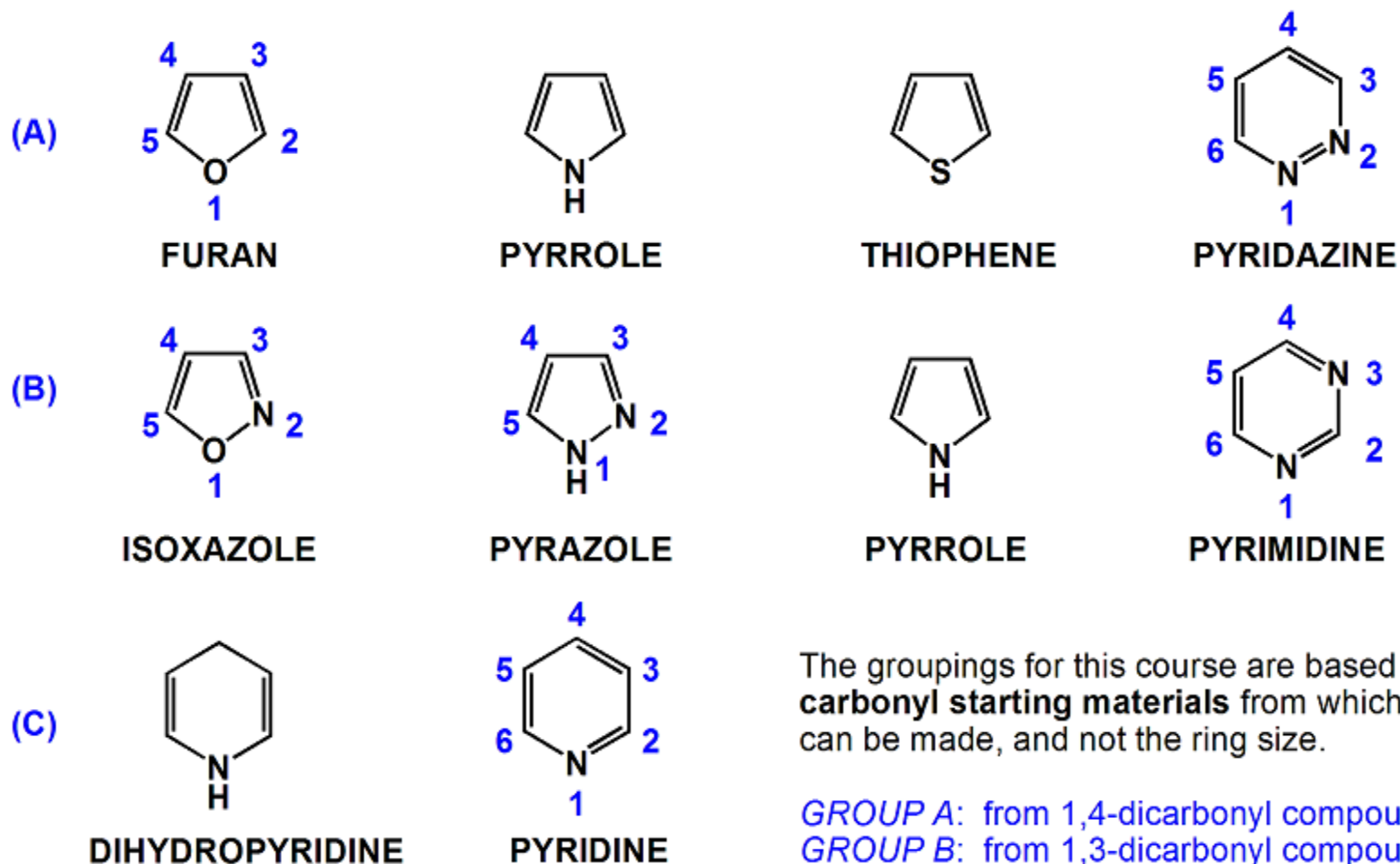


Classes of heterocycles covered in this course

1a



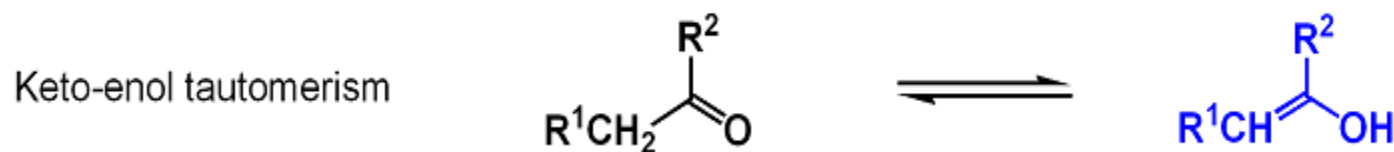
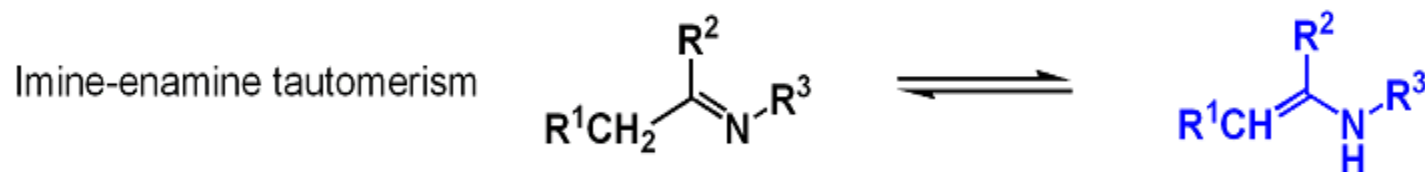
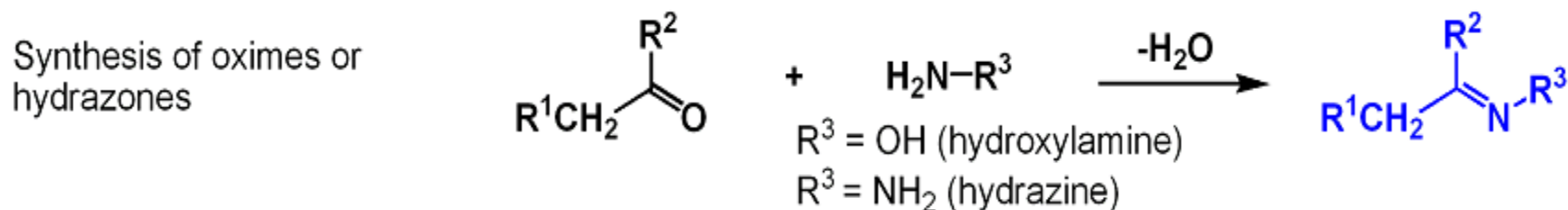
The groupings for this course are based on the **carbonyl starting materials** from which they can be made, and not the ring size.

GROUP A: from 1,4-dicarbonyl compounds
GROUP B: from 1,3-dicarbonyl compounds
GROUP C: from 1,5-dicarbonyl compounds

You've done the hard work already!

