UNIT-3

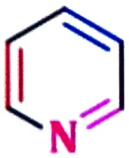
Heterocyclic Compound-I

Points to be covered in this topic

- ❖ INTRODUCTION
- ❖ CLASSIFICATION AND NOMENCLATURE
- ❖ SYNTHESIS, REACTIONS AND MEDICINAL USES OF
  - ➢ PYRROLE,
  - ➢ FURAN,
  - ➢ THIOPHENE

❑ INTRODUCTION

- Heterocyclic compound is the class of **cyclic organic compounds** those having **at least one hetero atom** (i.e. atom other than carbon) in the **cyclic ring system.**
- The most common **heteroatoms** are **nitrogen (N), oxygen (O) and sulphur (S)**



Heterocyclic pyridine
with one nitrogen heteroatom

❑ CLASSIFICATION OF HETEROCYCLIC COMPOUNDS

Heterocyclic compounds may be classified into three types: (i) Five Membered, (ii) Six Membered and (iii) Fused or Condensed Heterocyclic compounds.

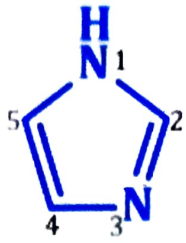
❖ Five-membered heterocyclic compounds bearing one heteroatom

HETEROATOM	SATURATED	UNSATURATED
Nitrogen	Pyrrolidine	Pyrrole
Oxygen	Tetrahydrofuran	Furan

PYRROLE PYRROLINE PYRROLIDINE FURAN DIHYDRO FURAN TETRAHYDRO FURAN

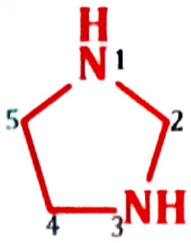
❖ Five-membered heterocyclic compounds bearing two heteroatom

HETEROATOM	SATURATED	UNSATURATED
Nitrogen – Nitrogen	Imidazolidine Pyrazolidine	Imidazole Pyrazole
Oxygen - Sulfur	Oxathiolidine Isoxthiolidine	Oxathiole Isoxathiole
Nitrogen - Sulfur	Thiazolidine Isothiazolidine	Thiazole Isothiazole

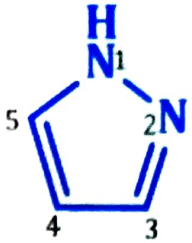


IMIDAZOLE

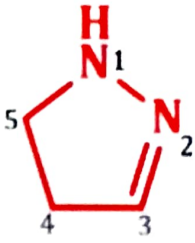
IMIDAZOLINE



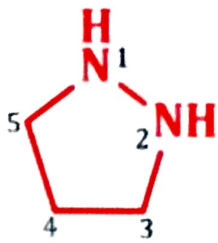
IMIDAZOLIDINE



PYRAZOLE



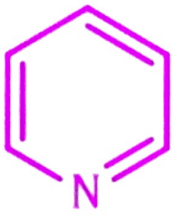
PYRAZOLINE



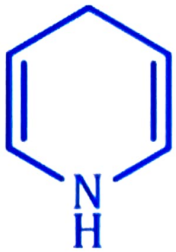
PYRAZOLIDINE

❖ Six-membered heterocyclic compounds bearing one heteroatom

HETEROATOM	SATURATED	UNSATURATED
Nitrogen	Piperidine	Pyridine
Oxygen	Oxane	Pyran
Sulfur	Thiane	Thiopyran

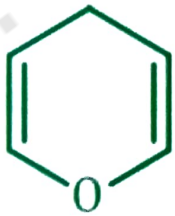


PYRIDINE

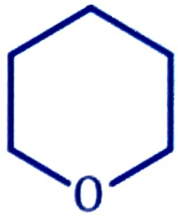


DIHYDRO PYRIDINE

PIPERIDINE

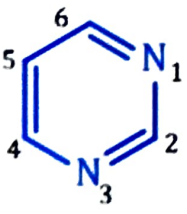


PYRAN

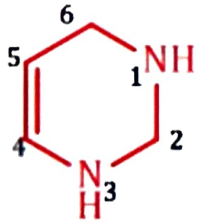


OXANE

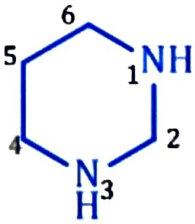
❖ Six-membered heterocyclic compounds bearing two heteroatom



