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Chemistry

SUB. CODE- BSCC2402

For B.Sc. 4th Semester

(Heterocycles)

Module-IV

Synthesis of isoquinolines

By

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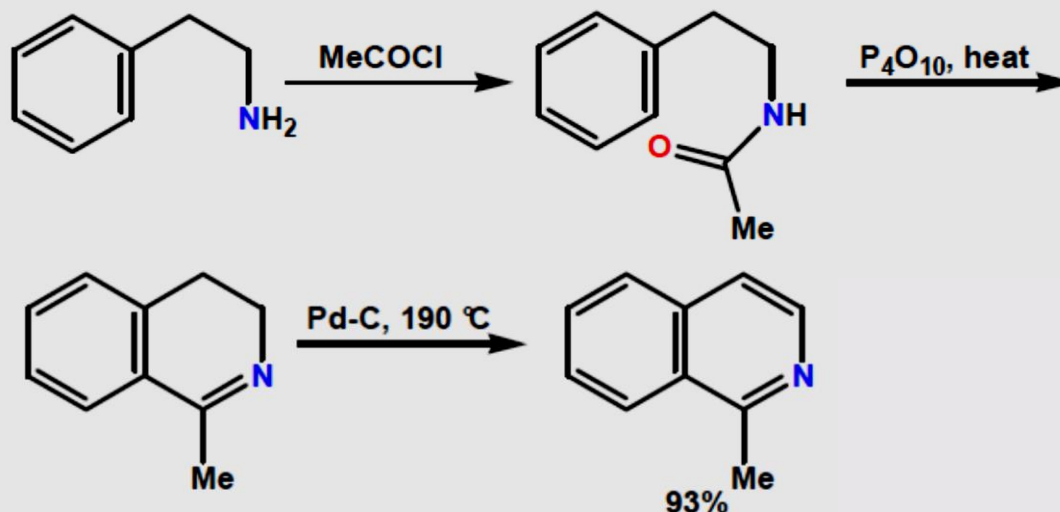
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Synthesis of isoquinolines

Bischler-Napieralski

The Bischler-Napieralski reaction involves the cyclization of **phenethyl amides** in the presence of dehydrating agents such as P_2O_5 or $POCl_3$ to afford 3,4-dihydroisoquinoline products.





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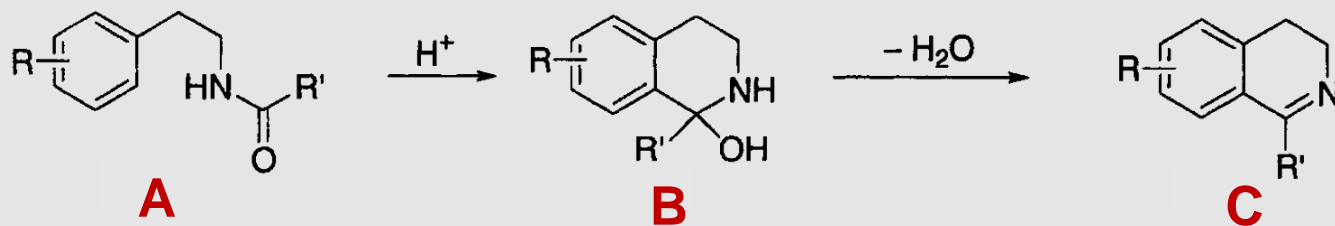
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Mechanism

Early mechanistic proposals regarding the Bischler-Napieralski reaction involved protonation of the amide oxygen by traces of acid present in P_2O_5 or $POCl_3$ followed by electrophilic aromatic substitution to provide intermediate **B**, which upon dehydration would afford the observed product **C**.

However, this proposed mechanism fails to account for the formation of several side products that are observed under these conditions.

