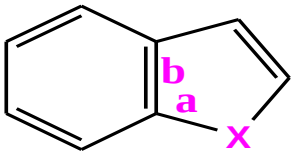
CH-2-II

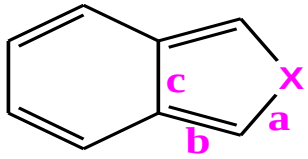
Indoles and Isoindoles

Introduction

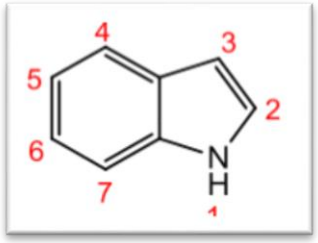
- As a result of the fusion between benzene ring and 5-memebered heterocyclic ring (annulation) there are two possible aromatic structures differ in position of fusion:

(a) Indole and its analogs (b) Isoindole and its analogs





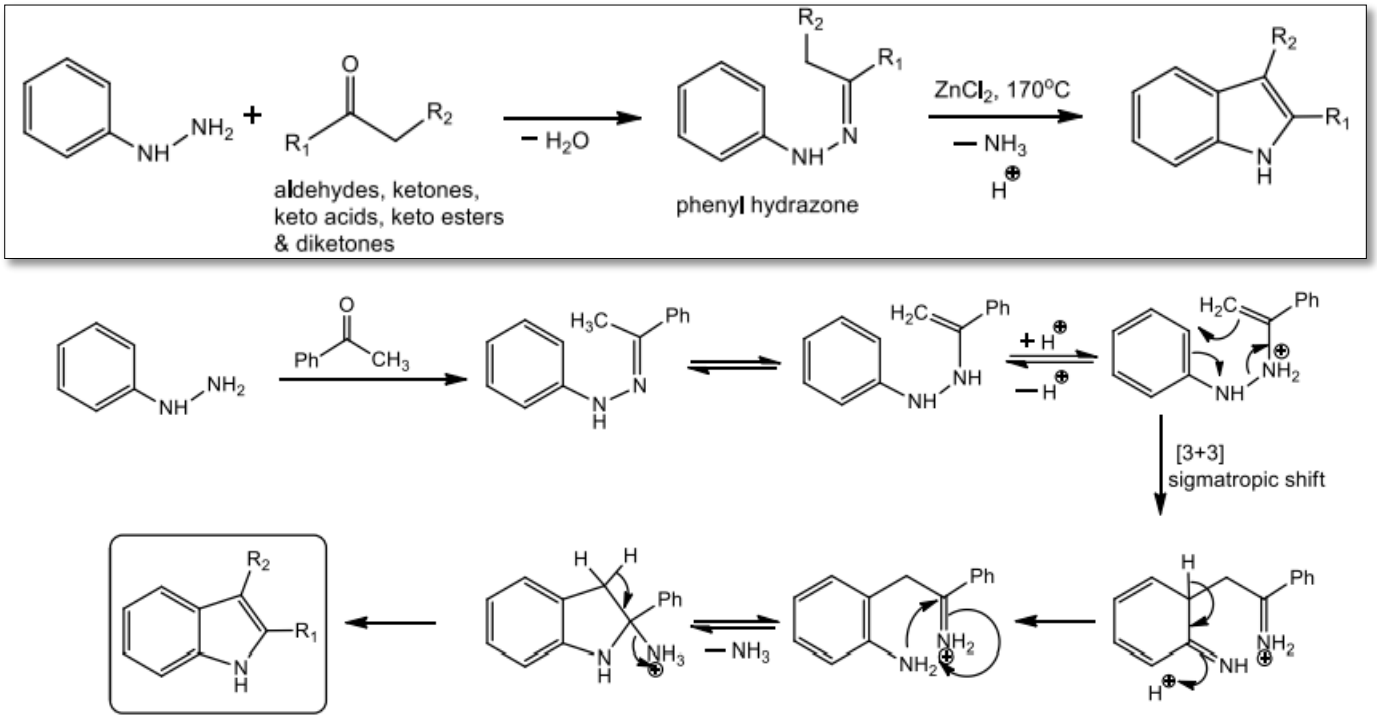
	X	
Indole	N	Isoindole
Benzo[b]thiophene	S	Benzo[c]thiophene
Benzo[b]furan	O	Benzo[c]furan