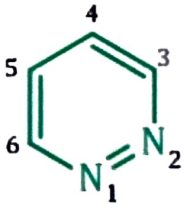
PYRIMIDINE



TETRAHYDRO PYRIMIDINE



PERHYDRO PYRIMIDINE

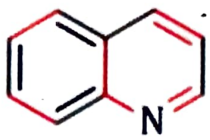


PYRIDAZINE

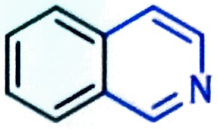
PYRAZINE

PIPERAZINE

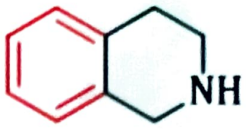
❖ Fused polycyclic system



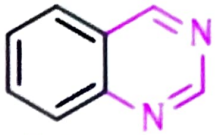
Quinoline



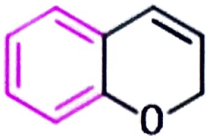
Isoquinoline



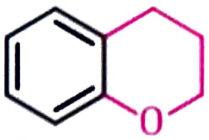
Tetrahydro isoquinoline



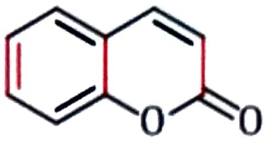
Quinazoline



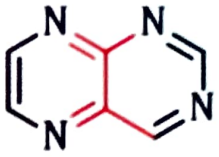
Chromene



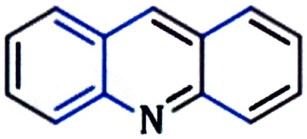
Chromane



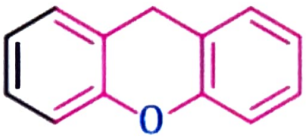
Coumarin



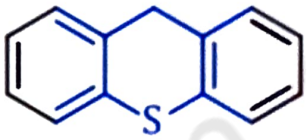
Pteridine



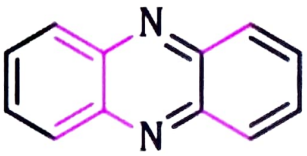
Acridine



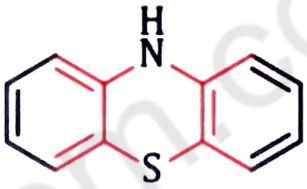
Xanthene



Thioxanthene



Phenazine



Phenothiazine

❑ NOMENCLATURE OF HETEROCYCLIC COMPOUNDS (HANTZCH-WIDMANN SYSTEM)

- This nomenclature system **specifies the nature**, **position, ring size, number,** and **types of heteroatoms** present in any heterocyclic compounds.
- This system of nomenclature **applies to monocyclic three-to-ten-membered** ring heterocycles
- The nomenclature of heterocyclic compounds are assigned **by combining 'prefix' (that indicate the heteroatom present)** with **'stem'** (that **indicate the ring size** as well as the **saturation and unsaturation in the ring**) and **'suffixes'**.

Prefix + Stem + Suffix

❖ Common Prefix for Heteroatoms (arranged in the preferential order)

HETEROATOM	SYMBOL	PREFIX
Oxygen	O	Oxa
Sulphur	S	Thia
Selenium	Se	Selena
Nitrogen	N	Aza
Phosphorous	P	Phospha
Arsenic	As	Arsa
Antimony	Sb	Stiba
Bismuth	Bi	Bisma
Silicon	Si	Silia
Tin	Sn	Stanna
Lead	Pb	Plumba

❖ Ring size

RING SIZE	SUFFIX
3	ir
4	et
5	ol
6	in
7	ep
8	oc
9	on
10	ec

❖ Size and degree of unsaturation

Ring size	Saturated	Unsaturated	Saturated (with Nitrogen)
3	-irane	-irene	-iridine
4	-etane	-ete	-etidine
5	-olane	-ole	-olidine
6	-inane	-ine	-
7	-epane	-epine	-
8	-ocane	-ocine	-
9	-onane	-onine	-
10	-ecane	-ecine	-

Oxa + irane= Oxirane

Thia+ irane= Thiirane

Aza+ iridine= Aziridine

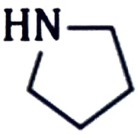
Oxa + etane= Oxetane

Thia + etane= Thietane

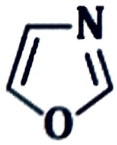
Aza+ etidine= Azetidine

Oxa + olane= Oxolane

Thia+ olane= Thiolane



Aza+ olidine= Azolidine



Oxa + aza + ol + e = Oxazole

1,3 Thia + aza + ol + e = 1,3-thiazole

Oxa + aza + ir + idine = Oxaziridine

❑ PYRROLE

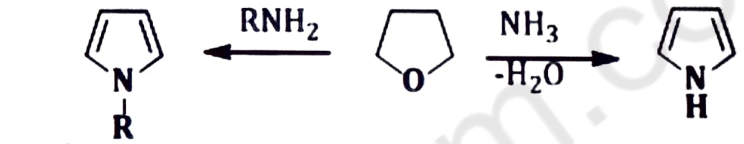
- Pyrrole is a heterocyclic aromatic organic compound, a **five-membered** ring with the formula C_4H_4NH.
- It is a **colorless volatile liquid** that darkens readily upon exposure to air.
- Pyrrole has **three pairs of delocalized π electrons.**
- It is an **aromatic heterocycle** having **weak aniline like odour.**


Pyrrole

❖ Method of preparation

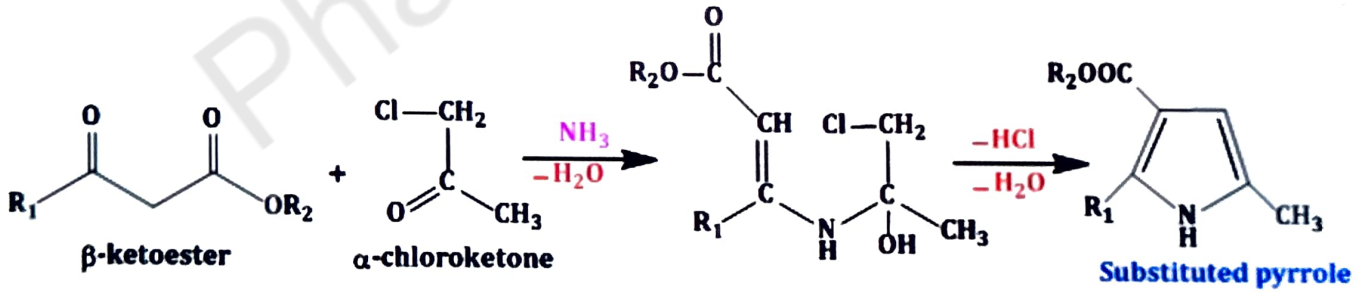
1. Industrial method

- Pyrrole is prepared industrially from furan by passing it over **ammonia and steam** and **heated at 400°C** in the presence of solid acid catalysts like SiO_2 and Al_2O_3



