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# Chemistry

## SUB. CODE- BSCC2402

*For B.Sc. 4<sup>th</sup> Semester*

### **(Heterocycles)**

### **Module-IV**

## ***Indole: Synthesis***

***By***

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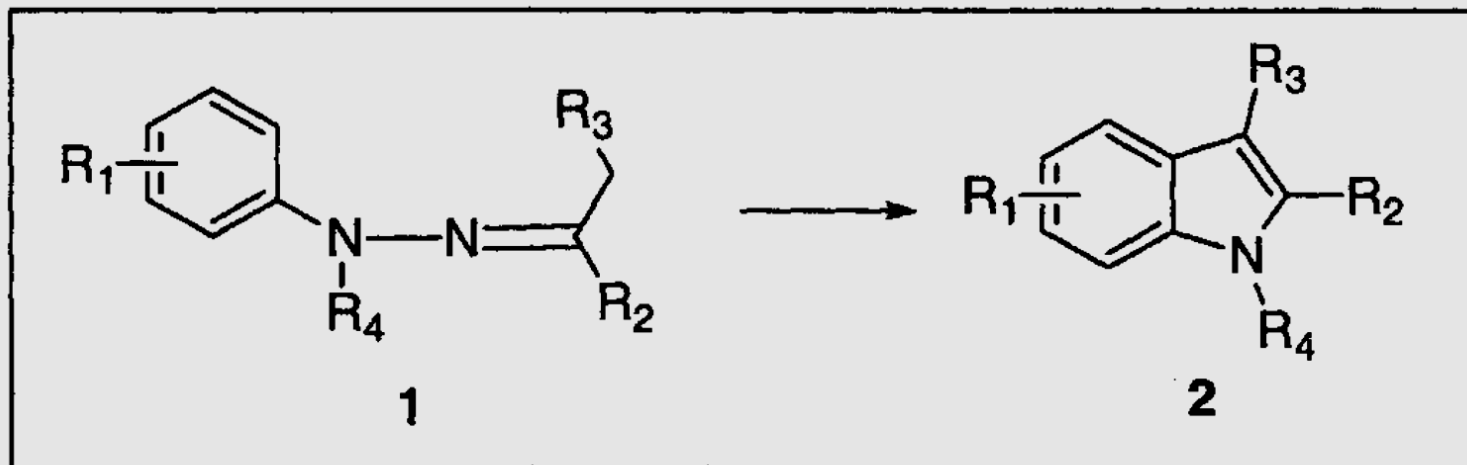


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# Fischer indole synthesis

The Fischer indole synthesis can be regarded as the cyclization of an arylhydrazone **1** of an aldehyde or ketone by treatment with acid catalyst or effected thermally to form the indole nucleus.