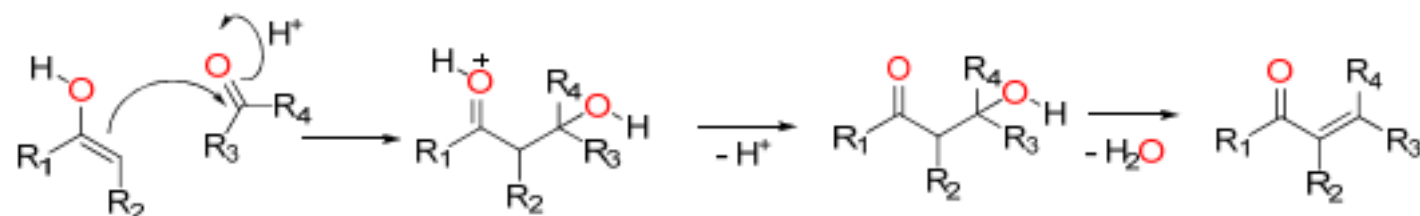
1b

A refresher of the key transformations:

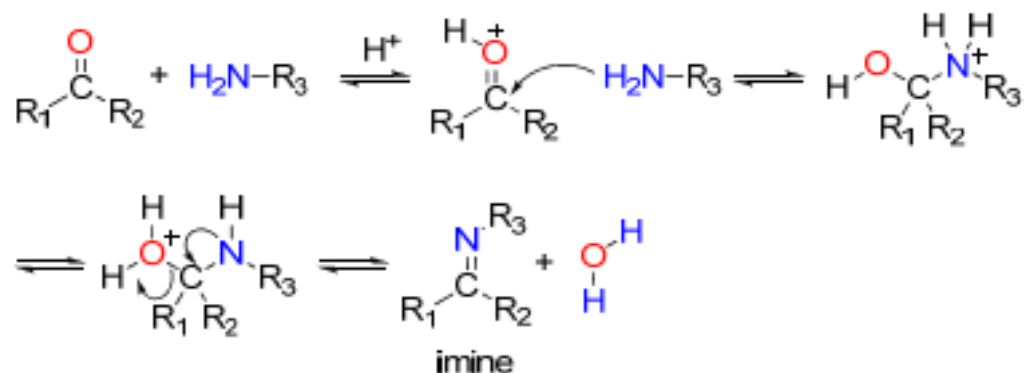


Reactions used in heterocyclic ring synthesis

- Aldol-type reactions of enols or enolate anions with electrophiles.

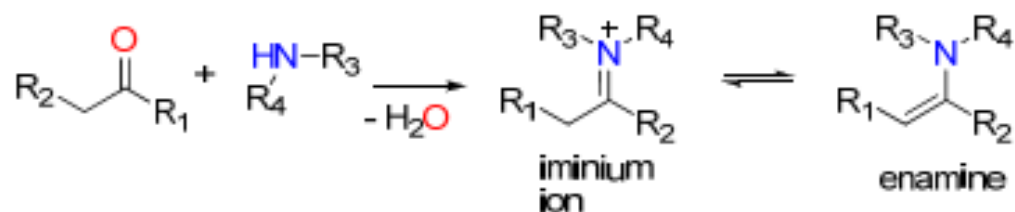


- Imine/enamine formation

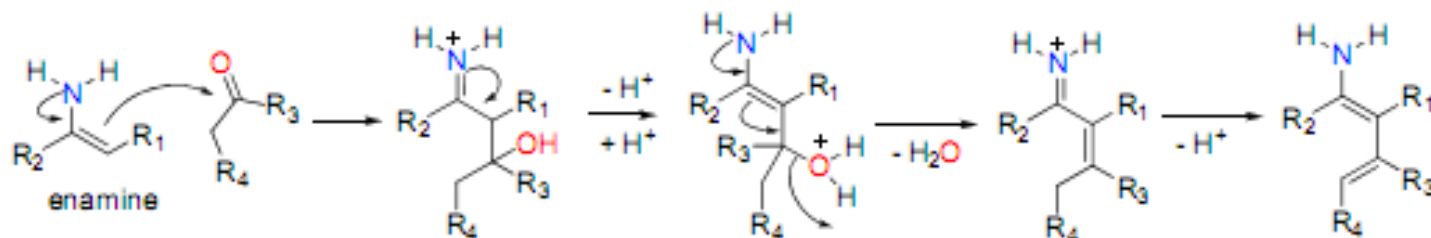


Reactions used in heterocyclic ring synthesis

- Enamine is tautomeric form of imine. If dialkylamine is used, enamine is formed

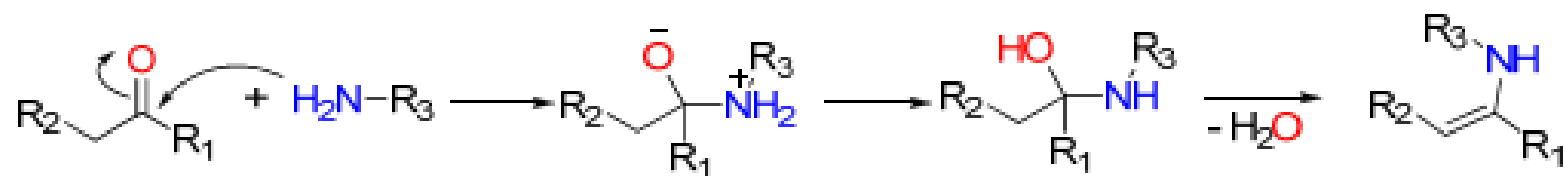
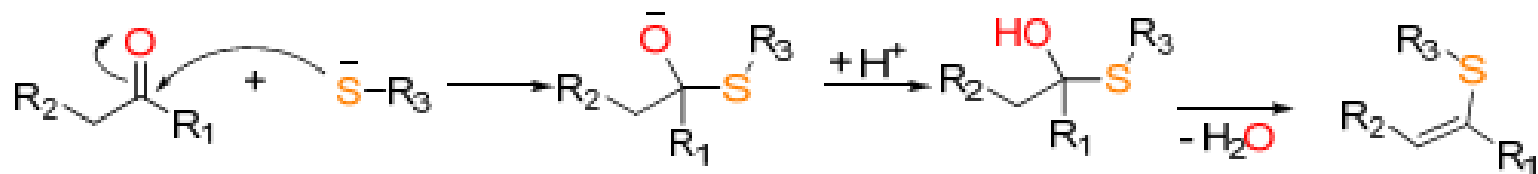


- Enamines can function as enolates



Reactions used in heterocyclic ring synthesis

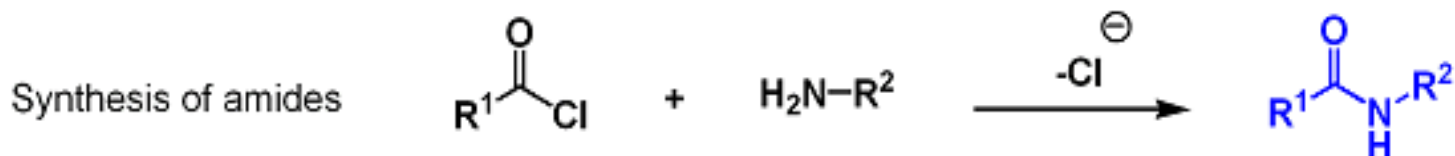
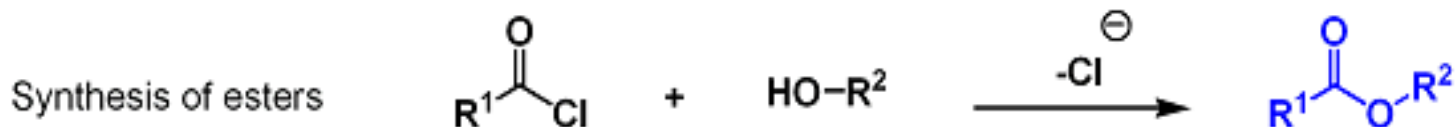
- When the process leads to C-heteroatom bond formation, then the nucleophile is an appropriate heteroatom.



