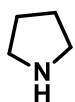


3.11. Heterocyclic Compounds

3.11.1. Introduction

- Compounds which contain one or more hetero atoms (other than carbon atom) in the ring, are called heterocyclic compounds.
- Classification:** (a) Non-aromatic heterocyclic compounds, (b) Aromatic heterocyclic compounds and (c) Partially saturated non-aromatic heterocyclic compounds.

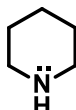
(a) Non-aromatic heterocyclic compounds:



Pyrrolidine



Tetrahydrofuran

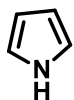


Piperidine



Aziridine

(b) Aromatic heterocyclic compounds:



Pyrrole



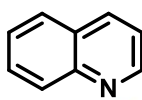
Furan



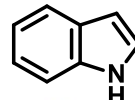
Thiophene



Pyridine



Quinoline



Indole



Oxazole

(c) Non-aromatic heterocyclic compounds:



dihydropyrrole



azirine



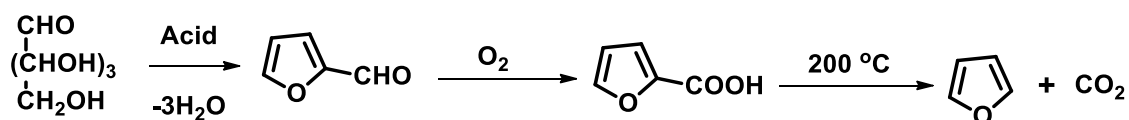
oxetane

3.11.2. Furan

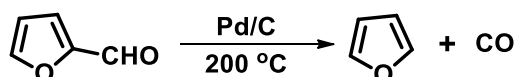
- It is a five membered heterocyclic compound having oxygen atom as the hetero atom.

3.11.2a. Synthesis:

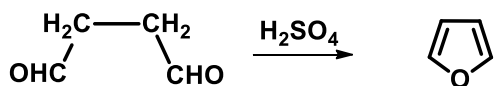
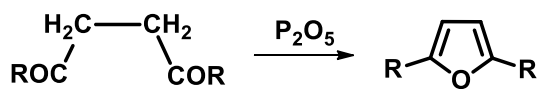
(a) The pentose fragment of naturally occurring substances like starch or corn cobs upon acid hydrolysis produces furfural from which furan is synthesized.



(b) It can also be prepared by the catalytic decomposition of furfural.

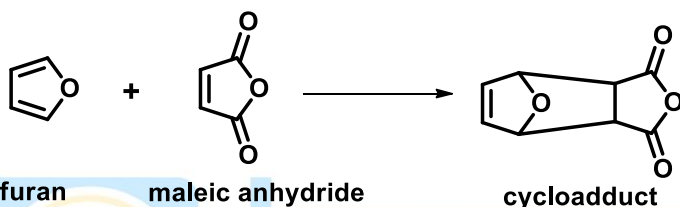


(c) **Paal-Knorr synthesis:** It is synthesized by dehydrating 1,4-diketones or aldehydes with P_2O_5 or conc. H_2SO_4 .

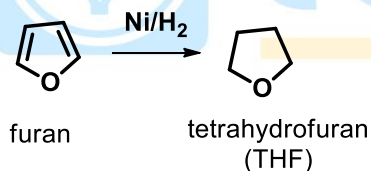


3.11.2b. Reactions of furan

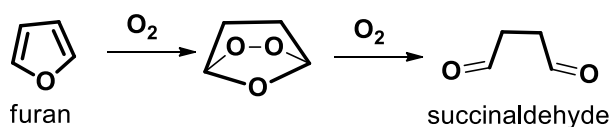
(i) **Diels-Alder reaction:** Furan undergoes Diels-Alder reaction with maleic anhydride to form the following cycloadduct.



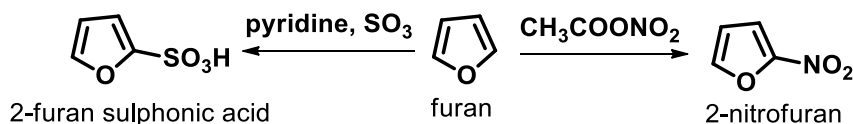
(ii) **Reduction reaction:** Furan is reduced to form tetrahydrofuran by metal-catalyzed hydrogenation reaction.



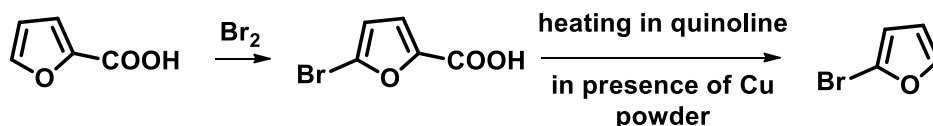
(iii) **Oxidation reaction:** Under oxidation reaction furan is transformed to succinaldehyde.



(iv) **Electrophilic Substitution Reaction:** Furan undergoes electrophilic substitution reaction at C2-position of the ring, it is also very labile to acids.

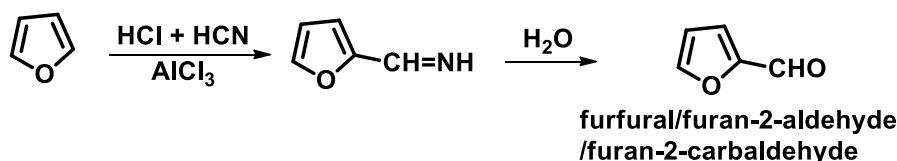


Furan cannot be halogenated directly as it is highly prone to polymerization to form the polymer.

