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ARTICLE TYPE

Tetrahydropyranyl ether (THPE) formation in hydroxyl group protection and conversion to other useful functionalities

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The short review highlights the various methods of formation of tetrahydropyranyl ethers (THPEs) as a method for the protection of simple alcohols as well as a diverse range of complex molecules using a variety of reagents and reaction conditions i.e., acid catalysed, heterogeneous catalyst and neutral reagent mediated reactions including their direct conversion to other useful functionalities.

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),[13] oxathiolanes (O,S),[14] 1,1-diacetates nitrogenous derivatives (imines, enamines, oximes, hydrazones, semicarbazones)[15] and *O*-methoxycarbonyl-cyanohydrin[16] have proven to be the most useful.

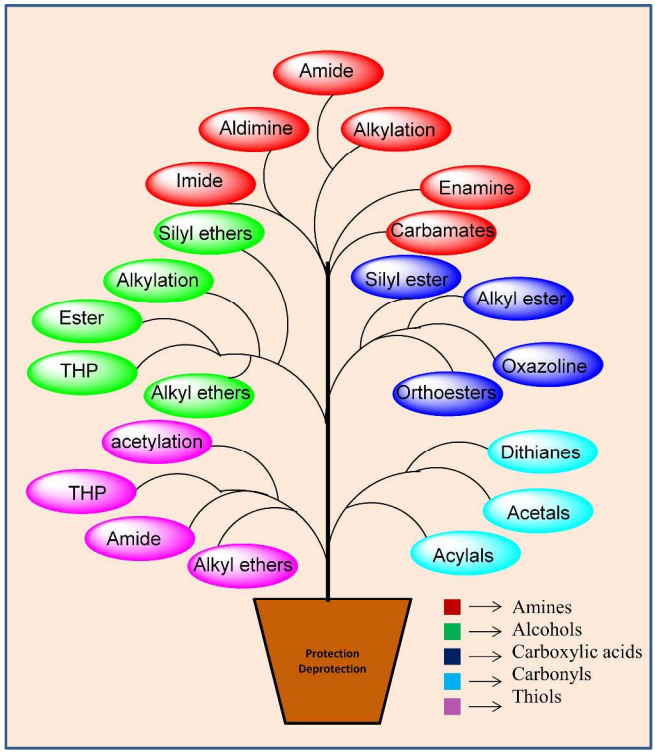


Figure 1: General demonstration of protection-deprotection strategies

2. 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, neomycim, erythromycin, tetracycline, gentamycin); anti-AIDs (crixivan, 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.[17]

Though more than 150 hydroxy-protecting groups have been reported,[18] 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.[19] 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,[20] metal exchanged as well as LaY zeolites,[21] phosphorus pentoxide supported on silica gel (SiO_2/P_2O_5)[22] *etc*. For acylation with acyl chlorides or anhydrides, bases the use of 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,[23] zinc chloride,[24] cobaltous chloride,[25] distannoxane,[26] scandium triflate[27] and silica supported fluoroboric acid (SiO_2/HBF_4) are used as catalysts.[28] 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 *et al*. reported acetylation of structurally varied alcohols and phenols catalyzed competently by numerous perchloric acids absorbed on silica gel (e.g., $SiO_2/HClO_4$).[29]

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[30] or by levulinate esters formation.[31] 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.[32] 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.[33] 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.[34]

