

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



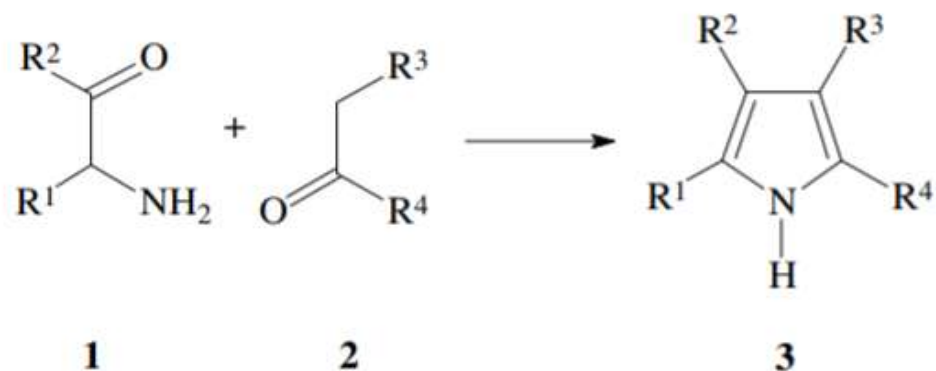
## **III. Heterocyclic Compounds 2. Knorr Pyrrole Synthesis**



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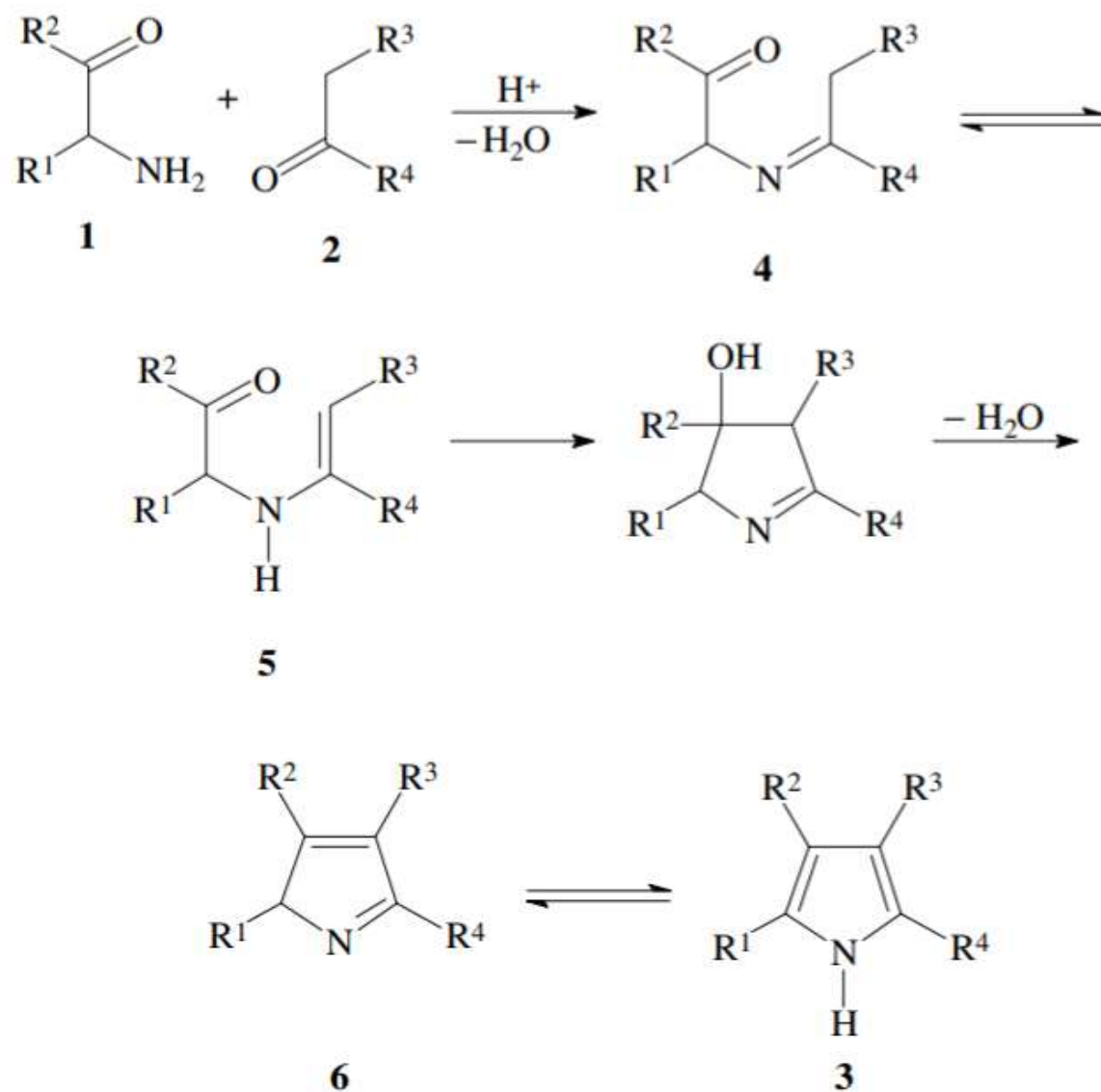
## Knorr Pyrrole Synthesis

