

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

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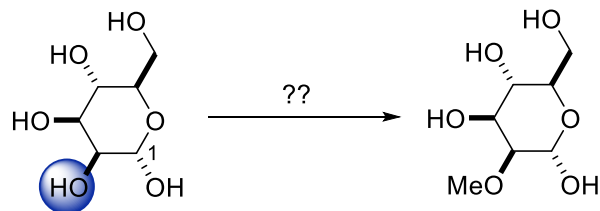
Recommended texts:

1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

The Logic of Organic Synthesis: The use of Protecting Groups:

The need for protecting group:

Suppose you are required to carry out the following transformation in the course of a multi-step synthesis:



The target is to etherify the C-2 oxygen selectively.

The reagent is known to you. It is a simple etherification and can be done by Williamson's method.

But the biggest challenge is to etherify the C-2 alcohol and keep the other primary and secondary hydroxyl groups intact so that they do not participate in the methylation reaction.

How to do this?

You can adopt either of the two following techniques.

One, you can employ a chemoselective reagent that seeks out the C-2 hydroxyl and does not touch the other -OH groups.

Or, two, you can make the other hydroxyls unreactive by protecting them in a form that is unresponsive towards the etherification condition, do your necessary reaction on C-2 hydroxyl, and finally, deprotect the protected -OH groups to achieve the target.

This is the protecting group (PG) strategy.

Notice that the installation of the PG by itself requires a *selective reaction that happens on every -OH groups except the one at C-2* but as you will see, it is doable.

The first option of using a *chemoselective reagent* is better as the PG strategy adds two non-productive steps (putting on the PG and removing the PG after the desired transformation is done) to the sequence and reduces the overall yield and efficiency of the synthesis.

But the trouble is, chemoselective reagents are rather difficult to find, and so, one is almost invariably stuck with using the PGs, especially when carrying out a long-drawn, multi-step synthesis of a complex target molecule bearing a large number of functional groups.

On these occasions, sometimes the PG strategy has to be adopted multiple times which eventually leads to drastic compromises with the synthetic efficiency of the scheme and in some cases the situation gets so bad that many synthetic chemists refer to PGs as a necessary evil.

"Like [death](#) and [taxes](#), [protecting groups](#) have become a consecrated obstruction which we cannot elude".

Philip J. Kocienski - Organic Chemist and author of the book "Protecting Groups"

Note that:

1. Every protecting group adds at least one, if not two steps to a synthesis.
2. They only detract from the overall efficiency and beauty of a route, but, without them, there are certainly transformations which we would not be able to do at all.

The Logic of Organic Synthesis: The use of Protecting Groups:

What makes a good PG?

The primary purpose of a PG is to temporarily "block" (or more fancily put, "mask") the other reactive sites when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound.

A proper selection of appropriate PGs therefore plays an important role in planning an organic synthesis. For a protecting group to find wide application in organic synthesis, it must fulfil several criteria. These are listed below:

- i) The PG must be introduced into the molecule to be protected under mild conditions in a selective manner and in high yield; functional groups other than that to be protected must not be attacked,
- ii) Once installed, the PG must be stable under all the conditions used during the synthesis, including those of the purification steps, up to the step in which it is removed. The PG should, as far as possible, have a stabilizing effect on the molecule and should suppress racemization or epimerization.
- iii) The removal of the PG (unmasking, or, deprotection) should be achieved under very mild conditions in a highly selective manner and in high yield; other protecting groups present in the molecule and the unprotected functionalities (if any) should not be affected by the deprotection conditions.

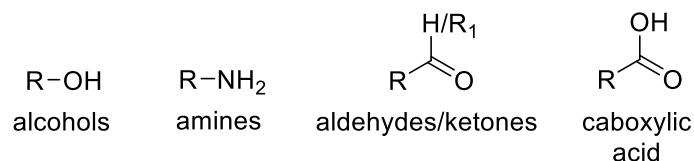
In addition to these minimum requirements, the protecting group should ideally have some additional characteristics:

- iv) It should be introduced and removed with the help of readily available reagents, such that in both transformations the products can be easily purified,
- v) The PG should introduce no additional stereocenters,
- vi) A "perfect" PG should lend the protected intermediates advantageous physical properties; for example, the compounds should be easily crystallized and/or readily soluble.

Only a few protecting groups, however, meet all of these demands, and in most cases a compromise must be found, in which the most important criteria (the first three - easy-to-put-on, stable under reaction condition from which it protects its intended targets, and easy-to-put-off) are addressed.

In most cases guaranteeing that the protecting group is very stable and, at the same time, readily liberated (an apparent contradiction!) is the crucial problem and overshadows the requirements for efficient introduction and the provision of desirable physical and chemical properties.

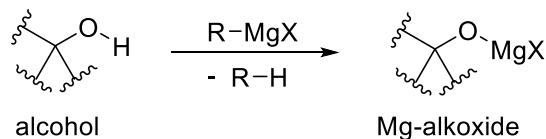
The following is a list of the commonly encountered functional groups in organic synthesis that are reactive to nucleophilic or electrophilic reagents. Selective transformation of these may present challenges that regularly require deactivation by masking with a protecting group. We shall discuss these one by one.



The Logic of Organic Synthesis: The use of Protecting Groups:

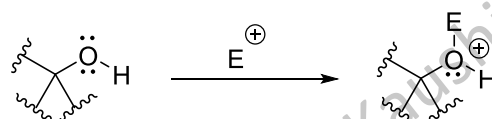
A] Protection of alcohols:

A common requirement in synthesis is that a hydroxy group be masked as a derivative lacking the proton. Examples of this requirement are reactions involving Grignard or other strongly basic organometallic reagents. The acidic proton of a hydroxy group will destroy one equivalent of a strongly basic organometallic reagent.



hydroxyl group acting as a proton source - an acid

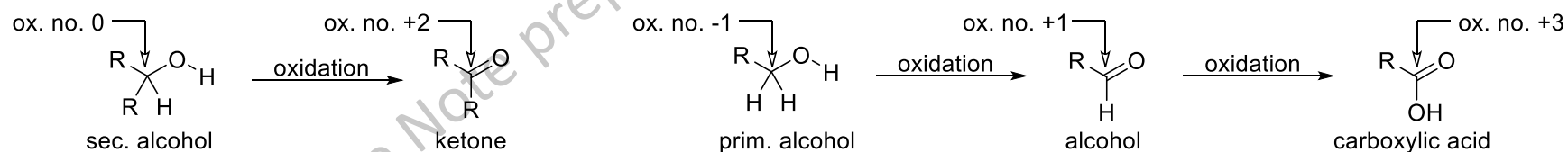
Due to the presence of the lone pair on oxygen in its lowest oxidation state, alcohols also react readily with most electrophiles.



hydroxyl group acting as a nucleophile

If electrophilic reagents are required and reactions at selected hydroxyl sites are to be avoided, this nucleophilic behaviour must be deactivated.

Primary and secondary alcohols are prone to oxidation, so protection on that count often also become necessary.



In some cases, protection of the hydroxy group also improves the solubility of alcohols in nonpolar solvents.

The most important protecting groups for alcohols are ethers and mixed acetals. The proper choice of the protecting group is crucial if chemoselectivity is desired. The reactivity of alcohols follows the order: primary > secondary > tertiary, and it is possible to selectively block a primary alcohol in presence of less reactive and sterically more demanding secondary hydroxyls using a bulky PG.

The stability of ethers and mixed acetals as protecting groups for alcohols varies from the very stable methyl ether to the highly acid-labile trityl ether. However, all ethers are stable to basic reaction conditions. Hence, ether or mixed acetal protecting groups specifically tolerate: i) RMgX and RLi reagents, ii) nucleophilic reducing reagents such as LiAlH₄, and NaBH₄, iii) oxidizing agents such as CrO₃, 2 pyridine, pyridinium chlorochromate (PCC), and MnO₂, iv) Wittig reagents, v) strong bases such as LDA.

The Logic of Organic Synthesis: The use of Protecting Groups:

A] Protection of alcohols:

I] Protection of alcohol as ethers:

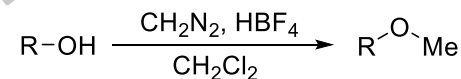
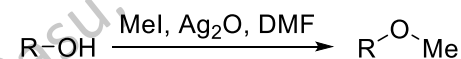
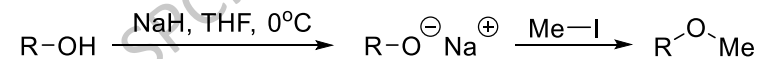
a) Alkyl ethers:

i) Methyl ethers: RO-CH₃:

Protection:

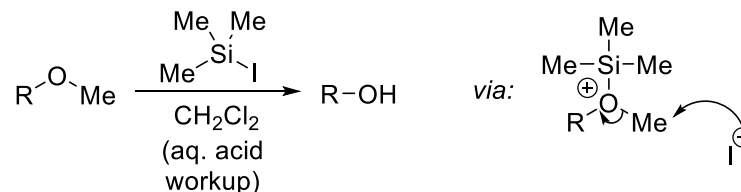
Methyl ethers are readily accessible via the Williamson ether synthesis, but harsh conditions are required to deprotect them. For hindered alcohols, the methylation should be carried out in the presence of KOH/DMSO. Methylation of secondary-OH groups in sugars with methyl iodide and silver oxide is often the method of choice.

A speciality protocol uses diazomethane in presence of fluoroboric acid and avoids the use of any base.



Deprotection:

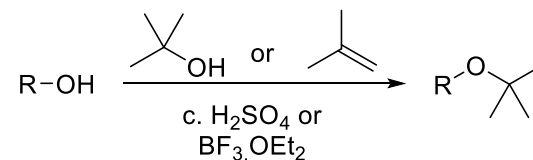
Reagents for cleaving methyl ethers include Me₃SiI (or Me₃SiCl+NaI) in CH₂Cl₂ and BBr₃ (or the solid BBr₃-SMe₂ complex) in CH₂Cl₂. BBr₃ is especially effective for cleaving PhOCH₃.



ii) *tert*-Butyl ethers: ROC(CH₃)₃:

Protection:

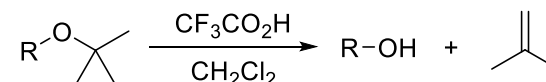
t-Butyl ethers are readily prepared and are stable to nucleophiles, hydrolysis under basic conditions, organometallic reagents, metal hydrides, and mild oxidations. The *t*-butyl group is normally introduced by reaction of the alcohol with isobutylene in the presence of an acid catalyst.



In case of alkene it is an acid-catalysed addition of H-OR across C=C; for *t*-butanol, it is an S_N1

Deprotection:

Owing to the stability of the *t*-butyl cation, *t*-butyl ethers can be cleaved under moderately acidic conditions (S_N1 reaction). Trifluoroacetic acid in an inert solvent is frequently used. Aq. phosphoric acid or 4N HCl is also useful.



The Logic of Organic Synthesis: The use of Protecting Groups:

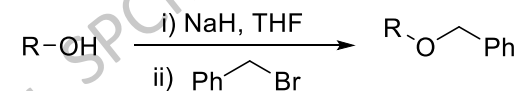
A] Protection of alcohols:

I] Protection of alcohol as ethers:

b) Benzylic ethers, RO-Bn: (Bn = benzyl):

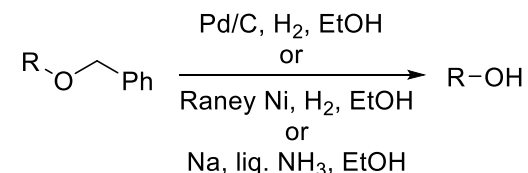
Protection:

Benzyl ethers are made in Williamson's method. They are quite stable under both acidic and basic conditions and toward a wide variety of oxidizing and reducing reagents. Hence, they are frequently used in organic syntheses as protecting groups. It should be noted, however, that *n*-BuLi may deprotonate a benzylic hydrogen, especially in the presence of TMEDA (tetramethylethylenediamine) or HMPA (hexamethylphosphoramide).



Deprotection:

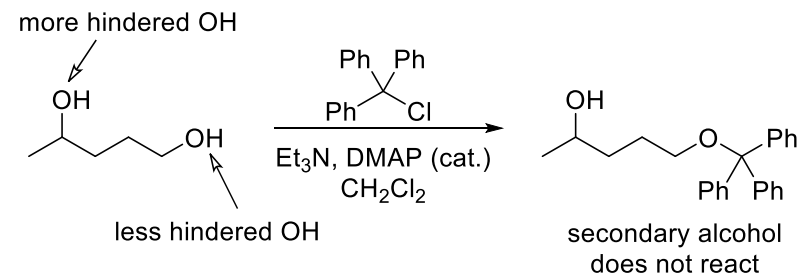
Catalytic hydrogenolysis offers the mildest method for deprotecting benzyl ethers. The benzyl C-O bond is also cleaved by electron-transfer reduction using sodium in liquid ammonia:



c) Trityl (/triphenylmethyl) ethers (RO-CPh₃ / RO-Tr):

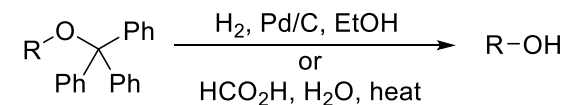
Protection:

Trityl ethers have played an important role in the selective protection and manipulation of -CH₂OH groups in carbohydrate chemistry. This group is introduced by reaction of the alcohol with triphenylmethyl chloride via an S_N1 substitution. Owing to their steric bulk, triarylmethyl groups are usually introduced only at primary hydroxy groups. For the same reason, the trityl group prevents the approach of anything but the smallest electrophiles such as H⁺ and deactivating the nucleophilic nature of the oxygen almost completely.



Deprotection:

Trityl ethers are stable to bases and nucleophiles but are **readily cleaved by hot aqueous acids or by hydrogenolysis**:



With formic acid, the cleavage happens in S_N1 fashion.

Deprotection by catalytic hydrogenation involves free radical intermediates.

The Logic of Organic Synthesis: The use of Protecting Groups:

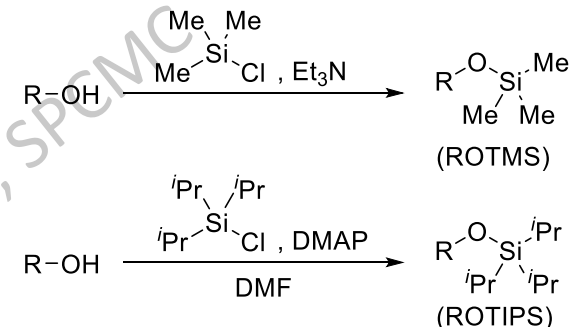
A] Protection of alcohols:

l] Protection of alcohol as ethers:

d) Silyl ethers:

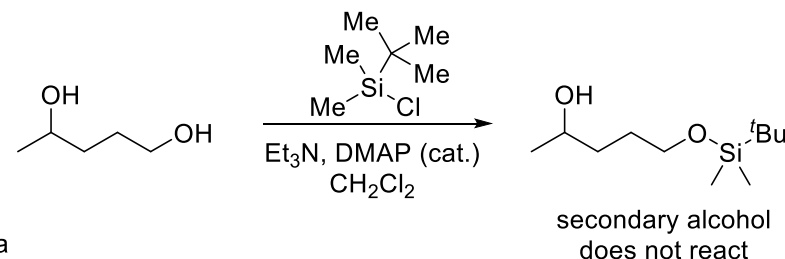
Protection:

The popularity of silicon protecting groups stems from the fact that they are readily introduced and removed under mild conditions. Moreover, a wide variety of silylating agents are available for tailor-made protection of ROH groups. In addition, silicon-based PGs reduce the effective nucleophilicity of the oxygen atom both sterically and electronically. The reaction of an alcohol (ROH) with a trialkylsilyl chloride (R_3SiCl such as trimethylsilyl chloride, TMSCl) and base makes the protected silyl ether (with TMSCl we get ROTMS). Bases generally employed for the preparation of silyl ethers include R_3N , imidazole, DMAP, and DBU. Variation of the alkyl groups on the silicon (e.g., triisopropylsilyl TIPS, or *t*-butyldimethylsilyl TBDMS/TBS) increases the silyl ether's stability, especially toward acidic conditions, and also allows for selective protection of the less hindered alcohols.



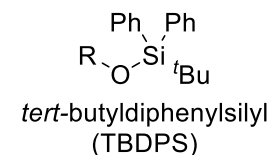
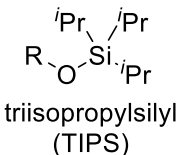
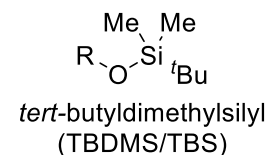
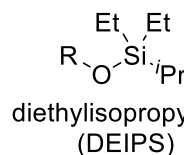
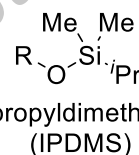
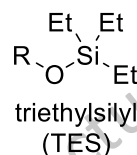
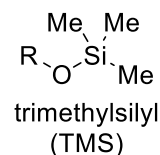
The *t*-butyldimethylsilyl group is the most widely used of the silicon protecting groups.

The rate of silylation of alcohols with TBSCl follows the trend: *prim.* > *sec.* > *tert.*. The large difference in rate of silylation between primary and secondary OH groups makes the TBSCl reagent well suited for the selective protection of the $-CH_2OH$ group in carbohydrate chemistry. For protecting a primary OH group in the presence of a secondary OH group, one should use TBSCl and Et_3N with DMAP as a catalyst.



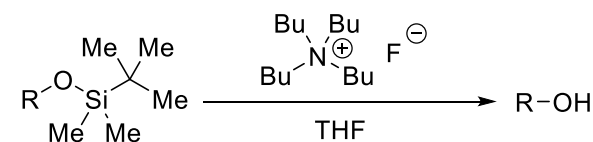
Triisopropylsilyl chloride (TIPSCl) is another excellent reagent for the selective protection of a primary OH in the presence of a secondary OH.

Commonly used silyl ether PGs:



Deprotection:

Depending on the structure of silyl ethers, they can be deprotected by water, aqueous acids, and fluoride salts. Since silicon has a strong affinity for fluoride ion (bond energy, kcal/mol: Si-F, 143; Si-O, 111), the O-SiR₃ bond is especially prone to cleavage by fluoride salts, such as **tetrabutylammonium fluoride ($n-Bu_4N^+F^-$, TBAF)** which is soluble in organic solvents such as THF and CH_2Cl_2 .



The Logic of Organic Synthesis: The use of Protecting Groups:

A] Protection of alcohols:

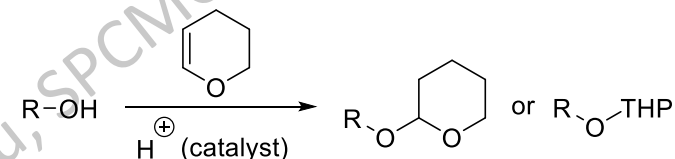
II] Protection of alcohol as acetals:

a) Tetrahydropyanyl ethers: RO-THP:

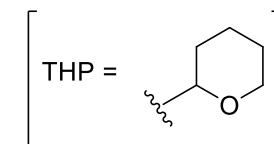
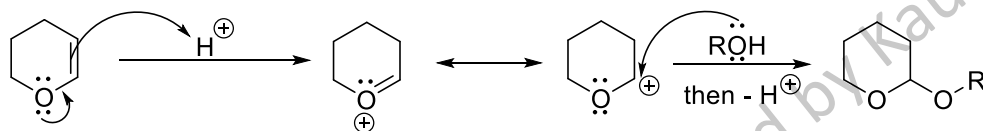
[note the name *ether*, but the functional group is actually an acetal]

Protection:

The THP group is a widely used protecting group; it is readily introduced by reaction of the enol ether dihydropyran with an alcohol in the presence of an acid catalyst, such as TsOH, $\text{BF}_3 \cdot \text{OEt}_2$, or POCl_3 . For sensitive alcohols such as allylic alcohols, PPTS (pyridinium *p*-toluenesulfonate) is used as a catalyst for THP derivative formation:

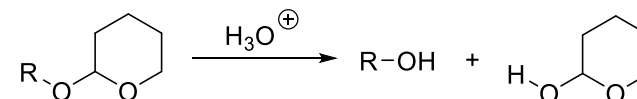


The installation of the THP moiety is an example of acid-catalysed, regioselective addition of alcohol across the C=C of the enol ether. The protonation is guided by the formation of the resonance-stabilized oxocarbenium ion:



Deprotection:

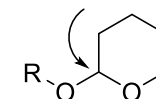
As an acetal, the THP group is readily hydrolyzed under aqueous acidic conditions with AcOH-THF, TsOH, PPTS-EtOH, or Dowex-H (cation exchange resin).



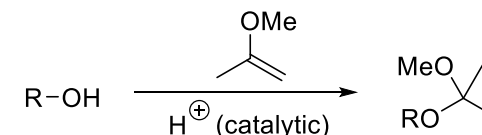
The mechanism is the acid-catalysed hydrolysis of acetals, try it out. Recall in this regard that acetals are acid-labile but base stable.

A disadvantage of the THP group is the fact that a new stereogenic center is produced at C-2 of the tetrahydropyran ring. This presents no difficulties if the alcohol is achiral, since a racemic mixture results. However, if the alcohol is chiral, the reaction gives a mixture of diastereomers, which may complicate purification and/or characterization.

new chiral centre



One way of avoiding this problem is to use methyl 2-propenyl ether in place of dihydropyran (abbreviated MOP, for methoxypropyl). No new chiral center is introduced, and this acetal offers the further advantage of being hydrolyzed under somewhat milder conditions than those required for THP ethers:



The Logic of Organic Synthesis: The use of Protecting Groups:

A] Protection of alcohols:

II] Protection of alcohol as acetals:

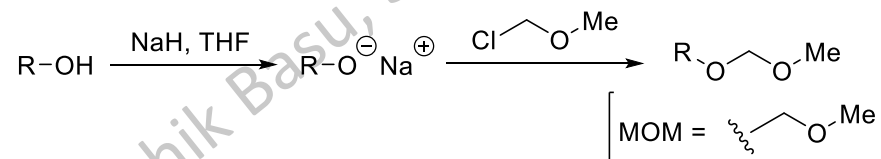
b) Methoxymethyl ethers: RO-MOM:

[note the name *ether*, but the functional group is actually an acetal]

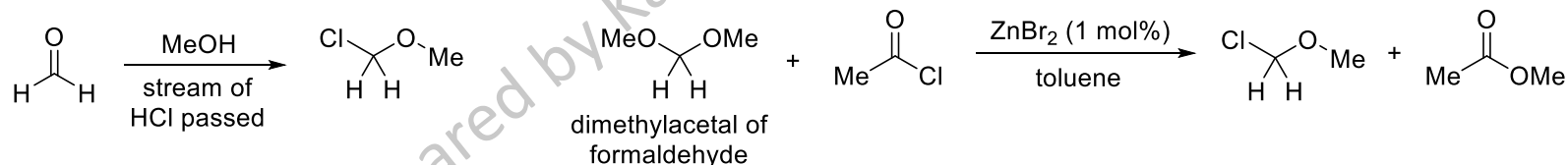
Protection:

α -halo ethers are often used for the protection of alcohols. The high reactivity of α -halo ethers in nucleophilic displacement reactions by alkoxides permits the protection of alcohols under mild conditions. Moreover, as acetals the alkoxy-substituted methyl ethers are cleaved with a variety of reagents.

The reaction of chloromethyl methyl ether (methoxymethyl chloride, MeOCH_2Cl , MOM-Cl, a carcinogen) with an alkoxide or with an alcohol in the presence of *i*- Pr_2NEt (Hünig's base) furnishes the corresponding formaldehyde acetal. Alkylation of *tert*-alcohols requires the more reactive MOM-I, derived *in situ* from MOM-Cl and NaI in the presence of *i*- Pr_2NEt .

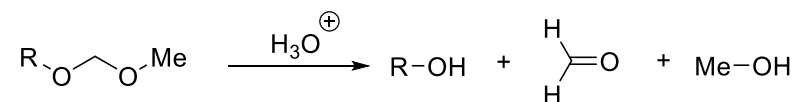


Preparation of MOM-Cl:



Deprotection:

Cleavage of the MOM group with dilute acids or with **PPTS** in *t*- BuOH regenerates the alcohol.

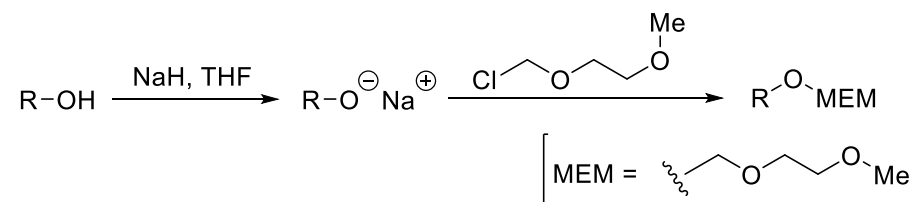


c) 2-Methoxyethoxymethyl ethers: RO-MEM:

[note the name *ether*, but the functional group is actually an acetal]

Protection:

MEM ethers are excellent protecting groups for *prim.*, *sec.* and *tert.* alcohols and even *tert.* allylic alcohols. They are stable toward strong bases, organometallic reagents, and many oxidizing agents and are more stable to acidic conditions than THP ethers. They are installed by reacting the corresponding alkoxide with 2-methoxyethoxymethyl chloride ($\text{MeOCH}_2\text{CH}_2\text{OCH}_2\text{Cl}$):



The Logic of Organic Synthesis: The use of Protecting Groups:

A] Protection of alcohols:

II] Protection of alcohol as acetals:

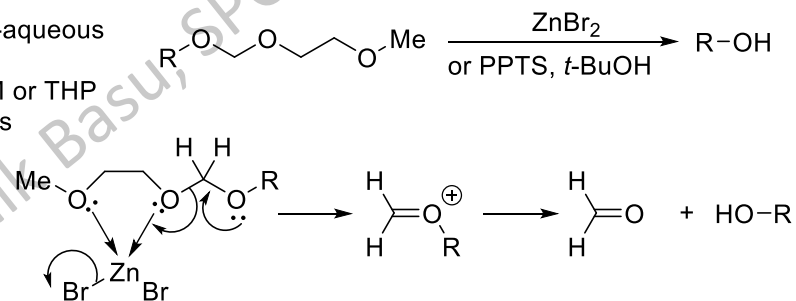
c) 2-Methoxyethoxymethyl ethers: RO-MEM (contd.):

[note the name *ether*, but the functional group is actually an acetal]

Deprotection:

An attractive feature of the MEM group is the ease with which it can be removed under non-aqueous conditions. Reagents such as zinc bromide, magnesium bromide, titanium tetrachloride, or trimethylsilyl iodide permit its removal. The MEM group is cleaved in preference to the MOM or THP groups under these conditions. Conversely, the MEM group is more stable to acidic aqueous hydrolysis than the THP group. MEM group can also be removed by PPTS in *t*-BuOH:

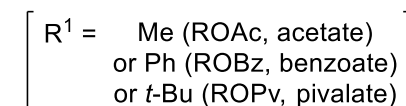
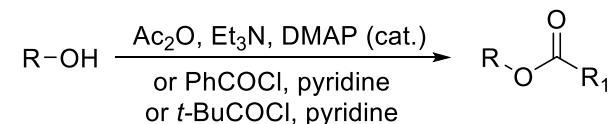
The cleavage induced by the Lewis acid such as ZnBr_2 is believed to proceed via an NGP mechanism:



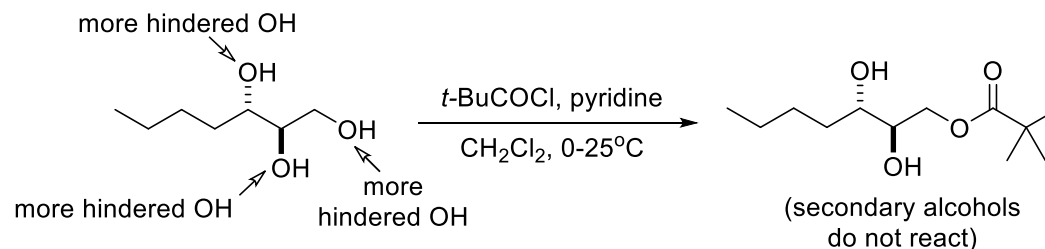
III] Protection of alcohol as esters: RO-COR¹:

Protection:

The use of carboxylic acid esters as protective groups for alcohols is limited since they may undergo acyl substitution, hydrolysis or reduction. However, esterification sometimes offers advantages over use of acetal or ether groups because esters are generally stable under acidic conditions (while acetals and most ethers are not), and they are especially useful in protection during oxidations. **Acetates, benzoates, and pivalates**, which are the most commonly used derivatives, can be conveniently prepared by reaction of unhindered alcohols with acetic anhydride, benzoyl chloride, or pivaloyl chloride, respectively, in the presence of pyridine or other tertiary amines. 4-Dimethylaminopyridine (DMAP) is often used as a catalyst.



A simple, convenient method for the selective acylation of a primary OH in the presence of a secondary OH group is its conversion into the *t*-butanoyl (i.e. pivalate) ester.



The Logic of Organic Synthesis: The use of Protecting Groups:

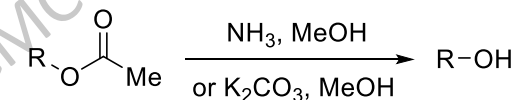
A] Protection of alcohols:

III] Protection of alcohol as esters: RO-COR¹ (contd.):

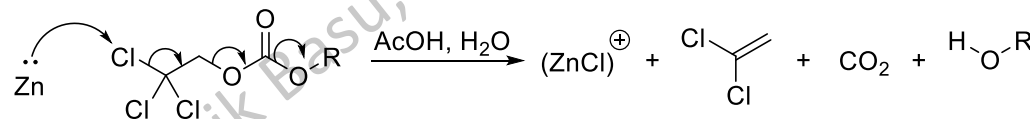
Deprotection:

Esters can be removed easily with **hydrolysis or alcoholysis in basic medium**. Relative reactivities of different esters toward hydrolysis and nucleophilic reagents follows the order RCOOMe > RCOOPh > RCOO*t*-Bu.

The steric bulk of the *t*-butyl group makes the pivalate esters resistant to nucleophilic attack, including hydrolysis under mild basic conditions. These are therefore cleaved using harsher conditions or by using metal hydride reagents.

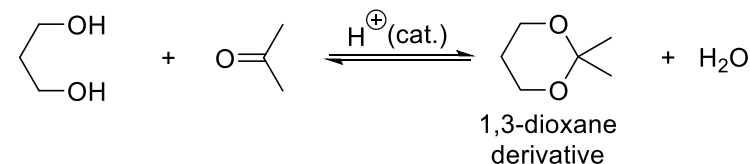
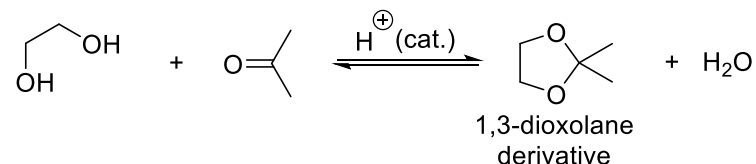


When basic hydrolysis is inappropriate, special acyl groups are required. 2,2,2-Trichloroethyl carbonate (Troc) esters, for example, can be reductively removed with zinc:



IV] Protection of diol as acetals:

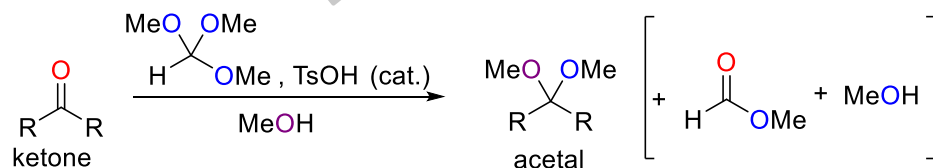
Acetalization of 1,2- and 1,3-diols plays an important role in manipulating the reactivity of cyclic and acyclic polyhydroxy compounds. Acetals derived from 1,2- and 1,3-diols are readily accessible via their reactions with ketones or aldehydes in the presence of an acid catalyst. Once they are formed, acetals are very stable to basic conditions but are labile toward acids. So deprotection requires just acid hydrolysis. Acetal formation allows the selective blocking of pairs of HO groups in polyhydroxy compounds. Five- and six-membered rings are formed preferentially.



The equilibrium of diol acetalization is shifted to the acetal side by removing the H₂O.

This may be accomplished by either -

- azeotropic distillation (via a Dean-Stark or Merlic trap),
- addition of molecular sieves, anhydrous CuSO₄, or Drierite, or
- transacetalization: acetal exchange with acetals, orthoesters, or enol ethers, where formation of water is either entirely avoided, or the water produced is utilised in a secondary reaction:



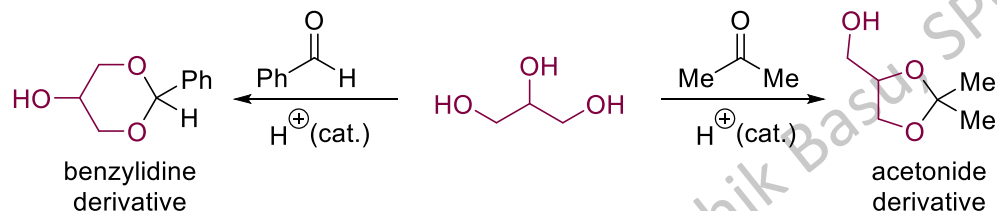
water produced is used to generate methyl formate and methanol for the orthoformate (try the mechanism of the whole reaction!)

The Logic of Organic Synthesis: The use of Protecting Groups:

A] Protection of alcohols:

IV] Protection of diol as acetals (contd.):

The selective protection of 1,2 and 1,3-diols in sugars has been developed using cyclic acetals based on acetone derivatives (isopropylidines or acetonides) and benzaldehyde derivatives (benzylidene). There is an interesting contrast between these two PGs in the protection of the triol glycerol which forms a 1,3-benzylidene derivative with benzaldehyde and a 1,2-acetonide with acetone.

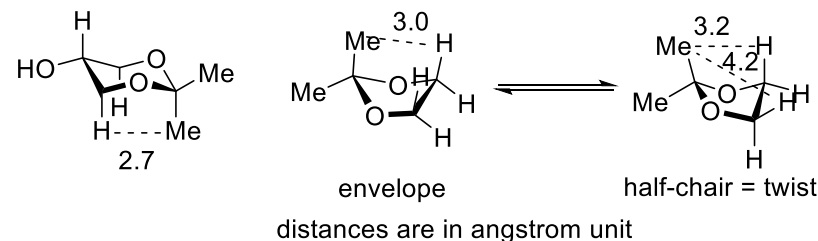


This selectivity is guided by the destabilisation of the six-membered ring system that can be constructed with acetone where a methyl group must be placed at the sterically demanding axial position:

The 1,3-diaxial interaction destabilises this cyclic ketone acetal although the dioxane (six-membered) ring is inherently more stable than a comparable dioxolane (five-membered) ring.

With benzaldehyde, the destabilising effect can be avoided by placing the bulkier phenyl group at the relatively free equatorial position:

In a five-membered dioxolane ring system the axial and equatorial sites are less clearly defined and, on average, substituents on the acetal carbon are further away and therefore less able to interact unfavourably with other atoms around the ring.



So, with benzaldehyde we get a six-membered cyclic acetal involving the hydroxyl groups that are 1,3 to each other, but with acetone only a five-membered cyclic acetal is formed using the vicinal (i.e. 1,2) hydroxyl groups.

The Logic of Organic Synthesis: The use of Protecting Groups:

A] Protection of alcohols:

IV] Protection of diol as acetals (contd.):

We have seen that with benzaldehyde we get a six-membered cyclic acetal involving the hydroxyl groups that are 1,3 to each other, but with acetone only a five-membered cyclic acetal is formed using the vicinal (i.e. 1,2) hydroxyl groups.

This allows for the following selective oxidations:

