Heterocyclic Chemistry

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South Valley Univeristy
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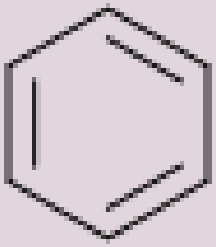
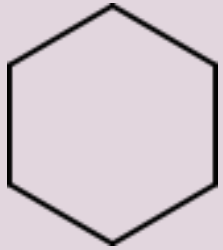
- Aromatic properties
- Nomenclature of heterocyclic compounds
- Furan
- Pyrrole
- Thiophene
- Pyridine
- Indole

WHAT IS HETEROCYCLIC CHEMISTRY?

What are carbocyclic compounds?

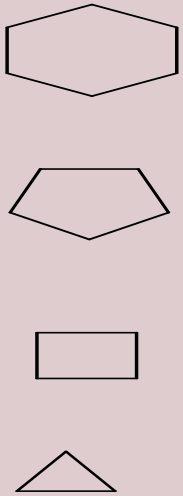
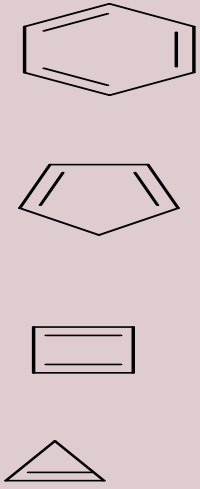


benzene



cyclohexane

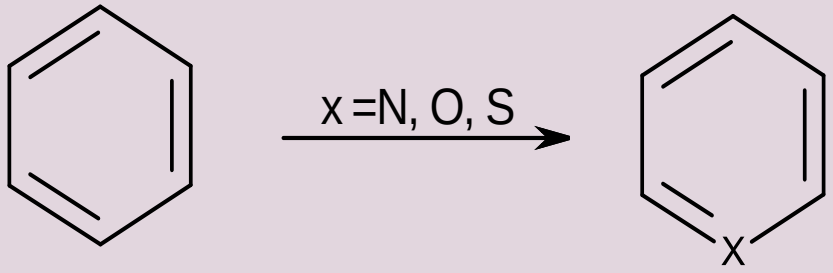
Carbocyclic Compound

Carboxylic Compound	
Cyclic Compound	Aromatic Compound
	

What's aheterocyclic compound?

If the ring system is made up of carbon atoms and at least one other element, the compound can be classified as hetero cyclic.

The elements that are found most commonly together with carbon in a ring system are Nitrogen (N), Oxygen(O), and Sulfur(S).



Heterocyclic Chemistry

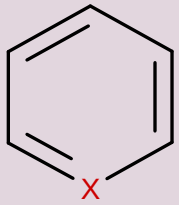
Heterocyclic compounds
are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom.

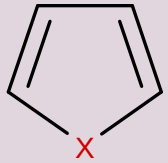
Heterocyclic Chemistry

Heterocyclic classification

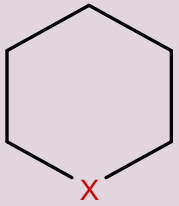
It can be classified into

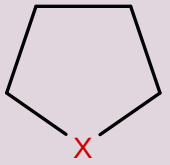
Heterocyclic compounds





Heteroaromatic



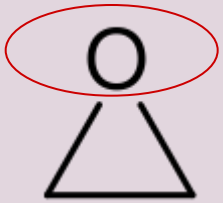


Heteroalicyclic

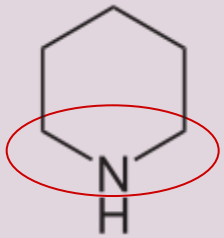
Heterocyclic Chemistry

Heterocyclic classification

1- Aliphatic heterocycles :-



Oxirane

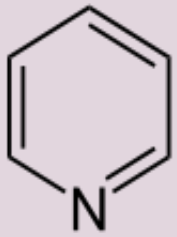


Piperidine

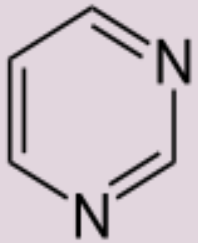
Heterocyclic Chemistry

2- Aromatic heterocycles :-

a- six-membered aromatic hetrocycles



Pyridine

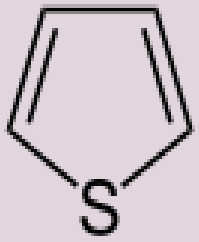


Pyrimidine

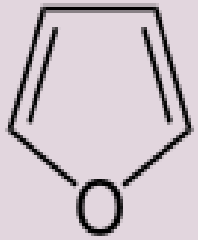
Heterocyclic Chemistry

2- Aromatic heterocycles :-

b- five-membered aromatic hetrocycles



Thiophen

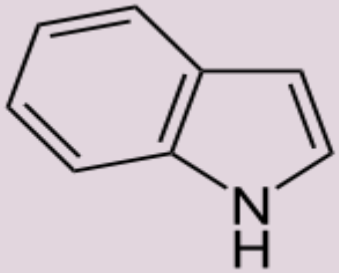


Furan

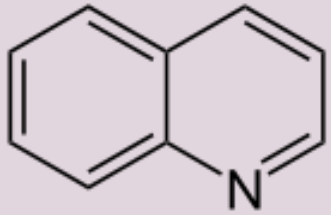
Heterocyclic Chemistry

2- Aromatic heterocycles :-

c- bicyclic heteroaromatic compounds



Indol



Quinoline

Heterocyclic Chemistry

Importantce and uses of Heterocyclic compounds:-

- *Biosynthesized*
- *Essential for life (haem, chlorophyll)*
- *Their metabolitis used as*
  - *toxin towords off predators*
  - *colouring agents to attact mates*

In general various important compounds such as:- alkaloids, vitamins, antibiotics, essential amino acids, hormones, drugs and dyes contain heterocyclic structure.

Heterocyclic Chemistry

- in general: nucleic acids, amino acids (proteins),
- feeding: proteins, carbohydrates, vitamins
- alkaloids: nicotine, caffeine

Application:

- antibiotics (penicillins, sulfonamides)
- insecticides (triazoles)
- herbicides (triazines, pyridines)

HETEROCYCLIC NOMENCLAUTURE

Nomenclature of heterocyclic compounds

- There are three systems for naming heterocylic compounds:

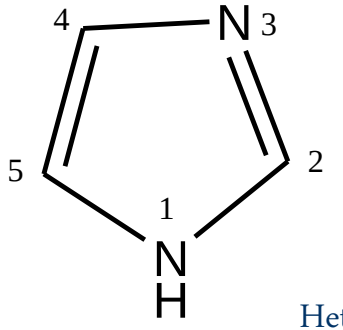
1) **The common nomenclature:** which convey little or no structural information but it still widely used.

2) **The Hantzsch-Widman (IUPAC or Systematic)** method which in contrast is designed so that one may deduce from it the structure of the compound.

I-Common Nomenclature

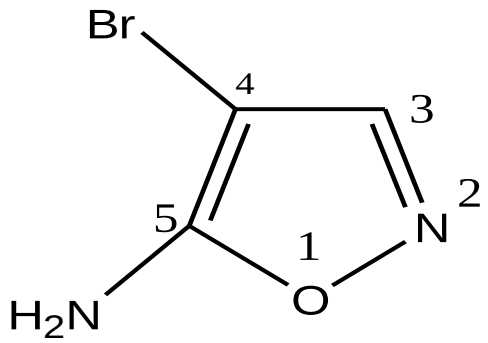
1) Each compound is given the corresponding trivial name (which should be memorized, see the following slides). This usually originates from the compounds occurrence, its first preparation or its special properties.

2) If there is more than one hetroatom of the same type numbering starts at the saturated one, e.g. imidazole.



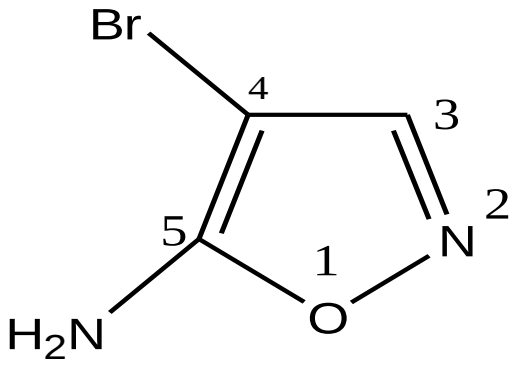
Common Nomenclature

3) If there is more than one type of the heteroatoms, the ring is numbered starting at the hetroatom of the higher priority (O>S>N) and it continues in the direction to give the other hetroatoms the lower numbers as possible.



Common Nomenclature

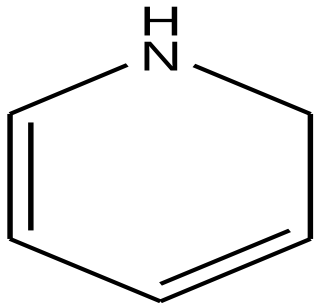
4) If substituents are present, their position should be identified by the number of the atoms bearing them and then they should be listed in alphabetical order.



5-Amino-4-bromoisoxazole

Common Nomenclature

5) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated trivial name.