Formation of pyrroles by condensation of ketones with  $\alpha$ -aminoketones

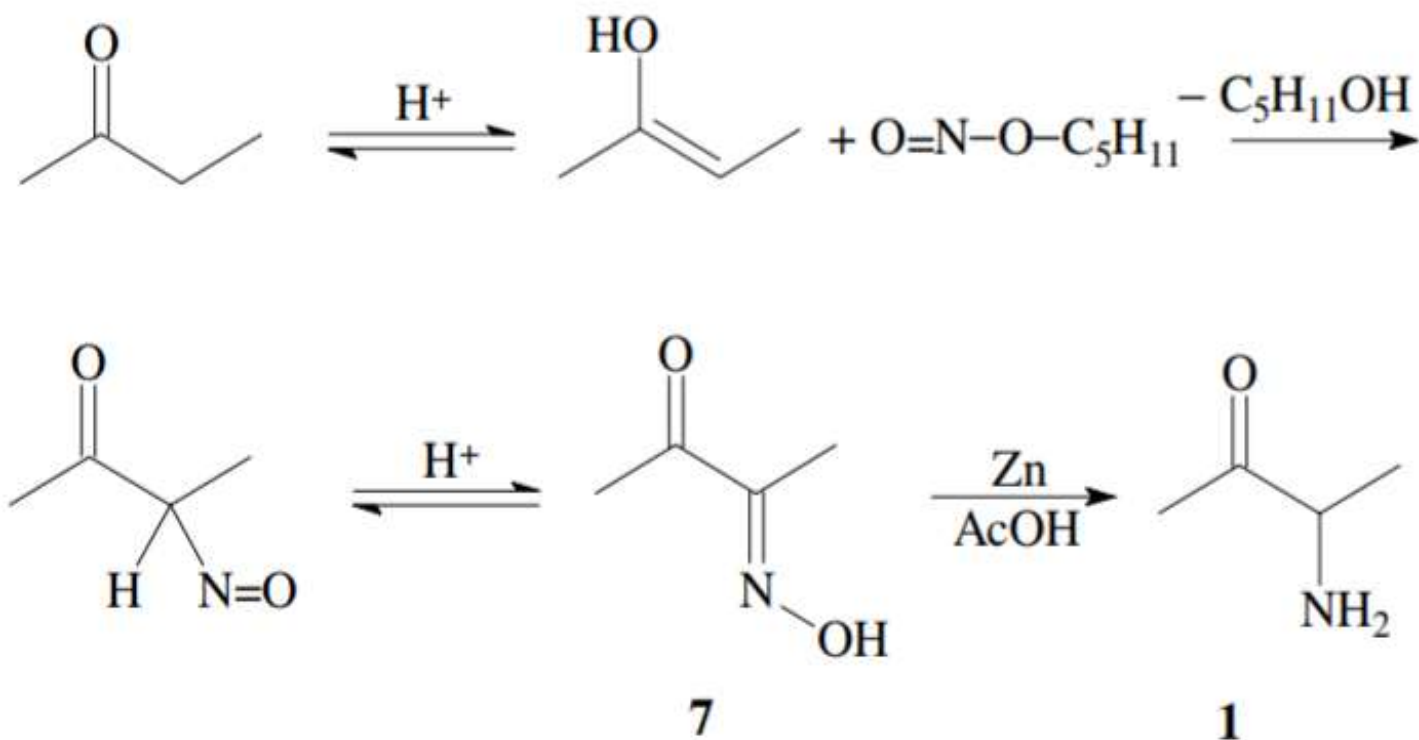


By a condensation reaction of an  $\alpha$ -aminoketone **1** with a ketone **2**, a pyrrole **3** can be obtained. This reaction is known as the Knorr pyrrole synthesis.<sup>1,2</sup>

