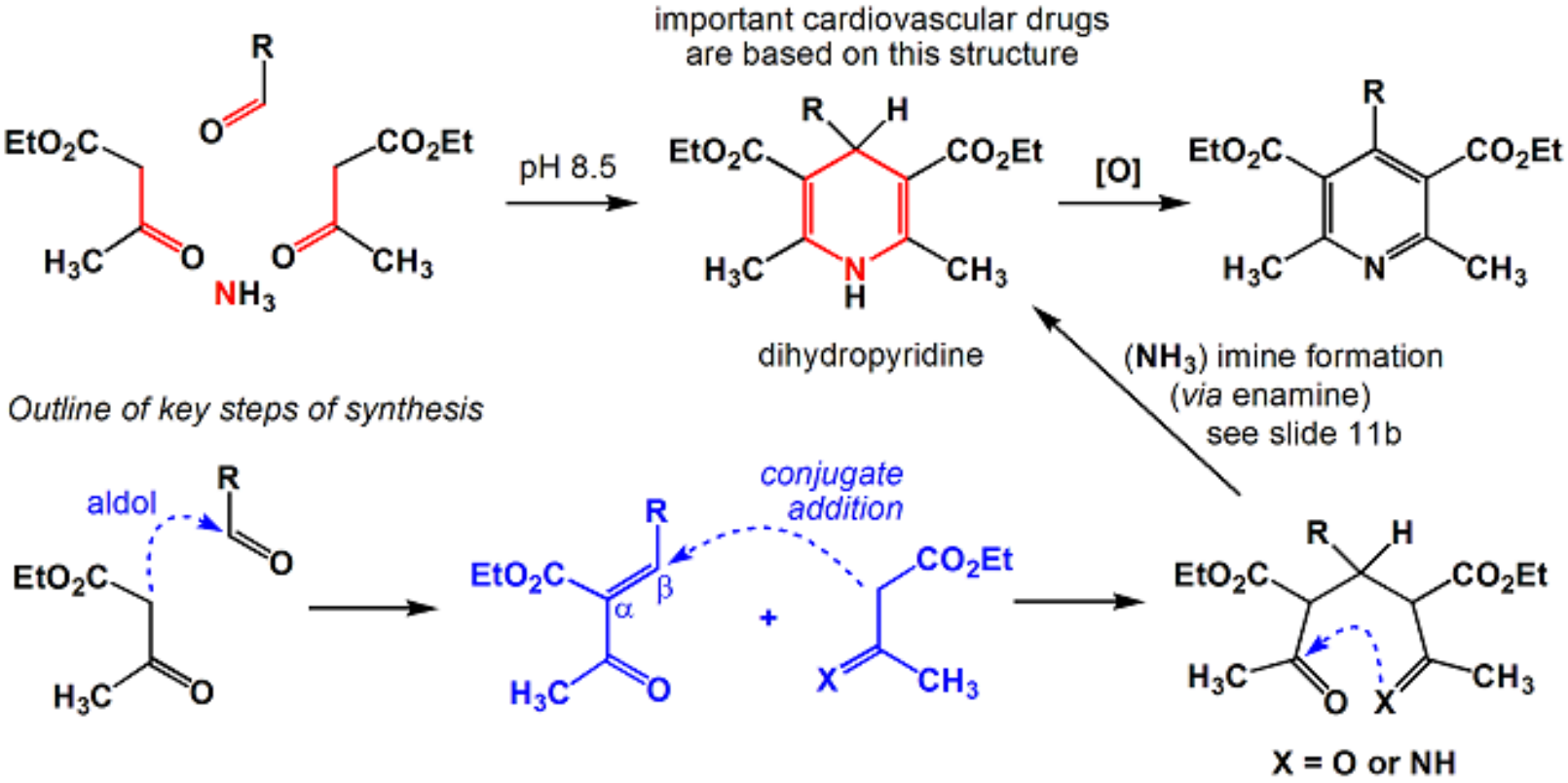
The Hantzsch pyridine synthesis

As with the Paal-Knorr pyrrole synthesis, making pyridines from 1,5 diketones depends on the availabilty (accessibility) of the starting material. An alternative muliti-component approach, the Hantzsch synthesis, enables pyridines to be made from two β-keto esters (cf. the Knorr pyrrole route). The extra carbon atom comes in the form of the carbonyl carbon of an aldehyde.

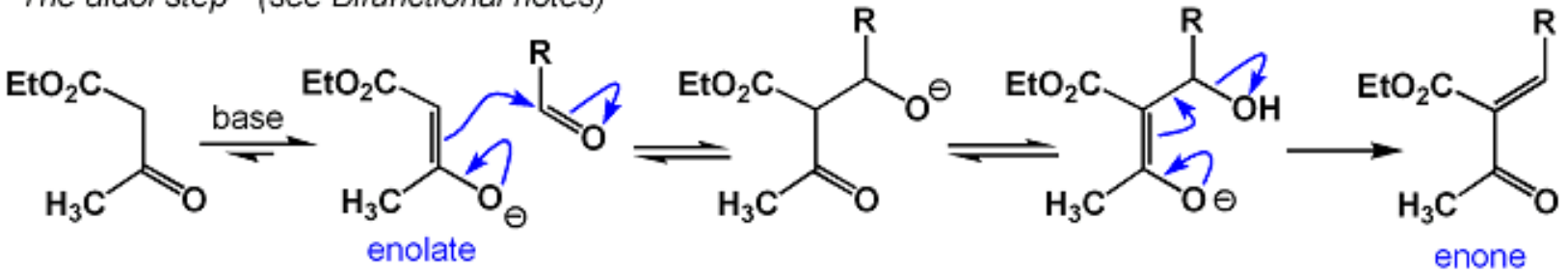
The Hantzsch synthesis



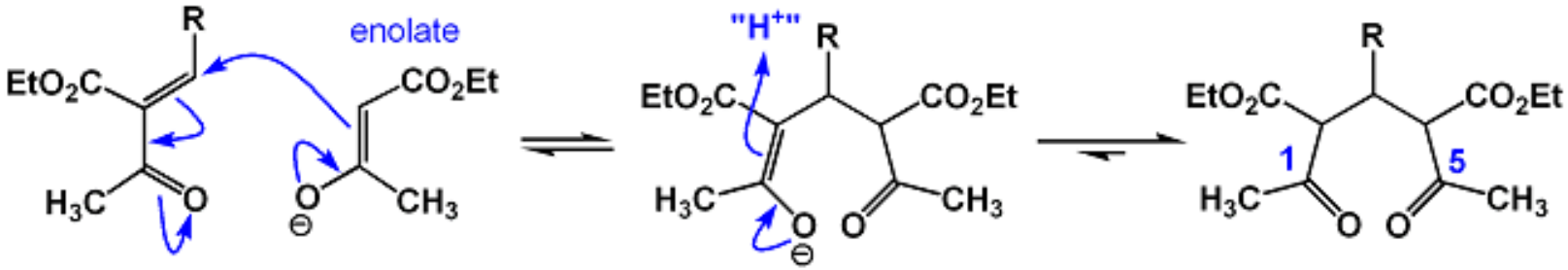
Mechanism of the Hantzsch synthesis

The exact sequence of events in a heterocyclic synthesis may vary depending on the conditions. In most cases a sensible guess can be made using knowledge of the chemistry of individual steps.

