Pharmaceutical Chemistry – I (Organic Chemistry)

REACTION MECHANISM

---

1. FRIEDEL-CRAFT REACTIONS

Introduction:

The Friedel-Craft reactions are a set of reactions developed by Charles Friedel and James Craft in 1877 to attach substituents to an aromatic ring. There are two main types of Friedel-Craft reactions.

i. Friedel-Craft Acylation
ii.
iii. Friedel-Craft Alkylation

Both reactions proceed by electrophilic aromatic substitutions.

Catalysts Used:

- Metal Halides ○ $AlCl_3$ > BF_3 > $SbCl_3$ > $FeCl_3$ > $SnCl_3$ > $ZnCl_2$
- Proton Acids ○ HF > H_2SO_4 > H_3PO_4

Definition:

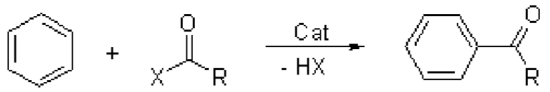
It is an effective means of introducing an acyl group into benzene ring.

Catalyst:

Mostly Ammonium chloride (NH_4Cl) or Aluminium chloride ($AlCl_3$) is used.

General Reaction:

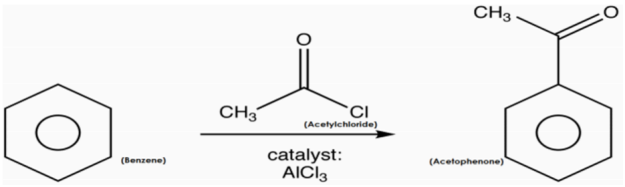
Benzene reacts with acid chloride (or anhydride) in the presence of $AlCl_3$ to give aromatic ketones e.g.



(Benzene) **(Acylchloride)** **(Acylbenzene)**

Example:

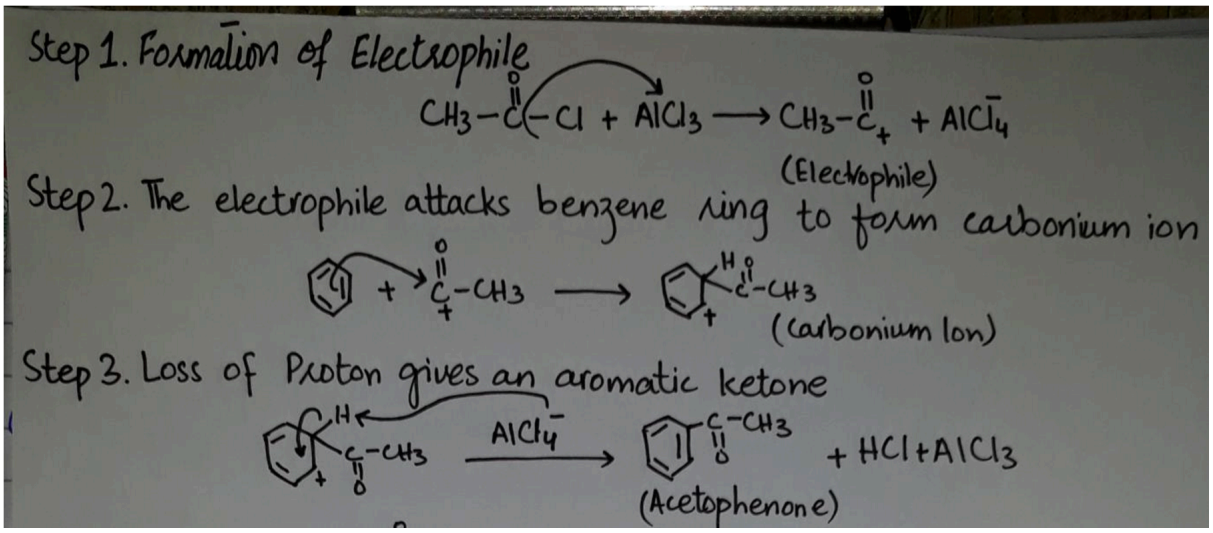
Benzene reacts with acetyl chloride in the presence of aluminium chloride to give acetophenone.



(Benzene) (Acetophenone)

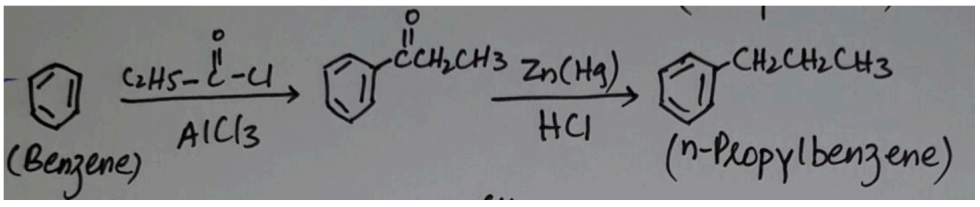
Mechanism:

The reaction is carried out in three steps.



Modifications or Applications:

Since alkyl benzenes other than methyl, ethyl or t-alkyl cannot be prepared from alkyl halides without rearrangement, they're best prepared by Friedel-CraftsAcylation-Clemenson reduction sequence e.g.



Friedel-Craft Alkylation Reaction:

Definition:

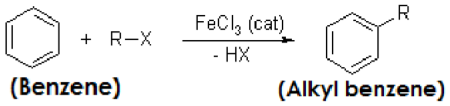
It is an effective means of introducing an alkyl group into the benzene ring.

Catalyst:

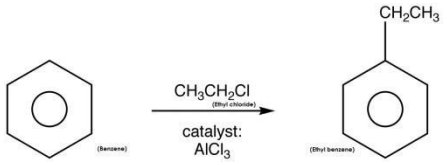
- $AlCl_3$
- $FeCl_3$

General Reaction:

Benzene reacts with alkyl halides to form alkyl-benzene in the presence of catalyst.



Example:



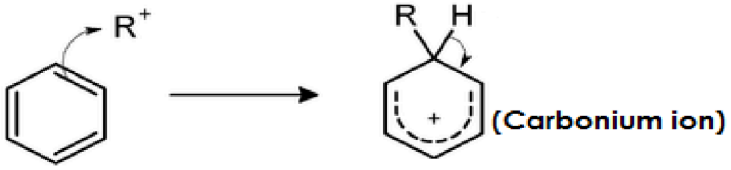
(Benzene) (Ethylbenzene)

Mechanism:

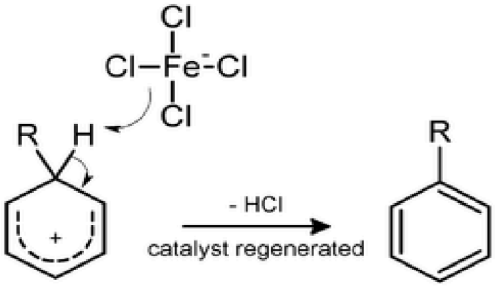
Three steps are involved in the reaction.

Step 1: Formation of an electrophile

Step 2: The electrophile attacks on benzene to give a carbonium ion



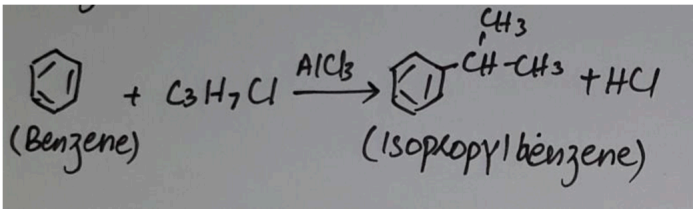
Step 3: Loss of proton gives alkylbenzene



Drawbacks:

While Friedel-Craft alkylation is useful in synthesis of certain alkyl benzenes, the reaction has two serious drawbacks.

- It is difficult to stop the reaction when one alkyl group has entered the ring. Di- or tri- alkyl-benzenes are formed.
- The alkyl groups often tend to rearrange e.g. when benzene is treated with npropyl chloride in the presence of $AlCl_3$, the product is iso-propyl benzene (cumene) rather than expected product n-propylbenzene.



---

2. MANNICH REACTION

Introduction:

The reaction is named after chemist (1917) Carl Mannich. It is basically an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia.