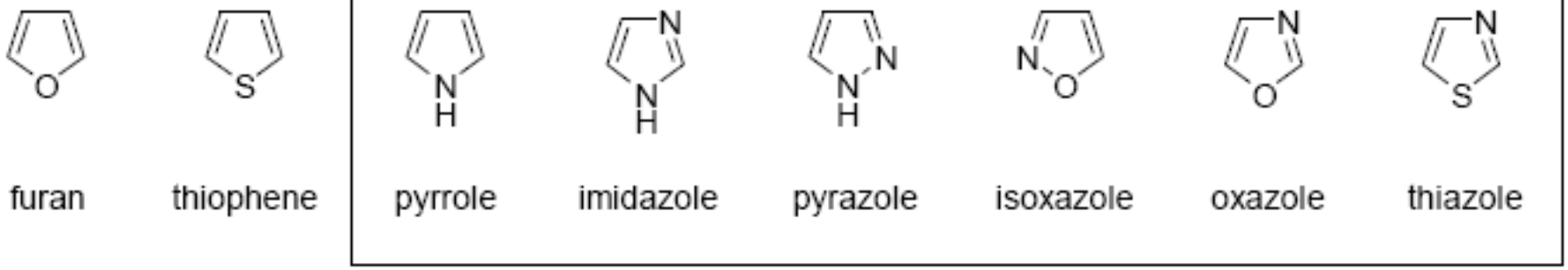


1,2-Dihydro-pyridine

Trivial names

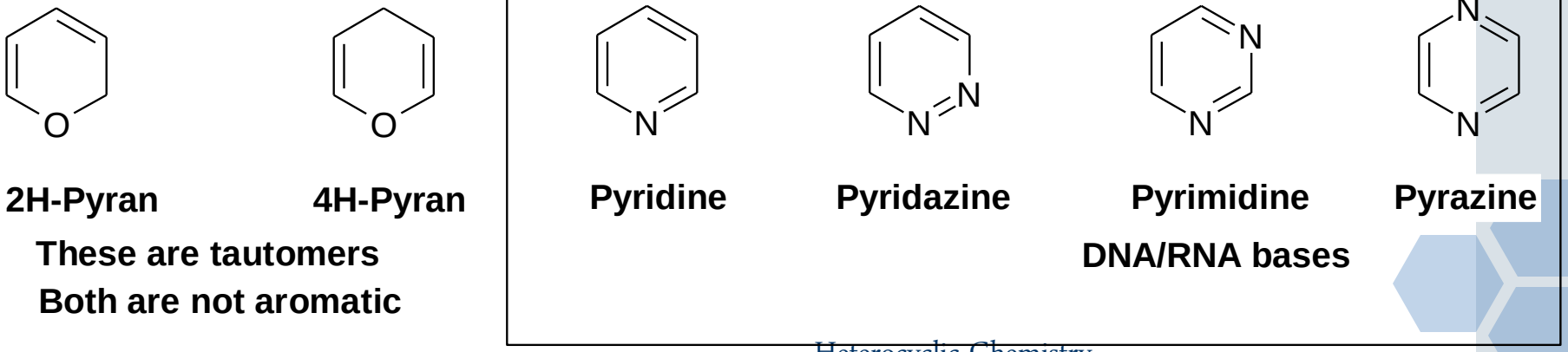
1) 5-membered heterocycles with one or two heteroatoms

common azoles - five-membered aromatic nitrogen heterocycles



2) 6-membered heterocycles with one or two heteroatoms

Common azines-six-membered aromatic nitorgrn heterocycles



These are tautomers

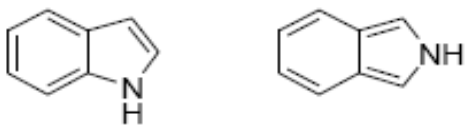
Both are not aromatic

DNA/RNA bases

Trivial Names

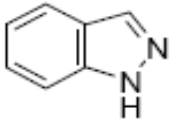
3) Fused heterocycles

common ring-fused azoles

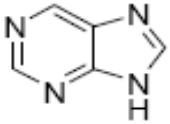


indole (found in the amino acid tryptophan)

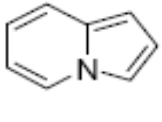
isoindole



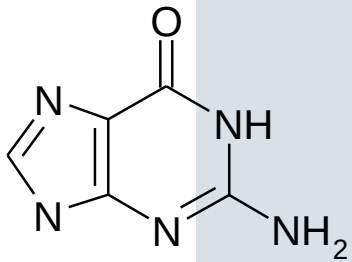
indazole



purine (DNA/RNA base)

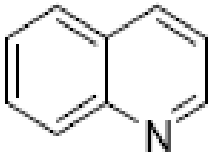


indolizidine

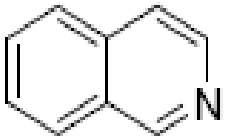


Guanine

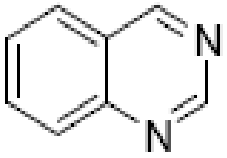
common ring-fused azines



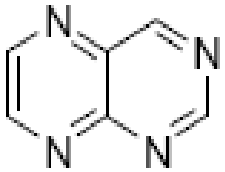
quinoline



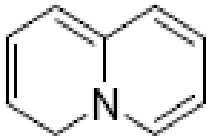
isoquinoline



quinazoline

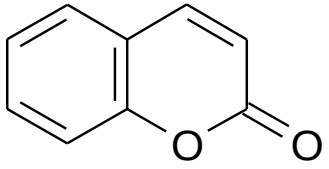


pteridine (found in the B vitamin riboflavin)

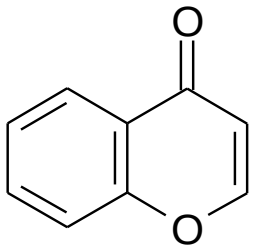


quinolizidine

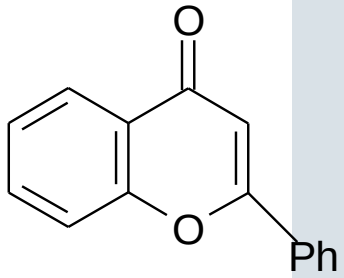
Trivial Names



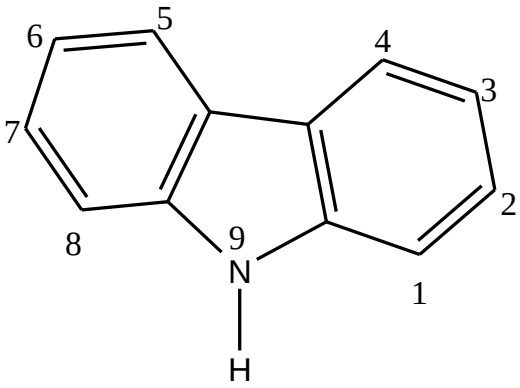
Coumarine
Chromen-2-one



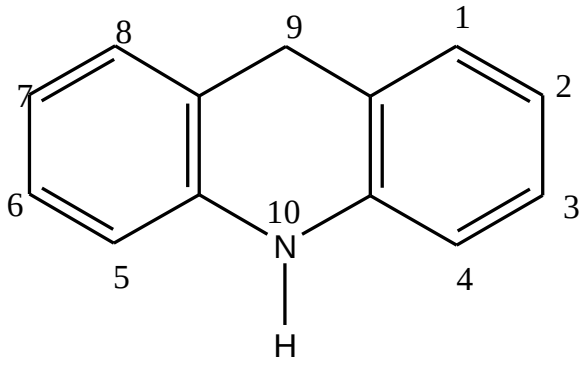
Chromen-4-one



Flavone



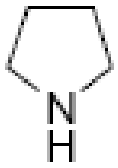
9H-Carbazole



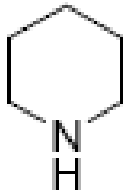
9,10-Dihydro-acridine

Trivial Names

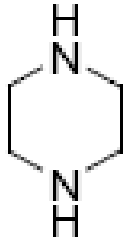
4) Saturated heterocycles



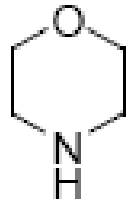
pyrrolidine



piperidine



piperazine



morpholine

II-Hantzsch-Widman nomenclature (IUPAC)

- Hantzsch-Widman nomenclature is named after the German chemists Arthur Hantzsch and Oskar Widman, who proposed similar methods for the systematic naming of heterocyclic compounds in 1887 and 1888 respectively.

- According to this system three to ten-membered rings are named by combining the appropriate prefix (or prefixes) that denotes the type and position of the heteroatom present in the ring with suffix that determines both the ring size (depending on the total number of atoms in the ring) and the degree of unsaturation (note that fully saturated and fully unsaturated have certain rules for nomenclature while partially unsaturation will be indicated in certain ways). In addition, the suffixes distinguish between nitrogen-containing heterocycles and heterocycles that do not contain nitrogen

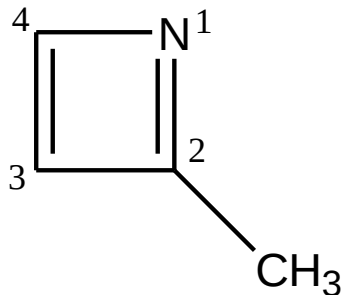
- **IUPAC name = locants +Prefix + suffix**

Hantzsch-Widman rules for fully saturated and fully unsaturated heterocycles

1) Identify the hetroatom present in the ring and choose from (table 1 on slide 11) the corresponding prefix (e.g. thia for sulfur, aza for nitrogen and oxa for oxygen).

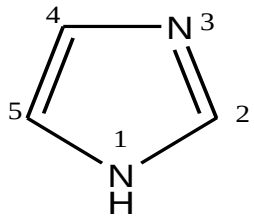
2) The position of a single heteroatom control the numbering in a monocyclic compound. The heteroatom is always assigned position 1 and if substituents present are then counted around the ring in a manner so as to take the lowest possible numbers.

For example:



Hantzsch-Widman rules

3) A multiplicative prefix (di, tri, ect.) and locants are used when two or more similar heteroatoms contained in the ring(two nitrogen indicated by diaza) and the numbering preferably commenced at a saturated rather than an unsaturated atom, as depicted in the following example: 1,3-diaza….

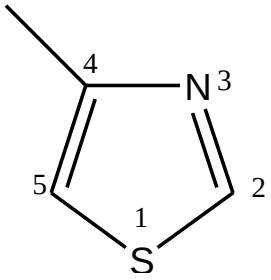


4) If more than one type of hetroatoms present in the ring the name will include more than one prefix with locants to indicate the relative position of the heteroatoms.

