

**B.Sc. Semester-IV
Core Course-IX (CC-IX)
Organic Chemistry-III**



III. Heterocyclic Compounds

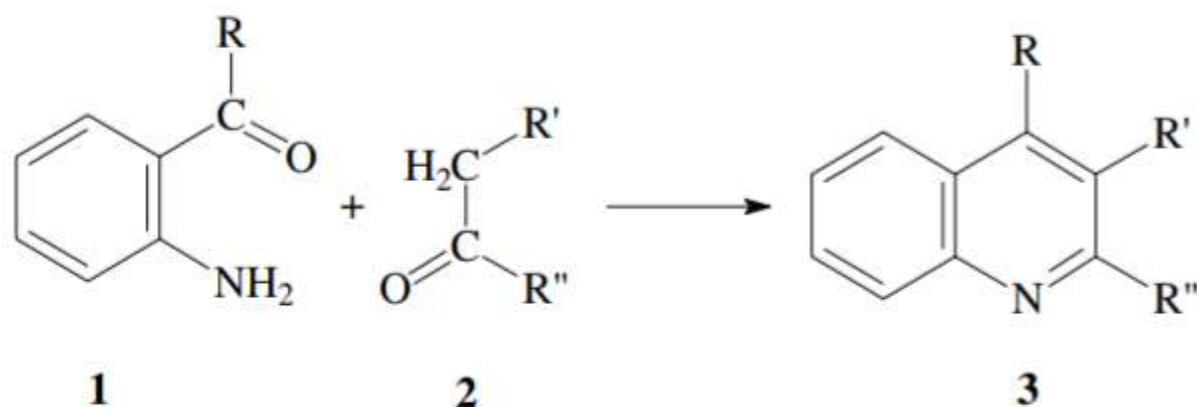
8. Friedlander Quinoline Synthesis



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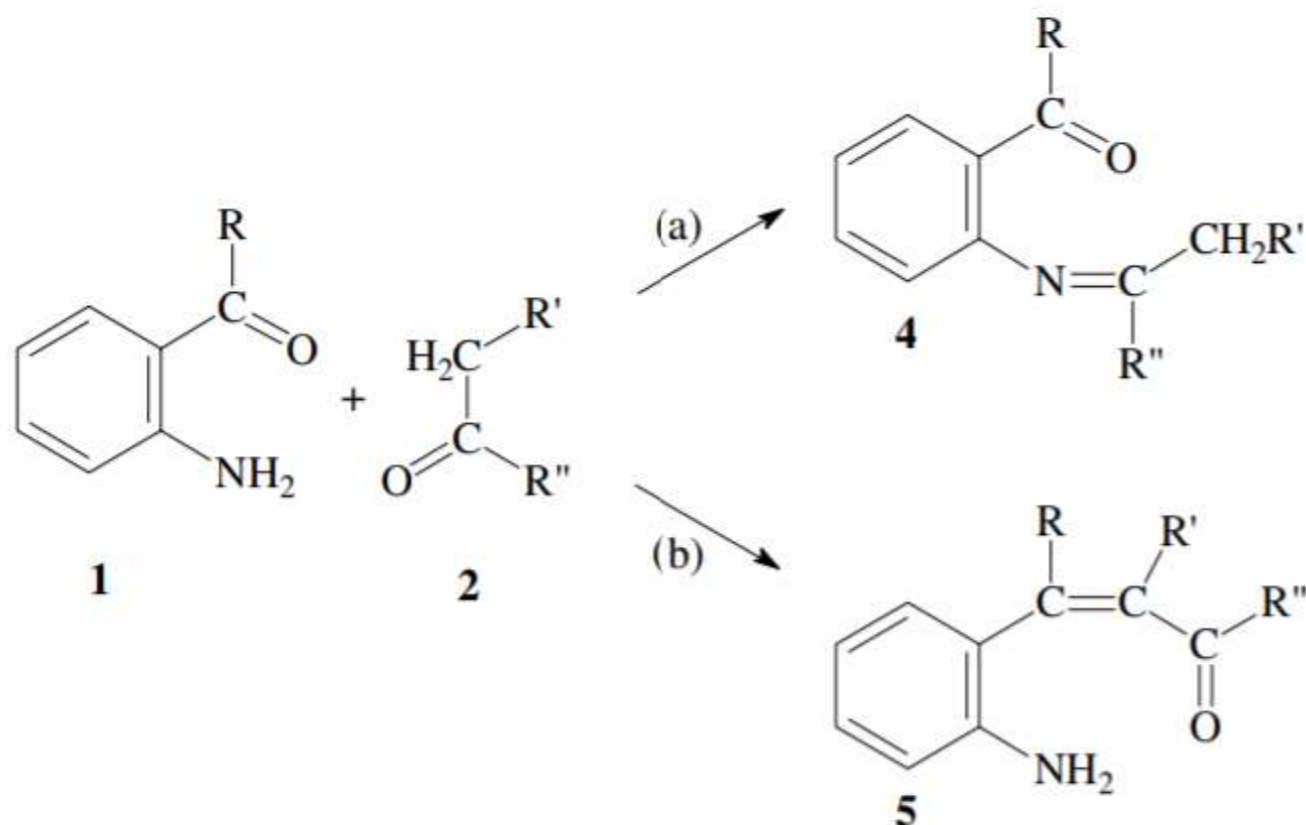
Friedländer Quinoline Synthesis

Condensation of *o*-aminobenzaldehydes with α -methylene carbonyl compounds



Quinolines **3** can be obtained from reaction of *ortho*-aminobenzaldehydes or *o*-aminoarylketones **1** with α -methylene carbonyl compounds.¹⁻³ Various modified procedures are known; a related reaction is the *Skraup quinoline synthesis*.

