SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

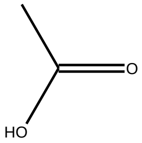
UNIT – I - CARBOXYLIC ACIDS AND THEIR DERIVATIVES - SCY1315

1. CARBOXYLIC ACIDS AND THEIR DERIVATIVES

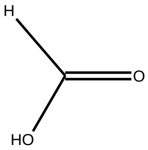
Structure and nomenclature - General methods of preparation of carboxylic acids – acidity – Effect of substituents on acidity – Physical and Chemical properties –Hell-Volhard-Zelinsky Reaction –Dicarboxylic acids - oxalic, malonic succinic, glutaric, adipic, phthalic, acrylic, crotonic and cinnamic acids – Stereospecific addition to maleic and fumaric acids – Derivatives of carboxylic acids – Acid halides, esters, anhydrides and amides – Preparation and Properties – Relative reactivity - Acid and alkaline hydrolysis of esters – trans-esterification.

Organic compounds containing carboxylic group are known as carboxylic acids. Their general formulae is RCOOH.

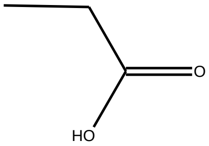
NOMENCLATURE



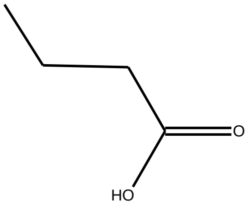
Ethanoic acid



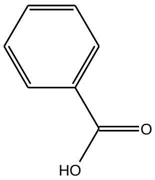
methanoic acid



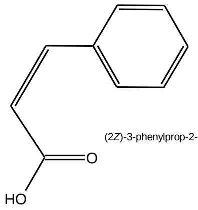
Propanoic acid



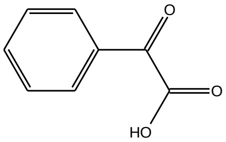
Butanoic acid



Benzoic acid

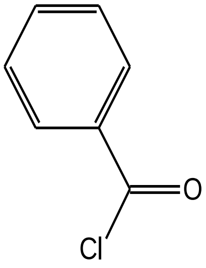


(2Z)-3-phenylprop-2-enoic acid

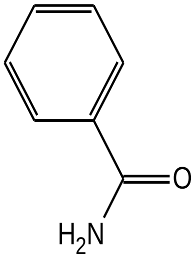


oxo(phenyl)acetic acid

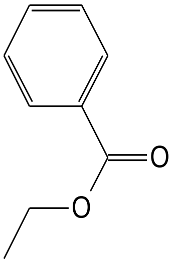
ACID DERIVATIVES



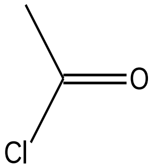
benzoyl chloride



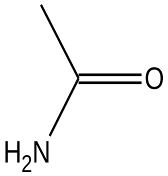
benzamide



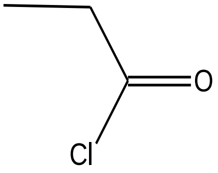
ethyl benzoate



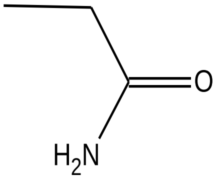
acetyl chloride



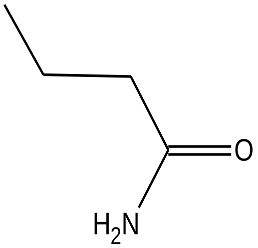
acetamide



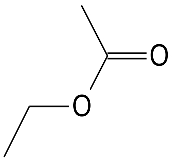
propanoyl chloride



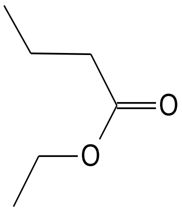
propanamide



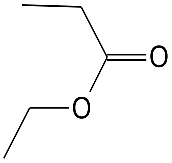
butanamide



ethyl acetate

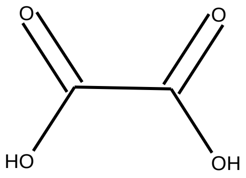


ethyl butanoate

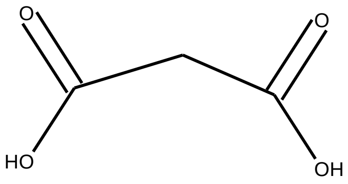


ethyl propanoate

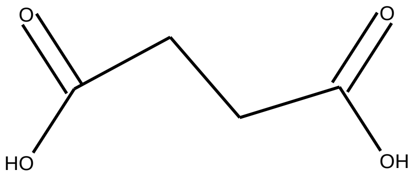
DICARBOXILIC ACIDS



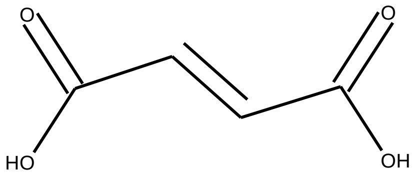
oxalic acid



propanedioic acid



butanedioic acid

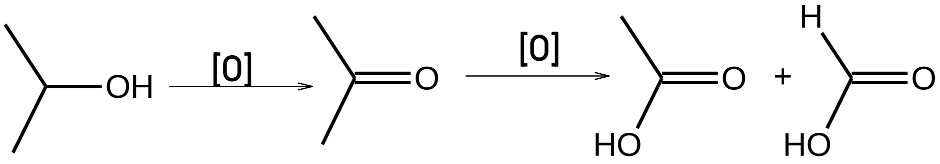


(2*E*)-but-2-enedioic acid

GENERAL PREPARATION METHODS

1. Oxidation of alcohols, aldehydes and ketones

$$CH_3CH_2OH \xrightarrow[{[0]}]{} CH_3CHO \xrightarrow[{[0]}]{} CH_3COOH$$



2. Hydrolysis of cyanides and amides

$$CH_3CN \xrightarrow{H_3O^+} CH_3CONH_2 \xrightarrow{H_3O^+} CH_3COOH$$

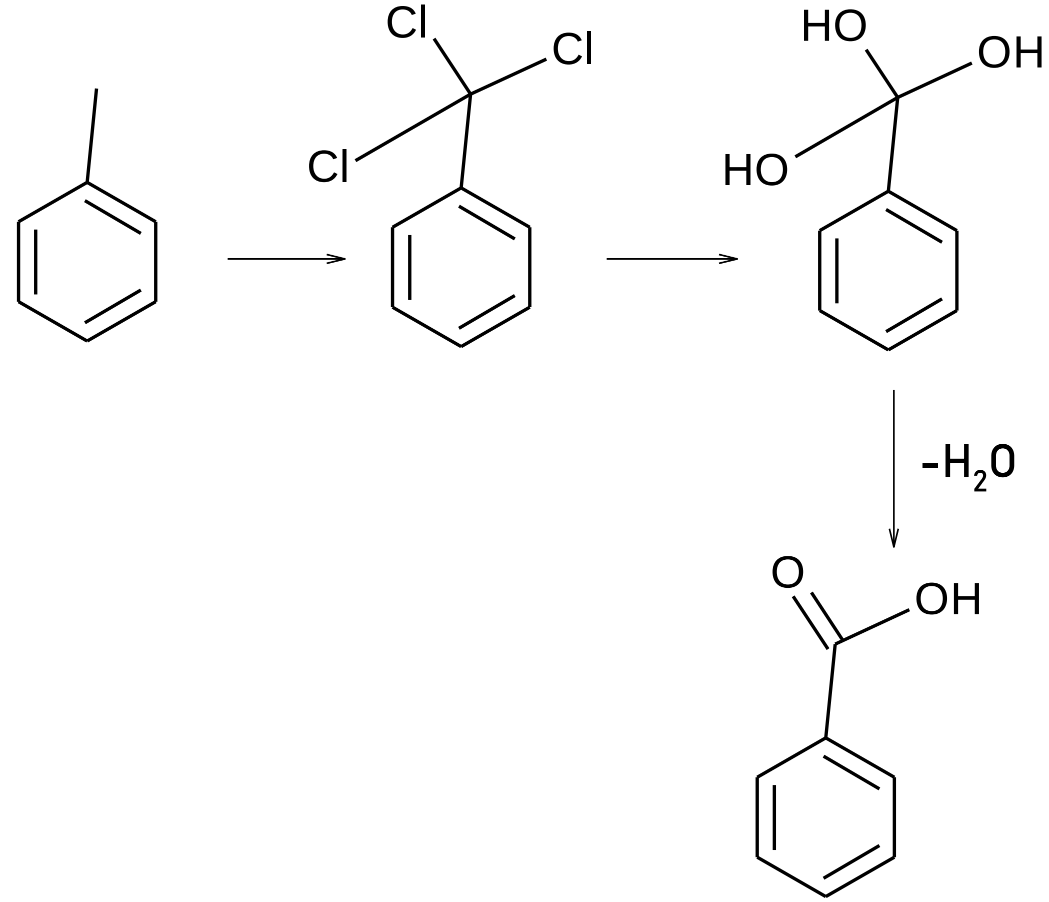
$$C_6H_5SO_3K + KCN \longrightarrow C_6H_5CN$$

3. Hydrolysis of esters

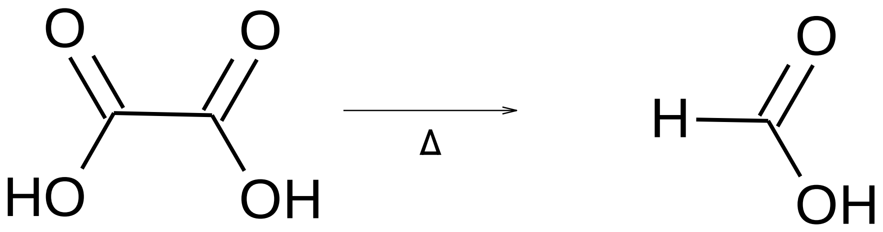
$$CH_3COOC_2H_5 \xrightarrow[KOH]{\Delta} CH_3COOH + C_2H_5OH$$

4. Hydroloysis of trihalgen derivates of alkanes

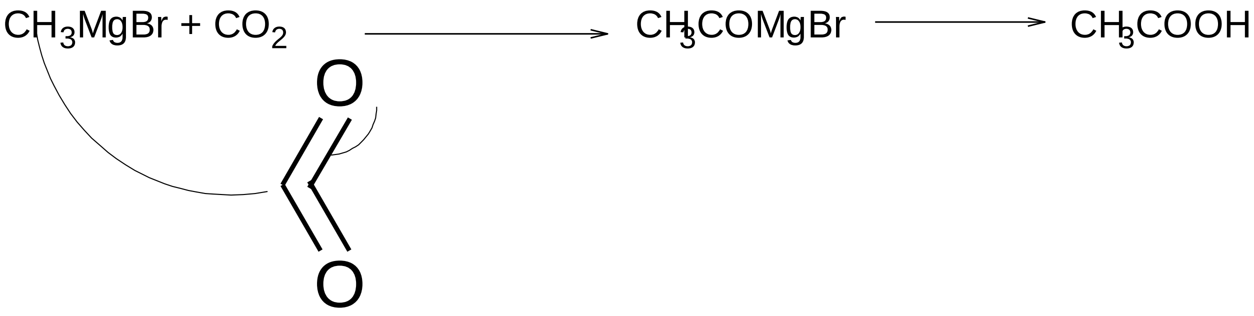
$$CHCl_3 \longrightarrow CH(OH)_3 \longrightarrow HCOOH$$



5. Heating dicarboxylic acids

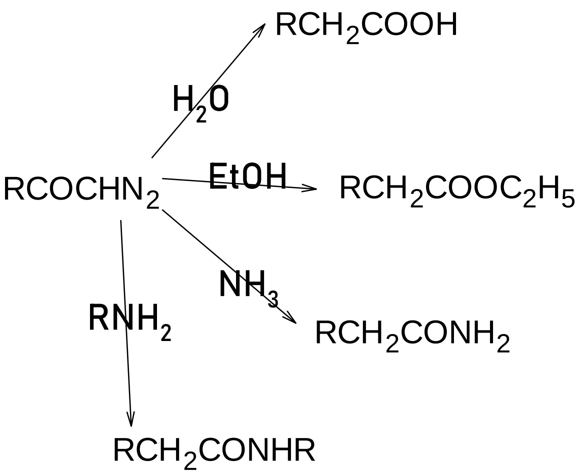


6. Carbonatin of Grignard reagent



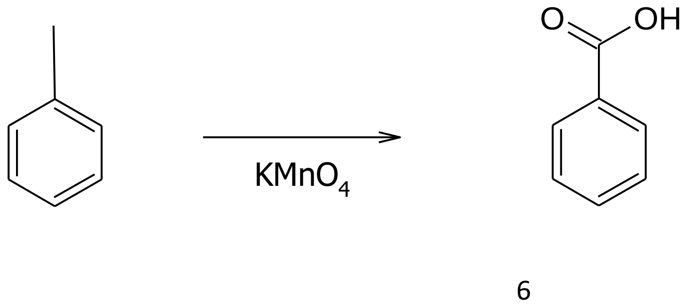
7. Arndt-Eistert Synthesis

$$RCOOH + SOCl_2 \longrightarrow RCOCl \xrightarrow[CH_2N_2]{} RCOCHN_2 \xrightarrow[Ag_2O,\ H_3O^+]{} RCH_2COOH$$

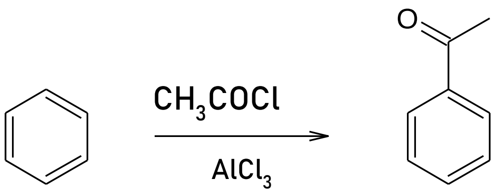


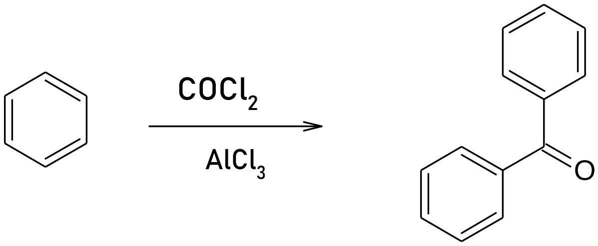
SPECIAL METHODS OF PREPARATION OF AROMATIC ACIDS

1. Oxidation of alkyl benzene

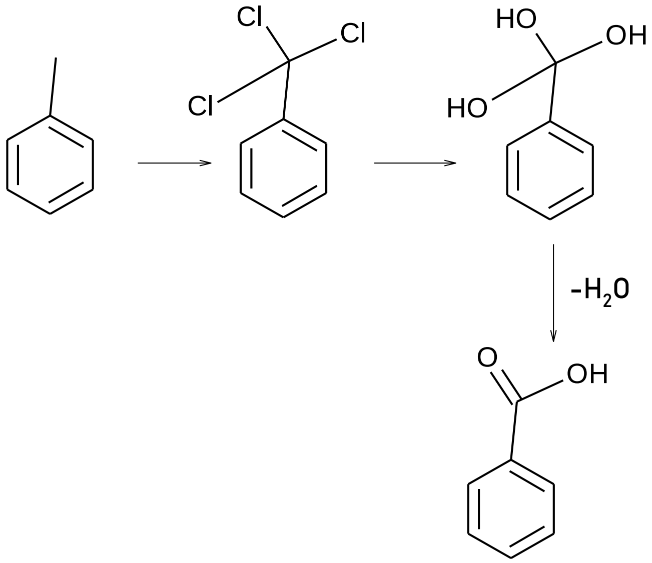


2. Friedel Craft reaction

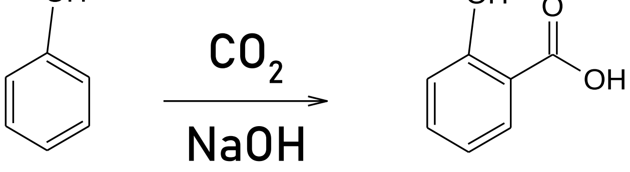




3. Hydrolysis of Benzotrichloride



4. Kolbe Reaction



PROPERTIES

1. The first three members are colourless, pungent smelling liquids. C4 to C8 have unpleasant odours. Acids above C7 have no smell.
2. Carboxylic acids are free soluble in water due to hydrogen bonding with water molecule
3. Boiling points of acid lower member are higher than alcohols of comparable molecular masses.
4. The even member carbon have markedly high melting points than the odd member preceding or following acid.
5. Acidity of carboxylic acid and substituent's on acidity

REACTIONS OF CARBOXYLIC ACIDS

A. INVOLVING HYDROGEN ATOM OF COOH GROUP

Reaction with metals

$$CH_3COOH + Na \longrightarrow CH_3COONa + 1/2\ H_2$$

$$CH_3COOH + Ca \longrightarrow (CH_3COO)Ca + 1/2\ H_2$$

$$CH_3COOH + Ca \longrightarrow (CH_3COO)Ca + 1/2\ H_2$$

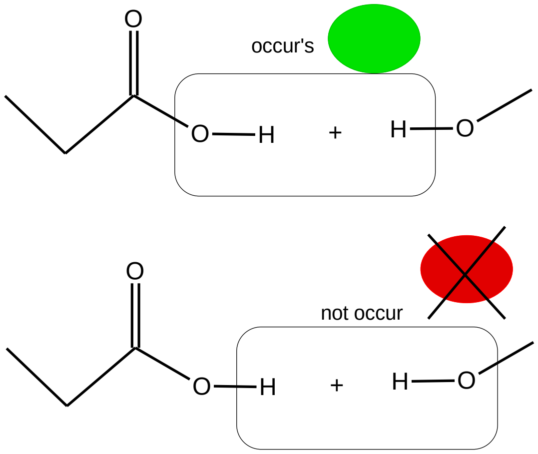
$$CH_3COOH + NaHCO_3 \longrightarrow CO_2 + H_2O + CH_3COONa$$

$$CH_3COOH + NaOH \longrightarrow CH_3COONa + H_2O$$

$$C_6H_5COOH + NaOH \longrightarrow C_6H_5COONa + H_2O$$

B. INVOLVING –OH OF THE –COOH GROUP

i. Reaction with Alcohols (Breakage of Carbonyl and oxygen of –COOH group)



$$RCOOH + R^{1}OH \xrightarrow[H_2SO_4]{\text{anhydrous } ZnCl_2} RCOOR^{1} + H_2O$$

$$CH_3COOH + CH_3OH \xrightarrow[H_2SO_4]{\text{anhydrous } ZnCl_2} CH_3COOCH_3 + H_2O$$

Decreasing reactivity order of alcohol

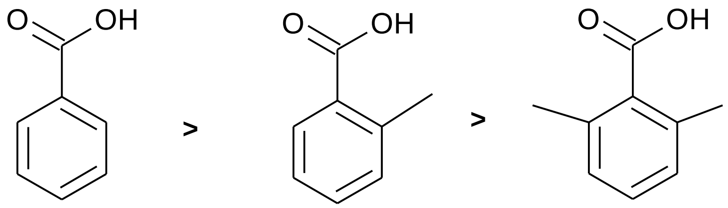
$CH_3OH > C_2H_5OH > (CH_3)_2CHOH > (CH_3)_3OH$

Decreasing reactivity order of acid

$HCOOH > CH_3COOH > C_2H_5COOH > (CH_3)_3COOH$

$$C_6H_5COOH + C_2H_5OH \xrightarrow{H^+} C_6H_5COOC_2H_5 + H_2O$$

Decreasing reactivity order of acid



ii. Rection with PCl5, PCl3 or SOCl2

$$CH_3COOH + PCl_5 \longrightarrow CH_3COCl + HCl + POCl_3$$

$$CH_3COOH + PCl_3 \longrightarrow CH_3COCl + H_3PO_3$$

$$CH_3COOH + SOCl_2 \longrightarrow CH_3COCl + SO_2 + HCl$$

$$C_6H_5COOH + SOCl_2 \longrightarrow C_6H_5COCl + SO_2 + HCl$$

iii. Reaction with ammonia

$$RCOOH + NH_3 \longrightarrow RCOONH_4 \xrightarrow[\Delta]{} RCONH_2 + H_2O$$

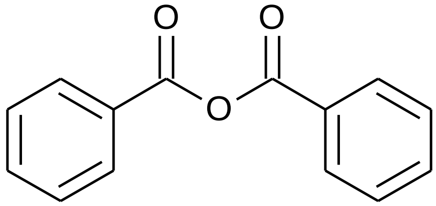
$$HCOOH + NH_3 \longrightarrow HCOONH_4 \xrightarrow[\Delta]{} HCONH_2 + H_2O$$

$$C_6H_5COOH + NH_3 \longrightarrow C_6H_5COONH_4 \xrightarrow[\Delta]{} C_6H_5CONH_2 + H_2O$$

iv. Dehydration

$$2CH_3COOH \longrightarrow CH_3COOCOCH_3$$

$$2C_6H_5COOH \xrightarrow{P_2O_5} C_6H_5COOCOC_6H_5$$



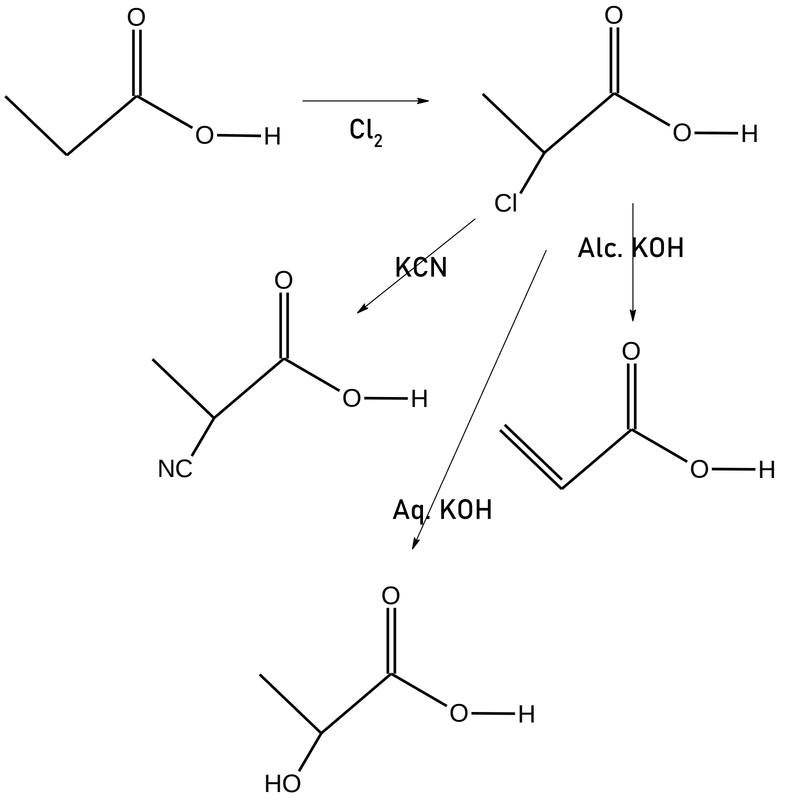
C. INVOLVING –C=O GROUP OF –COOH GROUP

Reduction

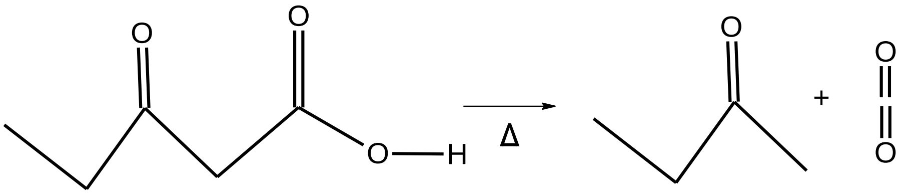
$$RCOOH + LiAlH_4 \longrightarrow RCH_2OH$$

D. INVOLVING ALKYL GROUP OF THE ACID

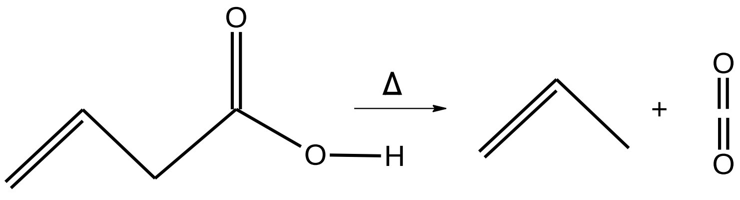
Hell-Volhard-Zelinsky Reaction (HVZ reaction)

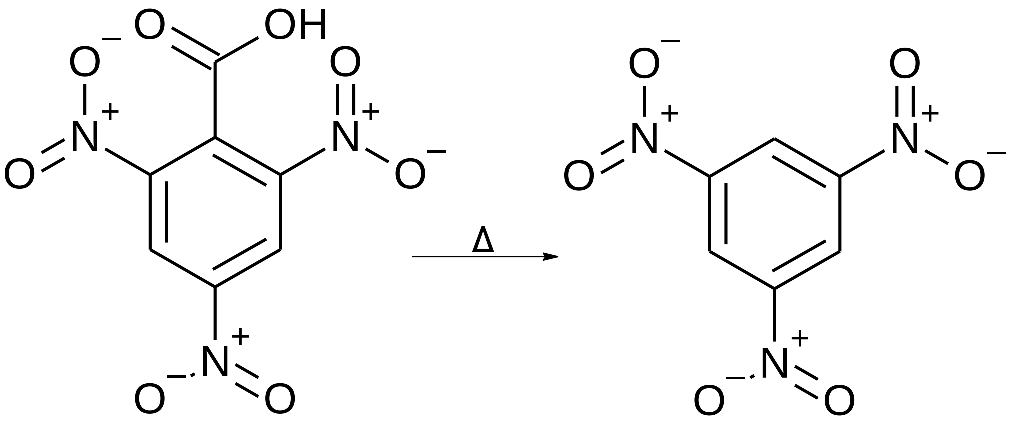


E. DECARBOXYLATION

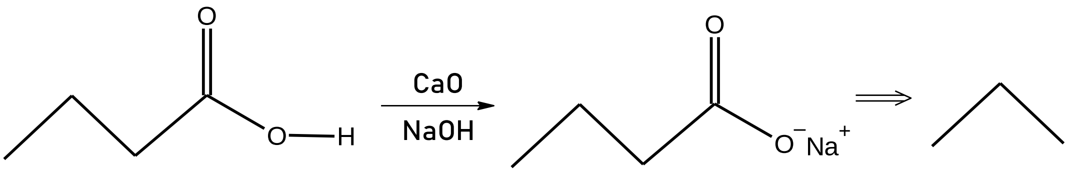


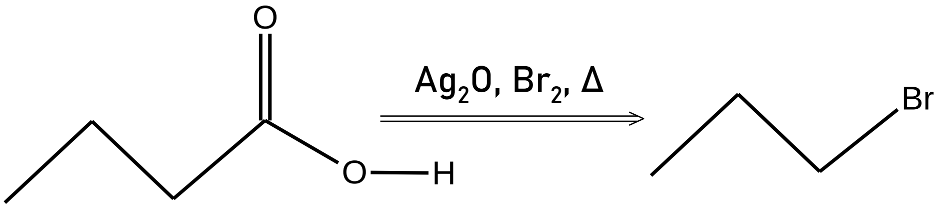
3 keto pentanoic acid



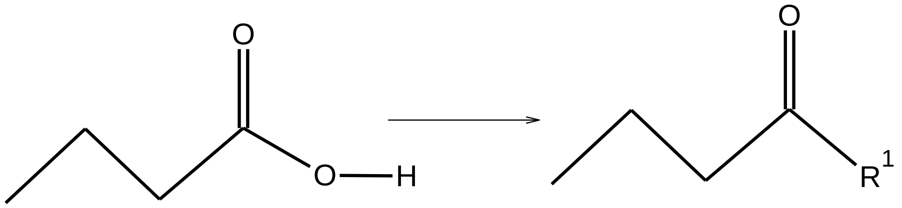


F. SALTS OF CARBOXYLIC ACID





ACID CHLORIDES



= X, NH2, OCOR, OR

Preparation: These are prepared by treating caroxylicl acid with SOCl2, PCl5 and PCl3.

$CH_3COOH + PCl_5 \longrightarrow CH_3COCl + HCl + POCl_3$

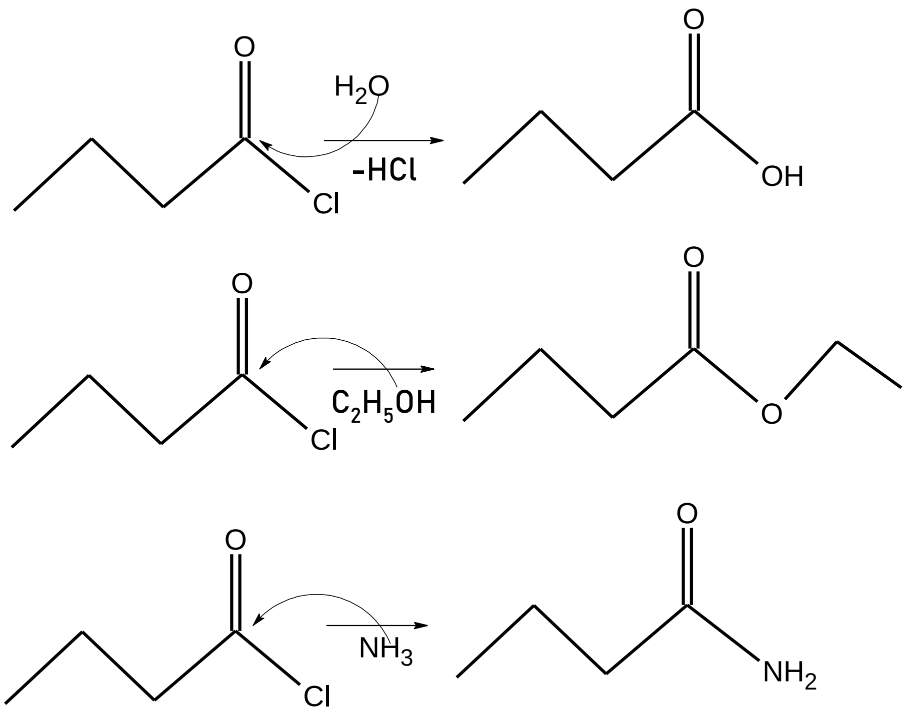
$CH_3COOH + PCl_3 \longrightarrow CH_3COCl + H_3PO_3$

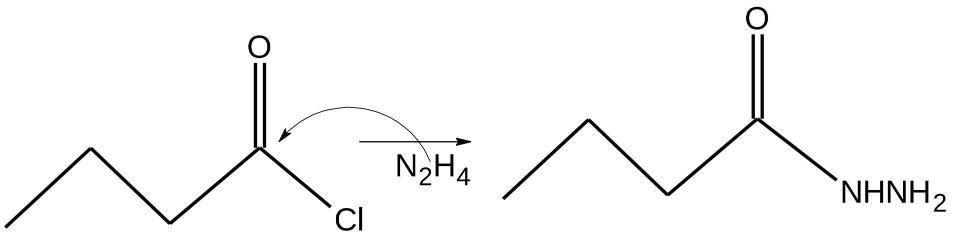
$CH_3COOH + SOCl_2 \longrightarrow CH_3COCl + SO_2 + HCl$

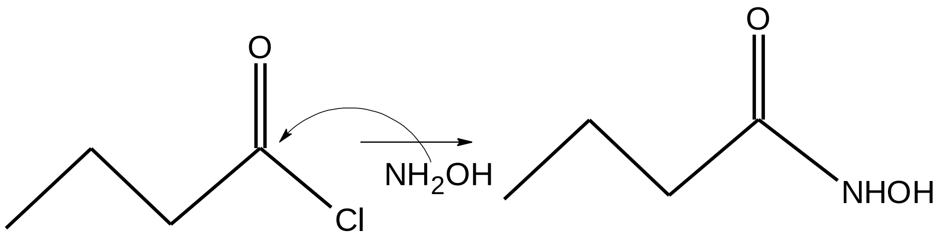
$C_6H_5COOH + SOCl_2 \longrightarrow C_6H_5COCl + SO_2 + HCl$

Chemical Reactions

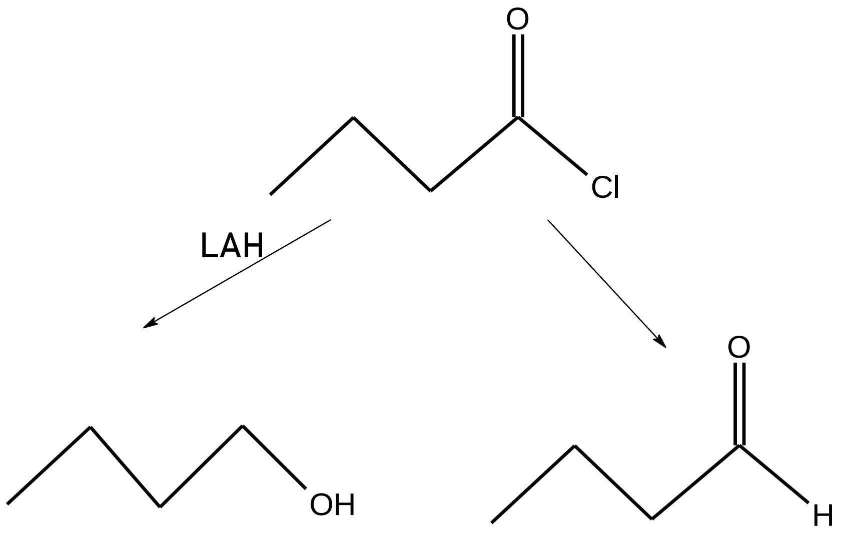
1. Nucleophilic substitution



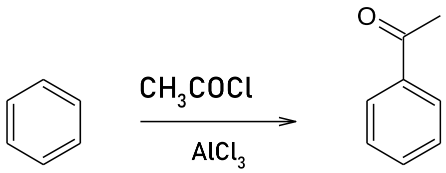


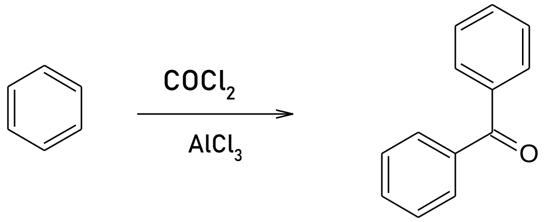


2. Reduction

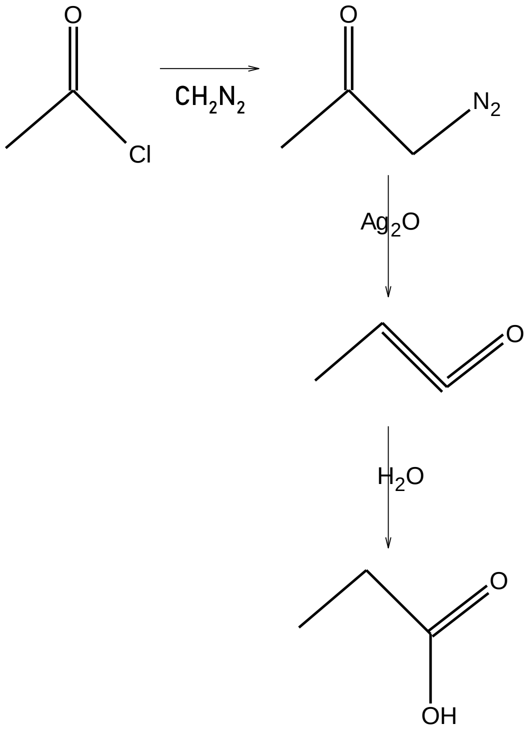


3. Friedel-Craft reaction



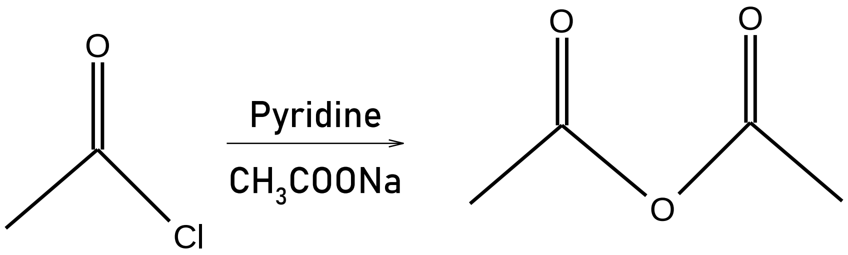


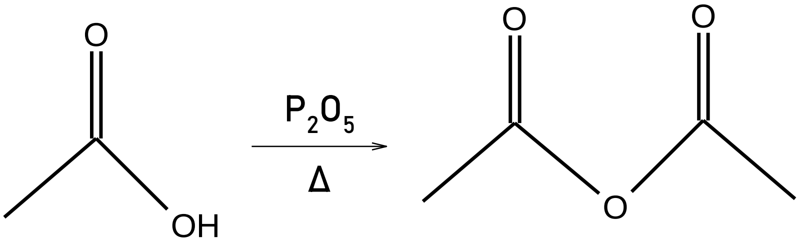
4. Diazomethane

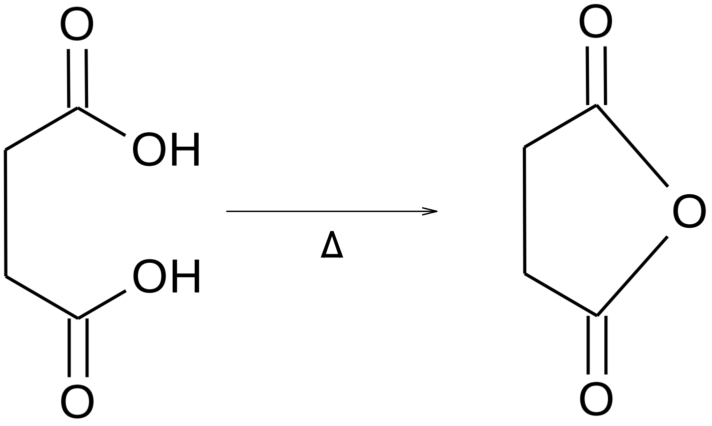


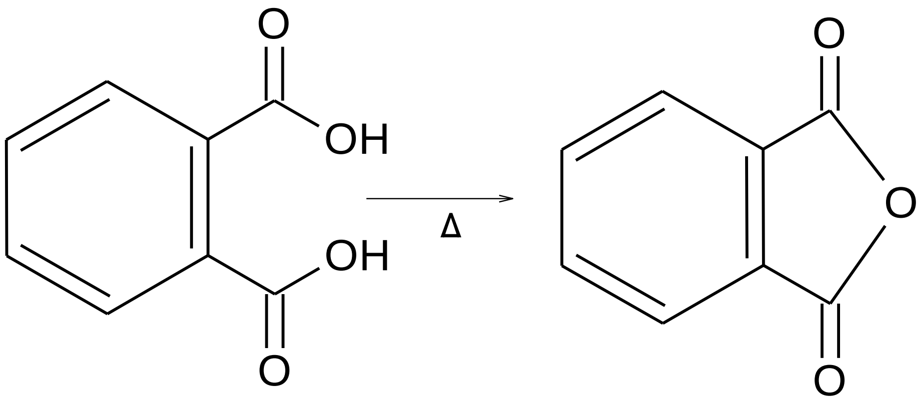
ACETIC ANHYDRIDE

Preparation







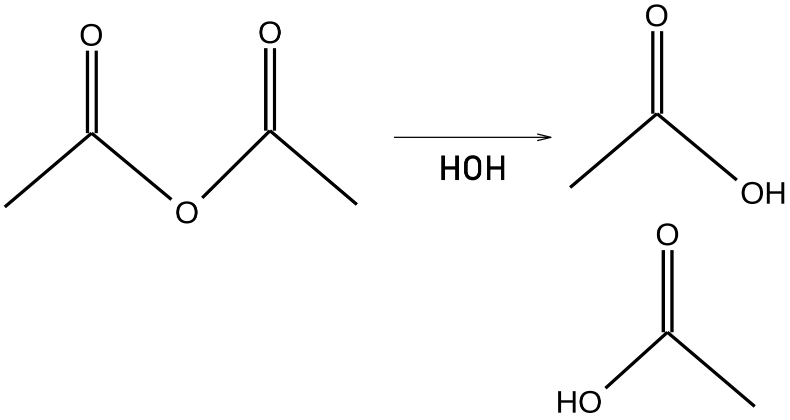


Properties:

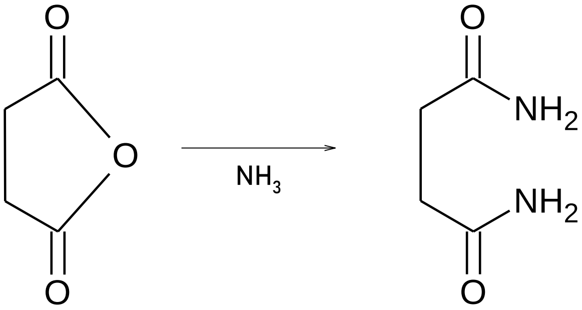
It is a colourless sweet smelling liquid. There is no intermolecular hydrogen bonding in esters. Hence their M.P. and B.P. are low as compared to those of the corresponding carboxylic acids.

