can be protected chemoselectively in presence of a secondary hydroxyl group (**153**). All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis and their characterization data were included in the experimental part.

Chapter II is divided again into two parts as usual **Part I** and **Part II.**

Part I of the second chapter contains the important method developed so far for oxidative deprotection of tetrahydropyranyl (THP) and *tert*-butyldimethylsilyl (TBS) ethers into the carbonyl compounds and chemoselective benzylic C-H oxidation. Further, it also highlights reasons for selecting the present research problem for investigation.

Part II of the second chapter consists of two sections viz., **Section A** and **Section B.** Each section describes the new methods for oxidation of various organic substrates.

Section A describes an expedient and efficient method for the direct oxidation of TBS- and THP ethers to the corresponding carbonyl compounds in good yields using a combination of BDMS and 30% H_2O_2 in CH_2Cl_2 at room temperature.

As per our expectation, when a mixture of TBS ether of benzyl alcohol (**58**) and BDSB (0.2 equiv.) was treated with 30% hydrogen peroxide (2 equiv.) in dichloromethane (2 mL) at room temperature, it gave benzaldehyde (**66**) with 85% yield. The product was characterized by recording IR and ^{1}H NMR spectra and the spectra were compared with the authentic spectra. Similarly the TBS ether of 4-nitrobenzyl alcohol **18** was converted to 4-nitrobenzaldehyde (**19**) within 50 minutes in 90% yield by following the same procedure. Interestingly, we have also observed that the combination is highly chemoselective towards the oxidative deprotection of benzylic TBS ether in presence of phenolic TBS ether (**64** and **65**). Likewise, various TBS ethers of secondary alcohols **66-69** were also converted smoothly to the corresponding carbonyl compounds **74-77,** respectively, by our protocol. On the other hand, the TBS ethers of aliphatic alcohol **70** provided the ester **78** instead of giving aldehyde. Similarly, THP ethers of a series of primary and secondary alcohols **79-84** were also converted to the corresponding carbonyl compounds with good to excellent yields. However, the THP ether of aliphatic primary alcohol **85** afforded the ester **78** rather than providing the expected aldehyde.

Section B describes a new method for transition metal free benzylic C-H oxidation as well as chemoselective oxidation of secondary hydroxyl group in presence of a primary hydroxyl group.

When a mixture of 2 mmol of toluene (**87**) and 30% hydrogen peroxide (1 mL) in 4 mL of CH_2Cl_2 was treated with BDSB (0.4 equiv) at room temperature, it was smoothly converted into 32% benzaldehyde (**71**) and 56% benzyl bromide (**100**). Both the products were characterized by recording IR and ^{1}H NMR spectra and also compared with the authentic spectra. Subsequently, we examined the substrate ethyl benzene (**88**) with the same combination under identical conditions, it provided (1-bromoethyl)benzene (14%), 1-phenylethanol (37%) and the oxidized product acetophenone (17%) after 3.5 h. Interestingly, when the same reaction was prolonged over a period of 10 h, it mainly afforded the oxidized product acetophenone (**101**) in 79% yield. Similarly various alkyl arenes **89-91** and cycloalkyl arenes **37** and **92** were oxidized into the corresponding ketones **76, 102, 103, 38,** and **5**, respectively, in good yields under identical reaction conditions. Similarly, other substrates having acetate and benzoyl protecting group such as **95-99** were also converted to the desired ketones **107-111** without any difficulty under similar reaction conditions. Interestingly, chemoselective oxidation at the benzylic position is possible in presence of a non-activated primary hydroxyl by employing our protocol. We have noted that various substrates **112** and **113** can be oxidized chemoselectively at the benzylic position without any difficulty by keeping intact the primary hydroxyl groups. In addition, various diols **116-119** can be oxidized chemoselectively in the presence of primary hydroxyl group. All the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.

Chapter III of the dissertation is again divided into two parts viz. **Part I** and **Part II.**

Part I of the third chapter provides a brief review on Michael addition of thiols to the electron deficient alkenes and also highlights their importance in organic synthesis.

Part II describes about perchloric acid impregnated on silica gel ($HClO_4$-SiO_2): a versatile catalyst for Michael addition of thiols to the electron deficient alkenes.

Thia-Michael reaction is an important reaction in organic synthesis. We were interested to develop a new method for thia-Michael reaction by employing solid supported reagents *e. g.* perchloric acid impregnated on silica gel because it has unique properties such as high efficiency due to more surface area, more stability and reusability, greater selectivity and ease of handling. We examined the thia-Michael reaction of 2-cyclopenten-1-one (**56**) with ethanethiol using 0.5 mol% of catalyst in dichloromethane at room temperature. We noticed that the reaction was complete within 5 min and the pure product 3-[ethylthio]-cyclopentanone (**64**) was isolated in 92% yield as a gummy liquid just by filtration through a short silica gel column. The product was characterized by recording IR, ^{1}H NMR, ^{13}C spectra and elemental analysis. Similarly, some other enones such as **30** and **57** gives the thia-Michael addition products **67-70** on reaction with a variety of thiols. Remarkably, the enone 16-dehydropregnenolone (16-DPA, **58**) was also reacted with ethanethiol and thiophenol independently to give the 1,4-addition products **71** and **72**, respectively, in fairly good yields using the same catalyst under similar reaction conditions. The product **72** was also confirmed by X-ray crystallography. In addition, by using methanol as the solvent, it is possible to access Michael addition products **73** and **74** from the corresponding chalcone (**41**) in very good yields. Notably, by employing our protocol, the naturally occurring α,β-unsaturated ketones such as *S* (+)-carvone (**59**) and *R*-(+) pulegone (**1**) were afforded corresponding Michael addition products **75**, **76** and **2** respectively as diastereomeric mixture on treatment with thiols under identical reaction conditions. By employing the present protocol, various α,β-unsaturated esters namely methyl acrylate (**5**), methyl methacrylate (**60**) and ethyl acrylate (**61**) furnished the desired Michael addition products **77-79**, respectively, on reaction with thiophenol in good yields. Furthermore, our methodology can be extended for 1,4-conjugate addition reaction of thiols with acrylonitrile (**62**) and acrylamide (**63**) providing the corresponding products **80** and **81** under identical conditions. All the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis, as well as their characterization data are included in the experimental part.

CONTENTS

CHAPTER II

PART II

SECTION A Transition metal-free oxidative deprtection of THP and TBS ethers using bromodimethylsulfonium bromide and hydrogen peroxide

CHAPTER III

PART II New synthetic method for thia-Michael reaction using silica supported perchloric acid

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam, from July 22, 2002 to May 5, 2006 as a research scholar.

The analytical samples were routinely dried *in vacuo* at 50 °C for 8 hours. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Buechi R-114V instrument. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent and spots were detected by staining with iodine vapour or under UV light or charring 15% Conc. H_2SO_4 in MeOH or MOSTAIN solution [by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulphate in 400 mL 10% H_2SO_4 solution]. ^{1}H-Nuclear Magnetic Resonance spectra and ^{13}C-Nuclear Magnetic Resonance spectra were recorded on Varian (60 MHz), Bruker (300 MHz), and Jeol (400 MHz), instruments using tetramethyl silane (TMS) as an internal standard and $CDCl_3$ as solvent. The chemical shift values were expressed in δ scale and their multiplications were described using the following symbols: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, *m*-multiplet, br-broad, brs-broad singlet.

The infrared spectra were recorded in KBr pellets or in liquid film on a Perkin Elmer 1330 and Nicolet Impact 410 instruments, respectively. Melting points were determined on a sulphuric acid bath or Buechi B-545 instrument and were uncorrected. Elemetal analysis has been done by Perkin Elmer CHNS/O-2400 instrument. All the solvents and reagents employed were purified using recommended procedures in literature.

X-ray diffraction data were collected with a Bruker Apex II smart diffractometer with CCD area detectors using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å).

Abbreviations

QFC	quinolium fluorochromate
CH_2Cl_2	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethyl sulfoxide
m-CPBA	*m*-chloroperbenzoic acid
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
PCC	pyridiniumchloro chromate
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TMSCl	trimethylchlorosilane
TBATB	tetrabutylammonium tribromide
CPCC	3-carboxypyridinium chlorochromate
NHPI	*N*-hydroxyphthalimide
DHP	3,4-dihydro-*2H*-pyran
PTSA	*p*-toluenesulfonic acid
PPTS	pyridinium *p*-toluenesulfonate
ATPB	acetonyltriphenylphosphonium bromide
THP	tetrahydropyranyl
MW	micro wave
β-CD	β-cyclo dextrin
Bz	benzoyl
Ts	*p*-toluenesulfonyl
Tr	trityl
py	pyridine
TMS	trimethylsilyl
THF	tetrahydrofuran
BDMS	bromodimethylsulfonium bromide
EG	ethylene glycol

A BRIEF LITERATURE SURVEY ON THE IMPORTANCE OF TETRAHYDROPYRANYL ETHERS AND METHODS OF PRYRANYLATION/ DEPYRANYLATION OF ALCOHOLS AND PHENOLS

REVIEW OF LITERATURE

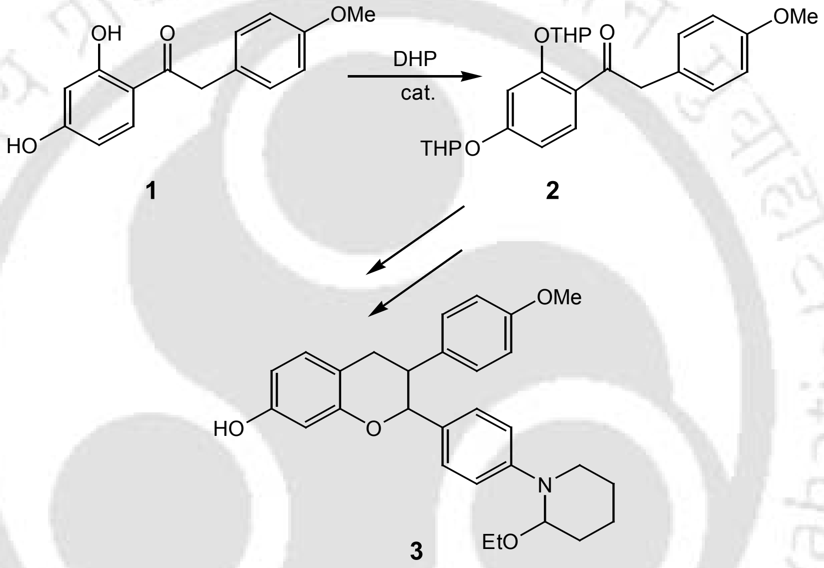
Introduction

Many natural and non-natural multifunctional molecules, which are synthesized through multi-step sequences in liquid phase, frequently involve protection-deprotection strategy during their synthesis. The concept of blocking functional groups temporarily has been used in organic synthesis for nearly 100 years, although it requires at least two additional steps to achieve the final product. This makes the entire synthetic plan more complex in case good methods are not available for protection-deprotection. At the same time, environmental and economic considerations have created interest in both academic and industrial research, in designing synthetic procedures that are clean, selective, high yielding and easy to handle. In fact, as clearly stated by Sheldon, "-------traditional concepts of process efficiency are changing from an exclusive focus on chemical yield to one that assigns economic value to eliminating waste----."[1]

The hydroxyl group is present in a number of biologically active compounds such as nucleosides, carbohydrates, steroids, macrolides, polyethers, peptides and amino acids. Sometimes the protection-deprotection strategy for a free hydroxyl group becomes an essential job to manipulate other functional groups particularly in polyfunctional natural and non-natural product synthesis. Therefore, high selectivity is frequently requested for a given hydroxyl group in polyol chemistry. Several protecting groups have been cited in the literature for the protection of hydroxyl groups. Among them, tetrahydropyranyl (THP) ether[2] is often used for protection of hydroxyl groups in organic synthesis.

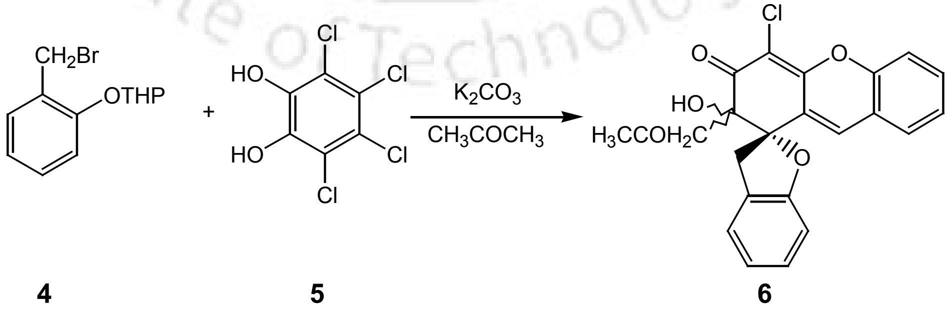
The particular advantages for using THP group as protecting group are: its ease of introduction, the low cost of dihydropyran, stable under a variety of reaction conditions such as reaction with metal hydrides, metal triflates, Grignard reagents, acylating agents, oxidative reagents and alkylating agents. In addition it can be easily deprotected at a later stage. Many times it is also the protecting group of choice in peptide,[3] nucleotide,[4] carbohydrate,[5] and steroid chemistry.[6] Unfortunately, its two greatest limitations are: the complexity of the NMR spectra and formation of diastereoisomers on reaction with alcohols. The tetrahydropyranylation is usually achieved with protonic or Lewis acid catalyst in an aprotic solvent such as CH_2Cl_2, THF, dioxan etc. or in solvent-free conditions. On the other hand, depyranylation is carried out with an acidic reagent in a protic solvent such as methanol, ethanol, isopropanol etc. Over the years, a large number of methods have been developed for tetrahydropyranylation/depyranylation, still there is a need to develop a better methodology, which might work under mild conditions. The importance of THP ether as a protecting group in various organic syntheses can be realized from the examples given below.

Hajela *et al* reported[7] the novel synthesis of 2-(4-alkoxyphenyl)-3-substituted phenyl-7-(hydroxy)-2*H*-1-benzopyran (**3**) by involving THP as the protecting group as depicted in Scheme 1.



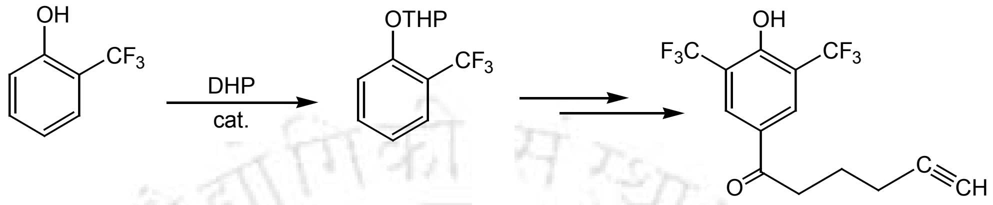
Scheme 1

Kasturi *et al* exploited[8] the THP ether of 2-bromomethylphenol for the synthesis of polycyclic heterocycle **6** as shown in Scheme 2.



Scheme 2

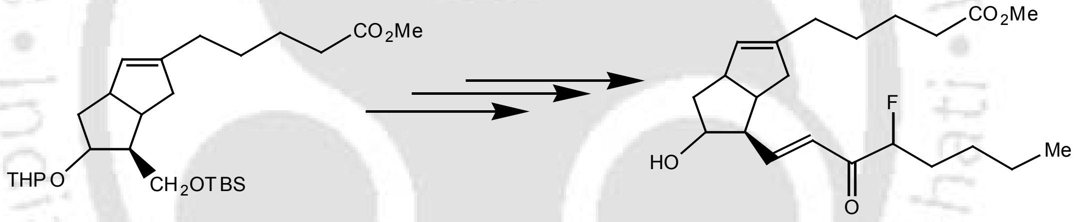
Miller *et al* also preferred[9] THP ether as the choice of protecting group for the hydroxyl functionality during the synthesis of metabolism-resistant analogue of tebufelone as depicted in Scheme 3.



7 **8** **9**

Scheme 3

Ueno *et al* utilized[10] THP group as protecting for the hydroxyl group in the synthesis of prostaglandins, which are useful as blood platelet aggregation inhibitors and antihypertensives, as shown in Scheme 4.

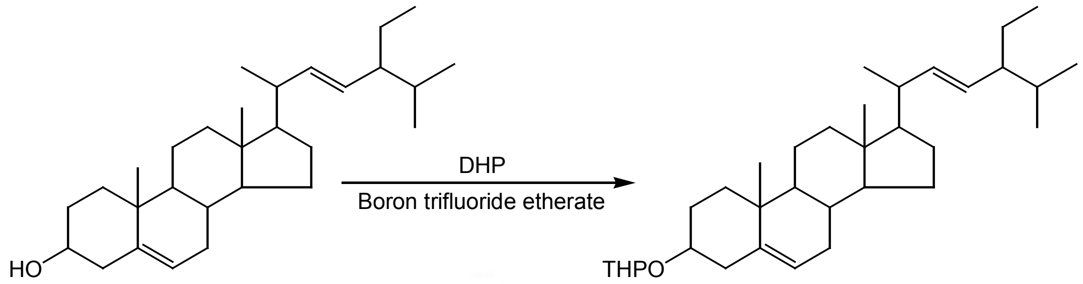


10 **11**

Scheme 4

Some of the examples, which are mentioned in the Schemes from 1 to 4, reflect the utility of the THP ethers in organic synthesis. Then we were interested to look for what are the methods available for their preparation and cleavage. Interestingly, over the years a large number of methods have been developed for tetrahydropyranylation of alcohols and phenols as well as depyranylation into the corresponding parent compounds and some of them are highlighted below.

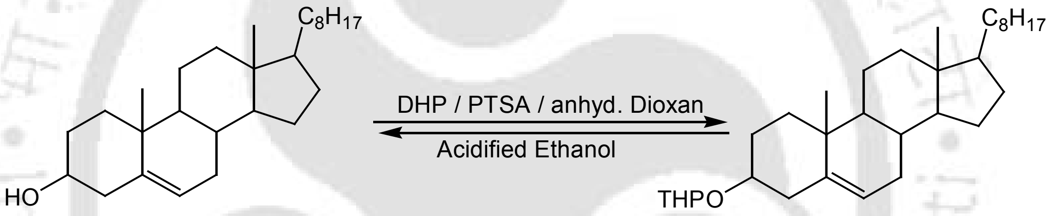
Dinkes *et al* used boron trifluoride[11] etherate as a catalyst for tetrahydropyranylation of stigmasterol as shown in Scheme 5. Although this method gives satisfactory results but it needs excess amount of dihydropyran (DHP).



12 **13**

Scheme 5

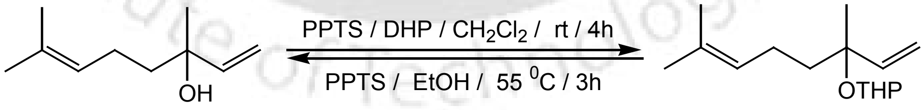
Boom *et al* introduced[12] an efficient method for the tetrahydropyranylation of cholesterol (**14**) using *p*-toluenesulfonic acid as a catalyst as represented in Scheme 6. The main drawback is requirement of large excess amount of dihydropyran.



14 **15**

Scheme 6

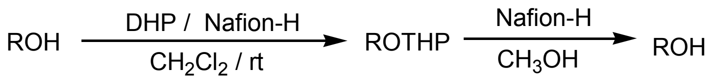
Yoshikoshi *et al* have shown[13] pyridinium *p*-toluenesulfonate is a useful catalyst for tetrahydropyranylation of alcohols as depicted in Scheme 7. Though the method provides excellent yields but it requires longer reaction time.



16 **17**

Scheme 7

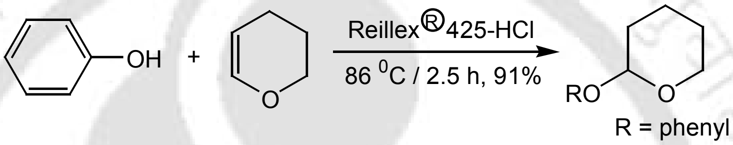
Olah and his group demonstrated[14] that Nafion-H, a solid superacid, can be utilized as catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols as shown in Scheme 8. This method is very good in terms of yield but it takes relatively much longer time for completion.



18 **19** **18**

Scheme 8

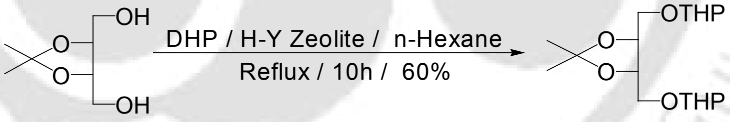
Later on Marston *et al* introduced[15] one commercially available copolymer Reillex® 425-HCl for tetrahydropyranylation of alcohols and phenols as shown in Scheme 9. Though the yields of this method are quite satisfactory, but the main disadvantage of this method is that the reaction has to be carried out at higher temperature.



20 **21**

Scheme 9

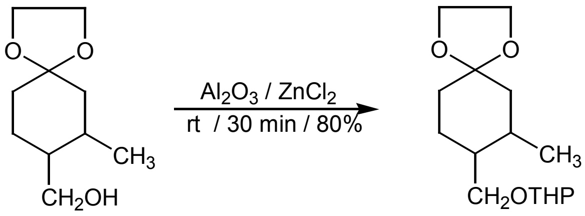
Kumar *et al* showed that H-Y Zeolite[16] is also a good and reusable catalyst for tetrahydropyranylation of alcohols and phenols as shown in Scheme 10. This method requires reflux condition and longer reaction time.



22 **23**

Scheme 10

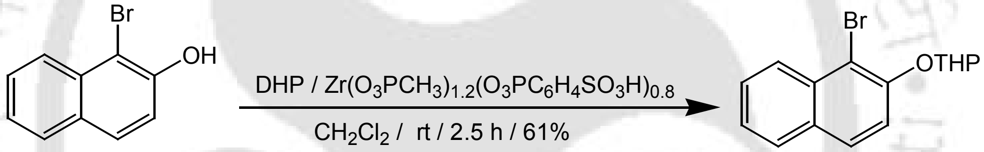
Ranu *et al* introduced[17] that alumina impregnated with $ZnCl_2$ is a useful catalyst for tetrahydropyranylation as represented in Scheme 11. Though they have shown that *O,O*-ketal can survive under the reaction conditions, still the method suffers from several drawbacks such as long reaction time, requires excess amount of reagent and N_2 atmosphere to preserve the reagent.



24 **25**

Scheme 11

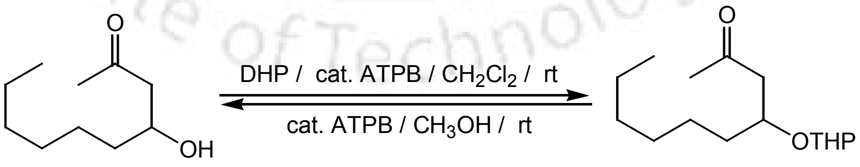
Curini *et al* reported[18] a method for tetrahydropyranylation of alcohols and phenols using zirconium sulfophenyl phosphonate as a heterogeneous catalyst as depicted in Scheme 12. The main advantage is the method is useful for protection of *tert*-alcohols as THP ether.



26 **27**

Scheme 12

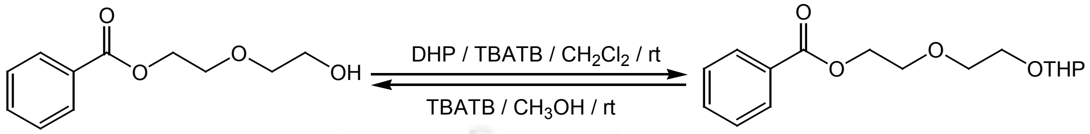
Later on, Hon *et al* reported polymer-supported acetonyltriphenylphosphonium bromide[19] as a catalyst for tetrahydropyranylation/depyranylation of alcohols phenols as shown in Scheme 13. This method is excellent in terms of yield and reaction time. But the major disadvantage of this method is that the catalyst has to be prepared prior to use.



28 **29**

Scheme 13

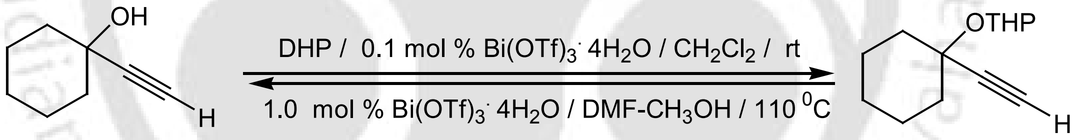
Recently, Patel *et al* demonstrated[20] another method for the chemoselective protection of the hydroxyl group as tetrahydropyranyl ether and their cleavage to the corresponding parent hydroxyl compounds using *n*-tetrabutylammonium tribromide (TBATB) as a catalyst as depicted in Scheme 14. Although this method gives satisfactory results, still it has the following disadvantage such as the reagent is expensive and it has to be prepared prior to use.



30 **31**

Scheme 14

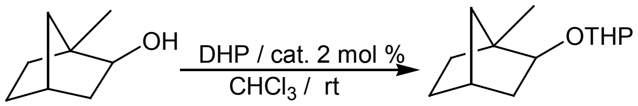
In the year 2003, Mohan *et al* used bismuth triflate[21] as an efficient catalyst for the formation and cleavage of tetrahydropyranyl ethers. This method suffers from several drawbacks such as involvement of expensive catalyst, high temperature particularly for deprotection and failure to produce the desired product in case of β-naphthol. Remarkably, this method successfully protects the tertiary alcohols in good yields as represented in Scheme 15.



32 **33**

Scheme 15

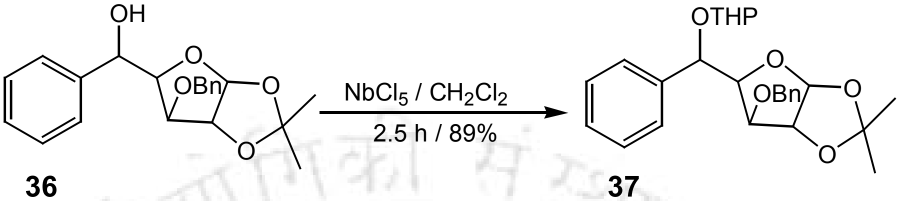
Karimi *et al* also have shown very recently that solid silica-based sulfonic acid[22] is an efficient and recoverable catalyst for selective tetrahydropyranylation of alcohols and phenols as represented in Scheme 16. In fact, the method is highly efficient, but the only drawback is that the reagent has to be made prior to use.



34 **35**

Scheme 16

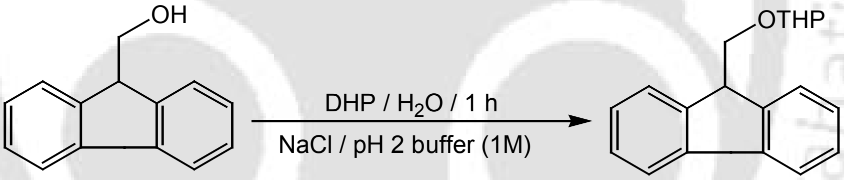
Nagaiah *et al* used niobium(V) chloride[23] as an active Lewis acid catalyst for tetrahydropyranylation of alcohols and phenols, as shown in Scheme 17. The main disadvantage of this method is longer reaction time.



36 **37**

Scheme 17

Very recently, Patel *et al* have shown[24] that water can be used as catalyst and solvent for tetrahydropyranylation of alcohols, which is shown in Scheme 18. Although the method is economically viable still it suffers from some drawbacks such as long reaction time, failure in case of phenols to react under the experimental condition.

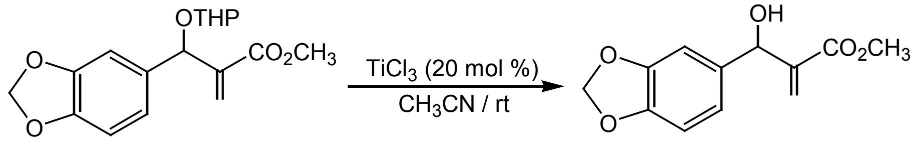


38 **39**

Scheme 18

Over the years, some more methods have also been reported for tetrahydropyranylation and depyranylation using various reagents such as: Amberlyst H-15,[25] Heteropoly acid,[26] bis[trimethylsilyl] sulfate,[27] iodotrimethylsilane,[28] copper(II) chloride,[29] K-10 Clay,[30] CBr_4,[31] dialkylimidazolium tetrachloroaluminate,[32] ATPB,[33] Li(OTf)[34a], TCCA[34b] etc.

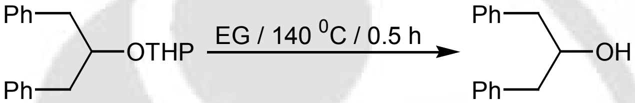
Some methods are also known in the literature exclusively for depyranylation into the corresponding alcohols as well as phenols and some of them are given below. Very recently Nayak *et al* have shown[35] that Ti(III) chloride is an effective catalyst for deprotection of tetrahydropyranyl ethers as shown in Scheme 19. Although this method gives satisfactory results but it takes longer time for completion of the reaction.



40 **41**

Scheme 19

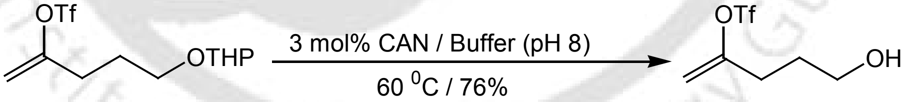
Miyake *et al* have introduced an efficient method[36] for depyranylation under neutral condition using ethylene glycol (EG) or propylene glycol, represented in Scheme 20. Although the method is highly efficient, still the drawback is that it requires higher temperature.



42 **43**

Scheme 20

Marko *et al* proposed a highly chemoselective method[37] for deprotection of THP ethers in presence of enol triflates using catalytic amount of cerium(IV) ammonium nitrate as shown in Scheme 21. The major disadvantages of this method are reflux condition and long reaction time.



44 **45**

Scheme 21

Unfortunately, many of these methods have serious drawbacks such as harsh reaction conditions, low yield, longer reaction time, the catalyst is not readily available and involvement of highly expensive reagent as catalyst. Therefore, we have chosen our research topic to develop some new methodologies for tetrahydropyranylation /depyranylation, which will be easy to handle and economically viable.

SECTION A

A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS USING BROMODIMETHYLSULFONIUM BROMIDE

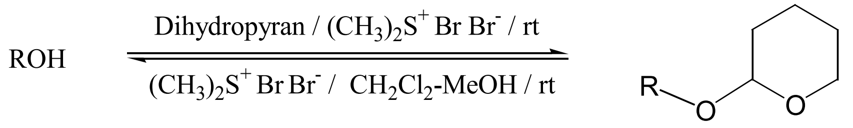
RESULTS AND DISCUSSION

Results and Discussion

Some of the importance and usefulness of tetrahydropyranyl ethers as well as their preparation and cleavage have been discussed in Part I of the Chapter I. It seems to us that there is a further scope to develop a new methodology for tetrahydropyranylation /depyranylation, which will be simple, efficient and economic.

In addition, some of the recently used reagents that can catalyze both tetrahydropyranylation and depyranylation are: $ZrCl_4$,[38] I_2,[39] LiBr,[40] acetonyltriphenylphosphonium bromide,[33] TBATB,[20] aluminium chloride hexahydrate,[41] $In(OTf)_3$,[42] dialkylimidazolium tetrachloroaluminates,[32] and $InCl_3$ immobilized in ionic liquids.[43] However, some of the earlier reported procedures have some drawbacks such as requirement of higher reaction temperatures, much longer reaction times, involvement of volatile organic solvents and expensive catalysts as well as incompatibility with other acid-sensitive functional groups. In an endeavor to gradually change the current working practices to greener alternatives and environmental demands,[44] there is a need for a solvent-free and catalytically efficient alternative for protection and deprotection of hydroxy functionality as THP ether, which might work under mild and economically cheaper reaction conditions. As a part of our ongoing research programme to develop new synthetic methodologies,[45] we conceived that bromodimethylsulfonium bromide (BDMS), which can generate HBr in the reaction medium on reaction with alcohol, might be a useful catalyst for tetrahydropyranylation and depyranylation of alcohols and phenols. The catalyst bromodimethylsulfonium bromide has been utilized in various organic transformations such as conversion of alcohols to the corresponding bromides,[46] oxidation of sulfides to the disulfides,[47] deprotection of dithioacetals,[48] preparation of α-bromoenones,[49] etc. In this section, we would like to discuss a simple and convenient synthetic protocol for tetrahydropranylation of alcohols and phenols catalyzed by bromodimethylsulfonium bromide under solvent-free conditions and their depyranylation to the corresponding parent hydroxyl compounds using the same catalyst in CH_2Cl_2-MeOH as shown in Scheme 22.

For our study, we prepared the reagent bromodimethylsulfonium bromide by following literature procedure.[48] Subsequently, the mixture of 1-decanol (0.79 g, 5 mmol) and 3,4-

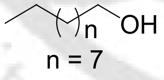
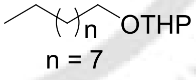
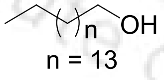
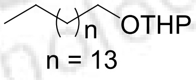
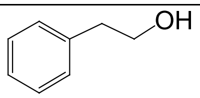
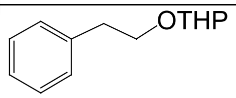
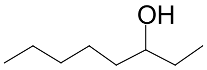
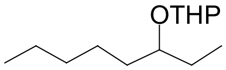
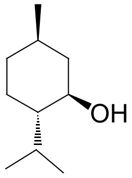
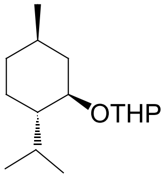


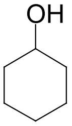
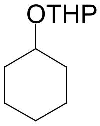
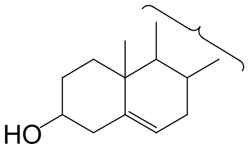
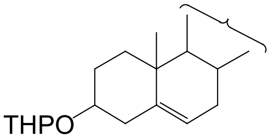
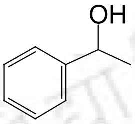
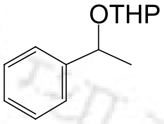
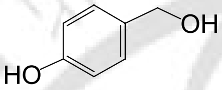
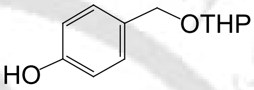
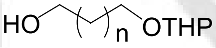
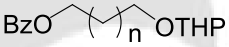
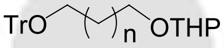
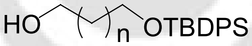
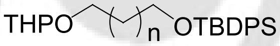
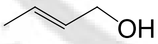
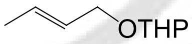
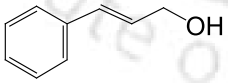
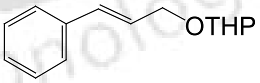
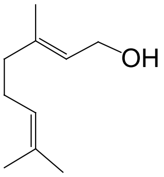
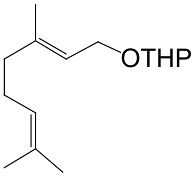
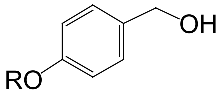
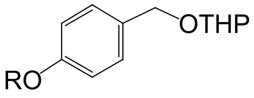
R = alkyl / aryl / sugar residue / nucleoside residue

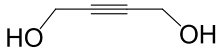
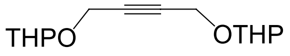
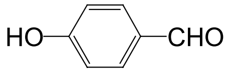
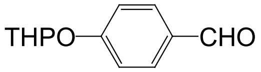
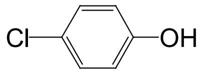
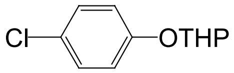
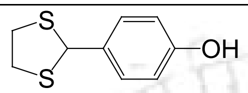
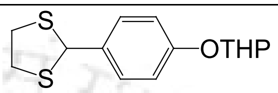
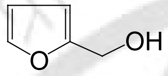
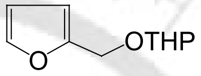
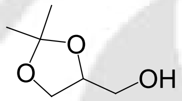
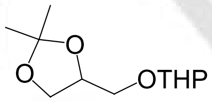
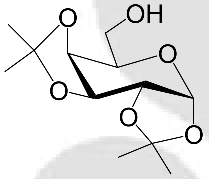
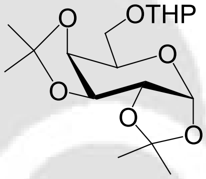
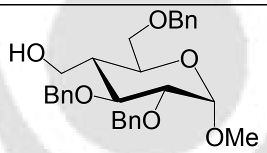
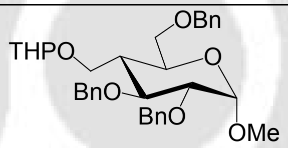
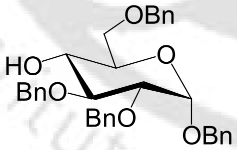
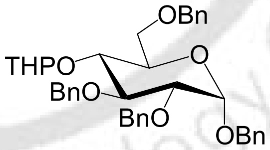
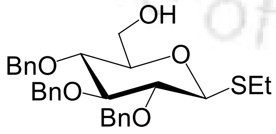
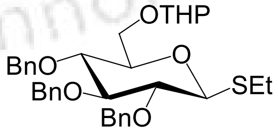
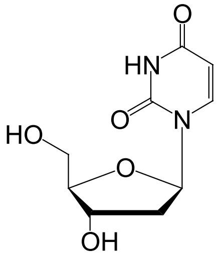
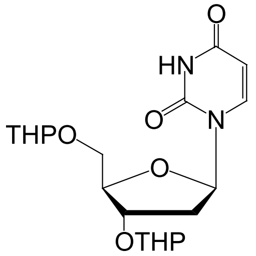
Scheme 22

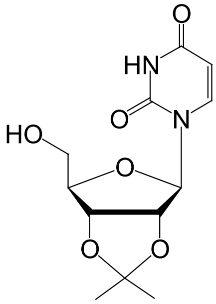
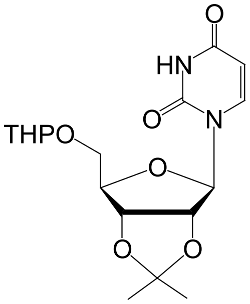
dihydro-2*H*-pyran (0.55 mL, 6 mmol) was treated with catalytic amount of bromo-dimethylsulfonium bromide (11 mg, 0.05 mmol) at room temperature and it was smoothly converted into the corresponding tetrahydropyranyl ether of 1-decanol (**75**) within 5 min in 97% yield. The product was characterized by recording IR, ^{1}H NMR and ^{13}C NMR spectra and elemental analysis. In IR spectrum, it exhibits absorbance values at 2919, 2854, 1469, 1354, 1218, 1127, 1037 cm^{-1} (Fig. 1). The disappearance of hydroxyl absorption frequency in the IR spectrum clearly indicates the formation of THP ether. Similarly, ^{1}H NMR spectrum gives the signals at δ 0.85 (t, 3H, J = 6.8 Hz), 1.24 (bs, 14H), 1.51-1.58 (m, 6H), 1.66-182 (m, 2H), 3.35 (dt, 1H, J = 6.8 Hz, J = 13.4 Hz), 3.46-3.48 (m, 1H), 3.70 (dt, 1H, J = 6.8 Hz, J = 13.9 Hz), 3.82-3.86 (m, 1H), 4.56 (dd, 1H, J = 3.0 Hz, J = 7.3 Hz) ppm (Fig. 2). The following new signals at δ 3.35, 3.46-3.48, 3.70, 3.82-3.86 and 4.56 clearly indicate the formation of THP ether. In ^{13}C NMR spectrum, it shows peaks at δ 14.07, 19.65, 22.65, 25.49, 26.21, 29.29, 29.46, 29.54, 29.57, 29.73, 30.75, 31.86, 62.27, 67.66, 98.79 ppm (Fig 3). The appearance of a new signal at δ 98.79 in the ^{13}C NMR spectrum support the formation of THP ether. Next, a mixture of cetyl alcohol (**47**) and 3,4-dihydro-2*H*-pyran (DHP) provided the corresponding THP ether **76** within 15 min in 98% yield under identical reaction conditions. By following the above typical procedure, various secondary alcohols (**14** and **49-52**) were transformed easily to the corresponding THP ethers (**15** and **78-81**) in good yields. Interestingly, mono protection of alcoholic hydroxyl group is possible in the presence of phenolic OH group (**53**) and other alcoholic OH group (**54**) by leaving 10% starting material unreacted. It is pertinent to mention that the conversion (**75**) is highly efficient in terms of yield, reaction time than the recently reported procedure.[20] Moreover, a wide variety of protected alcoholic (**55-58**) compounds were transformed into the corresponding THP ethers (**84-87**) under identical reaction conditions using the same catalyst. It is important to mention that various other protecting groups such as acetyl, benzoyl, trityl, and TBDPS groups remain unaffected during reaction conditions. Additionally, various double bonded and triple bonded substrates (**59-63**) also provided the corresponding THP ethers (**88-92**) under identical reaction conditions. It is important to highlight that no brominations take place at the double bond or triple bond. It is also important to mention that geraniol was smoothly transformed at a much faster rate to the corresponding THP ether (**90**) than recently reported procedure,[41] which also shows the efficiency of our protocol. Subsequently, various phenolic compounds (**64-66**) were also converted into the corresponding THP ethers (**93-95**) using the same catalyst under solvent-free conditions. It is noteworthy to point out that no brominations occur in the aromatic ring as well as dithioacetal group does not (as in case of substrate **66**) undergo deprotection under the experimental condition. Remarkably, highly acid sensitive substrates (**67-69**) can be protected to the corresponding THP ethers (**96-98**) by using the same catalyst. Furthermore, various carbohydrate and nucleosidic compounds (**69-74**) were transformed smoothly to the corresponding THP ethers (**98-103**) by following the same reaction procedure and the results are summarized in the Table 1. The products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. It is worthy to mention that benzyl, isopropylidene and a thio group at the anomeric position remain unaffected during the experimental conditions.

Table 1 Protection of various hydroxyl compounds to the corresponding tetrahydro-pyranyl ethers using catalytic amount of bromodimethylsulfonium bromide

Substrate No.	Substrate	Time min/ [h]	Product[a]	Product No.	Yield[b] /%
46		5		**75**	97
47		15		**76**	98
48		5		**77**	85
49		5		**78**	87
50		10		**79**	88

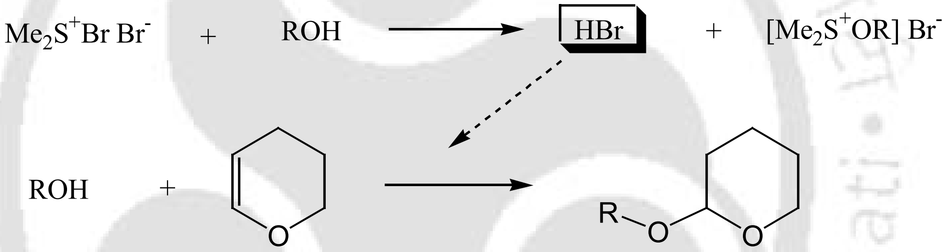
51		5		**80**	90
14		20		**15**	90
52		10		**81**	84
53		7		**82**	85^c
54	 n = 3	40	 n = 3	**83**	88^c
55	 n = 3	15	 n = 3	**84**	81
56	 n = 3	15	 n = 3	**85**	87
57	 n = 3	5	 n = 3	**86**	85
58	 n = 3	20	 n = 3	**87**	89
59		15		**88**	83
60		15		**89**	92
61		12		**90**	78
62	 R = -$CH_2CH=CH_2$	10	 R = -$CH_2CH=CH_2$	**91**	95

63		25		**92**	95
64		[4]		**93**	90
65		[6]		**94**	92
66		35		**95**	94
67		5		**96**	93
68		7		**97**	81
69		20		**98**	84
70		15		**99**	93
71		[1]		**100**	95
72		[1]		**101**	96
73		[3.5]		**102**	83

74		30		**103**	95

[a] The final products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. [b] Isolated yield. [C] Reaction was carried out by keeping 10% starting material unreacted.

The formation of the product can be explained as follows. It has been shown that bromodimethylsulfonium bromide can generate HBr on reaction with alcohol.[47] We believe that *in situ* generated HBr actually catalyzes the conversion of hydroxyl compounds into the corresponding tetrahydropyranyl ethers. We have observed that pH of the solution was ~ 2-3 while carrying out the reaction.

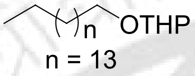
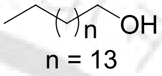
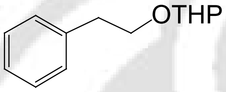
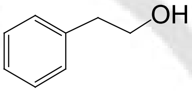
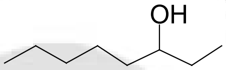
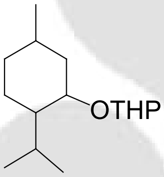
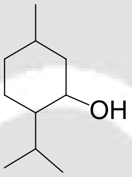
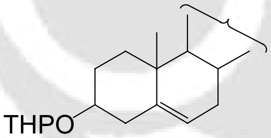
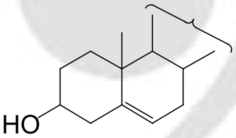
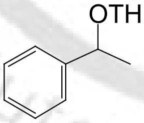
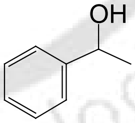
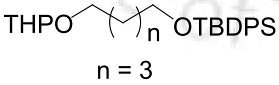
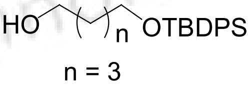
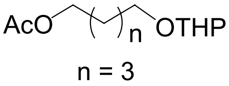
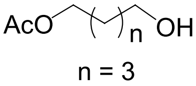
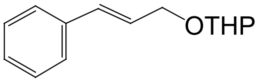
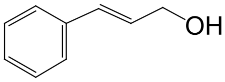


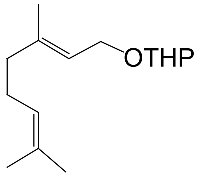
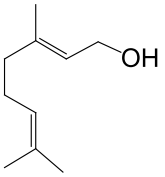
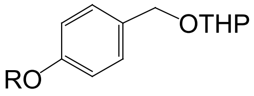
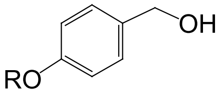
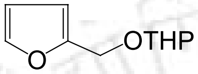
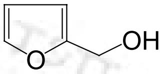
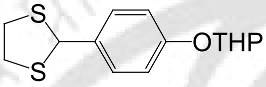
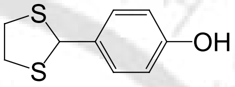
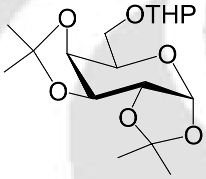
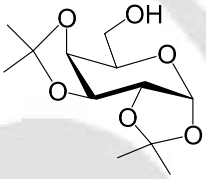
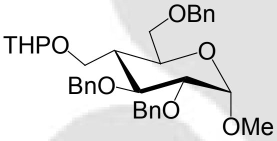
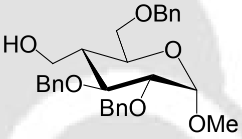
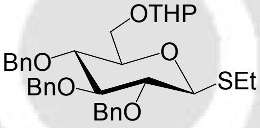
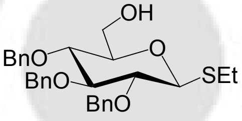
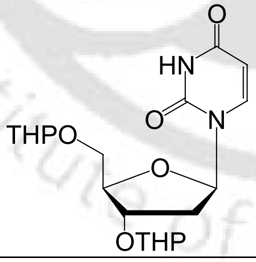
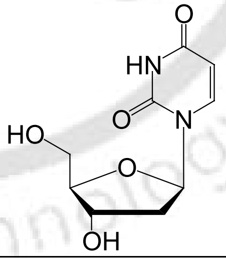
Scheme 23: Proposed mechanism for protection of hydroxy functionality as THP ether.

Next, we searched for suitable reaction conditions for deprotection of THP ethers to the parent hydroxyl compounds. The THP ether of cetyl alcohol (**76**) was deprotected smoothly to the parent hydroxyl compound cetyl alcohol (**47**) within 30 min on treatment with 0.05 equivalents of bromdimethylsulfonium bromide in dichloromethane-methanol at room temperature. Likewise, we converted successfully various THP ethers to the parent hydroxyl compounds under identical reaction conditions. The results are summarized in Table 2. The products were characterized by IR, ^{1}H NMR spectroscopy and elemental analyses as well as by comparison with the authentic compounds. It has also been observed that various protecting groups such as acetyl, benzoyl, benzyl, TBDPS, thioketal, allyl and isopropylidene remain unaffected during the deprotection reaction conditions. Moreover, no brominations occur at the double bond or triple bond or in the aromatic ring.

Similarly, the deprotection of THP ethers can be explained as follows: Bromodimethylsulfonium bromide can generate HBr on reaction with methanol, which is utilized for cleavage of THP ethers to the corresponding hydroxyl compounds.

Table 2 Deprotection of various tetrahydropyranyl ethers to the corresponding hydroxyl compounds using catalytic amount of bromodimethylsulfonium bromide in dry dichloromethane-methanol

Substrate No.	Substrate	Time min/ [h]	Product[a]	Product No	Yield[b] /%
76		30		**47**	90
77		25		**48**	97
78		25		**49**	92
79		15		**50**	95
15		40		**14**	70
81		25		**52**	70
87		30		**58**	90
84		15		**55**	90
89		[1]		**60**	90

90		[2]		**61**	98
91	 R = $-CH_2CH=CH_2$	50	 R = $-CH_2CH=CH_2$	**62**	93
96		35		**67**	80
95		40		**65**	82
98		30		**69**	76
99		[2]		**70**	85
101		[1]		**72**	73
102		[1.5]		**73**	80

[a]Final products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. [b]Isolated yield.

In summary, we have demonstrated a simple and convenient method for preparation of tetrahydropyranyl (THP) ethers from the corresponding alcohols and phenols under solvent-free conditions as well as deprotection to the parent hydroxyl compounds chemoselectively using the same catalyst by tuning the amount of the reagent and reaction conditions. In addition, this method is very simple and mild, easy to handle and compatible in the presence of a large number of other protecting groups. It is noteworthy that no brominations take place at the double or triple bond, and even in the aromatic rings. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for interconversion of various hydroxyl compounds to the corresponding tetrahydropyranyl (THP) ethers and vice-versa.

A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS

FIGURE

SECTION A

A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS USING BROMODIMETHYLSULFONIUM BROMIDE

EXPERIMENTAL

Experimental

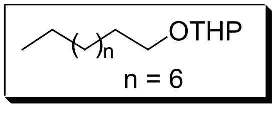
Preparation of bromodimethylsulfonium bromide:

Dimethyl sulfide (1.83 mL, 25 mmol) was taken in 5 mL of dry dichloromethane into a 150 mL standard joint conical flask. Then, 1.3 mL of bromine (25 mmol) was dissolved in 5 mL of dry dichloromethane and added slowly into the above solution at ice-bath temperature over a period of 5 min. During the addition, light orange crystals of bromodimethylsulfonium bromide begin to separate out. After the addition of bromine was completed, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. The crystalline product was obtained 4.3 g in 77% yield, m.p. 80 ^{o}C.

General procedure for Tetrahydropyranylation:

Bromodimethylsulfonium bromide (0.011 g, 0.05 mmol) was added to a mixture of 1-decanol (0.790 g, 5 mmol) and 3,4-dihydro-*2H*-pyran (0.550 mL, 6 mmol) and the resulting mixture was stirred at room temperature. The reaction was completed within 5 min as monitored by TLC and it was neutralized by addition of saturated $NaHCO_3$ solution (2-3 drops). The mixture was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the crude residue was purified through a short alumina column. The pure product was obtained (1.170g) in 97% yield as a colorless liquid.

THP ether of 1-decanol (75):



Nature: Colorless liquid

Yield: 97%

Reaction time: 5 min

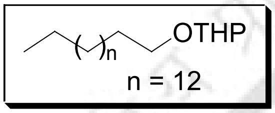
IR (Neat): cm^{-1} 2919, 2854, 1469, 1354, 1218, 1127, 1037

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J* = 6.8 Hz), 1.24 (bs, 14H), 1.51-1.58 (m, 6H), 1.66-182 (m, 2H), 3.35 (dt, 1H, *J* = 6.8 Hz, *J* = 13.4 Hz), 3.46-3.48 (m, 1H), 3.70 (dt, 1H, *J* = 6.8 Hz, *J* = 13.9 Hz), 3.82-3.86 (m, 1H), 4.56 (dd, 1H, *J* = 3.0 Hz, *J* = 7.3 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 14.07, 19.65, 22.65, 25.49, 26.21, 29.29, 29.46, 29.54, 29.57, 29.73, 30.75, 31.86, 62.27, 67.66, 98.79 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{30}O_2$	C 74.33	C 74.02
242.40	H 12.47	H 12.38

THP ether of 1-hexadecanol (76):



Nature: Colorless liquid

Yield: 98%

Reaction time: 15 min

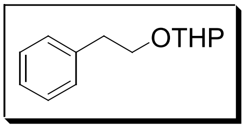
IR (Neat): cm^{-1} 2930, 2858, 1460, 1358, 1209, 1132, 1081, 1040, 989

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.85 (t, 3H, *J* = 6.6 Hz), 1.22-1.32 (m, 26H), 1.47-1.58 (m, 6H), 1.65-182 (m, 2H), 3.35 (dt, 1H, *J* = 6.6 Hz, *J* = 13.4 Hz), 3.44-3.49 (m, 1H), 3.69 (dt, 1H, *J* = 6.8 Hz, *J* = 13.9 Hz), 3.81-3.87 (m, 1H), 4.54 (dd, 1H, *J* = 2.7 Hz, *J* = 7.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 14.05, 19.63, 22.64, 25.46, 26.19, 29.31, 29.44, 29.57 (2C), 29.62 (3C), 29.64 (3C), 29.71, 30.73, 31.87, 62.24, 67.62, 98.76 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{21}H_{42}O_2$	C 77.24	C 77.08
326.56	H 12.96	H 12.87

THP ether of 2-phenylethanol (77):



Nature: Colorless liquid

Yield: 85%

Reaction time: 5 min

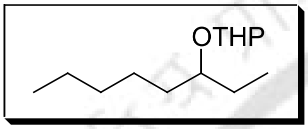
IR (Neat): cm^{-1} 2942, 2869, 1600, 1465, 1357, 1127, 1038

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.47-1.82 (m, 6H), 2.91 (t, 2H, *J* = 7.2 Hz), 3.43-3.46 (m, 1H), 3.61 (dt, 1H, *J* = 7.2, *J* = 14.4 Hz), 3.72-3.77 (m, 1H), 3.94 (dt, 1H, *J* = 7.6 Hz, *J* = 14.8 Hz), 4.58 (t, 1H, *J* = 3.2 Hz), 7.16-7.28 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.63, 25.58, 30.78, 36.47, 62.21, 68.30, 98.65, 126.00, 128.13 (2C), 128.85 (2C), 140.00 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_2$	C 75.69	C 75.43
206.28	H 8.79	H 8.73

THP ether of 3-octanol (78):



Nature: Colorless liquid

Yield: 87%

Reaction time: 5 min

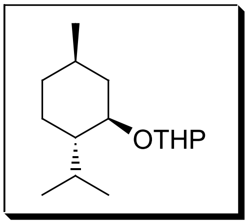
IR (Neat): cm^{-1} 2935, 2873, 1460, 1347, 1204, 1132, 1030

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 0.83 (t, 3H, *J* = 7.3 Hz), 0.90 (t, 3H, *J* = 7.3 Hz), 1.25-1.31 (m, 6H), 1.39-1.57 (m, 8H), 1.65-1.83 (m, 2H), 3.42-3.56 (m, 2H), 3.85-3.91 (m, 1H), 4.62 (dd, 1H, *J* = 2.4 Hz, *J* = 4.4 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 9.07, 9.95, 14.01, 14.05, 19.91, 19.96, 22.62 (2C), 24.70, 25.32, 25.55 (2C), 25.75, 27.71, 31.14, 31.20, 32.03, 32.08, 32.97, 34.32, 62.59, 62.65, 77.38, 78.02, 97.21, 97.66 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{26}O_2$	C 72.85	C 72.78
214.35	H 12.23	H 12.19

THP ether of menthol (79):



Nature: Colorless liquid

Yield: 88%

Reaction time: 10 min

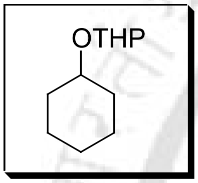
IR (Neat): cm^{-1} 2955, 2879, 1465, 1383, 1189, 1137, 1035

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 0.76-1.10 (m, 12H), 1.19-1.78 (m, 10H), 2.05-2.37 (m, 2H), 3.28-3.50 (m, 2H), 3.82-4.00 (m, 1H), 4.54-4.80 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 15.57, 16.23, 19.66, 20.23, 21.15, 21.20, 22.22, 22.34, 23.20, 25.14, 25.47, 25.58, 31.14, 31.28, 31.38, 31.60, 34.37, 34.53, 40.09, 43.52, 45.05, 48.12, 48.86, 50.10, 62.36, 63.01, 74.06, 79.88, 94.29, 101.26 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{28}O_2$	C 74.95	C 75.17
240.38	H 11.74	H 11.83

THP ether of cyclohexanol (80):



Nature: Colorless liquid

Yield: 90%

Reaction time: 5 min

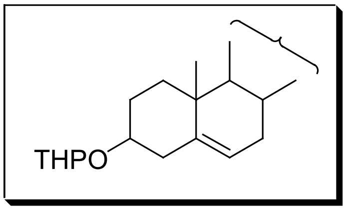
IR (Neat): cm^{-1} 2934, 2867, 1454, 1362, 1203, 1132, 1116, 1024,1004

^{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) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.95, 24.13, 24.40, 25.47, 25.68, 31.24, 31.72, 33.68, 62.67, 74.31, 96.52 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{20}O_2$	C 71.70	C 71.93
184.28	H 10.94	H 11.02

THP ether of cholesterol (15):



Nature: White solid

Yield: 90%

Reaction time: 20 min

M.P: 149 ^{0}C

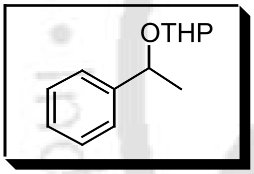
IR (KBr): cm^{-1} 2945, 2868, 1470, 1373, 1117, 1030, 979

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 0.70 (s, 3H), 0.83 (d, 3H, *J* = 2.0 Hz), 0.84 (d, 3H, *J* = 1.7 Hz), 0.88 (d, 3H, *J* = 6.7 Hz), 0.91-0.94 (m, 1H), 0.98 (s, 3H), 1.00-2.34 (m, 33H), 3.44-3.55 (m, 2H), 3.87-3.91 (m, 1H), 4.68-4.69 (m, 1H), 5.32 (t, 1H, *J* = 5.4 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 11.84, 18.70, 19.37, 20.02, 21.06, 22.55, 22.80, 23.81, 24.28, 25.49, 28.00 (2C), 28.22, 29.69, 31.27, 31.89, 35.77, 36.18, 36.76, 37.21, 39.51, 39.78, 40.25, 42.31, 50.16, 56.14, 56.76, 62.80, 76.02, 96.83, 121.48, 141.08 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{32}H_{54}O_2$	C 81.64	C 81.42
470.78	H 11.56	H 11.41

THP ether of 1-phenylethanol (81):



Nature: Colorless liquid

Yield: 84%

Reaction time: 10 min

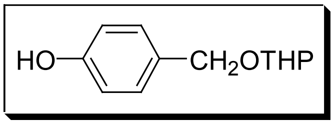
IR (Neat): cm^{-1} 2945, 2873, 1455, 1383, 1214, 1122, 1030, 984, 702

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 1.36 (d, 3H, *J* = 6.3 Hz), 1.40 (d, 3H, *J* = 6.6 Hz), 1.43-1.83 (m, 12H), 3.28-3.33 (m, 1H), 3.37-3.47 (m, 2H), 3.58-3.64 (m, 1H), 3.78-3.91 (m, 2H), 4.31-4.33 (m, 1H), 4.80-4.82 (m, 1H), 7.15-7.33 (m, 10H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.2, 19.8, 21.9, 24.3, 25.4, 25.5, 30.7, 30.8, 61.9, 62.7, 73.0, 73.2, 96.0, 96.2, 125.9 (2C), 126.4 (2C), 126.9, 127.3, 128.1 (2C), 128.3 (2C), 143.6, 144.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_2$	C 75.69	C 75.94
206.28	H 8.80	H 8.89

THP ether of 4-hydroxybenzyl alcohol (82):



Nature: Colorless liquid

Yield: 85%

Reaction time: 7 min

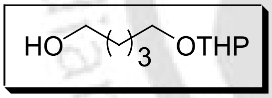
IR (Neat): cm^{-1} 3345, 2950, 2868, 1619, 1516, 1455, 1363, 1276, 1219, 1127

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.90 (m, 6H), 3.58-3.61 (m, 1H), 3.94-3.99 (m, 1H), 4.46 (d, 1H, *J* =11.5 Hz), 4.72-4.75 (m, 2H), 6.81 (d, 2H, *J* = 8.4 Hz), 7.25 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 25.4, 30.6, 62.2, 68.6, 97.5, 115.2 (2C), 129.5 (2C), 129.9, 155.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_3$	C 69.21	C 69.49
208.26	H 7.74	H 7.83

Mono THP ether of 1, 5 -pentane diol (83):



Nature: Colorless liquid

Yield: 88%

Reaction time: 40 min

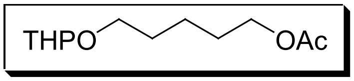
IR (Neat): cm^{-1} 3406, 2945, 2873, 1455, 1352, 1276, 1204, 1122, 1086, 979

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43-1.85 (m, 13H), 3.41(dt, 1H, *J* = 6.4 Hz, *J* = 9.6 Hz), 3.48-3.52 (m, 1H), 3.65 (t, 2H, *J* = 6.8 Hz), 3.76 (dt, 1H, *J* = 6.4 Hz, *J* = 9.2 Hz), 3.84-3.89 (m, 1H), 4.57-4.58 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0, 22.8, 25.8, 29.8, 31.1, 32.9, 62.7, 63.1, 67.8, 99.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{20}O_3$	C 63.80	C 63.53
188.27	H 10.71	H 10.82

THP ether of 5-acetyloxy-1-pentanol (84):



Nature: Colorless liquid

Yield: 81%

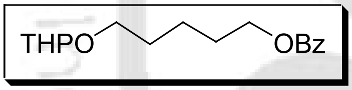
Reaction time: 15 min

IR (Neat): cm^{-1} 2945, 2873, 1742, 1471, 1460, 1439, 1372, 1250, 1034

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.39-1.84 (m, 12H), 2.04 (s, 3H), 3.36-3.41 (m, 1H), 3.48-3.51 (m, 1H), 3.71-3.76 (m, 1H), 3.82-3.88 (m, 1H), 4.06 (t, 2H, *J* = 6.8 Hz), 4.56-4.58 (m, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{22}O_4$	C 62.58	C 62.72
230.30	H 9.63	H 9.57

THP ether of 5-benzoyloxy-1-pentanol (85):



Nature: Gummy liquid

Yield: 81%

Reaction time: 15 min

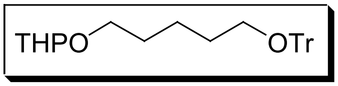
IR (Neat): cm^{-1} 2950, 2868, 1721, 1609, 1455, 1276, 1122, 1030

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.25 (bs, 2H), 1.51-1.84 (m, 10H), 3.41-3.44 (m, 1H), 3.47-3.55 (m, 1H), 3.73-3.79 (m, 1H), 3.82-3.92 (m, 1H), 4.32 (t, 2H, *J* = 6.4 Hz), 4.56-4.57 (m, 1H), 7.41 (t, 2H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 7.2 Hz), 8.02 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.8, 23.0, 25.6, 28.7, 29.5, 30.8, 62.3, 65.0, 67.3, 98.8, 128.2 (2C), 129.4 (2C), 130.4, 132.6, 166.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{24}O_4$	C 69.84	C 69.62
292.37	H 8.27	H 8.39

THP ether of 5-trityloxy-1-pentanol (86):



Nature: Gummy liquid

Yield: 85%

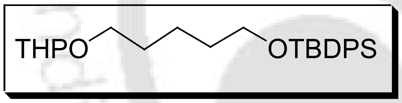
Reaction time: 5 min

IR (Neat): cm^{-1} 2950, 2868, 1598, 1496, 1450, 1332, 1163, 1071, 1030

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 1.38-1.83 (m, 12H), 3.02 (t, 2H, *J* = 6.6 Hz), 3.31-3.36 (m, 1H), 3.45-3.50 (m, 1H), 3.66-3.69 (m, 1H), 3.80-3.86 (m, 1H), 4.50- 4.52 (m, 0.3H), 4.90-4.92 (m, 0.7H), 7.15-7.28 (m, 12H), 7.39-7.41 (m, 3H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{34}O_3$	C 80.90	C 80.66
430.58	H 7.96	H 7.89

THP ether of 5-*tert*-Butyldiphenylsilyloxy 1-pentanol (87):



Nature: Colorless liquid

Yield: 89%

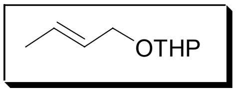
Reaction time: 20 min

IR (Neat): cm^{-1} 2940, 2858, 1475, 1440, 1393, 1117, 1035, 702

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.04 (bs, 4H), 1.07 (s, 9H), 1.41-1.83 (m, 8H), 3.32-3.38 (m, 1H), 3.42-3.50 (m, 1H), 3.65 (t, 2H, *J* = 6.4 Hz), 3.68-3.72 (m, 1H), 3.82-3.86 (m, 1H), 4.55-4.56 (m, 1H), 7.33-7.39 (m, 6H), 7.64 (dd, 2H, *J* = 1.6 Hz, *J* = 7.6 Hz), 7.69 (dd, 2H, *J* = 1.6 Hz, *J* = 7.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{26}H_{38}O_3Si$	C 73.19	C 73.48
426.67	H 8.98	H 8.91

THP ether of crotylalcohol (88):



Nature: Colorless liquid

Yield: 83%

Reaction time: 15 min

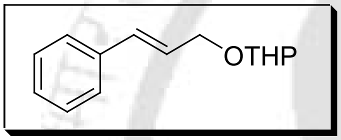
IR (Neat): cm^{-1} 3022, 2950, 2884, 1460, 1393, 1358, 1214, 1127, 1035, 984, 907

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.50-1.63 (m, 4H), 1.69-1.85 (d + m, 5H, *J* = 6.4 Hz), 3.47-3.52 (m, 1H), 3.84-3.92 (m, 2H), 4.14-4.19 (m, 1H), 4.62 (t, 1H, *J* = 4.0 Hz), 5.53-5.63 (m, 1H), 5.68-5.76 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 17.9, 19.6, 25.5, 30.7, 62.1, 67.8, 97.6, 127.2, 129.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{16}O_2$	C 69.20	C 69.01
156.22	H 10.32	H 10.23

THP ether of cinnamyl alcohol (89):



Nature: Colorless liquid

Yield: 92%

Reaction time: 15 min

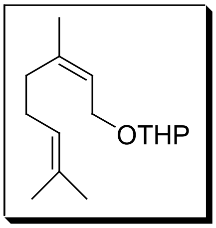
IR (Neat): cm^{-1} 3037, 2943, 2863, 1609, 1501, 1447, 1352, 1204, 1126, 1027, 969

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.48-1.81 (m, 6H), 3.46-3.49 (m, 1H), 3.82-3.87 (m, 1H), 4.10 (ddd, 1H, *J* = 1.2 Hz, *J* = 6.6 Hz, *J* = 12.9 Hz), 4.34 (ddd, 1H, *J* = 1.5 Hz, *J* = 5.4 Hz, *J* = 12.7 Hz), 4.65 (t, 1H, *J* = 3.9 Hz), 6.26 (dt, 1H, *J* = 5.6 Hz, *J* = 15.9 Hz), 6.56 (d, 1H, *J* = 15.8 Hz), 7.14-7.19 (m, 1H), 7.24 (t, 2H, *J* = 7.6 Hz), 7.32 (d, 2H, *J* = 7.3 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 25.4, 30.5, 62.1, 67.5, 97.8, 125.9, 126.4 (2C), 127.5, 128.4 (2C), 132.2, 136.7 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{18}O_2$	C 77.03	C 77.31
218.29	H 8.31	H 8.42

THP ether of geraniol (90):



Nature: Colorless liquid

Yield: 78%

Reaction time: 12 min

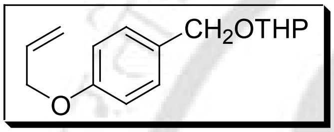
IR (Neat): cm^{-1} 2940, 2873, 1675, 1455, 1388, 1271, 1132, 1040, 984, 917

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.40-1.80 (m, 15H), 1.95-2.20 (m, 4H), 3.30-4.20 (m, 4H), 4.56 (bs, 1H), 5.16 (m, 1H), 5.34 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 16.4, 17.7, 19.7, 25.6, 25.7, 26.4, 30.8, 39.7, 62.2, 63.6, 97.7, 120.7, 124.2, 131.5, 140.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{26}O_2$	C 75.58	C 75.32
238.37	H 10.99	H 11.07

THP ether of 4-allyloxybenzyl alcohol (91):



Nature: Colorless liquid

Yield: 95%

Reaction time: 10 min

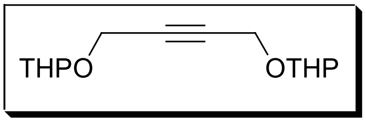
IR (Neat): cm^{-1} 2952, 2926, 2869, 1617, 1516, 1470, 1250, 1096, 1034, 855

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.46-1.86 (m, 6H), 3.46-3.50 (m, 1H), 3.82-3.92 (m, 1H), 4.49 (s, 2H), 4.65-4.70 (m, 3H), 5.24 (dd, 1H, J = 1.4 Hz, J = 10.5 Hz), 5.37 (dd, 1H, J = 1.7 Hz, J = 17.3 Hz), 5.97-6.06 (m, 1H), 6.86 (d, 2H, J = 8.5 Hz), 7.24 (d, 2H, J = 8.3 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 25.4, 30.5, 62.1, 68.4, 68.8, 97.4, 114.5 (2C), 117.6, 129.4 (2C), 130.4, 133.2, 158.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{20}O_3$	C 72.55	C 72.38
248.32	H 8.12	H 8.01

Di-THP ether of butyne 1, 4-diol (92):



Nature: Colorless liquid

Yield: 95%

Reaction time: 25 min

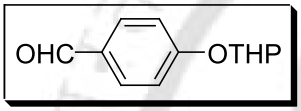
IR (Neat): cm^{-1} 2940, 2873, 1445, 1399, 1352, 1271, 1209, 1127, 1025, 968

^{1}H 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) ppm.

^{13}C NMR (100 MHz, CDCl3): δ 18.9(2C), 25.2(2C), 30.1(2C), 54.2(2C), 61.8(2C), 81.8(2C), 96.7(2C) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{22}O_4$	C 66.12	C 66.21
254.32	H 8.72	H 8.69

THP ether of 4-hydroxybenzaldehyde (93):



Nature: Colorless gummy liquid

Yield: 90%

Reaction time: 4 h

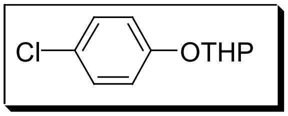
IR (Neat): cm^{-1} 2945, 2858, 1696, 1609, 1511, 1358, 1306, 1250, 1209, 1163, 1112

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.49-1.78 (m, 4H), 1.81-1.99 (m, 2H), 3.57-3.62 (m, 1H), 3.80-3.86 (m, 1H), 5.47-5.51 (m, 1H), 7.12 (d, 2H, *J* = 8.8 Hz), 7.79 (d, 2H, *J* = 8.8 Hz), 9.84 (s, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 18.4, 24.9, 30.6, 62.0, 96.0, 116.4 (2C), 131.8 (2C), 132.3, 162.1, 191.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{14}O_3$	C 69.89	C 69.78
206.24	H 6.84	H 6.78

THP ether of 4-chlorophenol (94):



Nature: Colorless liquid

Yield: 92%

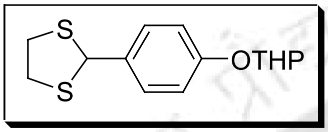
Reaction time: 6 h

IR (Neat): cm^{-1} 2944, 2873, 1594, 1490, 1454, 1356, 1237, 1203, 1182, 1037

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.58-1.99 (m, 6H), 3.58-3.62 (m, 1H), 3.84-3.90 (m, 1H), 5.36 (t, 1H, *J* = 3.2 Hz), 6.98 (d, 2H, *J* = 8.8 Hz), 7.22 (d, 2H, *J* = 8.8 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{13}ClO_2$	C 62.12	C 62.41
212.67	H 6.16	H 6.28

2-(4′-Tetrahydropyranyloxy phenyl) 1,3-dithiolane (95):



Nature: Colorless liquid

Yield: 94%

Reaction time: 35 min

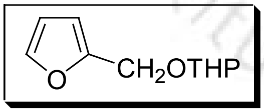
IR (Neat): cm^{-1} 2930, 1614, 1511, 1255, 1240, 1122, 1040

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46-2.00 (m, 6H), 3.31-3.41 (m, 2H), 3.48-3.63 (m, 3H), 3.89-3.93 (m, 1H), 5.41 (t, 1H, *J* = 3.0 Hz), 5.64 (s, 1H), 7.00 (d, 2H, *J* = 8.8 Hz), 7.44 (d, 2H, *J* = 8.7 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 19.1, 25.6, 30.7, 40.6 (2 C), 56.5, 62.4, 96.7, 116.8 (2 C), 129.8 (2C), 133.1, 157.3 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{18}O_2S_2$	C 59.54	C 60.05
282.41	H 6.42	H 6.39
	S 22.70	S 22.54

THP ether of furfuryl alcohol (96):



Nature: Colorless liquid

Yield: 93%

Reaction time: 5 min

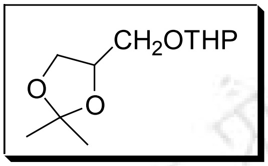
IR (Neat): cm^{-1} 2945, 2873, 1506, 1450, 1347, 1209, 1158, 1127, 1025, 984

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50-1.88 (m, 6H), 3.51-3.56 (m, 1H), 3.87-3.92 (m, 1H), 4.48 (d, 1H, *J* =13.2Hz), 4.66 (d, 1H, *J* = 12.8 Hz), 4.69-4.71 (m, 1H), 6.31 (bs, 2H), 7.39 (d, 1H, *J* =1.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 25.5, 30.4, 60.6, 61.9, 97.1, 109.1, 110.1, 142.5, 151.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{14}O_3$	C 65.92	C 65.67
182.22	H 7.74	H 7.64

THP ether of 2, 3-*O*-isopropylidene-*D*-(±)-glycerol (97):



Nature: Colorless liquid

Yield: 81%

Reaction time: 7 min

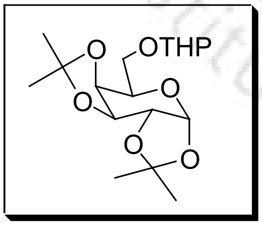
IR (Neat): cm^{-1} 2986, 2945, 2873, 1460, 1378, 1265, 1209, 1132, 1066, 1035

^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ 1.37 (s, 3H), 1.42 (s, 3H), 1.54-1.88 (m, 6H), 3.45-3.57 (m, 2H), 3.71-3.76 (m, 1H), 3.78-3.89 (m, 2H), 4.04-4.10 (m, 1H), 4.28-4.32 (m, 1H), 4.62-4.64 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 19.8, 25.7, 25.8, 25.9, 27.0, 27.1, 30.7, 62.3, 62.5, 67.0, 67.2, 68.2, 68.8, 74.9, 75.1, 99.1, 99.3, 109.4, 109.6 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{20}O_4$	C 61.09	C 61.38
216.28	H 9.32	H 9.43

THP ether of 1,2,3,4-di-*O*-isopropylidene-D-galactose (98):



Nature: Colorless liquid

Yield: 84%

Reaction time: 20 min

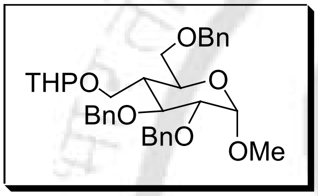
IR (Neat): cm^{-1} 2945, 1470, 1388, 1271, 1230, 1076, 1009

^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ 1.28 (s, 3H), 1.29 (s, 3H), 1.39 (s, 3H), 1.49 (s, 3H), 1.50-1.82 (m, 6H), 3.43-3.49 (m, 1H), 3.56-3.85 (m, 2H), 3.93-3.98 (m, 1H), 4.20 (dd, 1H, J = 1.7, J = 7.8 Hz), 4.23-4.29 (m, 1H), 4.52-4.61 (m, 2H), 4.88 (d, 1H, J = 4.9 Hz), 5.48 (dd, 1H, J = 5.2, J = 9.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 19.5, 19.7 (2C), 24.4, 24.5, 24.9, 25.4 (2C), 25.9, 26.0, 30.5, 30.7(2C), 62.2, 62.4, 62.9, 65.9, 66.1, 66.5, 67.4, 70.5, 70.6, 70.7, 71.0, 71.4, 94.6, 96.3, 96.4, 99.0, 99.1, 108.5, 109.1, 109.2 ppm

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{28}O_7$	C 59.29	C 59.52
344.40	H 8.19	H 8.23

THP ether of methyl-2,3,6-tri-*O*-benzyl-4-hydroxymethyl-1-*α*-D-glucopyranoside (99):



Nature: Viscous liquid

Yield: 93%

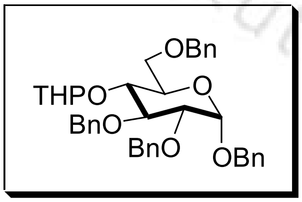
Reaction time: 15 min

IR (Neat): cm^{-1} 2941, 2873, 1453, 1354, 1202, 1074, 1033

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.43-1.95 (m, 6H), 3.39 (s, 3H), 3.40-4.02 (m, 12H), 4.47-4.77 (m, 5H), 4.95-5.02 (m, 1H), 7.24-7.37 (m, 15H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{34}H_{42}O_7$	C 72.57	C 72.63
562.70	H 7.52	H 7.48.

THP ether of benzyl-2,3,6-tri-*O*-benzyl-1-*α*-D-glucopyranoside (100):



Nature: Colorless liquid

Yield: 95%

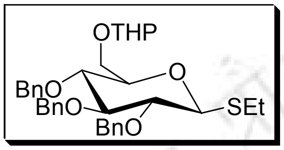
Reaction time: 1 h

IR (Neat): cm^{-1} 2935, 2858, 1634, 1470, 1383, 1265, 1086, 1030, 974

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.41-1.94 (m, 6H), 3.49-4.15 (m, 10H), 4.51-4.96 (m, 7H), 5.20-5.30 (m, 1H), 7.15-7.40 (m, 20H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{39}H_{44}O_7$	C 74.98	C 74.73
624.77	H 7.10	H 7.01

THP ether of ethyl-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (101):



Nature: Colorless liquid

Yield: 96%

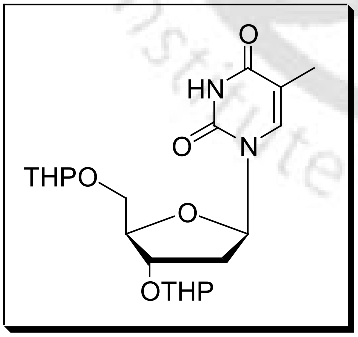
Reaction time: 1 h

IR (Neat): cm^{-1} 2925, 2858, 1552, 1460, 1358, 1143, 1076, 1035, 989, 758, 707

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.33 (t, 3H, *J* = 7.2 Hz), 1.49-1.72 (m, 6H) 2.72-2.78 (m, 2H), 3.43-3.51 (m, 4H), 3.53-3.74 (m, 2H), 3.86-4.03 (m, 2H), 4.47 (dd, 1H, *J* = 5.4 Hz, *J* = 9.7 Hz), 4.61 (d, 1H, *J* = 11.2 Hz), 4.70-4.76 (m, 2H), 4.83-4.95 (m, 4H), 7.23-7.39 (m, 15H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{34}H_{42}O_6S$	C 70.56	C 70.28
578.76	H 7.31	H 7.43
	S 5.54	S 5.78

Di-THP ether of Thymidine (102):



Nature: Colorless liquid

Yield: 83%

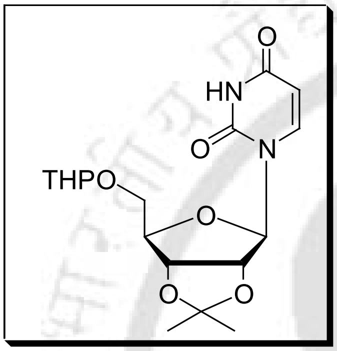
Reaction time: 3.5 h

IR (Neat): cm^{-1} 3437, 2950, 2879, 1737, 1450, 1358, 1271, 1214, 1137, 1081, 1040

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 1.53-1.80 (m, 24H), 1.88 (s, 3H), 1.91 (s, 3H), 1.97-2.52 (m, 4H), 3.48-3.68 (m, 6H), 3.80-4.14 (m, 8H), 4.26 (dd, 1H, *J* = 2.2, *J* =13.4 Hz), 4.42-4.44 (m, 2H), 4.56-4.57 (m, 1H), 4.60-4.69 (m, 1H), 4.87-4.89 (m, 1H), 6.26-6.36 (m, 2H), 7.53-7.65 (m, 2H), 8.50 (bs, 2H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{20}H_{30}N_2O_7$	C 58.52	C 58.39
410.46	H 7.37	H 7.29
	N 6.83	N 6.56

THP ether of 2,3-*O*-isopropylidene uridine (103):



Nature: Colorless liquid

Yield: 95%

Reaction time: 30 min

IR (Neat): cm^{-1} 3235, 3109, 2966, 2935, 2817, 1788, 1690, 1481, 1409, 1271, 1209, 1107, 1055, 989

^{1}H 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) ppm.

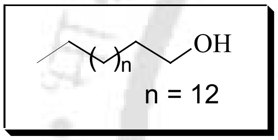
^{13}C NMR (100 MHz, $CDCl_3$): δ 20.01,20.84, 25.56, 25.58, 25.62, 25.78, 25.84, 27.64, 30.81, 32.42, 63.05, 63.11, 64.22, 67.52, 67.78, 80.99, 81.20, 85.45, 85.68, 85.91, 92.89, 94.85, 99.22, 99.84, 102.05, 102.33, 114.24, 114.44, 140.88, 141.48, 150.46 (2C), 163.86 (2C) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{24}N_2O_7$	C 55.43	C 55.61
368.38	H 6.57	H 6.59
	N 7.60	N 7.53

General procedure for Depyranylation:

Bromodimethylsulfonium bromide (0.056 g, 0.25 mmol) was added to a well stirred solution of THP ether of 2-phenylethanol (1.060 g, 5 mmol) in CH_2Cl_2/MeOH (5:2; 10 mL) at room temperature. The reaction was complete within 25 min as monitored by TLC. The mixture was neutralized by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The organic layer was concentrated in vacuo and finally purified by silica gel column chromatography. The pure product was obtained in 97% yield.

Cetyl alcohol (47):



Nature: White solid

Yield: 90%

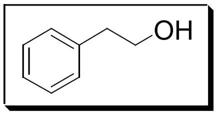
Reaction time: 30 min

IR (Neat): cm^{-1} 3324, 2924, 2858, 1470, 1065, 727

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.56 Hz), 1.23 (bs, 27H), 1.50-1.55 (m, 2H), 3.62 (t, 2H, *J* = 6.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{34}O$	C 79.27	C 79.34
242.44	H 14.13	H 14.20

2-phenylethanol (48):



Nature: Colorless liquid

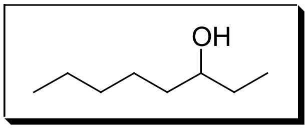
Yield: 97%

Reaction time: 25 min

IR (Neat): cm^{-1} 3324, 3027, 2870, 1510, 1460, 1214, 1019

Elemental Analysis	**Calculated**	**Found**
$C_8H_{10}O$	C 78.65	C 78.92
122.17	H 8.25	H 8.32

3-Octanol (49):



Nature: Colorless liquid

Yield: 92%

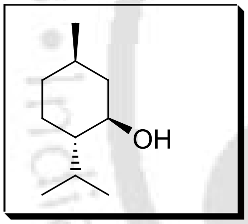
Reaction time: 25 min

IR (Neat): cm^{-1} 3350, 2930, 1460, 1010

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.88 (t, 3H, *J* = 7.2 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 1.28-1.58 (m, 10H), 1.72 (s, 1H), 3.49 (m, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{18}O$	C 73.78	C 73.92
130.23	H 13.93	H 13.87

Menthol (50):



Nature: Solid

Yield: 95%

Reaction time: 15 min

M.P.: 42 ^{0}C

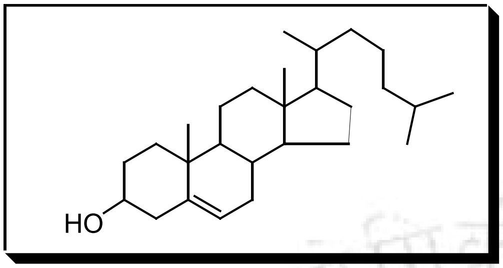
IR (KBr): cm^{-1} 3314, 2930, 2873, 1455, 1368, 1265, 1050

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.78 (d, *J* = 6.8 Hz, 3H), 0.82-0.83 (m, 1H), 0.88 (d, 3H, *J* = 6.4 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 0.92-0.96 (m, 2H), 1.05-1.12 (m, 1H), 1.38-1.40 (m, 1H), 1.52-1.65 (m, 3H), 1.92-1.95 (m, 1H), 2.11-2.17 (m, 1H), 3.35-3.44 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 16.1, 20.9, 22.2, 23.0, 25.8, 31.6, 34.5, 44.9, 50.1, 71.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{20}O$	C 76.86	C 76.65
156.27	H 12.90	H 13.02

Cholesterol (14):



Nature: White solid

Yield: 70%

Reaction time: 40 min

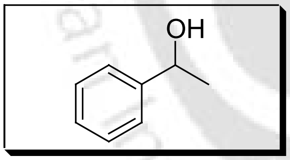
M.P.: 148 ^{0}C

IR (KBr): cm^{-1} 3342, 2930, 2863, 1619, 1465, 1378, 1137, 1061, 1030, 963, 810

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.68 (s, 3H), 0.86 (d, 3H, *J* = 1.68 Hz), 0.87 (d, 3H, *J* = 1.72 Hz), 0.91 (d, 3H, *J* = 6.6 Hz), 1.01 (s, 3H), 1.07-1.22 (m, 4H), 1.23-1.51 (m, 2H), 1.56 (bs, 17H), 1.78-1.87 (m, 2H), 1.95-2.03 (m, 2H), 2.20-2.31 (m, 2H), 3.49-3.55 (m, 1H), 5.35-5.36 (t, 1H, *J* = 2.7 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{27}H_{46}O$	C 83.87	C 84.02
386.66	H 11.99	H 12.08

1-Phenylethanol (52):



Nature: Colorless liquid

Yield: 70%

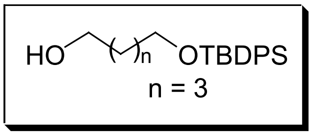
Reaction time: 25 min

IR (Neat): cm^{-1} 3396, 3042, 2981, 2940, 1609, 1501, 1460, 1373, 1301, 1204, 1081, 1025, 907, 769

^{1}H 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) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{10}O$	C 78.65	C 78.86
122.17	H 8.25	H 8.43

5-*tert*-Butyldiphenylsilyloxy-1-pentanol (58):



Nature: Colorless liquid

Yield: 90%

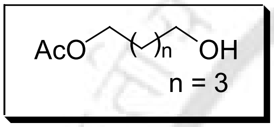
Reaction time: 30 min

IR (Neat): cm^{-1} 3396, 3068, 2940, 2863, 1598, 1470, 1429, 1399, 1112, 820, 712

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.05 (s, 9H), 1.56 (m, 7H), 3.62 (t, 2H, *J* = 6.4 Hz), 3.67 (t, 2H, *J* = 6.2 Hz), 7.40 (m, 5H), 7.68 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{21}H_{30}O_2Si$	C 73.63	C 73.87
342.55	H 8.83	H 8.89

5-*O*-Acetyl-1-pentanol (55):



Nature: Colorless liquid

Yield: 90%

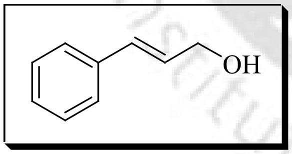
Reaction time: 15 min

IR (Neat): cm^{-1} 3447, 2935, 2868, 1742, 1465, 1404, 1368, 1235, 1045, 897, 851

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.35-1.74 (m, 7H), 2.05 (s, 3H), 3.67 (t, 2H, *J* = 6.4 Hz), 4.08 (t, 2H, *J* = 6.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_7H_{14}O_3$	C 57.52	C 57.68
146.18	H 9.65	H 9.57

Cinnamyl alcohol (60):



Nature: Light yellow liquid

Yield: 90%

Reaction time: 60 min

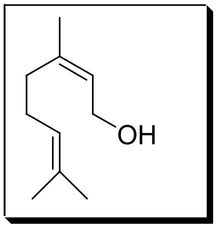
IR (Neat): cm^{-1} 3356, 3026, 2923, 2849, 1654, 1599, 1496, 1452, 1093, 1014, 970

^{1}H 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) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 63.69, 126.44, 127.67, 128.46, 128.57, 131.12, 136.63 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}O$	C 80.56	C 80.23
134.18	H 7.51	H 7.66

Geraniol (61):



Nature: Colorless liquid

Yield: 98%

Reaction time: 120 min

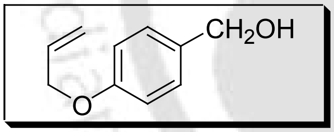
IR (Neat): cm^{-1} 3380, 2970, 2925, 2868, 1670, 1465, 1385,1020

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 3H), 1.66 (s, 3H), 1.73 (s, 3H), 1.92-2.15 (m, 5H), 4.20 (d, 2H, *J* = 6.4 Hz), 5.07 (t, 1H, *J* = 6.6 Hz), 5.34 (t, 1H, *J* = 6.4 Hz,) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 17.7, 29.6, 30.7, 39.6, 59.8, 124.0, 124.8, 131.6, 140.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{18}O$	C 77.87	C 77.62
154.25	H 11.76	H 11.85

4-Allyloxybenzylalcohol (62):



Nature: Colorless liquid

Yield: 93%

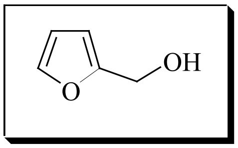
Reaction time: 50 min

IR (Neat): cm^{-1} 3350, 2930, 2879, 1619, 1511, 1460, 1424, 1373, 1301, 1240, 1189, 1122, 1009, 1034, 938, 825

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 1H), 4.53-4.55 (m, 2H), 4.56 (s, 2H), 5.27 (dd, 1H, *J* = 1.0 Hz, *J* = 10.5 Hz), 5.40 (dd, 1H, *J* = 1.4 Hz, *J* = 15.8 Hz), 6.04 (m, 1H), 6.89 (d, 2H, *J* = 8.5 Hz), 7.30 (d, 2H, *J* = 8.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}O_2$	C 73.15	C 72.90
164.20	H 7.37	H 7.17

Furfuryl alcohol (67):



Nature: Colorless liquid

Yield: 80%

Reaction time: 35 min

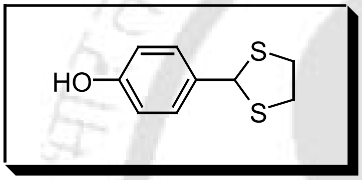
IR (Neat): cm^{-1} 3375, 2940, 2879, 1634, 1501, 1429, 1158, 1009, 922, 815, 748

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.02 (bs, 1H), 4.59 (s, 2H), 6.28 (d, 1H, *J* =3.2 Hz), 6.32 (d, 1H, *J* =3.2 Hz), 7.38 (d, 1H, *J* = 2.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 57.5, 107.8, 110.3, 142.6, 153.9 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_5H_6O_2$	C 61.22	C 61.47
98.10	H 6.16	H 6.23

2-[4′-Hydroxyphenyl]-1,3-dithiolane (66):



Nature: White solid

Yield: 82%

Reaction time: 40 min

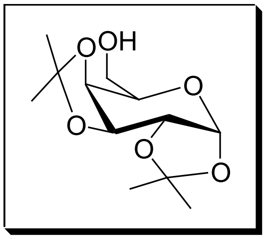
IR (KBr): cm^{-1} 3396, 2914, 1603, 1511, 1450, 1368, 1250, 1178, 1102, 851

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.31-3.37 (m, 2H), 3.45-3.52 (m, 2H), 5.23 (s, 1H), 5.62 (s, 1H), 6.75 (d, 2H, *J* = 7.8 Hz), 7.39 (d, 2H, *J* = 8.5 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 40.18 (2C), 56.03, 115.34 (2C), 129.40 (2C), 131.96, 155.30 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}OS_2$	C 54.51	C 54.65
198.30	H 5.08	H 5.15
	S 32.33	S 32.21

1,2,3,4-Di-*O*-isopropylidene-D-galactose (69):



Nature: Yellowish gummy liquid

Yield: 76%

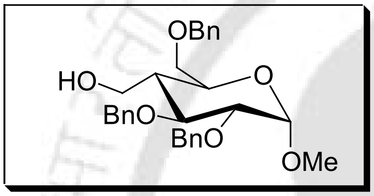
Reaction time: 30 min

IR (Neat): cm^{-1} 3493, 2991, 2935, 1460, 1383, 1255, 1219, 1173, 1076, 1009, 892

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.34 (s, 6H), 1.46 (s, 3H), 1.54 (s, 3H), 2.28 (bs, 1H), 3.75 (t, 1H, *J* = 7.3 Hz), 3.82-3.90 (m, 2H), 4.27 (d, 1H, *J* = 7.9 Hz), 4.34 (dd, 1H, *J* = 2.3 Hz, *J* = 4.9 Hz), 4.62 (dd, 1H, *J* = 2.3 Hz, *J* = 7.9 Hz), 5.57 (d, 1H, *J* = 5.0 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{20}O_6$	C 55.38	C 55.46
260.28	H 7.74	H 7.68

Methyl-2,3,6-tri-*O*-benzyl-4-hydroxymethyl-*α*-D-glucopyranoside (70):



Nature: Gummy liquid

Yield: 85%

Reaction time: 120 min

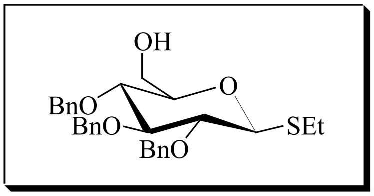
IR (Neat): cm^{-1} 3457, 3032, 2930, 2894, 1609, 1455, 1358, 1096, 1050, 743, 702

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.68 (bs, 1H), 1.86 (m, 1H), 3.37 (s, 3H), 3.55 (d, 1H, *J* = 3.4 Hz), 3.58 (t, 2H, *J* = 2.4 Hz), 3.61 (m, 2H), 3.68 (dd, 1H, *J* = 3.4 Hz, *J* = 11.4 Hz), 3.83 (m, 1H), 3.58 (t, 1H, *J* = 10.24 Hz), 4.47 (d, 1H, *J* = 11.96 Hz), 4.61 (d, 1H, *J* = 11.96 Hz), 4.66 (m, 1H), 4.69 (d, 1H, *J* = 3.2 Hz), 4.77 (d, 1H, *J* = 11.96 Hz), 4.99 (d, 1H, *J* = 11.2 Hz), 7.32 (m, 15H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 46.07, 55.19, 59.50, 68.20, 70.48, 72.88, 73.53, 75.19, 75.44, 81.49, 98.45, 127.76, 127.87, 128.09, 128.35, 128.39, 128.43, 128.51, 137.66, 138.18, 138.42 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{34}O_6$	C 72.78	C 72.57
478.58	H 7.16	H 7.25

Ethyl-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (72):



Nature: White solid

Yield: 73%

Reaction time: 60 min

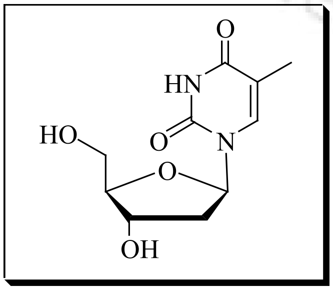
IR (Neat): cm^{-1} 3355, 3032, 2909, 2863, 1608, 1459, 1362, 1219, 1080, 1034, 1004, 845, 747, 701

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32 (t, 3H, *J* = 7.3 Hz), 1.95 (bs, 1H), 2.71-2.80 (m, 2H), 3.35-3.39 (m, 1H), 3.41 (t, 1H, *J* = 9.3 Hz), 3.58 (t, 1H, *J* = 9.3 Hz), 3.70 (t, 1H, *J* = 8.8 Hz), 3.87 (d, 1H, *J* = 11.5 Hz), 4.50 (d, 1H, *J* = 9.8 Hz), 4.65 (d, 1H, *J* = 11 Hz), 4.74 (d, 1H, *J* = 11 Hz), 4.86 (d, 2H, *J* = 12.4 Hz), 4.89 (d, 1H, *J* = 10.0 Hz), 4.92 (dd, 2H, *J* = 6.8 Hz, *J* = 11 Hz), 7.25-7.38 (m, 15 H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 15.16, 25.20, 62.15, 75.17, 75.57, 75.74, 75.76, 77.69,79.27, 81.77, 85.27, 86.47, 127.71, 127.77, 127.89, 127.96, 128.07, 128.29, 128.41,128.46, 128.52, 137.90 (2C), 138.41 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{34}O_5S$	C 70.42	C 70.64
494.65	H 6.93	H 7.08
	S 6.48	S 6.10

Thymidine (73):



Nature: White solid

Yield: 80%

Reaction time: 90 min

M.P.: 187 ^{0}C.

IR (Neat): cm^{-1} 3324, 3165, 3032, 2843, 1711, 1481, 1445, 1286, 1117, 1071, 1020, 968, 897

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{14}O_5N_2$	C 49.59	C 49.67
242.23	H 5.83	H 5.98
	N 11.57	N 11.36

SECTION B

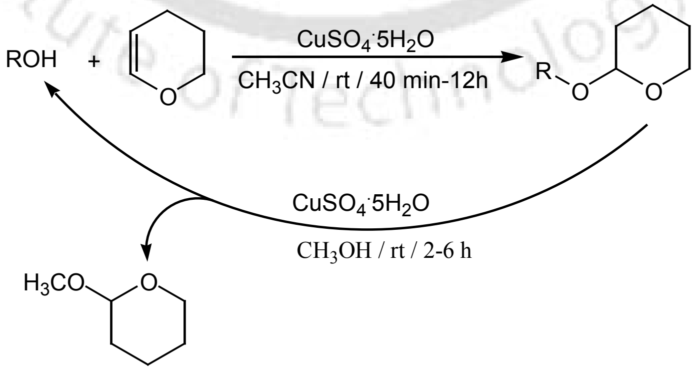
A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS USING CUPRIC SULFATE PENTAHYDRATE

RESULTS AND DISCUSSION

Results and Discussion

Though we have developed[50] highly efficient methodology for tetrahydropyranylation /depyranylation of alcohols and phenols using bromodimethylsulfonium bromide (BDMS) as pre-catalyst, still the main disadvantage of this method is that the catalyst has to be prepared prior to use. This drawback prompted us to investigate further whether the present drawback can be circumvented developing an alternative protocol.

In the present scenario, the heterogeneous catalysts find extensive application in organic synthesis due to several advantages over homogeneous catalysts such as high catalytic activity and selectivity, ready availability, simple work-up procedure, minimum corrosion and formation of less by-product etc. Many protection-deprotection methods for various functional groups have been developed using various heterogeneous catalysts, which has been reviewed recently.[51] Taking into the accounts of all advantages, we were interested to study whether some new heterogeneous catalyst can be exploited for tetrahydropyranylation /depyranylation of alcohols and phenols or not. In an endeavor to gradually change the current working practices to greener alternatives and to meet environmental demands,[44] there is a need for a catalytically efficient, greener and economically cheaper alternative protocol for protection of hydroxyl compounds as THP ethers. Therefore, the search is for simple and convenient way to generate these compounds in large amounts. As a part of our ongoing research program to develop new synthetic methodologies involving various new reagents,[52,53] we perceived that cupric sulfate pentahydrate, which is readily and commercially available, might be a useful heterogeneous catalyst for tetrahydropyranylation due to its mild Lewis acidity.



R = alkyl / aryl / sugar residue / nucleoside residue

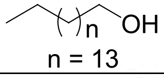
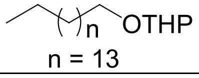
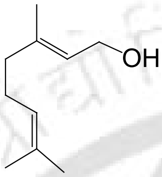
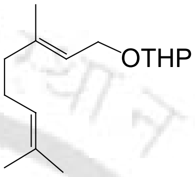
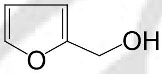
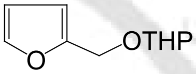
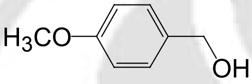
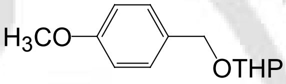
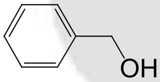
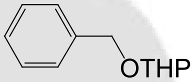
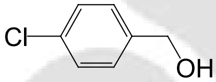
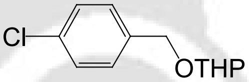
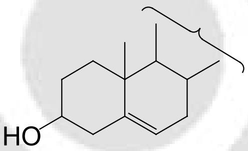
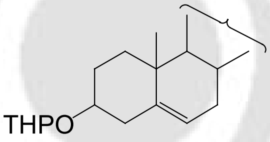
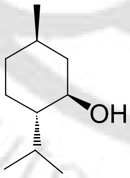
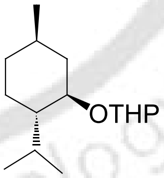
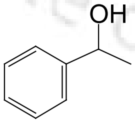
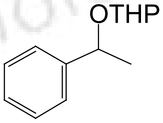
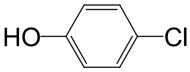
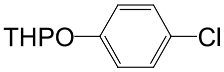
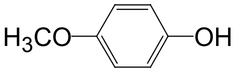
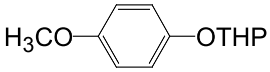
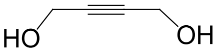
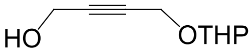
Scheme 24

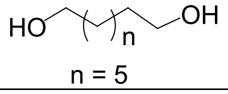
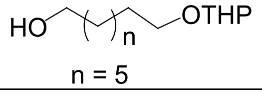
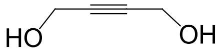
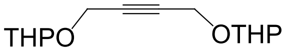
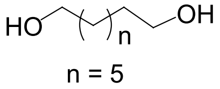
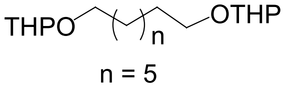
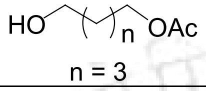
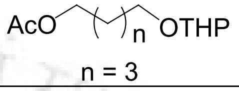
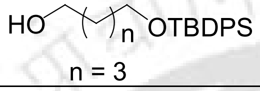
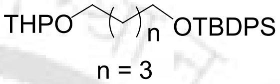
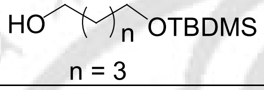
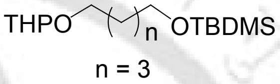
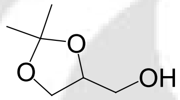
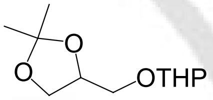
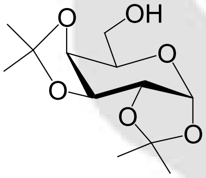
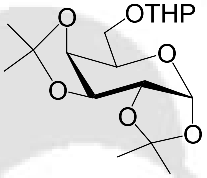
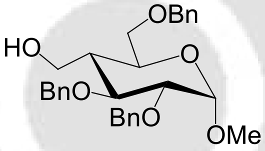
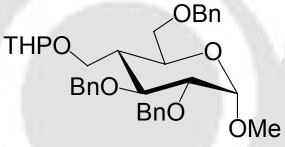
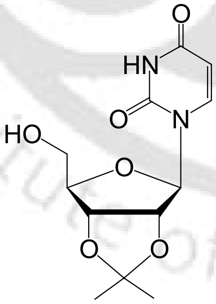
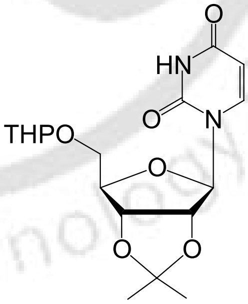
In this chapter, we would like to elaborate that cupric sulfate pentahydrate can be used as an efficient heterogeneous catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols as shown in Scheme 24.

When a mixture of cetyl alcohol (**47**) and 3,4-dihydro-2*H*-pyran was treated with 20 mol% of cupric sulfate pentahydrate in acetonitrile as solvent, it was smoothly converted into the corresponding THP ether (**76**) within 40 min in 90% yield. Similarly, 4-methoxybenzyl alcohol (**104**) was converted into the corresponding THP ether **110** within 40 min under identical reaction conditions. Although dichloromethane can also be used, we employed acetonitrile as choice of solvent because dichloromethane is a halogenated solvent and harmful. The tetrahydropyranylation could be achieved on a large-scale between 10-100 mmol without any difficulty. By following above typical reaction procedure, various benzylic, allylic and secondary alcohols (**61, 67, 104, 105, 106, 14, 50, 52**) as well as phenols (**65** and **107**) were smoothly transformed to the corresponding THP ethers (**90, 96, 110, 111, 112, 15, 79, 81**) and (**94** and **113**) respectively in very good yields. Remarkably, various diols (**63** and **108**) were transformed to mono THP ethers (**114** and **115**) along with 5-8% di-THP ether by using 20 mol% catalyst instead of 40 mol% catalyst. All the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and by elemental analyses. The IR spectrum of the THP ether **115** exhibits absorption frequency values 3422, 2931, 2858, 1454, 1354, 1276, 1127, 1030 cm^{-1} (Fig.4). ^{1}H NMR spectrum of compound **115** gives the signals at δ 1.30-1.40 (bs, 8H), 1.50-1.61 (m, 6H), 1.69-1.74 (m, 2H), 1.80-1.90 (m, 2H), 2.05 (bs, 1H, D_2O exchangeable), 3.35-3.41 (m, 1H), 3.48-3.51 (m, 1H), 3.64 (t, 2H, *J* = 6.8 Hz), 3.70-3.74 (m, 1H), 3.84-3.89 (m, 1 H), 4.56-4.58 (m, 1H) ppm (Fig. 5). The following new signals at δ 3.35-3.41 (m, 1H), 3.48-3.51 (m, 1H), 3.70-3.74 (m, 1H), 3.84-3.89 (m, 1 H), 4.56-4.58 (m, 1H) clearly indicate the formation of mono THP ether. The same compound shows peak in the ^{13}C NMR spectrum at δ 19.7, 25.5, 25.7, 26.2, 29.3, 29.4, 29.7, 30.7, 32.7, 62.2, 62.7, 67.6, 98.7 ppm (Fig. 6). The appearance of new signals at δ 98.7 in ^{13}C NMR as well as absorption at 3422 cm^{-1} in the IR spectrum support the formation of mono THP ether. The diols could be converted to the di-THP ethers (**92** and **116**) in good yields in the similar manner. In various substrates containing other functional groups such as acetyl, TBDPS, isopropylidene protected diols, benzyl ethers and TBDMS ethers were smoothly converted to the desired THP ethers (**84**, **87**, **97**,

98, **99, 103, 117**) in good yields as shown in the Table 3. All the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and by elemental analyses.

Table 3 Tetrahydropyranylation of alcohols and phenols in presence of a catalytic amount of $CuSO_4 \cdot 5H_2O$

Substrate No.	Substrate	Time min	Product[a]	Product No.	Yield[b] / %
47		40		**76**	90
61		55		**90**	87
67		40		**96**	90
104		40		**110**	89
105		40		**111**	91
106		45		**112**	92
14		80		**15**	85
50		60		**79**	89
52		55		**81**	91
65		95		**94**	87
107		90		**113**	89
63		60		**114**	55

108		12 h		**115**	83[c]
63		90		**92**	92
108		12h		**116**	93
55		40		**84**	84
58		40		**87**	82
109		40		**117**	82
68		50		**97**	85
69		85		**98**	83
70		90		**99**	81
74		45		**103**	90

[a]The products were characterized by IR, ^{1}H NMR and elemental analysis. [b]Isolated yields. [c]Yield based on starting material recovery

The tetrahydropyranylation of 4-methoxybenzyl alcohol (**104)** was investigated with the various forms of cupric sulfate to find out the relative efficiencies (Table 4). Cupric sulfate pentahydrate showed the highest catalytic activity in terms of reaction time and yield.

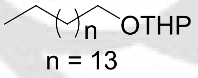
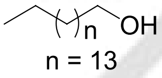
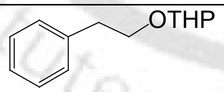
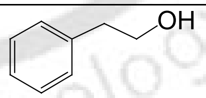
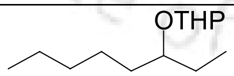
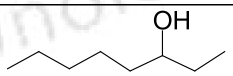
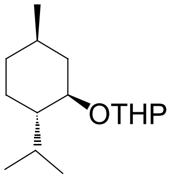
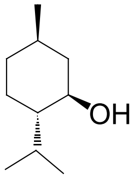
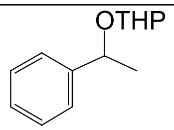
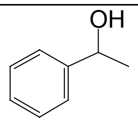
Table 4 Tetrahydropyranylation of 4-methoxybenzyl alcohol **104** using various forms of cupric sulfate.[a]

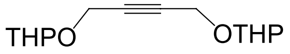
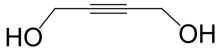
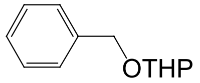
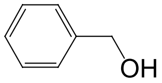
Run	Catalyst	Conversion %	Time min/ [h]
1	$CuSO_4 \cdot 5H_2O$	100	45
2	$CuSO_4$	80	[3]
3	$CuSO_4 \cdot SiO_2$	90	[2.5]
4	SiO_2	0	[3]

[a]Reactions were monitored by GC

After getting these successful results, we were interested to investigate whether the same catalyst can be used for the regeneration of the parent hydroxyl compounds from the corresponding THP ethers. The THP ether of cetyl alcohol (**76**) was deprotected smoothly to the parent hydroxyl compound cetyl alcohol (**47**) within 5 h on treatment with 0.2 equivalents of catalyst in methanol in 85% yield at room temperature. Likewise, we converted successfully various THP ethers (**77**, **78**, **79**, **81**, **84**, **92**, **111**) to the parent hydroxyl compounds (**48**, **49**, **50**, **52**, **55, 63**, **105**) under identical reaction conditions. The results have been summarized in Table 5 and the products were characterized by IR, ^{1}H-NMR spectroscopy and elemental analyses as well as by comparison with the authentic compounds.

Table 5 Deprotection of various tetrahydropyranyl ethers to the corresponding hydroxyl compounds using catalytic amount of $CuSO_4 \cdot 5H_2O$ in methanol

Substrate No.	Substrate	Time [h]	Product[a]	Product No	Yield[b] /%
76		5		**47**	85
77		5		**48**	82
78		6		**49**	80
79		6		**50**	84
81		6		**52**	80

84	 n = 3	5	 n = 3	**55**	81
92		8		**63**	88
111		5		**105**	86

[a]The products were characterized by IR, ^{1}H NMR and elemental analysis. [b]Isolated yields.

In summary, the present methodology demonstrates $CuSO_4 \cdot 5H_2O$ as an effective heterogeneous catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. The main advantages of our protocol are: mild, clean, environmentally benign reaction condition as well as good yields. In addition, our methodology might be useful for the substrates containing acid sensitive protecting groups because of the almost neutral reaction conditions. Furthermore, this method is also expected to have better applicability in organic synthesis due to the low cost of the reagent. We believe this protocol will be a useful addition to the modern synthetic methodologies.

SECTION B

A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS USING CUPRIC SULFATE PENTAHYDRATE

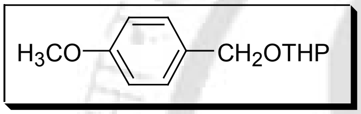
EXPERIMENTAL

Experimental

Typical procedure of protection:

Into a mixture of 3,4-dihydro-*2H*-pyran (1.1 mmol) and alcohol or phenol (1 mmol) in acetonitrile (2 mL) was added cupric sulfate pentahydrate (0.05 g, 0.2 mmol) at room temperature and the mixture stirred until completion of the reaction was ascertained by the disappearance of the alcohol spot on TLC. The product was isolated in almost pure form from the reaction mixture by simply filtering through a Whatman 42 filter paper without aqueous work-up. The pure product was obtained from the reaction mixture by passing it through a short column of basic alumina.

THP ether of 4-methoxybenzyl alcohol (110):



Nature: Colorless liquid

Yield: 89%

Reaction time: 40 min

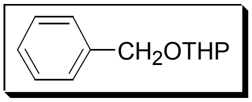
IR (**Neat**)**:** cm^{-1} 2940, 2858, 1619, 1516, 1460, 1358, 1255, 1132, 1030

^{1}H NMR (**400 MHz, $CDCl_3$**)**:** δ 1.48-1.90 (m, 6H), 3.51-3.57 (m, 1H), 3.79 (s, 3H), 3.88-3.93 (m, 1H), 4.43 (d, 1H, *J* = 12.0 Hz), 4.66-4.69 (m, 1H), 4.71 (d, 1H, *J* = 11.2 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.8 Hz) ppm.

^{13}C NMR (**100 MHz, $CDCl_3$**): δ 19.9, 25.9, 31.0, 55.6, 62.5, 68.8, 97.7, 113.9 (2C), 129.7 (2C), 130.5, 159.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_3$	C 70.25	C 70.02
222.28	H 8.16	H 8.04

THP ether of benzyl alcohol (111):



Nature: Colorless liquid

Yield: 91%

Reaction time: 40 min

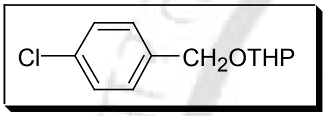
IR (Neat): cm^{-1} 3041, 2930, 1452, 1351

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.48-1.90 (m, 6H), 3.53-3.56 (m, 1H), 3.89-3.94 (m, 1H), 4.50 (d, 1H, *J* = 12.0 Hz), 4.71 (t, 1H, *J* = 3.3 Hz), 4.79 (d, 1H, *J* = 12.0 Hz), 7.27 - 7.38 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.3, 25.4, 30.5, 62.0, 68.7, 97.7, 127.4, 127.7 (2C), 128.3 (2C), 138.3 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_2$	C 74.97	C 74.74
192.26	H 8.39	H 8.48

THP ether of 4-chlorobenzyl alcohol (112):



Nature: Colorless liquid

Yield: 92%

Reaction time: 45 min

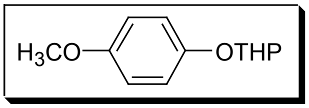
IR (Neat): cm^{-1} 2942, 2865, 1595, 1465, 1357, 1130, 1075, 1038

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.51-1.87 (m, 6H), 3.51-3.55 (m, 1H), 3.86-3.91 (m, 1H), 4.46 (d, 1H, *J* = 12.0 Hz), 4.68-4.69 (m, 1H), 4.74 (d, 1H, *J* = 12.0 Hz), 7.30 (bs, 4H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 25.5, 30.6, 62.1, 68.0, 97.7, 128.3 (2C), 128.9 (2C), 133.0, 136.7 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{15}ClO_2$	C 63.58	C 63.38
226.70	H 6.67	H 6.59

THP ether of 4-methoxyphenol (113):



Nature: Colorless liquid

Yield: 89%

Reaction time: 1.5 h

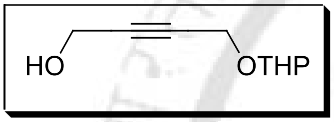
IR (Neat): cm^{-1} 2940, 2879, 1506, 1470, 1399, 1368, 1230, 1122, 1076, 1045, 968

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.61-2.01 (m, 6H), 3.58-3.61 (m, 1H), 3.77 (s, 3H), 3.91-3.97 (m, 1H), 5.29 (t, 1H, *J* = 3.6 Hz), 6.82 (d, 2H, *J* = 9.2 Hz), 6.99 (d, 2H, *J* = 9.6 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 25.7, 30.9, 56.0, 62.4, 97.6, 114.7 (2C), 117.9 (2C), 151.2, 158.8 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_3$	C 69.21	C 69.48
208.26	H 7.74	H 7.82

Mono THP ether of 1,4-butyne diol (114):



Nature: Colorless liquid

Yield: 55%

Reaction time: 1 h

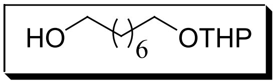
IR (Neat): cm^{-1} 3411, 2945, 2863, 1450, 1393, 1358, 1271, 1127, 1020

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.52-1.85 (m, 7H), 3.53-3.56 (m, 1H), 3.81-3.86 (m, 1H), 4.23-4.37(m, 4H), 4.81 (t, 1H, *J* = 3.2 Hz) ppm.

^{13}C NMR (100 MHz, CDCl3): δ 19.4, 25.7, 30.6, 51.5, 54.7, 62.3, 82.1, 84.6, 97.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{14}O_3$	C 63.51	C 63.64
170.21	H 8.29	H 8.24.

8-Tetrahydropyranyloxy-1-octanol (115):



Nature: Colorless liquid

Yield: 83%

Reaction time: 12 h

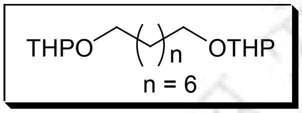
IR (Neat): cm^{-1} 3422, 2931, 2858, 1454, 1354, 1276, 1127, 1030

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.30-1.40 (bs, 8H), 1.50-1.61 (m, 6H), 1.69-1.74 (m, 2H), 1.80-1.90 (m, 2H), 2.05 (bs, 1H, D_2O exchangeable), 3.35-3.41 (m, 1H), 3.48-3.51 (m, 1H), 3.64 (t, 2H, *J* = 6.8 Hz), 3.70-3.74 (m, 1H), 3.84-3.89 (m, 1H), 4.56-4.58 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.5, 25.7, 26.2, 29.3, 29.4, 29.7, 30.7, 32.7, 62.2, 62.7, 67.6, 98.7 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{26}O_3$	C 67.79	C 67.65
230.35	H 11.38	H 11.29

Di-THP ether of 1,8-octanediol (116):



Nature: Colourless liquid

Yield: 93%

Reaction time: 12 h

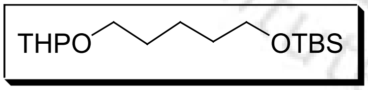
IR (Neat): cm^{-1} 2935, 2863, 1465, 1358, 1265, 1209, 1137, 1081, 1040, 979

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (bs, 8H), 1.50-1.86 (m, 16H), 3.37 (dt, 2H, J = 6.8 Hz, J = 9.6 Hz), 3.46-3.51 (m, 2H), 3.72 (dt, 2H, J = 6.8 Hz, J = 9.6 Hz), 3.83-3.88 (m, 2H), 4.55-4.56 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8 (2C), 25.6 (2C), 26.3 (2C), 29.5 (2C), 29.8 (2C), 30.9 (2C), 62.3 (2C), 67.6 (2C), 98.8 (2C) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{34}O_4$	C 68.75	C 68.98
314.46	H 10.90	H 10.79

THP ether of 5-tert-Butyldimethylsilyloxy-1-pentanol (117):



Nature: Colorless liquid

Yield: 82%

Reaction time: 40 min

IR (Neat): cm^{-1} 2932, 2862, 1462, 1358, 1259, 1112, 1033

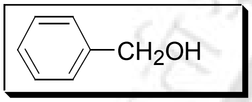
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.37-1.42 (m, 4H), 1.49-1.92 (m, 8H), 3.36-3.40 (m, 1H), 3.42-3.51 (m, 1H), 3.61 (t, 2H, J = 6.8 Hz), 3.71-3.76 (m, 1H), 3.82-3.90 (m, 1H), 4.56-4.58 (m, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{34}O_3Si$	C 63.52	C 63.79
302.53	H 11.33	H 11.41

Typical procedure of deprotection:

To a solution of THP ether of cetyl alcohol (0.325 g, 1 mmol) in methanol (5 mL) was added cupric sulfate pentahydrate (0.05 g, 0.2 mmol) and the mixture stirred at room temperature. The reaction was completed within 5 h and the solid cupric sulfate was filtered off. The solid residue was washed with methanol (2 x 5 mL). After concentration of the combined filtrate, the crude residue was purified through a short silica gel column. The desired cetyl alcohol was obtained 0.206 g in 85% yield.

Benzyl alcohol (105):



Nature: Colorless liquid

Yield: 82%

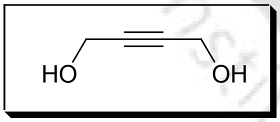
Reaction time: 4.5 h

IR (Neat): cm^{-1} 3339, 3027, 2868, 1506, 1460, 1209, 1019

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.78 (bs, 1H), 4.69 (s, 2H), 7.25-7.37 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
C_7H_8O	C 77.75	C 77.58
108.14	H 7.46	H 7.42

2-Butyne-1,4-diol (63):



Nature: Light yellow solid

Yield: 76%

Reaction time: 40 min

IR (Neat): cm^{-1} 3370, 2925, 2868, 1434, 1358, 1230, 1132, 1015

^{1}H NMR (400 MHz, Acetone-d$_6$): δ 4.23 (bs, 4H), 4.39 (bs, 2H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_4H_6O_2$	C 55.81	C 55.73
86.09	H 7.02	H 7.07

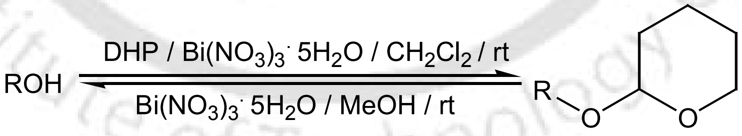
SECTION C

A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS USING BISMUTH(III) NITRATE PENTAHYDRATE

RESULTS AND DISCUSSION

Results and Discussion

In section B of chapter I, we have discussed about the potentiality of cupric sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$)[54] as a mild and efficient heterogeneous catalyst for tetrahydropyranylation /depyranylation of alcohols and phenols. But, the method suffers from one major drawback — the method is not applicable for compounds having sulfur containing group. As a part of our ongoing research programme to develop new synthetic methodologies by using various new reagents,[55] we realized that there is a further scope for a cleaner and greener methodology for tetrahydropyranylation/depyranylation, which might work under mild catalytic conditions as well as economically cheaper. In recent years, bismuth compounds have been gaining interest in various organic transformations.[56,57] We thought that bismuth(III) nitrate pentahydrate, which is commercially available at a very low cost and is relatively nontoxic, might be a useful catalyst for tetrahydropyranylation /depyranylation. So far, bismuth(III) nitrate pentahydrate has been utilized in various organic transformations: i) acetylation and benzoylation of alcohols and phenols,[58a] ii) guanidylation of *N*-benzoylthiourea,[58b] iii) conversion of thiocarbonyl compounds to the corresponding carbonyl compounds,[58c] iv) Michael reaction,[58d] v) oxidation of thiols to disulfides,[58e] and vi) for the synthesis of acylals[58f] and dihydropyrimidinone.[58g] In this section, we would like to discuss the tetrahydropyranylation of alcohols and phenols and depyranylation in the presence of catalytic amounts of bismuth(III) nitrate pentahydrate,[59] as shown in Scheme 25.