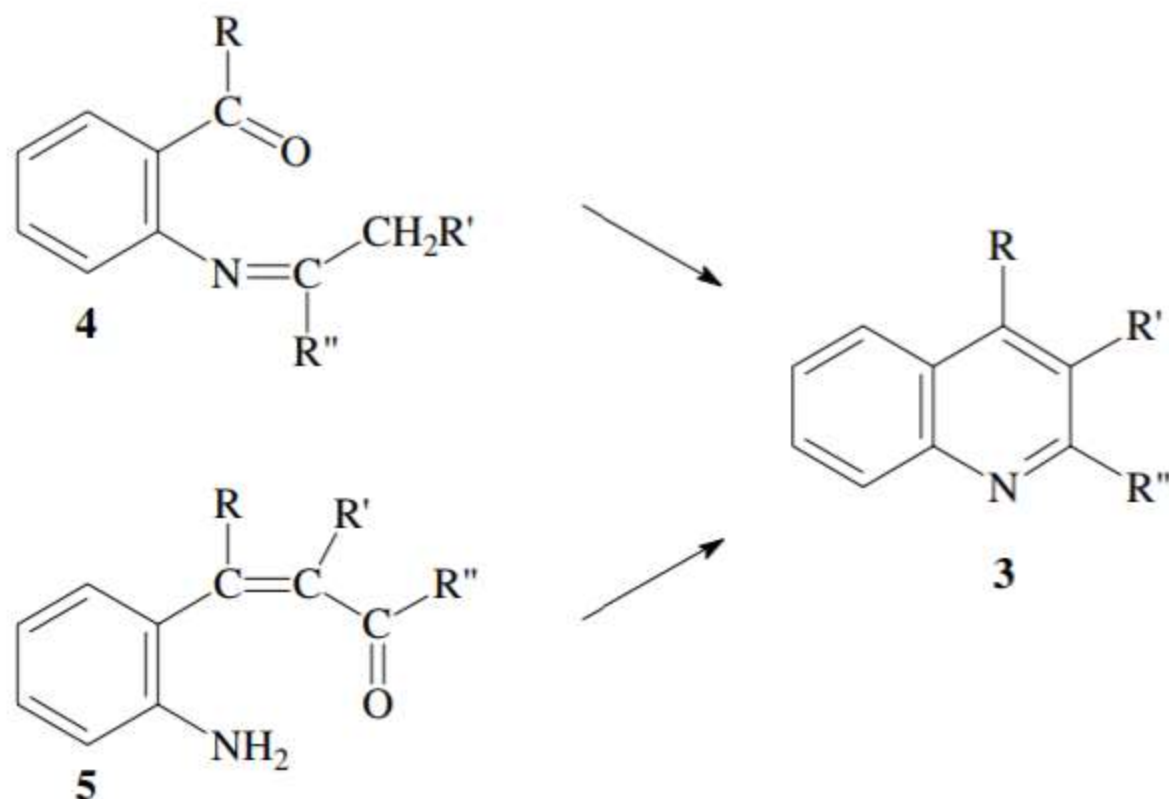
The mechanistic pathway of the ordinary Friedländer synthesis is not rigorously known. Two steps are formulated. In a first step a condensation reaction, catalyzed by acid or base, takes place, that can lead to formation of two different types of products: (a) an imine (Schiff base) **4**, or (b) an α,β -unsaturated carbonyl compound **5**:



Although that reaction has been known for more than one hundred years, it is not clear whether the reaction proceeds *via* pathway (a) or (b) or both. Since the reaction works with a large number of different substrates and under various

reaction conditions, e.g. catalyzed by acid or base, or without a catalyst, it is likely that the actual mechanistic pathway varies with substrate and reaction conditions.³

The next step in both cases is a dehydrative cyclization to yield the quinoline **3**:



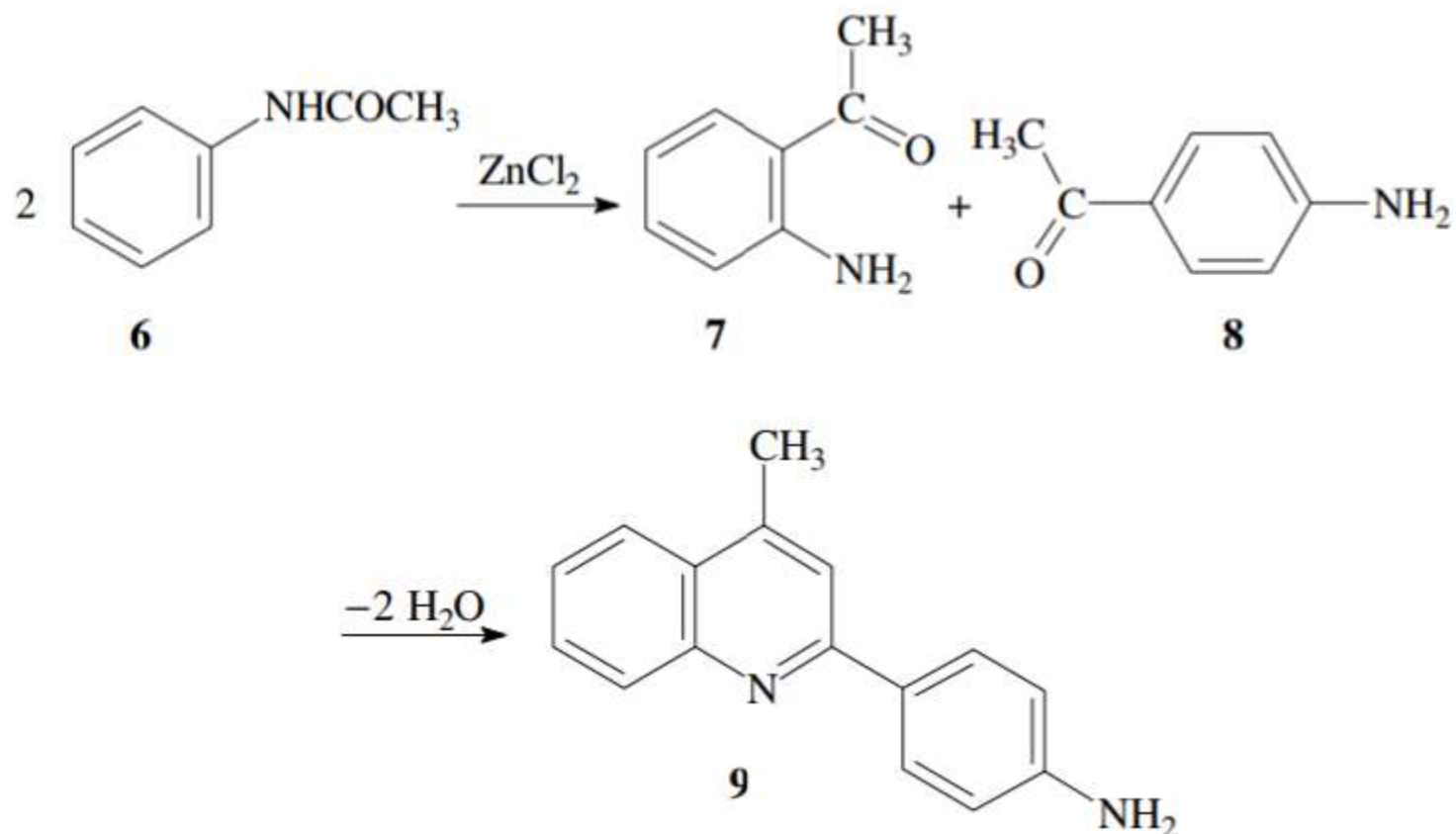
Since various substituents are tolerated, the Friedländer reaction is of preparative value for the synthesis of a large variety of quinoline derivatives. The benzene ring may bear for example alkyl, alkoxy, nitro or halogen substituents. Substituents R, R' and R'' also are variable.³ The reaction can be carried out with various carbonyl compounds, that contain an enolizable α -methylene group. The reactivity of that group is an important factor for a successful reaction.

Usually the reaction is carried out in the presence of a basic catalyst, or simply by heating the reactants without solvent and catalyst.

As basic catalysts KOH, NaOH or piperidine are used. As acidic catalysts are used HCl, H₂SO₄, polyphosphoric acid or *p*-toluenesulfonic acid.

Although the uncatalyzed Friedländer reaction requires more drastic conditions, i.e. temperatures of 150–200 °C, it often gives better yields of quinolines.³

Certain quinolines can be prepared by heating a single suitable compound. For example acetanilide **6** rearranges upon heating in the presence of zinc chloride as catalyst, to give a mixture of *o*- and *p*-acetylaniline **7** and **8**. These two reactants then do undergo the condensation reaction to yield flavaniline **9** that has found application as a dyestuff:⁴



The Friedländer quinoline synthesis is particularly useful for the preparation of 3-substituted quinolines, which are less accessible by other routes. A drawback however is the fact that the required *o*-aminobenzaldehydes or *o*-aminoarylketones are not as easy to prepare as, e.g., the anilines that are required for the Skraup synthesis.

1. P. Friedländer, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 1833–1839.
2. G. Jones, *Chem. Heterocycl. Compd.* **1977**, *32(1)*, 181–207.
3. C. Cheng, S. Yan, *Org. React.* **1982**, *28*, 37–201.
4. E. Besthorn, O. Fischer, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 68–75.

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