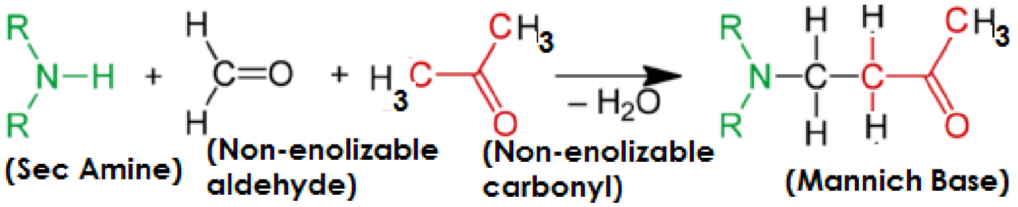
Definition:

It is a multi-potent condensation reaction of enolizable carbonyl compound, non-enolizable aldehyde and primary or secondary amine to yield compounds known as Mannich bases or β-amino carbonyl compounds.

Conditions:

- Acidic Medium (1970)
- Basic solution can also be used (modification)

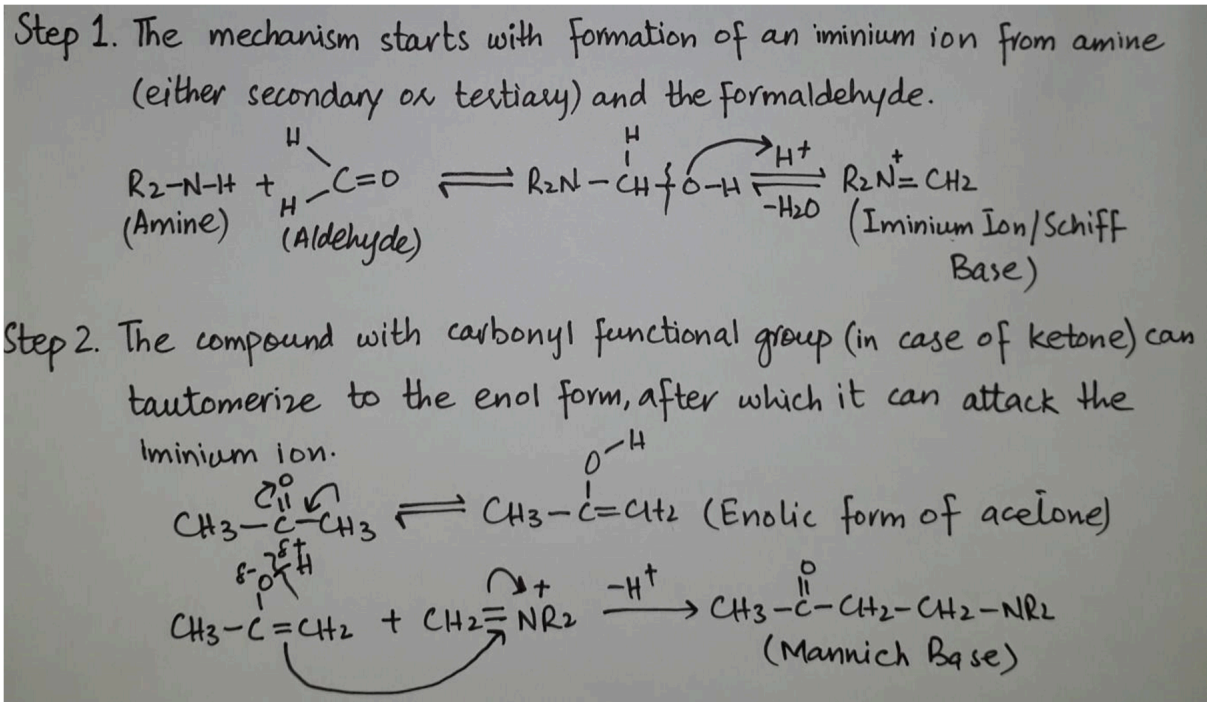
General Reaction:



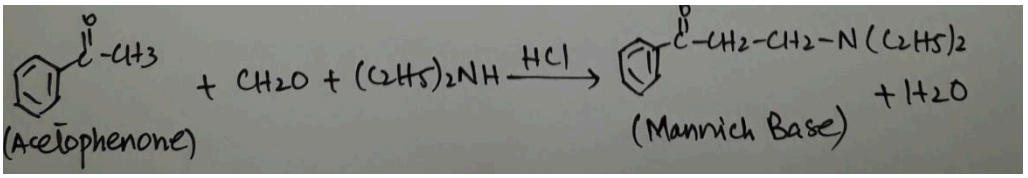
Explanation:

- This reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base.
- The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become an enol).
- In the Mannich reaction, primary or secondary amines or ammonia are employed for the activation of the formaldehyde. Tertiary amine lacks an N-H proton to form the intermediate enamine.

Mechanism:



Example:



Applications:

The Mannich reaction is employed in organic synthesis of numerous compounds like:

- Alkyl amines, polymers, catalysts
- Peptides, nucleotides, antibiotics and alkaloids (e.g. tropione)
- Agrochemicals (plant growth regulators)
- Pharmaceutical drugs like rolitetracyline (Mannich base of tetracycline) 🎬 Soaps and detergents

---

3. DIELS-ALDER REACTION

(2015)

Introduction:

The Diels-Alder reaction is an organic chemical reaction specifically a [4+2] cyclo-addition, which was first described by Otto Diels and Kurt Alder in 1928, for which they were awarded the Nobel Prize in Chemistry in 1950.

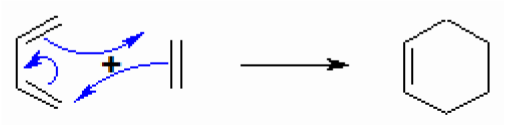
Definition:

It is an organic chemical reaction between a conjugated diene and a substituted alkene, commonly termed the dienophile (diene-lover), to form a substituted cyclohexene system (adduct).

Conjugated Diene (Substituted) + Olefin (Substituted) → Cyclohexene (Substituted)

General Reaction:

The simplest example of this reaction is the reaction of 1, 3-Butadinen with ethylene.



(Diene) (Dienophile) (Cyclohexene)- Adduct

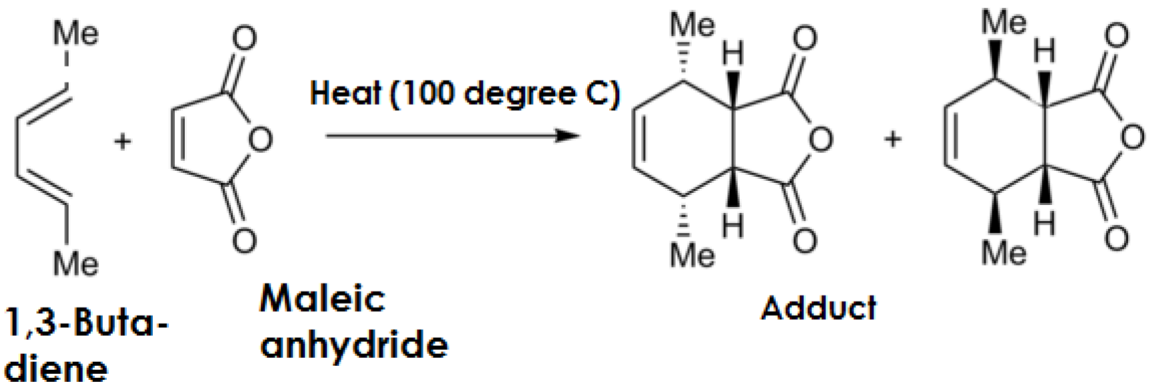
Catalyst:

No catalyst is required.

Mechanism:

- A diene and a dienophile combine to make rings and bicyclic compounds.
- The tree bonds in the starting two materials are converted into two new sigma bonds and one pi-bond.
- Typically this reaction works best when either the diene is substituted with electron-donating groups (-OR, -NR_2) or when the dienophile is substituted with electron withdrawing groups (-NO_2, -CN, -COR).

Example:



Applications:

- This reaction is particularly used in synthetic organic chemistry as a reliable method for forming 6-membered systems with good control over regio- and stereo- chemical properties.
- Diels-Alder reactions can be reversible under certain conditions, the reverse reaction is known as the retro-Diels-Alder reaction.