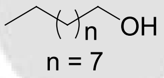
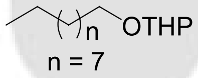
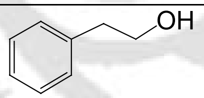
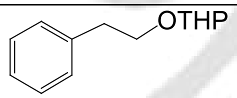
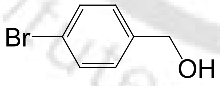
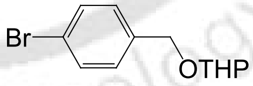
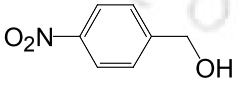
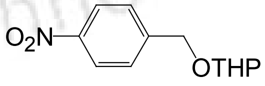
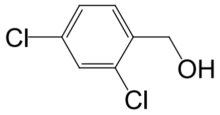
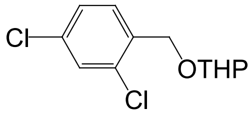
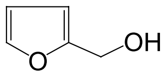
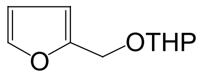
R = alkyl / aryl / sugar residue / nucleoside residue

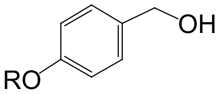
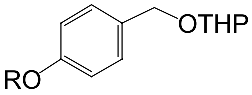
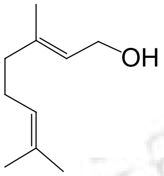
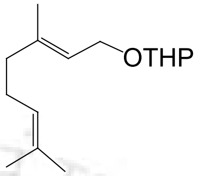
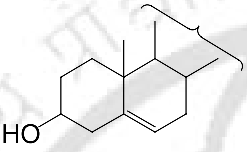
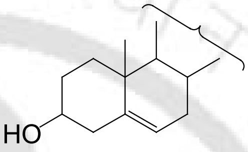
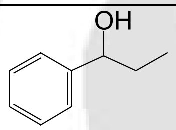
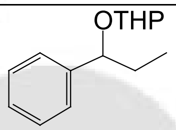
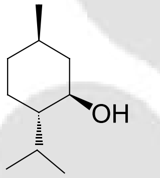
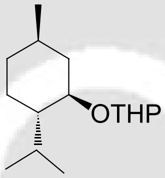
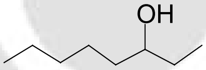
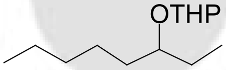
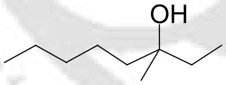
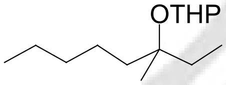
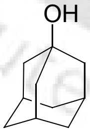
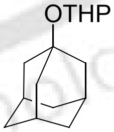
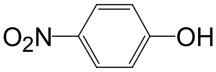
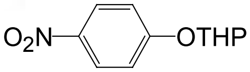
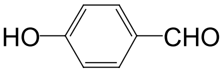
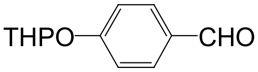
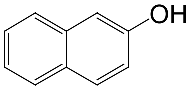
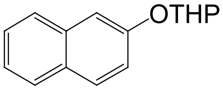
Scheme 25

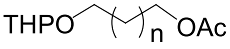
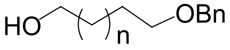
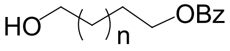
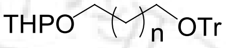
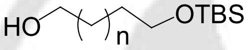
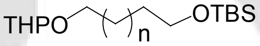
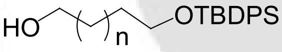
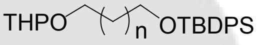
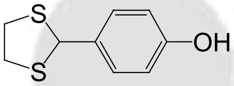
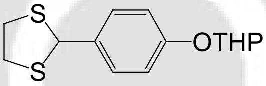
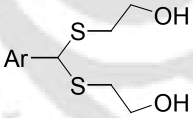
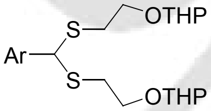
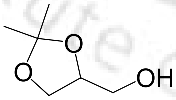
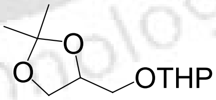
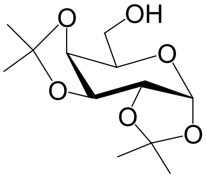
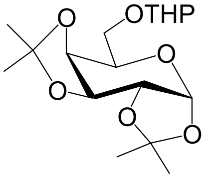
When a mixture of 1-decanol (**46**) and 3,4-dihydro-2*H*-pyran (DHP) in dichloromethane was treated with 5 mol-% of bismuth (iii) nitrate pentahydrate, it was smoothly converted into the corresponding THP ether **75** within 15 min in 92% yield. Similarly, 2-phenylethanol (**48**) was converted into the corresponding THP ether **77** in fairly good yield under identical reaction conditions. Various benzylic alcohols (**118**, **119**, **120**, **67**,

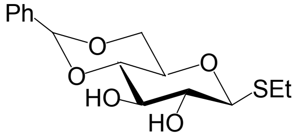
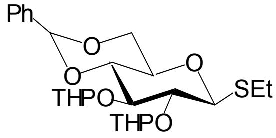
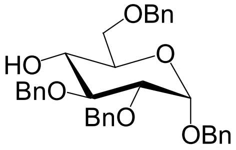
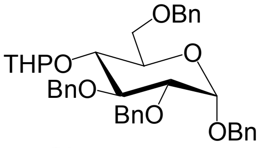
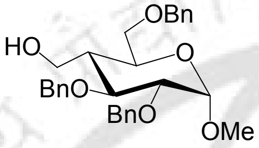
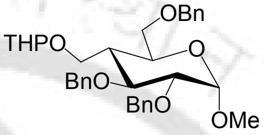
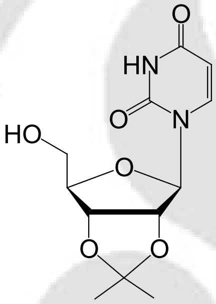
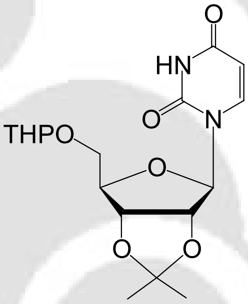
62), allyl alcohols (**61**), secondary alcohols (**14**, **120**, **50**, **49**), and tertiary alcohols (**122** and **123**) were smoothly converted into the corresponding THP ethers **133**, **134**, **135**, **96**, **91**, **90**, **15**, **136**, **79**, **78**, **137** and **138** respectively, in very good yields, as shown in Table 6. Here, it is worth mentioning that our procedure is highly efficient in terms of reaction times and yields obtained than some of the recently reported procedures.[21,26,27] For example, tetrahydropyranylation of 4-nitrobenzylalcohol (**119**), geraniol (**61**), and (–) menthol (**50**) form the corresponding THP ethers (**134**, **90**, **79**) much more quickly giving better yields than the bismuth triflate method.[21] We were then interested to investigate whether the same catalyst could be employed for tetrahydropyranylation of phenolic compounds. By following identical reaction procedures, various phenols (**124**, **64**, **125**) were smoothly converted into the corresponding THP ethers **139**, **93** and **140** in good yields. The THP ether **140** exhibits absorption frequency in the IR spectrum at 2919, 2854, 1469, 1354, 1218, 1127, 1037 cm^{-1} (Fig. 7). The disappearance of hydroxyl frequency in the IR spectrum clearly indicates the formation of THP ether. In ^{1}H NMR spectrum the compound **140** gives the signals at δ 1.60-1.73 (m, 3H), 1.89-1.92 (m, 2H), 1.99-2.08 (m, 1H), 3.62-3.66 (m, 1H), 3.91-3.97 (m, 1H), 5.56 (t, J = 3.3 Hz, 1H), 7.21-7.25 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.39-7.43 (m, 2H), 7.72-7.76 (m, 3H) ppm (Fig. 8). The following new signals at δ 1.60-1.73 (m, 3H), 1.89-1.92 (m, 2H), 1.99-2.08 (m, 1H), 3.62-3.66 (m, 1H), 3.91-3.97 (m, 1H) and 5.56 (t, J = 3.3 Hz, 1H) clearly indicate the formation of THP ether. Similarly, ^{13}C NMR spectrum it shows peaks at δ 18.7, 25.2, 30.4, 61.9, 96.4, 110.4, 119.1, 123.8, 126.2, 127.0, 127.5, 129.2, 129.4, 134.5, 154.8 ppm (Fig. 9). The appearance of new signals at δ 18.7, 25.2, 30.4, 61.9 and 96.4 also support the formation of THP ether. It had been observed previously that the formation of the THP ether **140** from β-naphthol (**125**) by employing Bi(OTf)$_3$ as catalyst was a failure,[21] whereas we have shown that it can be easily accessible by our method; this offers an additional advantage. We then turned our attention on whether the same catalyst could be useful for tetrahydropyranylation of substrates containing other protecting groups. We observed that various protected alcohols (**55**, **126**, **127**, **57**, **128**, **129** and **130**) containing protecting groups such as acetyl, benzyl, benzoyl, trityl, tosyl, TBS and TBDPS ethers were smoothly converted into the corresponding THP ethers **84**, **141**, **142**, **86**, **143**, **144** and **145** without affecting the other protecting groups. Furthermore, substrates with thioacetal groups (**66** and **131**), and isopropylidene protected alcohols (**68** and **69**) and benzylidene protected diol (**132**) can be easily transformed into the desired THP ethers **146**, **97**, **98** and **147** in good yields as shown in the Table 6. Interestingly, it was observed that the formation of THP ethers **95**, **146** and **147** from the compounds **66**, **131** and **132**, respectively, was difficult by our recently reported procedure, where we used cupric sulfate pentahydrate as catalyst.[54] Remarkably, by employing our present protocol, various carbohydrates (**69**, **132**, **71** and **70**), as well as a nucleoside compound (**74**), were smoothly converted into the corresponding THP ethers (**98**, **147**, **100**, **99** and **103**) in good yields, as shown in Table 6. The formation of the products was confirmed by IR, 1H and ^{13}C NMR spectroscopy and by elemental analysis. In addition, we have also compared some of the spectroscopic data with that obtained by a method reported earlier.[30]

Table 6 Tetrahydropyranylation of alcohols and phenols in presence of a catalytic amount of bismuth(III) nitrate pentahydrate [$Bi(NO_3)_3 \cdot 5H_2O$]

Substrate No	Substrate	Time /min	Product[a]	Product No.	Yield[b], [c] [/%]
46		15		**75**	92
48		15		**77**	84
118		15		**133**	91
119		20		**134**	90
120		25		**135**	77
67		12		**96**	85

62	 R = $-CH_2CH=CH_2$	22	 R = $-CH_2CH=CH_2$	**91**	84
61		18		**90**	88
14		45		**15**	82
121		18		**136**	90
50		22		**79**	90
49		18		**78**	90
122		22		**137**	65
123		25		**138**	76
124		30		**139**	83
64		25		**93**	87
125		45		**140**	74

55	 n = 3	16	 n = 3	**84**	83
126	 n = 5	18	 n = 5	**141**	86
127	 n = 5	15	 n = 5	**142**	87
57	 n = 3	15	 n = 3	**86**	81
128	 n = 3	12	 n = 3	**143**	86
129	 n = 5	15	 n = 5	**144**	87
130	 n = 5	12	 n = 6	**145**	85
66		27		**95**	83
131	 Ar = 4-methoxy phenyl	18	 Ar = 4-methoxy phenyl	**146**	81
68		20		**97**	84
69		35		**98**	79

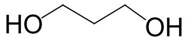
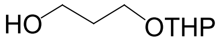
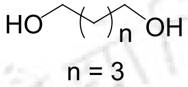
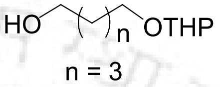
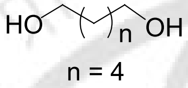
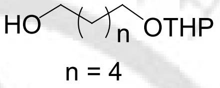
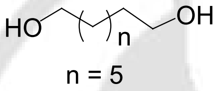
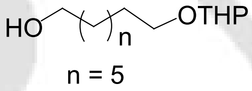
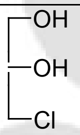
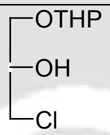
132		55		**147**	60
71		32		**100**	79
70		25		**99**	84
74		40		**103**	83

[a]All starting material and final products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. [b]Isolated yield.

The most significant advantage of this protocol is that various symmetric diols (**148**, **54**, **149**, **110** and **63**) can be chemoselectively protected when transformed into the mono THP ethers **(151, 83, 152, 114** and **115**) with 5–10% di-THP ethers by using 5 mol-% catalyst under identical conditions; this is sometimes difficult to achieve with other methods. It should also be noted that primary alcohols can be protected chemoselectively in the presence of a secondary alcohol (**153**). These results have been summarized in Table 7.

An additional feature of our protocol is that tetrahydropyranylation can be carried out even on a large scale (for example, on 10–100 mmol) without any difficulty. The formation of the product can be explained as follows. We believe that the actual catalyst is nitric acid, which is generated from bismuth(III) nitrate pentahydrate in the reaction medium. This fact is verified in two ways: i) the tetrahydropyranylation of 4-nitrobenzyl-

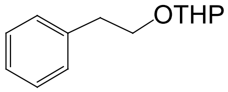
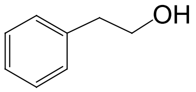
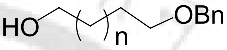
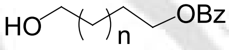
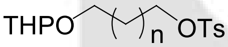
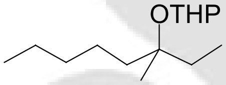
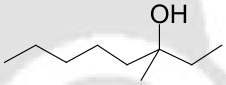
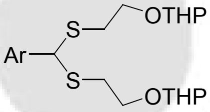
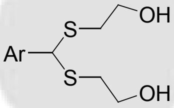
Table 7 Selective tetrahydropyranylation of diols using catalytic amount of $Bi(NO_3)_3 \cdot 5H_2O$

Substrate No	Substrate	Time /min	Product[a]	Product No.	Yield[b] [%]
148		12		**151**	73
54		15		**83**	70
149		12		**152**	83
108		20		**115**	75
63		15		**114**	62
150		18		**153**	76

[a]All starting material and final products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. [b]Isolated yield.

alcohol (**119**) in the presence of bismuth(III) nitrate pentahydrate (0.05 mmol) and potassium carbonate (1 mmol) did not show the formation of any product; ii) the formation of THP ether **134** from 4-nitrobenzyl alcohol is possible in 72% yield in the presence of a catalytic amount of concentrated HNO_3. However, Banik et al. reported[58d] while studying Michael reactions that bismuth(III) nitrate pentahydrate acts only as a Lewis acid because they did not observe any Michael addition product in the presence of other metal nitrates which can also readily generate nitric acid in the medium. Notably, the same catalyst can be used for depyranylation reactions. For example, the THP ether **96** undergoes cleavage in methanol within 35 min in 79% yield with 5 mol-% of catalyst. Likewise, various THP ethers **77**, **84**, **141**, **142**, **143**, **137** and **136** were converted into the parent hydroxyl compounds **48, 55, 126, 127, 128, 122** and **131** respectively, within 35-50 min in 66–90% yields under similar reaction conditions, which are given in the Experimental Section. The results are shown in Table 8.

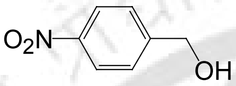
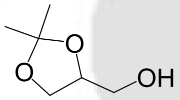
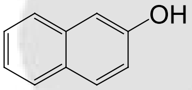
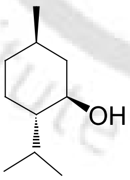
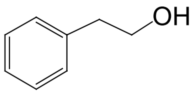
Table 8 Deprotection of various tetrahydropyranyl ethers to the corresponding hydroxyl compounds using catalytic amount of $Bi(NO_3)_3 \cdot 5H_2O$ in methanol

Substrate No.	Substrate	Time min /[h]	Product[a]	Product No	Yield[b] /%
77		45		**48**	82
84	 n = 3	45	 n = 3	**55**	90
141	 n = 5	40	 n = 5	**126**	80
142	 n = 5	40	 n = 5	**127**	82
143	 n = 3	45	 n = 3	**128**	85
137		35		**122**	66
146	 Ar = 4-methoxy phenyl	50	 Ar = 4-methoxy phenyl	**131**	81

[a] All final products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis.
[b] Isolated yield.

The efficiency and generality of the present method can be realized at a glance by comparing our results with those of some recently reported procedures (shown in Table 9). The results have been compared with respect to the reaction times, mol-% of the catalyst used, and yields. Here we have chosen some of the substrates as model substrates. In case of **119**, the yields are comparable, but the reaction time proves the efficiency of our protocol. For substrate **125**, the desired THP ether **140** was difficult to obtain when $Bi(OTf)_3 \cdot 4H2O$ was used, but it can be prepared in good yield and without any difficulty by employing our protocol. For entries **68**, **50** and **48**, the yields are better and reaction times are lower when our protocol is used. The protocol with $Bi(OTf)_3 \cdot 4H_2O$ requires not only an inert atmosphere, but also $Bi(OTf)_3 \cdot 4H_2O$ has to be prepared prior to use. Therefore, considering all these facts we believe that bismuth(III) nitrate pentahydrate is a relatively better catalyst for tetrahydropyranylation of hydroxyl compounds.

Table 9 Comparison of results of tetrahydropyranylation of alcohols and phenols with other catalyst

Substrate No.	Alcohol / Phenol	Catalyst	Mol %	Time	Yield
119		LiOTf	60-70	3 h	92[36]
		$Bi(OTf)_3\cdot 4H_2O$	0.1	4 h	85[21]
		$Bi(NO_3)_3\cdot 5H_2O$	5	20 min	90[61]
68		H_2O	-	9 h	55[27]
		$Bi(OTf)_3\cdot 4H_2O$	0.1	3.25 h	78[21]
		$Bi(NO_3)_3\cdot 5H_2O$	5	20 min	84[61]
125		LiOTf	60-70	6 h	92[36]
		$Bi(OTf)_3\cdot 4H_2O$	0.1	-	0[21]
		$Bi(NO_3)_3\cdot 5H_2O$	5	45 min	74[61]
50		$NbCl_5$	10	3 h	89[26]
		H_2O	-	10 h	76[27]
		$Bi(OTf)_3\cdot 4H_2O$	0.1	2 h	74[21]
		$Bi(NO_3)_3\cdot 5H_2O$	5	22 min	90[61]
48		TBATB	2.5	45 min	88[20]
		LiOTf	60-70	2.5 h	94[36]
		$Bi(OTf)_3\cdot 4H_2O$	0.1	1h	82[21]
		$Bi(NO_3)_3\cdot 5H_2O$	15	22 min	90[61]

In conclusion, the present methodology demonstrates $Bi(NO_3)_3 \cdot 5H_2O$ as an effective catalyst for tetrahydropyranylation /depyranylation of alcohols and phenols. The main advantages of this method are: mild, clean and simple reaction conditions, good yields, non-aqueous work-up and environmentally benign reagent. In addition, our methodology might be useful for the substrates containing a wide variety of other protecting groups. Furthermore, this method is also expected to have much better applicability in organic synthesis due to the very low cost and non-toxic nature of the reagent. We believe, this methodology will be a valuable addition to the area of modern synthetic methodologies.

SECTION C

A HIGHLY EFFICIENT AND CHEMOSELECTIVE SYNTHETIC PROTOCOL FOR TETRAHYDROPYRANYLATION / DEPYRANYLATION OF ALCOHOLS AND PHENOLS USING BISMUTH(III) NITRATE PENTAHYDRATE

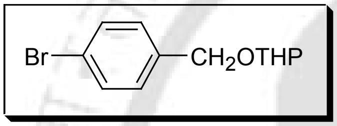
EXPERIMENTAL

Experimental

Typical procedure for Tetrahydropyranylation:

Bismuth(III) nitrate pentahydrate (0.024 g, 0.05 mmol) was added to a mixture of alcohol or phenol (1 mmol) and 3,4-dihydro-*2H*-pyran (109 μL, 1.2 mmol) in dichloromethane. The mixture was stirred at room temperature. After completion of the reaction as confirmed by TLC, the reaction mixture was reduced to approximately 1 mL, and then it was passed through a short basic alumina column to afford the desired THP ether.

THP ether of 4-bromobenzyl alcohol (133):



Nature: Colorless liquid

Yield: 91%

Reaction time: 15 min

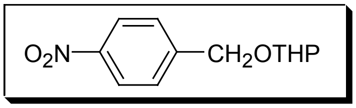
IR (Neat): cm^{-1} 2942, 2865, 1595, 1465, 1357, 1130, 1075, 1038

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.53-1.87 (m, 6H), 3.50-3.56 (m, 1H), 3.85-3.91 (m, 1H), 4.44 (d, 1H, *J* = 12.4 Hz), 4.66-4.68 (m, 1H), 4.71 (d, 1H, *J* = 12.0 Hz), 7.23 (d, 2H, *J* = 8.8 Hz), 7.46 (d, 2H, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 25.5, 30.6, 62.2, 68.0, 97.7, 121.2, 129.2 (2C), 131.3 (2C), 137.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{15}O_2Br$	C 53.16	C 53.24
271.15	H 5.58	H 5.49

THP ether of 4-nitrobenzyl alcohol (134):



Nature: Yellowish liquid

Yield: 90%

Reaction time: 20 min

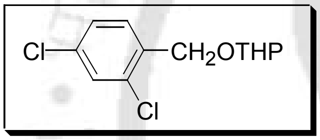
IR (Neat): cm^{-1} 2943, 2869, 1605, 1522, 1346, 1202, 1127, 1036

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.52-1.92 (m, 6H), 3.51-3.59 (m, 1H), 3.86-3.92 (m, 1H), 4.61 (d, 1H, *J* = 13.6 Hz), 4.73-4.74 (m, 1H), 4.89 (d, 1H, *J* = 13.2 Hz), 7.53 (d, 2H, *J* = 9.2 Hz), 8.20 (d, 2H, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.4, 25.4, 30.5, 62.3, 67.6, 98.2, 123.4 (2C), 127.6 (2C), 145.9, 147.3 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{15}NO_4$	C 60.75	C 60.54
237.25	H 6.37	H 6.29
	N 5.90	N 5.78

THP ether of 2,4-dichlorobenzyl alcohol (135):



Nature: Colorless liquid

Yield: 77%

Reaction time: 25 min

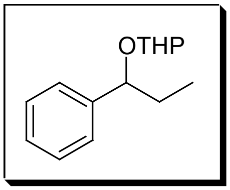
IR (Neat): cm^{-1} 2942, 2862, 1591, 1468, 1382, 1350, 1200, 1129, 1073, 1034, 972

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.55-1.92 (m, 6H), 3.55-3.59 (m, 1H), 3.87-3.94 (m, 1H), 4.56 (d, 1H, *J* = 13.6 Hz), 4.75 (t, 1H, *J* = 3.6 Hz), 4.81 (d, 1H, *J* = 13.6 Hz), 7.24 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz), 7.37 (d, 1H, *J* = 2.0 Hz), 7.46 (d, 1H, *J* = 8.0 Hz) ppm.

^{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 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{14}Cl_2O_2$	C 55.19	C 55.48
261.15	H 5.40	H 5.51

THP ether of 1-phenyl-1-propanol (136):



Nature: Colorless liquid

Yield: 90%

Reaction time: 18 min

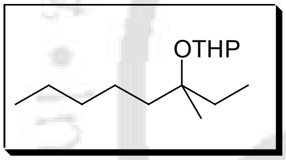
IR (Neat): cm^{-1} 3042, 2938, 2874, 1614, 1501, 1456, 1383, 1204, 1121,1026

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.93 (t, 3H, J = 7.6 Hz), 1.44 -1.90 (m, 8H), 3.47-3.50 (m, 1H), 3.93-3.98 (m, 1H), 4.40 (t, 1H, J = 4.0 Hz), 4.59 (t, 1H, J = 7.6 Hz), 7.25-7.35 (m, 5H) ppm.

^{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 (2C), 128.2 (2C), 142.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{20}O_2$	C 76.33	C 76.52
220.31	H 9.15	H 9.21

THP ether of 3-methyl-3-octanol (137):



Nature: Light yellow liquid

Yield: 65%

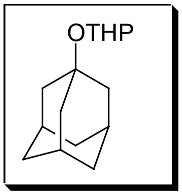
Time : 22 min

IR (Neat): cm^{-1} 2945, 2863, 1460, 1378, 1281, 1204, 1132, 1086, 1030, 994

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.84 (t, 3H, J = 6.8 Hz), 0.89 (t, 3H, J = 7.2 Hz), 1.15 (s, 3H), 1.26-1.39 (m, 6H), 1.41-1.84 (m, 10H), 3.42-3.45 (m, 1H), 3.93-3.97 (m, 1H), 4.70 (bs, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{28}O_2$	C 73.63	C 73.84
228.37	H 12.36	H 12.29

THP ether of 1-adamantanol (138):



Nature: Light yellow liquid

Yield: 76%

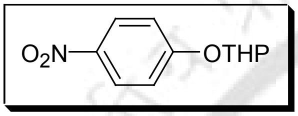
Reaction time: 25 min

IR (Neat): cm^{-1} 2935, 2858, 1440, 1245, 1204, 1158, 1132, 1068, 1046, 979

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.47-1.54 (m, 4H), 1.56-1.66 (m, 8H), 1.76-1.85 (m, 6H), 2.12 (s, 3H), 3.40-3.48 (m, 1H), 3.91-3.99 (m, 1H), 4.82-4.85 (m, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{24}O_2$	C 76.23	C 76.03
236.35	H 10.23	H 10.29

THP ether of 4-nitrophenol (139):



Nature: Yellowish liquid

Yield: 83%

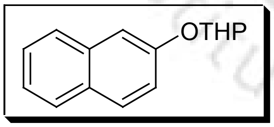
Reaction time: 30 min

IR (Neat): cm^{-1} 2948, 1495, 1173, 849, 823

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.54-2.01 (m, 6H), 3.50-3.65 (m, 1H), 3.78-3.88 (m, 1H), 5.53-5.55 (m, 1H), 7.11 (d, 2H, J = 9.2 Hz), 8.19 (d, 2H, J = 9.2 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{13}NO_4$	C 59.19	C 59.44
223.23	H 5.87	H 5.79
	N 6.27	N 6.43

THP ether of 2-naphthol (140):



Nature: Light yellow solid

Yield: 74%

Reaction time: 45 min

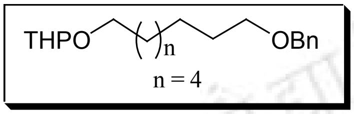
IR (Neat): cm^{-1} 2919, 2854, 1469, 1354, 1218, 1127, 1037

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.60-1.73 (m, 3H), 1.89-1.92 (m, 2H), 1.99-2.08 (m, 1H), 3.62-3.66 (m, 1H), 3.91-3.97 (m, 1H), 5.56 (t, 1H, J = 3.3 Hz), 7.21-7.25 (m, 1H), 7.32 (d, 1H, J = 8.0 Hz), 7.39-7.43 (m, 2H), 7.72-7.76 (m, 3H) ppm.

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.7, 25.2, 30.4, 61.9, 96.4, 110.4, 119.1, 123.8, 126.2, 127.0, 127.5, 129.2, 129.4, 134.5, 154.8 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{16}O_2$	C 78.92	C 78.71
228.29	H 7.06	H 6.98

THP ether of 8-benzyloxy-1-octanol (141):



Nature: Colorless liquid

Yield: 86%

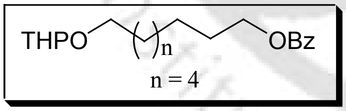
Reaction time: 18 min

IR (Neat): cm^{-1} 2937, 2855, 1454, 1123, 1034, 968

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-1.37 (m, 8H), 1.53-1.90 (m, 10H), 3.37 (dt, 1H, *J* = 6.4 Hz, *J* = 9.2 Hz), 3.46 (t, 2H, *J* = 6.8 Hz), 3.48-3.62 (m, 1H), 3.72 (dt, 1H, *J* = 6.4 Hz, *J* = 9.2 Hz), 3.83-3.89 (m, 1H), 4.50 (s, 2H), 4.56-4.57 (m, 1H), 7.26-7.36 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{20}H_{32}O_3$	C 74.96	C 74.68
320.47	H 10.06	H 10.17

THP ether of 8-benzoyloxy-1-octanol (142):



Nature: Gummy liquid

Yield: 87%

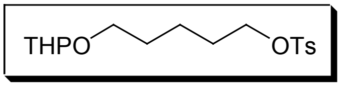
Reaction time: 15 min

IR (Neat): cm^{-1} 2930, 2857, 1719, 1453, 1276, 1217, 1114, 1038

^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ 1.36-1.86 (m, 18H), 3.35-3.41 (m, 1H), 3.50-3.56 (m, 1H), 3.70-3.78 (m, 1H), 3.86-3.89 (m, 1H), 4.31 (t, 2H, *J* = 6.8 Hz), 4.56-4.60 (m, 0.5H), 4.94-4.98 (m, 0.5H), 7.43 (t, 2H, *J* = 7.2 Hz), 7.55 (t, 1H, *J* = 7.2 Hz), 8.04 (d, 2H, *J* = 8.4 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{20}H_{30}O_4$	C 71.83	C 71.56
334.45	H 9.04	H 9.10

THP ether of 5-tosyloxy-1-octanol (143):



Nature: Gummy liquid

Yield: 86%

Reaction time: 12 min

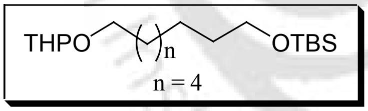
IR (Neat): cm^{-1} 2945, 2868, 1603, 1465, 1362, 1183, 1132, 1081, 1050, 968, 963

^{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) ppm.

^{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 (2C), 129.6 (2C), 133.0, 144.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{26}O_5S$	C 59.63	C 59.40
342.45	H 7.65	H 7.71
	S 9.36	S 9.14

THP ether of 8-(*tert*-butyldimethylsilyloxy)-1-octanol (144):



Nature: Colorless liquid

Yield: 87%

Reaction time: 15 min

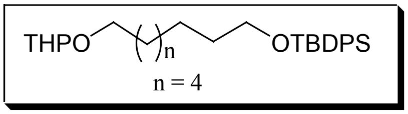
IR (Neat): cm^{-1} 2937, 2860, 1465, 1358, 1254, 1106, 1031

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.25-1.30 (m, 6H), 1.48-1.87 (m, 12H), 3.34-3.40 (m, 1H), 3.47-3.50 (m, 1H), 3.59 (t, 2H, *J* = 6.4 Hz), 3.69-3.73 (m, 1H), 3.84-3.89 (m, 1H), 4.56-4.57 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ –5.3 (2C), 18.3, 19.6, 25.5, 25.7, 25.9 (3C), 26.1, 29.3, 29.4, 29.7, 30.7, 32.8, 62.2, 63.2, 67.6, 98.8 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{19}H_{40}O_3Si$	C 66.22	C 66.46
344.61	H 11.70	H 11.62

THP ether of 5-(*tert*-Butyldiphenylsilyloxy)-1-octanol (145):



Nature: Colorless liquid

Yield: 85%

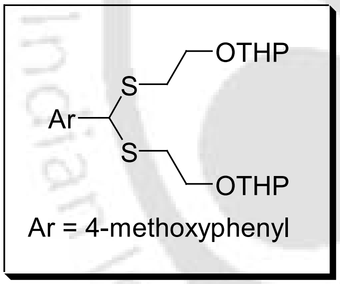
Reaction time: 12 min

IR (Neat): cm^{-1} 2935, 2858, 1475, 1440, 1388, 1363, 1204, 1112, 1030, 979

^{1}H NMR (200 MHz, CDCl$_3$): (mixture of diastereomers): δ 1.04 (s, 9H), 1.10-1.35 (m, 8H), 1.52-1.85 (m, 10H), 3.35-3.54 (m, 2H), 3.64 (t, 2H, *J* = 6.4 Hz), 3.70-3.92 (m, 2H), 4.52-4.62 (m, 0.4H), 4.90-5.00 (m, 0.6H), 7.30-7.46 (m, 6H), 7.61-7.71 (m, 4H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{44}O_3Si$	C 74.31	C 74.09
468.75	H 9.46	H 9.40

Spectroscopic data for compound 146:



Nature: Colorless liquid

Yield: 81%

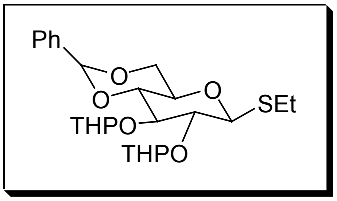
Reaction time: 18 min

IR (Neat): cm^{-1} 2966, 2925, 2843, 1619, 1516, 1450, 1327, 1260, 1178, 1086, 1030

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.53-1.87 (m, 12H), 2.70-2.80 (m, 2H), 2.92-2.98 (m, 2H), 3.45-3.60 (m, 4H), 3.85-3.88 (m, 4H), 3.88 (s, 3H), 4.85-4.95 (m, 2H), 6.22 (s, 1H), 7.00 (d, 2H, *J* = 8.8 Hz), 7.84 (d, 2H, *J* = 8.0 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{22}H_{34}O_5S_2$	C 59.70	C 59.56
442.63	H 7.74	H 7.67
	S 14.49	S 14.32

Spectroscopic data for compound 147:



Nature: Colorless liquid

Yield: 60%

Reaction time: 55 min

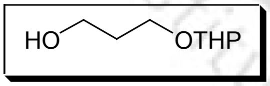
IR (Neat): cm^{-1} 2935, 2858, 1634, 1470, 1383, 1265, 1086, 1030, 974

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 1.33 (t, 3H, *J* = 7.6 Hz), 1.42-1.76 (m, 12H), 2.63-2.67 (m, 2H), 3.23-3.67 (m, 7H), 3.90-4.00 (m, 1H), 4.22-4.27 (m, 1H), 4.38-4.48 (m, 3H), 4.64-4.70 (m, 1H), 5.44 (s, 1H), 7.21-7.27 (m, 3H), 7.34-7.38 (m, 2H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 15.04, 15.16, 19.03, 19.63, 20.03, 21.13, 24.44, 24.87, 25.22, 25.44, 29.03, 30.69, 31.00, 65.40, 65.63, 66.96, 68.65, 70.09, 70.83, 72.15, 73.29, 79.34, 80.57, 83.97, 84.20, 84.87, 86.23, 101.24, 101.72, 102.35, 102.79, 125.98, 126.33, 128.21, 137.28 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{25}H_{36}SO_7$	C 62.48	C 62.71
480.62	H 7.55	H 7.59
	S 6.67	S 6.62

3-Tetrahydropyranyloxy-1-propanol (151):



Nature: Colorless liquid

Yield: 73%

Reaction time: 12 min

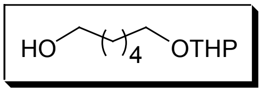
IR (Neat): cm^{-1} 3416, 2950, 2879, 1455, 1352, 1209, 1127, 1081, 1035

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.51-1.63 (m, 3H), 1.67-1.89 (m, 3H), 2.25 (bs, 1H), 3.48-3.61 (m, 2H), 3.78 (t, 2H, *J* = 5.2 Hz), 3.83-3.95 (m, 2 H), 4.57-4.59 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.8, 25.4, 30.7, 32.1, 61.5, 62.6, 66.3, 99.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{16}O_3$	C 59.98	C 60.05
160.21	H 10.07	H 10.12

6-Tetrahydropyranyloxy-1-hexanol (152):



Nature: Colorless liquid

Yield: 83%

Reaction time: 12 min

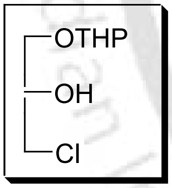
IR (Neat): cm^{-1} 3412, 2942, 2862, 1454, 1352, 1274, 1127, 1082

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.40 (q, 4H, J = 4.0 Hz), 1.50-1.85 (m, 11H), 3.40 (dt, 1H, J = 6.4 Hz, J = 9.6 Hz), 3.47-3.55 (m, 1H), 3.64 (t, 2H, J = 6.8 Hz), 3.74 (dt, 1H, J = 6.4 Hz, J = 9.2 Hz), 3.84-3.90 (m, 1H), 4.56-4.58 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 20.0, 25.8, 25.9, 26.4, 30.0, 31.1, 33.0, 62.6, 62.9, 67.8, 99.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{22}O_3$	C 65.31	C 65.43
202.29	H 10.96	H 10.92

1-Tetrahydropyranyloxy-3-chloro-2-propanol (153):



Nature: Colorless liquid

Yield: 76%

Reaction time: 18 min

IR (Neat): cm^{-1} 3416, 2940, 2873, 1445, 1393, 1265, 1204, 1132, 1081, 1035, 979

^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ 1.52-1.83 (m, 6H), 3.27-3.37 (bs, 1H, D_2O exchangeable), 3.51-3.99 (m, 7H), 4.51-4.53 (m, 0.5H), 4.57-4.59 (m, 0.5H) ppm.

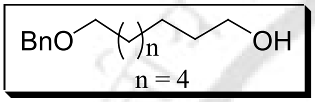
^{13}C NMR (100 MHz, CDCl$_3$): δ 20.3, 20.6, 25.5, 25.6, 31.0, 31.1, 45.8, 46.2, 63.5, 64.0, 70.1, 70.5, 70.8 (2 C), 100.4, 100.9 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{15}O_3Cl$	C 49.36	C 49.52
194.66	H 7.77	H 7.84

Typical procedure for Depyranylation:

Bismuth(III) nitrate pentahydrate (0.024 g, 0.05 mmol) was added into a stirred solution of THP ether of 8-Benzyloxy-1-octanol (0.320 g, 1 mmol) in methanol (2 mL) at room temperature. The reaction was complete within 40 min and the mixture was concentrated in rotavapor. The crude residue was purified through a short silica gel column. The desired 8-Benzyloxy-1-octanol was obtained (0.194 g) in 82% yield.

8-Benzyloxy-1-octanol (126):



Nature: Colorless liquid

Yield: 82%

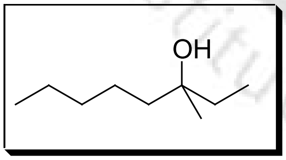
Reaction time: 45 min

IR (Neat): cm^{-1} 3334, 2928, 2857, 1598, 1458, 1127, 1038

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.32-1.37 (m, 8H), 1.55-1.63 (m, 5H), 3.46 (t, 2H, *J* = 6.8 Hz), 3.62 (t, 2H, *J* = 6.8 Hz), 4.50 (s, 2H), 7.25- 7.37 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{24}O_2$	C 76.23	C 76.42
236.35	H 10.24	H 10.29

3-Methyl-3-octanol (122):



Nature: Light yellow liquid

Yield: 61%

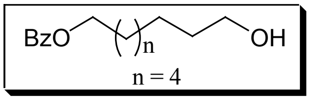
Reaction time: 30 min.

IR (Neat): cm^{-1} 3412, 2947, 1462, 1275, 1078

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, 3H, *J* = 7.2 Hz), 0.90 (t, 3H, *J* = 7.2 Hz), 1.14 (s, 3H), 1.28-1.35 (m, 7H), 1.41-1.44 (m, 2H), 1.48 (q, 2H, *J* = 7.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{20}O$	C 74.93	C 74.71
144.26	H 13.97	H 13.91

8-Benzoyloxy-1-octanol (127):



Nature: Gummy liquid

Yield: 81%

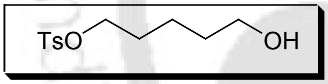
Reaction time: 40 min

IR (Neat): cm^{-1} 3396, 2930, 2857, 1719, 1453, 1276, 1114, 1069

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.35-1.45 (m, 7H), 1.61-1.04 (m, 4H), 1.77 (quin, 2H, *J* = 6.8 Hz), 3.62 (t, 2H, *J* = 7.2 Hz), 4.32 (t, 2H, *J* = 6.8 Hz), 7.44 (t, 2H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 8.0 Hz), 8.04 (d, 2H, *J* = 7.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{22}O_3$	C 71.97	C 71.61
250.34	H 8.86	H 8.79

5-Tosyloxy-1-octanol (128):



Nature: Gummy liquid

Yield: 85%

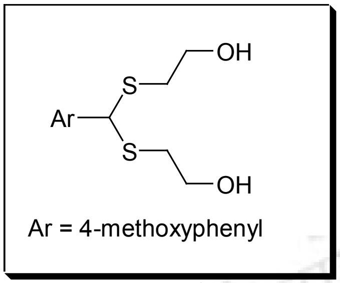
Reaction time: 35 min

IR (Neat): cm^{-1} 3401, 1598, 1475, 1373, 1189, 1071, 963

^{1}H 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 (bs, 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) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}O_4S$	C 55.79	C 55.98
258.33	H 7.02	H 7.13
	S 12.41	S 12.62

Spectroscopic data for compound 131:



Nature: Colorless liquid

Yield: 81%

Reaction time: 18 min

IR (Neat): cm^{-1} 3334, 2914, 2848, 2745, 1609, 1516, 1455, 1255, 1173, 1076, 1020

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.58-2.90 (m, 6H), 3.71 (m, 4H), 3.80 (s, 3H), 5.06 (s, 1H), 6.87 (d, 2H, J = 8.6 Hz), 7.38 (d, 2H, J = 8.6 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 36.1, 33.2, 55.9, 99.5, 114.7, 129.5, 132.0, 160.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}O_3S_2$	C 52.53	C 52.69
274.40	H 6.61	H 6.65
	S 23.37	S 23.40

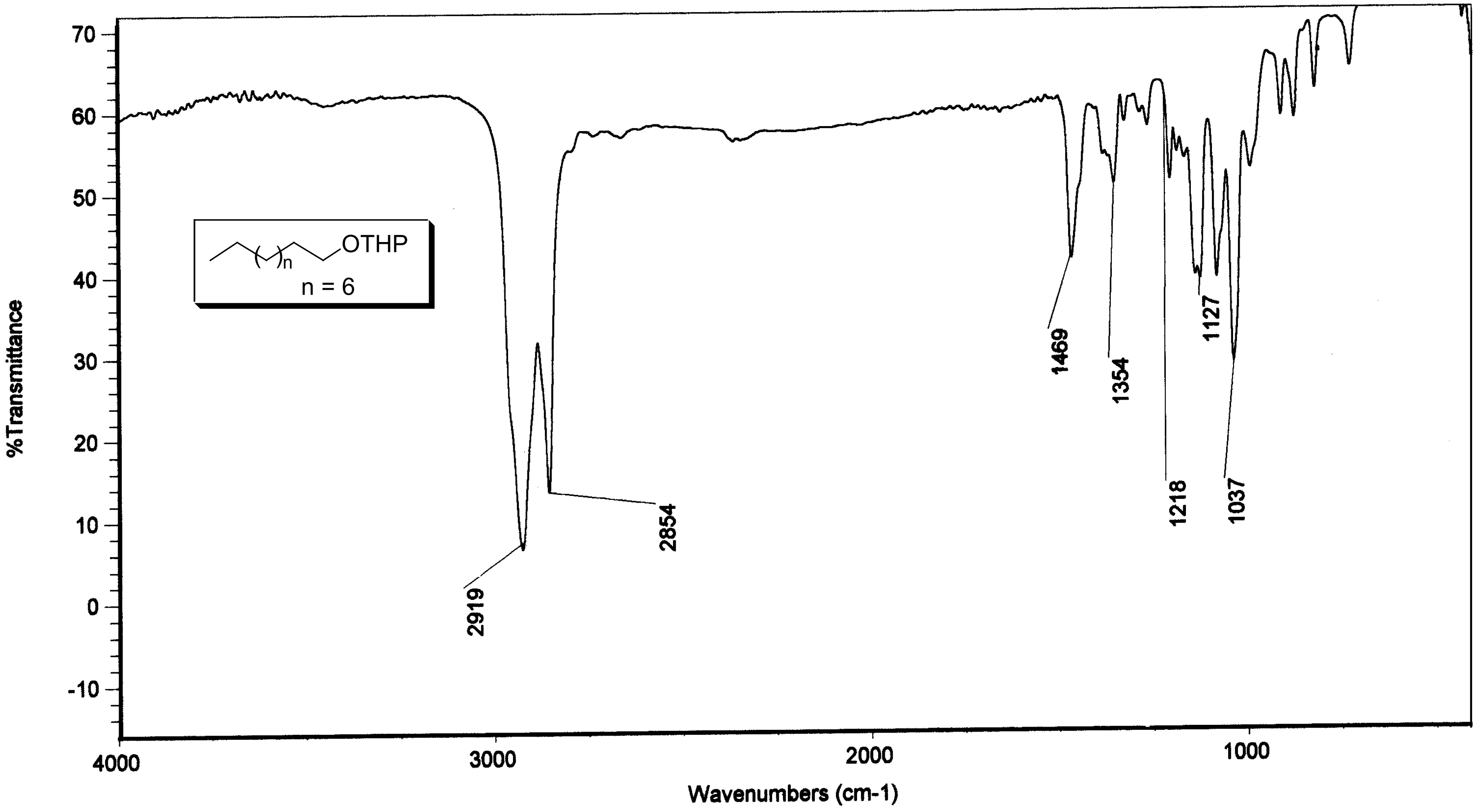


Figure 1: IR spectrum of THP ether of 1-decanol (75)

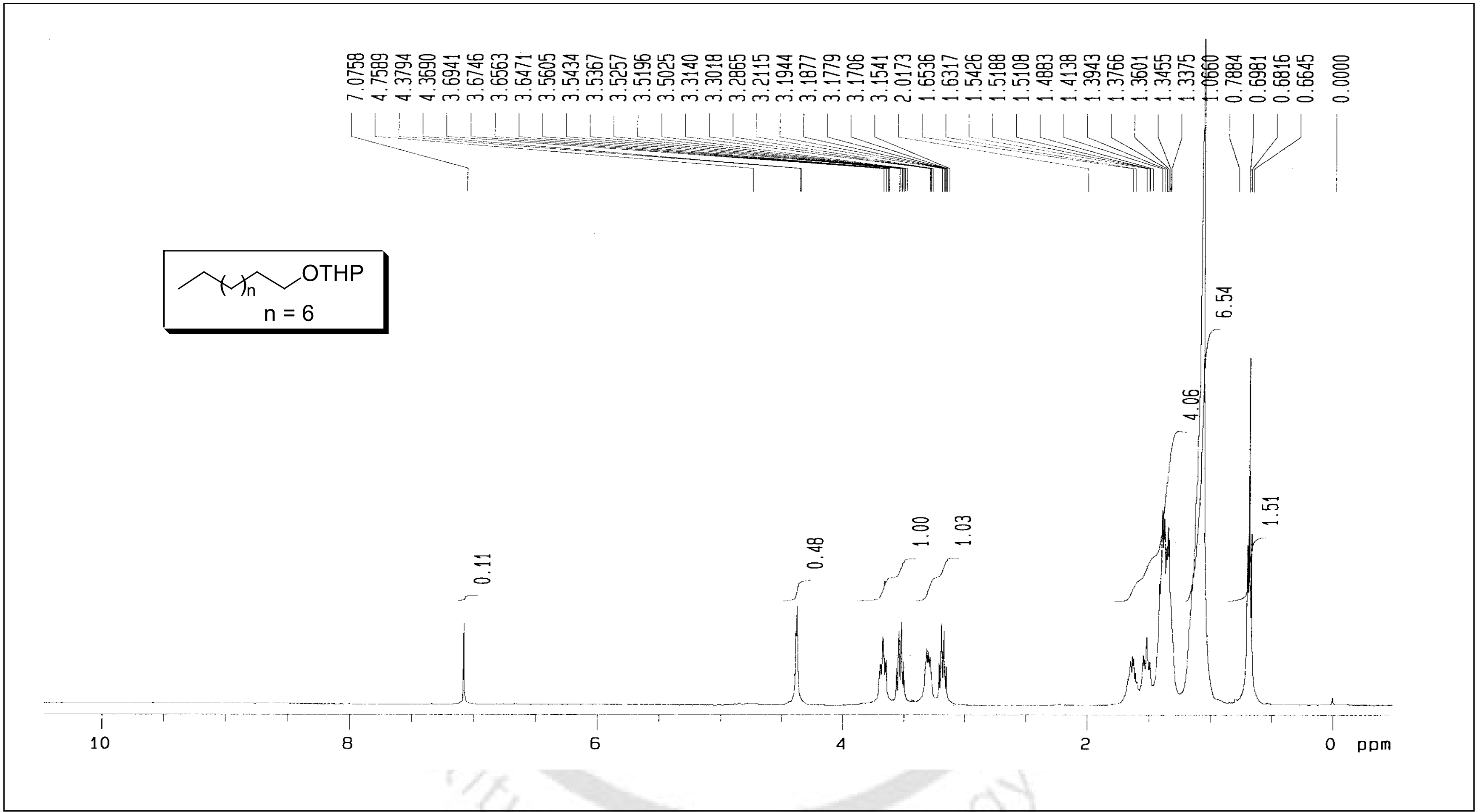


Figure 2: ^{1}H NMR spectrum of THP ether of 1-decanol (75)

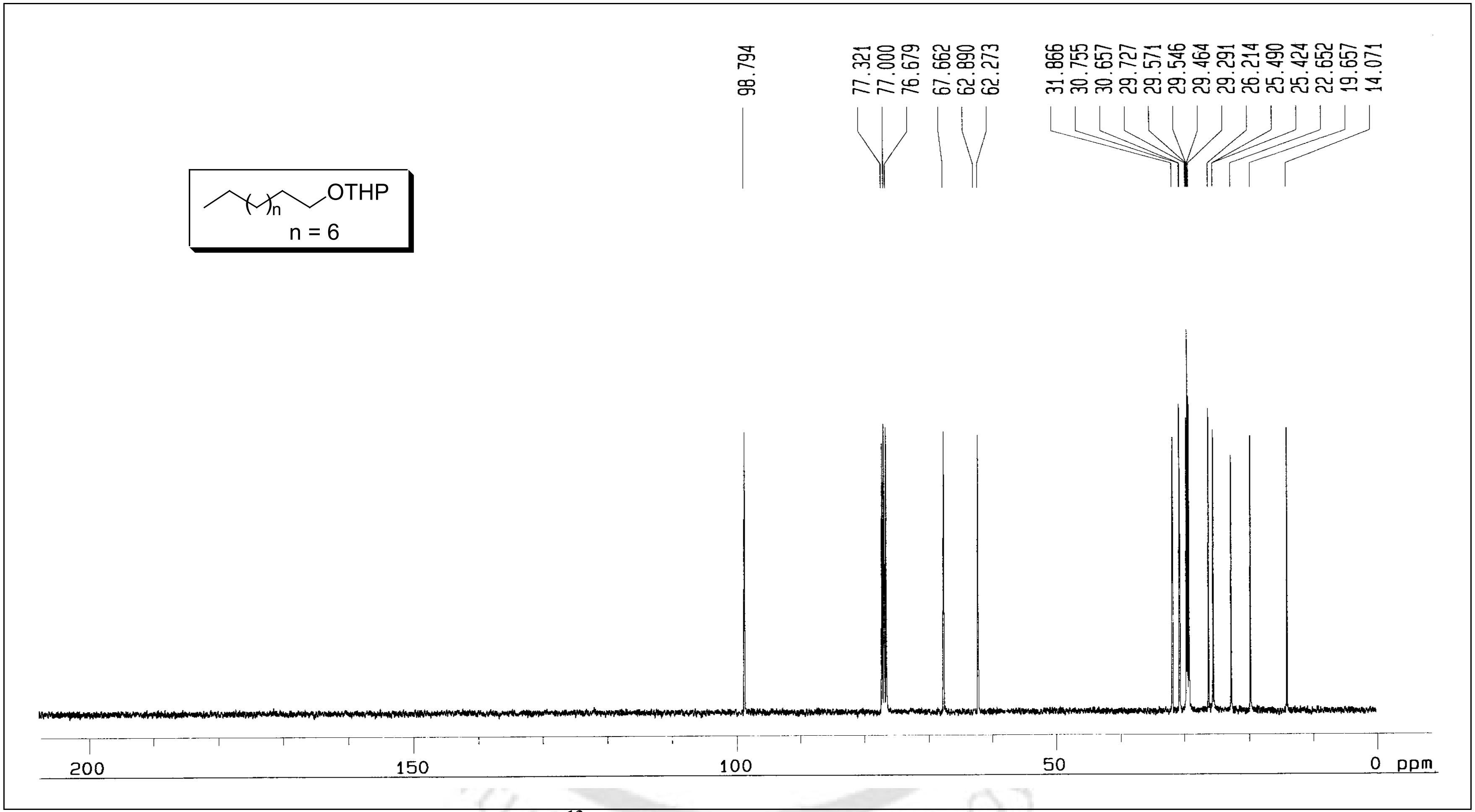


Figure 3: ^{13}C NMR of THP ether of 1-decanol (75)

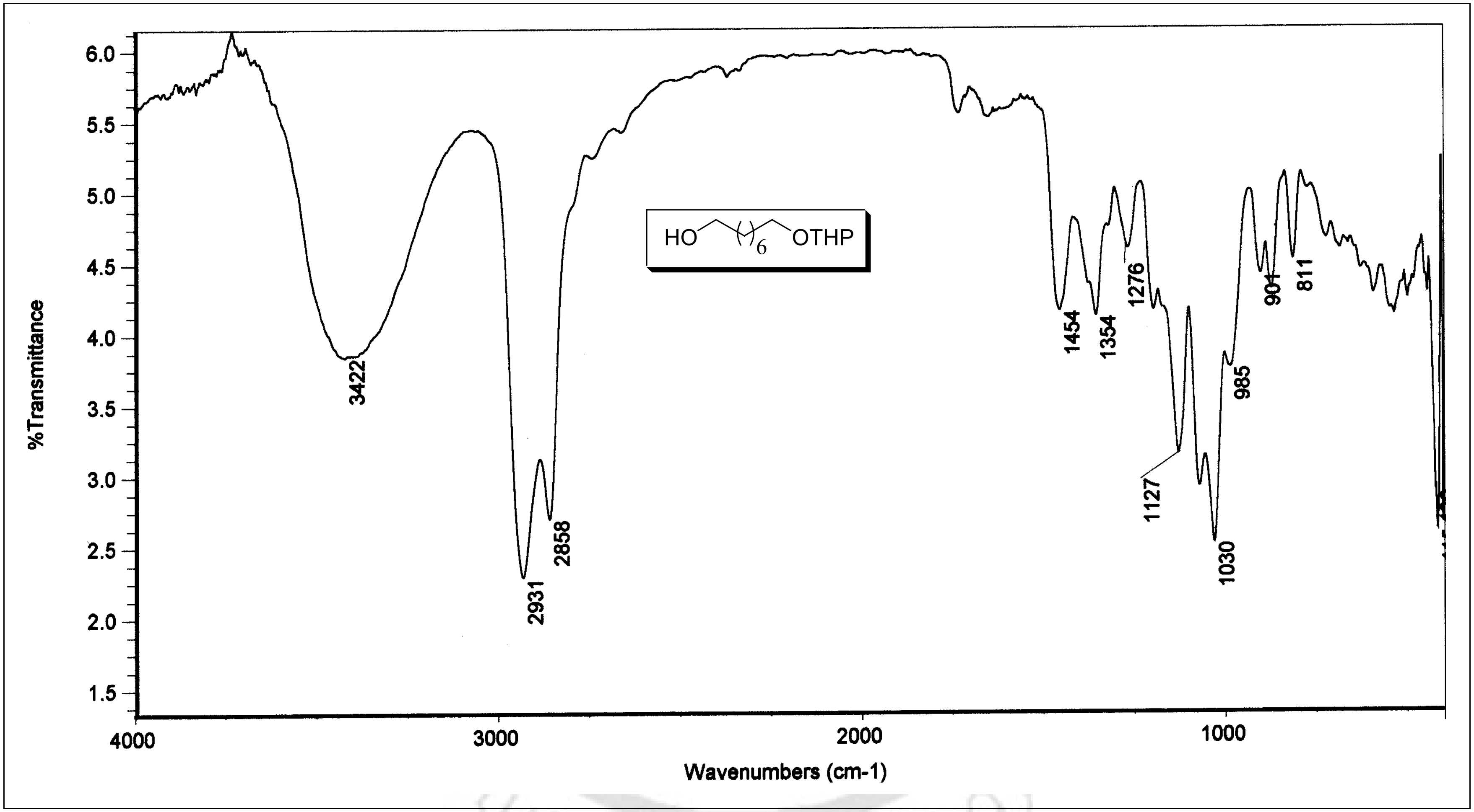


Figure 4: IR spectrum of mono THP ether of 1,8-octanediol (115)

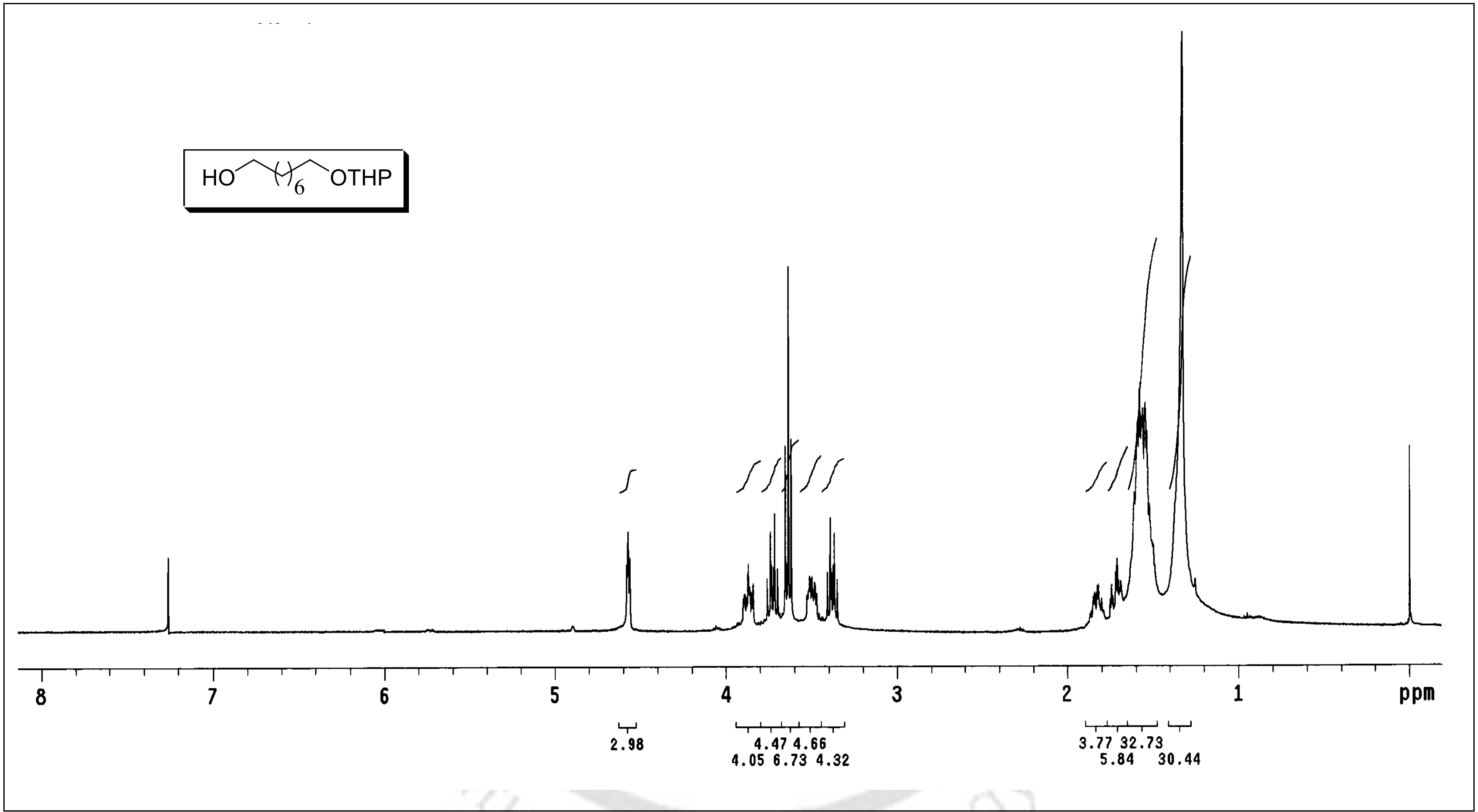


Figure 5: ^{1}H NMR spectrum of mono THP ether of 1,8-octanediol (115)

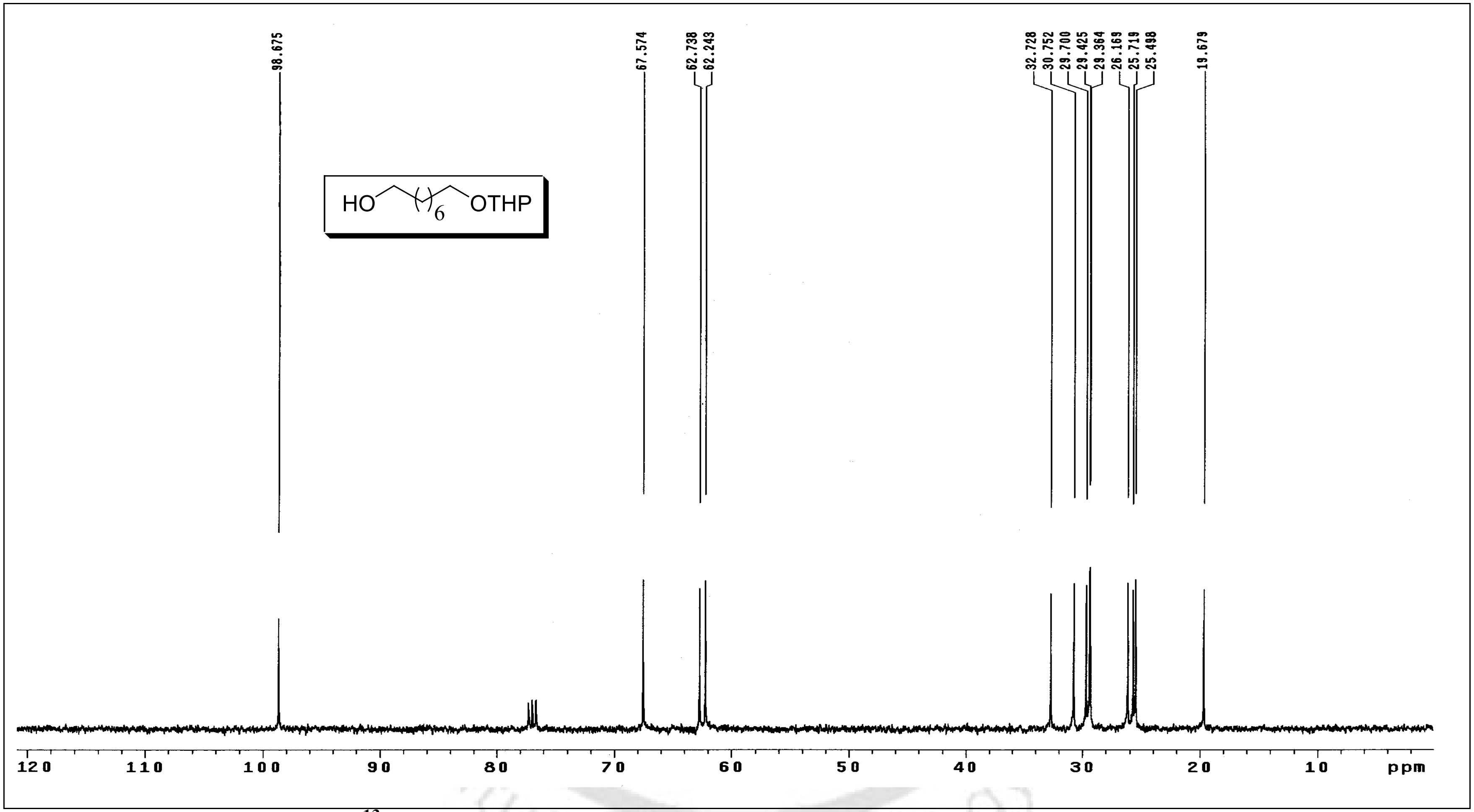


Figure 6: ^{13}C NMR spectrum of THP ether of mono THP ether of 1,8-octanediol (115)

