Protecting groups in organic synthesis

Protecting groups for amino, hydroxyl, thiol, carboxyl and carbonyl groups

The use of protecting groups is of great importance in synthetic organic chemistry, when we want reactions to take place at only a particular functional group when other reactive groups are also present. This concept can be easily illustrated by considering the synthesis of a desired dipeptide molecule from the starting aminoacid molecules (the concept can be extended to polypeptide synthesis). Let the dipeptide to be synthesized be

H_2N-**A**-CO-NH-**B**-COOH (or abbreviated as **AB**)

starting from

H_2N-**A**-COOH (abbreviated as **A**) and NH_2-**B**-COOH (abbreviated as **B**)

If one mixes together **A** and **B** and allow them to react, one can easily see that many other products such as **BA**, **AA**, **BB**, **AAA**, **BBB**, **ABA**, **BAB**, **AAB …** will all be produced and the reaction will be a total loss. On the other hand, if we block the amino group of **A** and the acid group of **B**,

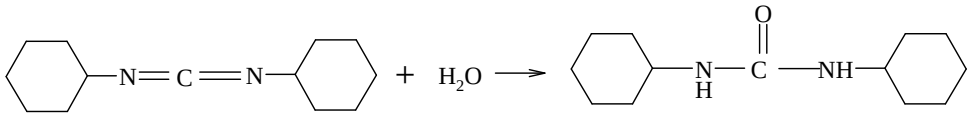
P_1-HN-**A**-COOH and NH_2-**B**-COO-P_2

Then only the acid group of **A** and the amino group of **B** are free to react, giving only the desired product **AB**. The protecting groups are removed after reaction.

Desirable properties of a protecting group:

(1) Must react easily with the functional group to be protected under mild conditions.
(2) Must be stable to the reaction conditions after protection.
(3) Must be easily removable when required without affecting other parts of the molecule.

In peptide synthesis, after introducing the protecting groups, the amide (or peptide) linkages are produced by reacting in presence of a **coupling agent** such as **N,N-dicyclohexyl carbodiimide** (or **DCC**). The water molecule produced by the condensation of the amino and carboxylic acid group is absorbed by DCC, which is converted to a urea derivative that can be easily removed, for example by chromatography.



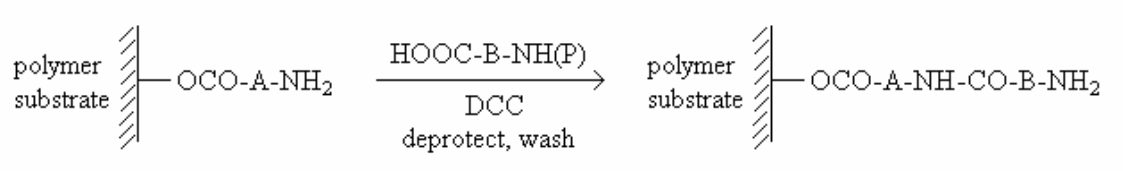
DCC DCC.H_2O

P_1-HN-**A**-COOH + NH_2-**B**-COO-P_2 + DCC → P_1-HN-**A**-CO-NH-**B**-COO-P_2 + DCC.H_2O

↓ deprotect

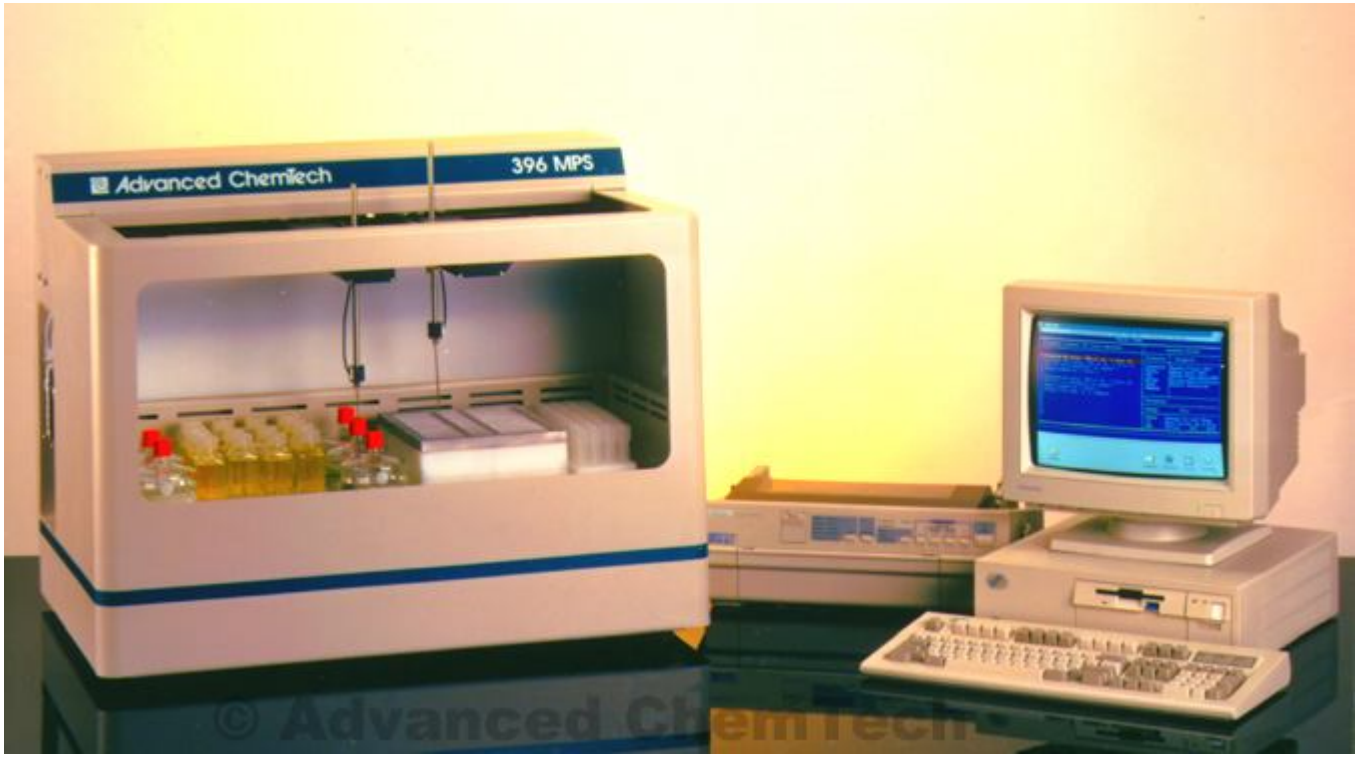
H_2N-**A**-CO-NH-**B**-COOH

All these reactions are usually carried out in solution (known as **solution-phase polypeptide synthesis**) and isolation / purification steps are necessary after each condensation step. This process is thus very laborious. Professor Merrifield (Nobel Prize 1984) introduced a new easier method for peptide synthesis, in which the first aminoacid molecule is attached to a solid resin at the COOH group (NH_2 group is free). The resin is then treated successively with the required sequence of amino-protected aminoacid solutions in presence of DCC. After each treatment, the resin is simply *washed* free of the excess reagents and the protecting group at the end is removed. The peptide chain thus "grows" as a branch from the solid polymer substrate. The protecting group usually employed is FMOC.



This method is commonly known as the **Merrifield synthesis** or **solid-phase peptide synthesis** (**SPPS**), and automated machines that can be programmed to produce the required peptide when supplied with the aminoacid solutions are now available (see picture on next page).

There are many reagents for protecting the amino group as the carbamate (carbamic acid is H_2N-COOH), such as the **benzyloxycarbonyl** group (abbreviated as **Cbz** or simply **Z**), the **t-butoxycarbonyl** group (abbreviated as **Boc**) and the **9-fluorenylmethoxycarbonyl** group (abbreviated as **Fmoc**). All these are stable in acid medium, but can be easily removed by hydrogenolysis or weakly basic medium.

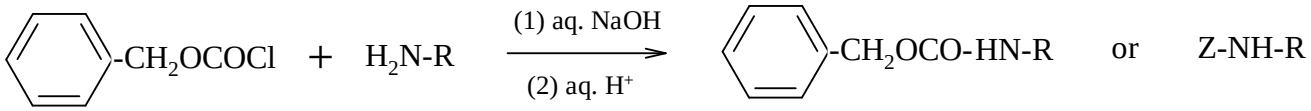


The Advanced ChemTech (ACT) model 396MPS automatic peptide synthesizer.

1. **Benzyloxycarbonyl** group (abbreviated as **Cbz** [old name carbobenzyloxy] or simply **Z**):

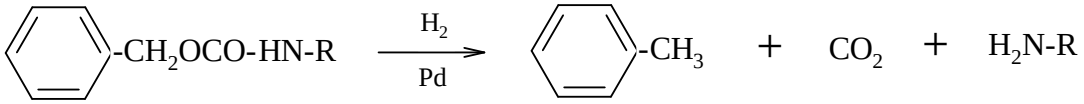
The reagent used is benzyloxycarbonyl chloride.

Protection:

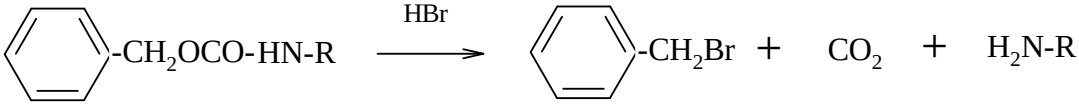


benzyloxycarbonyl chloride

Deprotection:



or

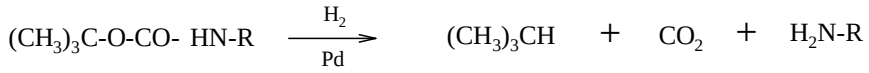


2. **t-butoxycarbonyl** group (**BOC**): The reagent used is tertiary butoxy carbonyl azide.

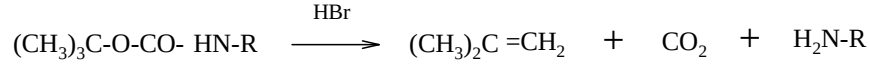
Protection:

t-butoxycarbonyl azide

Deprotection:

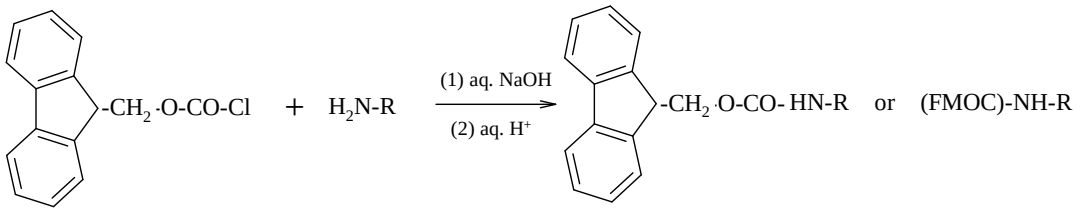


or



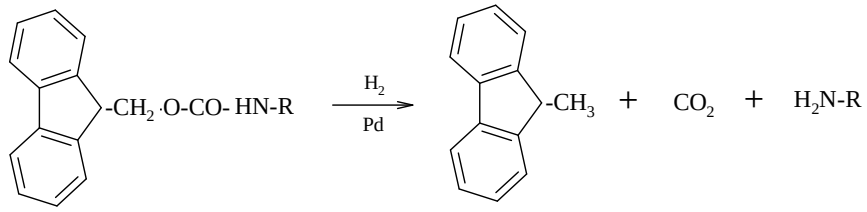
3. **9-fluorenylmethoxycarbonyl** group (**FMOC**):

Protection:



9-fluorenyl methoxycarbonyl chloride

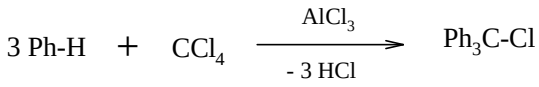
Deprotection:

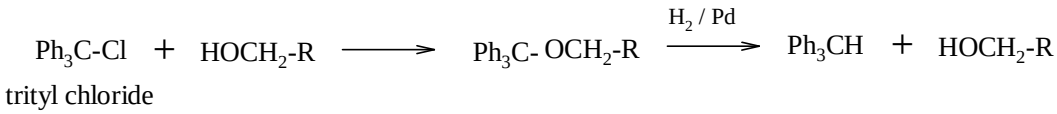


FMOC protecting group can also be easily removed by treating with several amines such as piperidine through a β-elimination.

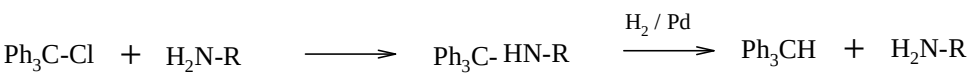
4. **Triphenylmethyl** group (**trityl** group):

The triphenylmethyl group is a good protecting group for alcohols and amines, and can be easily removed by hydrogenolysis or mild acid hydrolysis. It is selective for primary alcohols in presence of secondary and tertiary alcoholic groups, and has been utilized in the synthesis of adenosine triphosphate.





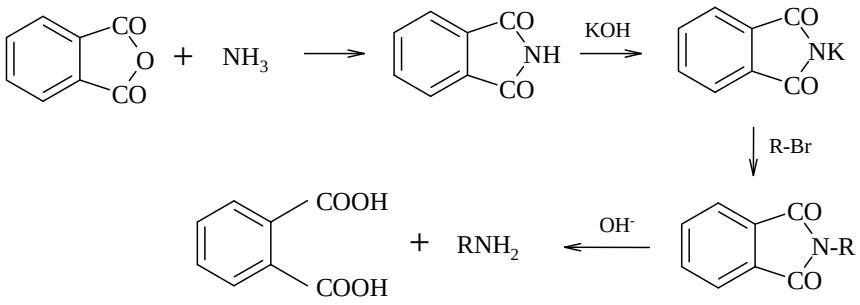
trityl chloride



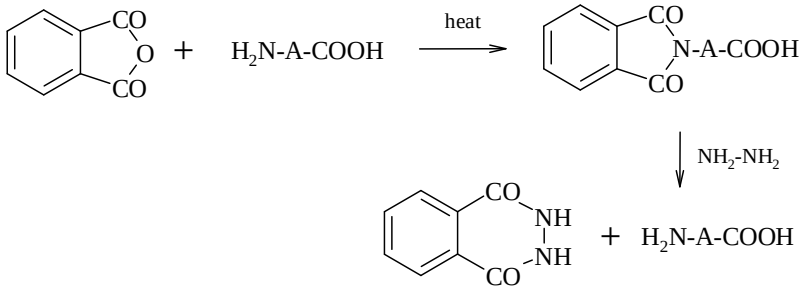
Triphenylmethyl chloride can be prepared from benzene and carbon tetrachloride through Friedel-Craft's reaction.

5. **Phthalic anhydride**:

Phthalimide has been used extensively in the Gabriel synthesis of amino acids for generating amino groups.

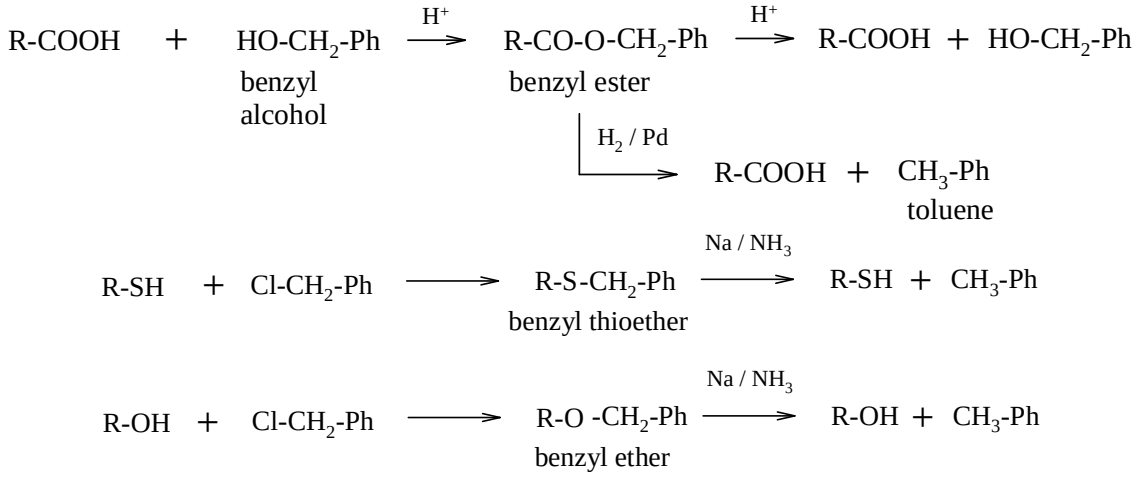


The phthaloyl group can also act as a protecting group for the amino group if it can be introduced and removed under milder conditions in which the peptide linkage is not affected. The phthaloyl group can be introduced by heating the aminoacid with phthalic anhydride, and can be removed under mild conditions by treating with hydrazine as shown in the following sequence of reactions:



6. The **benzyl** group:

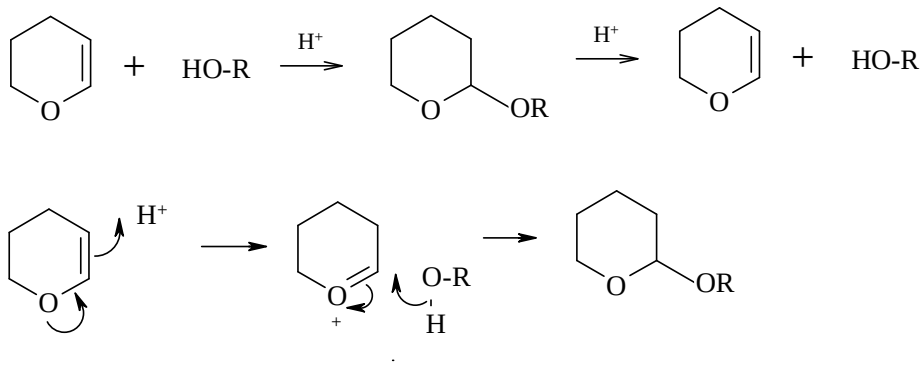
The benzyl group can be used to protect –COOH, -OH and –SH groups. The reagent used is usually benzyl chloride.



Deprotection of the acid ester is achieved by acid hydrolysis or catalytic hydrogenation. The thioether and ether are converted back to thiol and alcohol by reduction with metallic sodium in liquid ammonia.

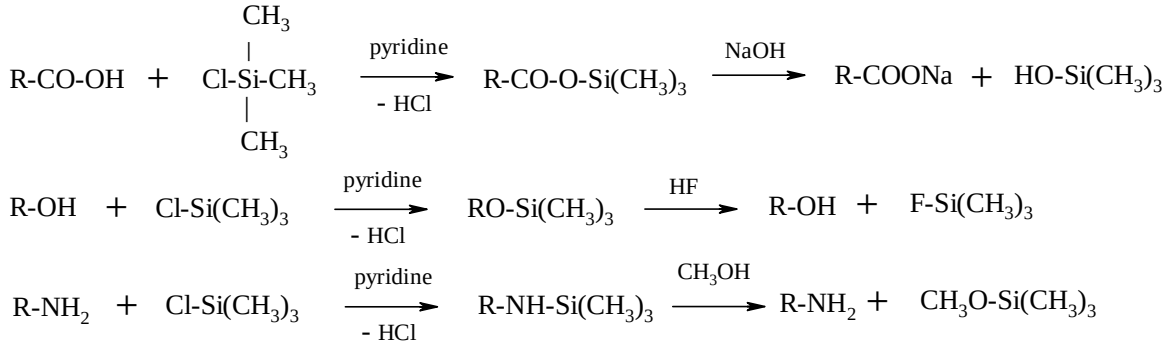
7. The **tetrahydropyranyl** group:

This is a protecting group for alcohols. The reagent used is dihydropyran, which forms an acetal with alcohols in anhydrous acid medium. The group can be removed using aqueous mineral acid.

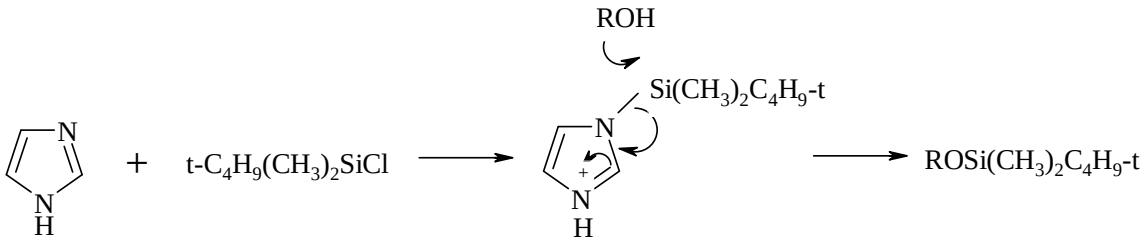


8. The **trialkyl silyl** group:

The trimethylsilyl group is a good protecting group for amino, hydroxyl and carboxylic acid groups. The derivatives are easily made by the reaction of the carboxylic acid, alcohol or amine with chlorotrimethylsilane (same as trimethylsilyl chloride) in the presence of a tertiary amine base like pyridine.

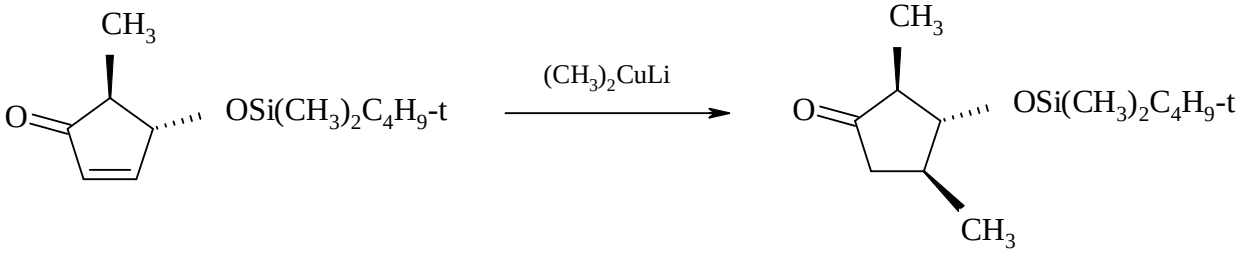


In general the trimethylsilyl ethers of alcohols are very susceptible to solvolysis in protic media and cannot endure the reaction conditions of a multi-step synthesis. t-butyldimethylsilyl ethers give better results, and can be prepared by the reaction of alcohols with t-butylchlorodimethylsilane in presence of imidazole.



These derivatives are not affected by conditions of synthetic transformations and more resistant to hydrolysis than trimethylsilyl ethers. They can be reconverted in to the alcohol by treatment with HF (cleavage of a Si-O bond by nucleophylic attack by fluoride ion and formation of an even stronger Si-F bond).

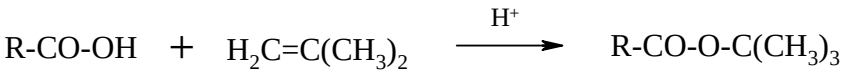
Another advantage of t-butyldimethylsilyl ethers is that the bulky protecting group can sometimes be used to control the stereochemistry of a reaction at a nearby functional group. For example,



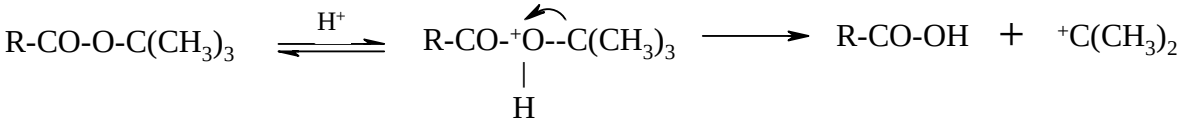
The attack of lithium dimethylcuprate on the cyclopentanone is directed entirely to the top face of the molecule.

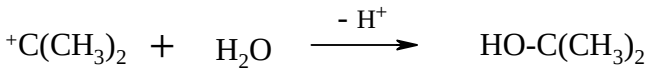
9. The **t-butyl** group:

The carboxylic acid group is normally protected by converting into the t-butyl ester using isobutylene (same as 2-methyl propene) in presence of sulphuric acid.



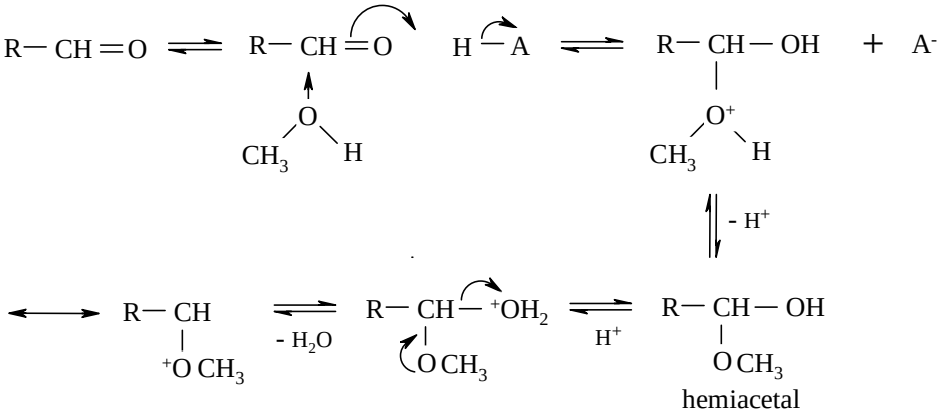
The protecting group may be removed by mild acid hydrolysis through the readily-formed carbonium ion.

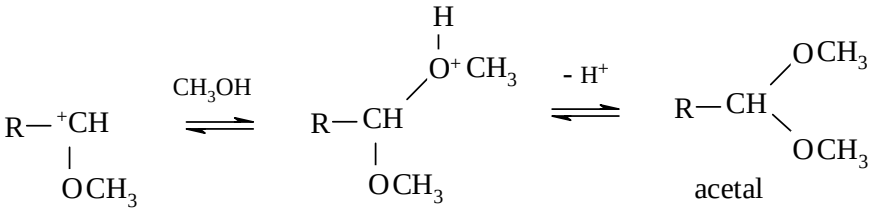




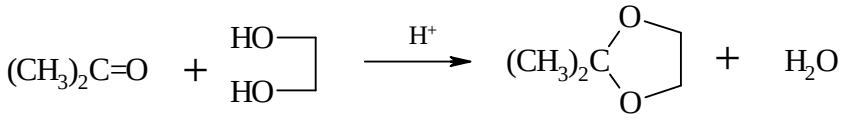
10. **Acetals** and **thioacetals**:

Aldhydes react with primary alcohols in *anhydrous* acid medium to give acetals which can be isolated. Since all steps in the reaction are reversible, *aqueous* acid hydrolyses the acetal, reverting it back to the aldehyde and alcohol. Therefore the formation of acetals can be used as protecting groups for both the carbonyl group as well as alcohols.





Ketones do not give acetals with monohydric alcohols, but react with glycols (or 1,2-diols) to give cyclic ketals. Thus ketones can form protecting groups for 1,2-diols.



Both aldehydes and ketones give the thio-acetals and thio-ketals when treated with mercaptans in presence of acid. Therefore both can act a protecting groups for –SH groups.