Fused Ring Heterocycles

Part (II)

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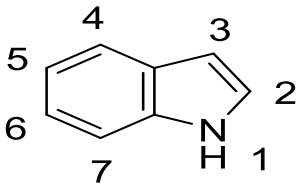
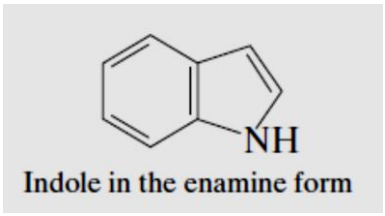
Indole (benzo[b]pyrrole)

Indole is an aromatic heterocyclic organic compound with formula C_8H_7N. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered pyrrole ring.



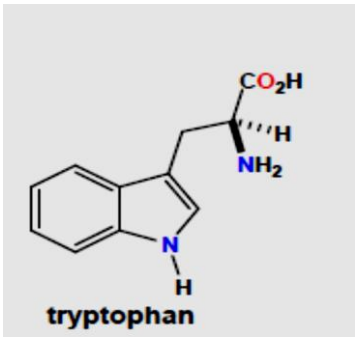
Indole ring occurs widely in nature as alkaloids. The alkaloids have medicinal values. In these compounds, a benzene ring is fused with a pyrrole ring and hence behaves as an aromatic heterocyclic compound. Because of the aromatic stability of the benzene ring, the most important contributing structure of indole to its resonance hybrid is its enamine form.



Indole in the enamine form

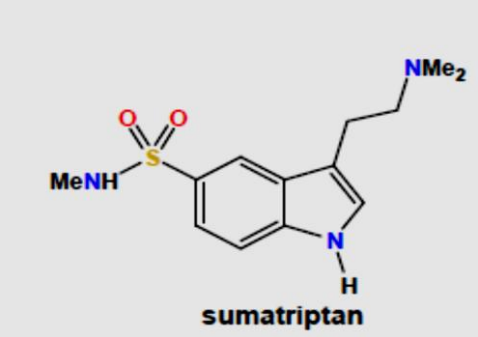
Bioactive Indoles

- Tryptophan is one of the essential amino acids and a constituent of most proteins.



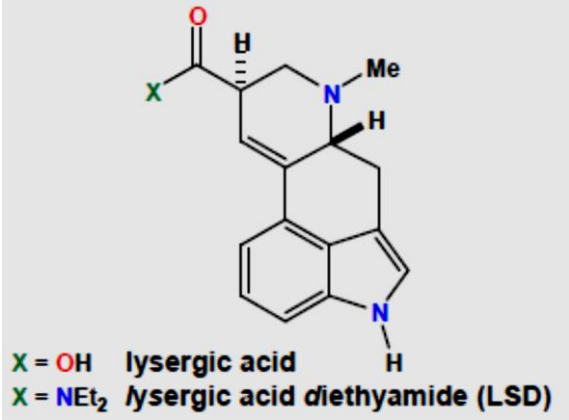
tryptophan

- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS.



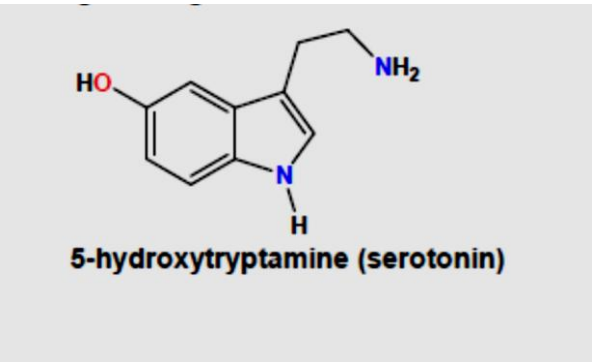
sumatriptan

- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus.



X = OH lysergic acid
X = NEt_2 *l*ysergic acid *d*iethyamide (LSD)