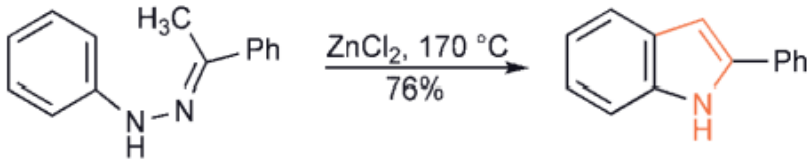
Synthesis of Indole

1) Fischer Synthesis

From heating aryl-hydrazones of Aldehydes and Ketones with protic acid or lewis acids such as $ZnCl_2$, PCl_3, $FeCl_3$, PPA etc, in an inert solvent gives an indole with the loss of ammonia.



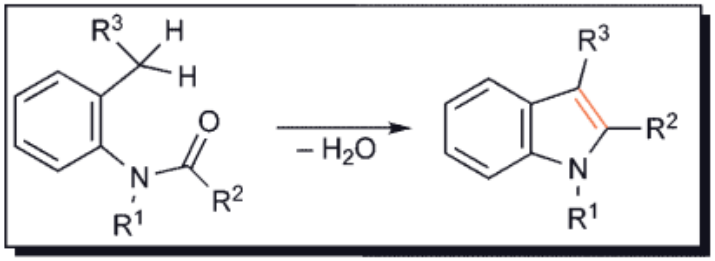
Example:



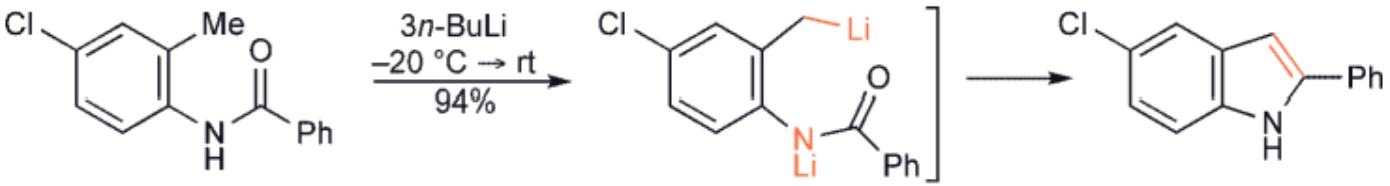
Synthesis of Indole

2) Madelung Synthesis

Base-catalyzed cyclo-condensation of an ortho-alkylacetamide with alkyllithiums as bases, gives an indole.

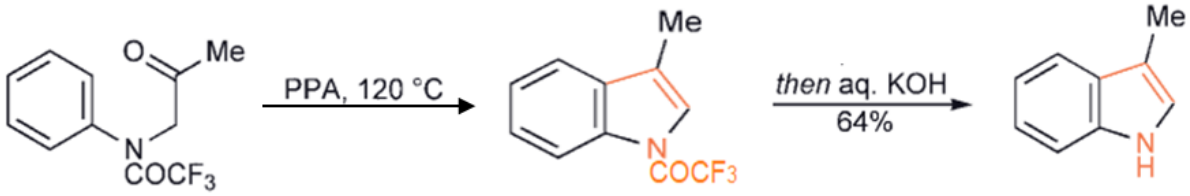


Example:



3) Bischler Synthesis

An α-arylamino-ketone is cyclized under acidic conditions.



Comparison with pyrrole

- Pyrroles, indoles and isoindoles have a partially positive nitrogen, and partially negative carbons therefore these carbons react easily with electrophilic reagents, and resist substitution by nucleophilic reagents.
- Indoles, like pyrroles are non basic due to if protonation on nitrogen occurs, the aromaticity would be lost.