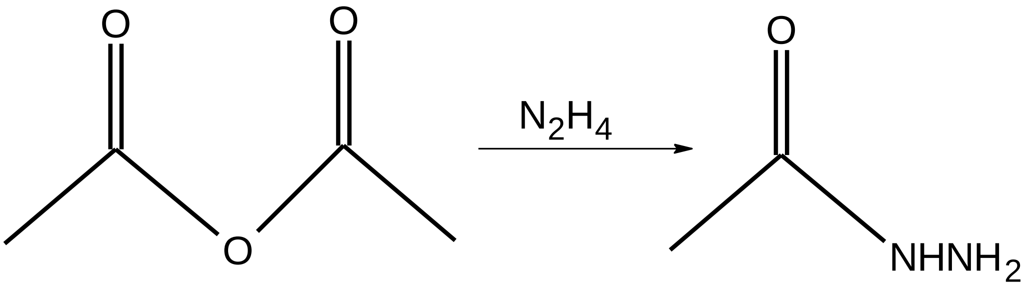
CHEMICAL REACTIONs

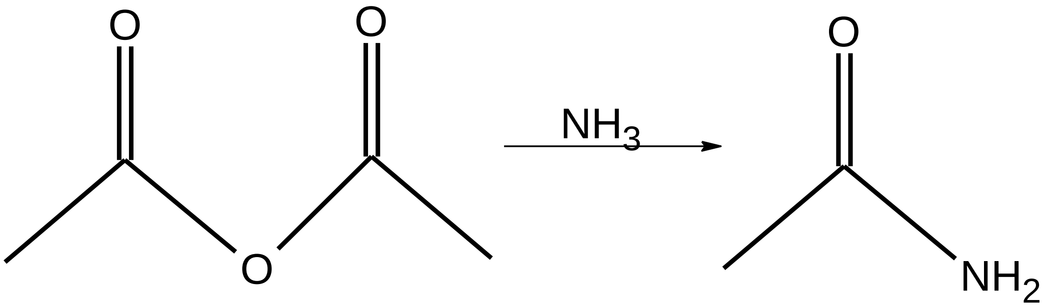
a. **Hydrolysis in presence of acid**
b. **Hydrolysis in presence of base**



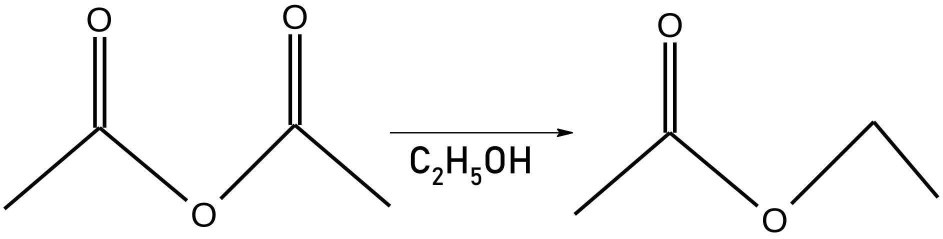
c. **Ammonolysis**



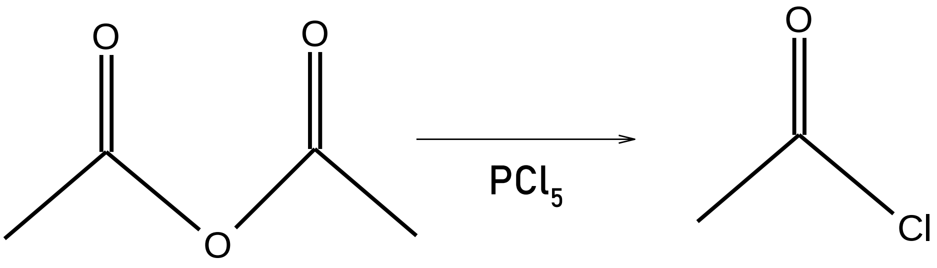




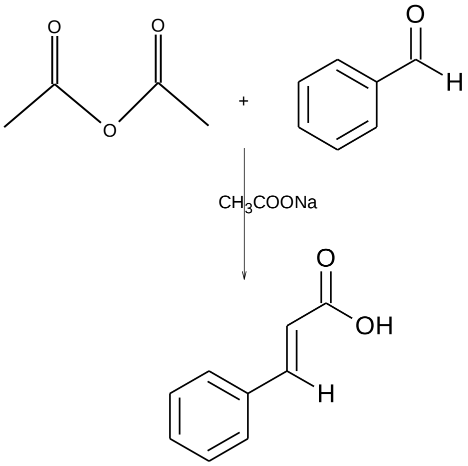
d. Alcoholysis



e. PCl5



f. Claisen Condensation reaction

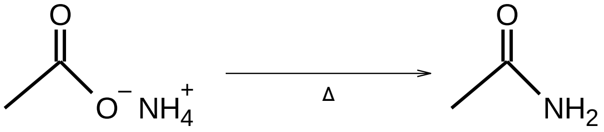


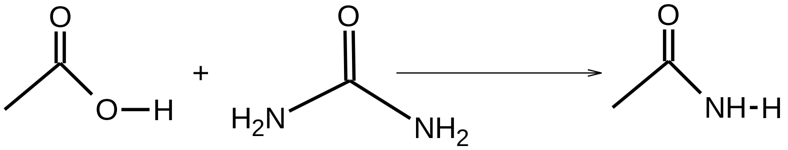
ACID AMIDES (ACETAMIDE)

Preparation

1. Ammonium salts of fatty acids

2. Ammonia and acid chlorides





3. Glacial acetic acid with urea
4. Wilgerdot reaction

$$CH_3CN \quad + H_2O \xrightarrow[\text{COLD } H_2SO_4]{\text{ALKALINE } H_2O_2} CH_3CONH_2$$

5. Diazoacetone with ammonia

Properties: Among the four derivates of acids, only acid amide molecules are capable of forming hydrogen bonds with each other because they have hydrogen atoms linked to nitrogen. Impure acetamide has mosy odour. Important chemical properties of acied amides are summarized below.

1. Hydrolysis

$$CH_3CONH_2 \xrightarrow{H^+} CH_3COOH \; + NH_3$$

2. HNO2

$$CH_3CONH_2 \xrightarrow{HNO_2} CH_3COOH + N_2 + H_2O$$

3. Dehydration

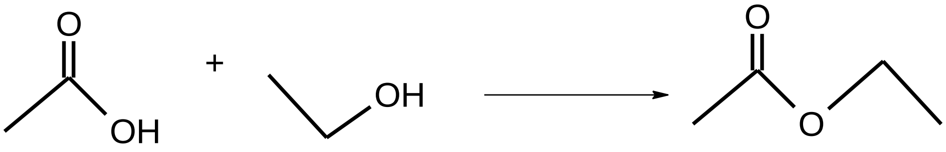
$$CH_3CONH_2 \longrightarrow CH_3CN + H_2O$$

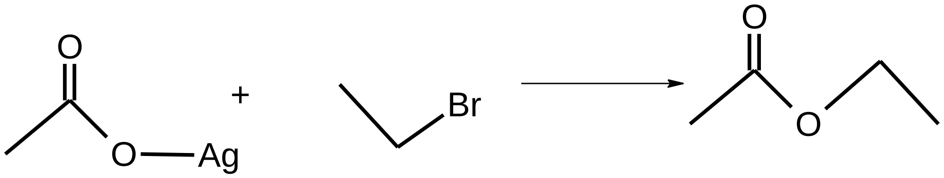
4. Hofmann degradation reaction

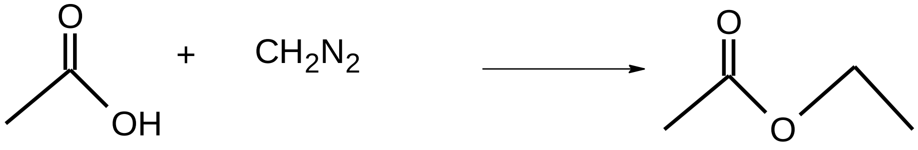
$$CH_3CON_2 + Br_2 + 4KOH \longrightarrow CH_3NH_2 + 2KBr + K_2CO_3 + H_2O$$

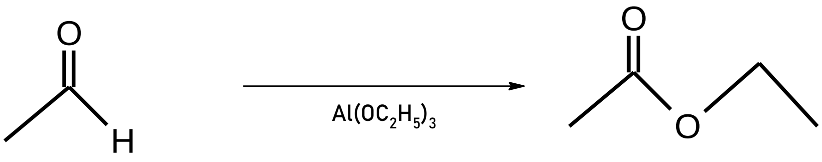
ESTERS (ETHYL ACETATE)

Preparation

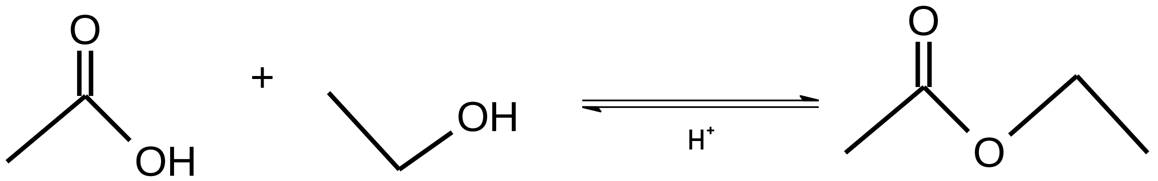


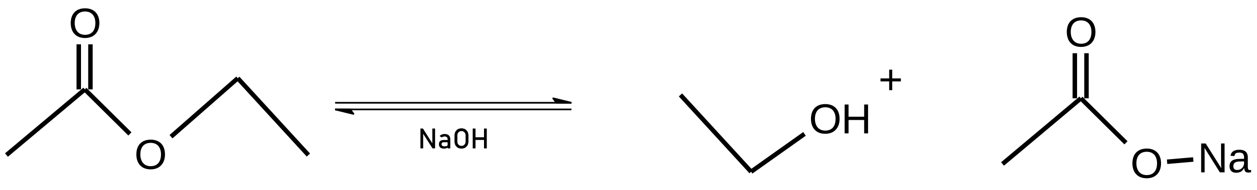




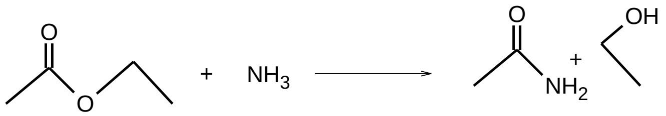


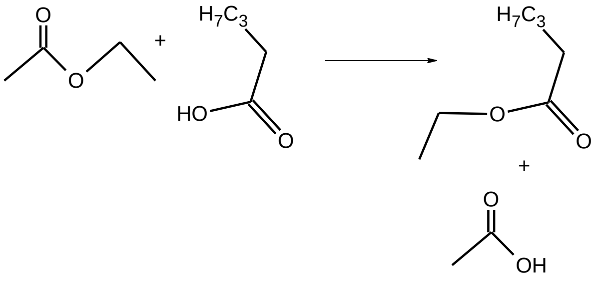
Esterification and hydrolysis of ester

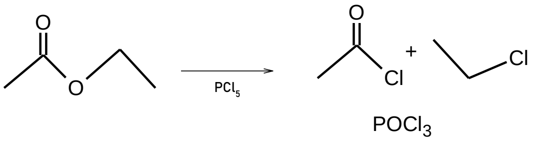




REACTIONS OF ESTERS







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2. O. P. Agarwal, Unified Chemistry text book, Volume 2; Jai Prash Nath Publication, Meerut, India.
3. O. P. Agarwal, Unified Chemistry text book, Volume 3; Jai Prash Nath Publication, Meerut, India.
4. O. P. Agarwal, Unified Chemistry text book, Volume 4; Jai Prash Nath Publication, Meerut, India.

Question Bank

1. Write the any four Synthetic methods for Aliphatic carboxylic acids?
2. Write the any four Synthetic methods for Aromatic carboxylic acids?
3. Write a short note on Arndt Eistert Synthesis
4. Write a short note on Hell-Volhard-Zelinsky Reaction?
5. Write an essay on chemical properties of carboxylic acid group?
6. Write a short note derivatives of carboxylic acids.
7. Write an essay on dicarboilic acids and their synthesis, properties and applications.

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – II - Reactive Methylene Groups – SCY1315

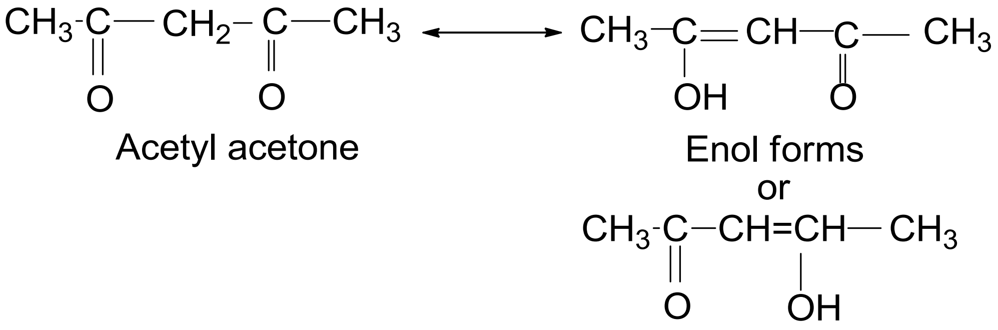
UNIT-2

REACTIVE METHYLENE GROUPS

2.0 INTRODUCTION

When a methylene group is presentr between two electronegative groups such as CO or CN, the hydrogen atoms of methylene group becomes acidic. Such compounds exhibit keto-enol equilibrium. The migration of hydrogen atoms to keto group depends on the inductive effect of the alkyl group or other groups on either side of the $-CH_2$-group.

Example 1:



$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\underset{\underset{OH}{|}}{C}=CH-\underset{\underset{O}{\|}}{C}-CH_3$$

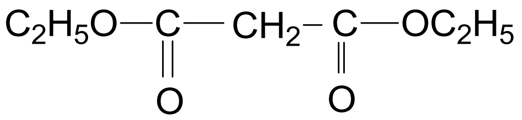
Acetyl acetone

Enol forms

or

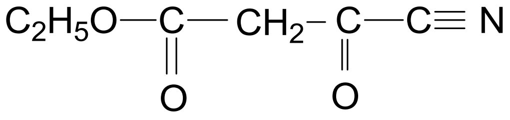
$$CH_3-\underset{\underset{O}{\|}}{C}-CH=\underset{\underset{OH}{|}}{CH}-CH_3$$

Other Examples:



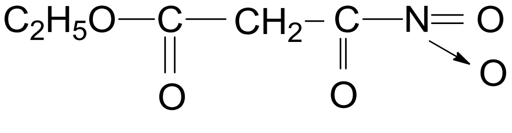
$$C_2H_5O-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-OC_2H_5$$

Diethyl Malonate



$$C_2H_5O-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-C\equiv N$$

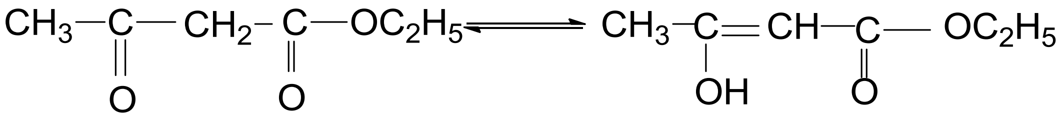
Ethyl Cyanoacetate



$$C_2H_5O-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-N\overset{\searrow O}{=}O$$

Another example of unsymmetrical compound-

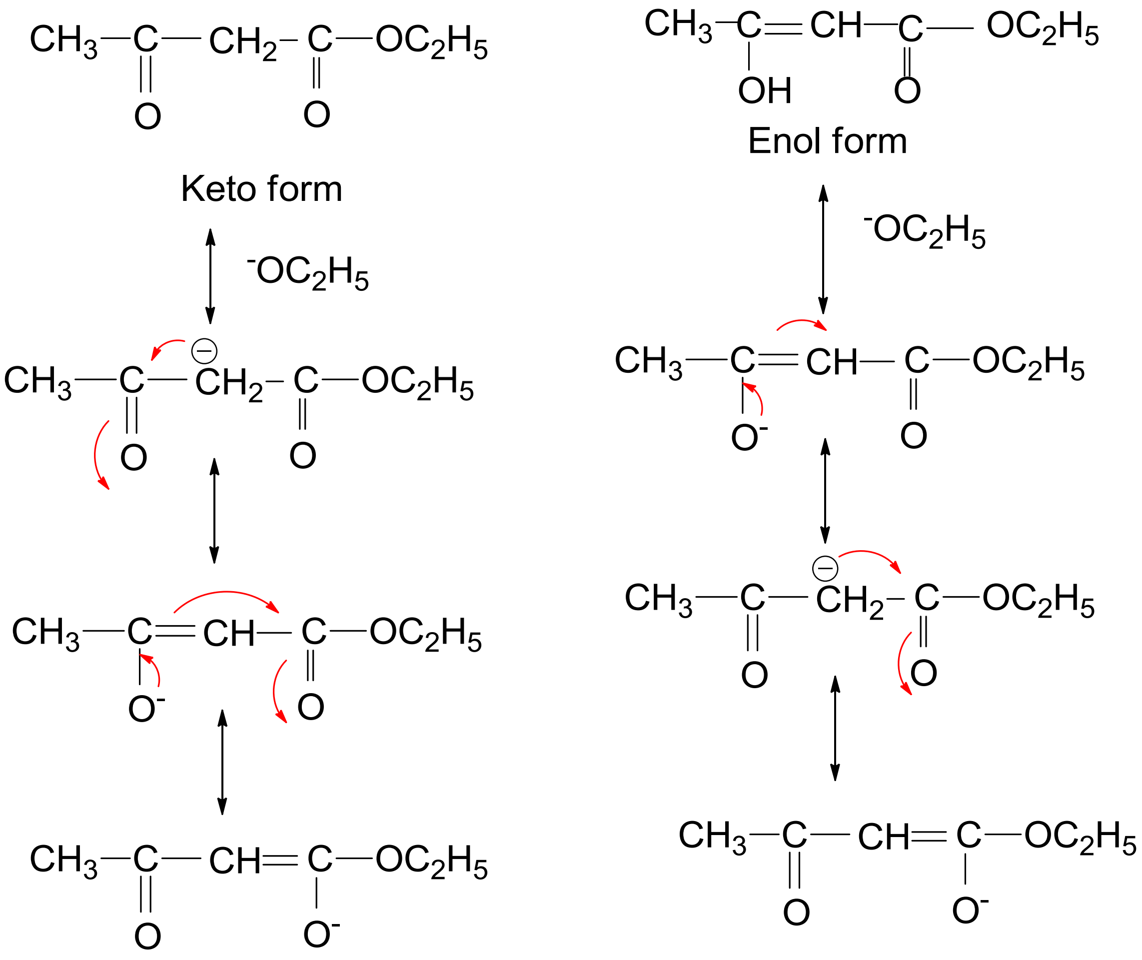
When a compound containing active methylene groups reacts with a strong base the proton removal takes place from both keto and enol form and the resulting enolate is stabilised by resonance.



Ethylacetoacetae
Keto form

Enol form

Reactions of EAA with strong base:



2.1 KETO-ENOL TAUTOMERISM

Compounds of structurally distinct molecules which are present as equilibrium mixture and the two forms are readily interconvertible and the removal of one form from the mixture results in the conversion to other from in order to restore equilibrium.

The term Tautomerism is coined by Laar in 1885 to describe the phenomemon of substance reacting chemically according to the two possible structures. (*Tauto*-same *meros*-parts).

“The property exhibited by compounds of behaving in different reactions as they possessed two or m ore different structures.”

It is a special type of functional isomerism where the isomers are in equilibrium and are interconvertible in anture. It is therefore considered as dynamic isomerism. When both tautomers are detected and isolated it is known as desmotropism.

Tautomerism is a heterolytic in nature, involving the migration of one or group of atoms from one atom to another atom in close proximity with the rearrangement of linkages.

Types of Tautomerism:

Cationotropic- Migrating groups are cations

Anionotropic- Migrating groups are anions.

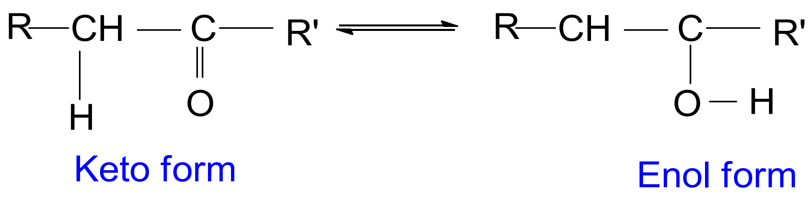
Prototropic -Migrating groups are protons.

Tautomerism can also be classified as

Dyad system- If the oscillation of hydrogen atom takes places between two polyvalent atoms linked together.

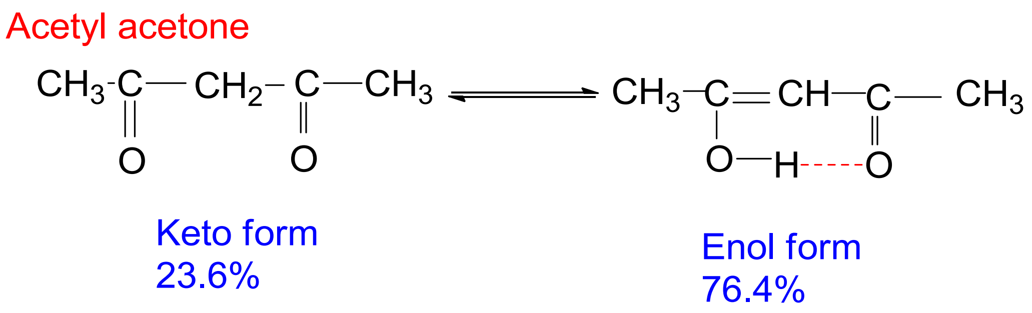
Triad system-if the oscillation of hydrogen atoms takes place between first and third of three polyvalent atoms linked together.

Keto-enol tautomerism: Common type of tautomerism involving a carbonyl compound having an α-hydrogen atom (keto form) and its enol form (having an double bond and an –OH).



Eg1: Acetyl acetone:

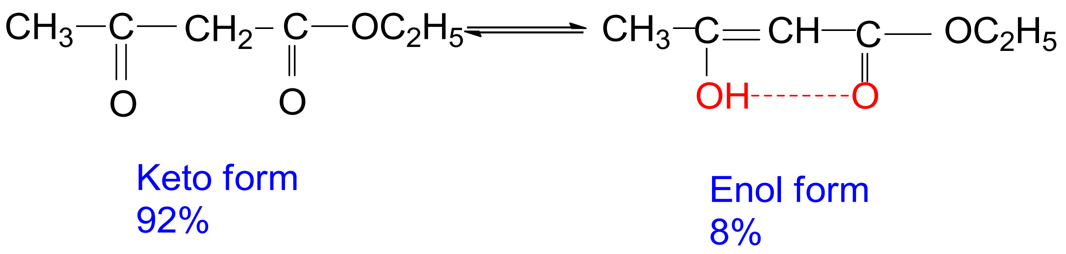
It exhibits keto-enol tautomerism. The enol from is stabilized by intramolecular hydrogen bonding.



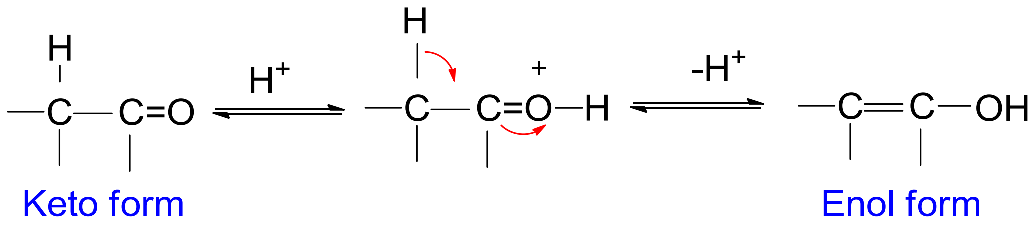
Eg 2: Ethyl acetoacetate:

It also exhibits keto-enol tautomerism. The enol form is stabilized by intramolecular hydrogen bonding.

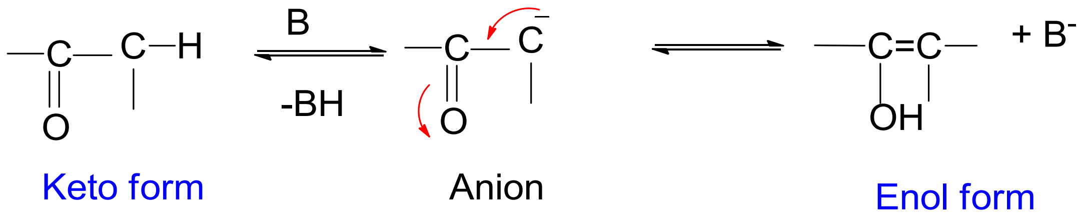
Ethylacetoacetate



Acid catalyzed reaction:



Base catalyzed Reaction:



2.1.1Characteristics of tautomerism:

Discrete chemical entities capable of isolation under suitable conditions.

Migration of proton between three polyvalent atoms.

Reversible intramolecular hydrogen bonding.

They differ in their stability, less stable is known as labile form.

It is catalyses by acids and bases.

Exist in dynamic equilibrium. Separated by special methods.

2.1.2 Difference between resonance and Tautomerism

Tautomerism	Resonance
Tautomers have real existence	Contributing structures are hypothetical

Migration of atoms or protons.	Contributing structures differ only in the placement of electrons
Dynamic equilibrium	No equilibrium exists
No change in bond length occurs	Shortening of single bond and lengthening of double bond occurs.
Shape of the molecule doesn't play an role.	Molecule should be planar and it lowers the energy
Tautomerism is represented by reversible arrow.	Resonance is indicated by double headed arrow

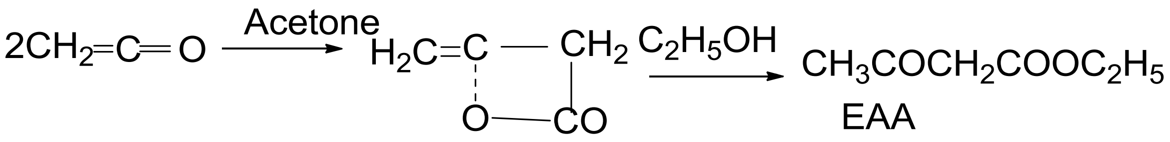
2.2 ACETOACETIC ESTER, ETHYL ACETOACETATE- EAA

2.2.1 Preparation:

A) Condensation of two molecules of ethyl acetate in the presence of a base like sodium ethoxide- Claisen condensation.

$$\underset{\text{Ethyl acetate}}{CH_3COOC_2H_5} + CH_3COOC_2H_5 \xrightarrow{C_2H_5ONa} \underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + C_2H_5OH$$

B) Polymerising of ketene in acetone solution to form diketen and alcohol.



$$2CH_2{=}C{=}O \xrightarrow{\text{Acetone}} H_2C{=}C - CH_2 \xrightarrow{C_2H_5OH} \underset{\text{EAA}}{CH_3COCH_2COOC_2H_5}$$

2.2..2 Physical properties-

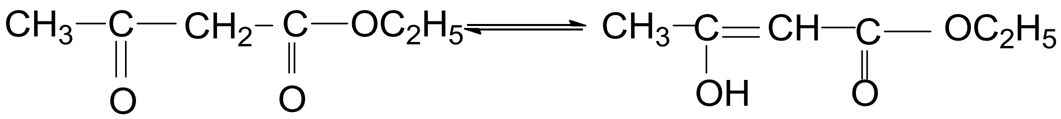
Colourless, pleasant smelling liquid (b.pt 181^0c);

Sparingly soluble in water, soluble in alcohol and ether.

Soluble in sodium hydroxide in its enol form which dissolves to give sodium salt.

2.2. 3 Chemical properties-

These compounds behave as a ketone as well as an alcohol and exhibits keto-enol tautomerism.



$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-OC_2H_5 \rightleftharpoons CH_3-\underset{\underset{OH}{|}}{C}=CH-\underset{\underset{O}{\|}}{C}-OC_2H_5$$

Ethylacetoacetae
Keto form

Enol form

2.2.4. Reactions involving ketonic form-

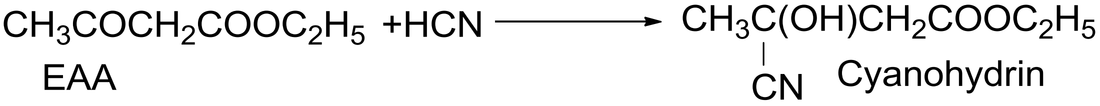
1)Reductions: on reduction with sodium amalgam it form hydroxy butyric ester.

$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + 2H \xrightarrow{Na/Hg} \underset{\beta\text{–hydroxybutyric acid}}{CH_3CHOHCH_2COOC_2H_5}$$

2) With $LiAlH_4$ it forms 1,3 butane diol.

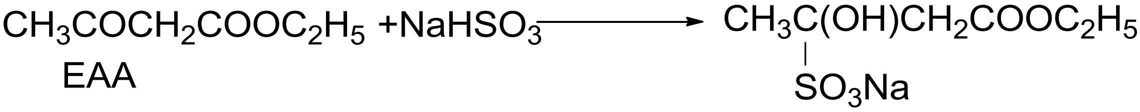
$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + 6H \xrightarrow{LiAlH_4} CH_3CHOHCH_2CH_2OH + C_2H_5OH$$

3) Addition reaction with HCN- like other ketones it forms cyanohydrins.



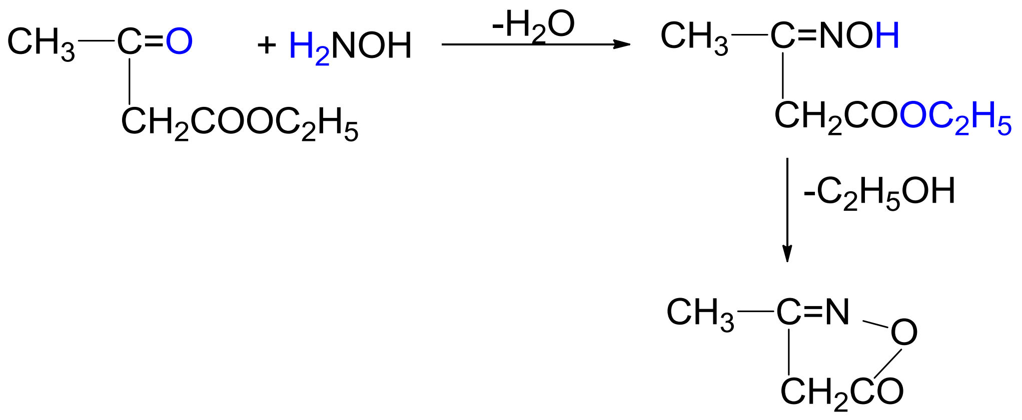
$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + HCN \longrightarrow CH_3\underset{\underset{CN}{|}}{C}(OH)CH_2COOC_2H_5 \quad \text{Cyanohydrin}$$

4) With sodium bisulphite- it forms crystalline addition compound.



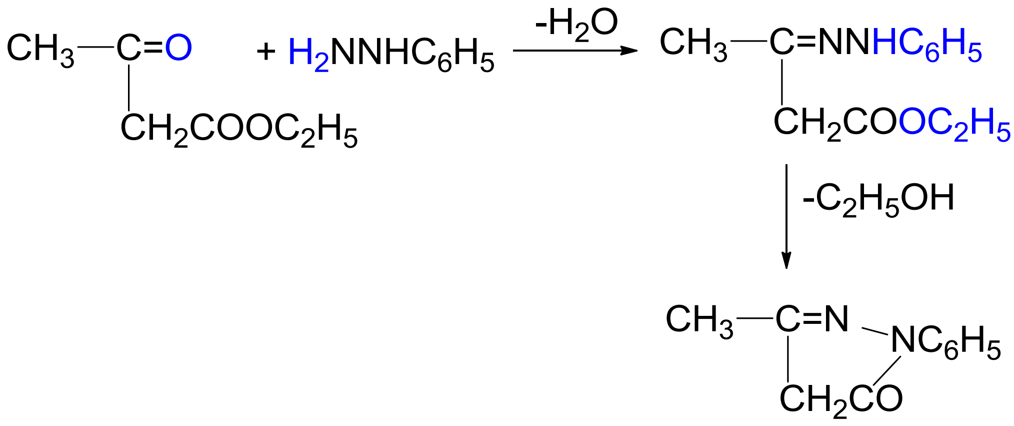
$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + NaHSO_3 \longrightarrow CH_3\underset{\underset{SO_3Na}{|}}{C}(OH)CH_2COOC_2H_5$$

5) Reactions with hydroxyl amine- It forms an oxime and immediately loses an alcohol to form methyl isoxazolone.


Methyl isoxazolone

6) Reactions with phenyl hydarzine-

It form phenyl hydrazone and forms 3-methyl-1-phenyl-pyrazolone.


3-Methyl 1-Phenyl pyrazolone

2.2.5 Hydrolysis of EAA

1)Ketonic hydrolysis: When boiled with dilute aqueous or alcoholic KOH , dilute H_2SO_4, acetoacetic ester is hydrolysed to form ketone .

$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} \xrightarrow{H_2O} CH_3COCH_3 + CO_2 + C_2H_5OH$$

2)Acid Hydrolysis: When boiled with concentrated alcoholic KOH it is hydrolysed to acids.

$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + KOH \longrightarrow 2CH_3COOK + C_2H_5OH$$

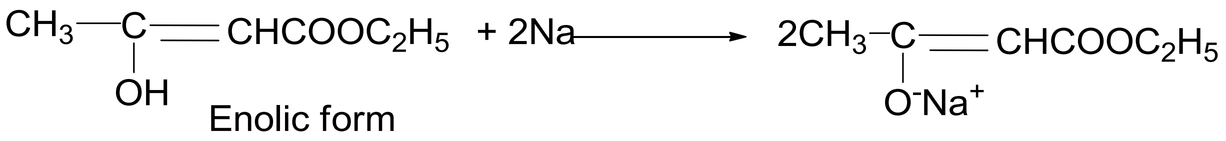
3) **Normal Hydrolysis:** With cold and dilute KOH, hydrolysis takes place resulting in the formation of potassium acetoacetate.

$$\underset{\text{EAA}}{CH_3COCH_2COOC_2H_5} + KOH \longrightarrow CH_3COCH_2COOK + C_2H_5OH$$

2.2.6 Reactions of Enol:

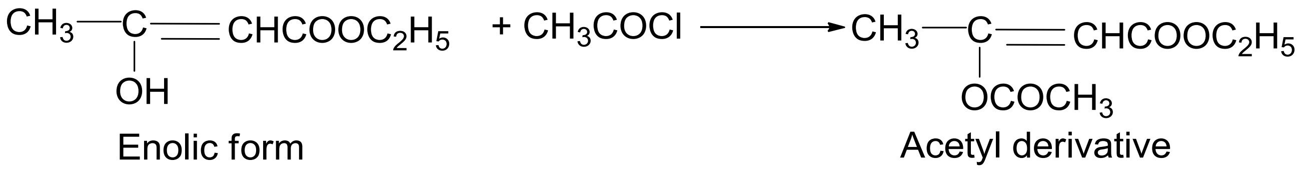
1)With Neutral Ferric chloride: It gives violet colour with $FeCl_3$ characteristic of enol

2) With sodium metal:The enolic form reacts with sodium to from sodium derivatives.



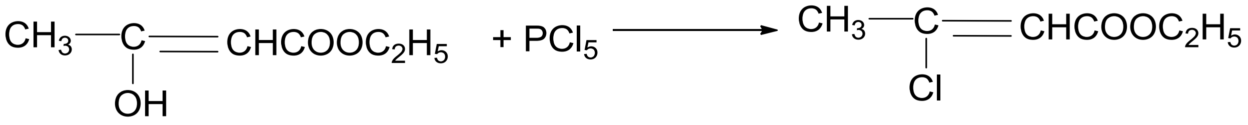
$$\underset{\text{Enolic form}}{CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5} + 2Na \longrightarrow 2CH_3-\underset{O^-Na^+}{\underset{|}{C}}=CHCOOC_2H_5$$

3) with acetyl chloride:It reacts to from acetyl derivatives.



