Chapter 2

Allyl Tetrahydropyranyl Ether: A versatile Alcohol/Thiol Protecting Reagent

1. Introduction:

The protecting groups play an indispensable part in the synthesis of complex multifunctional molecules. The continuing efforts worldwide to develop ideal protecting methodologies has lead to the introduction of a number of protecting groups over the years and several books\(^1\) and reviews\(^2\) have appeared on the subject. The functional groups that have attracted the most attention are the amino, thio, carboxylic, carbonyl and hydroxyl (Figure-1). Amino group finds its presence in a number of biologically significant compounds like peptides, nucleosides, amino acids etc., likewise, thiol (-SH), carboxyl groups etc., also constitute as an important part of various drug moieties interacting with receptors or antigens involved in the development of disease.

A tremendous amount of work has gone in developing suitable strategies towards the protection and deprotection of these functional groups. The most frequently used methods of amino group protection are \(N\)-alkylation using alkyl halides, amide or imide formation using acetic acid/ acetyl chloride/ acetic anhydride or phthaloyl anhydride,\(^3\) aldimines and enamines formation,\(^4\) while thiols are generally protected by acetylation or tetrahydropyranylation (THPRN),\(^5,6,7\) the protection of carboxylic acids is normally facilitated by ester formation with alcohols,\(^8,9\) alkyl halides,\(^10\) chloroformates\(^11\) and dimethyl carbonate.\(^12\)

However, in the protection of aldehydes and ketones, relatively a small repertoire of protecting groups has been employed and of these acetals (O,O), thiocetals (S,S),

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oxathiolanes (O,S), 1,1-diacetates nitrogenous derivatives (imines, enamines, oximes, hydrazones, semicarbazones) and O-methoxycarbonyl-cyanohydrin have proven to be the most useful.

1.1. Hydroxy group protection:

Hydroxy compounds (alcohols, phenols, steroids, sugars etc.) have an immense significance in our life. Most of these compounds are used for many scientific, medical and industrial applications. Many compounds with alcoholic and phenolic functionalities are associated with pharmacological activities, for example anti-tumor (podophyllotoxin, etoposide, taxol, vinca alkaloids, bleomycin, doxorubicin); antibiotics (amoxicillin, kanamycin, neomycin, erythromycin, tetracycline, gentamycin); anti-AIDs (crivixan, zidovudine); normalizing cardiac vascular system (digoxin, digitoxin, gitoxin, quinidine, propranolol, atenolol); anti-pyretic (paracetamol); anaesthetic (propofol); analgesic (morphine); acting on central nervous system (L-dopa) and vitamins (pyridoxine, Vitamin B6, Riboflavin/ Vitamin B2, ascorbic acid, Vitamin C). Moreover, steroids (cholesterol, stigmasterol, oestrone, and testosterone) are also used as medicines and generally they also bear one or more hydroxyl groups (Figure-2). The protection of hydroxy groups is a key step in both the synthesis of various polyfunctional organic molecules and further reactions of these compounds.

Though more than 150 hydroxy-protecting groups have been reported, the search for novel OH protective groups is still highly desirable, as molecular targets increase in their complexities and new fields such as supported-oligosaccharide synthesis are emerging. This has lead to the development of a variety of techniques, such as ester formation (acylation, tosylation), ether formation (silyl ethers, allyl ethers, THP ethers and other alkoxyalkyl ethers) etc., for their protection. The acylation

(acetate, benzoate, pivaloate and levulinate formation) is the most frequently used method of protection, which is generally carried out using carboxylic acids or acyl chlorides or corresponding anhydrides.

Esterification of carboxylic acids is potentiated by various catalysts like montmorillonite,\(^{21}\) metal exchanged as well as LaY zeolites,\(^{22}\) phosphorus pentoxide supported on silica gel (SiO\(_2\)/P\(_2\)O\(_5\))\(^{23}\) etc. For acylation with acyl chlorides or anhydrides, bases such as triethylamine, pyridine or 4-(dimethylamino)-pyridine (DMAP) as a catalyst are essential. In the case of base sensitive substrates, Lewis acids,


such as p-toluene-sulfonic acid,\textsuperscript{24} zinc chloride,\textsuperscript{25} cobaltous chloride,\textsuperscript{26} distannoxane,\textsuperscript{27} scandium triflate\textsuperscript{28} and silica supported fluoroboric acid (SiO$_2$/HBF$_4$) are used as catalysts.\textsuperscript{29} Protic and Lewis acids which are absorbed on different organic or inorganic polymeric materials can also be used and prepared by mixing the reagents and the support materials. Chakraborti \textit{et al.} reported acetylation of structurally varied alcohols and phenols catalyzed competently by numerous perchloric acids absorbed on silica gel (e.g., SiO$_2$/HClO$_4$).\textsuperscript{30}

In the synthesis of various naturally occurring glycosides and other glycol-conjugates, protection of hydroxyl group is an essential step which is effected either by acetylation\textsuperscript{31} or by levulinate esters formation.\textsuperscript{32} In addition, pivaloyl esters are formed if high hydrolytic stability of an ester is required. Neutral alumina is used where solventless conditions are needed and also with microwave irradiations.\textsuperscript{33} Phenols bearing electron-donating groups can be protected using methyl benzoate in the presence of iron (III) sulfate supported silica, which as such cannot be acetylated.\textsuperscript{34} Besides, basic alumina is also used as an efficient catalyst for the esterification of phenols even in the absence of solvent, using microwave irradiations in 4-5 min in the presence of pyridine.\textsuperscript{35}

Tosylation is another frequently used method of hydroxyl group protection,\textsuperscript{36} generally carried out using p-toluenesulfonic acid, sulfonyl chloride and sulfonyl anhydrides in the presence of pyridine, tri-ethylamine and 1,4-diazabicyclo [2.2.2.] octane (DABCO). The assorted alcohols are protected by treating with p-toluenesulfonic acid in the presence of silica chloride.\textsuperscript{37} Primary hydroxy groups in polyhydroxy compounds can be selectively tosylated in the presence of TsOH in combination with Fe$^{3+}$ exchanged montmorillonite clay K10.\textsuperscript{38} In case of symmetrical

\begin{thebibliography}{99}
\bibitem{27} Orita, A; Sakamoto, K; Hamada, y. \textit{Tetrahedron} \textbf{1999}, 55, 2899.
\bibitem{36} Kocienski, P. \textit{Protecting Groups}; Thieme: Stuttgart, Germany, 1994.
\end{thebibliography}
diols, selectivity of tosylation depends upon concentration of TsOH in a reaction mixture.

The protection of hydroxyl group can also be facilitated by forming their ethers like silyl ethers, allyl ethers, benzyl ethers, THP ethers and alkoxyalkyl ethers. The formation of silyl ether is an excellent method of protection of alcohols and phenols and plentiful silylating methods are known and among them, trimethylsilylation (TMS) and trimethylsilylethoxymethyl (SEM) are commonly used. Trimethylsilylation is generally carried out using hexamethyldisilazane (HMDS) in presence of kaolinitic clay, montmorillonite K10, envirocat EPZG and zirconium sulfophenyl phosphonate. The SEM ethers are formed using SEMCl in the presence of alumina supported potassium fluoride (Al₂O₃/KF) and can be efficiently used in the protection of both electron-rich and electron-poor phenols, but they cannot be used in the protection of alcohols.

Protection using benzyl ethers, diphenyl-methyl (DPM) ether, 9-fluorenyl ether and allyl ethers are the most frequently used methods in carbohydrate chemistry, since these ethers are very stable under both acidic and basic conditions. Benzyl ethers are formed using benzyl bromide in the presence of NaH, whereas DPM ethers are formed by reacting with diphenyl-methanol in the presence of Yb(OTf)₃ or FeCl₃. Although, allyl ether formation is the most popular method, but its utilization has some limitations because the double bond present in allyl group makes it susceptible to various reactions like halogenations, catalytic hydrogenation etc. Allyl ethers are formed using allyl bromide in the presence of NaH or allyl trichloroacetimidate catalysed by triflormethane sulfonic acid or allyl chloroformate followed by Pd catalyzed decarboxylation. Besides, allyl ethers can be selectively cleaved by oxidation with DDQ. Alkoxyalkyl ether formation is another method of protection of

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hydroxyl groups. It is highly preferable method, because the alkoxyalkyl ethers are very stable and are resistant to strong bases, alkyllithiums, LAH and Grignard reagents.\(^{50}\) Methoxymethyl (MOM) ethers, methoxypropyl ethers and THP ethers are the most commonly prepared alkoxyalkyl ethers. MOM ethers are prepared by using chloromethyl methyl ether (MOMCl) or dimethoxymethane in the presence of catalysts like, enirocat EPZG,\(^{51}\) montmorillonite K10\(^{52}\) and zeolites\(^{53}\) (e.g., NaY zeolite, acid Y zeolite, ZSM-5, mordenite). As MOMCl is highly carcinogenic, dimethoxymethane is preferred over it. However, deprotection of MOM ethers requires harsh acidic conditions because of the high stability of such ethers.