- Atom prefixes have a strict order of priority (preference) in which they are to be listed. For example,‘’Oxa’’(for oxygen) always comes before ‘’aza’’ (for nitrogen) in a name (see table 1).
- When combining the prefixes (e.g. oxa and aza) two vowels may end up together, therefore the vowel on the end of the first part should be omitted (oxaza).

Hantzsch-Widman rules

- The numbering is started from the heteroatom of the highest priority in such a way so as to give the smallest possible numbers to the other heteroatoms in the ring (the substituents are irrelevant). For example the prefix corresponding to the following compound is 4-Methyl-1,3-Thiaza….



5) Choose the appropriate suffix from (table 2) depending on whether or not nitrogen atom is present in the ring, the size of the ring and presence or absence of any double bonds

6) Combine the prefix(s) and suffix together and drop the first vowel if two vowels came together.

Hantzsch-Widman rules

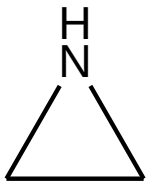
Table 2

Ring size	N-present		N-absent	
	Unsat	sat	Unsat	sat
	irine	iridine	irene	irane
	ete	etidine	ete	etane
	ole	olidine	ole	olane
	ine	a	in	ane
	epine	a	epin	epane
	ocine	a	ocin	ocane
9	onine	a	onin	onane
10	ecine	a	ecin	ecane

a: means use the prefix perhydro followed by the fully unsaturated name

Hantzsch-Widman rules

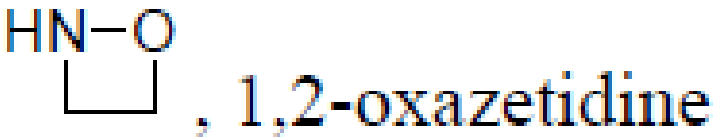
- Examples



- This ring contains (N) ⟹ Prefix is aza
- The ring is 3-membered and fully saturated ⟹ suffix is iridine
- By combining the prefix and suffix, two vowels ended up together (azairidine), therefore the vowel on the end of the first part should be dropped. This gives the correct name: **Aziridine**

III-Hantzsch-Widman nomenclature (IUPAC)

- **Example 2:**

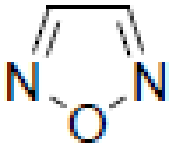


, 1,2-oxazetidine

- **This ring contains nitrogen = aza-**
- **And oxygen = oxa-**
- **And is a fully saturated four-membered**
- **ring = -etidine**
- **Drop the vowels in oxa & aza**
- **The name = 1,2-Oxazetidine**

III-Hantzsch-Widman nomenclature (IUPAC)

- **Example 3:**

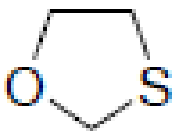


, 1,2,5-oxadiazole

- **This ring contains nitrogen = aza-**
- **And oxygen = oxa-**
- **And Unsaturated five-membered rings with nitrogen = –ole**
- **Oxygen is higher priority than nitrogen, so it is in position 1.**
- **The two nitrogens are therefore at positions 2 and 5**
- **The name = 1,2,5-Oxadiazole**

III-Hantzsch-Widman nomenclature (IUPAC)

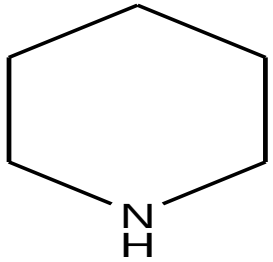
- **Example 4:**



, 1,3-oxathiolane

- **This ring contains sulpher= thia-**
- **And oxygen = oxa-**
- **And saturated five-membered rings without nitrogen = –olane**
- **Oxygen is higher priority than sulpher, so it is in position 1.**
- **Drop the vowel in thia**
- **The name = 1,3-Oxathiolane**

Hantzsch-Widman rules



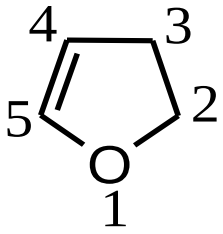
- The ring is 6-memberd, fully saturated with N
Prefix perhydro followed by the name of fully unsaturated 6-memberd ring with nitrogen azine

- Thus the full name is perhydroazine

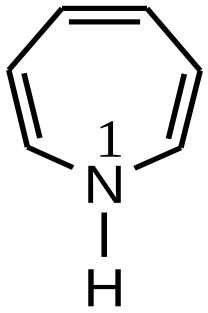
Hantzsch-Widman rules for partially unsaturated heterocycles

- **Partial unsaturation in heterocyclic compounds can be indicated by one of the following methods:**

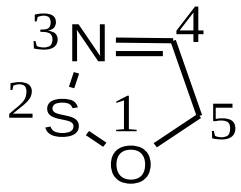
a) The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. 1*H*, 2*H*, etc.) followed by the name of maximally unsaturated ring.



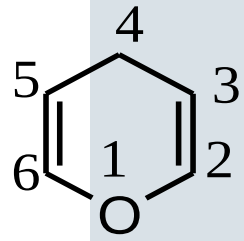
2*H*, 3*H*-Oxole



1*H*-Azepine



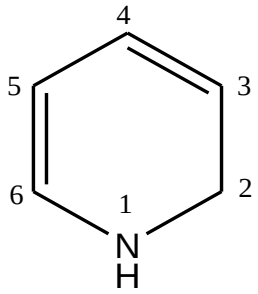
5H-1,2,3-Oxathiazole



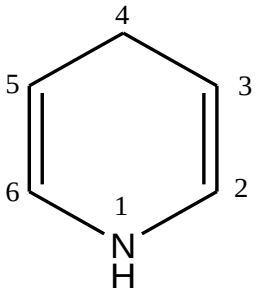
4*H*-Oxin

Hantzsch-Widman rules for partially unsaturated heterocycles

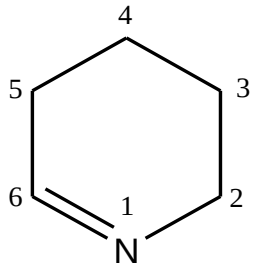
b) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



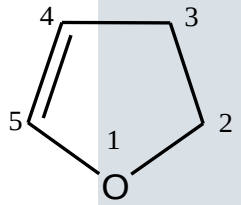
1,2-Dihydroazine



1,4-Dihydroazine



2,3,4,5-Tetrahydroazine



2,3-Dihydrooxole

Isomers have the same M.F. but differ in the position of the double bond

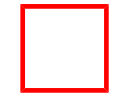
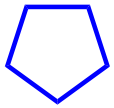
Hantzsch-Widman rules for partially unsaturated heterocycles

c) Alternatively, the partially unsaturated 4 and 5 rings (i.e. rings contain one double bond) are given special Hantzsch-Widman suffixes as in table 3 and the double bond is specified as Δ^1, Δ^2, Δ^3, etc.. Which indicates 1 and ; 2 and 3; 3 and 4 atoms respectively have a double bond

(i.e. **Name : Δ^x + Prefix + special suffix)**

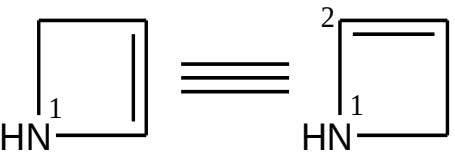
(x= locant of the double bond)

Table 3

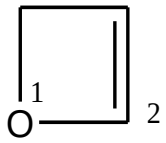
Ring size	With N	Without N
	-etine	-etene
	-oline	-olene

Hantzsch-Widman rules for partially unsaturated heterocycles

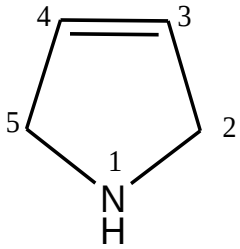
❖ Examples



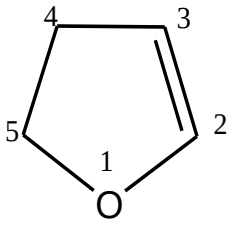
Δ^2 -Azetine



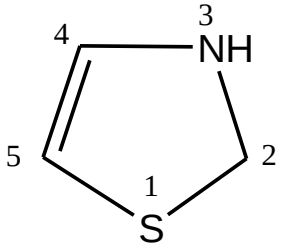
Δ^2 -Oxetene



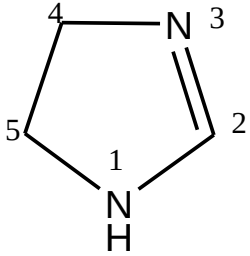
Δ^3 -Azoline



Δ^2 -Oxolene



Δ^4 -1,3-Thiazoline



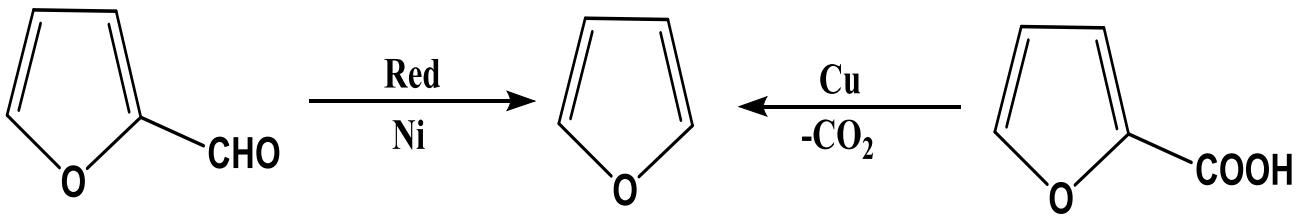
Δ^2 -1,3-Diazoline

Furan

Physical properties

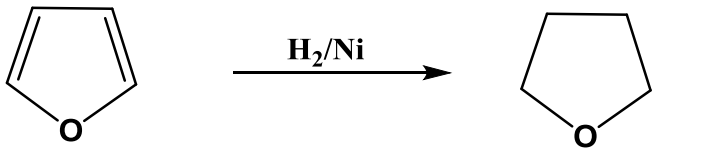
- **Furan may be as ethers but it is aromatic compoud because the lone pair of electrons on oxygen atom contribute in aromaticity.**
- **Furan has low melting point less than pyrrole because there's no hydrogen bonds.**
- **Furan is a liquid boiled at 31c and has odour as chloroform.**
- **Furan is springily soluble in water but it is miscible with most organic solvents.**