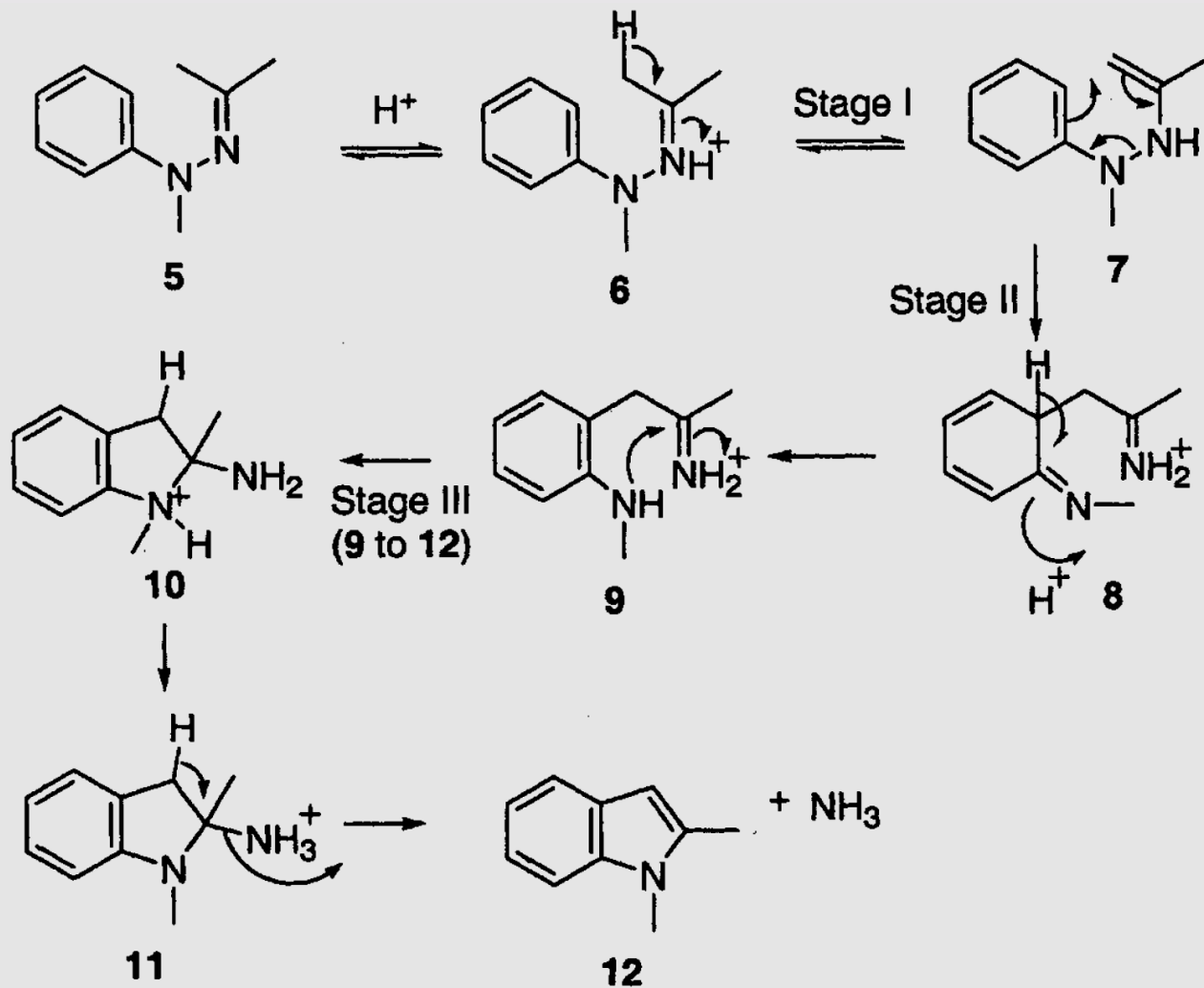




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# Mechanism





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# Mechanism

Step 1: Under acidic conditions, protonation of the imine nitrogen followed by tautomerization to form an ene-hydrazine intermediate **(7)**.

Step 2: After the tautomerization, a **[3,3]** -sigmatropic rearrangement occurs, which provides intermediate **8**.

Step 3: Rearomatization then occurs *via* a proton shift to form the imine **9** which cyclizes to form the 5-membered ring **10**. Finally, loss of ammonia from **11** generates the indole nucleus in **12**.



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## Commonly used catalysts for the Fischer indole synthesis