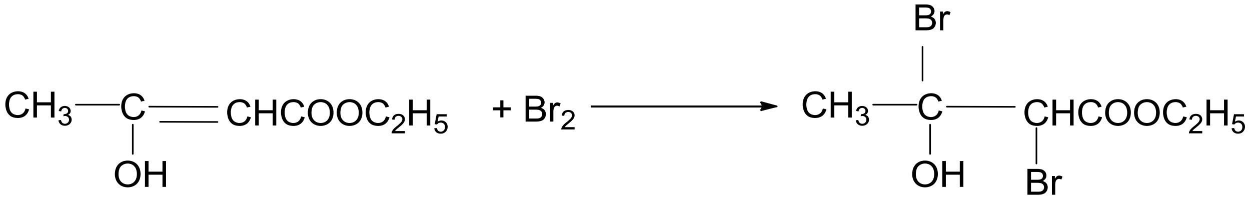
$$\underset{\text{Enolic form}}{CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5} + CH_3COCl \longrightarrow \underset{\text{Acetyl derivative}}{CH_3-\underset{OCOCH_3}{\underset{|}{C}}=CHCOOC_2H_5}$$

4)With PCl_5:The enolic form reacts with PCl_5 to from β-chloro derivatives.



$$CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5 + PCl_5 \longrightarrow CH_3-\underset{Cl}{\underset{|}{C}}=CHCOOC_2H_5$$

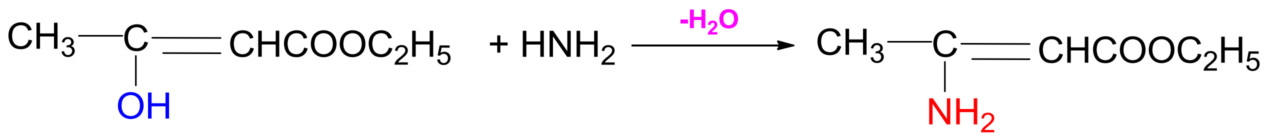
5) Addition with Bromine:It adds with Bromine to form α,β-dibromo derivative.



$$CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5 + Br_2 \longrightarrow CH_3-\overset{Br}{\overset{|}{\underset{OH}{\underset{|}{C}}}}-\underset{Br}{\underset{|}{C}}HCOOC_2H_5$$

6)Reactions with amine compounds:

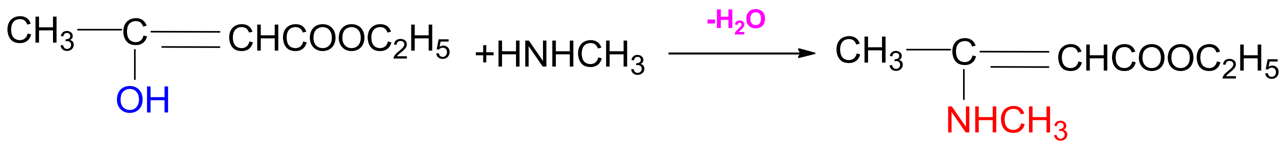
It reacts with ammonia as well as 1 and 2 amine to from β-amino crotonic esters.



$$CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5 + HNH_2 \xrightarrow{-H_2O} CH_3-\underset{NH_2}{\underset{|}{C}}=CHCOOC_2H_5$$

Enolic form

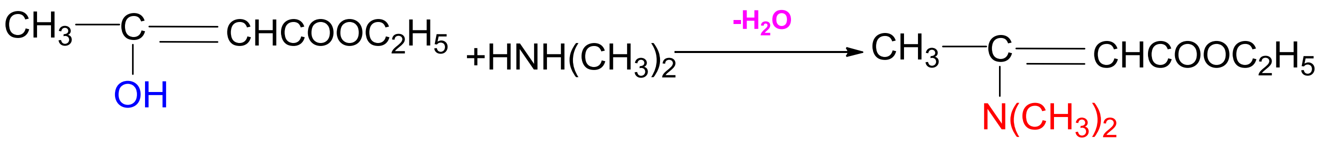
β–amino crotonic ester



$$CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5 + HNHCH_3 \xrightarrow{-H_2O} CH_3-\underset{NHCH_3}{\underset{|}{C}}=CHCOOC_2H_5$$

Enolic form

β–methylamino crotonic ester

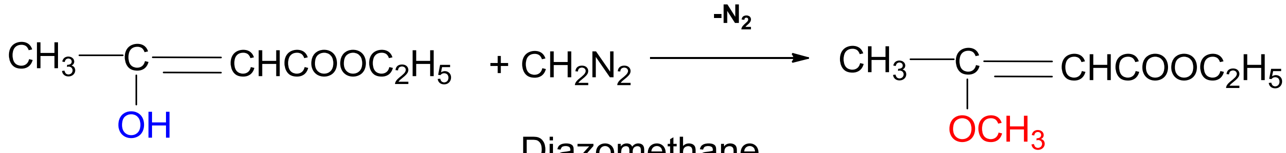


$$CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5 + HNH(CH_3)_2 \xrightarrow{-H_2O} CH_3-\underset{N(CH_3)_2}{\underset{|}{C}}=CHCOOC_2H_5$$

Enolic form

β–dimethylamino crotonic ester

7) Reactions with diazomethane:With diazomethane it forms methylether of ethyl crotonate.



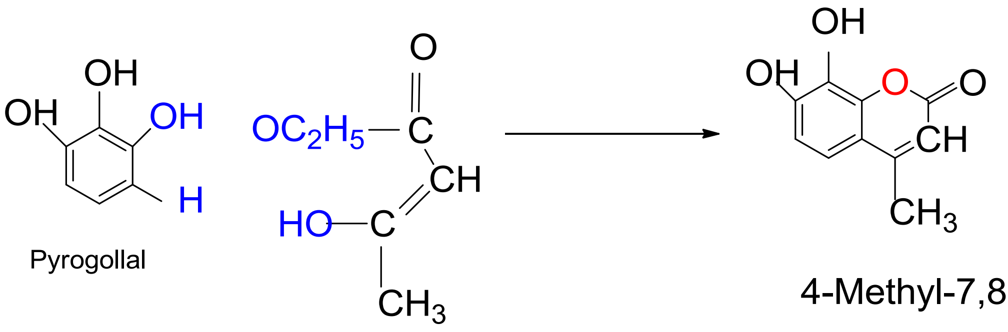
$$CH_3-\underset{OH}{\underset{|}{C}}=CHCOOC_2H_5 + CH_2N_2 \xrightarrow{-N_2} CH_3-\underset{OCH_3}{\underset{|}{C}}=CHCOOC_2H_5$$

Enolic form

Diazomethane

Methyl ether of crotonate

8) Reactions with Pyrogallol: It forms coumarin



Pyrogollal

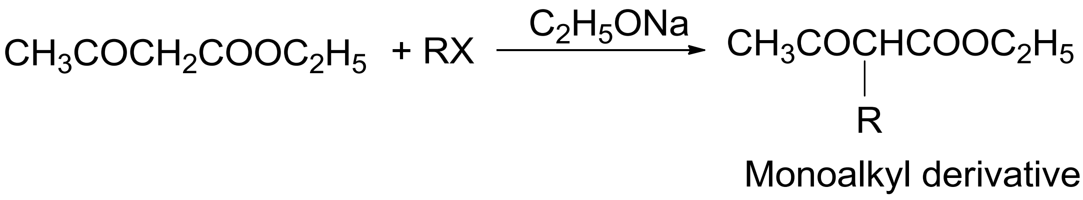
4-Methyl-7,8-dihydroxy coumarin

2.2.7 Synthetic Applications:

Acetoacetic ester behaves as an acid forming carbanion, resonance stabilized and can undergo nucleophilic substitution reaction..

1) Reactions with alkyl halide- It follows S_N2 mechanism and the attack is at the carbon atom. Both the alkyl groups can’t be added simultaneously in one single step because the hydrogen can be displaced by sodium ethoxide which contains one hydrogen atom. The enolic form is formed twice which changes to carbanion for the reaction with alkyl halide.

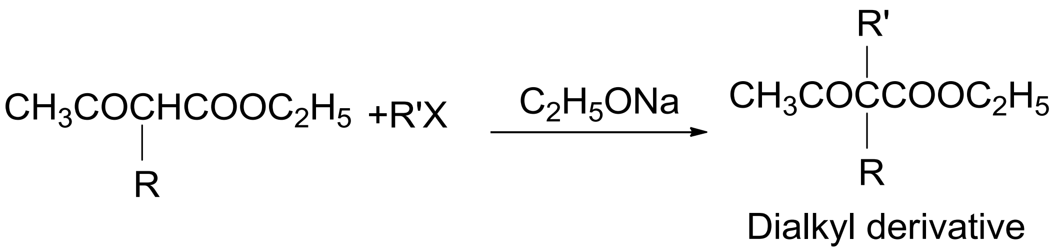
Reaction with first alkyl halide:



$$CH_3COCH_2COOC_2H_5 + RX \xrightarrow{C_2H_5ONa} CH_3CO\underset{\substack{|\\ R}}{C}HCOOC_2H_5$$

Monoalkyl derivative

Reaction with second alkyl halide:

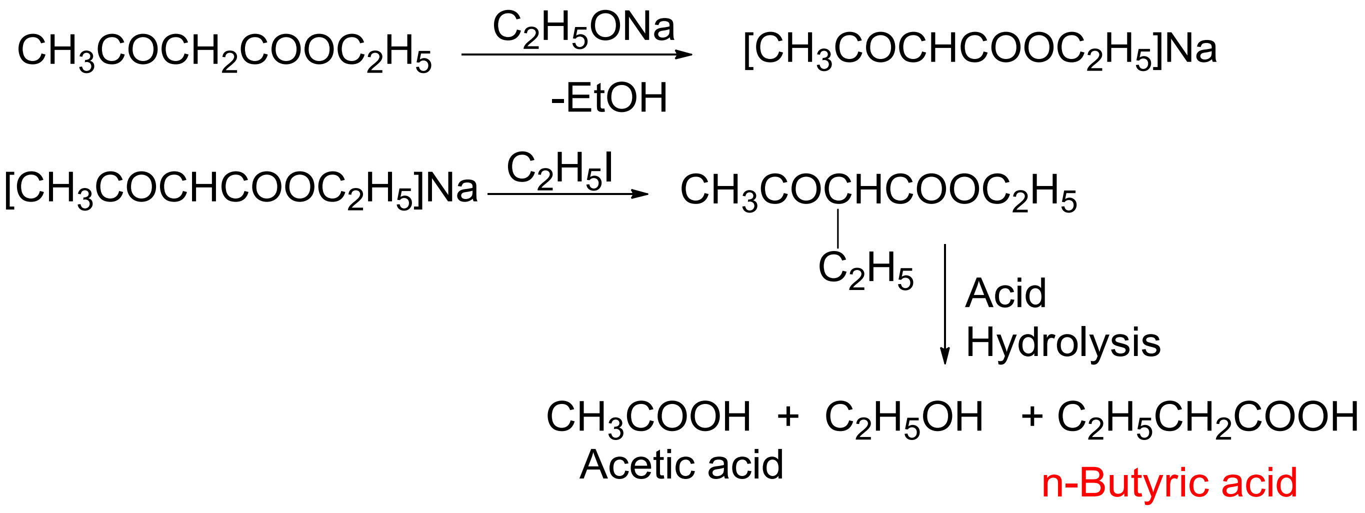


$$CH_3CO\underset{\substack{|\\ R}}{C}HCOOC_2H_5 + R'X \xrightarrow{C_2H_5ONa} CH_3CO\overset{\substack{R'\\ |}}{\underset{\substack{|\\ R}}{C}}COOC_2H_5$$

Dialkyl derivative

2) Synthesis of Monocarboxylic acids:

a)n-Butyric acid:Dialkyl derivative of acetoacetic ester is prepared and it is subjected to acid hydrolysis.



$$CH_3COCH_2COOC_2H_5 \xrightarrow[-EtOH]{C_2H_5ONa} [CH_3COCHCOOC_2H_5]Na$$

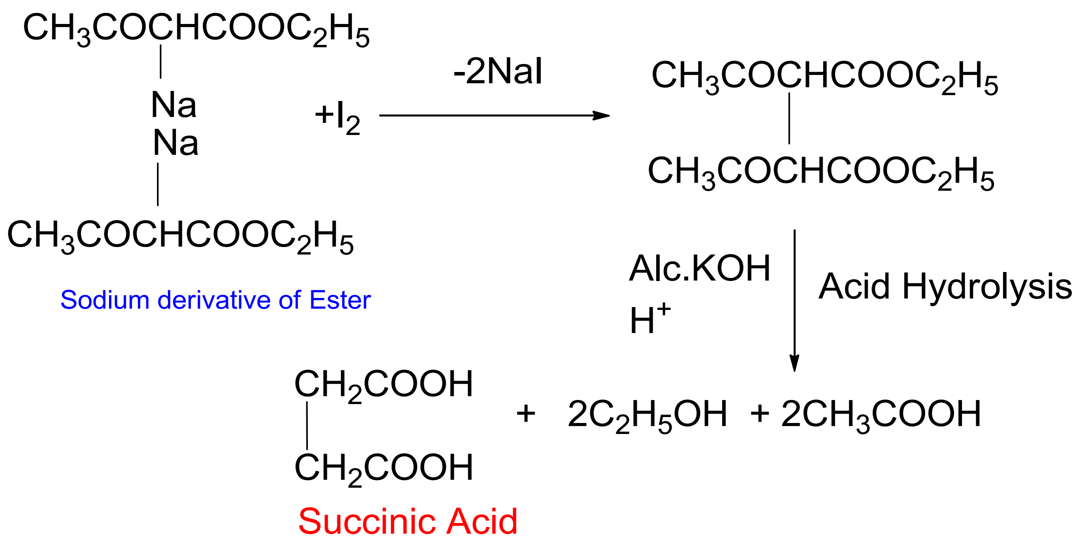
$$[CH_3COCHCOOC_2H_5]Na \xrightarrow{C_2H_5I} CH_3CO\underset{\substack{|\\ C_2H_5}}{C}HCOOC_2H_5$$

$$\xrightarrow{\text{Acid Hydrolysis}} \underset{\text{Acetic acid}}{CH_3COOH} + C_2H_5OH + \underset{\text{n-Butyric acid}}{C_2H_5CH_2COOH}$$

3) Synthesis of dicarboxylic acids:

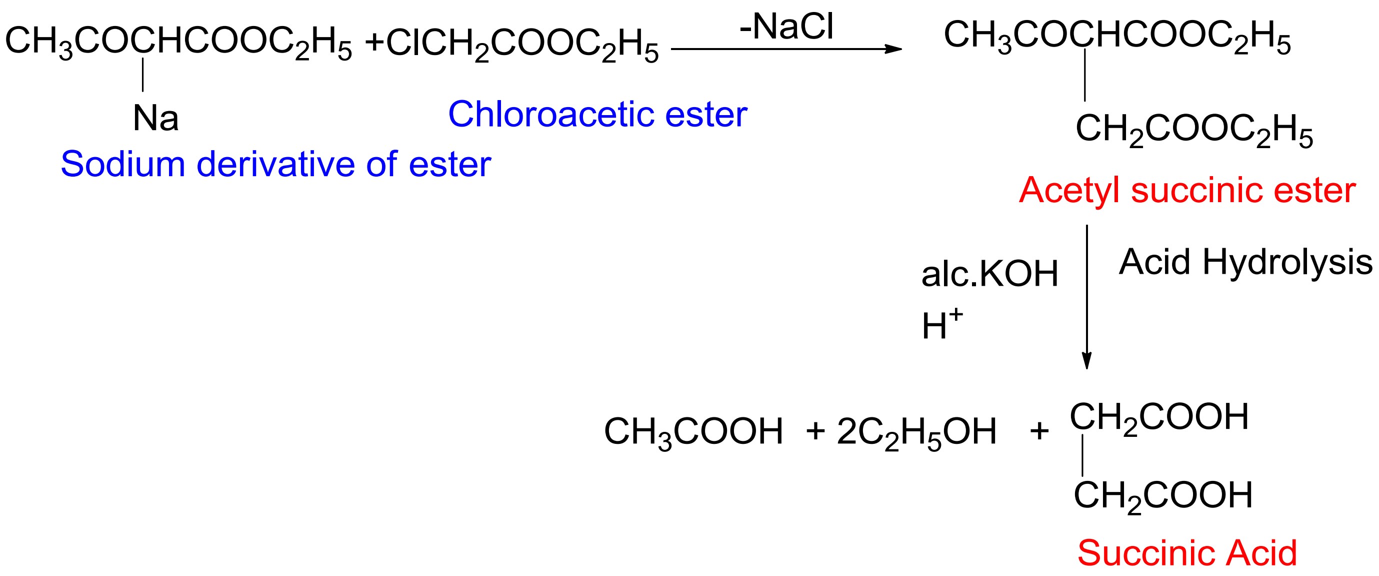
Succinic acid: Prepared by treating monosodium derivative of ester i) with Iodine or ii) Chloroacetic ester followed by acid hydrolysis

i) With Iodine:



$$\begin{array}{c} CH_3COCHCOOC_2H_5 \\ | \\ Na \\ Na \\ | \\ CH_3COCHCOOC_2H_5 \end{array} + I_2 \xrightarrow{-2NaI} \begin{array}{c} CH_3COCHCOOC_2H_5 \\ | \\ CH_3COCHCOOC_2H_5 \end{array} \xrightarrow[\text{Acid Hydrolysis}]{\text{Alc.KOH},\ H^+} \begin{array}{c} CH_2COOH \\ | \\ CH_2COOH \end{array} + 2C_2H_5OH + 2CH_3COOH$$

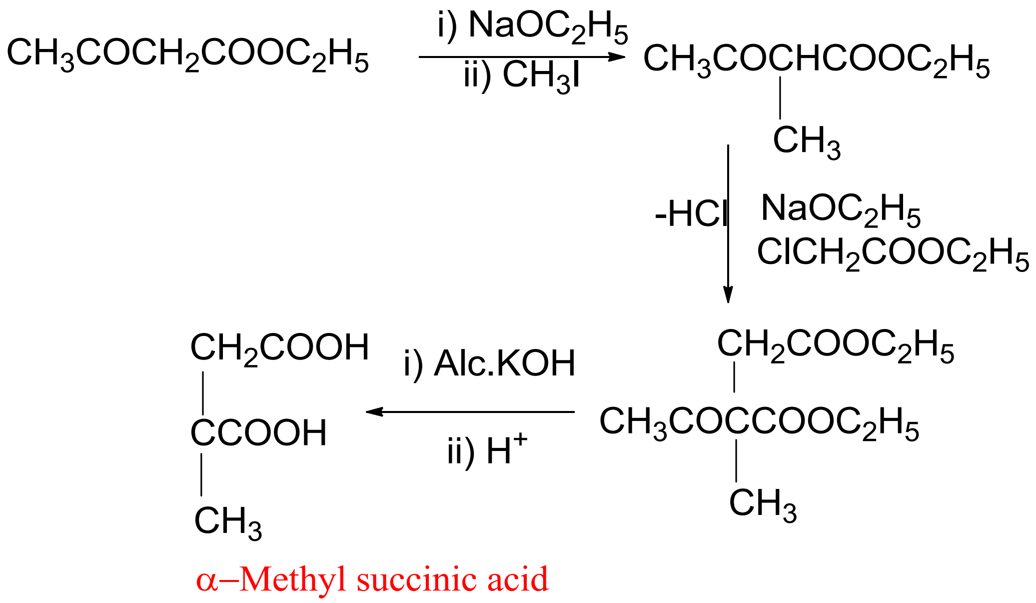
ii) With chloroacetic ester:



$$\begin{array}{c} CH_3COCHCOOC_2H_5 \\ | \\ Na \end{array} + ClCH_2COOC_2H_5 \xrightarrow{-NaCl} \begin{array}{c} CH_3COCHCOOC_2H_5 \\ | \\ CH_2COOC_2H_5 \end{array} \xrightarrow[\text{Acid Hydrolysis}]{\text{alc.KOH},\ H^+} CH_3COOH + 2C_2H_5OH + \begin{array}{c} CH_2COOH \\ | \\ CH_2COOH \end{array}$$

(iii) Substituted succinic acids:

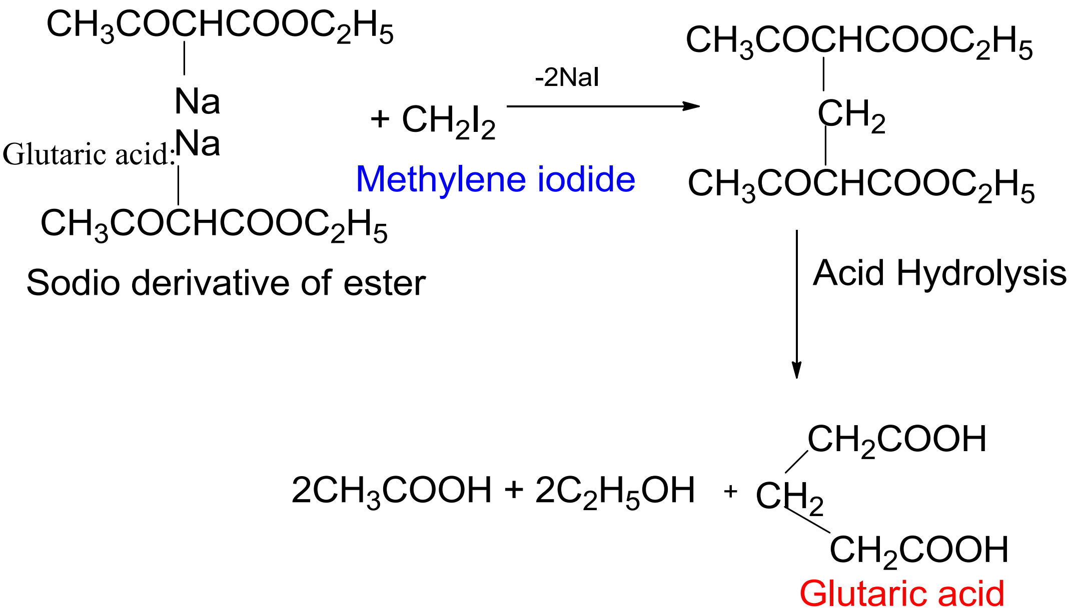
Sodium derivative of alkylacetoacetic ester with suitable α-halogen substituted ester- methyl substituted succinic acids.



(iv) Higher dibasic acids:

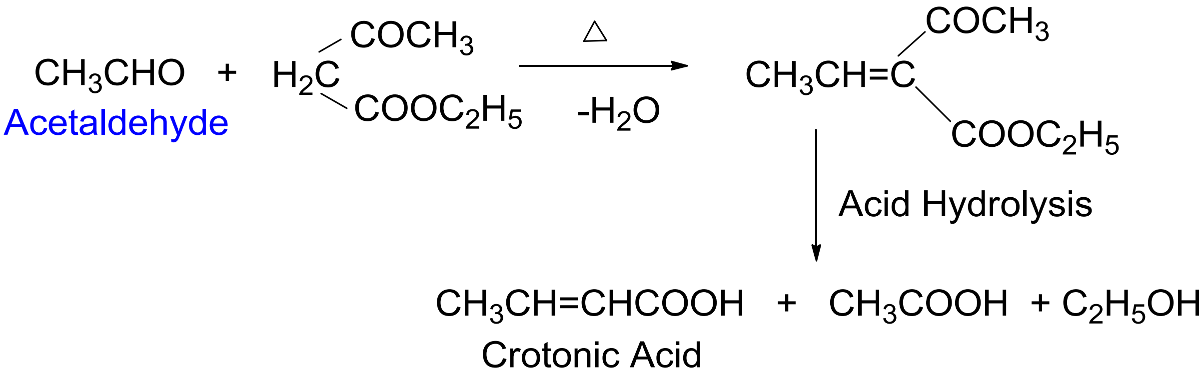
Sodium derivative of the ester with alkylene halide followed by acid hydrolysis.

Glutaric acid:



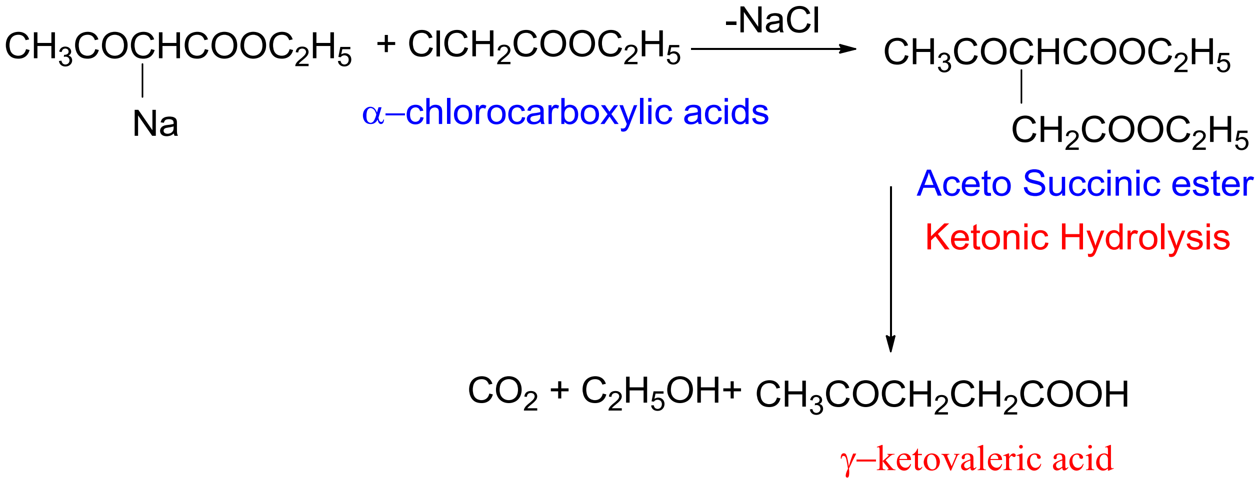
4) Synthesis of α,β-unsaturated acids:

Condensation of acetoacetic esterw ith aldehyde and ketones gives α,β unsaturated acids on acid hydrolysis.



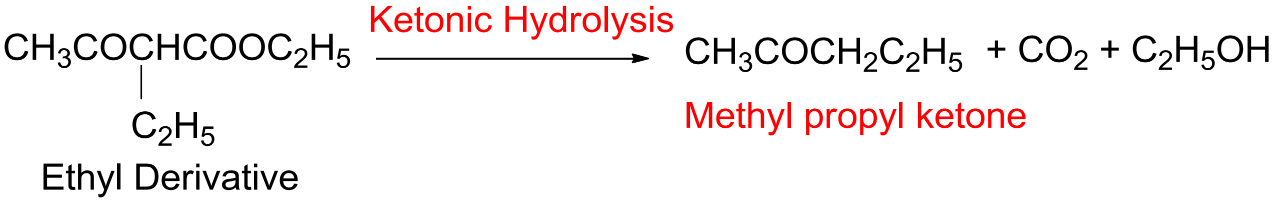
5) Synthesis of γ-ketonic acids:

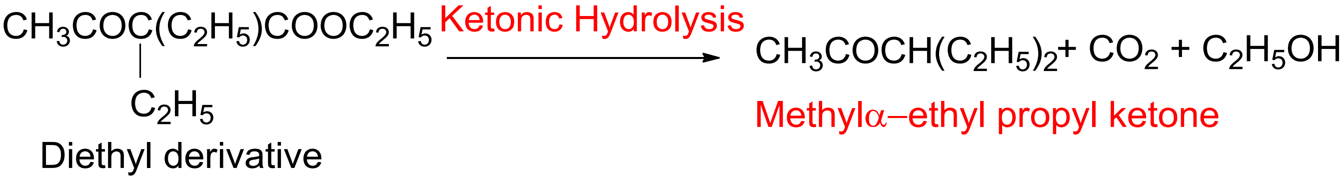
Condensation of sodio derivative of α-chlorocarboxylic acid ester followed by ketonic hydrolysis.



6) Synthesis of methyl ketones:

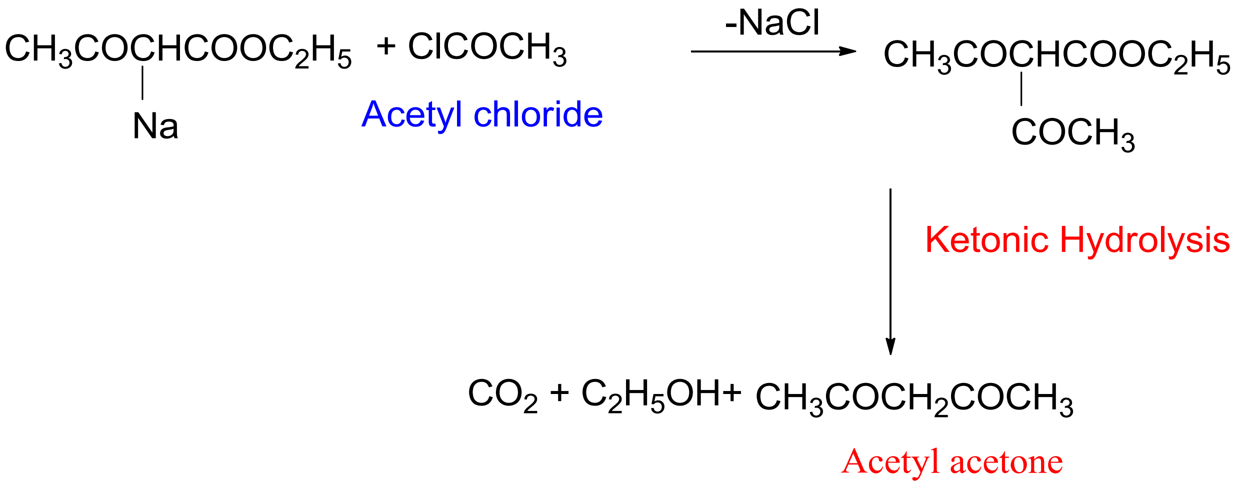
Mono and di alkyl derivatives of acetoacetic ester on ketonic hydrolysis forms higher methyl ketones.



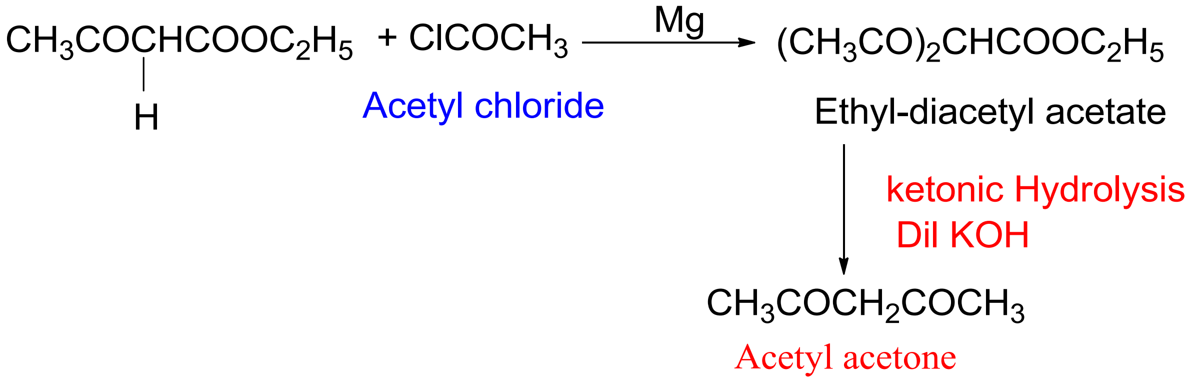


7) Synthesis of 1,3-diketones:

i) sodio derivative of ester is treated with acyl halide to form 1,3 –diketone.

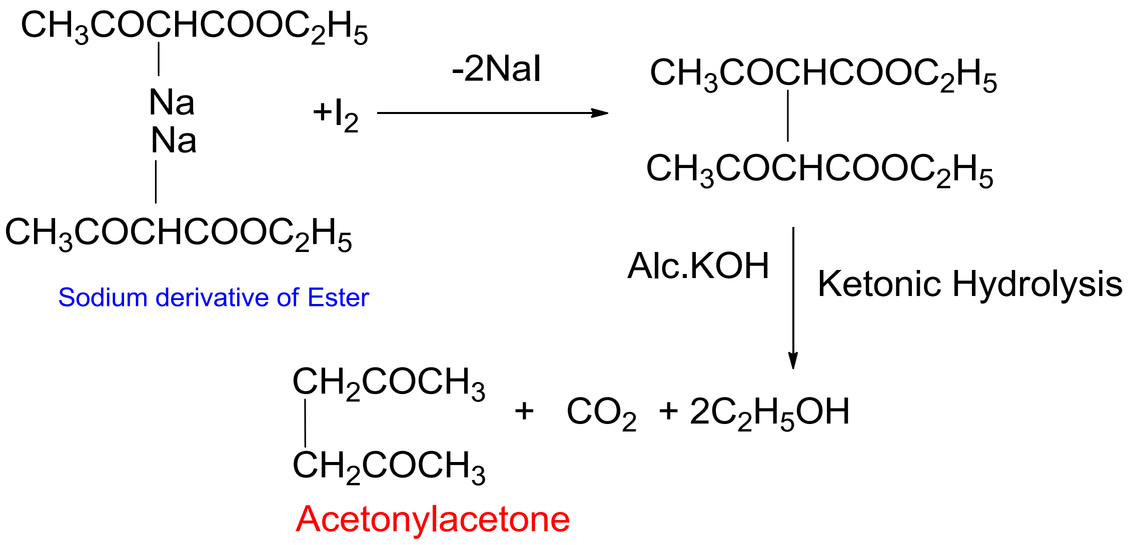


ii) Treating the ester with acid chloride and Mg to form the product which on ketonic hydrolysis forms 1,3 diketones.



8) Synthesis of 1,4-diketone(acetonyl acetone)

Acetoacetic ester is treated with iodine followed by ketonic hydrolysis, acetonyl acetone is obtained.

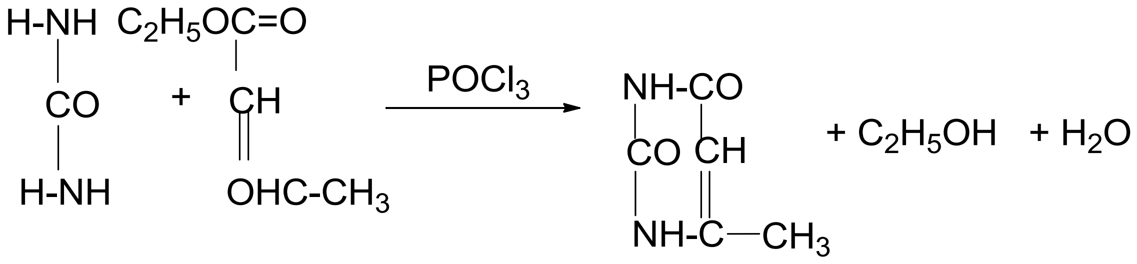


9) Synthesis of hydrocarbons:

Esters and its alkyl derivatives forms paraffins on electrolytic reduction.

$$CH_3COCH_2COOC_2H_5 + 10[H] \longrightarrow CH_3CH_2CH_2CH_3 + 2H_2O + C_2H_5OH$$

10) Synthesis of cyclic compounds:It condenses with urea to from 4-methyl uracil.



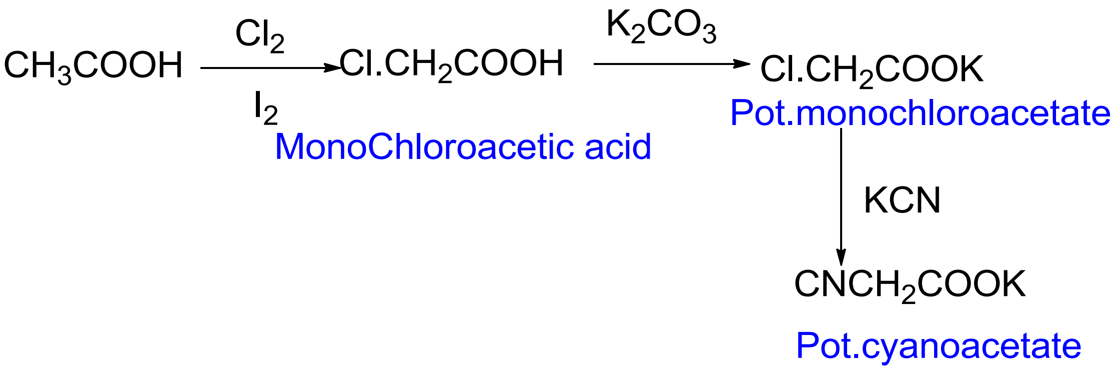
4-Methyluracil

2.3 MALONIC ESTER, DIETHYL MALONATE-$CH_2(COOC_2H_5)_2$

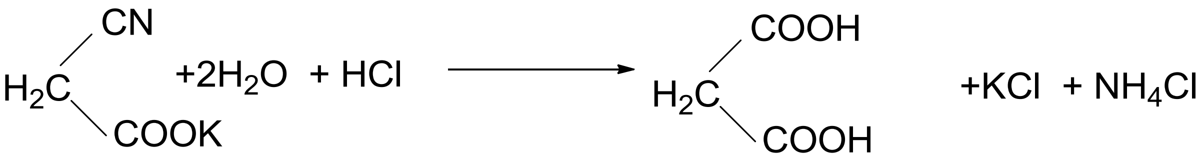
2.3.1 Preparation:

By passing dry hydrogen chloride gas through a mixture containing alcohol and potassium cyanoacetate, is prepared *insitu* from chloroacetic acid.

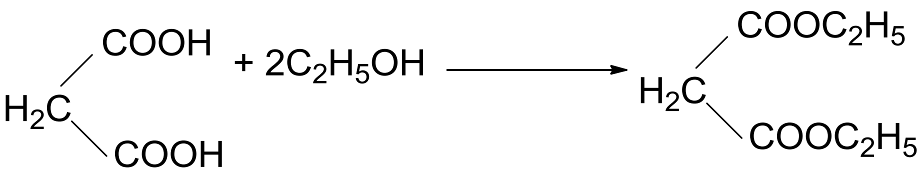
(1) Preparation of Potasium cyanoacetate:



ii) Synthesis of malonic acid and its ester



Malonic Acid



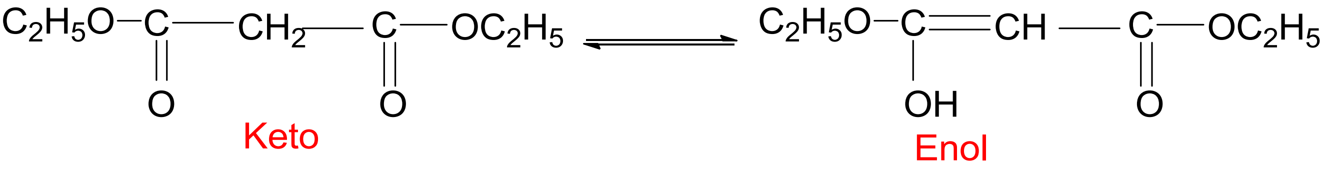
Malonic Ester

2.3.2 Physical properties:

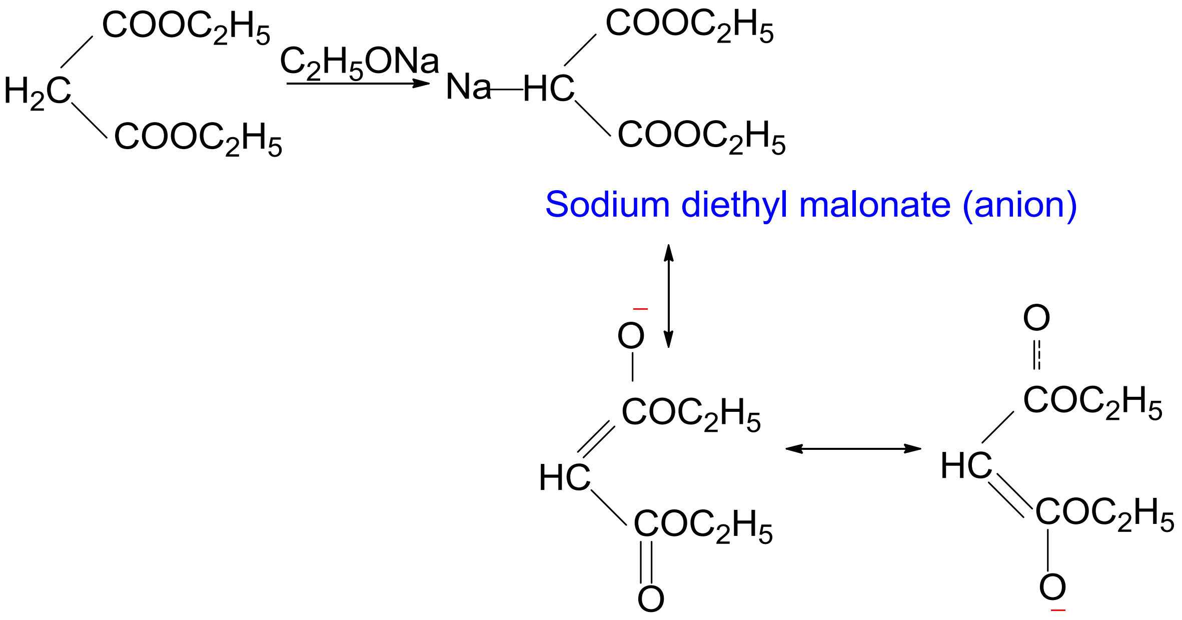
Colourless, pleasant smelling liquid, sparingly soluble in water but soluble in alcohol, benzene.