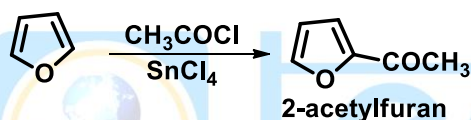


Chlorination of furan even at -40°C produces a mixture of 2- and 2,5-dichloro furan. So, direct halogenations is restricted for furan.

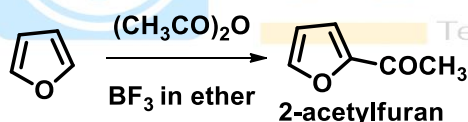
(v) **Gattermann reaction:** It is used for the synthesis of furfural from furan.



(vi) **Friedel-Crafts reaction:** Furan undergoes Friedel-Crafts reaction in presence of SnCl_4 , not using AlCl_3 , because it attacks the ring.



When anhydride is used as acylating agent, then boron trifluoride in ether is used as the catalyst.

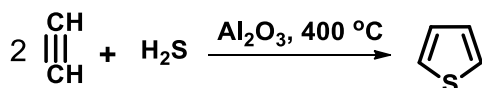


3.11.3. Thiophene

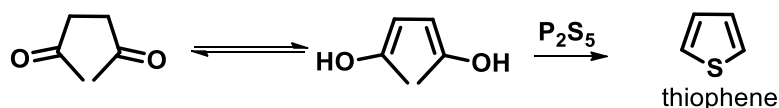
- It is a five membered heterocyclic compound having sulphur atom as the hetero atom.

3.11.3a. Synthesis

(a) Thiophene is commercially prepared by passing a mixture of acetylene and H_2S gas through a tube containing alumina at 400°C .

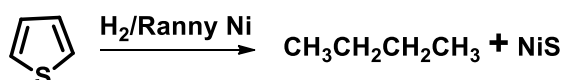
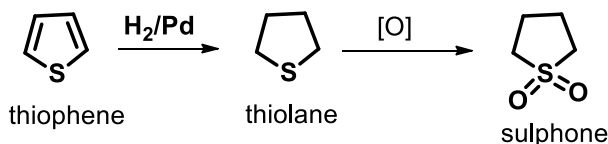
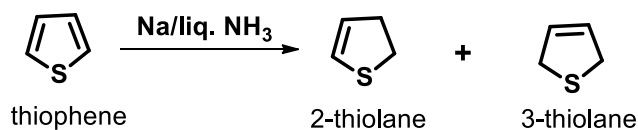


(b) **Paal-Knorr synthesis:** 1,4-diketone upon heating with P_2S_5 forms thiophene.



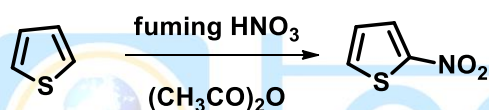
3.11.3b. Reactions of thiophenes

(i) **Reduction:** Thiophene can be reduced by Na/liq. NH_3 , H_2/Pd and $\text{H}_2/\text{Ranny nickel}$.

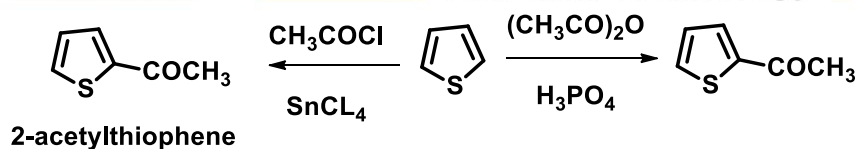


(ii) **Electrophilic substitution reaction:**

- Thiophene undergoes electrophilic substitution reaction to afford 2- or 5-substituted thiophene derivative.

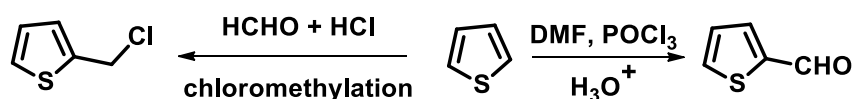


- Thiophene can also be acetylated either using acid chloride in presence of stannic chloride (SnCl_4) or acid anhydride in presence of phosphoric acid (H_3PO_4).



(iii) **Vilsmier-Haack reaction:**

- Thiophene undergoes formylation reaction at 2-position of the ring using dimethyl formamide and phosphorus oxychloride.
- It also undergoes chloromethylation reaction at the 2-position upon treatment with formaldehyde and HCl.



- Mercury, lithio and bromo derivatives of thiophene are used as the useful intermediate for the synthesis of various 2-substituted thiophene derivatives.

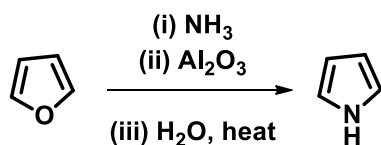


3.11.4. Pyrrole

- It is a five membered heterocyclic compound having nitrogen atom as the hetero atom.