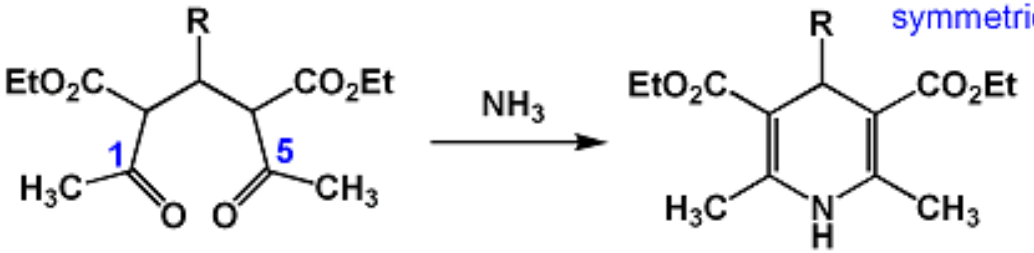
The aldol step - (see Bifunctional notes)



The conjugate addition step - (see Bifunctional notes)



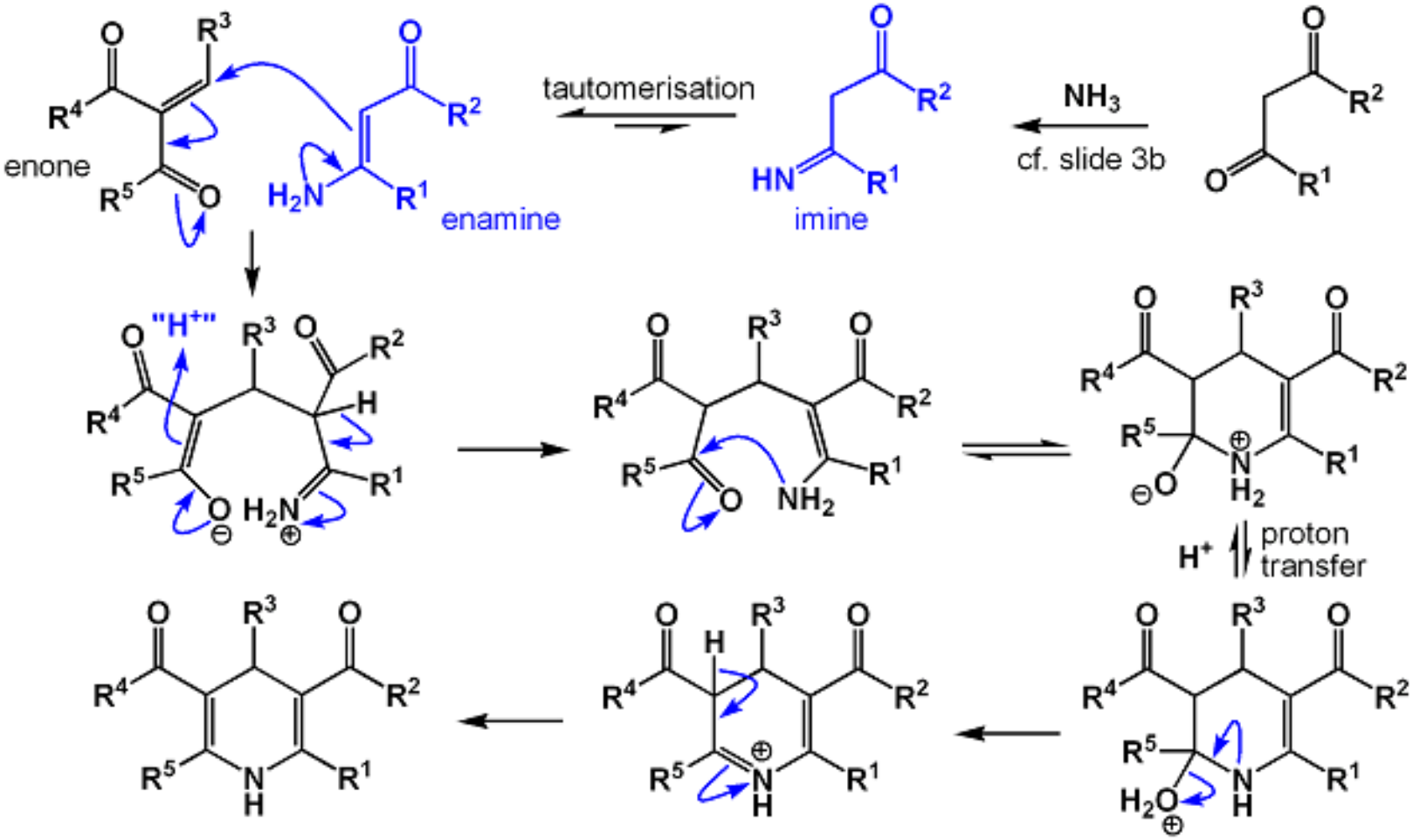
The cyclisation step - (see these notes - slide 12a)



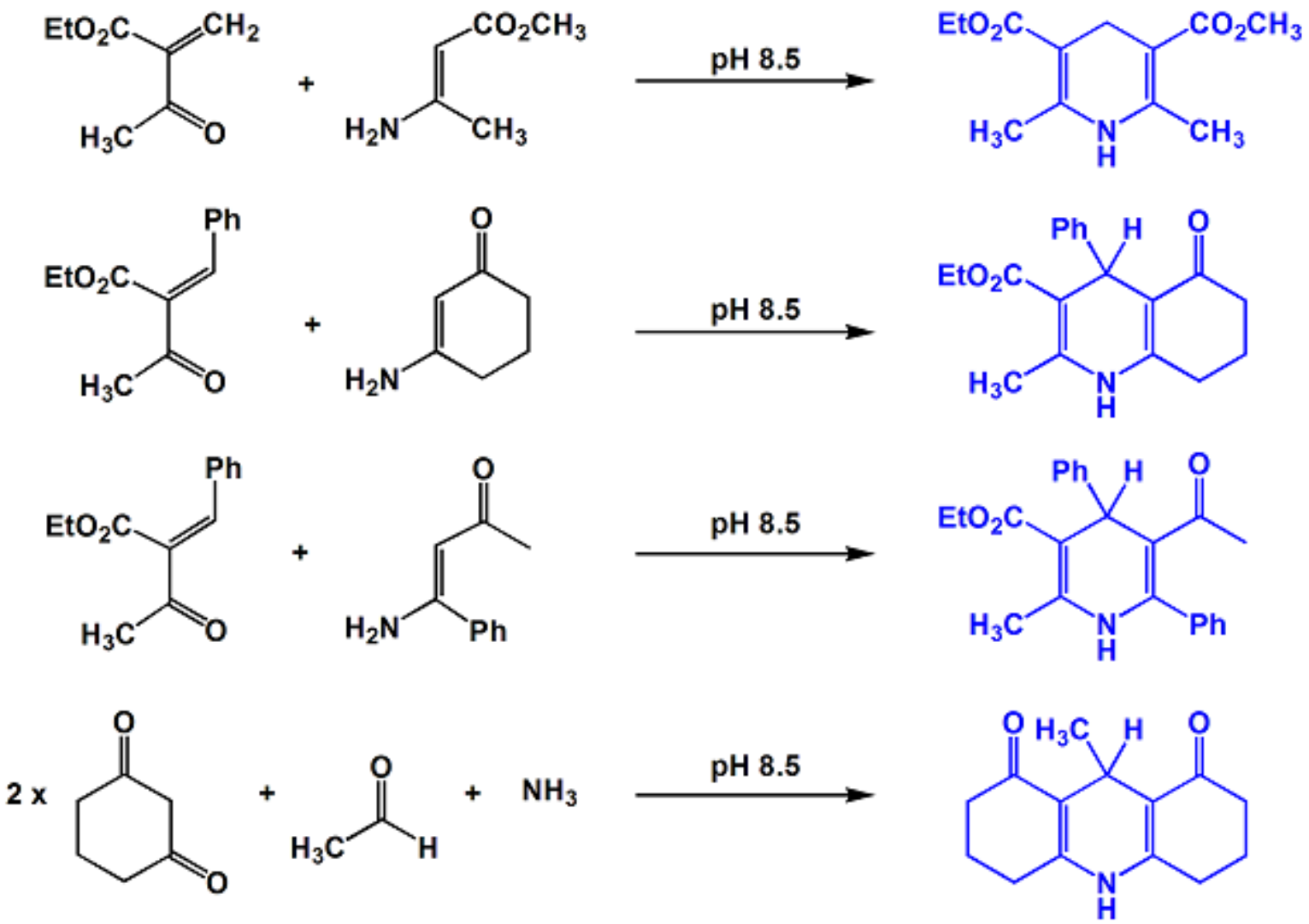
If there was a way to make the enone and enolate separately then unsymmetrical dihydropyridines could be made (cf. Knorr pyrrole synthesis).