2.3.3 Chemical Properties:

Presence of two carbonyl groups on either side of methylene group exerts –I effect which adds to the resonance stabilised anion resulting in the hydrogen of the methylene group to be acidic thereby malonic ester exhibits keto-enol tautomerism.

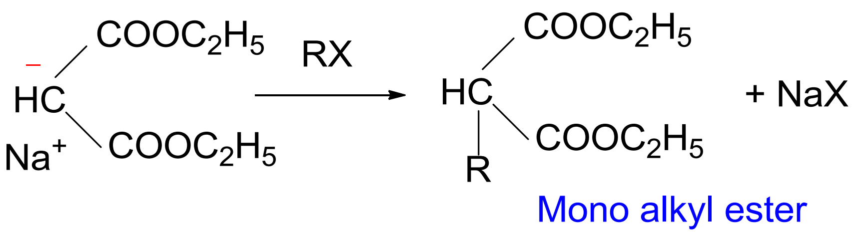


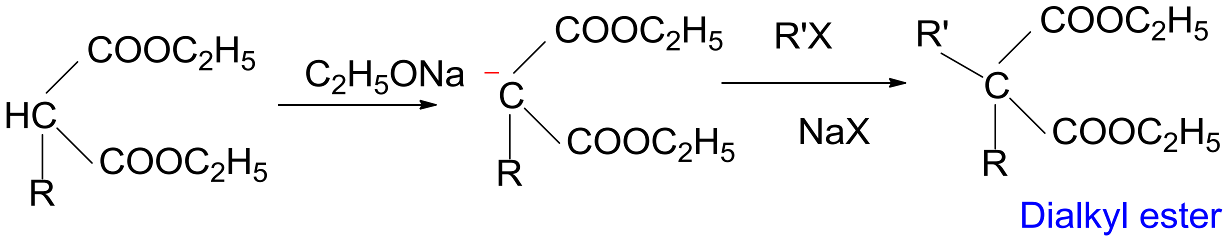
The presence of active methylene group behaves as an acid. It reacts with ethoxide to form sodiomalonic ester the anion is resonance stabilized. The anion act as nucleophile reacts with alkyl halide.



1) Reaction with alkyl halide:

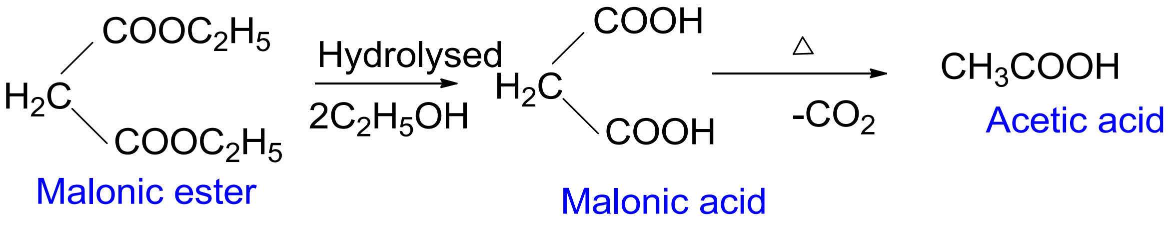
The anion of malonic ester reats with alkyl halide to from monoalkyl and dialkyl ester.



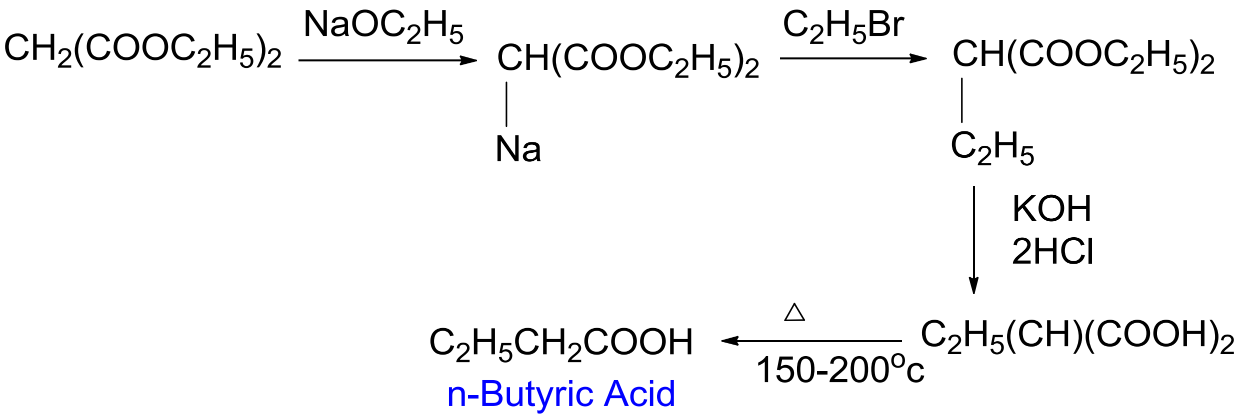


2) Synthesis of Monocarboxylic acid:

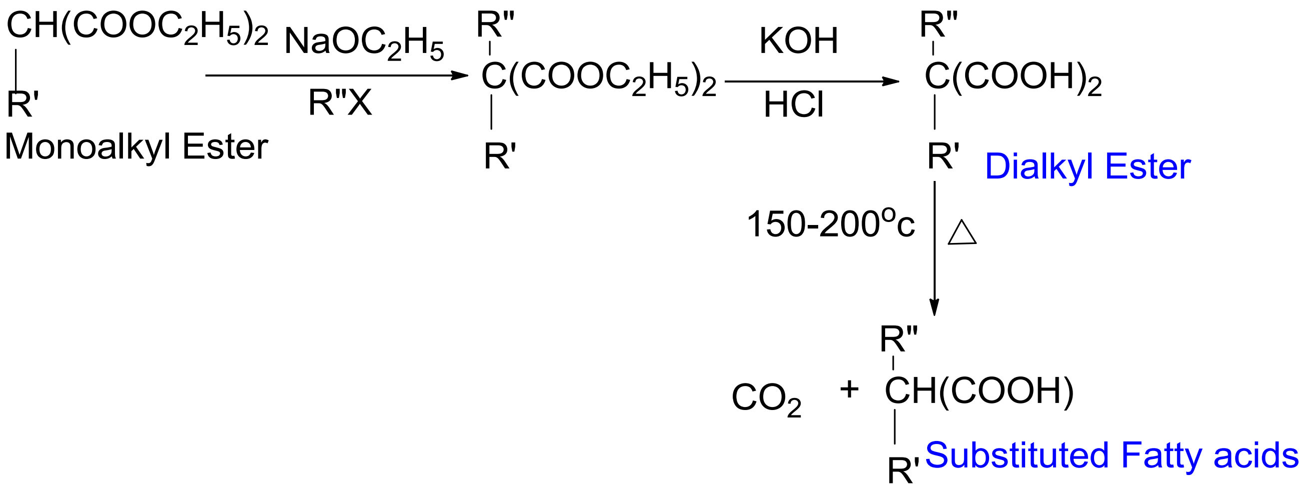
i)Acetic acid: Malonic ester on hydrolysis followed by heating at 150-200^{o}c yields acetic acid.



ii) Butyric acid: Treating sodio derivative of the ester with alkyl halide followed by hydrolysis and decarboxylation.

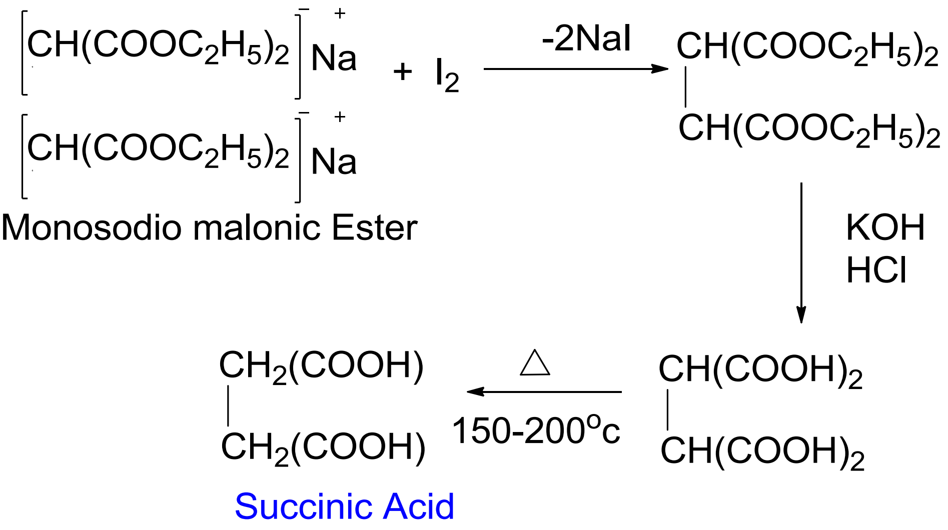


iii) Substituted Fatty acids: Reaction of dialkyl ester of malonic acid on hydrolysis followed by decarboxylation gives substituted fatty acids.

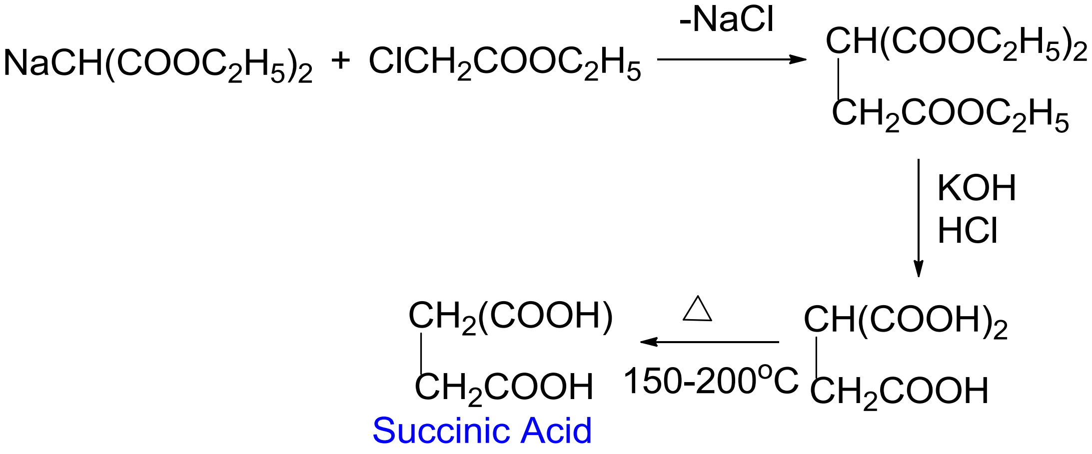


3) Synthesis of dicarboxylic acid:

Heating monosodium malonic ester with iodine followed by hydrolysis and decarboxylation.

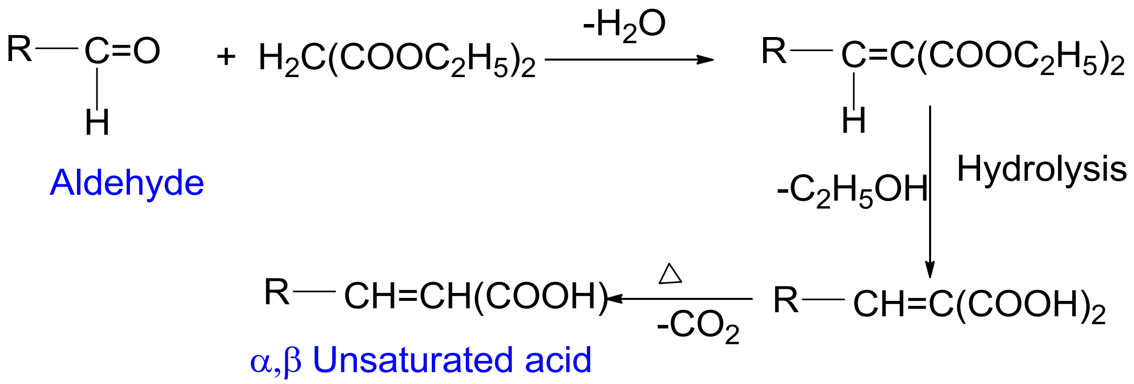


ii) Monosodio malonic ester is treated with chloroester, the product is hydrolysed followed by decarboxylation.

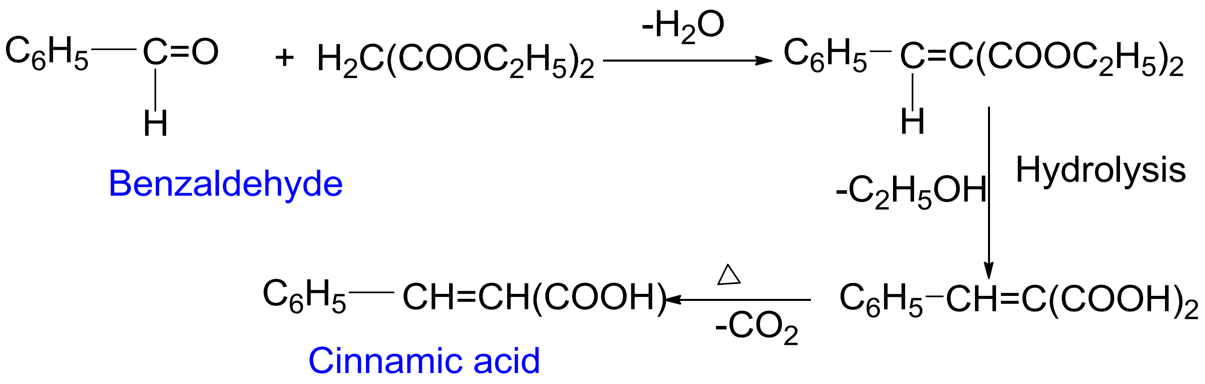


4)Synthesis of α,β unsaturated acids:

Malonic ester condenses with an aldehyde or ketone and the product on heating forms an unsaturated acid.

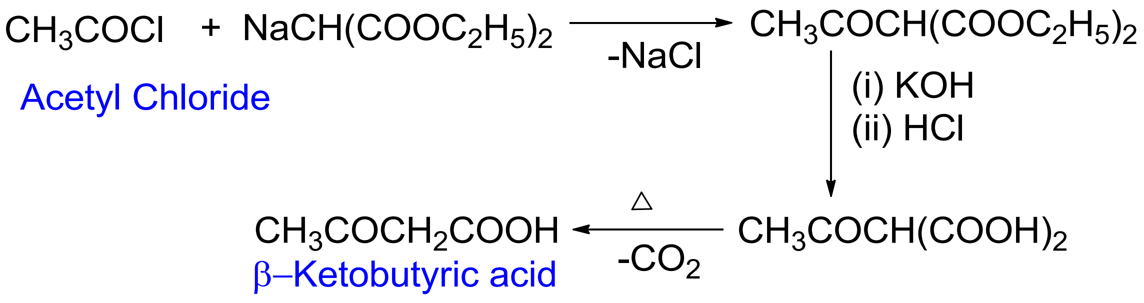


Reactions with benzaldehyde



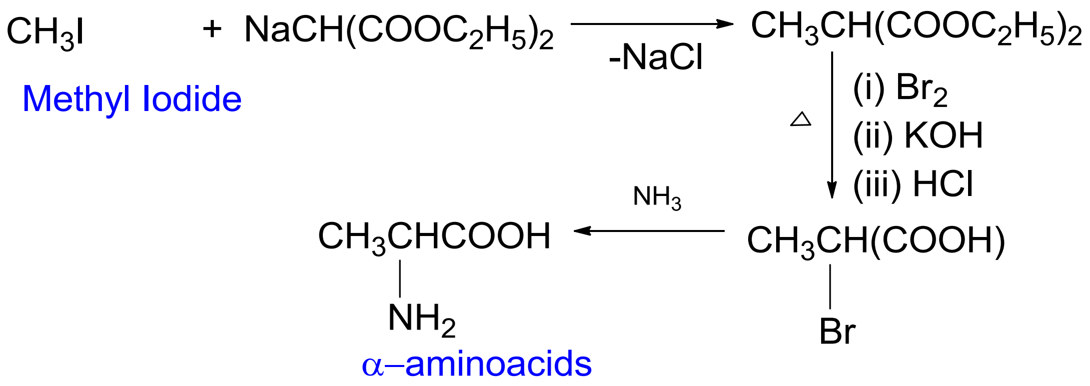
5) Synthesis of β ketoacids:

When sodiomalonic ester is treated with acid chloride, a keto acid is formed by hydrolysing the product.



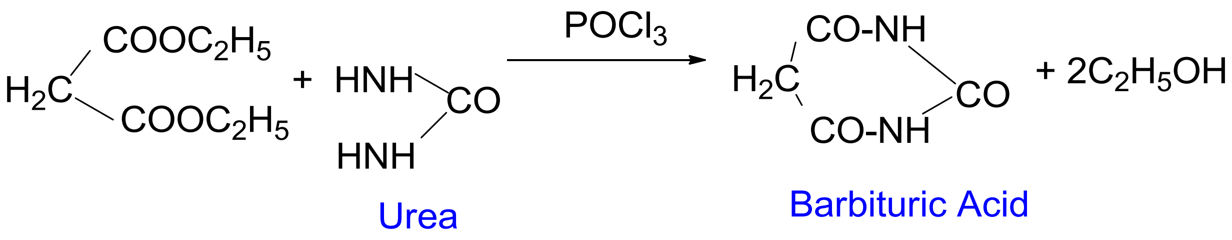
6)Synthesis of α aminoacids:

Alkyl iodide on treating with malonic ester forms a product which on bromination follwed by hydrolysis, decarboxylation and animation forms an α-aminoacids.



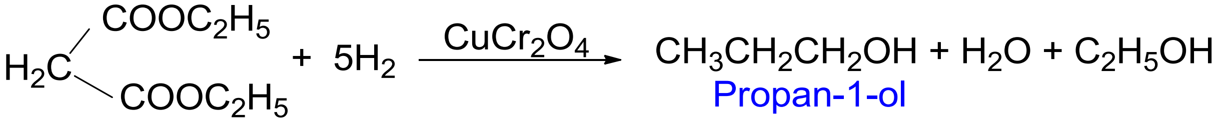
7) Synthesis of heterocyclic compounds:

In the presence of $POCl_3$, malonic ester condenses with urea to from malonyl urea, barbituric acid.



8) Synthesis of primary alcohol:

Malonic ester is treated with hydrogen in the presence of copper chromite, carboethoxy group is reduced to I^o alcohol.



2.4 CYANOACETIC ESTER,ETHYL CYANOACETATE- $CN.CH_2COOC_2H_5$

2.4.1 Preparation:

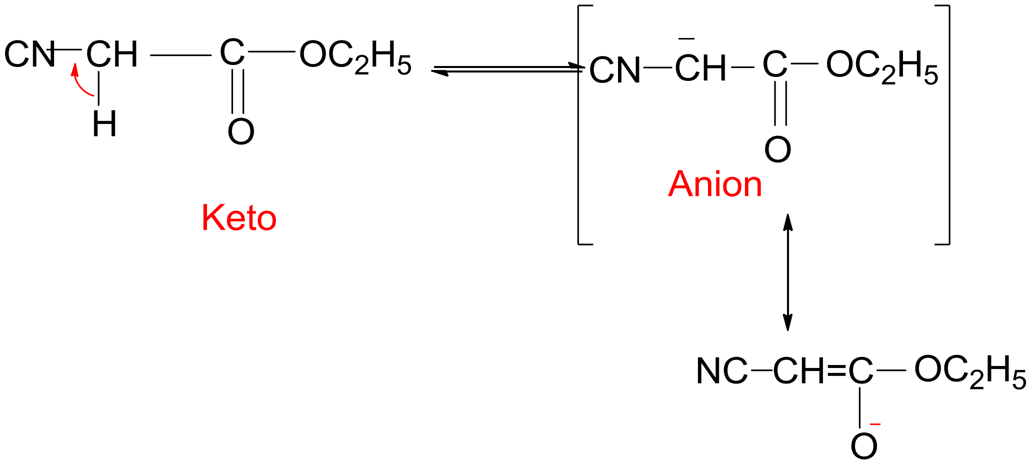
Heating Chloroacetic ester with KCN.

$$KCN + ClCH_2COOC_2H_5 \longrightarrow CNCH_2COOC_2H_5 + KCl$$

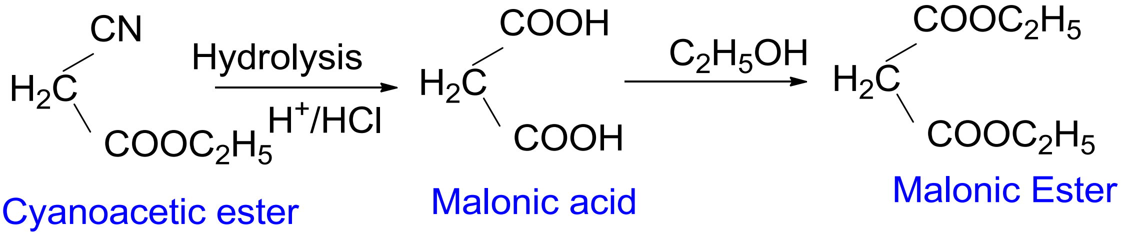
2.4.2 Physical: Colourless liquid, slightly soluble in water, soluble in alcohol and ether.

2.4.3 Chemical: Exhibits Keto-enol tautomerism.

Reactions:The methylene group is acidic due to the presence of CN and CO groups which are resonance stabilized.

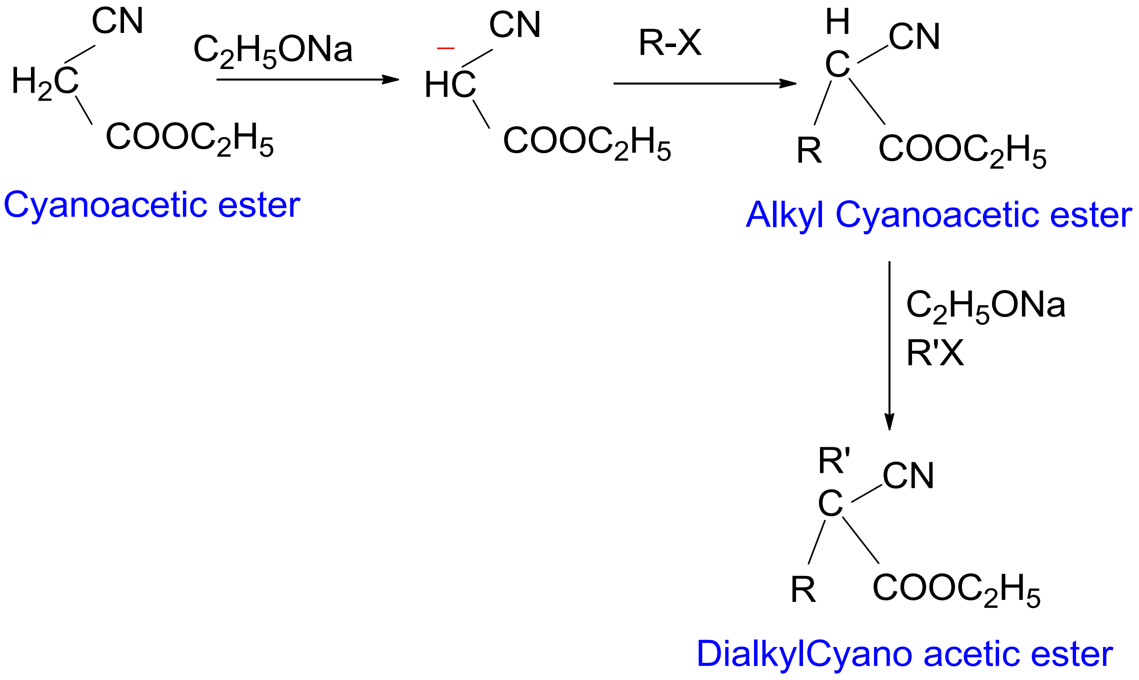


On hydrolysis it produces malonic acid, its reactions are similar to those of malonic ester.



2.4.4.Synthetic Importance:

1)With alkyl halide: It forms carbanion readily, can undergo nucleophilic substitutions to from alkyl derivative.



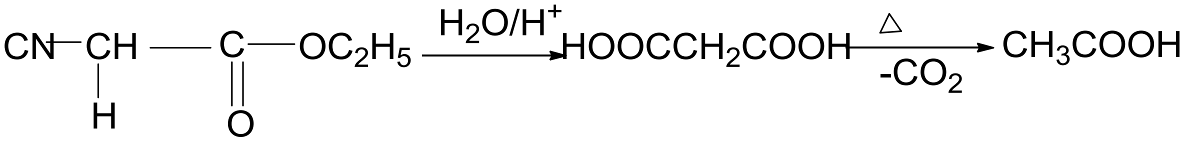
Cyanoacetic ester

Alkyl Cyanoacetic ester

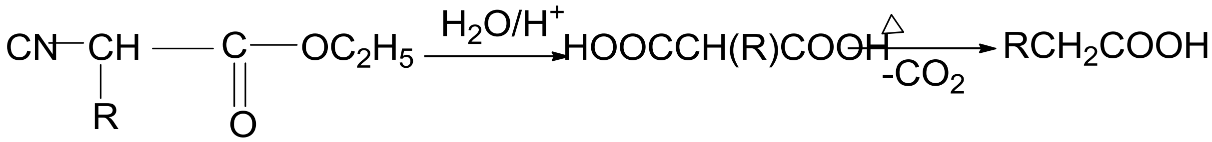
DialkylCyano acetic ester

2)Synthesis of monocarboxylic acid:

Ester or its alkyl derivative on hydrolysis yields acids.



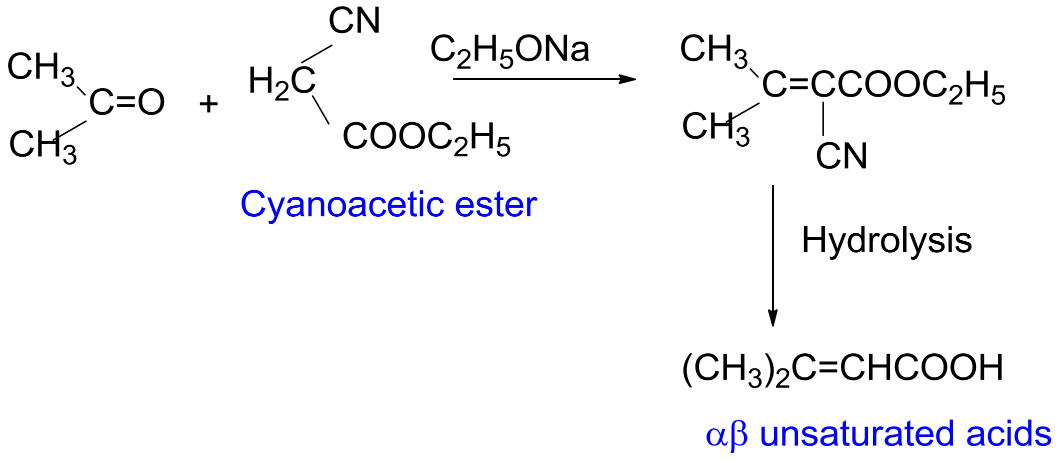
$$\mathrm{CN{-}\underset{\displaystyle H}{\underset{|}{C}H}{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OC_2H_5 \xrightarrow{H_2O/H^+} HOOCCH_2COOH \xrightarrow[-CO_2]{\triangle} CH_3COOH}$$



$$\mathrm{CN{-}\underset{\displaystyle R}{\underset{|}{C}H}{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OC_2H_5 \xrightarrow{H_2O/H^+} HOOCCH(R)COOH \xrightarrow[-CO_2]{\triangle} RCH_2COOH}$$

3) Knoevenagel Reaction:

Ester condenses with aldehyde or ketone to form α,β unsaturated acids.

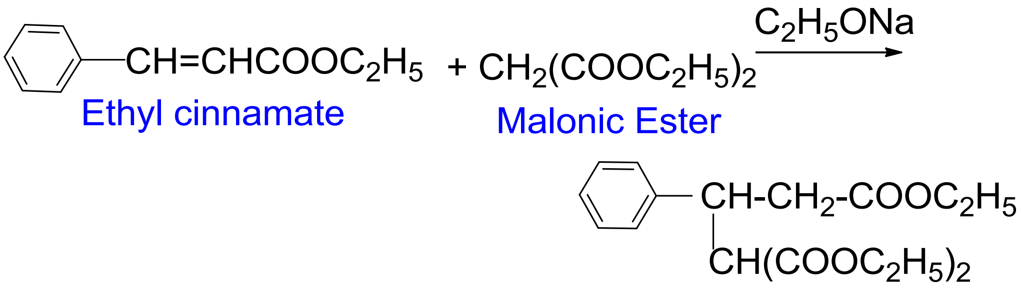


Cyanoacetic ester

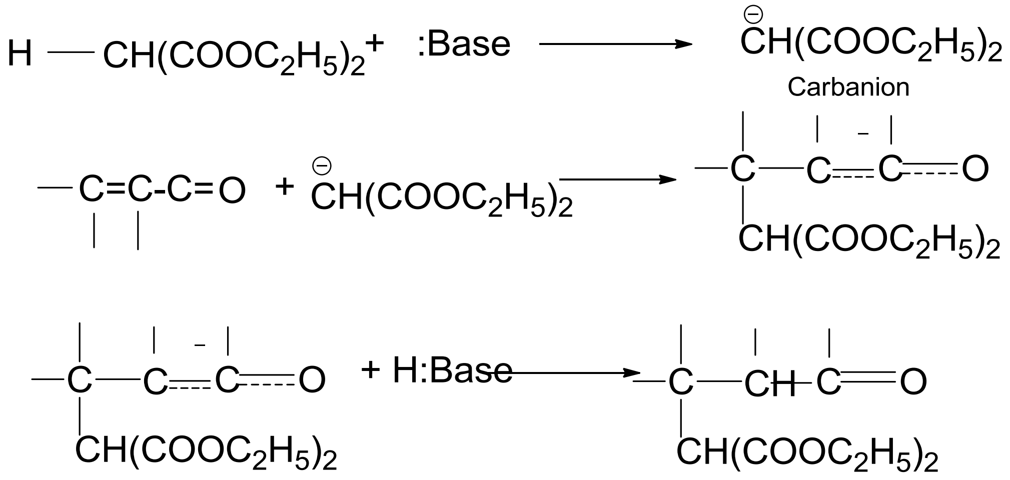
αβ unsaturated acids

2.5 MICHAEL ADDITION:

Nucleophilic addition of carbanions to αβ unsaturated carbonyl compounds to from conjugate addition poroduct, 1,5 dicarbonyl compound.



Malonic ester


$$H-CH(COOC_2H_5)_2 + :Base \longrightarrow \overset{\ominus}{C}H(COOC_2H_5)_2$$

$$-C=C-C=O + \overset{\ominus}{C}H(COOC_2H_5)_2 \longrightarrow -\underset{CH(COOC_2H_5)_2}{C}-C\overset{-}{=}C=O$$

$$-\underset{CH(COOC_2H_5)_2}{C}-C\overset{-}{=}C=O + H:Base \longrightarrow -\underset{CH(COOC_2H_5)_2}{C}-CH-C=O$$

TEXT / REFERENCE BOOKS

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – III - CHEMISTRY OF NITROGEN CONTAINING COMPOUNDS
SCY1315

2. CHEMISTRY OF NITROGEN CONTAINING COMPOUNDS

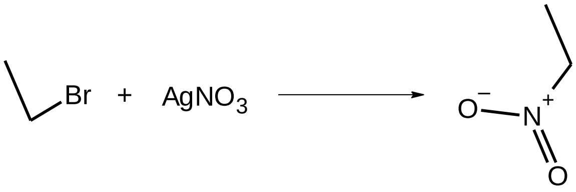
Amines – Structure, nomenclature and classification - Methods of preparation of primary, secondary and tertiary amines - Physical and chemical properties – Basicity of amines, effect of substituents on basicity of aromatic amines – Quaternary ammonium salts – Hinsberg test – Carbylamine test, Schotten-Baumann reaction. Nitrocompounds – Structure - Aliphatic and Aromatic nitro compounds – Methods of preparation - Physical and Chemical Properties – Substitution of aromatic nitro compounds. Diazo compounds- Diazotisation and its mechanism. Cyanides and isocyanides – Structure, preparation and properties.

NITROCOMPOUNDS

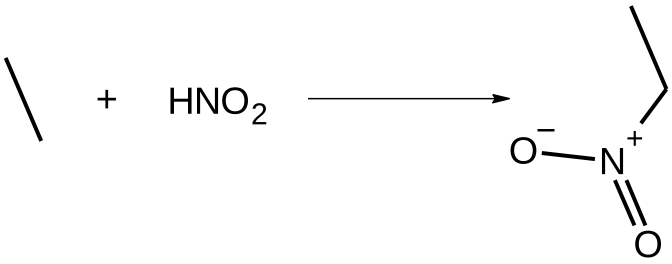
The important nitrogen containing organic compounds discussed here are alkyl nitriles, nitroalkanes, aromatic nitro compounds, alkyl cyanides, alkyl isocyanides, amines and aryl diazonium salts.

General Methods of Preparation

1. By heating an alkyl halide with aqueous alcoholic solution of silver nitrate



2. By the direct vapour phase nitration of paraffin's

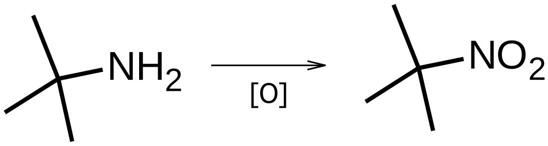


3. By the action of sodium nitrite on alpha-halo carboxylates

$$ClCH_2COONa + NaNO_2 \longrightarrow NO_2CH_2COONa + NaCl$$

$$NO_2CH_2COONa \xrightarrow[\Delta]{} CH_3NO_2$$

4. Tertiary nitroalkanes are obtained by the oxidation of tertiary-amine with $KMnO_4$



Properties:

1. Physical properties
   - (i) Nitroalkanes are colourless pleasant smelling liquids
   - (ii) These are sparingly soluble in water but readily soluble in organic solvents
   - (iii) Due to their polar nature, they have appreciable electrostatic attraction and hence posses high boiling point. Again due to polar nature, nitroalkanes are excellent solvents for polar and ionic compounds
2. Chemical Properties:
   - A. Acidic Nature
   - B. Action of Nitrous Acid

$$CH_3NO_2 + HNO_2 \xrightarrow[NaOH]{} CH_3(NO)NO_2$$

   - C. Condensation with Aldehydes

$$CH_3CHO + CH_3NO_2 \longrightarrow \underset{\text{b-hydroxy nitropropane}}{CH_3CH(OH)CH_2NO_2}$$

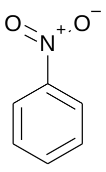
   - D. Mannich Reaction & Reaction with Grignard Reagent
   - E. Reduction & Hydrolysis
   - F. Halogination & Action of Heat

Applications of nitroalkanes:

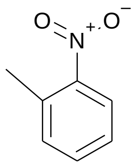
- Solvents for oils, fats, resins, dyes, lacquers, rubbers, etc..
- As explosives
- As intermediates for the synthesis of many organic compounds

AROMATIC NITROCOMPOUNDS

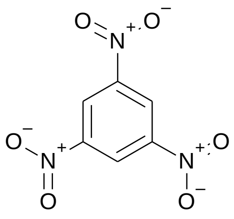
Nomenclature



nitrobenzene



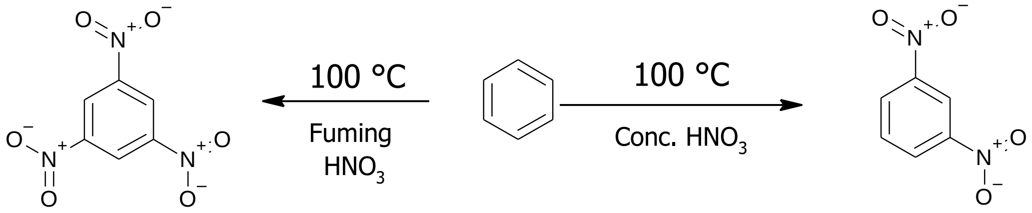
1-methyl-2-nitrobenzene

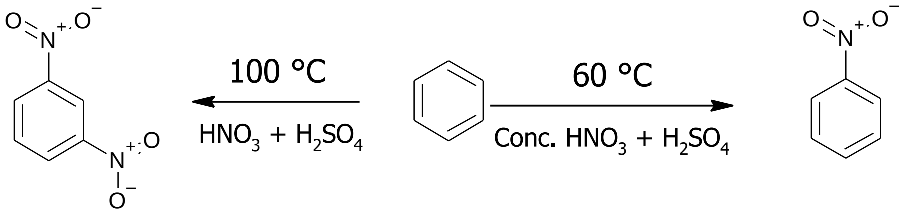


1,3,5-trinitrobenzene

AROMATIC NITRO COMPOUNDS

Preparation of Aromatic Nitrocompounds





Nitration Mechanism

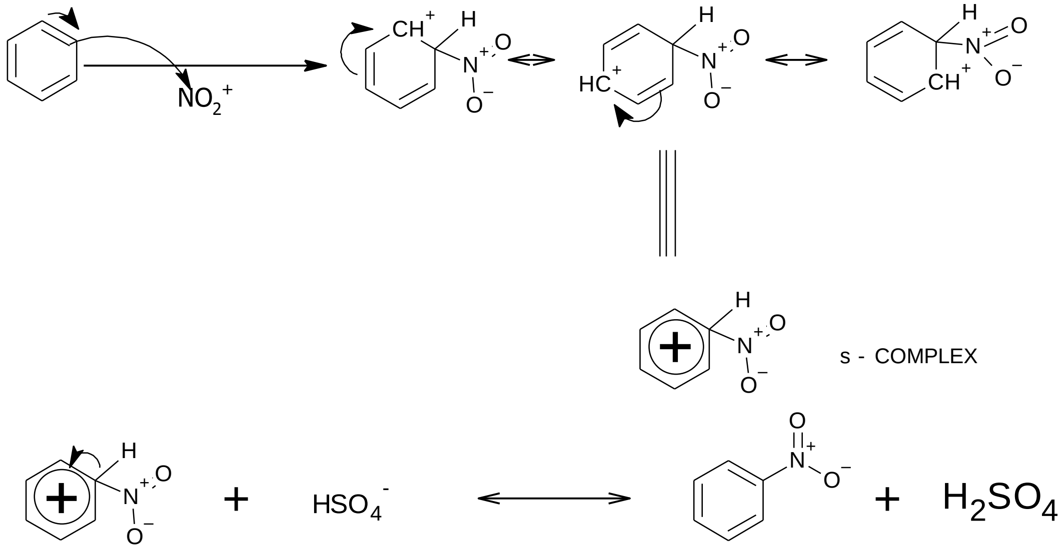
Generation of Nitrosonium ion:

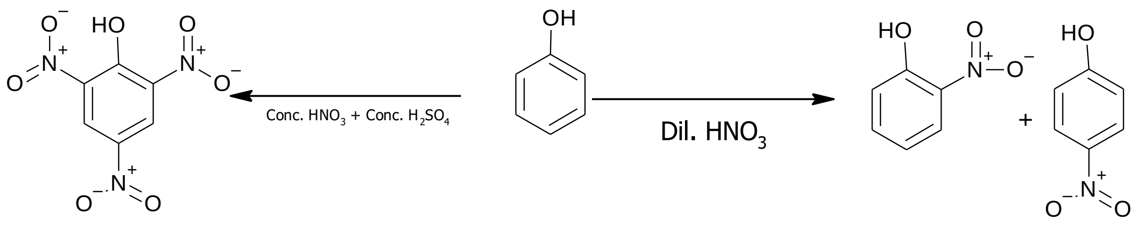
$$OH - NO2 + H_2SO_4 \rightleftharpoons H_2O - NO_2 \;+\; HSO_4^-$$

$$H_2O - NO_2 \rightleftharpoons H_2O \;+\; NO_2^+$$

$$H_2O \;+ H_2SO_4 \rightleftharpoons H_3O^+ \;+ HSO_4^-$$

Formation of sigma complex and nitro benzene





PHYSICAL PROPERTIES

(i) Most of the nitro compounds are yellow crystalline solids, except few (nitrobenzene) which are liquids

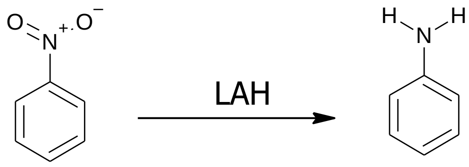
(ii) They are insoluble in water but soluble in organic solvents

(iii) They high boiling and melting points

(iv) They are highly toxic in nature

CHEMICAL PROPERTIES

A. Reduction

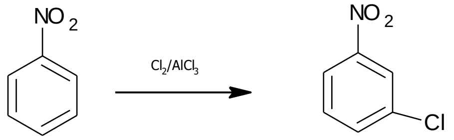


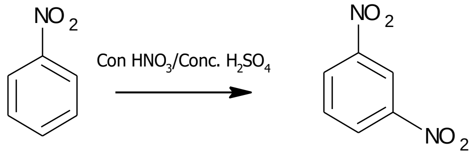
ACIDIC CONDITION:
Sn/HCl or Zn/HCl or Fe/HCl

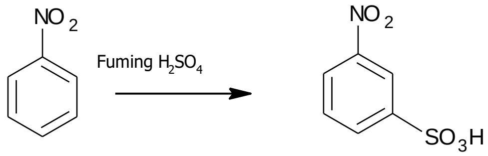
BASIC CONDITION
Zn dust/NaOH

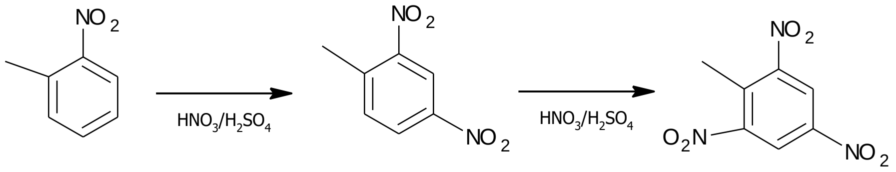
Neutral condition :
Zn dust/NH4Cl or Al-Hg/H2O

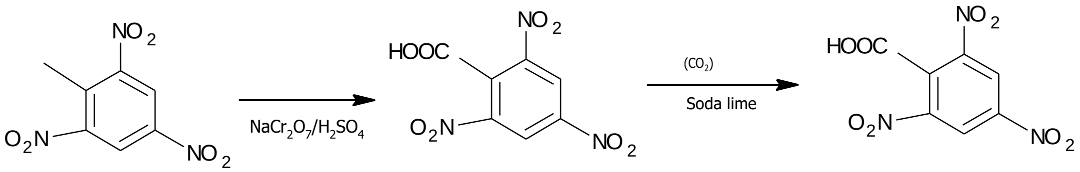
B. Electrophilic substitution



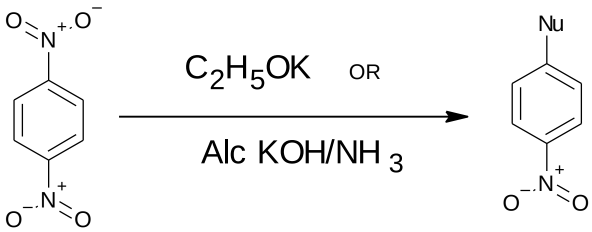




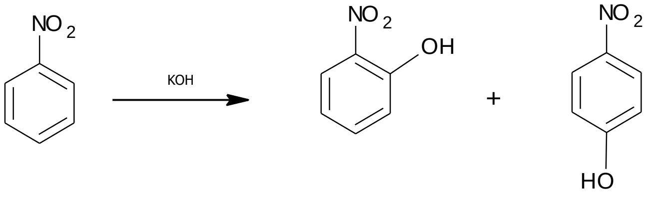


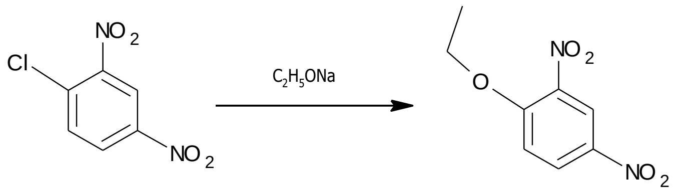


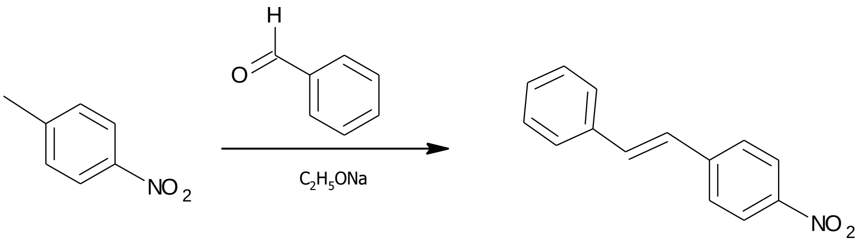
C. Nucleophlic substitution



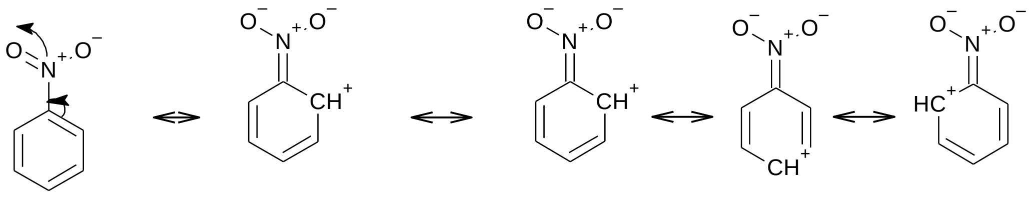
Nu = OH, NH_2, OC_2H_5

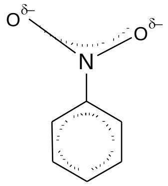






Resonance forms of Nitrobenzene



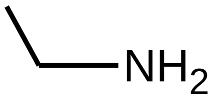


ALIPHATIC AMINES

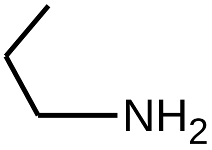
Alkyl amines may be regarded as derivatives of ammonia in which one or more hydrogen atoms have been replaced by alkyl groups. Amines are classified into primary, secondary and tertiary amines depending upon the number of alkyl groups attached to the nitrogen atom. Thus, a primary amine has only one alkyl group, secondary two and tertiary three attached to nitrogen atom.

Nomenclature of Aliphatic amines

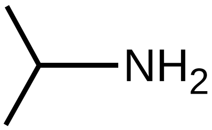
methanamine



ethanamine

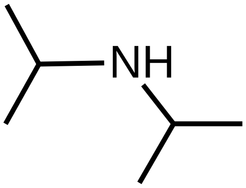


propan-1-amine

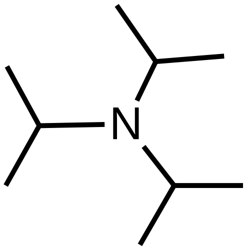


propan-2-amine

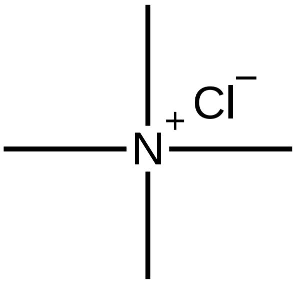
isopropyl amine



N-(propan-2-yl)propan-2-amine



N,*N*-di(propan-2-yl)propan-2-amine



Quarternary ammonium chloride

PREPARATION METHODS:

1. Ammonolysis of alkyl halides
2. Reduction of acid amides
3. Hofmann degradation of amides
4. Gabriel phthalimide reaction
5. Curtius reaction

1. Ammonalysis of alkylhalides

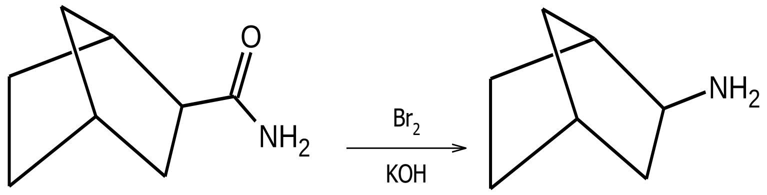
$$C_2H_5I + HNH_2 \longrightarrow C_2H_5NH_2 + HI$$

2. Reduction of acid amides

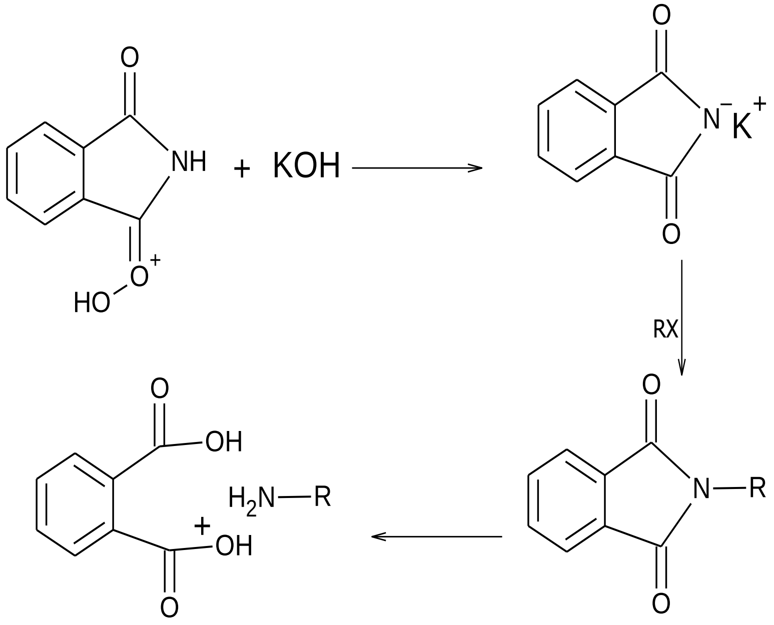
$$CH_3CONH_2 \longrightarrow CH_3CH_2NH_2 + H_2O$$

3. Hofmann degradation of amides

$$CH_3CONH_2 + Br_2 + KOH \longrightarrow CH_3NH_2 + 2KBr + K_2CO_3 + 2H_2O$$



4. Gabrlal pthalidamide reaction



5. CURTIUS REACTION

$$RCOOH \xrightarrow[C_2H_5OH]{H^+} RCOOEt \xrightarrow[N_2H_4]{} RCONHNH_2 \xrightarrow[HNO_2]{} RCON_3$$

$$RCON_3 \xrightarrow{CHCl_3} RN{=}C{=}O$$

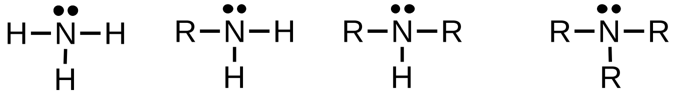
$$RNH_2 + K_2CO_3 \xleftarrow[KOH]{} RN{=}C{=}O \xleftarrow[KOH]{} RN{=}C{=}O$$

PHYSICAL PROPERTIES

1. The lower members are combustible gases i.e. C3 to C11 are volatile liquids and C12 onwards are solids
2. The lower members have fishy ammonical odour
3. The lower member is readily soluble in water, the solubility in water decreases and in organic solvents.
4. The boiling point increases with the increase in molecular weight.

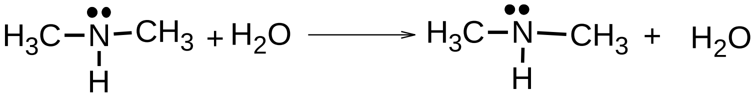
CHEMICAL PROPERTIES

1. Basic character



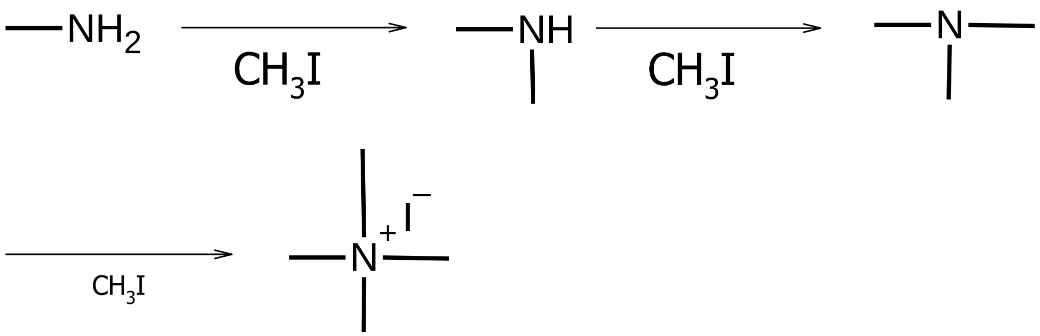
$NH_3 + H_2O \longleftrightarrow NH_4OH \longleftrightarrow NH_4^+ + OH^-$

$CH_3NH_2 + H_2O \longleftrightarrow CH_3NH_3OH \longleftrightarrow CH_3NH_4^+ + OH^-$

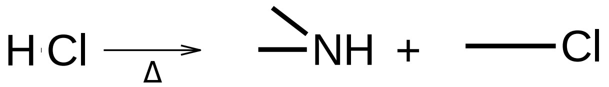


$H_3C-\underset{H}{\overset{\bullet\bullet}{N}}-CH_3 + H_2O \longrightarrow H_3C-\underset{H}{\overset{\bullet\bullet}{N}}-CH_3 + H_2O$

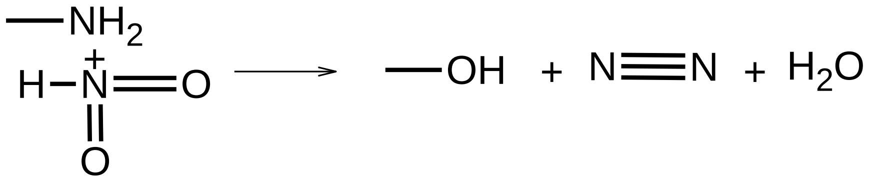
2. Alkylation and acylation

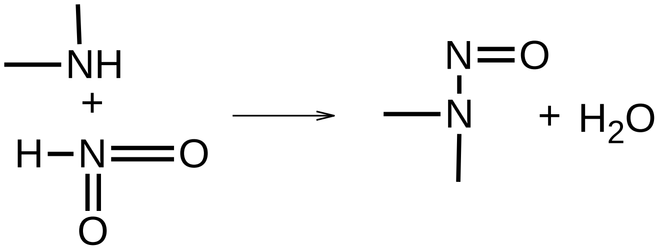


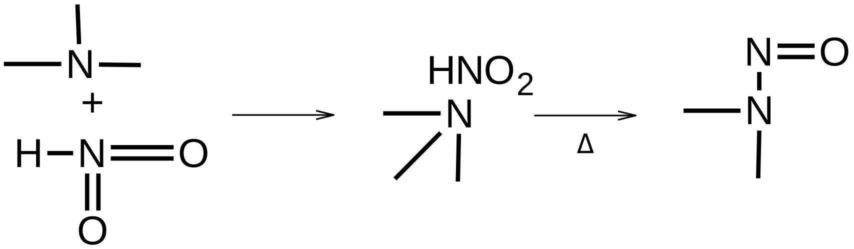
3. Dealkylation

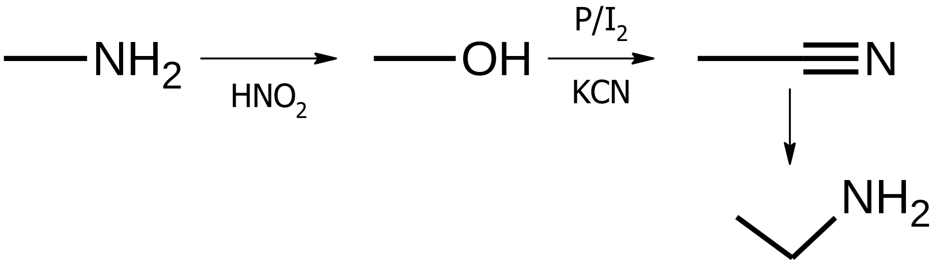


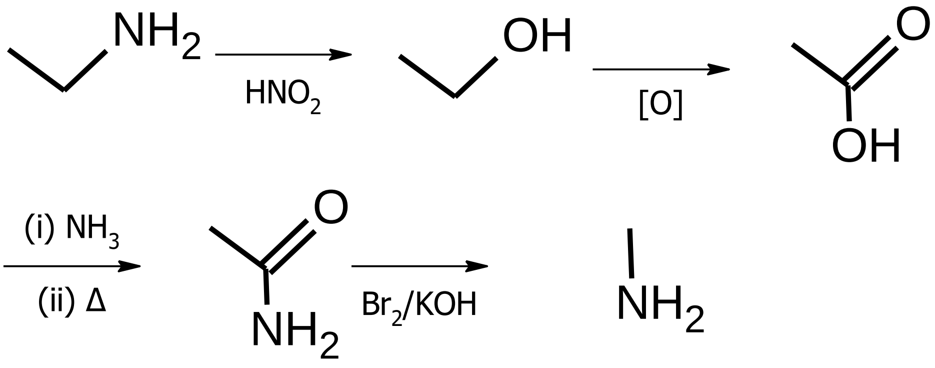
4. Reaction with nitrous acid



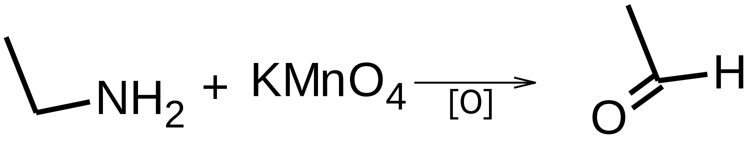


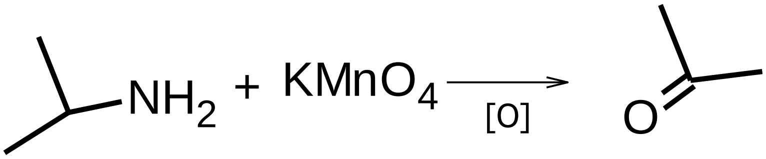


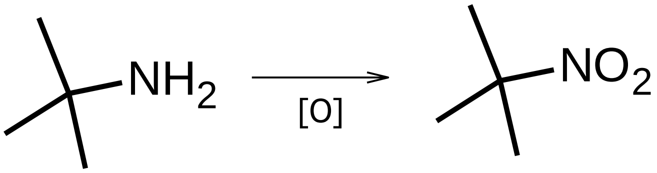




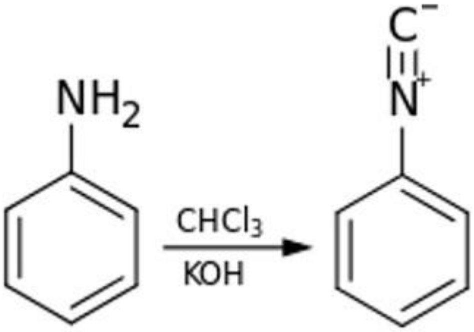
5. Oxidation



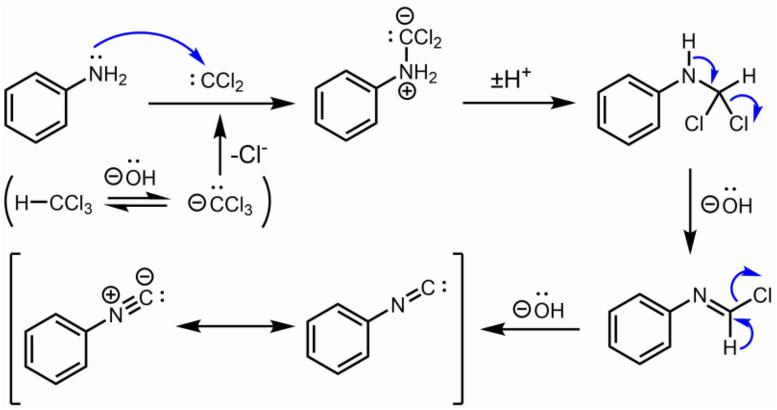




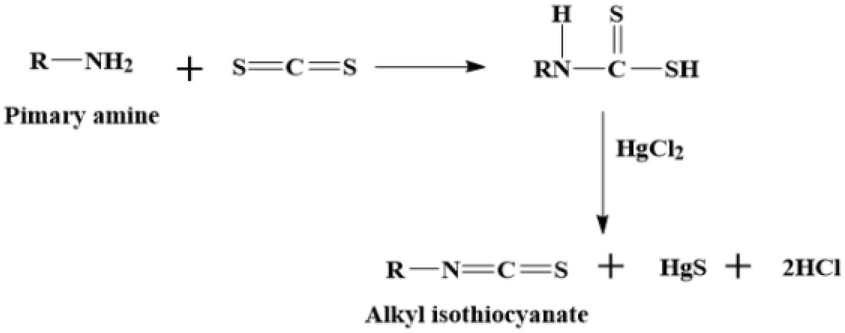
6. Carbylamine reaction



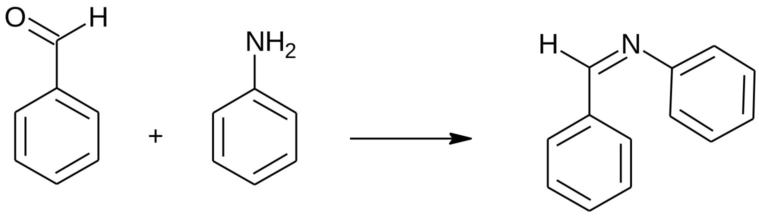
MECHANISM:



7. Hofmann’s mustard oil reaction



8. Reaction with aldehydes and ketones



Aldemine

The differences between Primary, Secondary and Tertiary amine

REACTION	PRIMARY	SECONDARY	TERTIARY
HNO_2	ALCOHOL + N_2	Nitroso amines - Libermann's reaction	Nitroso amines - Libermann's reaction
$CHCl_3$ + KOH	Carbyl amine	No reaction	No reaction
CS_2 + $HgCl_2$ Mustard Oil reaction	alkylisothiocyanate	No reaction	No reaction
Hinsburg reagent	Monoalkyl sulphonamide	Dialkyl sulphonamide	No reaction
diethyl oxalate	diethyl oxamide	diethyl oxamic ester	No reaction
Acetyl chloride	Amide	Amide	No reaction
CH_3I	3 MOLES	2 MOLES	1 MOLES

AROMATIC AMINE

Aromatic amino compounds are the derivatives of ammonia in which one or more hydrogen atom are replaced by aryl group. Like other classes of aromatic compounds. They can be of two types.

(i) Nuclear substituted aromatic amines
(ii) Side-chain substituted aromatic amines

Preparation of Primary aromatic amines

1. Reduction of the nitro compounds
2. Ammonolysis of aryl halides
3. Ammonolysis of phenols
4. Hofmann's hypobromite method
5. Isomerisation of alkylanilines
6. Schmidt reaction

CHEMICAL REACTION OF AMINO GROUP

A. REACTION OF AMINO GROUP
   (i) Basic character
   (ii) Alkylation & Acylation
   (iii) Sulphonylation
   (iv) Reaction with Grignard reagents
   (v) Condensation with aldehydes
   (vi) Carbylamines reaction
   (vii) Diazotisation
   (viii) Mustard oil reaction
   (ix) Carbonyl chloride

B. REACTIONS OF BENZENE NUCLEUS

   Electrophilic substitution reaction

   - Halogination

- Nitration
- Sulphonation
- Coupling reaction
- Oxidation

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2. O. P. Agarwal, Unified Chemistry text book, Volume 2; Jai Prash Nath Publication, Meerut, India.
3. O. P. Agarwal, Unified Chemistry text book, Volume 3; Jai Prash Nath Publication, Meerut, India.
4. O. P. Agarwal, Unified Chemistry text book, Volume 4; Jai Prash Nath Publication, Meerut, India.

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – IV - Molecular Rearrangements – SCY1315

UNIT-4

MOLECULAR REARRANGEMENTS

4.0 INTRODUCTION

Rearrangement: Reactions in which the carbon skeleton of the molecule is rearranged to give a structural isomer of the original molecule.

Sequence of steps involving substitution, elimination and addition reactions.

Atom or group which is migrates- Migrating Group.

Atom which is initially attached – Migration origin

Atom or group which it finally joins- Migration terminus.

Intermolecular Rearrangement:

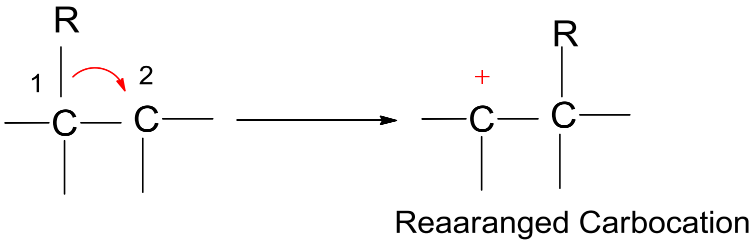
When the migratory group is completely detached from the molecule and go the migration terminus of the other molecule.

Intramolecular rearrangement:

When the migratory group remains attached to the molecule in some or the other way throughout the process of rearrangement.

Anionotropic Migration:

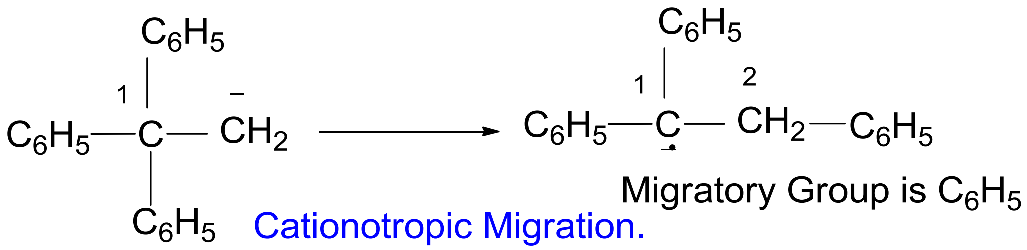
If the migratory atoms or groups may occur with the pair of electrons.



(C1= Migration Origin, C2- Migration Terminus)

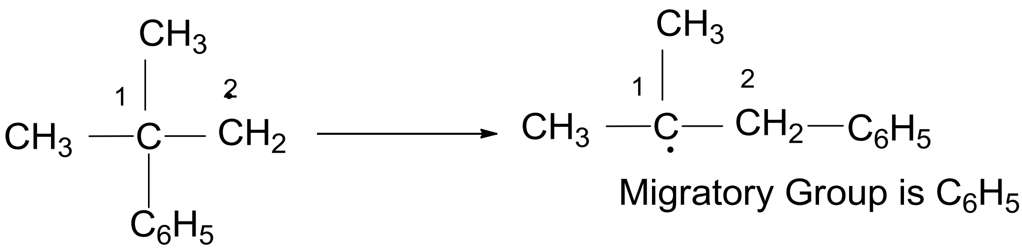
Cationotropic Migration:

If the migratory atoms or groups may occur without this pair of electrons.



Free Radical Migration:

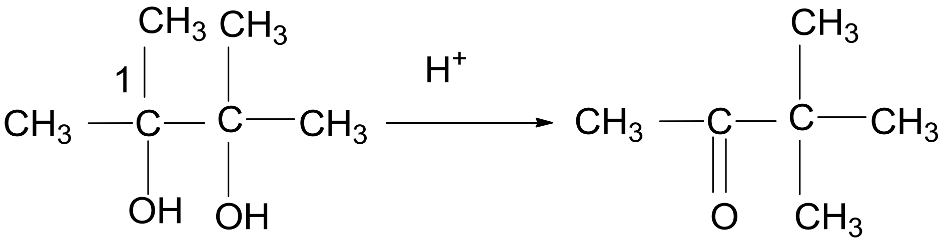
If the migratory group moves with one unpaired electron.



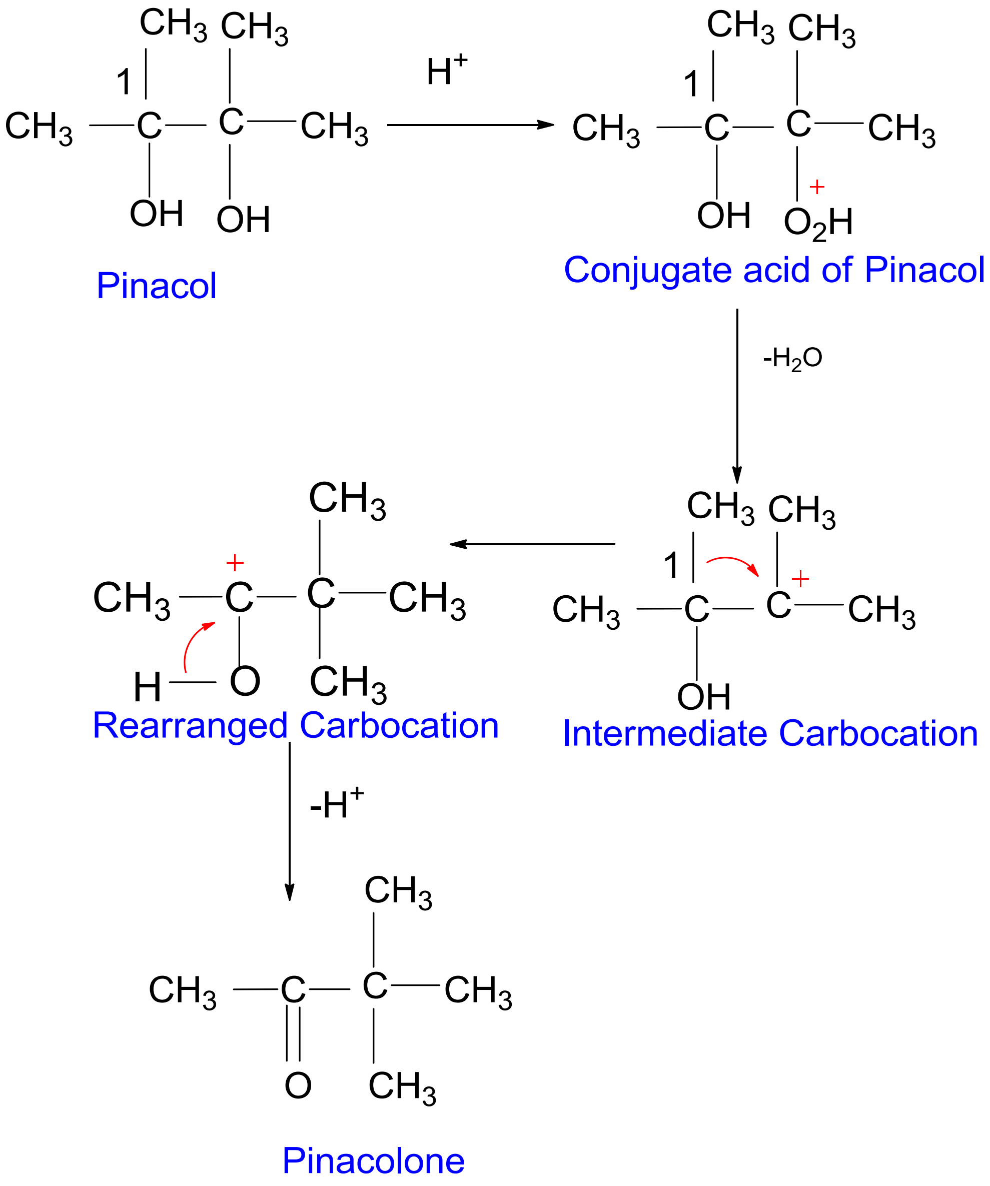
4.1 C-C Migration-

4.1.1Pinacol-Pinacolone Rearrangement

The acid-catalyzed elimination of water from pinacol gives *t*-butyl methyl ketone.

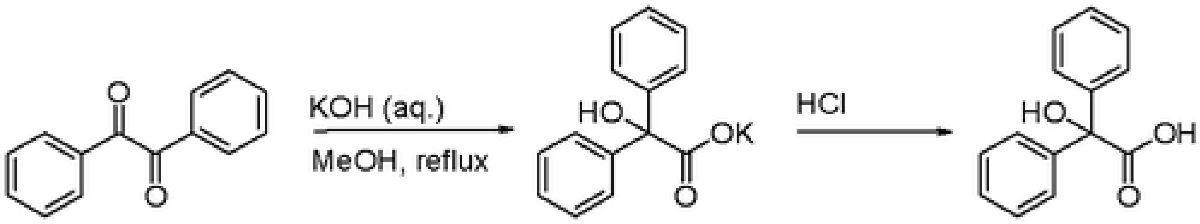


Mechanism: This reaction occurs with a variety of fully substituted 1,2-diols, and can be understood to involve the formation of a carbenium ion intermediate that subsequently undergoes a rearrangement. The first generated intermediate, an α-hydroxycarbenium ion, rearranges through a 1,2-alkyl shift to produce the carbonyl compound. If two of the substituents form a ring, the Pinacol Rearrangement can constitute a ring-expansion or ring-contraction reaction



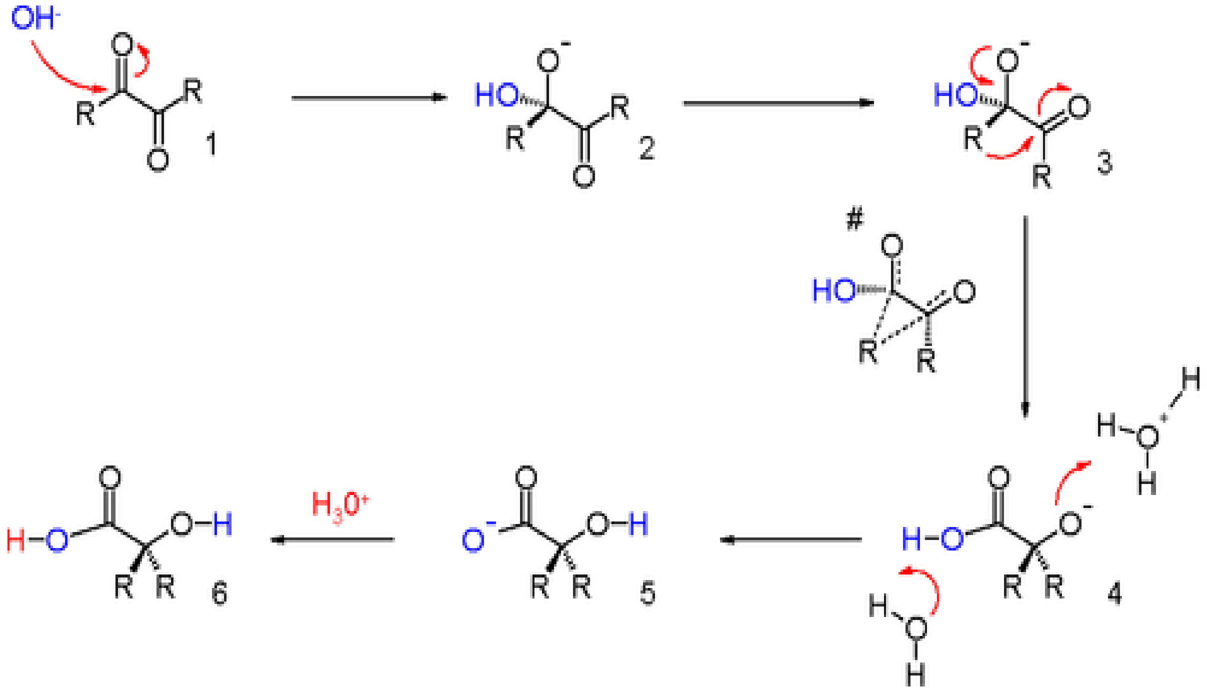
4.1.2 Benzil-Benzilic Rearrangement

The **benzilic acid rearrangement** is the rearrangement reacion of benzil with potassium hydroxide to benzilic acid.



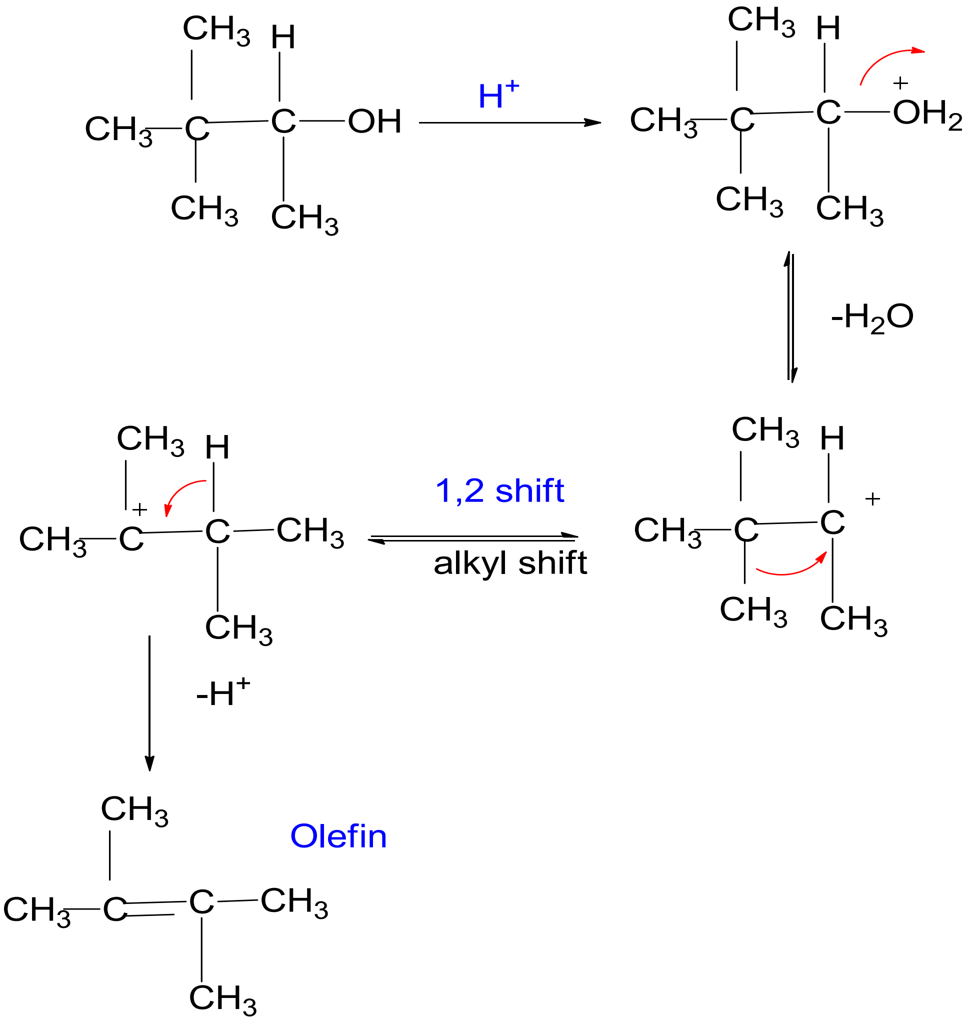
Mechanism:

A hydroxide anion attacks one of the ketone groups in **1** in a nucleophilic addition to the hydroxyl anion **2**. The next step requires a bond rotation to conformer **3** which places the migrating group R in position for attack on the second carbonyl group in a concerted step with reversion of the hydroxyl group back to the carbonyl group. This sequence resembles a nucleophilic acyl substitution.