3.11.4a. Synthesis

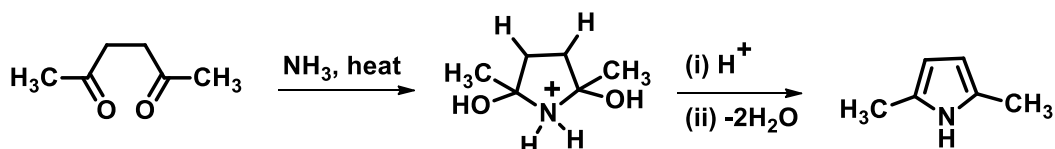
(a) Pyrrole is commercially synthesized by passing a mixture of furan, ammonia and steam over heated Al_2O_3 .



(b) Pyrrole is also synthesized by heating ammonium mucate in glycerol at 200°C .



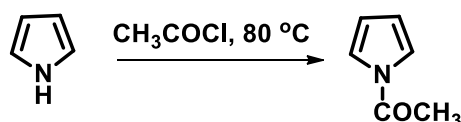
(c) **Paul-Knorr synthesis:** This involved the heating of a mixture of 1,4-diketone with ammonia or a primary amine. 2,5-dimethyl Pyrrole is obtained from acetonyl acetone and ammonia.




3.11.4b. Reactions of Pyrrole

- Basic structure:** (i) It is weaker base as the nitrogen lone pair is involved in the delocalization with the ring to make it $(4n+2)\pi$ electron system. (ii) In acid solution protonation occurs at the carbon centre. (iii) In dilute acid, Pyrrole forms trimer.

- CN1C=CC=C1.CI>>CN1C=CC=C1.[K+].[OH-]>>[K+]1C=CC=C1



- $$\text{Pyrrolidine} \xleftarrow[200\text{ }^{\circ}\text{C}]{\text{Ni/H}_2} \text{Pyrrole} \xrightarrow[\text{(ii) HI/red P}]{\text{(i) Zn/AcOH}} \text{Pyrrolidine}$$

- 
- Pyrrole** **Maleic imide**

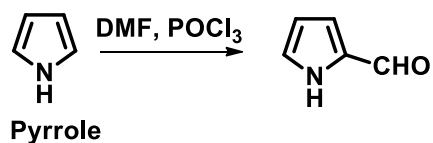
-
- Iodole

 Pyrrole

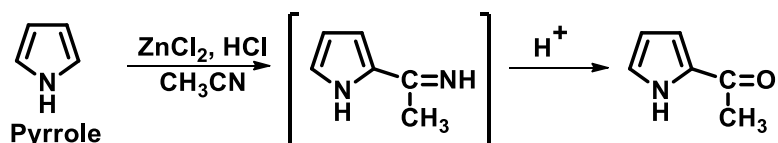
 2-bromo pyrrole

 2-nitro pyrrole

- **Vilsmier-Haack reaction:** Pyrrole can be formylated at 2-position with the help of DMF and POCl_3 .

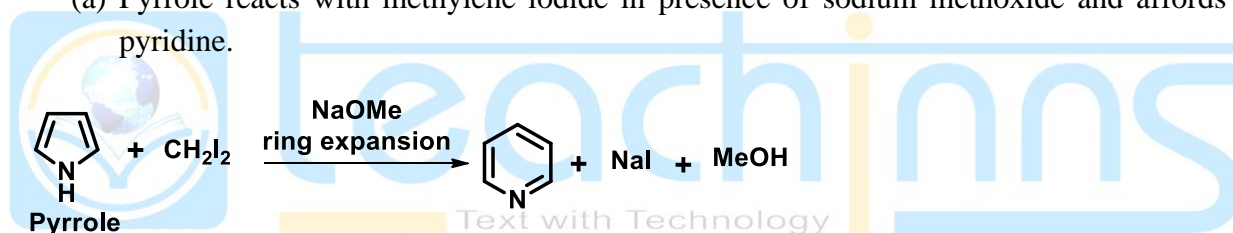


- **Houben-Hoesch reaction:** Pyrrole undergoes Houben-Hoesch reaction to produce 2-substituted ketones.

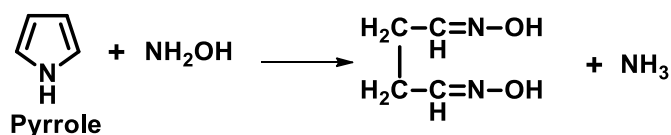


- Some other reactions:

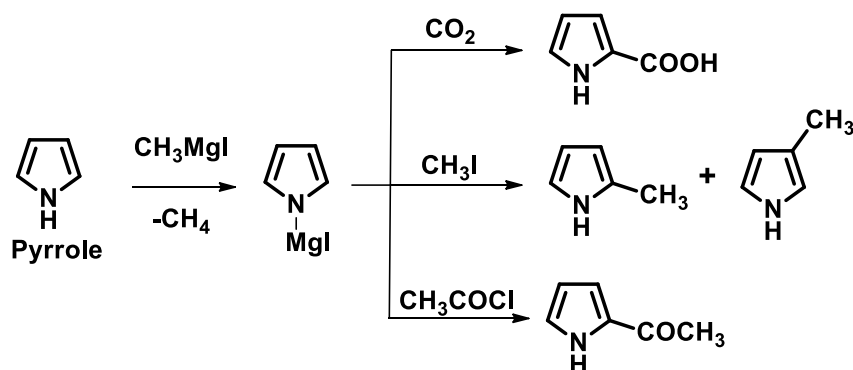
(a) Pyrrole reacts with methylene iodide in presence of sodium methoxide and affords pyridine.