Tetrahydropyranyl ethers (THPE) have found extensive applications in organic synthesis as they can be easily synthesized from a variety of hydroxy group containing compounds by acid catalyzed reaction using 3,4-dihydro-2\(H\)-pyran (DHP). Tetrahydropyranylation is one of the preferable methods in organic synthesis, due to high stability of THP ethers in different reaction conditions, like strongly acidic or basic pH; presence of oxidizing or reducing agents etc., besides, due to easy deprotection (Table-1).

Table 1: Showing stabilities of THP ethers under various conditions.

<table>
<thead>
<tr>
<th>Bases</th>
<th>LDA</th>
<th>NEt(_3), Py</th>
<th>t-BuOK</th>
<th>KOH</th>
<th>DCC</th>
<th>Pyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleophiles</td>
<td>RLi</td>
<td>RMgX</td>
<td>RCuLi</td>
<td>Enolates</td>
<td>NH(_3), RNH(_2)</td>
<td>NaOCH(_3)</td>
</tr>
<tr>
<td>Electrophiles</td>
<td>RCOCl</td>
<td>RCHO</td>
<td>CH(_3)I</td>
<td>NXS</td>
<td>:CCl(_2)</td>
<td>Bu(_3)SnH</td>
</tr>
<tr>
<td>Reduction</td>
<td>H(_2)/Ni</td>
<td>H(_2)/Rh</td>
<td>H(_2)/Pd</td>
<td>Na / NH(_3)</td>
<td>LiAIH(_4)</td>
<td>NaBH(_4)</td>
</tr>
<tr>
<td>Oxidation</td>
<td>KMnO(_4)</td>
<td>OsO(_4)</td>
<td>CrO(_3) / Py</td>
<td>RCOOOH</td>
<td>I(_2), Br(_2), Cl(_2), MnO(_2) / CH(_3)Cl(_2)</td>
<td></td>
</tr>
</tbody>
</table>

THPEs are stable to bases and the deprotection is done through acid hydrolysis. It is important to point out that the introduction of the THP ether onto a chiral molecule results in the formation of diastereoisomers due to an additional stereogenic centre present in the tetrahydropyran ring, which can make both the NMR interpretation and the handling of the reaction products somewhat troublesome.

\(^{50}\) Yardley, J. P.; Fletcher, H. *Synthesis* **1976**, 244.


1.2. THP as a protecting group

Tetrahydropyranyl ethers are prepared from dihydrodropyran (versatile vinyl ether) by reacting with alcohols under mild acid catalysis (p-toluenesulfonic acid or more effectively boron trifluoride etherate).

![Scheme 1: General reaction of THP protection](image1)

The THP protection can be catalyzed by a long range of catalysts (Scheme-2) and the methodology may be broadly divided into following categories.

![Scheme 2: Mechanistic pathway of THP protection](image2)

1.2.1. Acid mediated
1.2.2. Neutral reagent mediated
1.2.3. Heterogeneous catalyst mediated
1.2.4. Miscellaneous

**1.2.1. Acid mediated**

The acid mediated reaction has a special relevance in numerous chemical reactions. There are several possible chemical compounds that can act as sources for the protons to be transferred in an acid catalysis system. Usually this is done to create a more likely electron abstraction from the double bond of DHP to produce oxonium ion intermediate, which further abstracts the electron from the nucleophile to produce THP ethers.

![Scheme 3: Mechanistic pathway of acid mediated THP protection](image3)
Usually, tetrahydropropylation has been carried out by acid-catalyzed addition of alcohols and phenols to 2,3-dihydro-2H-pyran (DHP) in an organic solvent at room temperature. Various methods for the formation of THP ethers in acidic conditions have been reported and been frequently used for protecting hydroxy groups in multi-step organic synthesis. Most of these reported methods use acidic reagents in an aprotic solvent, such as CH$_2$Cl$_2$, THF, acetone and toluene. In 1934, R. Paul$^{54}$ observed that 2-methoxytetrahydropyran was formed while adding methyl alcohol to dihydropyran with HCl. Later, Woods and Kramer$^{55}$ modified the procedure developed by Paul and synthesized a number of acetals from 2,3-dihydropyran, while, Schwalm et al.$^{56}$ used PTSA for THPRN.

THPRN of alcohols has also been reported under solvent-free conditions using catalytic amounts of SnCl$_2$-2H$_2$O$^{57}$ and InCl$_3$ immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate (ionic liquid) in excellent yields and mild reaction conditions.$^{58}$ The use of ionic liquid offers the advantage of compatibility with a wide range of functional and protecting groups such as THP, TBDMS, TBDPS, PMB, MOM ethers, acetonides, olefins and epoxides. Moreover, aluminum chloride hexahydrate as a catalyst also enables to carry out solvent-free THPRN of alcohols and phenols at moderate temperatures with the simple addition of methanol, regenerating corresponding alcohols and phenols, rendering these protection and deprotection sequences as very efficient transformations at high substrate to catalyst ratios.$^{59}$ Yadav et al. employed THPRN in monoprotection of diols using InCl$_3$.$^{58}$ One such method affected highly selective monoprotection of symmetrical diols using a catalytic amount of polystyrene supported AlCl$_3$.$^{60}$ Nagaiah et al.$^{61}$ used niobium (V) chloride to convert a diversity of alcohols and phenols into their corresponding THP-ethers in excellent yields. THPRN of alcohols and phenols with dihydropyran (DHP) has also been performed by using a catalytic amount of ZrCl$_4$ in CH$_2$Cl$_2$.$^{62}$ Pachamuthu and Vankar$^{63}$

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employed CAN in CH$_3$CN at room temperature to prepare corresponding THP ethers of a variety of alcohols.

Majid et al.$^{64}$ developed a simple, mild and efficient method of THPRN of alcohols using ferric perchlorate. The protection of hydroxy groups as tetrahydropyryl ethers and carbonyl functionalities as oxathioacetals and thioacetals has also been achieved by using a catalytic amount of silica-supported perchloric acid under solvent free conditions.$^{65}$ Bismuth triflate can also be efficiently employed in THPRN under solvent-free conditions, which is a non-toxic catalyst and is insensitive to air and small amounts of moisture.$^{66}$ Additionally, CeCl$_3$·7H$_2$O/NaI system under solvent-free conditions can also be employed in highly chemo-selective and environmentally benevolent THPRN of alcohols and phenols.$^{67}$ This reaction bears a great advantage of being performed under extremely mild conditions.$^{68}$ Majid and co-workers reported the method of chemo-selective tetrahydropyranylation of primary alcohols in the presence of secondary and tertiary alcohols and phenols,$^{69}$ using tin(IV) porphyrin triflate as catalyst in THF. Babak et al.$^{70}$ reported THRPN in the presence of catalytic amount of lithium trifluoromethanesulfonate (LiOTf) and also by using Brønsted acidic ionic liquids [BMIm][HSO$_4$] or [BMIm][H$_2$PO$_4$].$^{71}$ Sulfated zirconia (SO$_4^{2-}$/ZrO$_2$) has also been reported to catalyze tetrahydropranylation of alcohols and phenols under solvent-free reaction conditions and reusability of the catalyst.$^{72}$ In(OTf)$_3$ catalyzed THPRN formation of alcohols in dichloromethane is also described.$^{73}$ Tetrahydropyryl ethers can also be synthesized in a mild, chemoselective and convenient fashion, even in the presence of many acid-sensitive functional groups using acetyl chloride and dihydropyran.$^{74}$

1.2.2. Neutral reagents:

Neutral reaction conditions essentially involve the reaction at room temperature, atmospheric pressure and almost neutral pH. Such reaction conditions generally come

with an advantage of having no serious effects on other sensitive (acid/base) functionalities present in the reactants.

Kotke and co-workers\textsuperscript{75} reported tetrahydropyranylation of sterically hindered and acid-sensitive substrates in the presence of $N,N'$-bis[3,5-bis(trifluoromethyl)phenyl]thiourea catalyst. Bartoli et al.\textsuperscript{76} reported a highly chemoselective method for the protection of free hydroxy compounds with DHP using CeCl$_3$$\cdot$7H$_2$O/NaI as a catalyst under solvent-free conditions. Molecular iodine has also been employed as a highly efficient catalyst for tetrahydropyranylation using 3,4-dihydro-2H-pyran in DCM at room temperature. It was generated \textit{in situ} from Fe(NO$_3$)$_3$$\cdot$9H$_2$O/NaI.\textsuperscript{77} Kumar et al.\textsuperscript{78} also used molecular iodine for THP protection. Bernady et al.\textsuperscript{79} reported non-acidic condition for THP protection by using PPh$_3$, DEAD in THF; this method is also effective for phenols. Olah et al.\textsuperscript{80} reported synthesis of tetrahydropyranyl ethers with dihydropyran in the presence of Me$_3$SiI under mild, neutral conditions and short reaction times. Bismuth (III) nitrate pentahydrate [Bi(NO$_3$)$_3$$\cdot$5H$_2$O]\textsuperscript{81} has also been found to be an effective catalyst for THPRN of alcohols and phenols in the presence of a large number of other protecting groups like, isopropylidene, benzylicidene and thioacetal etc.

