# SEM III H_ORGANIC CHEMISTRY

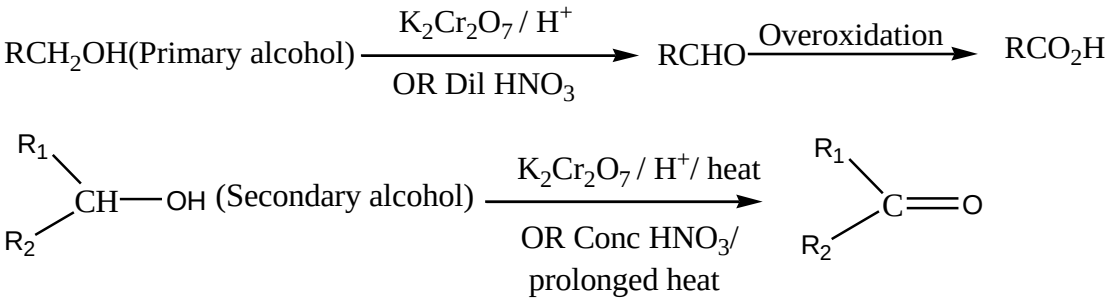
## Carbonyl and Related Compounds

## Addition to C=O:

### TOPICS: STRUCTURE, REACTIVITY AND PREPARATION OF CARBONYL COMPOUNDS.

**I ) PREPARATION :**

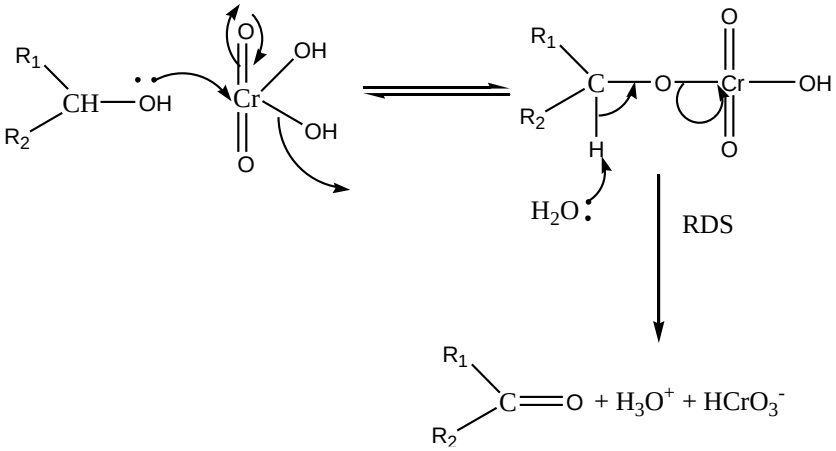
**A) OXIDATION REACTION**:




Oxidation of primary alcohols to aldehyde with acidic solutions of chromic acid is less satisfactory as –CHO is easily oxidised further to –COOH and more importantly unchanged alcohol reacts with produced –CHO to give hemiacetal under acidic condition. Hemiacetal rapidly oxidised to an ester. Satisfactory yield can be obtained by removing the aldehyde from the reaction medium by distillation or better by using Pyridine –Chromium VI oxide complex (PDC and PCC; Discussed later).

**MECHANISM:**

Oxidation of alcohols by chromic acid takes place by initial formation of chromate ester, followed by proton abstraction. By this process ketone is formed as the required product and generates Chromium (IV) specis, which itself thought to produce more ketone product. The reaction shows primary kinetic isotope effect with $k_H/k_D > 6$. So the second step i.e. cleavage of C-H bond is the rate determining step (RDS). Generally, tertiary alcohols remains unaffected by chromic acid.

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**JONES REAGENT:**

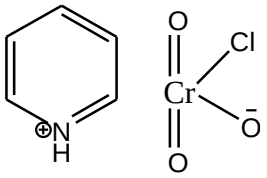
Oxidation with acid solutions of chromic acid is normally unsuitable for alcohols that contain acid-sensitive groups or either easily oxidisable groups such as allylic or benzylic C-H bonds elsewhere in the molecule. Dropwise addition of stoichiometric amount of a solution of Cromium(VI) oxide in aqueous $H_2SO_4$ to a cooled (0-20$^oC$) solution of alcohol in acetone. End point (Completion) of the reaction can easily be detected by persistence of red colour of chromic acid. Overoxidation thus can be prevented.

**COLLINS REAGENT:**

$CrO_3$, Pyridine in dry DCM. This is a relatively mild reagent but excess reagent is required

**PCC:** Modified reagent better if molecule has acid sensitive groups other than reactive centre.

Pyridinium ChloroChromate (Pyridine + $CrO_3$ + HCl)




Here, DCM is used as a solvent. It gives good yield when is used in little excess. PCC is mildly acidic so side reactions are less.

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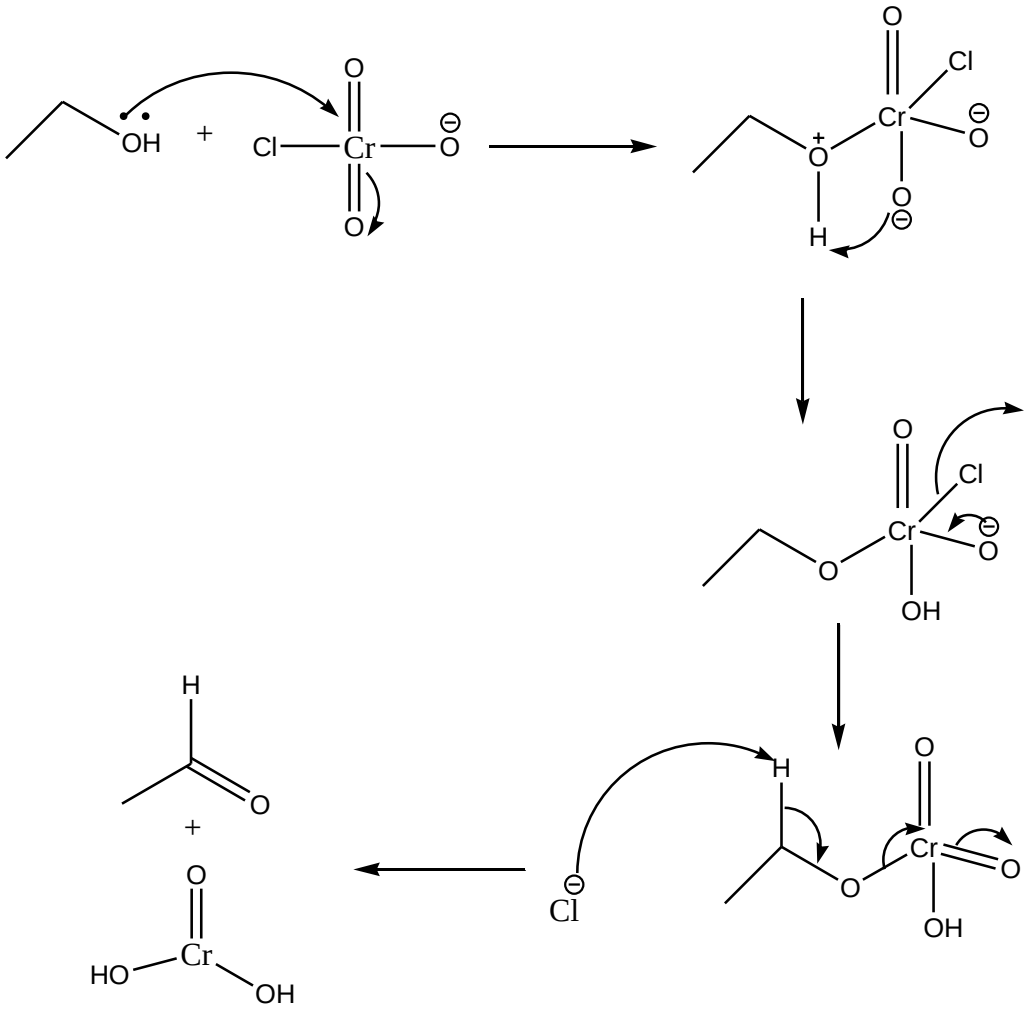
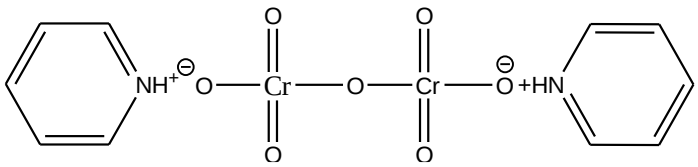
**MECHANISM:**




**PDC:**

Pyridinium DiChromate : Even less acidic than PCC so more selective. It is also used in dry DCM solvent. It is an excellent reagent for allylic and benzylic alcohols.




**LECTURE 2:**

**PREPARATION:**

**B. OPPENAUR OXIDATION:**

The Oppenauer Oxidation with aluminium alkoxides provides an alternative method for the oxidation of secondary alcohol. The reaction is reverse of Meerwin-Pondrof -Verely (MPV

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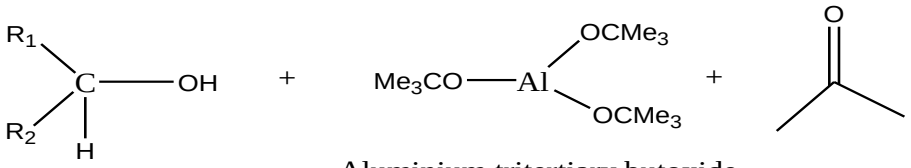
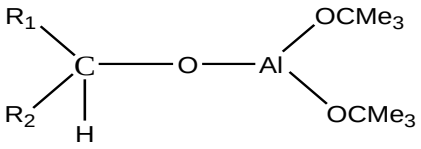
Reaction , discussed later) reduction. Generally, aluminium isopropoxide ( or aluminium tri-tert-butoxide) is used which forms the aluminium alkoxide of the alcohol which is the oxidised to ketone through cyclic transition state. By the use of excess acetone the equilibrium is shifted to right.