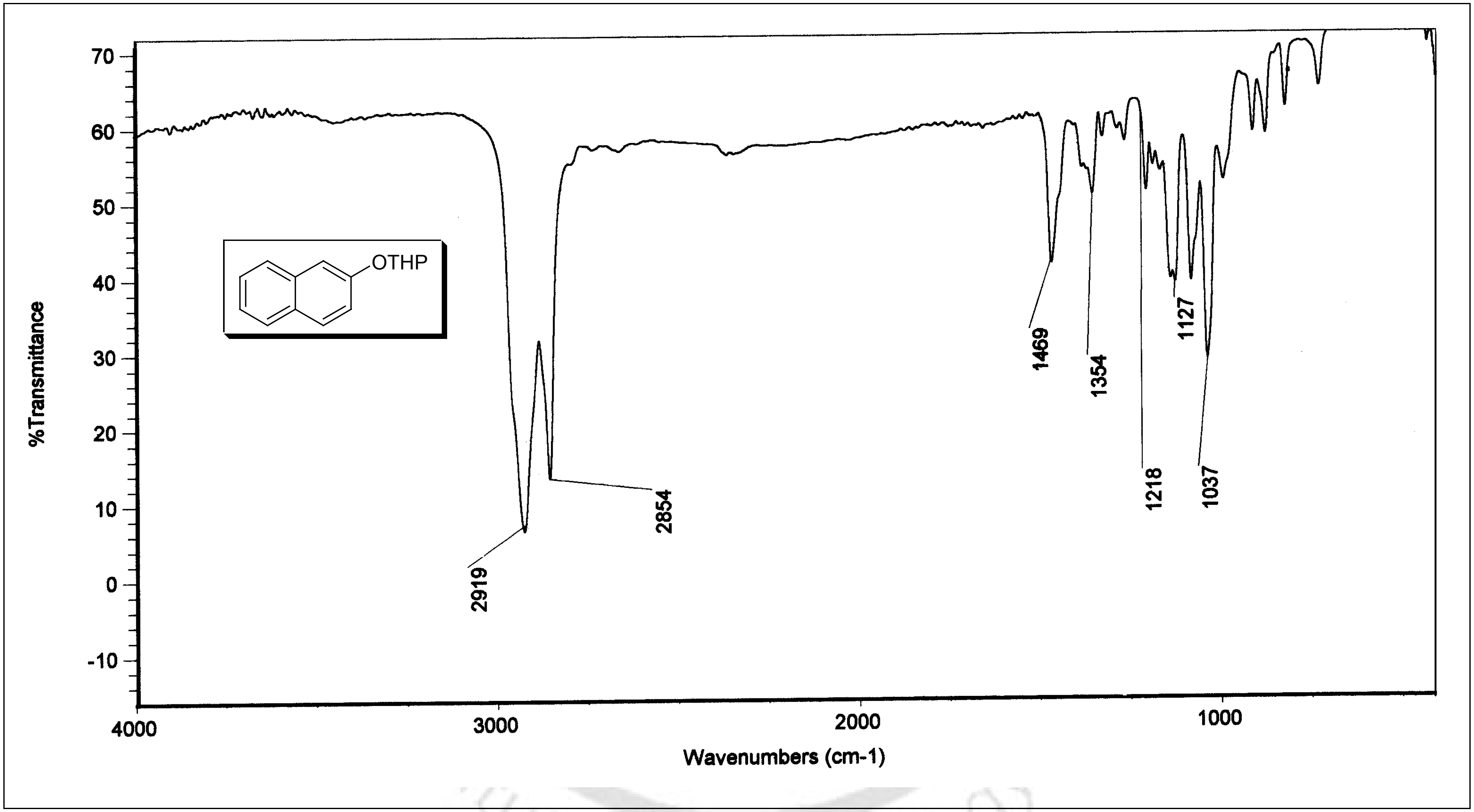


Figure 7: IR spectrum of THP ether of β-naphthol (139)

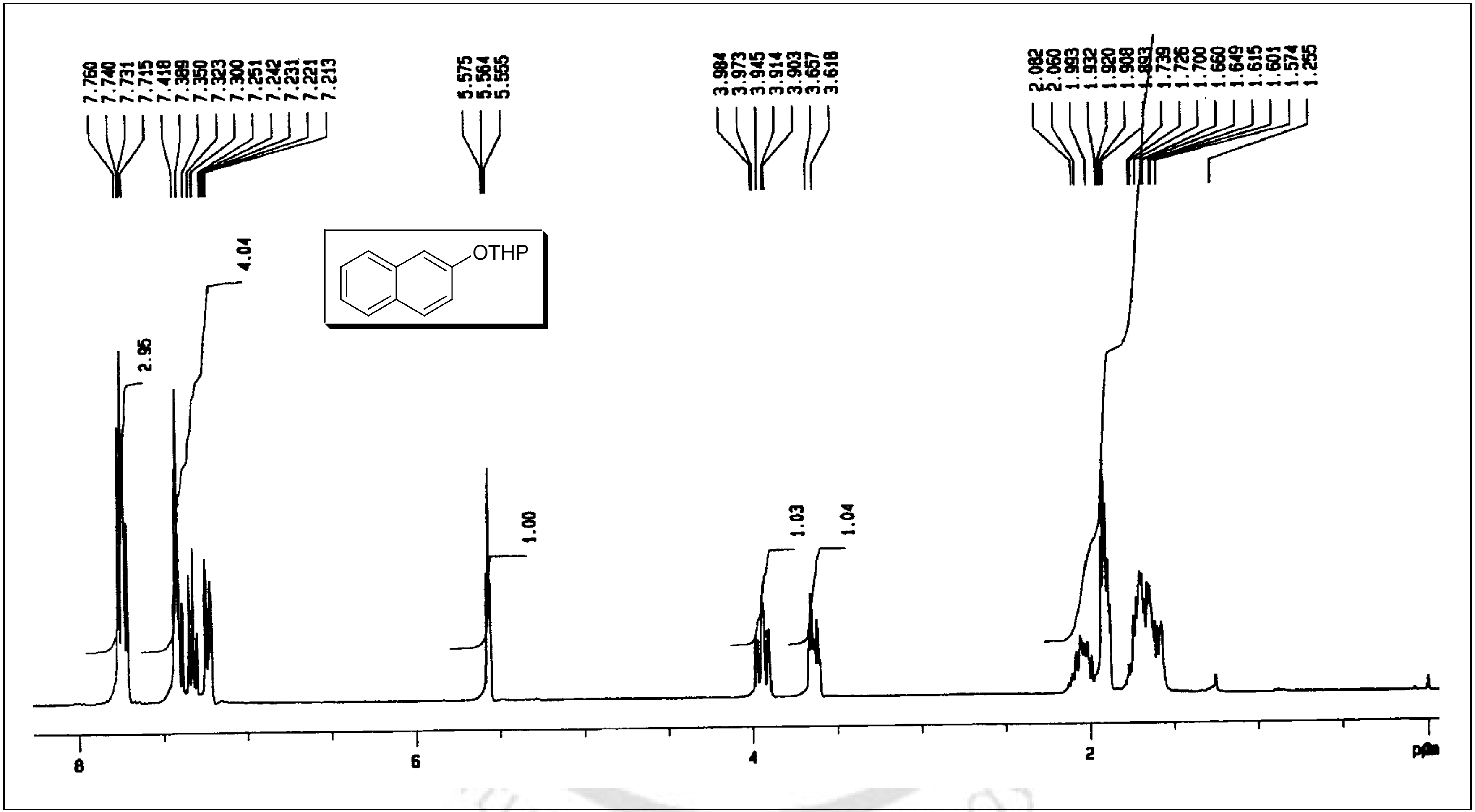


Figure 8: ^{1}H NMR spectrum of THP ether of β-naphthol (139)

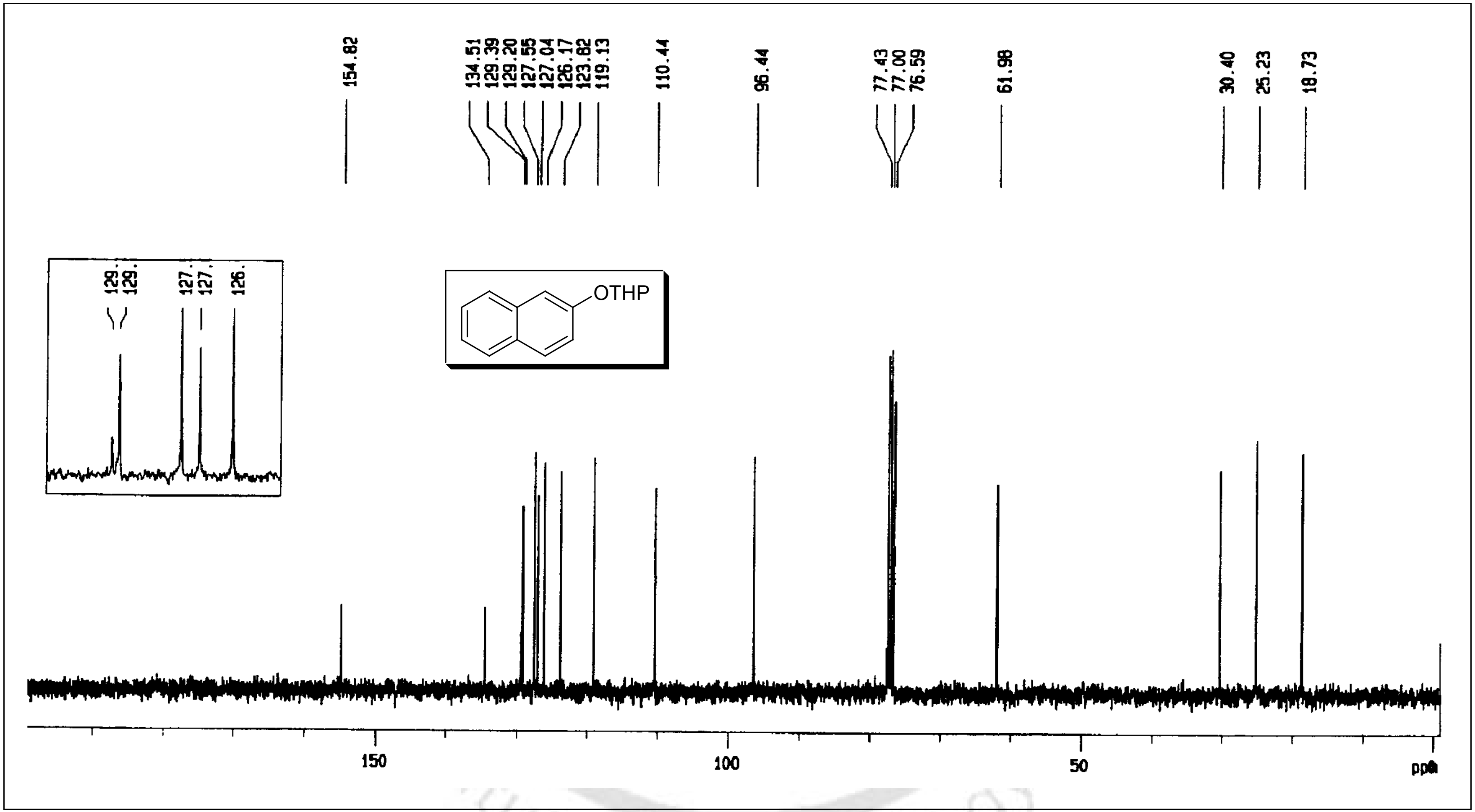


Figure 9: ^{13}C NMR spectrum of THP ether of β-naphthol (139)

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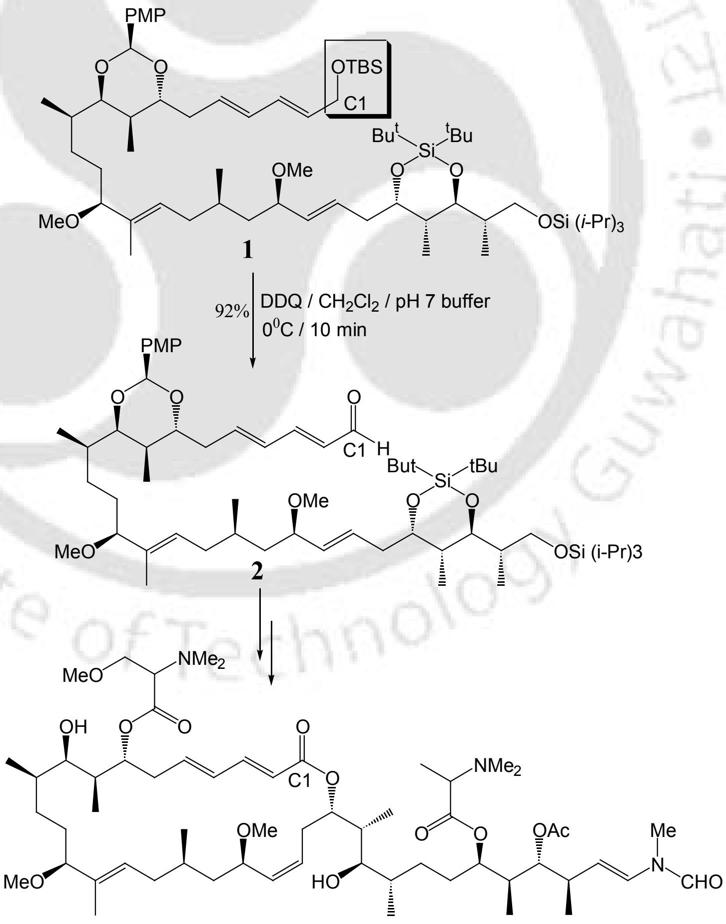
A BRIEF REVIEW ON DIRECT OXIDATION OF TETRAHYDROPYRANYL- AND *TERT*-BUTYLDIMETHYLSILYL ETHERS TO THE CORRESPONDING CARBONYL COMPOUNDS AND BENZYLIC C-H OXIDATIONS

LITERATURE SURVEY

Introduction

Carbonyl compounds are valuable building blocks in fine chemical industries having a wide variety of applications from drugs to fragrances. The carbonyl compounds can be easily obtained from the oxidation of alcohols and ethers. Sometimes alcohols are protected as tetrahydropyranyl (THP)- or *tert*-butyldimethylsilyl (TBS) ethers for manipulation of other functional groups. In case these ethers have to be converted to the corresponding carbonyl compounds then it can be achieved without deprotection followed by oxidation. Eventually, by this process we can minimize the over all steps. The conversion of the THP- and TBS ethers into the corresponding carbonyl compounds can be carried out by either a direct method or in two-step procedures, deprotection followed by oxidation of free alcohol. The use of a direct method to establish such a transformation increases the overall efficiency of the method.



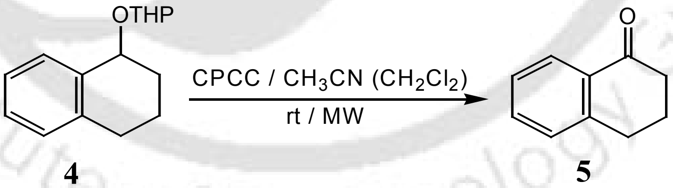
Aplyronine A

Scheme 1 3

During the synthesis of aplyronine A (**3**), a 24-membered cytotoxic macrolide, Paterson *et al* have demonstrated[1] silyl ethers as the protecting group for four hydroxyl groups of the intermediate **1**. To accomplish the target molecule, the C_1 TBS ether was converted directly into the corresponding aldehyde using DDQ instead of deprotection followed by oxidation strategy. They noted unsatisfactory yields when two steps sequences implemented as shown in Scheme 1.

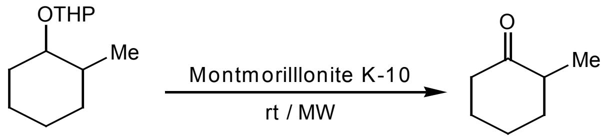
Therefore, sometimes it is necessary to perform the direct transformation of the TBS or THP ethers to the corresponding carbonyl compounds to avoid some side reactions in multi-step synthesis for multifunctional compounds. Many catalysts have been reported in the literature for the cleavage of THP and TBS ethers,[2] but much work has not been done on the direct synthesis of the carbonyl compounds from the corresponding THP- and TBS ethers in the literature. Some of the methods for the direct oxidation of THP ethers have been highlighted below:

Mohammadpoor-Baltork *et al* used[3] 3-carboxypyridinium chlorochromate (CPCC) for the oxidative transformation of the THP ethers into the corresponding carbonyl compounds as shown in Scheme 2. Though the method is efficient in terms of yields, still it suffers from a drawback such as requirement of excess amount of toxic chromium reagent.



Scheme 2

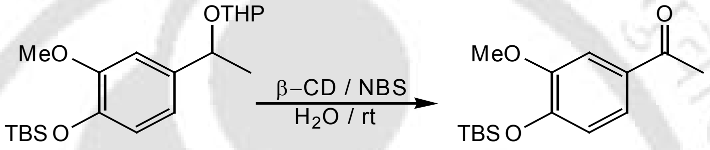
Heravi *et al* introduced[4] a new method for convenient oxidative deprotection of THP ethers using Fe(III) nitrate and clay under microwave irradiation in solvent-free conditions, shown in Scheme 3. The main drawback of this method is that it requires microwave irradiation, which is inconvenient for large-scale reaction.



6 **7**

Scheme 3

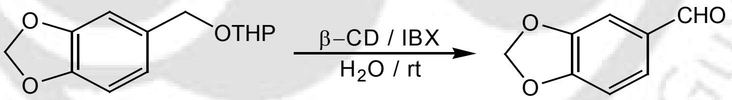
Later on, Rao *et al* have shown[5] a mild and efficient method for oxidative deprotection of THP ethers using NBS as a reagent in presence of β-cyclodextrin in water as represented in Scheme 4. This method suffers from the drawback that it requires stoichiometric amount of reagent.



8 **9**

Scheme 4

Very recently, the same group reported[6] another method for the oxidative deprotection of THP ethers using IBX as a reagent in presence of β-cyclodextrin in water, shown in Scheme 5. However, it also needs stoichiometric amount of reagent.



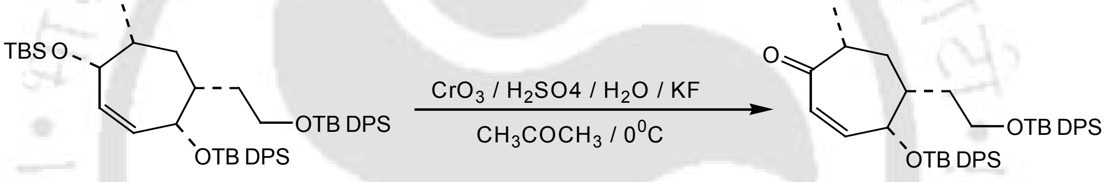
10 **11**

Scheme 5

Over the years, some more methods have also been developed for oxidative deprotection of THP ethers to the corresponding carbonyl compounds using other reagents such as PCC,[7] (n-BuPPh$_3$)$_2$S$_2$O$_8$,[8] AgBrO$_3$ and NaBrO$_3$ in presence of AlCl$_3$,[9] tetramethylammonium chlorochromate,[10] etc. Unfortunately, some of the methods have one or other limitations such as involvement of anhydrous organic solvents, longer reaction times, lower yields, use of expensive reagent and toxic Cr(VI) reagents. From this literature background, it is quite clear that still there is a scope to develop an efficient, mild and economically viable methodology for oxidative transformation of THP ethers to the corresponding carbonyl compounds.

On the other hand, the method for the oxidative deprotection of TBS ethers is rather poorly addressed in the literature as compared to the THP ethers. Some of them have been addressed below.

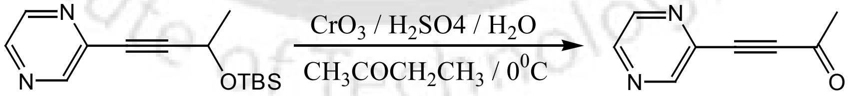
During the synthesis of tylosin subunit (**13**), Pearson *et al* demonstrated[11] the chemoselective oxidative transformation of TBS ethers in presence of TBDPS ethers using a combination of Jones reagent and KF, as shown in Scheme 6. This fact also measures directly the importance of the oxdative deprotection process in organic synthesis.



12 **13**

Scheme 6

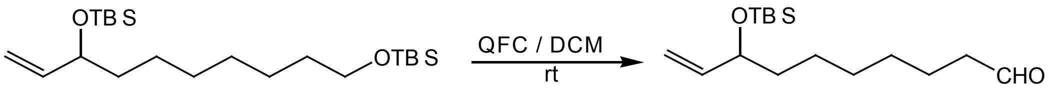
Taylor *et al* have shown[12] that Jones reagent can be used for the oxidative transformation of the TBS ethers to the corresponding carbonyl compounds, which has been shown in Scheme 7. The main disadvantage of this method is low yields.



14 **15**

Scheme 7

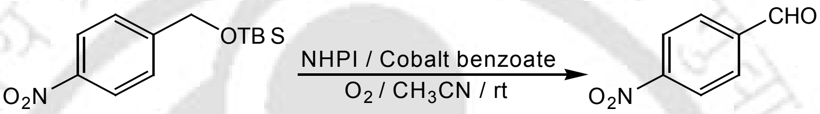
Chandrasekhar *et al* introduced[13] a method for regioselective oxidative deprotection of 1°-TBS ether in presence of a 2°-TBS ether using quinolinium fluorochromate (QFC) as depicted in Scheme 8. However, it requires excess amount of toxic reagent and longer reaction times although the method provides better selectivity.



16 **17**

Scheme 8

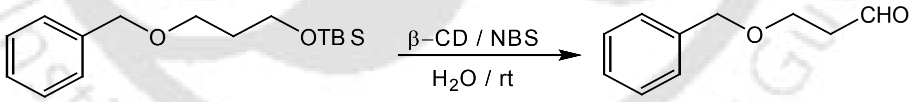
In recent past, Karimi *et al* demonstrated[14] a method for aerobic oxidation of silyl ethers to carbonyl compounds catalyzed with *N*-hydroxyphthalimide (NHPI) and lipophilic Co(II) complexes, shown in Scheme 9. The method is efficient in terms of yield and reaction time.



18 **19**

Scheme 9

Very recently, Rao *et al* reported[15] that β-cyclodextrin could be utilized further as a catalyst for oxidative deprotection of TBS ethers in presence of stoichiometric amount of NBS in water as represented in Scheme 10. The main advantage of this method is that the TBS ethers of aliphatic alcohols give the corresponding aldehydes rather than giving esters. But, the major drawback of this method is the requirement of longer reaction time.

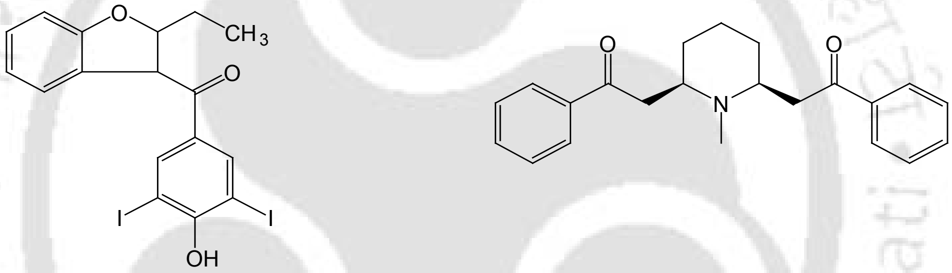


20 **21**

Scheme 10

Over the years, a few more methods have also been developed for oxidative deprotection of TBS ethers into the corresponding carbonyl compounds using other reagents such as $PdCl_2(CH_3CN)_2$,[16] $AlCl_3$ and MnO_2,[17] zinc chlorochromate nonahydrate,[18] $KMnO_4$ and $BaMnO_4$,[19a], solid silica chloride/$KMnO_4$[19b] etc. However, most of the methods suffer from severe drawbacks such as use of anhydrous organic solvents, longer reaction times, lower yields, use of expensive reagent and use of toxic Cr(VI) reagents. Therefore, there is a further scope for development of new protocol, which requires less polluting and inexpensive reagent for oxidative deprotection of TBS ethers into the corresponding carbonyl compounds.

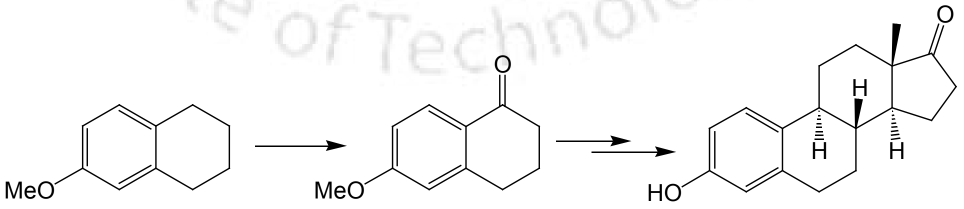
The oxidation of activated benzylic C-H bonds of alkyl- and cycloalkyl arenes as well as oxidation of alcohols is one of the most useful and fundamental organic transformations due to their wide applications as industrial intermediates for the manufacture of specialty chemicals in pharmaceuticals or agrochemicals.[20] It is also found in the literature that the carbonyl functionality particularly located at the benzylic position is an integral component of many natural and non-natural products. For example, benziodarone (**22**), a highly potent molecule having carbonyl moiety in the benzylic position, is used as a drug in cardiac diseases.[21] Similarly, lobelanine (**23**), a naturally occurring alkaloid, is widely used as drug for treatment of narcotic poisoning as well as respiratory illnesses.[22]



22 **23**

Scheme 11

In addition, oxidized product of 6-methoxy-1,2,3,4-tetrahydronaphthalene i.e, 6-methoxy-1-tetralone[23] (**25**) has been used as a key starting material for the synthesis of (±)-oestrone (**26**) as shown in Scheme 12.

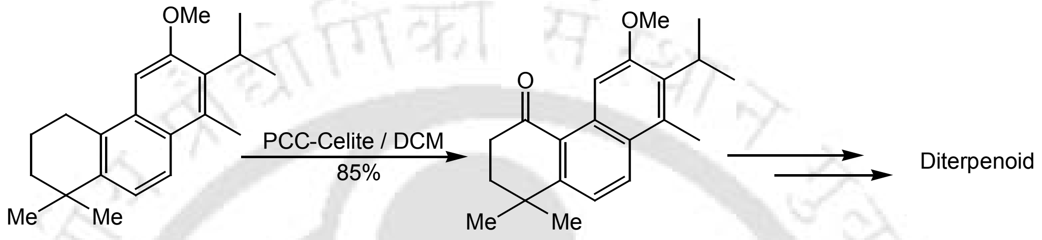


24 **25** **26**

Scheme 12.

Sometimes benzylic C-H oxidation has been used extensively during the synthesis of many natural and non-natural products.

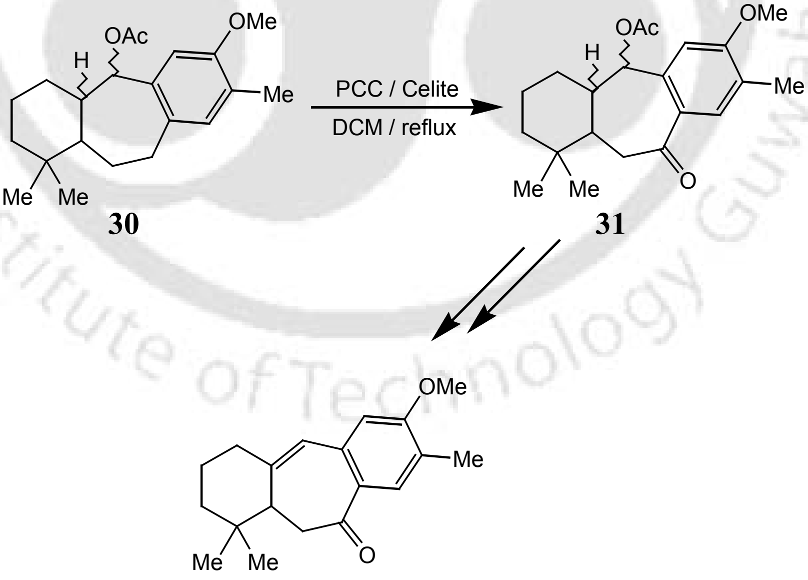
Ghatak *et al* prepared[24] the key intermediate **28**, which finds application in the total synthesis of diterpenoids, by performing benzylic C-H oxidation, which is presented in Scheme 13.



27 **28** **29**

Scheme 13

The same research group showed[25] another application of benzylic C-H oxidation during the synthesis of (±) faveline methyl ether (**32**), which is depicted in Scheme 14.

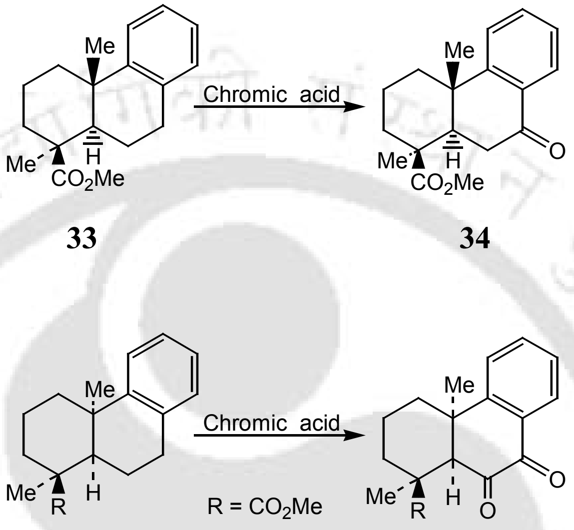


30 **31**

32

Scheme 14

Further, they have reported[26] another excellent observation on benzylic oxidation. In case of the following tricyclic compound, the *trans* racemate (**33**) gave monoketone (**34**) while carrying out the benzylic C-H oxidation, whereas the *cis* racemate (**35**) gave diketone (**36**), shown in Scheme 15.



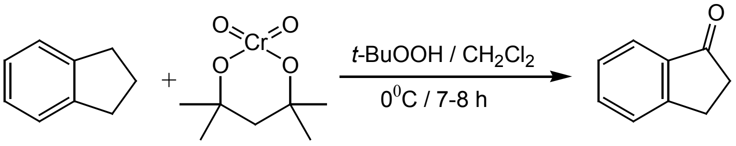
33 **34**

35 **36**

Scheme 15

All these wide applications prompted us to choose a research problem on development of a new method for benzylic C-H oxidation. Literature survey suggested that the following are methods available for the above oxidation. Most commonly, benzylic C-H oxidations of alkyl benzenes are performed by involving environmentally hazardous metal promoted oxidations mainly based on chromium(VI) reagents using either stoichiometric or excess quantities.[27] Over the years, only a few new methods are known in the literature for similar type of oxidation.

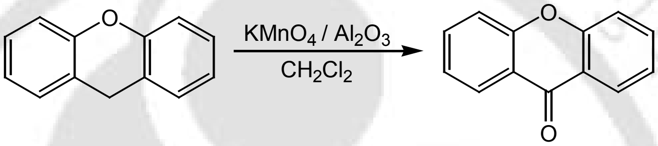
Muzart used Cr(VI) complex[28] as a catalyst for benzylic oxidation in presence of *tert*-butyl hydroperoxide, shown in Scheme 16. The method provides good yields. But the utility of Cr(VI) reagents is compromised due to their inherent toxicity and the cumbersome preparation as well as the potential danger of handling its complexes.



37 **38** **39**

Scheme 16

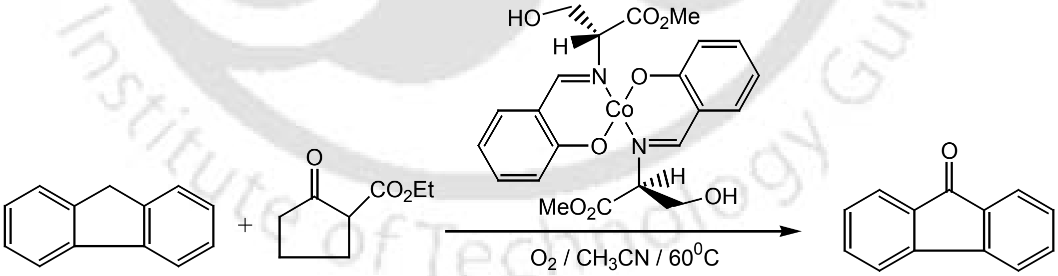
Lee *et al* introduced[29] a method for benzylic C-H oxidation using alumina supported $KMnO_4$ in dichloromethane, which is presented in Scheme 17. The method is efficient in terms of yield but it suffers from two drawbacks such as longer reaction times and use of excess reagent.



40 **41**

Scheme 17

Iqbal and his co-workers reported[30] molecular oxygen along with 2-oxocyclopentane-carboxylate and Co(II) complex for benzylic oxidation as shown in Scheme 18. The method suffers from several drawbacks such as requirement of expensive reagents, harsh reaction conditions and low yields.

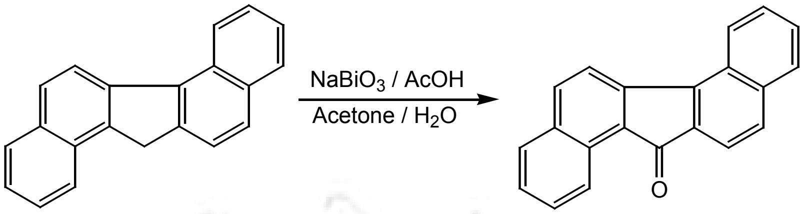


42 **43** **44**

Scheme 18

During the past few years the use of bismuth based reagents in several processes has gained popularity.[31] Indeed, despite being heavy metal, bismuth has low toxicity. Banik *et al* reported[32] the use of sodium bismuthate for benzylic oxidation as depicted in Scheme

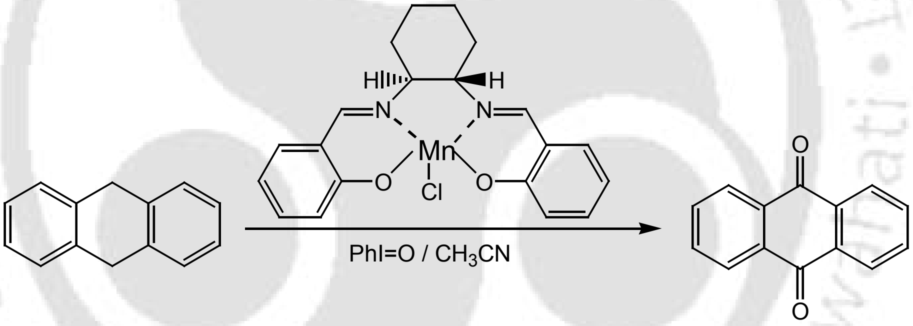
19. The major disadvantages of this process are the poor solubility of $NaBiO_3$, necessitating the use of a large excess of the salt and prolonged reaction times.



45 **46**

Scheme 19

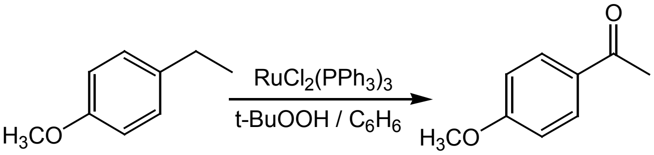
(Salen)Mn(III) complexes have been utilized enormously in organic synthesis. Lee *et al* utilized (salen)Mn(III) complex[33] for the synthesis of carbonyl compounds from hydrocarbons as represented in Scheme 20. The method suffers from the drawback that it provides low yields.



47 **48**

Scheme 20

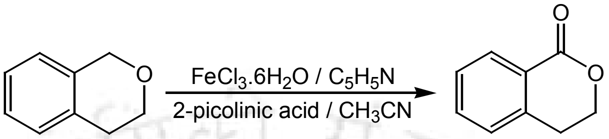
Murahashi *et al* demonstrated[34] a combination of $RuCl_2(PPh_3)_3$–*t*-BuOOH for benzylic oxidation, as shown in Scheme 21. Although the method efficiently oxidizes a series of alkyl or cycloalkyl arenes, still it includes the use of expensive reagent and requires dry solvent.



49 **50**

Scheme 21

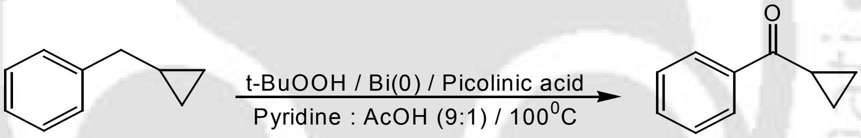
In recent past, Kim *et al* exploited[35] Gif reagent, represented by Fe(III)/*t*-BuOOH, for benzylic oxidation, which is shown in Scheme 22. This method is efficient in terms of reaction times as well as yields. But it requires many other co-catalysts, which is one of the disadvantages.



51 **52**

Scheme 22

Very recently Barrett *et al* have shown[36] that *in situ* generated Bi(0) can be used as an efficient catalyst for benzylic oxidation as depicted in Scheme 23. Though the method is highly efficient in terms of yields, still it suffers from some drawbacks such as extremely harsh reaction conditions, which is to be carried out in a sealed tube and requires many other co-catalysts.



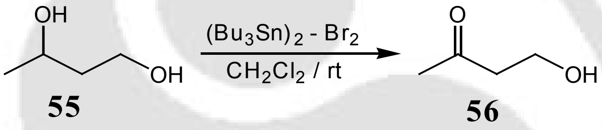
53 **54**

Scheme 23

Over the years, some more methods have also been developed for benzylic C-H oxidation using other reagents namely Mo(VI)-peroxo complex/H_2O_2,[37] tetrapyridinesilver peroxydisulfate,[38] PCC,[39] CrO_3,[40] etc.

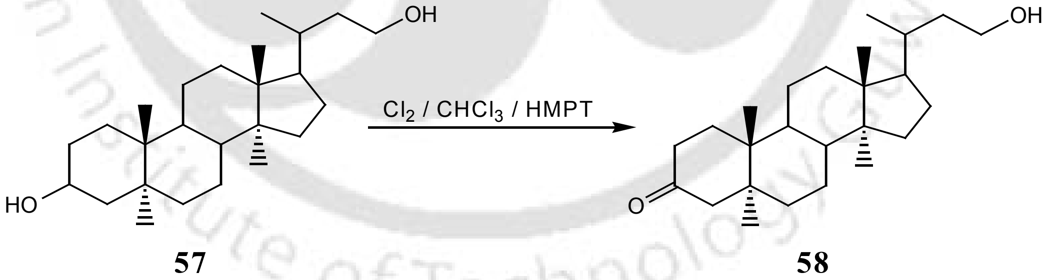
Similarly, a large number of methods and reagents are reported in the literature for the oxidation of alcohols to the carbonyl compounds,[20,41] still there is a need to find out better alternatives, which might work even under milder conditions. Recently some new synthetic methods have also been devised for the oxidation of alcohols to carbonyl compounds by employing the following reagents: polyoxometalate ion,[42] amphiphilic resin-dispersion of a nanopalladium,[43] oxodiperoxovanadate ion,[44] and vanadium pentoxide along with molecular oxygen.[45] In the synthesis of multifunctional natural and non-natural products, it is necessary to oxidize selectively one of the hydroxyl group in presence of other hydroxyl group present in the same molecule. Thus, selective transformation of hydroxyl group is a challenging target for synthetic chemists since it offers an alternative to synthesis *via* protection and deprotection. Only a few methods are known for the chemoselective oxidation of secondary hydroxyl groups in the presence of a primary hydroxyl group. Some of them have been highlighted below:

Ueno *et al* reported[46] that a combination of $(Bu_3Sn)_2O$ and Br_2 can be used for the selective oxidation of alcohols as shown in Scheme 24. The method suffers from several drawbacks such as longer reaction times, use of expensive reagent and use of excess amount of molecular bromine. Moreover, molecular bromine is difficult to handle and hazardous.



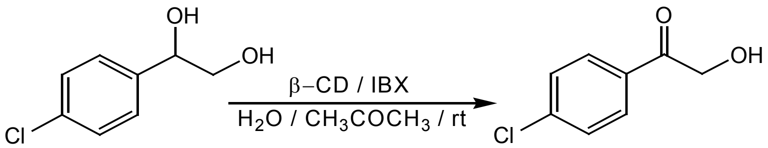
Scheme 24

Later on, Neirabeyeh *et al* introduced[47] two halogen based combinations, Cl_2-$CHCl_3$-HMPT or Br_2-$CHCl_2$-HMPT, for the selective oxidation of alcohols. This has been presented in Scheme 25. This method also requires excess amount of reagent.



Scheme 25

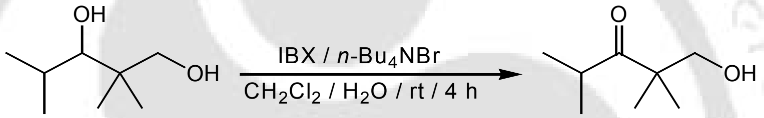
In recent past, Rao *et al* showed[48] the potentiality of *o*-iodoxybenzoic acid (IBX) as a selective oxidizing agent for alcohols in presence of β-cyclodextrin in water/acetone mixture, represented in Scheme 26. Though the method is highly efficient in terms of yield, still it suffers from the drawback such as longer reaction times.



59 **60**

Scheme 26

Very recently, Kuhakarn *et al* introduced[49] an efficient method for selective oxidation of secondary alcohols in presence of primary alcohols using a combination of IBX and tetrabutylammonium bromibe (*n*-Bu_4NBr) in CH_2Cl_2/H_2O biphasic system, which is shown in Scheme 27. The method shows an excellent chemoselectivity over a variety of substrates. However, it suffers from two major drawbacks such as longer reaction times and use of excess amount of reagent.



61 **62**

Scheme 27

Over the years, few more methods have been developed for selective oxidation of secondary alcohols in presence of primary alcohols such as Cl_2/pyridine,[50] $NOCl/CH_3CO_2H$,[51] $NaBrO_3/NaHSO_3$,[52] $Ce(SO_4)_2/NaBrO_3$[53] etc.

Nevertheless, all these procedures have one or the other drawbacks such as some of the reagents are highly toxic, quite expensive, require drastic reaction conditions and longer reaction time, difficulties in the work-up procedure and removal of the toxic by-products as well as metal residue from the final product, and provide low yields as well as mixtures of products. From this literature background on the usefulness of benzylic oxidation, our aim is to find out better synthetic methodologies for the oxidation of THP- and TBS ethers, benzylic oxidation and oxidation of alcohols, which will be transition metal-free, easy to handle, economically viable, and also work under mild reaction conditions.

SECTION A

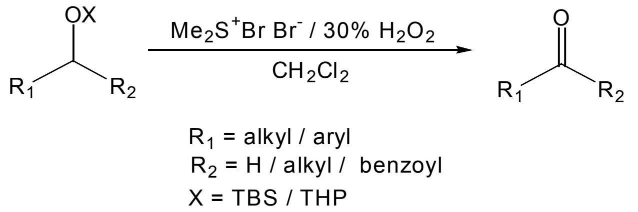
TRANSITION METAL-FREE OXIDATIVE DEPROTECTION OF THP- AND TBS ETHERS USING BROMODIMETHYLSULFONIUM BROMIDE AND HYDROGEN PEROXIDE

RESULTS AND DISCUSSION

Results and Discussion

After going through the literature, it is quite clear that the oxidative deprotection of THP and TBS ethers is an important transformation in organic synthesis. Over the years, many methods have been developed for oxidative deprotection of THP- and TBS ethers to the corresponding carbonyl compounds. Unfortunately, many of these procedures have one or other disadvantages such as longer reaction time, use of excessive and expensive catalyst, harsh reaction conditions etc. Therefore, development of an efficient and mild synthetic protocol is always in great demand to make the available procedures more convenient and attaractive. It was reported in the literature that molecular bromine and hydrogen peroxide is a good combination[54] for the regioselective bromination at the benzylic position as well as for the oxidation of alcohols. However, elemental bromine is associated with hazards because of its rapid vaporization. Besides, it is difficult to maintain the stoichiometric ratio during the reactions. Therefore, there has been much interest in developing some methods, which will not include the direct use of elemental bromine. On the other hand, BDMS can be considered as a convenient storage of molecular bromine molecule, less hazardous, easy to handle and to maintain stoichiometric ratio during the reactions. Very recently, Sain *et al* have demonstrated[55] that aqueous 48% hydrobromic acid along with hydrogen peroxide is also a good combination for the selective oxidation of secondary alcohols to ketones. From the above two observations as well as in continuation of our research programme to develop newer synthetic methodologies using bromodimethylsulfonium bromide (BDSB),[56] we conceived that BDMS along with hydrogen peroxide might be a useful combination for one pot conversion of THP- and TBS ethers to the corresponding carbonyl compounds. In Section A of the Chapter I, we have shown that BDMS is a versatile reagent in organic synthesis. In this Section, we wish to report that BDSB and H_2O_2 is a hitherto unreported combination for oxidative deprotection of THP and TBS ethers to the corresponding carbonyl compounds as depicted in Scheme 28.

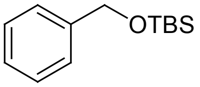
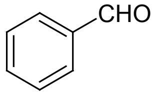
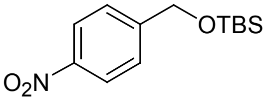
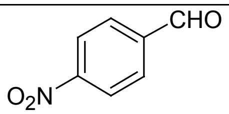
The preparation of the catalyst, bromodimethylsulfonium bromide (BDSB), is already mentioned in page 19.[57] As per our expectation, when a mixture 1 equivalent of TBS ether of benzyl alcohol (**63**) and BDSB (0.2 equiv.) was treated with 30% hydrogen per-

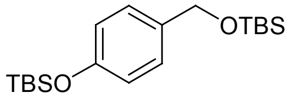
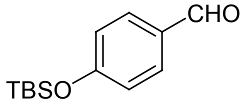
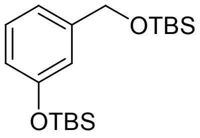
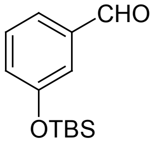
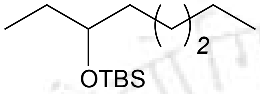
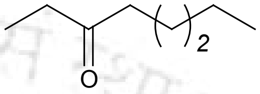
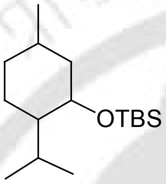
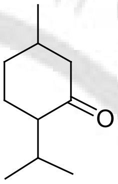
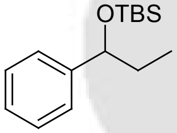
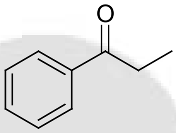
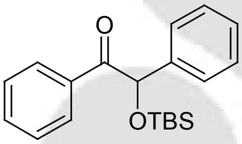
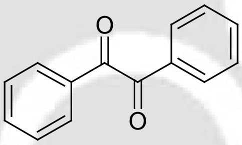
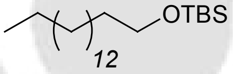
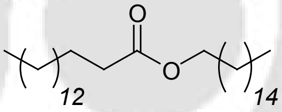


Scheme 28

oxide (2 equiv.) in dichloromethane (2 mL) at room temperature, it gave benzaldehyde (**71**) with 85% yield. The product was characterized by recording IR and ^{1}H NMR spectra and those spectra were also compared with the authentic spectra. Similarly, the TBS ether of 4-nitrobenzyl alcohol (**18**) was converted to 4-nitrobenzaldehyde (**19**) within 50 minutes in 90% yield by following the same procedure. Interestingly, we have also observed that the combination is highly chemoselective towards the oxidative deprotection of benzylic TBS ether in presence of phenolic TBS ether. When the di-TBS ethers of 4-hydroxybenzyl alcohol (**64**) as well as 3-hydroxybenzyl alcohol (**65**) were treated with the same combination, the corresponding benzaldehydes **72** and **73,** respectively, were obtained keeping the phenolic TBS ether intact. Likewise, various TBS ethers of secondary alcohols **66-68** were also converted smoothly to the corresponding carbonyl compounds **74-76**, respectively, by using our protocol. Moreover, a highly hindered TBS ether **69** can provide desired oxidized product **77** within a very short time. However, the TBS ethers of primary alcohol **70** afforded the ester **78** instead of expected aldehyde. The results are summarized in Table 1.

Table 1 Oxidation of various TBS ethers of alcohols by bromodimethylsulfonium bromide and hydrogen peroxide

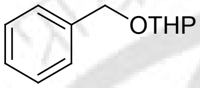
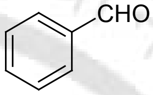
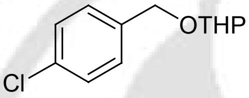
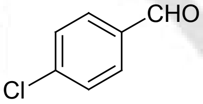
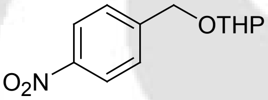
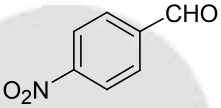
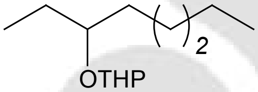
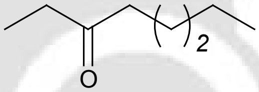
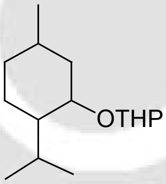
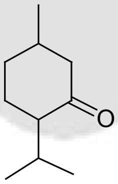
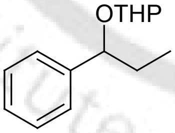
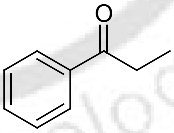
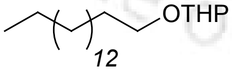
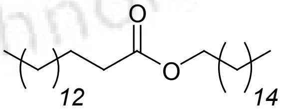
Substrate No.	Substrate[a]	Time min/[h]	Product[b]	Product No.	Yield[c] [%]
63	 OTBS	30	 CHO	**71**	85
18	 O2N, OTBS	50	 O2N, CHO	**19**	90

64		22		**72**	64
65		20		**73**	66
66		25		**74**	90
67		[1]		**75**	89
68		25		**76**	81
69		[1]		**77**	94
70		[8]		**78**	92

[a]The TBS ethers were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. [b]The oxidized products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. [c]Isolated yield.

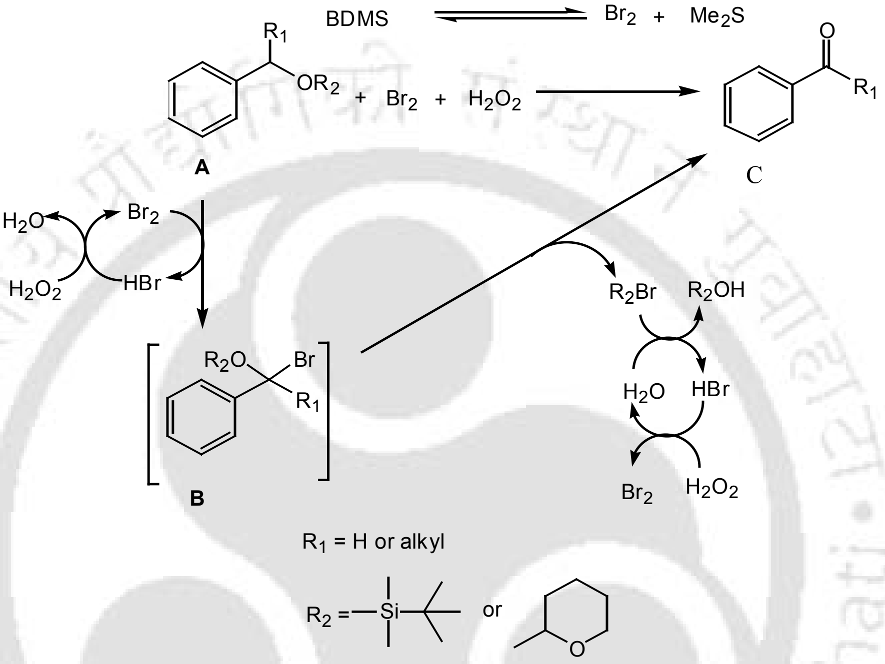
Next, we switched our attention to investigate the one pot conversion of THP ethers of alcohols into the corresponding carbonyl compounds. When a mixture of THP ether of benzyl alcohol (**79**) and BDSB (0.2 equiv) was treated with 30% H_2O_2 (2 equiv.) in dichloromethane (2 mL) at room temperature, it gave benzaldehyde (**71**) with 81% yield by avoiding the deprotection step. The product was characterized by IR and ^{1}H NMR spectra as well as comparing with the authentic spectra. Similarly, the THP ether of 4-chlorobenzyl alcohol (**80**) was converted smoothly to 4-chlorobenzaldehyde (**86**) within 50 min in 91% yield. The THP ether of 4-nitrobenzyl alcohol (**81**) was also transformed into 4-nitrobenzaldehyde (**19**) within 60 min in 90% yield by following the same procedure. Likewise, various THP ethers of secondary alcohols **82-84** also provided the desired ketones **74-76**, respectively, with good to excellent yields. On the other hand, the THP ether of aliphatic primary alcohol **85** gave ester **78** rather than giving aldehyde. The results are summarized in Table 2.

Table 2 Oxidation of various THP ethers of alcohols by bromodimethylsulfonium bromide and 30% hydrogen peroxide in dichloromethane

Substrate No.	Substrate[a]	Time min/[h]	Product[b]	Product No.	Yield[c] [%]
79		45		**71**	82
80		50		**86**	91
81		[1]		**19**	90
82		50		**74**	81
83		[1.5]		**75**	81
84		30		**76**	90
85		[9]		**78**	92

[a]The THP ethers were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. [b]The oxidized products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. [c]Isolated yield.

The formation of the product might be explained as follows. At first, bromine molecule might generate bromine radicals in the presence of hydrogen peroxide, which can generate a radical at the benzylic positions of the THP or TBS ethers. Subsequently, bromine radical is probably captured to provide an unstable intermediate **B** as shown in Scheme 29. Finally, it is converted to the ketones (**C**). The over all reactions are represented in Scheme 29.



Scheme 29: Plausible mechanism for oxidative deprotection of THP- and TBS ethers.

Alternatively, it can undergo hydrolysis first to the corresponding alcohol followed by oxidation gave the desired oxidation product.[54]

In summary, we have devised a new, efficient, and practical synthetic protocol for the oxidation of various TBS and THP ethers of alcohols to the corresponding carbonyl compounds in presence of 30% H_2O_2 in dichloromethane at room temperature. Over oxidation of aldehydes to carboxylic acids has not been observed under this reaction condition. The significant features of the present method include the ease of operation, high efficiency and mild condition, which may be useful in organic synthesis. We believe that our protocol will be a good addition in the oxidation field of organic chemistry.

SECTION A

TRANSITION METAL-FREE OXIDATIVE DEPROTECTION OF THP AND TBS ETHERS USING BROMODIMETHYLSULFONIUM BROMIDE AND HYDROGEN PEROXIDE

EXPERIMENTAL

General procedure for the preparation of *tert*-butyldimethylsilyl ethers of alcohols:[58]

To a mixture of alcohol (1 mmol) and TBDMSCl (1.2 mmol) in dry CH_2Cl_2 (3 mL) was added imidazole (3 mmol) at room temperature. After the completion of the reaction as monitored by TLC, the reaction mixture was neutralized with dilute 2N HCl and extracted with dichloromethane. The aqueous part was extracted once more with CH_2Cl_2. The combined organic part was dried over anhydrous Na_2SO_4 and concentrated in rotavapor. Finally, the residue was passed through a silica gel column to obtain the desired silyl ether.

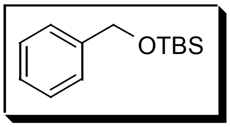
General procedure for the preparation of tetrahydropyranyl (THP) ethers of alcohols:

The THP ethers are prepared using bismuth(III) nitrate pentahydrate,[59] which is described in Section C of the Chapter I.

Typical procedure for oxidative deprotection of THP and TBS ethers:

To a well-stirred solution of THP or TBS ether (1 mmol) and BDMS (45 mg, 0.2 eq) in 2 mL of dichloromethane was added 30% H_2O_2 (0.225 mL, 2 mmol) at room temperature and kept for stirring. After completion of the reaction as monitored by TLC, saturated solution of sodium metabisulphite (1 mL) was added and the reaction mixture was extracted with dichloromethane (10 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under Vacuum to get the crude product, which was finally purified by silica gel column chromatography using a suitable combination of hexane/ethyl acetate as eluent.

TBS ether of benzyl alcohol (63):



Nature: Viscous liquid

Yield: 85%

Reaction time: 2 h

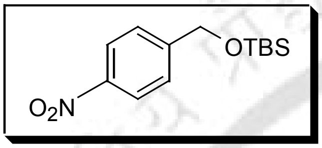
IR (Neat): cm^{-1} 2962, 2936, 2860, 1483, 1377, 1256, 1210, 1099, 1073, 845, 780, 729

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.94 (s, 9H), 4.75 (s, 2H), 7.20-7.36 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ -5.3 (2C), 18.4, 25.9 (3C), 65.0, 126.0 (2C), 126.8, 128.2 (2C), 141.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{22}OSi$	C 70.21	C 70.39
222.40	H 9.97	H 9.91

TBS ether of 4-nitrobenzyl alcohol (18):



Nature: Viscous liquid

Yield: 79%

Reaction time: 4 h

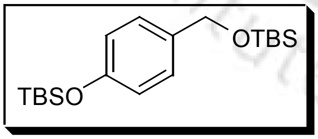
IR (Neat): cm^{-1} 2955, 2935, 2863, 1614, 1521, 1475, 1352, 1265, 1102, 1020, 856

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.13 (s, 6H), 0.96 (s, 9H), 4.83 (s, 2H), 7.49 (d, 2H, J = 8.7 Hz), 8.20 (d, 2H, J = 9.0 Hz) ppm.

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.4, 18.3, 25.8, 64.0, 123.5, 126.3, 146.0, 149.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{21}O_3NSi$	C 58.39	C 58.15
267.40	H 7.92	H 7.84
	N 5.24	N 5.08

TBS ether of 4-hydroxybenzyl alcohol (64):



Nature: Viscous liquid

Yield: 85%

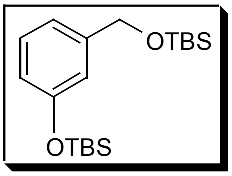
Reaction time: 6 h

IR (Neat): cm^{-1} 2960, 2945, 2899, 2868, 1614, 1516, 1475, 1255, 1091, 922, 851, 779

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.08 (s, 6H), 0.18 (s, 6H), 0.93 (s, 9H), 0.98 (s, 9H), 4.66 (s, 2H), 6.79 (d, 2H, J = 8.4 Hz), 7.17 (d, 2H, J = 8.4 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{19}H_{36}O_2Si_2$	C 64.71	C 64.83
352.66	H 10.29	H 10.36

TBS ether of 3-hydroxybenzyl alcohol (65):



Nature: Viscous liquid

Yield: 78%

Reaction time: 6 h

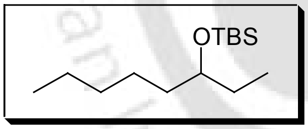
IR (Neat): cm^{-1} 2959, 2934, 2860, 1597, 1479, 1370, 1282, 1163, 1104, 1015, 971, 848

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.10 (s, 6H), 0.20 (s, 6H), 0.85 (s, 9H), 0.89 (s, 9H), 4.60 (s, 2H), 6.51 (dd, 1H, *J* = 2.4, *J* = 7.8 Hz), 6.65 (s, 1H), 6.69 (d, 1H, *J* = 7.6 Hz), 6.98 (t, 1H, *J* = 7.8 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): -5.3, -4.4, 18.2, 18.4, 25.7, 25.9, 64.7, 117.6, 118.6, 118.8, 129.1, 143.1, 155.7 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{19}H_{36}O_2Si_2$	C 64.71	C 64.82
352.66	H 10.29	H 10.32

TBS ether of 3-octanol (66):



Nature: Colorless liquid

Yield: 82%

Reaction time: 1.5 h

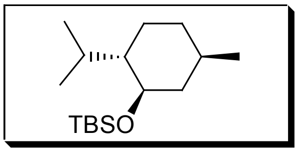
IR (Neat): cm^{-1} 2960, 2940, 2863, 1475, 1378, 1255, 1132, 1061, 835

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.00 (s, 6H), 0.83 (t, 6H, *J* = 7.6 Hz), 0.85 (s, 9H), 1.22-1.30 (m, 6H), 1.34-1.43 (m, 4H), 3.53 (quin, 1H, *J* = 5.9 Hz) ppm

^{13}C NMR (100 MHz, CDCl$_3$): δ -4.5, -4.5, 9.6, 14.0, 18.1, 22.6, 25.0, 25.9, 29.7, 32.0, 36.5, 73.5 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{32}OSi$	C 68.78	C 68.91
244.49	H 13.19	H 13.06

TBS ether of menthol (67):



Nature: Colourless gummy liquid

Yield: 75%

Time: 2 h

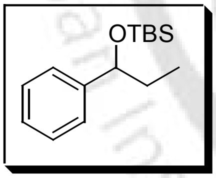
IR (Neat): cm^{-1} 2960, 2930, 2858, 1460, 1373, 1255, 1112, 1071

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.70 (d, 3H, *J* = 6.8Hz), 0.84-1.13 (m, 20H), 1.53-1.62 (m, 2H), 1.81-1.85 (m, 1H), 2.15-2.20 (m, 1H), 3.32-3.37 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ -4.8, -3.7, 15.7, 18.1, 21.3, 22.4, 22.7, 24.9, 25.9 (3C), 31.7, 34.6, 45.5, 56.2, 72.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{16}H_{34}OSi$	C 71.04	C 70.86
270.53	H 12.67	H 12.56

TBS ether of 1-phenyl 1-propanol (68):



Nature: Viscous liquid

Yield: 83%

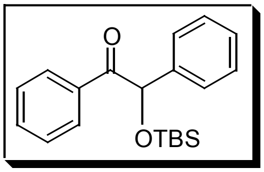
Reaction time: 2 h

IR (Neat): cm^{-1} 3039, 2956, 2940, 2865, 1475, 1359, 1263, 1100, 1038, 965, 847, 778

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.00 (s, 3H), 0.16 (s, 3H), 0.99 (t, 3H, *J* = 7.6 Hz), 1.02 (s, 9H), 1.78-1.82 (m, 2H), 4.69 (t, 1H, *J* = 6.3 Hz), 7.32-7.40 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{26}OSi$	C 71.93	C 71.77
250.46	H 10.46	H 10.51

TBS ether of benzoin (69):



Nature: Viscous liquid

Yield: 72%

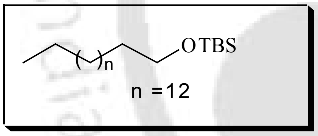
Reaction time: 6 h

IR (Neat): cm^{-1} 3035, 2958, 2857, 1692, 1467, 1359, 1261, 1100

^{1}H NMR (400 MHz, $CDCl_3$): 0.00 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 5.72 (s, 1H), 7.23 (d, 1H, J = 8.0 Hz), 7.31 (d, 4H, J = 7.6 Hz), 7.42 (t, 1H, J = 7.6 Hz), 7.49 (d, 2H, J = 7.6 Hz), 7.97 (d, 2H, J = 7.2 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{20}H_{26}O_2Si$	C 73.57	C 73.69
326.51	H 8.03	H 8.09

TBS ether of cetylalcohol (70):



Nature: Colorless liquid

Yield: 80%

Time: 1.5 h

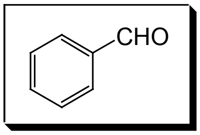
IR (Neat): cm^{-1} 2930, 2858, 1470, 1393, 1265, 1107, 1015, 846, 784

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (t, 3H, J = 7.2 Hz), 0.89 (s, 9H), 1.25 (bs, 26H), 1.51(quin, 2H, J = 6.6 Hz), 3.60 (t, 2H, J = 6.6 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3, 14.1, 22.7, 25.8, 25.9, 29.4, 29.5, 29.7, 31.9, 32.9, 63.4 ppm

Elemental Analysis	**Calculated**	**Found**
$C_{22}H_{48}OSi$	C 74.08	C 74.26
356.71	H 13.56	H 13.62

Benzaldehyde (71):



Nature: Liquid

Yield: 85%

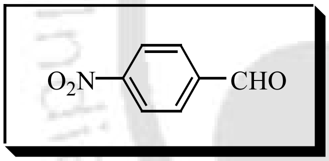
Reaction time: 30 min

IR (Neat): cm^{-1} 1706, 1598

^{1}**H NMR (400 MHz, CDCl$_3$):** δ 7.47 (t, 1H, *J* = 7.6 Hz), 7.54 (t, 2H, *J* = 7.8 Hz), 7.89 (d, 2H, *J* = 7.6 Hz), 10.02 (s, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
C_7H_6O	C 79.23	C 79.42
106.12	H 5.70	H 5.62

4-Nitrobenzaldehyde (19):



Nature: Light yellow solid

Yield: 90%

Reaction time: 50 min

Melting point: 102-105°C

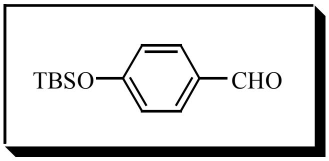
IR (Neat): cm^{-1} 1710, 1609, 1541, 1352, 1203

^{1}**H NMR (400 MHz, CDCl$_3$):** δ 8.08 (d, 2H, *J* = 8.7 Hz), 8.40 (d, 2H, *J* = 8.6 Hz), 10.17 (s, 1H) ppm.

