Heterocyclic Chemistry

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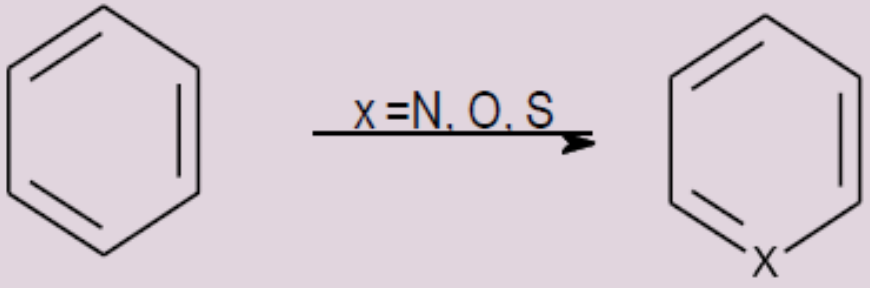
What's aheterocyclic compound?

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).



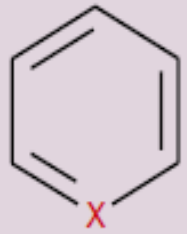
Heterocyclic Chemistry

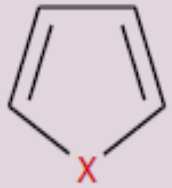
Heterocyclic compounds
are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom.

Heterocyclic classification

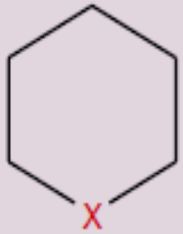
It can be classified into

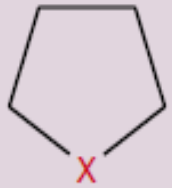
Heterocyclic compounds





Heteroaromatic

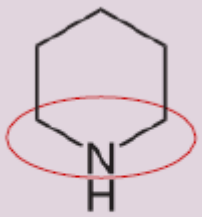




Heteroalicyclic

1- Heteroalicyclic or aliphatic heterocyclic

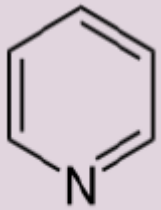
Oxirane



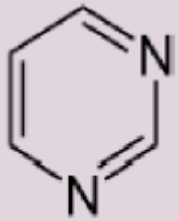
Piperidine

2- Aromatic heterocyclic :

A- Six-membered heteroaromatic compounds :

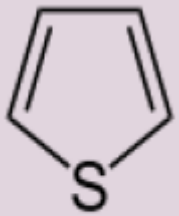


Pyridine



Pyrimidine

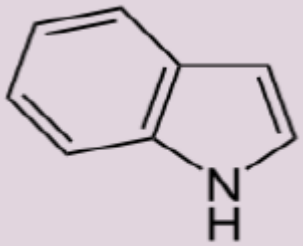
B- Five-membered heteroaromatic compounds :



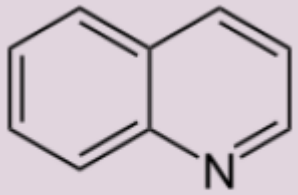
Thiophen

Furan

C- Bicyclic heteroaromatic compounds :

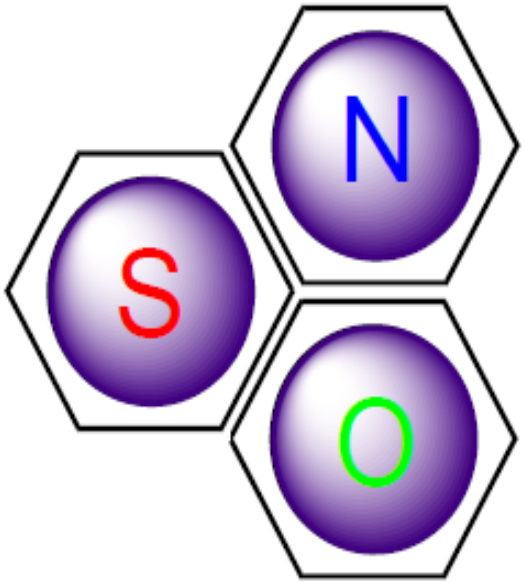


Indol



Quinoline

Heterocyclic Chemistry



Nomenclature of Heterocyclic compounds

Nomenclature of heterocyclic compounds

- Three systems for naming heterocylic compounds:

1- Common name

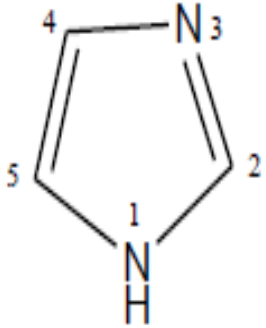
2- Replacement methaod

3- IUPAC or systematic method

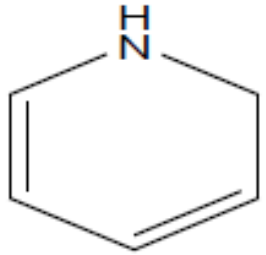
I- Common Nomenclature

- Each compound is given the corresponding trivial name. This usually originates from the compounds occurrence, its first preparation or its special properties.

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

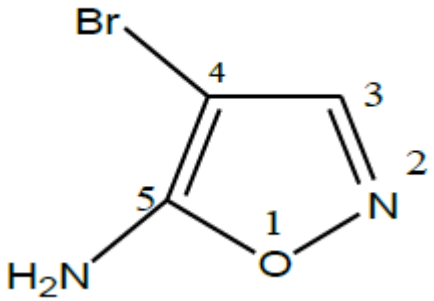


❖ The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated trivial name.

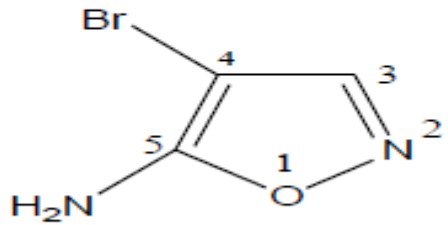


1,2-Dihydro-pyridine

❖ 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.



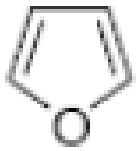
If subsituents present, their position should be identified by the number of the atoms bearing them and then they should be listed in alphabetical order.



5-Amino-4-bromoisoxazole

Trivial names

1) 5-membered heterocycles with one or two heteroatoms



furan

thiophene

pyrrole

imidazole

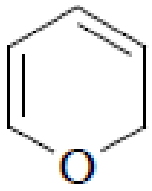
pyrazole

oxazole

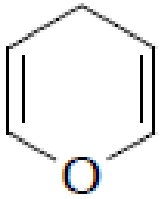
isoxazole

thiazole

2) 6-membered heterocycles with one or two heteroatoms



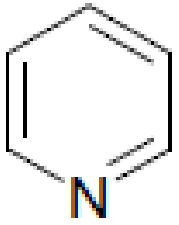
2H-Pyran



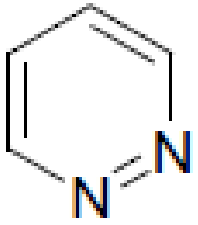
4H-Pyran

These are tautomers

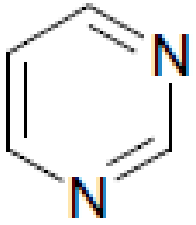
Both are not aromatic



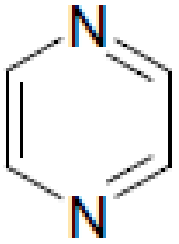
Pyridine



Pyridazine



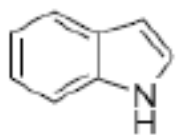
Pyrimidine



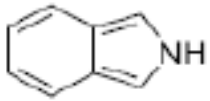
Pyrazine

3) Fused heterocycles

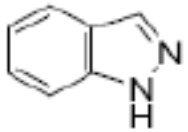
common ring-fused azoles



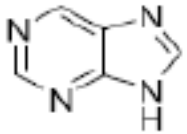
indole
(found in the amino acid tryptophan)



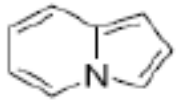
isoindole



indazole

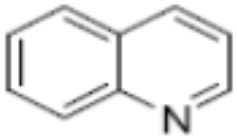


purine
(DNA/RNA base)

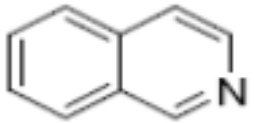


indolizidine

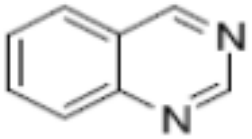
common ring-fused azines



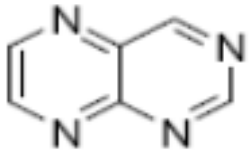
quinoline



isoquinoline

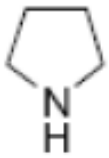


quinazoline

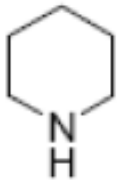


pteridine
(found in the B vitamin riboflavin)

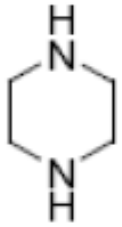
4) Saturated heterocycles



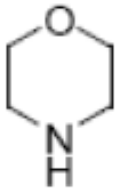
pyrrolidine



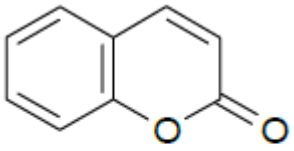
piperidine



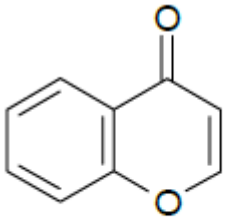
piperazine



morpholine



Coumarine
Chromen-2-one



Chromen-4-one

II- Replacement nomenclature

- Heterocycle's name is composed of the corresponding carbocycle's name and an elemental prefix for the heteroatom introduced (if more than one heteroatom is present they should be listed according to the priority order shown in (table 1).