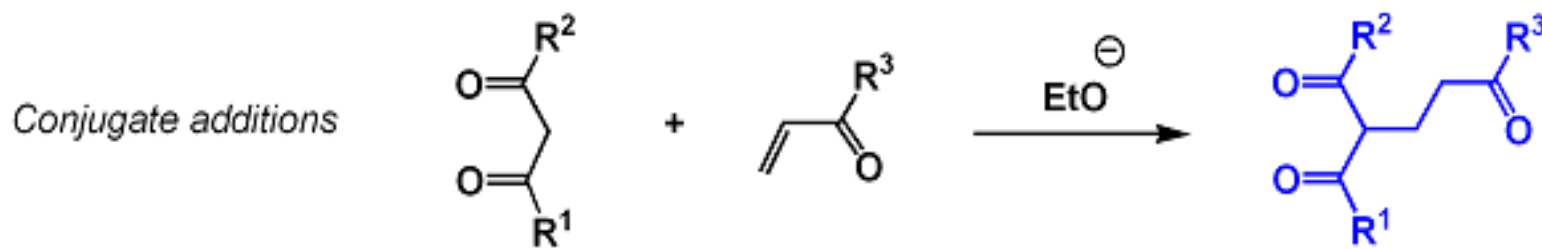
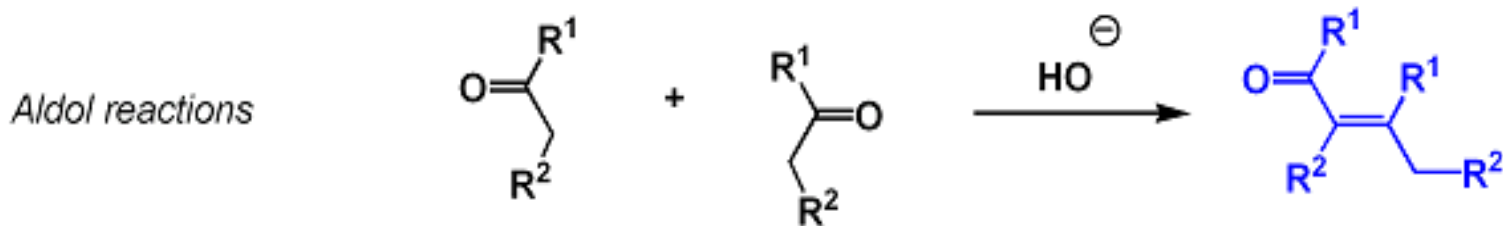
More key reactions in heterocycle synthesis

2a

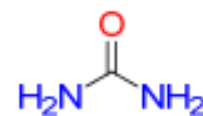
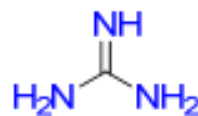
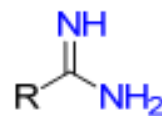
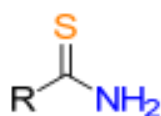
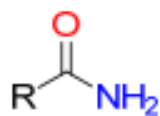
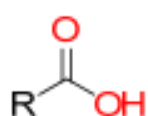
Interconversion of functional groups in the same oxidation state as carboxylic acids, as shown below, most commonly occurs through addition-elimination reactions *via* a tetrahedral intermediate.



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



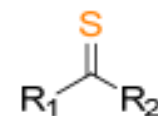
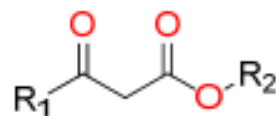
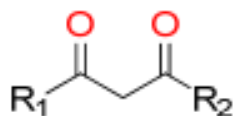
Common building-blocks for heterocyclic compounds



