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

III. Heterocyclic Compounds
4. Hantzsch Pyridine Synthesis

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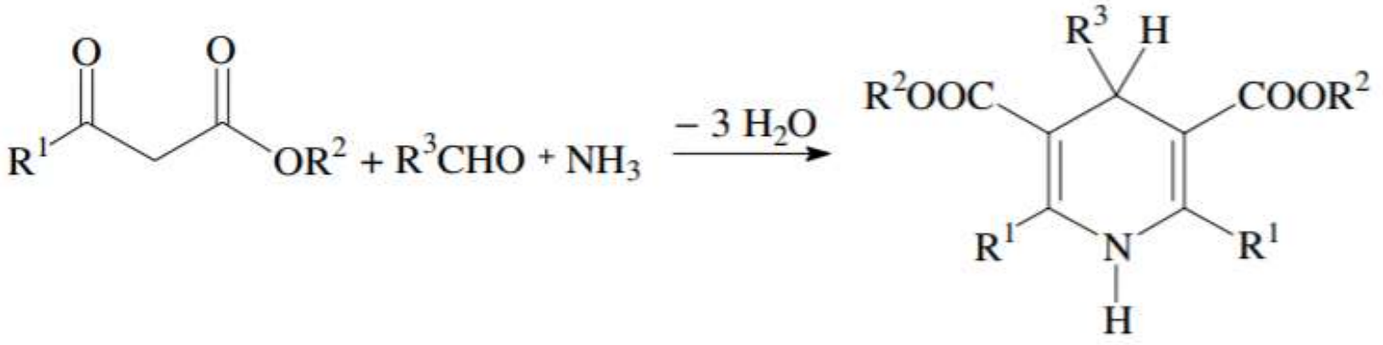
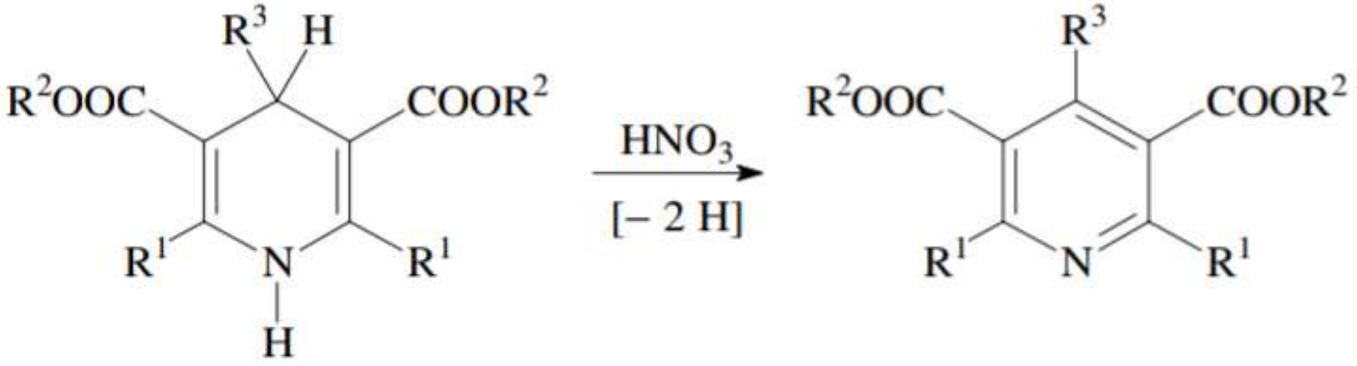
Hantzsch Pyridine Synthesis

1,4-Dihydropyridines from condensation of β-ketoesters with aldehydes and ammonia



1 **2** **3**

A general method for the construction of a pyridine ring is the *Hantzsch synthesis*.[1–4] A condensation reaction of two equivalents of a β-ketoester **1** with an aldehyde **2** and ammonia leads to a 1,4-dihydropyridine **3**, which can be oxidized to the corresponding pyridine **4**—for example by nitric acid:



3 **4**

In general the oxidation does not affect the substituent R^3 at C-4; however if R^3 is a benzyl group $PhCh_2-$, this will be cleaved from C-4, and a hydrogen is retained in that position (unusual oxidation to yield pyridine).