4.1.3 Wagner-Meerwein rearrangement

The Wagner-Meerwein rearrangement is an organic reaction used to convert an alcohol to an olefin using an acid catalyst. The mechanism begins with protonation of the alcohol by the acid which is then released as water to forms a carbocation. A 1,2-shift then occurs to form a more substituted and stabilized carbo-cation. A final deprotonation with water produces the final olefin product and regenerates the acid catalyst



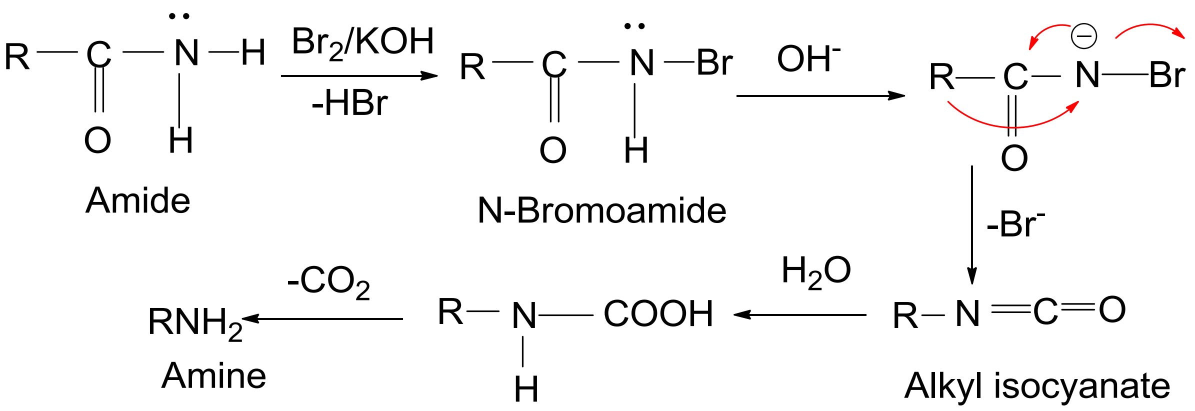
4.2 C-N Migration

4.2.1 Hoffmann Reaction:

The **Hofmann rearrangement** (**Hofmann degradation**) is the organic reaction of a primary amide to a primary amine with one fewer carbon atom. The reaction involves oxidation of the nitrogen followed by rearrangement of the carbonyl and nitrogen to give an isocyanate intermediate.

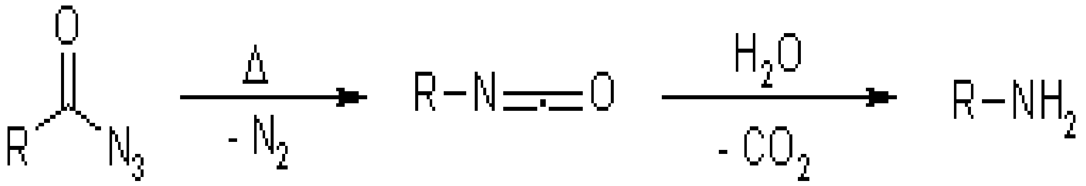
$$CH_3CH_2CONH_2 + Br_2 + 4KOH \longrightarrow CH_3CH_2NH_2 + 2KBr + K_2CO_3 + 2H_2O$$

Mechanism: The reaction involves the migration of aryl or aryl group from adjacent carbon atom to electron deficient nitrogen atom forming isocyanates.

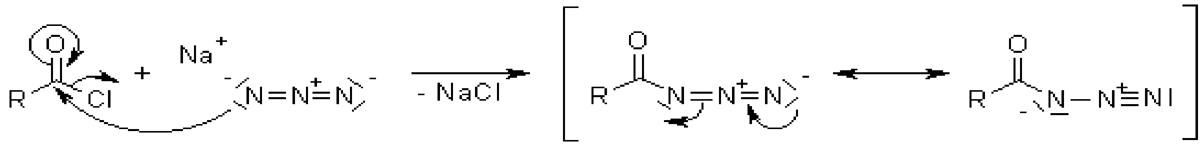


4.2.2 Curtius Rearrangement

The Curtius Rearrangement is the thermal decomposition of carboxylic azides to produce an isocyanate. These intermediates may be isolated, or their corresponding reaction or hydrolysis products may be obtained.

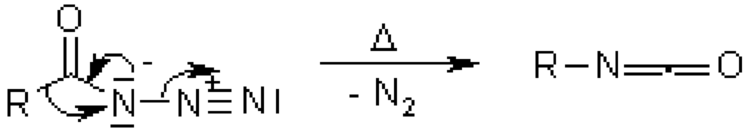


Preparation of azides:

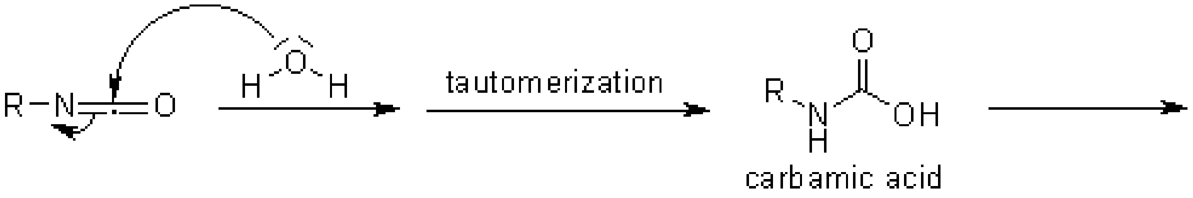


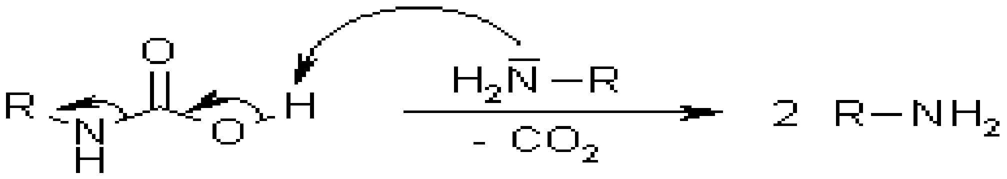
Mechanism-Curtius Rearrangement

Decomposition:



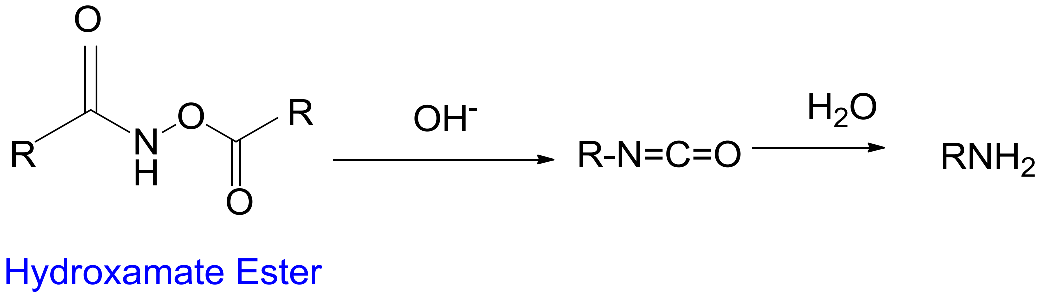
Reaction with water to the unstable carbamic acid derivative which will undergo spontaneous decarboxylation:



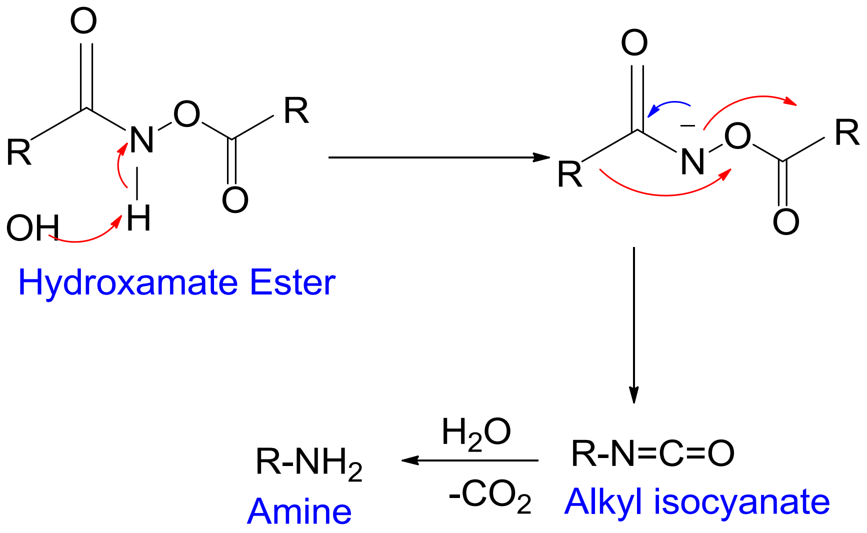


4.2.3 Lossen rearrangement

The **Lossen rearrangement** is the conversion of a hydroxamate ester to an isocyanate. Typically O-acyl, sulfonyl, or phosphoryl O-derivative are employed. The isocyanate can be used further to generate ureas in the presence of amines or generate amines in the presence of H_2O.

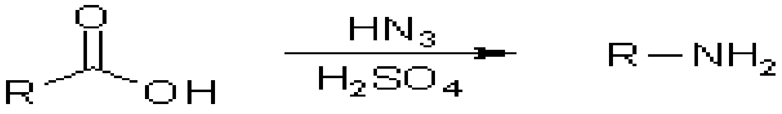


Mechanism:



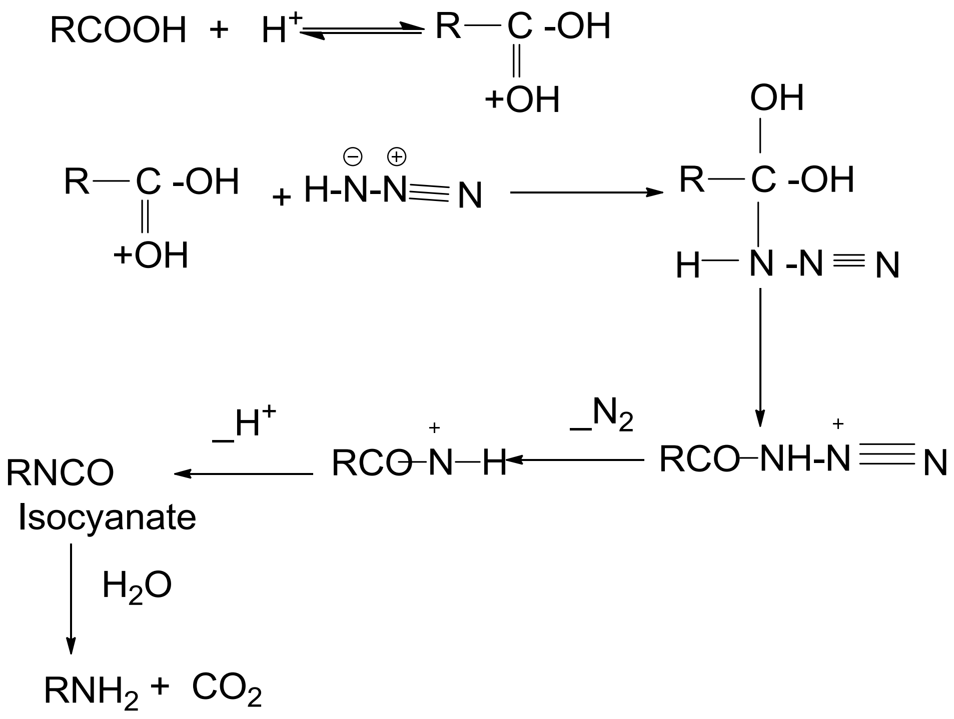
4.2.4 Schmidt Reaction

The acid-catalysed reaction of hydrogen azide with electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes. After a rearrangement and extrusion of N_2, amines, nitriles, amides or imines are produced.



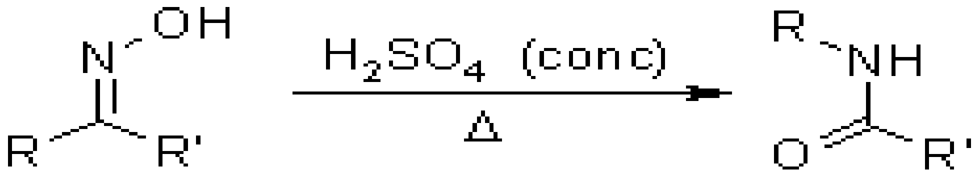
Mechanism Reaction of carboxylic acids gives acyl azides, which rearrange to isocyanates, and these may be hydrolyzed to carbamic acid or solvolysed to carbamates. Decarboxylation leads to amines.

$$\mathrm{RCOOH} + \mathrm{N_3H} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{RNH_2} + \mathrm{CO_2} + \mathrm{N_2}$$



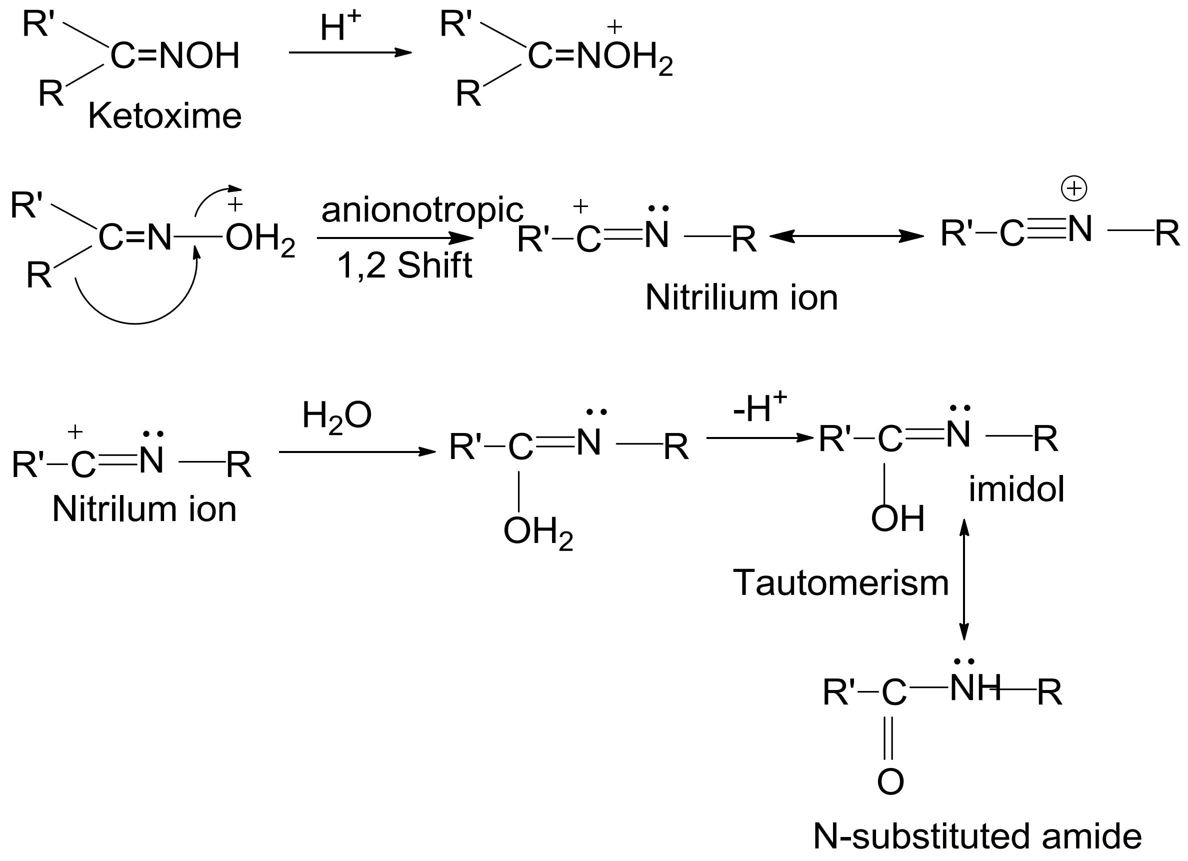
4.2. 5 Beckmann Rearrangement

An acid-induced rearrangement of oximes to give amides.

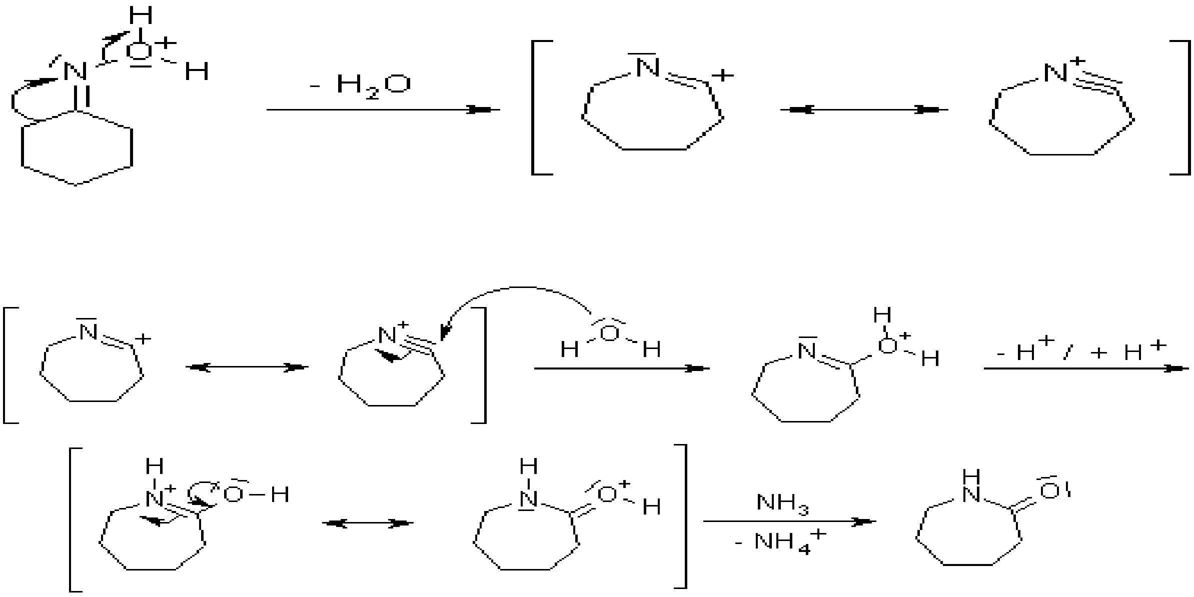


Mechanism:

Conversion of ketoxime to better leaving group in the presence of H^{+}.


R'
R
C=NOH
Ketoxime
H+
R'
R
C=NOH2
R'
R
C=N—OH2
anionotropic
1,2 Shift
R'–C=N—R
R'–C≡N—R
Nitrilium ion
R'–C=N—R
Nitrilum ion
H2O
R'–C=N—R
OH2
-H+
R'–C=N—R
OH
imidol
Tautomerism
R'–C—NH—R
O
N-substituted amide

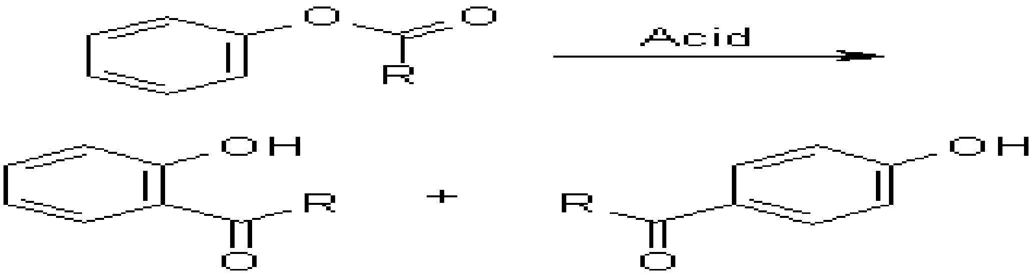
Mechanism:


H
O
H
N
- H2O
N
N
H O H
H
O
H
- H+ / + H+
H
N
O–H
H
N
O
H
NH3
- NH4+
H
N
O

4.3 Miscellaneous Rearrangements:

4.3.1 Fries Rearrangement

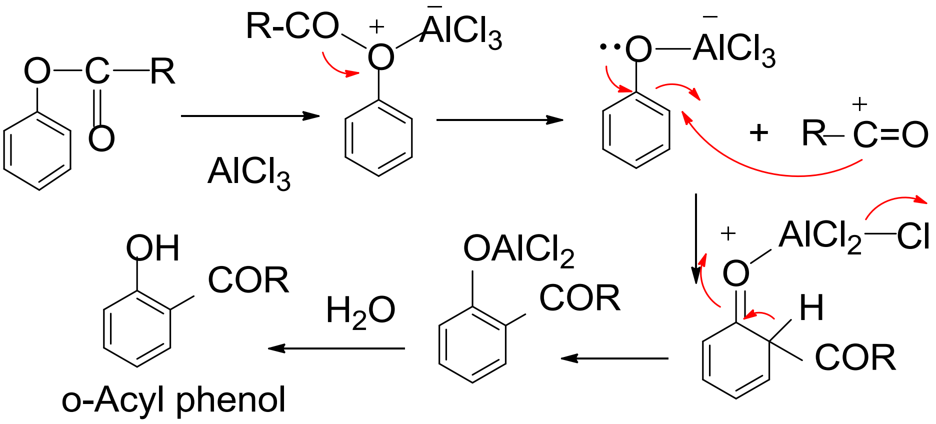
The Fries Rearrangement enables the preparation of acyl phenols

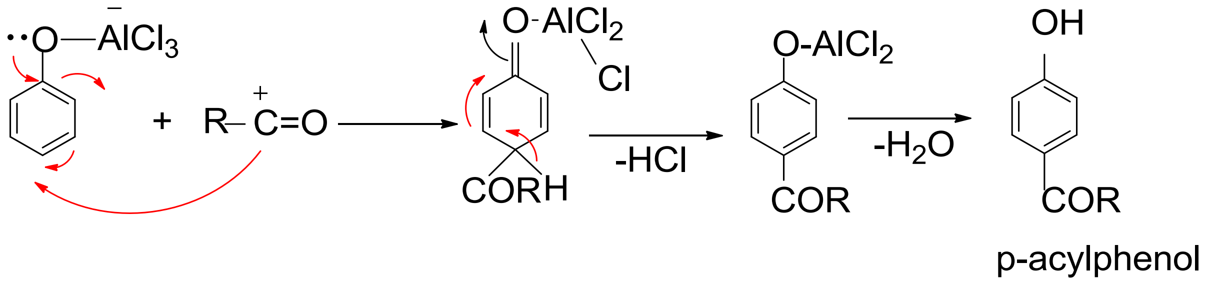


Mechanism of the Fries Rearrangement

The reaction is catalyzed by Brønsted or Lewis acids such as HF, $AlCl_3$, BF_3, $TiCl_4$ or $SnCl_4$. The acids are used in excess of the stoichiometric amount, especially the Lewis acids, since they form complexes with both the starting materials and products. The complex can dissociate to form an acylium ion. Depending on the solvent, an ion pair can form, and the ionic species can react with each other within the solvent cage

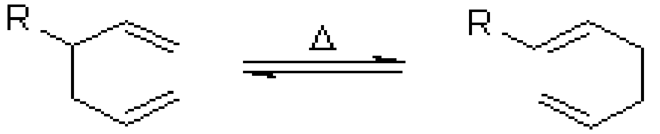
After hydrolysis, the product o and p acyl phenol is liberated



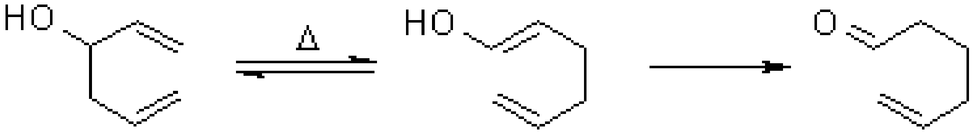


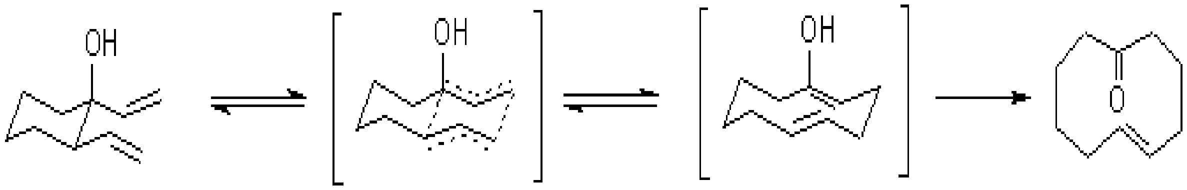
4.3.2 Cope Rearrangement (Anionic) Oxy-Cope Rearrangement

The Cope Rearrangement is the thermal isomerization of a 1,5-diene leading to a regioisomeric 1,5-diene. The main product is the thermodynamically more stable regioisomer. The Oxy-Cope has a hydroxyl substituent on an sp^3-hybridized carbon of the starting isomer.



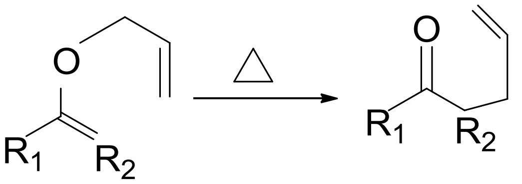
The driving force for the neutral or anionic Oxy-Cope Rearrangement is that the product is an enol or enolate (resp.), which can tautomerize to the corresponding carbonyl compound. This product will not equilibrate back to the other regioisomer.





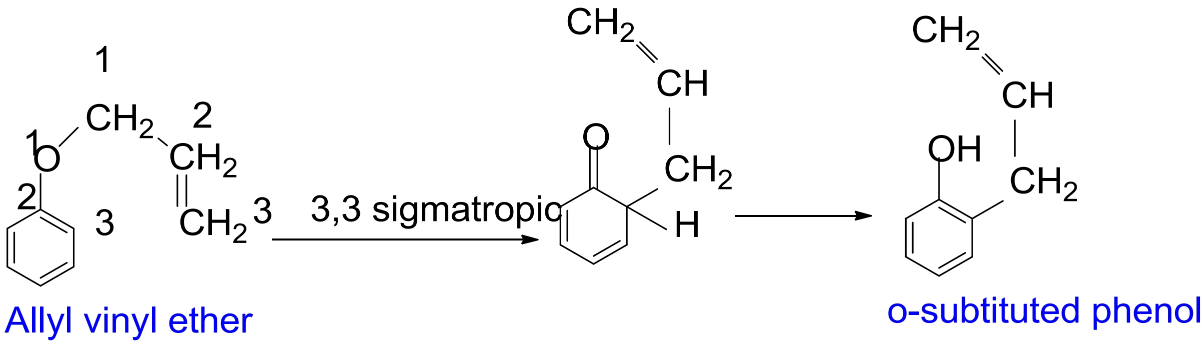
4.3.3 Claisen Rearrangement:

The **Claisen rearrangement** is a powerful carbon–carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen. The heating of an allyl vinyl ether will initiate a [3,3]-sigmatropic rearrangement to give a γ,δ-unsaturated carbonyl.



Reaction:

The [3,3]-sigmatropic rearrangement of an allyl phenyl ether to intermediate 1, which quickly tautomerizes to an ortho-substituted phenol.



TEXT / REFERENCE BOOKS

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SCHOOL OF SCIENCE AND HUMANITIES

DEPARTMENT OF CHEMISTRY

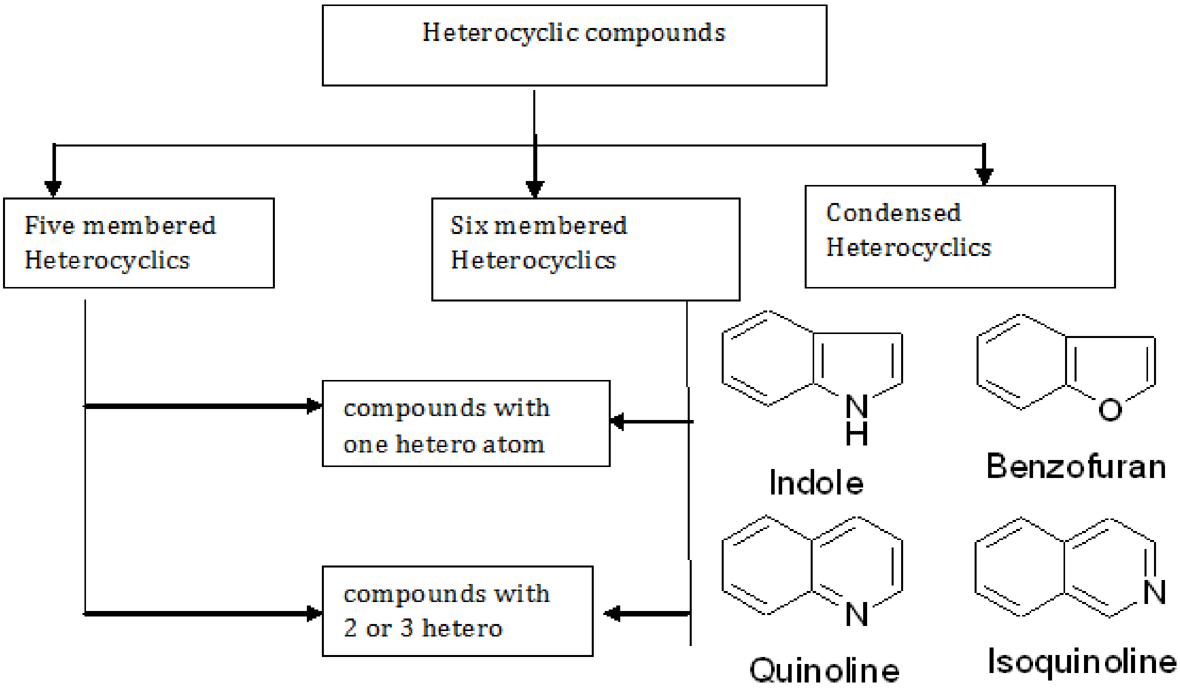
UNIT – V - Heterocycl;ic compounds – SCY1315

UNIT-5

HETEROCYCLIC COMPOUNDS

2.0 INTRODUCTION

Heterocyclic compounds are compounds with atleast one heteroatom as the ring member which are relatively stable and exhibits aromatic character.

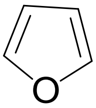


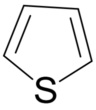
2.1 NOMENCLATURE

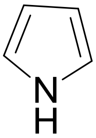
Rings with one hetero atom follows the following rule:

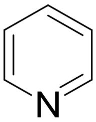
Hetero atom	Prefix	No.of atoms	Suffix	UnSaturated Other Atoms N	UnSaturated N	Saturated Other Atoms	N
N	Aza	3	Ir	ene	ine	Ane	dine
O	Oxa	4	Et	e	e	Ane	dine
S	Thia	5	Ol	e	e	ane	dine

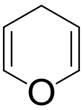
P	Phospha	6	In	e	e		
As	arsa	7	epin	e	e		


Furan /Oxole

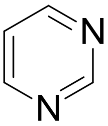

Thiophene /Thiole

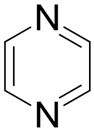

Pyrrole /azole

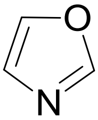

Pyridine /Azine

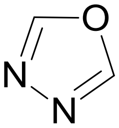

Pyran /Oxine

Rings with more than one heteroatom, the order of priority is O>S>N.

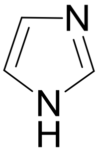

1,3 diazine pyrazine

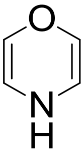

1,4 diazine pyrimidine

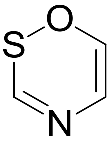

1,3 oxazole

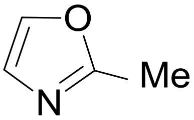

1,3,4oxadiazole

A saturated heteroatom with an extra-hydrogen attached is given priority over an unsaturated form of the same atom.

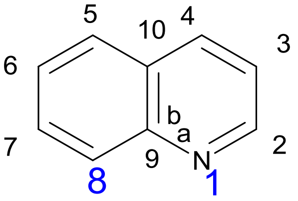

1-H 1,3-diazole Imidiazole


1-H 1,4 Oxazine

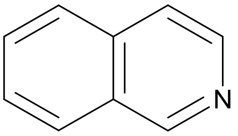

1,2,4-oxathiazine

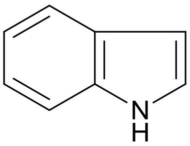

2-methyl 1,3 oxazole

Systems where two rings share a common single or double bond, which are said to be fused rings.A common case is where a benzene ring is fused to a heterocyclic ring. The name begins with the prefix “benzo.” The point of attachment is indicated by a letter that defines the “face” of the heterocycle involved Thus, the1,2- position on the heterocyclic ring is always the “a- face,” 2,3- is the “b-face,” 3,4- is the “c-face,” and so on.



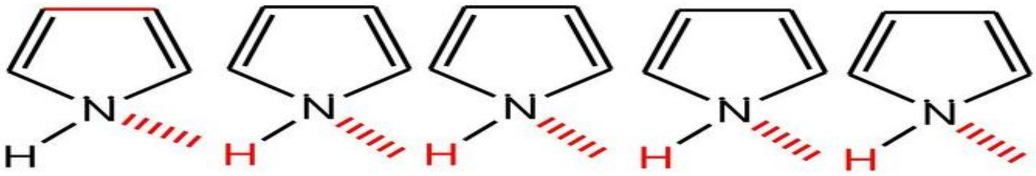
Benzo[b]pyridine Quinoline


Benzo[c]pyridine isoquinoline

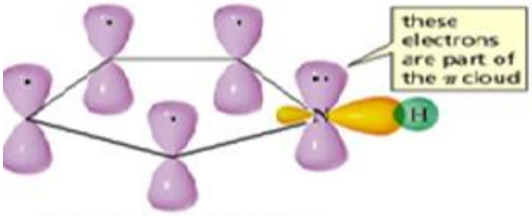

1H-benzo[b]pyrrole Indole

2.2 GENERAL CHARACTERISTICS

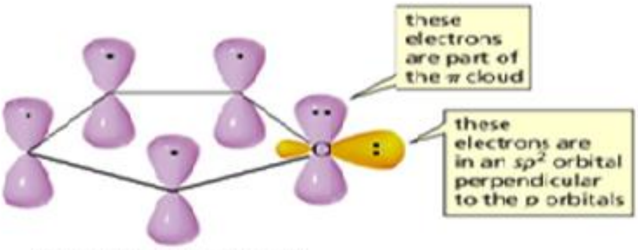
Pyrrole, furan and thiophene are colorless liquids of boiling points 126°, 32°, and 84° respectively. Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



Pyrrole furan and thiophene are aromatic because:1) they fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, thus the grading of aromaticity is in the order of: furan< pyrrole < thiophene< benzene .oxygen (3.44), nitrogen (3.04) and thiophene (2.56).

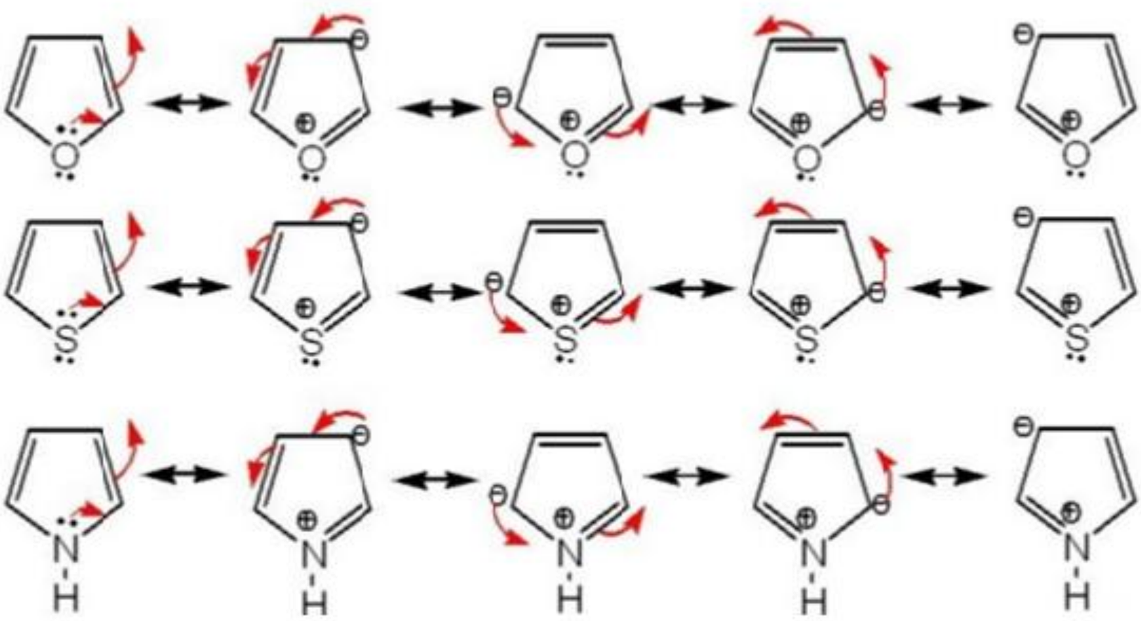


orbital structure of pyrrole



orbital structure of furan

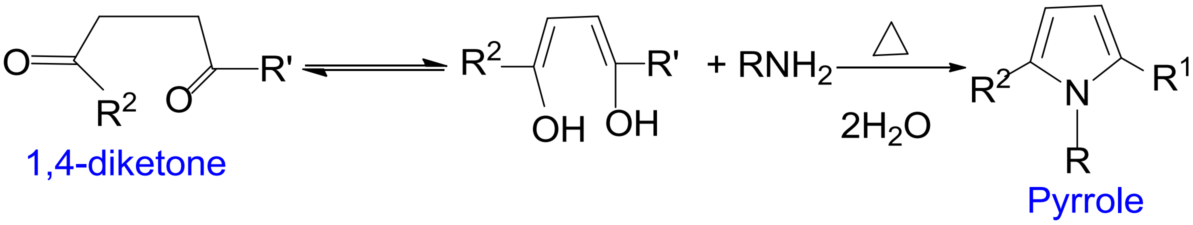
They tend to react by electrophilic substitution due appearance of –ve charge on carbon atoms due to delocalization as shown in the following resonance structures.