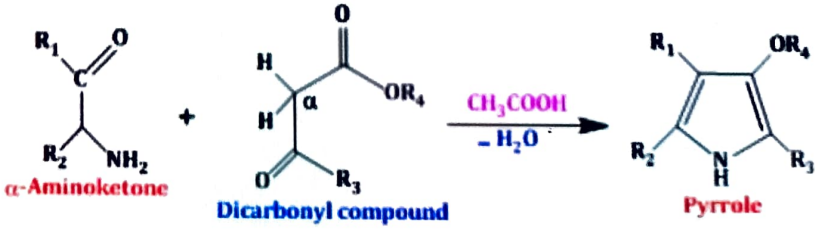
2. Hantzsch Pyrrole synthesis

- When **α- haloketone** or **aldehyde** is **reacted** with a **β-ketoester or β-chloroketone** and a base like ammonia/primary amine, it **gives pyrrole**



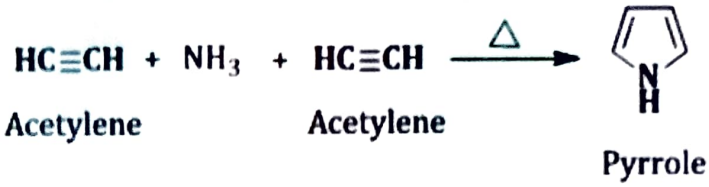
3. Knorr Pyrrole synthesis

- **α - amino ketone** is **condensed** with **another dicarbonyl compound** containing an electron withdrawing group a to a carbonyl group (i.e., **activated methylene group**) in the **presence of acetic acid**.



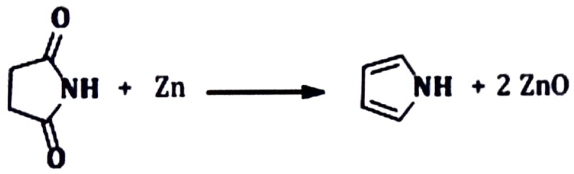
4. From acetylene

- Pyrrole is obtained by passing **acetylene and ammonia** through **a red hot tube**



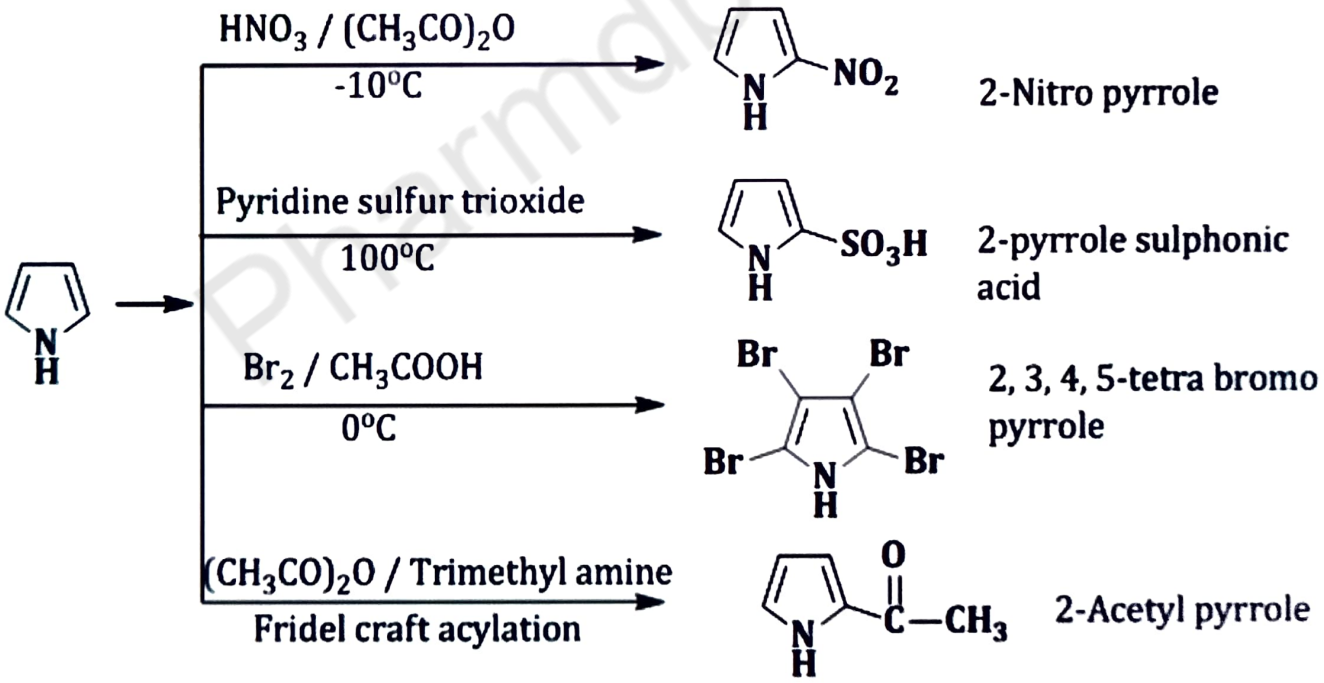
5. From distillation of succinimide

- Pyrrole is obtained by the **distillation of succinimide** with zinc dust.