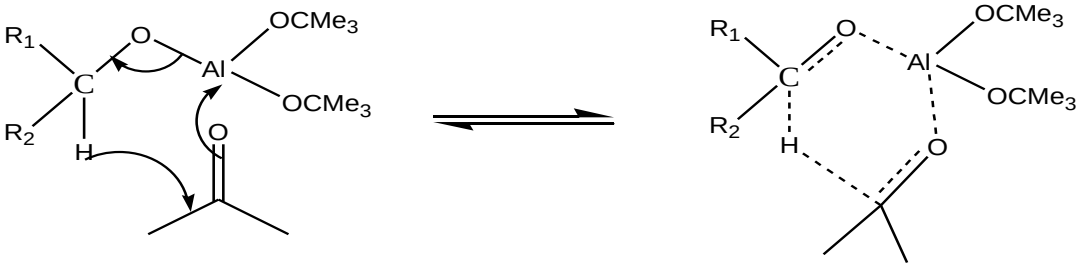

Aluminium tritertiary butoxide

Step-I

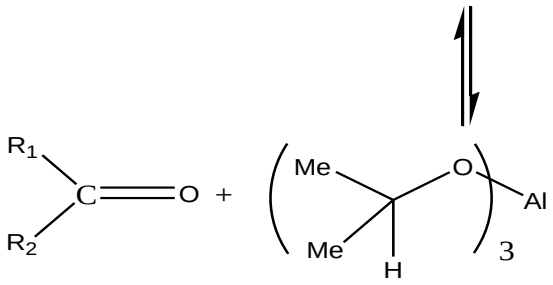
Rapid Exchange of Proton




Step-II




6-membered transition state




Aluminium isopropxide

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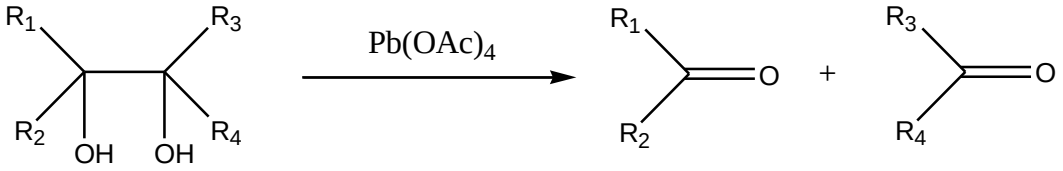
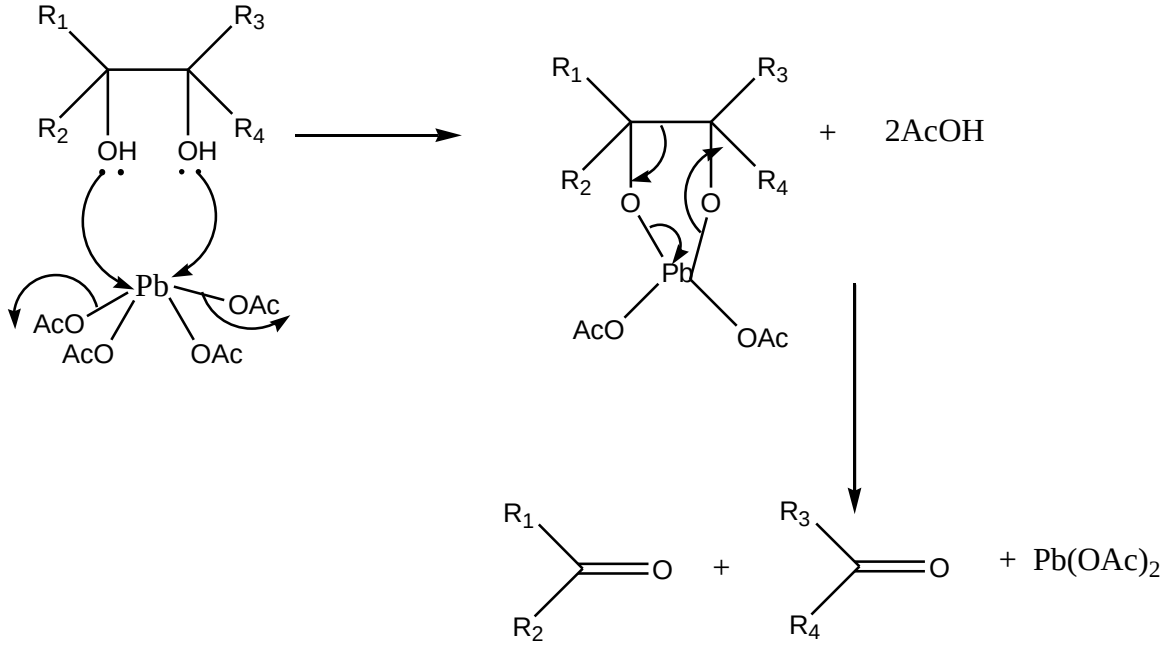
**C. Oxidation of 1,2-glycols by $Pb(OAc)_4$ or $HIO_4$:** The ability of the diol to form an intermediate cyclic diester with periodic acid is critical for the successful cleavage of vicinal diol.

- 1,2- or vicinal diols are cleaved by periodic acid, $HIO_4$ or $Pb(OAc)_4$, into two carbonyl compounds.
- The reaction is selective for 1,2-diols.
- The reaction occurs via the formation of a cyclic periodate ester.
- This can be used as a functional group test for 1,2-diols.

**By $Pb(OAc)_4$**




**MECHANISM:**

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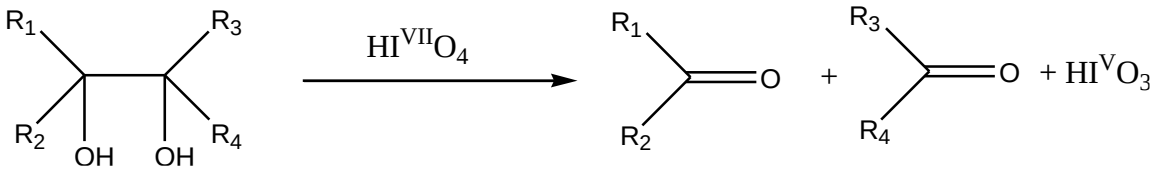
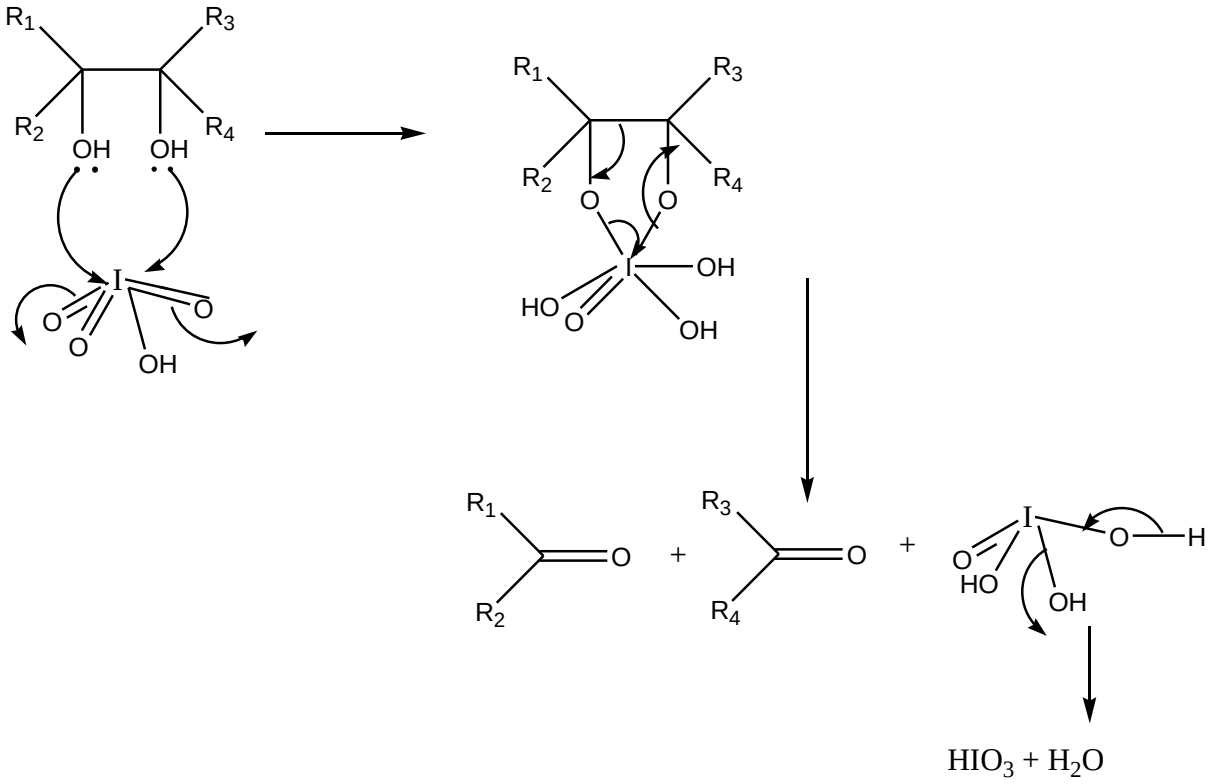
**By $HIO_4$ :**




**MECHANISM:**




**CARBONYL CHEMISTRY STUDY MATERIAL (APS)**

**LECTURE 3:**

**PREPARATION:**

**E. ROSENMUND REACTION:**

The catalytic hydrogenation of acid chlorides allows the formation of aldehydes The Pd catalyst must be poisoned, for example with $BaSO_4$, because the untreated catalyst is too reactive and will give some over reduction of aldehyde to alcohol. Some of the side products can be avoided if the reaction is conducted in strictly anhydrous solvents.