Tetrahydropyranylation of primary alcohols has also been selectively carried out in the presence of secondary and tertiary alcohols and phenols using PdCl$_2$(CH$_3$CN)$_2$ as a catalyst in tetrahydrofuran (THF), while other protection groups such as p-toluenesulfonyl, tert-butyldiphenylsilyl, benzoxycarbonyl, allyl, benzyl, and benzyol remained intact under these conditions.\textsuperscript{82} Miyashita et al.\textsuperscript{83} used PPTS for THPRN under very mild reaction condition. CuSO$_4$.5H$_2$O has also been reported to bring about smooth conversions of various alcohols and phenols into their corresponding THP ethers under mild reaction conditions.\textsuperscript{84} Moreover, the preparation and catalytic application of $N,N$-dibromo-$N,N$-1,2-ethanediyl-bis(benzene sulfonamide)

\textsuperscript{75} Kotke, M.; Schreiner, P. R. \textit{Synthesis}, \textbf{2007}, 790.
\textsuperscript{77} Amin; R.; Sadegh, R.; Ardestehr, K. \textit{Monatshefie fuer Chemie} \textbf{2009}, 140, 667.
for THPRN of different alcohols and phenols has also been reported.\textsuperscript{85} Catalytic behavior of water-insoluble cesium and rubidium tungstosilicates has also been studied in THPRN of phenols.\textsuperscript{86} Cesium salts were found to be more active than rubidium salts. Besides, THPRN has also been reported using 3,4-dihydro-2H-pyran in the presence of various other catalysts such as anhydrous calcium chloride,\textsuperscript{87} LiBr,\textsuperscript{88} or dicyanoketene ethylene acetal,\textsuperscript{89} lithium perchlorate in diethyl ether (LPDE),\textsuperscript{90} (TBA)$_2$S$_2$O$_8$,\textsuperscript{91} etc.

1.2.3. Heterogenous catalyst mediated:

The ion-exchange resin Dowex 50WX4–100 efficiently catalyzed the protection of a variety of alcohols with DHP in dichloromethane at ambient conditions.\textsuperscript{92} Silica-gel-supported aluminium chloride as a heterogeneous Lewis acid catalyst has proven to be a simple, effective, highly chemoselective and reusable catalyst for the preparation of 2-tetrahydropyranyl ethers of alcohols and phenols.\textsuperscript{93} Shimizu \textit{et al.}\textsuperscript{94} used sulfonic acid group-functionalized silica as a highly effective and reusable catalyst for THPRN of alcohols. Solid silica-based sulfonic acid catalysts have also been employed in the conversion of alcohols and phenols into corresponding THP ether. The catalyst shows high thermal stability (up to 300 °C) and can be recovered and reused for at least eight reaction cycles without the loss of reactivity.\textsuperscript{95} Vanadyl (IV) acetate has also been utilized in the synthesis of THPE of a variety of alcohols, thiols and phenols under mild conditions and excellent yields at a faster rate in a heterogeneous medium.\textsuperscript{96} Molybdophosphoric and tungstophosphoric acids supported on silica-alumina, obtained by means of sol–gel method, catalyzed the phenol THPRN in environmentally benign reaction conditions.\textsuperscript{97}

\textsuperscript{87} Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S.; Patil, S. V. \textit{Monatshefte fuer Chemie} 2003, 134, 428.
Some inexpensive and readily available naturally occurring clays, frequently utilized as competent and versatile catalysts like K10 clay\textsuperscript{98} or Spanish sepiolite clay\textsuperscript{99} or natural kaolinitic clay for organic reactions,\textsuperscript{100} have also been utilized for the THPRN of hydroxy compounds. Likewise, enirocat (EPZG exhibiting both Bronsted and Lewis acid characteristics)\textsuperscript{101} and acid zeolites (e.g., Y zeolite with silica/alumina ratio of 4.86)\textsuperscript{102} has also been utilized for the highly efficient THPRN of alcohols and phenols in short reaction times. Moreover, the protection of phenols and alcohols could be performed under solventless conditions by using zeolites with different SARs (5.9 and 13.9, respectively).\textsuperscript{103} Corma \textit{et al.}\textsuperscript{104} utilized the zeolitic material (ITQ-2) as catalyst to protect alcohols and phenols, including naphthols and steroids. Mesoporous (H-MCM-41) molecular sieves (SAR 51.8) represent another zeolite-type material, utilized for the reaction with bulky molecules.\textsuperscript{105} Sulfuric acid adsorbed on silica gel has also been very efficiently exploited for the preparation of THP ethers of alcohols.\textsuperscript{106} Steroids, cinnamic and propargylic alcohols were quantitatively converted into the corresponding THP ethers by using this reagent system (\(\text{SiO}_2/\text{H}_2\text{SO}_4\)).\textsuperscript{107} The same reaction could be performed selectively by using silica chloride, prepared by treating silica with thionyl chloride.\textsuperscript{108} Besides, silica-supported Lewis acid \(\text{SiO}_2/\text{TaCl}_5\), affected THPRN at very low concentration and short reaction time.\textsuperscript{109} This protocol is highly useful in the case of protection of benzyloxy and acid-labile sugar substrates containing acetal groups. Ranu \textit{et al.} used alumina-supported zinc chloride for THPRN of alcohols through a simple solvent-free reaction.\textsuperscript{110}

Zirconia in its pure as well as modified form has also been employed in microwave-accelerated THPRN of alcohols and phenols. Moreover, THP ethers of allylic and acetylenic alcohols were formed without isomerization of double and triple bonds, as well as bulky substrates, such as cholesterol and naphthols in high yields and

\textsuperscript{98} Hoyer, S.; Laszlo, P.; Orlovic`, M.; Polla, E. \textit{Synthesis} 1986, 655.
\textsuperscript{100} Cornelis, A.; Laszlo, P. \textit{Synlett} 1994, 155.
\textsuperscript{102} Kumar, P.; Dinesh, C. U.; Reddy, R. S.; Pandey, B. \textit{Synthesis} 1993, 1069.
\textsuperscript{104} Rodriguez, I.; Climent, M. J.; Iborra, S.; Forne`s, V.; Corma, A. \textit{J. Catal.} 2000, 192, 441.
\textsuperscript{108} Ravindranath, N.; Ramesh, C.; Das, B. \textit{Synlett} 2001, 1777.
short reaction times. Additionally, treatment of a variety of alcohols and phenols with DHP in the presence of a catalytic amount of sulfated zirconia (\(\text{ZrO}_2/\text{SO}_4\)) (a popular solid superacid catalyst, which exhibits the highest acid strength) gave corresponding THP ethers in high yields.\(^{111}\) The procedure had also been efficiently applied to highly acid-sensitive alcohols such as allyl and propargyl alcohols.\(^{112}\) This solid catalyst has also been utilized for the THPRN of hydroquinone protected as the benzyl ether.\(^{113}\) Similarly, tetrahydropranylation was also reported with \(\alpha\)-\(\text{Zr(O}_3\text{PCH}_3\)\(_2\)\(\text{O}_3\text{PC}_6\text{H}_4\text{SO}_3\text{H})\)\(_0.8\), even in presence of C-C double and triple bonds with the yields not being affected by the steric hindrance of reagents.\(^{114}\) ZrO\(_2\)-pillared clay (Zr-PILC) has been used for the selective mono THPRN of symmetrical diols and simple alcohols with good selectivity and conversion under solvent-free conditions as a mild recyclable solid Lewis acid catalyst both by heating and microwave irradiation.\(^{115}\)

Campelo et al.\(^{116}\) employed AlPO\(_4\) as a solid acid catalyst using an excess of DHP for the protection of alcohols and phenols in short reaction times and without the formation of the troublesome olygomeric pyrenes. Sulfated charcoal in combination with 3-Å molecular sieve has been used in the protection of the diversity of alcohols and phenols as THP ethers.\(^{117}\) Recently, the tetrahydropranylation was performed using catalyst supported on organic polymers e.g., Hon et al.\(^{118}\) used acetonyltriphenylphosphonium bromide (ATPB) supported on polystyrene. Olah et al.\(^{119}\) reported the use of Nafion for the THPRN of primary and secondary alcohols. Zeolite H-beta, as a recyclable acid catalyst has been suggested to be a useful alternative to the known methods for the production of THP ethers with mild reaction conditions.\(^{120}\) Small pore size zeolite \(\text{viz.}\), modified zeolite-type adsorbent E4A has been found to be a simple, recyclable and environmentally friendly catalyst for THPRN of various alcohols and phenols.\(^{121}\)


