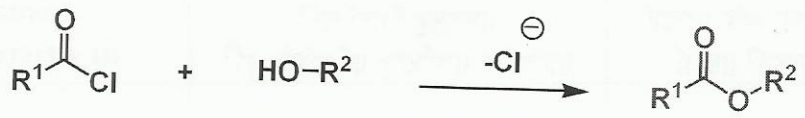
More key reactions in heterocycle synthesis

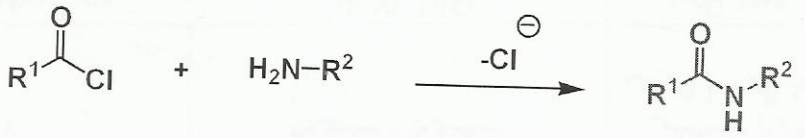
2a

Interconversion of functional groups in the same oxidation state as carboxylic acids, as shown below, most commonly occurs through addition-elimination reactions *via* a tetrahedral intermediate.

Synthesis of esters

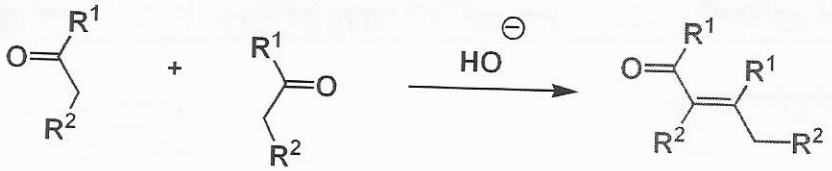


Synthesis of amides

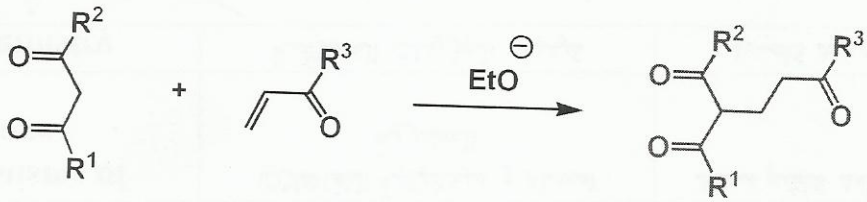


Carbon-carbon bond forming reactions covered in the *Bifunctional Chemistry* course are also important.

Aldol reactions



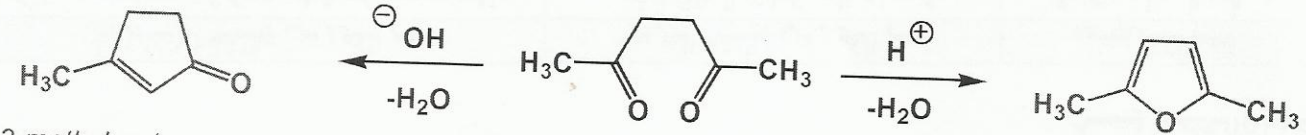
Conjugate additions



Heterocycles from 1,4-diketones: the Paal-Knorr synthesis

2b

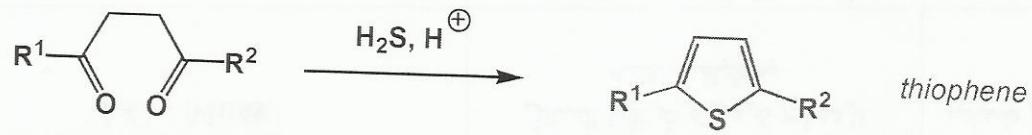
When hexan-2,5-dione is treated with base an aldol-dehydration takes place, *via* the enolate, yielding an α,β-unsaturated ketone (3-methylcyclopentenone). Treatment with a strong acid however yields a furan (2,5-dimethylfuran) *via* the enol.