(b) Pyrrole upon refluxing with ethanolic hydroxylamine produces succinaldehyde dioxime.



(c) Pyrrole reacts with Grignard reagent to form a salt with evolution of methane.



3.11.5. Pyridine

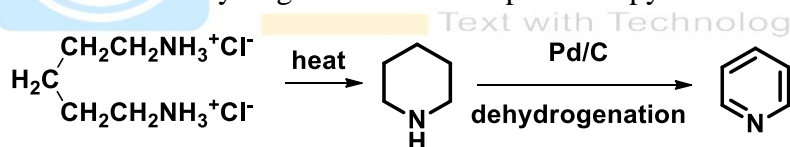
It is a six membered heterocyclic compound with nitrogen as the hetero atom.

3.11.5a. Synthesis of pyridine

(a) By distillation of 3-carboxy pyridine with sodalime

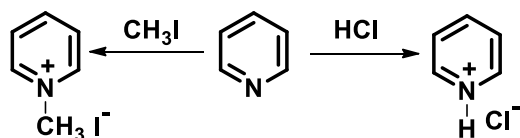


(b) Pentamethylene diamine hydrochloride salt under heating condition affords piperidine which under dehydrogenation reaction produces pyridine.

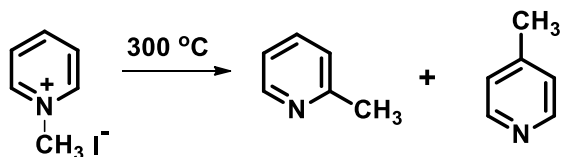


3.11.5b. Reactions of pyridine

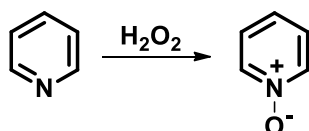
(i) **Basic structure:** Pyridine is highly basic, because the nitrogen lone pair is totally free for attacking an electrophile as it does not take part in the resonance with the ring itself. So it reacts with inorganic acids/alkyl halide and gives quaternary salts.



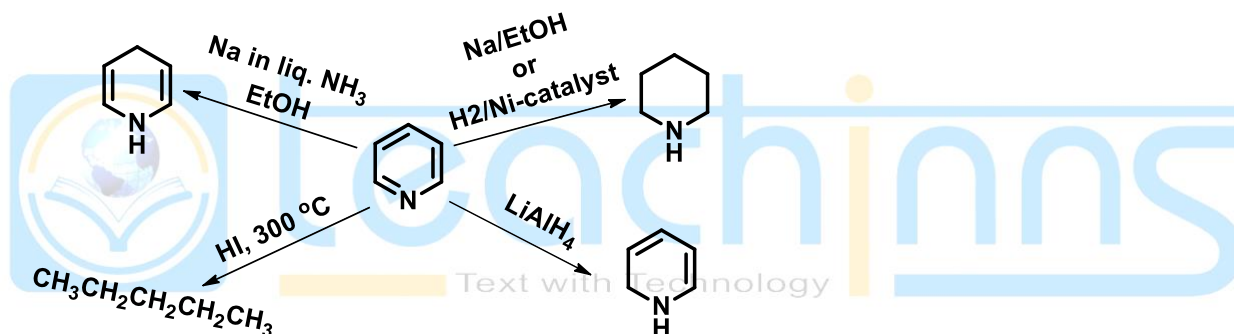
The quaternary salt of pyridine undergoes Hofmann-Martius reaction to form 2- and 4-methyl pyridines.



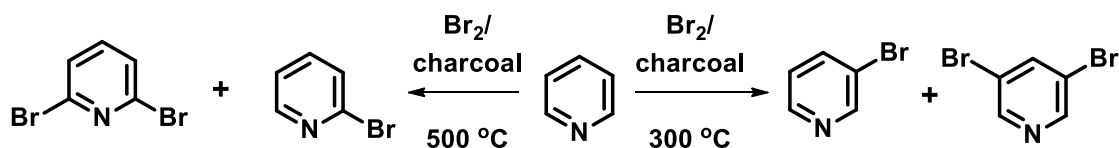
(ii) **Oxidation:** Pyridine undergoes oxidation reaction very easily in presence of hydrogen peroxide or perbenzoic acid to ultimately produce pyridine N-oxide.



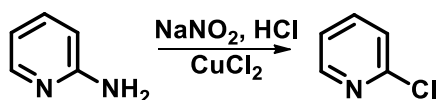
(iii) **Reduction:** Pyridine under different reduction conditions affords different products like below.