---

4. GRIGNARD REAGENT

Introduction:

- Organo-magnesium halides are called as Grignard reagent.
- They're named after Victor Grignard (Nobel Prize, 1912).
- Organo-magnesium halides include alkyl- or aryl- magnesium halides.
- They're highly reactive, greater use in organic synthesis than any other single organic reagent.
- They're used in synthesis of alkanes, alkenes, alcohols, ketones and carboxylic acids etc.
- They are represented as RMgX, R-MgX, RMg-X, ArMgX etc.

Preparation:

- They're prepared in laboratory by the action of alkyl halides on magnesium metal in the presence of dry ether.

Physical Properties:

- Non-volatile, colorless solids

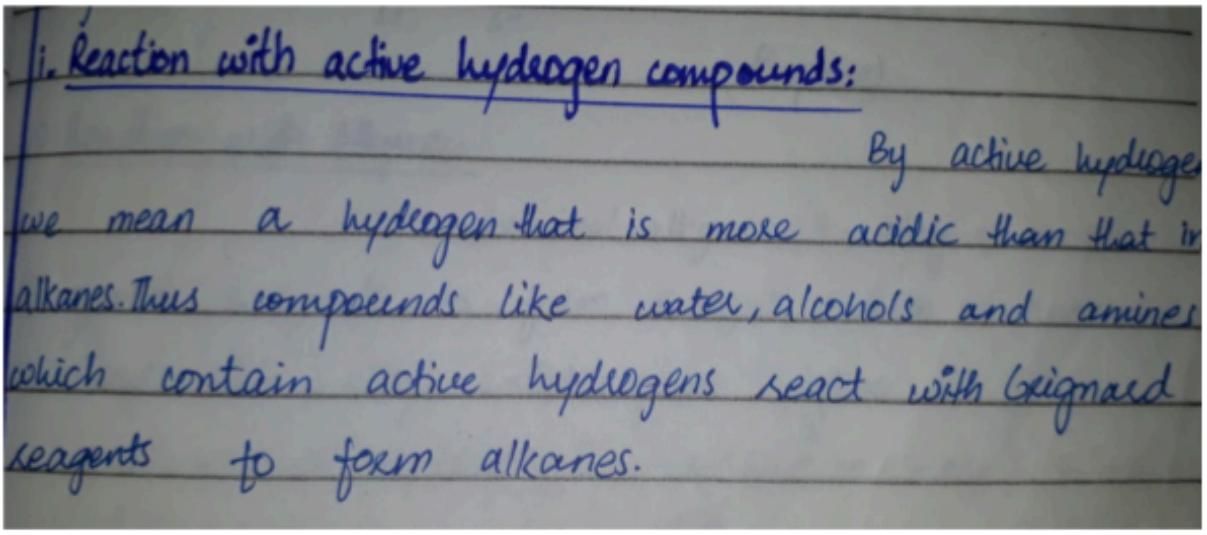
- Seldom isolated in free state on account of their explosive nature
- Always prepared in ether solution

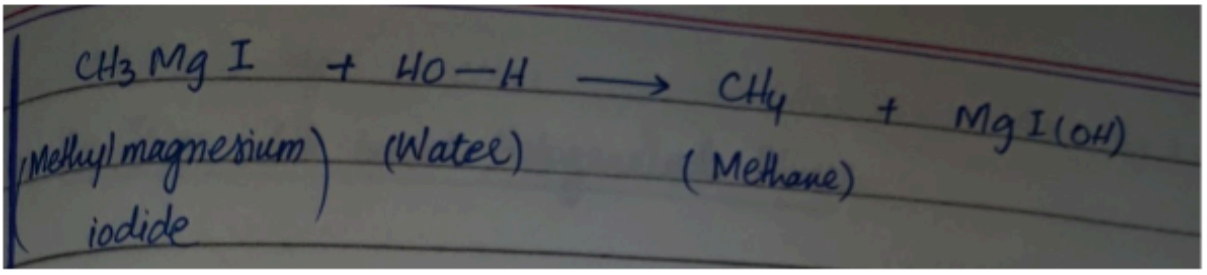
Chemical Properties:

The C-Mg bond in Grignard reagent is covalently bonded but highly polar. The carbon atom is more electronegative than Mg. the electrons of C-Mg bond are drawn towards the C atom. Thus the Grignard reagent gives nucleophilic addition and substitution reactions.

Synthetic Importance:

Grignard reagent reacts with a variety of compounds yielding almost the entire range of organic substances.





$CH_3MgI + C_2H_5O-H \longrightarrow CH_4 + MgI(OC_2H_5)$

(Ethanol)

$CH_3MgI + C_2H_5NH-H \longrightarrow CH_4 + MgI(NHC_2H_5)$

(Ethylamine)

$CH_3MgI + H-NH_2 \longrightarrow CH_4 + MgI(NH_2)$

(Ammonia)

• Since CH_4 evolved in above reactions can be measured, it gives a method for the estimation of -OH and $-NH_2$ group in organic compounds.

ii. Reaction with Alkyl Halides:

Grignard reagents react with saturated alkyl halides to form higher alkanes or alkenes.

$CH_3\overset{\delta-}{Mg}\overset{\delta+}{I} + CH_3\overset{\delta+}{CH_2}-\overset{\delta-}{Br} \longrightarrow CH_3CH_2CH_3 + MgI(Br)$

(Propane)

iii. Reaction with Alkynes:

Terminal alkynes (1-alkynes) react with Grignard reagents to form R-Mg-X which on subsequent treatment with alkyl halides form higher alkynes.

$CH_3\equiv C-H + CH_3MgI \longrightarrow CH_3C\equiv C-MgI + CH_4$

(Propyne) (Propylmagnesium iodide)

$CH_3C\equiv C-MgI + CH_3I \longrightarrow CH_3C\equiv C-CH_3 + MgI_2$

iv. Reaction with lower Halogenated Ethers:

Grignard reagents attack with lower halogenated ethers to form higher ethers.

$CH_3CH_2MgBr + ClCH_2OCH_3 \longrightarrow CH_3CH_2CH_2OCH_3 + MgBrCl$

(Ethylmagnesium bromide) (Chloromethyl ether) (Methyl propyl ether)

V. Reaction with Ethylene Oxide:

Grignard reagents react with ethylene oxide to give an addition product which on hydrolysis forms primary alcohols.

$$CH_3MgI + \underset{\diagdown O \diagup}{CH_2-CH_2} \longrightarrow [CH_3CH_2CH_2\bar{O}\overset{+}{M}gI] \xrightarrow[-MgI(OH)]{H_2O/H^+} CH_3CH_2CH_2OH$$

(Addition Product) (1-Propanol)

(1° Alcohol)

VI. Reaction with Aldehydes: (Primary or Secondary Alcohols are obtained).

A- Formaldehyde reacts with Grignard reagent to give addition products which on hydrolysis yield primary alcohols

$$H-\overset{\overset{\delta-}{O}}{\overset{\|}{C}}-H + \overset{\delta-}{CH_3}-\overset{\delta+}{MgI} \longrightarrow \left[H-\underset{\underset{CH_3}{|}}{\overset{\overset{\bar{O}\overset{+}{M}gI}{|}}{C}}-H\right] \xrightarrow[-MgI(OH)]{H_2O/H^+} H-\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-H$$

(Addition Product)

(unstable)

(Ethanol) (1° Alcohol)

From R-MgX

B. Other aldehydes react with Grignard reagents to give addition products which on hydrolysis produce secondary alcohols.

$$CH_3-\overset{\overset{\delta-}{O}}{\overset{\|}{C}}-H + \overset{\delta-}{CH_3}-\overset{\delta+}{MgI} \longrightarrow \left[CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{\bar{O}\overset{+}{M}gI}{|}}{C}}-H\right] \xrightarrow[-MgI(OH)]{H_3O^+} CH_3-\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-H$$

From RMgX

(Acetaldehyde)

(Addition product)

(UNSTABLE)

Isopropyl alcohol

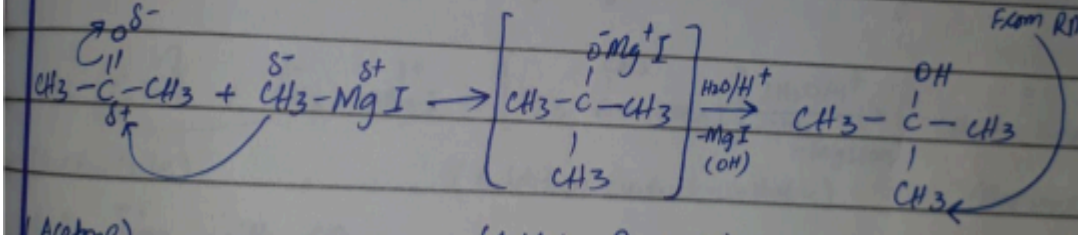
(2° Alcohol)

C. Reaction with Ketones:

(UNSTABLE)

vii. Reaction with Ketones:

Grignard reagents react with ketone to give addition products which on hydrolysis form tertiary alcohols.