amidine

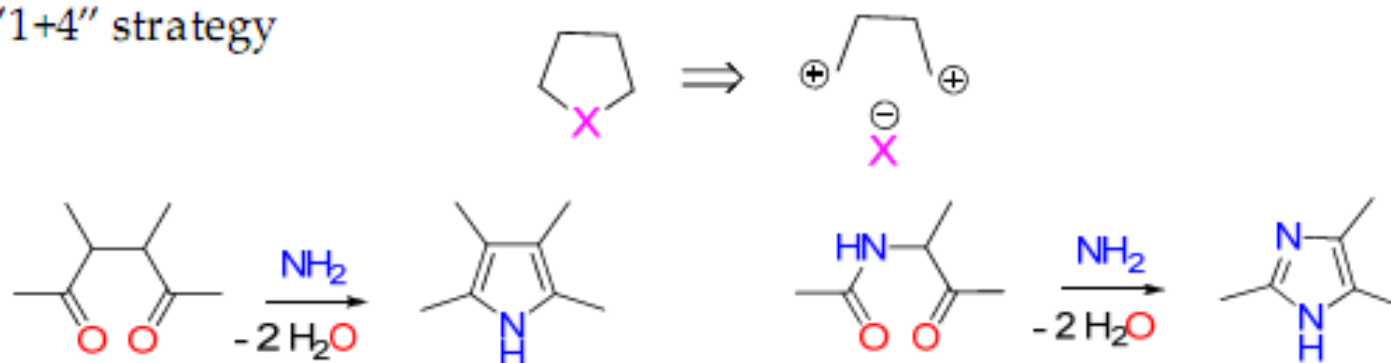
guanidine

urea

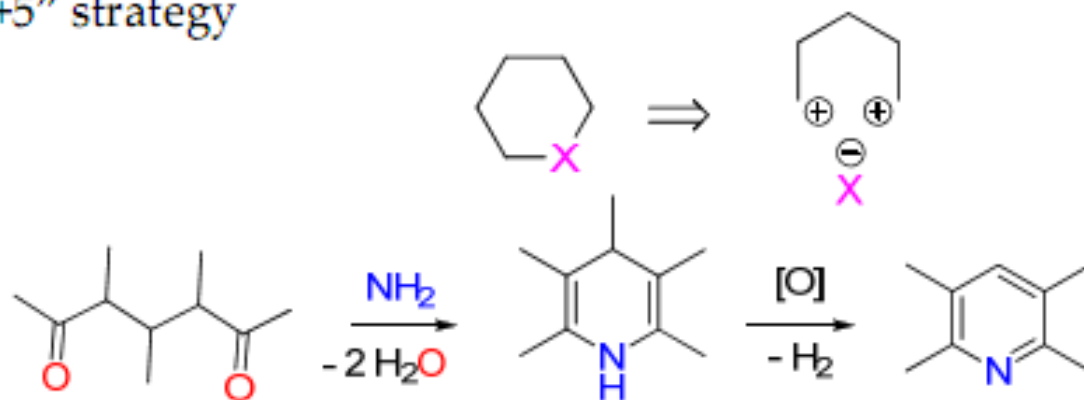


General strategies for heterocycle synthesis

- "1+4" strategy

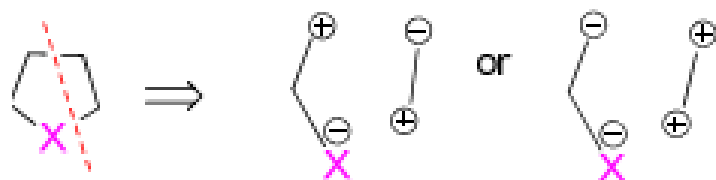


- "1+5" strategy

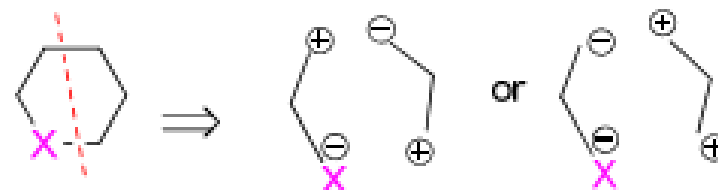


General strategies for heterocycle synthesis

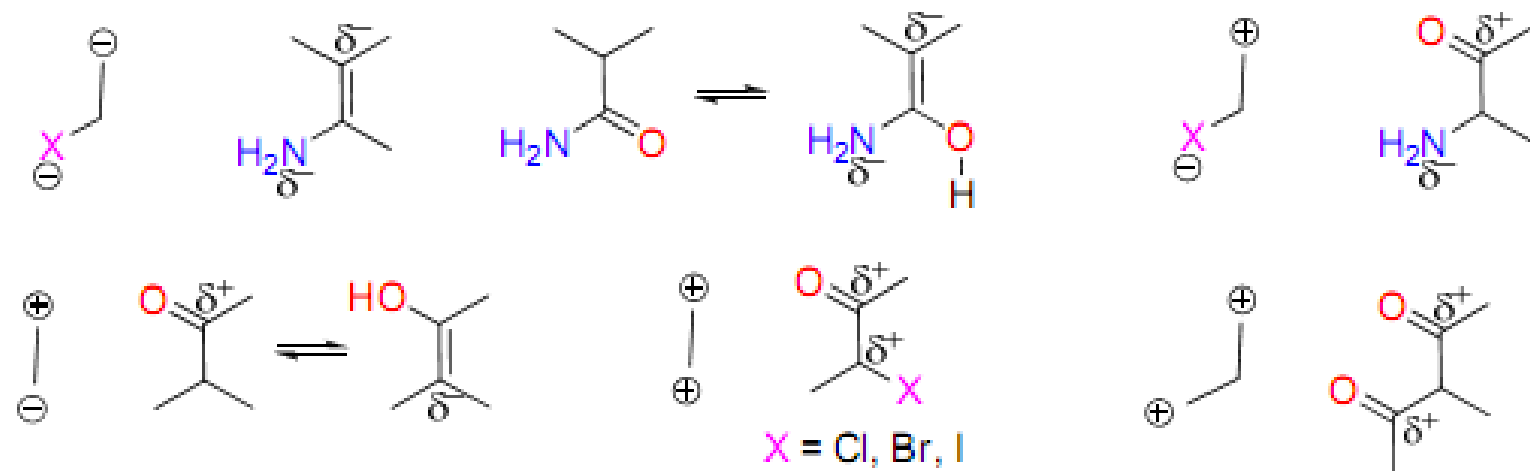
■ "2+3" strategy



■ "3+3" strategy



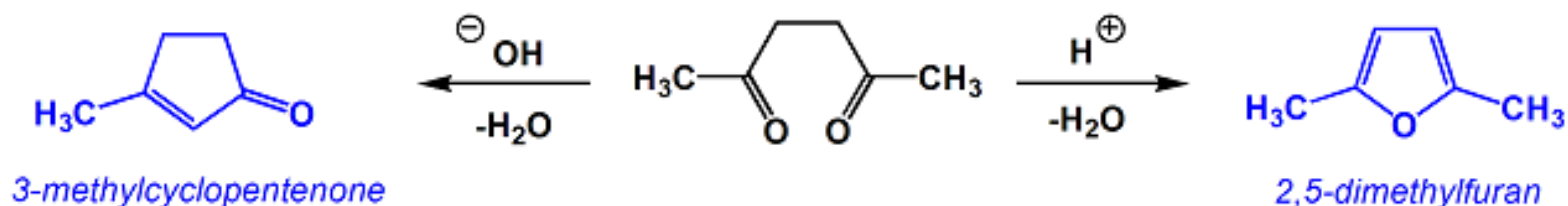
■ Examples



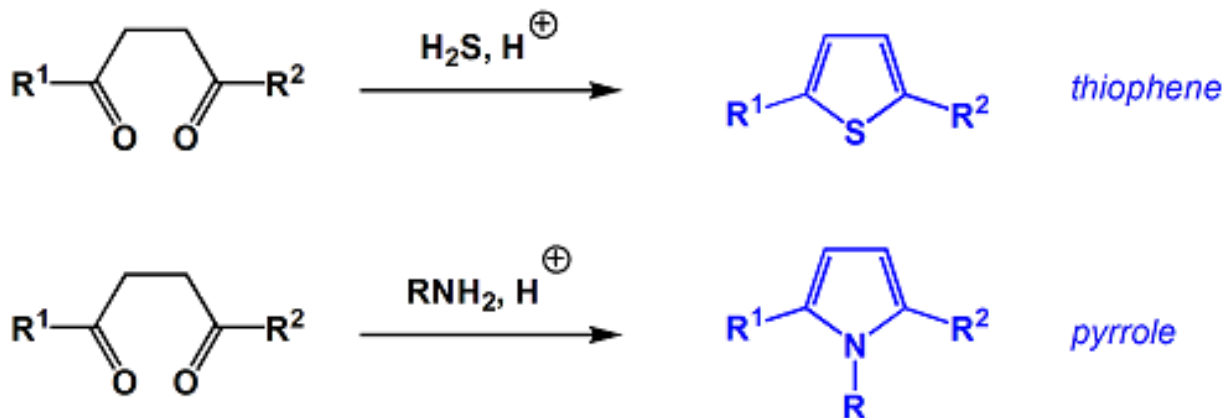
Heterocycles from 1,4-diketones: the Paal-Knorr synthesis

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.

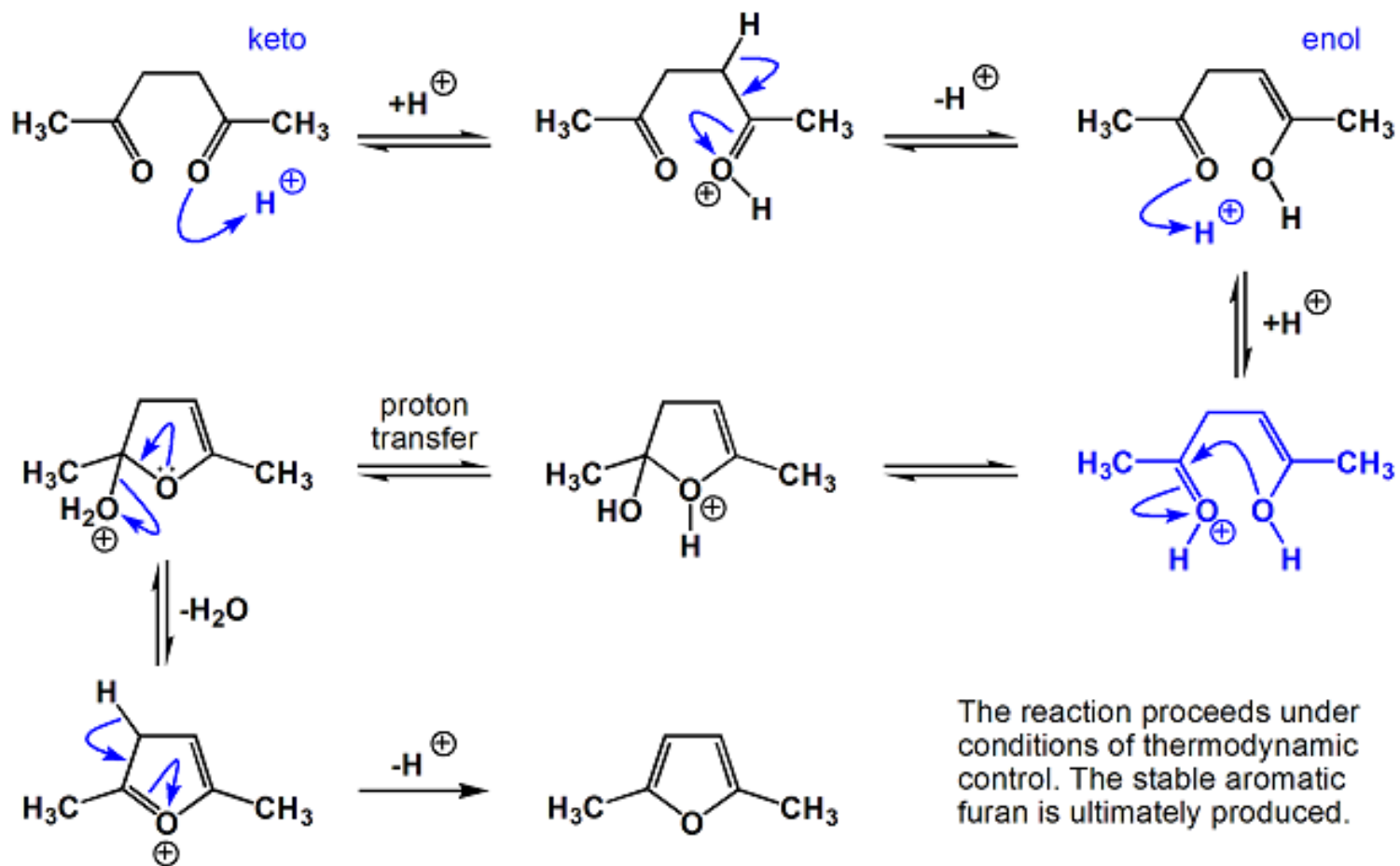


Related reactions under acidic conditions can yield pyrroles and thiophenes.