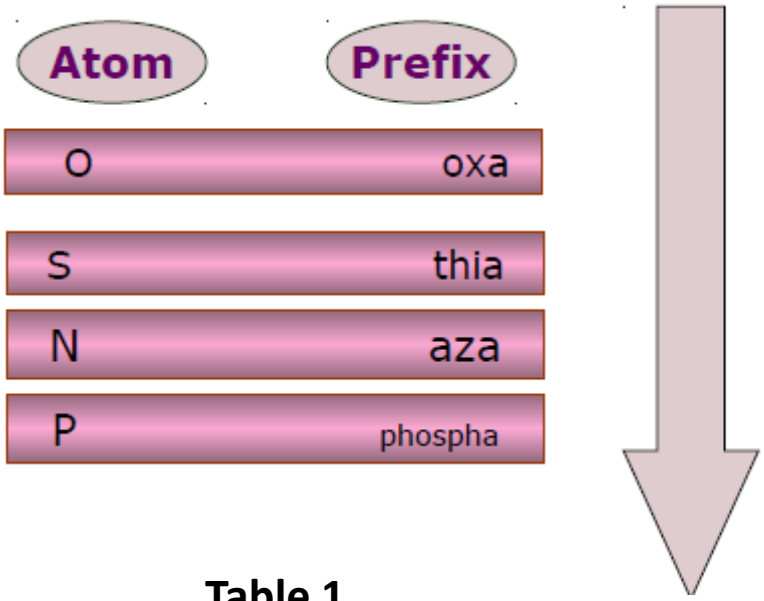
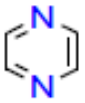


Table 1

Replacement methods


Benzene

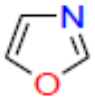


1,4-Diazabenzene

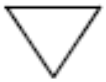

Cyclopentadiene

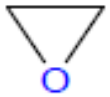
Oxacyclopenta-2,4-diene


Cyclopentadiene

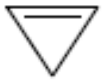


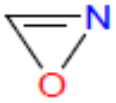
1-Oxa-3-azacyclopenta-2,4-diene


Cyclopropane



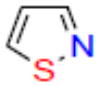
Oxacyclopropane


Cyclopropene



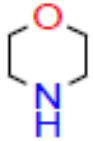
Oxazacyclopropene


Cyclopentadiene

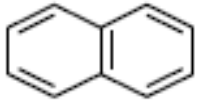


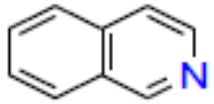
1-Thia-2-azacyclopenta-2,4-diene


Cyclohexane



1-Oxa-4-azacyclohexane


Naphthalene



2-Azanaphthalene

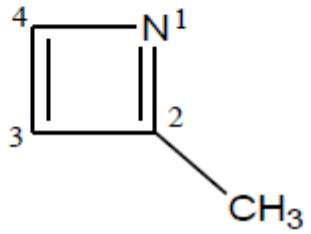
IUPAC method

1) **Identify the heteroatom present in the ring and choose from the corresponding prefix.**

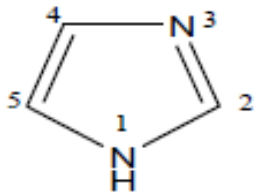
e.g. thia for sulpher, aza for nitogen and oxa for oxygen.

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:



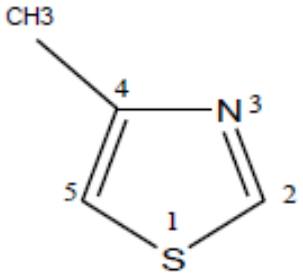
3) A multiplicative prefix (di, tri, ect.) and locants are used when two or more similar heteroatoms contained in the ring(two nitrogen indicated by diaza) and the numbering preferably commenced at a saturated rather than an unsaturated atom, as depicted in the following example: 1,3-diaza….



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.

- 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).

- 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

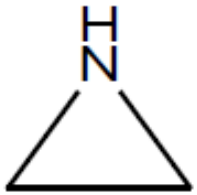
6) Combine the prefix(s) and suffix together and drop the first vowel if two vowels came together**.**

Table 2

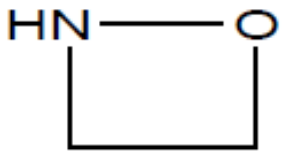
Ring size	N-present		N-absent	
	Unsat	sat	Unsat	sat
	irine	iridine	irene	irane
	ete	etidine	ete	etane
	ole	olidine	ole	olane
	ine	a	in	ane
	epine	a	epin	epane
	ocine	a	ocin	ocane
9	onine	a	onin	onane
10	ecine	a	ecin	ecane

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

- 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**



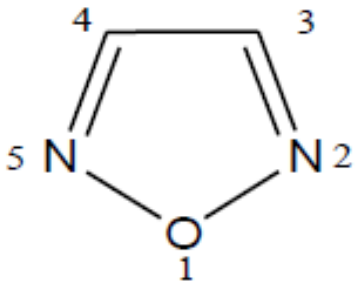
- This ring contains (O ,N) and (o) has higher priority than (N) and by starting numbering the ring at (O) → Prefix is 1,2-Oxaaza, but the first vowel must be omitted to give

  1,2-Oxaza

- The ring is 4-membered and fully saturated → suffix is etidine

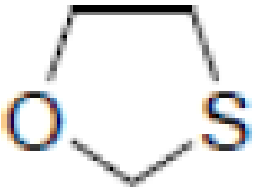
- By combining the prefix and suffix, two vowels ended up together (1,2-oaxazaetidine), therefore the vowel on the end of the first part should be dropped. This gives the correct name:

  1,2-oxazetidine

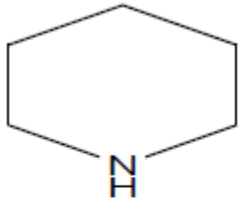


- This ring contains (O) → prfix1 (oxa), and two (N) → prfix2 diaza
- Locants, since (O) is higher priority than (N) so it is in position 1 by default and the two (N) are therefore at positions 2 and 5, this gives the combined prefixes as 1,2,5-oxadiaza (note that the a in oxa is not dropped)
- It is 5-membered,fully unsaturated ring with (N) → the suffix is ole
- By combining the prefixes and the suffix and dropping the appropriate vowels we get the correct name as

1,2,5-Oxadiazole



- 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

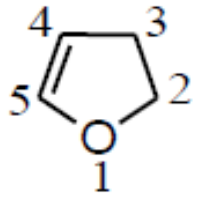


- The ring is 6-memberd, fully saturated with N ⇒ Prefix perhydro followed by the name of fully unsaturated 6-memberd ring with nitrogen ⇒ azine

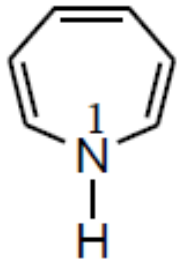
- Thus the full name is **perhydroazine**

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

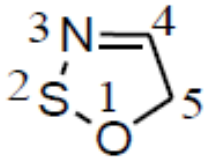
a) The position of nitrogen or carbon atoms which bear extra hydrogen atoms must be indicated by numbers and italic capital H (e.g. 1*H*, 2*H*, etc.) followed by the name of maximally unsaturated ring.



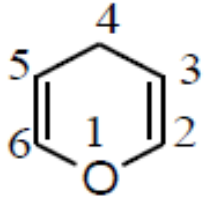
2*H*, 3*H*-Oxole



1*H*-Azepine

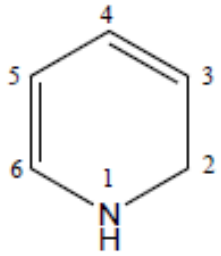


5*H*-1,2,3-Oxathiazole

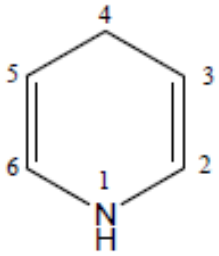


4*H*-Oxin

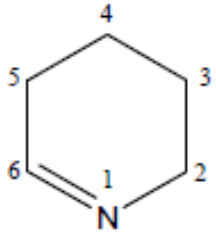
b) The words dihydro, or trihydro, or tetrahydro are used if two or three or four atoms are saturated. These words are preceded by numbers indicate the position of saturated atoms as low as possible and followed by the corresponding fully unsaturated Hantzsch-Widman name.