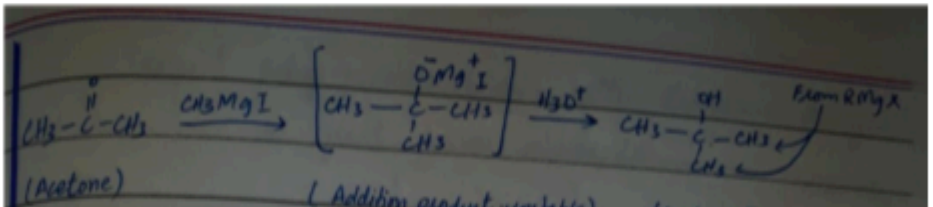
(Acetone) (Addition Product I) (unstable) tert-butyl-alcohol (3°-alcohol)

viii. Reaction with Esters:

Grignard reagents react with formic esters to form secondary alcohols while other esters yield tertiary alcohols.

A. Reaction with Ethyl formate.

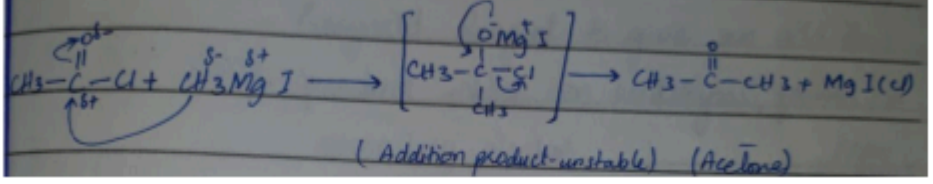
Two steps are involved.



(Acetone) (Addition product-unstable) (tert-Butyl alcohol)

ix. Reaction with Acid Chlorides:

Grignard reagents react with acid chloride to form ketones.



(Addition product-unstable) (Acetone)

5. WOLFF-KISHNER REDUCTION

(2007, 2009, 2012, 2016)

Introduction:

The Wolff-Kishner reduction is a reduction first reported by Nikolai Kishner (1911) and Ludwing Wolff (1912).

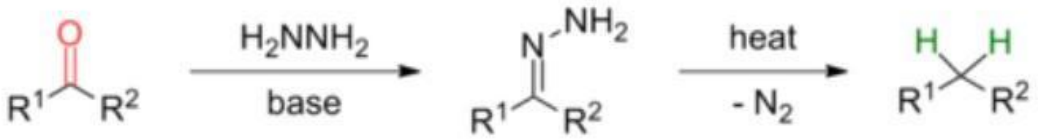
Definition:

The Wolff-Kishner reduction is a reaction used in organic chemistry to convert carbonyl functionalities (i.e. aldehydes and ketones) into methylene group.

Conditions:

- Hydrazones (or simple semicarbazones)
- Heat
- Base (e.g. NaOH / KOH) – mostly KOH is used.

General Reaction:



Mechanism:

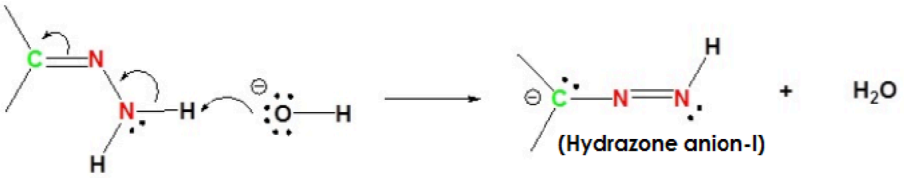
Step 1: Reaction of Aldehydes or Ketones with hydrazine (hydrazones are produced):

$$R_2C{=}O + N_2H_4 \rightarrow R_2C{=}N\text{-}NH_2 + H_2O$$

(Hydrazone) **Step 2:**

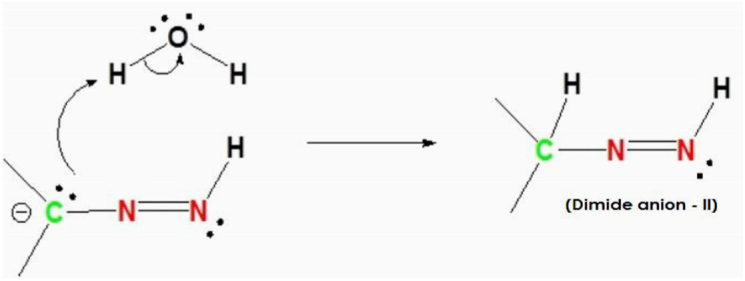
Deprotonation of Nitrogen from Hydrazone:

Hydrazone anion – I is formed by the deprotonation of the terminal nitrogen by base (KOH) and a molecule of water is released.



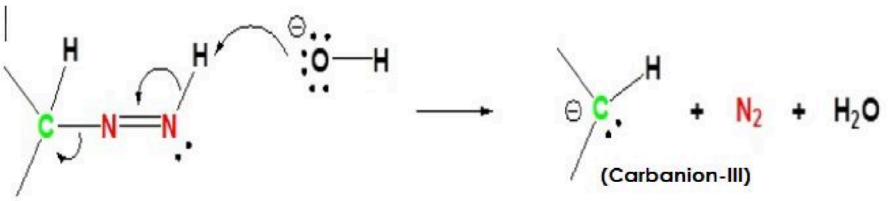
Step 3: Protonation of Carbon:

Water produced in upper step donates a proton to the carbon of hydrazone anion –I to form anion – II.



Step 4: Deprotonation of Nitrogen:

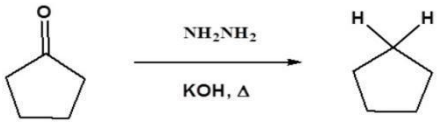
Nitrogen is removed from dimide anion – II to form sp^3 hybridized carbanionIII via OH^-.



Step 5: Protonation of Carbon:

In the presence of proton, carbanion-III is converted into alkane.

Example:



(Cyclopentanone) (Cyclopentane)

(Add other relevant examples)

Uses:

This reaction has been applied to the total synthesis of Scopadulic acid B, Asipidospermidine and Dysidolidc.

---

6. ARNDT-EISTERT REACTION

Introduction:

Arndt-Eistert reaction is named after the German chemists Fritz Arndt (18851969) and Bernd Eistert (1902-1978).

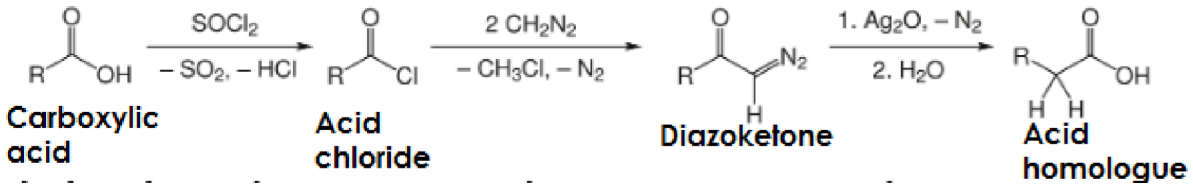
Definition:

The Arndt-Eistert synthesis is a series of chemical reactions, designed to convert a carboxylic acid into a higher acid homologue (i.e. it contains one additional carbon atom) is considered a homologation process.