1.2.4. Miscellaneous:
THP ethers of alcohols have also been prepared by photolysis of DHP, using 1,5-dichloro-9,10-anthraquinone as catalysts under visible light. The reaction could be conducted under ambient fluorescent lighting or with sunlight as well as in a Rayonet reactor (Scheme-4).<sup>122</sup>

![Scheme 4: THP protection under photochemical condition](image)

Microwave assisted organic synthesis became an increasingly popular technique in academic and industrial research, due to advantages like particularly shorter reaction times and rapid optimization of chemical reactions. Besides, iodine-catalyzed THPRN under microwave irradiation has also been achieved for selective protection of one hydroxyl group in \(n\)-symmetrical diol.<sup>123</sup>

![Figure 3: Various methods of THPRN](image)

1.3. Deprotection of tetrahydropyranyl ether:
The selective removal of a protecting group is of equal importance and significance as its introduction in an organic synthesis. Acetals and ketals are generally deprotected by reducing them to either ethers or hydrocarbons under a variety of reducing conditions, e.g. trialkysilanes in the presence of Bronsted or Lewis acids.<sup>122</sup> Oates. R. P.; Jones, P. B. J. Org. Chem. 2008, 73, 4745.  
THP ethers are mixed acetals, while for the deprotection of the THP ethers a transacetalization methodology is preferred. Owing to great impact THP ethers on the protection of hydroxyl groups, the development of its deprotection methods has also received considerable attention. Liu and Wong\textsuperscript{124} achieved the deprotection of THP ethers by selectfluor catalysis in an efficient fashion (Scheme-5).

\begin{center}
\textbf{Scheme 5:} Selectfluor catalysed THP protection
\end{center}

Bismuth triflate has been found to bring about deprotection of THP ethers of a range of alcohols and phenols under solvent-free conditions.\textsuperscript{125} Williams \textit{et al.}\textsuperscript{126} developed a simple and efficient method for the deprotection of THPE in a facile manner using Al(OTf)$_3$ in the presence of methanol. Also, Tajbakhsh and co-workers\textsuperscript{127} reported a chemoselective and competent method for the deprotection of THP ethers with H$_2$O$_2$/Mn(III) Schiff-base complex. Hiromichi \textit{et al.}\textsuperscript{128} carried out the reaction of tetrahydropyranyl (THP) ethers with triethylsilyl trifluoromethanesulfonate (TESOTf)-2,4,6-collidine to chemoselectively afford alcohol and 4-triethylsiloxybutanal in good yields. The weakly basic reaction conditions facilitate deprotection without affecting acid-labile protecting groups. Maulide \textit{et al.}\textsuperscript{129} achieved chemoselective, catalytic deprotection of tetrahydropyranyl (THP) ethers in the presence of enol triflates by the action of cerium (IV) ammonium nitrate (CAN). Ti(III) chloride was found to be a mild and effective catalyst for the deprotection of tetrahydropyranyl ethers of alcohols and phenols not effecting allyl ether, benzyl ether, tert-butylidiphenylsilyl (TBDPS) ether, $p$-toluenesulfonate ester and isomerizable double bonds.\textsuperscript{130} Narender \textit{et al.}\textsuperscript{131} reported oxidative deprotection of tetrahydropyranyl ethers with $N$-bromosuccinimide using (-)-

\textsuperscript{130} Nayak, A.; Kumar, S. \textit{Synthesis} \textbf{2005}, \textit{1}, 74.
cyclohextrin in water. Pore et al.\textsuperscript{132} employed silica-sulfuric acid as a reusable solid acid catalyst for the deprotection of tetrahydropyranyl ethers. Various THP ethers can be deprotected to the parent alcoholic or phenolic compounds in CH$_2$Cl$_2$/MeOH (5:2) by employing bromomethylsulfonylum bromide as catalyst.\textsuperscript{133} THP ethers of alcohols in absolute MeOH have also been converted to the corresponding alcohols using a catalytic amount of decaborane.\textsuperscript{134} Mohammadpoor and co-workers\textsuperscript{135} reported that the treatment of tetrahydropyranyl (THP) ethers with Bi(III) salts like BiCl$_3$, Bi(TFA)$_3$ and Bi(OTf)$_3$ in MeOH provided a simple and efficient process for the conversion of ethers into corresponding alcohols. Cupric chloride dihydrate in MeOH has also been used in the deprotection of tetrahydropyranyl ethers to the corresponding alcohols.\textsuperscript{136} Tomoko Mineno\textsuperscript{137} reported Indium triflate-mediated deprotection of tetrahydropyran ethers in aqueous MeOH.

1.4. Direct conversion of THP ether in different functionalities:

THP-ethers have an immense advantage of being easily convertible to corresponding functionalities such as halides, sulphides, esters, cyanides, alkyl ethers, silyl ethers, isothiocyanate and carbonyl compounds using a variety of methods.

The interconversion of THPE into acetate is a useful transformation in organic synthesis. Das et al.\textsuperscript{138} developed an efficient and direct method for the conversion of THP ethers into the corresponding acetates using acetic anhydride in the presence of Amberlyst-15 as a catalyst. Rafiee and co-workers\textsuperscript{139} converted THPE derived from primary alcohols into the corresponding acetates and formates by the action of EtOAc, HOAc, acetic anhydride and ethyl formate in the presence of K$_5$CoW$_{12}$O$_{40}$·3H$_2$O as catalyst. Tetrahydropyranyl ethers derived from secondary alcohols and phenols could be transformed into the corresponding acetates, using acetic anhydride, However K$_5$CoW$_{12}$O$_{40}$·3H$_2$O was ineffective for esterification with EtOAc, HOAc, and ethyl


formate. Movassagh et al.\textsuperscript{140} reported conversion of tetrahydropyranyl ethers into their corresponding esters with acid chlorides in the presence of montmorillonite K-10. A green chemical method for the direct conversion of alcohol tetrahydropyranyl ethers into the corresponding acetates has been reported with various substituted acetyl chlorides and sodium iodide in high yields.\textsuperscript{141} Bi(III) salts such as BiCl$_3$, Bi(TFA)$_3$ and Bi(OTf)$_3$ were found to be efficient catalysts for the transformation of THPE to their corresponding acetates and formates with acetic acid and ethyl formate.\textsuperscript{142} Ranu et al.\textsuperscript{143,144} developed a highly selective conversion of THPE to acetates by indium tri-iodide. Chandrasekhar et al.\textsuperscript{145} used TiCl$_4$/Ac$_2$O and Bacos et al.\textsuperscript{146} used acid chlorides and a catalytic amount of ZnCl$_2$ for the conversion of THPE to acetates.

Direct conversion of alcohol silyl ethers to diphenylmethyl (DPM) ethers can be easily performed by reaction with diphenylmethyl formate in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate.\textsuperscript{147} The reaction of THP ethers with Ac$_2$O, Bi(NO$_3$)$_3$ and a catalytic amount of DABCO under microwave irradiation led to the corresponding acetates.\textsuperscript{148}

Direct transformation of tetrahydropyranyl ethers into the corresponding halides is an attractive method. Sonnet et al.\textsuperscript{150} developed a protocol for the conversion of alcohol tetrahydropyranyl ether into a bromide, chloride, methyl ether, nitrile or trifluoroacetate. Varrious reagents systems viz., 4-aminophenyldiphenylphosphinite,\textsuperscript{151} SiO$_2$-Cl/NaI, NaI (or LiBr) BF$_3$OEt$_2$ (or ClSiMe$_3$)\textsuperscript{152} and CBr$_4$-Ph$_3$P\textsuperscript{153} have been widely used for this transformation. THPE using pyridinium chlorochromate and TFA has been employed for their direct conversion to aldehydes.\textsuperscript{154}

PPh₃/DDQ)[n-Bu₄N]OCN has been used as a reagent system for the conversion of THPE to the corresponding alkyl isocyanates.¹⁵⁵ Naser et al.¹⁵⁶ exploited 4-aminophenyl diphenylphosphinite for the conversion of THPE to their corresponding thiocyanates or isothiocyanates in the presence of Br₂ and NH₄SCN. A combination of triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone has also been provided for the conversion of THPE to their corresponding thiocyanates.¹⁵⁷ In-situ generated Ph₃P(SCN)₂ has also been used for the conversion of THPE viz., primary and secondary alkyls and also benzylic to their corresponding thiocyanates.¹⁵⁸

Direct conversion of THPE into the corresponding benzyl ethers can be achieved in one pot with Et₃SiH and PhCHO in the presence of a catalytic amount of TMSOTf.¹⁵⁹ Oriyama et al.¹⁶⁰ developed a reagent system of trialkylsilyl trifluoromethanesulfonate and NEt₃ to readily convert THP ethers into corresponding trialkylsilyl ethers, e.g. Ph(CH₂)₃OSiR₃ in good yields. Direct conversion of THP ethers into tert-butyldimethylsilyl ethers has also been facilitated with CF₃SO₂SiMe₂CMe₃ and Me₂S.¹⁶¹

Akhlaghinia et al.¹⁶² reported triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone /tetrabutylammonium azide as an efficient reagent system for conversion of THP ethers to corresponding alkyl azides. For the conversion of tetrahydropyranyl ethers to their corresponding alkyl cyanides, triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone/n-Bu₄NCN system has been employed.¹⁶³ THP ethers of primary fatty alcohols can be converted in to the corresponding fatty acids using Jones reagents.¹⁶⁴

Figure 4 summarized the types of one step transformation of tetrahydropyranyl ether into various functionalities.