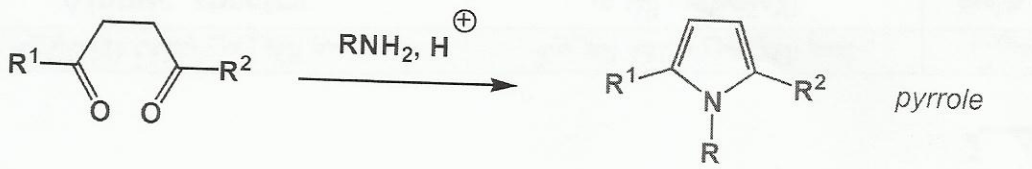
3-methylcyclopentenone

2,5-dimethylfuran

Related reactions under acidic conditions can yield pyrroles and thiophenes.



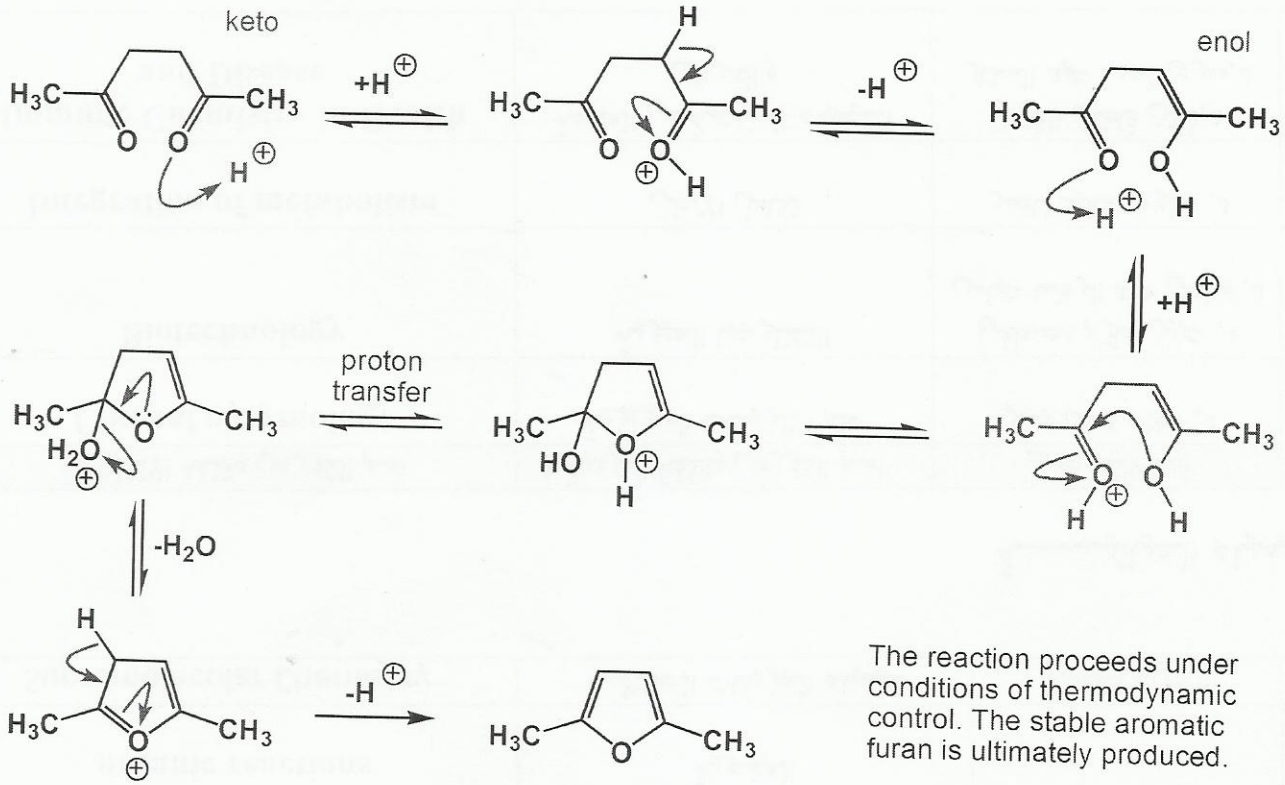
thiophene



pyrrole

Mechanism of the Paal-Knorr synthesis

3a

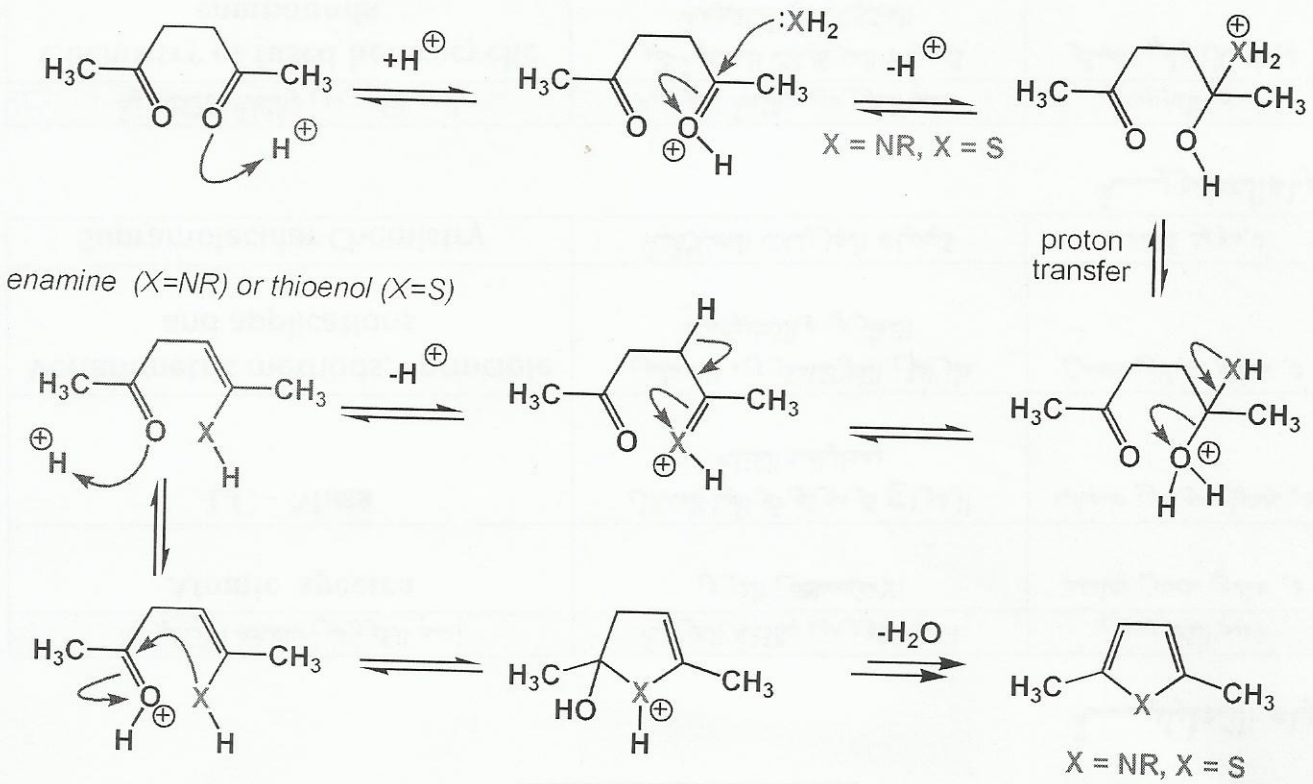


The reaction proceeds under conditions of thermodynamic control. The stable aromatic furan is ultimately produced.

Paal-Knorr synthesis: pyrroles and thiophenes

3b

The chemistry involved here is essentially the same as the furan example before, but an enamine or thioenol intermediate is needed.