Tosylation is another frequently used method of hydroxyl group protection,[35] 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.[36] Primary hydroxy groups in polyhydroxy compounds can be selectively tosylated in the presence of TsOH in combination with Fe^{3+} exchanged montmorillonite clay K10.[37] In case of symmetrical 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,[38] montmorillonite K10,[39] envirocat EPZG[40] and zirconium sulfophenyl phosphonate.[41] The SEM ethers are formed using SEMCl in the presence of alumina supported potassium fluoride (Al_2O_3/ KF) and can be efficiently used in the protection of both electron-rich and electron-poor phenols,[42] 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,[43] whereas DPM ethers are formed by reacting with diphenyl-methanol in the presence of $Yb(OTf)_3$ or $FeCl_3$.[44] 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*.[45] Allyl ethers are formed using allyl bromide in the presence of NaH or allyl trichloroacetimidate catalysed by trifloromethane sulfonic acid[46] or allyl chloroformate followed by Pd catalyzed decarboxylation.[47] Besides, allyl ethers can be selectively cleaved by oxidation with DDQ.[48] Alkoxyalkyl ether formation is another method of protection of 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.[49] 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, envirocat EPZG,[50] montmorillonite K10[51] and zeolites[52] (e.g., NaY zeolite, acid Y zeolite, ZSM-5, mordenite). As MOMCl is highly carcinogenic, dimemethoxymethane 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 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).

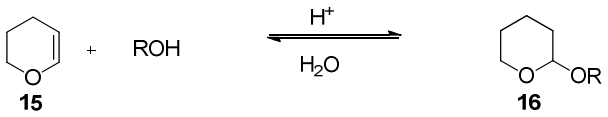
Table 1: Showing stabilities of THP ethers under various conditions.

Bases	LDA	NEt3, Py	t-BuOK	KOH	DCC	Pyridine
Nucleophiles	RLi	RMgX	RCuLi	Enolates	NH_3, RNH_2	$NaOCH_3$
Electrophiles	RCOCl	RCHO	CH_3I	NXS	$:CCl_2$	Bu_3SnH
Reduction	H2 / Ni	H_2 / Rh	H_2/Pd	Na / NH_3	$LiAlH_4$	$NaBH_4$
Oxidation	$KMnO_4$	OsO_4	CrO_3 / Py	RCOOOH	I_2. Br_2, Cl_2	MnO_2 / $CH2Cl_2$

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.

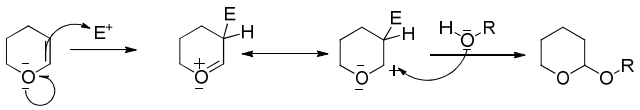
3. THP as a protecting group

Tetrahydropyranyl ethers are prepared from dihydropyran (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

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

1.3.1. Acid mediated
1.3.2. Neutral reagent mediated
1.3.3. Heterogeneous catalyst mediated
1.3.4. Miscellaneous

3.1. 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.

Usually, tetrahydropranylation has been carried out by acid-catalyzed addition of alcohols and phenols to 2,3-dihydro-2*H*-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_2Cl_2, THF, acetone and toluene. In 1934, R. Paul[53] observed that 2-methoxytetrahydropyran was formed while adding methyl alcohol to dihydropyran with HCl. Later, Woods and Kramer[54] modified the procedure developed by Paul and synthesized a number of acetals from 2,3-dihydropyran, while, Schalm *et al.,*[55] used PTSA for THPRN.

THPRN of alcohols has also been reported under solvent-free conditions using catalytic amounts of $SnCl_2$-$2H_2O$[56] and $InCl_3$ immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate (ionic liquid) in excellent yields and mild reaction conditions. 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.[57] Yadav *et al*.[58] employed THPRN in monoprotection of diols using $InCl_3$. One such method affected highly selective monoprotection of symmetrical diols using a catalytic amount of polystyrene supported $AlCl_3$.[59] Nagaiah *et al.*[60] 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_2Cl_2.[61] Pachamuthu and Vankar[62] employed CAN in CH_3CN at room temperature to prepare corresponding THP ethers of a variety of alcohols.