Unsymmetrical pyridines from the Hantzsch synthesis 13b

Making the enone component is relatively straightforward (see slide 13a), but in place of the enolate a (semi)stable enamine is used. The enamine is simply the tautomer of the imine derived from ammonia and in this way unsymmetrical dihydropyridines can be made.



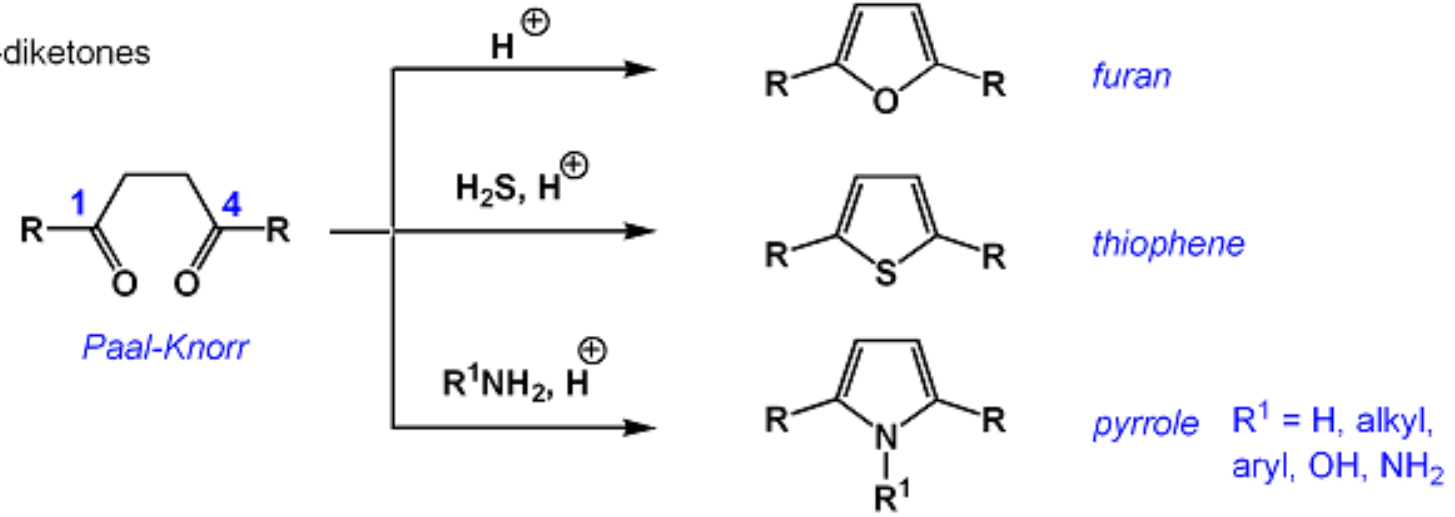
Hantzsch pyridine synthesis: examples



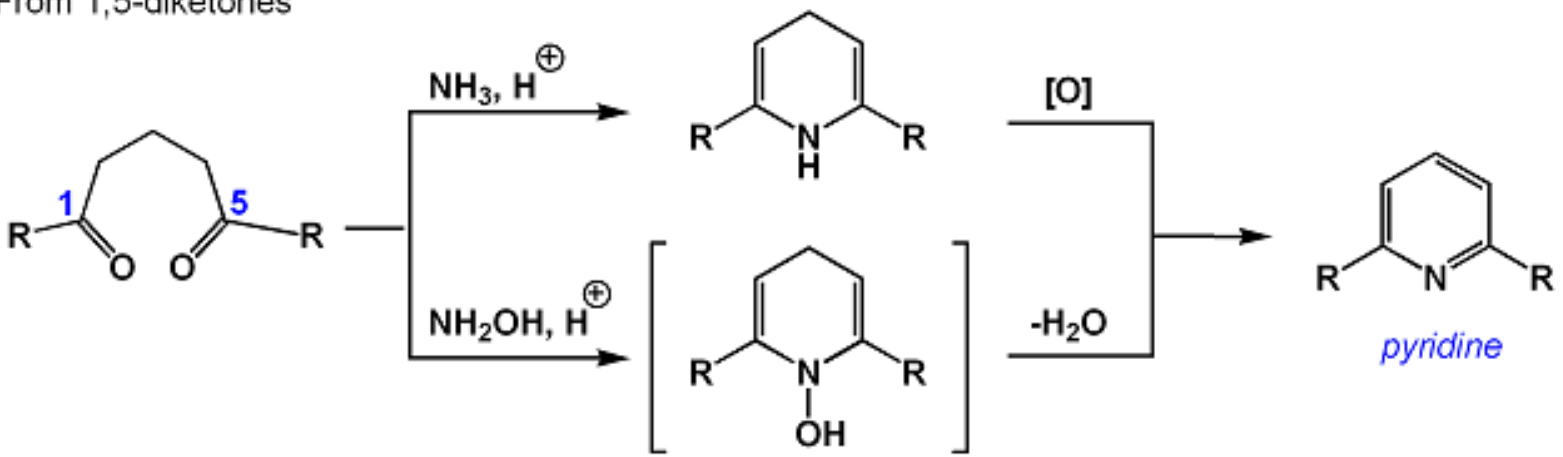
Course summary: Rings with one heteroatom