^{13}**C NMR (100 MHz, CDCl$_3$):** δ 124.3 (2C), 130.5 (2C), 140.0 (2C), 190.3 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_7H_5O_3N$	C 55.64	C 55.49
151.12	H 3.33	H 3.23
	N 9.27	N 9.13

4-*tert*-Butyldimethylsilyloxy benzaldehyde (72):



Nature: Colourless liquid

Yield: 64%

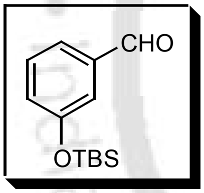
Reaction time: 22 min

IR (Neat): cm^{-1} 1705, 1603, 1511, 1275, 1157, 912, 845

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.25 (s, 6H), 0.99 (s, 9H), 6.94 (d, 2H, *J* = 8.5 Hz), 7.89 (d, 2H, *J* = 8.6 Hz), 9.88 (s, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{20}O_2Si$	C 66.05	C 66.22
236.39	H 8.53	H 8.45

3-*tert*-Butyldimethylsilyloxy benzaldehyde (73):



Nature: Colorless liquid

Yield: 66%

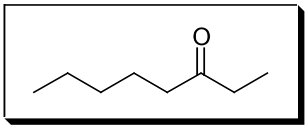
Reaction time: 20 min

IR (Neat): cm^{-1} 2955, 2859, 1700, 1591, 1491, 1390, 1283, 1167

^{1}H NMR (400 MHz, CDCl$_3$): 0.23 (s, 6H), 0.99 (s, 9H), 7.09-7.12 (m, 1H), 7.32-7.33 (m, 1H), 7.40 (t, 1H, *J* = 8.0 Hz), 7.46-7.48 (m, 1H), 9.95 (s, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{20}O_2Si$	C 66.05	C 66.28
236.39	H 8.53	H 8.47

3-octanone (74):



Nature: Colorless liquid

Yield: 90%

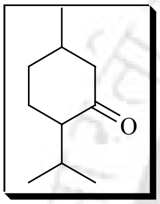
Reaction time: 25 min

IR (Neat): cm^{-1} 2940, 2868, 1716, 1460, 1373, 1260, 1071

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, 3H, J = 7.0 Hz), 1.05 (t, 3H, J = 7.2 Hz), 1.26-1.33 (m, 4H), 1.59 (quin, 2H, J = 7.2 Hz), 2.40 (t, 2H, J = 7.2 Hz), 2.43 (q, 2H, J = 7.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{16}O$	C 74.95	C 74.58
128.21	H 12.58	H 12.64

Menthone (75):



Nature: Colourless gummy liquid

Yield: 89%

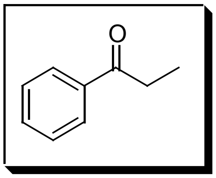
Time: 1 h

IR (Neat): cm^{-1} 2955, 2884, 1716, 1460, 1373, 1209, 1137, 1030

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.85 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.3 Hz), 1.33-1.50 (m, 2H), 1.79-2.53 (m, 7H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{18}O$	C 77.87	C 77.63
154.25	H 11.76	H 11.83

Propiophenone (76):



Nature: Viscous liquid

Yield: 81%

Reaction time: 25 min

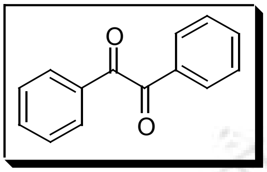
IR (Neat): cm^{-1} 1690, 1598, 1460, 1362, 1270

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.22 (t, 3H, J = 7.2 Hz), 2.99 (q, 2H, J = 7.2 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.52 (t, 1H. J = 7.6 Hz), 7.94 (d, 2H, J = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 8.4, 31.9, 127.8 (2C), 128.4 (2C), 132.7, 136.8, 200.5 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}O$	C 80.56	C 80.39
134.18	H 7.51	H 7.59

Benzil (77):



Nature: Solid

Yield: 94%

Reaction time: 60 min

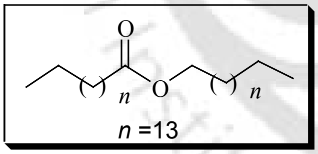
M.P.: 94 ^{0}C

IR (Neat): cm^{-1} 3073, 2935, 1670, 1593, 1450, 1322, 1214, 1178

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51 (t, 4H, *J* = 7.8 Hz), 7.66 (t, 2H. *J* = 8.0 Hz), 7.98 (d, 4H, *J* = 7.8 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{10}O_2$	C 79.99	C 79.74
210.23	H 4.79	H 4.87

Hexadecyl hexadecanoate (78):



Nature: White solid

Yield: 92%

Time: 8 h

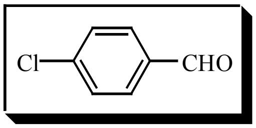
M.P.: 56 ^{0}C

IR (Neat): cm^{-1} 2926, 2856, 1739, 1462, 1169, 1112

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.86 (t, 6H, *J* = 6.6 Hz), 1.23 (bs, 50H), 1.58 (quin, 4H, *J* = 7.2 Hz), 2.26 (t, 2H, *J* = 7.6 Hz), 4.03 (t, 2H, *J* = 6.8 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{32}H_{64}O_2$	C 79.93	C 79.72
480.86	H 13.41	H 13.49

4-Chlorobenzaldehyde (86):



Nature: White Solid

Yield: 91%

Reaction time: 50 min

Melting point: 48 °C

IR (Neat): cm^{-1} 2924, 2852, 1706, 1587, 1393, 1290, 1208, 1162, 1091, 1019

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52 (d, 2H, *J* = 8.3 Hz), 7.83 (d, 2H, *J* = 8.3 Hz), 9.98 (s, 1H) ppm.

Elemental Analysis	**Calculated**	**Found**
C_7H_5OCl	C 59.81	C 59.63
140.57	H 3.58	H 3.62

SECTION B

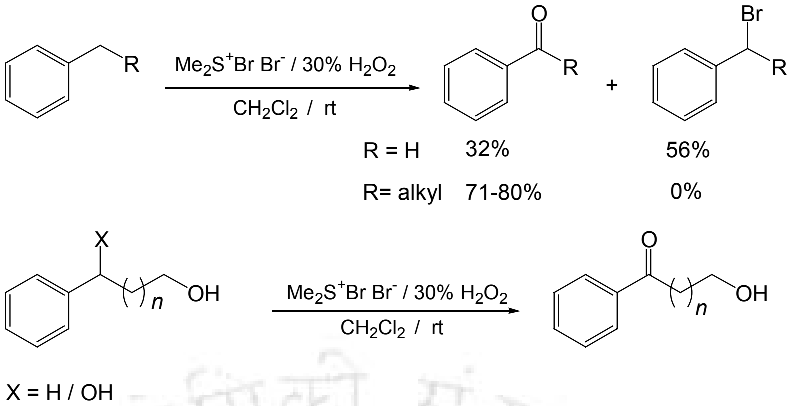
TRANSITION METAL-FREE BENZYLIC C-H OXIDATION AND CHEMOSELECTIVE OXIDATION OF SECONDARY HYDROXYL GROUP IN PRESENCE OF PRIMARY HYDROXYL GROUP USING BROMODIMETHYLSULFONIUM BROMIDE AND 30% HYDROGEN PEROXIDE

RESULTS AND DISCUSSION

Results and Discussion

The literature review of this chapter clearly provides an idea about the importance of benzylic C-H oxidation. Over the years, many methods have been developed for benzylic C-H oxidation and chemoselective oxidation of secondary alcohols to the carbonyl compounds. Interestingly, most of the methods involve the use of transition metal based reagents, which are already mentioned in the review section. Unfortunately, the main disadvantages of these procedures are harsh reaction conditions, longer reaction time, low yields and requirement of expensive reagents. On the other hand, only a few methods are known for the chemoselective oxidation of secondary hydroxyl groups in the presence of a primary hydroxyl group. Despite all these readily available procedures, development of a better selective oxidation method is highly desirable. We have described in the previous section that TBS ethers as well as THP ethers can be converted to the corresponding carbonyl compounds using a combination of bromodimethylsulfonium bromide and 30% hydrogen peroxide.[60] We thought if alkyl arenes can be brominated at the benzylic position by the same combination tuning the reaction condition and subsequently it can undergo hydrolysis to the alcohol, which can provide the oxidized product in a single step. With this aim in mind, we wanted to develop a new synthetic methodology using bromodimethylsulfonium bromide along with hydrogen peroxide for selective benzylic oxidation of alkyl- and cycloalkyl arenes. The present reagent has more advantages over molecular bromine because it can be considered as a convenient storage of molecular bromine molecule, less hazardous, easy to handle and maintain stoichiometric ratio during the reactions. In this section we wish to report that BDSB and H_2O_2 is a hitherto unreported combination for selective benzylic C-H oxidation of alkyl and cycloalkyl arenes and oxidation of secondary hydroxyl group located at the benzylic position over a primary hydroxyl group as depicted in Scheme 30.

As per our assumption, when a mixture of 2 mmol of toluene (**87**) and 30% hydrogen peroxide (1 mL) in CH_2Cl_2 (4 mL) was treated with BDSB (89 mg, 0.4 mmol) at room temperature, it was smoothly converted into 32% benzaldehyde (**71**) and 56% benzyl bromide (**100**). Both the products were characterized by recording IR and ^{1}H NMR spectra and also compared with the authentic spectra. Subsequently, we examined the substrate ethyl benzene (**88**) with above combination under identical conditions, it provided (1-bromoethyl) benzene (14%), 1-phenylethanol (37%) and the oxidized product acetophe-

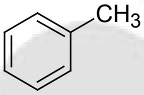
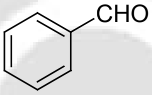
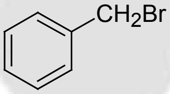
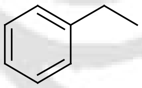
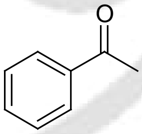
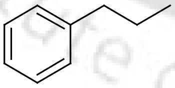
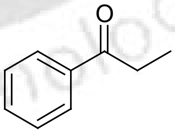
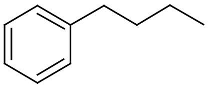
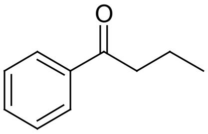
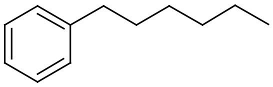
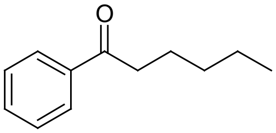


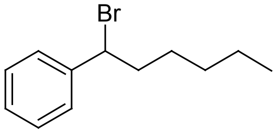
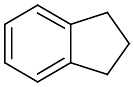
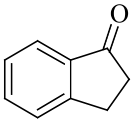
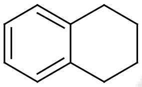
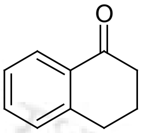
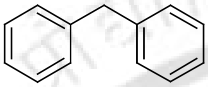
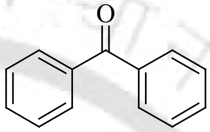
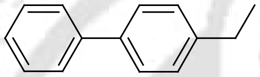
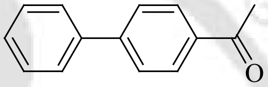
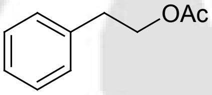
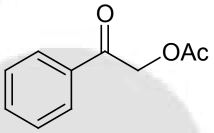
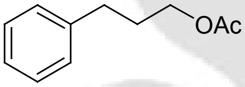
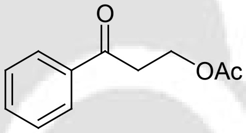
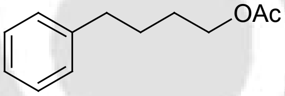
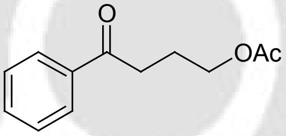
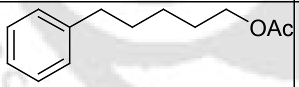
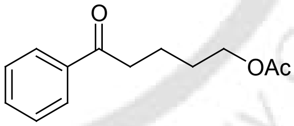
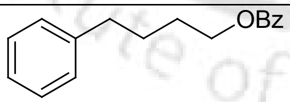
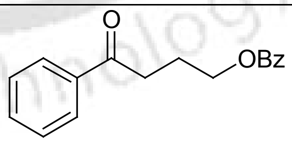
Scheme 30

-none(17%)after 3.5 h. Interestingly, when the same reaction was prolonged over a period of 10 h, it mainly afforded the oxidized product acetophenone (**101**) in 79% yield. From this observation, it is quite clear that the conversion proceeds through benzylic bromination, followed by hydrolysis to the alcohol and finally it gets oxidized to the ketone. In the present case (1-bromoethyl) benzene can undergo hydrolysis much faster to the 1-phenylethanol as compared to the hydrolysis of benzyl bromide to the benzyl alcohol. It was also observed[54] by Minisci *et al*. that the reaction of ethyl benzene (**88**) with molecular bromine and hydrogen peroxide provides exclusively brominated product (1-bromoethyl)benzene in 89% yield under reflux conditions. Remarkably, the same substrate provides only acetophenone by our method. These successful results further encouraged us to study the other substrates. Similarly, *n*-propylbenzene and *n*-butylbenzene (**89** and **90**) were converted into the corresponding benzylic oxidized product **76** and **102,** by following same reaction conditions in good yields. However, *n*-hexylbenzene (**91**) provided oxidized product **103** in 62 % yield along with 24% brominated product **104** when it was treated with same combination under identical conditions. It is important to mention that oxidation becomes sluggish if side chain in the aromatic ring increases, which may be due to slow hydrolysis of the brominated product. Likewise, various cycloalkyl arenes such as indan (**37**) and 1,2,3,4-tetrahydronaphthalene (**92**) were also oxidized to the corresponding ketones such as 1-indanone (**39**) and α-tetralone (**5**) in good yields under identical reaction conditions. Similarly, diphenyl methane (**93**), 4-ethylbiphenyl (**94**) and other substrates having acetate and benzoyl protecting group **95**, **96**, **97**, **98** and **99** were also converted to the desired ketones **105**, **106**, **107**, **108**, **109**, **110** and **111** without any difficulty under similar reaction conditions.

The results are summarized in Table 3 and all the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra as well as by comparing with authentic spectra. The IR, ^{1}H-NMR and ^{13}C NMR spectra of compound **110** are shown in figure 1-3. It is important to mention, when ethylbenzene was treated with other brominating agent such as n-tetrabutylammonium tribromide (TBATB) along with hydrogen peroxide, then only 20% acetophenone is obtained as oxidized product along with major amount of starting material after 48 h of stirring at room temperature. On the other hand, when the same reaction was carried out with NBS and hydrogen peroxide, it provided only (1-bromoethyl)benzene in 80% yield. This observation clearly demonstrates that the combination of BDMS and H_2O_2 has a unique property for the transposition of carbonyl functionality at the benzylic position from the corresponding alkyl and cycloalkyl arenes as compared to the other brominating reagents.

Table 3 Transition metal free C-H oxidation of alkyl arenes using bromodimethylsufonium bromide-H_2O_2 under biphasic condition at room temperature.

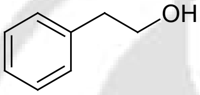
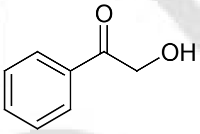
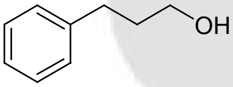
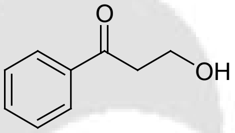
Substrate No.	Substrate	Time/h	Product[a]	Product No.	Yield[b] [%]
87		12	 	**71** **100**	32 56
88		10		**101**	79
89		10		**76**	77
90		10		**102**	74
91		20		**103**	62

				**104**	24
37		6		**38**	78
92		6		**5**	77
93		7		**105**	91
94		8		**106**	84
95		23		**107**	83
96		21		**108**	78
97		22		**109**	77
98		25		**110**	80
99		24		**111**	74

[a]All the products were characterized by analysis of spectral data and elemental analysis. [a]Isolated yields after chromatographic separation.

Next, we were interested to investigate whether the chemoselective oxidation at the benzylic position is possible in the presence of a non-activated primary hydroxyl group or not. We have noted that various substrates **112** and **113** can be oxidized chemoselectively at the benzylic position to yield products, **114** and **115,** without any difficulty by keeping the primary hydroxyl groups intact. The results are shown in Table 4 and the products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analysis (Fig. 4-6). Various aliphatic alcohols such as 1-decanol and cetyl alcohol provide higher ester after oxidation while treating with BDMS and 30% aqueous H_2O_2 at room temperature. The similar observation was also observed by Minisci *et al.* while using molecular bromine and hydrogen peroxide.[54] To the best of our knowledge, this is the first example demonstrating that carbonyl group transposition might be possible at the benzylic position regioselectively in the presence of a non-activated primary hydroxyl groups.

Table 4 Chemoselective benzylic C-H oxidation in presence of a non-activated primary hydroxyl group using the same combination.

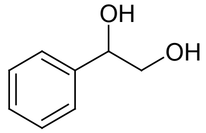
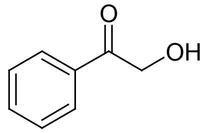
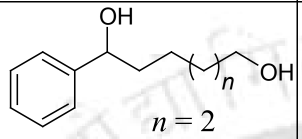
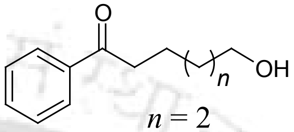
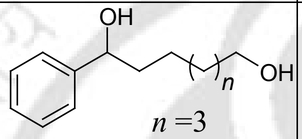
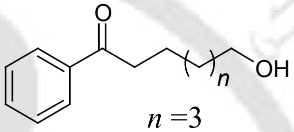
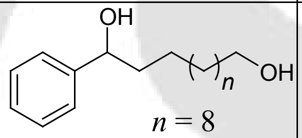
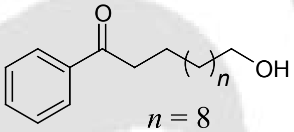
Substrate No.	Substrate	Time/h	Product[a]	Product No.	Yield[b] [%]
112		11		**114**	51
113		9		**115**	69

[a]All the products were characterized by analysis of spectral data and elemental analysis.
[a]Isolated yields after chromatographic separation.

Finally, we were keen to find out whether the secondary hydroxyl group can be oxidized in the presence of a primary hydroxyl group or not. We have found that benzylic secondary hydroxyl group of various diols **116**, **117**, **118** and **119** can be oxidized chemoselectively into the corresponding products **114**, **120**, **121** and **122** in the presence of primary hydroxyl group using 0.2 mmol of BDMS per mmol of the substrate, respectively. The results are summarized in Table 5 and all the products were characterized by usual spectroscopic technique and elemental analyses. It is worthwhile to mention that primary hydroxyl group did not undergo oxidation under the experimental conditions.

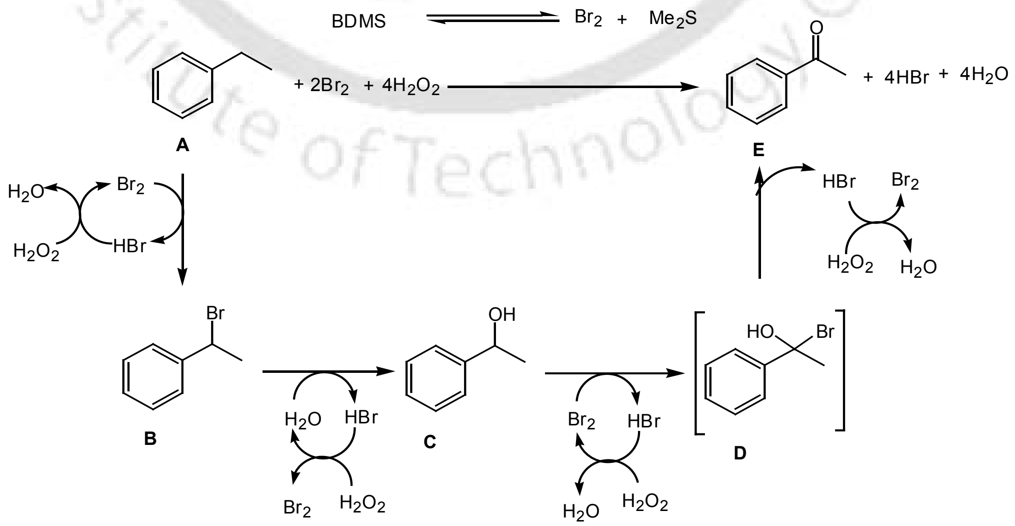
The formation of the product can be explained as follows. At first bromine molecule might generate bromine radicals in the presence of hydrogen peroxide, which can generate a radical at the benzylic position of the alkylarene. Subsequently, the bromine radical is captured to provide the brominated product at the benzylic position and slowly

Table 5 Selective oxidation of benzylic secondary alcohols to the ketones using bromodimethylsul-fonium bromide and hydrogen peroxide at room temperature.

Substrate No.	Substrate	Time/ min	Product[a,b]	Product No.	Yield[c] [%]
116		18		**114**	79
117		22		**120**	84
118		25		**121**	80
119		25		**122**	81

[a]The products were characterized by analysis of spectral data and elemental analysis. [b]Isolated yields after chromatographic separation.

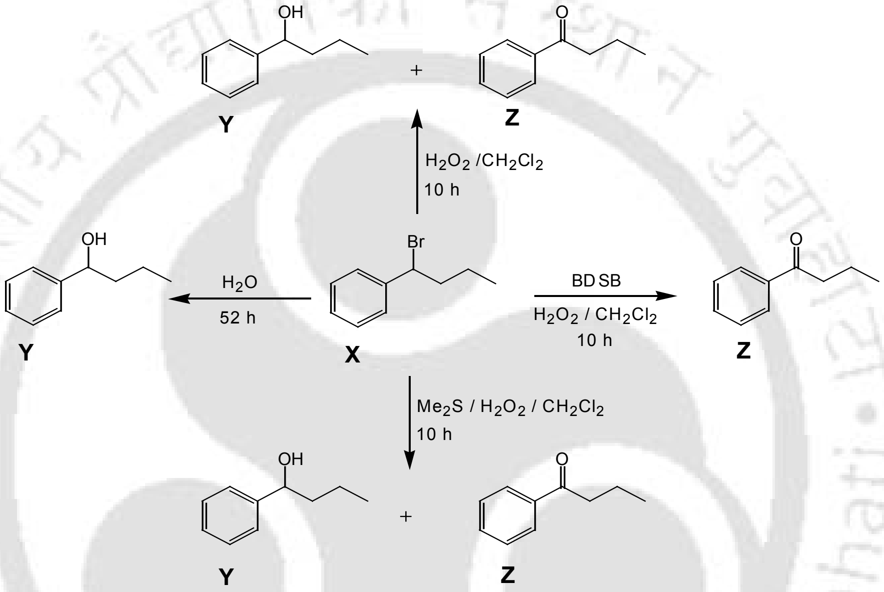
it can undergo hydrolysis to the alcohol. Again, it is possible to generate a benzyl radical, which can capture bromine radical to provide unstable intermediate **D** as shown in Scheme 31. Finally, it is converted to the ketones.



Scheme 31: Plausible mechanism for benzylic C-H oxidation by using BDSB-H_2O_2

In some of the cases we have isolated brominated product (**100** and **104**) along with oxidized product, which indicates that the reaction proceeds through benzylic bromination. To further confirm the generation of alcohol intermediate, we have done the following sets of experiment.

The compound (1-bromobutyl) benzene (**X**) was prepared from butylbenzene by benzylic bromination using NBS and alkyl peroxide. When the compound **X** was stirred with water at room temperature, it provided the hydrolyzed product **Y** after 52 h.



Scheme 32: Results, which support our plausible mechanism.

Table 6 Mechanistic investigations by different catalytic combination on the model substrate **X**

Entry	Catalytic combination	Reaction time/ h	% Product **Y**	% product **Z**
1.	H_2O	52	78	0
2.	H_2O_2 (2 eq) /CH_2Cl_2 / rt	10	66	22
3.	Me_2S (0.2 eq) / H_2O_2 (2 eq) / CH_2Cl_2 / rt	10	62	27
4.	BDSB (0.2 eq) /H_2O_2 (2 eq) / CH_2Cl_2 / rt	10	0	73

On the other hand, the substrate **X** gave the hydrolyzed product **Y** along with oxidized product **Z** when it was treated with hydrogen peroxide only. This result indicates that after hydrolysis HBr is eliminated, which plays a vital role in the formation of oxidized product ketone. Next, we were interested to find out whether dimethylsulfide has any role in the following transformation. When the substrate **X** was treated with hydrogen peroxide and dimethyl sulfide, it gave almost similar result as shown in Table 6. It shows that dimethylsulfide does not have any significant role in the transformation of **X** into **Y** and **Z**. However, it has been used for the formation of charge transfer complex with molecular bromine for maintaining stoichiometric ratio of molecular bromine. Lastly, the compound **X** was treated with BDMS and hydrogen peroxide, which gave exclusively the product **Z**. From this experiment, we may conclude that the reaction proceeds through alcohol intermediate as shown in Scheme 32.

The superiority and generality of this present protocol can be realized at a glance by comparing our results with those of some recently reported procedures (shown in Table 7). For this comparison we have chosen the oxidation of diphenyl methane (**93**) to benzophenone (**105**) as a model reaction. From the Table 7, it is evident that our protocol is better in terms of cost-effectiveness, reaction conditions as well as yields obtained.

Table 7 Comparison of results of oxidation of diphenyl methane with other catalysts

Entry	Oxidant (equivalents)	Catalyst (equivalents)	Solvent used	Reaction condition / time	% Yields[a]
1.	PhI=O (3.0)	Mn(III) salen complex (0.15)	CH_3CN	0 ^{0}C/ 3 h	72[33]
2.	H_2O_2 (40.0)	Mo(VI) peroxo complex (0.05)	CH_3CN	60 ^{0}C under O_2 atmosphere/ 12 h	25[c,37]
3.	Ethyl-2-Oxo cyclopentane carboxylate (2.0)	[bis(salicylidene-N-(methyl-3-hydroxy propionate)] (0.05)	CH_3CN	60 ^{0}C under O_2 atmosphere/ 15 h	69[30]

4.	*t*-BuOOH (30)	Fe(III) compound (0.2 eq) and 2-picolinic acid (0.5)	CH_3CN and C_5H_5N	room temp. / 24 h	92[35]
5.	*t*-BuOOH (4)	$RuCl_2(PPh_3)_3$ (0.01)	Dry C_6H_6	20 ^{0}C under argon atmosphere / 2h	95[34] Total conversion is 75%
6.	-	$KMnO_4/Al_2O_3/$ (3 gm per mmol)	CH_2Cl_2	Room temp. / 282 h	91[29]
7.	H_2O_2 (4)	BDSB (0.4)	CH_2Cl_2	Room temp. / 7 h	91
8.	*t*-BuOOH (5)	Bi_2O_3 (0.08) + $NaBH_4$ (0.5) and picolinic acid (0.2 mmol)	C_5H_5N and CH_3COOH	First sonication for 30 min., then heat in a sealed tube at 100 ^{0}C / 16 h	95[36]

[a] Corresponding references.

In conclusion, we have devised a novel and useful synthetic protocol for the oxidation of various alkyl- and cycloalkyl arenes to the corresponding carbonyl compounds using a catalytic amount of bromodimethylsulfonium bromide and 30% H_2O_2 in dichloromethane at room temperature. Remarkably, a carbonyl group transposition is also possible at the benzylic position in the presence of non-activated primary hydroxyl groups. Various benzylic alcohols can be chemoselectively converted into ketones in high yields in the presence of non-activated primary hydroxyl groups. This is the first synthetic procedure, which does not involve any transition metal. The significant features of the present method include the ease of operations, high efficiency and mild conditions, which may be extensively useful in organic synthesis. We believe that our protocol will be a good addition in the field of oxidation chemistry.

SECTION B

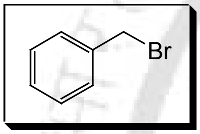
TRANSITION METAL-FREE BENZYLIC C-H OXIDATION AND CHEMOSELECTIVE OXIDATION OF SECONDARY HYDROXYL GROUP IN PRESENCE OF PRIMARY HYDROXYL GROUP USING BROMODIMETHYLSULFONIUM BROMIDE AND 30% HYDROGEN PEROXIDE

EXPERIMENTAL

General procedure for benzylic C-H oxidation:

To a well-stirred solution of ethyl benzene (212 mg, 2 mmol) and bromo-dimethylsulfonium bromide (178 mg, 0.4 equiv) in 4 mL of dichloromethane was added 30% H_2O_2 (0.450 mL, 4 mmol) at room temperature and kept for stirring. After completion of the reaction as monitored by TLC, saturated solution of sodium metabisulphite (1 mL) was added and the reaction mixture was extracted with dichloromethane (10 mL x 2). The organic layers were dried over anhydrous Na_2SO_4. The organic extract was concentrated in vacuum to get the crude product, which was finally purified by column chromatography on silica gel (eluent: hexane/ ethyl acetate, 9.8: 0.2). The product acetophenone was obtained as colourless liquid (178 mg, 74%).

Benzyl bromide (100):



Nature: liquid

Yield: 56%

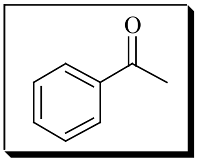
Reaction time: 12 h

IR (Neat): cm^{-1} 3043, 2976, 1506, 1463, 1241, 1208, 1085

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.11 (s, 2H), 7.11-7.35 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
C_7H_7Br	C 49.16	C 49.38
171.04	H 4.12	H 4.21

Acetophenone (101):



Nature: Liquid

Yield: 79%

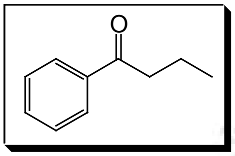
Reaction time: 10 h

IR (Neat): cm^{-1} 1690, 1598, 1460, 1362,1270

^{1}H NMR (300 MHz, CDCl$_3$): δ 2.61 (s, 3H), 7.45 (t, 2H, *J* = 7.6 Hz), 7.55 (t, 1H, *J* = 7.2 Hz) 7.95 (d, 2H, *J* = 7.2 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
C_8H_8O	C 79.97	C 79.78
120.15	H 6.71	H 6.85

Butyrophenone (102):



Nature: Viscous liquid

Yield: 74%

Reaction time: 10 h

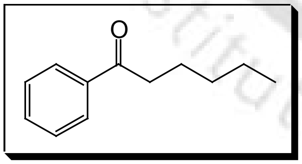
IR (Neat): cm^{-1} 1688 (CO)

^{1}**H NMR (400 MHz, CDCl$_3$):** δ 1.00 (t, 3H, *J* = 7.2 Hz), 1.77 (sex, 2H, *J* = 7.2 Hz), 2.94 (t, 2H, *J* = 7.2 Hz), 7.43 (t, 2H, *J* = 8.0 Hz), 7.52 (t, 1H, *J* = 7.2 Hz) 7.94 (d, 2H, *J* = 7.2 Hz) ppm.

^{13}**C-NMR (100 MHz, CDCl$_3$):** 14.0, 17.9, 40.6, 127.9 (2C), 128.4 (2C), 132.7, 136.8, 200.5 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}O$	C 81.05	C 81.32
148.20	H 8.16	H 8.22

Hexanophenone (103):



Nature: Viscous liquid

Yield: 62%

Reaction time: 20 h

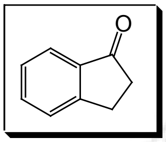
IR (Neat): cm^{-1} 1685(CO)

^{1}**H NMR (400 MHz, CDCl$_3$):** δ 0.91 (t, 3H, *J* = 6.8 Hz), 1.34-1.39 (m, 4H), 1.74 (quin, 2H, *J* = 7.2 Hz), 2.95 (t, 2H, *J* = 7.6 Hz), 7.43 (t, 2H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.94 (d, 2H, *J* = 8.4 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): 14.1, 22.6, 24.2, 31.6, 38.7, 127.9 (2C), 128.4 (2C), 132.7, 136.9, 200.3 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O$	C 81.77	C 81.61
176.26	H 9.15	H 9.06

Indanone (39):



Nature: Viscous liquid

Yield: 78%

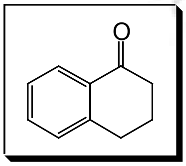
Reaction time: 6 h

IR (KBr): cm^{-1} 1715(CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (t, 2H, *J* = 6.0 Hz), 3.14 (t, 2H, *J* = 6.0 Hz), 7.37 (t, 1H, *J* = 7.6 Hz), 7.46 (d, 1H, *J* = 7.6 Hz), 7.57 (d, 1H, *J* = 7.6 Hz), 7.74 (d, 1H, *J* = 7.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
C_9H_8O	C 81.79	C 81.52
132.16	H 6.10	H 6.18

α-Tetralone (5):



Nature: Viscous liquid

Yield: 77%

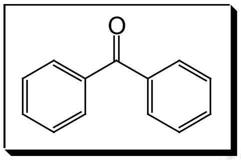
Reaction time: 6 h

IR (Neat): cm^{-1} 1675 (CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09-2.16 (m, 2H), 2.63-2.66 (m, 2H), 2.94-2.97 (m, 2H), 7.22 (d, 1H, *J* = 7.6 Hz), 7.27 (t, 1H, *J* = 7.6 Hz), 7.41-7.45 (m, 1H), 8.00 (d, 1H, *J* = 7.6 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{10}O$	C 82.16	C 82.43
146.19	H 6.89	H 6.96

Benzophenone (105):



Nature: White solid

Yield: 91%

Reaction time: 7 h

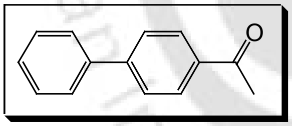
M. P.: 47 ^{0}C

IR (KBr): cm^{-1} 1665 (CO)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47 (t, 4H, *J* = 8.0 Hz), 7.57 (t, 2H, *J* = 8.0 Hz), 7.78 (d, 4H, *J* = 8.4 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{10}O$	C 85.69	C 85.91
182.22	H 5.53	H 5.41

4-Phenyl acetophenone (106):



Nature: White solid

Yield: 84%

Reaction time: 8 h

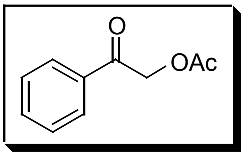
M. P.: 118 °C

IR (Neat): cm^{-1} 1688 (CO)

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.64 (s, 3H), 7.39 (t, 1H, *J* = 7.2 Hz), 7.47 (t, 2H, *J* = 6.8 Hz), 7.62 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.0 Hz), 8.02 (d, 2H, *J* = 8.0 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{12}O$	C 85.68	C 85.43
196.25	H 6.16	H 6.07

(1-benzoyl)methylacetate (**107**):



Nature: Viscous liquid

Yield: 83%

Reaction time: 23 h

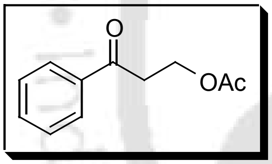
IR (Neat): cm^{-1} 1752 ($OCOCH_3$), 1706 (CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 5.33 (s, 2H), 7.46 (t, 2H, *J* = 7.6 Hz), 7.59 (t, 1H, *J* = 7.6 Hz), 7.89 (d, 2H, *J* = 7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 66.0, 127.6 (2C), 128.7 (2C), 133.7, 133.9, 170.2 (CO), 191.8 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{10}O_3$	C 67.41	C 67.63
178.19	H 5.66	H 5.72

(2-benzoyl)ethylacetate (**108**):



Nature: White solid

Yield: 78%

Reaction time: 21 h

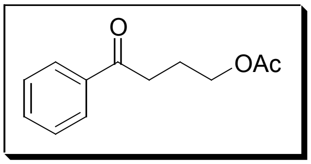
IR (Neat): cm^{-1} 1742 ($OCOCH_3$), 1680 (CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 3.31 (t, 2H, *J* = 6.4 Hz), 4.51 (t, 2H, *J* = 6.4 Hz), 7.46 (t, 2H, *J* = 7.6 Hz), 7.55-7.58 (m, 1H), 7.94 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 37.4, 59.7, 127.9 (2C), 128.6 (2C), 133.3, 136.5, 170.8 (CO), 196.8 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{12}O_3$	C 68.74	C 68.91
191.21	H 6.29	H 6.37

(3-benzoyl)propylacetate (**109**):



Nature: Viscous liquid

Yield: 77%

Reaction time: 22 h

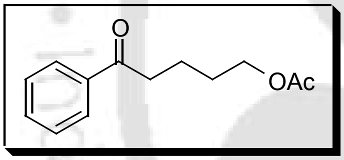
IR (Neat): cm^{-1} 1742 ($OCOCH_3$), 1690 (CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.10 (quin, 2H, *J* = 7.2 Hz), 3.07 (t, 2H, *J* = 7.2 Hz), 4.16 (t, 2H, *J* = 6.4 Hz), 7.45 (t, 2H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.94 (d, 2H, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 23.3, 34.9, 63.8, 127.8 (2C), 128.5 (2C), 132.9, 136.6, 170.9 (CO), 198.8 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{14}O_3$	C 69.89	C 69.67
206.24	H 6.84	H 6.93

(4-benzoyl)butylacetate (**110**):



Nature: White solid

Yield: 80%

Reaction time: 25 h

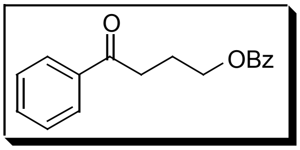
IR (KBr): cm^{-1} 1752 ($COCH_3$), 1706 (CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.76 (m, 2H), 1.79-1.86 (m, 2H), 2.04 (s, 3H), 3.01 (t, 2H, *J* = 7.2 Hz), 4.10 (t, 2H, *J* = 6.4 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.94 (d, 2H, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 20.8, 21.1, 28.3, 37.9, 64.2, 127.9 (2C), 128.5 (2C), 132.9, 136.8, 170.9, 199.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{16}O_3$	C 70.89	C 71.11
220.27	H 7.32	H 7.41

(3-benzoyl)propylbenzoate (111):



Nature: Solid

Yield: 74%

Reaction time: 24 h

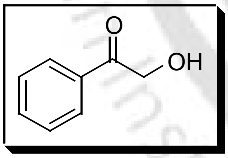
IR (neat): cm^{-1} 1716 (OCOPh), 1680 (CO)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (quin, 2H, *J* = 6.8 Hz), 3.16 (t, 2H, *J* = 7.2 Hz), 4.43 (t, 2H, *J* = 6.4 Hz), 7.39-7.46 (m, 4H), 7.52-7.56 (m, 2H), 7.95 (d, 2H, *J* = 8.4 Hz), 8.01 (d, 2H, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 35.0, 64.3, 127.9 (2C), 128.2 (2C), 128.5 (2C), 129.4 (2C), 130.0, 132.8, 132.9, 136.6, 166.3, 198.8 (CO) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{16}O_3$	C 76.10	C 76.32
268.31	H 6.01	H 6.12

2-hydroxy-1-phenylethanone (114):



Nature: White Solid

Yield: 51%

Reaction time: 11 h

M. P.: 88 ^{0}C

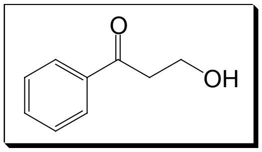
IR (neat): cm^{-1} 3428, 1685, 1592

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50 (bs, 1H), 4.88 (s, 2H), 7.49 (t, 2H, *J* = 7.6 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.91 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 65.5, 127.6 (2C), 128.8 (2C), 133.3, 134.1, 198.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_8O_2$	C 70.58	C 70.71
136.15	H 5.92	H 5.83

3-hydroxy-1-phenyl-1-propanone (115):



Nature: Viscous liquid

Yield: 69%

Reaction time: 9 h

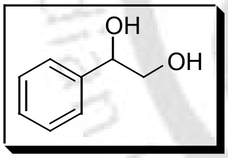
IR **(Neat):** cm^{-1} 3411, 3073, 2945, 2894, 1685, 1603, 1582, 1449, 1362, 1260, 1214

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (bs, 1H), 3.23 (t, 2H, *J* = 5.6 Hz), 4.02 (t, 2H, *J* = 5.6), 7.45 (t, 2H, *J* = 7.6 Hz), 7.54-7.58 (m, 1H), 7.94 (d, 2H, *J* = 7.6 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): 40.5, 58.1, 127.9 (2C), 128.5 (2C), 133.4, 136.5, 200.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{10}O_2$	C 71.98	C 71.72
150.18	H 6.71	H 6.79

1-phenyl-1,2-ethanediol (116):



Nature: White Solid

Yield: 68%

Reaction time: 10 min

M. P.: 66°C

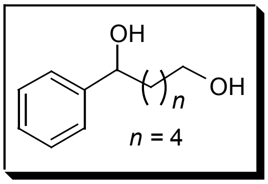
IR (KBr): cm^{-1} 3211, 2935, 1455, 1096, 1061

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (bs, 1H), 3.17 (bs, 1H), 3.62 (dd, 1H, *J* = 8.0 Hz, *J* = 11.2 Hz), 3.71 (dd, 1H, *J* = 3.2 Hz, *J* = 11.2 Hz), 4.78 (dd, 1H, *J* = 3.6 Hz, *J* = 8.4 Hz), 7.25-7.36 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 68.0, 74.7, 125.9 (2C), 127.8, 128.4 (2C), 140.3 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{10}O_2$	C 69.54	C 69.72
138.17	H 7.29	H 7.38

1-phenyl-1,6-hexaanediol (117):



Nature: Viscous liquid.

Yield: 62%

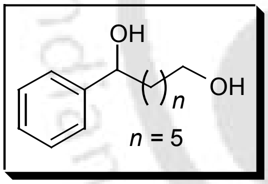
Reaction time: 15 min

IR (neat): cm^{-1} 3336, 2930, 1456, 1054

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.25-1.40 (m, 4H), 1.53 (q, 2H, *J* = 6.8 Hz), 1.68-1.85 (m, 4H), 3.60 (t, 2H, *J* = 6.8 Hz), 4.65 (dd, 1H, *J* = 5.6 Hz, *J* = 7.2 Hz), 7.26-7.34 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}O_2$	C 74.19	C 74.33
194.27	H 5.56	H 5.47

1-phenyl-1,7-heptanediol (118):



Nature: Viscous liquid.

Yield: 64%

Reaction time: 15 min

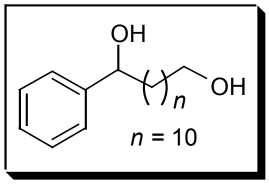
IR (neat) cm^{-1}: 3334, 2930, 2855, 1614, 1453, 1271, 1052

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.34-1.82 (m, 12H), 3.62 (t, 2H, *J* = 6.8 Hz), 4.67 (dd, 1H, *J* = 6.0 Hz, *J* = 7.2 Hz), 7.26-7.35 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 26.1, 26.2, 29.7, 33.1, 39.4, 63.3, 74.9, 126.1 (2C), 127.7, 128.6 (2C), 145.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{20}O_2$	C 74.96	C 74.68
208.30	H 9.68	H 9.76

1-phenyl-1,12-dodecanenediol (119):



Nature: White Solid

Yield: 65%

Reaction time: 15 min

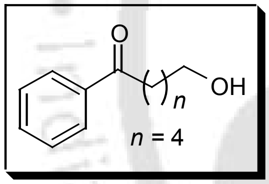
M. P.: 49°-50°C

IR (KBr): cm^{-1} 3353, 3027, 2927, 2854, 1603, 1457, 1363, 1056

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-1.41(m, 16H), 1.52-1.85 (m, 6H), 3.63 (t, 2H, *J* = 6.8 Hz), 4.66 (dd, 1H, *J* = 5.6 Hz, *J* = 7.2 Hz), 7.26-7.35 (m, 5H) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{30}O_2$	C 77.65	C 77.92
278.43	H 10.86	H 10.95

6-hydroxy-1-phenyl-1-hexanone (120):



Nature: Viscous liquid.

Yield: 84%

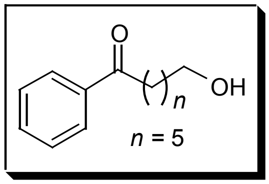
Reaction time: 22 min

IR (neat): cm^{-1} 3421, 2940, 1685, 1593, 1050

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44-1.52 (m, 2H), 1.58-1.66 (m, 3H), 1.78 (q, 2H, *J* = 7.2 Hz), 3.00 (t, 2H, *J* = 7.2 Hz), 3.68 (t, 2H, *J* = 6.4 Hz), 7.46 (t, 2H, *J* = 7.8 Hz), 7.57 (t, 1H, *J* = 6.9 Hz), 7.96 (d, 2H, *J* = 7.5 Hz) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{16}O_2$	C 74.97	C 74.72
192.26	H 8.39	H 8.31

7-hydroxy-1-phenyl-1-heptanone (121):



Nature: Viscous liquid

Yield: 80%

Reaction time: 25 min

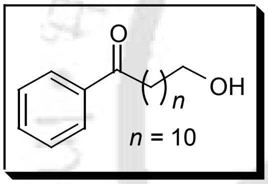
IR (neat): cm^{-1} 3398, 3062, 2933, 2859, 1682, 1591, 1452, 1366, 1265, 1219, 1185

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.40-1.44 (m, 5H), 1.58-1.61 (m, 2H), 1.74-1.77 (m, 2H), 2.98 (t, 2H, *J* = 7.2 Hz), 3.65 (t, 2H, *J* = 7.2 Hz), 7.46 (t, 2H, *J* = 8.4 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.95 (d, 2H, *J* = 8.4 Hz) ppm. .

^{13}C NMR (75 MHz, CDCl$_3$): δ = 24.7, 26.0, 29.5, 32.9, 38.9, 63.2, 128.2 (2C) , 128.8 (2C), 133.1, 137.1, 200.6 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{13}H_{18}O_2$	C 75.69	C 75.81
206.28	H 8.79	H 8.87

12-hydroxy-1-phenyl-1-dodecanone (122):



Nature: White Solid

Yield: 81%

Reaction time: 25 min

M. P.: 67°-69°C

IR (KBr): cm^{-1} 3350, 2919, 2848, 1690, 1588, 1475, 1383, 1066

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.24-1.38 (m, 14H), 1.53-1.76 (m, 5H), 2.96 (t, 2H, *J* = 7.2 Hz), 3.64 (t, 2H, *J* = 6.8 Hz), 7.46 (t, 2H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 8.0 Hz), 7.95 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 24.8, 26.1, 29.7, 29.8, 29.9, 30.0, 33.2, 39.0, 63.4, 128.2, 128.7, 132.9, 137.3, 200.6. ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{18}H_{28}O_2$	C 78.21	C 78.02
276.42	H 10.21	H 10.31

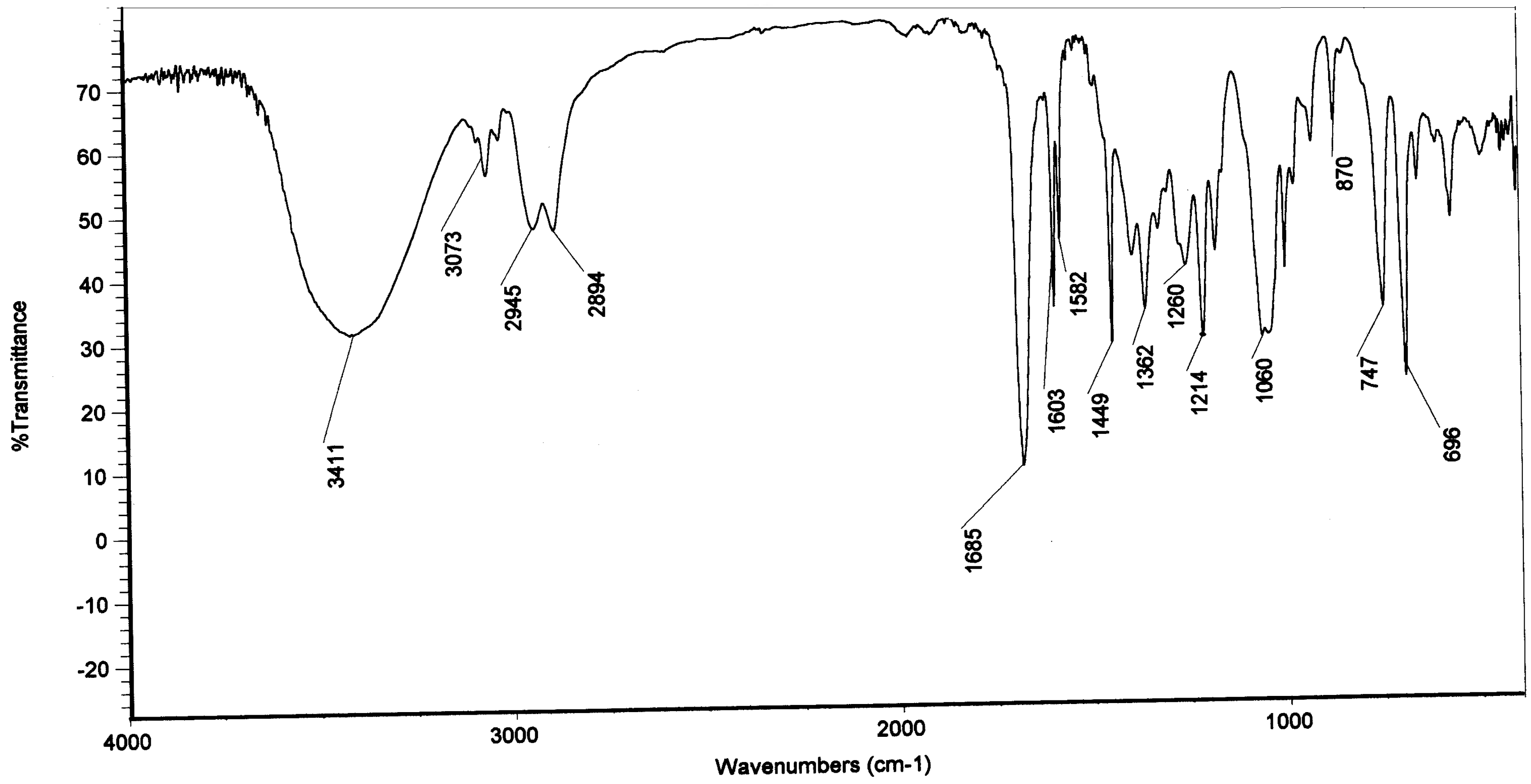


Figure 1: IR spectrum of 3-hydroxy-1-phenyl-1-propanone (115)

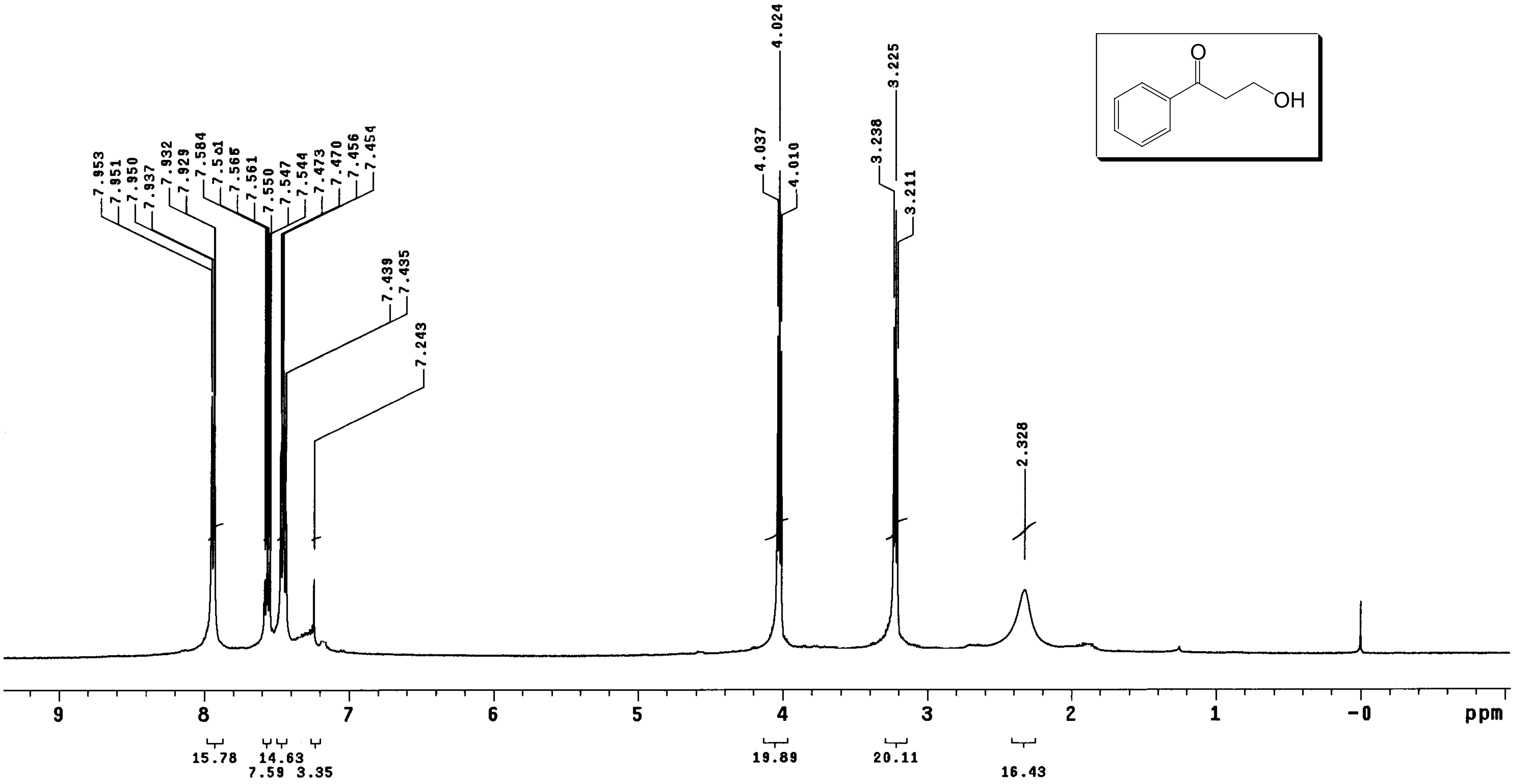


Figure 2: ^{1}H NMR spectrum of 3-hydroxy-1-phenyl-1-propanone (115)

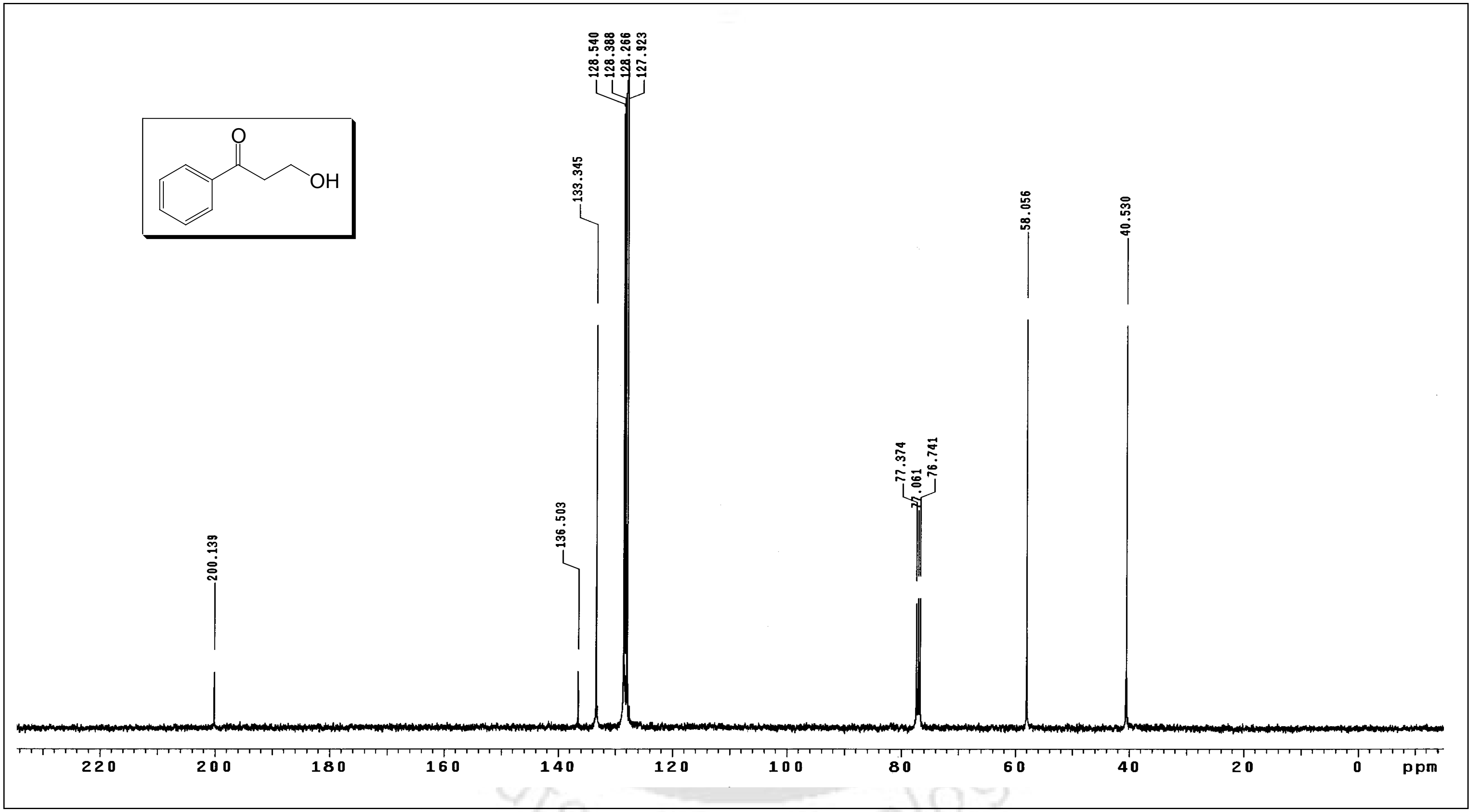


Figure 3: ^{13}C NMR spectrum of 3-hydroxy-1-phenyl-1-propanone (115)

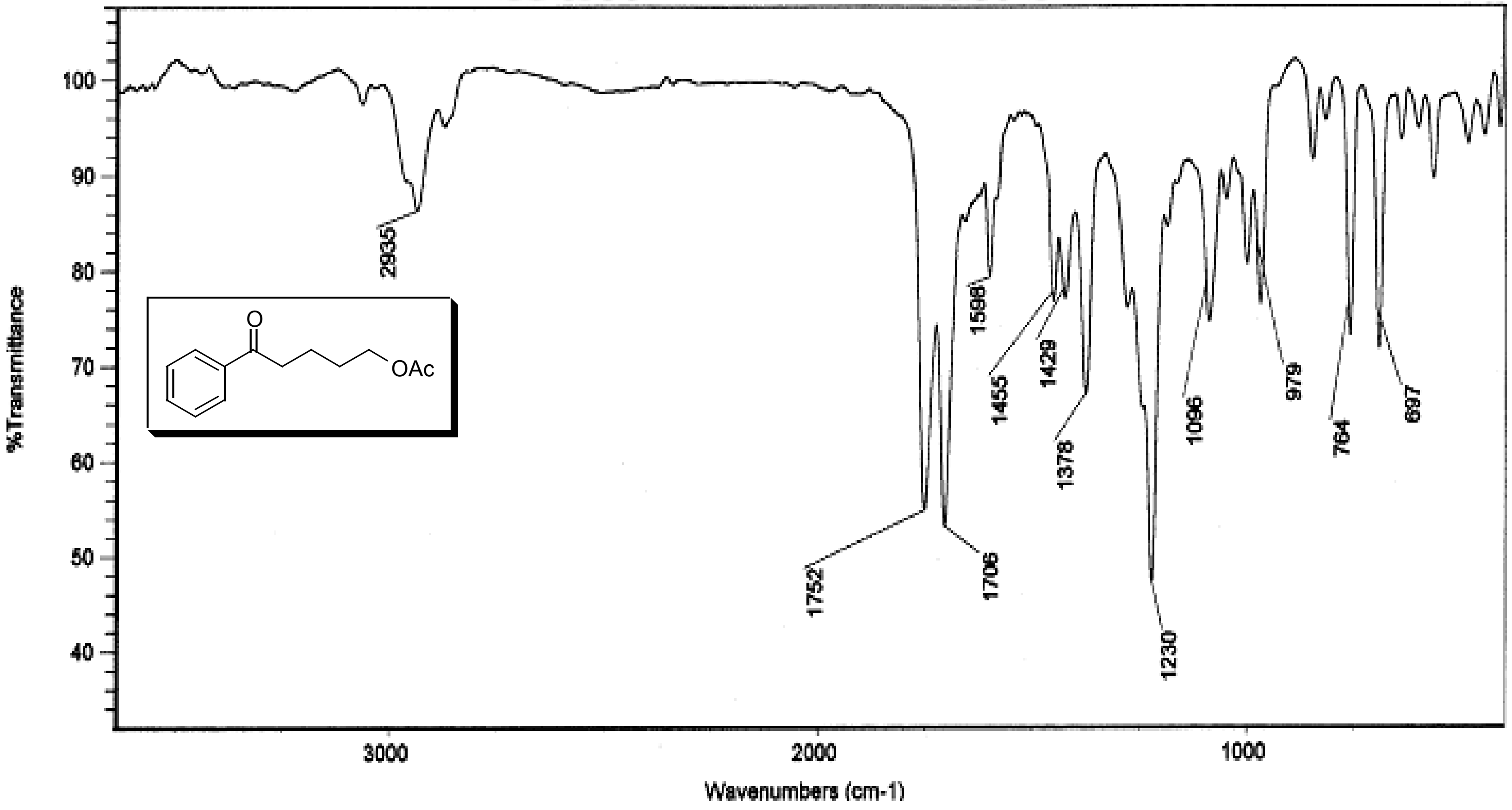


Figure 4: IR spectrum of (4-benzoyl) butylacetate (110)