Majid *et al*.[63] developed a simple, mild and efficient method of THPRN of alcohols using ferric perchlorate. The protection of hydroxy groups as tetrahydropyranyl 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.[64] 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.[65] Additionally, $CeCl_3 \cdot 7H_2O$/NaI system under solvent-free conditions can also be employed in highly chemo-selective and environmentally benevolent THPRN of alcohols and phenols.[66] This reaction bears a great advantage of being performed under extremely mild conditions.[67] Majid and co-workers reported the method of chemo-selective tetrahydropranylation of primary alcohols in the presence of secondary and tertiary alcohols and phenols,[68] using tin(IV) porphyrin triflate as catalyst in THF. Babak *et al.*[69] 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_2PO_4].[70] 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.[71] $In(OTf)_3$ catalyzed THPRN formation of alcohols in dichloromethane is also described.[72] Tetrahydropyranyl 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.[73]

3.2. 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.

In 2009, Taneja and Coworkers[74] used allyl tetrahydropyranyl ether (ATHPE) as a versatile THP protecting reagent. In combination with NBS/I_2, O-allyl group can be easily substituted by hydroxyls (including tertiary OH) or thiols in presence of other reactive groups such as halogens, nitro, acetonide, alkenes etc. under mild reaction conditions (near neutral pH and ambient temperature).

Kotke and co-workers[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*.[76] reported a highly chemoselective method for the protection of free hydroxy compounds with DHP using $CeCl_3{\cdot}7H_2O$/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 *in situ* from $Fe(NO_3)_3 9H_2O$/NaI.[77] Sampath *et al*.[78] also used molecular iodine for THP protection. Bernady *et al*.[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*.[80] reported synthesis of tetrahydropyranyl ethers with dihydropyran in the presence of Me_3SiI under mild, neutral conditions and short reaction times. Bismuth (III) nitrate pentahydrate [$Bi(NO_3)_3{\cdot}5H_2O$][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, benzylidene and thioacetal *etc*.

Tetrahydropyranylation of primary alcohols has also been selectively carried out in the presence of secondary and tertiary alcohols and phenols using $PdCl_2(CH_3CN)_2$ as a catalyst in tetrahydrofuran (THF), while other protection groups such as p-toluenesulfonyl, tert-butyldiphenylsilyl, benzyloxycarbonyl, allyl, benzyl, and benzoyl remained intact under these conditions.[82] Miyashita *et al*.[83] used PPTS for THPRN under very mild reaction condition. $CuSO_4.5H_2O$ has also been reported to bring about smooth conversions of various alcohols and phenols into their corresponding THP ethers under mild reaction conditions.[84] Moreover, the preparation and catalytic application of *N,N*-dibromo-*N,N*-1,2-dethanediylbis(benzene sulfonamide) for THPRN of different alcohols and phenols has also been reported.[85] Catalytic behavior of water-insoluble cesium and rubidium tungstosilicates has also been studied in THPRN of phenols.[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,[87] LiBr,[88] or dicyanoketene ethylene acetal,[89] lithium perchlorate in diethyl ether (LPDE),[90] $(TBA)_2S_2O_8$,[91] *etc*.

3.3. Heterogeneous 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.[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.[93] Shimizu *et al*.[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 ºC) and can be recovered and reused for at least eight reaction cycles without the loss of reactivity.[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.[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.[97]

Some inexpensive and readily available naturally occurring clays, frequently utilized as competent and versatile catalysts like K10 clay[98] or Spanish sepiolite clay[99] or natural kaolinitic clay for organic reactions,[100] have also been utilized for the THPRN of hydroxy compounds. Likewise, envirocat (EPZG exhibiting both Brønsted and Lewis acid characteristics)[101] and acid zeolites (e.g., Y zeolite with silica/ alumina ratio of 4.86)[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).[103] Corma *et al*.[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.[105] Sulfuric acid adsorbed on silica gel has also been very efficiently exploited for the preparation of THP ethers of alcohols.[106] Steroids, cinnamic and propargylic alcohols were quantitatively converted into the corresponding THP ethers by using this reagent system (SiO_2/H_2SO_4).[107] The same reaction could be performed selectively by using silica chloride, prepared by treating silica with thionyl chloride.[108] Besides, silica-supported Lewis acid $SiO_2/TaCl_5$, affected THPRN at very low concentration and short reaction time.[109] This protocol is highly useful in the case of protection of benzyloxy and acid-labile sugar substrates containing acetal groups. Ranu *et al.* used alumina-supported zinc chloride for THPRN of alcohols through a simple solvent-free reaction.[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 short reaction times. Additionally, treatment of a variety of alcohols and phenols with DHP in the presence of a catalytic amount of sulfated zirconia (ZrO_2/SO_4) (a popular solid super acid 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 α-$Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$, 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 tetrahydropyranylation 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 *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]