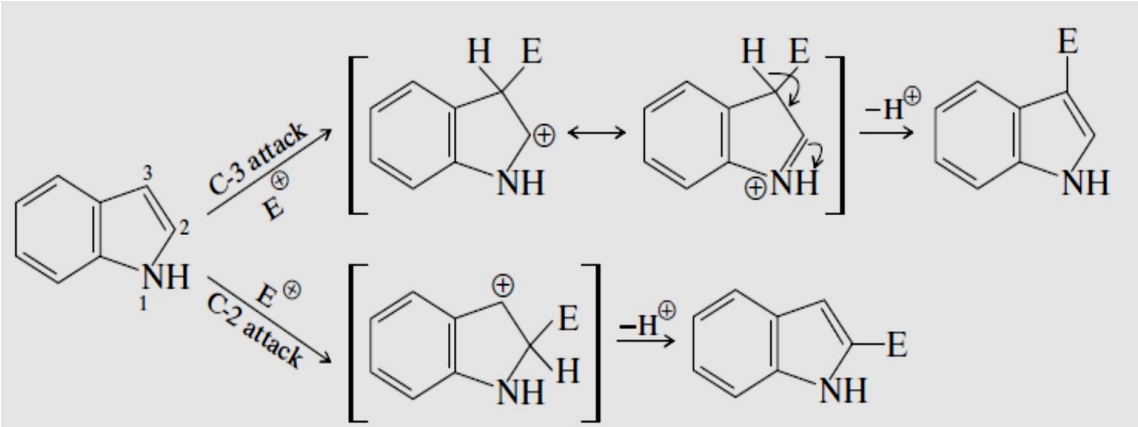
- Serotonin, which is an indole, occurs naturally in the body.



5-hydroxytryptamine (serotonin)

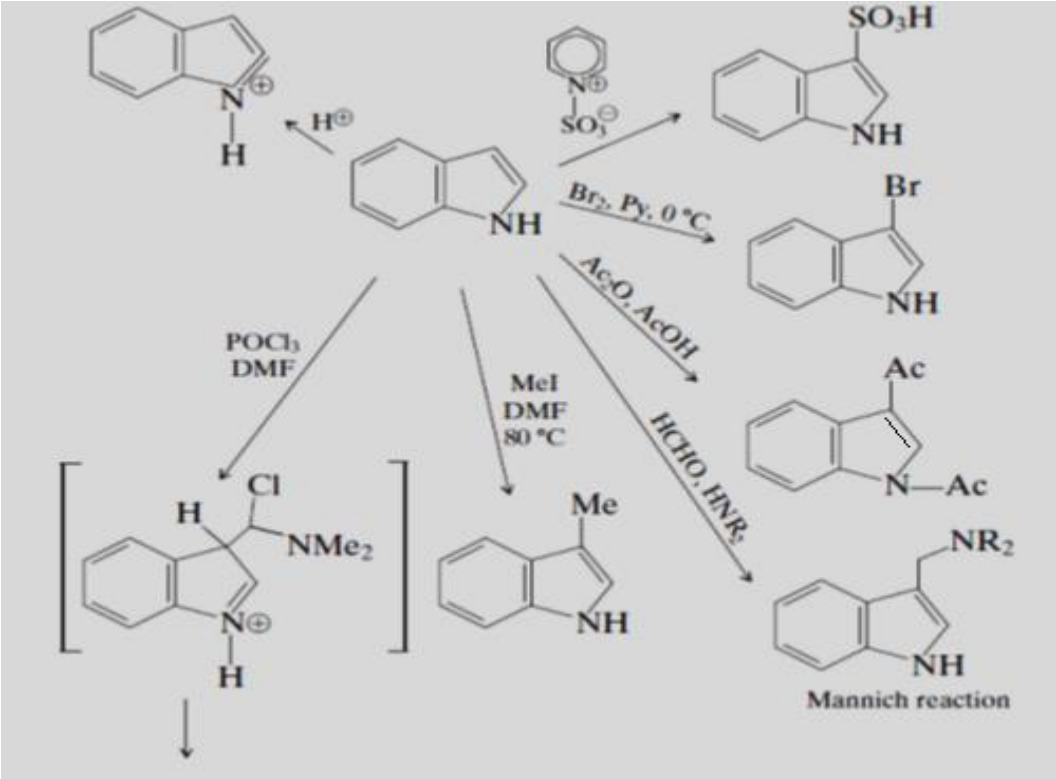
Electrophilic Substitution

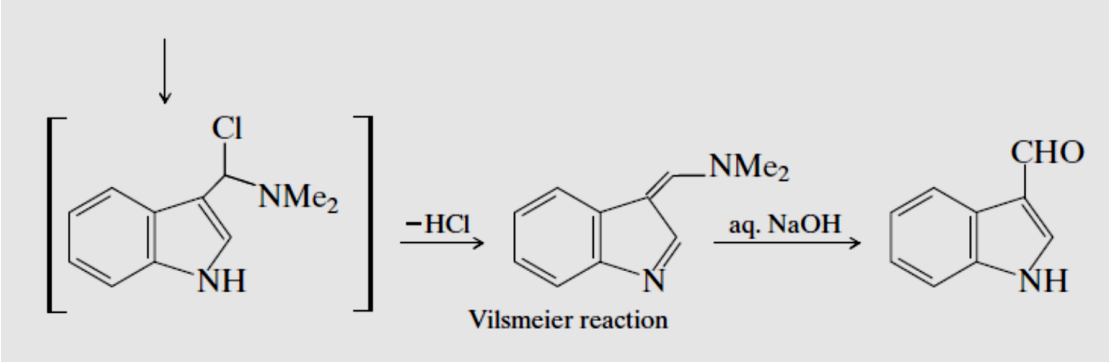
Because of the higher electron density in the heteroring, indole undergoes electrophilic substitution at C-2 in the pyrrole ring and Regio selectively at C-3 due to higher resonance stabilization of the intermediate formed by C-3 attack.



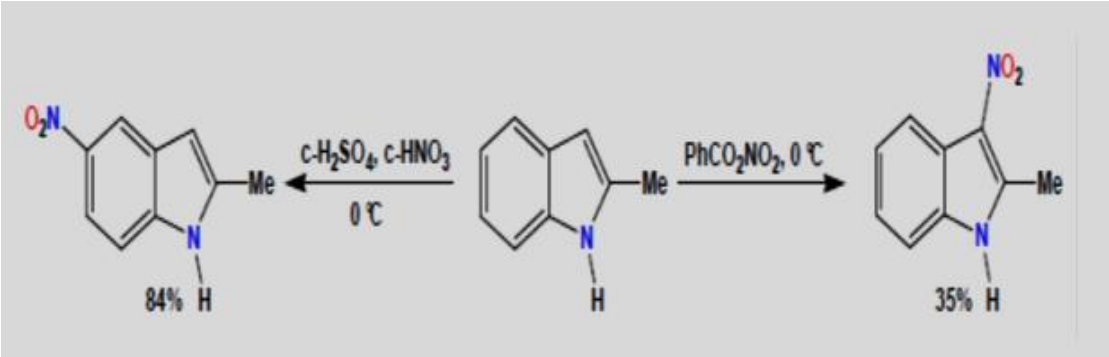
However, indole easily undergoes **protonation** to give indolenium cation for which the electrophilic substitutions of indole cannot be carried out under the similar conditions as are used in benzene series. For example:

- indole is **sulfonated** at **C-3** with pyridinium–*N*-sulfonate,
- **Brominated** at **C-3** with bromine in pyridine at 0°C,
- **Acetylated** at **C-1 and C-3** to give diacetyl derivative with acetic anhydride in acetic acid,
- **Methylated** at **C-3** with methyl iodide in DMF at 80°C,
- **Formylated** at **C-3** with $POCl_3$ and *N*, *N*-Dimethyl formamide at 5°C followed by alkaline hydrolysis (Vilsmeier reaction),
- **Amino methylated** at **C-3** with HCHO and amines (Mannich reaction).





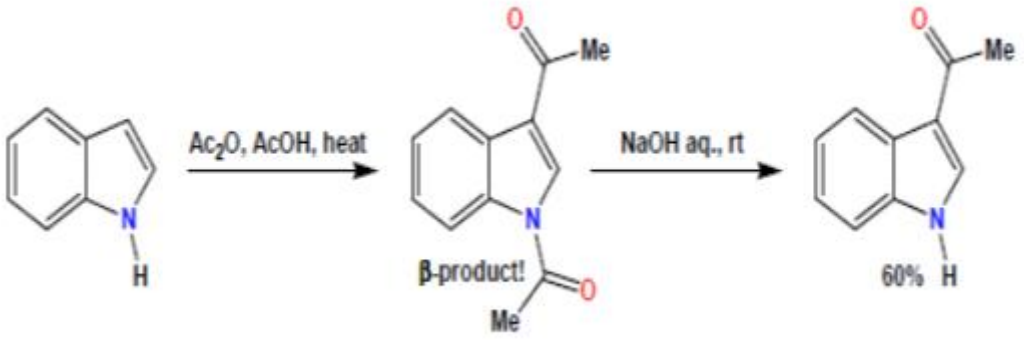
Nitration of Indoles



- Polymerization occurs when there is no substituent at the 2-position.