14b

From 1,4-diketones

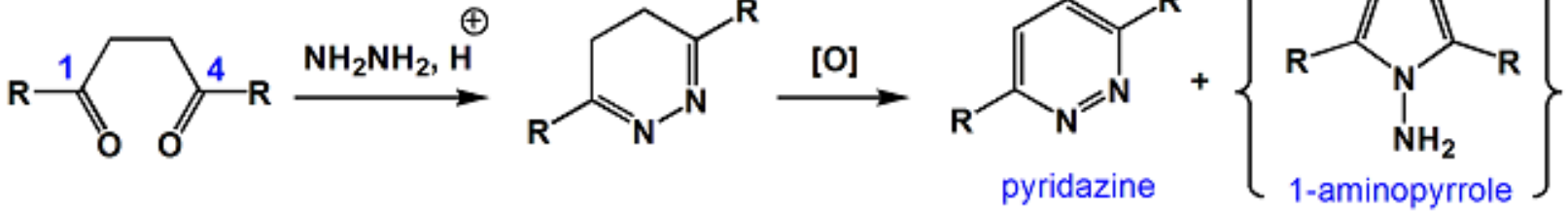


From 1,5-diketones

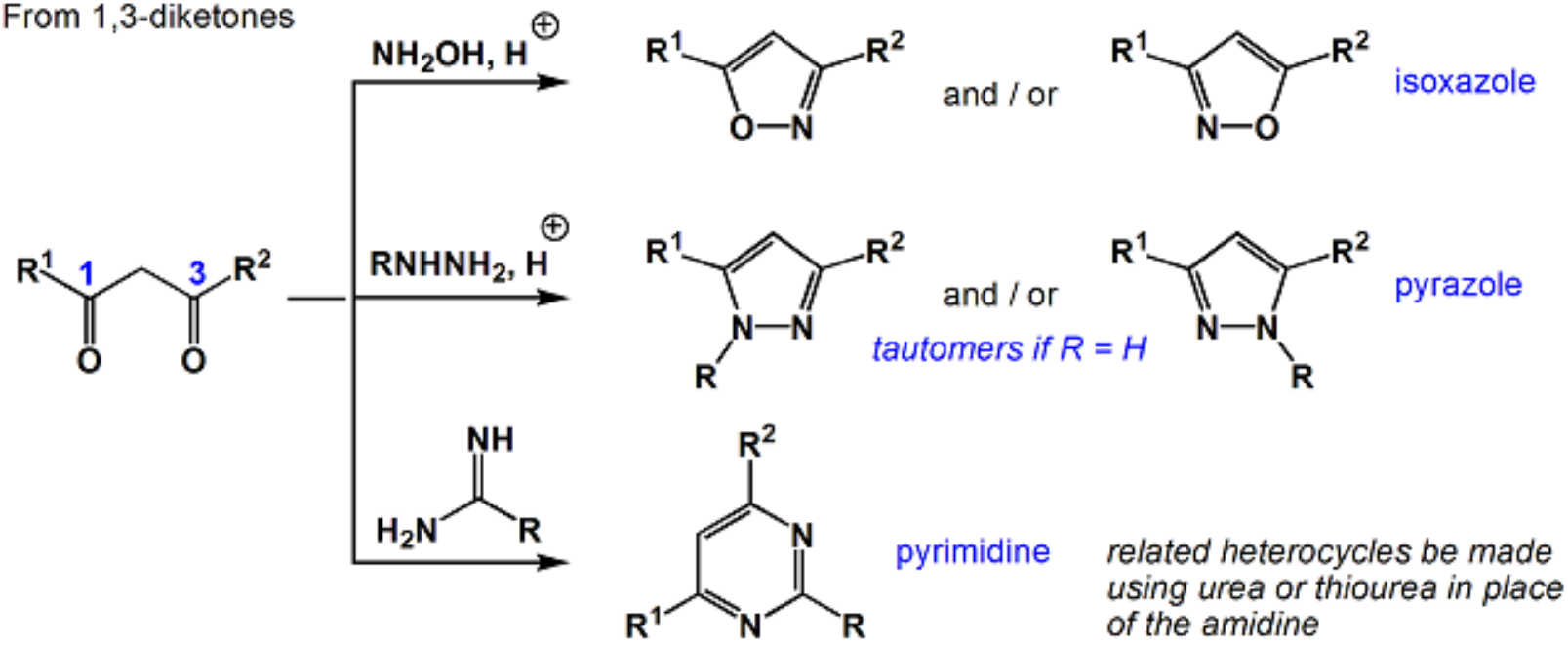


Course summary: Rings with two heteroatoms

From 1,4-diketones



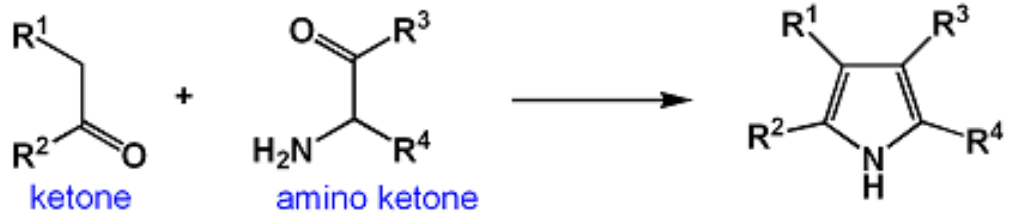
From 1,3-diketones



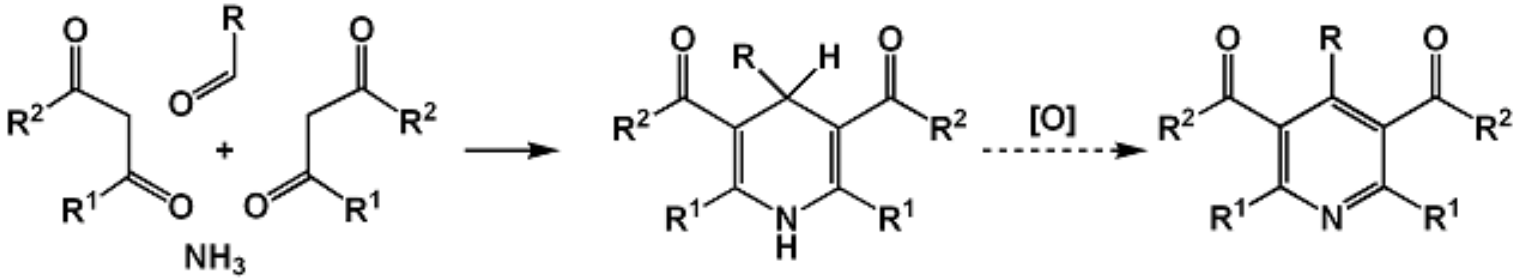
related heterocycles be made using urea or thiourea in place of the amidine