Conditions:

- Nucleophile (H_2O, alcohol or amine)
- Alternate catalysts include (light, Pt, Ag, Copper salts)

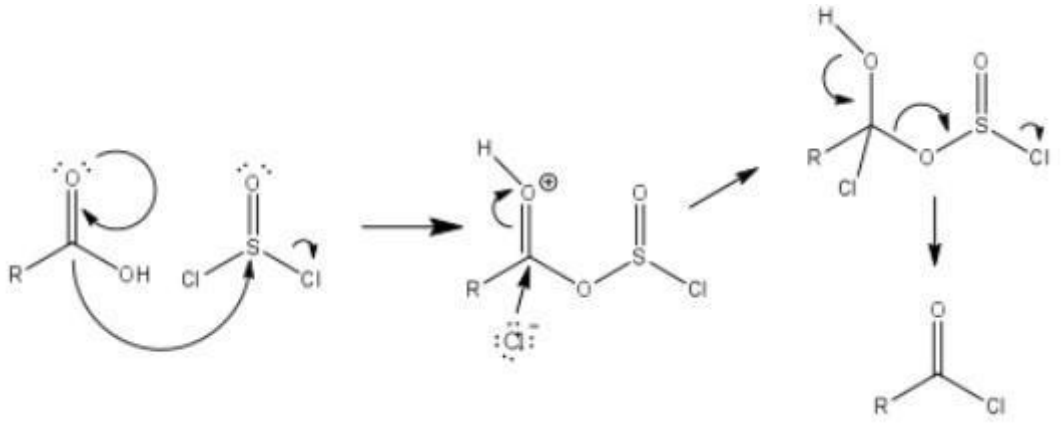
General Reaction:



Mechanism:

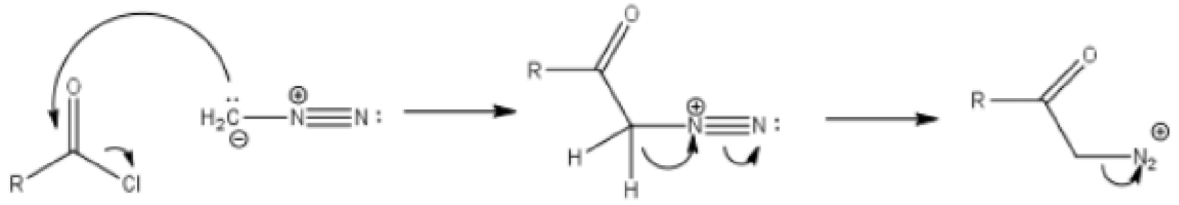
Step 1: Activation of Carboxylic acid group by chlorination with $SOCl_2$

Classic Arndt-Eistert synthesis uses thionyl chloride to convert starting acid into an acid chloride. Any procedure can be used that will generate an acid chloride.



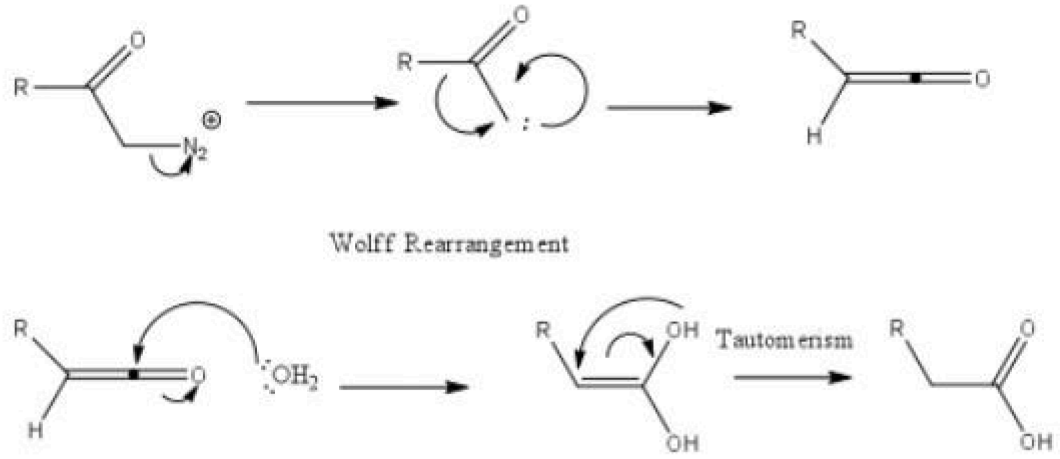
Step 2: Homologation of Diazomethane

Acid chloride reacts with diazomethane to give diazoketone. Diazoketones are typically produced by the method described here but other methods such as diazogroup transfer can also be used. Excess diazomethane can be destroyed by the addition of small amounts of acetic acid or vigorous stirring.

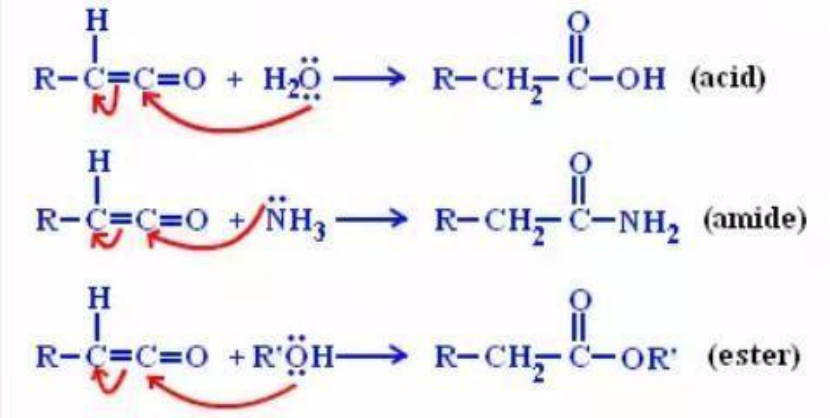


Step 3: Wolff Rearrangement of Diazoketone to Ketones and Finally in Acid Homologue

After interference of nucleophile (water) and metal catalyst (Ag_2O), diazoketone will form the desire acid homologue. Since diazomethane is toxic and violent explosive, many safer alternatives have been developed, such as usage of ynolates or diazomethane. Tautomerism finally plays a role in getting to the product.



This final step can be conducted in the presence of various nucleophiles e.g. water (to give carboxylic acid), alcohol (to give ester), amines (to give amides).



Applications:

- It is a popular method of preparing or producing β-amino acids from α-amino acids.
- Peptides that contain beta-amino acids feature a lower rate of metabolic degradation and are therefore of interest for pharmaceutical applications. This reaction is used for synthesis of dienic acids.

---

7. BAYER-VILLIGER OXIDATION

(2013, 2014, 2015)

Introduction:

The reaction is named on the two scientists Adolf Bayer and Victor Villiger who first reported this reaction is 1899-1900.

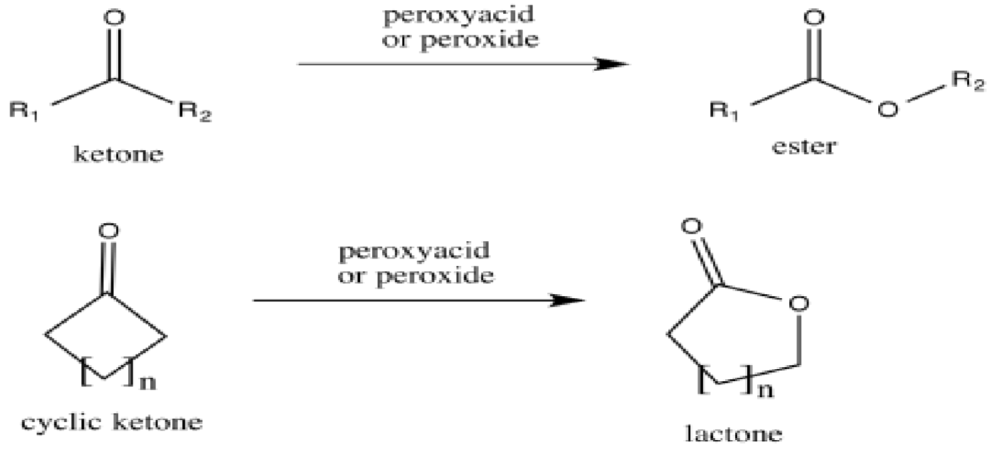
Definition:

The Bayer-Villiger oxidation (or rearrangement) is an organic reaction that forms an ester from a ketone (aliphatic) or lactone from a cyclic ketone.

Oxidizing Agent:

- First, Caro's acid (permonosulphuric acid – H_2SO_5) was used
- Organic peracids (per-benzoic acid, per-acetic acid) or Peroxide

Overall Reaction:



Mechanism:

Step 1: Protonation

- In the first step per-oxyacid protonates the oxygen of the carbonyl group.
- This makes the carbonyl group more susceptible to attack by the per-oxyacid.
- Than per-oxyacid attacks the carbonyl group forming known as adduct-I. Hydrogen ion leaves at the end.