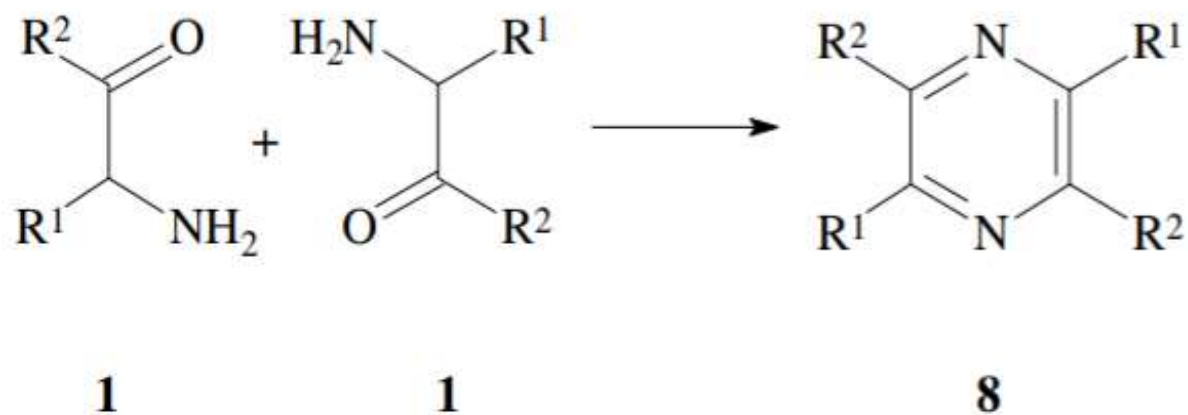
A mechanism has been formulated, starting with a condensation to give the imine **4**, that can tautomerize to the corresponding enamine **5**. The latter can be isolated in some cases, thus supporting the formulated mechanism. A cyclization and subsequent dehydration leads to the imine **6**, which tautomerizes to yield the aromatic pyrrole **3**:



The aminoketone **1**, required as starting material, can be obtained by a *Neber rearrangement* from a *N*-tosylhydrazone. Another route to  $\alpha$ -aminoketones starts with the nitrosation of an  $\alpha$ -methylene carbonyl compound—often *in situ*—to give the more stable tautomeric oxime **7**, which is then reduced in a subsequent step to yield **1**:



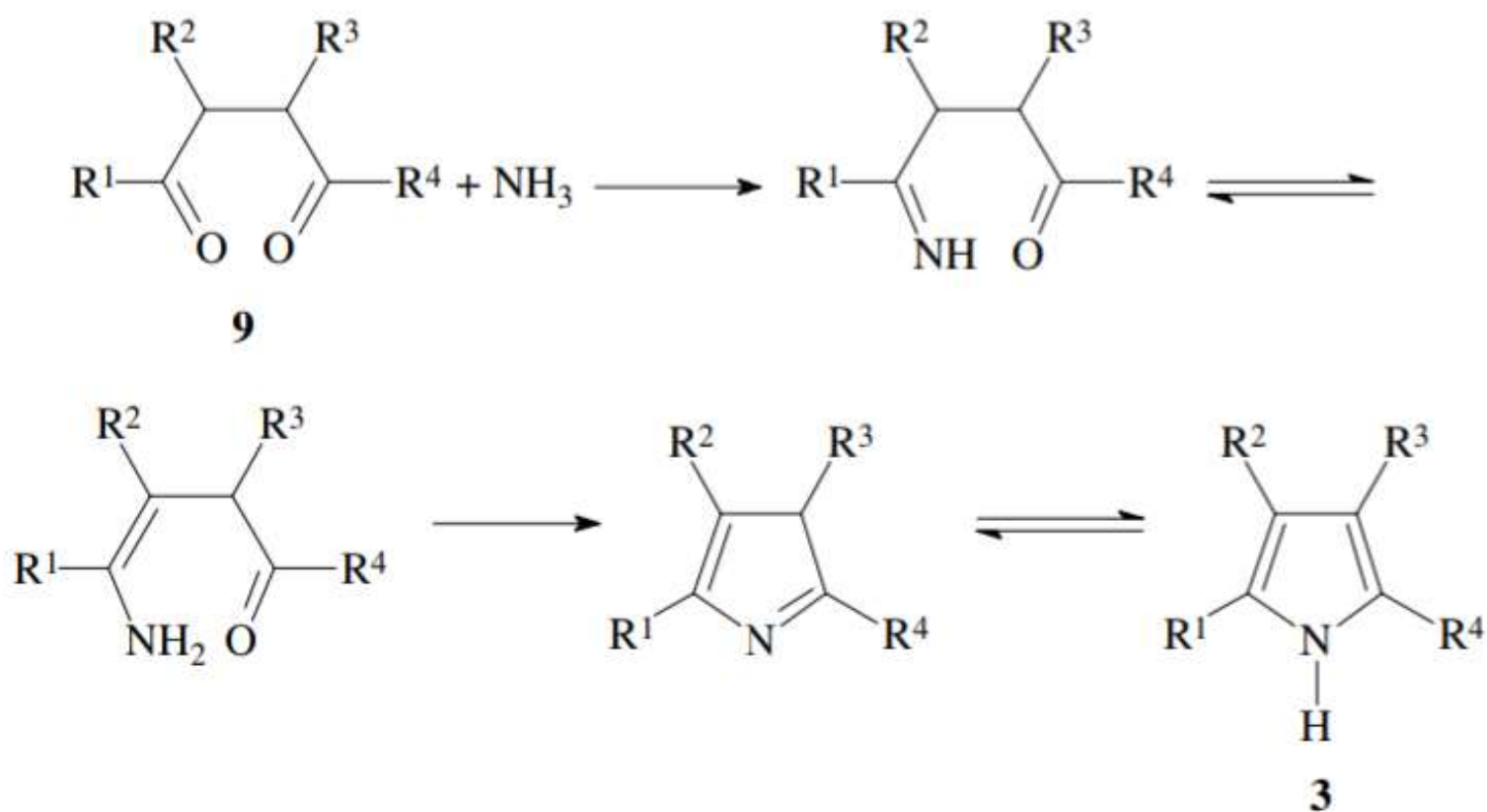
With excess ketone, the preparation of the aminoketone and subsequent condensation to a pyrrole can be conducted in one pot. In a side-reaction  $\alpha$ -aminoketones can undergo a self-condensation to give pyrazines **8**:



The self-condensation is largely suppressed in reactions with those ketones **2**, that are activated by an electron-withdrawing substituent  $R^3$  or  $R^4$ . The carbonyl activity is then increased, and the enamine-intermediate **5** is favored over the imine **4**, by conjugation with the electron-withdrawing group.<sup>3</sup>

Mainly C-substituted pyrroles have been synthesized by application of the Knorr pyrrole synthesis; however N-substituted pyrroles can also be prepared, when starting with secondary aminoketones, e.g. bearing an N-methyl or N-phenyl substituent.

Another important route to pyrroles is offered by the *Paal-Knorr reaction*;<sup>4</sup> where the pyrrole system is formed by condensation of a 1,4-diketone **9** with ammonia:<sup>5</sup>



This reaction is of wide scope; it is limited only by the availability of the appropriate 1,4-diketone. 1,4-Diketones are easily accessible, e.g. by the *Nef reaction*.

Methods for the synthesis of pyrroles are of importance, since the pyrrole unit is found in natural products widespread in nature. For example a pyrrole unit is the building block of the porphyrin skeleton, which in turn is the essential structural subunit of chlorophyll and hemoglobin.

1. L. Knorr, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635–1642.
2. R. P. Bean in *The Chemistry of Pyrroles* (Ed.: R. A. Jones), Wiley, New York, **1990**, *Vol. 48/1*, p. 108–113.
3. A. H. Corwin, *Heterocyclic Compounds*, Wiley, New York, **1950**, *Vol. 1*, p. 287–290.
4. C. Paal, *Ber. Dtsch. Chem. Ges.*, **1885**, *18*, 367–371.
5. R. P. Bean in *The Chemistry of Pyrroles* (Ed.: R. A. Jones), Wiley, New York, **1990**, *Vol. 48/1*, p. 206–220.

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