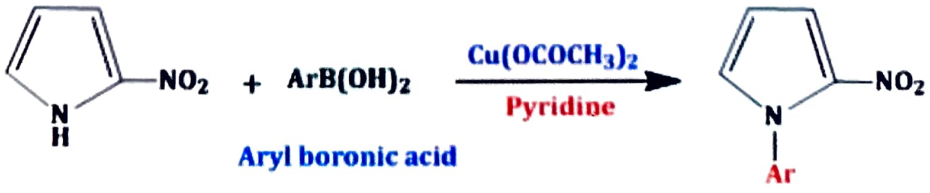


❖ Chemical reaction

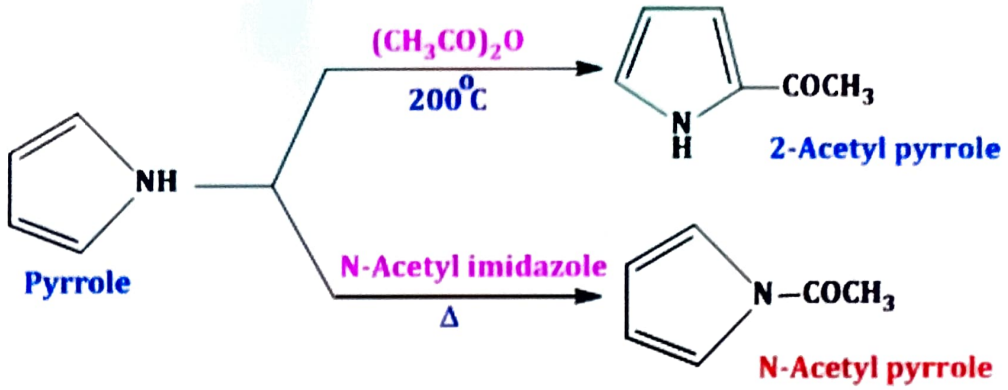
1. Electrophilic substitution reactions: Pyrrole undergoes electrophilic substitution reactions and substitution chiefly **at C-2 position.**



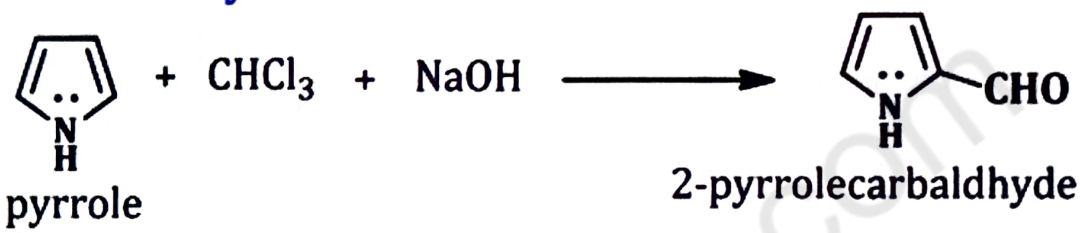
2. Alkylation & Arylation



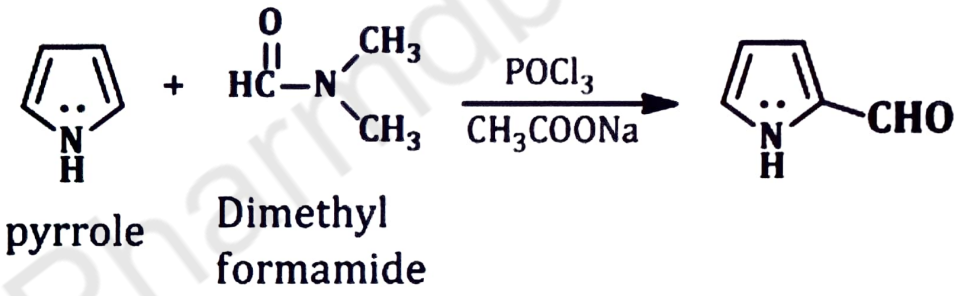
3. Acylation



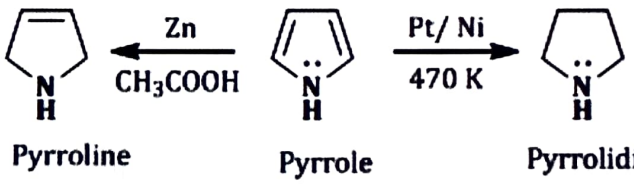
4. Reimer – Tiemann reaction: In the presence of **a strong base** and **chloroform, pyrrole undergoes** Reimer – Tiemann reaction to form **pyrrole – 2 – aldehyde**



5. Gatterman-Koch reaction: When **pyrrole is heated** with **phosphorus oxychloride** and **dimethyl formamide** it gives **2-pyrrolecarbaldehyde**



6. Reduction: Pyrrole is **reduced with Pt, Pd and Ni** at 470 K to yield **pyrrolidine**



❖ Use

- Pyrrole is a structural constituent of **haem, chlorophyll, Vitamin B_{12}** and **bile pigments.**
- Pyrrole ring is also present in the drug tolmetin **(NSAID),** ketorolac **(NSAID),** sunitinib **(anti-cancer),** ageliferin **(anti-bacterial),** elopiprazole **(antipsychotic),** procyclidine **(antimuscarinic drug to treat parkinsonism)** and atorvastatin **(lipid lowering agent).**

❑ FURAN

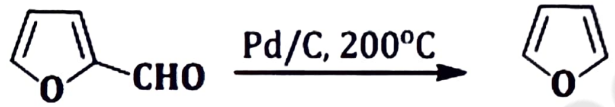
- Furan is a **heterocyclic organic compound**, consisting of a **five-membered aromatic ring** with **four carbon** atoms and **one oxygen** atom
- It is a **colourless, inflammable, volatile, liquid** with **boiling point of 32°C.**