Step 2: Migration of Peroxide Group

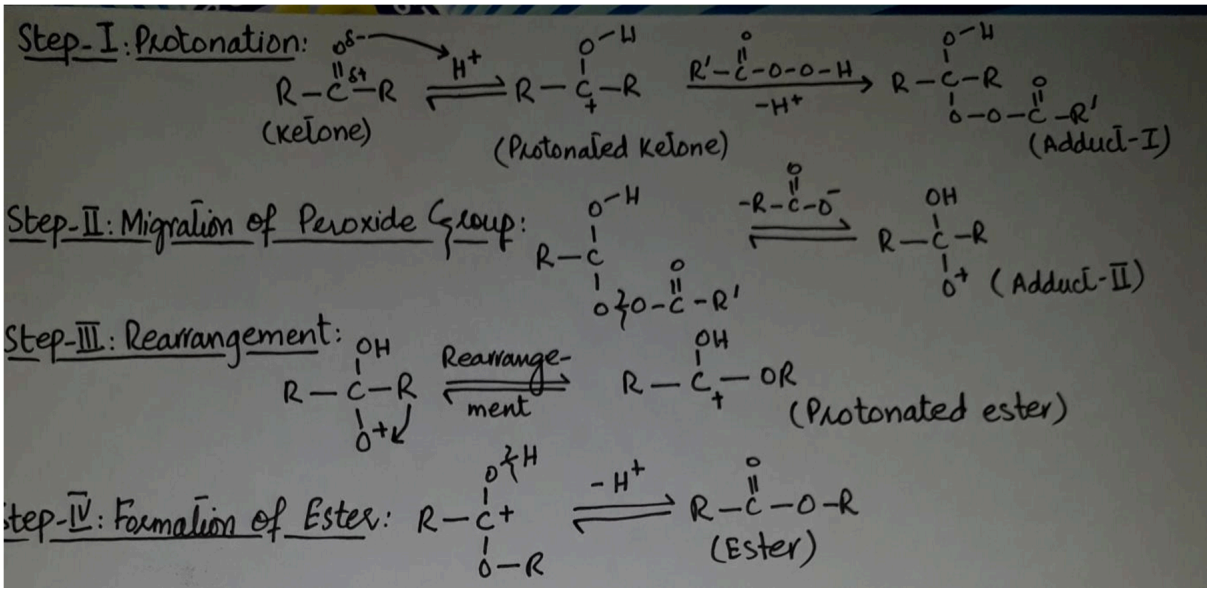
One of the substituents on the ketone migrates to the oxygen of the peroxide group while a carboxylic acid leaves and adduct-II is formed.

Step 3: Rearrangement

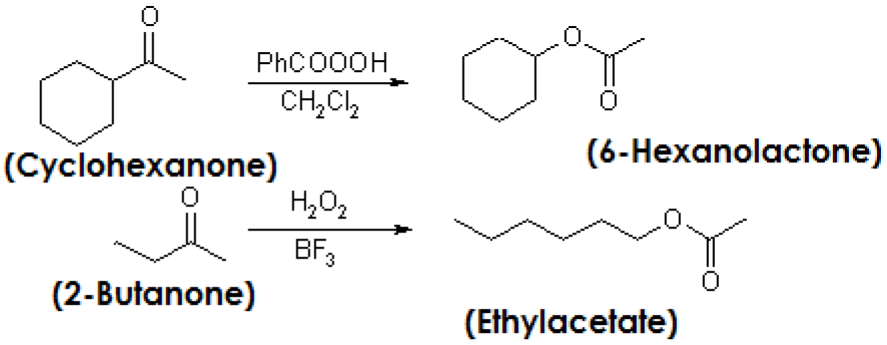
Adduct-II rearranges itself and protonated ester is formed.

Step 4: Formation of Ester

In the final step, deprotonation of the oxygen of the carbonyl group produces the ester.



Examples:



Uses:

The yield produced in this reaction is reasonable, and so this reaction is useful in structure determination, and may also be used as a method of preparing acids.

- It is used in making Zoapatanol a biological active molecule used to induce menstruation and labor.
- Steroidal hormones can be made by this reaction.

---

8. CANNIZZARO'S REACTION

(2007, 2012, 2013, 2014, 2015, 2016)

Introduction:

This reaction is named after its discoverer Stanislo Cannizzaro in 1853 i.e. is a redox chemical nucleophilic addition reaction.

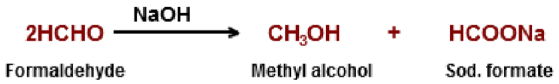
Definition:

It is a disproportionation (self oxidation-reduction) reaction in which two molecules of the aldehyde are involved, one molecule being converted into the corresponding alcohol (reduced product) and the other into the acid in salt form (the oxidized product) in the presence of strong alkali.

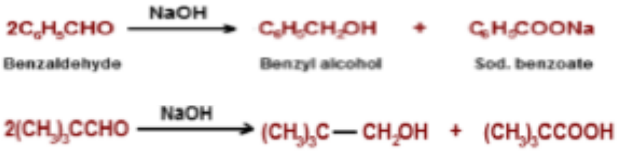
Conditions:

- Strong base i.e. 50% NaOH, Room temperature (25 to 30^0C)
- Aldehyde with α-hydrogen don't undergo this reaction
- Normally, ketones don't undergo this reaction

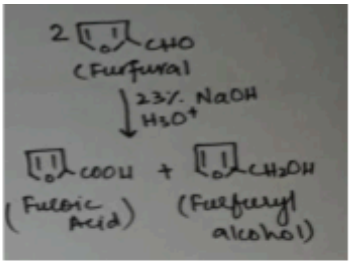
General Reaction:

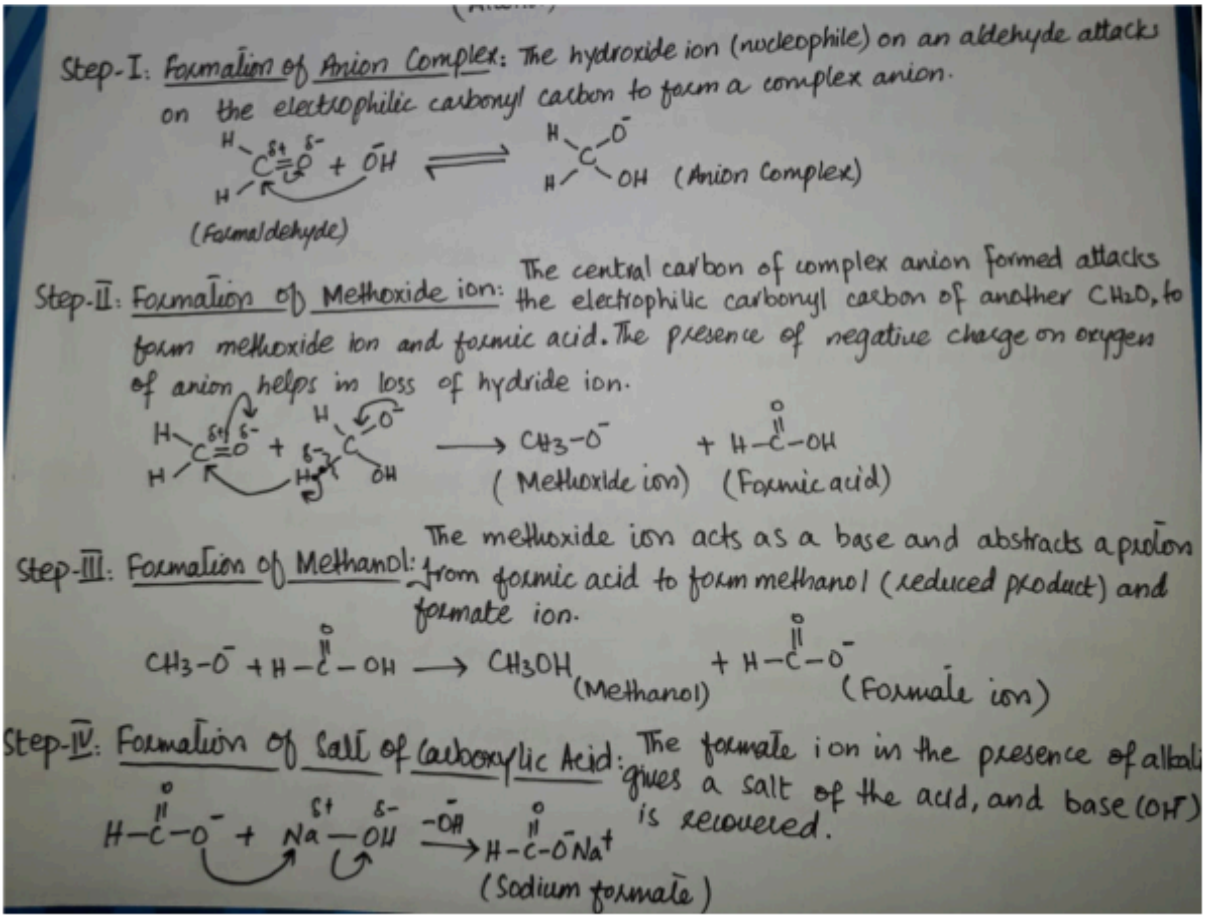


Example:



Mechanism:



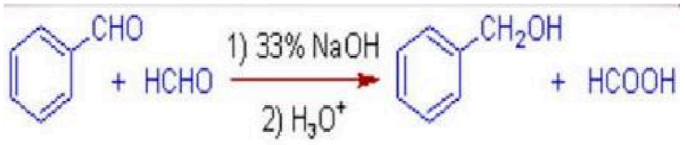


Note:

The reaction is mainly applicable to aromatic aldehydes.

Crossed Cannizzaro's Reaction:

The Cannizzaro's reaction can be take place between two different aldehydes and then known as "Crossed Cannizzaro's Reaction". E.g. Benzaldehyde and formaldehyde react to form benzyl alcohol and formic acid.



9. METAL HYDRIDE REDUCTION

(2010, 2017)

Introduction:

In recent years, inorganic hydrides have become extremely important as reducing agent. These reagents have considerable uses with expensive and sensitive carbonyl compounds.

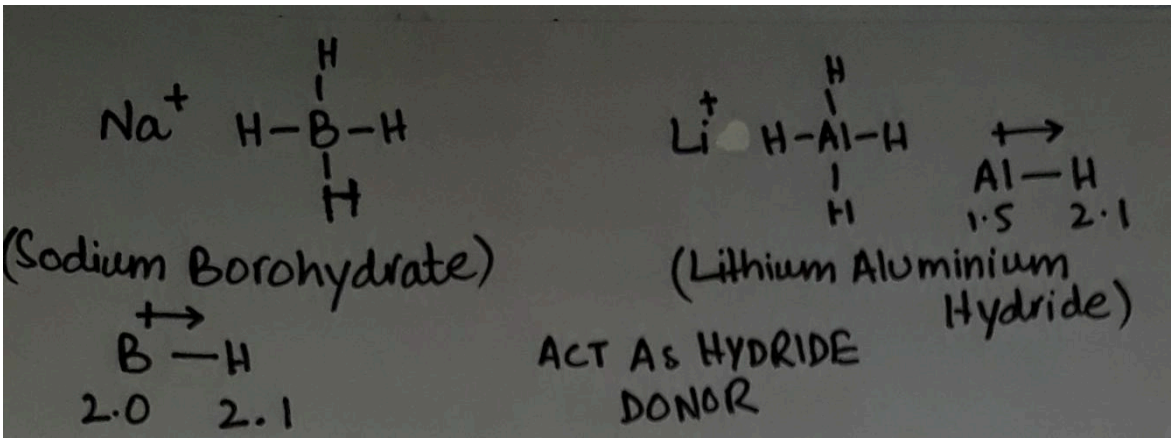
Common Reducing Agents:

These agents also act as nucleophile.

- $NaBH_4$ (Sodium borohydrate)
- $LiAlH_4$ (Lithium aluminium hydride)

Limitations of Reagents:

Forming aldehydes from carboxylic acid derivatives is often a challenge, because weaker reducing agents ($NaBH_4$) are incapable of reducing esters and carboxylic acid, which are relatively stable; and stronger agents ($LiAlH_4$) immediately reduce the formed aldehyde to alcohol.

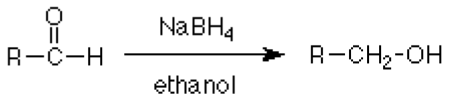


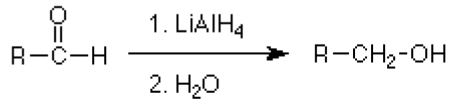
Sketch:

Metal Hydride Reduction	
$LiAlH_4$	**$NaBH_4$**
Strong reducing agent	Weak reducing agent

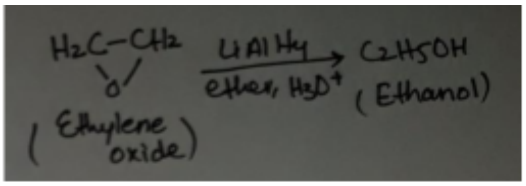
Reduces aldehydes, ketones, carboxylic acids, esters, Epoxides, nitriles, amides	Reduces only aldehydes and ketones
Use solvents like ether, diethyl ether and THF	Use solvents like alcohol and water

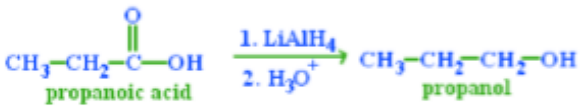
General Reaction:

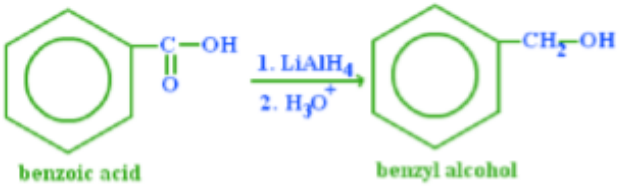




Examples:

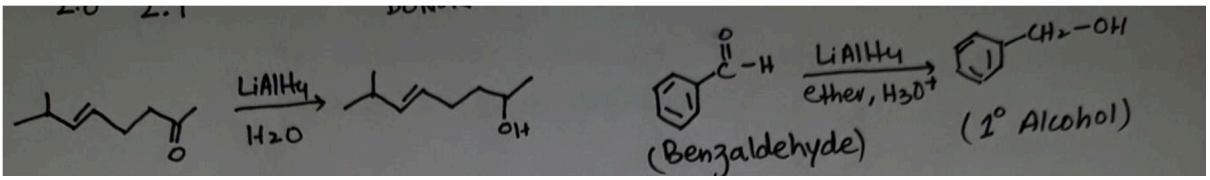




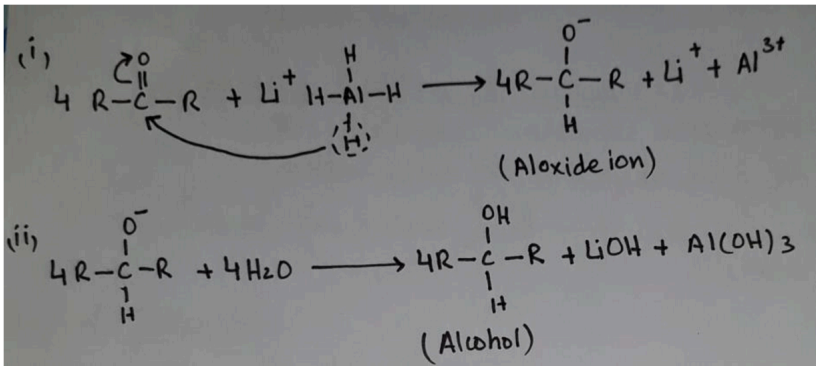


Note:

Neither $NaBH_4$ nor $LiAlH_4$ reduces the isolated double bonds.