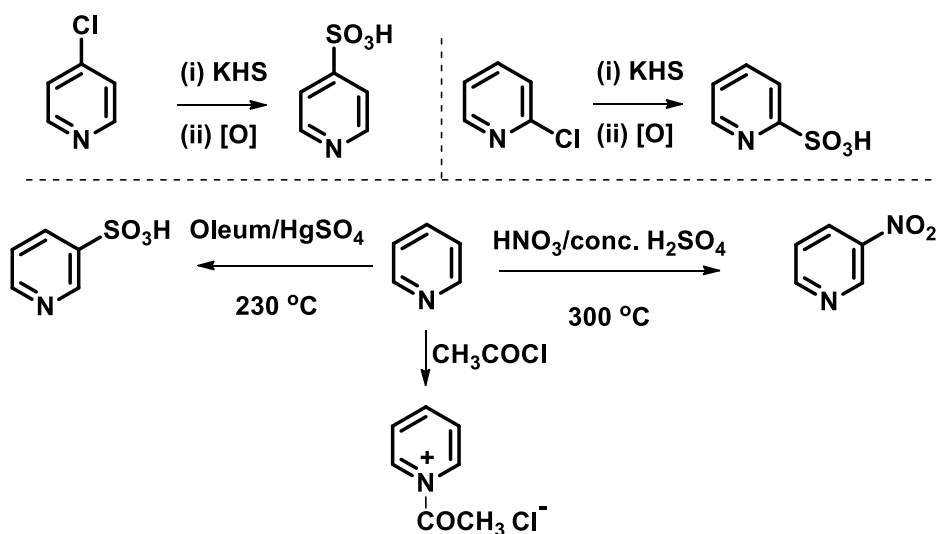
(iv) **Electrophilic Substitution reactions:** Pyridine forms 3-bromo and 3,5-dibromo pyridine upon reaction with Br_2 at $300\text{ }^{\circ}\text{C}$, however it produces a mixture of 2-bromo and 2,6-dibromo pyridine when the reaction is performed at $500\text{ }^{\circ}\text{C}$.



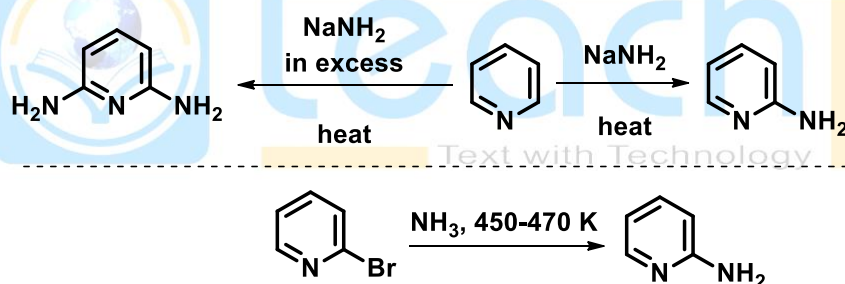
- 2-chloro pyridine is not obtained by the similar reaction condition. This can be synthesized by diazotization reaction of 2-aminopyridine.



- Some other electrophilic substitution reactions:

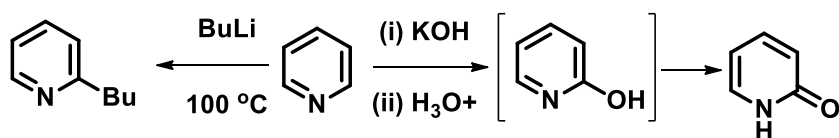


(v) **Nucleophilic Substitution reactions:** Pyridine upon treatment with sodamide under heating condition gives 2-aminopyridine, this reaction is known as Chichibabin reaction.



(vi) **Some other reactions:**

- Pyridine is transformed into pyridone by treating it with potassium hydroxide at 320 °C to form 2-hydroxypyridine which undergoes tautomerization reaction.
- Pyridine forms 2-butylpyridine when treated with n-butyl lithium at 100 °C.

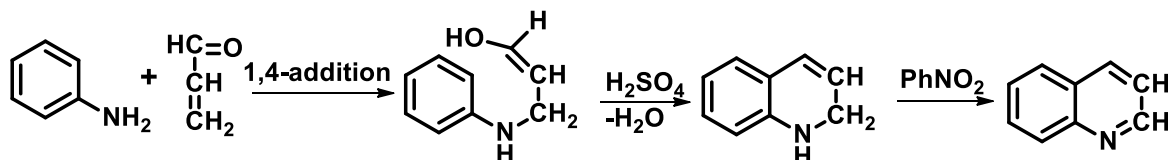


3.11.6. Quinoline

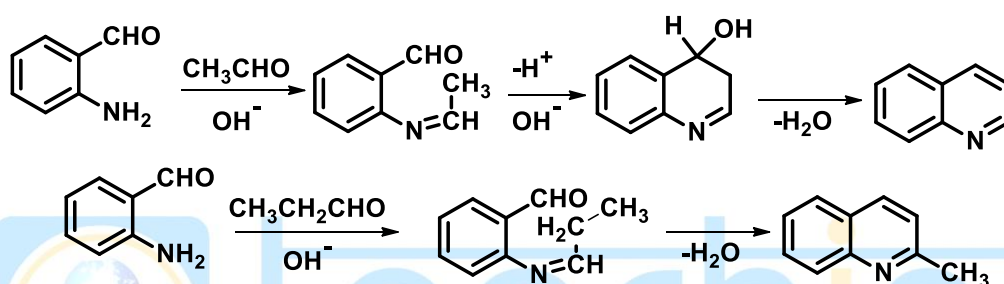
- It is nothing but 2,3-benzopyridine in which one benzene ring is fused with a pyridine ring at α, β -position.