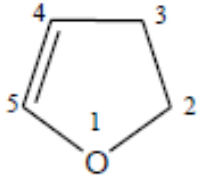
1,2-Dihydroazine



1,4-Dihydroazine



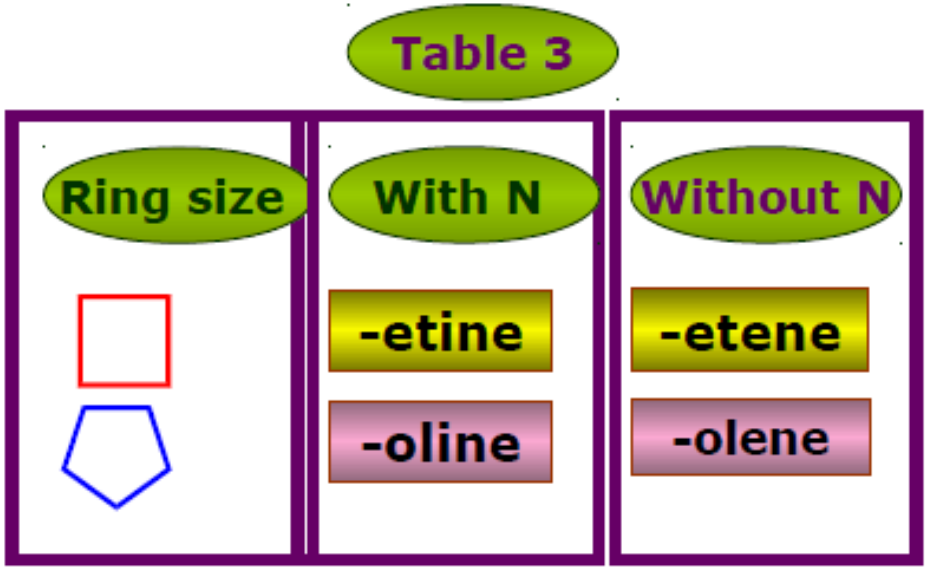
2,3,4,5-Tetrahydroazine



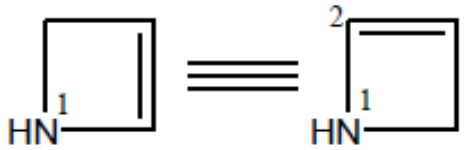
2,3-Dihydrooxole

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; 2 and 3; 3 and 4 atoms respectively have a double bond

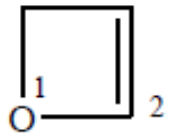
(i.e. Name : Δ^x + Prefix + special suffix)
(x= locant of the double bond)



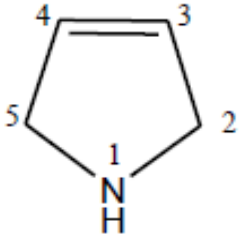
- Examples



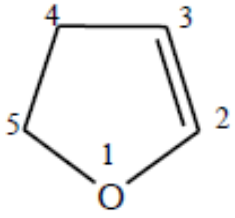
Δ^2 -Azetine



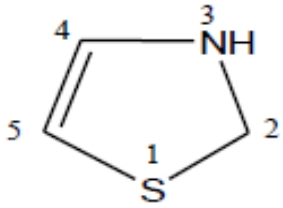
Δ^2 -Oxetene



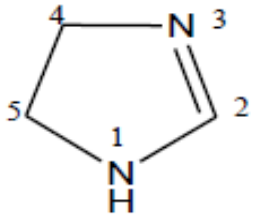
Δ^3 -Azoline



Δ^2 -Oxolene



Δ^4 -1,3-Thiazoline

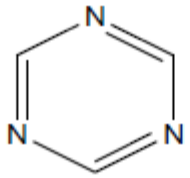


Δ^2 -1,3-Diazoline

- Exercise:

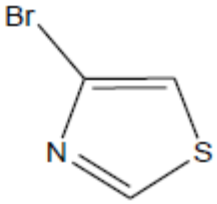
  Explain how can you name the following heterocycles.

1,3-Oxathiolane



1,3,5 triazine

Oxirene



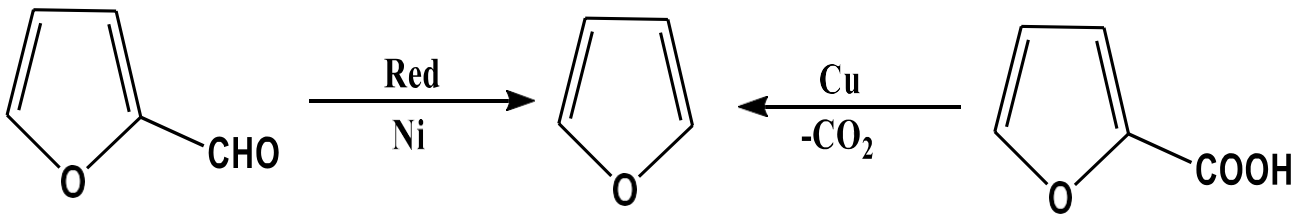
4 bromo 1,3 thiazole

Furan

Physical properties

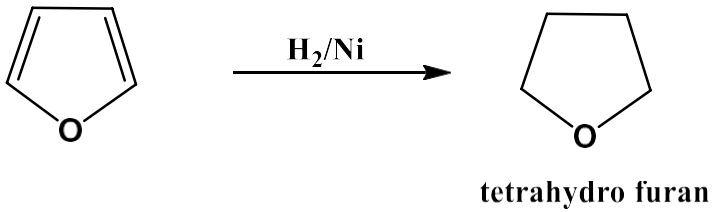
- **Furan may be as ethers but it is aromatic compoud because the lone pair of electrons on oxygen atom contribute in aromaticity.**
- **Furan has low melting point less than pyrrole because there's no hydrogen bonds.**
- **Furan is a liquid boiled at 31c and has odour as chloroform.**
- **Furan is springily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