¹⁵⁵ Akhlaghinia, B.; Samiei, S. Phosphorus, Sulfur and Silicon and the Related Elements 2009, 184, 2529.
2. Objectives of the present work:

It is quite evident from the review of literature that tetrahydropyranylation (THPRN) is a useful protecting strategy for alcohols and thiols, offering stability towards strongly basic reaction conditions, organometallics, hydrides, acylating reagents and alkylating reagents. THP protection has mostly been achieved through harsh acidic condition. Moreover, many of the earlier employed strategies suffer from one or the other disadvantages such as (a) high cost of preparation, (b) hygroscopicity of the reagents (DDQ, triflates and iron perchlorate), (c) high acidity of the medium, (d) instability of the reagents (inorganic complexes and PPTC), (e) photosensitivity (DDQ), (f) requirement of complex experimental conditions and (g) tedious work-up etc.

It is apparent from the review of literature, that there are only a few reports related to mild tetrahydropyranylation of alcohols and thiols. Therefore, there are sufficient grounds to look for a mild and neutral approach for an improved THP protection of acid sensitive and natural product moieties. We therefore, envisaged developing a versatile, mild and efficient methodology for tetrahydropyranyl protection of alcohols and thiols using allyl tetrahydropyranyl ether (ATHPE) as a novel reagent.
3. Results and discussion:

In order to meet the objectives, allyl tetrahydropyrylan ether (ATHPE) was selected as a suitable reagent for tetrahydropyryl protection of alcohols and thiols. Initially, our studies were focused towards the determination of suitable experimental conditions for the replacement of O-allyl group in ATHPE (20) with hydroxyl group. Using various permutations of the mild reagents/catalysts, it was observed that halogenating reagents such as NXS and I\(_2\) in aqueous acetonitrile smoothly facilitated the formation of 2-hydroxytetrahydropyran (21) in almost quantitative yield (Scheme-6). The other expected byproducts such as bromohydrin, dibromo, allylic bromination of 20 were not formed.

![Scheme 6: Formation of 2-Hydroxytetrahydropyran from ATHPE](image)

This led us to believe that the replacement of water with suitable nucleophiles, such as alcohol/thiol may facilitate the transfer of THP from THP-allyl ether to alcohol/thiol under mild reaction conditions in the presence of suitable activators.

To verify the feasibility of the envisaged conversion, ATHPE was stirred with bromopropanol in the presence of various catalysts under different reaction conditions. The effect of the solvents, halogenating agents and lewis acid catalysts on the reaction time and the yields were also studied. The following reaction was taken as a model for optimization of the protocol.

![Scheme 7: Reaction for optimization of the protocol](image)
In this methodology we successfully used halogenating agents such as NBS, NCS, NIS and I$_2$. NBS also finds application in regeneration of alcohols from their allylic ethers under mild photochemical conditions.\textsuperscript{165} In general, NBS was found superior to other halogenating agents with respect to reaction time and yield (Table-2). Addition of catalytic amount of lewis acid dramatically reduced the reaction time. Thus, the reaction was completed in just 2 h at rt with the addition of 1 mol\% BF$_3$.OEt$_2$ in acetonitrile or CH$_2$Cl$_2$, affording the product in a practicable yield.

**Table 2:** Reaction of tetrahydropyranyl allyl ether (1 eq.), 3-bromopropanol-1 (2.0 eq.), with BF$_3$.OEt$_2$ in acetonitrile in the presence of different halogenating agents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halogenating agent$^a$</th>
<th>Time (h)</th>
<th>Yields$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS</td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>NIS</td>
<td>2.0</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>NCS</td>
<td>4.0</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>I$_2$</td>
<td>6.0</td>
<td>71</td>
</tr>
</tbody>
</table>

$^a$ NBS, NIS and NCS were used 1.2 equivalent and I$_2$ was used in catalytic amount.

$^b$ Isolated yield of the compound 23 after column chromatography.

The use of other lewis acids, such as InCl$_3$, In(OTf)$_3$, SnCl$_4$ and TiCl$_4$ as catalysts, resulted in comparatively lower yields of the products (Table-3).

**Table 3:** Reaction of tetrahydropyranyl allyl ether (1 eq.), 3-bromopropanol-1 (2.0 eq.), with NBS (1.2 eq.) in the presence of different lewis acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid catalyst$^a$</th>
<th>Time(h)</th>
<th>Yields$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$.OEt$_2$</td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>InCl$_3$</td>
<td>4.0</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)$_3$</td>
<td>4.0</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>TiCl$_4$</td>
<td>6.0</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>SnCl$_4$</td>
<td>6.0</td>
<td>70</td>
</tr>
</tbody>
</table>

$^a$ Catalyst loading 1 mol %

$^b$ Isolated yield of the compound 23 after column chromatography.

The experiments were also carried out for the optimization of the BF$_3$.OEt$_2$ load along with NBS during the formation of THP ethers. The results are depicted in table 4.

**Table 4:** Reaction of tetrahydropyranyl allyl ether (1 eq.), 3-bromopropanol-1 (2.0 eq.), with NBS (1.2 eq.) in the presence of different proportion of lewis acid BF$_3$.OEt$_2$ in acetonitrile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Loading of acid catalyst (mol %)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>

In this methodology, the amount of catalyst loading also played an important role. The best result was obtained by using 1% BF$_3$.OEt$_2$, while with a higher amount of the Lewis acid (1.0 eq.), no improvements in the yield or selectivity were observed, even when the reaction was performed at room temperature for 6 h.

For the optimization of such a methodology, the role of the solvent is also very significant. Transfer of THP took place efficiently in the solvents acetonitrile, CH$_2$Cl$_2$ with 81% and 72% yields, respectively. However, switching the solvent to N,N-dimethylformamide led to the complete decomposition of the product (Table-5).

**Table 5:** Solvent effect on reaction of tetrahydropyranyl allyl ether (1 eqv.), 3-bromopropanol-1(2.0eq.), with NBS (1.2 eq.).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time( h)</th>
<th>Yields$^b$ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>8.0</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Dichloromethane</td>
<td>10.0</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Dichloroethane</td>
<td>10.0</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>Diethyl Ether</td>
<td>24.0</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Tetrahydrofuran</td>
<td>24.0</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Ionic Liquid</td>
<td>8.0</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>N,N-dimethylformamide</td>
<td>-</td>
<td>trace</td>
</tr>
</tbody>
</table>

a. In every case 3 mL/mmol of solvent was used.
b. Isolated yield after column chromatography.

After the optimization of the reaction conditions, the application of the THP transfer methodology was explored on various substrates. A variety of alcohols including thiols (nucleophiles) produced corresponding tetrahydropyranyl ethers in high yields (60–91%) when treated with ATHPE at room temperature in the presence of NBS (with 1% BF$_3$.OEt$_2$) or I$_2$ (Figure-5).
Primary, secondary, tertiary, benzylic alcohols and thiols were conveniently protected as tetrahydropyranyl ethers at room temperature and neutral pH. Iodine alone could bring about the transformation in moderate yield (Table-7). Table 6 depicts the results of THP protection with less sensitive substrates while in the next table (Table-7), THP protection of comparatively more acid sensitive substrates under optimized conditions are shown.

The tolerance of various functional groups under the optimized reaction conditions was studied in the substrates bearing substituents such as nitro, halo and alkenes. It was observed that the reagent is mild enough to be used in systems containing acid sensitive multifunctional groups. Thus, we have encountered no serious difficulty for the tetrahydropyranylation of alcohols such as tertiary butanol, cholesterol, citronellol, 1-phenyl ethanol and furfuryl alcohol respectively (Table 6 and 7), possessing acid sensitive functional groups, effecting smooth transformations at room temperature without the formation of side products. However, with the substrates comprising double bond such as cholesterol and citronellol, I\textsubscript{2} gave the best results, while NBS was unsuitable due to the formation of side products.