Mechanism:1



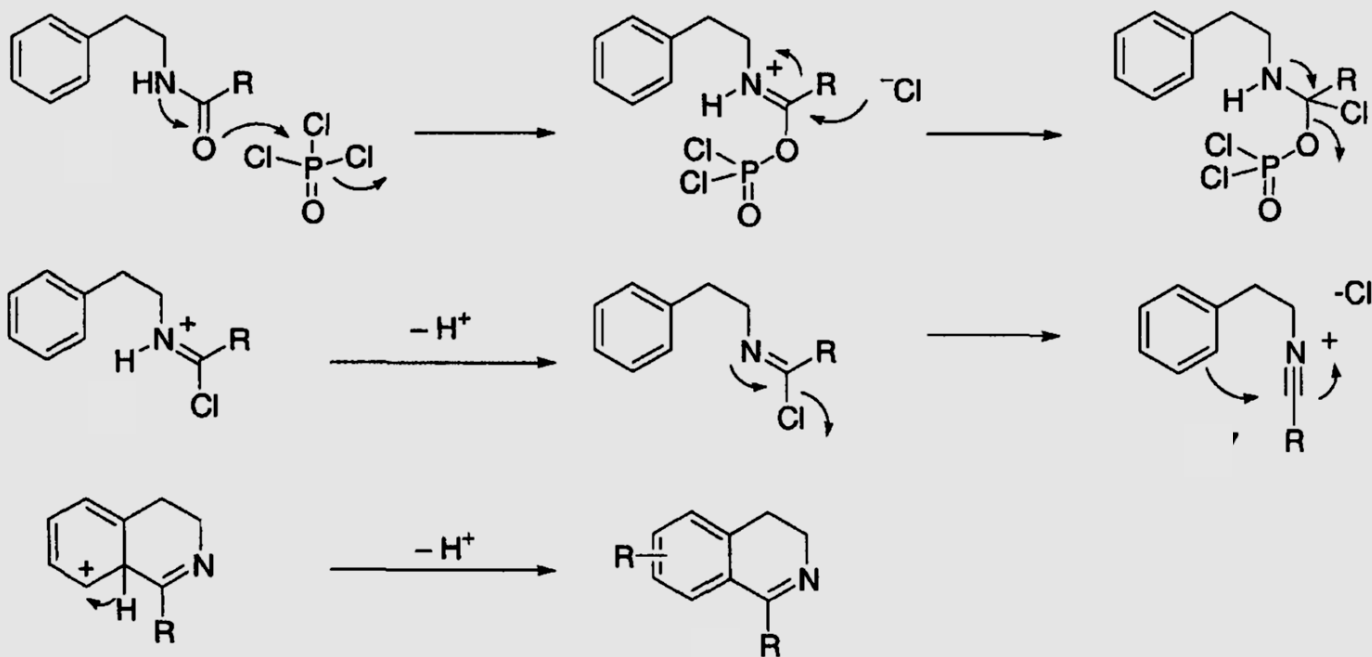


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Mechanism

Mechanism: 2



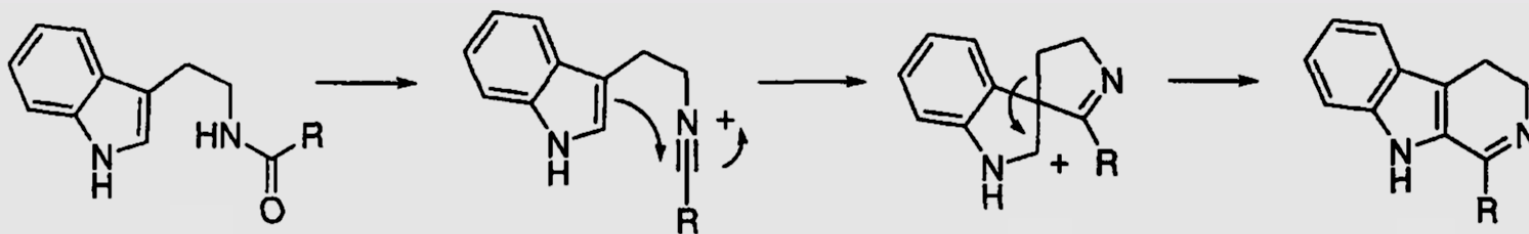


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This reaction is one of the most commonly employed and versatile methods for the synthesis of the isoquinoline ring system, which is found in a large number of alkaloid natural products.

The Bischler-Napieralski reaction is also frequently used for the conversion of N-acyl tryptamine derivatives into p-carbolines.





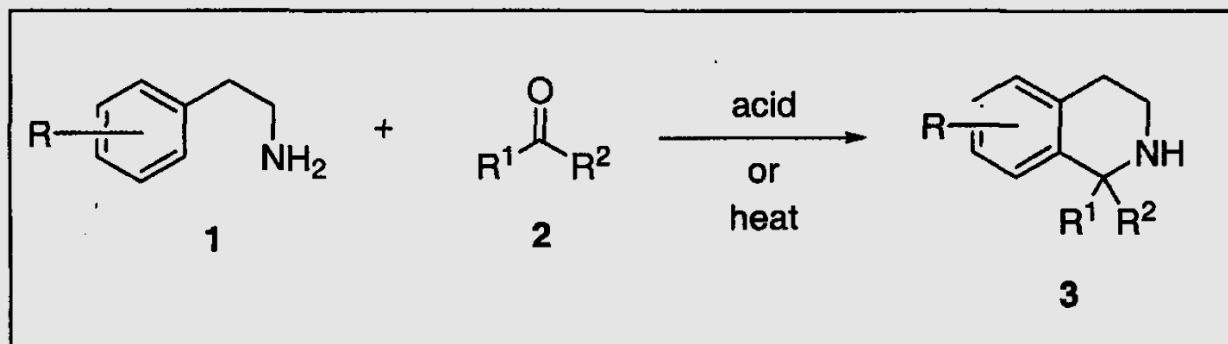
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Pictet-Spengler reaction

This reaction involves the condensation of a P-arylethyl amine **1** with an aldehyde, ketone, or 1,2-dicarbonyl compound **2** to give the corresponding tetrahydroisoquinoline **3**.

These reactions are generally catalyzed by protic or Lewis acids, although numerous thermally-mediated examples are found in the literature.

Aromatic compounds containing electron-donating substituents are the most reactive substrates for this reaction.



R = H, hydroxy, alkoxy, alkyl

R₁, R₂ = H, alkyl, Ar, carbonyl



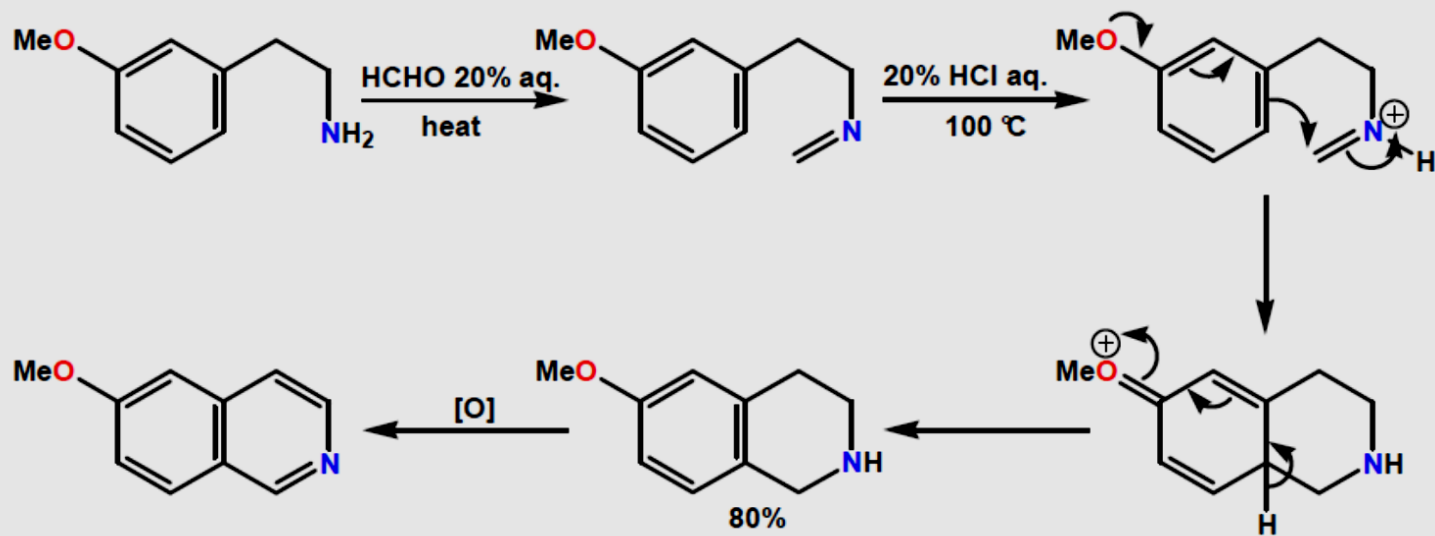
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Pictet-Spengler reaction

Mechanism

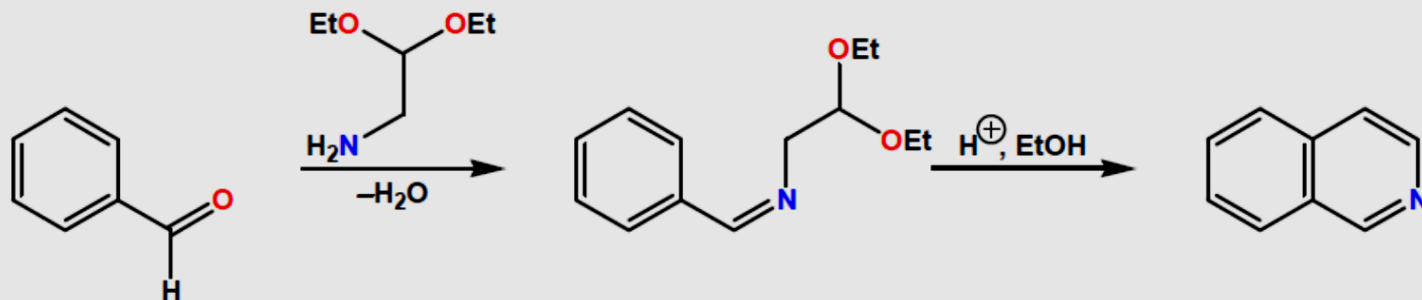




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Pomeranz-Fritsch Synthesis





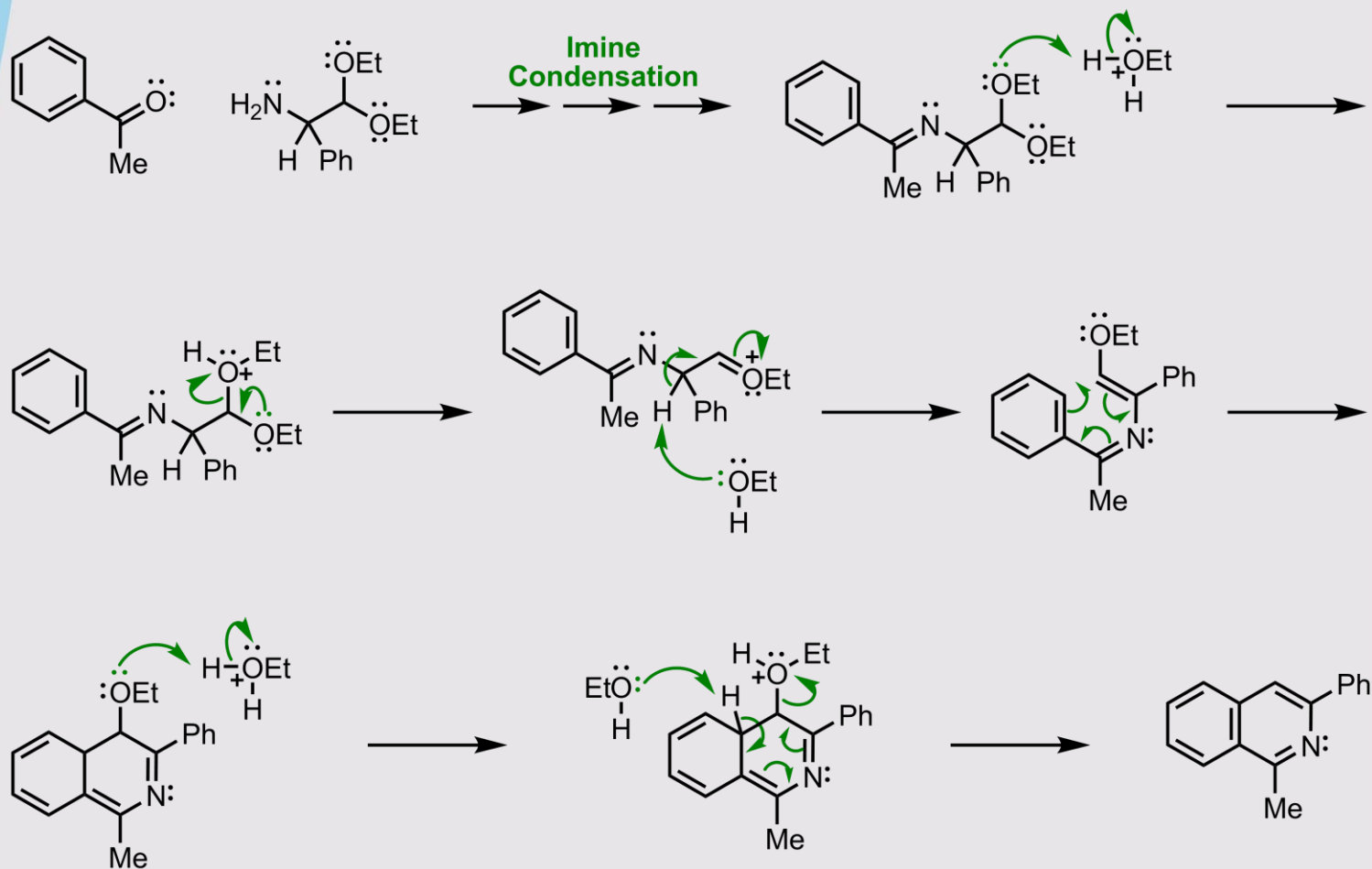
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Pomeranz-Fritsch Synthesis

Mechanism

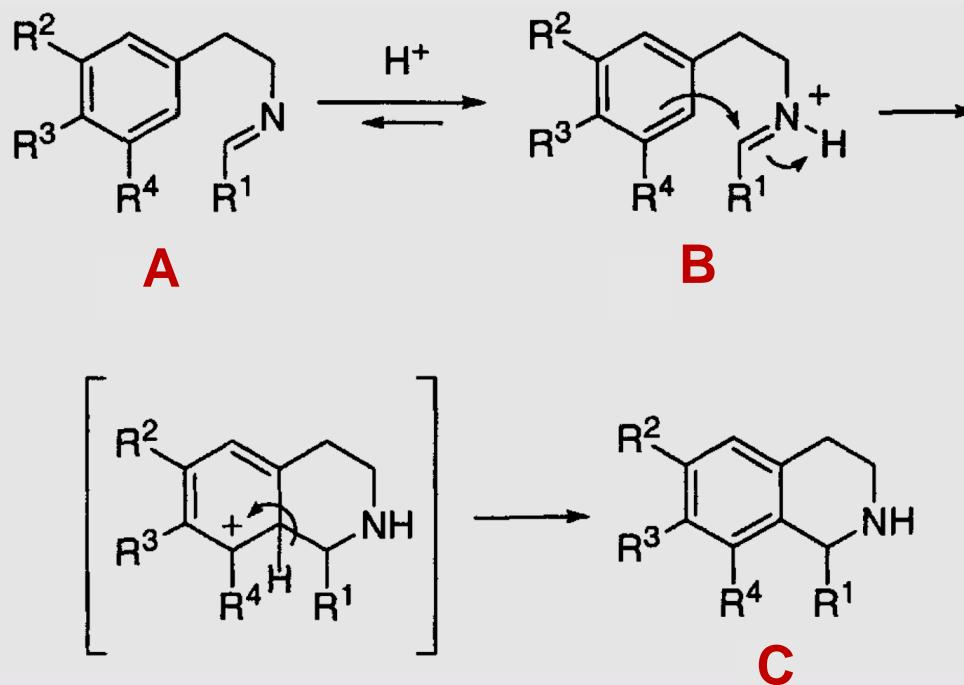




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Under acidic conditions, imine **A** is protonated to give the iminium ion **B** which undergoes an electrophilic aromatic substitution reaction to form the new carbon-carbon bond. Rapid loss of a proton and concomitant re-aromatization gives the tetrahydroisoquinoline **C**.





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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. K. K. Ojha, Himalaya Publishing house, Unit IV, page-379