Preparation of furan



Reactions of furan

Reduction of furan❖

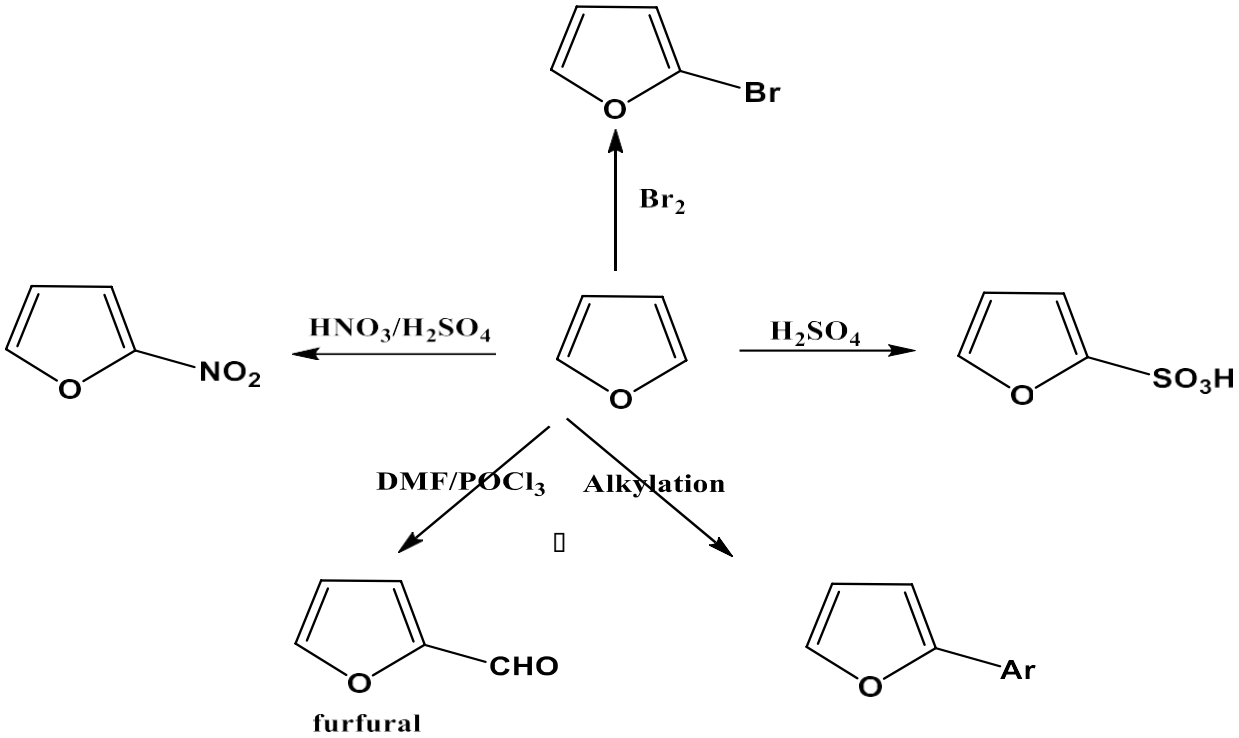


tetrahydro furan

Reactions of furan

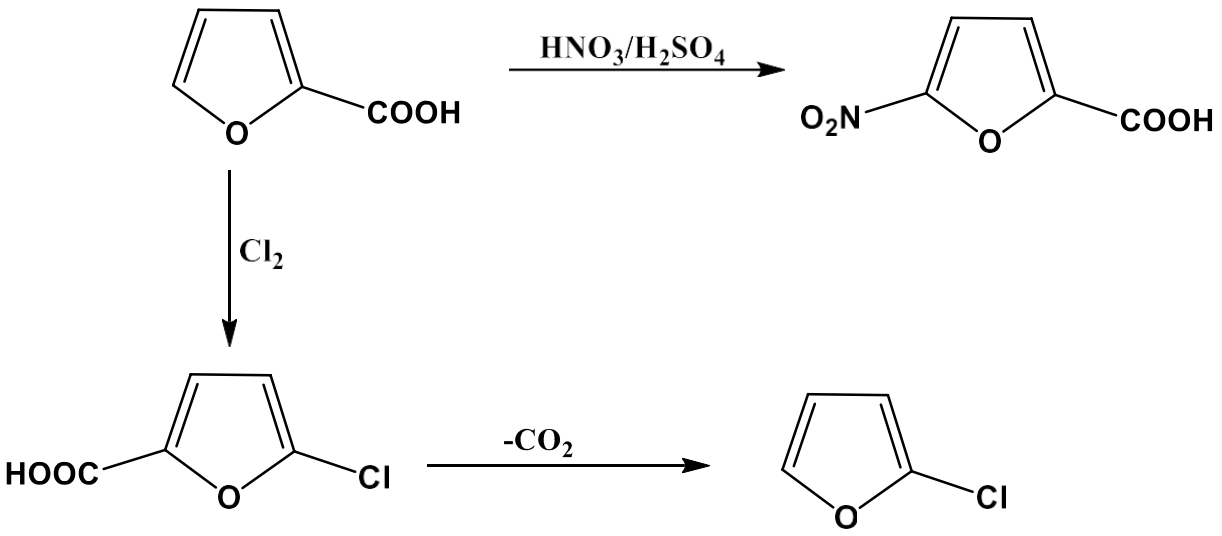
Electrophilic substitution reactions: ❖

The substitution occurred in position 2 ❖



Reactions of furan

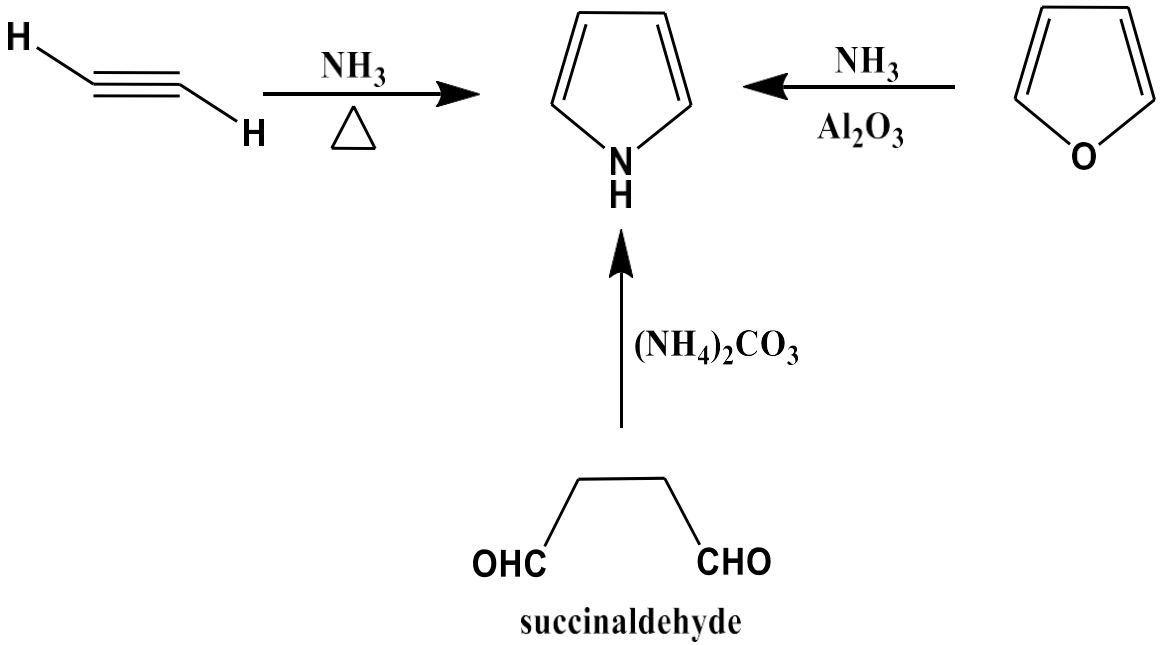
Reactions of furan-2-carboxylic acid:



Pyrrole

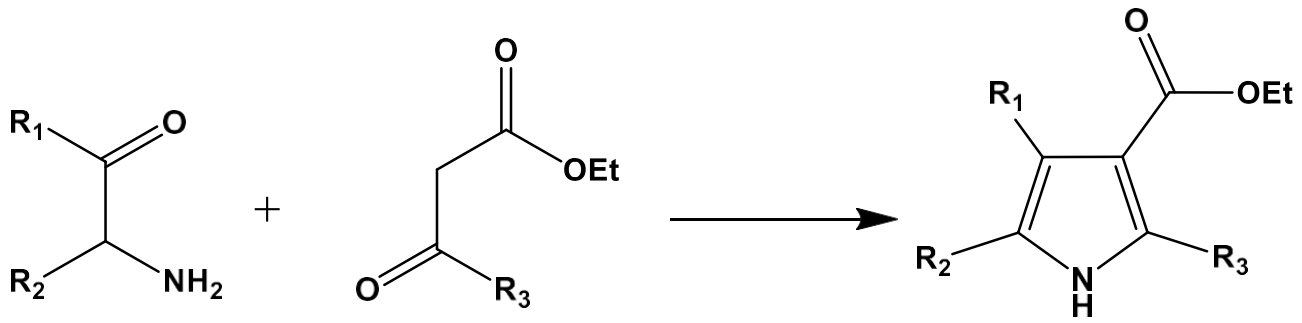
- Pyrrole is a colorless liquid which has an odour as chloroform.
- If it is exposed to air give brown color.
- The lone pairs of electrons on nitrogen atom contribute in aromatic properties.

Preparation of pyrrole



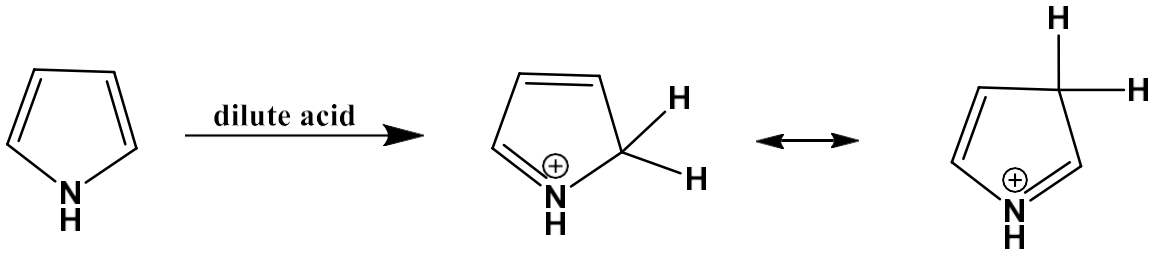
Preparation of pyrrole

Knorr synthesis:



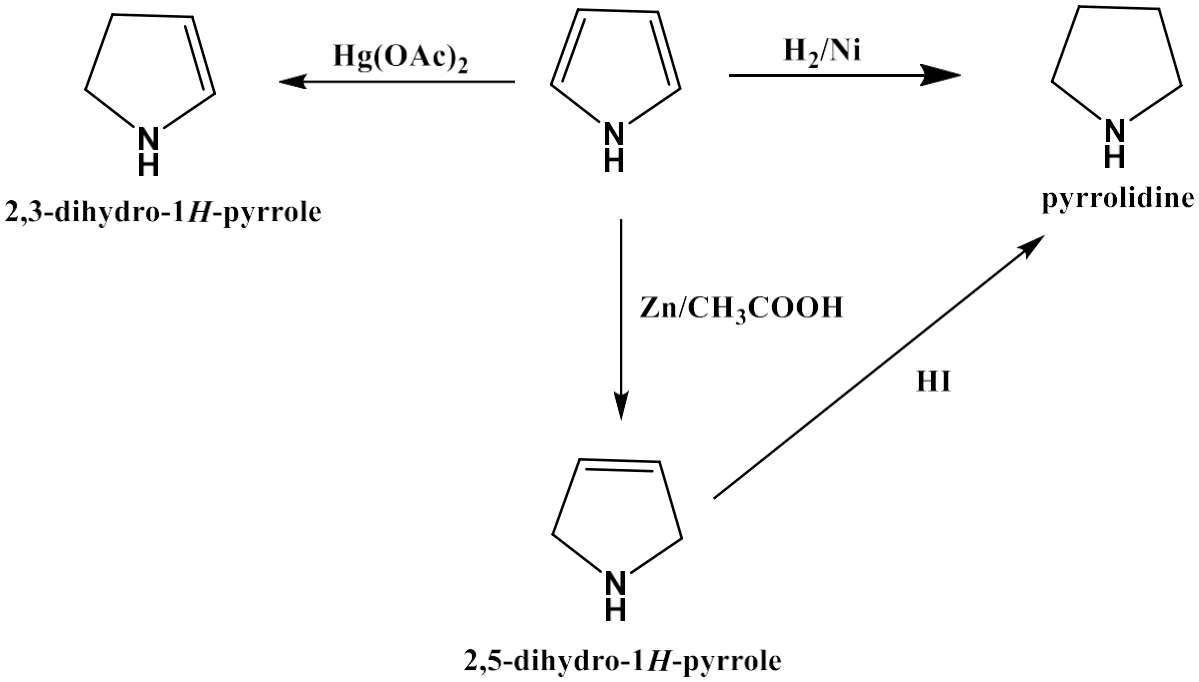
Reactions of pyrrole

Basicity:



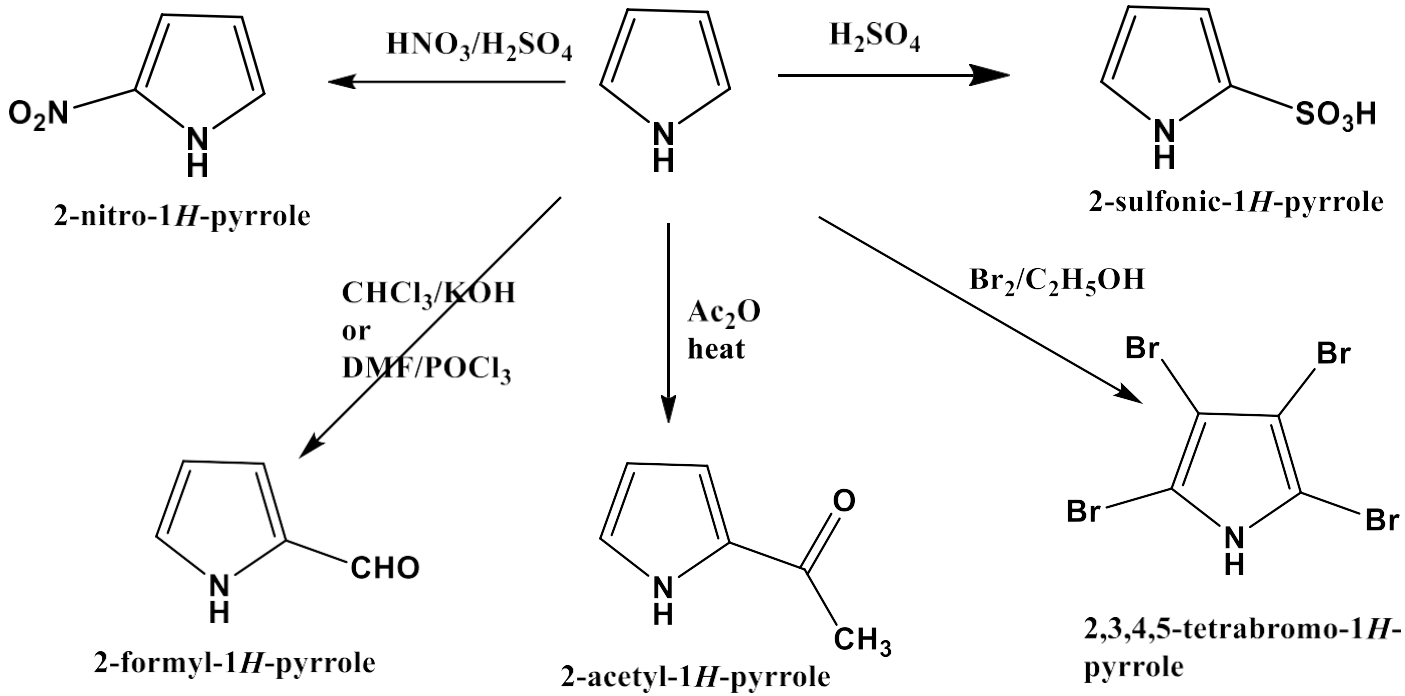
Reactions of pyrrole

Reduction of pyrrole:



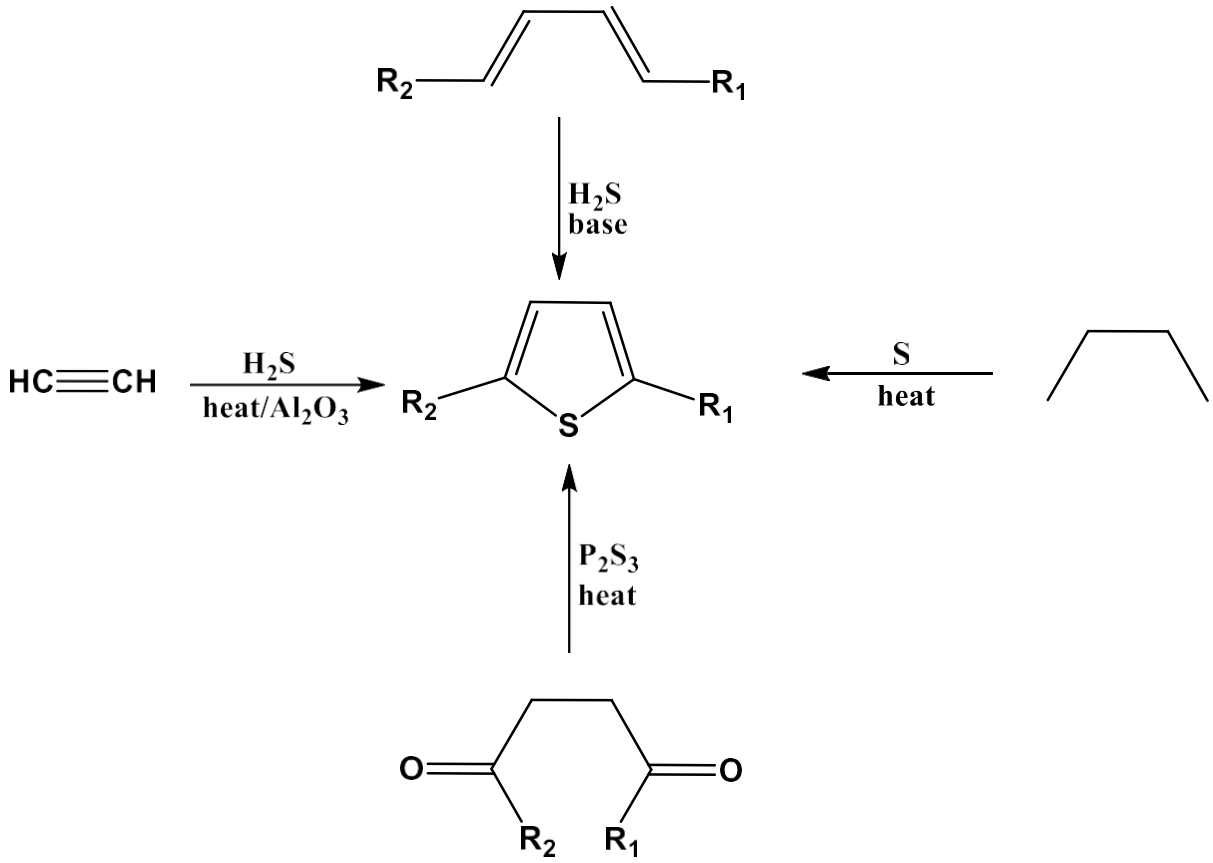
Reactions of pyrrole

Electrophilic substitution:



Thiophene

Preparation of thiophene

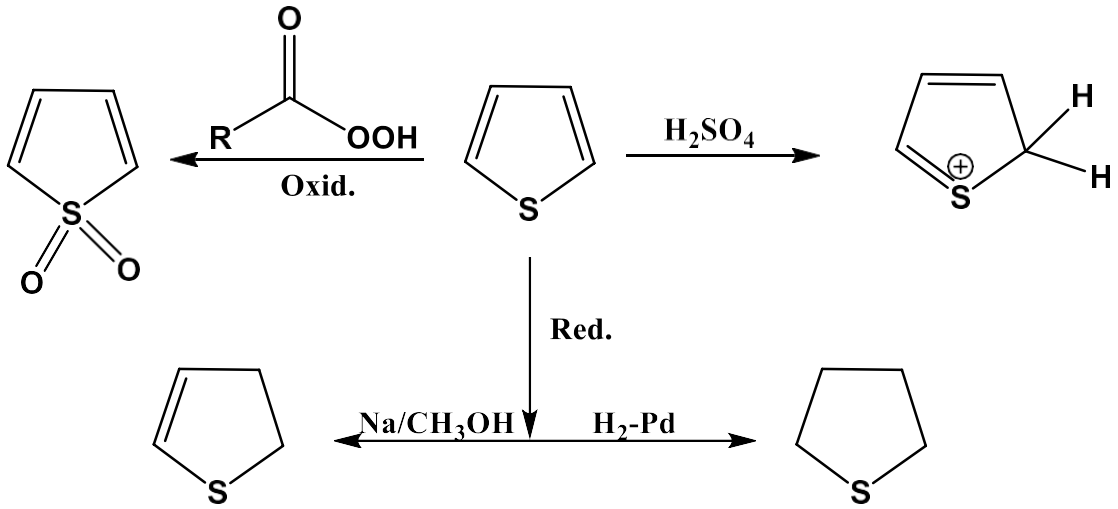


Reactions of thiophene

1- addition reactions.