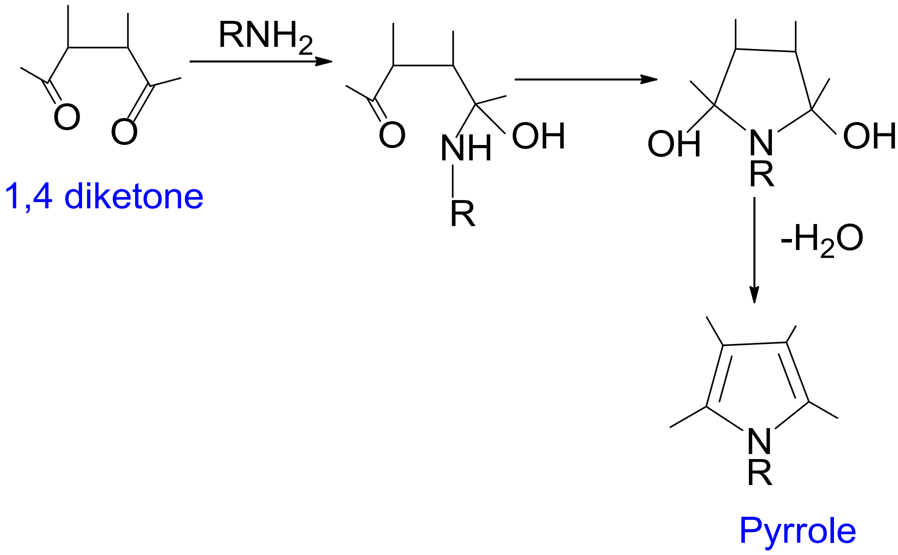
2.3 PYRROLE

2.3.1 Synthesis:

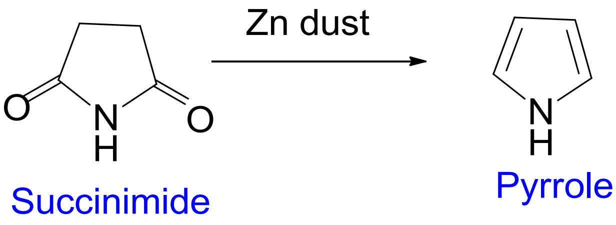
1) Pall-Knorr synthesis: Heating diketone with ammonia or aliphatic amine.



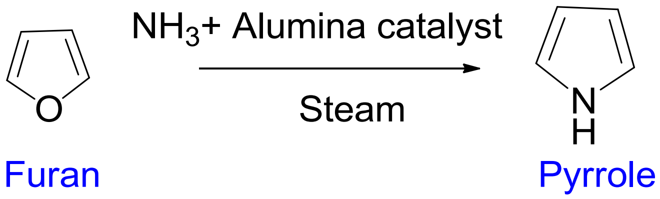
Mechanism:



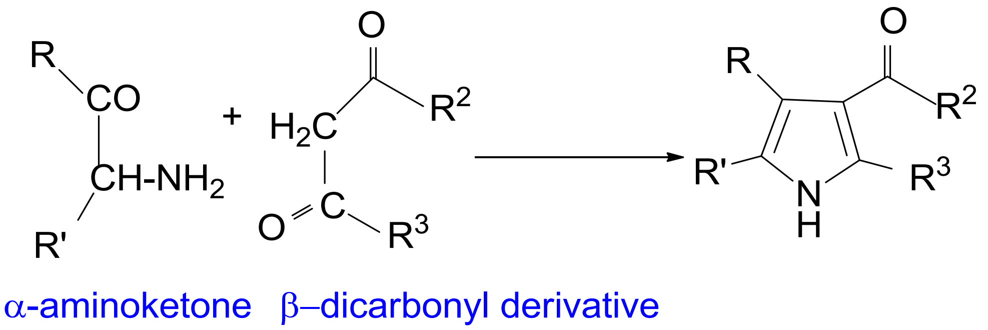
2) Pyrrole is obtained by distillation of succinimide over zinc dust



3) By heating a mixture of furan, ammonia, steam over the presence of alumina catalyst

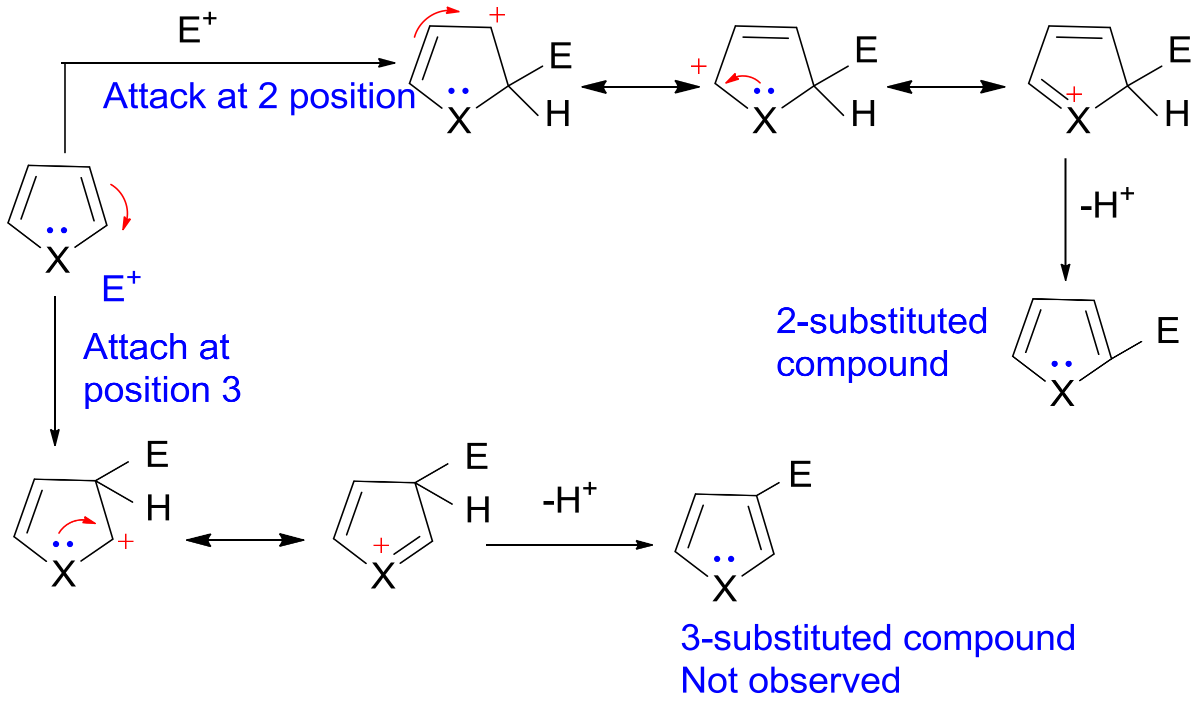


4) Knorr-Pyrrole synthesis: Reaction between α- amino ketone and β-keto ester.

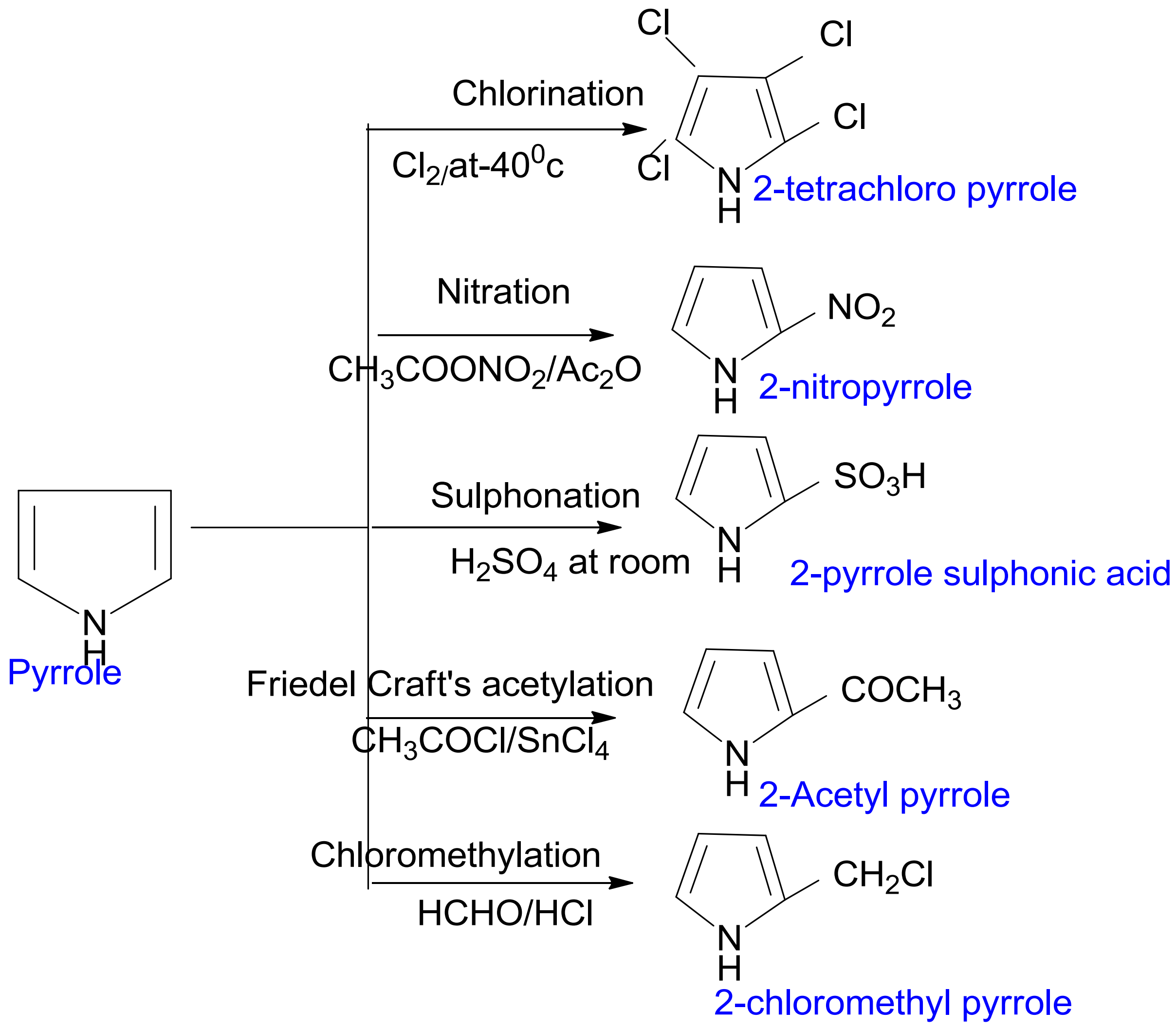


2.3.2 Electrophilic Substitution:

Electrophilic substitution in 5 membered ring occurs at C2 and not at C3. The resonance structures are more at C2 than at C3.



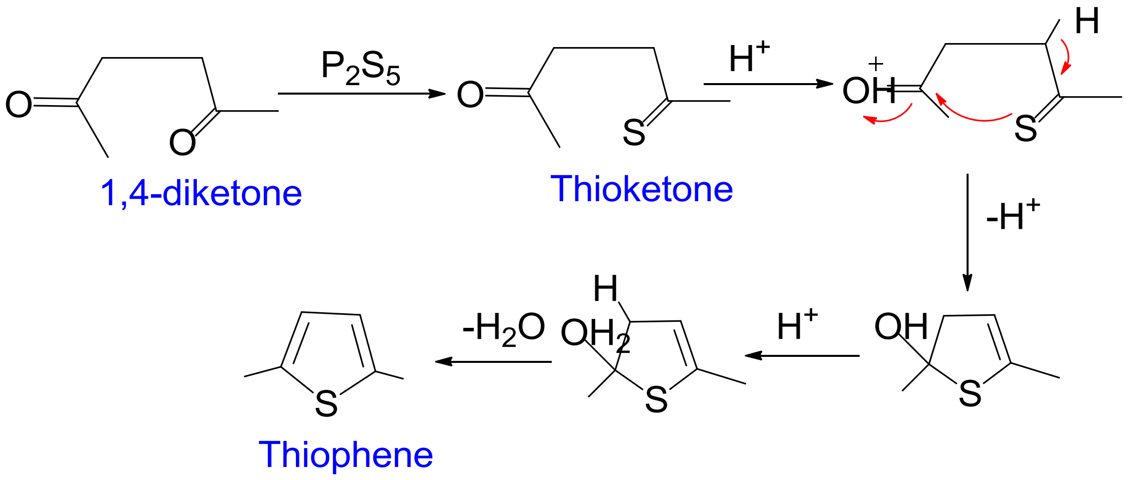
Electrophilic reactions in Pyrrole



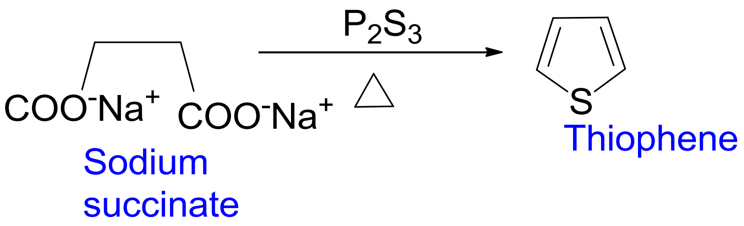
2.4 THIOPHENE

2.4.1 Synthesis:

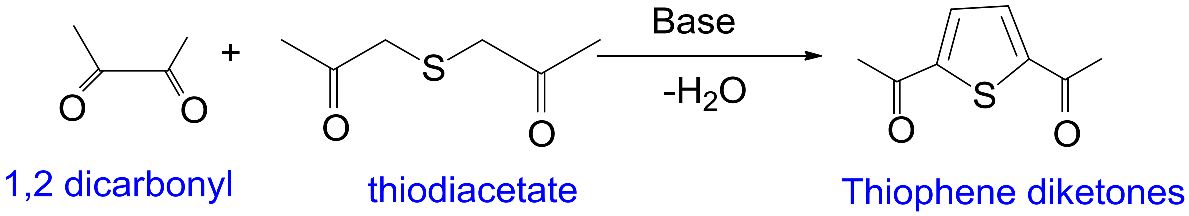
1) Pall-Knorr synthesis: Heating diketone with Phosphorus penta sulphide.



2. Laboratory Synthesis: Heating a mixture of sodium succinate with phosphorus tri sulphide

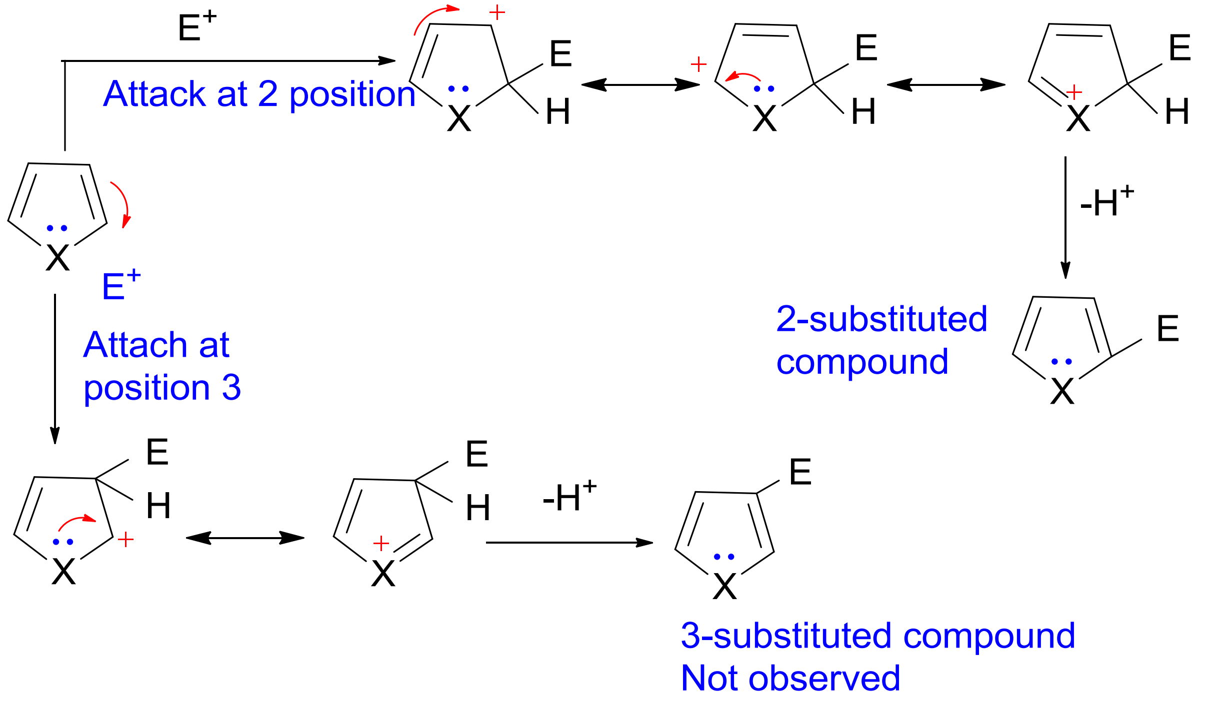


3. Hinsberg Synthesis: Condensation between 1,2 dicarbonyl and thiodiacetate in the presence of a base gives thiophene 2,5 diacids(-diketone)

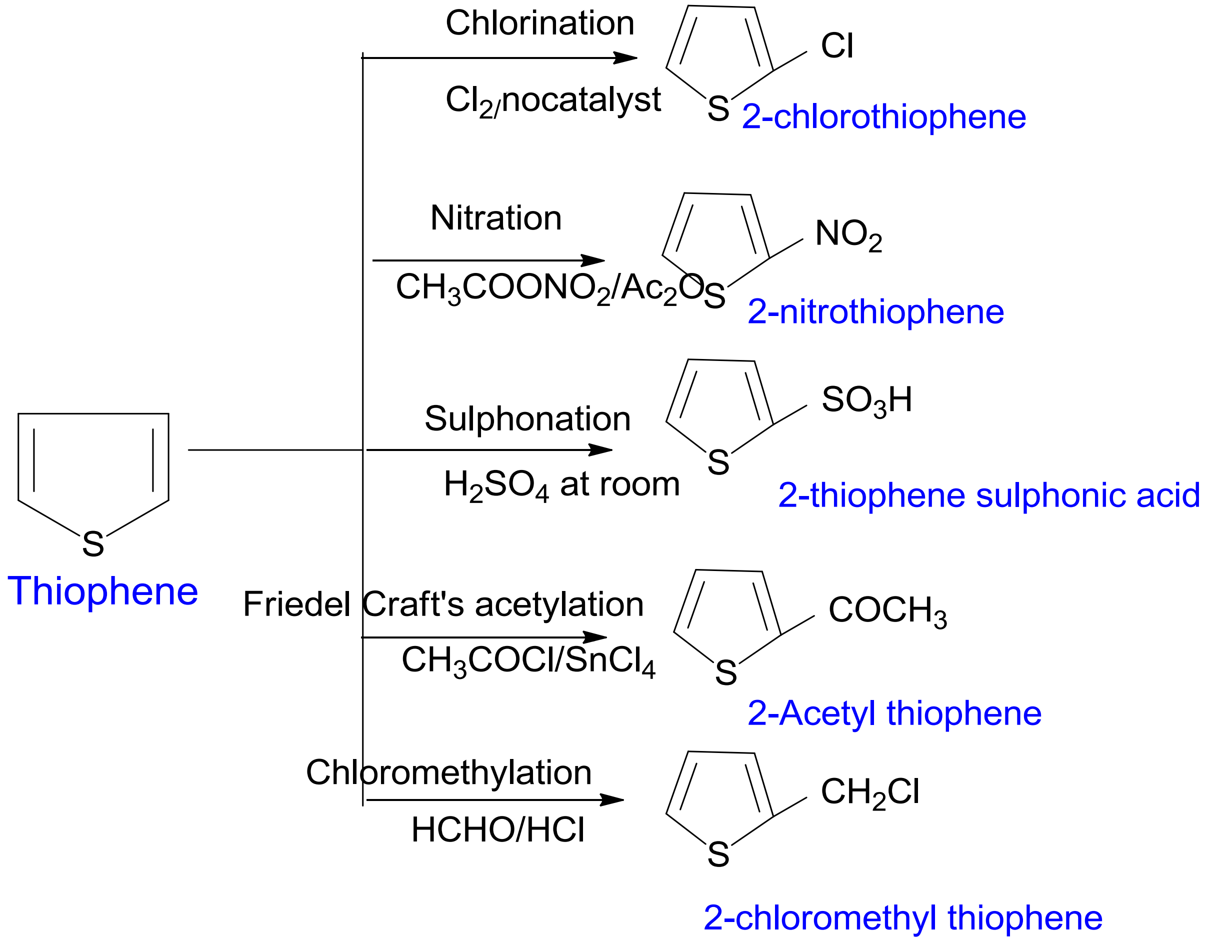


2.4.2 Electrophilic substitution:

Electrophilic substitution in 5 membered ring occurs at C2 and not at C3. The resonance structures are more at C2 than at C3.



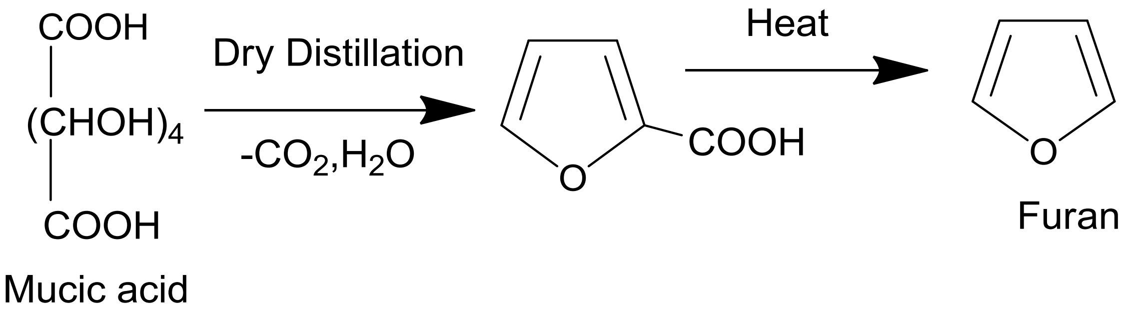
Electrophilic substitution reactions of thiophene:



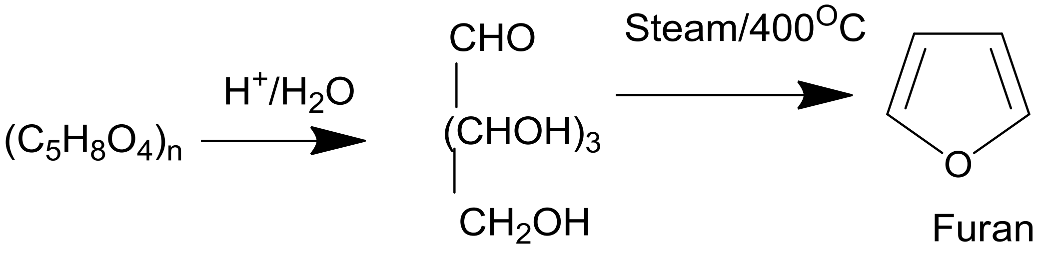
2.5 FURAN

2.5.1 Synthesis:

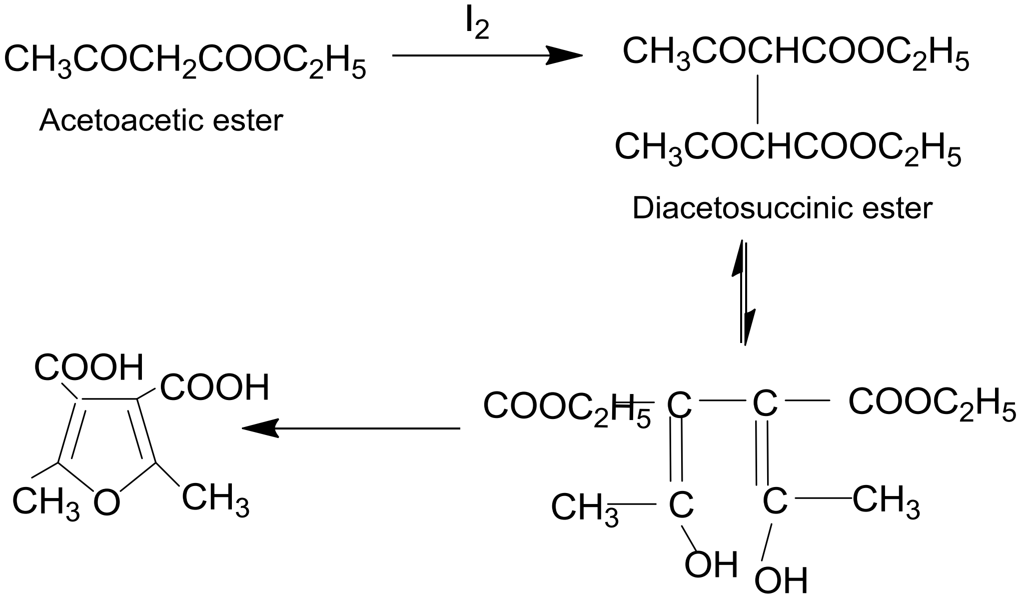
1)Dry distillation of mucic acid followed by decarboxylation



2) Pentosan are hydrolysed to xylose followed by dehydration and cyclization to furfural, steam distillation to furan.

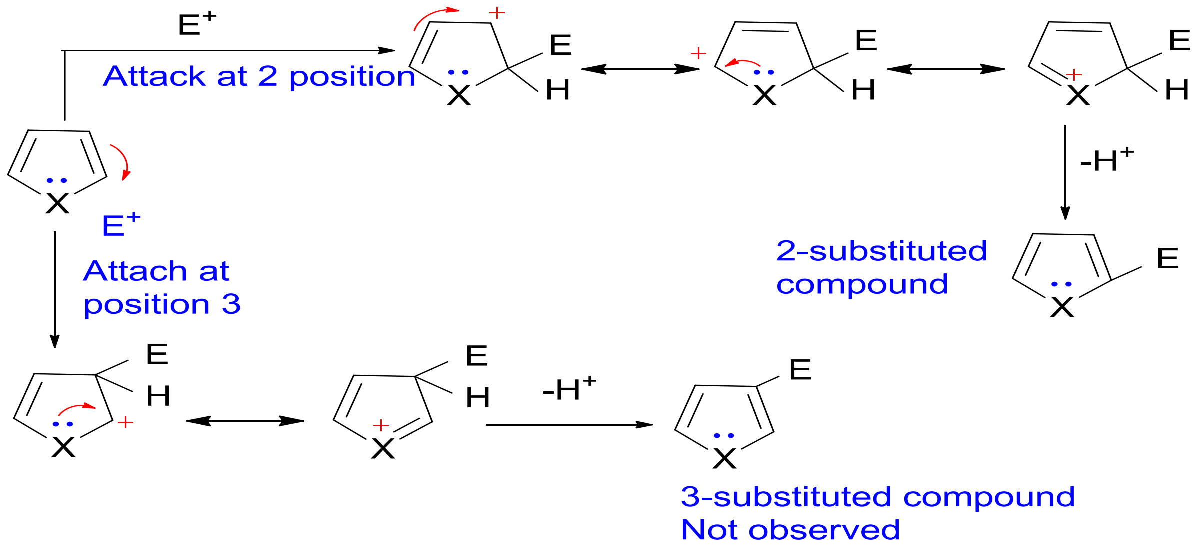


3) Furan derivatives is obtained from acetoacetic ester.

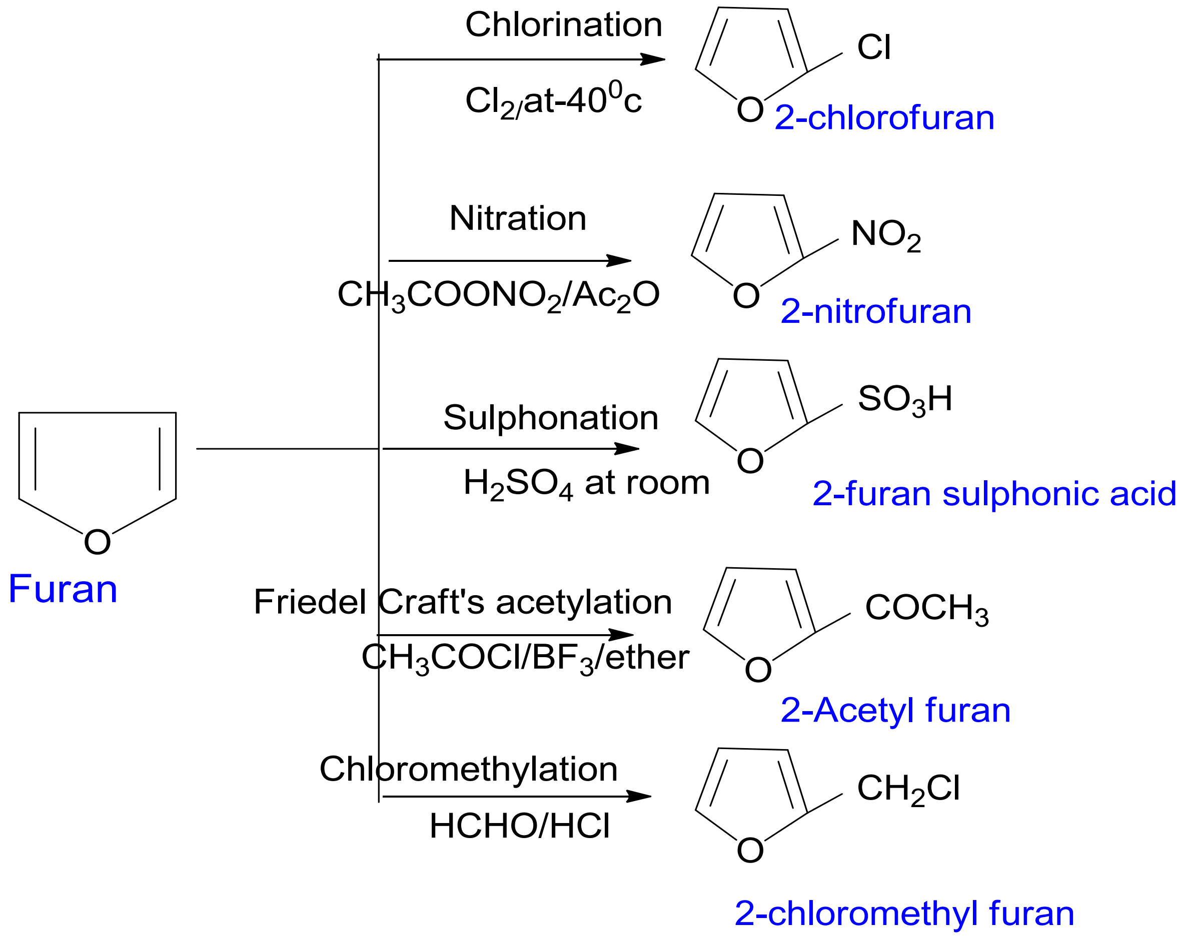


2.5.2 Electrophilic substitution

Electrophilic substitution in 5 membered ring occurs at C2 and not at C3. The resonance structures are more at C2 than at C3.



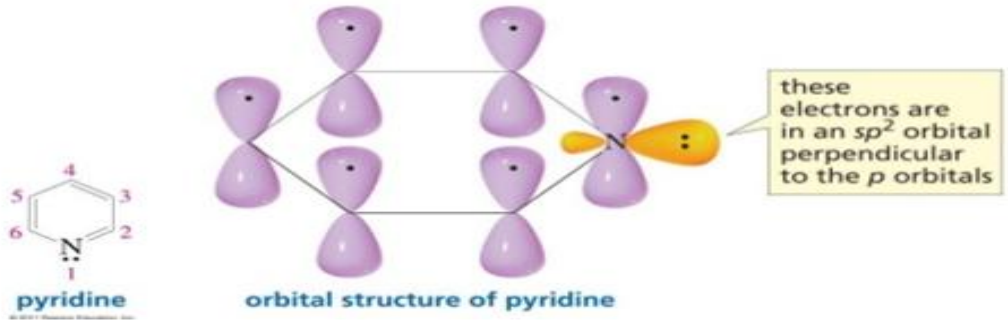
Electrophilic substitution at position 2.



2.6 SIX-MEMBERED RING (PYRIDINE)

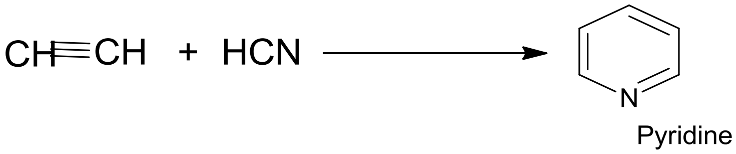
Pyridine is a 6 membered ring , with one heteroatom, Nitrogen.Aromatic in nature.

Carbon are in sp^2 hybridisation, planar in nature.

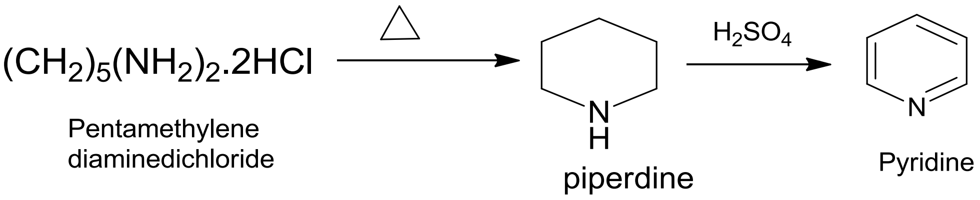


2.6.1 Synthesis:

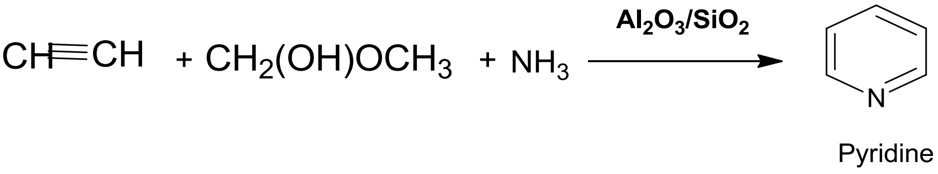
1) Passing acetylene and HCN through a red hot tube.



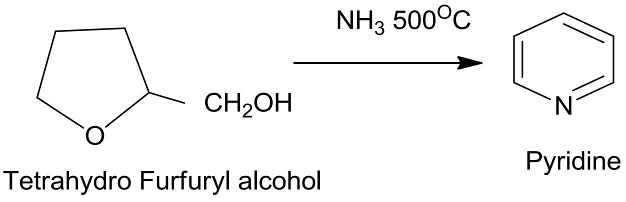
2) Heating pentamethylene diamine hydrochloride followed by heating with conc.H_2SO_4



3) Passing acetylene, HCHO and NH_3 over alumina catalyst.



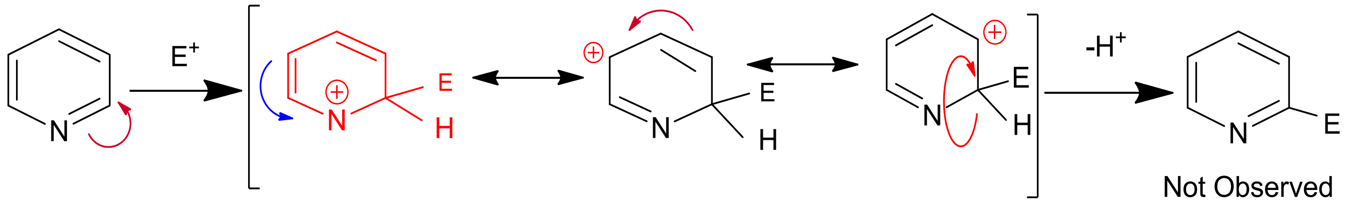
4) Heating tetrahydrofurfuryl alcohol with NH_3



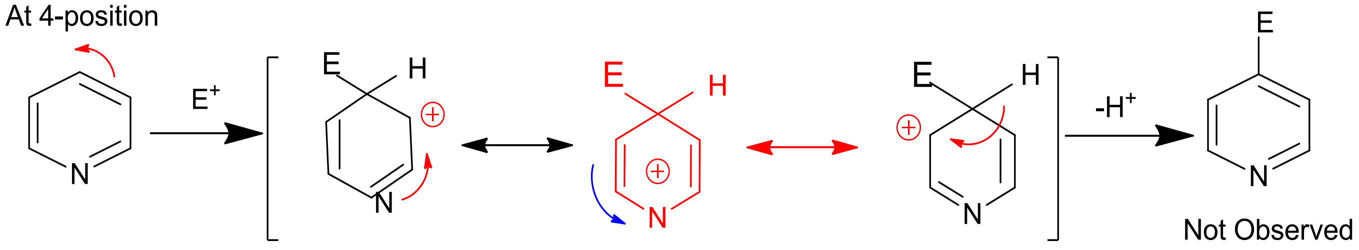
2.6.2 Electrophilic substitution-Π electron excess reaction

The attack of 2 and 4 position involves the formation of positive charge on the highly electronegative nitrogen atom. The cations from these structures are highly unstable. Hence, substitution occurs only at 3-position.

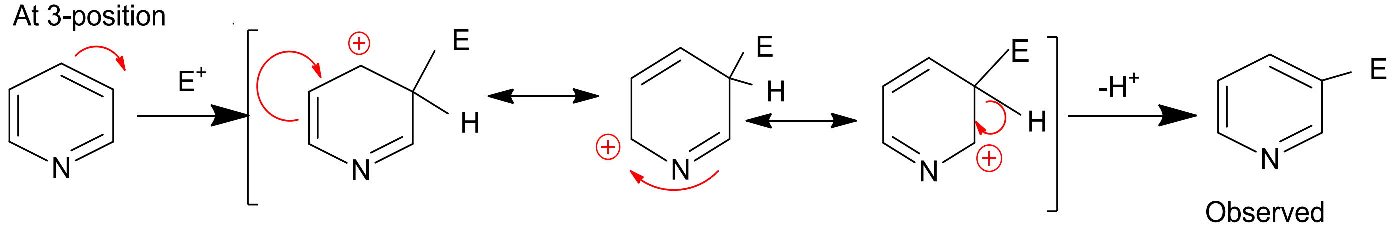
At 2-position



At 4-position



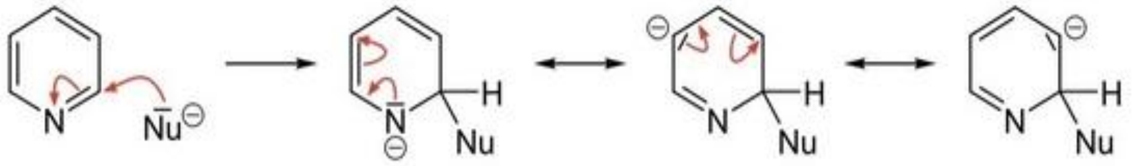
At 3-position



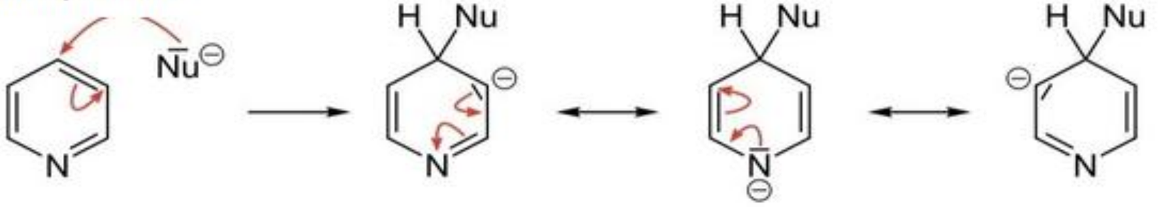
2.6.3 Nucleophilic substitution-Π electron deficient

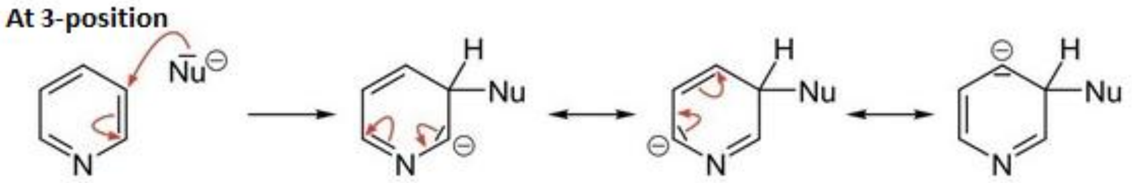
The electron density at position 2 and 4 is less.The negative charge on nitrogen is more resonance stabilized. Nucleophilic substitution occurs at 2 and 4 position.

At 2-position

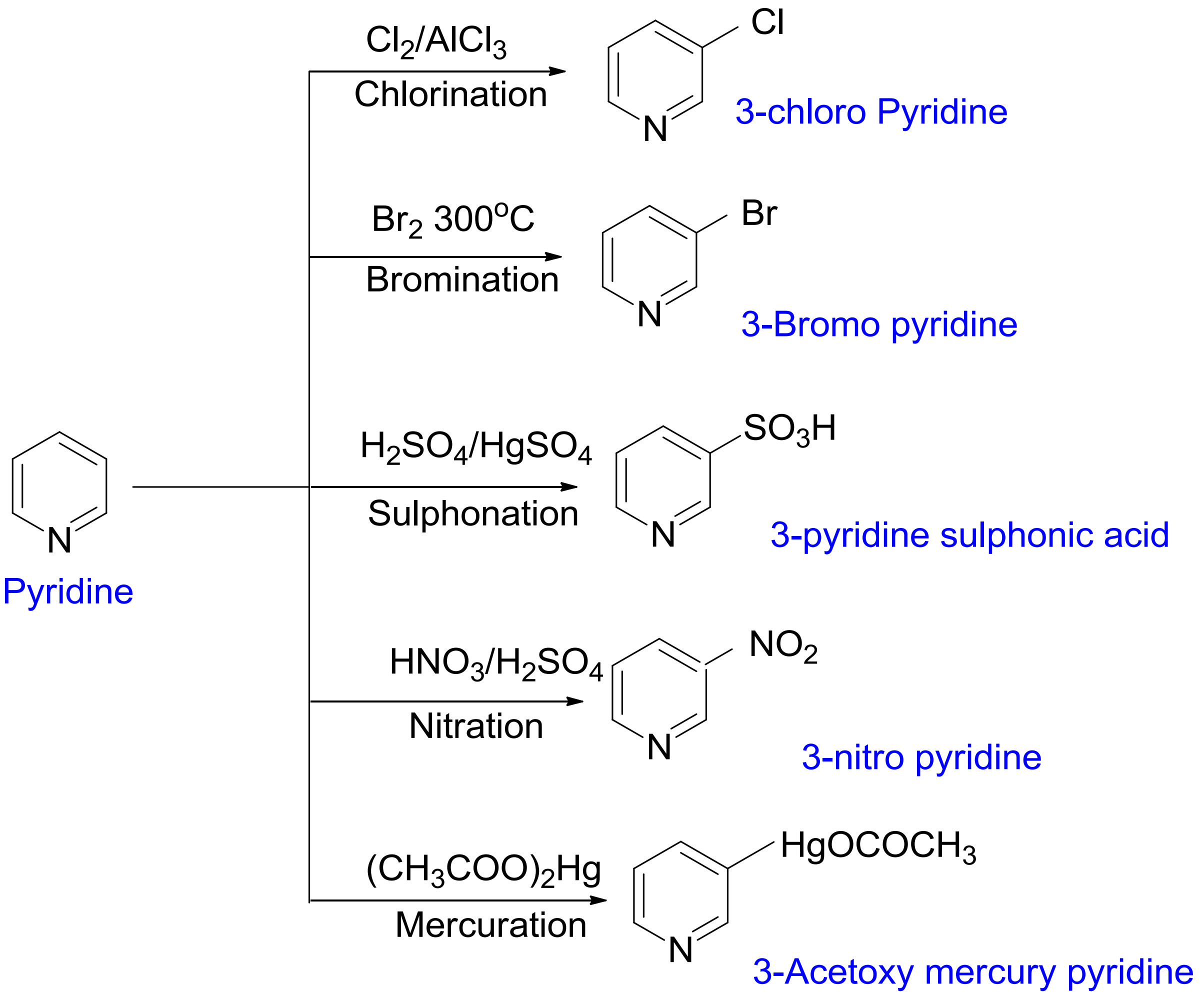


At 4-position

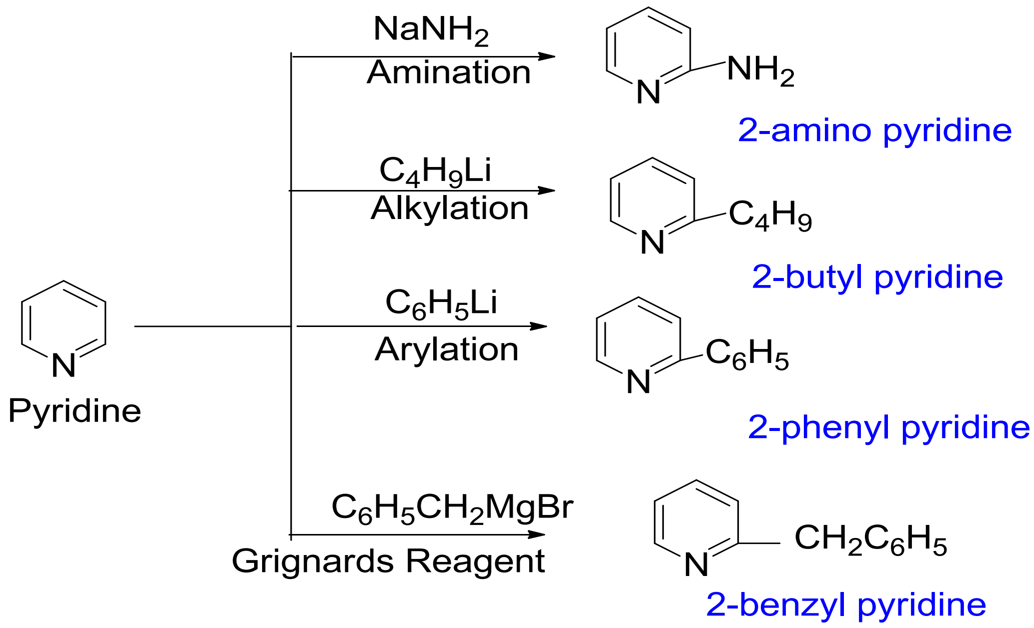




Electrophilic substitution-Π electron excess reaction

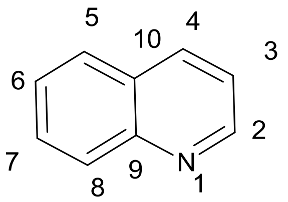


Nucleophilic substitution-Π electron deficient

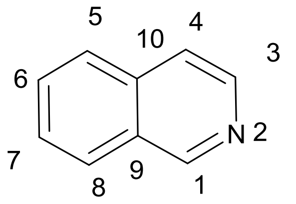


2.7 QUINOLINE AND ISOQUINOLINE

Quinoline: Isoquinoline:



Benzo[b]pyridine



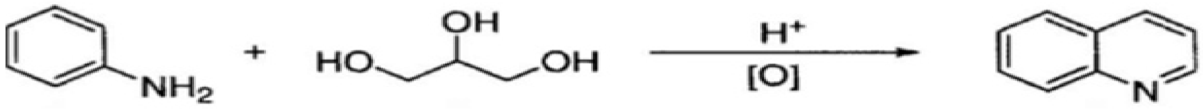
Benzo[c]pyridine

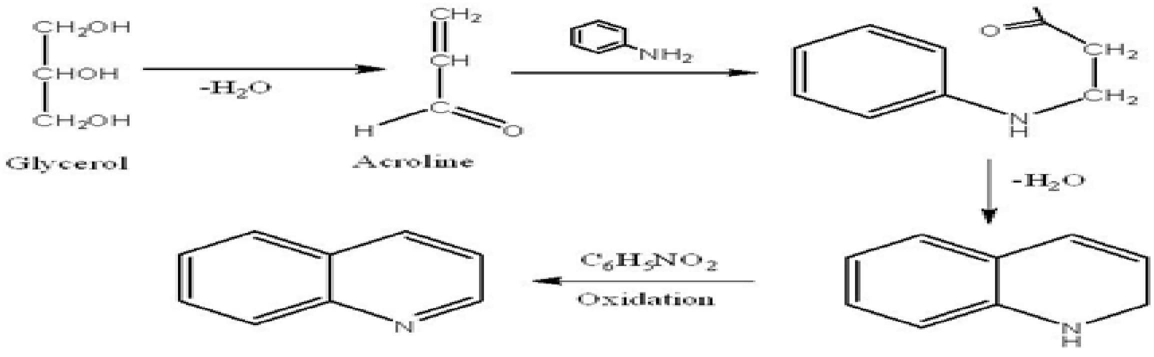
Aromatic; sp^2 hydridization; 10e-s; Planar Basic in nature.

2.7.1 Synthesis of quinoline

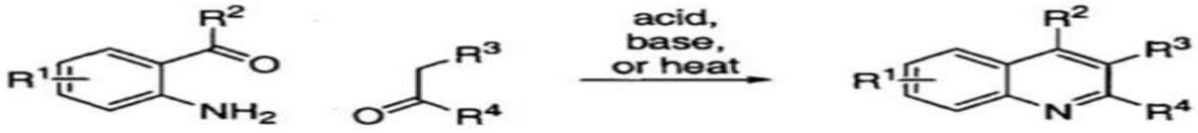
1) Skraup synthesis:

Reaction of aniline and glycerol in the presence of acid and oxidant.

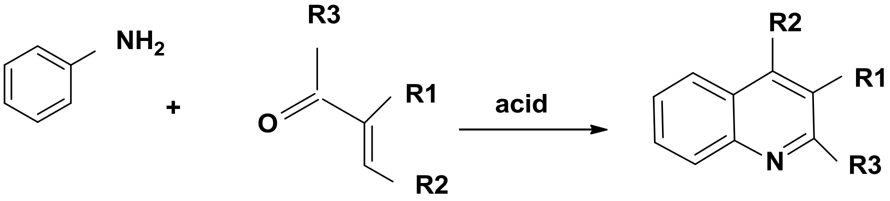




2) Friedlander's synthesis: Condensation of O-aminobenzaldehyde and aldehyde in the presence of alkali.

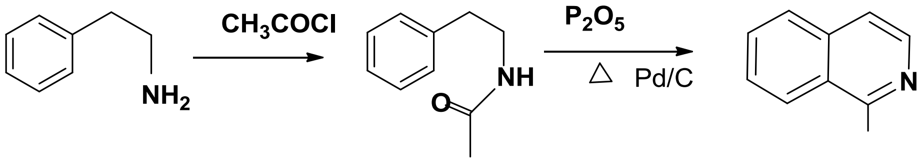


3) Doebner-Miller synthesis: Condensation of aniline with α,β- unsaturated carbonyl compound.

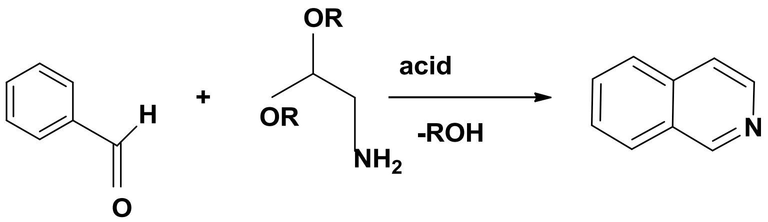


2.7.2 Synthesis of Isoquinoline

1) Bischler-Napieralski synthesis: Reaction of 2-aryl ethanamine with acylchloride followed by cyclization and reduction.

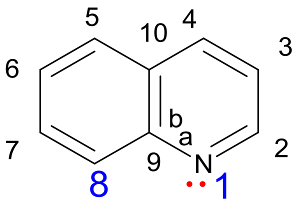


2) Pomeranz-Fritsch synthesis: Reaction of benzaldehyde with dialkoyethylamine.

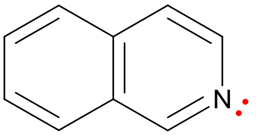


2.7.3 Resonance structures

Quinoline and Isoquinoline contains a pyridine ring fused to a benzene ring.



Benzo[b]pyridine
Quinoline

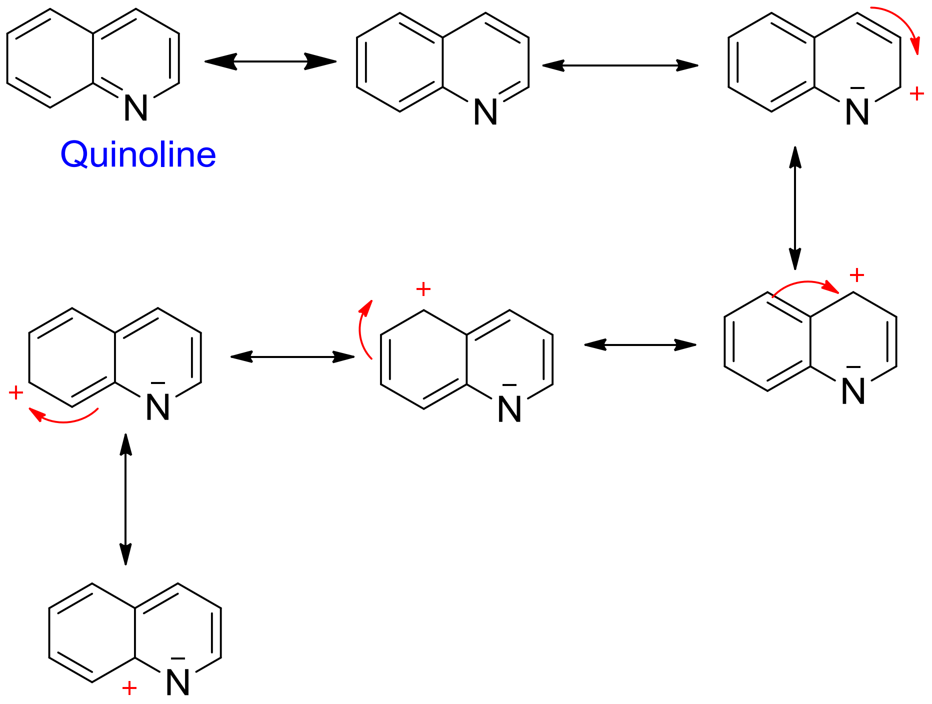


Benzo[c]pyridine
isoquinoline

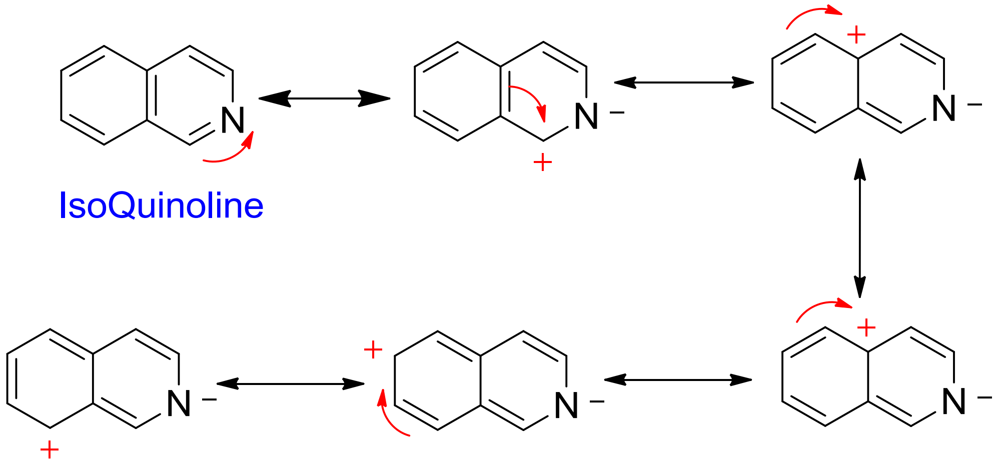
The Nitrogen has a deactivating effect on the ring towards electrophilic substitution.

Hence, it takes place less vigorously at position 5 and 8 in the benzene ring.Nitrogen lone pair is not released into the aromatic system. The nitrogen withdraws electrons makes it an Π electron deficient systems.

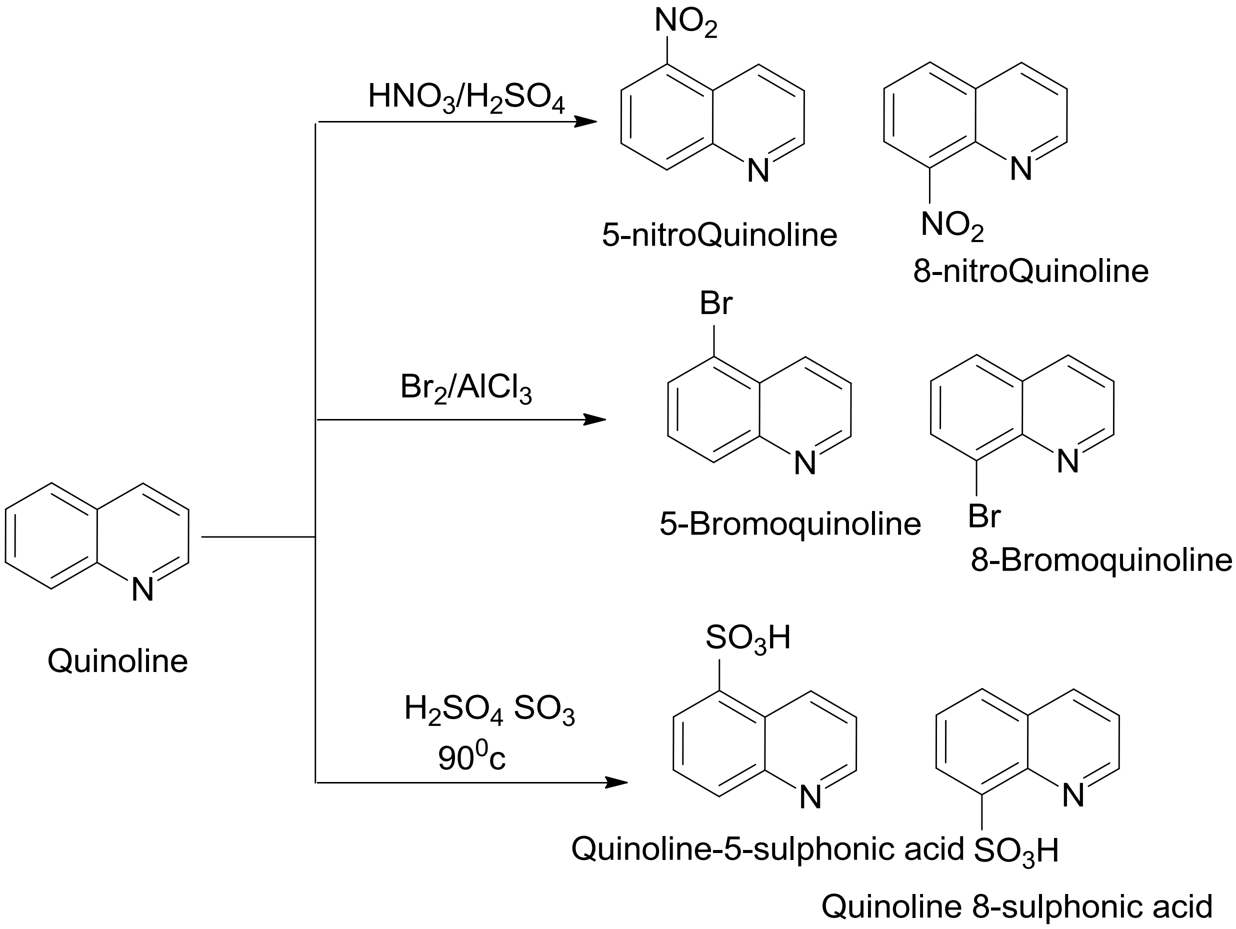
Quinoline:



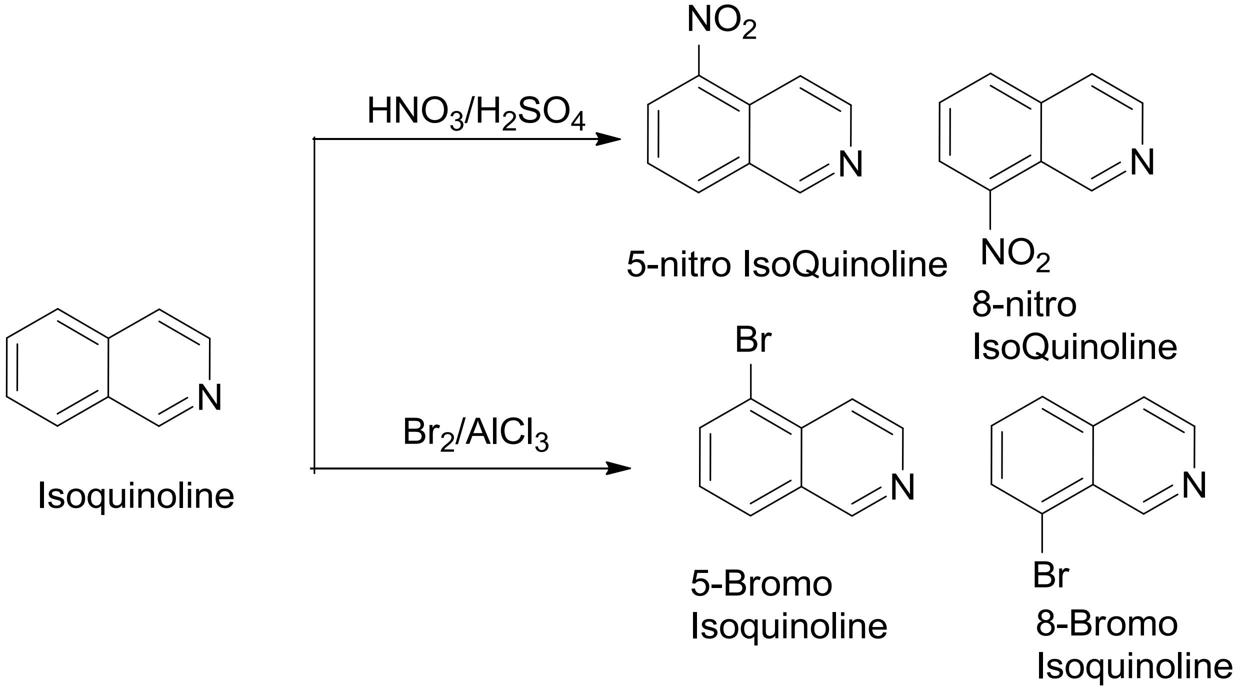
Isoquinoline



Electrophilic substitution at 5 and 8 position

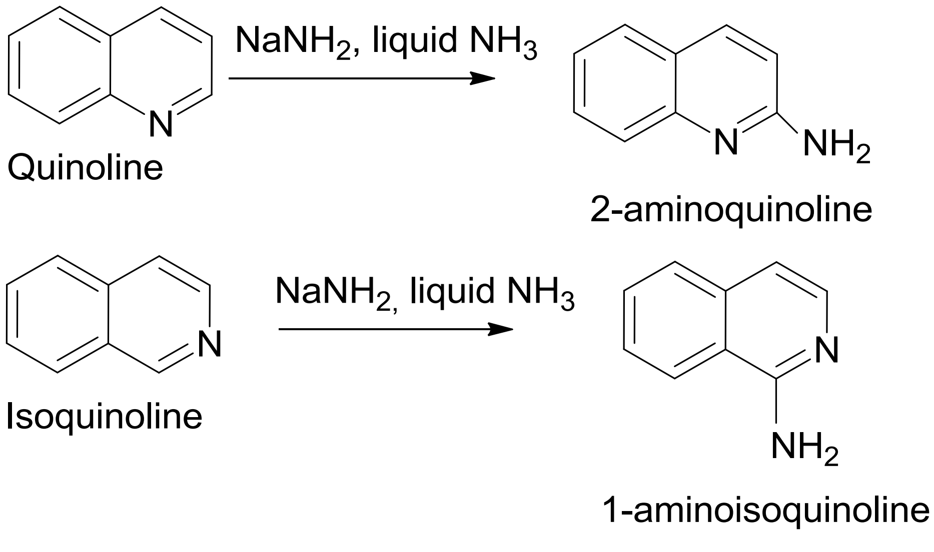


Isoquinoline



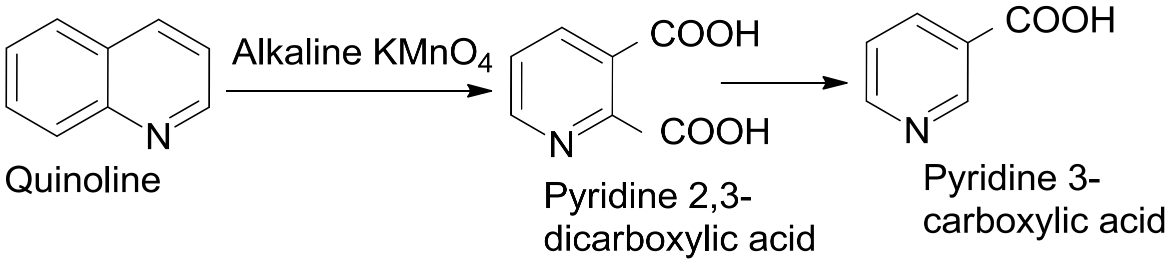
2.7.4 Nucleophilic Substitution

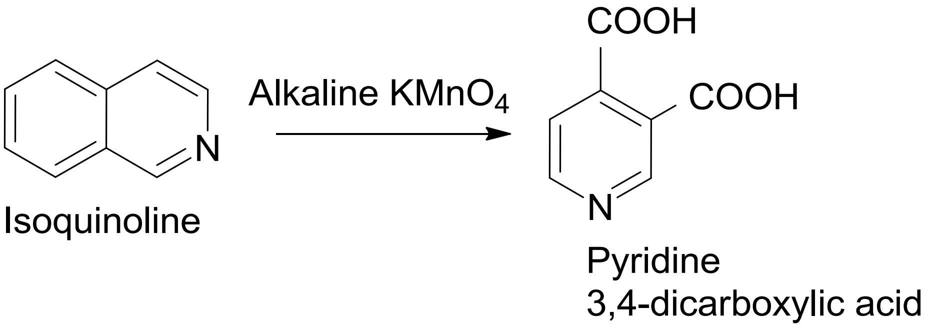
Quinoline and Isoquinoline undergoes facile nucleophilic substitution same as in pyridine. Quinoline gives 2-aminoquinoline while isoquinoline gives 1-aminoisoquinoline.



2.7.5 Oxidation

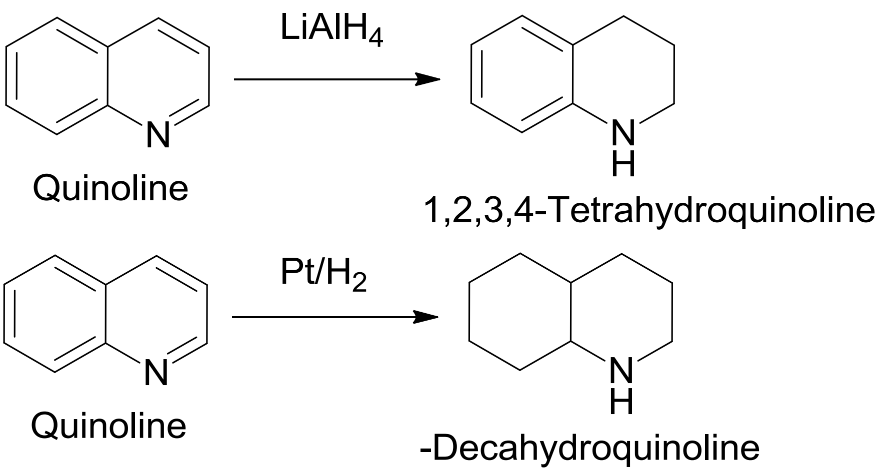
Quinoline and isoquinoline undergoes oxidative cleavage with alkaline $KMnO_4$ to form pyridine 2,3 and pyridine 3,4-dicarboxylic acids.



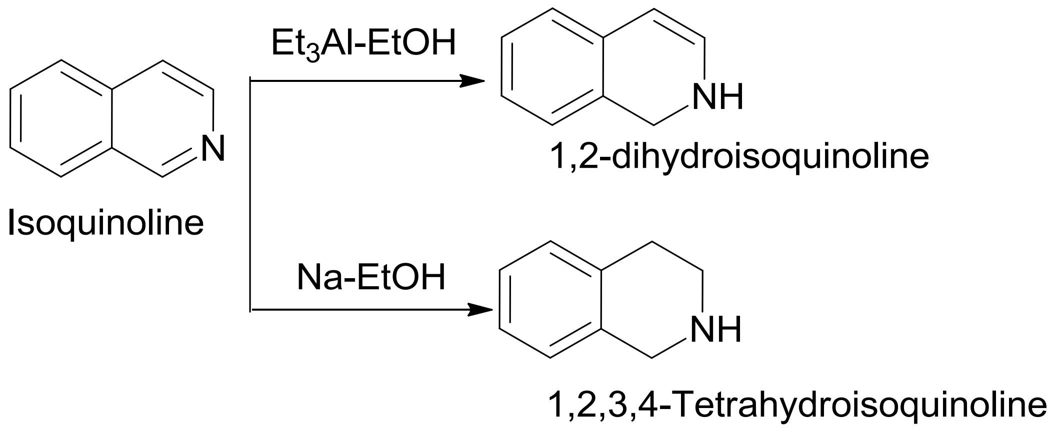


2.7.6 Reduction

Quinoline on reduction give 1,2,3,4-tetrahydro quinoline.



Isoquinoline on reduction gives 1,2-dihydo and 1,2,3,4-tetrahydro isoquinoline.

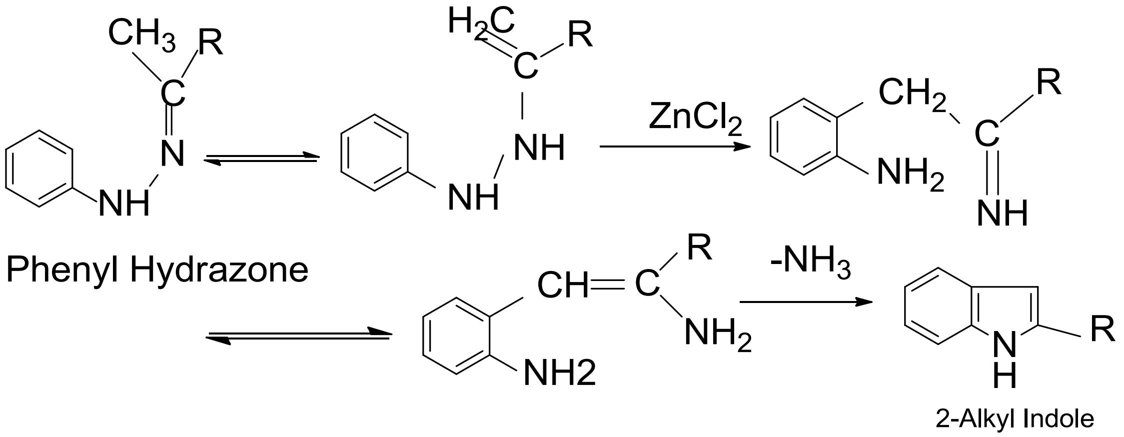


2.8 INDOLE

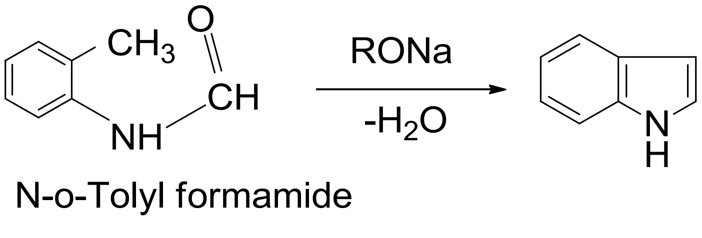
Condensed Rings containing 5 memebered Heterocyclics.Occurs in coal tar, orange blossoms, jasmine flowers.

2.8.1 Preparation:

1) Fischer's Indole Synthesis: Indole is prepared when phenylhtdrazone of a carbonyl group is heated in the presence of $ZnCl_2$, BF_3,

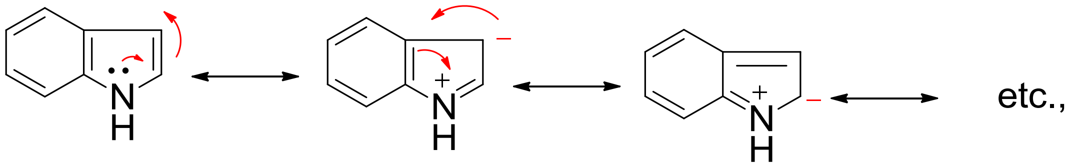


2) Madelung synthesis:Intramolecular condensation of N-o-tolylformamide in the presence of a base like sodium ethoxide,sodamide



2.8.2 Structure of Indole:

All the ring atoms in indole are in sp2 hybridised with 10 e-s follows Huckel's rule of 4n+2, aromatic in nature.



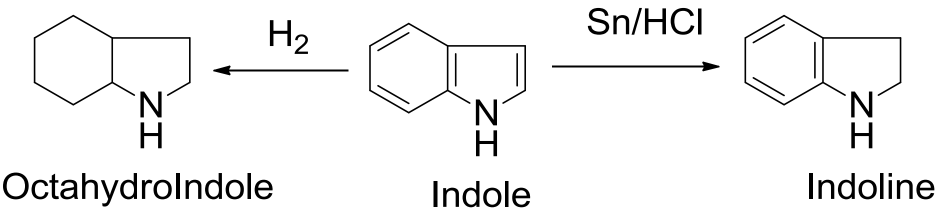
2.8.3 Properties:

Crystalline solid with a melting point 52^{0}C.

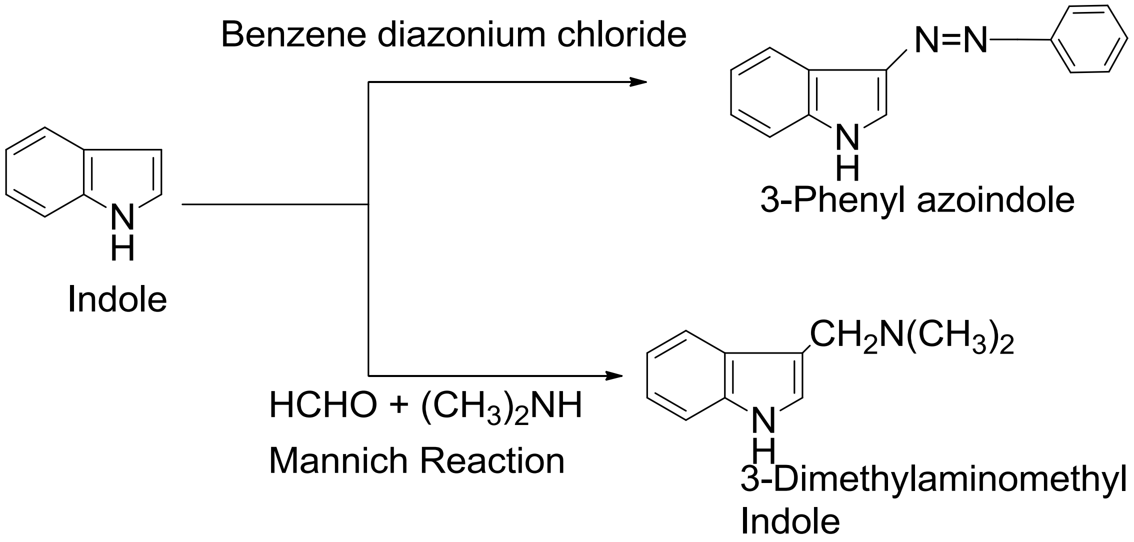
Resembles pyrrole undergoes electrophilic substitution at position 3 due to greater stabilization of carbocation as compared to position 2.

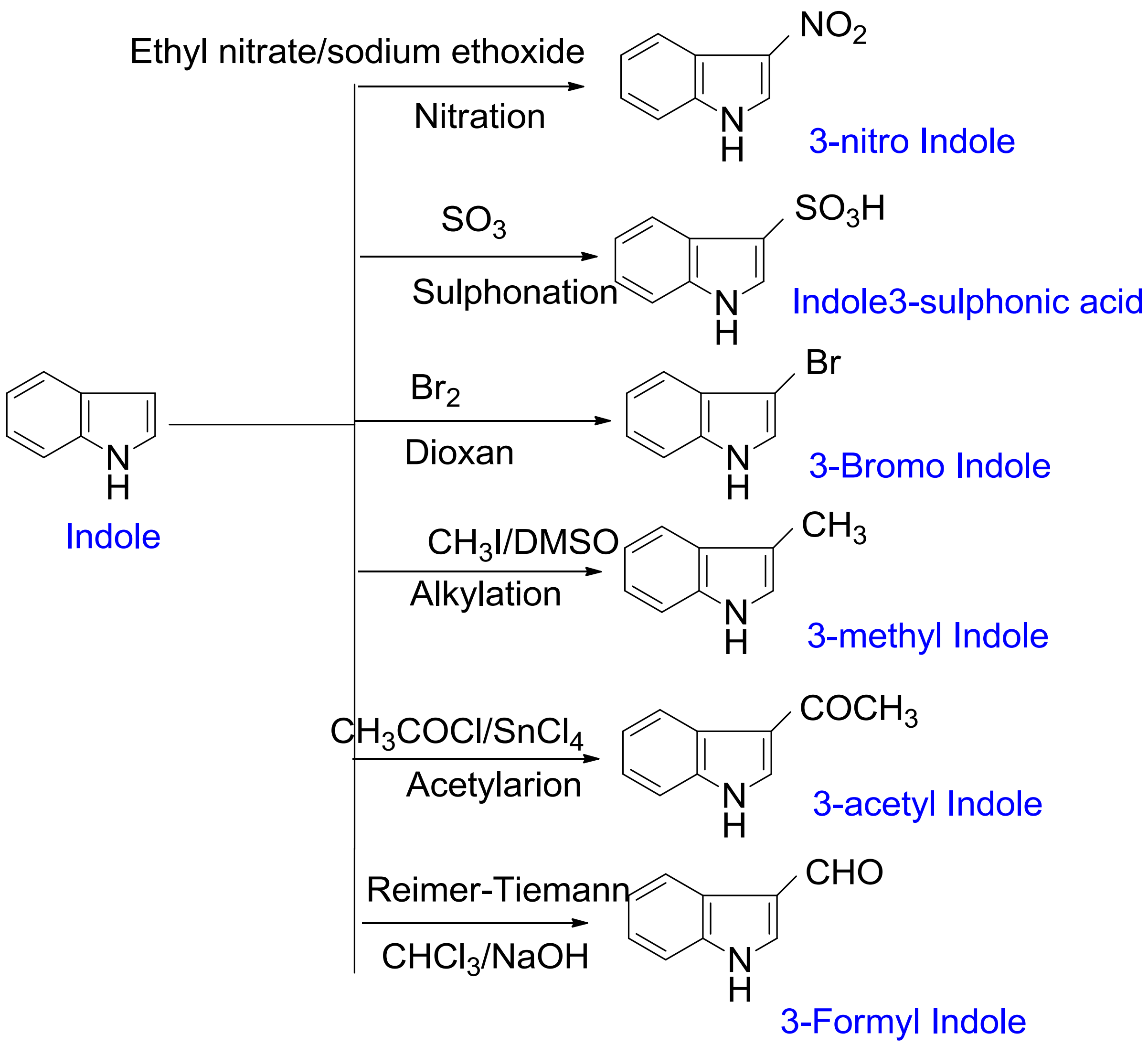
2.8.4 Reduction:

It forms Indoline and octahydroindole.



2.8.5 Electrophilic substitution of Indole





TEXT / REFERENCE BOOKS

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