Glacial acetic acid

Boron trifluoride in acetic acid

Copper (I) chloride

Formic acid

Conc. hydrochloric acid

Hydrogen chloride in ethanol

Hydrogen chloride in acetic acid

Polyphosphoric acid

Conc. sulfuric acid in ethanol

Conc. sulfuric acid in acetic acid

Zinc chloride

p-Toluenesulfonic acid

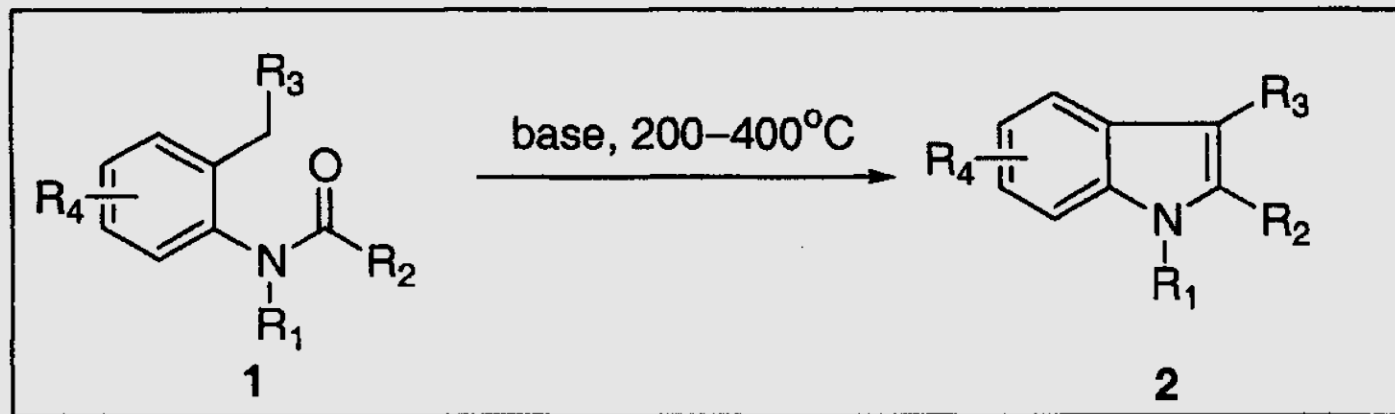


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## Madelung Indole Synthesis

The intramolecular cyclization of **N-acylated-o-alkylanilines** in the presence of a strong base at elevated temperatures is known as the Madelung indole synthesis

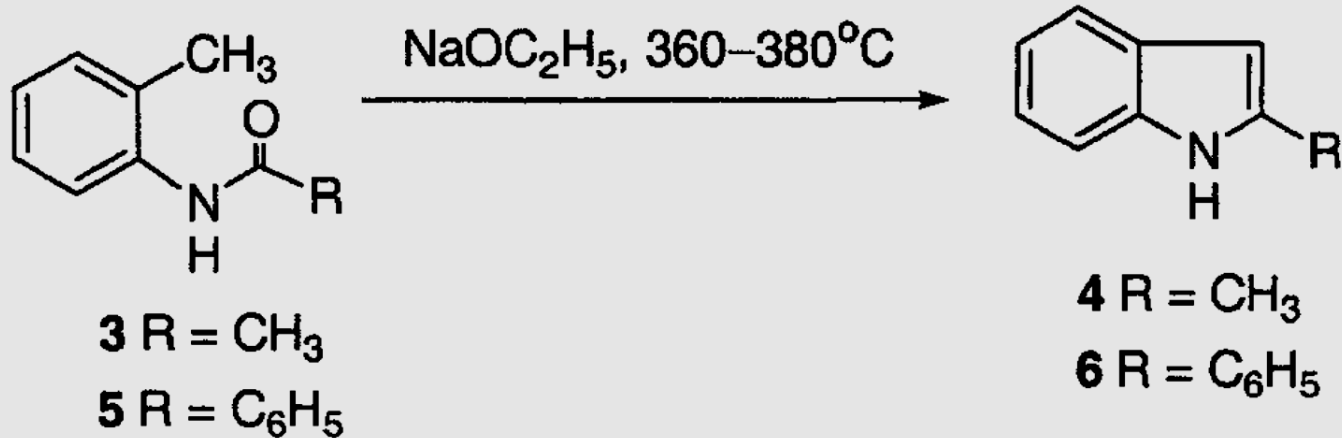




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## First reported Madelung indole synthesis