The classical synthesis started from acetoacetic ester (**1**, $R^1 = CH_3$, $R^2 = C_2H_5$) and acetaldehyde (**2**, $R^3 = CH_3$). By subsequent cleavage of the substituents from C-3 and C-5, the collidine **5** was obtained ($R^1 = R^3 = CH_3$):[1]

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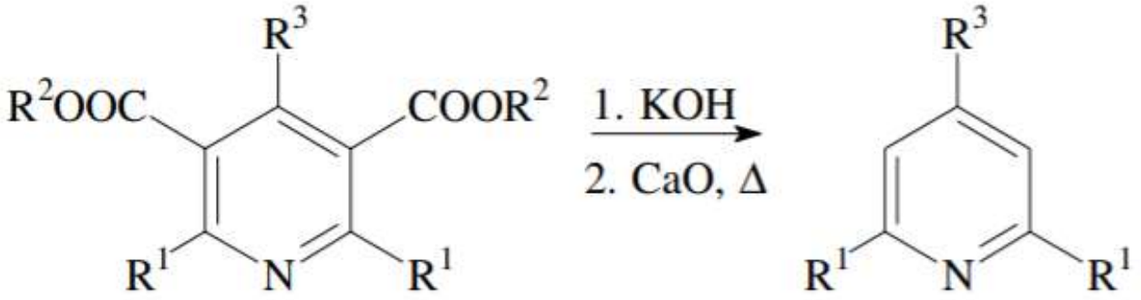
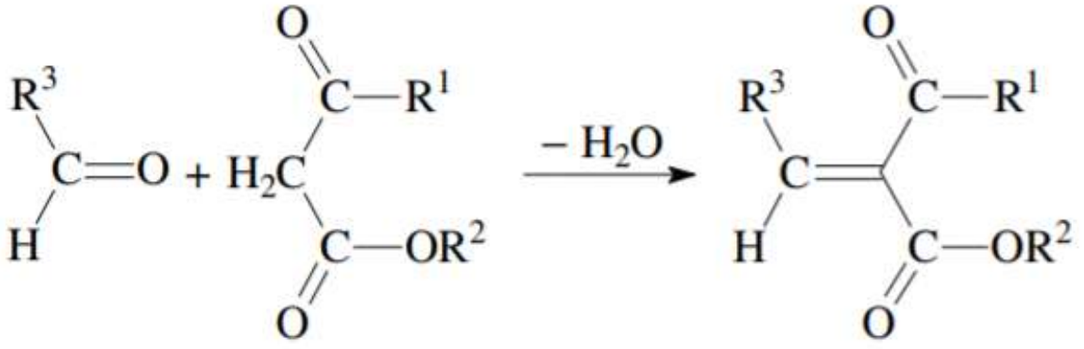


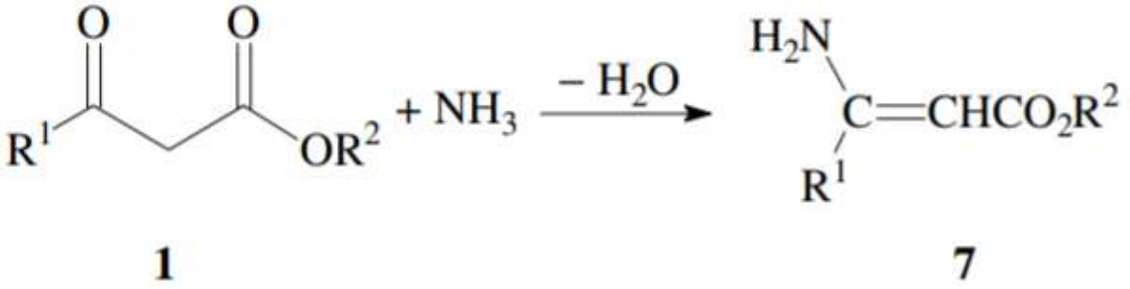
4 **5**

The initial step of the Hantzsch synthesis is likely to be a *Knoevenagel condensation* reaction of aldehyde **2** and β-ketoester **1** to give the α,β-unsaturated ketoester **6**:



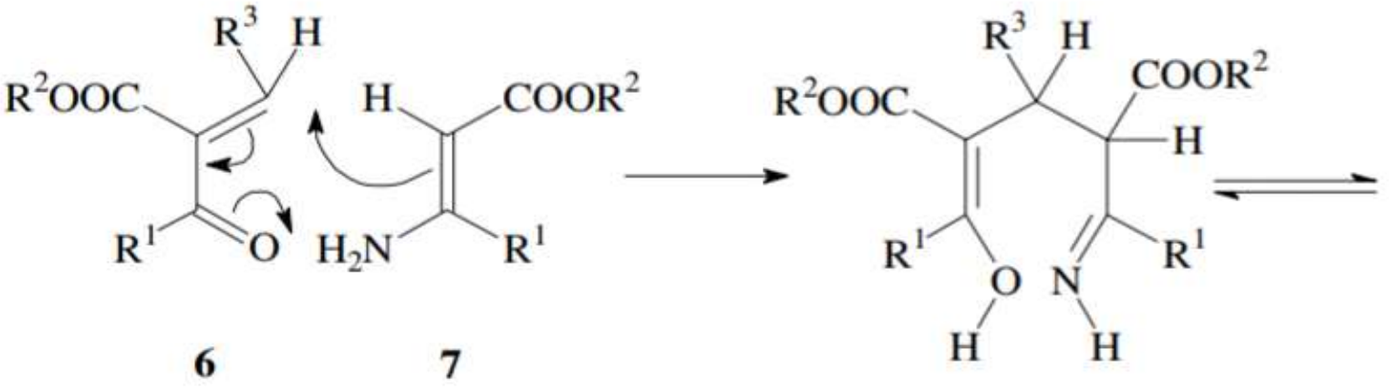
2 **1** **6**

From β-ketoester **1** and ammonia the enamine **7** and water is formed:

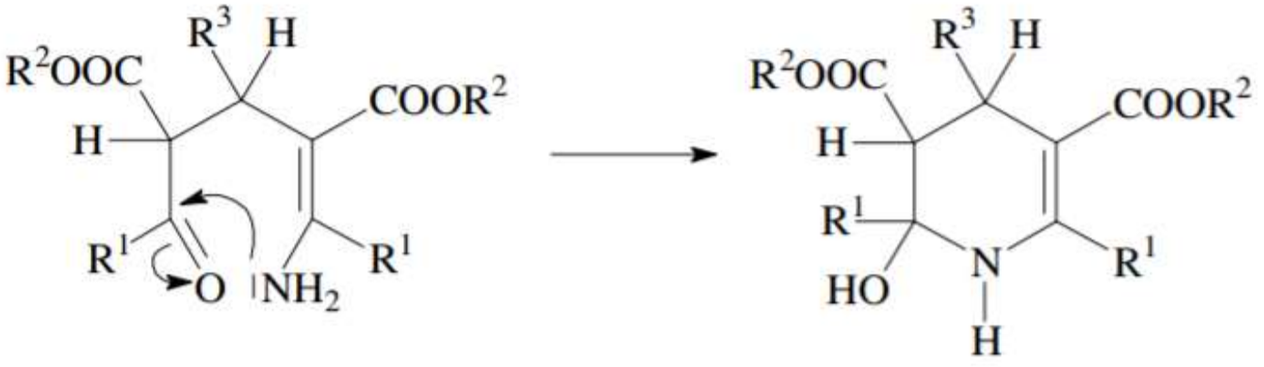


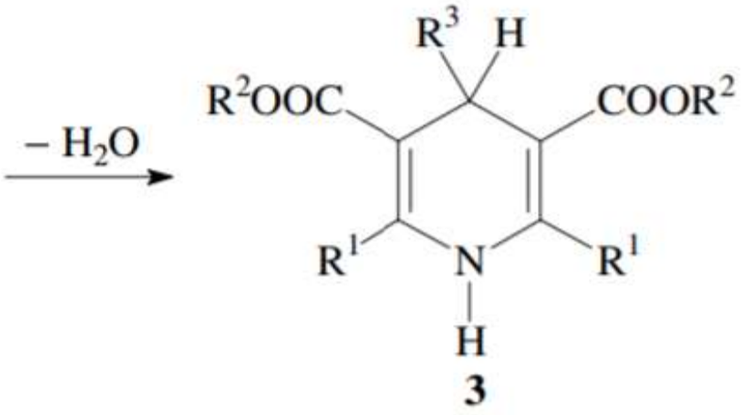
1 **7**

The ring synthesis then proceeds in subsequent steps by condensation of the unsaturated ketoester **6** and enamine **7** to yield a 1,4-dihydropyridine **3**:



6 **7**





3

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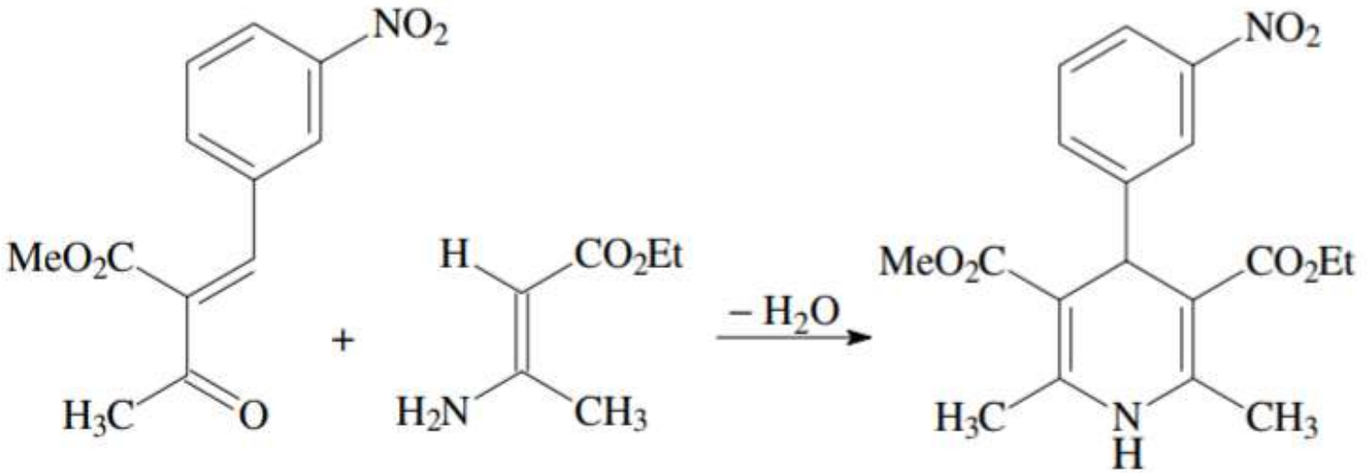
1,4-Dihydropyridines not only are intermediates for the synthesis of pyridines, but also are themselves an important class of N-heterocycles;[5,6] an example is the coenzyme NADH. Studies on the function of NADH led to increased interest in the synthesis of dihydropyridines as model compounds. Aryl-substituted dihydropyridines have been shown to be physiologically active as calcium antagonists. Some derivatives have found application in the therapy of high blood pressure and angina pectoris.[7] For that reason the synthesis of 1,4-dihydropyridines has been the subject of intensive research and industrial use. The Hantzsch synthesis has thus become an important reaction.

Many dihydropyridines that are of therapeutic interest are unsymmetrically substituted at C-3 and C-5. The synthesis of such compounds is possible from separately prepared Knoevenagel condensation products **6**, as is outlined in the following scheme for nitrendipine **8**, which is used in the medical treatment of high blood pressure.[4]



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The reaction is of wide scope. Instead of ester groups as substituents at C-3 and C-5, other acceptor substituents—e.g. oxo, cyano, sulfonyl or nitro groups—can be employed in order to stabilize the 1,4-dihydropyridine system.

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4. F. Bossert, H. Meyer, E. Wehinger, *Angew. Chem.* **1981**, *93*, 755–763; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762.
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