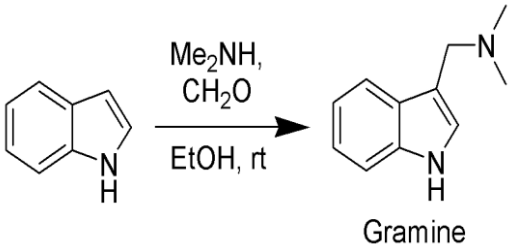
Acylation of Indoles

- Acylation occurs at *C* before *N*



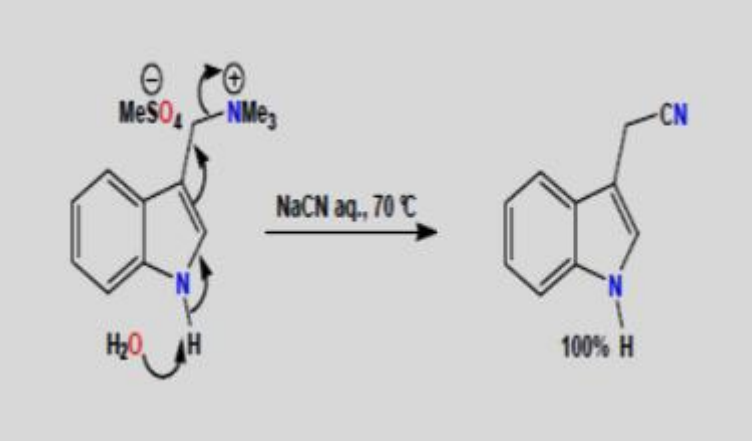
Mannich Reaction

- A very useful reaction for the synthesis of 3-substituted indoles.
- The product (gramine) can be used to access a variety of other 3-substituted indoles.
- Gramine, a useful synthetic intermediate, is produced via a Mannich reaction of indole with dimethylamine and formaldehyde. It is the precursor to indole-3-acetic acid and synthetic tryptophan.

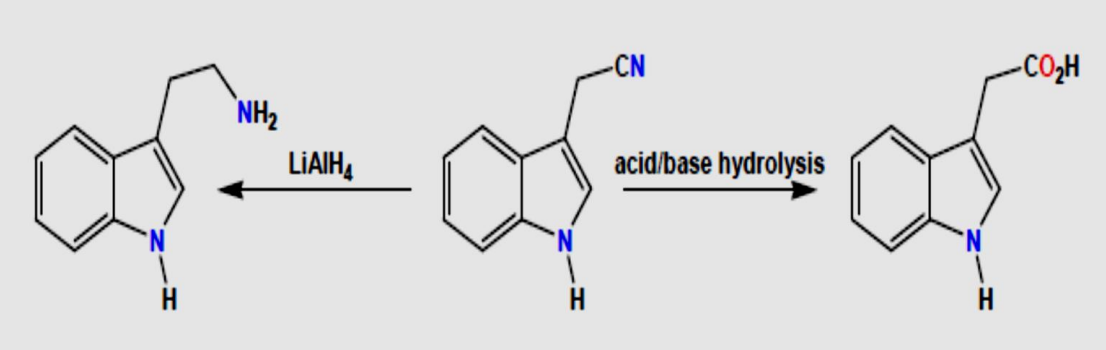


Gramine

Other 3-Substituted Indoles from Gramine

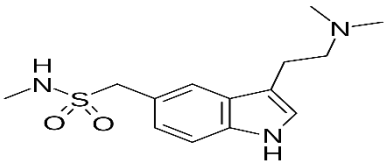


The nitrile group can be modified to give other useful functionality.

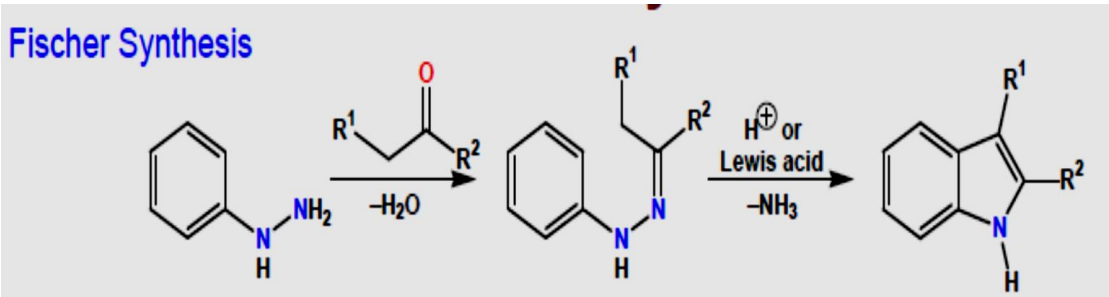


Synthesis of indole (Fischer's indole synthesis)