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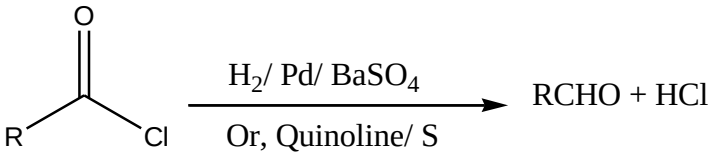
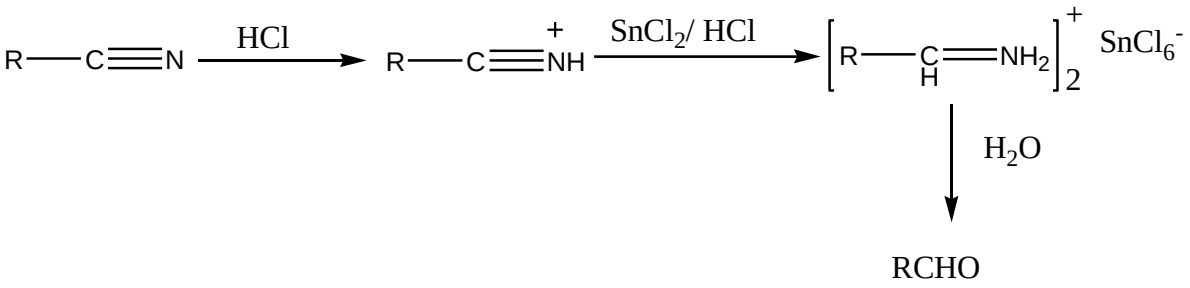


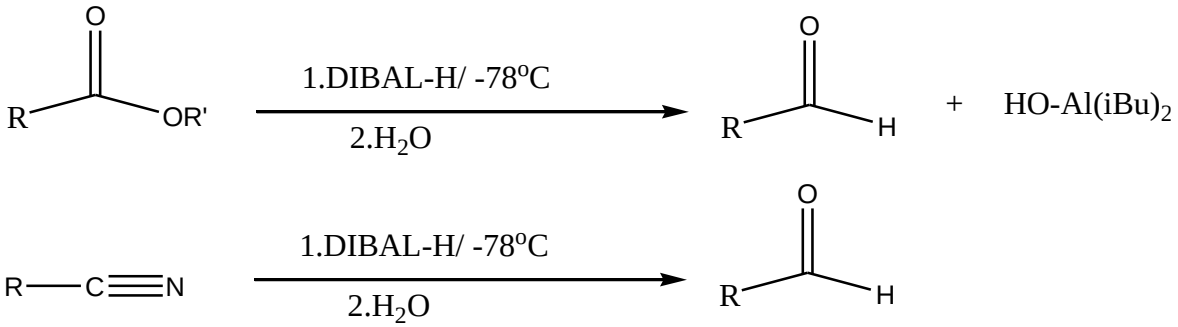

**F. STEPHEN'S REACTION:**

This reaction involves the preparation of aldehydes (R-CHO) from nitriles (R-CN) using tin(II)) chloride ($SnCl_2$), HCl and quenching the resulting iminium salt ([R-$CH{=}NH_2]^+Cl^-$) with water ($H_2O$). During the synthesis, ammonium chloride is also produced.




**G. REDUCTION by HYDRIDE DONOR**

**DIBAL-H Diisobutyl aluminium hydride:** DIBAL-H is a strong, bulky reducing agent. It's most useful for the reduction of esters to aldehydes. Unlike lithium aluminum hydride, it will not reduce the aldehyde further to alcohol if only one equivalent is added. It will also reduce other carbonyl compounds such as amides, aldehydes, ketones, and nitriles.

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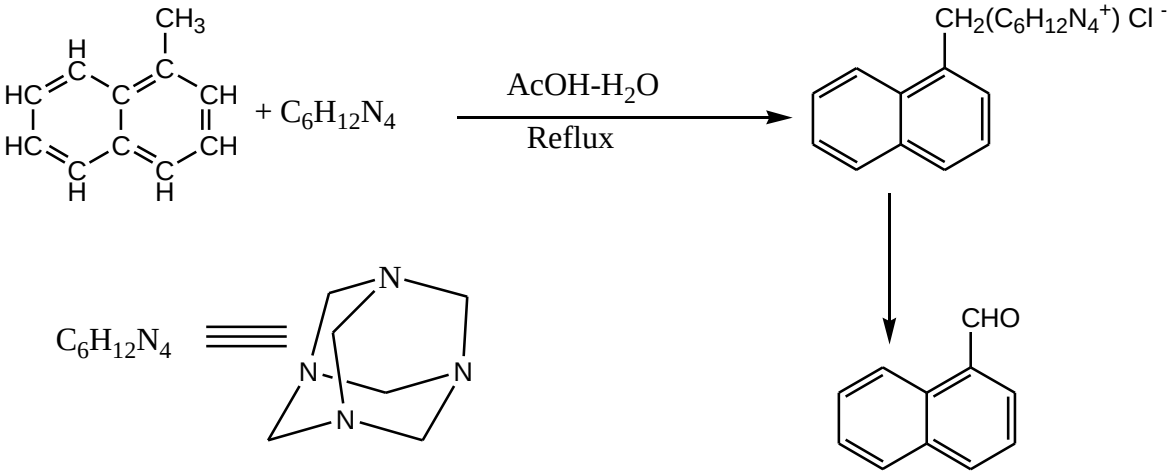
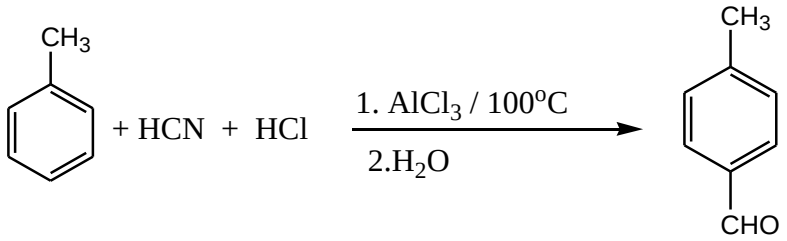
## H. SOMMELET'S REACTION:

The Sommelet reaction uses hexamethylenetetramine (HMT) to convert benzylic halides into aldehydes. The reaction requires mild acidic conditions, and halo, nitro, alkyl, alkoxy, and ester groups are unaffected. *Ortho*-substituents usually give lower yields, and 2,6-disubstituted benzyl halides usually fail to react.




## I.GATTERMANN ALDEHYDE SYNTHESIS:

The preparation of aromatic aldehydes containing hydroxyl or alkyloxyl groups on the aromatic ring by treatment of the aromatics with hydrogen cyanide and hydrogen chloride in anhydrous solvent (e.g., ether) with or without the presence of a Lewis acid (e.g., $ZnCl_2$, $AlCl_3$) as a catalyst, in which aldimine hydrochloride functions as an intermediate, is generally referred to as the Gattermann aldehyde synthesis or simply as the Gatterman synthesis.

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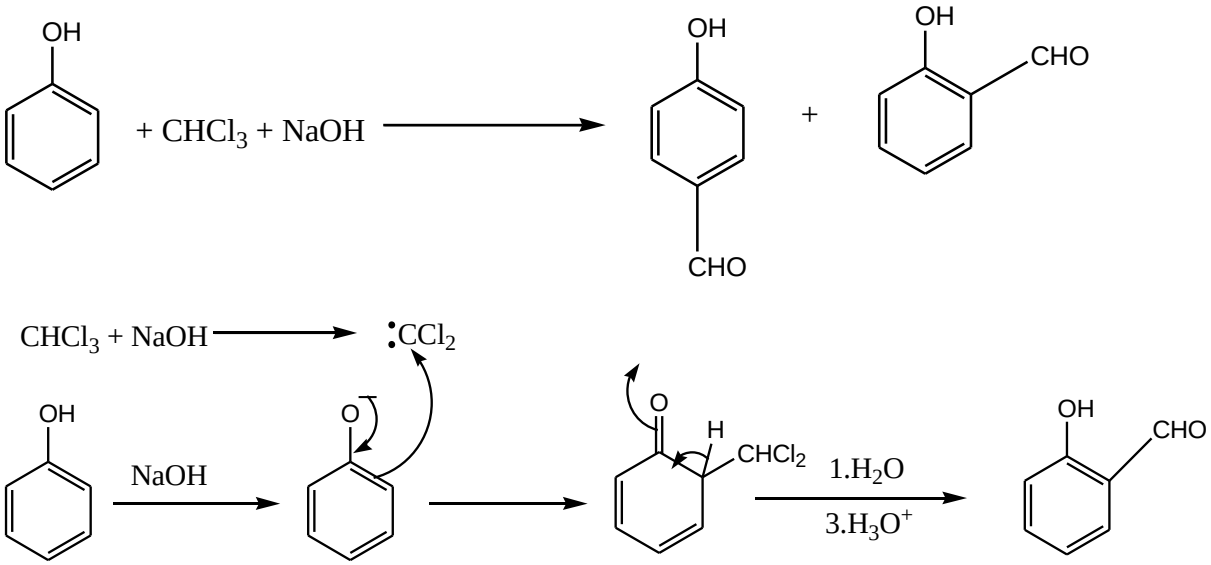
## H. REIMER-TIMANN REACTION:

The Reimer-Tiemann reaction is an organic reaction used to convert a phenol to an o/p-hydroxy benzaldehyde using chloroform, a base, and acid work-up. The mechanism begins with abstraction of the proton from chloroform with the base to form a trichlorocarbanion which spontaneously loses a chloride ion to form a dichlorocarbene. The base also deprotonates the phenol reagent which then attacks the carbene. A series of steps and a final acid work-up result in the o-hydroxy benzaldehyde product.

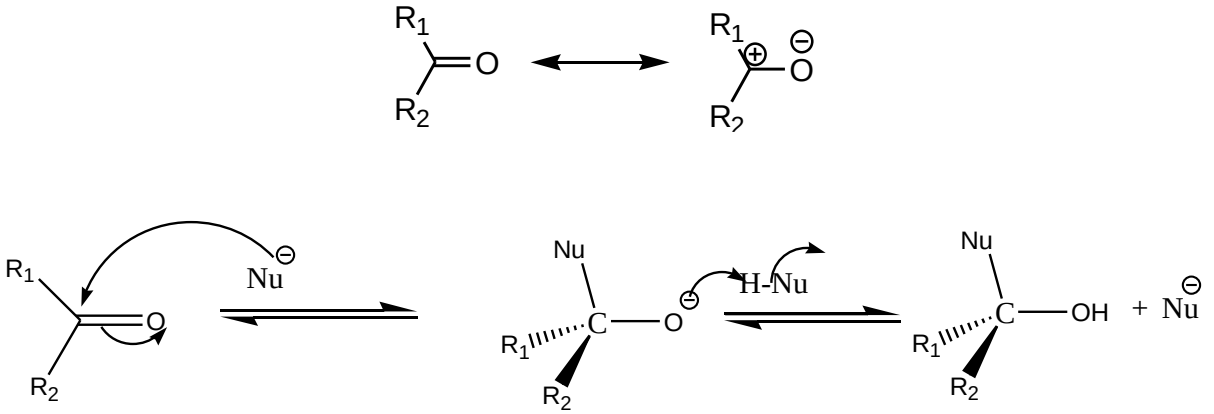





## LECTURE 4:

## NUCLEOPHILIC ADDITION TO CARBONYL GROUP:

( Addition Nucleophilic Bimolecular Reaction)

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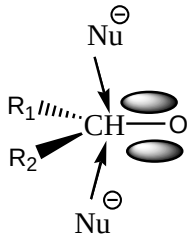
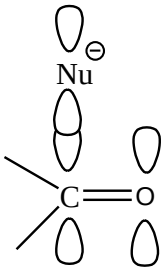
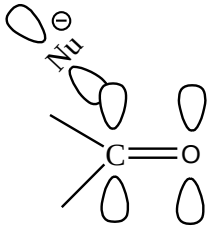
Nucleophile can attack from either side of carbonyl group depending on $R_1$ or $R_2$ groups.