3.11.6a. Synthesis of Quinoline

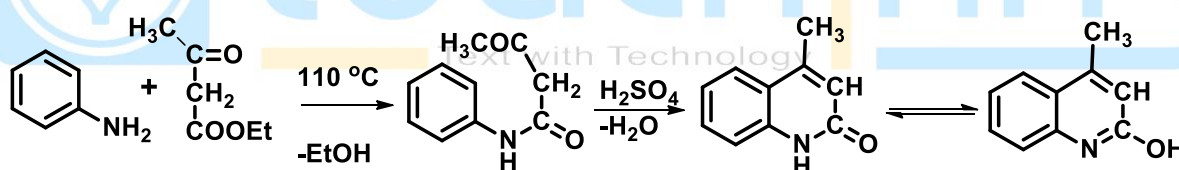
(1) **Skraup synthesis:** It is the commercial method for the synthesis of quinoline which involves heating a mixture of aniline, nitrobenzene, glycerol, concentrated sulphuric acid and FeSO_4 . Nitrobenzene acts as oxidizing agent whereas ferrous sulphate makes the reaction less violent. Glycerol loses water to afford acrolein.



(2) **Friedlander's synthesis:** This reaction involves the alkaline condensation of 2-aminobenzaldehyde with a carbonyl compound having active methylene group.

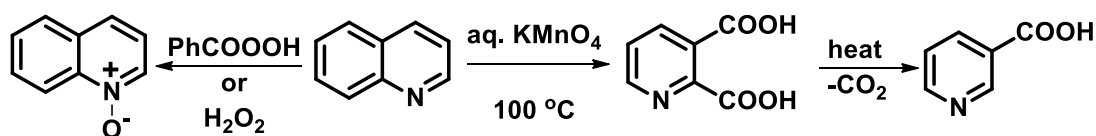


(3) **Knorr-quinoline synthesis:**

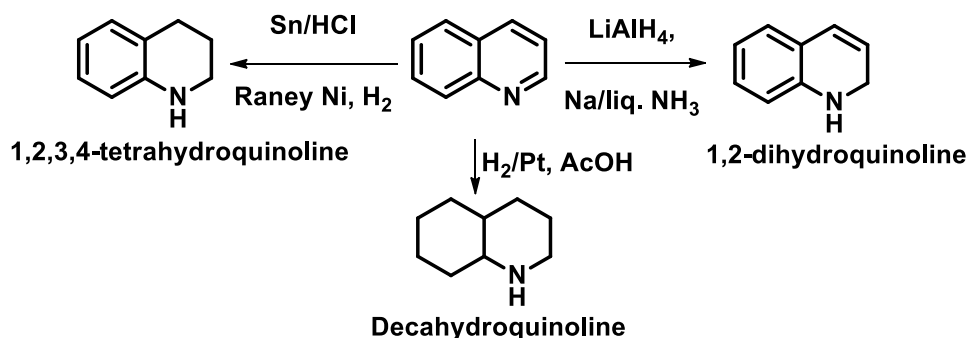


3.11.6b. Reactions of Quinoline

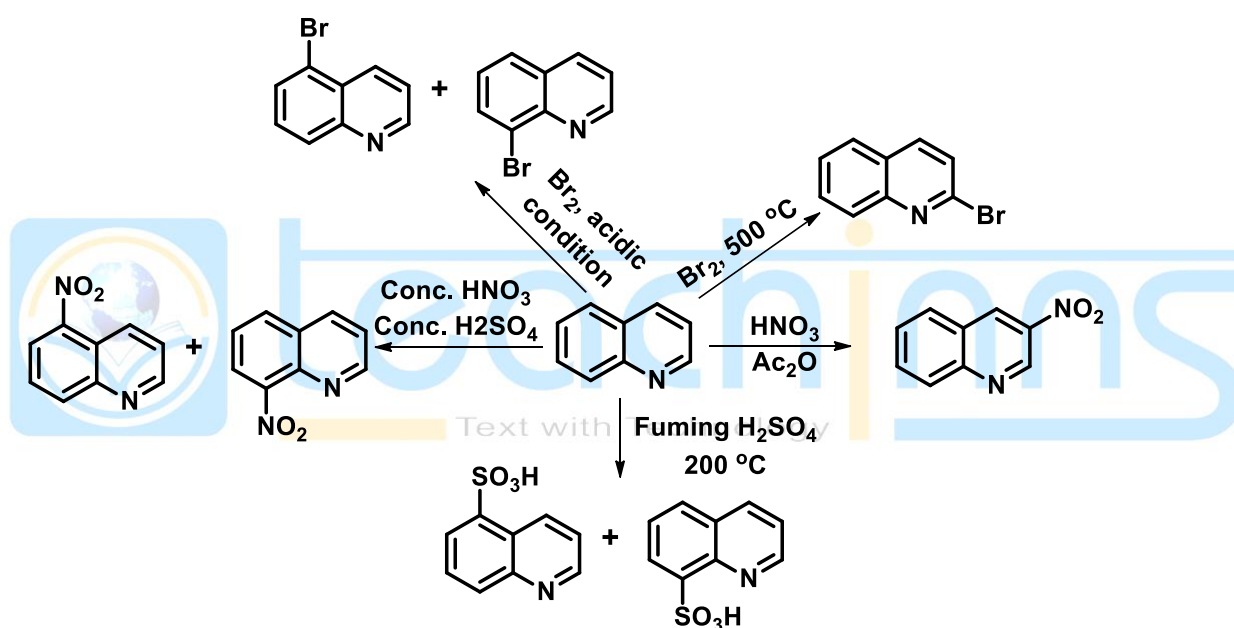
(1) **Oxidation:** quinoline is oxidized to nicotinic acid by the reaction with KMnO_4 and it reacts perbenzoic acid to form quinoline N-oxide.