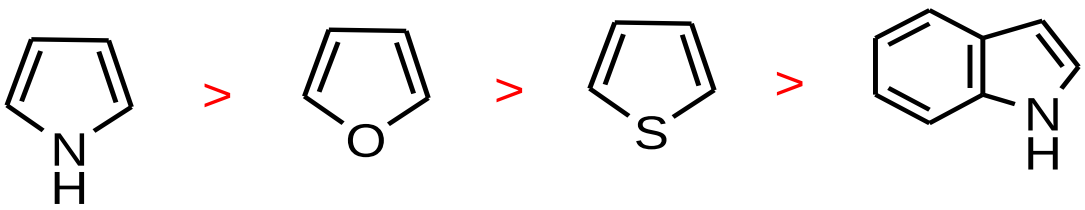
The main differences between indole and pyrrole include:

1. The reactivity order in the electrophilic substitution
2. The regioselectivity in electrophilic substitution

The reactivity order in the electrophilic substitution

- Generally indole and its analogs are less reactive compared to the corresponding single heterocyclic rings therefore the electrophilic aromatic substitution is slower with these compounds.
- This can be attributed to the fact that the share of each carbon atom of the –ve charge in these compound is lesser due to delocalization of the charge on the benzene.

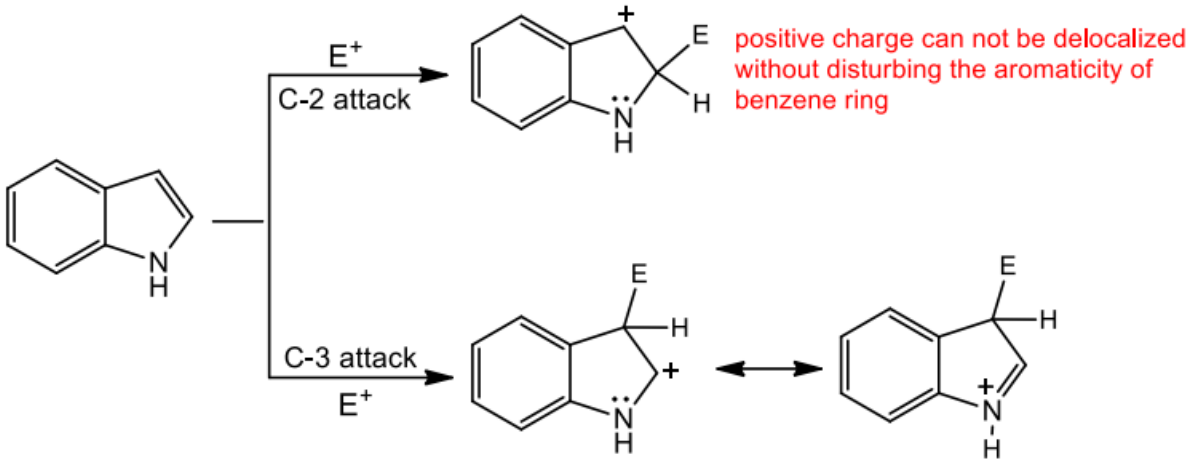
Reactivity order in electrophilic aromatic substitution:



The regioselectivity in electrophilic.substitution

- Fusion of the benzene ring with heterocyclic rings alter the regioselectivity from the 2- position in the single heterocylic compounds (e.g. pyrrole) to 3- position in indole.

- The preferred site of electrophilic substitution is C-3, because the cation formed by the C-3 attack of electrophile is more stable than that of the C-2 attack. In case of C-3 attack,transition intermediate formed has positive charge adjacent to N atom that can be stabilized by the delocalization of lone pair of electrons of nitrogen. Whereas, the positive charge of transition intermediate formed by the C-2 attack, cannot be stabilized without disturbing aromaticity of benzene ring. If C-3 position is occupied, then electrophilic substitution takes place at C-2.