Mechanism of the Paal-Knorr synthesis

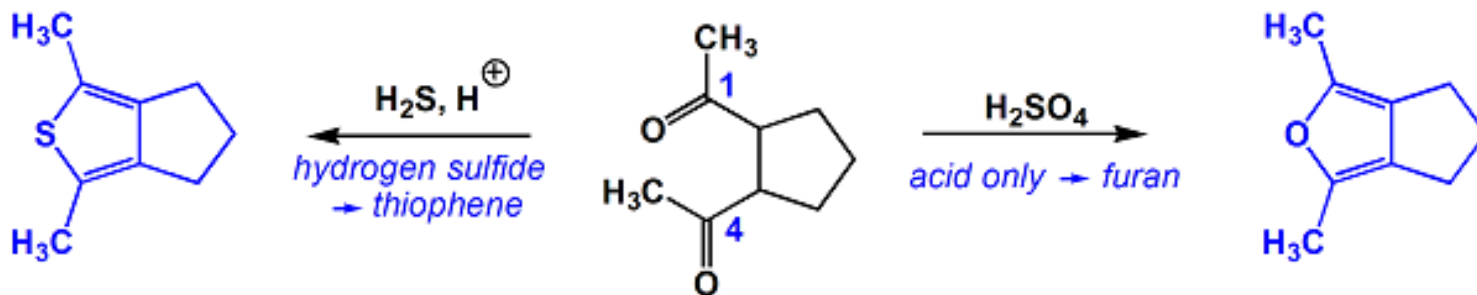
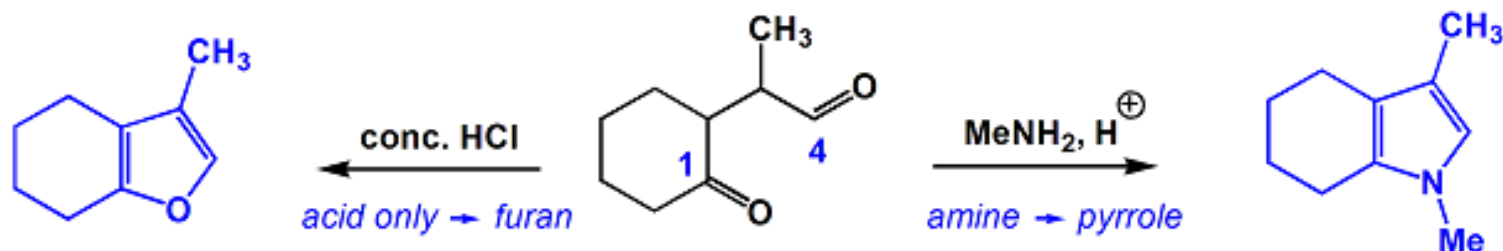
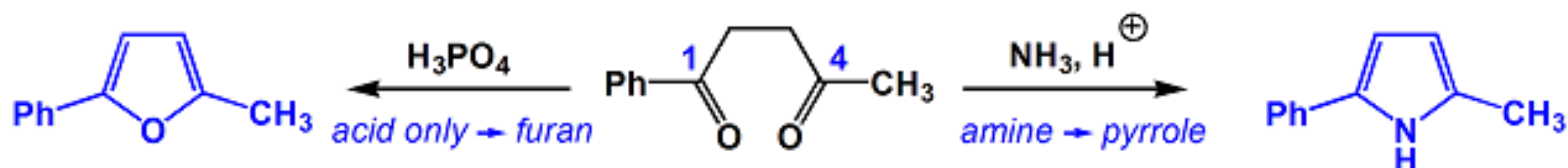
3a



Paal-Knorr synthesis: examples

4a

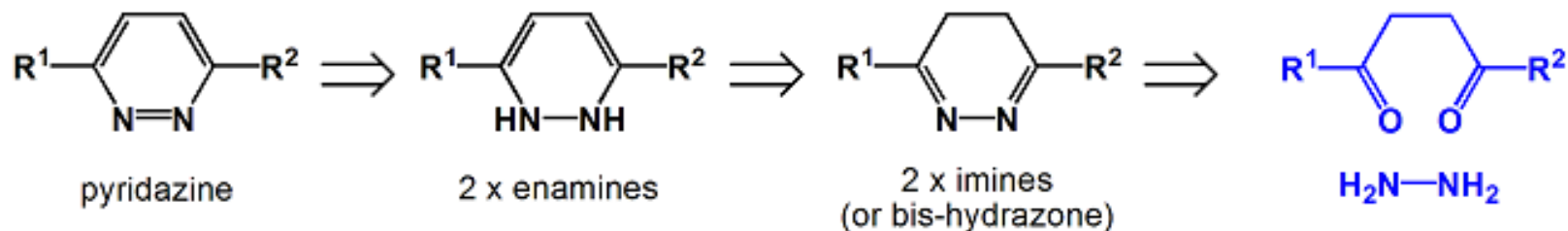
Work out the products from the following reactions:



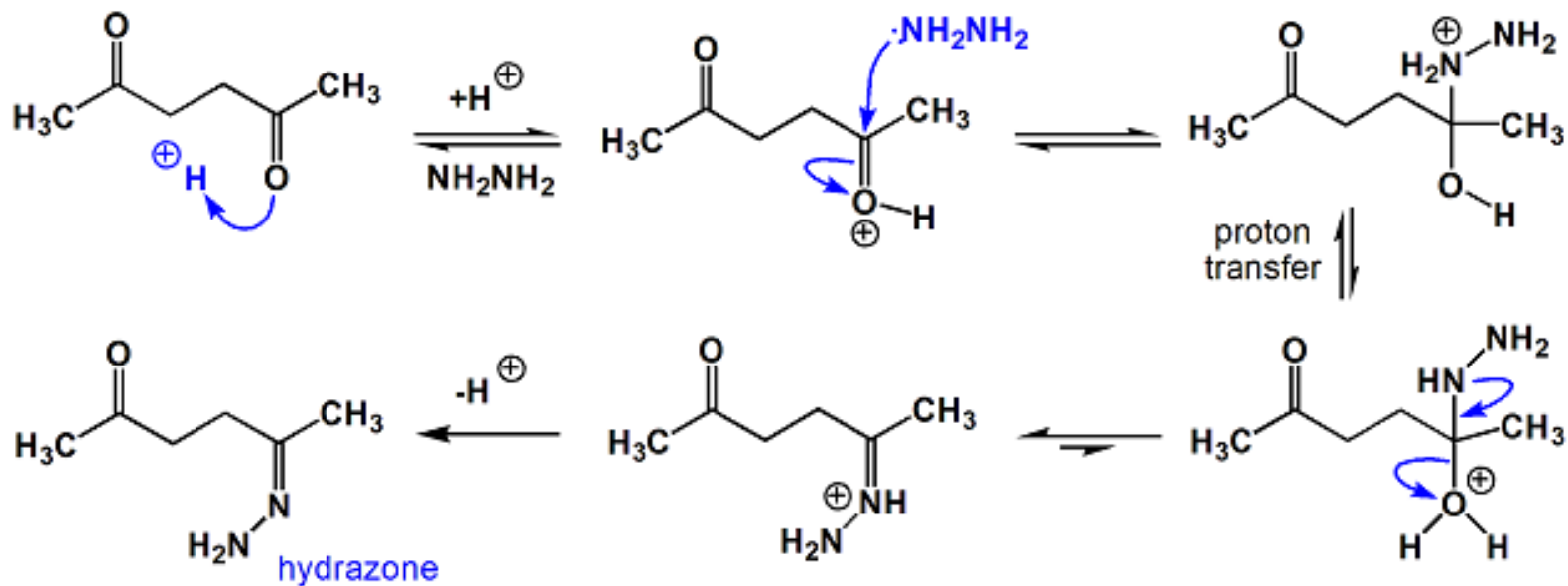
Heterocycles from 1,4-diketones: pyridazines

4b

retro-synthetic analysis

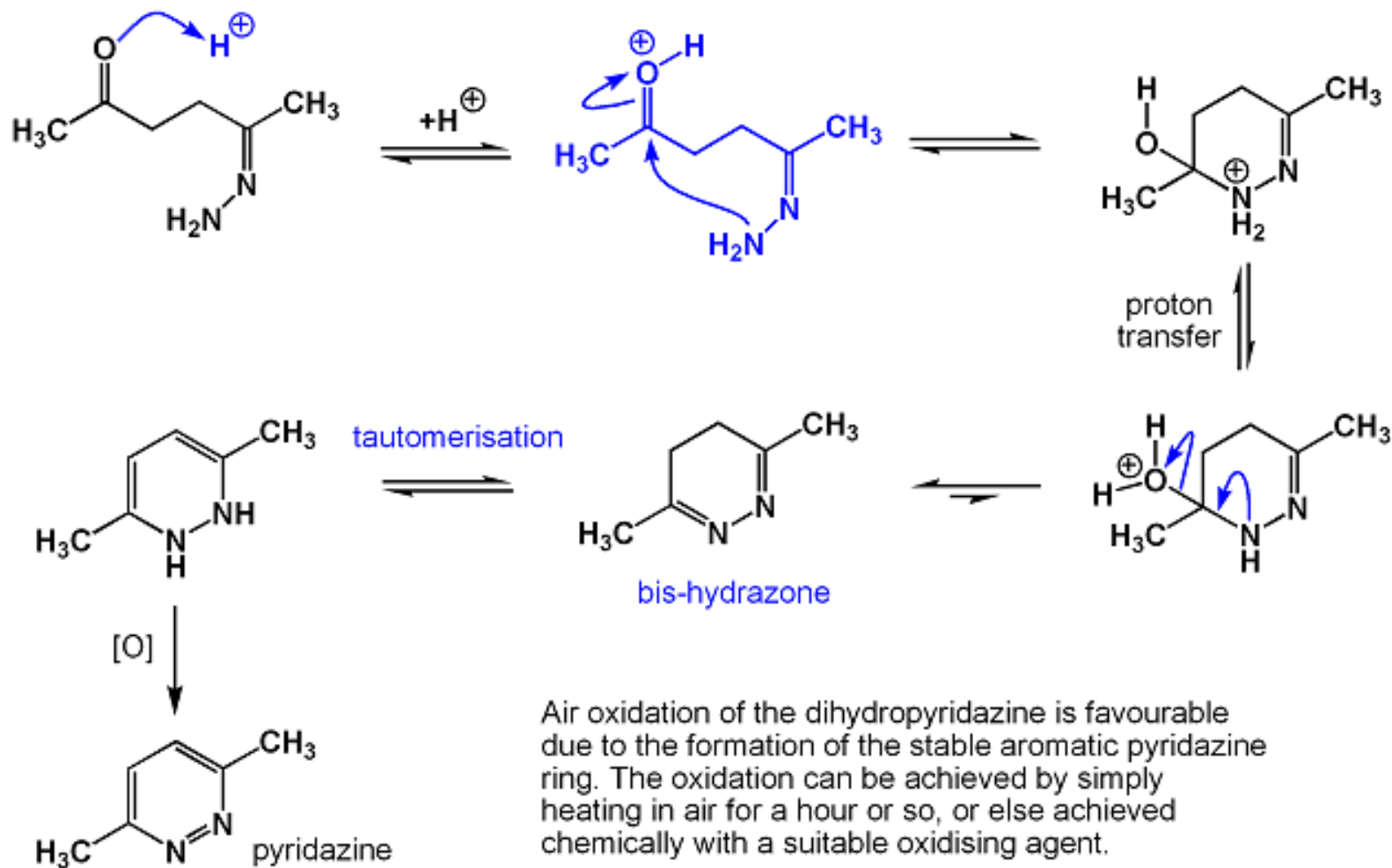


Synthesis of the first hydrazone intermediate



Mechanism of pyridazine synthesis (cont.)

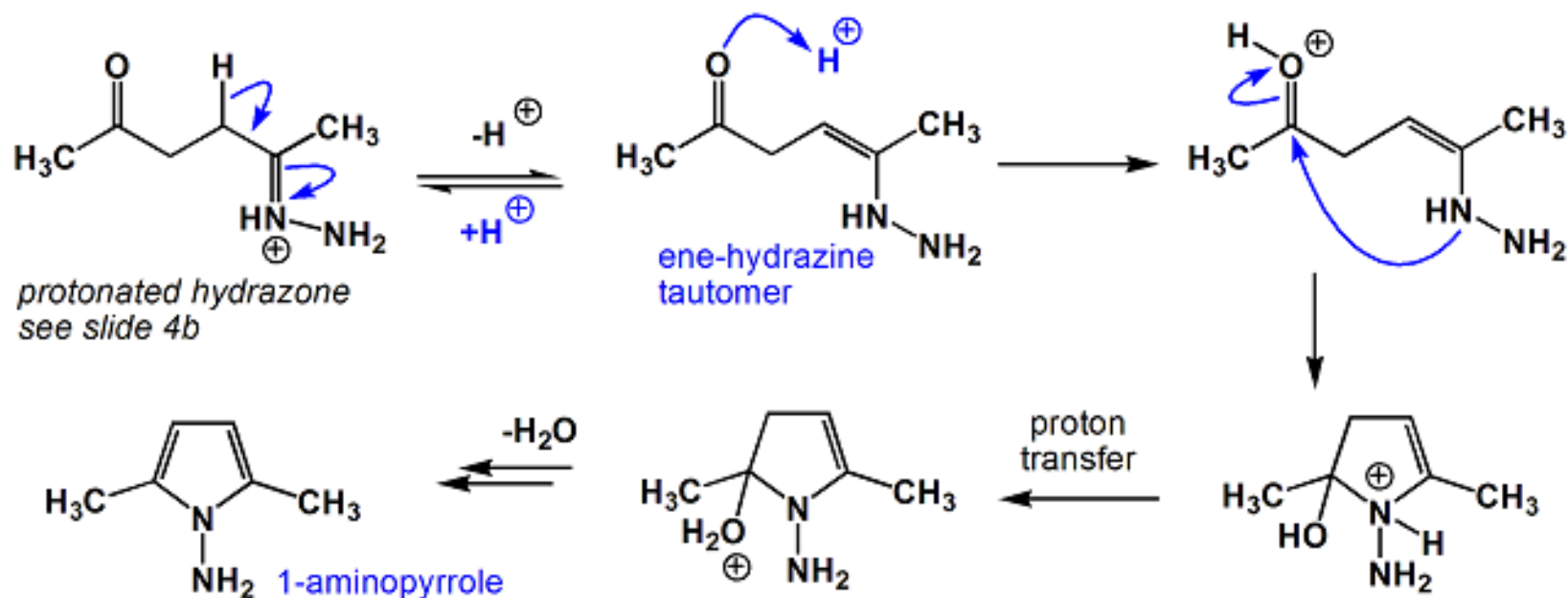
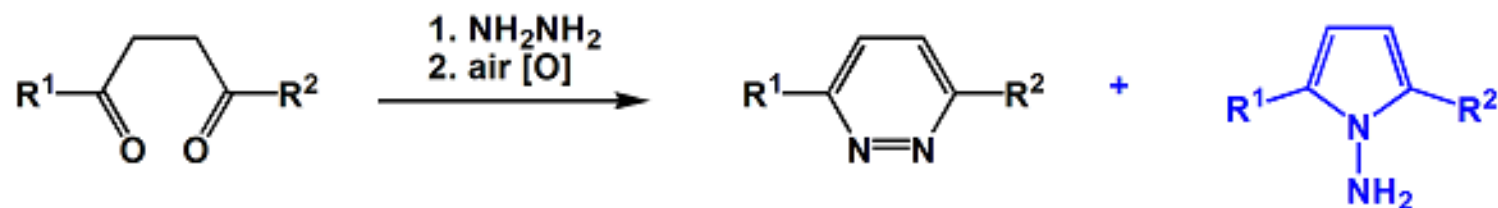
5a



By-product formation: 1-aminopyrroles

5b

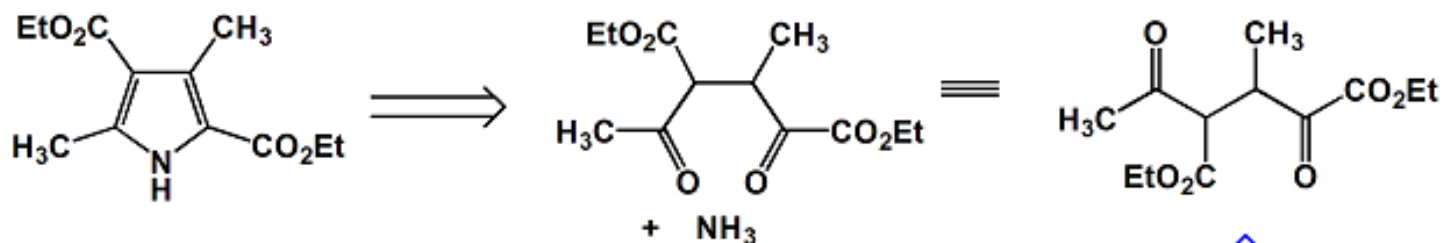
Synthesis of pyridazines from 1,4-diketones by this method may be accompanied by a 1-aminopyrrole by-product arising from a Paal-Knorr type mechanism.



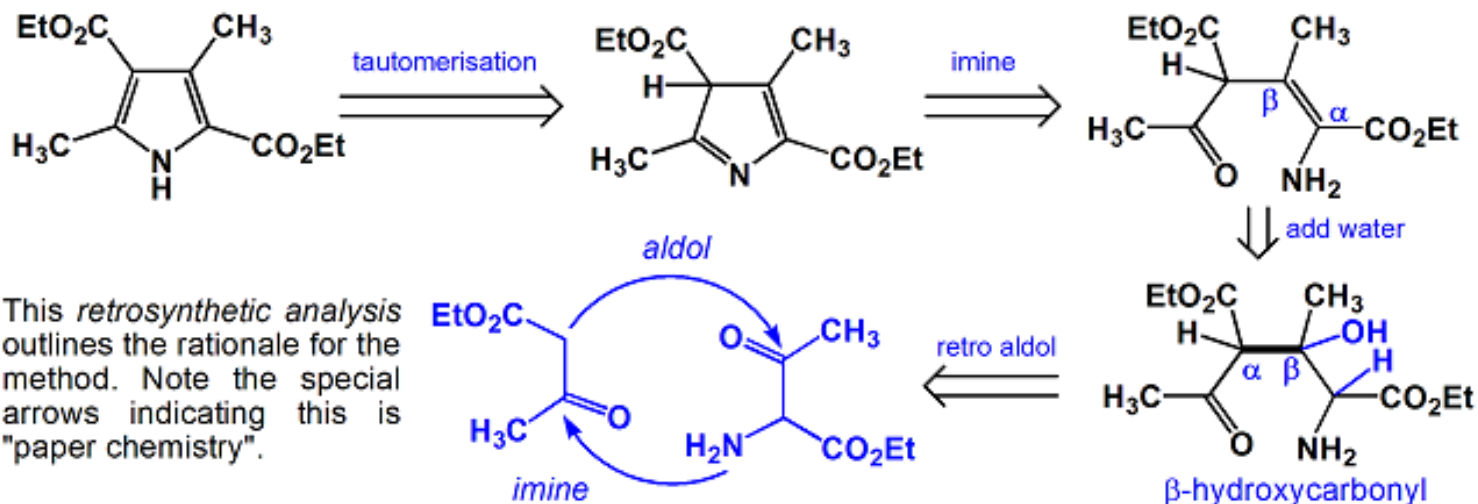
Knorr pyrrole synthesis

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.

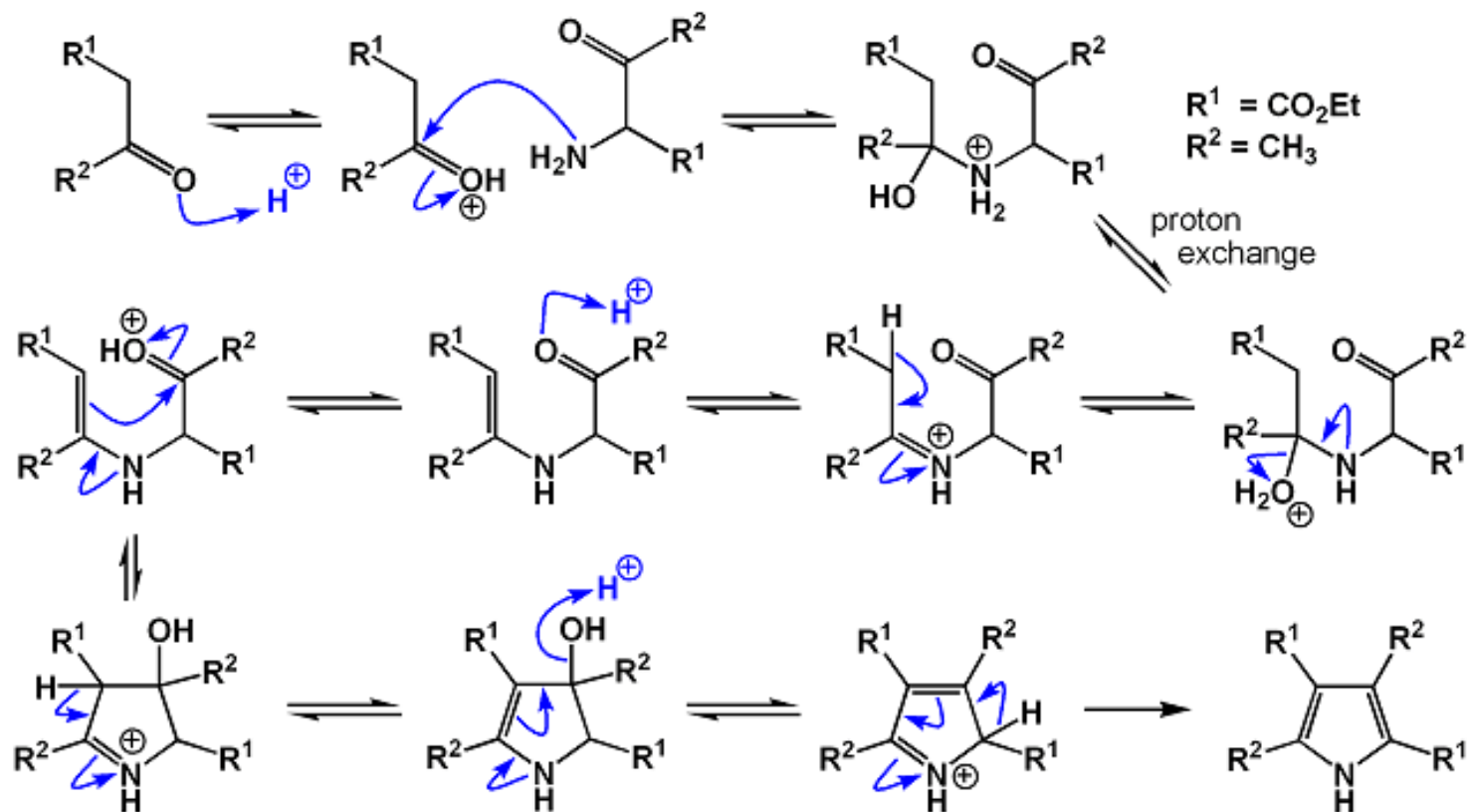


This *retrosynthetic analysis* outlines the rationale for the method. Note the special arrows indicating this is "paper chemistry".

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.