**Figure 5:** Nucleophiles employed in the reaction with tetrahydropyranyl allyl ether
**TABLE 6: Results of Protection of Alcohols and Thiols with ATHPE**

<table>
<thead>
<tr>
<th>Entry</th>
<th>NuH</th>
<th>Product</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-Bromopropanol-1</td>
<td><img src="23" alt="Image" /></td>
<td>2.0</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Hexanol-1</td>
<td><img src="44" alt="Image" /></td>
<td>2.0</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Decanol-1</td>
<td><img src="45" alt="Image" /></td>
<td>2.0</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Tetradecanol-1</td>
<td><img src="46" alt="Image" /></td>
<td>2.0</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>Benzyl alcohol</td>
<td><img src="47" alt="Image" /></td>
<td>2.5</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>4-Chlorobenzyl alcohol</td>
<td><img src="48" alt="Image" /></td>
<td>3.0</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>4-Nitrobenzyl alcohol</td>
<td><img src="49" alt="Image" /></td>
<td>3.0</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>5-Hydroxymethyl benzo[d][1,3]dioxole</td>
<td><img src="50" alt="Image" /></td>
<td>3.0</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>2-Phenylethanol</td>
<td><img src="51" alt="Image" /></td>
<td>2.0</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Compound</td>
<td>Yield (%)</td>
<td>Isolated Yield (%)</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-----------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Cyclohexanol</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1-Phenylethanol</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Ethanethiol</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Glycerol</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2-Aminobutanol</td>
<td>No reaction</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*a Time taken using 1.5 eq NuH, 1.0 eq tetrahydropyranyl allyl ether, 1.2 eq NBS, 1 mol% BF$_3$.OEt$_2$ in acetonitrile. *b* isolated yield.

A tertiary alcohol, as anticipated takes longer time than a secondary alcohol that in turn takes more time than a primary alcohol, presumably due to their reactivity and steric factors. One of the other important applications of the present protection methodology has been the THP protection of sugar alcohols bearing acid sensitive acetonide protections (Table 7, entries 3 and 4). The preparation of THP protected sugar derivatives in good yields (70–75%) may find useful applications in carbohydrate chemistry.

As THP is only a protecting group, therefore, it has minimal implications on the formation of diastereoisomers and the stereochemical outcome of the products. Thus, in the substrates having chiral centre/s, the formation of more than one diastereoisomers cannot be ruled out. For example, both 1-phenyl ethanol and cholesterol gave a mixture of two diastereoisomers in unequal proportions (3:1 and 2:1, respectively) as calculated from NMR spectra; whereas, other chiral molecules (Table-7) gave two diastereoisomers in approximately equal ratios. As expected, glycerol (Table-6) gave a mixture of three diastereoisomers in almost equal amounts. Here, the role of steric
factors could be important in deciding about the stereochemistry and the number of
diastereoisomers.

\[
\begin{array}{cccc}
\text{Scheme: 9 Protection of sensitive alcohols by using 20} \\
\end{array}
\]

**TABLE 7: Results of Protection of Some Acid Sensitive Alcohols and Thiol with 20.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>NuH</th>
<th>Product</th>
<th>( t^a ) (h)</th>
<th>Yield (%)(^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Furfuryl alcohol</td>
<td><img src="image" alt="56" /></td>
<td>1.5</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>tert-Butanol</td>
<td><img src="image" alt="57" /></td>
<td>8.0</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Glucose diacetonide</td>
<td><img src="image" alt="58" /></td>
<td>6.0</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Galactose diacetonide</td>
<td><img src="image" alt="59" /></td>
<td>6.0</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>Furan methane thiol</td>
<td><img src="image" alt="60" /></td>
<td>1.5</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Glycerol acetonide</td>
<td><img src="image" alt="61" /></td>
<td>6.0</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Citronellol</td>
<td><img src="image" alt="62" /></td>
<td>8.0(^b)</td>
<td>80</td>
</tr>
</tbody>
</table>
8. Cholesterol

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td></td>
<td>8.0</td>
<td>60</td>
</tr>
</tbody>
</table>

\( ^{\text{a}} \) Time taken using 1.5 eq N\text{uH}, 1.0 eq allyl tetrahydropyranyl ether, 1.2 eq NBS, in acetonitrile.

\( ^{\text{b}} \) Time taken using 1.5 eq N\text{uH}, 1.0 eq allyl tetrahydropyranyl ether, 1.0 eq allyl tetrahydropyranyl ether, 1 mol % I\text{2}\text{c} isolated yield

### 3.1. Mechanism:

Based on our own experiments and a recent study on glycosylation by propargyl glycosyl donor,\(^{166}\) which is analogous to the mechanism earlier proposed for the glycosylation of 4-penten-1-ol donor,\(^{167}\) we suggest the following possible mechanism for tetrahydropyranylation using ATHPE in the presence of halogenating agents.

The proximity of NBS and allyl tetrahydropyranyl ether facilitates the attack of a bromonium ion and the formation of the intermediate A, which equilibrates with the unstable intermediate B. The elimination of C (epihalohydrin) from B generates reactive oxocarbenium D, which can easily capture the attacking nucleophiles (i.e., ROH and RSH), giving the desired product. The development of yellowish colour (with NBS), which slowly disappears after the addition of alcohols and thiols support the formation of halonium ion intermediate. Moreover, while working with NCS in a controlled experiment, we observed the formation of C (X = Cl) in the NMR-spectra of the reaction mixture. When the same reaction was performed on molecule comprising basic nitrogen, for example 2-aminobutanol (Table 6, entry 14), the reaction did not proceed, because the NH\text{2} group prevented the formation of the halonium ion intermediate A. This observation also supports the proposed mechanistic pathway.

---


**SCHEME 10:** Plausible mechanism of replacement of O-allyl group by alcohols and thiols

4. Conclusions:* 

In summary, we have demonstrated the usefulness of allyl tetrahydropyranyl ether (ATHPE) as a new tetrahydropyran protecting agent for alcohols and thiols under neutral conditions. The tolerance of various sensitive functional groups under mild and neutral conditions is the added advantages over classical THP protection using dihydropyran. The reagent system may also prove useful in the protection protocols in polyfunctional molecules. As shown in the literature and discussed earlier, a diverse range of catalysts and reagent system have been utilized in the field of THP protection chemistry during the past decades. Since, there has always been a consistent requirement of developing more mild and environmentally friendly methods for the protection-deprotection protocols in synthetic organic chemistry, the present methodology of THP protection may prove to be a positive step in that direction.

*This work has been published in *Tetrahedron Lett.* 2009, 50, 6236.
5. Experimental:

5.1. General Information:

\(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on 200 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts were expressed in parts per million (\(\delta \) ppm). MS were recorded on Mass spectrometer. Elemental analyses were performed on Elementar Vario EL-III. MPs were measured in a Buchi-510 apparatus. Silica gel coated aluminium plates were used for TLC. Reagents and solvents used were mostly of LR grade.

5.2. Experimental procedure:

(1) General procedure of THP protection using ATHPE as a reagent and NBS:

A solution of tetrahydropyranyl allyl ether (1 eq.), nucleophiles (1.5 eq.) in acetonitrile (3 mL/mmol substrate), NBS (1.2 eq.), BF\(_3\).OEt\(_2\),(1 mol \%) were added and the reaction mixture was allowed to stir for specified time (Tables 6 and 7) at room temperature. The reaction mixture was concentrated, extracted in diethyl ether (10 mL) and washed with saturated sodium bicarbonate solution (10 mL). The organic layer separated, dried over anhydrous Na\(_2\)SO\(_4\), evaporated, and finally the crude mixture was purified by column chromatography on alumina to afford corresponding pure product.

(2) General procedure of THP protection using ATHPE as a reagent and I\(_2\):

A mixture of tetrahydropyranyl allyl ether (1.0 eq.), citronellol (1.5 eq.) in acetonitrile (3 mL/mmol substrate), I\(_2\) (1 mol \%) added and the contents allowed to stir for specified time (Tables 6 and 7) at room temperature. The reaction mixture was evaporated under reduced pressure, extracted in diethyl ether (10 mL) and washed successively with saturated sodium bisulphite solution (10 mL), water (10 mL). The organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and evaporated. The crude mixture was purified by column chromatography on alumina to afford corresponding pure product.

5.3. Spectral analysis:

5.3.1. 2-(Allyloxy)-tetrahydro-2\(H\)-pyran (20): \(^1\)H NMR(200 MHz,CDC\(_3\)), \(\delta\) 5.84 (m,1H), 5.16 (m, 2H), 4.57 (t, 1H, \(J = 3.13\) Hz), 4.14 (m, 1H), 3.91 (m, 1H), 3.78 (m, 1H), 3.43 (m, 1H), 1.45-
1.75 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 134.7, 116.6, 97.8, 67.7, 62.0, 30.6, 25.2, 20.6, ESI-MS (M+Na)= 165; Anal. Calc for C$_8$H$_{14}$O$_2$: C, 67.57; H, 9.92; Found; C, 67.67; H, 9.88.