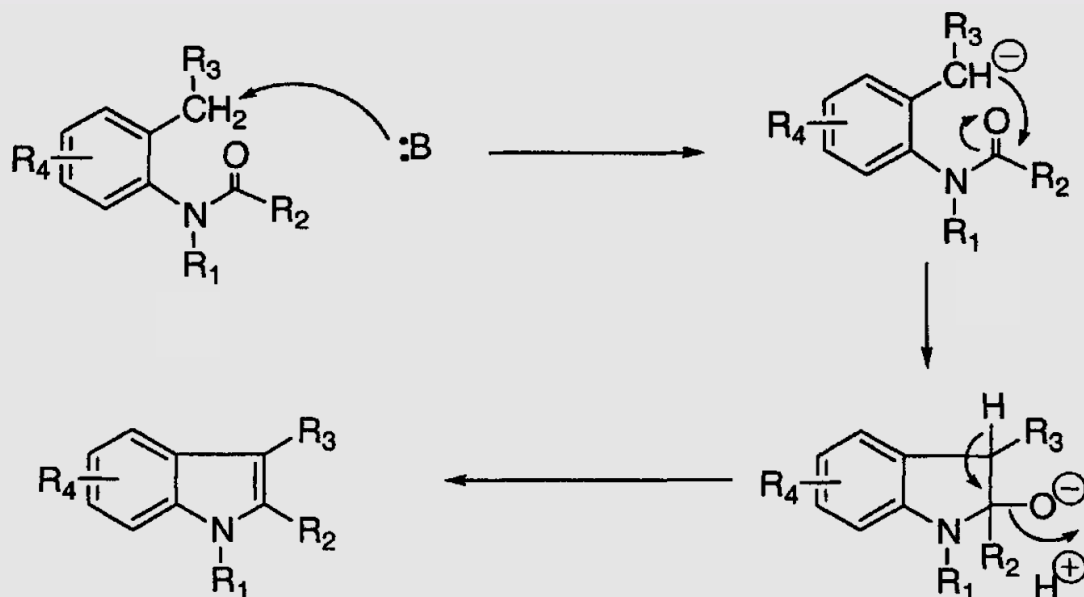


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# Mechanism

The mechanism of the Madelung indole synthesis has not been fully established. Presumably it involves an intramolecular Claisen type condensation.



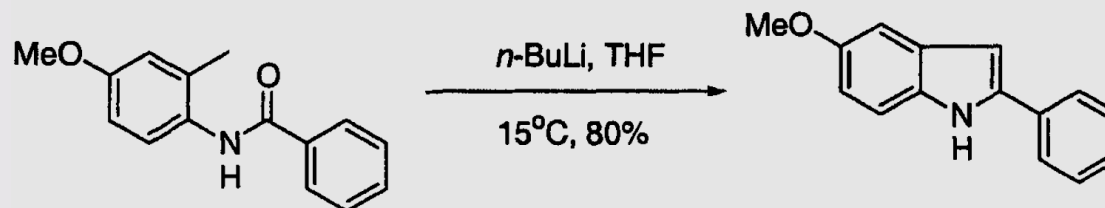
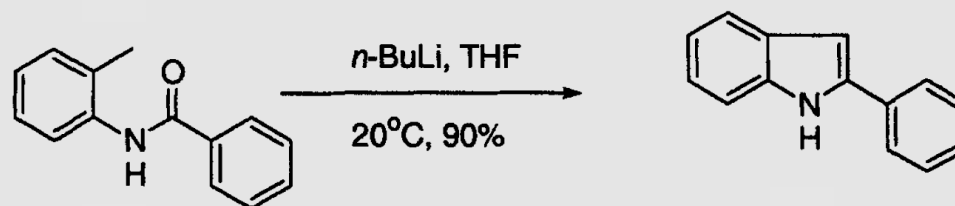
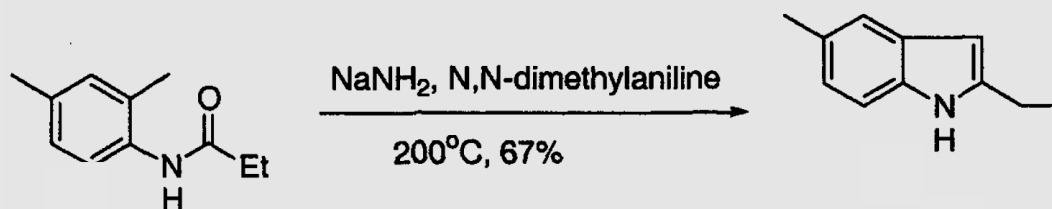
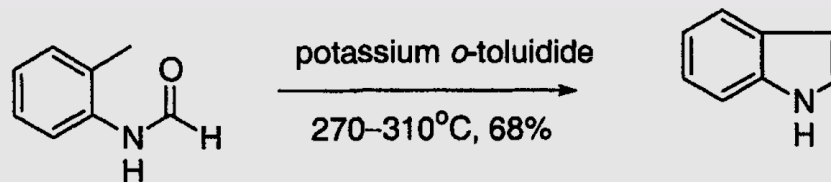




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# Examples of Madelung Indole Synthesis





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# References

1. K.D Sharma and Y. R. Sharma, Kalyani Publishers, Unit-III page-278;
2. University Chemistry, Vol-IV, Dr. U. N. Dash, Dr. KK. Ojha, Himalaya Publishing house, Unit IV, page-378