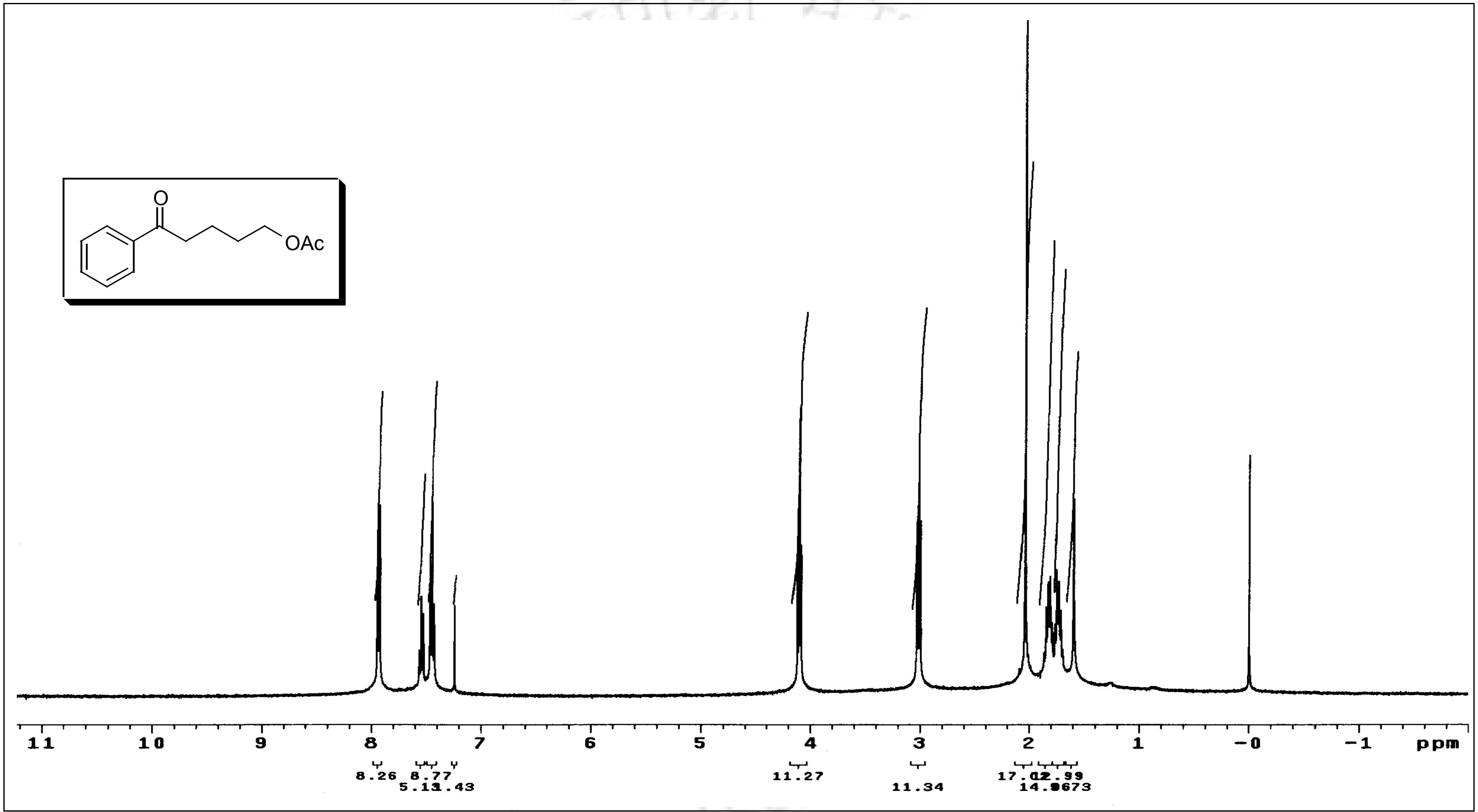


Figure 5: ^{1}H NMR spectrum of (4-benzoyl)butylacetate (110)

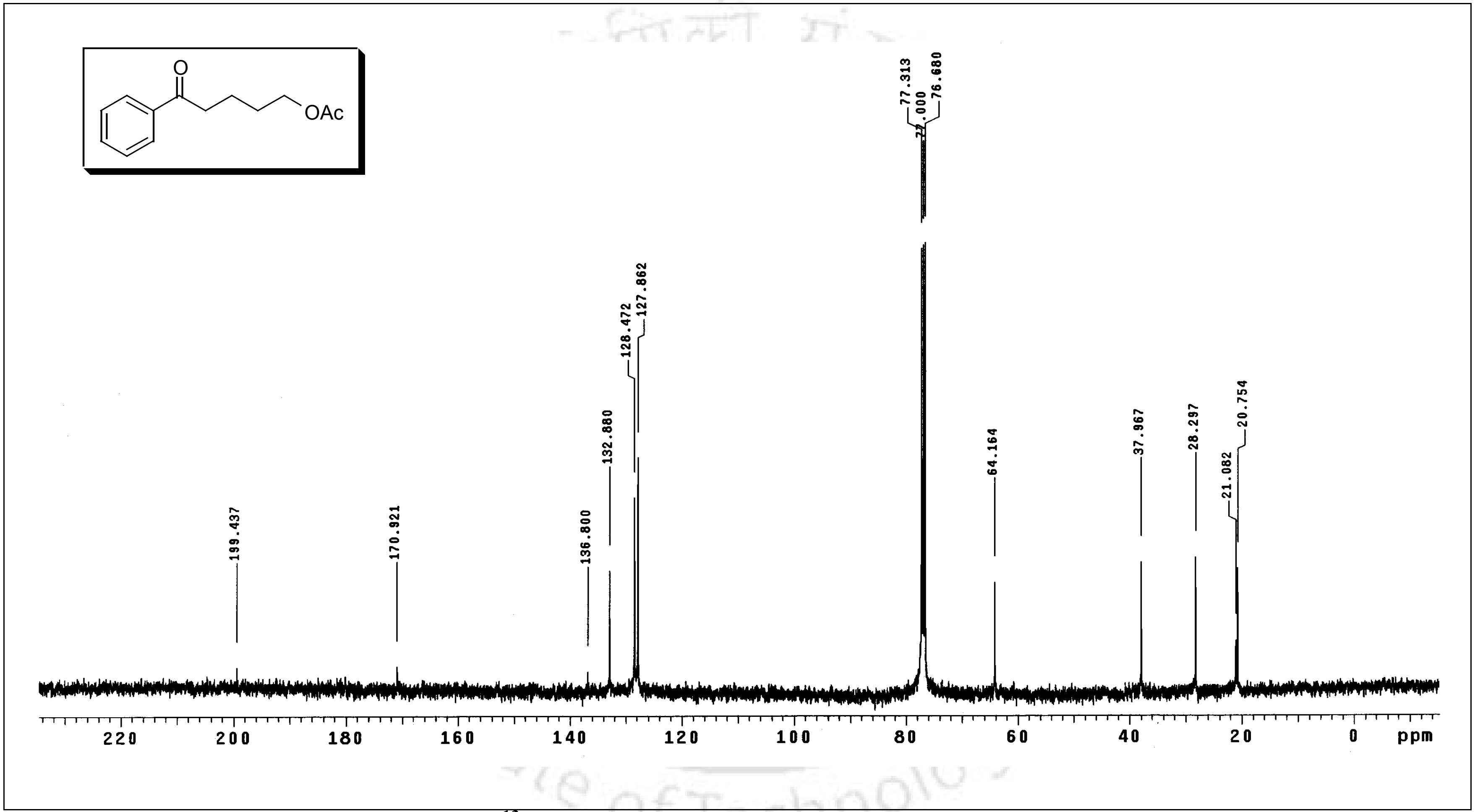


Figure 6: ^{13}C NMR spectrum of (4-benzoyl)butylacetate (110)

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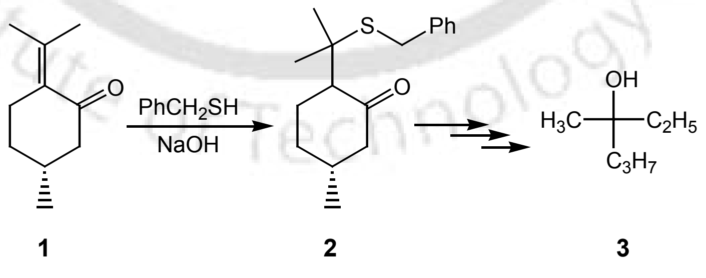
A BRIEF LITERATURE SURVEY ON THE MICHAEL ADDITION REACTION OF THIOLS TO THE ELECTRON DEFICIENT ALKENES

REVIEW OF LITERATURE

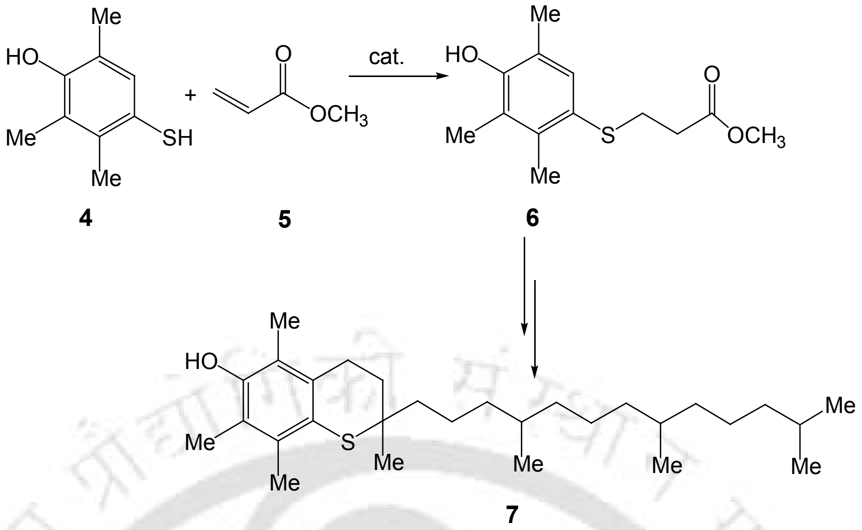
The Michael reaction since its discovery in 1889[1] has been used as one of the most useful methods for carbon-carbon bond formation and later on it has been further extended for carbon-sulfur, carbon-oxygen and carbon-nitrogen bond forming reactions. Addition of thiols to α,β-unsaturated carbonyl compounds is a very important process for carbon-sulfur bond formation.[2] Organosulfur compounds are useful and important in the synthesis of some compounds having promising biological activities. Recently, conjugate addition of thiols to α,β-unsaturated carbonyl compounds has attracted considerable interest as it leads to the synthesis of biologically active compounds such as calcium antagonist diltiazem.[3] Further this type of conjugate addition gains importance by protecting selectively the olefinic double bond of a conjugated carbonyl compound and the deprotection can be done easily either by copper(I)-induced elimination[4] or by oxidation followed by thermolytic elimination.[5] Moreover, the resultant β-sulfido carbonyl compounds serve as starting materials for the generation of β-acylvinyl cation equivalents[6] and homoenolate equivalents.[7] On the other hand, the thia-Michael addition product(s) of α,β-unsaturated carbonyl compounds are very important building blocks for the synthesis of bioactive compounds,[8] heterocycles,[9] and are also used as chiral auxiliary for the synthesis of optically active α-hydroxy aldehydes.[10] Some of the applications of thia-Michael reaction have been highlighted below.

Eliel *et al* showed[11] the importance of thia-Michael reaction through the synthesis of (*R*)-(+)-ethylmethyl-n-propylcarbinol starting from (+)-Pulegone, depicted in Scheme 1.



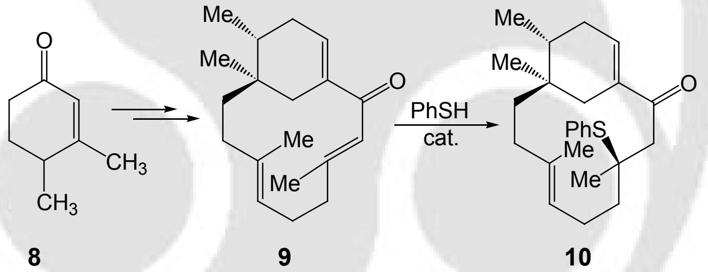
Scheme 1

Later on, Robillard *et al* synthesized 2-substituted 5,7,8-trimethyl-6-hydroxythiochromans[12] using the thia-Michael adduct between methyl acrylate and 2,3,5-trimethyl-4-hydroxybenzenethiol, shown in Scheme 2.



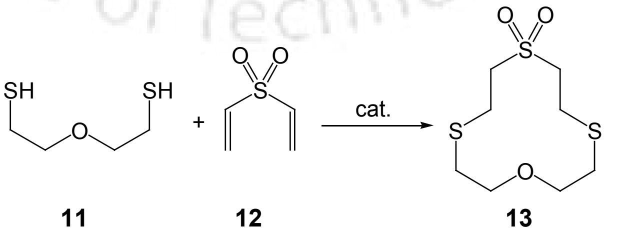
Scheme 2

The importance of the thia-Michael reaction can also be realized from the synthesis of the phomactin core,[2] achieved by Houghton *et al*. This has been shown in Scheme 3.



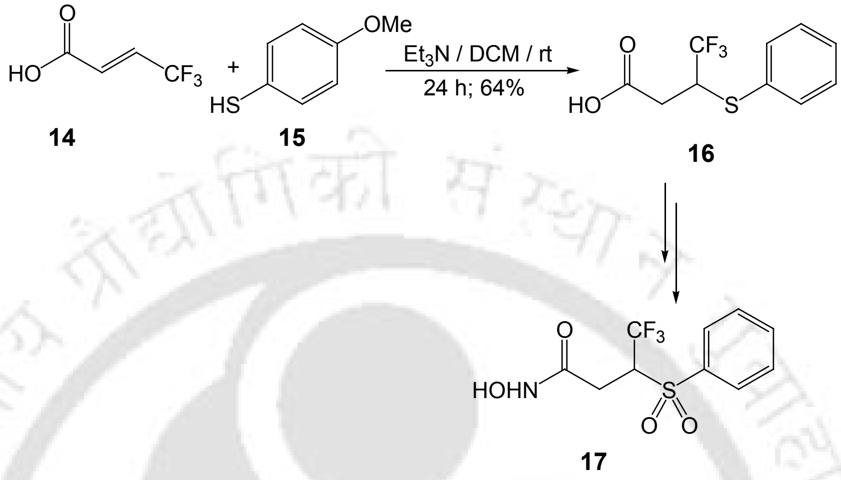
Scheme 3

According to Teyssot *et al*, bis-heteronucleophilic Michael addition to divinyl sulfone gives macrocycles[13] in good yields, shown in Scheme 4.



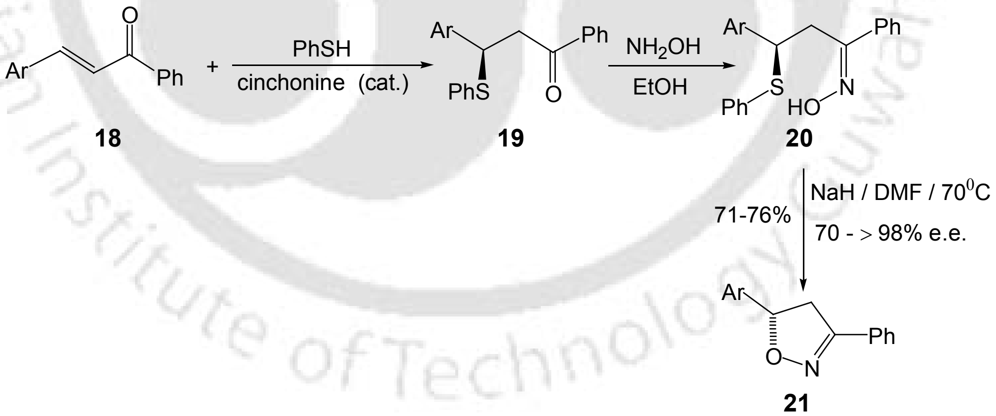
Scheme 4

In the recent past, Zanda *et al* used thia-Michael reaction during the synthesis of γ-trifluoromethyl γ-sulfone hydroxamate[14] inhibitor of stromelysin-1 (MMP-3), which is depicted in Scheme 5.



Scheme 5

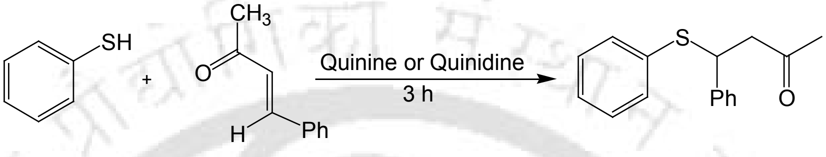
Very Recently Skarzewski *et al* utilized thia-Michael reaction for the stereospecific synthesis of 4,5-dihydroisoxazoles,[9] shown in Scheme 6.



Scheme 6

Considering all these wide applications, it is quite clear that the development of an efficient and selective catalyst for the construction of carbon-sulfur bond is of interest in organic synthesis. Thia-Michael reaction is classically carried out either by the activation of thiols by a base or by the activation of the acceptor olefins with Lewis acids. Over the years many methods have been developed for thia-Michael reaction. Some of them have been highlighted below.

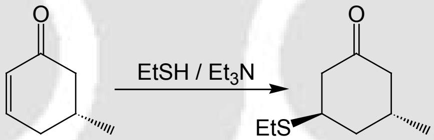
Gogte *et al* performed[15] thia-Michael using quinine and quinidine bases as catalyst under reflux condition, which has been shown in Scheme 7. The main disadvantages of this method are harsh reaction condition, longer reaction time and considerable amount of disulfide formation.



22 **23** **24**

Scheme 7

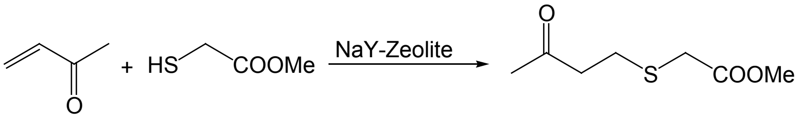
Djerassi *et al*, during optical rotatory dispersion studies,[16] performed thia-Michael reaction by using Et_3N as a base, shown in Scheme 8. In most of the cases, the base catalyzed thia-Michael reactions encounter many side reactions such as polymerization, disulfide formation, bis-addition, self-condensations etc.



25 **26**

Scheme 8

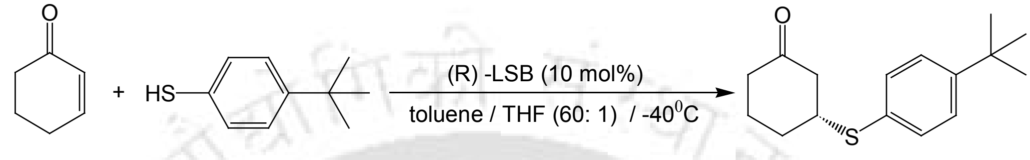
Sreekumar *et al* reported[17] that NaY-Zeolite can be used as a heterogeneous catalyst for thia-Michael reaction which has been presented in Scheme 9. Though the reaction takes less reaction time but it gives poor yields.



27 **28** **29**

Scheme 9

In recent years, the catalytic asymmetric thia-Michael addition promoted by chiral metal complexes has been recognized as an efficient method for enantioselective carbon-sulfur bond formation. Shibasaki *et al* used $LaNa_3$-tris(binaphthoxide)[18] (LSB) as an efficient catalyst for asymmetric Michael addition of thiols to cycloalkenones. The method gives an excellent enantioselectivity, shown in Scheme 10.



30 **31** **32**

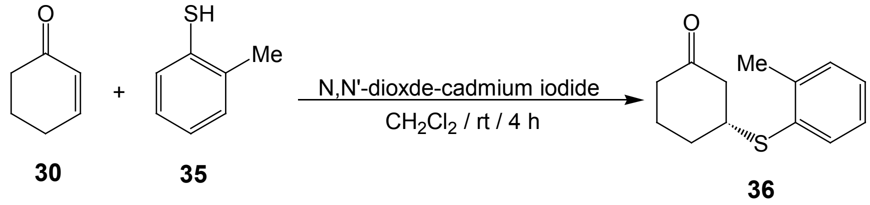
Scheme 10

Later on Kanemasa *et al* introduced[19] another chiral ligand, 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph), for asymmetric conjugate addition of thiols to a 3-(2-alkenoyl)-2-oxazolidinone, presented in Scheme 11. This method also provides an excellent enantioselectivity.

22 **33** **34**

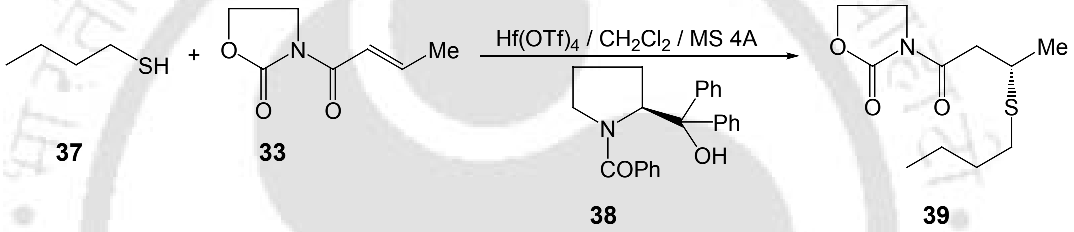
Scheme 11

Chiral *N, N*′-dioxde-cadmium iodide complex was used by Nakajima *et al* as a chiral catalyst[20] for enantioselective conjugate addition of thiols to cyclic enones and enals which has been depicted in Scheme 12. The major disadvantages of this method are longer reaction time, requirement of excess amount of thiols etc.



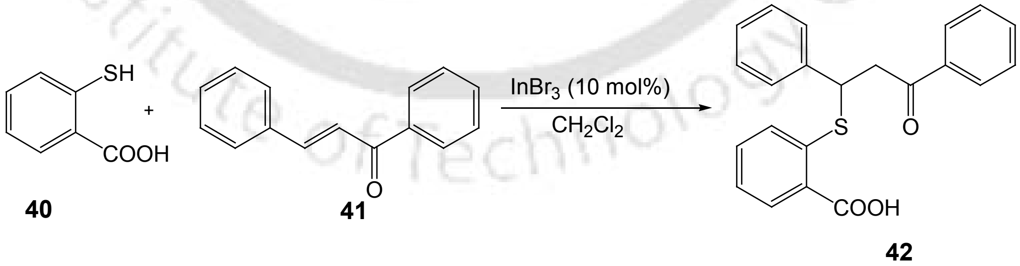
Scheme 12

By employing Ligand-acceleration strategy, Kobayashi *et al* introduced[21] ligand-accelerated chiral Lewis acid catalyst for asymmetric Michael addition of thiols to α,β-unsaturated carbonyls which is shown in Scheme 13. Though the method gives satisfactory enantioselectivity still it suffers from the drawback such as longer reaction time.



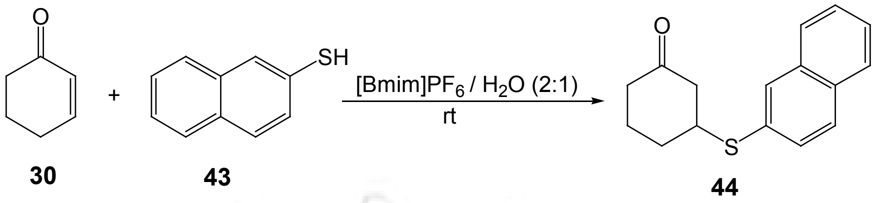
Scheme 13

Umani-Ronchi *et al* reported[22] that $InBr_3$ can be used as a catalyst for thia-Michael reaction which is shown in Scheme 14. The most interesting feature of this method is that the highly deactivated substituted aryl thiol such as thiolsalicylic acid affords the desired thia-Michael product in excellent yield. The main drawback is the reagent is highly expensive reagent.



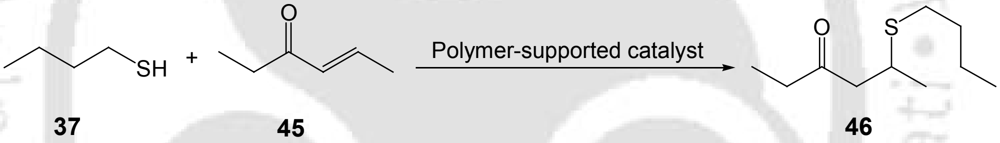
Scheme 14

In recent times, ionic liquids have emerged as an alternative reaction media for the immobilization of transition-metal catalysts, Lewis acids and enzymes. They are being used as green solvents and referred to as 'designer solvents' because of their versatile properties. Yadav *et al* demonstrated[23] ionic liquid as a green solvent for the thia-Michael reaction in excellent yields under mild and neutral conditions, shown in Scheme 15.



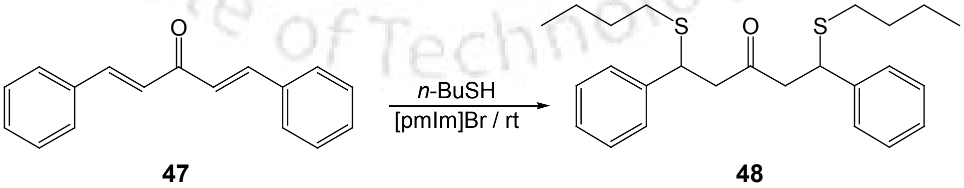
Scheme 15

Polymer supported catalysts have attracted much attention in organic synthesis because of the easy workup procedures and minimization of cost and waste generation by recycling the catalyst. Spencer *et al* introduced[24] a method for thia-Michael reaction using polymer-supported acid as a catalyst, which is shown in Scheme 16. The main disadvantage of this method is longer reaction time.



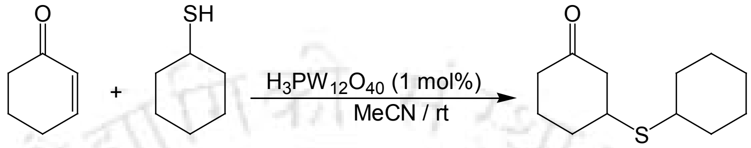
Scheme 16

Ranu *et al* reported[25] the novel application of an inexpensive ionic liquid, 1-pentyl-3-methylimidazolium bromide [pmIm]Br as an efficient catalyst as well as reaction medium for thia-Michael reaction, as shown in Scheme 17. The main disadvantage of this method is longer reaction time.



Scheme 17

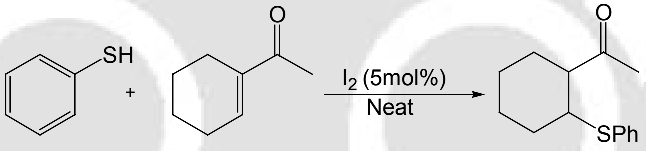
In recent years, heteropolyacids (HPAs) are gaining interest as catalysts in organic synthesis because of their more catalytic activity compared to the conventional inorganic and organic acids. Firouzabadi *et al* used dodecatangstophosphoric acid ($H_3W_{12}O_{40}$) [26] as a recyclable heterogeneous catalyst for thia-Michael reaction. This has been depicted in Scheme 18. The method is efficient in terms of reaction time and yield.



30 **49** **50**

Scheme 18

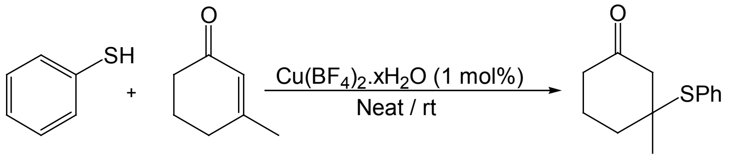
Over the past few years, molecular (I_2) has emerged as an efficient catalyst for various organic transformations. Yao *et al* reported[27] a method for thia-Michael reaction using molecular iodine (I_2) as catalyst; this has been shown in Scheme 19. Though the method is highly efficient in terms of reaction time and yield, still it suffers from one major drawback that it includes a tedious workup procedure.



22 **51** **52**

Scheme 19

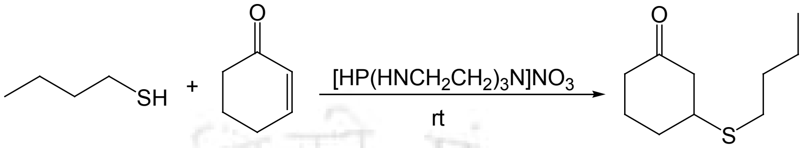
In Lewis acid catalyzed thia-Michael reaction, probably the Lewis acid coordinates with the carbonyl oxygen of the α,β-unsaturated carbonyl compound and makes it more susceptible to nucleophilic attack at the β-carbon. Chakraborti *et al* performed[28] thia-Michael reaction using copper(II) tetrafluoroborate as a novel and highly efficient Lewis acid catalyst, shown in scheme 20. The method is efficient in terms of yield and reaction.



22 **53** **54**

Scheme 20

Very recently, Verkade *et al* disclosed[29] that azaphosphatrane nitrate salt, $[HP(HNCH_2CH_2)_3N]NO_3$ can be used as an efficient homogeneous and solid-supported promoter for thia-Michael reaction which has been depicted in Scheme 21. The major disadvantage of this method is longer reaction time.



37 **30** **55**

Scheme 21

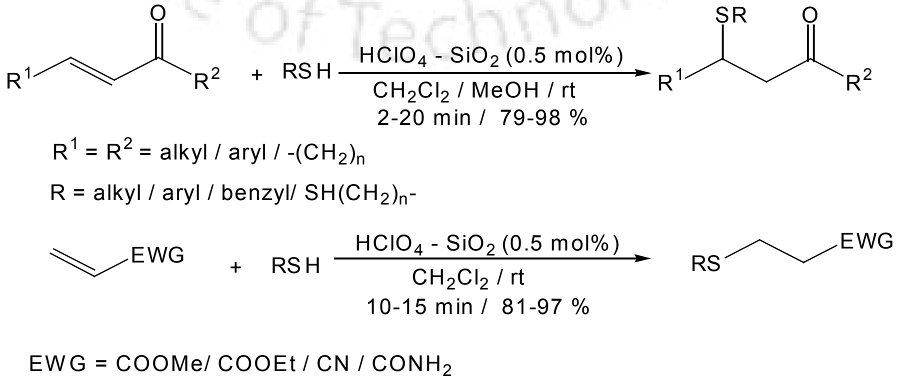
Over the years, some other methods have also been developed for thia-Michael reaction using other reagents such as: modified cinchona alkaloid,[30] potassium fluoride,[31] clay-supported $NiBr_2$ and $FeCl_3$,[32] Fluorapatite,[33] $InCl_3$,[34] $Bi(NO_3)_3$,[35] $Bi(OTf)_3$,[36] $RuCl_3$,[37] molten tetrabutylammonium bromide,[38] etc. Recently, Firouzabadi and his group demonstrated that SDS[39a] can be employed as an efficient catalyst for Michael addition of mercaptans. Very recently, Chakraborti *et al* reported[39b] the catalyst-free conjugated addition of thiols to α,β-unsaturated carbonyl compounds in water. Unfortunately, many of these methods have serious drawbacks such as harsh reaction condition, low yield, longer reaction time, the catalyst is not readily available and involvement of highly expensive reagent as catalyst. Therefore, with this literature background on the utility of thia-Michael reaction our aim is to find out better synthetic methodology for thia-Michael reaction which will be easy to handle, economically viable, and functional under mild condition.

NEW SYNTHETIC METHOD FOR THIA-MICHAEL REACTION USING SILICA SUPPORTED PERCHLORIC ACID

RESULTS AND DISCUSSION

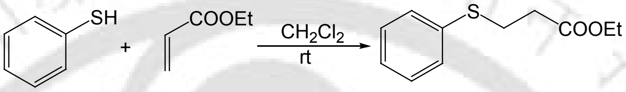
Results and discussion

From the review of the literature it is quite clear that thia-Michael reaction is a very important reaction in organic synthesis. Over the years, many methods have been developed for thia-Michael reaction. Unfortunately, many of these procedures have one or other disadvantages such as longer reaction time, use of excessive expensive catalyst, harsh reaction conditions, sometimes fails to provide addition product and tedious experimental procedure. Therefore, development of an efficient and mild synthetic protocol is always in great demand to make the available procedures more convenient and simple. Very recently solid supported reagents[40] have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, greater selectivity and ease of handling. In continuation of our ongoing research programme to develop better and newer synthetic methodologies, we perceived that perchloric acid impregnated on silica gel ($HClO_4$-SiO_2) might be a very useful solid supported catalyst for the thia-Michael reaction. The catalyst, $HClO_4$-SiO_2 has so far been utilized for acetylation of phenols, thiols, alcohols and amines,[41] peracetylation of carbohydrates,[42] acetalization followed by acetylation,[43] glycosylation reaction[44] and for Ferrier rearrangement of glycals.[45] Very recently, we also noticed that the same catalyst is highly effective for the *gem* diacylation of aldehydes.[46] Therefore, we became interested to study whether the same catalyst is useful or not for the thia Michael reaction. In this section, we want to discuss that $HClO_4$-SiO_2 is an efficient and valuable catalyst for 1, 4-conjugate addition of thiols to a wide variety of conjugated alkenes[47] such as α,β-unsaturated ketones, carboxylic esters, nitriles and amides as shown in scheme 22.



Scheme 22

For our investigations, $HClO_4$-SiO_2 was prepared according to the literature procedure.[41] To evaluate the better catalytic activity of $HClO_4$-SiO_2 over silica gel or aqueous perchloric acid, a model study was carried out with thiophenol and ethyl acrylate using various catalytic conditions, as shown in Table 1. From the study, it clearly demonstrated that the silica-supported perchloric acid is indeed an effective catalyst in terms of reaction time and yield.



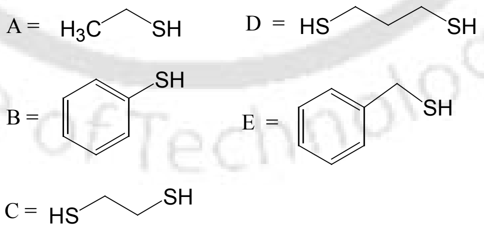
Scheme 23

Table 1. The result of the reaction of ethyl acrylate (2 mmol) with thiophenol (2.2 mmol) under different catalytic conditions in dichloromethane at room temperature.

Run	Catalyst	Time	Yield[a,b] [/%]
I	No catalyst	24 h	52
II	SiO_2 (10 mg /mmol)	24 h	63
III	Aqueous $HClO_4$ (0.5 mol%)	1 h	82
IV	$HClO_4$-SiO_2 (10mg/mmol, 0.5 mol%)	10 min	95

a. Isolated yield. b. All the compounds were characterized by recording IR, ^1H NMR, ^{13}C NMR and elemental analyses

Thia-Michael reaction of 2-cyclopenten-1-one (**56**) with ethanethiol (**A**) using 0.5 mol% of catalyst in dichloromethane at room temperature proceeded within 5 min and the pure product 3-[ethylthio]-cyclopentanone (**64**) was isolated in 92% yield as a gummy liquid by filtration through a short silica gel column. The product was characterized by IR, ^1H NMR, ^{13}C NMR spectra and elemental analysis and it was agreeable with the 1,4-addition product. The enone **56** also reacted with thiophenol (**B**) in the presence of same catalyst under identical conditions to provide the desired addition product **65** in 98% yield, in quicker time with better yield compared to the recently reported procedure.[22] Likewise, 1,2-ethanedithiol (**C**) on reaction with two molecules of enone **56** smoothly provided the *bis*-Michael addition product **66** within 5 min in good yield without any difficulty. By following identical reaction procedure, 2-cyclohexen-1-one (**30**) also reacted with ethanethiol (**A**), thiophenol (**B**) and 1,3-propanedithiol (**D**) to furnish the desired Michael addition products **67**, **68** and **69** respectively in good yields. We observed that the present protocol is highly efficient in terms of mol% of the catalyst used and yields than the very recently reported procedure.[22] 4,4-Dimethyl-2-cyclohexen-1-one (**57**) was readily converted into **70** on reaction with thiophenol (**B**) in good yields. The results are summarized in Table 2. Next, we were interested to see whether the same catalyst is useful for the Michael reaction of acyclic α,β-unsaturated ketones or not. Remarkably, the enone 16-dehydropregnenolone (16-DPA) (**58**) was also reacted with ethanethiol (**A**) and thiophenol (**B**) independently to give the 1,4-addition products **71** and **72** respectively in fairly good yields using the same catalyst under similar reaction conditions. In addition, by using methanol as the solvent, it is possible to access Michael addition products **73** and **74** from the corresponding chalcone (**41**) in very good yields. Notably, by employing our protocol, the naturally occurring α,β-unsaturated ketones such as *S* (+)-carvone (**59**) and *R*-(+) pulegone (**1**) were afforded corresponding Michael addition products **75**, **76** and **2** respectively as diastereomeric mixture on treatment with thiols under identical reaction conditions. It is noteworthy to point out that the addition reaction of *R*-(+)- pulegone (**1**) with benzylthiol (**E**) took much longer reaction time under basic conditions.[11] One more advantage of the present method is that the reaction does not need to be carried out under N_2 atmosphere.



Scheme :

All the final products were characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. The structure of compound **72** was determined by X-ray crystallography. The ORTEP diagram is shown in Figure 1.

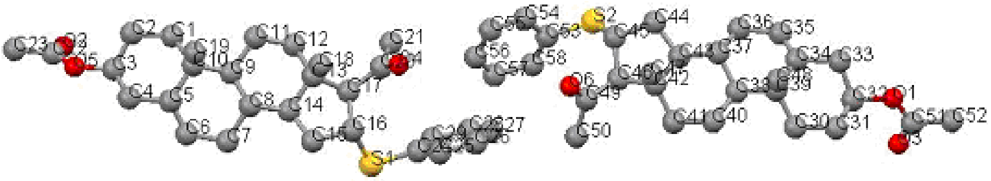


Figure 1: ORTEP plot of the molecule with atom numbering scheme. Hydrogen atoms are omitted for clarity.

Each unit cell contains two identical molecules. The torsion angles between H_{32}-C_{16}-C_{17}-H_{46}, S_1-C_{16}-C_{17}-H_{46}, H_{32}-C_{16}-C_{17}-C_{20} and C_{20}-C_{17}-C_{16}-S_1 are 155.27°, 31.32°, 32.44° and 92.49° respectively. These results are in accordance with the fact that H_{46} and H_{32} as well as C_{20} and S_1 are in *anti* orientation as shown in Figure 2.

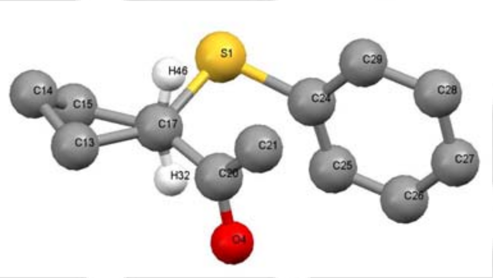
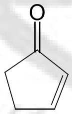
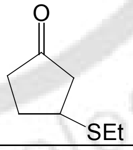
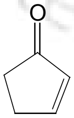
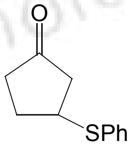
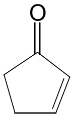
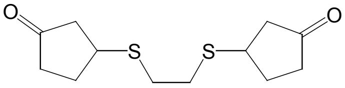
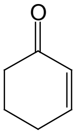
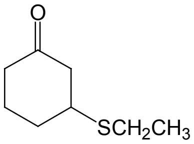
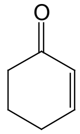
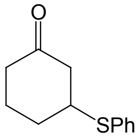
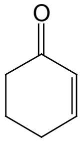
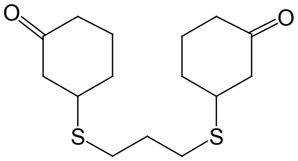
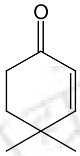
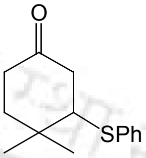
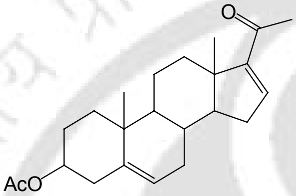
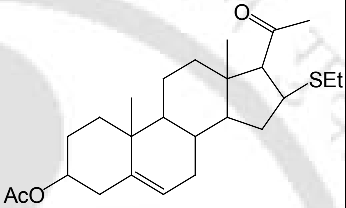
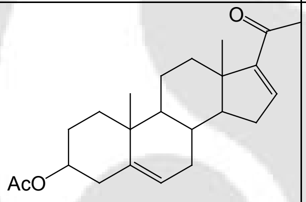
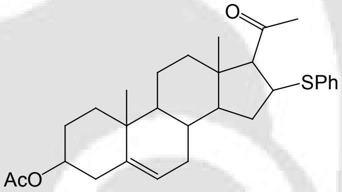
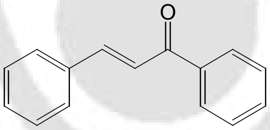
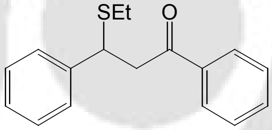
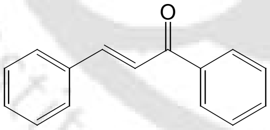
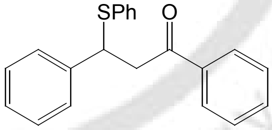
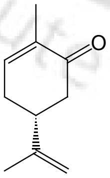
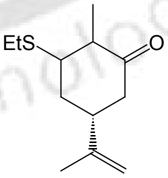
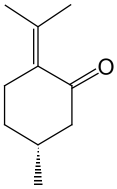
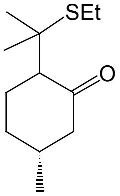


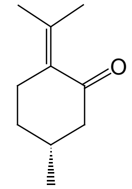
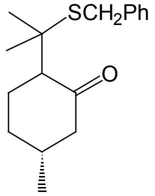
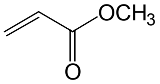
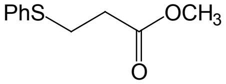
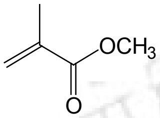
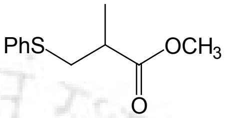
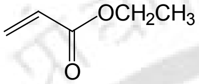
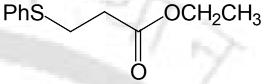
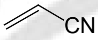
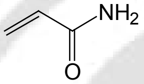
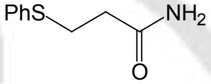
Figure 2: Front view of some selected portion

Moreover, by employing the present protocol, various α,β-unsaturated esters namely methyl acrylate (**5**), methyl methacrylate (**60**) and ethyl acrylate (**61**) furnished the desired Michael addition products **77**, **78** and **79** respectively, on reaction with thiophenol (**B**) in good yields. Furthermore, our methodology can be extended for 1,4-conjugate addition reaction of thiols with acrylonitrile (**62**) and acrylamide (**63**) providing the products **80** and **81** respectively under identical conditions. We have also studied the recyclability of the catalyst by the following way. The reaction of acrylonitrile (100 mmol) with thiophenol (110 mmol) was carried out in the presence of $HClO_4$-SiO_2 (0.5 mol%, 1 g). After completion, the catalyst was filtered off and activated by heating at 80 ^{0}C under vacuum for 1 hour and reused for thia-Michael reaction of a fresh lot of acrylonitrile (100 mmol) with thiophenol (110 mmol) affording 85% yield of the desired product after 20 min. Again, the catalyst was recovered, reactivated and reused repeatedly for three more consecutive runs for thia-Michael reactions with acrylonitrile (100 mmol) affording 81%, 76% and 70 % yields respectively, in 25, 30 and 35 min. From this observation, it is clear that the reaction can be performed in a large-scale as well as the catalyst can be reused although efficiency of the catalyst is lesser in further cycles. To check whether the catalyst looses its activity by leaching the actual catalyst perchloric acid during the experiment since it gave lesser yield and took longer time during reusability test. To verify it, a reaction of ethylacrylate (2 mmol) and thiophenol (2.2 mmol) was carried out following the same experimental procedure. After completion of the reaction, the catalyst was removed by filtration through Whatman 40 filter paper. To the filtrate was added another 2.2 mmol of thiophenol and 2 mmol of cyclohexenone and stirring was continued. A parallel reaction was performed with 2.2 mmol of thiophenol and 2 mmol of cyclohexenone in dichloromethane without any catalyst. The isolated yield of **68** from the above two reactions were 30% and 27% respectively after five hours. From this observation, it is clear that no leaching has occurred during the experiment. But may be due to the poisoning of the surface of the catalyst isolated yields are less and required longer reaction time in the recycling experiments.

Table 2. Michael addition of thiols to conjugated alkenes catalyzed by silica supported perchloric acid ($HClO_4$-SiO_2)

Substrate No	Substrate	Time min	Product^a	Product No	Yield %
56		5		**64**	92
56		2		**65**	98
56		5		**66**	80
30		5		**67**	94

30		2		**68**	97
30		5		**69**	81
57		20		**70**	82
58		20		**71**	79
58		20		**72**	82
41		15		**73**	93^b
41		15		**74**	95^b
59		10		**75**	95
1		10		**76**	80

1		10		**2**	86
5		10		**77**	88
60		10		**78**	91
61		10		**79**	95
62		10		**80**	97
63		15		**81**	91

[a]All the compounds were characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. Yield refers to isolated yield. [b]The reaction was carried out in methanol instead of dichloromethane.

In conclusion, the unique properties of silica supported perchloric acid allowed us to demonstrate a new synthetic methodology for the thia Michael addition reaction. The significant advantages of our protocol are: very good yields, mild conditions, short reaction times, non-aqueous work-up procedure and involvement of non-expensive reusable catalyst.

PART II

NEW SYNTHETIC METHOD FOR THIA-MICHAEL REACTION USING SILICA SUPPORTED PERCHLORIC ACID

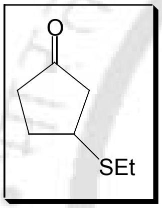
EXPERIMENTAL

Experimental

Typical experimental procedure for thia-Michael reaction:

To a magnetically stirred solution of 2-cyclohexene-1-one (0.192 g, 2 mmol) and thiophenol (0.242 g, 2.2 mmol) in dichloromethane (2 mL) was added $HClO_4$-SiO_2 (20 mg, 0.5 mol%). The reaction was instantly completed as checked by TLC. After completion of the reaction, the reaction mixture was directly passed through a silica gel column to obtain pure desired Michael addition product (0.400 g, 97%) as a colourless oily liquid. In case of solid product, it was obtained by removing the catalyst by filtration followed by recrystallization.

3-Thioethylcyclopentanone (64):



Nature: Viscous liquid

Yield: 92%

Reaction time: 5 min

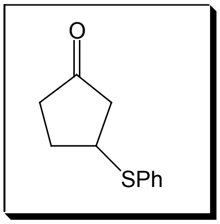
IR (Neat): cm^{-1} 3068, 2966, 1752, 1583, 1481, 1399, 1286, 1153, 1030

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H, J = 7.2 Hz), 1.89-1.98 (m, 1H), 2.15-2.23 (m, 2H), 2.31-2.48 (m, 2H), 2.56-2.62 (m, 3H), 3.46 (quin, 1H, J = 6.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 25.1, 29.7, 36.9, 39.8, 45.5, 216.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_7H_{12}OS$	C 58.29	C 58.08
144.23	H 8.39	H 8.35
	S 22.23	S 22.01

3-Thiophenylcyclopentanone (65):



Nature: Viscous liquid

Yield: 98%

Reaction time: 2 min

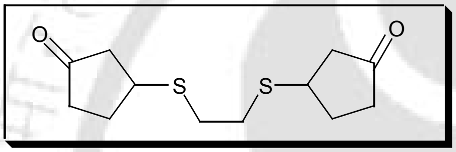
IR (Neat): cm^{-1} 3068, 2966, 1752, 1583, 1475, 1399, 1286, 1245, 1153, 1020

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.00-2.06 (m, 1H), 2.16-2.38 (m, 3H), 2.44-2.52 (m, 1H), 2.61 (dd, 1H, *J* = 7.2 Hz, *J* = 18.8 Hz), 3.89 (quin, 1H, *J* = 6.0 Hz), 7.24-7.33 (m, 3H), 7.40 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$): δ 29.3, 36.8, 43.4, 45.2, 127.4, 129.1 (2C), 131.9 (2C), 134.2, 216.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{12}OS$	C 68.71	C 68.86
192.28	H 6.29	H 6.38
	S 16.68	S 16.52

Spectroscopic data for compound 66:



Nature: Viscous liquid

Yield: 80%

Reaction time: 5 min

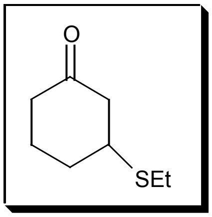
IR (Neat): cm^{-1} 3012, 2955, 1747, 1434, 1363, 1235, 1045

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.71-1.76 (m, 1H), 1.91-2.00 (m, 2H), 2.12-2.27 (m, 3H), 2.33-2.50 (m, 3H), 2.58-2.66 (m, 2H), 2.71-2.86 (m, 5H), 3.29-3.34 (m, 1H), 3.47-3.52 (m, 1H) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$): δ 30.3 (2C), 31.8 (2C), 37.4 (2C), 41.0 (2C), 46.1 (2C), 216.5 (2C) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{18}O_2S_2$	C 55.78	C 55.91
258.40	H 7.02	H 7.13
	S 24.82	S 24.67

3-thioethylcyclohexanone (67):



Nature: Viscous liquid

Yield: 94%

Reaction time: 5 min

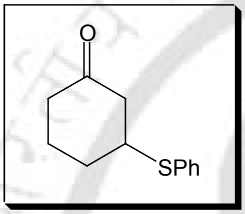
IR (Neat): cm^{-1} 2935, 2873, 1711, 1445, 1327, 1271, 1224, 979, 748

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.68-1.79 (m, 2H), 2.10-2.16 (m, 2H), 2.31-2.39 (m, 3H), 2.57 (q, 2H, *J* = 7.2 Hz), 2.70 (dd, 1H, *J* = 4.5 Hz, *J* = 14.2 Hz), 3.02-3.12 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 24.4, 24.6, 31.7, 41.0, 42.5, 48.2, 208.6 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_8H_{14}OS$	C 60.72	C 60.93
158.26	H 8.92	H 8.81
	S 20.26	S 20.04

3-thiophenylcyclohexanone (68):



Nature: Viscous liquid

Yield: 97%

Reaction time: 2 min

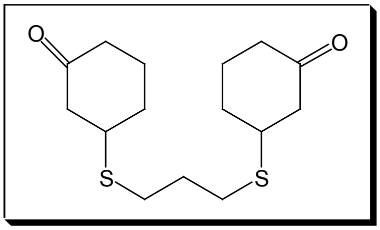
IR (Neat): cm^{-1} 2950, 2858, 1716, 1583, 1475, 1445, 1317, 1235, 1030

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68-1.75 (m, 2H), 2.11-2.18 (m, 2H), 2.29-2.34 (m, 3H), 2.68 (dd, 1H, *J* = 4.4 Hz, *J* = 18.8 Hz), 3.39-3.44 (m, 1H), 7.26-7.32 (m, 3H), 7.39-7.42 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.2, 31.4, 40.9, 46.2, 47.9, 127.7, 128.9 (2C), 132.9 (2C), 133.1, 208.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{14}OS$	C 69.86	C 69.64
206.31	H 6.84	H 6.91
	S 15.54	S 15.72

Spectroscopic data for compound 69:



Nature: Viscous liquid

Yield: 81%

Reaction time: 5 min

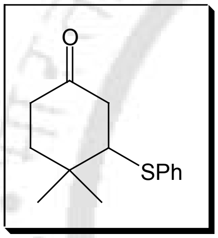
IR (Neat): cm^{-1} 3016, 2958, 1712, 1438, 1369, 1241, 1039

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.66-1.77 (m, 4H), 1.84 (quin, 2H, *J* = 7.2 Hz), 2.10-2.18 (m, 4H), 2.27-2.40 (m, 6H), 2.65 (t, 4H, *J* = 7.2 Hz), 2.71 (dd, 2H, *J* = 4.4 Hz, *J* = 14.4 Hz), 3.02-3.08 (m, 2H) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$): 24.6 (2C), 29.7 (2C), 29.8 (2C), 32.0 (2C), 41.3 (2C), 43.3, 48.5 (2C), 208.7 (2C) ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{15}H_{24}O_2S_2$	C 59.96	C 59.78
300.49	H 8.05	H 8.13
	S 21.34	S 21.22

4, 4-Dimethyl-3-thiophenylcyclohexanone (70):



Nature: White solid

Yield: 82%

Reaction time: 20 min

M. P.: 68 ^{0}C

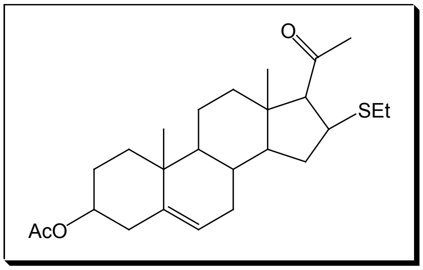
IR (KBr): cm^{-1} 3058, 2966, 2935, 2873, 1711, 1583, 1481, 1450, 1409, 1306, 1245, 1163, 1091, 1025, 743, 697

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.17 (s, 3H), 1.23 (s, 3H), 1.59-1.62 (m, 1H), 1.82-1.86 (m, 1H), 2.23-2.28 (m, 1H), 2.37-2.41 (m, 1H), 2.50-2.58 (m, 2H), 3.11-3.15 (m, 1H), 7.17-7.37 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 21.0, 29.0, 34.61, 37.8, 38.6, 45.4, 57.6, 127.4, 129.1 (2C), 132.7 (2C), 134.6, 209.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{14}H_{18}OS$	C 71.75	C 71.49
234.36	H 7.74	H 7.67
	S 13.68	S 13.45

Spectroscopic data for compound 71:



Nature: White solid

Yield: 79%;

Reaction time: 20 min

M. P.: 126 °C

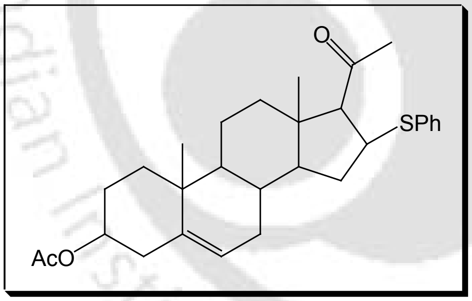
IR (KBr): cm^{-1} 2935, 2863, 1731, 1706, 1455, 1373, 1250, 1178, 1040

^{1}H NMR (300 MHz, CDCl$_3$): δ 0.62 (s, 3H), 0.98-1.10 (m, 10H), 1.01(s, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.23 (t, 6H, *J* = 7.2 Hz), 1.49-1.58 (m, 16H), 1.86 (d, 3H, *J* = 9.6 Hz), 1.97 (d, 3H, *J* = 9.3 Hz), 2.03 (s, 6H), 2.16 (s, 3H), 2.19 (s, 3H), 2.32 (d, 2H, *J* = 9.6 Hz), 2.41-2.62 (m, 4H), 2.69 (d, 2H, *J* = 9.9 Hz), 3.42-3.48 (m, 1H), 3.72-3.76 (m, 1H), 4.61 (m, 2H), 5.37 (m, 2H) ppm.

^{13}C NMR (75 MHz, CDCl$_3$): δ 207.4 (2C), 170.5(2C), 139.9, 139.6, 122.1 (2C), 73.8, 73.7, 72.1, 67.2, 55.8, 54.9, 50.1, 49.7, 45.3, 42.8, 42.7, 40.5, 38.7, 38.5, 38.0, 37.8, 36.9, 36.6, 28.0, 27.7, 26.4, 21.4 (2C), 20.8, 20.4, 19.3, 17.6, 14.7, 14.6, 14.2, 13.88 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{25}H_{38}O_3S$	C 71.73	C 71.48
418.64	H 9.15	H 9.10
	S 7.66	S 7.42

Spectroscopic data for compound 72:



Nature: White solid

Yield: 82%

Reaction time: 20 min

M.P.: 134 ^{0}C

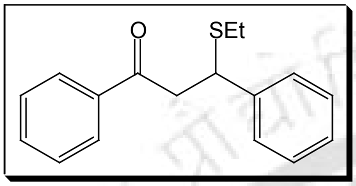
IR (KBr): cm^{-1} 2971, 2950, 2899, 2848, 2817, 1731, 1711, 1635, 1589, 1481, 1440, 1378, 1245, 1035, 753, 702

^{1}H NMR (400 MHz, CDCl$_3$): 0.66 (s, 3H), 1.00 (s, 3H), 0.92-1.02 (m, 5H), 1.40-1.80 (m, 8H), 1.82 (d, 2H, *J* = 10.8Hz), 1.83-1.97 (m, 4H), 2.01 (s, 3H), 2.29-2.32 (m, 1H), 2.60 (d, 1H, *J* = 8.4 Hz), 4.10-4.22 (m, 1H), 4.55-4.62 (m, 1H), 5.35-5.37 (m, 1H), 7.10-7.20 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 14.2, 19.4, 20.9, 21.5, 27.8, 31.4, 31.7, 31.8, 34.7, 36.6, 36.9, 38.1, 38.9, 43.6, 45.4, 49.7, 54.9, 70.9, 73.9, 121.9, 126.4, 128.7 (2C), 130.8 (2C), 135.9, 139.4, 170.2, 206.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{29}H_{38}O_3S$	C 74.64	C 74.35
466.68	H 8.21	H 8.14
	S 6.87	S 6.82

1, 3-Diphenyl-3-thioethyl-propan-1-one (73):



Nature: White solid

Yield: 93%

Reaction time: 15 min

M. P.: 61-62 °C

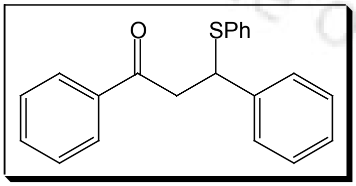
IR (KBr): cm^{-1} 3065, 2966, 2929, 1693, 1594, 1454, 1340, 1223, 978, 761, 693

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.16 (t, 3H, J = 7.2 Hz), 2.30-2.39 (m, 2H), 3.52 (d, 2H, J = 7.6 Hz), 4.57 (t, 1H, J= 7.2 Hz), 7.18 (t, 1H, J= 7.2 Hz), 7.28 (t, 2H, J= 8.0 Hz), 7.38 -7.43 (m, 4H), 7.52 (t, 1H, J= 7.2 Hz), 7.89 (d, 2H, J= 7.6 Hz) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$): 14.8, 25.9, 44.4, 45.8, 127.4, 128.0 (2C), 128.3 (2C), 128.7 (2C), 128.8 (2C), 133.4, 137.0, 142.4, 196.9 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{18}OS$	C 75.52	C 75.18
270.39	H 6.71	H 5.65
	S 11.86	S 11.58.

1, 3-Diphenyl-3-thiophenyl-propan-1-one (74):



Nature: White solid

Yield: 95%

Reaction time: 15 min

M. P.: 114-115°C

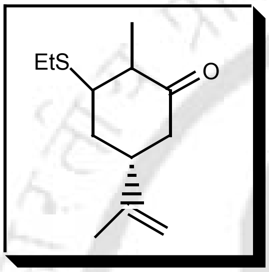
IR (KBr): cm^{-1} 3068, 2955, 2904, 1685, 1588, 1486, 1455, 1404, 1342, 1230, 1086

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.56 (dd, 1H, J = 6.0 Hz, J = 17.2 Hz), 3.64 (dd, 1H, J = 8.4 Hz, J = 17.2 Hz), 4.93 (dd, 1H, J = 6.0 Hz, J = 8.4 Hz), 7.14-7.23 (m, 6H), 7.28-7.31 (m, 4H), 7.40 (t, 2H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.85 (d, 2H, J = 8.0 Hz) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$): δ 44.8, 48.3, 127.2, 127.4, 127.6 (2C), 127.9 (2C), 128.3 (2C), 128.4 (2C), 128.7 (2C), 132.6 (2C), 133.1, 134.1, 136.6, 141.0, 196.7 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{21}H_{18}OS$	C 79.21	C 78.95
318.43	H 5.70	H 5.65
	S 10.07	S 9.87

3-thioethylcarvone (75):



Nature: Viscous liquid

Yield: 95%

Reaction time: 10 min

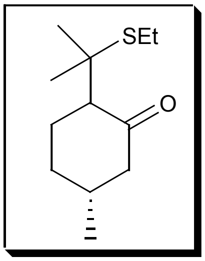
IR (Neat): cm^{-1} 3078, 2981, 2930, 2873, 1711, 1450, 1378, 1271, 1214, 1153, 892

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.15 (d, 3H, J = 7.2 Hz), 1.22-1.27 (m, 4H), 1.76 (s, 3H), 1.95-2.02 (m, 1H), 2.15-2.25 (m, 1H), 2.43-2.57 (m, 3H), 2.78-2.82 (m, 1H), 2.87-2.92 (m, 1H), 3.42 (q, 1H, J = 4.4 Hz), 4.73 (d, 1H, J = 20 Hz), 4.81 (d, 1H, J = 15.2 Hz) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$): 12.7, 14.8, 15.4, 20.9, 21.5, 24.9, 26.03, 32.71, 35.9, 40.2, 40.7, 43.3, 46.0, 46.2, 48.8, 49.2, 49.9, 110.0, 111.4, 146.2, 146.9, 209.5, 211.0 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{20}OS$	C 67.87	C 67.55
212.35	H 9.49	H 9.40
	S 15.10	S 14.95

7-Thioethylpulegone (76)



Nature: Viscous liquid

Yield: 80%

Reaction time: 10 min

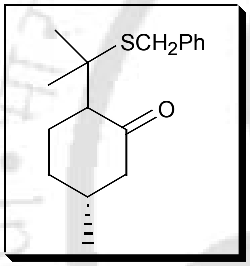
IR (Neat): cm^{-1} 2965, 2929, 2875, 1718, 1458, 1390, 1214, 1137, 1042

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.00 (d, 3H, *J* = 6.8 Hz), 1.21 (t, 3H, *J* = 7.2 Hz), 1.36 (s, 3H), 1.37-1.50 (m, 1H), 1.51 (s, 3H), 1.57-1.63 (m, 1H), 1.86-1.93 (m, 3H), 2.03 (t, 1H, *J* = 12.4 Hz), 2.27-2.30 (m, 1H), 2.42 (dd, 1H, *J* = 3.6 Hz, *J* = 11.6 Hz), 2.50 (q, 2H, *J* = 7.2 Hz) ppm.