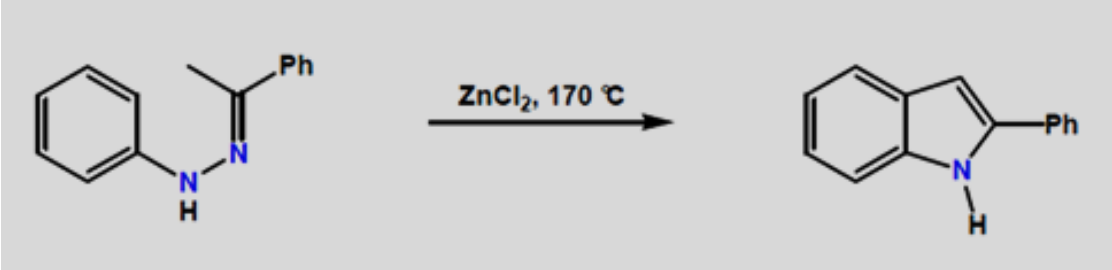
The **Fischer indole synthesis** is a chemical reaction that produces the aromatic heterocycle indole from a (substituted) phenyl hydrazine and an aldehyde or ketone under acidic conditions. The reaction was discovered by Emil Fischer. Today antimigraine drugs of the triptan class are often synthesized by this method.