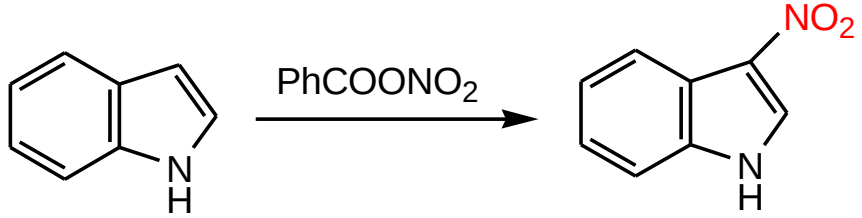


C-2 Vs. C-3 attack

Electrophilic substitution reactions

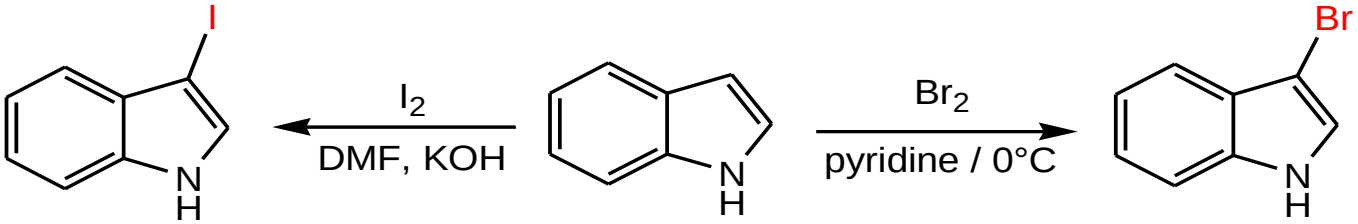
1) Nitration

nitration of indole is carried out using non-acidic nitrating agent such as benzoyl nitrate and ethyl nitrate.



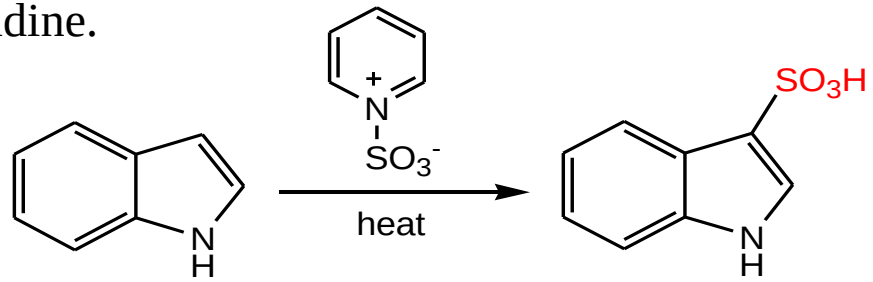
2) Halogenation

3-Halo- and 2-halo-indoles are unstable therefore, must be utilized immediately after their preparation.



3) Sulphonation

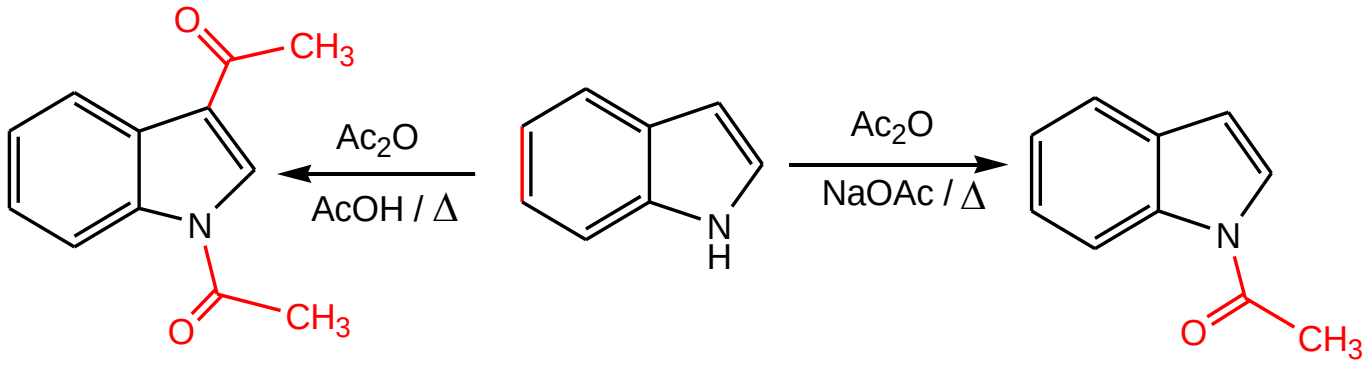
Sulfonation of indole, at C-3, is performed using the pyridine-sulfur trioxide complex in hot pyridine.