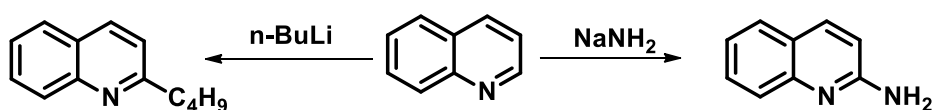
(2) **Reduction:** Quinoline undergoes reduction reaction under various reaction condition and affords partially- and fully-reduced products.



(3) **Electrophilic substitution reactions:**



(4) **Other reactions:**

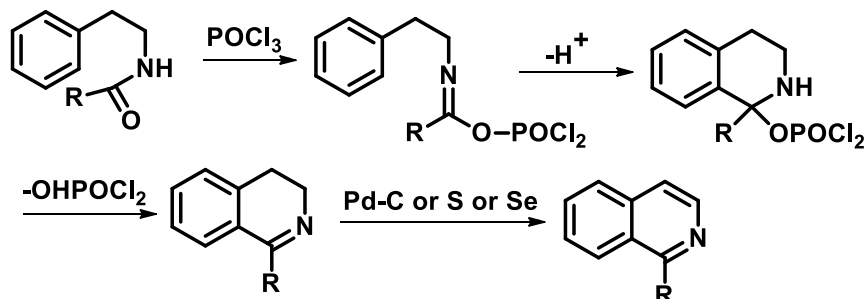


3.11.7. Isoquinoline

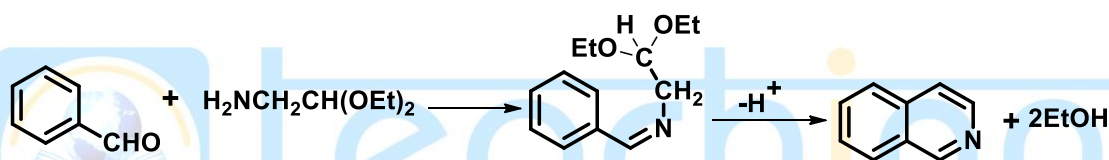
- This is a bicyclic heterocyclic compound with nitrogen atom as the heteroatom and it is isomeric with quinoline.

3.11.7a. Synthesis of Isoquinoline

(1) **Bischler-Napieralski synthesis:** This reaction involves the cyclodehydration of an acyl derivative of β -phenylethylamine.

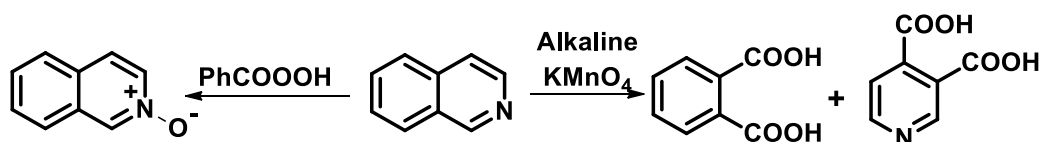


(2) **Pomeranz-Fritsch synthesis:** This reaction involves the cyclization of a Schiff's base which is formed by the condensation reaction of an aromatic aldehyde and aminoacetal, in presence of catalytic amount of an acid.

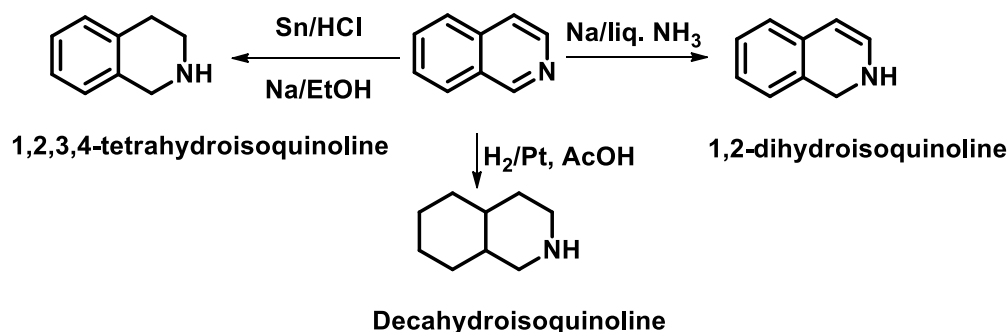


3.11.7b. Reactions of Isoquinoline

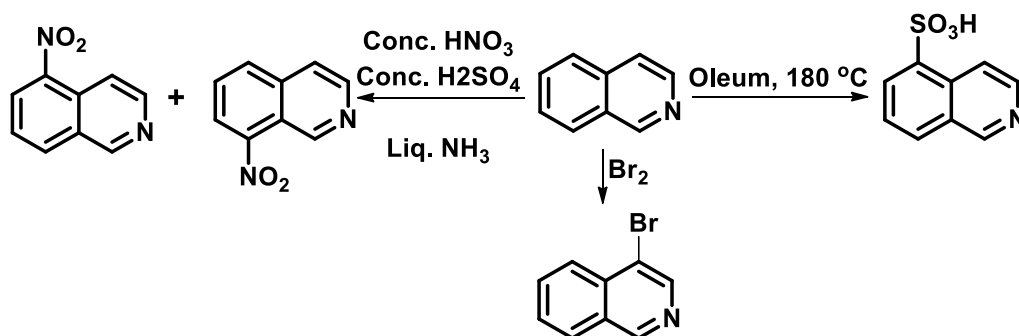
(1) **Oxidation:** Isoquinoline is oxidized in presence of alkaline KMnO_4 to afford phthalic acid and cinchomeric acid. Like pyridine, isoquinoline also produces the corresponding N-oxide under treatment with perbenzoic acid.