The Nucleophile does not attack at 90°. The actual attack angle is 107° to the carbonyl group, which is known as Burgi-Dunitz trajectory. B.D. Trajectory is due to balance between maximum overlap with π* and minimum repulsion of HOMO by electron density of carbonyl π bond.




Maximum overlap with
$\Pi^*$, perpendicular to C=O bond




Nucleophilic attacks C=O
at 107° angle

**EFFECT OF STRUCTURE ON REACTIVITY:**

1. Steric Factor: Increasing bulk in R groups will slow the reaction as the $SP_2$ hybridised carbon atom in the original carbonyl compound (R-C-R bond angle ≈ 120°) is converted to SP3 hybridised carbon atom (R-C-R bond angle ≈ 109°). The R groups thus move closer together as the reaction proceeds, i.e. Transition State becomes more crowded. So, the reaction rate dercreases as size of R increases.

2. Electronic Factor: It is expected that nucleophilic addition reaction is reduced by electron donating group R groups and enhanced by electron withdrawing R groups.

- So, according to both steric and electronic effect , the order of observed reaction rate is

  $H_2C=O>RCH=O>R_2C=O$ (when R= alkyl group)

- When C=O group is conjugated with C=C bond or benzene ring, it reacts at a slower rate compared to their saturated analogues as electrophilic character of C=O is reduced.

  So, the reactivity order of cyanohydrins formation of the following compounds is

  $CH_3COCH_2CH_3$ (38) > $PhCOCH_3$ (0.8) > PhCOPh (very very small)

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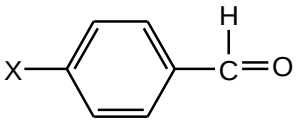
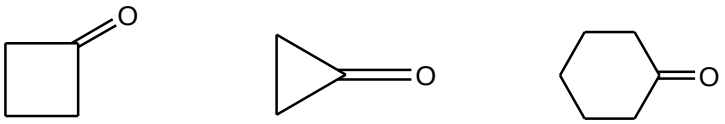
- However, EWG in para position increases the eaction rate and EDG in para position reduces the reaction rate.



Relative rate: X= $NO_2$ > H> OMe

- Relative reaction rates of $CF_3CHO$ > $CH_3CHO$ >$CH_3CH$=CH-CHO

-

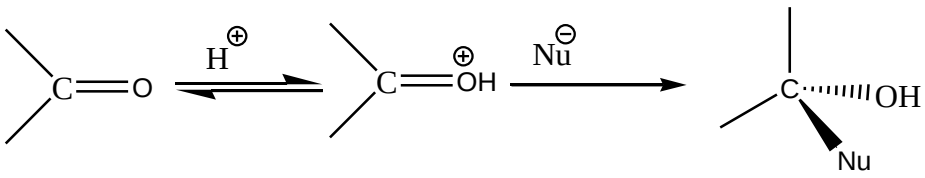


I II III

| | | | | |
|---|---|---|---|---|
| Bond Angle | : | $90^o$ | $60^o$ | $116^o$ |
| Ideal $SP^2$ C=O angle | | $120^o$ | $120^o$ | $120^o$ |
| Angle Strain: | | $30^o$ | $60^o$ | $4^o$ |

More the releief of angle strain after reaction more will be the reaction rate.
Here, relative rate of reactivity : II > I > III.

**EFFECT OF pH:**



Protonation will clearly increase the positive character of the carbonyl carbon, thereby facilitate the nucleophilic attack. In absence of this activation weak nucleophile (like $H_2O$) may react very slowly but strong nucleophile e.g. $CN^-$ does not require this help.

Attack of Nucleophile could also be base catalysed by enhancing the nucleophilicity.

e.g. HCN + base → $CN^-$

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So acid can activate carbonyl group, but it can also reduce the effective concentration Nucleophile by protonation.

e.g. $CN^- + H^+ \rightarrow HCN$ or $RNH_2 + H^+ \rightarrow RN^+H_3$

On the otherhand, in highly basic pH electrophilicity of carbonyl bond is reduced.

So, optimum pH is required for nucleophilic addition reaction to carbonyl. In some cases Sodium acetate is used as the buffer to maintain the pH.

## CARBONYL CHEMISTRY

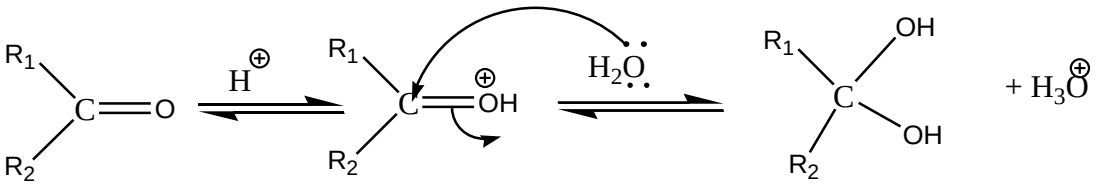
### LECTURE 5:

### NUCLEOPHILIC ADDITION TO CARBONYL GROUP:

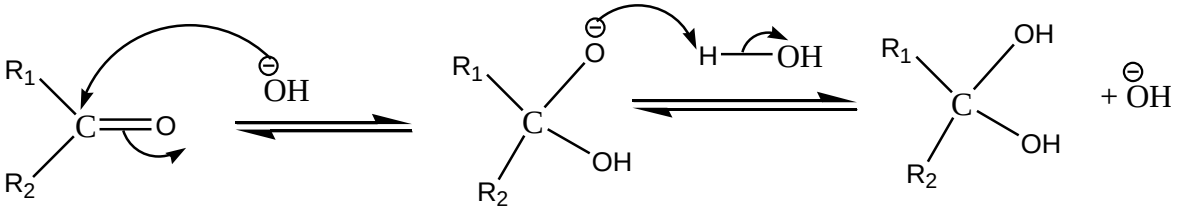
### SIMPLE ADDITION REACTIONS TO CARBONYL:

**HDRATION:** Hydration could be both acid catalysed and base catalysed.

Acid-catalysed Hydration:

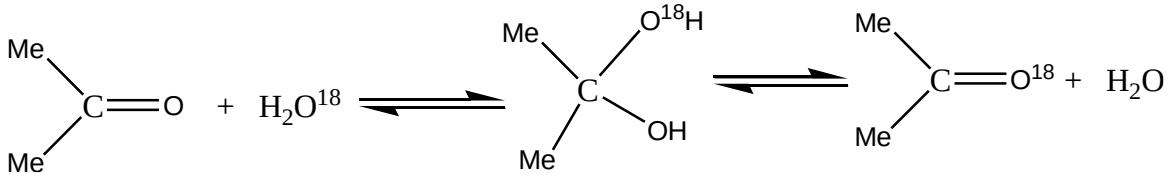



Base-catalysed Hydration:




The total process is reversible.

Proof:




Incorporation of $O^{18}$ into ketone occurs under all conditions proves the reversibility of the hydration reaction.

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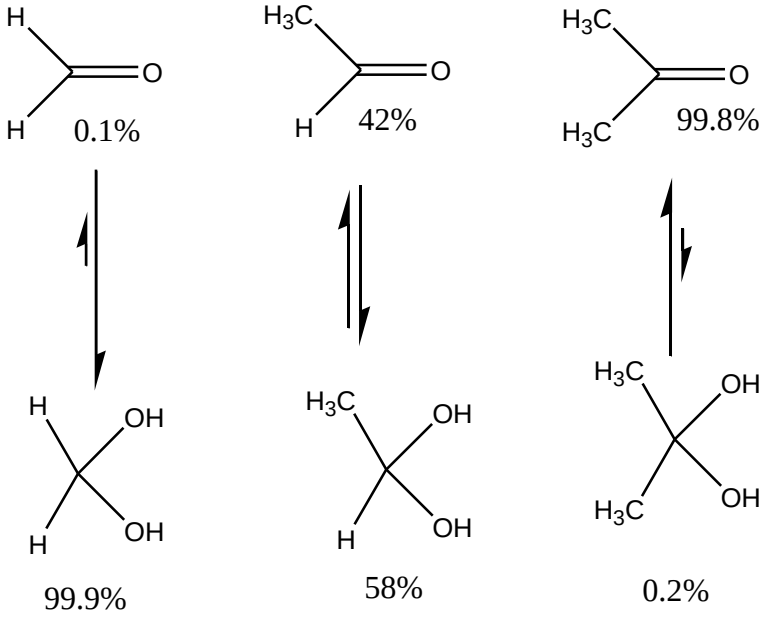
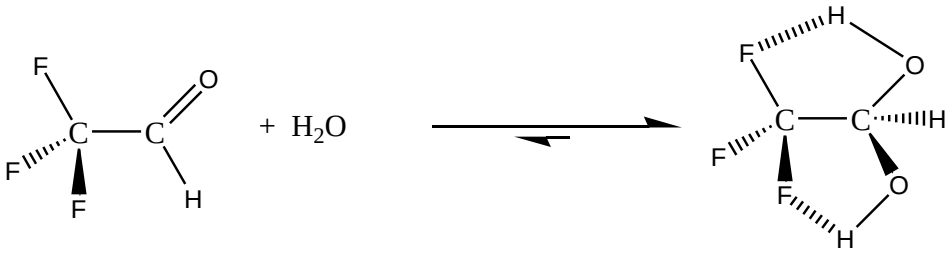
Acid or base i.e. the catalyst affects the rate at which an aldehyde or a ketone is converted to hydrate, it has no effect on the amount of aldehyde or ketone converted to its hydrate. EDGs in carbonyl compounds inhibit hydration and EWGs promote it.