Preparation of furan



Reactions of furan

Reduction of furan ❖

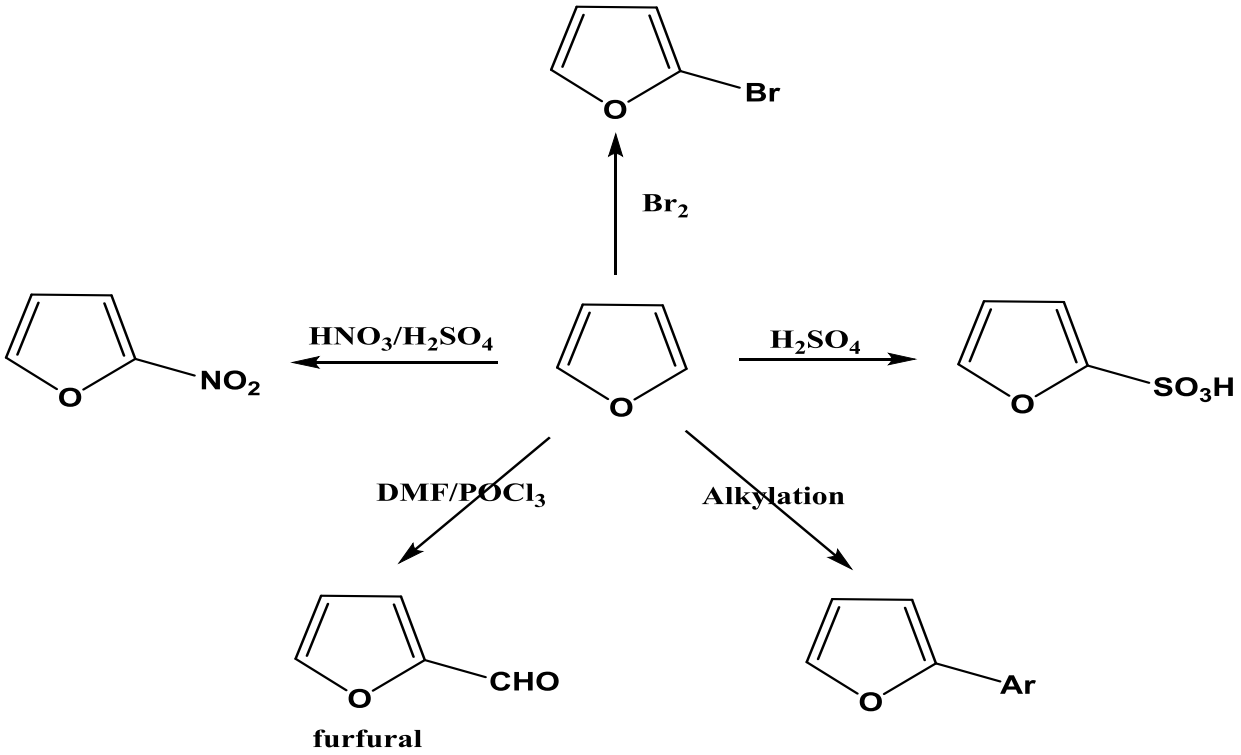


tetrahydro furan

Reactions of furan

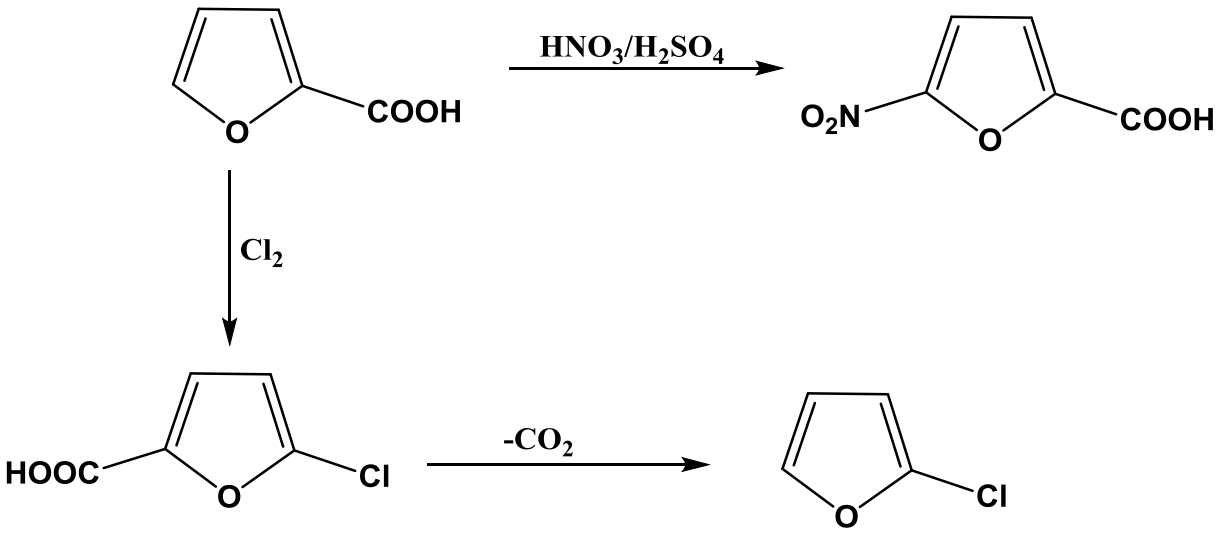
Electrophilic substitution reactions: ❖

The substitution occurred in position 2 ❖



Reactions of furan

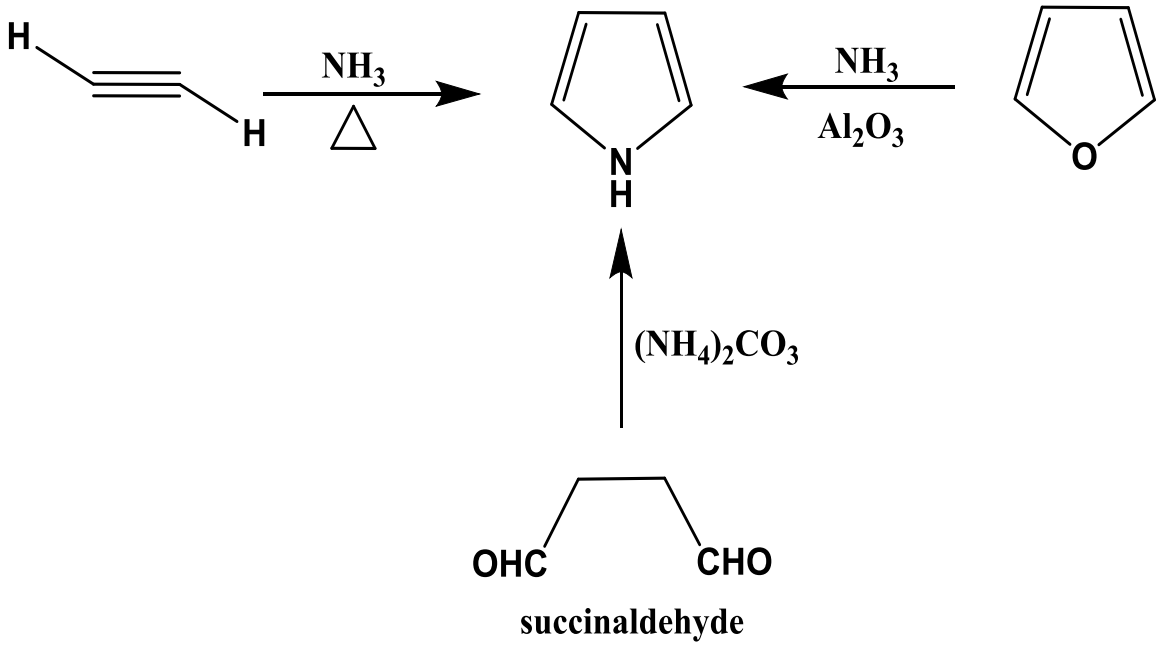
Reactions of furan-2-carboxylic acid:



Pyrrole

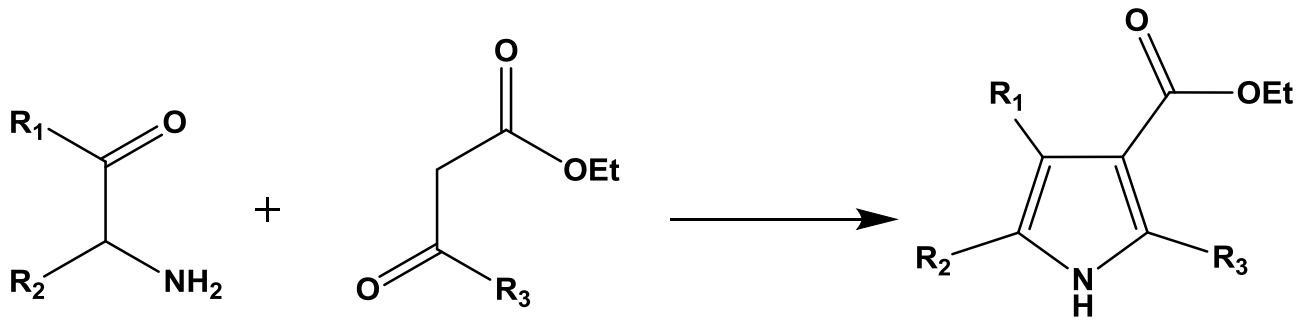
- Pyrrole is a colorless liquid which has an odour as chloroform.
- If it is exposed to air give brown color.
- The lone pairs of electrons on nitrogen atom contribute in aromatic properties.