^{13}C NMR (75 MHz, CDCl$_3$): δ 14.5, 19.3, 21.7, 21.8, 22.3, 24.1, 24.8, 25.5, 28.0, 28.3, 29.7, 31.5, 32.7, 34.8, 36.7, 46.9, 47.1, 50.4, 52.4, 58.1, 58.3, 210.3, 211.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{12}H_{22}OS$	C 67.24	C 67.01
214.37	H 10.34	H 10.28
	S 14.96	S 14.68

7-Thiabenzyl pulegone (2):



Nature: Viscous liquid

Yield: 86%

Reaction time: 10 min

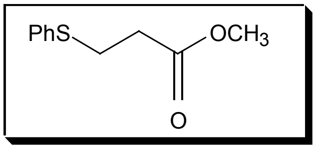
IR (Neat): cm^{-1} 2960, 2925, 2868, 1711, 1609, 1455, 1388, 1363, 1127, 1091, 707

^{1}H NMR (400 MHz, CDCl$_3$): δ 0.92 (d, 3H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 7.2 Hz), 1.37 (s, 3H), 1.39 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.73-1.92 (m, 6H), 2.02-2.06 (m, 2H), 2.21-2.54 (m, 8H), 3.72 (s, 4H), 7.20-7.33 (m, 10H) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 19.2, 22.3, 24.0, 24.6, 25.6, 27.9, 28.2, 29.8, 31.4, 32.7, 33.3, 34.6, 36.7, 48.1, 50.4, 52.4, 57.8, 58.1, 126.7, 128.3, 128.8, 138.4, 210.5, 211.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{17}H_{24}OS$	C 73.86	C 73.62
276.44	H 8.75	H 8.82
	S 11.60	S 11.85

3-Thiophenyl-methyl propanoate (77):



Nature: Viscous liquid

Yield: 88%

Reaction time: 10 min

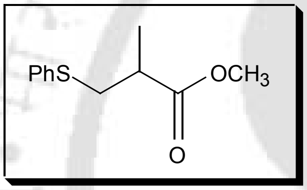
IR (Neat): cm^{-1} 3002, 2949, 1744, 1584, 1472, 1440, 1365, 1248, 1219, 1173, 1034, 746, 709

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (t, 2H, *J* = 7.5 Hz), 3.17 (t, 2H, *J* = 7.5 Hz), 3.68 (s, 3H), 7.19-7.39 (m, 5H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 29.0, 34.2, 51.8, 126.6, 129.0 (2C), 130.1 (2C), 135.1, 172.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{10}H_{12}O_2S$	C 61.20	C 61.01
196.27	H 6.16	H 6.12
	S 16.34	S 16.12

3-Thiophenyl-2-methyl-methyl propanoate (78):



Nature: Viscous liquid

Yield: 91%

Reaction time: 10 min

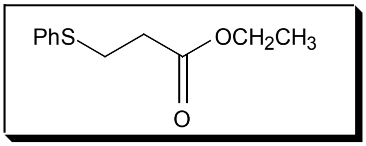
IR (Neat): cm^{-1} 3001, 2952, 1742, 1583, 1470, 1442, 1360, 1243, 1220, 1170, 1029, 746, 709

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, 3H, *J* = 6.9 Hz), 2.70 (dd, 1H, *J* = 6.9 Hz, *J* = 13.8 Hz), 2.93 (dd, 1H, *J* = 6.9 Hz, *J* = 13.2 Hz), 3.27 (dd, 1H, *J* = 6.9 Hz, *J* = 13.2 Hz), 3.67 (s, 3H), 7.20-7.38 (m, 5H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 37.4, 39.7, 51.9, 126.3, 128.8 (2C), 129.8 (2C), 135.5, 175.1 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{14}O_2S$	C 62.83	C 62.61
210.29	H 6.71	H 6.68
	S 15.25	S 14.95

3-Thiophenyl-ethyl propanoate (79):



Nature: Viscous liquid

Yield: 95%

Reaction time: 10 min

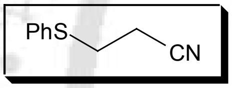
IR (Neat): cm^{-1} 3005, 2948, 1743, 1583, 1472, 1441, 1362, 1221, 1171, 1030, 745, 709

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.24 (t, 3H, *J* = 7.2 Hz), 2.61 (t, 2H, *J* = 7.2 Hz), 3.15 (t, 2H, *J* = 7.2 Hz), 4.13 (q, 2H, *J* = 7.2 Hz), 7.18 (t, 1H, *J* = 7.6 Hz), 7.27 (t, 2H, *J* = 7.6 Hz), 7.34 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (75 MHz, CDCl$_3$): δ 14.2, 29.0, 34.4, 60.6, 126.3, 128.8 (2C), 129.8 (2C), 135.0, 171.4 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_{11}H_{14}O_2S$	C 62.83	C 62.66
210.29	H 6.71	H 6.62
	S 15.25	S 14.99

1-Cyano-2-thiophenylethane (80):



Nature: Viscous liquid

Yield: 97%

Reaction time: 10 min

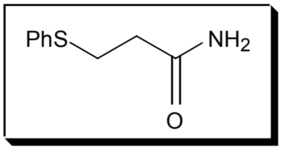
IR (Neat): cm^{-1} 3057, 2931, 2250, 1582, 1479, 1437, 1248, 1090, 743, 693

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.58 (t, 2H, *J* = 7.2 Hz), 3.12 (t, 2H, *J* = 7.2 Hz), 7.26-7.34 (m, 3H), 7.40 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 18.4, 30.4, 117.8, 127.6, 129.2 (2C), 131.3 (2C), 133.0 ppm.

Elemental Analysis	**Calculated**	**Found**
C_9H_9NS	C 62.22	C 62.01
163.24	H 5.56	H 5.47
	S 19.64	S 19.39

3-Thiophenylpropioamide (81):



Nature: White solid

Yield: 91%

Reaction time: 15 min

M.P. 125 ^{0}C

IR (KBr): cm^{-1} 3359, 3182, 2924, 2793, 1657, 1580, 1426, 1309, 1282, 1128, 748

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.53 (t, 2H, *J* = 7.2 Hz), 3.22 (t, 2H, *J* = 7.2 Hz), 5.56 (bs, 2H), 7.20 (t, 1H, *J* = 8.4 Hz), 7.29 (t, 2H, *J* = 8.8 Hz), 7.36 (d, 2H, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ 29.2, 35.4, 126.3, 128.9 (2C), 129.6 (2C), 135.1, 173.2 ppm.

Elemental Analysis	**Calculated**	**Found**
$C_9H_{11}NOS$	C 59.64	C 59.40
181.25	H 6.12	H 6.04
	N 7.73	N 7.49
	S 17.69	S 17.51

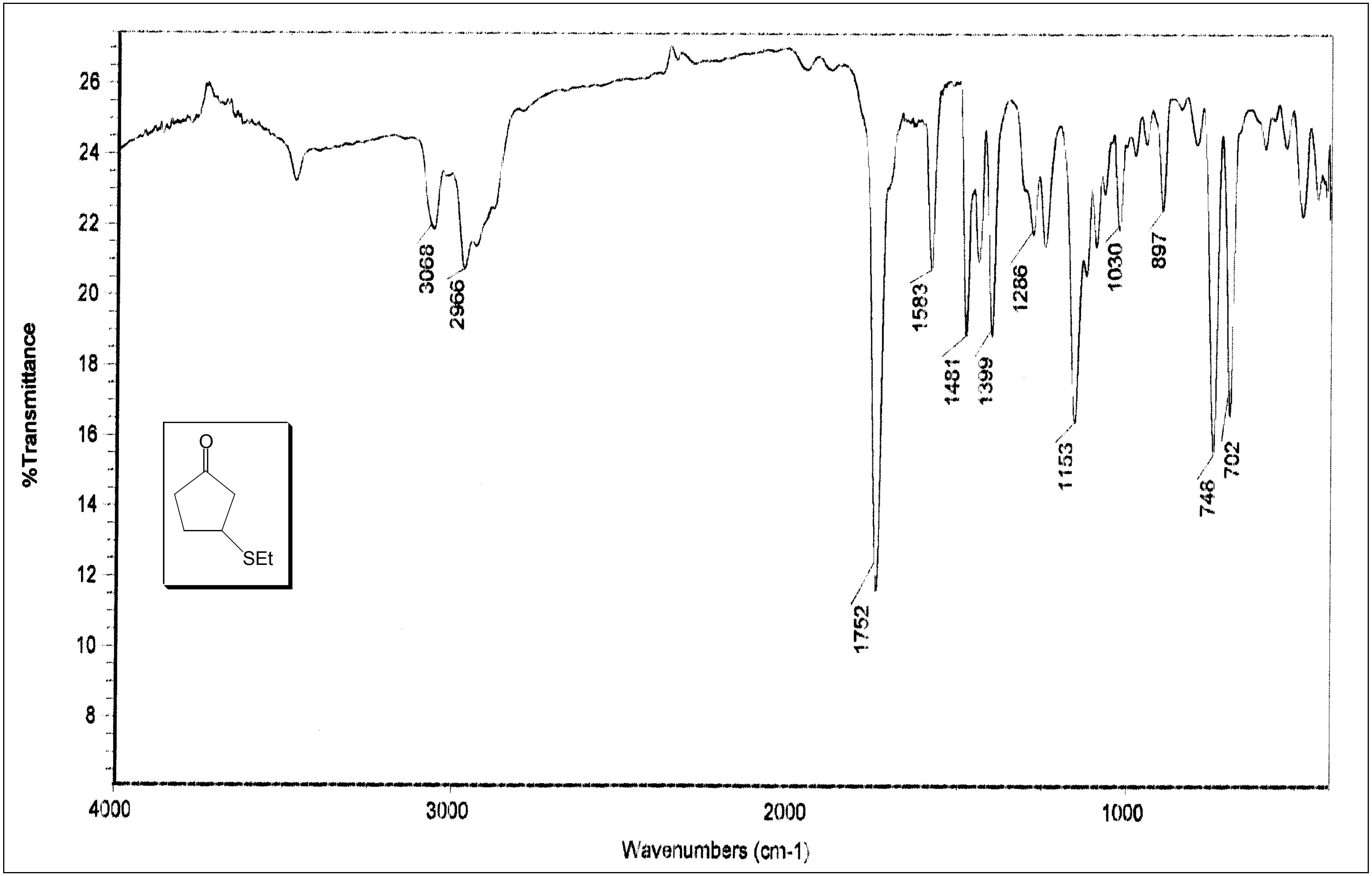


Fig 1: IR spectrum of 3-Thioethylcyclopentanone (64)

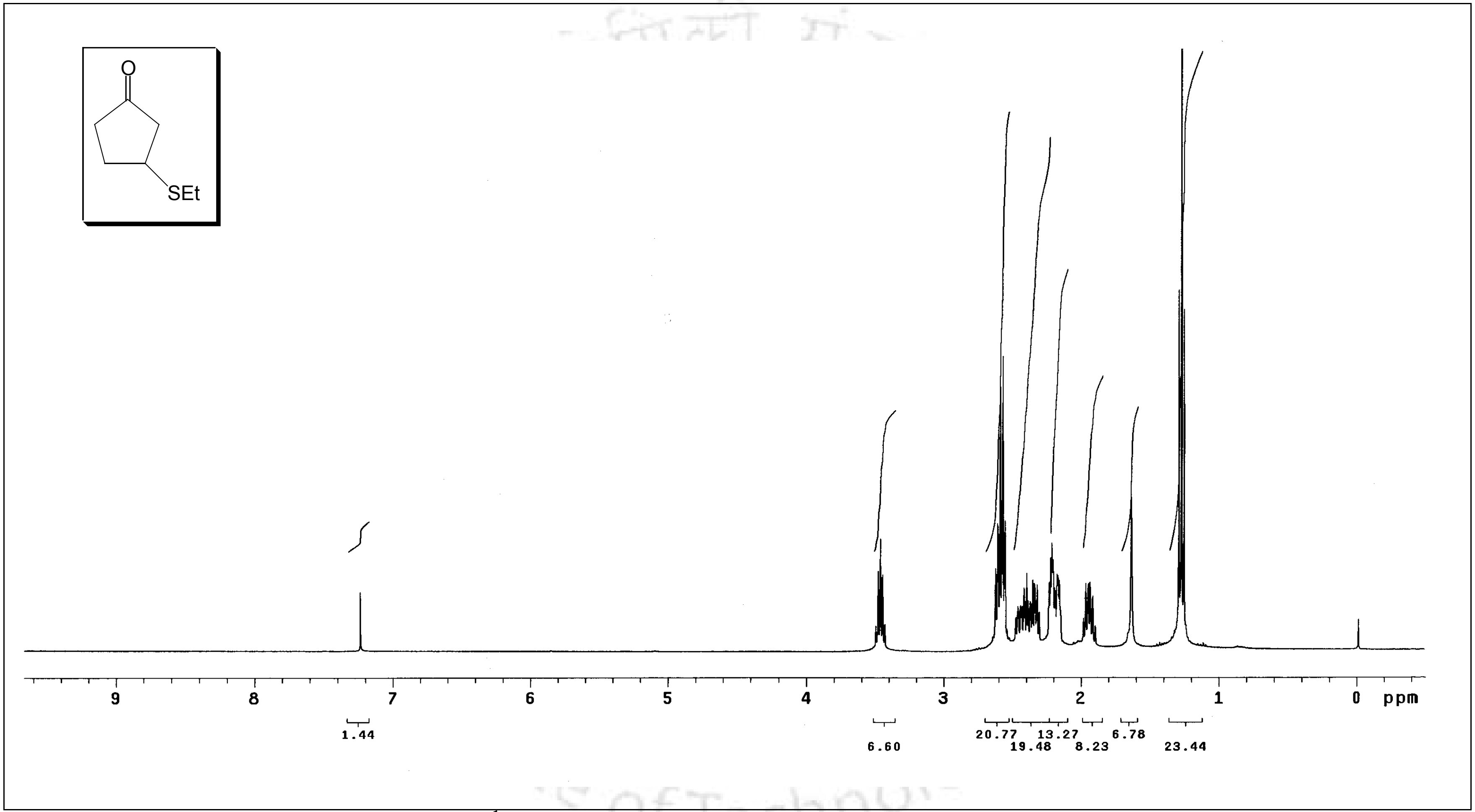


Figure 2: ^{1}H NMR spectrum of 3-Thioethylcyclopentanone (64)

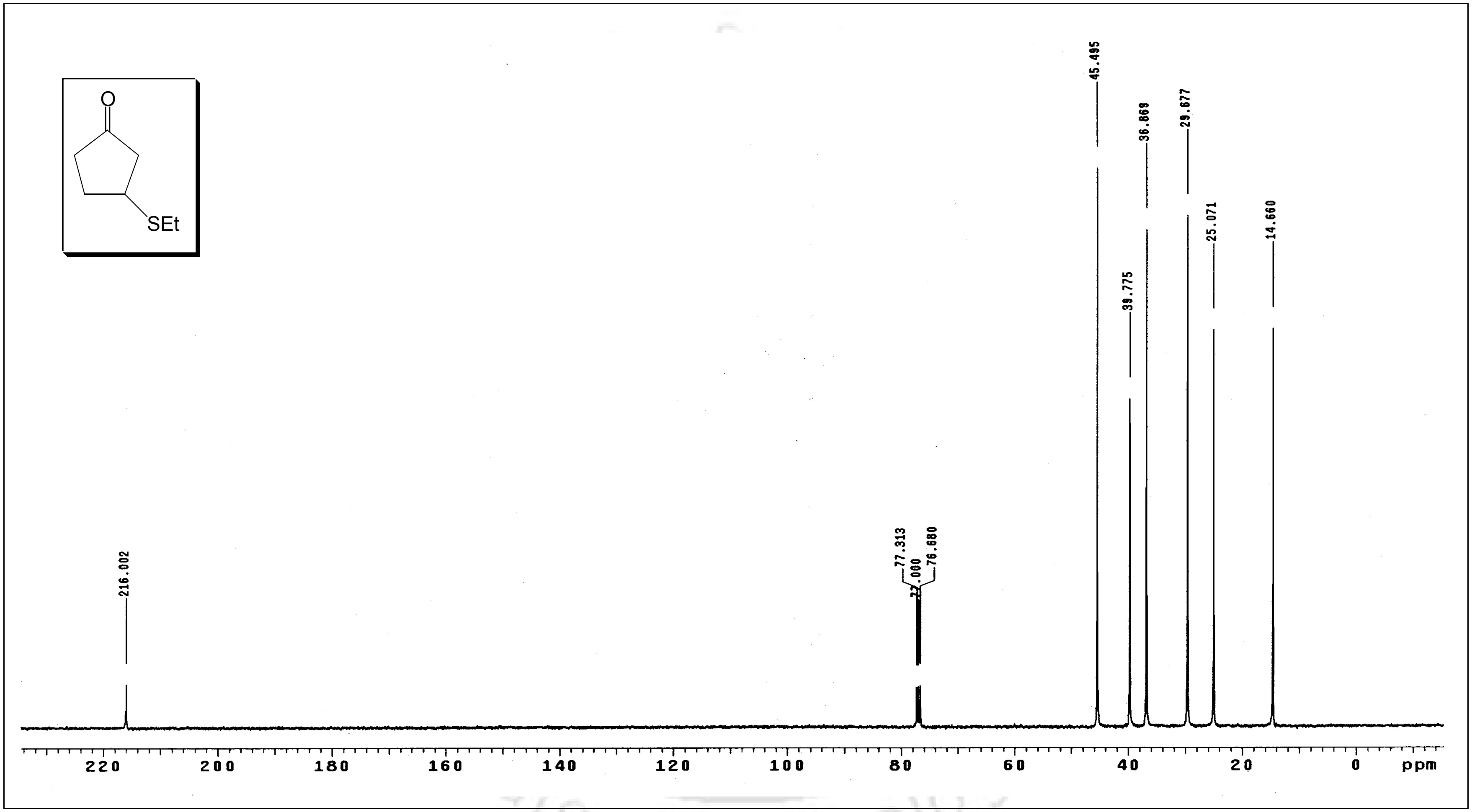


Figure 3: ^{13}C NMR spectrum of 3-Thioethylcyclopentanone (64)

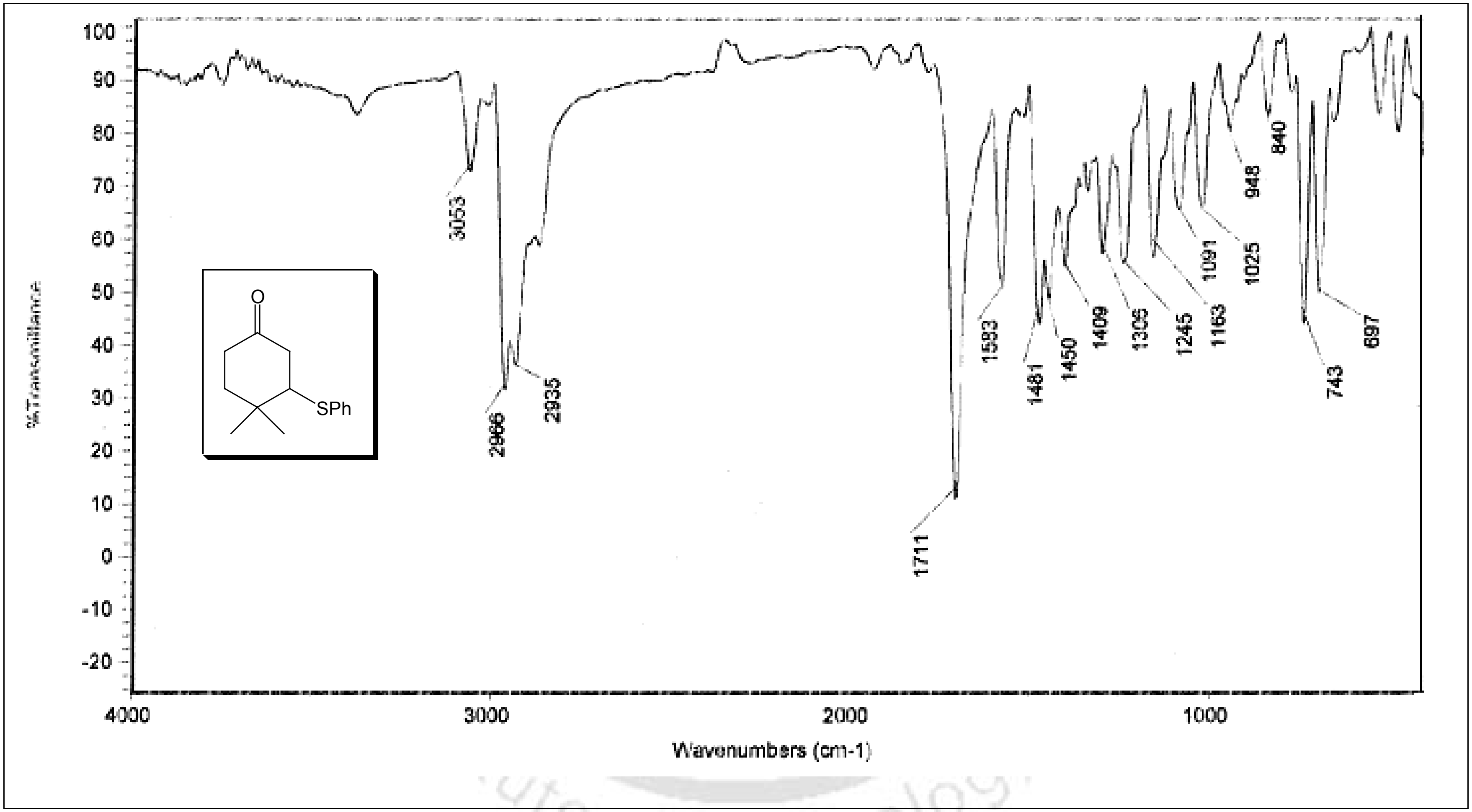


Figure 4: IR spectrum of 4, 4-Dimethyl-3-thiophenylcyclohexanone (70)

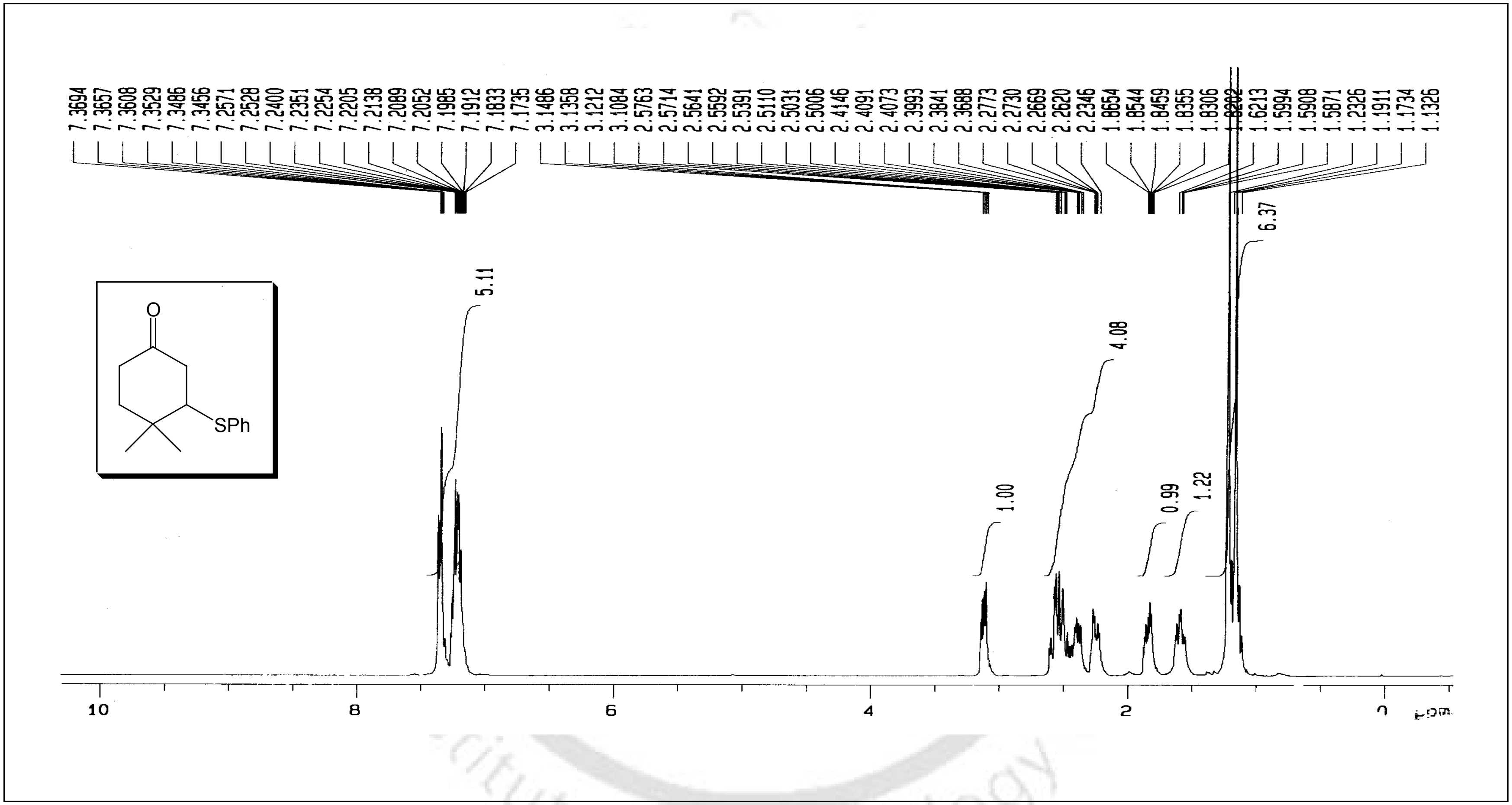


Figure 3: ^{1}H NMR spectrum of 4,4-Dimethyl-3-thiophenylcyclohexanone (70)

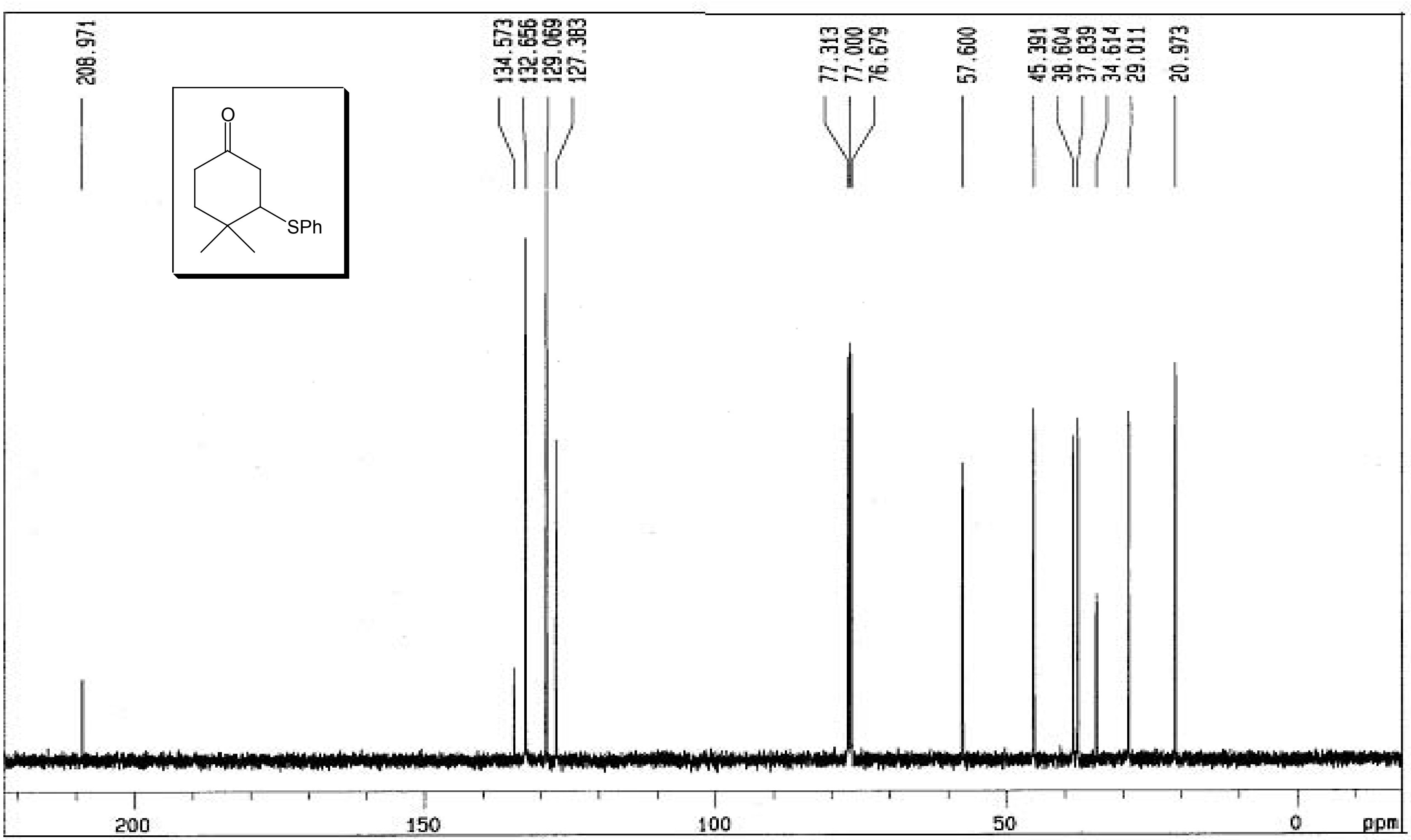


Figure 3: ^{13}C NMR spectrum of 4,4-Dimethyl-3-thiophenylcyclohexanone (70)

NEW SYNTHETIC METHOD FOR THIA-MICHAEL REACTION USING SILICA SUPPORTED PERCHLORIC ACID

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Appendix

Conclusion and future scope

We have developed three new synthetic methodologies for tetrahydropyranylation and depyranylation of hydroxyl compounds by using bromodimethylsulfonium bromide, cupric sulfate pentahydrate and bismuth(III) nitrate pentahydrate as pre-catalyst or catalyst, which are discussed in Part II of the Chapter I in Section A, Section B and Section C, respectively. The salient features of these methodologies are: mild reaction conditions, good yields, no side reactions such as bromination either at the double bond or triple bond or even in the aromatic rings using bromodimethylsulfonium bromide, which are some of the major advantages. The method developed by using bismuth(III) nitrate pentahydrate is highly effective in terms of reaction time and yields. Moreover, work-up procedure is hassle free as compared to the earlier reported procedures. In addition, these protected compounds will be used in natural product synthesis. These successful results might open up to look for a new catalyst or reagents for tetrahydropyranylation and depyranylation reactions.

We have successfully demonstrated that oxidation of THP- and TBS ethers into the carbonyl compounds using bromodimethylsulfonium bromide and 30% hydrogen peroxide. The same combination is further useful for benzylic C-H oxidation. All these successful results were presented in Part II of the Chapter II. The benzylic oxidation can be implemented towards natural product synthesis such as Lobelanine or other natural product synthesis having carbonyl functionality at the benzylic position. Moreover, we have demonstrated a new method for thia-Michael addition using silica-supported perchloric acid, which is discussed in Part II of the Chapter III. The thia-Michael addition product of 16-DPA will be utilized for asymmetic synthesis and presently, we are working on the same line.

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1. A Highly Efficient and Chemoselective Synthetic Protocol for Tetrahydropyranylation/ Depyranylation of Alcohols and Phenols
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5. A catalytic amount of nickel (II) chloride hexahydrate and 1, 2- ethanedithiol is a good combination for the cleavage of tetrahydropyranyl (THP) and tert-butyldimethylsilyl (TBS) ethers
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6. Acetonyltriphenylphosphonium Bromide (ATPB): A Versatile Reagent for the Acylation of Alcohols, Phenols, Thiols and Amines and for 1,1-Diacylation of Aldehydes under Solvent-Free Conditions
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7. Bromodimetylsulfonium bromide: A useful reagent for acylation of alcohols, phenols, amines, thiols, thiophenols and 1,1-diacylation of aldehydes under solvent free conditions
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8. Highly Efficient Synthetic Protocol for Tetrahydropyranylation /depyranylation of Alcohols and Phenols

   Abu T. Khan, **Subrata Ghosh** and Lokman H. Choudhury, *Eur. J. Org. Chem.* **2005**, 4891.

9. Perchloric acid impregnated on silica gel ($HClO_4$- SiO_2): A versatile catalyst for Michael addition of thiols to the electron deficient alkenes

   Abu T. Khan, **Subrata Ghosh** and Lokman H. Choudhury, *Eur. J. Org. Chem.* **2006,** 2226.

10. Silica supported perchloric acid ($HClO_4$- SiO_2): An efficient and reusable catalyst for geminal diacylation of aldehydes under solvent free conditions

    Abu T. Khan, Lokman H. Choudhury and **Subrata Ghosh,** *J. Mol. Cat. A: Chem.* **2006**, 0000.

11. Transition metal-free oxidative deprotection of THP and TBS ethers by bromodimethylsulfonium bromide and hydrogenperoxide: A greener approach

    A. T. Khan, **Subrata Ghosh** and Ejabul Mondal (submitted for publication)

12. A highly regioselective synthetic protocol for benzylic C-H oxidations of alkyl- and cycloalkyl arenes and secondary alcohols to ketones using bromodimethylsulfonium bromide and hydrogen peroxide

    A. T. Khan, **Subrata Ghosh** and Lokman H. Choudhury (submitted for publication).

A Highly Efficient and Chemoselective Synthetic Protocol for Tetrahydropyranylation/Depyranylation of Alcohols and Phenols

Abu T. Khan,*[a] Ejabul Mondal,[a] Ballav M. Borah,[a] and Subrata Ghosh[a]

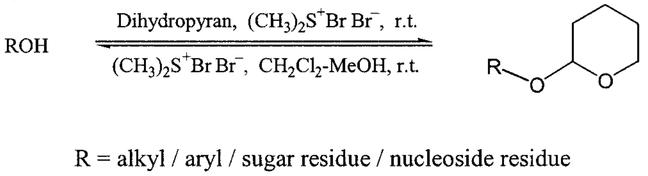
Dedicated to the late Mr. Gadadhar Mondal[‡]

Keywords: Protecting groups / Deprotecting groups / Hydroxyl compounds / Ethers / Catalysis / Alcohols

Various alcohols and phenols can be converted efficiently to the corresponding tetrahydropyranyl (THP) ethers in good yields using catalytic amounts of bromodimethylsulfonium bromide (0.005–0.02 equivalent) at room temperature. On the other hand, various THP ethers can also be deprotected to the parent alcoholic or phenolic compounds in CH_2Cl_2/MeOH (5:2) by employing 0.05 equivalent of the same catalyst. Some of the major advantages of this procedure are its mild conditions, that it is highly selective and efficient, high yielding, and cost-effective, that it needs no solvent and is compatible with the presence of other protecting groups. Furthermore, no brominations occur at a double or triple bond, at an allylic position or even at an aromatic ring.

Introduction

The protection−deprotection of hydroxyl compounds as tetrahydropyranyl (THP) ethers is one of the most frequently employed transformations in multi-step organic syntheses[1] because of their low cost, ease of preparation, stability towards basic media and ease of removal of protecting groups at a later stage. Over the years, numerous methods have been developed for the protection of hydroxyl groups as THP ethers[2] and their deprotection,[3] but there is still a need to find better alternatives that work under mild conditions. Some of the recently used reagents that can catalyze both tetrahydropyranylation and depyranylation are $ZrCl_4$,[4] I_2,[5] LiBr,[6] acetonylphenylphosphonium bromide,[7] TBATB,[8] aluminum chloride hexahydrate,[9] In(OTf)$_3$,[10] dialkylimidazolium tetrachloroaluminates,[11] and $InCl_3$ immobilized in ionic liquids.[12] However, some of the reported procedures have drawbacks, such as requiring higher reaction temperatures, much longer reaction times and the use of volatile organic solvents, being incompatible with other acid-sensitive functional groups, and involving expensive catalysts. In an endeavor to gradually change the current working practices to greener alternatives and to meet environmental demands,[13] there is a need for a solvent-free and catalytically efficient alternative for protection and deprotection of the hydroxy functionality as a THP ether, which works under mild and economically cheaper reaction conditions. As part of our research program to develop new synthetic methodologies,[14] we conceived that bromodimethylsulfonium bromide, which can generate HBr in the reaction medium on reaction with alcohol, might be a useful catalyst for tetrahydropyranylation and depyranylation of alcohols and phenols. The catalyst bromodimethylsulfonium bromide has been utilized so far for the transformation of alcohols to the corresponding bromides,[15] oxidation of sulfides to disulfides,[16] deprotection of dithioacetals,[17] and preparation of α-bromoenones.[18] In this communication, we report a simple and convenient synthetic protocol for tetrahydropyranylation of alcohols and phenols catalyzed by bromodimethylsulfonium bromide under solvent-free conditions, and their depyranylation to the corresponding parent compounds using the same catalyst in CH_2Cl_2/MeOH (Scheme 1).



Scheme 1

Results and Discussion

As expected, a mixture of 1-decanol (5 mmol) and 3,4-dihydro-2*H*-pyran (6 mmol) in the presence of bromodime-

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thylsulfonium bromide (0.05 mmol) at room temperature was converted smoothly to the corresponding tetrahydropyranyl ether of 1-decanol within 5 min in 97% yield (run 1). Similarly, a mixture of cetyl alcohol (5 mmol) and 3,4-dihydro-2*H*-pyran (DHP) (6 mmol) provided the corresponding THP ether within 15 min in 98% yield (run 2) under identical reaction conditions. Using the above typical procedure, various secondary alcohols (runs 3−8) were transformed easily to the corresponding THP ethers in good yields. Interestingly, mono protection of an alcoholic hydroxyl group is possible in the presence of a phenolic OH group (run 9) and other alcoholic OH group (run 10) if 10% of the starting material is left unchanged. The conversion (run 1) is more efficient in terms of yield and reaction time than another recently reported procedure.[8] Moreover, a wide variety of protected alcoholic compounds were transformed to the corresponding THP ethers under identical reaction conditions using the same catalyst (runs 11−15). It should be noted that various other protecting groups such as acetyl, benzoyl, trityl, ester and TBDPS groups remain unaffected during the reaction. In addition, various double bonded and triple bonded substrates also provided the corresponding THP ethers under identical reaction conditions (runs 16−20). Importantly, no brominations took place at the double or triple bonds. It is worth mentioning that geraniol was smoothly transformed to the corresponding THP ether at a much faster rate than it was by a recently reported procedure,[9] which also shows the efficiency of our protocol. Subsequently, various phenolic compounds were converted into the corresponding THP ethers (runs 21−24) using the same catalyst without solvent. It is noteworthy that no brominations take place in the aromatic ring even for an electron-rich aromatic substrate (run 24) and that there is no cleavage of the dithioacetal group (run 23). Remarkably, a highly acid-sensitive substrate can be protected to the corresponding THP ethers using the same catalyst (runs 25 and 26). Furthermore, various carbohydrate and nucleosidic compounds were transformed smoothly to the corresponding THP ethers (runs 27−32) by the same reaction procedure. The results are summarized in Table 1. The products were fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and by elemental analyses. It is worth mentioning that benzyl, isopropylidene, and a thio group at the anomeric position were unaffected by the experimental conditions.

Next, we searched for suitable reaction conditions for deprotection of THP ethers to the parent hydroxyl compounds. The THP ether of cetyl alcohol was deprotected smoothly to the parent cetyl alcohol within 30 min on treatment with 0.05 equivalents of bromodimethylsulfonium bromide in dichloromethane/methanol at room temperature (run 1). Similarly, we successfully converted various THP ethers to the parent hydroxyl compounds under identical reaction conditions (runs 2−18). The results are summarized in Table 2 and the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analyses, as well as by comparison with the authentic compounds. We also observed that various protecting groups such as acetyl, benzoyl, benzyl, TBDPS, ester, thioketal, allyl, and isopropylidene were unaffected by the deprotection reaction conditions. Moreover, no brominations occurred at a double or triple bond or in the aromatic ring.

The formation of the product can be explained as follows. It has been shown that bromodimethylsulfonium bromide can generate HBr on reaction with alcohol.[14] We believe that in situ-generated HBr catalyzes the conversion of hydroxyl compounds into the corresponding tetrahydropyranyl ethers (Scheme 2). We have observed that the pH of the solution was ca. 2−3 while the reaction was proceeding.

Similarly, the deprotection of THP ethers can be explained by the fact that bromodimethylsulfonium bromide generates HBr on reaction with methanol, which is utilized for cleavage of THP ethers to the corresponding hydroxyl compounds.

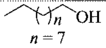
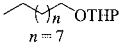
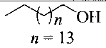
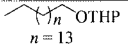
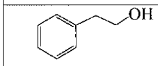
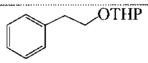
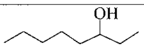
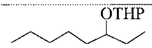
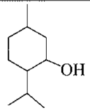
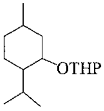
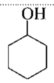
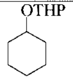
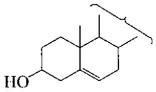
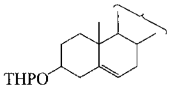
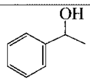
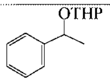
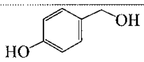
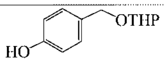
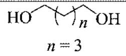
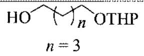
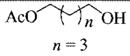
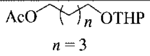
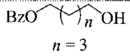
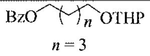
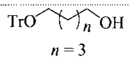
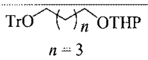
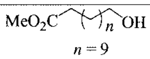
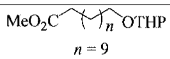
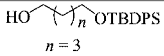
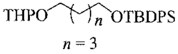
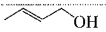
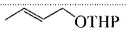
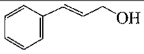
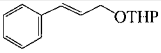
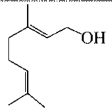
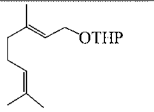
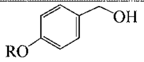
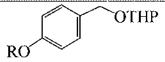
Conclusion

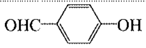
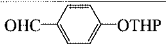
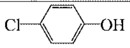
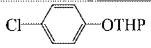
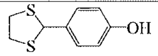
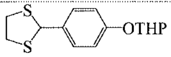
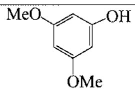
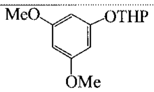
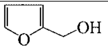
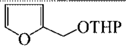
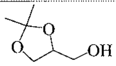
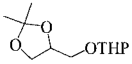
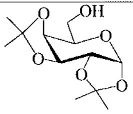
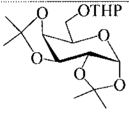
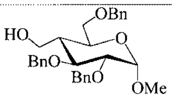
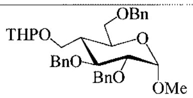
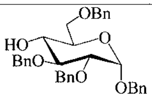
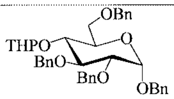
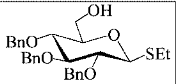
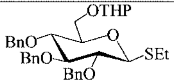
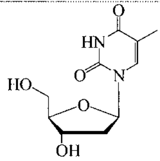
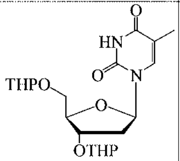
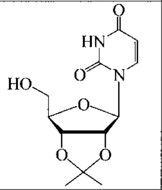
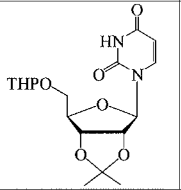
We have demonstrated a simple and convenient method for preparation of tetrahydropyranyl (THP) ethers from the corresponding alcohols and phenols under solvent-free conditions as well as deprotection to the parent hydroxyl compounds chemoselectively using the same catalyst by tuning the amount of reagent and the reaction conditions. In addition, this method is very simple and mild, easy to handle, and compatible with the presence of a large number of other protecting groups. It is noteworthy that no brominations take place at double or triple bonds, or even in aromatic rings. Because of its operational simplicity, generality, and efficacy, this method is expected to have wide applicability for the conversion of various hydroxyl compounds to the corresponding tetrahydropyranyl (THP) ethers and vice-versa.

Experimental Section

General Procedure for Tetrahydropyranylation: Bromodimethylsulfonium bromide (0.011 g, 0.05 mmol) was added to a mixture of 1-decanol (0.790 g, 5 mmol, run 1) and 3,4-dihydro-2*H*-pyran (0.550 mL, 6 mmol) and the resulting mixture was stirred at room temperature. The reaction was complete within 5 min as monitored by TLC and it was neutralized by addition of saturated $NaHCO_3$ solution (2−3 drops). The mixture was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed with water (10 mL), brine (10 mL), and dried with Na_2SO_4. The organic layer was concentrated in vacuo and the crude residue was purified through a short alumina column. The pure product was obtained (1.170 g) in 97% yield as a colorless liquid. Spectroscopic data of THP ether of *p*-allyloxybenzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46-1.86$ (m, 6 H, CH_2), 3.46−3.50 (m, 1 H, OCH_2), 3.82−3.92 (m, 1 H, OCH_2), 4.49 (s, 2 H, OCH_2), 4.65−4.70 (m, 3 H, OCH_2, OCHO-), 5.24 (dd, $J = 1.4$, $J = 10.5$ Hz, 1 H, $CH{=}\mathit{CH_2}$), 5.37 (dd, $J = 1.7$, $J = 17.3$ Hz, 1 H, $CH{=}\mathit{CH_2}$), 5.97−6.06 (m, 1 H, $\mathit{CH}{=}CH_2$), 6.86 (d, $J = 8.5$ Hz, 2 H, ArH), 7.24 (d, $J = 8.3$ Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.35$, 25.39, 30.53, 62.08, 68.44, 68.76, 97.44, 114.54 (2 C), 117.58, 129.41

Table 1. Protection of various hydroxyl compounds to the corresponding tetrahydropyranyl ethers using catalytic amount of bromodimethylsulfonium bromide

Run	Substrate	Catalyst used	Time min/ [h]	Product[a]	Yield[b] /%
1		0.01	5		97
2		0.01	15		98
3		0.01	5		85
4		0.01	5		87
5		0.01	10		88
6		0.01	5		90
7		0.01	20		90
8		0.01	10		84
9		0.01	7		85[c]
10		0.01	40		88[c]
11		0.01	15		81
12		0.01	15		87
13		0.01	5		85
14		0.01	15		87
15		0.01	20		89
16		0.01	15		83
17		0.01	15		92
18		0.01	12		78
19	 R = $-CH_2CH=CH_2$	0.01	10	 R = $-CH_2CH=CH_2$	95
20		0.01	25		95

Run	Substrate	Catalyst used	Time min/ [h]	Product[a]	Yield[b] /%
21		0.01	[4]		90
22		0.01	[6]		92
23		0.01	35		94
24		0.01	20		83
25		0.005	5		93
26		0.005	7		81
27		0.01	20		84
28		0.01	15		93
29		0.02	[1]		95
30		0.02	[1]		96
31		0.02	[3.5]		83
32		0.01	30		95

[a] All final products were characterized by IR, ^1H NMR, ^{13}C NMR spectroscopy, and elemental analysis. [b] Isolated yield. [c] Reaction was carried out by keeping 10% starting material unchanged.

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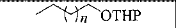
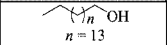
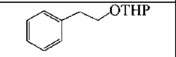
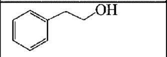
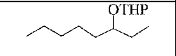
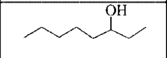
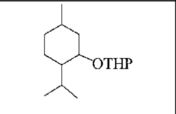
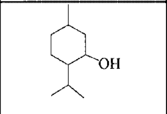
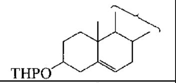
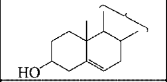
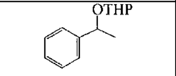
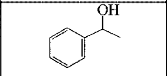
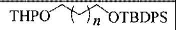
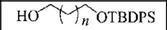
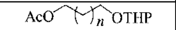
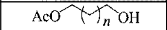
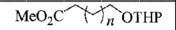
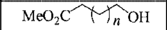
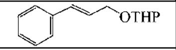
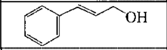
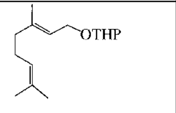
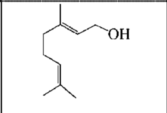
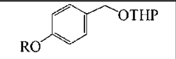
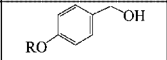
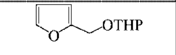
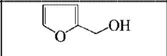
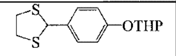
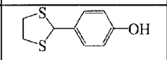
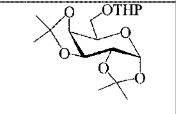
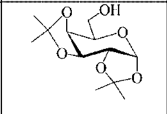
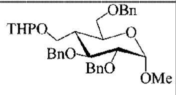
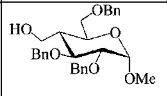
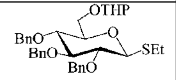
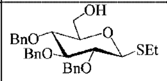
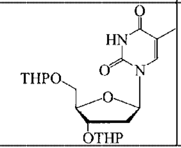
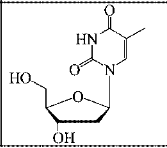
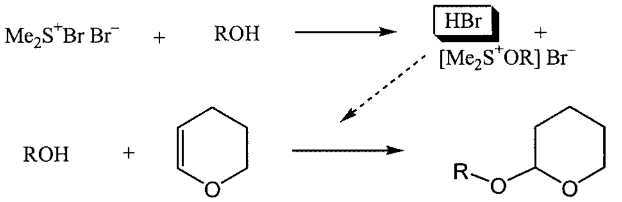
Table 2. Deprotection of various tetrahydropyranyl ethers to the corresponding hydroxyl compounds using catalytic amount of bromodimethylsulfonium bromide in dry dichloromethane/methanol

Run	Substrate	Catalyst used	Time min/ [h]	Product[a]	Yield[b] /%
1	 n = 13	0.05	30	 n = 13	90
2		0.05	25		97
3		0.05	25		92
4		0.05	15		95
5		0.05	40		70
6		0.05	25		70
7	 n = 3	0.05	30	 n = 3	90
8	 n = 3	0.05	15	 n = 3	90
9	 n = 9	0.05	[1]	 n = 9	72
10		0.05	[1]		90
11		0.05	[2]		98
12	 R = -$CH_2CH=CH_2$	0.05	50	 R = -$CH_2CH=CH_2$	93
13		0.05	35		80
14		0.05	40		82
15		0.05	30		76
16		0.05	[2]		85
17		0.05	[1]		73
18		0.05	[1.5]		80

[a] All final products were characterized by IR, ^1H NMR, ^{13}C NMR spectroscopy, and elemental analysis. [b] Isolated yield.



Scheme 2. Proposed mechanism of protection

(2 C), 130.42, 133.23, 158.07 ppm. $C_{15}H_{20}O_3$ (248.32): calcd. C 72.55, H 8.12; found: C 72.38, H 8.01%.

General Procedure for Depyranylation: Bromodimethylsulfonium bromide (0.056 g, 0.25 mmol) was added to a well-stirred solution of the THP ether of 2-phenylethanol (1.060 g, 5 mmol, run 2) in CH_2Cl_2/MeOH (5:2; 10 mL) at room temperature. The reaction was complete within 25 min as monitored by TLC. The mixture was neutralized with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), and dried with Na_2SO_4. The organic layer was concentrated in vacuo and finally purified by silica-gel column chromatography. The pure product was obtained in 97% yield. Spectroscopic data of *p*-allyloxybenzyl alcohol: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80 (br. s, 1 H, OH, D_2O exchangeable), 4.38−4.40 (m, 2 H, OCH_2), 4.45 (s, 2 H, OCH_2), 5.15 (dd, J = 1.4, J = 10.5 Hz, 1 H, CH=CH_2), 5.28 (dd, J = 1.5, J = 17.8 Hz, 1 H, CH=CH_2), 5.86−5.96 (m, 1 H, CH=CH_2), 6.76 (d, J = 8.0 Hz, 2 H, ArH), 7.12 (d, J = 8.3 Hz, 2 H, ArH) ppm. $C_{10}H_{12}O_2$ (164.20): calcd. C 73.15, H 7.37; found: C 72.87, H 7.28%.

Acknowledgments

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Cupric sulfate pentahydrate ($CuSO_4{\cdot}5H_2O$): a mild and efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols

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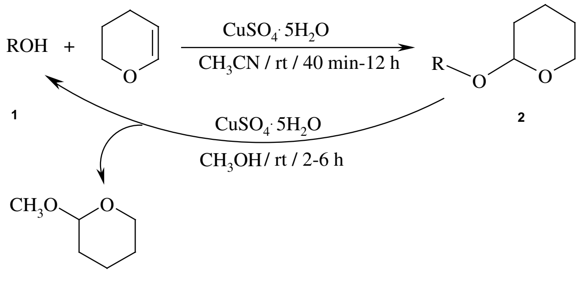
This paper is dedicated to Professor H. Ila on the occasion of her 60th birthday

Abstract—Various alcohols and phenols can be smoothly converted to the corresponding THP ethers using 20 mol% $CuSO_4{\cdot}5H_2O$ under mild reaction conditions at room temperature. Some of the major advantages of this procedure are nonaqueous work-up, very good yields, less expensive catalyst and compatibility with other protecting groups.

The tetrahydropyranyl (THP) group is frequently used for the protection of alcohols and phenols due to their ease of preparation and stability under a wide variety of reaction conditions such as with hydrides, alkylating reagents, Grignard reagents and organometallic reagents.[1] In addition, they also serve as stable protecting group in peptide, nucleoside and nucleotide, carbohydrate and steroid chemistry. Tetrahydropyranylation of alcohols can be accomplished by using *p*-TSA,[2] $BF_3{\cdot}OEt_2$[3] and PPTS.[4] Some of the recently used reagents that can catalyze both tetrahydropyranylation and depyranylation are $ZrCl_4$,[5] I_2,[6] LiBr,[7] acetonyltriphenylphosphonium bromide (ATPB),[8] TBATB,[9] aluminium chloride hexahydrate,[10] $In(OTf)_3$,[11] dialkylimidazolium tetrachloroaluminates,[12] $InCl_3$ immobilized in ionic liquids[13] and bromodimethylsulfonium bromide.[14] On the other hand, many methods have also been developed by using heterogeneous catalysts, and these have been reviewed recently.[15] However, some of these procedures have some difficulties such as requirement of much longer reaction times, incompatibility with other acid-sensitive functional groups,[3,9,10,13] involvement of expensive and moisture sensitive catalysts and some of them have to be prepared prior to use.[4,8,9,14] There is a need for a greener catalytically efficient method, which might work under mild and economically cheaper conditions. As a part of our ongoing research program to develop new synthetic methodologies involving various new reagents,[16,17] we perceived that cupric sulfate pentahydrate, which is readily available, might be a useful catalyst for tetrahydropyranylation because of its mild Lewis acidity. In this paper we disclose that cupric sulfate pentahydrate can be used as an efficient catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols as shown in Scheme 1.

When a mixture of 1-hexadecanol **1a** and 3,4-dihydro-2*H*-pyran was treated with 20 mol% of cupric sulfate pentahydrate in acetonitrile as solvent, it was smoothly converted to the corresponding THP ether **2a** within



Scheme 1. R = alkyl/aryl/sugar residue/nucleoside residue.

Keyword: Protection of hydroxyl compounds.

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40 min in 90% yield. Similarly, 4-methoxybenzyl alcohol **1b** was converted to the corresponding THP ether **2b** within 40 min under identical reaction conditions. Although dichloromethane can also be used, we employed acetonitrile as solvent because dichloromethane is a halogenated solvent and harmful. The tetrahydropyranylation could be achieved on a large scale between 10 and 100 mmol without any difficulty. Following the typical reaction procedure,[18] various benzylic, allylic and secondary alcohols **1c–i** as well as phenols **1j–k** were smoothly transformed to the corresponding THP ethers **2c–k**, respectively, in very good yields. Remarkably, various diols were transformed to mono THP ethers **2l–n** along with 5–8% di-THP ether by using 20 mol% catalyst instead of 40 mol% catalyst. The diols could be converted to the di-THP ethers **2o–p** in good yields in a similar manner. In various substrates containing other functional groups such as acetyl, TBDMS and TBDPS ethers, isopropylidene protected diols and benzyl ethers were smoothly converted to the desired THP ethers **2q–w** in good yields as shown in Table 1. All the products were fully

Table 1. Tetrahydropyranylation of alcohols and phenols in presence of a catalytic amount of $CuSO_4{\cdot}5H_2O$

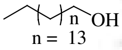
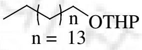
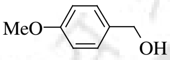
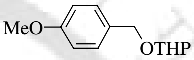
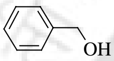
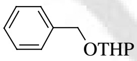
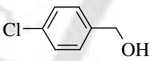
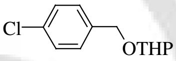
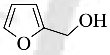
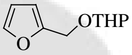
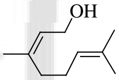
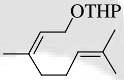
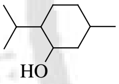
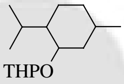
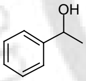
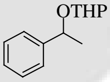
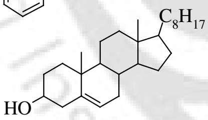
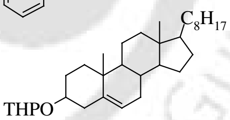
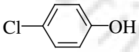
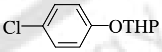
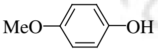
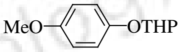
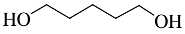
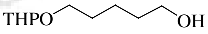
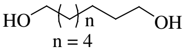
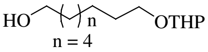
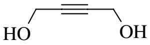
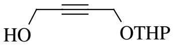
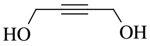
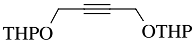
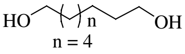
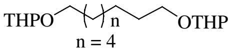
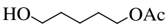
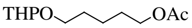
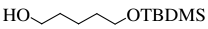
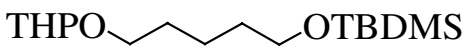
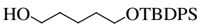
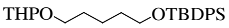
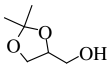
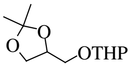
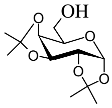
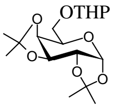
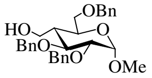
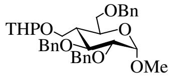
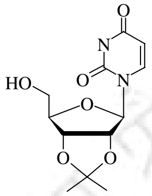
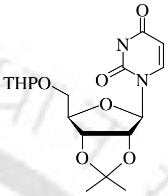
Entry	Substrate **1**	Time (min)	Product **2**[a]	Yield[b] (%)
a		40		90
b		40		89
c		40		91
d		45		92
e		40		90
f		55		87
g		60		89
h		55		91
i		80		85
j		95		87
k		90		89
l		45		70
m		12 h		83[c]
n		60		55
o		90		92
p		12 h		93
q		40		84
r		40		82
s		40		82

Table 1 (*continued*)

Entry	Substrate **1**	Time (min)	Product **2**[a]	Yield[b] (%)
t		50		85
u		85		83
v		90		81
w		45		90

[a] All products were characterized by IR, ^{1}H NMR and elemental analysis.
[b] Isolated yields.
[c] Yield based on starting material recovery.

Table 2. Tetrahydropyranylation of 4-methoxybenzyl alcohol **1b** using various forms of cupric sulfate[a]

Run	Catalyst	Conversion (%)	Time (min/[h])
1	$CuSO_4{\cdot}5H_2O$	100	45
2	$CuSO_4$	80	[3]
3	$CuSO_4{\cdot}SiO_2$	90	[2.5]
4	SiO_2	0	[3]

[a] Reactions were monitored by GC.

characterized by IR, ^{1}H NMR spectroscopy and by elemental analyses. The most interesting feature is that the THP ether **2a** undergoes cleavage within 5h using same catalyst (20mol%) in methanol in 85% yield.[19] Other THP ethers **2b**, **2c**, **2f** and **2k** were converted to the respective hydroxyl compounds **1b**, **1c**, **1f** and **1k** within 2–6h in 80–85% yields under identical reaction conditions.

The tetrahydropyranylation of 4-methoxybenzyl alcohol **1b** was investigated with the various forms of cupric sulfate to find out the relative efficiencies (Table 2). Cupric sulfate pentahydrate showed the highest catalytic activity in terms of reaction time and yield.

In summary, the present methodology demonstrates $CuSO_4{\cdot}5H_2O$ as an effective catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. The main advantages of our protocol are: mild, clean, environmentally benign reaction conditions as well as good yields. In addition, our methodology might be useful for the substrates containing acid-sensitive protecting groups because of the almost neutral reaction conditions. Furthermore, this method is also expected to have better applicability in organic synthesis due to the low cost of the reagent. We believe this protocol will be a useful addition to the modern synthetic methodologies.

Acknowledgements

A.T.K. thanks the DST, New Delhi for a financial grant (Grant No SP/S1/G-35/98), L.H.C. and S.G. are grateful to IITG for their research fellowships. The authors are also grateful to the referee for his valuable comments and suggestions.

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18. Typical procedure of protection: Into a mixture of 3,4-dihydro-2*H*-pyran (1.1 mmol) and alcohol or phenol (1 mmol) in acetonitrile (2 mL) was added cupric sulfate pentahydrate (0.05 g, 0.2 mmol) at room temperature and the mixture stirred until completion of the reaction was ascertained by the disappearance of the alcohol spot on TLC. The product was isolated in almost pure form from the reaction mixture by simply filtering through a Whatman 42 filter paper without aqueous work-up. The pure product was obtained from the reaction mixture by passing it through a short column of basic alumina. Compound **2a**: IR (Neat): 2919, 2854, 1469, 1354, 1228, 1122, 1071, 1037; ^{1}H NMR ($CDCl_3$): 0.85 (t, 3H, $J = 6.6$ Hz), 1.22–1.32 (m, 26H), 1.47–1.81 (m, 8H), 3.32–3.38 (m, 1H), 3.44–3.49 (m, 1H), 3.65–3.73 (m, 1H), 3.81–3.87 (m, 1H), 4.54 (m, 1H). Elemental analysis: calcd for, $C_{21}H_{42}O_2$ (326.56); C 77.24, H 12.96, found C 77.08, H 12.87.
19. Typical procedure of deprotection: To a solution of THP ether **2a** (0.325 g, 1 mmol) in methanol (5 mL) was added cupric sulfate pentahydrate (0.05 g, 0.2 mmol) and the mixture stirred at room temp. The reaction was completed within 5 h and the solid cupric sulfate was filtered off. The solid residue was washed with dry methanol (2 × 5 mL). After concentration of the combined filtrate, the crude residue was purified through a short silica gel column. The desired cetyl alcohol **1a** was obtained 0.206 g in 85% yield.

A Highly Efficient Synthetic Protocol for Tetrahydropyranylation/Depyranylation of Alcohols and Phenols

Abu T. Khan,*[a] Subrata Ghosh,[a] and Lokman H. Choudhury[a]

Dedicated to Professor K. Dey on the occasion of his 65th birthday

Keywords: Tetrahydropyranylations / Alcohols / Phenols / Bismuth(III) nitrate pentahydrate / Synthetic methods

Bismuth(III) nitrate pentahydrate [$Bi(NO_3)_3{\cdot}5H_2O$] is found to be an effective catalyst for both tetrahydropyranylation and depyranylation of alcohols and phenols. Some of the major advantages of this protocol are: non-aqueous workup, good yields, the involvement of a less-expensive and nontoxic catalyst, and compatibility in the presence of a large number of other protecting groups. Notably, isopropylidene, benzylidene, and thioacetal groups are also unaffected under the experimental conditions. Remarkably, a selective mono-protection of diols and primary alcohols can be achieved chemoselectively by employing the same catalyst.

Introduction

The protection/deprotection strategy is a very common practice for manipulation of other functional groups during multistep organic synthesis. Among various functional groups, the protection of the hydroxy group as tetrahydropyranyl (THP) ether is usually preferred because of its low cost, ease of preparation, and stability of THP ethers towards metal hydrides, and acylating, alkylating, Grignard, and organometallic reagents.[1] Sometimes THP ethers also serve as a stable protecting groups in peptide, nucleoside and nucleotide, carbohydrate, and steroid chemistry. Tetrahydropyranylation of alcohols or phenols is usually achieved by using *p*TsA,[2] $BF_3{\cdot}OEt_2$,[3] or PPTS.[4] Many other reagents, such as $ZrCl_4$,[5] I_2,[6] LiBr,[7] acetonyltriphenylphosphonium bromide (ATPB),[8] TBATB,[9] aluminium chloride hexahydrate,[10] LiOTf,[11] $In(OTf)_3$,[12] dialkylimidazolium tetrachloroaluminates,[13] $InCl_3$ immobilized in ionic liquids,[14] $Bi(OTf)_3$,[15] bromodimethylsulfonium bromide,[16] cupric sulfate pentahydrate,[17] and $NbCl_5$,[18] have also been employed for both tetrahydropyranylation/depyranylation in recent years. Though metal triflates have been found to be effective catalysts for the above transformations, they still have some drawbacks, such as they are relatively expensive, difficult to handle, and not readily available. They also require harsh[11] and inert reaction conditions.[15] Very recently, one more method has been reported that involves a heterogeneous catalyst such as a solid silica-based sulfonic acid.[19] Further, more methods have recently been reviewed that employ various heterogeneous catalysts.[20] Unfortunately, many of these procedures have a disadvantage such as harsh reaction conditions, long reaction times, incompatibility with other acid-sensitive functional groups,[3,9,10,13] the involvement of more expensive and moisture sensitive reagents, and some also have to be freshly prepared prior to use.[4,8,9,15,16] As part of our ongoing research to develop new synthetic methodologies by using various new reagents,[21–23] we realized that there is further scope for a cleaner and greener methodology for tetrahydropyranylation/depyranylation, one that might work under mild catalytic conditions and that is economically cheaper. In recent years, bismuth compounds have been gaining interest in various organic transformations.[24,25] We thought that bismuth(III) nitrate pentahydrate, which is commercially available at a very low cost and is relatively nontoxic, might be a useful catalyst for tetrahydropyranylation/depyranylation. So far, bismuth(III) nitrate pentahydrate has been utilized in various organic transformations: i) acetylation and benzoylation of alcohols and phenols,[26a] ii) guanidylation of *N*-benzoylthiourea,[26b] iii) conversion of thiocarbonyl compounds to the corresponding carbonyl compounds,[26c] iv) Michael reaction,[26d] v) oxidation of thiols to disulfides,[26e] and vi) for the synthesis of acylals[26f] and dihydropyrimidinone.[26g] In this paper, we report the tetrahydropyranylation of alcohols and phenols and depyranylation in the presence of catalytic amounts of bismuth(III) nitrate pentahydrate, as shown in Scheme 1.