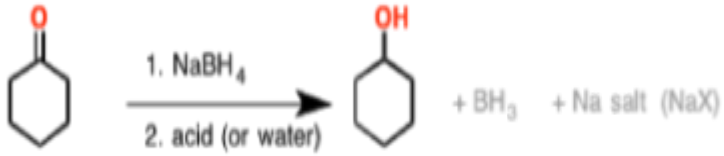


General Mechanism:



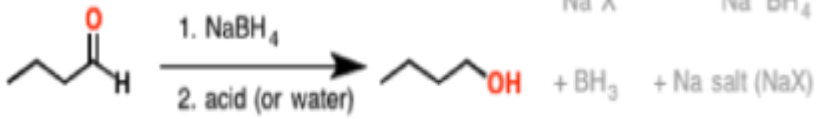
Other Examples:

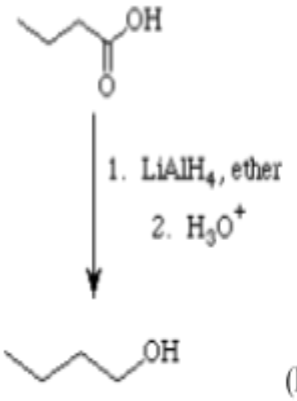
Example 1: Reduction of ketones



	Form	Break
	C–H	C–O
	O–H	B–H
	Na X	Na BH4

Example 2: Reduction of aldehydes





(Preparation of Alcohol from Carboxylic Acids)

10. PERKIN REACTION

(2009, 2017)

Introduction:

The first aldehyde reaction is associated with specific investigator of Cannizzaro's reaction. The next was developed by William Henry Perkin in 1867 for the preparation of various unsaturated aromatic acids.

Definition:

When benzaldehyde (or any other aromatic aldehyde) is heated with the anhydride of an aliphatic acid (containing two α-hydrogen atoms) in the presence of sodium salt, condensation (aldol) takes place to form a β-acrylic acid i.e. Cinnamic acid (α-β-unsaturated acid).

Conditions:

- Temperature (170 – 175^{0}C)
- Aromatic aldehyde
- Acid anhydride
- Alkali salt (acts as base catalyst – other bases can be used instead) 🎬 This reaction is not carried out by aliphatic aldehydes.

Note:

- Only the alpha-hydrogen atoms of the anhydride are involved in the condensation.
- The acyloxyl ion acts as a base and in some cases triethylamine as base give better yield.

General Reaction:

When benzaldehyde reacts with acetic anhydride and sodium acetate, Cinnamic acid is formed.

$$C_6H_5CHO + (CH_3CO)_2O \xrightarrow[170-180^0C]{CH_3COONa} C_6H_5\text{-}CH{=}CHCOOH + CH_3COOH$$

(Benzaldehyde) (Acetic anhydride) (Cinnamic Acid)

Substitution and Yield Percentage:

If different compounds are substituted on benzaldehyde, yield percentage is changed e.g.

Position of Aromatic Aldehyde on which Group is Substituted	Group which is Substituted	Percentage Yield
3	Nitro ($-NO_2$) Group	75%
2	Nitro ($-NO_2$) Group	75%
4	Nitro ($-NO_2$) Group	82%
2	Chloro (-Cl) Group	71%
3	Chloro (-Cl) Group	63%
4	Chloro (-Cl) Group	52%
2	Methyl ($-CH_3$) Group	15%
3	Methyl ($-CH_3$) Group	23%
4	Methyl ($-CH_3$) Group	33%

Mechanism:

Step-I: Formation of Carboxylate ion:

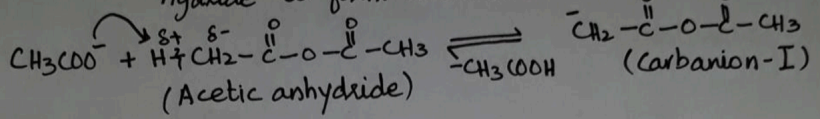
Sodium acetate is ionized to form acetate ion.

$CH_3COONa \rightleftharpoons CH_3COO^- + Na^+$

(Sodium Acetate) (Acetate ion)

Step-II: Formation of Carbanion-I:

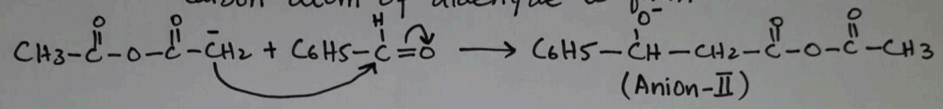
The carboxylate anion takes or abstracts from α-carbon of anhydride to form carbanion-I.



(Acetic anhydride) (Carbanion-I)

Step-III: Nucleophilic Addition of Carbanion-I:

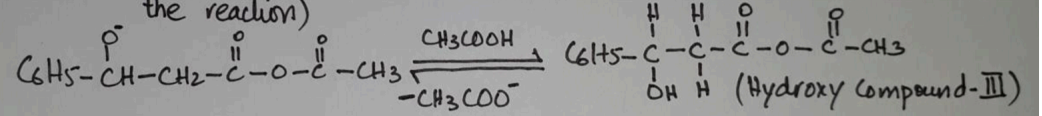
This carbanion undergoes nucleophilic addition at carbonyl carbon atom of aldehyde to form anion-II.



(Anion-II)

Step-IV: Protonation:

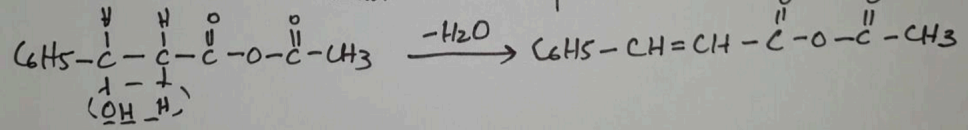
The anion takes up a proton from acetic acid (formed during the reaction)



(Hydroxy Compound-III)

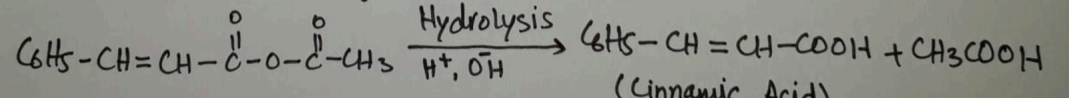
Step-V: Dehydration:

A water molecule is removed from hydroxy compound-III to create unsaturation in the compound.



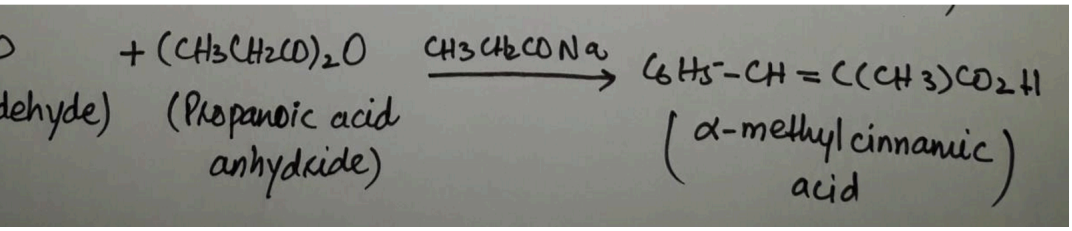
Step-VI: Formation of Cinnamic Acid:

Resulting dehydrated molecule is hydrolysed and desired product is formed.

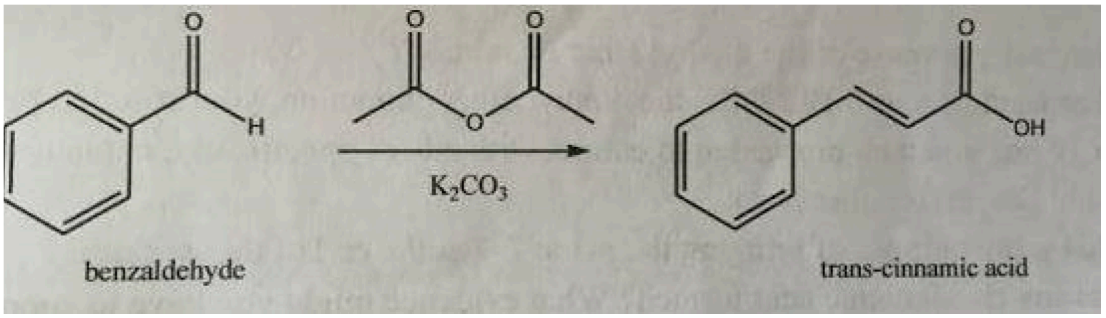


(Cinnamic Acid)

Examples:



(Benzaldehyde) (Propanoic acid anhydride) (α-methyl cinnamic acid)



Industrial Application:

When salicaldehyde reacts with acetic anhydride in the presence of sodium ethanoate, coumarin is formed which is used in perfume industry.