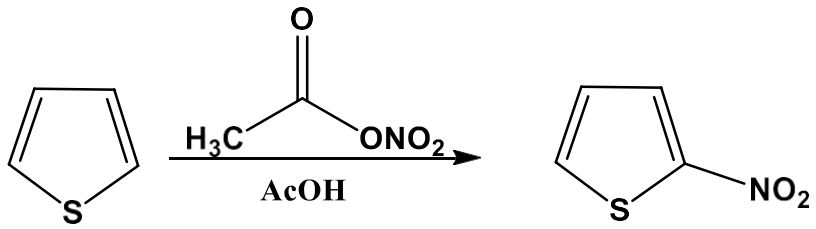
2- reduction reactions.

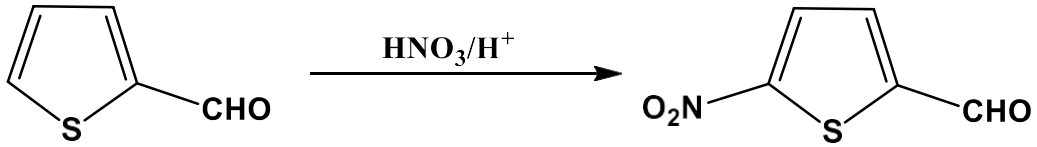
3- oxidation reactions.



Reactions of thiophene

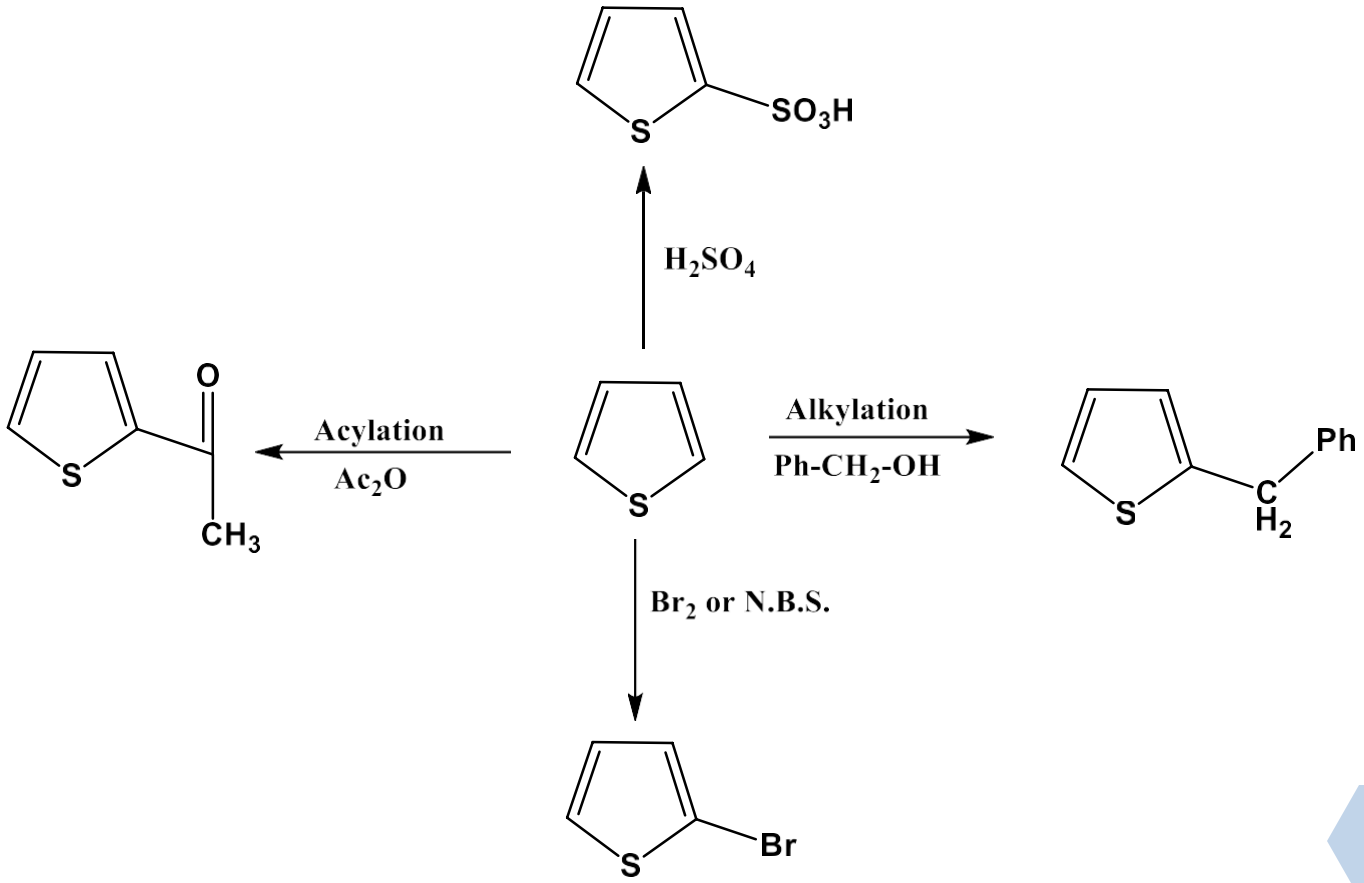
Electron withdrawing groups increase the stability of the ring and rate of reaction.





Reactions of thiophene

Electrophilic substitution reactions:



Pyridine

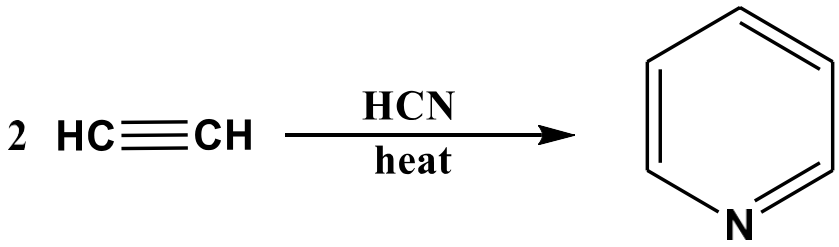
Physical properties

- 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.**

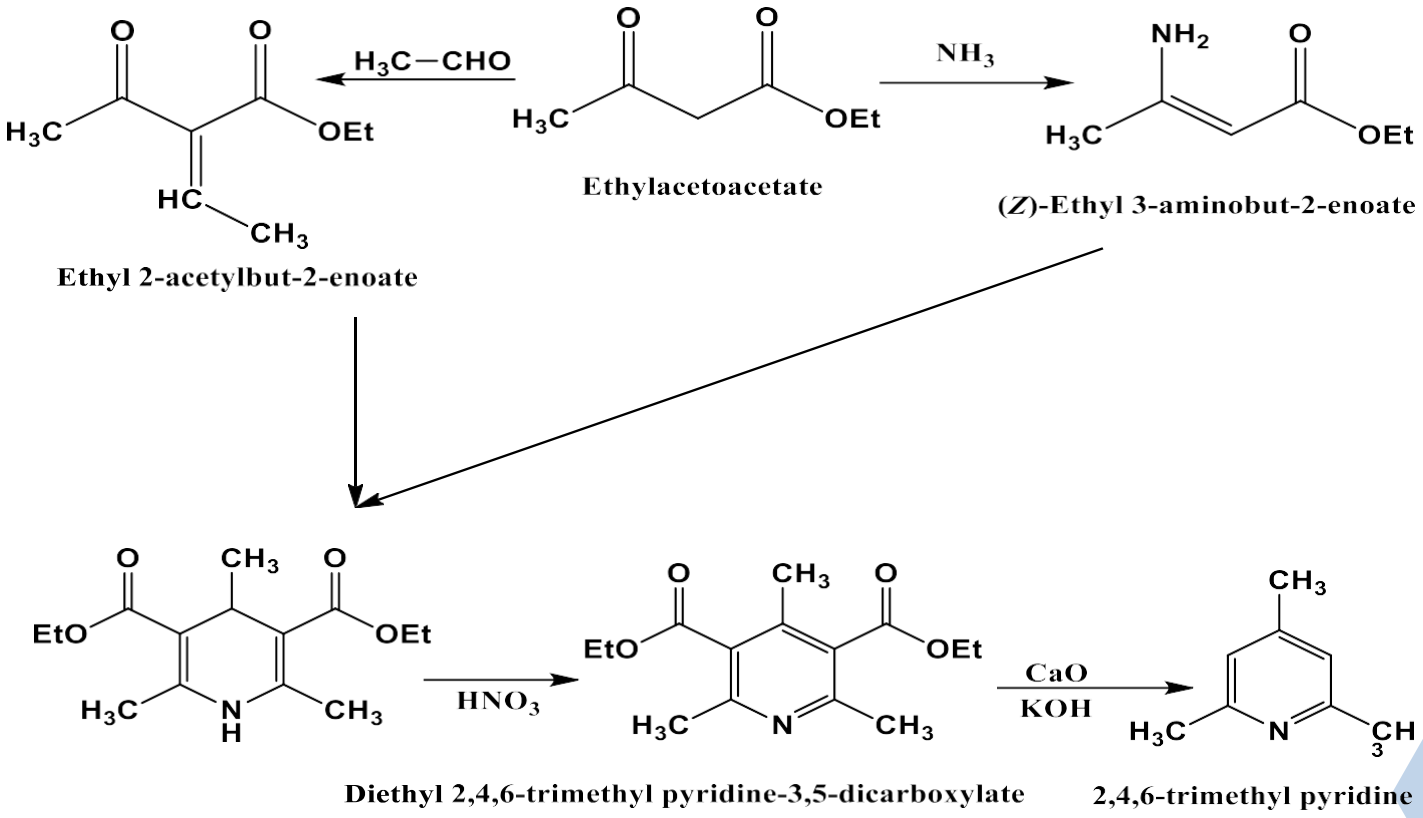
Preparation of pyridine

1- from acetylene:



Preparation of pyridine

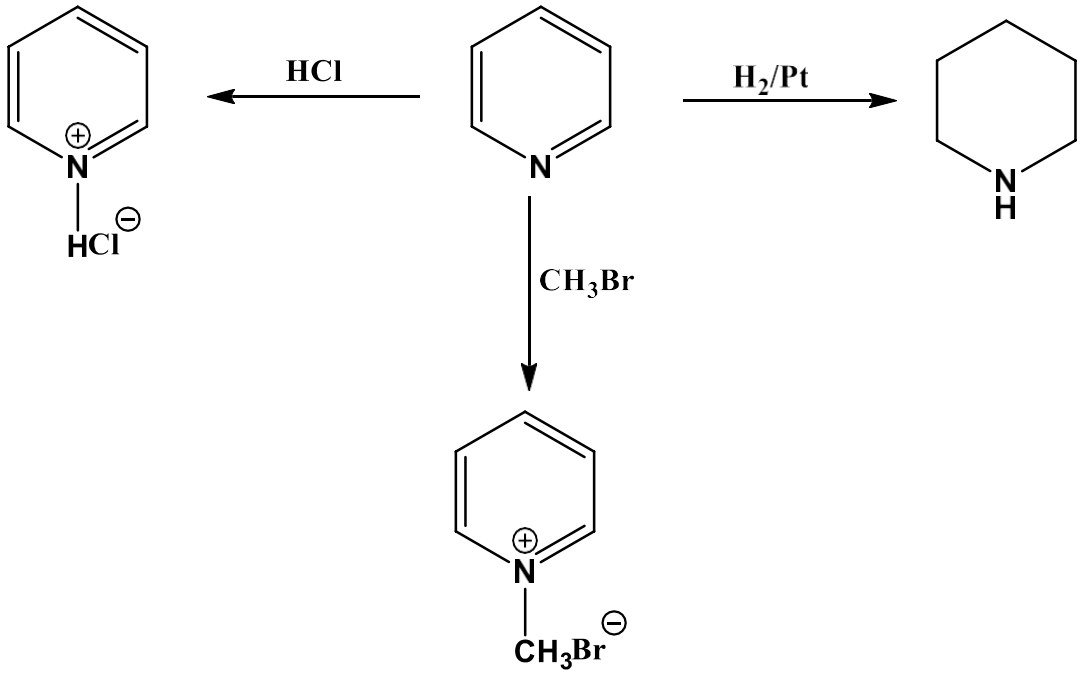
2- Hantzch synthesis:



Reactions of pyridine

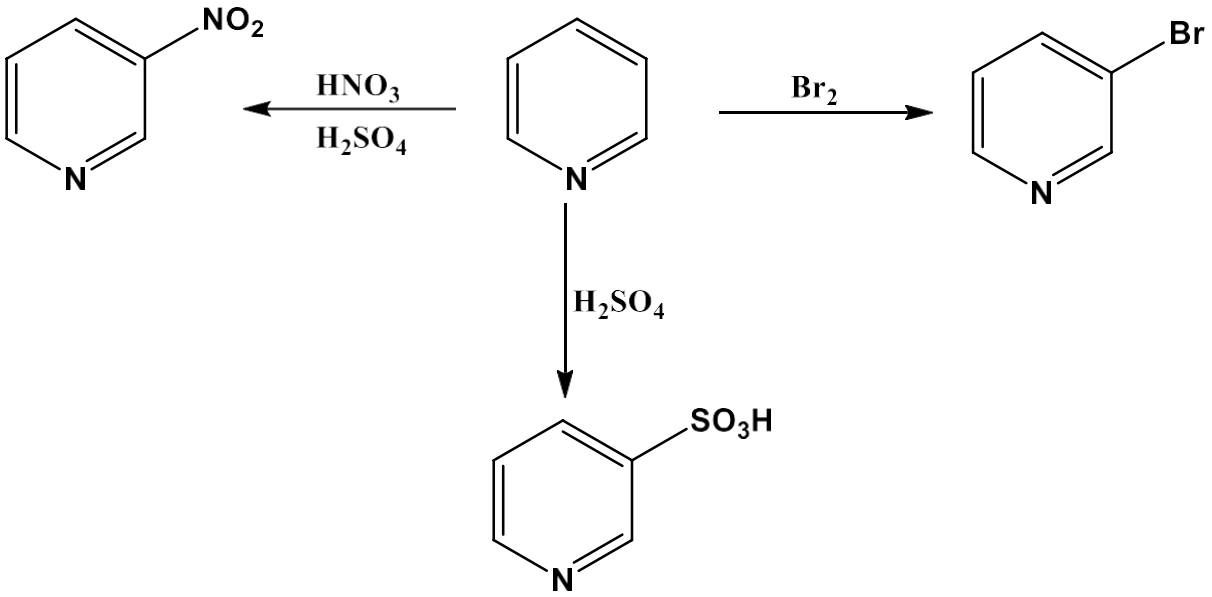
1- addition reactions:

A- reduction b- salt formation

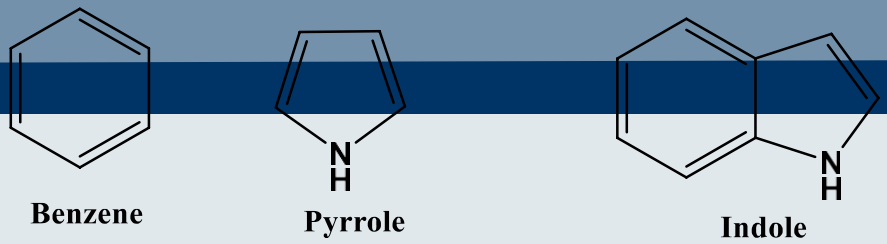


Reactions of pyridine

Electrophilic substitution reactions:



Indole



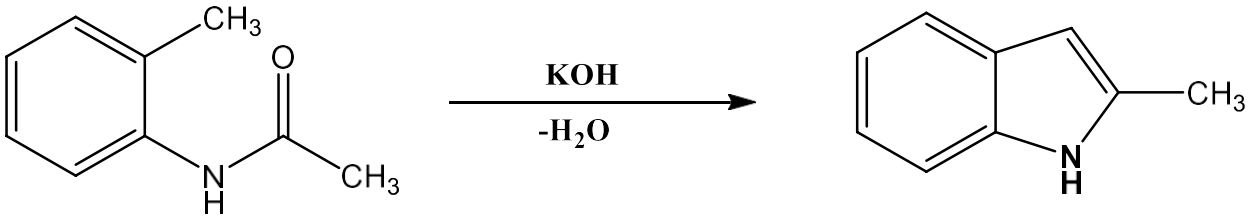
Benzene Pyrrole Indole

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

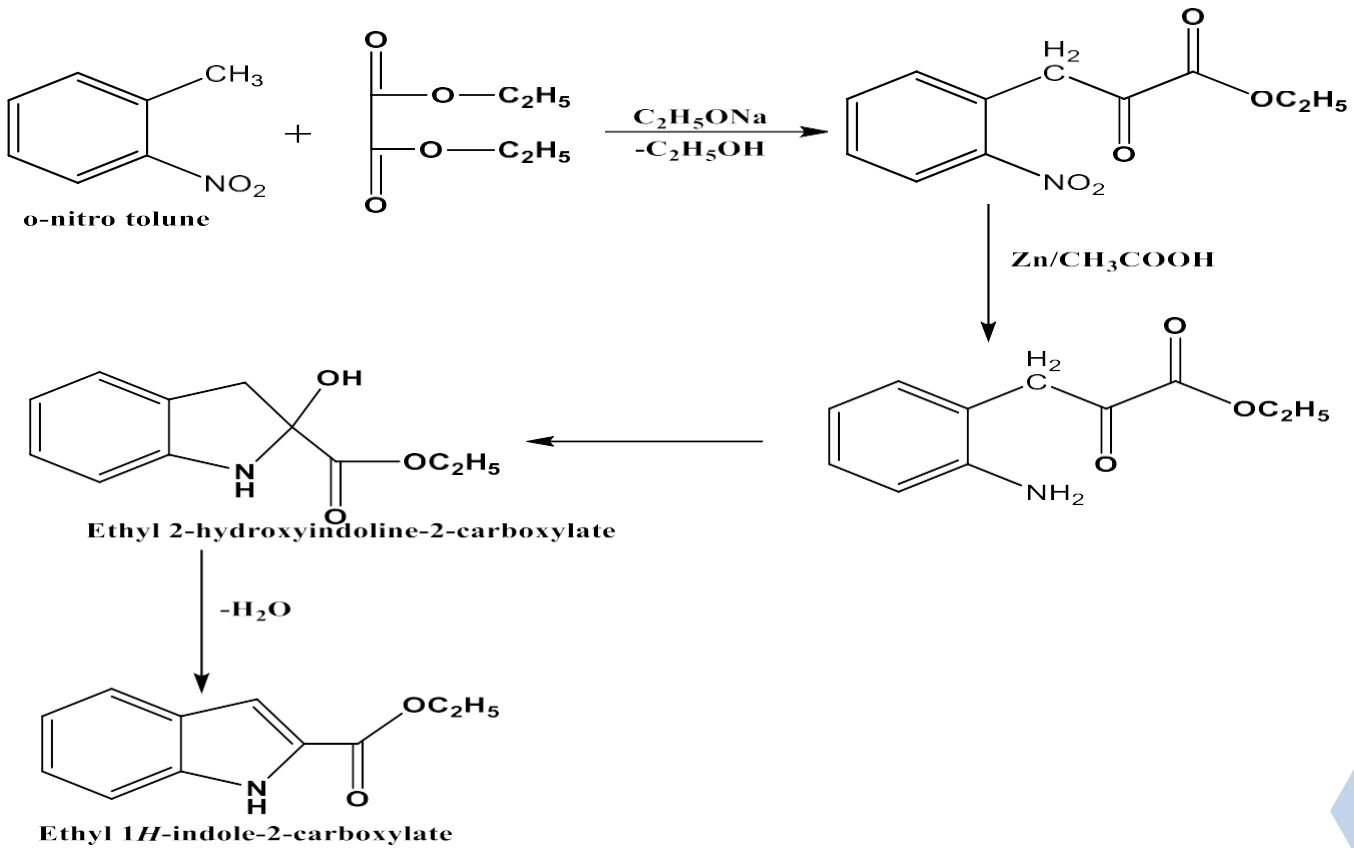


N-o-tolylacetamide

2-methyl indole

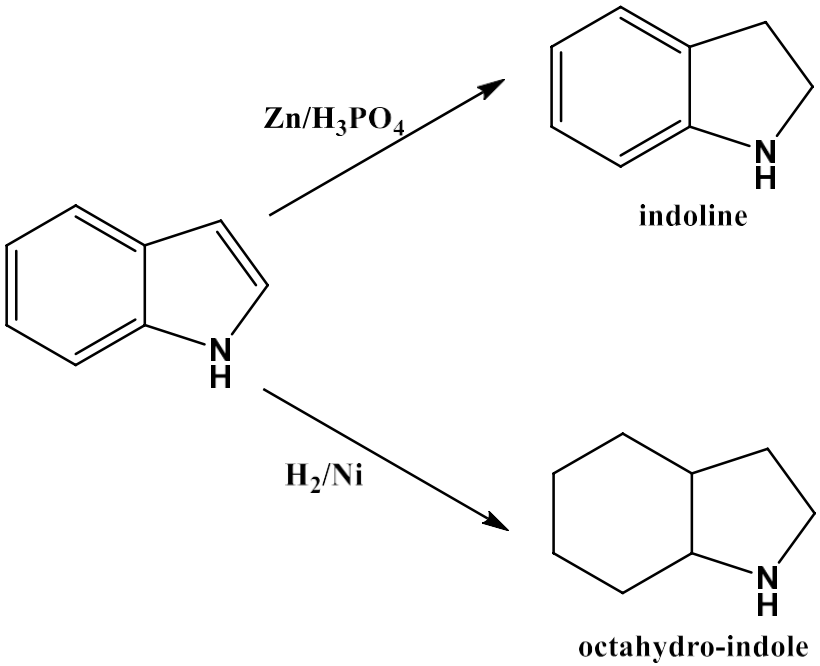
Preparation of indole

2- Reissert Synthesis



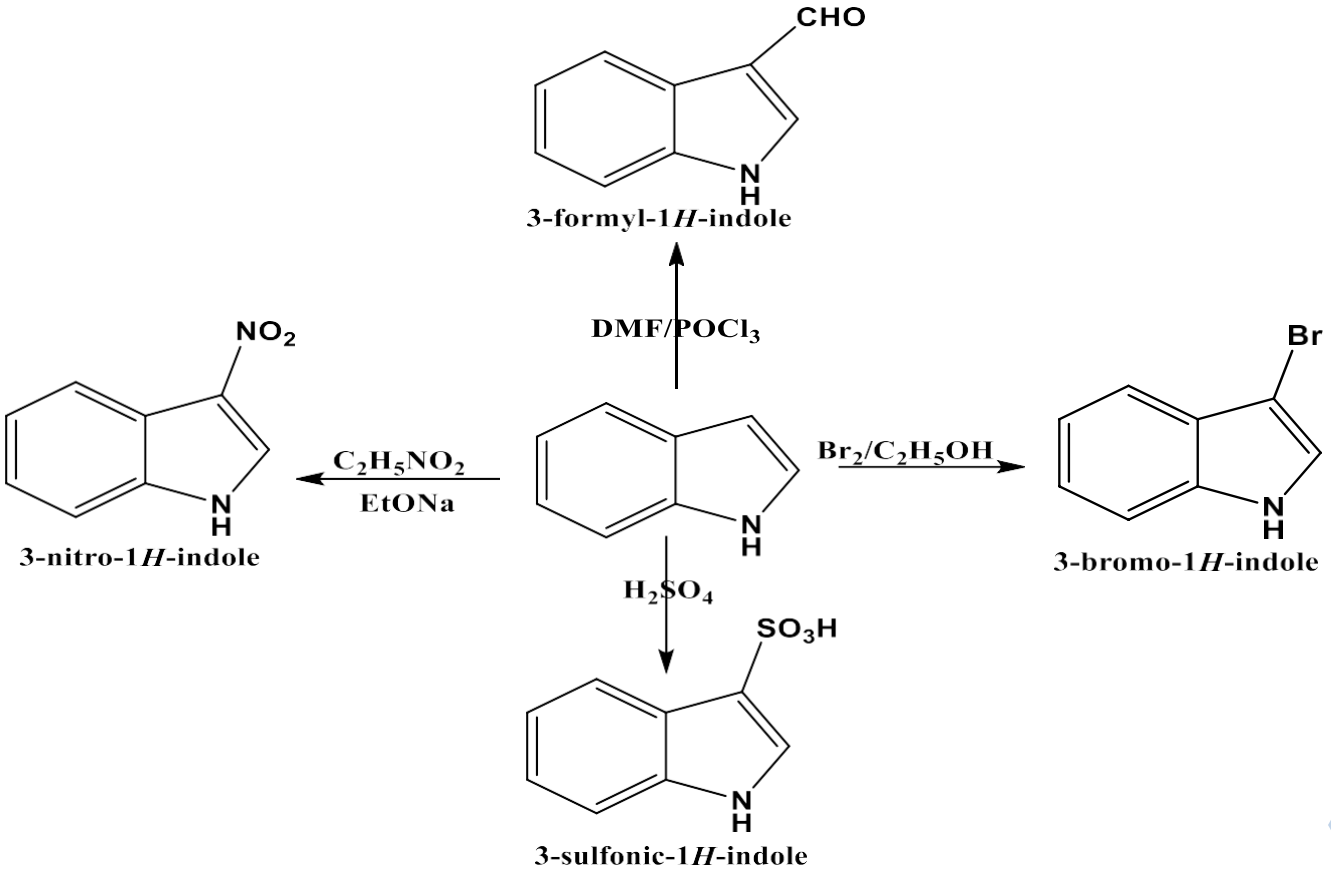
Reactions of indole

Reduction of indole:



Reactions of indole

Electrophilic substitution reactions:



References

- 1- Handbook of Heterocyclic chemistry (3rd Edition) 2014.
- 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).
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