Furan

❖ Method of preparation

1. Decarboxylation of furfural

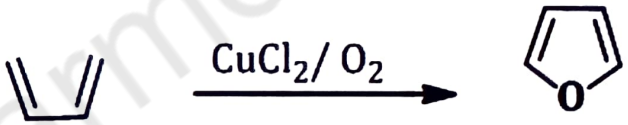
- The vapour phase **decarboxylation of furfural** in the **presence of palladium and charcoal gives furan**



Furfural Furan

2. From 1,3-Butadiene

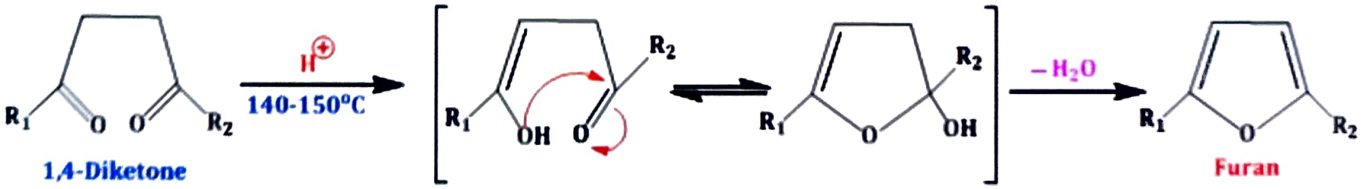
- 1,3-Butadiene can be converted **to furan** by the copper-catalyzed oxidation.



1,3-butadiene Furan

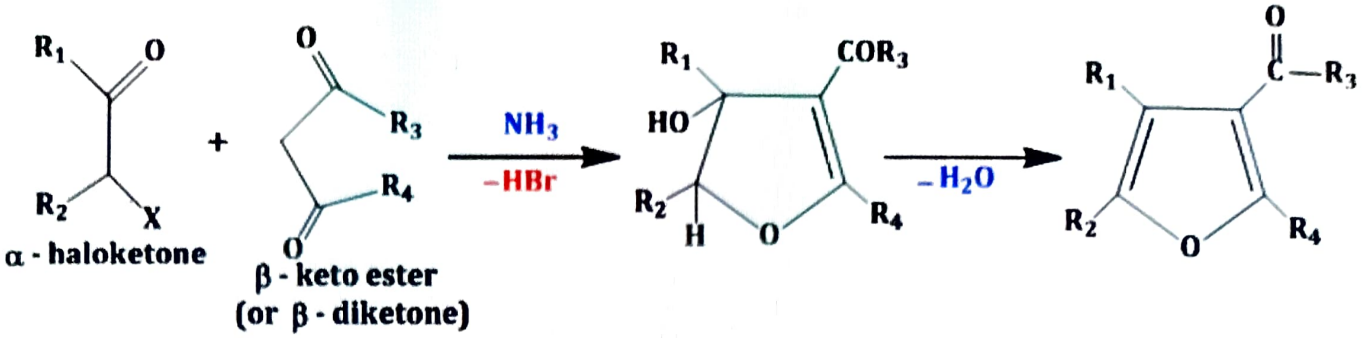
3. Pall knorr synthesis

- Under **non-aqueous acidic conditions, 1, 4 – diketones** undergo **cyclization** followed by **dehydration** to give **furans**



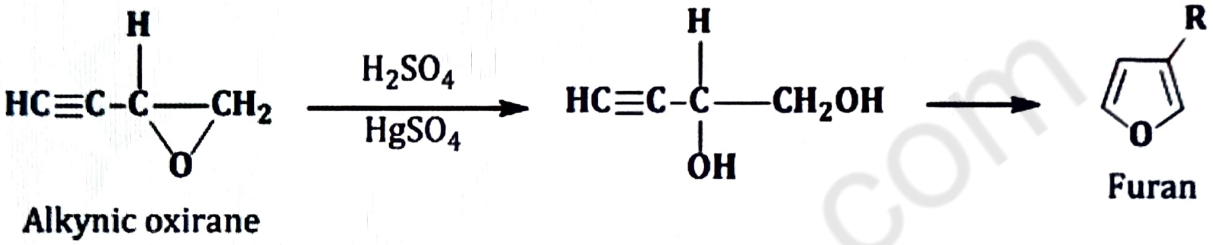
4. Fiest-Benary Synthesis

- It is a **condensation reaction** between an **α-haloketone** with a **β-ketoester** (or **α β - diketone**) in the presence of a base like **ammonia or pyridine**



5. Ring expansion

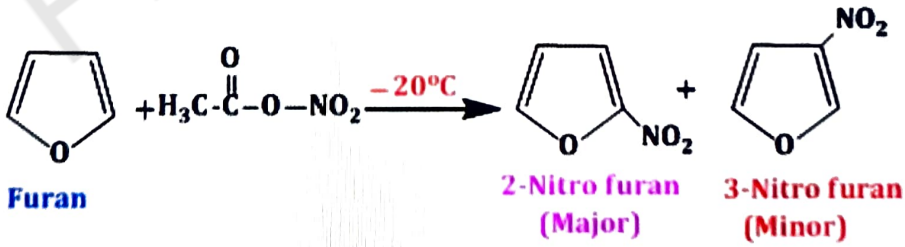
- **Alkynic oxirans** when treated with **sulfuric acid and mercury sulfate,** undergo ring expansion to produce furans



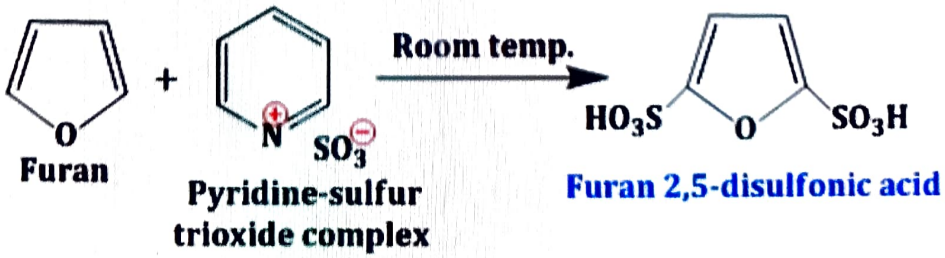
❖ Chemical reaction

1. Electrophilic substitution reactions: The **C-2 position of the furan** is preferentially reactive towards **electrophilic attack than C-3 position.**

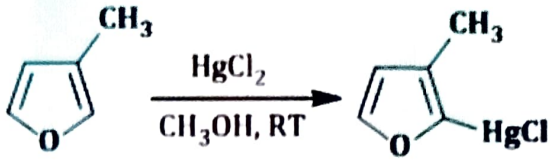
Nitration: Furan is nitrated with mild nitrating agent, acetyl nitrate, at low temperature.



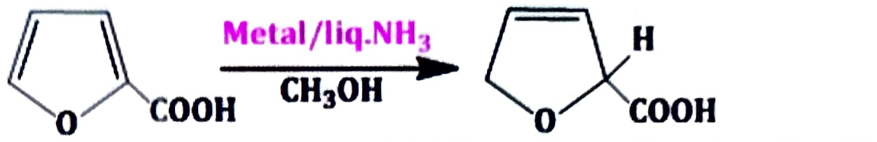
Sulfonation: Furan is sulfonated with the complex of sulfur trioxide and pyridine or dioxane to give **2, 5 – disubstituted furan** even at room temperature.



2. Mercuration

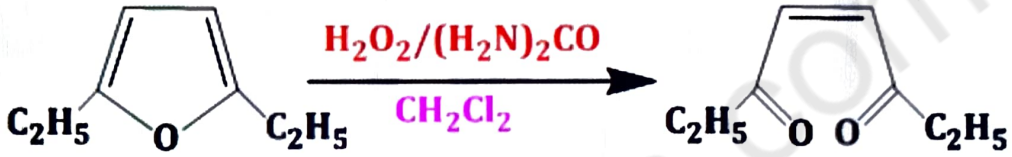


3. Reduction: Furoic acid can be reduced to dihydro derivative



Furoic acid — 2,5-dihydrofuran-2-carboxylic acid

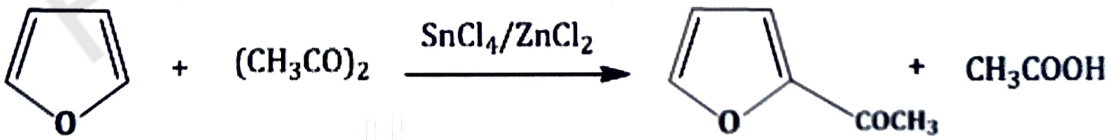
4. Oxidation: When **furan is treated** with sodium hypochlorite, hydrogen peroxide or meta chloroperbenzoic acid.



5. Reactions with diazonium salts

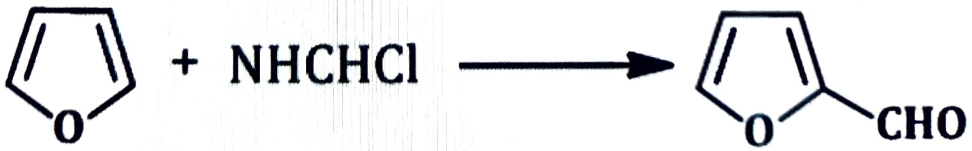
Furan — 2-methyl furan

6. Fridel crafts acylation



Furan — 2-Acetyl furan

7. Gatterman – koche reaction



❖ Use

Furan is an important scaffold present in drugs like, ranitidine (anit-ulcer), nitrofurazone (anti-bacterial), ascorbic acid (vitamin C) and many natural terpenoids.

❑ THIOPHENE

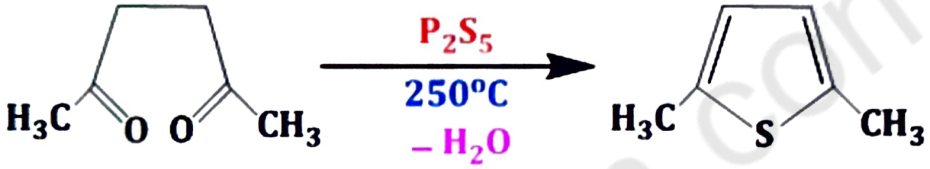
- Thiophene belongs to a class of heterocyclic compounds containing a **five membered ring** made up of **one sulfur as a heteroatom.**
- Thiophene is a **colourless liquid having** the **boiling point of 84°C.**

Thiophene

❖ Method of preparation

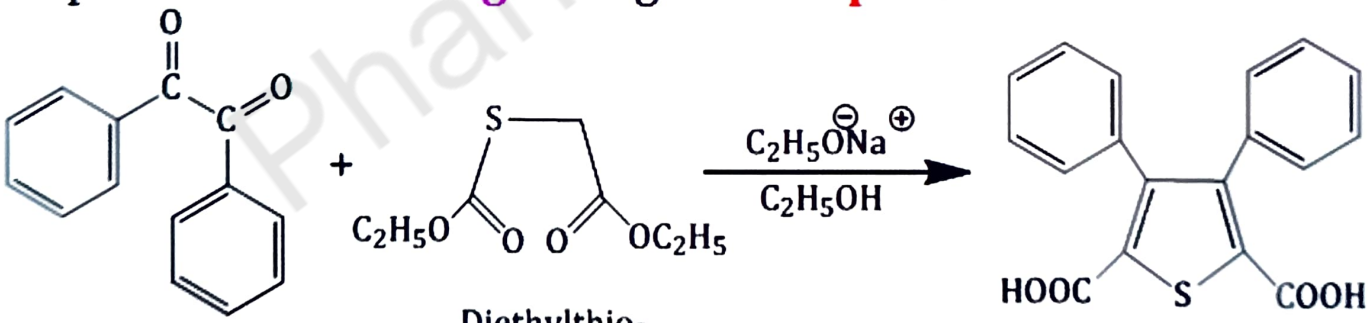
1. Paal-Knorr Synthesis

- In this method, **1, 4 – dicarbonyl compounds** can be heated with **phosphorus pentasulfide** (a source of sulfur) **to give thiophene**



2. Hinsberg Synthesis

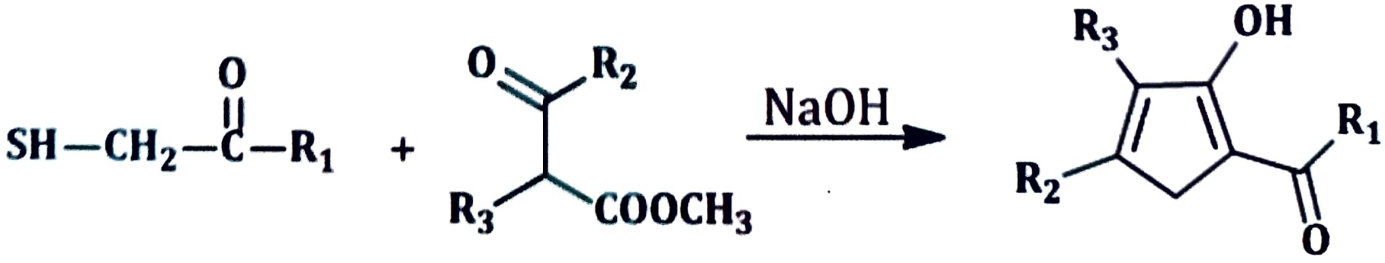
- Two consecutive **aldol condensations** between **1, 2-dicarbonyl compound** and **diethylthiodiacetate** in the presence of a **strong base** gives **thiophene**



1,2-Dicarbonyl compound

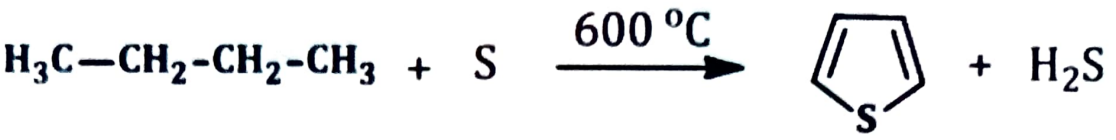
Diethylthio-diacetate

3. Fiesselmann Thiophene Synthesis



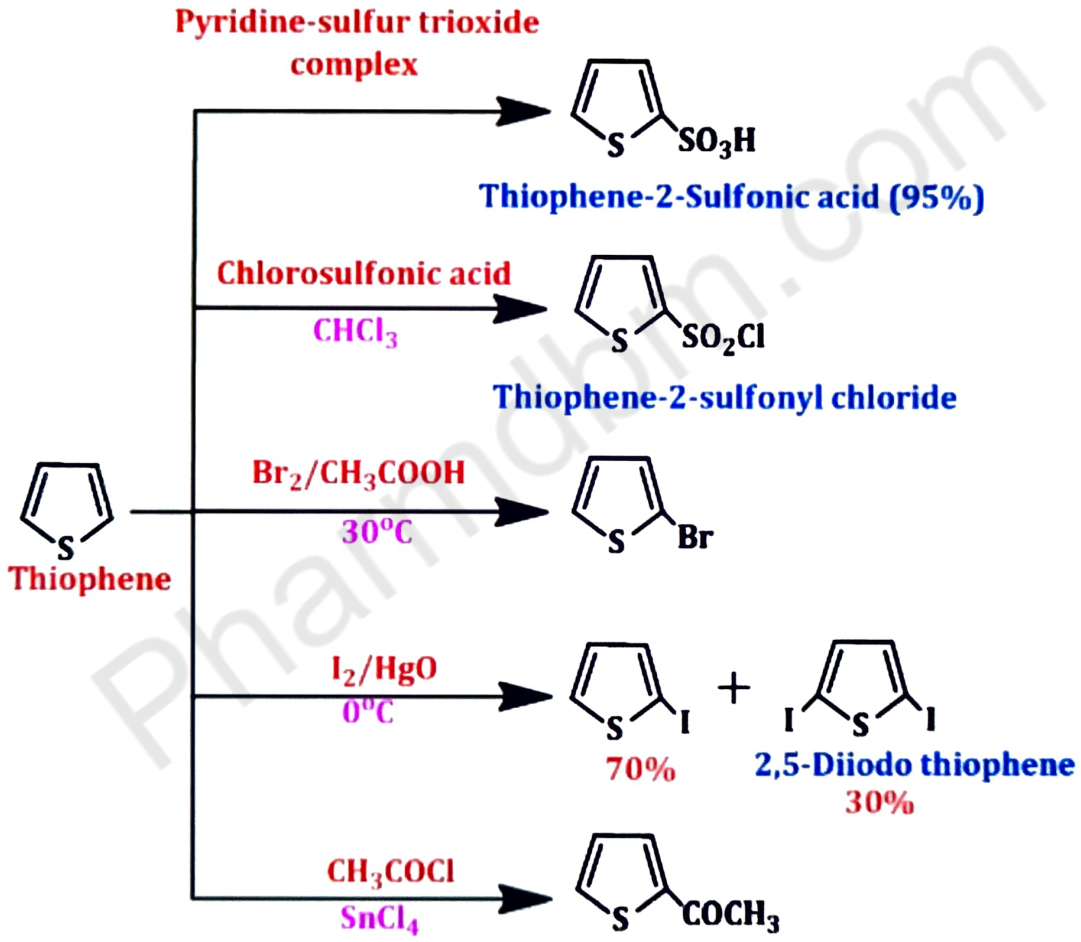
4. Industrial Methods

- Thiophene can be synthesized on industrial scale **heating n-butane** and **sulfur** at **high temperature.**

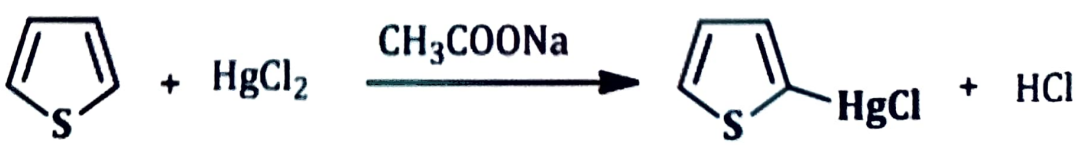


❖ Chemical reaction

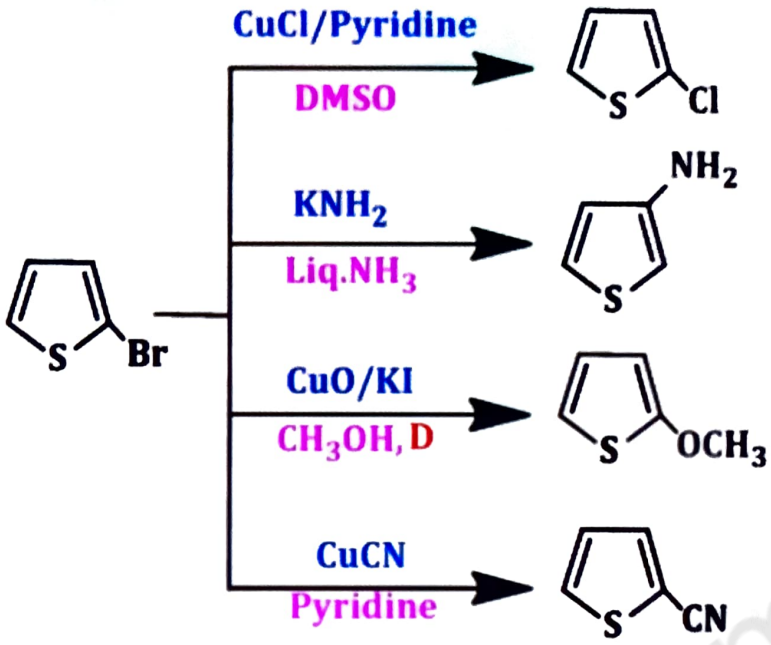
1. Electrophilic substitution reactions: The **preferred site of attack in thiophene is C2-position.**



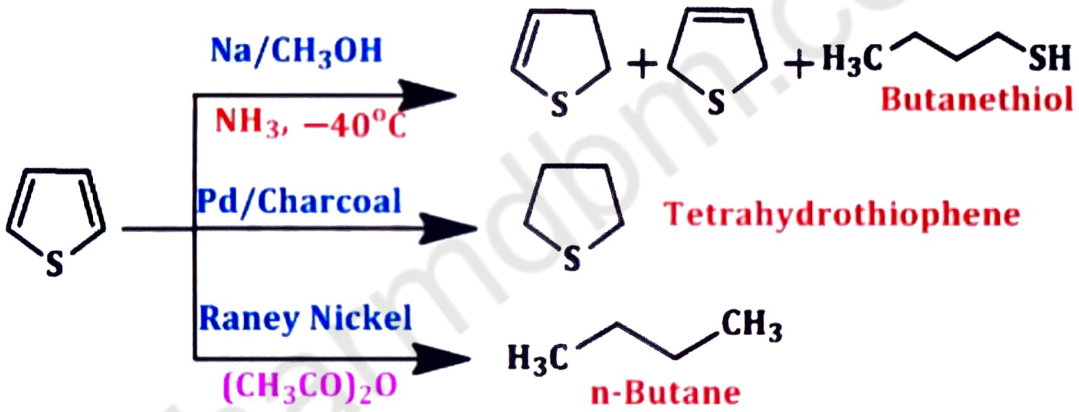
2. Mercuration: Thiophene react with **mercuric chloride** in the **sodium acetate** and gives **Thiophene-2-mercuric chloride**



3. Nucleophilic substitution



4. Reduction



5. Oxidation

- Thiophene is resistant **to mild oxidizing agent**, but it is oxidized to maleic acid and oxalic acid by the **treatment with HNO_3**

❖ Use

- Thiophene derivatives possess remarkable activities like **antibacterial, anti-inflammatory, anti-anxiety, anti-psychotic, anti-arrhythmic and anticancer.**