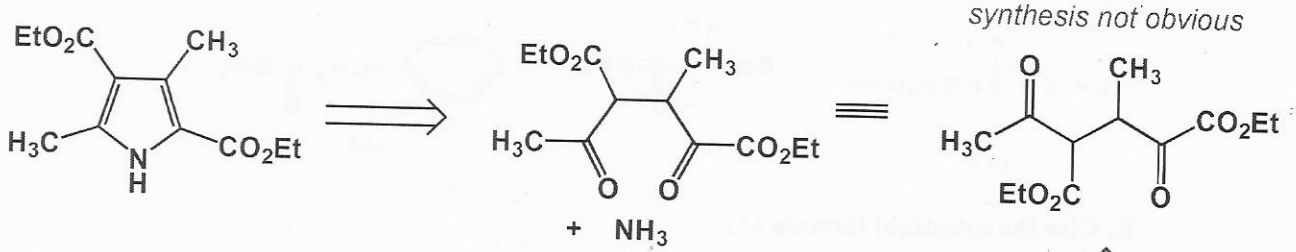
enamine (X=NR) or thioenol (X=S)

X = NR, X = S

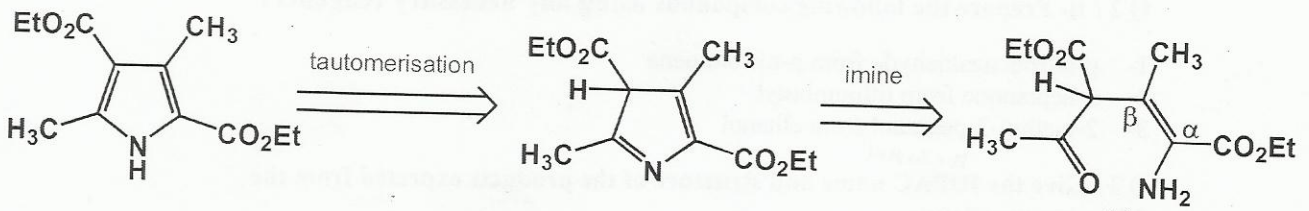
Knorr pyrrole synthesis

6a

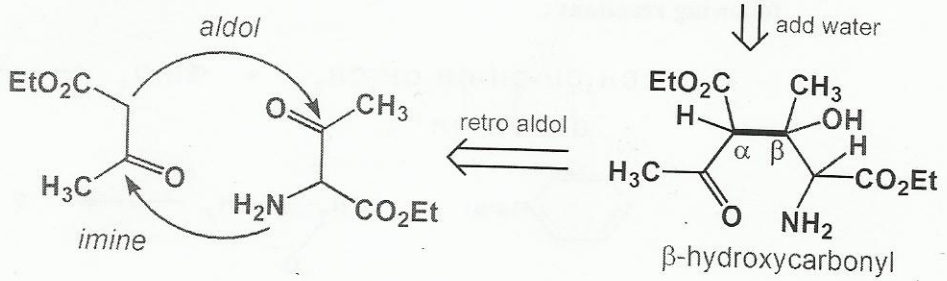
The Paal-Knorr pyrrole method is useful for making pyrrole rings *as long as the starting 1,4-dicarbonyl compound is readily available*. For example:



An alternative method, known simply as the **Knorr pyrrole synthesis**, involves the reaction of an α-aminoketone with another ketone.