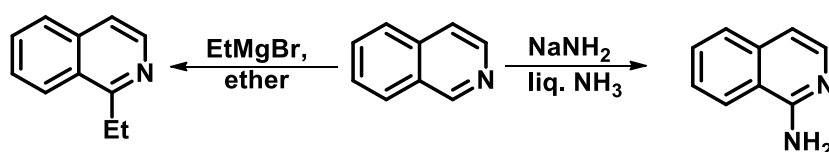
(2) **Reduction:**



(3) Electrophilic substitution reaction:



(4) Other reactions:

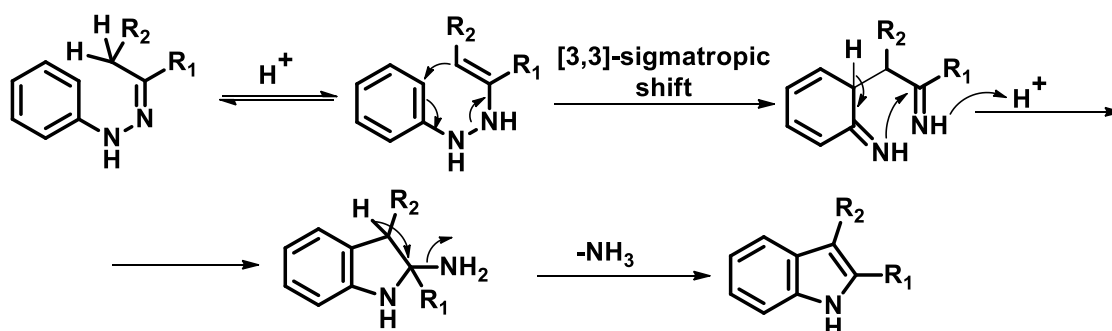


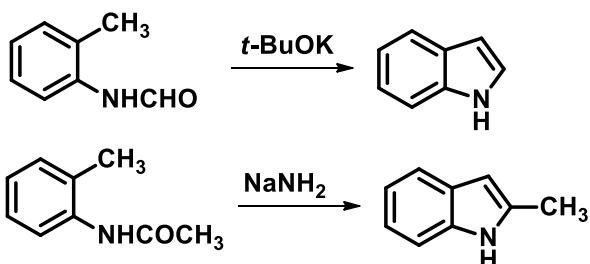
3.11.8. Indole

- Indole is a benzopyrrole, a bicyclic heterocyclic compound containing nitrogen as the hetero atom.

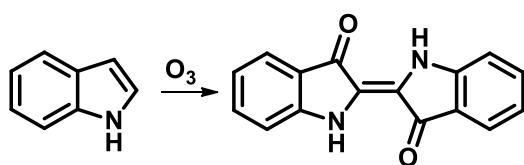
3.11.8a. Synthesis of Indole

(1) **Fischer's indole synthesis:** Phenyl hydrazones which has an α -methylene group upon treatment with mineral acid undergoes ring closure reaction followed by [3,3] sigmatropic shift and loses ammonia to ultimately afford indole.

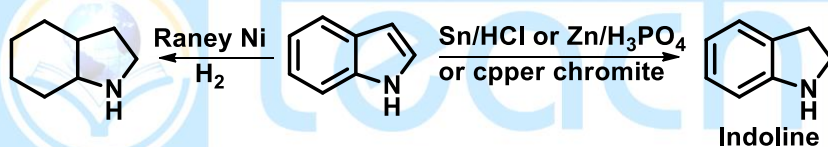


(2) **Madelung synthesis:****Reactions of indole:**

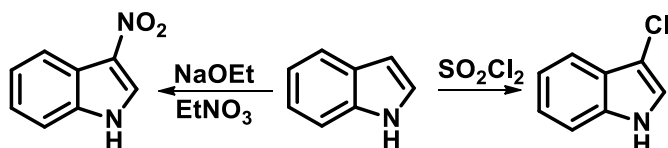
(1) **Oxidation:** Indole is oxidized to produce indigotin in presence of ozone.



(2) **Reduction:** Indole is reduced to indoline and octahydroindole depending upon the reduction condition.



(3) **Electrophilic substitution reaction:** Normally, electrophilic substitution occurs in 3-position, if it is already blocked, then substitution occurs at 2-position. However, if both 2- and 3-positions are blocked, then, substitution occurs at 6-position.



(4) **Reimer-Tiemann reaction:** Under Reimer-Tiemann reaction condition, indole produces indole-3-carbaldehyde. It is also synthesized by Gattermann reaction and Vilsmier-Haack reaction.