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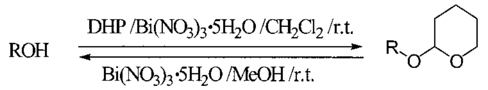


1 **2**

R = alkyl / aryl / sugar residue / nucleoside residue

Scheme 1.

Results and Discussion

When a mixture of 1-decanol (entry **1a**) and 3,4-dihydro-2*H*-pyran (DHP) in dichloromethane was treated with 5 mol-% of bismuth(III) nitrate pentahydrate, it was smoothly converted into the corresponding THP ether **2a** within 15 min in 92% yield. Similarly, 2-phenylethanol (entry **1b**) was converted into the corresponding THP ether **2b** in fairly good yield under identical reaction conditions. Various benzylic alcohols (entries **1c**–**g**), allyl alcohols (entry **1h**), secondary alcohols (entries **1i**–**l**), and tertiary alcohols (entries **1m** and **1n**) were smoothly converted into the corresponding THP ethers **2c**–**n**, respectively, in very good yields, as shown in Table 1. Here, it is worth mentioning that our procedure is more highly efficient in terms of reaction times and yields than some of the recently reported procedures.[15,18] For example, tetrahydropyranylation of 4-nitrobenzylalcohol (entry **1d**), geraniol (entry **1h**), and (–)menthol (entry **1k**) to form the corresponding THP ethers was completed much more quickly and also provided better yields than the bismuth triflate method.[15] We were then interested in whether the same catalyst could be employed for tetrahydropyranylation of phenolic compounds. By following identical reaction procedures, various phenols (entries **1o**–**q**) were smoothly converted into the corresponding THP ethers **2o**–**q** in good yields. It had been observed previously that the formation of the THP ether **2q** from β naphthol (entry **1q**) by employing Bi(OTf)$_3$ as catalyst was a failure,[15] whereas we have shown that it can be easily accessible by our method; this offers an additional advantage. We then turned our attention on whether the same catalyst could be useful for tetrahydropyranylation of substrates containing other protecting groups. We observed that various protected alcohols (entries **1r**–**x**) containing protecting groups such as acetyl, benzyl, benzoyl, trityl, tosyl, TBS and TBDPS ethers were smoothly converted into the corresponding THP ethers **2r**–**x** without affecting the other protecting groups. Furthermore, substrates with thioacetal groups (entries **1y** and **1z**), and isopropylidene protected alcohols (entries **1a′** and **1b′**) and benzylidene protected diol (entry **1c′**) can be easily transformed into the desired THP ethers in good yields as shown in the Table 1. Interestingly, it should be noted that the formation of THP ethers **2y** and **2z** from the compounds **1y** and **1z**, respectively, was difficult by our recently reported procedure, where we used cupric sulfate pentahydrate as catalyst.[17] Remarkably, by employing our current protocol, various carbohydrates (entries **1d′** and **1e′**), as well as a nucleoside compound (entry **1f′**), were smoothly converted into the corresponding THP ethers in good yields, as shown in Table 1. The formation of the products was confirmed by IR, ^{1}H- and ^{13}C NMR spectroscopy and by elemental analysis. In addition, we have also compared some of the spectroscopic data with that obtained by a method reported earlier.[28]

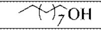
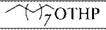
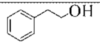
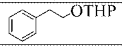
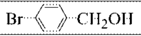
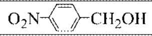
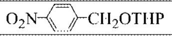
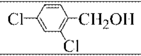
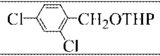
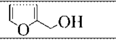
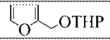
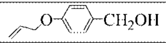
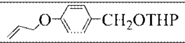
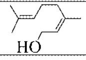
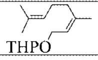
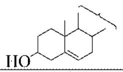
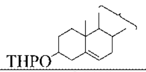
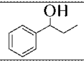
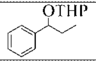
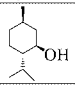
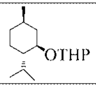
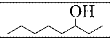
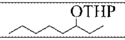
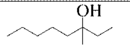
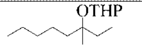
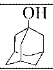
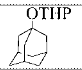
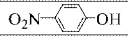
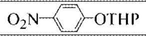
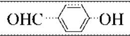
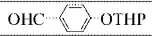
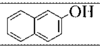
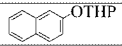
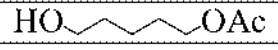
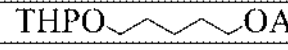
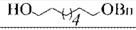
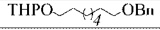
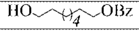
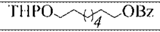
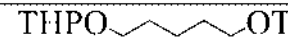
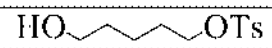
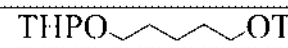
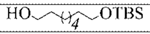
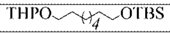
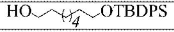
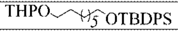
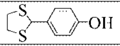
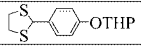
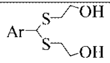
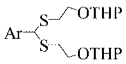
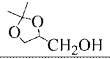
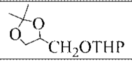
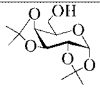
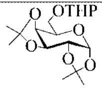
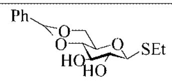
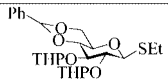
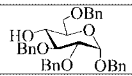
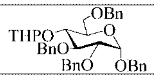
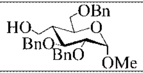
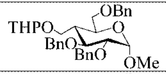
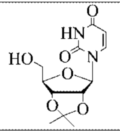
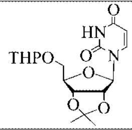
The most significant advantage of this protocol is that various symmetric diols can be chemoselectively protected when transformed into the mono THP ethers (**2g′**–**k′**) [with 5–10% di-THP ethers] by using 5 mol-% catalyst under identical conditions; this is sometimes difficult to achieve with other methods, see Table 2. It should also be noted that primary alcohols can be protected chemoselectively in the presence of a secondary alcohol (entry **1l′**). An additional feature of our protocol is that tetrahydropyranylation can be carried out even on a large scale (for example, on 10–100 mmol) without any difficulty.

The formation of the product can be explained as follows. We believe that the actual catalyst is nitric acid, which is generated from bismuth(III) nitrate pentahydrate in the reaction medium. This fact is verified in two ways: i) the tetrahydropyranylation of 4-nitrobenzyl alcohol (entry **1d**) in the presence of bismuth(III) nitrate pentahydrate (0.05 mmol) and potassium carbonate (1 mmol) did not show the formation of any product; ii) the formation of THP ether **2d** from 4-nitrobenzyl alcohol is possible in 72% yield in the presence of a catalytic amount of concentrated HNO$_3$. However, Banik et al. reported[26d] while studying Michael reactions that bismuth(III) nitrate pentahydrate acts only as a Lewis acid because they did not observe any Michael addition product in the presence of other metal nitrates that can readily generate nitric acid in the medium.

Notably, the same catalyst can be used for depyranylation reactions. For example, the THP ether **2b** undergoes cleavage in methanol within 45 min in 82% yield with 5 mol-% of catalyst. Likewise, various THP ethers **2c**, **2f**, **2n**, **2r**, and **2z** were converted into the parent hydroxyl compounds **1c**, **1f**, **1n**, **1r**, and **1z**, respectively, within 35–50 min in 80–90% yields under similar reaction conditions, which are given in the Experimental Section.

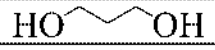
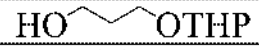
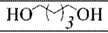
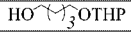
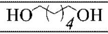
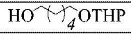
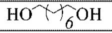
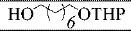
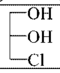
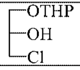
The efficiency and generality of the present method can be realized at a glance by comparing our results with those of some recently reported procedures (shown in Table 3). The results have been compared with respect to the reaction times, mol-% of the catalyst used, and yields. Here we have chosen some of the substrates as model substrates. In case of entry **1**, the yields are comparable, but the reaction time proves the efficiency of our protocol. For entry **2**, the desired THP ether **2q** was difficult to obtain when Bi(OTf)$_3$·4H$_2$O was used, but it can be prepared in good yield and without any difficulty by employing our protocol. For entries **3**, **4** and **5**, the yields are better and reaction times are lower when our protocol is used. The protocol with Bi(OTf)$_3$·4H$_2$O requires not only an inert atmosphere, but also Bi(OTf)$_3$·4H$_2$O has to be prepared prior to use. Therefore, considering all these facts we believe that bismuth(III) nitrate pentahydrate is a relatively better catalyst for tetrahydropyranylation of hydroxyl compounds.

Table 1. Tetrahydropyranylation of alcohols and phenols in the presence of a catalytic amount of bismuth(III) nitrate pentahydrate [$Bi(NO_3)_3 \cdot 5H_2O$].

Entry	Substrate (1)	Time [min]	Product[a] (2)	Yield[b,c] [/%]
a		15		92[18a]
b		15		84
c		15		91
d		20		90
e		25		77[18a]
f		12		85[27]
g		22		84[18a]
h		18		88[27]
i		45		82[8]
j		18		90[18a]
k		22		90[8]
l		18		90
m		22		65
n		25		76
o		30		83[28]
p		25		87
q		45		74
r		16		83
s		18		86[28]
t		15		87
u		15		81
v		12		86
w		15		87
x		12		85
y		27		83
z	 Ar = 4-Methoxyphenyl	18		81
a′		20		84[18b]
b′		35		79
c′		55		60
d′		32		79
e′		25		84
f′		40		83

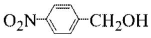
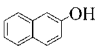
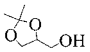
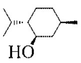
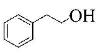
[a] All starting materials and final products were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy and by elemental analysis. [b] Isolated yield. [c] The reference refers to the spectroscopic data for the particular compound.

Table 2. Selective tetrahydropyranylation of diols using a catalytic amount of $Bi(NO_3)_3 \cdot 5H_2O$.

Entry	Substrate (1)	Time [min]	Product[a] (2)	Yield[b] [%]
g′		12		73
h′		15		70[18a]
i′		12		83[18a]
j′		20		75
k′		15		62
l′		18		76

[a] All starting materials and final products were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy and by elemental analysis. [b] Isolated yield.

Table 3. Comparison of results of tetrahydropyranylation of alcohols and phenols with other catalysts.

Entry	Alcohol/Phenol	Catalyst	Mol-%	Time	Yield [%]
1		LiOTf	60–70	3 h	92[11]
		$Bi(OTf)_3 \cdot 4H_2O$	0.1	4 h	85[15]
		$Bi(NO_3)_3 \cdot 5H_2O$	5	20 min	90
2		LiOTf	60–70	6 h	92[11]
		$Bi(OTf)_3 \cdot 4H_2O$	0.1	–	0[15]
		$Bi(NO_3)_3 \cdot 5H_2O$	5	45 min	74
3		H_2O	–	9 h	55[18a]
		$Bi(OTf)_3 \cdot 4H_2O$	0.1	3.25 h	78[15]
		$Bi(NO_3)_3 \cdot 5H_2O$	5	20 min	84
4		$NbCl_5$	10	3 h	89[18b]
		H_2O	–	10 h	76[18a]
		$Bi(OTf)_3 \cdot 4H_2O$	0.1	2 h	74[15]
		$Bi(NO_3)_3 \cdot 5H_2O$	5	22 min	90
		TBATB	0.1	1 h	74[9]
5		TBATB	2.5	45 min	88[9]
		LiOTf	60–70	2.5 h	94[11]
		$Bi(OTf)_3 \cdot 4H_2O$	0.1	1h	82[15]
		$Bi(NO_3)_3 \cdot 5H_2O$	15	22 min	90

Conclusions

In conclusion, the present methodology demonstrates $Bi(NO_3)_3 \cdot 5H_2O$ as an effective catalyst for tetrahydropyranylation/depyranylation of alcohols and phenols. The main advantages of this method are: mild, clean and simple reaction conditions, good yields, nonaqueous workup, and environmentally benign reagents. In addition, our methodology might be useful for substrates containing a wide variety of other protecting groups. Furthermore, this method is also expected to have much better application in organic synthesis because of the very low cost and nontoxic nature of the reagent. We believe this methodology will be a valuable addition to modern synthetic methodologies.

Experimental Section

Melting points were recorded on a Büchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 200 MHz, Bruker 300 MHz, and Jeol 400 MHz spectrometer in $CDCl_3$ by using TMS as internal reference. Elemental analyses were carried out with a Perkin–Elmer 2400 automatic carbon, hydrogen, nitrogen, and sulfur analyzer. Column chromatographic separations were done on SRL silica gel (60–120 mesh).

Typical Procedure for Tetrahydropyranylation: Bismuth(III) nitrate pentahydrate (0.024 g, 0.05 mmol) was added to a mixture of alcohol or phenol (1 mmol) and 3,4-dihydro-2*H*-pyran (109 µL, 1.2 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature. After completion of the reaction as confirmed by TLC, the reaction mixture was reduced to approximately 1 mL, and then it was passed through a short basic alumina column to afford the desired THP ether.

2b: Yield: 0.173 g, 84%. IR (Neat): 2942, 2869, 1600, 1465, 1357, 1127, 1038 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.47–1.82 (m, 6 H), 2.91 (t, J = 7.2 Hz, 2 H), 3.41–3.47 (m, 1 H), 3.61 (dt, J = 7.2, J = 4.0, 10.0 Hz, 1 H), 3.72–3.77 (m, 1 H), 3.94 (dt, J = 7.6, 5.2, 9.6 Hz, 1 H), 4.58 (t, J = 3.5 Hz, 1 H), 7.16–7.28 (m, 5 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.6, 25.6, 30.8, 36.5, 62.2, 68.3, 98.7, 126.0, 128.1 (2 C), 128.9 (2 C), 140.0 ppm. $C_{13}H_{18}O_2$ (206.28): calcd. C 75.69, H 8.79; found C 75.43, H 8.73%.

2c: Yield: 0.247 g, 91%. IR (Neat): 2942, 2865, 1595, 1465, 1357, 1130, 1075, 1038 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.53–1.87 (m, 6 H), 3.50–3.56 (m, 1 H), 3.85–3.91 (m, 1 H), 4.44 (d, J = 12.4 Hz, 1 H), 4.66–4.68 (m, 1 H), 4.71 (d, J = 12.0 Hz, 1 H), 7.23 (d, J = 8.8 Hz, 2 H), 7.46 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.4, 25.5, 30.6, 62.2, 68.0, 97.7, 121.2, 129.2 (2 C), 131.3 (2 C), 137.2 ppm. $C_{12}H_{15}O_2Br$ (271.15): calcd. C 53.16, H 5.58; found C 53.24, H 5.49%.

2d: Yield: 0.213 g, 90%. IR (Neat): 2943, 2869, 1605, 1522, 1346, 1202, 1127, 1036 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.52–1.92 (m, 6 H), 3.51–3.59 (m, 1 H), 3.86–3.92 (m, 1 H), 4.61 (d, J = 13.6 Hz, 1 H), 4.73–4.74 (m, 1 H), 4.89 (d, J = 13.2 Hz, 1 H), 7.53 (d, J = 9.2 Hz, 2 H), 8.20 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.4, 25.4, 30.5, 62.3, 67.6, 98.2, 123.4 (2 C), 127.6 (2 C), 145.9, 147.3 ppm. $C_{12}H_{15}NO_4$ (237.25): calcd. C 60.75, H 6.37, N 5.90; found C 60.54, H 6.29, N 5.78%.

2l: Yield: 0.193 g, 90%. IR (neat): 2935, 2873, 1460, 1347, 1204, 1132, 1030 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.83 (t, J = 7.3 Hz, 3 H), 0.90 (t, J = 7.3 Hz, 3 H), 1.25–1.31 (m, 6 H), 1.39–1.83 (m, 10 H), 3.42–3.56 (m, 2 H), 3.85–3.91 (m, 1 H), 4.61–4.63 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 9.1, 14.0, 19.7, 22.6, 24.7, 25.8, 31.1, 32.1, 32.9, 34.3, 62.6, 78.0, 97.2 ppm. $C_{13}H_{26}O_2$ (214.35): calcd. C 72.85, H 12.23; found C 72.78, H 12.19%.

2m: Yield: 0.148 g, 65%. IR (neat): 2945, 2863, 1460, 1378, 1281, 1204, 1132, 1086, 1030, 994 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.84 (t, J = 6.8 Hz, 3 H), 0.89 (t, J = 7.2 Hz, 3 H), 1.15 (s, 3 H), 1.26–1.39 (m, 6 H), 1.41–1.84 (m, 10 H), 3.42–3.45 (m, 1 H), 3.93–3.97 (m, 1 H), 4.70 (br. s, 1 H) ppm. $C_{14}H_{28}O_2$ (228.37): calcd. C 73.63, H 12.36; found C 73.84, H 12.27%.

2n: Yield: 0.180 g, 76%. IR (neat): 2935, 2858, 1440, 1245, 1204, 1158, 1132, 1068, 1046, 979 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.47–1.54 (m, 4 H), 1.56–1.66 (m, 8 H), 1.76–1.85 (m, 6 H), 2.12 (s, 3 H), 3.40–3.48 (m, 1 H), 3.91–3.99 (m, 1 H), 4.82–4.85 (m, 1 H) ppm. $C_{15}H_{24}O_2$ (236.35): calcd. C 76.23, H 10.23; found C 76.03, H 10.29%.

2p: Yield: 0.179 g, 87%. IR (neat): 2945, 2858, 1696, 1609, 1511, 1358, 1306, 1250, 1209, 1163, 1112, 1040 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.49–1.78 (m, 4 H), 1.81–1.99 (m, 2 H), 3.57–3.62 (m, 1 H), 3.80–3.86 (m, 1 H), 5.47–5.51 (m, 1 H), 7.12 (d, J = 8.8 Hz, 2 H), 7.79 (d, J = 8.8 Hz, 2 H), 9.84 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 18.4, 24.9, 30.6, 62.0, 96.0, 116.4 (2 C), 131.8 (2 C), 132.3, 162.1, 191.1 ppm. $C_{12}H_{14}O_3$ (206.24): calcd. C 69.89, H 6.84; found C 69.78, H 6.78%.

2q: Yield: 0.169 g, 74%. M.p. 44–46 °C. IR (KBr): 3056, 2941, 1617, 1599, 1510, 1466, 1390, 1253, 1217, 1173, 1037 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.60–1.73 (m, 3 H), 1.89–1.92 (m, 2 H), 1.99–2.08 (m, 1 H), 3.62–3.66 (m, 1 H), 3.91–3.97 (m, 1 H), 5.56 (t, J = 3.3 Hz, 1 H), 7.21–7.25 (m, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.39–7.43 (m, 2 H), 7.72–7.76 (m, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 18.7, 25.2, 30.4, 61.9, 96.4, 110.4, 119.1, 123.8, 126.2, 127.0, 127.5, 129.2, 129.4, 134.5, 154.8 ppm. $C_{15}H_{16}O_2$ (228.29): calcd. C 78.92, H 7.06; found C 78.71, H 6.98%.

2r: Yield: 0.191 g, 83%. IR (neat): 2945, 2873, 1471, 1460, 1439, 1372, 1250, 1034 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): 1.39–1.84 (m, 12 H), 2.04 (s, 3 H), 3.36–3.41 (m, 1 H), 3.48–3.51 (m, 1 H), 3.71–3.76 (m, 1 H), 3.82–3.88 (m, 1 H), 4.06 (t, J = 6.8 Hz, 2 H), 4.56–4.58 (m, 1 H) ppm. $C_{12}H_{22}O_4$ (230.30): calcd. C 62.58, H 9.63; found C 62.72, H 9.57%.

2t: Yield: 0.291 g, 87%. IR (neat): 2930, 2857, 1719, 1453, 1276, 1217, 1114, 1038 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ = 1.36–1.86 (m, 18 H), 3.35–3.41 (m, 1 H), 3.50–3.56 (m, 1 H), 3.70–3.78 (m, 1 H), 3.86–3.89 (m, 1 H), 4.31 (t, J = 6.8 Hz, 2 H), 4.56–4.60 (m, 0.5 H), 4.94–4.98 (m, 0.5 H), 7.43 (t, J = 7.2 Hz, 2 H), 7.55 (t, J = 7.2 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 2 H) ppm. $C_{20}H_{30}O_4$ (334.45): calcd. C 71.83, H 9.04; found C 71.56, H 9.10%.

2u: Yield: 0.291 g, 81%. IR (neat): 2950, 2868, 1598, 1496, 1450, 1332, 1163, 1071, 1030 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): (mixture of diastereomers): δ = 1.38–1.83 (m, 12 H), 3.02 (t, J = 6.6 Hz, 2 H), 3.31–3.36 (m, 1 H), 3.45–3.50 (m, 1 H), 3.66–3.69 (m, 1 H), 3.80–3.86 (m, 1 H), 4.50–4.52 (m, 0.3 H), 4.90–4.92 (m, 0.7 H), 7.15–7.28 (m, 12 H), 7.39–7.41 (m, 3 H) ppm. $C_{29}H_{34}O_3$ (430.58): calcd. C 80.90, H 7.96; found C 80.66, H 7.89%.

2v: Yield: 0.295 g, 86%. 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, 12 H), 2.45 (s, 3 H), 3.32–3.35 (m, 1 H), 3.49–3.50 (m, 1 H), 3.68–3.70 (m, 1 H), 3.80–3.89 (m, 1 H), 4.03 (t, J = 6.8 Hz, 2 H), 4.53–4.54 (m, 1 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.4 Hz, 2 H) ppm. ^{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 (2 C), 129.6 (2 C), 133.0, 144.5 ppm. $C_{17}H_{26}O_5S$ (342.45): calcd. C 59.63, H 7.65, S 9.36; found C 59.40, H 7.71, S 9.15%.

2w: Yield: 0.300 g, 87%. IR (neat): 2937, 2860, 1465, 1358, 1254, 1106, 1031 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.04 (s, 6 H), 0.89 (s, 9 H), 1.25–1.30 (m, 6 H), 1.48–1.87 (m, 12 H), 3.34–3.40 (m, 1 H), 3.47–3.50 (m, 1 H), 3.59 (t, J = 6.4 Hz, 2 H), 3.69–3.73 (m, 1 H), 3.84–3.89 (m, 1 H), 4.56–4.57 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = –5.3 (2 C), 18.3, 19.6, 25.5, 25.7, 25.9 (3 C), 26.1, 29.3, 29.4, 29.7, 30.7, 32.8, 62.2, 63.2, 67.6, 98.8 ppm. $C_{19}H_{40}O_3Si$ (344.61): calcd. C 66.22, H 11.70; found C 66.46, H 11.62%.

2x: Yield: 0.399 g, 85%. IR (neat): 2935, 2858, 1475, 1440, 1388, 1363, 1204, 1112, 1030, 979 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): (mixture of diastereomers): δ = 1.04 (s, 9 H), 1.10–1.35 (m, 8 H), 1.52–1.85 (m, 10 H), 3.35–3.54 (m, 2 H), 3.64 (t, J = 6.4 Hz, 2 H), 3.70–3.92 (m, 2 H), 4.52–4.62 (m, 0.4 H), 4.90–5.00 (m, 0.6 H), 7.30–7.46 (m, 6 H), 7.61–7.71 (m, 4 H) ppm. $C_{29}H_{44}O_3Si$ (468.75): calcd. C 74.31, H 9.46; found C 74.09, H 9.40%.

2y: Yield: 0.235 g, 83%. IR (neat): 2930, 1614, 1511, 1255, 1240, 1122, 1040 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.46–2.00 (m, 6 H), 3.31–3.41 (m, 2 H), 3.48–3.63 (m, 3 H), 3.89–3.93 (m, 1 H), 5.41 (t, J = 3.0 Hz, 1 H), 5.64 (s, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.44 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ =

19.1, 25.6, 30.7, 40.6 (2 C), 56.5, 62.4, 96.7, 116.8 (2 C), 129.8 (2 C), 133.1, 157.3 ppm. $C_{14}H_{18}O_2S_2$ (282.41): calcd. C 59.54, H 6.42, S 22.70; found C 60.05, H 6.39, S 22.54%.

2z: Yield: 0.359 g, 81%. IR (neat): 2966, 2925, 2843, 1619, 1516, 1450, 1327, 1260, 1178, 1086, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53–1.87 (m, 12 H), 2.70–2.80 (m, 2 H), 2.92–2.98 (m, 2 H), 3.45–3.60 (m, 4 H), 3.85–3.88 (m, 4 H), 3.88 (s, 3 H), 4.85–4.95 (m, 2 H), 6.22 (s, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.84 (d, J = 8.0 Hz, 2 H) ppm. $C_{22}H_{34}O_5S_2$ (442.63): calcd. C 59.70, H 7.74, S 14.49; found C 59.56, H 7.67, S 14.32%.

2b′: Yield: 0.272 g, 79%. IR (neat): 2945, 1470, 1388, 1271, 1230, 1076, 1009 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ = 1.28 (s, 3 H), 1.29 (s, 3 H), 1.39 (s, 3 H), 1.49 (s, 3 H), 1.50–1.82 (m, 6 H), 3.43–3.49 (m, 1 H), 3.56–3.85 (m, 2 H), 3.93–3.98 (m, 1 H), 4.20 (dd, J = 1.7, 7.8 Hz, 1 H), 4.23–4.29 (m, 1 H), 4.52–4.61 (m, 2 H), 4.88 (d, J = 4.9 Hz, 1 H), 5.48 (dd, J = 5.2, 9.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 19.5, 19.7 (2 C), 24.4, 24.5, 24.9, 25.4 (2 C), 25.9, 26.0, 30.5, 30.7 (2 C), 62.2, 62.4, 62.9, 65.9, 66.1, 66.5, 67.4, 70.5, 70.6, 70.7, 71.0, 71.4, 94.6, 96.3, 96.4, 99.0, 99.1, 108.5, 109.1, 109.2 ppm. $C_{17}H_{28}O_7$ (344.40): calcd. C 59.29, H 8.19; found C 59.52, H 8.23%.

2c′: Yield: 0.288 g, 60%. IR (neat): 2935, 2858, 1634, 1470, 1383, 1265, 1086, 1030, 974 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ = 1.33 (t, J = 7.6 Hz, 3 H), 1.42–1.76 (m, 12 H), 2.63–2.67 (m, 2 H), 3.23–3.67 (m, 7 H), 3.90–4.00 (m, 1 H), 4.22–4.27 (m, 1 H), 4.38–4.48 (m, 3 H), 4.64–4.70 (m, 1 H), 5.44 (s, 1 H), 7.21–7.27 (m, 3 H), 7.34–7.38 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.04, 15.16, 19.03, 19.63, 20.03, 21.13, 24.44, 24.87, 25.22, 25.44, 29.03, 30.69, 31.00, 65.40, 65.63, 66.96, 68.65, 70.09, 70.83, 72.15, 73.29, 79.34, 80.57, 83.97, 84.20, 84.87, 86.23, 101.24, 101.72, 102.35, 102.79, 125.98, 126.33, 128.21, 137.28 ppm. $C_{25}H_{36}SO_7$ (480.62): calcd. C 62.48, H 7.55, S 6.67; found C 62.71, H 7.59, S 6.62

2d′: Yield: 0.493 g, 79%. IR (neat): 2935, 2858, 1634, 1470, 1383, 1265, 1086, 1030, 974 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41–1.94 (m, 6 H), 3.49–4.15 (m, 10 H), 4.51–4.96 (m, 7 H), 5.20–5.30 (m, 1 H), 7.15–7.40 (m, 20 H) ppm. $C_{39}H_{44}O_7$ (624.77): calcd. C 74.98, H 7.10; found C 74.73, H 7.01

2e′: Yield: 0.473 g, 84%. IR (neat): 2941, 2873, 1453, 1354, 1202, 1074, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43–1.95 (m, 6 H), 2.47 (t, J = 6.0 Hz, 1 H, 4-H), 3.39 (s, 3 H), 3.40–4.02 (m, 11 H), 4.47–4.77 (m, 5 H), 4.95–5.02 (m, 1 H), 7.24–7.37 (m, 15 H) ppm. $C_{34}H_{42}O_7$ (562.70): calcd. C 72.57, H 7.52; found C 72.63, H 7.48.

2f′: Yield: 0.306 g, 83%. IR (neat): 3235, 3109, 2966, 2935, 2817, 1788, 1690, 1481, 1409, 1271, 1209, 1107, 1055, 989 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ = 1.33 (s, 3 H), 1.34 (s, 3 H), 1.49 (s, 3 H), 1.51 (s, 3 H), 1.47–1.90 (m, 12 H), 3.49–3.57 (m, 4 H), 3.65 (dd, J = 2.4, 11.2 Hz, 1 H), 3.78–3.83 (m, 2 H), 3.94 (dd, J = 3.2, 11.2 Hz, 1 H), 4.01–4.05 (m, 2 H), 4.37–4.42 (m, 1 H), 4.57–4.59 (m, 1 H), 4.73–4.74 (m, 1 H), 4.81–4.82 (m, 1 H), 4.87–4.88 (m, 1 H), 4.89–4.95 (m, 1 H), 5.64 (d, J = 8.0 Hz, 1 H), 5.66 (d, J = 8.0 Hz, 1 H), 5.88 (d, J = 2.4 Hz, 1 H), 5.90 (d, J = 2.4 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 8.58 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.01, 20.84, 25.56, 25.58, 25.62, 25.78, 25.84, 27.64, 30.81, 32.42, 63.05, 63.11, 64.22, 67.52, 67.78, 80.99, 81.20, 85.45, 85.68, 85.91, 92.89, 94.85, 99.22, 99.84, 102.05, 102.33, 114.24, 114.44, 140.88, 141.48, 150.46 (2 C), 163.86 (2 C) ppm. $C_{17}H_{24}$ N_2O_7 (368.38): calcd. C 55.43, H 6.57, N 7.60; found C 55.61, H 6.59, N 7.53.

2g′: Yield: 0.117 g, 73%. IR (neat): 3416, 2950, 2879, 1455, 1352, 1209, 1127, 1081, 1035 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51–1.63 (m, 3 H), 1.67–1.89 (m, 3 H), 2.25 (br. s, 1 H, D_2O exchangeable), 3.48–3.61 (m, 2 H), 3.78 (t, J = 5.2 Hz, 2 H), 3.83–3.95 (m, 2 H), 4.57–4.59 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 25.4, 30.7, 32.1, 61.5, 62.6, 66.3, 99.1 ppm. $C_8H_{16}O_3$ (160.21): calcd. C 59.98, H 10.07; found C 60.05, H 10.12.

2j′: Yield: 0.173 g, 75%. IR (neat): 3422, 2931, 2858, 1454, 1354, 1276, 1127, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.40 (br. s, 8 H), 1.50–1.61 (m, 6 H), 1.69–174 (m, 2 H), 1.80–1.90 (m, 2 H), 2.05 (br. s, 1 H, D_2O exchangeable), 3.35–3.41 (m, 1 H), 3.48–3.51 (m, 1 H), 3.64 (t, J = 6.8 Hz, 2 H), 3.70–3.74 (m, 1 H), 3.84–3.89 (m, 1 H), 4.56–4.58 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 25.5, 25.7, 26.2, 29.3, 29.4, 29.7, 30.7, 32.7, 62.2, 62.7, 67.6, 98.7 ppm. $C_{13}H_{26}O_3$ (230.35): calcd. C 67.79, H 11.38; found C 67.65, H 11.29.

2k′: Yield: 0.106 g, 62%. IR (neat): 3411, 2945, 2863, 1450, 1393, 1358, 1271, 1127, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.52–1.85 (m, 7 H), 3.53–3.56 (m, 1 H), 3.81–3.86 (m, 1 H), 4.23–4.37 (m, 4 H), 4.81 (t, J = 3.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 25.7, 30.6, 51.5, 54.7, 62.3, 82.1, 84.6, 97.2 ppm. $C_9H_{14}O_3$ (170.21): calcd. C 63.51, H 8.29; found C 63.64, H 8.24.

2l′: Yield: 0.148 g, 76%. IR (neat): 3416, 2940, 2873, 1445, 1393, 1265, 1204, 1132, 1081, 1035, 979 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): (mixture of diastereomers): δ = 1.52–1.83 (m, 6 H), 3.27–3.37 (br. s, 1 H, D_2O exchangeable), 3.51–3.99 (m, 7 H), 4.51–4.53 (m, 0.5 H), 4.57–4.59 (m, 0.5 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.6, 25.5, 25.6, 31.0, 31.1, 45.8, 46.2, 63.5, 64.0, 70.1, 70.5, 70.8 (2 C), 100.4, 100.9 ppm. $C_8H_{15}O_3Cl$ (194.66): calcd. C 49.36, H 7.77; found C 49.52, H 7.84.

Typical Procedure for Depyranylation: Bismuth(III) nitrate pentahydrate (0.024 g, 0.05 mmol) was added into a stirred solution of the THP ether of 4-bromobenzyl alcohol **2c** (0.271 g, 1 mmol) in methanol (2 mL) at room temperature. The reaction was complete within 40 min, and the mixture was concentrated in rotavapor. The crude residue was purified through a short silica gel column. The desired 4-bromobenzyl alcohol (**1c**) was obtained (0.170 g) in 91% yield.

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Perchloric Acid Impregnated on Silica Gel ($HClO_4/SiO_2$): A Versatile Catalyst for Michael Addition of Thiols to the Electron-Deficient Alkenes

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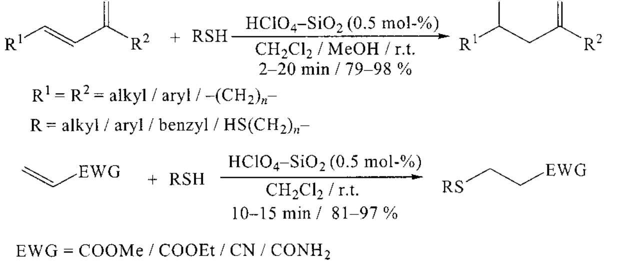
Keywords: Thiols / Electron-deficient alkenes / Michael addition / Silica-supported perchloric acid

Perchloric acid adsorbed on silica gel ($HClO_4/SiO_2$) has been found to be a highly efficient and versatile catalyst for the Michael addition of thiols to a wide variety of conjugated alkenes such as α,β-unsaturated ketones, carboxylic esters, nitriles, amides and chalcones in dichloromethane or methanol at room temperature. The reactions are completed within 2–20 min in high yields. Some of the additional advantages are: no aqueous work-up is necessary, and the catalyst is also reusable. Moreover, the solid product can be obtained without chromatographic separation.

Inltroduction

The addition of thiols to α,β-unsaturated carbonyl compounds is a very important process in carbon–sulfur bond formation.[1] By employing this process, the olefinic double bond of a conjugated carbonyl compound can selectively be protected, and deprotection can be easily done either by copper(I) induced elimination[2] or by oxidation followed by thermolytic elimination.[3] Thia-Michael addition product(s) of α,β-unsaturated carbonyl compounds are very important building blocks for the synthesis of bioactive compounds,[4] heterocycles,[5] and are also used as chiral auxiliary for the synthesis of optically active α-hydroxy aldehydes.[6] Therefore, the development of an efficient and selective catalyst for the construction of carbon–sulfur bond is of interest in organic synthesis. Thia-Michael reaction is classically carried out by employing a base under homogeneous conditions.[6a,7] Under heterogeneous conditions, various solid catalysts have been found to be useful. For example, natural phosphate or phosphate doped with potassium fluoride,[8] zeolite,[9] clay-supported $NiBr_2$ and $FeCl_3$,[10] Fluoroapatite,[11] polymer-supported Nafion® SAC-13[12] and dodecatungstophosphoric acid ($H_3PW_{12}O_{40}$).[13] Moreover, a wide variety of Lewis acid catalyst and other reagents have been used over the years for the similar transformation. Among them some of the reported catalysts are: $Hf(OTf)_4$,[14] $InBr_3$,[15] $InCl_3$,[16] $Bi(NO_3)_3$,[17] $Bi(OTf)_3$,[18] $Cu(BF_4)_2{\cdot}xH_2O$,[19] nickel(II) perchlorate,[20] [pmIm]Br,[21] $[Bmim]PF_6/H_2O$,[22] $RuCl_3$ in poly(ethyleneglycol),[23] molten tetrabutylammonium bromide,[24] chiral *N*,*N*′-dioxide–cadmium iodide,[25] I_2,[26] micellar solution of sodium dodecyl sulfate (SDS),[27] and azaphosphatrane nitrate salt.[28] Unfortunately, many of these procedures have one or the other disadvantages such as longer reaction time, use of excessive expensive catalyst, harsh reaction conditions, failure to provide addition product and tedious experimental procedure. Therefore, the development of an efficient and mild synthetic protocol is always in great demand to make the available procedures more convenient and simpler. Very recently, solid-supported reagents[29] have gained considerable interest in organic synthesis because of their unique properties of the reagents such as high efficiency due to more surface area, more stability and reusability, greater selectivity and ease of handling. In continuation of our ongoing research programme to develop better and newer synthetic methodologies, we perceived that $HClO_4/SiO_2$ might be a very useful catalyst for thia-Michael reaction. The catalyst, $HClO_4/SiO_2$ has been utilized so far by others for acetylation of phenols, thiols, alcohols and amines,[30] peracetylation of carbohydrates,[31] acetalization followed by acetylation,[32] glycosylation reaction[33] and for Ferrier rearrangement of glycals.[34] Very recently, we also noticed that the same catalyst is highly effective for the *gem* diacylation of aldehydes.[35] In this paper, we wish to report that $HClO_4/SiO_2$ is an efficient and valuable catalyst for the 1,4-



Scheme 1.

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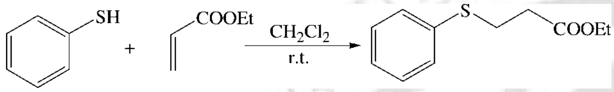
conjugate addition of thiols to a wide variety of conjugated alkenes such as α,β-unsaturated ketones, carboxylic esters, nitriles and amides as shown in Scheme 1.

Results and Discussion

For our investigations, $HClO_4/SiO_2$ was prepared according to the literature procedure.[30] To evaluate the better catalytic activity of $HClO_4/SiO_2$ over silica gel or aqueous perchloric acid, a model study was carried out with thiophenol and ethyl acrylate using various catalytic conditions, as shown in Scheme 2 and Table 1. From the study, it clearly demonstrated that the silica-supported perchloric acid is indeed an effective catalyst in terms of reaction time and yield.



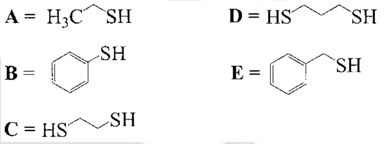
Scheme 2.

Table 1. The result of the reaction of ethyl acrylate (2 mmol) with thiophenol (2.2 mmol) under different catalytic conditions in dichloromethane at room temperature.

Run	Catalyst	Time	Yield [%][a,b]
I	No catalyst	24 h	52
II	SiO_2 (10 mg /mmol)	24 h	63
III	Aqueous $HClO_4$ (0.5 mol-%)	1 h	82
IV	$HClO_4/SiO_2$ (10 mg/mmol, 0.5 mol-%)	10 min	95

[a] Isolated yield. [b] All the compounds were characterized by recording IR, ^1H NMR, ^{13}C NMR and elemental analyses.

The thia-Michael reaction of 2-cyclopenten-1-one (**1**) with ethanethiol (**A**) using 0.5 mol-% of catalyst in dichloromethane at room temperature (run 1) proceeded within 5 min and the pure product 3-(ethylthio)cyclopentanone (**1a**) was isolated in 92% yield as a gummy liquid by filtration through a short silica gel column. The product was characterized by IR, ^1H NMR, ^{13}C NMR spectra and elemental analysis, and it was agreeable with the 1,4-addition product. Various thiols used for Michael addition are given in Scheme 3. The enone **1** also treated with thiophenol (**B**) in the presence of same catalyst under identical conditions to provide the desired addition product **1b** in 98% yield (run 2), in quicker time with better yield compared to the recently reported procedures.[15,22] Likewise, 1,2-ethanedithiol (**C**) on reaction with two molecules of the enone **1** smoothly provided the bis-Michael addition product **1c** within 5 min in good yield without any difficulty. By following identical reaction procedure, 2-cyclohexen-1-one (**2**) also treated with ethanethiol (**A**), thiophenol (**B**) and 1,3-propanedithiol (**D**) (run 4–6) to furnish the desired Michael addition products **2a**, **2b** and **2d**, respectively, in good yields. We observed that the present protocol is highly efficient in terms of mol-% of the catalyst used and yields, relative to a very recently reported procedure.[19] 4,4-Dimethyl-2-cyclohexen-1-one (**3**) was readily converted into **3b** on reaction with thiophenol (**B**) in good yields. The results are summarized in Table 2. Next, we were interested to see whether the same catalyst is useful for the Michael reaction of acyclic α,β-unsaturated ketones or not. Remarkably, an enone **4**, such as 16-dehydropregnenolone acetate (16-DPA), was also treated with ethanethiol (**A**) and thiophenol (**B**) independently to give the 1,4-addition products **4a** and **4b**, respectively, in fairly good yields using the same catalyst under similar reaction conditions. In addition, the use of methanol as the solvent, makes it possible to access the Michael addition products **5a** and **5b** from the corresponding chalcone (**5**) in very good yields. Notably, by employing our protocol, from naturally occurring α,β-unsaturated ketones such as (*S*)-(+)-carvone (**6**) and (*R*)-(+)-pulegone (**7**), we obtained the corresponding Michael addition products, **6a**, **7a** and **7e**, respectively, as a diastereomeric mixture on treatment with thiols under identical reaction conditions. It is noteworthy to point out that the addition reaction of (*R*)-(+)-pulegone (**7**) with phenylmethanethiol (**E**) took much longer reaction time under basic conditions.[6a] One more advantage of the present method is that the reaction does not need to be carried out under N_2.



Scheme 3.

All the final products were characterized by recording IR, ^1H NMR, ^{13}C NMR spectra and elemental analysis. The structure of compound **4b** was determined by X-ray crystallography. The ORTEP diagram is shown in Figure 1.

Each unit cell contains two identical molecules. The torsion angles between H^{32}–C^{16}–C^{17}–H^{46}, S^1–C^{16}–C^{17}–H^{46}, H^{32}–C^{16}–C^{17}–C^{20} and C^{20}–C^{17}–C^{16}–S^1 are 155.27°, 31.32°, 32.44° and 92.49°, respectively. These results are in accordance with the fact that H^{46} and H^{32} as well as C^{20} and S^1 are in an *anti* orientation as shown in Figure 2.

Moreover, by employing the present protocol, various α,β-unsaturated esters namely methyl acrylate (**8**), methyl methacrylate (**9**) and ethyl acrylate (**10**) furnished the desired Michael addition products **8b**, **9b** and **10b** respectively, on reaction with thiophenol (**B**) in good yields. Furthermore, our methodology can be extended for 1,4-conjugate addition reaction of thiols with acrylonitrile (**11**) and acrylamide (**12**) under identical conditions. We have also studied the recyclability of the catalyst by the following way. The reaction of acrylonitrile (100 mmol) with thiophenol (110 mmol) was carried out in the presence of $HClO_4/SiO_2$ (0.5 mol-%, 1 g). After completion, the catalyst was filtered off and activated by heating at 80 °C under vacuum for 1 hour and reused for thia-Michael reaction of a fresh lot of acrylonitrile (100 mmol) with thiophenol (110 mmol) affording 85% yield of the desired product after 20 min. Again, the catalyst was recovered, reactivated and reused repeatedly for three more consecutive times for thia-Michael reactions with acrylonitrile (100 mmol) affording

Table 2. Michael addition of thiols to conjugated alkenes catalyzed by silica-supported perchloric acid ($HClO_4/SiO_2$).

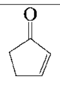
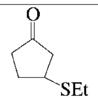
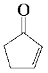
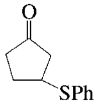
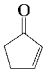
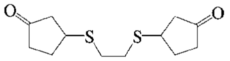
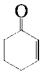
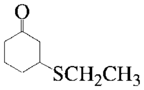
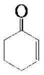
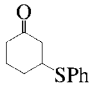
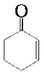
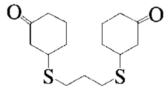
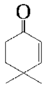
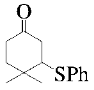
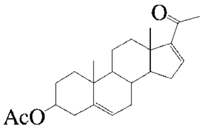
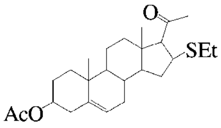
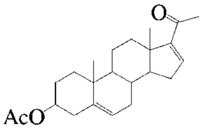
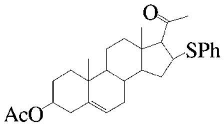
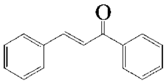
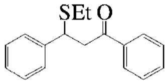
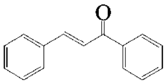
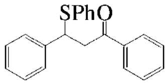
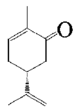
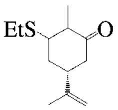
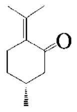
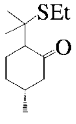
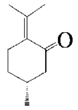
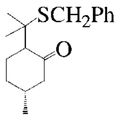
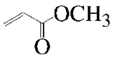
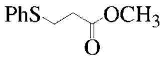
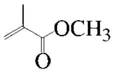
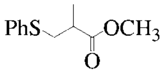
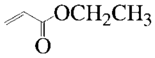
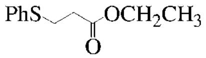
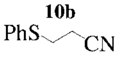
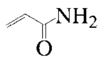
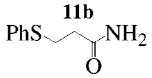
Run	Substrate	Time [min]	Product[a,b,c]	Yield[d] [%]
1	 **1**	5	 **1a**	92
2		2	 **1b**	98[26]
3		5	 **1c**	80[14]
4	 **2**	5	 **2a**	94[7c]
5		2	 **2b**	97[26]
6		5	 **2d**	81[14]
7	 **3**	20	 **3b**	82
8	 **4**	20	 **4a**	79
9		20	 **4b**	82
10	 **5**	15	 **5a**[c]	93
11		15	 **5b**[c]	95[15]
12	 **6**	10	 **6a**	95
13	 **7**	10	 **7a**	80

Table 2. (*Continued*).

Run	Substrate	Time [min]	Product[a,b,c]	Yield[d] [%]
14		10	 **7e**	86[6a]
15	 **8**	10	 **8b**	88
16	 **9**	10	 **9b**	91
17	 **10**	10	 **10b**	95
18	 **11**	10	 **11b**	97
19	 **12**	15	 **12b**	91

[a] All the compounds were characterized by recording IR, ^1H NMR, ^{13}C NMR and elemental analyses. [b] Isolated yield. [c] The reaction was carried out in methanol instead of dichloromethane. [d] The corresponding reference for spectroscopic data.

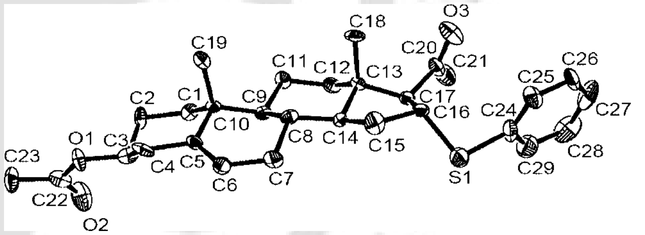


Figure 1. ORTEP plot of the molecule with atom numbering scheme; hydrogen atoms are omitted for clarity.

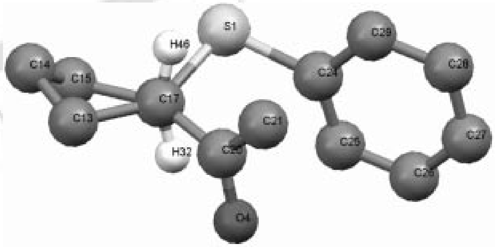


Figure 2. Front view of a selected portion.

81%, 76% and 70% yields respectively, in 25, 30 and 35 min. From this observation, it is clear that the reaction can be performed in a large scale as well as the catalyst can be reused although efficiency of the catalyst is lesser in further cycles. As the reaction took a longer time and gave lower yields during the reusability test, the following experiments were performed to rule out leaching of the actual catalyst perchloric acid. A reaction of ethyl acrylate

(2 mmol) and thiophenol (2.2 mmol) was carried out following the same experimental procedure. After completion of the reaction, the catalyst was removed by filtration through a Whatman 40 filter paper. To the filtrate was added another 2.2 mmol of thiophenol and 2 mmol of cyclohexenone and stirring was continued. A parallel reaction was performed with 2.2 mmol of thiophenol and 2 mmol of cyclohexenone in dichloromethane without any catalyst. The isolated yields of **2b** from the above two reactions were 30% and 27%, respectively, after five hours. From this observation, it is clear that no leaching has occurred during the experiment. But may be due to the poisoning of the surface of the catalyst, isolated yields are less and required longer reaction time in the recycling experiments.

Conclusion

In conclusion, the unique properties of silica-supported perchloric acid allowed us to demonstrate a new synthetic methodology for the thia-Michael addition reaction. The significant advantages of our protocol are: very good yields, mild conditions, short reaction times, non-aqueous work-up procedure and involvement of non-expensive reusable catalyst.

Experimental Section

Melting points were recorded with a Büchi B-545 melting point apparatus and were uncorrected. IR spectra were recorded in KBr or neat with a Nicolet Impact 410 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded either with a Jeol 300 MHz or Varian 400 spectrometer and Jeol 75 MHz or Varian 100 MHz, respectively, in $CDCl_3$ using TMS as internal reference. Elemental analyses were carried out in a Perkin–Elmer 2400 automatic carbon, hydrogen, nitrogen and sulfur analyzer. X-ray diffraction data were collected with a Bruker Apex II smart diffractometer with CCD area detectors using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Column chromatographic separations were done on SRL silica gel (60–120 mesh). CCDC-298160 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of $HClO_4/SiO_2$ Catalyst:[30] $HClO_4$ (1.8 g, 12.5 mmol, as a 70% aq. solution) was added to a suspension of SiO_2 (230–400 mesh, 23.7 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 hours under vacuum to furnish $HClO_4/SiO_2$ (0.5 mmol/g) as a free flowing powder (50 mg, 0.025 mmol of $HClO_4$).

Typical Experimental Procedure: To a magnetically stirred solution of 2-cyclohexene-1-one (**2**) (0.192 g, 2 mmol) and thiophenol (0.242 g, 2.2 mmol) in dichloromethane (2 mL) was added $HClO_4/SiO_2$ (20 mg, 0.5 mol-%). The reaction was instantly completed as checked by TLC. After completion of the reaction, the reaction mixture was directly passed through a silica gel column to obtain pure desired Michael addition product (**2b**) (0.400 g, 97%) as a colourless oily liquid. In case of solid product, it was obtained by removing the catalyst by filtration followed by recrystallization from the mixture of ethyl acetate/hexane (1:9) for compound **4a**, **4b**, and from methanol for compound **3b**, **5a**, **5b**, **12b**.

1a: Yield: 0.265 g, 92%. IR (neat): $\tilde{\nu}$ = 1748 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.2 Hz, 3 $HSCH_2\mathit{CH_3}$), 1.89–1.98 (m, 1 H), 2.15–2.23 (m, 2 H), 2.30–2.48 (m, 2 H), 2.56–2.62 (m, 3 H), 3.46 (quin, J = 6.8 Hz, 1 H, $=\mathit{CH}SCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 25.1, 29.7, 36.9, 39.8, 45.5, 216.2 ppm. $C_7H_{12}OS$ (144.23): calcd. C 58.29, H 8.39, S 22.23; found C 58.08, H 8.35, S, 22.01.

3b: Yield: 0.385 g, 82%, m.p. 68 °C. IR (KBr): $\tilde{\nu}$ = 1711 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (s, 3 H), 1.23 (s, 3 H), 1.59–1.62 (m, 1 H), 1.82–1.86 (m, 1 H), 2.23–2.28 (m, 1 H), 2.37–2.41 (m, 1 H), 2.50–2.58 (m, 2 H), 3.11–3.15 (m, 1 H), 7.17–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 29.0, 34.6, 37.8, 38.6, 45.4, 57.6, 127.4, 129.1 (2 C), 132.7 (2 C), 134.6, 209.0 ppm. $C_{14}H_{18}OS$ (234.36): calcd. C 71.75, H 7.74, S 13.68; found C 71.49, H 7.67, S 13.45.

4a: Yield: 0.660 g, 79%, m.p. 126 °C (mixture of diastereomers, 1:1). IR (KBr): $\tilde{\nu}$ = 1731, 1706 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.62 (s, 3 H), 0.98–1.10 (m, 12 H), 1.01(s, 3 H), 1.02 (s, 3 H), 1.06 (s, 3 H), 1.23 (t, J = 7.2 Hz, 6 H), 1.49–1.58 (m, 16 H), 1.86 (d, J = 9.6 Hz, 2 H), 1.97 (d, J = 9.3 Hz, 2 H), 2.03 (s, 6 H), 2.16 (s, 3 H), 2.19 (s, 3 H), 2.32 (d, J = 9.6 Hz, 2 H), 2.41–2.62 (m, 4 H), 2.69 (d, J = 9.9 Hz, 2 H), 3.42–3.48 (m, 1 H), 3.72–3.76 (m, 1 H), 4.61 (m, 2 H), 5.37 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.2, 14.6, 14.7, 19.3 (2 C), 20.4, 20.8, 21.4 (2 C), 26.4, 27.7 (2 C), 28.0, 30.9, 31.4, 31.5, 31.7, 31.8, 34.8, 36.5, 36.6 (2 C), 36.9, 37.8, 38.0 (2 C), 38.5, 38.7, 40.5, 42.7, 42.8, 45.3 (2 C), 49.7, 50.1, 54.9, 55.8, 67.2, 72.1, 73.7, 73.8, 122.1 (2 C), 139.6, 139.9, 170.5 (2 C), 207.4 (2 C) ppm. $C_{25}H_{38}O_3S$ (418.64): calcd. C 71.73, H 9.15, S 7.66; found C 71.48, H 9.10, S 7.42.

4b: Yield: 0.765 g, 82%, m.p. 134 °C. IR (KBr): $\tilde{\nu}$ = 1731 (C=O), 1711 ($COCH_3$) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (s, 3 H), 1.00 (s, 3 H), 0.92–1.02 (m, 5 H), 1.40–1.80 (m, 8 H), 1.82 (d, J = 10.8 Hz, 2 H), 1.83–1.97 (m, 4 H), 2.01 (s, 3 H), 2.29–2.32 (m, 1 H), 2.60 (d, J = 8.4 Hz, 1 H), 4.10–4.22 (m, 1 H), 4.55–4.62 (m, 1 H), 5.35–5.37 (m, 1 H), 7.10–7.20 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 19.4, 20.9, 21.5, 27.8, 31.4, 31.7, 31.8, 34.7, 36.6, 36.9, 38.1, 38.9, 43.6, 45.4, 49.7, 54.9, 70.9, 73.9, 121.9, 126.4, 128.7 (2C), 130.8 (2C), 135.9, 139.4, 170.2, 206.4 ppm. $C_{29}H_{38}O_3S$ (466.68): calcd. C 74.64, H 8.21, S 6.87; found C 74.35, H 8.14, S 6.62.

5a: Yield: 0.503 g, 93%, m.p. 61–62 °C. IR (KBr): $\tilde{\nu}$ = 1693 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.2 Hz, 3 H), 2.30–2.39 (m, 2 H), 3.52 (d, J = 7.6 Hz, 2 H), 4.57 (t, J = 7.2 Hz, 1 H), 7.18 (t, J = 7.2 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 2 H), 7.38–7.43 (m, 4 H), 7.52 (t, J = 7.2 Hz, 1 H), 7.89 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 25.9, 44.4, 45.8, 127.4, 128.0 (2 C), 128.3 (2 C), 128.7 (2 C), 128.8 (2 C), 133.4, 137.0, 142.4, 196.9 ppm. $C_{17}H_{18}OS$ (270.39): calcd. C 75.52, H 6.71, S 11.86; found C 75.18, H 6.63, S 11.58.

5b: Yield: 0.605 g, 95%, m.p. 114–115 °C. IR (KBr): $\tilde{\nu}$ = 1685 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (dd, J = 6.0 Hz, J = 17.2 Hz, 1 H), 3.64 (dd, J = 8.4 Hz, J = 17.2 Hz, 1 H), 4.93 (dd, J = 6.0 Hz, J = 8.4 Hz, 1 H), 7.14–7.23 (m, 6 H), 7.28–7.31 (m, 4 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.8, 48.3, 127.2, 127.4, 127.6 (2 C), 127.9 (2 C), 128.3 (2 C), 128.4 (2 C), 128.7 (2 C), 132.6 (2 C), 133.1, 134.1, 136.6, 141.0, 196.7 ppm. $C_{21}H_{18}OS$ (318.43): calcd. C 79.21, H 5.70, S 10.07; found C 78.95, H 5.65, S 9.87.

6a: (data for the major isomer), yield: 0.403 g, 95%. IR (neat): $\tilde{\nu}$ = 1711 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.15 (d, J = 7.2 Hz, 3 H), 1.24 (t, J = 7.6 Hz, 3 H), 1.76 (s, 3 H), 1.95–2.02 (m, 1 H), 2.15–2.25 (m, 2 H), 2.40–2.60 (m, 3 H), 2.76–2.84 (m, 1 H), 2.87–3.15 (m, 1 H), 3.42 (dd, J = 3.2 Hz, J = 8.4 Hz, 1 H), 4.73 (d, J = 20 Hz, 1 H), 4.81 (d, J = 15.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.7, 14.8, 20.9, 26.1, 35.9, 40.7, 46.0, 48.8, 49.2, 110.0, 146.9, 209.5 ppm. $C_{12}H_{20}OS$ (212.35): calcd. C 67.87, H 9.49, S 15.10; found C 67.55, H 9.40, S 14.95.

7a: (data for the major isomer), yield: 0.343 g, 80%. IR (neat): $\tilde{\nu}$ = 1718 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.00 (d, J = 6.0 Hz, 3 H), 1.21 (t, J = 7.6 Hz, 3 H, SCH$_2$*CH$_3$*), 1.36 (s, 3 H), 1.40–1.60 (m, 2 H), 1.52 (s, 3 H), 1.82–2.20 (m, 3 H), 2.27–2.30 (m, 1 H), 2.42 (dd, J = 3.6 Hz, J = 11.6 Hz, 1 H), 2.48–2.57 (m, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.5, 21.7, 22.3, 24.1, 28.0, 29.7, 34.8, 36.7, 46.9, 52.4, 58.1, 210.3, ppm. $C_{12}H_{22}OS$ (214.37): calcd. C 67.24, H 10.34, S 14.96; found C 67.01, H, 10.28, S 14.68.

8b: Yield: 0.345 g, 88%. IR (neat): $\tilde{\nu}$ = 1744 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.64 (t, J = 7.5 Hz, 2 H), 3.17 (t, J = 7.5 Hz, 2 H), 3.68 (s, 3 H), 7.19–7.39 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 29.0, 34.2, 51.8, 126.6, 129.0 (2 C), 130.1 (2 C), 135.1, 172.2 ppm. $C_{10}H_{12}O_2S$ (196.27): calcd. C 61.20, H 6.16, S 16.34; found C 61.01, H 6.12, S 16.12.

9b: Yield: 0.382 g, 91%. IR (neat): $\tilde{\nu}$ = 1742 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.27 (d, J = 6.9 Hz, 3 H), 2.70 (dd, J = 6.9 Hz, J = 13.8 Hz, 1 H), 2.93 (dd, J = 6.9 Hz, J = 13.2 Hz, 1 H), 3.27 (dd, J = 6.9 Hz, J = 13.2 Hz, 1 H), 3.67 (s, 3 H), 7.20–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.8, 37.4, 39.7, 51.9, 126.3, 128.8 (2 C), 129.8 (2 C), 135.5, 175.1 ppm. $C_{11}H_{14}O_2S$ (210.29): calcd: C 62.83, H 6.71, S 15.25; found C 62.61, H 6.68, S 14.95.

10b: Yield: 0.383 g, 95%. IR (neat): $\tilde{\nu}$ = 1743 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.24 (t, J = 7.2 Hz, 3 H), 2.61 (t, J = 7.2 Hz, 2 H), 3.15 (t, J = 7.2 Hz, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.27 (t, J = 7.6 H, 2 Hz), 7.34 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.2, 29.0, 34.4, 60.6, 126.3, 128.8 (2 C), 129.8 (2 C), 135.0, 171.4 ppm. $C_{11}H_{14}O_2S$ (210.29): calcd. C 62.83, H 6.71, S 15.25; found C 62.66, H 6.62, S 14.99.

11b: Yield: 0.317 g, 97%. IR (neat): $\tilde{\nu}$ = 2250 (CN) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.58 (t, J = 7.2 Hz, 2 H), 3.12 (t, J = 7.2 H, 2 Hz), 7.26–7.34 (m, 3 H), 7.40 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 18.4, 30.4, 117.8, 127.6, 129.2 (2 C), 131.3 (2 C), 133.0 ppm. C_9H_9NS (163.24): calcd. C 66.22, H 5.56, N 8.58, S 19.64; found C 66.01, H 5.47, N 8.49, S 19.39.

12b: Yield: 0.330 g, 91%, m.p. 125 °C. IR (KBr): $\tilde{\nu}$ = 1657 (CONH$_2$) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.53 (t, J = 7.2 Hz, 2 H), 3.22 (t, J = 7.2 Hz, 2 H), 5.56 (br. s, 2 H), 7.20 (t, J = 8.4 Hz, 1 H), 7.29 (t, J = 8.8 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.2, 35.4, 126.3, 128.9 (2 C), 129.6 (2 C), 135.1, 173.2 ppm. $C_9H_{11}NOS$ (181.25): calcd. C 59.64, H 6.12, N 7.73, S 17.69; found C 59.40, H 6.04, N 7.59, S 17.51.

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