Electrophilic substitution reactions

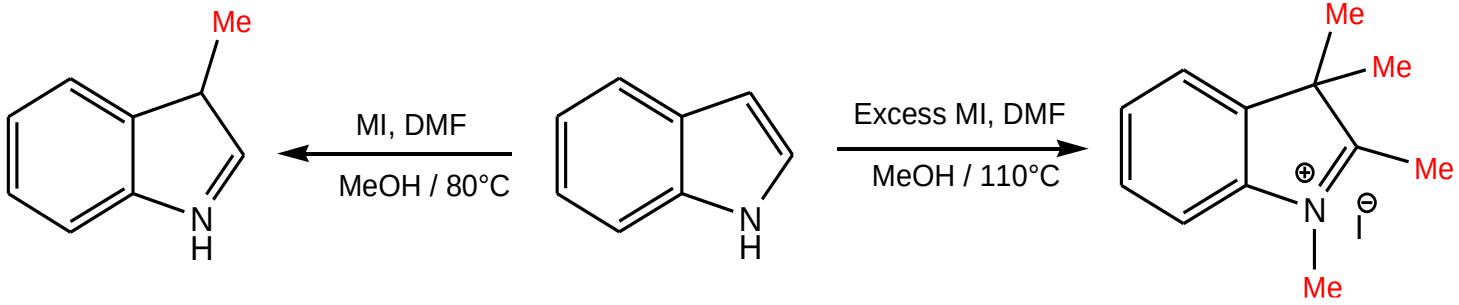
4) Acylation

Indoles react with acetic anhydride in acetic acid above 140°C to afford 1,3-diacetylindole. On the other hand, acetylation in the presence of sodium acetate affords 1-acetylindole.



5) Alkylation

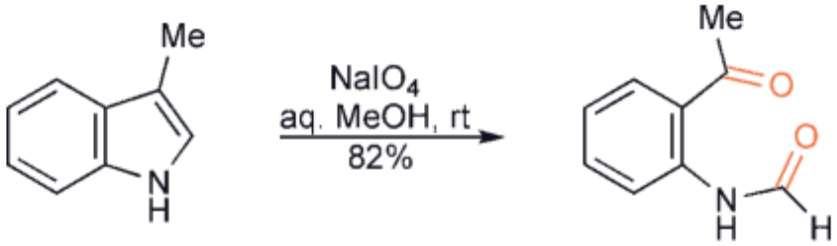
Indole itself begins to react with methyliodide in DMF at about 80°C, to give main product 3-methyl indole. As the temperature is increased, further methylation takes place resulting in 1,2,3,3- tetramethylindolium iodide.



Reaction of Indole

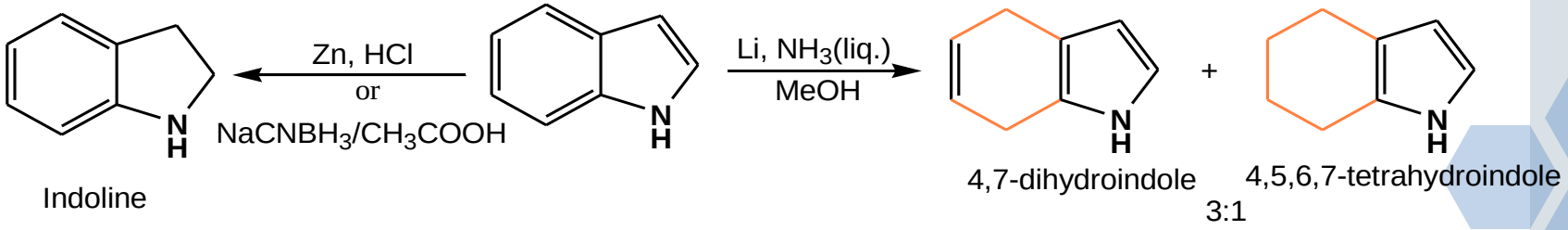
Oxidation

C2-C3 double bond of indole is oxidatively cleaved by the use of reagents such as ozone, sodium periodate, or potassium superoxide.



Reduction

The indole ring can be reduced selectively in carbocyclic or the heterocyclic ring. lithium/liquid ammonia reduces the benzene ring to 4,7-dihydroindole as major product. The heterocyclic ring can be reduced in acidic reagents such as Zn/HCl or $NaCNBH_3/CH_3COOH$ to give indoline.



Reaction of Indole

Mannich reaction (reaction with iminium ions)

- indole reacts with a mixture of formaldehyde and dimethylamine by substitution at the indole nitrogen. Under neutral conditions at higher temperature or in acidic medium acetic acid, N-substituted gets transformed into 3-dimethylaminomethylindole, gramine.

- The Mannich reaction is useful because the product gramine can be used as intermediates to access various 3-substituted indoles.