Course summary: Multicomponent approaches

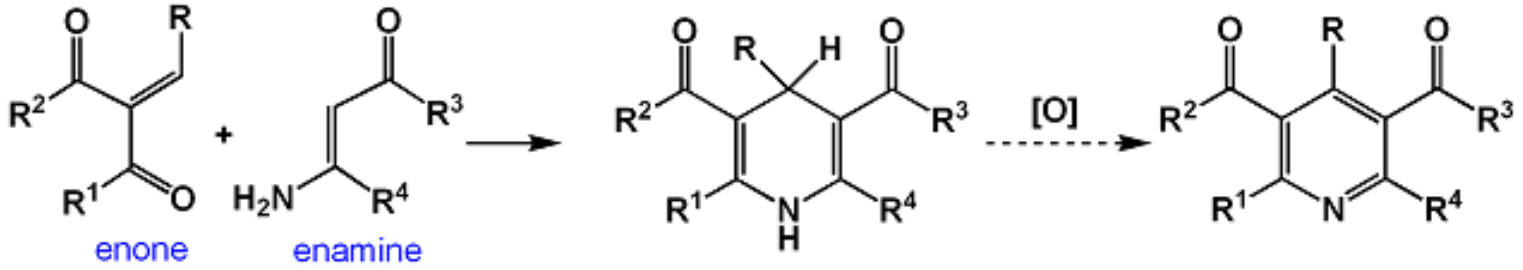
Knorr pyrrole synthesis



Hantzsch (dihydro)pyridine synthesis: *symmetrical*

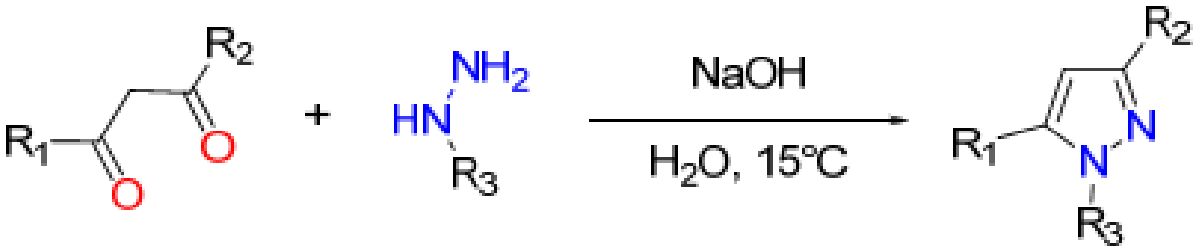


Hantzsch (dihydro)pyridine synthesis: *unsymmetrical*

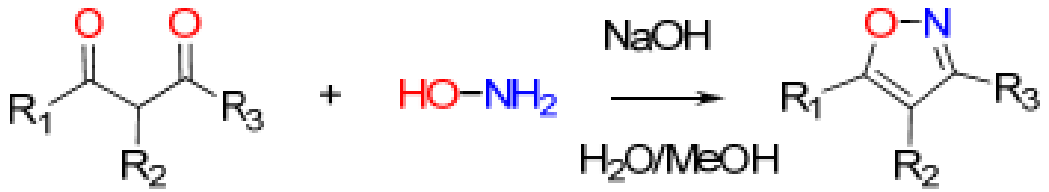


1,2-Azoles

- Pyrazoles can be synthesized from 1,3-dicarbonyls with hydrazine

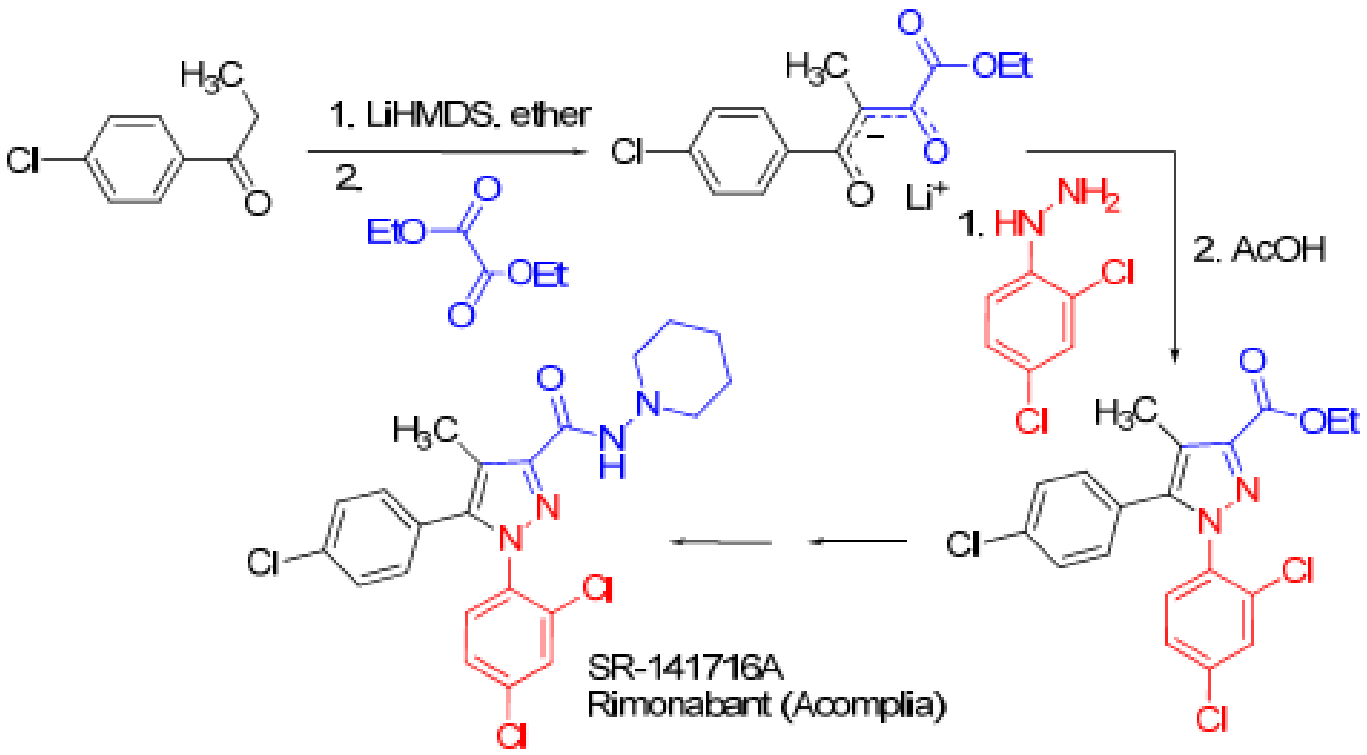


- Isoxazoles can be made from 1,3-dicarbonyl compounds or β-ketoesters with hydroxylamine