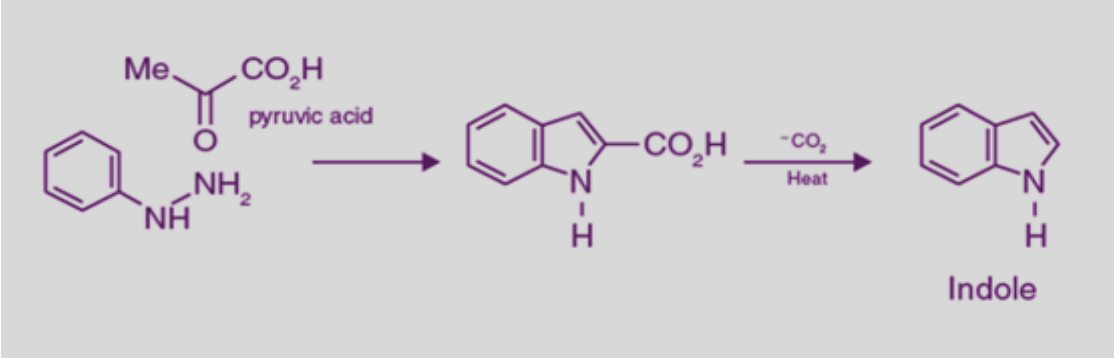


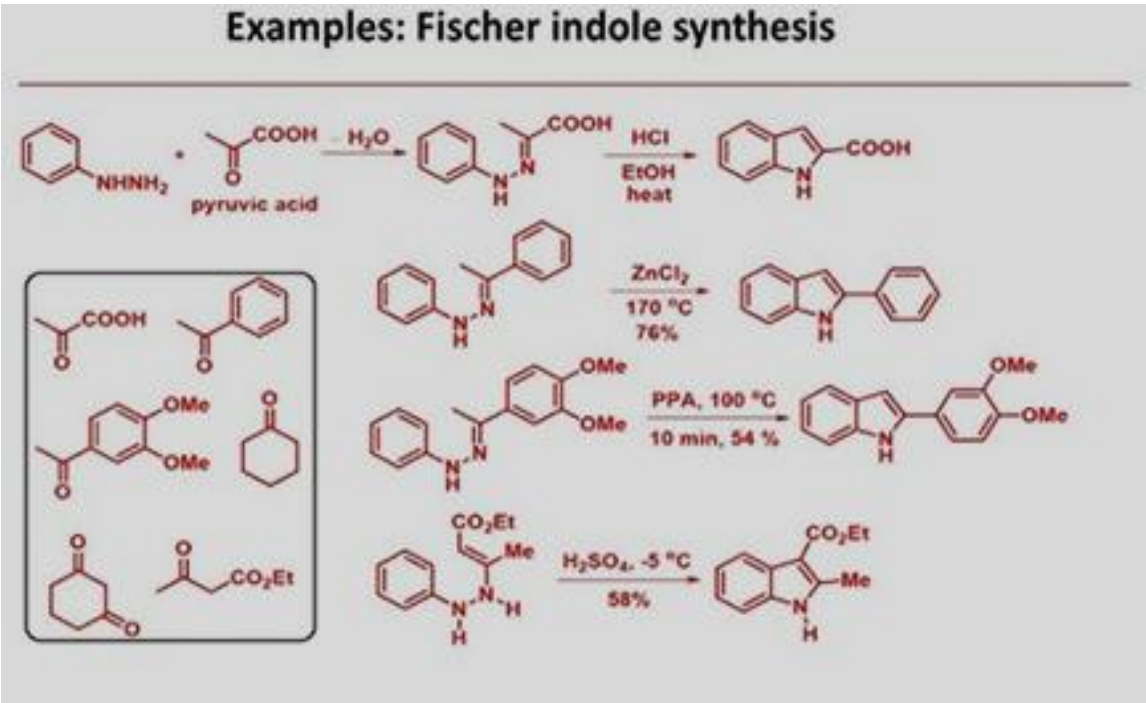
Triptan

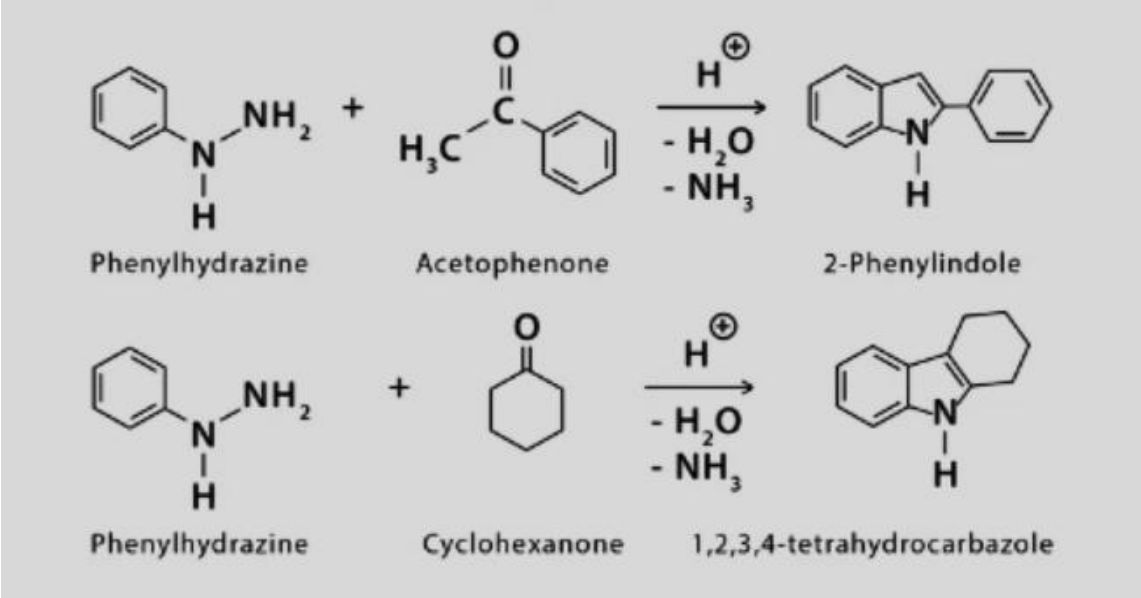

Fischer Synthesis
R1
O
R2
–H2O
NH2
N
H
H⊕ or
Lewis acid
–NH3

Example:


Ph
ZnCl2, 170 °C
N
H


Me
CO2H
pyruvic acid
NH2
NH
CO2H
-CO2
Heat
Indole


Examples: Fischer indole synthesis
NHNH2
COOH
pyruvic acid
H2O
HCl
EtOH
heat
ZnCl2
170 °C
76%
OMe
PPA, 100 °C
10 min, 54 %
CO2Et
H2SO4, -5 °C
58%



Mechanism

Phenylhydrazones having an α-methylene group on treatment with a mineral acid undergoes ring closure through a [3,3] sigma tropic shift with the loss of ammonia. The reaction is known as Fisher's indole synthesis.