5.3.2. Tetrahydro-$2H$-pyran-2-ol (21): Prepared by the general procedure 1 but here we used water instead of alcohol or thiol and purified on alumina (EtOAc/PE: 2/98) to obtain the product (80%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 4.93(t, 1H, $J$=2.80 Hz), 3.86 (m, 1H), 3.50 (m, 1H), 1.53-1.858 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 94.6, 62.9, 30.6, 25.4, 19.7, ESI-MS (M+Na)= 125; Anal. Calc for C$_5$H$_{10}$O$_2$: C, 58.80; H, 9.87, Found; C, 58.66; H, 10.06.

5.3.3. 2-(3-Bromopropoxy)-tetrahydro-$2H$-pyran (23):
Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (91%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 4.597 (t, 1H, $J$= 3.92 Hz), 4.41 (m, 2H), 3.50 (m, 4H), 2.126 (m, 2H), 1.514-1.787 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 99.2, 65.2, 62.6, 33.2, 31.0, 30.9, 25.7, 19.8 ESI-MS (M+Na)= 245 Anal. Calc for C$_8$H$_{15}$BrO$_2$: C, 43.07; H, 6.78; Found; C, 43.17; H, 6.71.

5.3.4. 2-(Hexyloxy)-tetrahydro-$2H$-pyran (44):
Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (92%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 4.56 (t, 1H, $J$= 3.4 Hz), 3.76(m, 2H), 3.41 (m, 2H), 1.29-1.81(m, 14H), 0.87(t, 3H, $J$ = 6.60 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) 98.8, 67.7, 62.3, 31.7, 30.5, 29.5, 25.96, 25.4, 22.6, 19.7, 14.0. ESI-MS (M+Na) 229; Anal. Calc for C$_{11}$H$_{22}$O$_2$: C, 70.92; H, 11.90; Found; C, 70.62; H, 12.00.

5.3.5. 2-(Decyloxy)-tetrahydro-$2H$-pyran (45):
Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (89%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 4.55 (t, 1H, $J$= 3.4 Hz), 3.64-3.84 (m, 2H), 3.29-3.49 (m, 2H), 1.24-1.80 (m, 16H), 0.85 (t, 3H, $J$= 6.6); $^{13}$C NMR (125 MHz, CDCl$_3$) 98.8, 67.6, 62.2, 31.9, 30.8, 29.8, 29.7, 29.6, 29.5, 19.3, 26.2,
5.3.6. 2-(Tetradecyloxy)-tetrahydro-2H-pyran (46): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (87%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): δ 4.57(t, 1H, J = 3.30), 3.87(m, 1H), 3.71(m, 1H), 3.49 (m, 1H), 3.38 (m, 1H), 1.25-1.85 (m, 30H), 0.84 (t, 3H, J=6.6); $^{13}$C NMR (125 MHz, CDCl$_3$) 98.74, 67.63, 62.1, 31.9, 30.8, 29.9, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 26.3, 25.5, 22.7, 19.6, 14.0 ESI-MS (M+Na)= 321; Anal. Calc for C$_{19}$H$_{38}$O$_2$: C, 76.45; H, 12.83; Found; C, 76.50; H, 12.80.

5.3.7. 2-(Benzyloxy)-tetrahydro-2H-pyran (47): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (85%) as oily liquid; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.200-7.35(m, 5H), 4.764 (d, 1H, J=13.2 Hz), 4.677 (t, 1H, J=3.5 Hz), 4.465 (d, 1H, J=12.4), 3.88 (m, 1H), 3.50(t, 1H, J=3.4 Hz), 1.47-1.69 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 138.5, 128.6, 128.2, 127.5, 97.7, 68.8, 62.0, 30.7, 25.6, 19.4 ESI-MS (M+Na)=115 Anal. Calc for C$_{12}$H$_{16}$O$_2$: C, 74.97; H, 8.39; Found; C, 74.93; H, 8.42.

5.3.8. 2-(4-Chlorobenzyloxy)-tetrahydro-2H-pyran (48): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 4/96) to obtain the product (81%) as oily liquid; $^1$H NMR(200 MHz,CDCl$_3$): δ 7.31(s, 4H), 4.76 (d,1H, J= 12.2 Hz),4.70 (t, 1H, J= 3.5 Hz), 4.47 (d, 1H, J=12.2 Hz), 3.50-3.60 (m, 1H), 1.28-1.82 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 136.9, 133.2, 129.1, 128.5, 97.8, 68.0, 62.2, 30.6, 25.5, 19.3 ESI-MS (M+Na)=249 Anal. Calc for C$_{12}$H$_{15}$ClO$_2$: C, 63.58; H, 6.67; Found; C, 63.56; H, 6.87.

5.3.9. 2-(4-Nitrobenzyloxy)-tetrahydro-2H-pyran (49): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 5/95) to obtain the product (80%) as oily liquid; $^1$H NMR(500 MHz,CDCl$_3$): δ 8.21(d, 2H, J= 8.70), 7.53 (d, 2H, J= 8.70), 4.89 (d, 1H, J=13.4), 4.73 (t, 1H, J= 3.50), 4.65 (d, 1H, J=13.40), 3.88 (m, 1H), 3.56 (t, 1H, J= 5.8), 1.55-1.89 (m, 6H); $^{13}$C NMR (125 MHz,
CDCl$_3$) 147.2, 146.1, 127.7, 123.6, 98.3, 67.6, 62.2, 30.4, 25.3, 19.2 ESI-MS (M+Na) = 260; Anal. Calc for C$_{12}$H$_{15}$NO$_4$: C, 60.75; H, 6.37; N, 5.96; Found: C, 60.65; H, 6.47; N, 6.08.

5.3.10. 5-(Tetrahydro-2H-pyran-2-yloxy)methyl  benzo[d] [1,3]dioxole (50): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (82%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): δ 6.83 (m, 1H), 6.75 (m, 2H), 5.92 (s, 2H), 4.65 (m, 2H), 4.37 (d, 1H, $J = 13.60$), 3.87 (m, 1H), 3.51 (m, 1H), 1.47-1.82 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 147.7, 147.0, 132.1, 121.4, 108.6, 108.0, 100.9, 97.5, 68.7, 62.1, 30.7, 25.3, 19.7. ESI-MS (M+Na) = 259; Anal. Calc for C$_{13}$H$_{16}$O$_4$: C, 66.09; H, 6.83; Found: C, 66.19; H, 6.73.

5.3.11. Tetrahydro-2-(phenethoxy)-2H-pyran (51): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (89%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): δ 7.10-7.27 (m, 5H), 4.56 (t, 1H, $J = 3.2$ Hz), 3.86-3.98 (m, 1H), 3.41(m, 1H), 1.88 (m, 2H), 1.45-1.71 (m, 6H); $^{13}$C NMR (50 MHz, CDCl$_3$) 139.6, 129.4, 128.7, 126.5, 99.0, 68.7, 62.4, 36.8, 31.1, 25.9, 19.9 ESI-MS (M+Na) = 229; Anal. Calc for C$_{13}$H$_{18}$O$_2$: C, 75.69; H, 8.80; Found: C, 75.60; H, 8.89.

5.3.12. 2-(Cyclohexyloxy)-tetrahydro 2H-pyran (52): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (86%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): δ 4.67 (t, 1H, $J = 3.4$ Hz), 3.87 (m, 1H), 3.37-3.52 (m, 1H), 1.29-1.90 (m, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) 96.3, 74.1, 62.3, 33.6, 31.6, 31.2, 25.7, 25.5, 19.8 ESI-MS (M+Na) = 207; Anal. Calc for C$_{11}$H$_{20}$O$_2$: C, 71.70; H, 10.94; Found: C, 71.81; H, 11.83.

5.3.13. 2-(1-Phenylethoxy)-tetrahydro-2H-pyran (53): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (81%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): δ 7.23-7.42 (m, 5H), 4.86 (m, 1H), 4.39 (t, 1H, $J = 4.30$ Hz), 3.90-3.52 (m, 1H), 1.29-1.90 (m, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) 147.7, 147.0, 132.1, 121.4, 108.6, 108.0, 100.9, 97.5, 68.7, 62.1, 30.7, 25.3, 19.7. ESI-MS (M+Na) = 259; Anal. Calc for C$_{13}$H$_{16}$O$_4$: C, 66.09; H, 6.83; Found: C, 66.19; H, 6.73.
5.3.14. 2-(Ethyl thio)-tetrahydro-2H-pyran (54): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (90%) as oily liquid; \( ^1 \text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta 4.78 \) (t, 1H, \( J= 3.6 \) Hz), 3.99 (m, 1H), 3.41(m, 1H), 2.59 (m,1H), 2.51(m, 1H), 1.82 (m,1H), 1.72 (m, 1H), 1.46-1.51 (m, 4H), 1.18 (t, 3H, \( J= 7.4 \) Hz); \( ^{13} \text{C NMR} \) (125 MHz, CDCl\(_3\)) 81.8, 64.4, 31.3, 25.1, 24.2, 21.7, 14.9 ESI-MS (M+Na)= 169; Anal. Calc for C\(_7\)H\(_{14}\)OS: C, 57.49; H, 9.65; S, 21.97.