1,2-Azoles

Example of pyrazole synthesis: Rimonabant

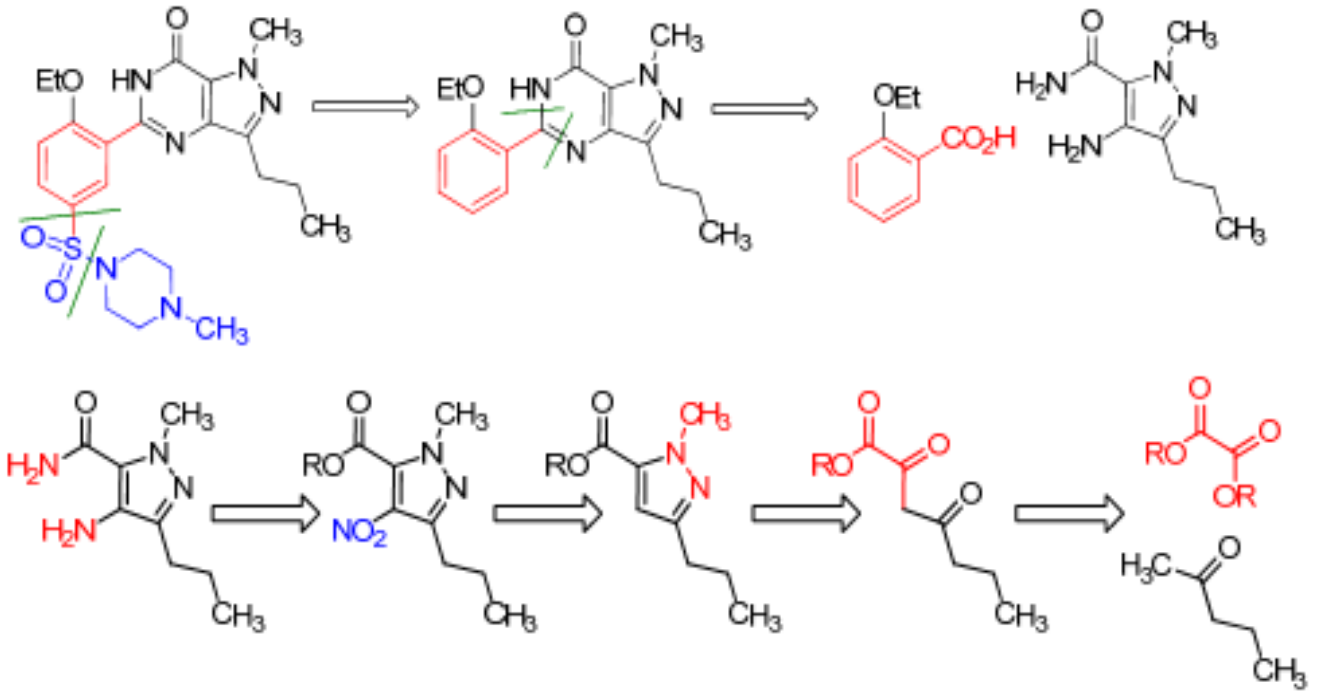


Org. Process Res. Dev., 2007, 11 (5), 910–912

1,2-Azoles

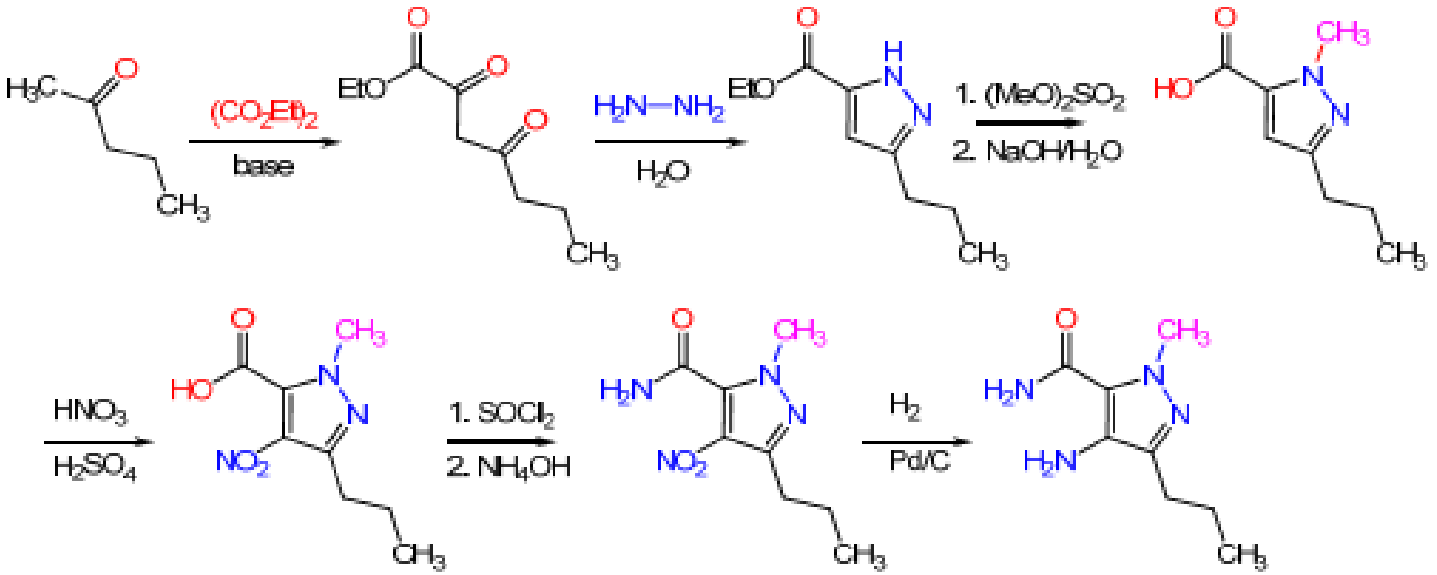
The synthesis of sildenafil

- Retrosynthesis



1,2-Azoles

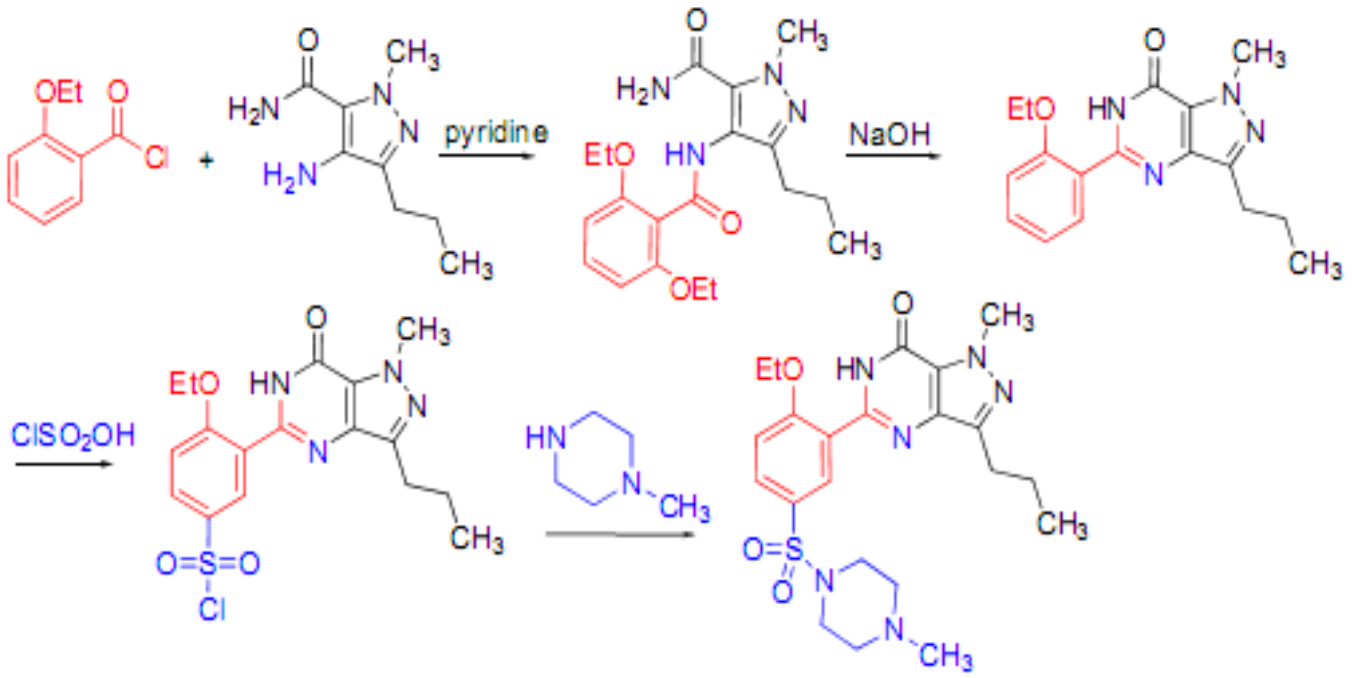
The synthesis of sildenafil



Bioorg. Med. Chem. Lett. 6, pp. 1819, 1996

1,2-Azoles

The synthesis of sildenafil

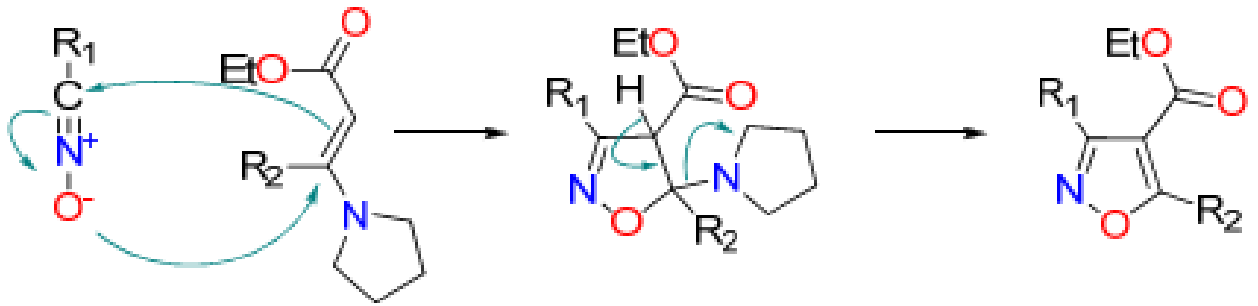


Bioorg. Med. Chem. Lett. 6, pp. 1819, 1996

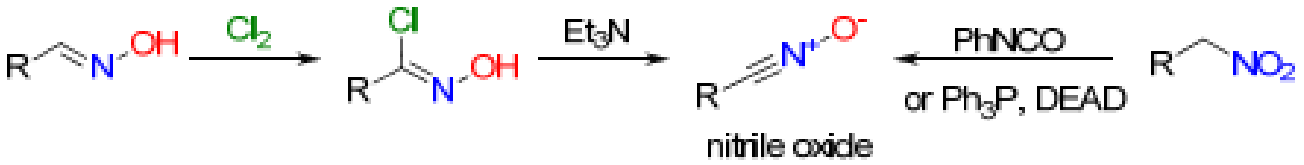
1,2-Azoles

synthesis of isoxazoles

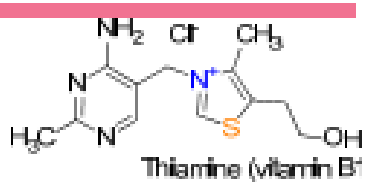
- By 1,3-cycloaddition from nitrile oxides and unsaturated compounds



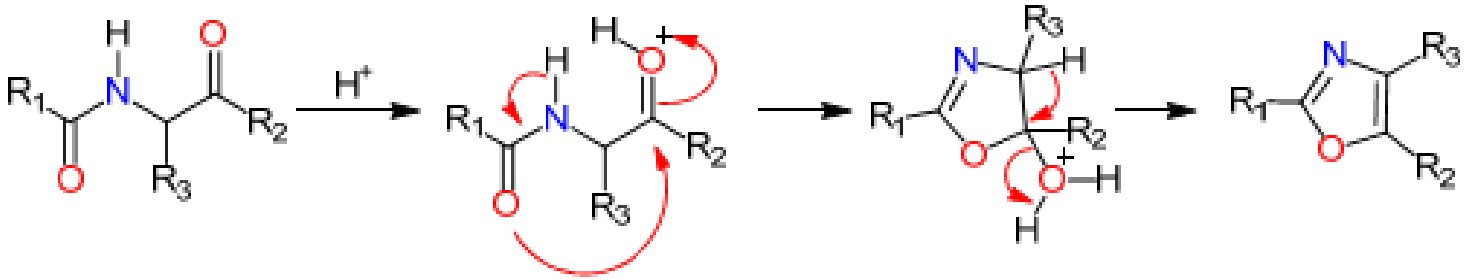
- Nitrile oxides can be prepared by the γ-elimination of chlorooximes or the dehydration of nitroalkanes



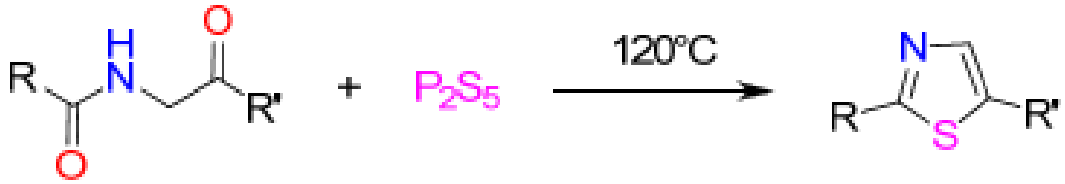
1,3-Azoles



- Oxazoles and thiazoles can be obtained by the Robinson-Gabriel synthesis from 2-acylamino-ketones.