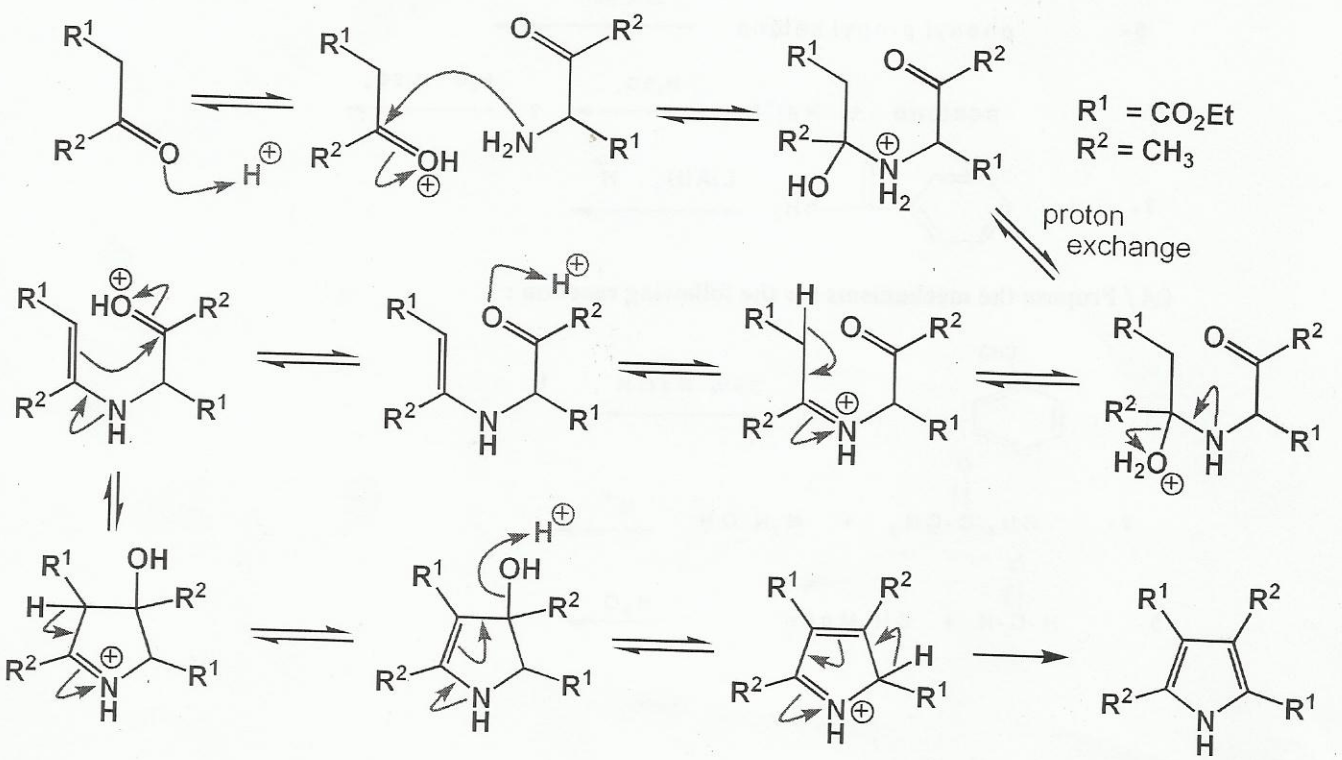
This *retrosynthetic analysis* outlines the rationale for the method. Note the special arrows indicating this is "paper chemistry".



Knorr pyrrole synthesis: mechanism

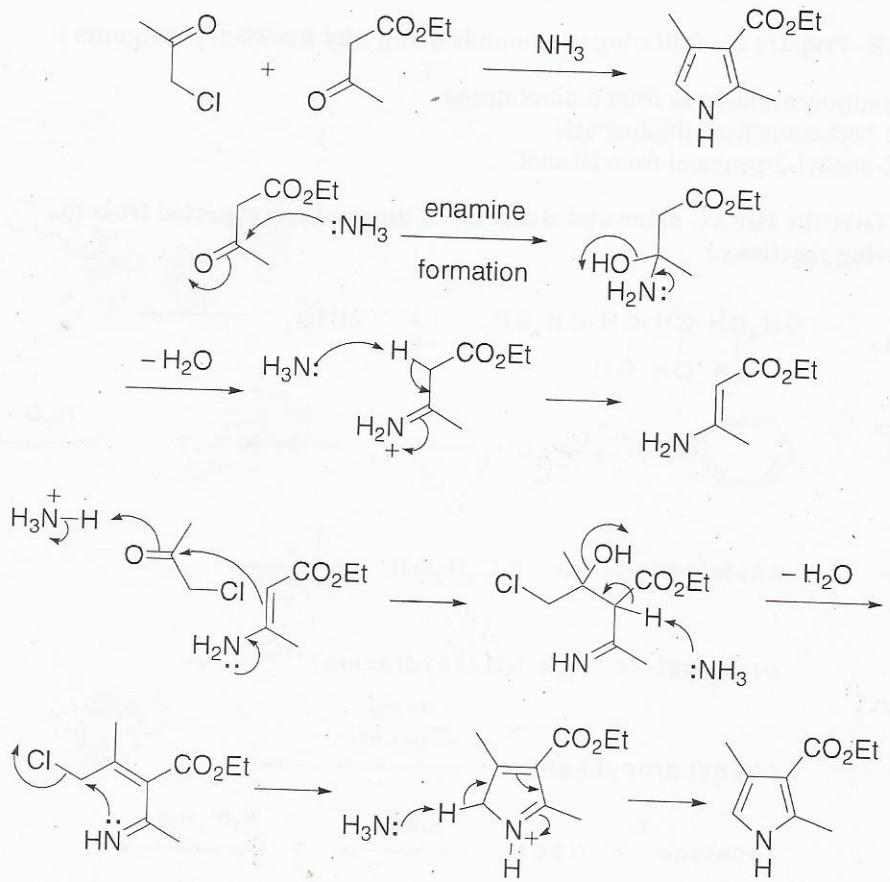
6b

Looking the example above we note that the α-amino-β-ketoester and β-ketoester have *the same carbon skeleton*. In this case the α-amino-β-ketoester can be made *in situ* with a second mole of the β-ketoester to yield the pyrrole directly.

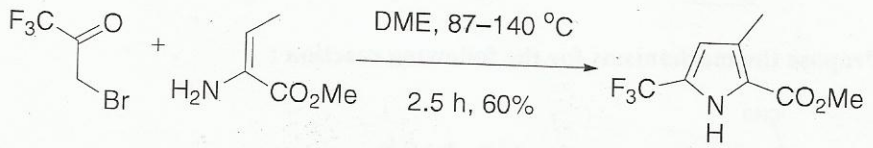


Hantzsch pyrrole synthesis

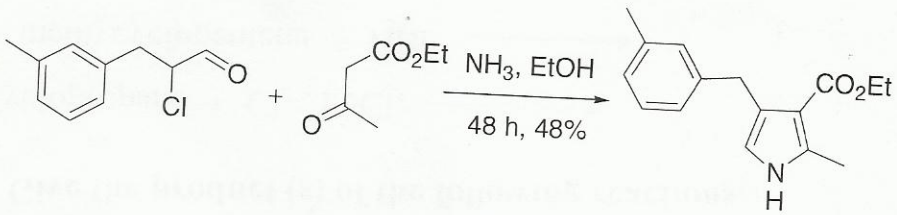
Reaction of α-chloromethyl ketones with β-ketoesters and ammonia to assemble pyrroles.



Example 1[5]



Example 2[8]