Preparation of pyrrole



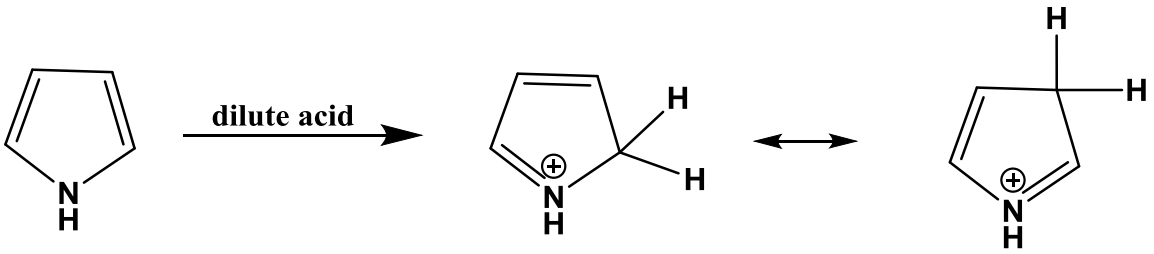
Preparation of pyrrole

Knorr synthesis:



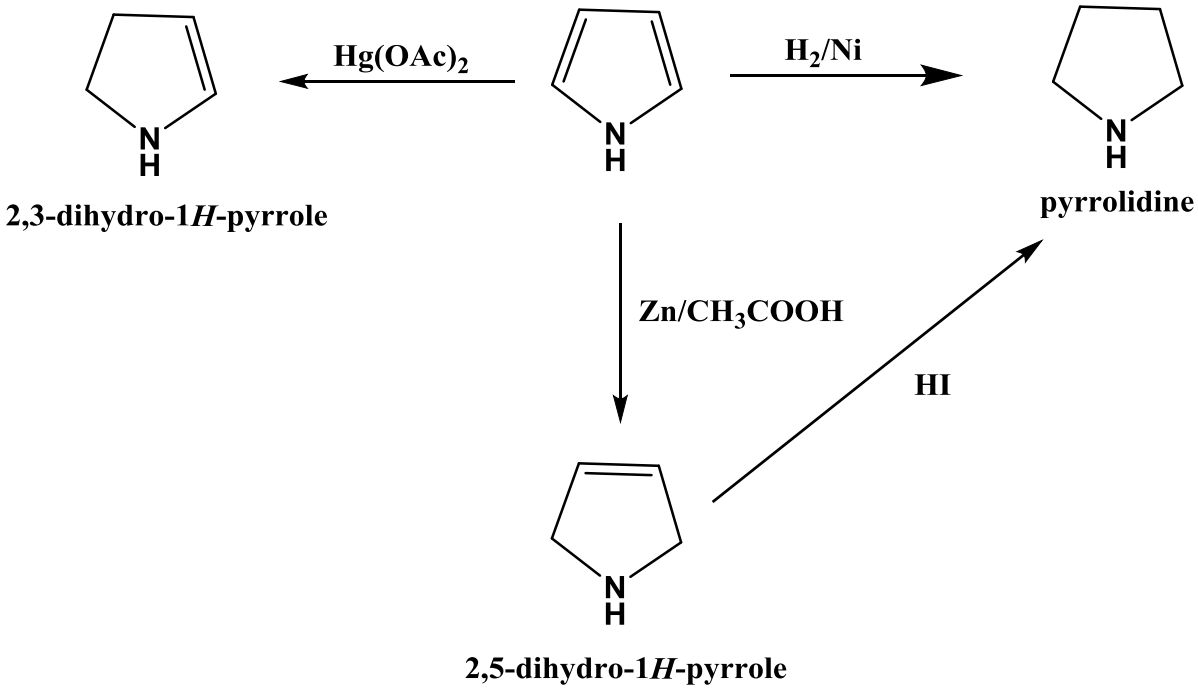
Reactions of pyrrole

Basicity:



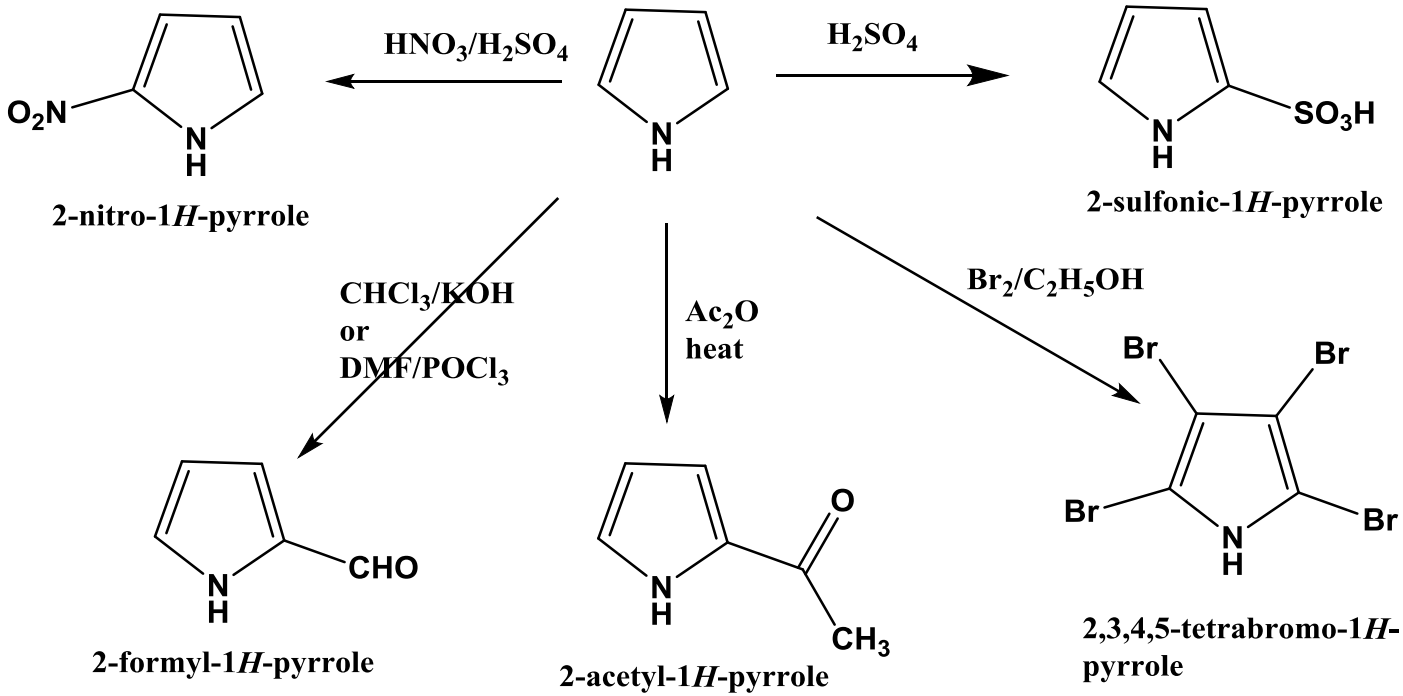
Reactions of pyrrole

Reduction of pyrrole:



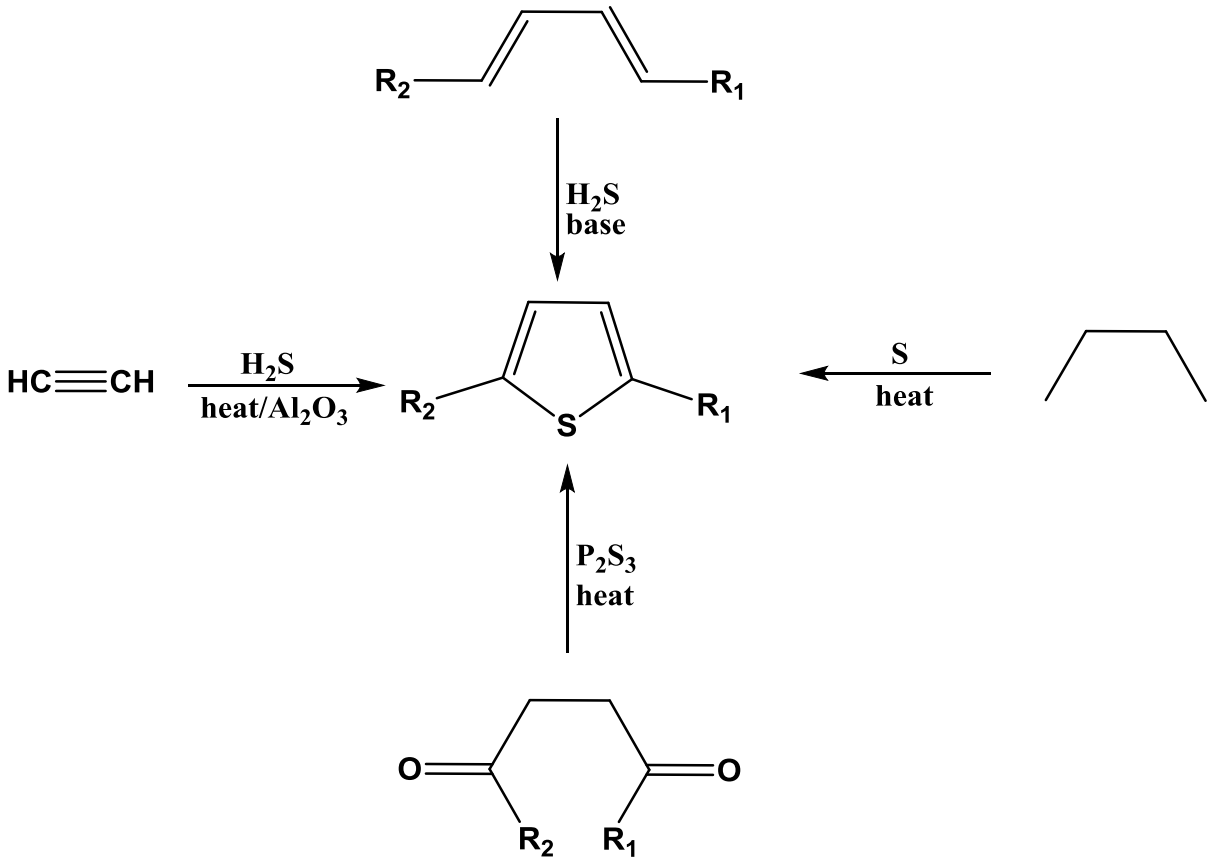
Reactions of pyrrole

Electrophilic substitution:



Thiophene

Preparation of thiophene

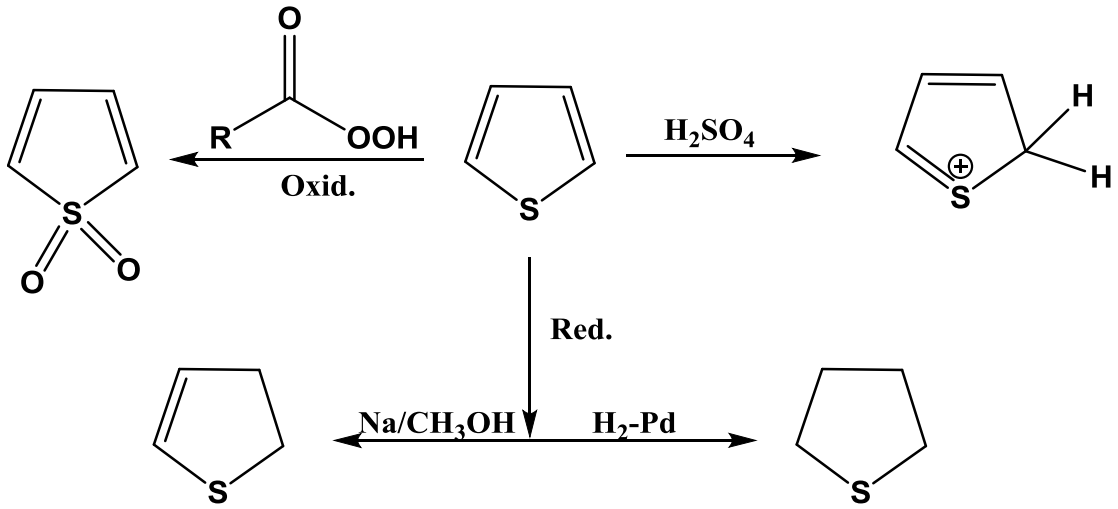


Reactions of thiophene

1- addition reactions.

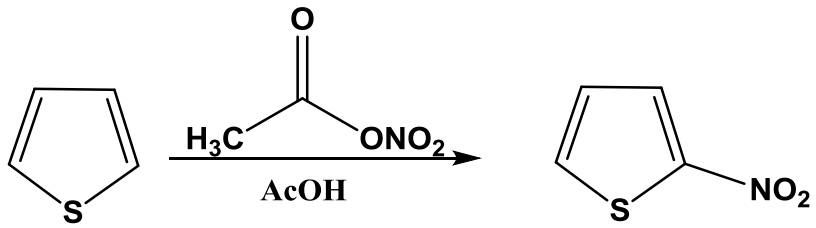
2- reduction reactions.

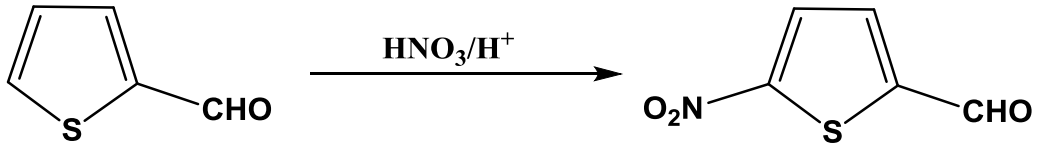
3- oxidation reactions.



Reactions of thiophene

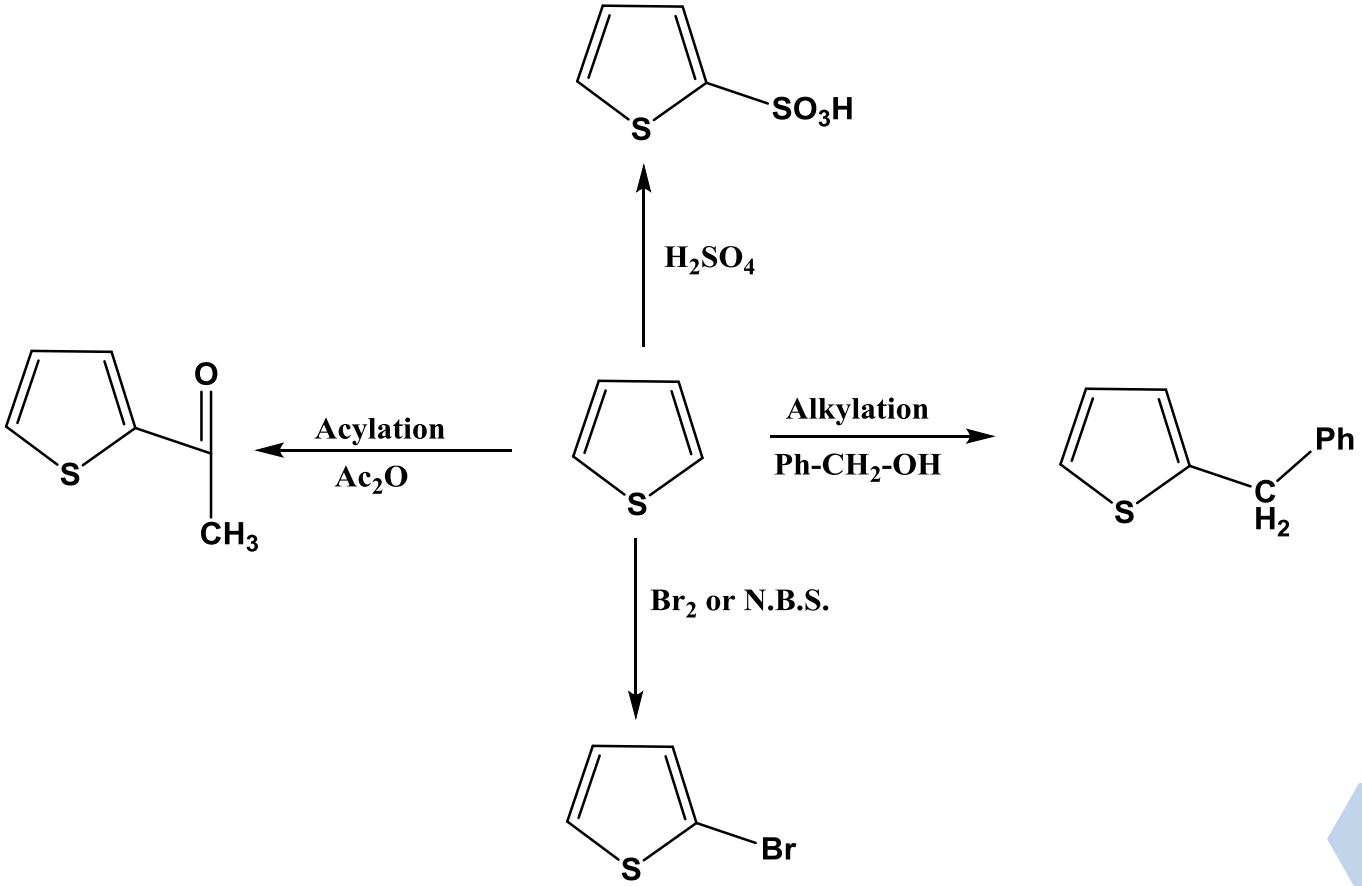
Electron withdrawing groups increase the stability of the ring and rate of reaction.





Reactions of thiophene

Electrophilic substitution reactions:



Pyridine

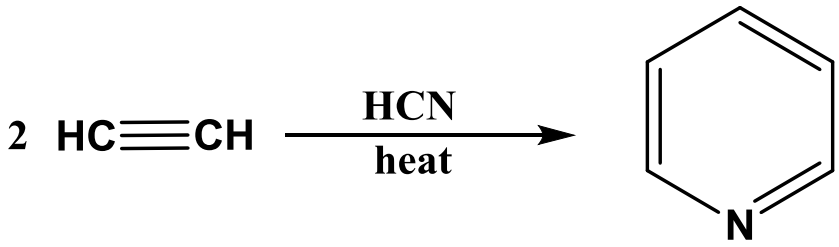
Physical properties

- In case of boiling point pyridine has less boiling point than pyrrole because the presence of hydrogen bonds in pyrrole.