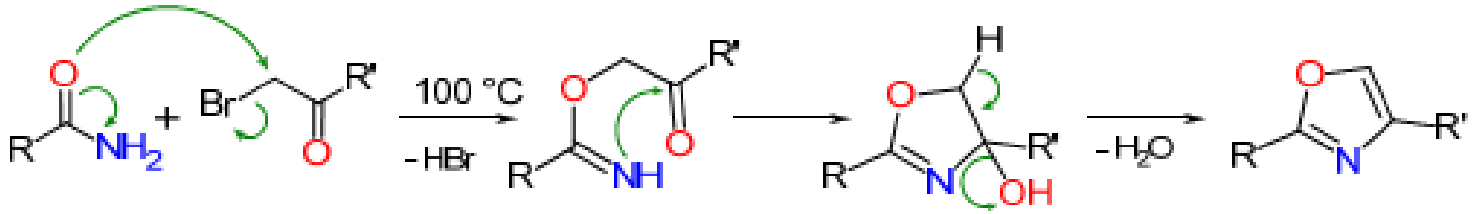


- 2-acylamino-ketones reacts with phosphorus pentasulfide to form thiazoles

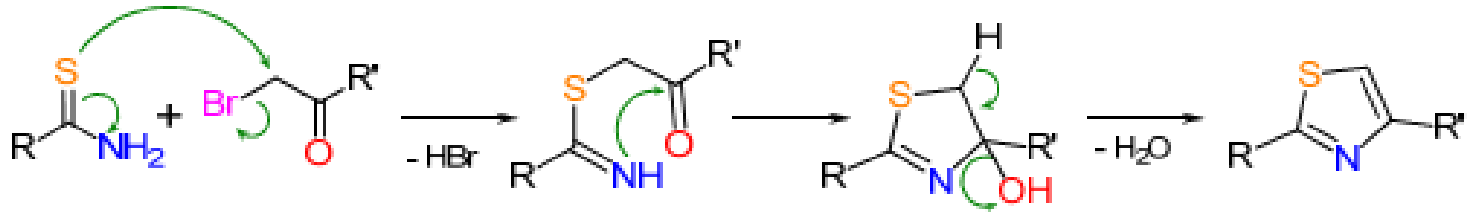


1,3-Azoles

- Oxazoles can be made by Blümlein-Lewy Synthesis: heating an α–haloketone with amide

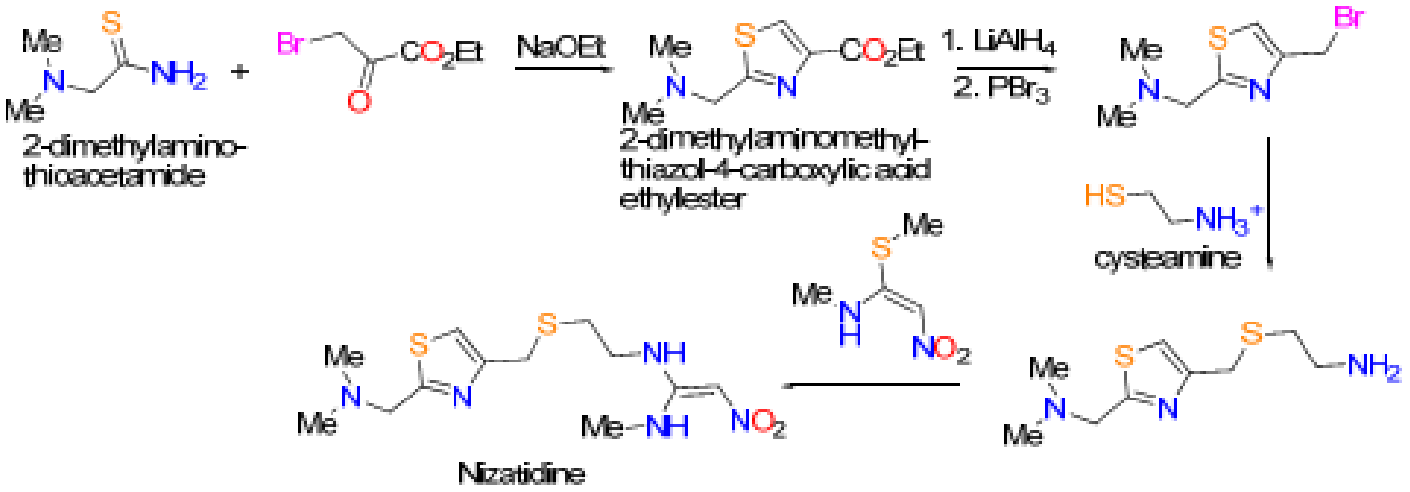


- **Most important method for thiazoles is Hantzsch thiazole synthesis from thioamides and a-halocarbonyl compounds**



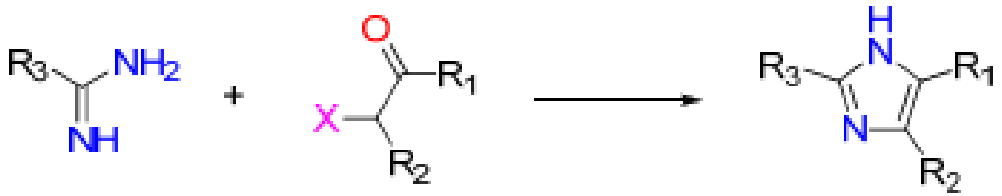
1,3-Azoles

- Example: synthesis of nizatidine



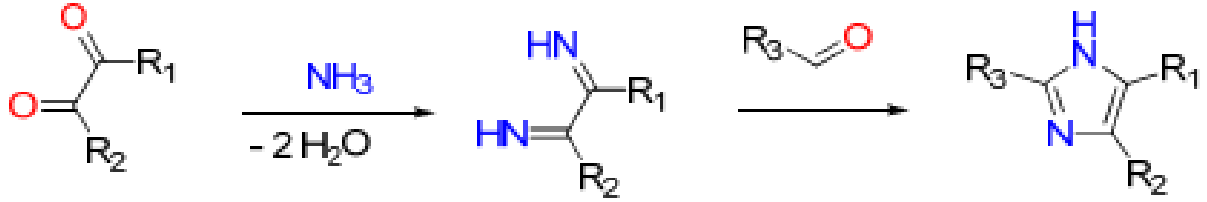
1,3-Azoles: Synthesis of imidazoles

- From amidines and hydroxy or halocarbonyl compounds



X = Br, Cl, OH

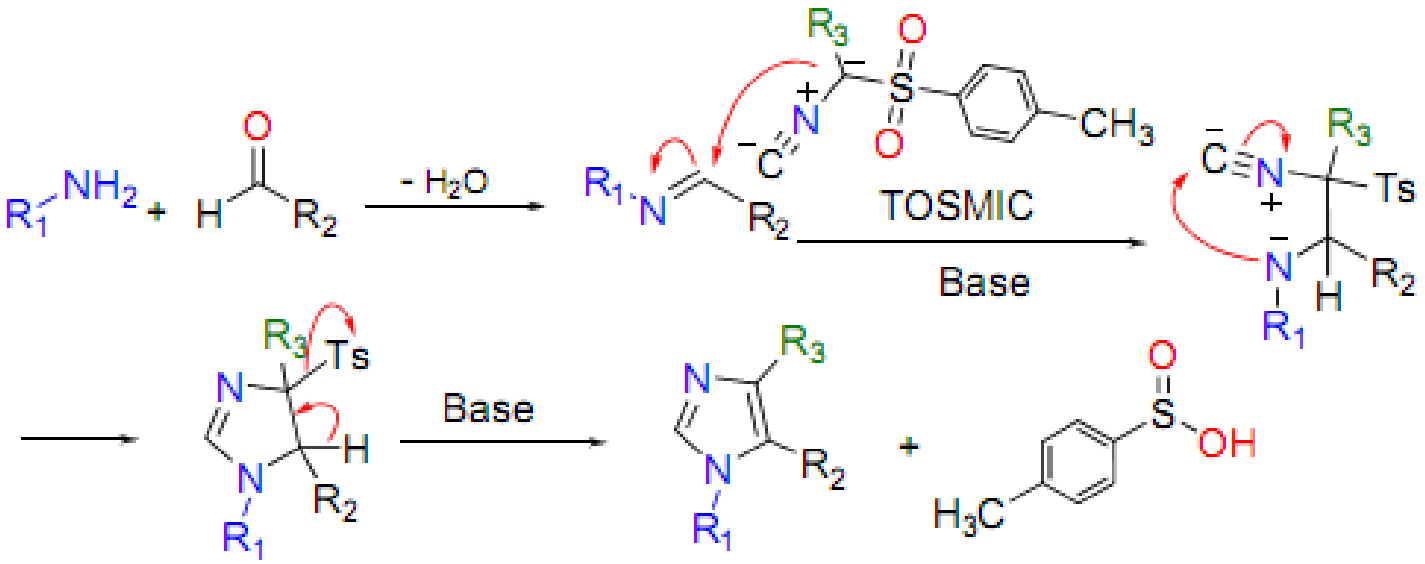
- **Debus-Radziszewski imidazole synthesis:** diketone and ammonia form an diimine, which condenses with the aldehyde