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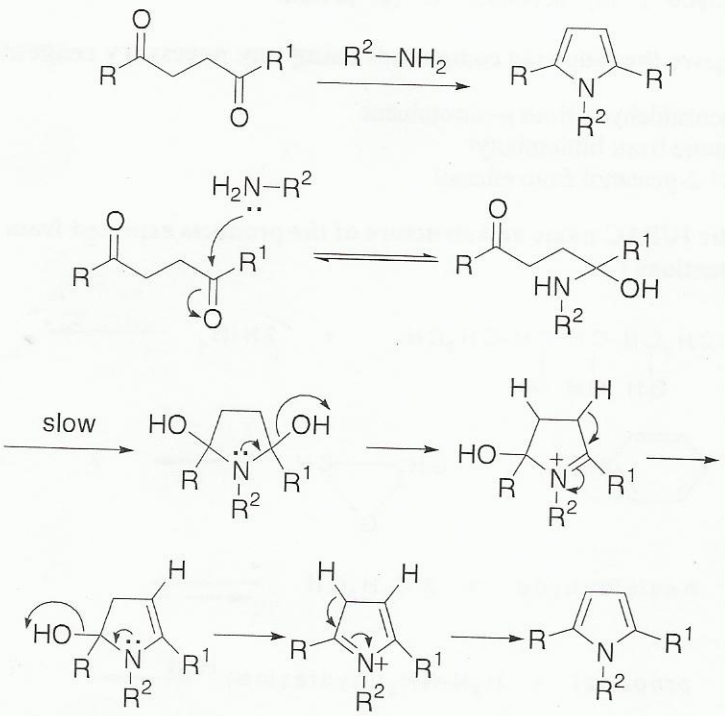
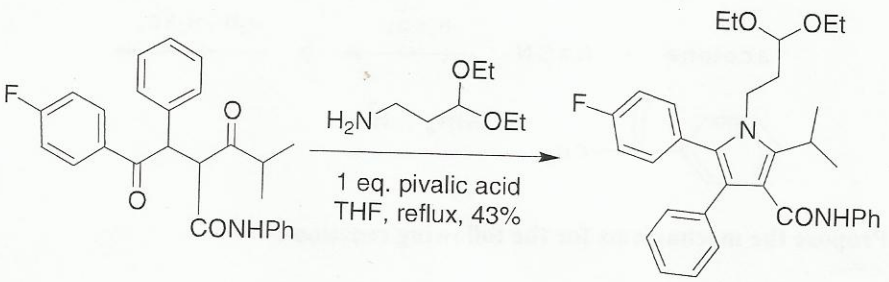
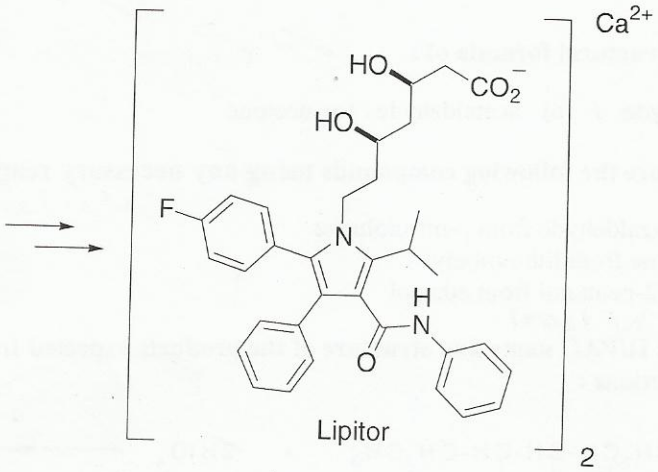
Paal–Knorr pyrrole synthesis

Reaction between 1,4-ketones and primary amines (or ammonia) to give pyrroles. A variation of the Knorr pyrazole synthesis (page 331).

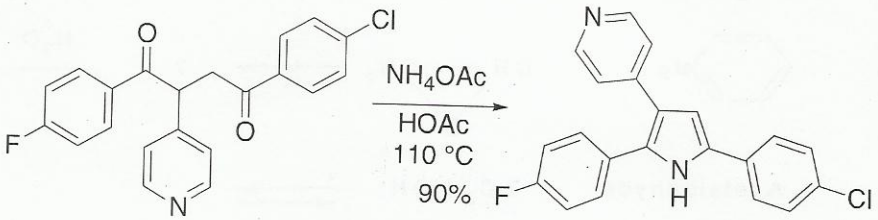


Example 1[5]





Example 2[7]



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