- **But in case of basicity pyridine is more basic than pyrrole because the presence of free lone pairs of electrons on nitrogen atom, but in case of pyrrole the lone pairs of electrons contributed in aromaticity.**
- **Pyridine is used as a solvent in organic synthesis.**

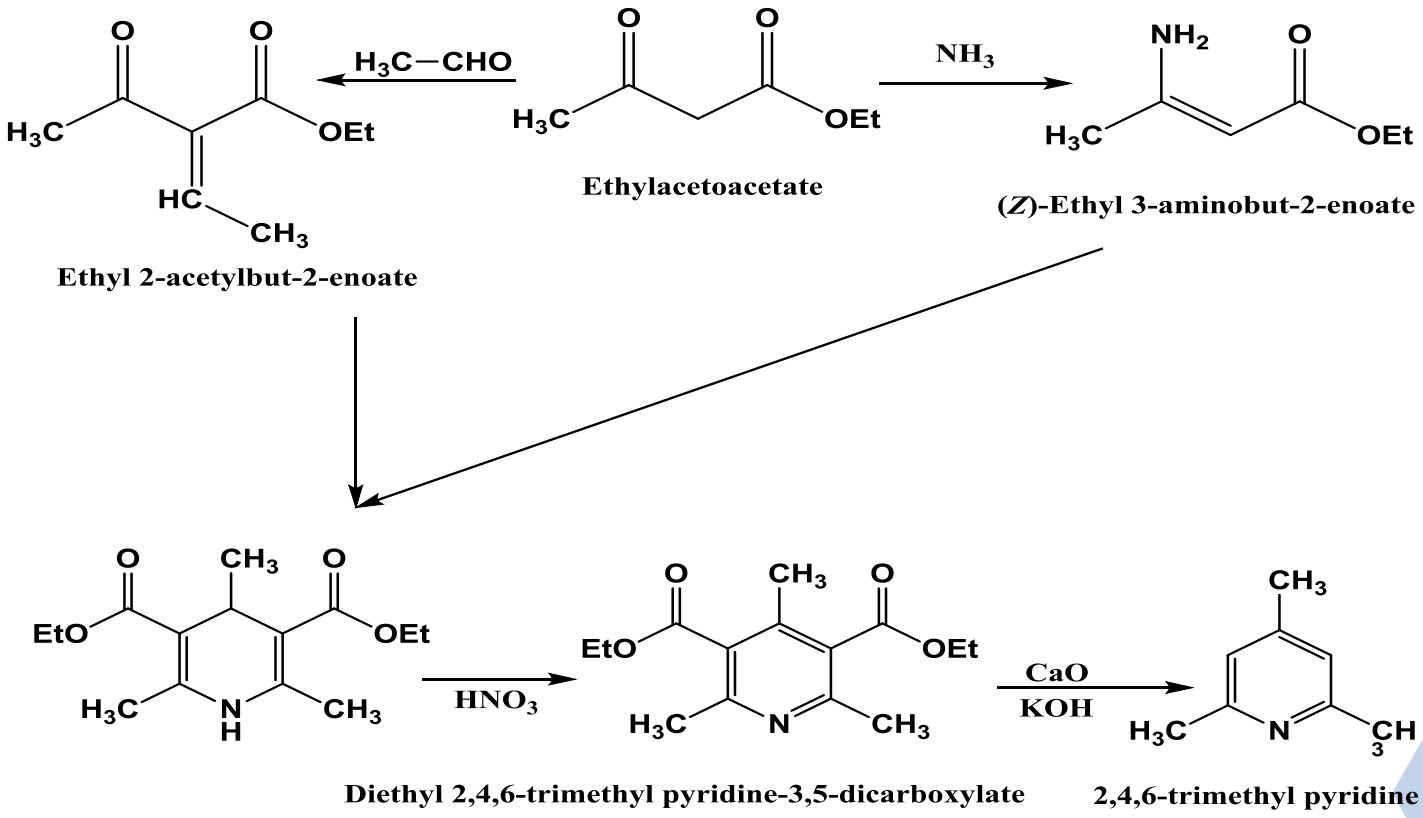
Preparation of pyridine

1- from acetylene:



Preparation of pyridine

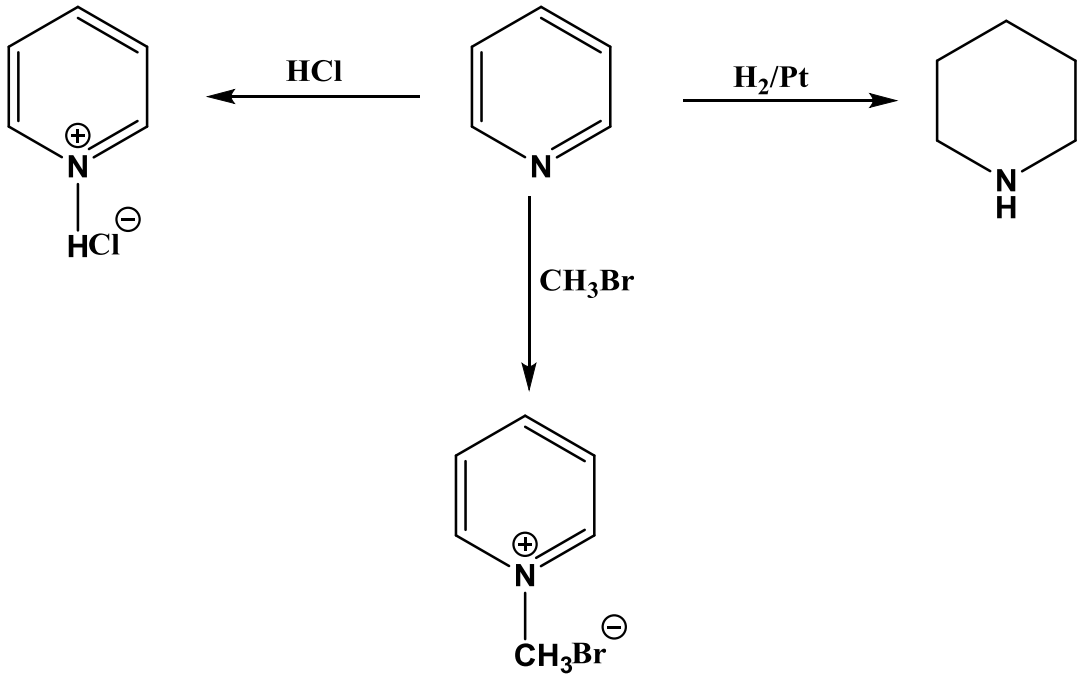
2- Hantzch synthesis:



Reactions of pyridine

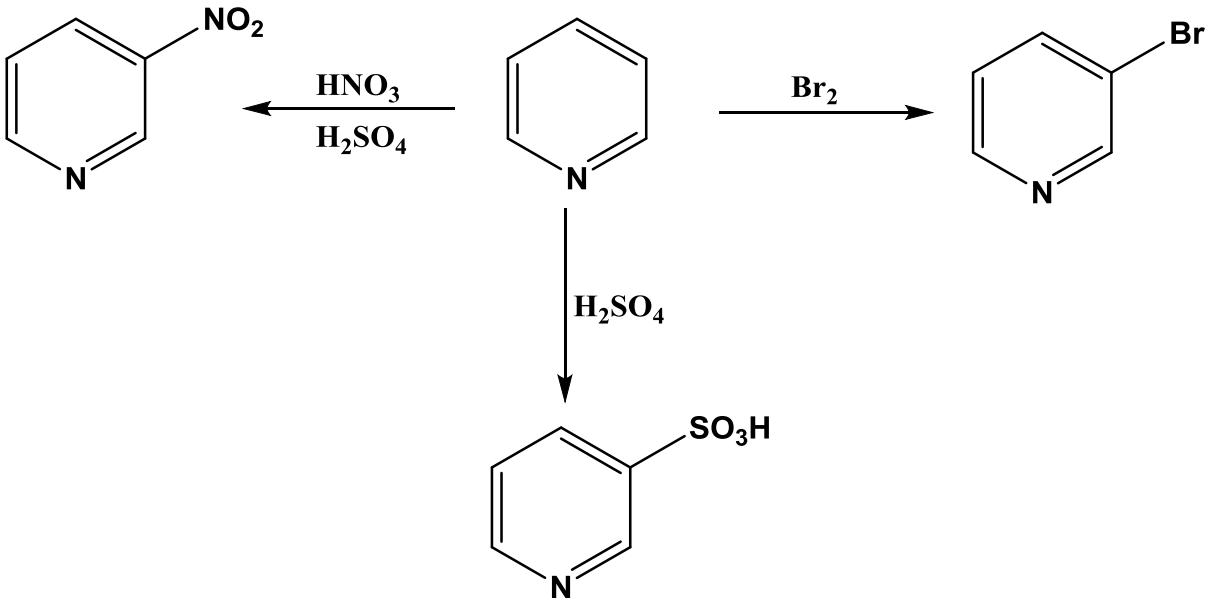
1- addition reactions:

A- reduction b- salt formation

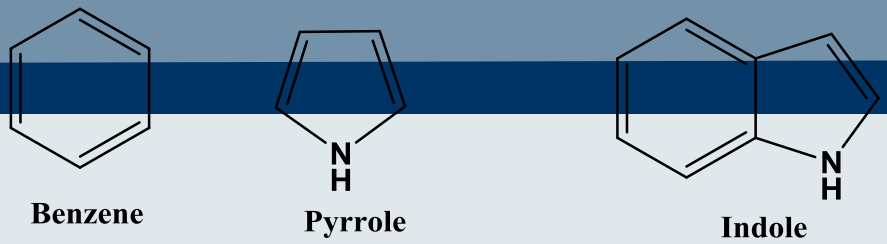


Reactions of pyridine

Electrophilic substitution reactions:



Indole



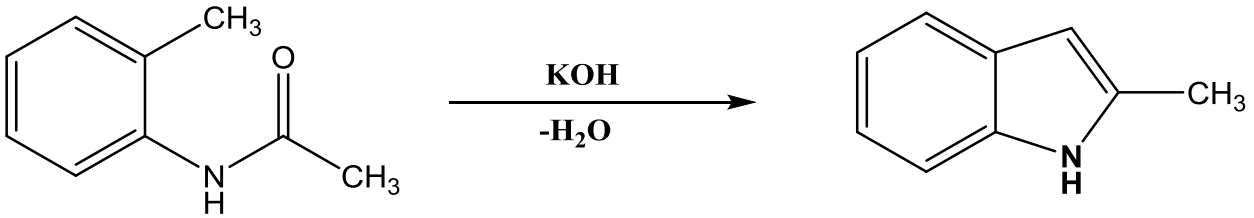
Benzene Pyrrole Indole

Physical properties

- Indole is a solid compound has melting point at 52c.
- More stable than pyrrole because of its molecular weight.
- Electrophilic substitution preferred position 3 than position 2.
- It is present in dyes and proteins.