5.3.15. 2-(1,3-Bis(tetrahydro-2H-pyran-2-yloxy)propane-2-yloxy)-tetrahydro-2H-pyran (55): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (83%) as oily liquid; \( ^1 \text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta 4.86-4.88 \) (m, 1H), 4.59-4.62 (m, 2H), 3.95-4.02 (m, 2H), 3.73-3.86 (m, 4H), 3.46-3.54 (m, 5H), 1.78-1.79 (m, 3H), 1.48-1.66 (m, 16H); \( ^{13} \text{C NMR} \) (125 MHz, CDCl\(_3\)) 100.5, 100.2, 100.0, 99.7, 99.7, 99.5, 99.2, 99.1, 98.8, 75.9, 75.7, 75.3, 75.3, 69.2, 69.1, 69.0, 68.9, 68.6, 68.4, 63.3, 63.3, 62.9, 62.9, 32.1, 31.9, 31.9, 31.8, 26.9, 26.8, 26.6, 20.7, 20.6, 20.4, 20.4, ESI-MS (M+Na)=367; Anal. Calc for C\(_{18}\)H\(_{32}\)O\(_6\): C, 62.77; H, 9.36; Found; C, 62.66; H, 9.46.

5.3.16. 2-((Furan-2-yl)-methoxy)-tetrahydro-2H-pyran (56): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (80%) as oily liquid; \( ^1 \text{H NMR} \) (200 MHz,CDCl\(_3\)): \( \delta 7.41\) (d, 1H, \( J=1.4 \) Hz), 6.34 (s, 2H), 4.71(t, 1H, \( J= 3.30 \) Hz), 4.67(d, 1H, \( J= 12.8 \) Hz), 4.49 (d, 1H, \( J= 12.8 \) Hz), 3.90 (m, 1H), 3.54 (m, 1H), 1.48-1.83 (m, 6H); \( ^{13} \text{C NMR} \) (125 MHz, CDCl\(_3\)) 151.8, 142.7, 110.2, 109.1, 61.8, 60.5, 30.3, 25.4, 19.1 ESI-MS (M+Na)= 205; Anal. Calc for C\(_{10}\)H\(_{14}\)O\(_3\): C, 65.91; H, 7.74; Found; C, 65.95; H, 7.84.

5.3.17. 2-(Tert butoxy)-tetrahydro-2H-pyran (57): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98)
to obtain the product (80%) as oily liquid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.70 (t, 1H, $J= 3.5$ Hz), 3.89-3.99 (m, 1H), 3.37-3.48 (m, 1H), 1.41-1.88 (m, 6H), 1.23 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) 94.3, 74.1, 63.4, 32.5, 28.7, 25.4, 21.0 ESI-MS (M+Na)= 181; Anal. Calc for C$_9$H$_{18}$O$_2$: C, 68.31; H, 11.47; Found; C, 68.21; H, 11.42.

5.3.18. (2,2,7,7-tetramethyl-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)tетрахидро-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (59): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (75%) as oily liquid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.53 (dd, 1H, $J=12.0, 5.0$ Hz), 4.64-4.66 (m, 1H), 4.58-4.61 (m, 1H), 4.24-4.31 (m, 1H), 4.00-4.02 (m, 1H), 3.87-4.01 (m, 2H), 3.6-3.72 (m, 1H), 3.48-3.50 (m, 1H), 1.71-1.71 (m, 1H), 1.60-1.61 (m, 1H), 1.57-1.54 (m, 4H), 1.54 (s, 1H), 1.44 (s, 1H), 1.32 (s, 1H); ($^{13}$C NMR(125 MHz, CDCl$_3$) 109.2, 109.1, 108.4, 99.1, 99.0, 96.4, 96.3, 71.3, 71.0, 70.7, 70.6, 70.5, 67.4, 66.4, 66.1, 65.9, 62.3, 62.2, 30.5, 29.6, 29.0, 25.9, 25.4,25.3, 24.9, 24.4, 24.43, 19.5,19.4; ESI-MS (M+Na)= 367; Anal. Calc for C$_{17}$H$_{28}$O$_7$: C, 59.25; H, 8.19 Found; C, 59.33, H, 8.11.

5.3.19. 2,2-Dimethyl-1,3 dioxalan-4- ylmethoxy, tetrahydropyran (61): Prepared by the general procedure 1 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (70%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.37-1.80 (m, 12H), 3.49 (m, 2H), 3.78 (m, 3H), 4.06 (m, 1H), 4.30 (m, 1H), 4.63 (t, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) 107.65, 107.50, 97.4, 97.1, 73.1, 72.9, 66.7, 66.1, 65.1, 64.9, 60.4, 60.3, 28.6, 24.9, 23.6, 17.6, 17.5 ESI-MS (M+Na)= 239; Anal. Calc for C$_{11}$H$_{20}$O$_4$: C, 61.09; H, 9.32 Found; C, 61.84; H, 8.78.

5.3.20. 2-(3,7-Dimethyl-6-enyloxy)-tetrahydro-2H-pyran (62): Prepared by the general procedure 2 and purified on alumina (EtOAc/PE: 2/98) to obtain the product (80%) as oily liquid; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 5.09 (t, 1H, $J= 7.01$ Hz), 4.58 (t, 1H, $J= 3.30$ Hz), 3.74-3.91 (m, 2H), 3.36-3.53 (m, 2H), 1.97 (m, 2H), 1.54-1.70 (m, 14H), 0.84-0.92 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) 130.3, 124.8, 98.8, 65.8, 62.1, 39.2, 37.2, 37.0, 30.7, 29.6, 25.5, 25.4, 24.8, 19.6, 17.5,
ESI-MS (M+Na) = 264; Anal. Calc for C\textsubscript{15}H\textsubscript{28}O\textsubscript{2}: C, 74.95; H, 11.74 Found; C, 74.84; H, 11.78.

5.3.21. 3-(Cyclohexyloxy)-17-tetradecahydro-13-dimethyl-6-methylheptan-2-yl)-1\textsubscript{H}-cyclopenta[\textit{a}] phenanthrene (63): Prepared by the general procedure 2 and purified on alumina (EtOAc/PE: 5/95) to obtain the product (60%) as white solid; \textsuperscript{1}HNMR(200 MHz,CDCl\textsubscript{3}) \(\delta\) 5.34 (t, 1H, \(J=8.55\) Hz), 4.71 (t, 1H, \(J=3.5\) Hz), 3.91 (m,1H), 3.49 (m,2H), 2.35 (d, 1H, \(J=7.50\) Hz ), 1.00-1.99 (m, 40H ), 0.91 (m, 4H), 0.86 (s, 3H), 0.67 (s, 3H); \textsuperscript{13}CNMR(125 MHz, CDCl\textsubscript{3}) 141.0, 121.5, 96.8, 76.0, 62.8, 56.7, 56.1, 50.2, 40.2, 39.8, 39.5, 38.7, 37.4, 37.2, 36.79, 36.2, 35.8, 31.9, 31.2, 29.7, 28.2, 28.0, 25.5, 24.3, 23.8, 22.8, 22.5, 21.0, 20.0, 20.0, 19.3, 19.7 ESI-MS (M+Na)= 494; Anal. Calc for C\textsubscript{33}H\textsubscript{56}O: C, 84.55; H, 12.04 Found; C, 84.51; H, 12.08.
$^1$H and $^{13}$C NMR spectra of compound 20:
$^{1}$H and $^{13}$C NMR spectra of compound 21:
$^1$H and $^{13}$C NMR spectra of compound 23:
$^1$H and $^{13}$C NMR spectra of compound 44:
\(^1\)H and \(^{13}\)C NMR spectra of compound 45:
$^1$H and $^{13}$C NMR spectra of compound 46:
$^1$H and $^{13}$C NMR spectra of compound 47:
$^1$H and $^{13}$C NMR spectra of compound 48:
$^1$H and $^{13}$C NMR spectra of compound 49:
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$^1$H and $^{13}$C NMR spectra of compound 55:
$^1$H and $^{13}$C NMR spectra of compound 56:
$^1$H and $^{13}$C NMR spectra of compound 57:
$^1$H and $^{13}$C NMR spectra of compound 59:
$^1$H and $^{13}$C NMR spectra of compound 61:
$^1$H and $^{13}$C NMR spectra of compound 62:
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra of compound $63$: