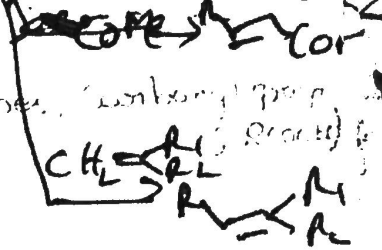


PART-A

A PROTECTING GROUPS: (R-OH, 1,2-diols, Amines, Carbonyl group)



* Protection of Carboxylic acids :-

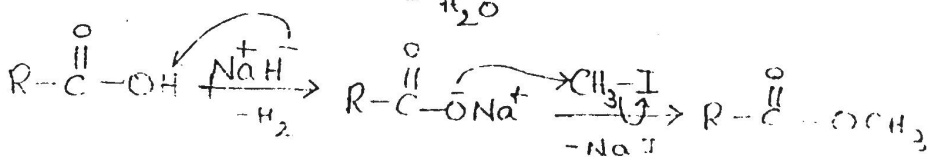
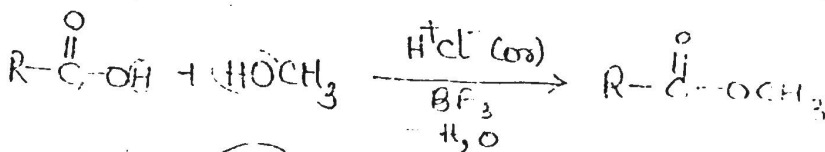
Carboxylic acids can be protected by converting them into esters (or) amides, out of which esters are preferred as the latter method is better as it can be easily cleaved to regenerate free carboxylic acids.

(A)

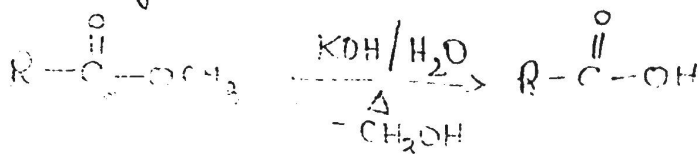
Ex:1 Protection as methyl ester :-

Carboxylic acids are protected as methyl esters by treating them with methanol (or) with sodium hydride (NaH) & methyl iodide (CH₃I).

The formed esters are easily cleaved into carboxylic acids by basic hydrolysis.

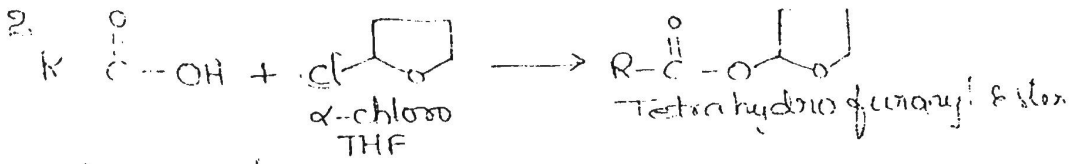


Cleavage :-

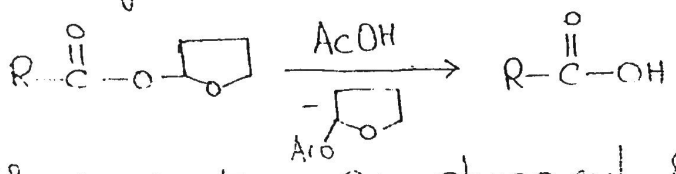


Ex:2 Protection as tetrahydropyridine

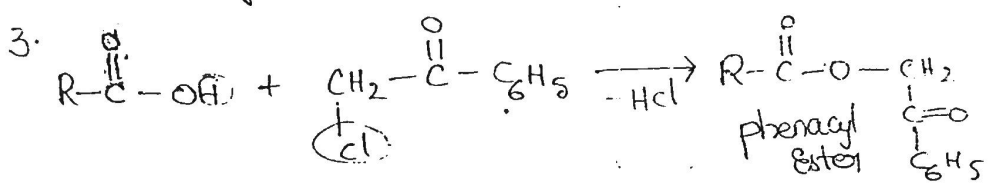
Carboxylic acids can be protected as tetrahydropyridine by reacting with ethylamine. The tetrahydropyridine formed is more stable than the corresponding amide. It can be easily cleaved to regenerate the free carboxylic acid.



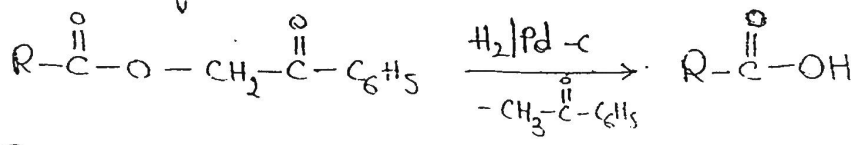
cleavage:-



Ex:3 protection as phenacyl ester
 Carboxylic Acids on reaction with α-halo Acetophenone forms phenacyl ester, which can be cleaved by hydrogenation in palladium catalyst.

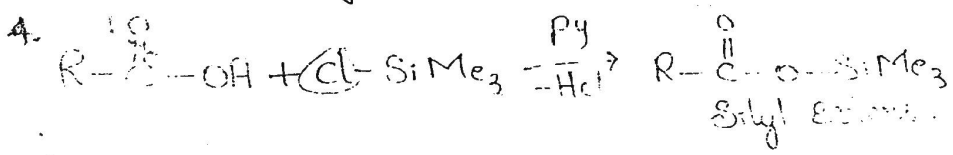


cleavage:-

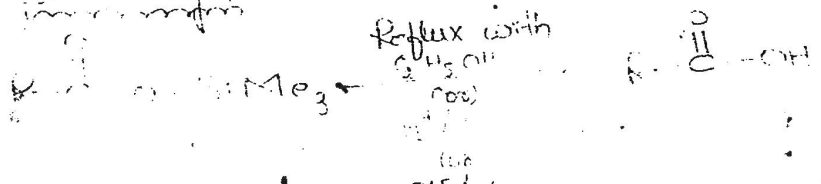


Ex:4:- protection as Silyl Ester:-

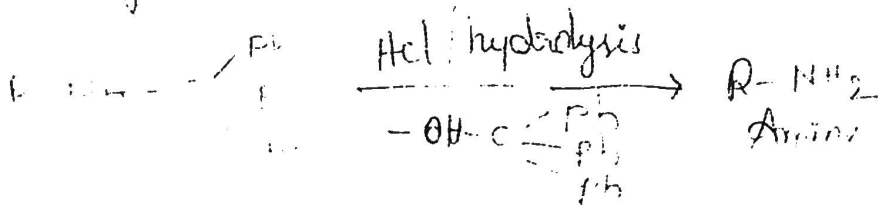
Carboxylic Acids on reaction with Trimethyl silyl chloride in presence of pyridine forms silyl esters. These, silyl esters can be cleaved by refluxing in alcohols (or) by acidic (or) basic hydrolysis.



cleavage:-



N-Tertiary metal amine is cleaved by acid
 catalyzed by catalytic hydrogenolysis.
 cleavage

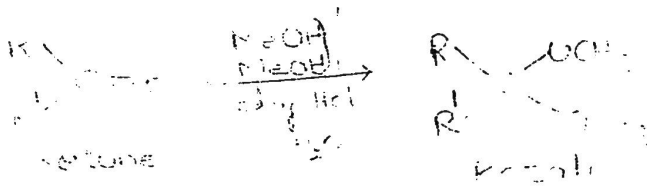
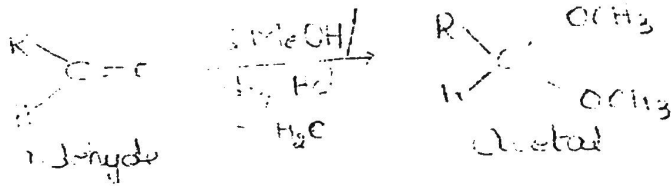


* Protection of Carbonyl Groups:-

During synthetic sequence a carbonyl group may have to be protected against attack by various reagents such as nucleophiles, organometallic compounds, acidic, basic, oxidising and reducing agents.

Protection of Carbonyl groups as Acetals & Ketals

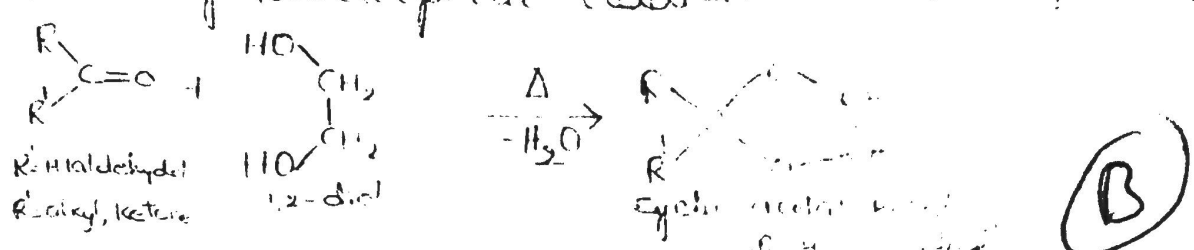
Aldehydes can be protected by reaction with methanol and Dry HCl as acetals
 Ketones on same procedure can be protected as ketals



Acetals & ketals are hydrolysed
 back to aldehydes & ketones by acid

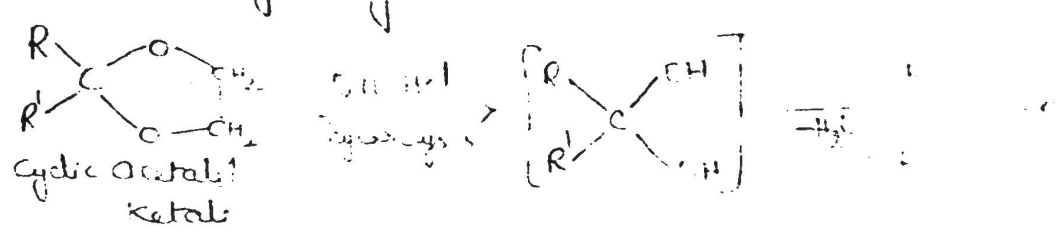


2. protection of carbonyl group as cyclic acetal
 Cyclic acetals (or) ketals are formed by treating carbonyl compounds with 1,2-diol. Cyclic acetals and ketals are used for preventing nucleophilic addition on carbonyl group.



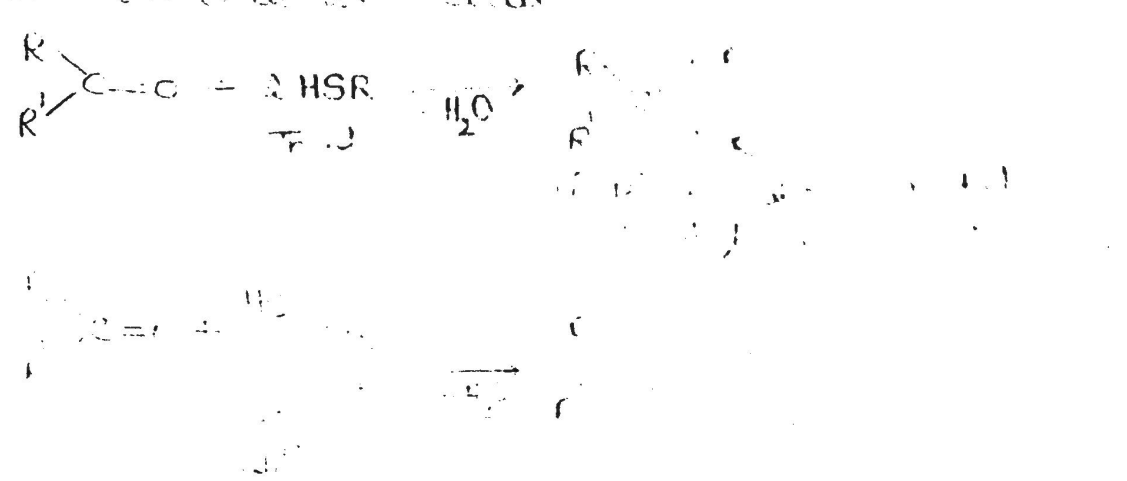
(B)

Cyclic acetals / Ketals are formed by acidic hydrolysis.

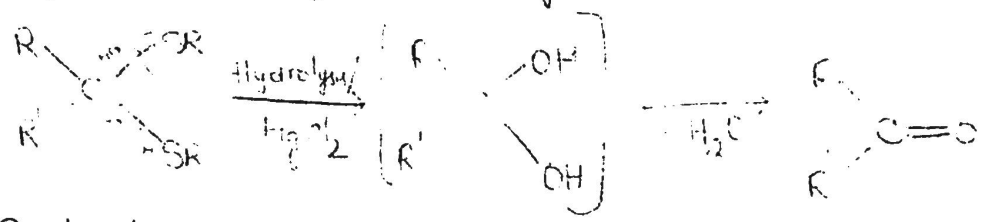


3. protection of carbonyl as the acetal / ketal
 Carbonyl group can be protected as acetal derivatives.

Reaction of carbonyl compounds in presence of acid catalyst with thiol (or) alcohol gives addition stable acetal (ketal).



Alkyl Halides are converted by hydrolysis in presence of mercury salts



* Protection of alcohols:-

The lone pair of electrons on the hydroxyl oxygen of alcohols impart nucleophilicity to them. Therefore, alcohols react readily with oxidising agents to give carbonyl compounds and react with other electrophiles like alkyl halides to give ethers.

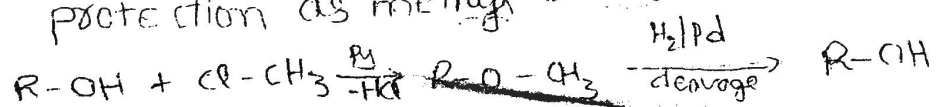
Replacement of OH proton with relatively inert group protects the OH group to react with various groups.

Hydroxyl group may be protected as ethers, silyl ethers, as acetals and as esters.

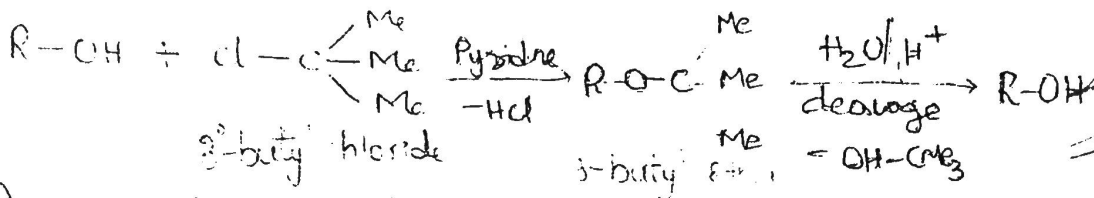
1. Ethers as protecting groups for alcohols:-

Alcohol are converted into ethers by nucleophilic attack on alkyl halides. Ethers are stable to basic & acidic conditions, they don't react with oxidising or reducing agent and do not react to organic metallic compounds. Ethers are removed from by hydrolysis to give alcohols.

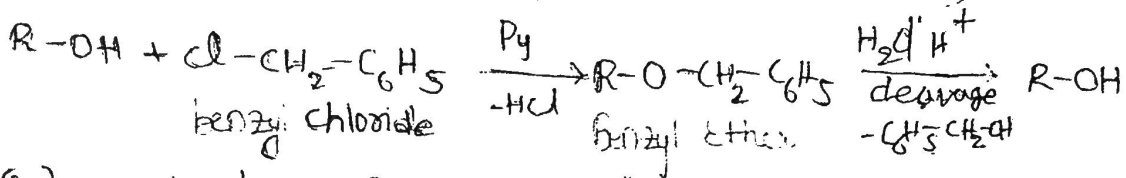
Protection as methyl ethers:-



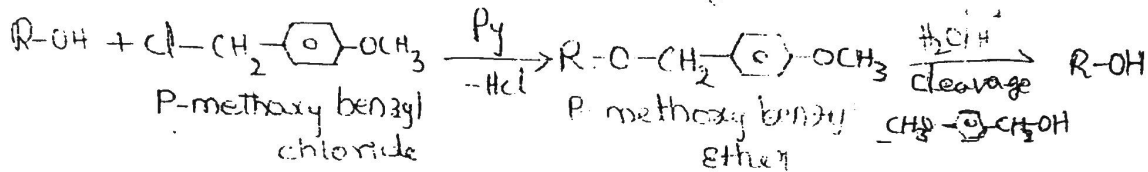
(ii) protection as 3°-butyl ether:-



(iii) protection as benzyl ether:-



(iv) protection as paramethoxy benzyl ether:-



2. Trialkyl Silyl Ethers As protecting groups for alcohols

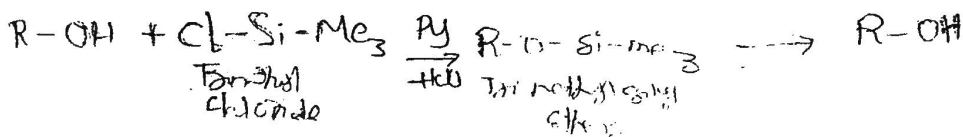
Trialkyl silyl ethers as protecting group for alcohols has found major appl. in organic synthesis.

These are prepared by reaction of an alcohol with trialkyl silyl halides in presence of base.

Trialkyl silyl group with bulky alkyl groups are more stable.

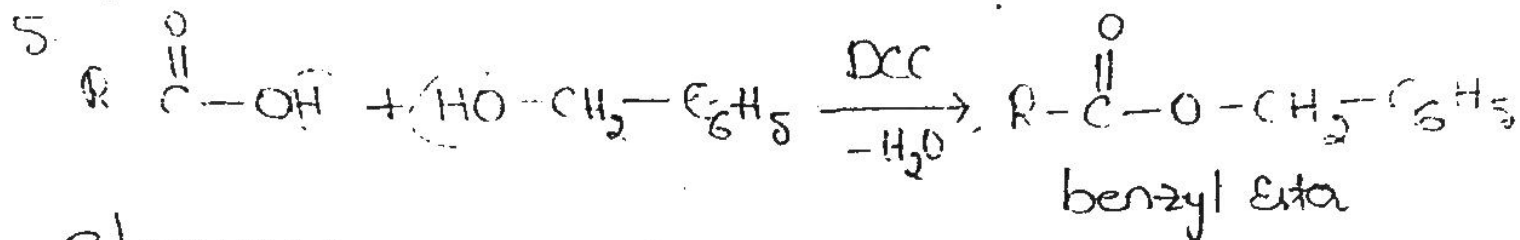
Silyl ethers are cleaved to their parent alcohols by treatment with fluoride ion.

"protection" as Trimethyl silyl ethers

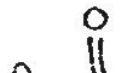


Ex: protection as benzyl Esters :-

Carboxylic acids on reaction with benzyl alcohol in presence of dehydrating agent forms benzyl Esters, which can be cleave by hydrolysis (Catalytic hydrogenation).

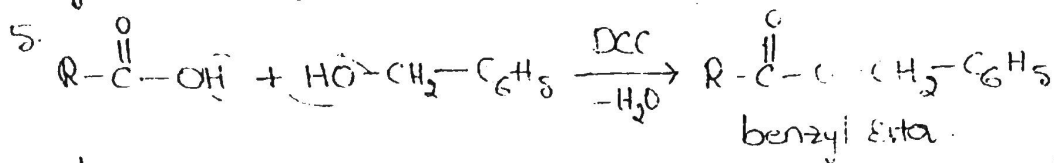


cleavage :-

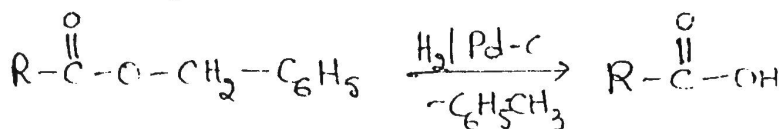


Ex:5 protection as benzyl Esters :-

Carboxylic acids on reaction with benzyl alcohol in presence of dehydrating agent forms benzyl Esters, which can be cleave by hydrogenolysis (Catalytic hydrogenation).



cleavage -



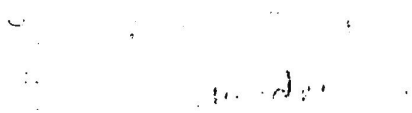
* protection of Amides :-

Amines compete effectively for electrophiles, because of its nucleophilic nature. It is difficult to handle the molecules that contain free amines therefore, it is better to keep the amines protected.

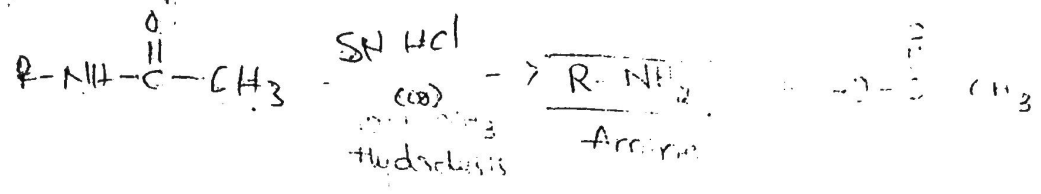
1. protection of Amine by acylation

Amines can be protected as amides which are readily prepared by acylation of amines with acid chlorides or acid anhydrides.

The amide is stable to most reagents and can be removed easily with acid or base. However, amides are not stable to strong acids.



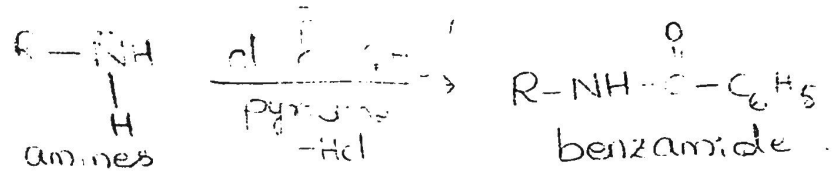
C=O group:



2. Protection of amine by benzoylation:-

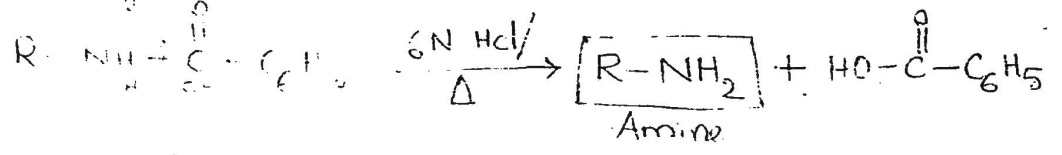
Amine is converted to benzamides.

It is done by benzoylation of amine with benzoyl chloride in presence of pyridine.



Benzamides are cleaved by heating in presence of strong acidic medium.

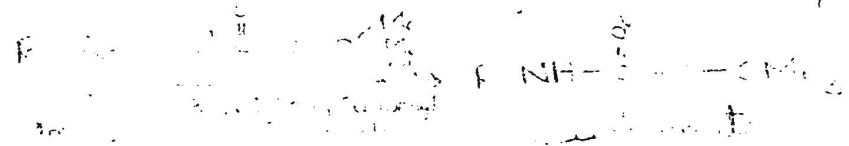
Reaction:-



3. Protection with BOC (B-tert-butyl Oxycarbonyl):-

Carbamates are used as protecting groups for amines and amino group in amino acids.

B-tert-butyl carbamate is prepared by treatment of amine with B-tert-butyl oxycarbonyl chloride.

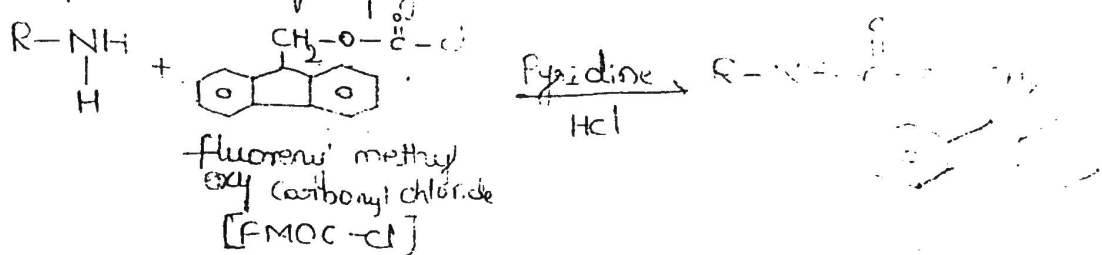


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4. protection with Fmoc (9-fluorenyl methoxy carbonyl)

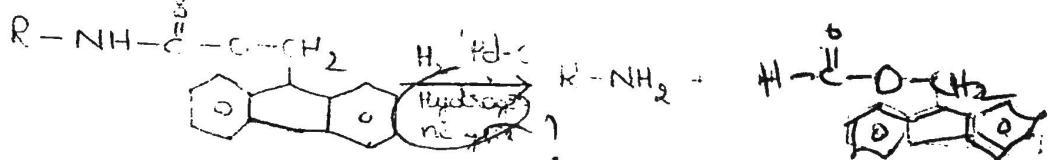
Fluorenyl methoxy carbonyl protection for N amine is carried out with reaction of amine with fluorenyl methoxy carbonyl chloride in presence of pyridine.



Fmoc group is widely used in the protection of amino acids during solid phase peptide synthesis.

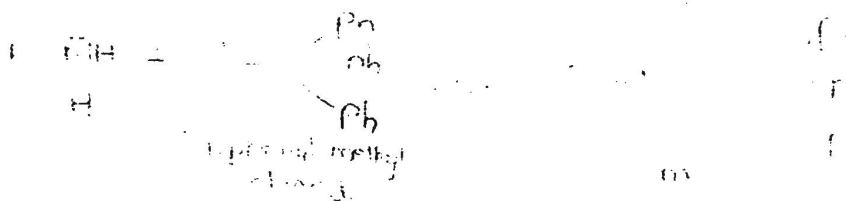
Fmoc can be cleaved by catalytic hydrogenolysis.

cleavage:-

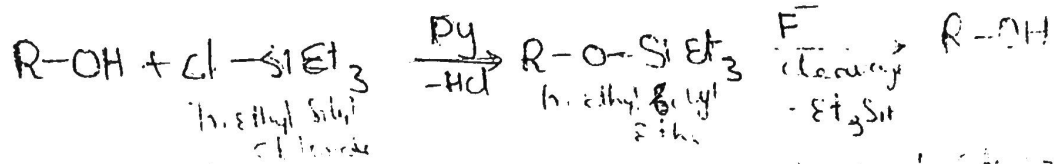


5. protection with diphenyl methyl halide

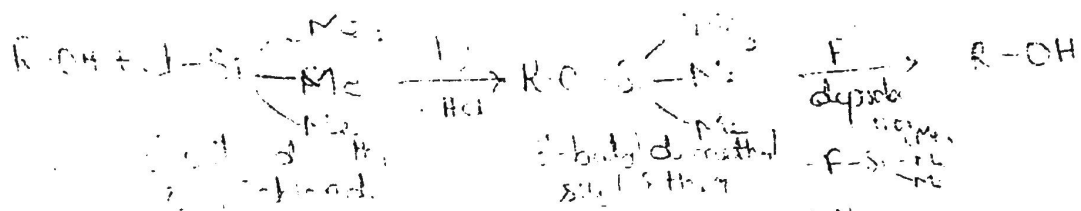
The bulky triphenyl methyl group is removed by mild acid hydrolysis. It is used to protect amino groups of amino acids in penicillin, cephalosporin etc.



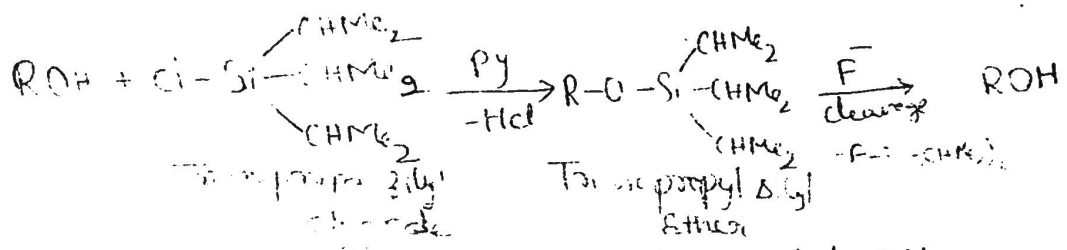
ii) Protection of primary alcohols using ethyl



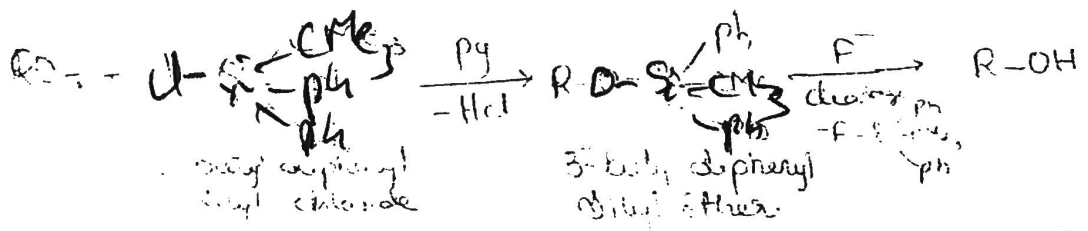
(iii) Protection of secondary alcohols using ethyl



(iv) Protection of tertiary alcohols using ethyl



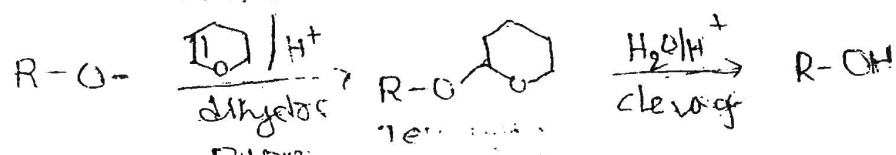
(v) Protection of secondary alcohols using ethyl



3. Acetals and Ketals as protecting groups for alcohols

Acetals and Ketals have many advantages in protection of alcohols. Tetrahydropyran derivatives and methoxy methyl ethers are commonly employed.

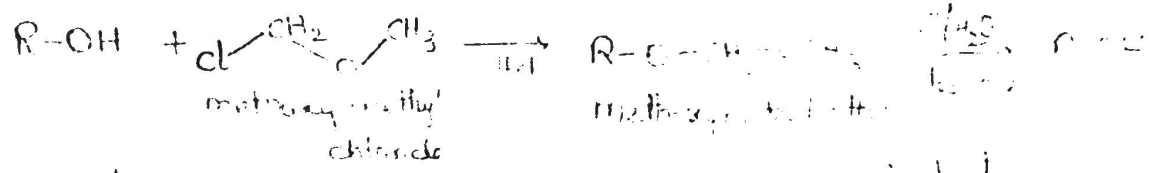
Acetals and Ketals can be easily removed by



Mechanism



(i) protection as methoxy methyl ether

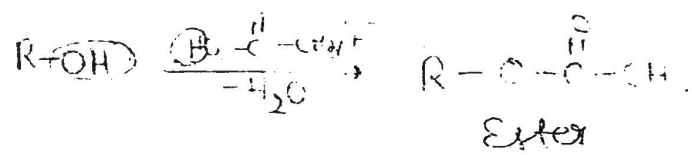
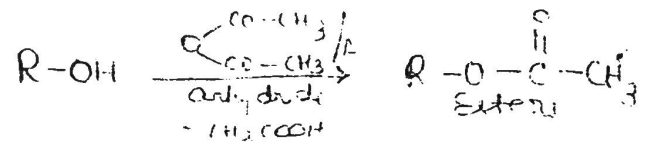
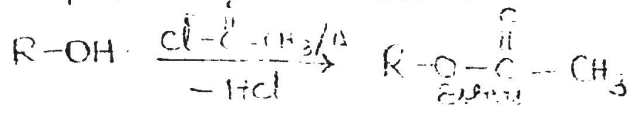


4. Esters as protecting groups for alcohols
 Alcohols are protected as esters, obtained by treating alcohols with acids, anhydrides or acetic anhydride.

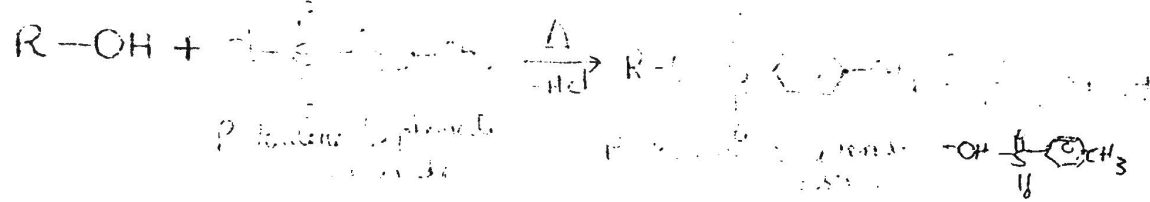
Esters are cleaved by base hydrolysis.

(i) protection as Acetate Ester

D



(ii) protection as p-Toluenesulphonyl ester



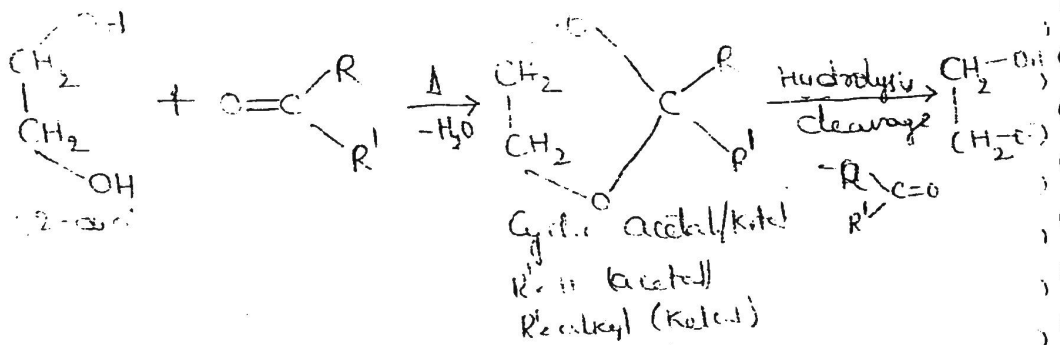
* Protection of 1,2-diols :-

1,2-diols are protected by cyclic acetals/ketals by carbonyl formation.

Acetals & ketals are cleaved by acidic conditions. Carbonyl is formed by basic hydrolysis.

(i) Protection as Cyclic Acetals/Ketals :-

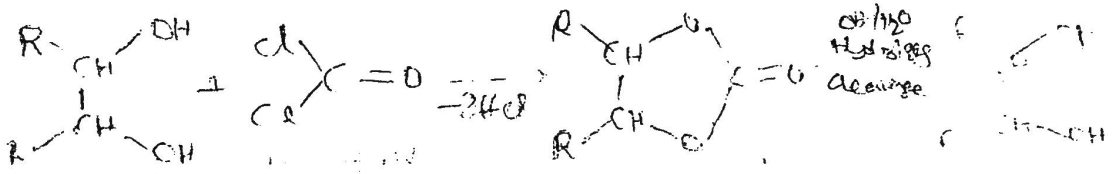
Cyclic acetals & ketals are formed by reaction of diol with a carbonyl compound in presence of acid catalyst. The formed acetals & ketals are stable to oxidation, reduction and alkaline conditions.

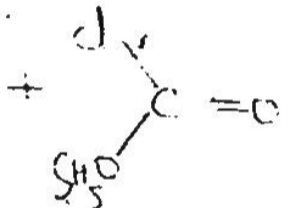
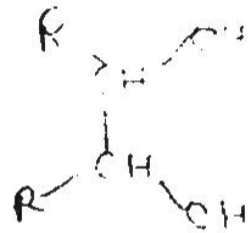


(ii) Protection as Cyclic Carbonates :-

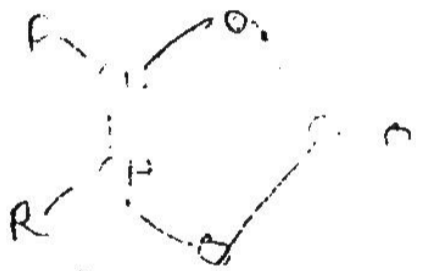
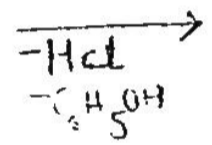
Cyclic carbonates are prepared from 1,2-diols and phosgene as a chloroformate are stable to acidic conditions.

They are easily cleaved by basic hydrolysis.

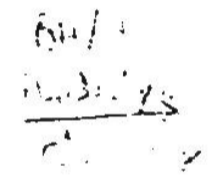




Chloroformate



Cyclic carbonate



PART-B