Preparation of Indole

1- Madelung Synthesis

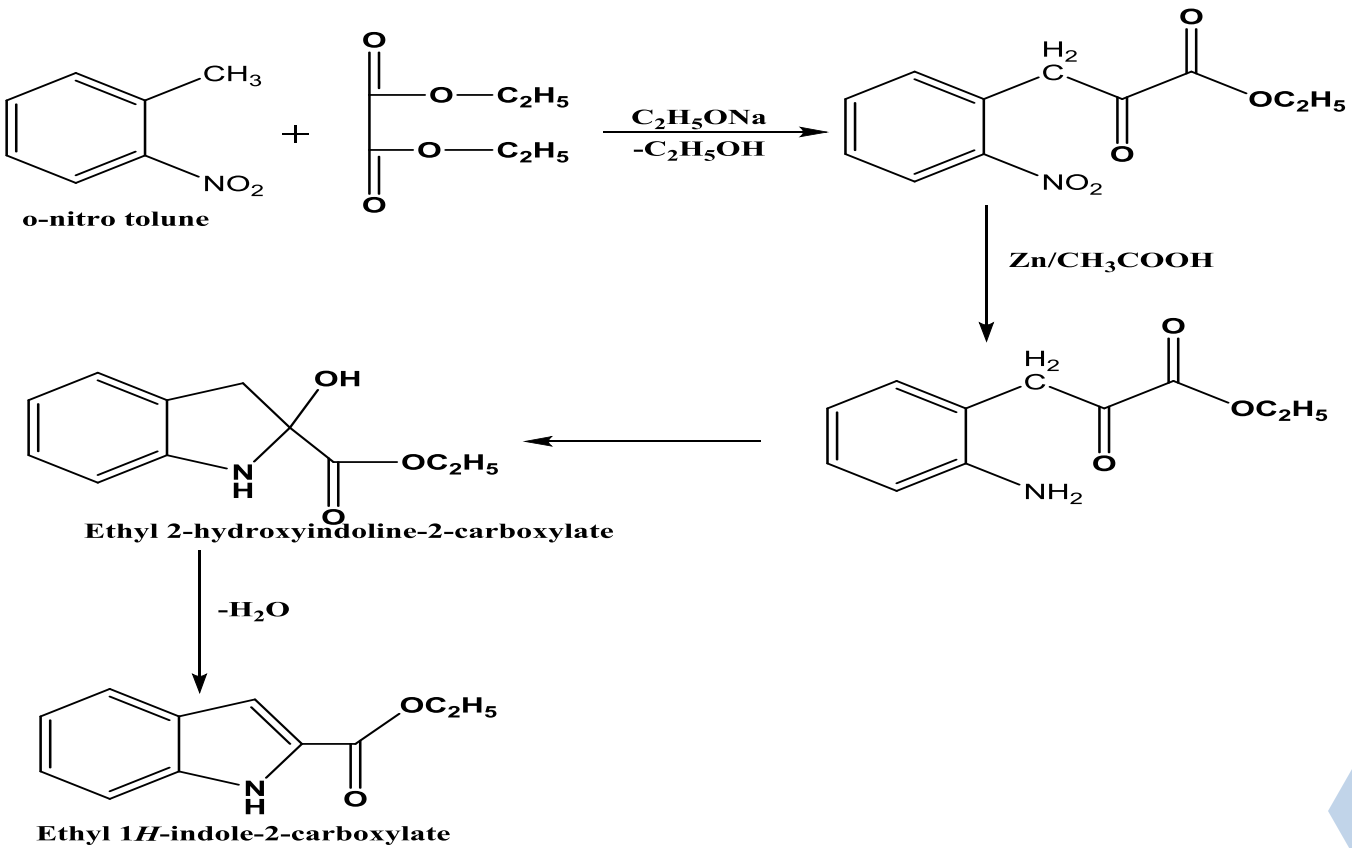


N-o-tolylacetamide

2-methyl indole

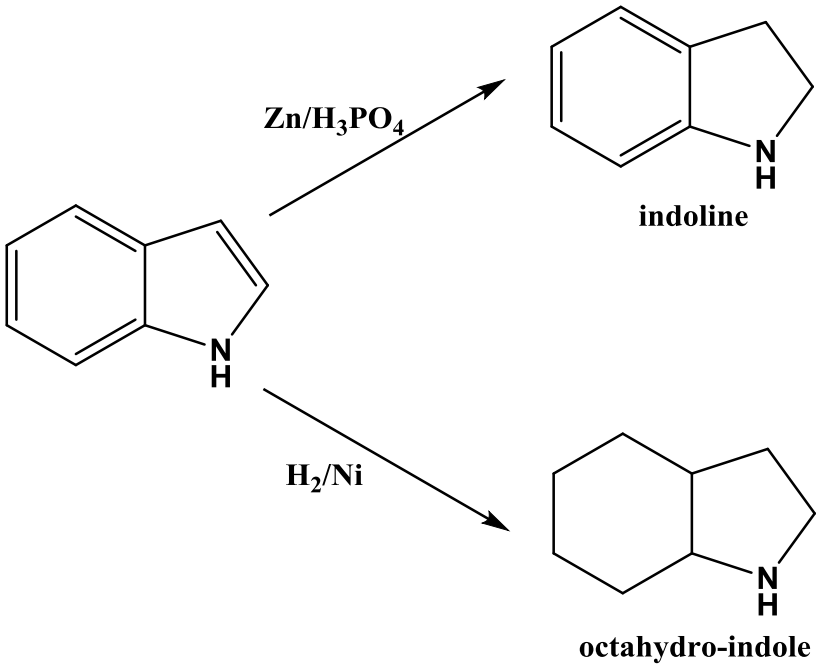
Preparation of indole

2- Reissert Synthesis



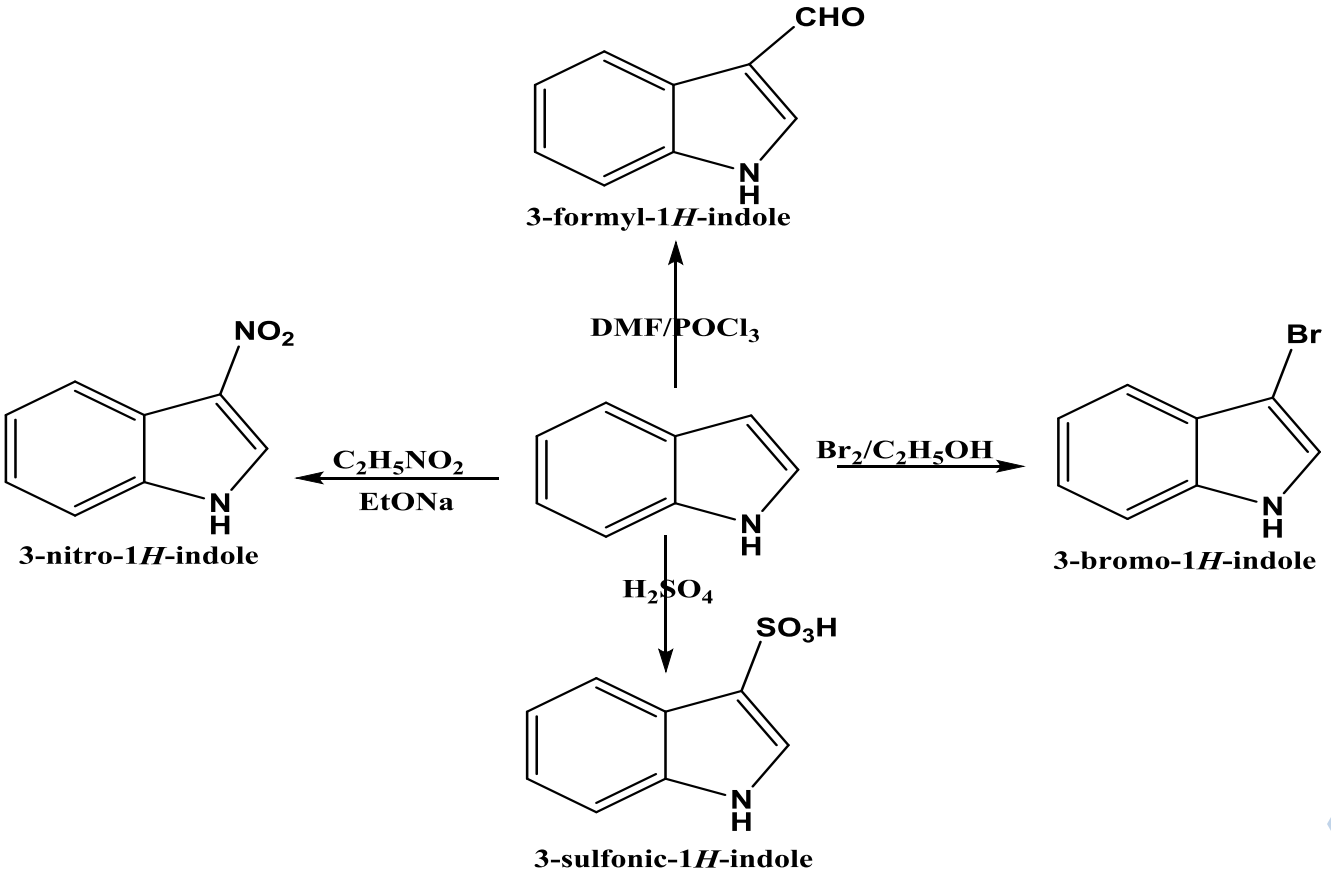
Reactions of indole

Reduction of indole:



Reactions of indole

Electrophilic substitution reactions:



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- 2- Comprehensive Heterocyclic Chemistry III: Alan Katritzky, Christopher Ramsden, Eric Scriven, Richard Taylor (2008).
- 3- Heterocyclic Chemistry I, Mahndra Kumar, Fandana Jupta, Radha Ar. Jupta (2011).
- 4- Heterocyclic Chemistry II, Mahndra Kumar, Fandana Jupta, Radha Ar. Jupta (1998).

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- 5- Advances in Heterocyclic Chemistry, Eric F. V. Scriven, (2016).
- 6- Modern Heterocyclic Chemistry, Julio Alvarez-Builla, Juan J. Vaquero, and Jose Barluenga, (2011).
- 7- The Chemistry of Heterocyclic compounds, R. Ian Fryer, (1991).