3.4. 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.[122]

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.[123]

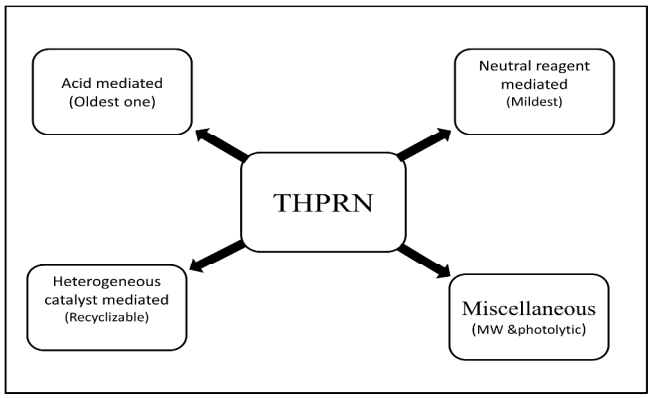


Figure 2: Various methods of THPRN

4. 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. trialkylsilanes in the presence of Bronsted or Lewis acids. 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[124] achieved the deportection of THP ethers by selectfluor catalysis in an efficient fashion.

Bismuth triflate has been found to bring about deprotection of THP ethers of a range of alcohols and phenols under solvent-free conditions.[125] Williams *et al.*[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[127] reported a chemoselective and competent method for the deprotection of THP ethers with H_2O_2/ Mn(III) Schiff-base complex. Hiromichi *et al.*[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 *et al.*[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-butyldiphenylsilyl (TBDPS) ether, *p*-toluenesulfonate ester and isomerizable double bonds.[130] Narender *et al.*[131] reported oxidative deprotection of tetrahydropyranyl ethers with *N*-bromosuccinimide using (-)-cyclodextrin in water. Pore *et al.*[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_2Cl_2/MeOH (5:2) by employing bromodimethylsulfonium bromide as catalyst.[133] THP ethers of alcohols in absolute MeOH have also been converted to the corresponding alcohols using a catalytic amount of decaborane.[134] Mohammadpoor and co-workers[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.[136] Tomoko Mineno[137] reported Indium triflate-mediated deprotection of tetrahydropyran ethers in aqueous MeOH.

5. 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.*[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[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 $K_5CoW_{12}O_{40}.3H_2O$ as catalyst. Tetrahydropyranyl ethers derived from secondary alcohols and phenols could be transformed into the corresponding acetates, using acetic anhydride, However $K_5CoW_{12}O_{40}.3H_2O$ was ineffective for esterification with EtOAc, HOAc, and ethyl formate. Movassagh *et al.*[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.[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.[142] Ranu *et al.*[143,144] developed a highly selective conversion of THPE to acetates by indium tri-iodide. Chandrasekhar *et al.*[145] used $TiCl_4$ /Ac_2O and Bacos *et al*.[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.[147] The reaction of THP ethers with Ac_2O, $Bi(NO_3)_3$ and a catalytic amount of DABCO under microwave irradiation led to the corresponding acetates.[148]

Direct transformation of tetrahydropyranyl ethers into the corresponding halides is an attractive method.[149] Sonnet *et al*.[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,[151] SiO_2-Cl/NaI, NaI (or LiBr) BF_3-Et_2O (or $ClSiMe_3$)[152] and CBr_4-Ph_3P.[153] have been widely used for this transformation. THPE using pyridinium chlorochromate and TFA has been employed for their direct conversion to aldehydes.[154]