For more imidazole syntheses, look:
http://www.scripps.edu/chem/baran/images/grpmtgpdf/Zografos_Feb_04.pdf

1,3-Azoles: Imidazoles from isocyanides

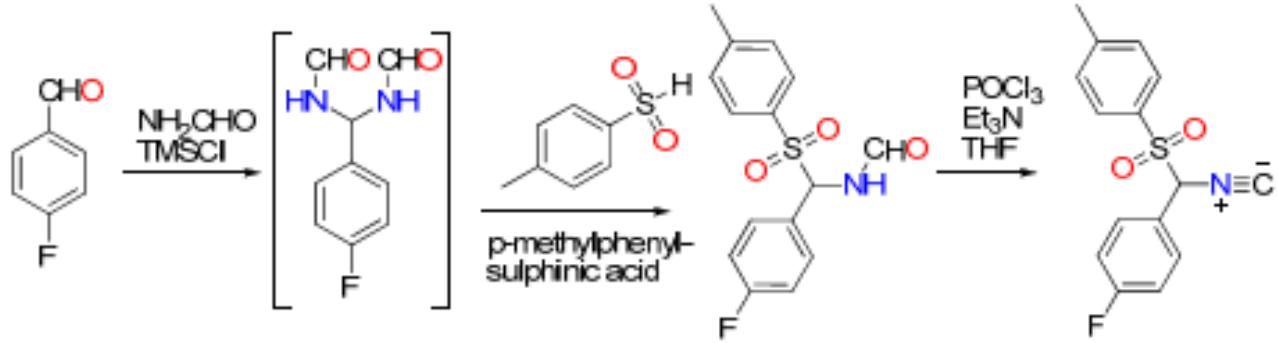
- The reaction of aldehydes, primary amines and toluenesulphonylmethyl isocyanide (TOSMIC) yield 1,4,5-trisubstituted imidazoles (van Leusen et al. *J. Org. Chem.* **1977**, *42*, 1153).



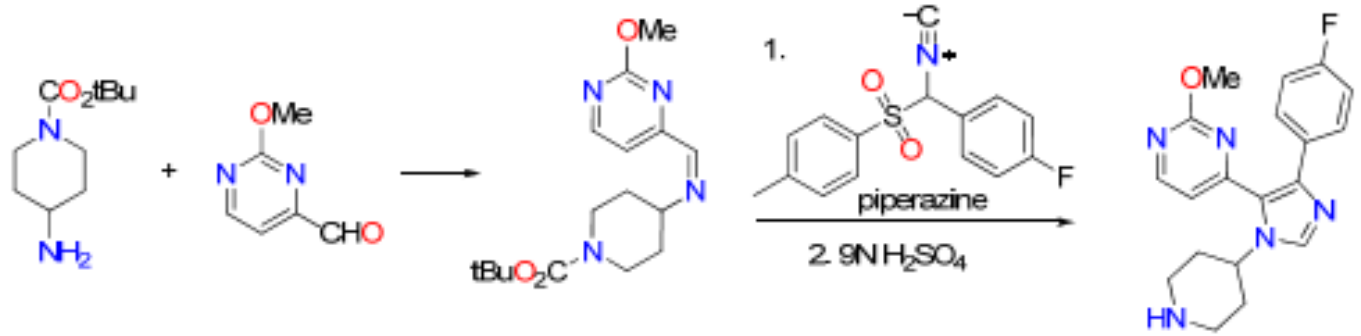
http://www.organic-chemistry.org/Highlights/2005/05May.shtm

1,3-Azoles: Imidazoles from isocyanides

- Substituted tosylmethyl isocyanides (TosMICs) are synthesized from tosylmethyl formamides and *p*-methylphenylsulphinic acid.

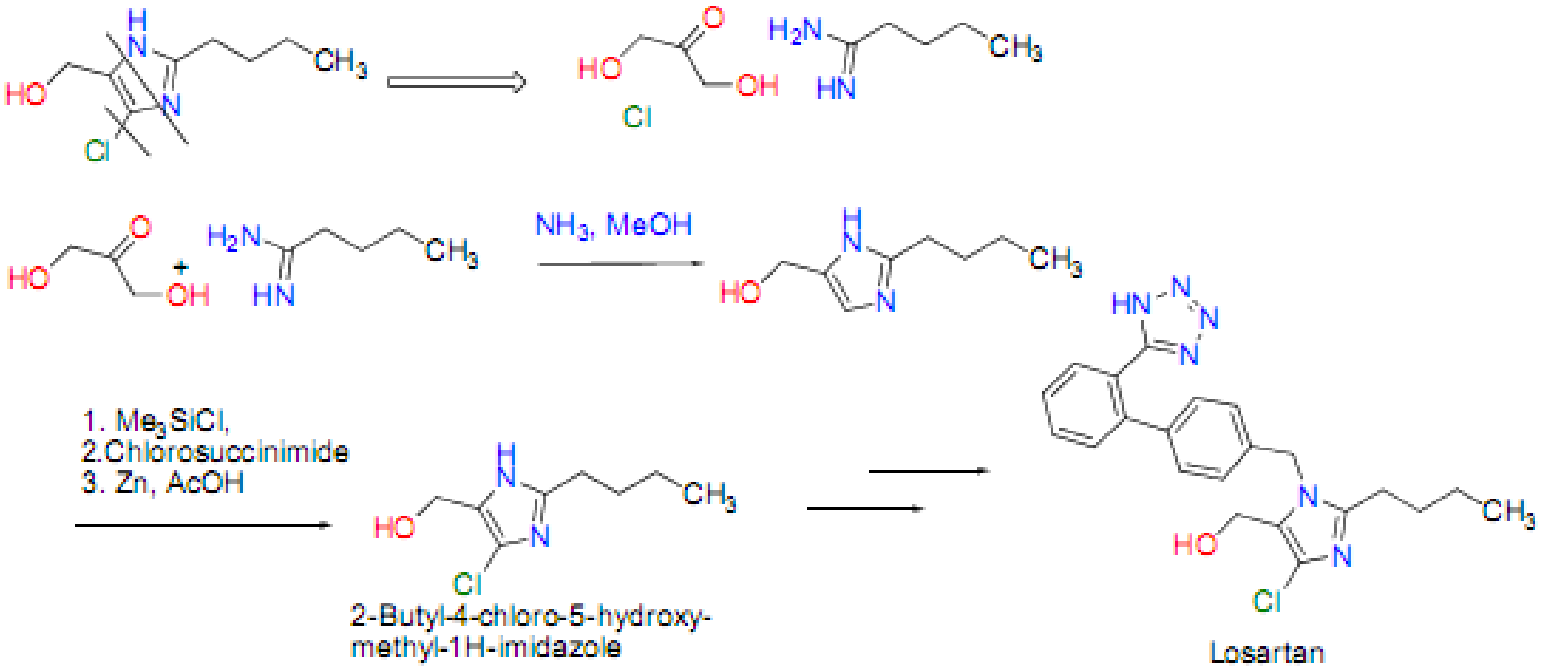


- Synthesis of the GSK p38 kinase inhibitor



1,3-Azoles

- Synthesis of 2-Butyl-4-chloro-5-hydroxymethyl-1H-imidazole



Synthetic Communications (1993), 23(16), 2623-30.