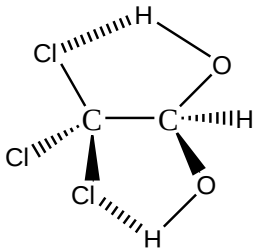

**FORMATION OF STABLE HYDRATES:**

**1.**




Trifluoro acetaldehyde hydrate, very stable due to intramolecular H-bonding

Hydrate of trichloro ethanal (Chloral) i.e. chloral hydrate is also stable , isolable crystalline hydrate due to same reason.

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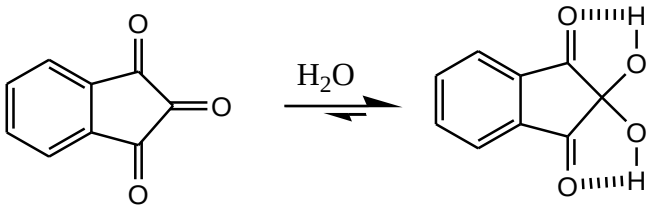
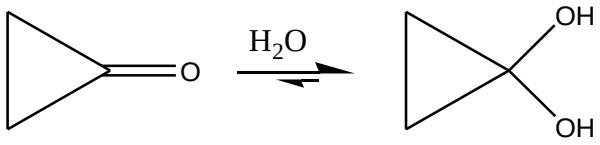
2.




Indane1,2,3- trione Ninhydrin

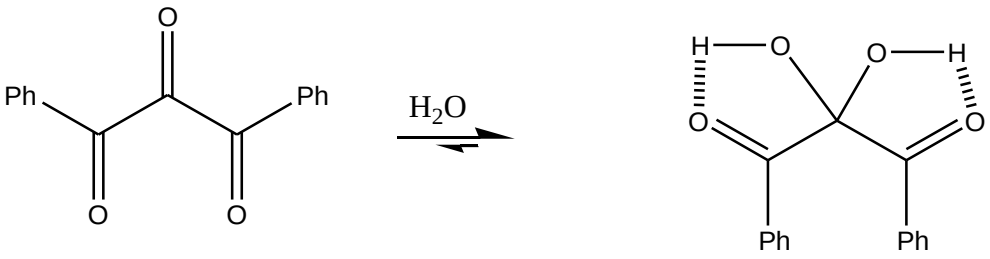
3.




Angle Strain: $120^o$ - $60^o$ $109^o$ - $60^o$

Release of angle strain makes this hydrate stable.

4.




**CARBONYL CHEMISTRY STUDY MATERIAL (APS)**

**LECTURE 6: NUCLEOPHILIC ADDITION TO CARBONYL GROUP:**

**SIMPLE ADDITION REACTIONS TO CARBONYL:**

2. ADDITION OF CYANIDE:

HCN is not itself a powerful neucleophile to attack, and the reaction requires base-catalysis in order to convert HCN into stronger nucleophile $CN^{-.}$

The reaction then obeys the rate law.

Rate= K [Carbonyl Compound][ $CN^{-.}$ ]

The reaction with $CN^-$ is reversible and tends to lie in favour of starting material unless a proton donor is present.

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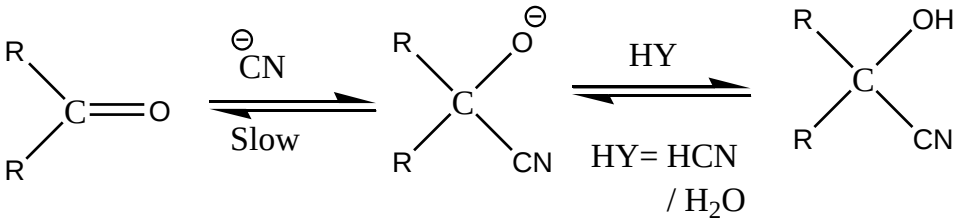


Synthetically Useful Reactions:

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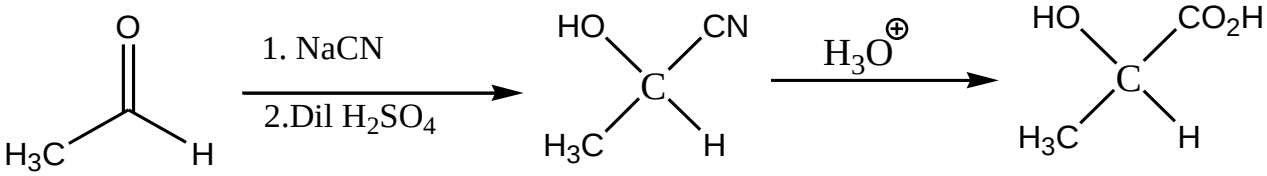
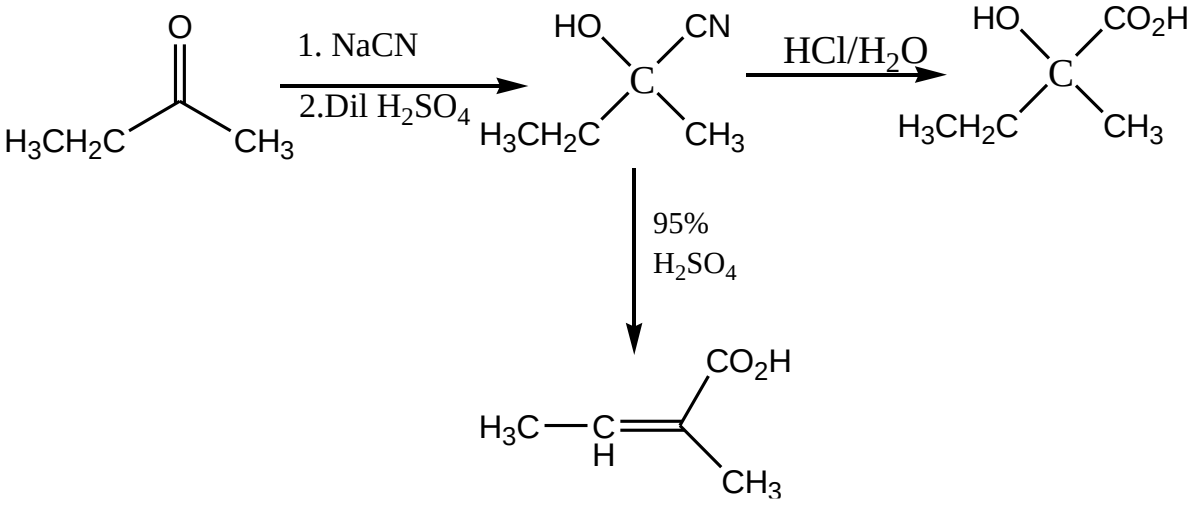
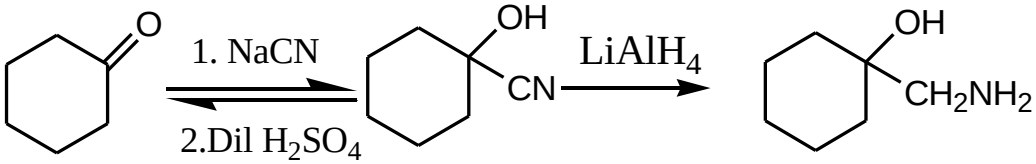



II.




III.

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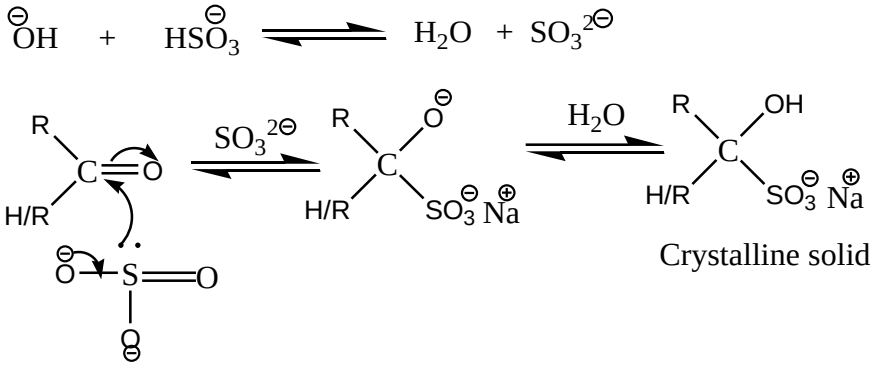
3. ADDITION OF BISULPHITE ($NaHSO_3$):

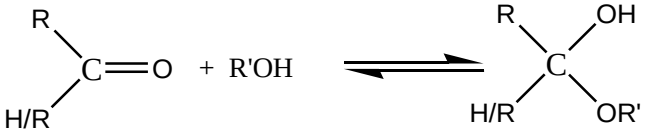
Effective Nucleophile is $SO_3^{2-}$ rather than $HSO_3^-$.




Crystalline solid

Neither acid nor base catalysis is required as $SO_3^{2-}$ is strong enough. Adduct is crystalline solid, insoluble in organic solvent. So, it can be separated from other organic compounds (which are soluble in organic solvents) by filtering the solid adduct and washing it with ether. Usually, alkalis are used to regenerate ketones and acids are used to regenerate aldehydes.

4. REACTIONS WITH ALCOHOLS:




Hemiacetal: When R=H
Hemiketal: when R= Alkyl

Reaction is just like as hydrate formation but rate is slow. Formation of acetal/ketal must require acid catalysis. Hemiacetal/ hemiketal formation could be done by both acid and base catalysis.

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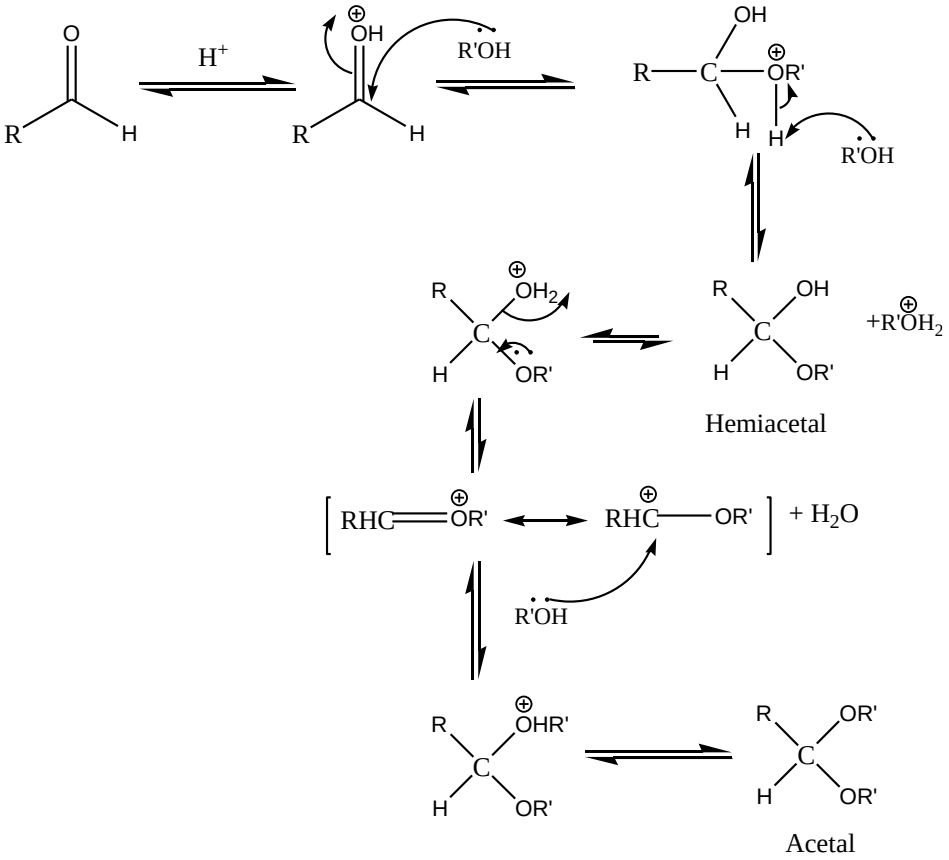
Acid catalysis:




Acetal formation is reversible but the equilibrium will be influenced by relative proportions of R'OH and $H_2O$ present. Preparatory acetal formation is thus normally carried out in excess R'OH with anhydrous acid catalyst.

$H_2O$ is produced in forward reaction so removal of $H_2O$ is important. Azeotropic mixture is used to remove $H_2O$ or conc HCl gas is passed to convert $H_2O$ into nonnucleophilic $H_3O^+$.

Conversion of acetal to aldehyde is done by dil acid. Acetals are not base sensitive as there is no acidic Hydrogen. So, acetals are used as protecting agent for aldehydes which are base sensitive.

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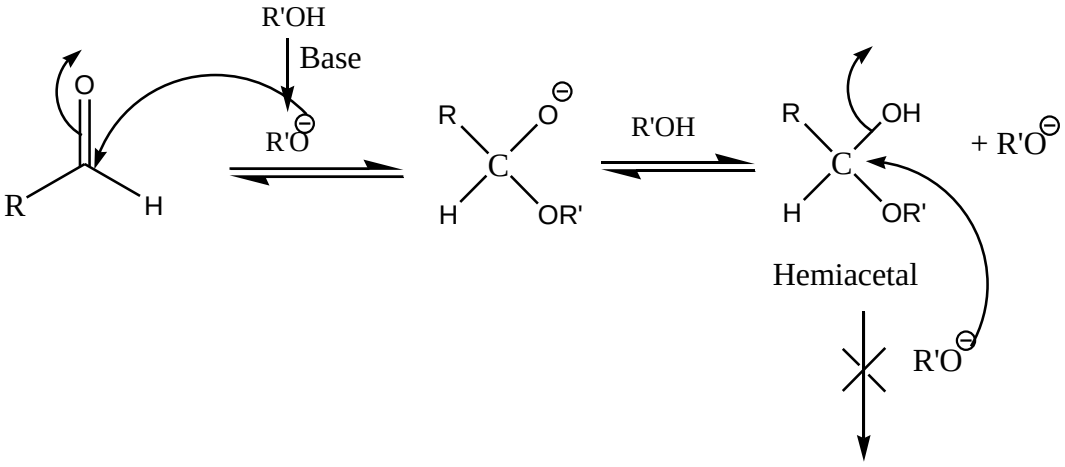
Base catalysis:

In case of base catalysis, acetal formation is not possible. Reaction will not progress further after hemiacetal formation.




**CARBONYL CHEMISTRY STUDY MATERIAL (APS)**

**LECTURE 7:**

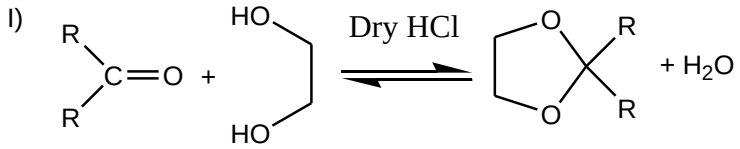
**NUCLEOPHILIC ADDITION TO CARBONYL GROUP:**

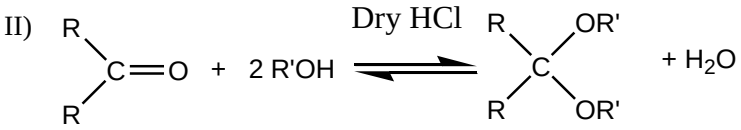
**SIMPLE ADDITION REACTIONS TO CARBONYL:**

4. REACTIONS WITH ALCOHOLS:

FORMATION OF KETAL:

Acetal formation is possible under acidic condition. But ketal formation is not that easy. We know due to both steric and electronic reason reactivity of ketones is much less than that of aldehydes. Ketal formation does not take place under normal acidic condition like acetal. They can be made by reacting with1,2 diol to form cyclic ketal.

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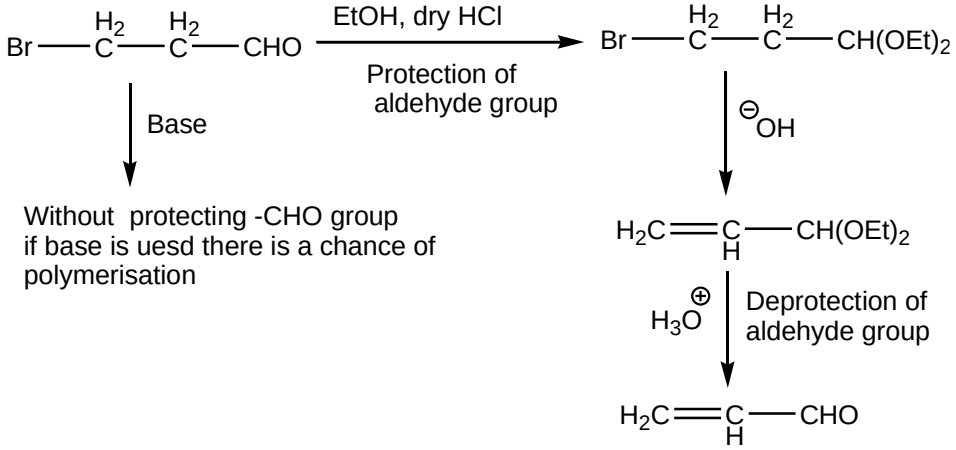
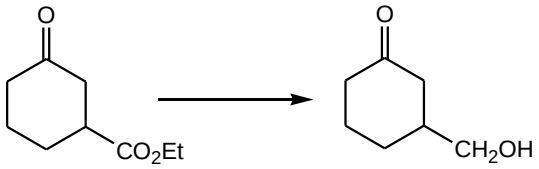
In reaction II), there is decrease in number of molecules going from reactant side to product side. So, entropically it is not favourable. But in case of reaction I) no decrease in number of molecules so entropically the reaction is favourable.

Acetal or ketal formation is synthetically very useful.

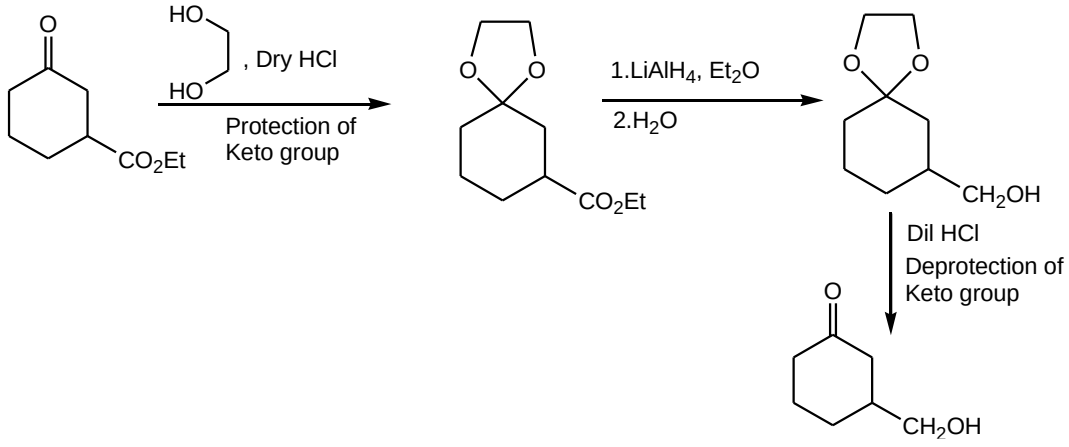
I.



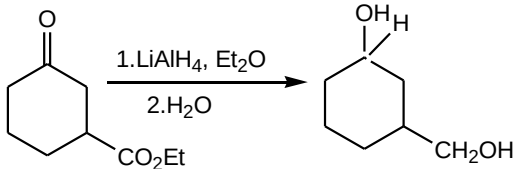

II.




To reduce ester group we have to use strong reducing agent like $LiAlH_4$. But it will also reduce keto group. So, to reduce ester group selectively we need to protect keto group. To protect keto group cyclic ketal should be made.




If no protection is used

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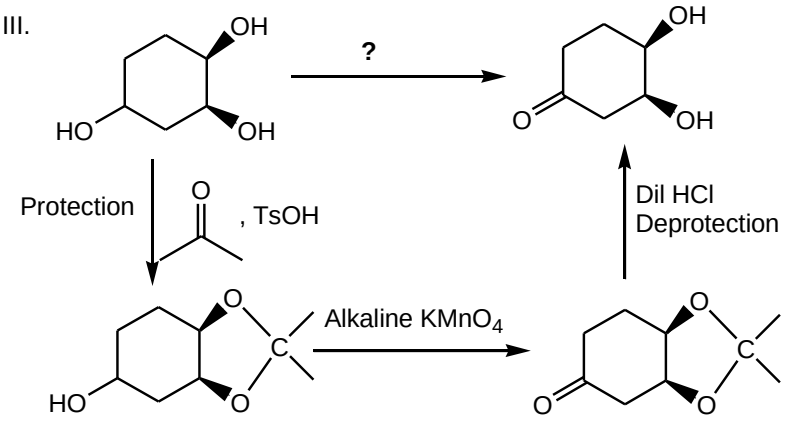
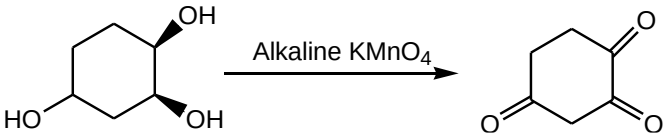
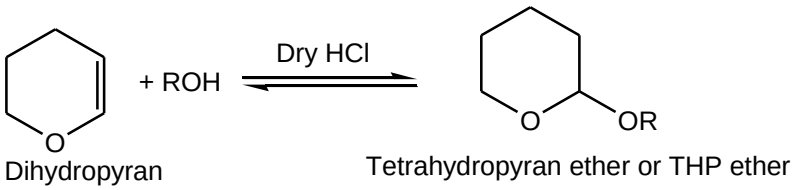
III.

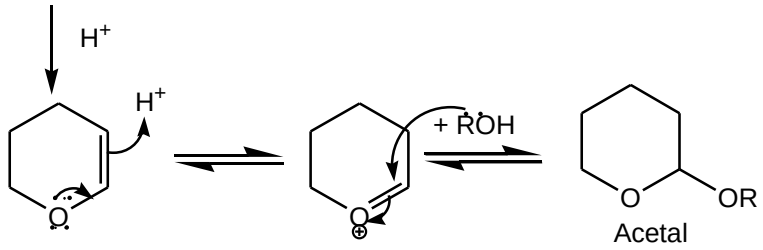



If protection is not used




ACETAL AS PROTECTING AGENT FOR ALCOHOLS:




So it can act as protecting agent for alcohol and phenol for the basic reaction condition. It can easily be deprotected using dilute acid.

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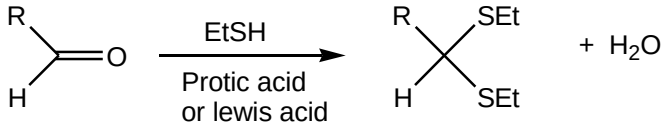
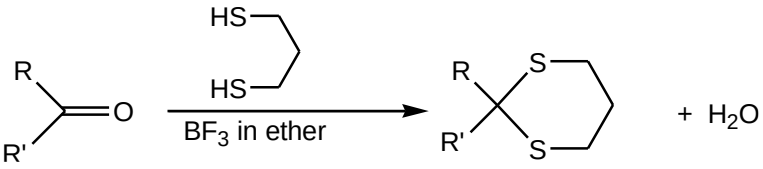
**CARBONYL CHEMISTRY STUDY MATERIAL (APS)**

**LECTURE 8: NUCLEOPHILIC ADDITION TO CARBONYL GROUP:**

**SIMPLE ADDITION REACTIONS TO CARBONYL:**

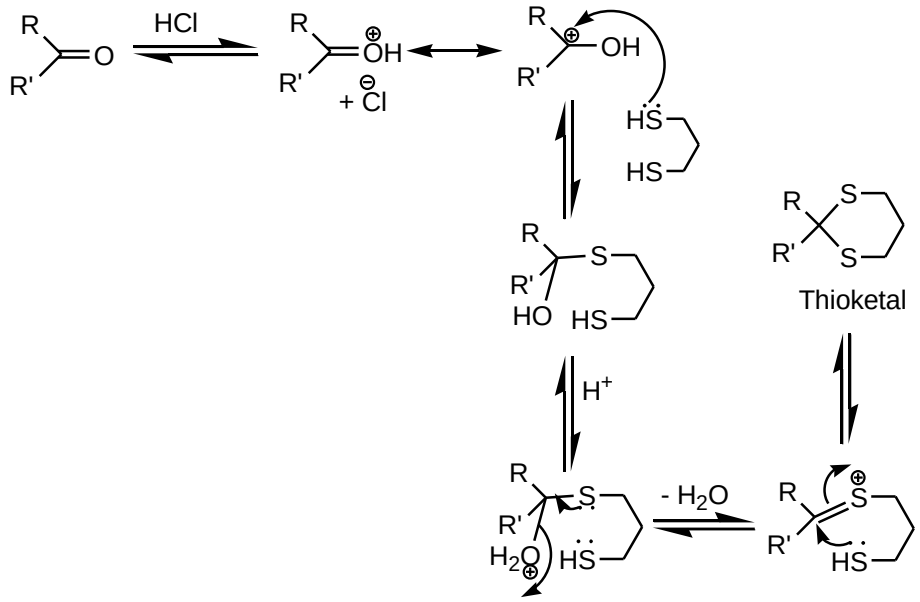
5. REACTIONS WITH SULPHUR NUCLEOPHILES:




In case of thioketal formation cyclic thioketal should be formed because it is entropically favourable to overcome the less reactivity of ketones.

Mechanism:




Advantages of thioacetal/ thioketal protection:

i) They are stable also in dilute acid.

ii) It can be deprotected by $HgCl_2$ ,$CdCl_2$/ $H_2O$ as Sulphur is soft centre and $Hg^{2+}$ and $Cd^{2+}$ are also soft.

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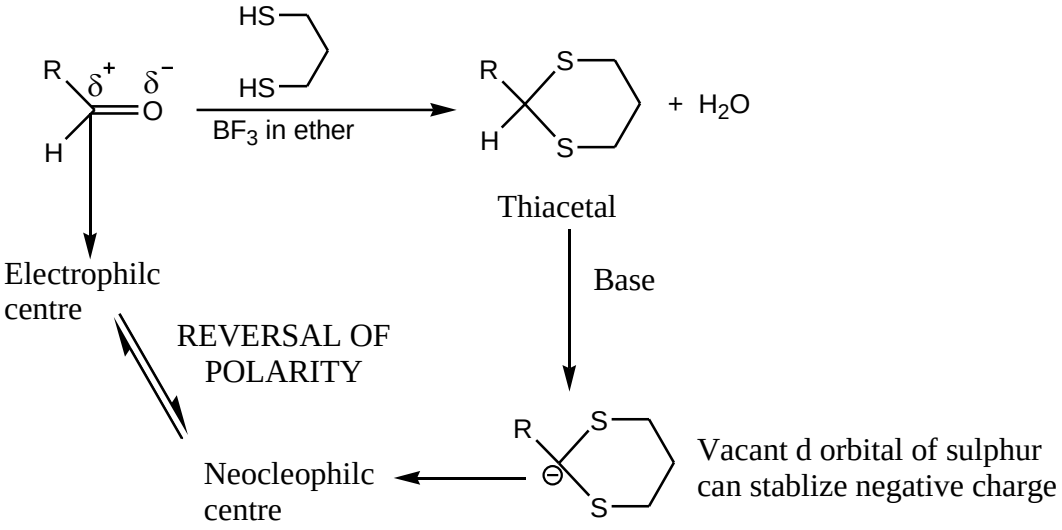
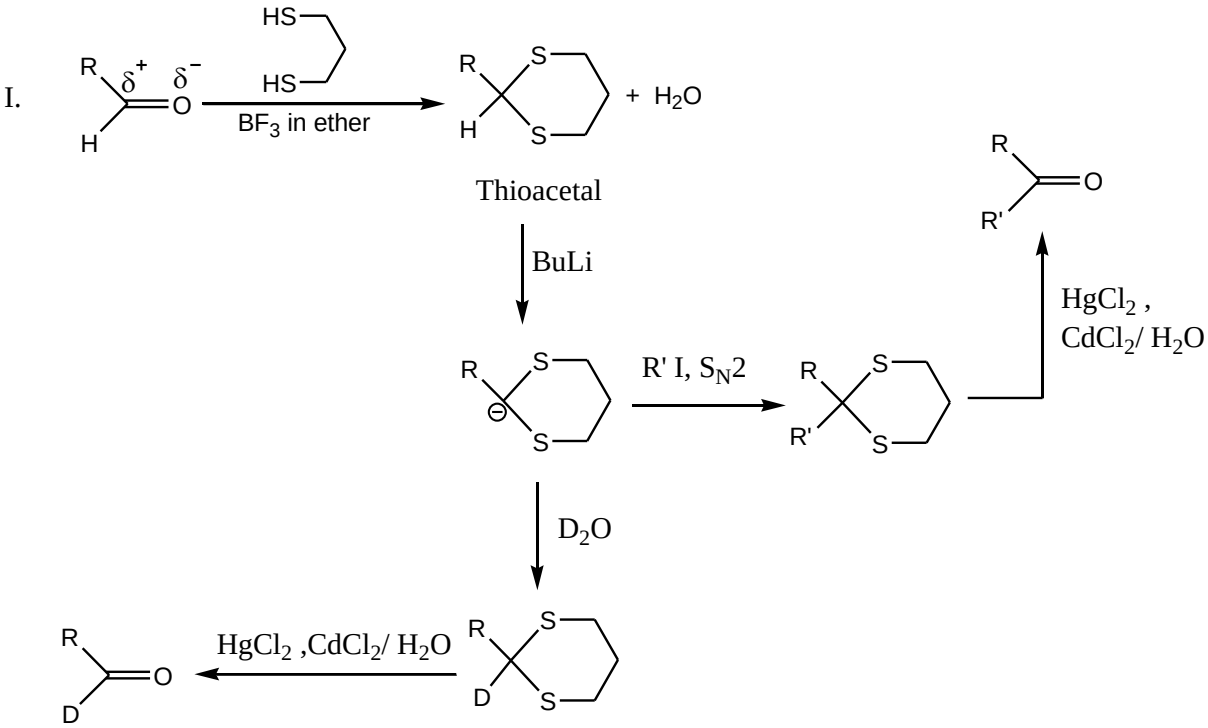
UMPOLUNG REACTION: Thioacetal can be used in Umpolung Reaction.

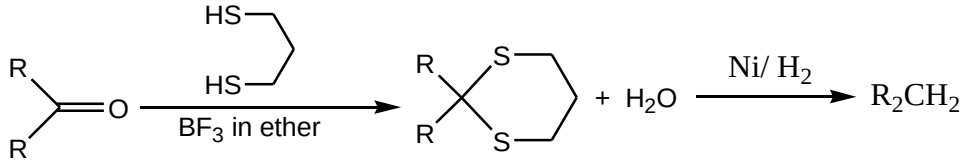



Synthetic Use of Umpolung Reaction:

I.




II.

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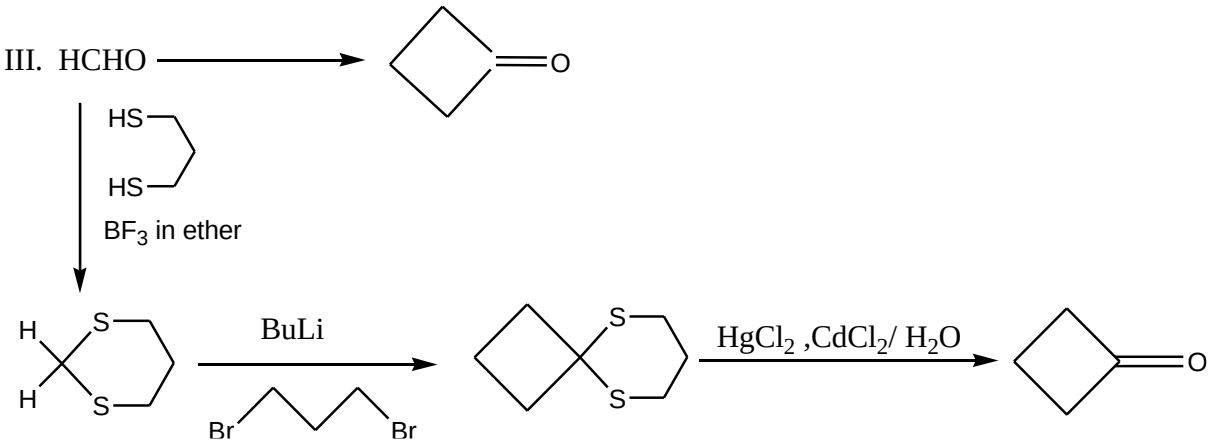
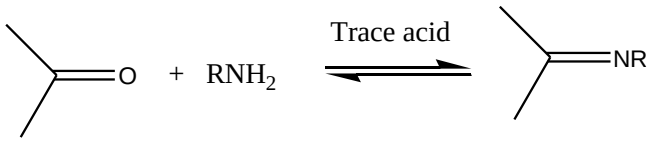
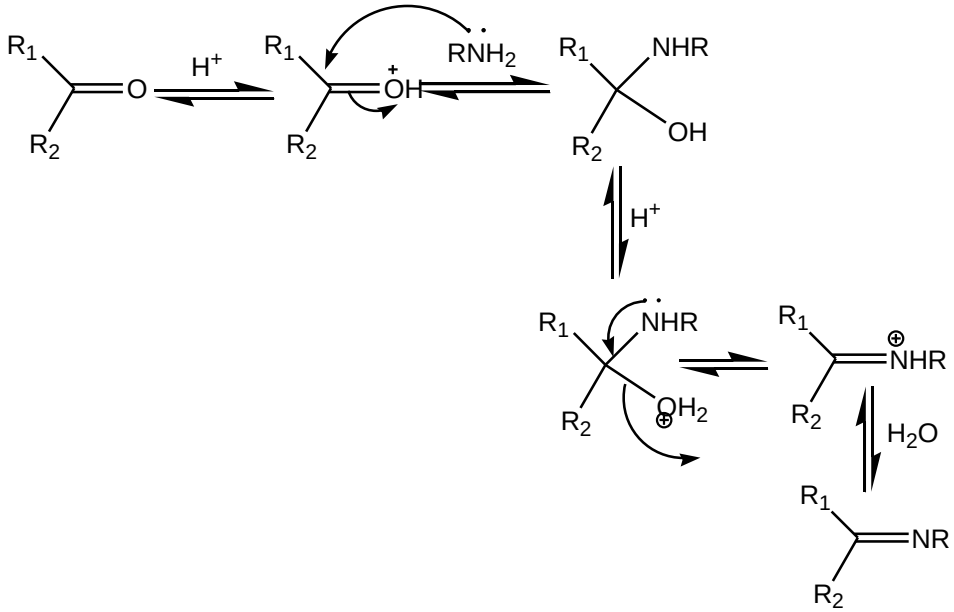



Addition of 'N' based Nucleophiles:

I. AMINE:




Addition-Elimination Mechanism




pH 4 – 5 is ideal for this reaction. At higher pH Step III is slower and at lower pH $RNH_2$ remains protonated $RN^+H_3$. Depending on $RNH_2$, different product can be obtained.

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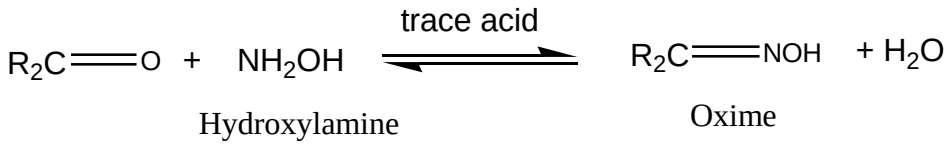
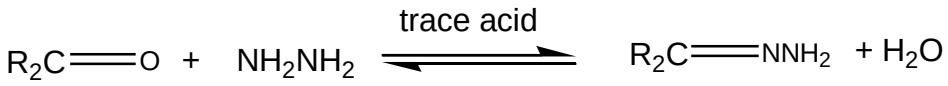
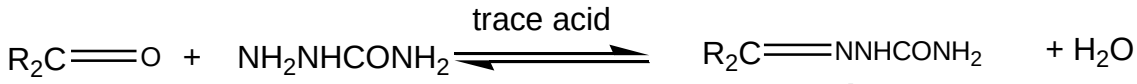


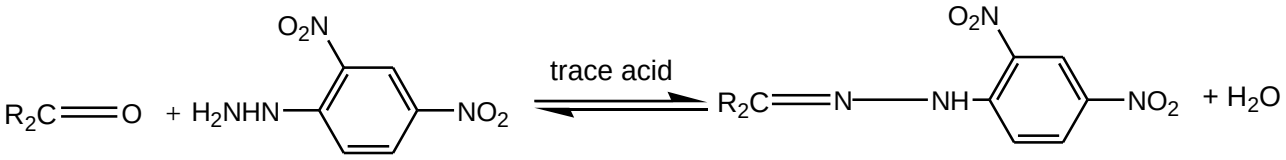

Hydroxylamine — Oxime




Hydrazine — Hydrazone




semicarbazide — Semicarbazone

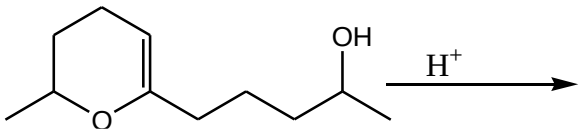



2,4 dintro phenyl hydrazine — 2,4 dintro phenyl hydrazone

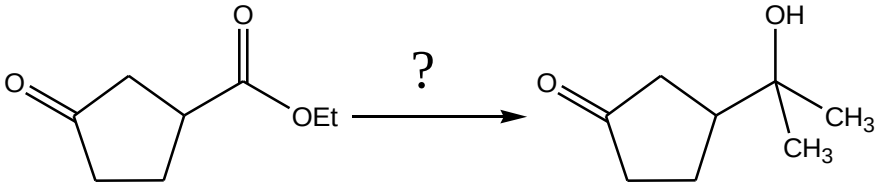
SOME PROBLEMS:

1. Hemiacetal formation is very fast for $CF_3CHO$ with $CH_3CH_2CHOH$ but acetal formation is very slow in anhydrous acid. Explai why?

2. Suggest product with mechanism.




3. How to Convert?

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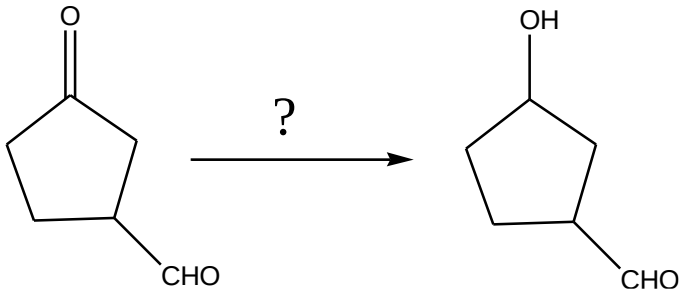
4.

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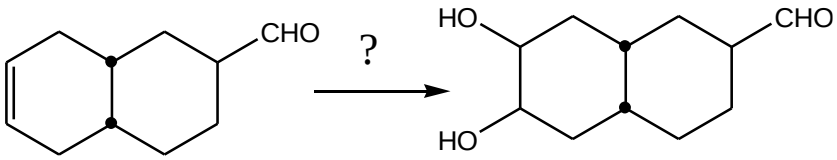


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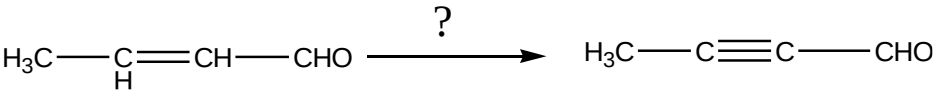


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