PPh_3/DDQ)[n-Bu_4N]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 their corresponding thiocyanates or isothiocyanates in the presence of Br_2 and NH_4SCN. 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 $Ph_3P(SCN)_2$ 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 Et_3SiH and PhCHO in the presence of a catalytic amount of TMSOTf.[159] Oriyama *et al.*[160] developed a reagent system of trialkylsilyl trifluoromethanesulfonate and NEt_3 to readily convert THP ethers into corresponding trialkylsilyl ethers, *e.g*. $Ph(CH_2)_3OSiR_3$ in good yields. Direct conversion of THP ethers into *tert*-butyldimethylsilyl ethers has also been facilitated with $CF_3SO_3SiMe_2CMe_3$ and Me_2S.[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-Bu_4NCN 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 3 summarized the types of one step transformation of tetrahydropyranyl ether into various useful functionalities.

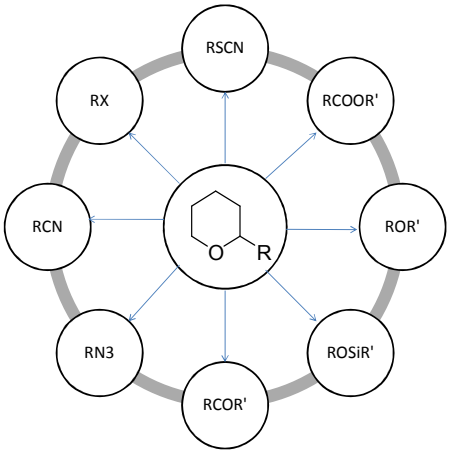


Figure 3: One step transformation of THP ethers into different functionalities

6. Conclusions

This review focussed on hydroxyl group protection via tetrahydropyranylation and deprotection of resulting THPE, and direct conversion of THPE into various useful functionalities.

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Notes and references

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Graphical abstract

Tetrahydropyranyl ether (THPE) formation in hydroxyl group protection and conversion to other useful functionalities

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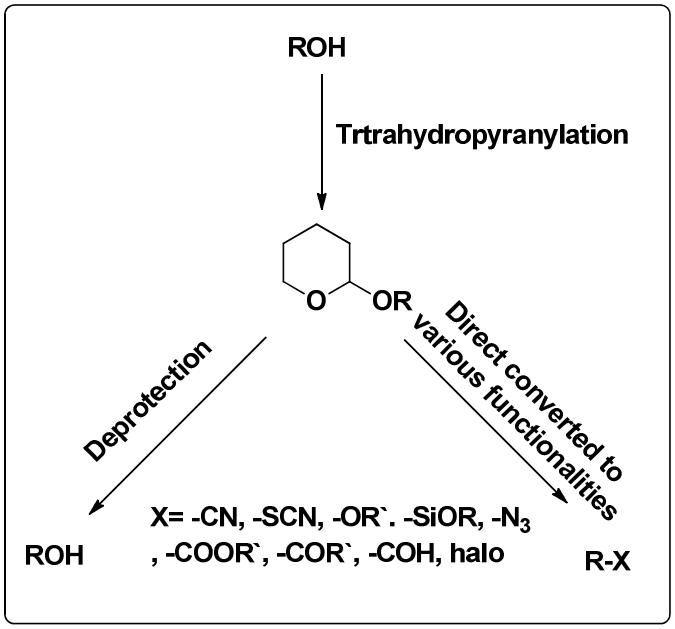

The short review highlights the various methods of formation of tetrahydropyranyl ethers (THPEs) as a method for the protection of simple alcohols as well as a diverse range of complex molecules using a variety of reagents and reaction conditions i.e., acid catalysed, heterogeneous catalyst and neutral reagent mediated reactions including their direct conversion to other useful functionalities.