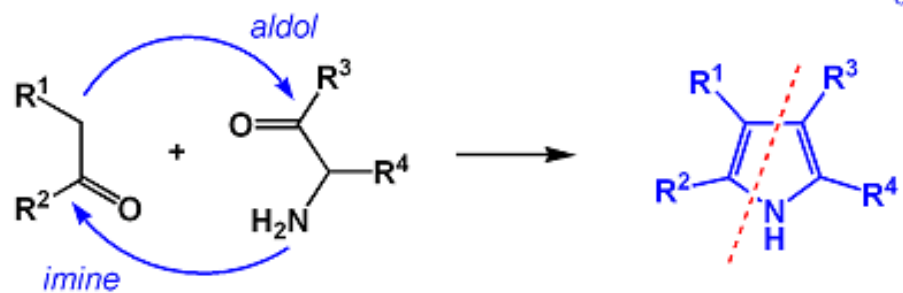
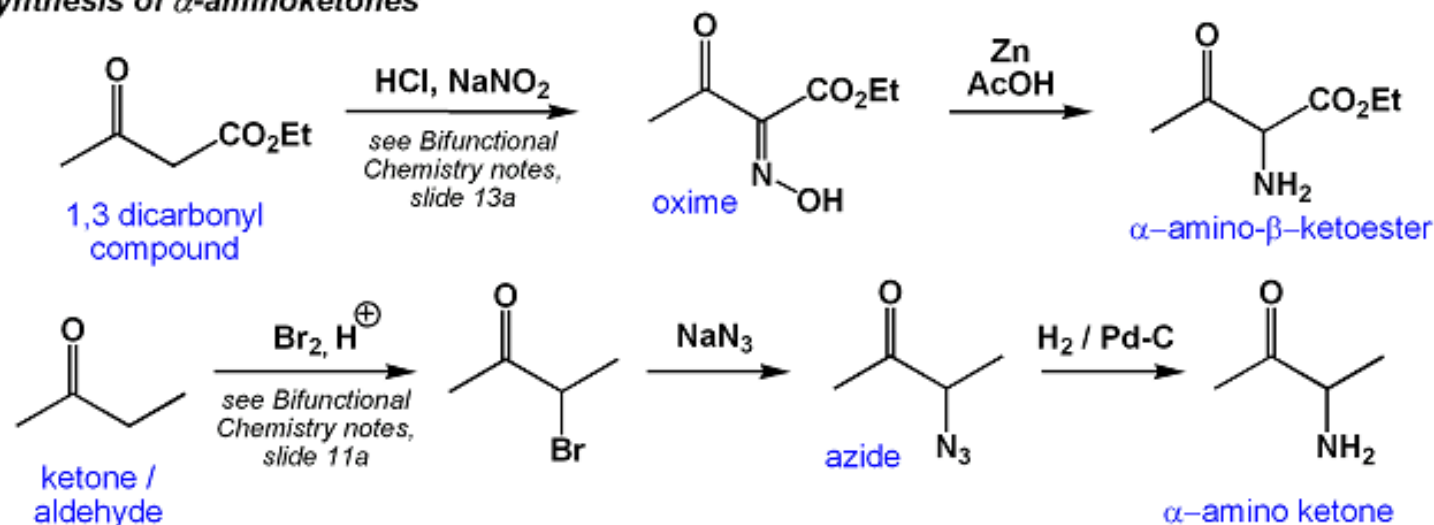


The Knorr pyrrole synthesis: "unsymmetrical" pyrroles

7a

The Knorr pyrrole synthesis does not need to be done in "one pot". The amino ketone component can be made separately, then condensed with another carbonyl containing compound, so giving access to a wider range of pyrroles.

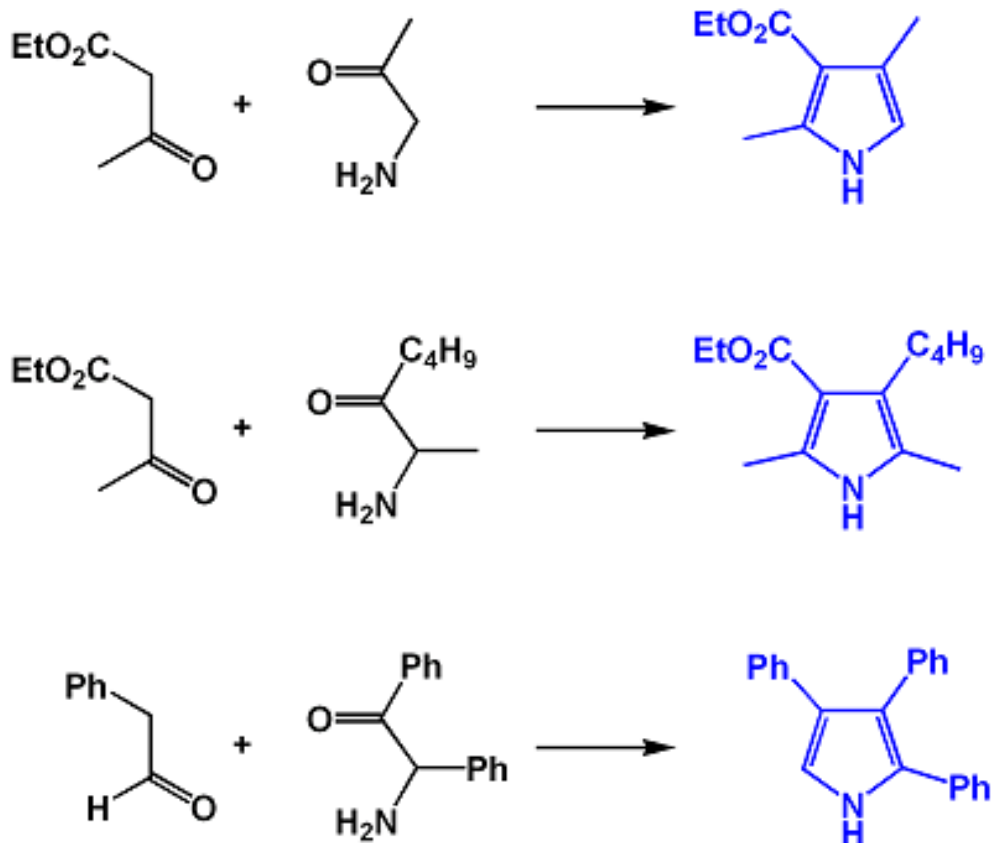
Synthesis of α -aminoketones



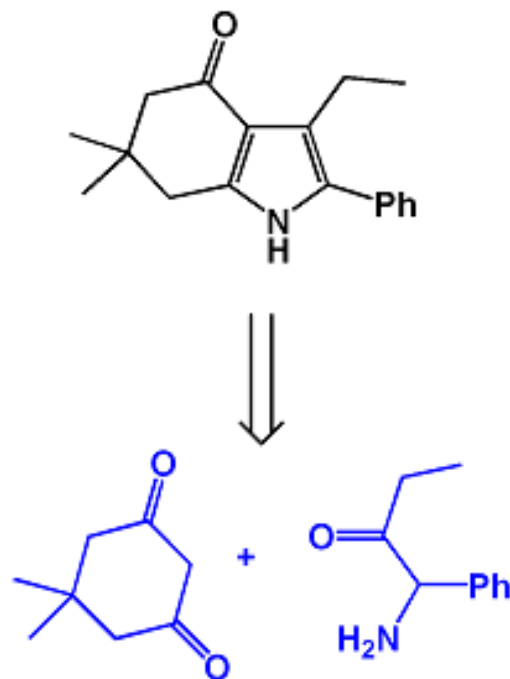
The Knorr pyrrole synthesis: examples

7b

Examples of pyrroles made using the Knorr method.



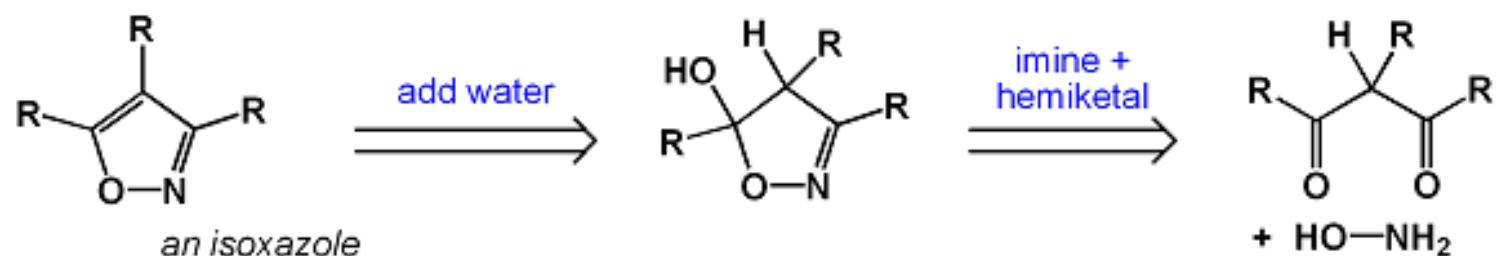
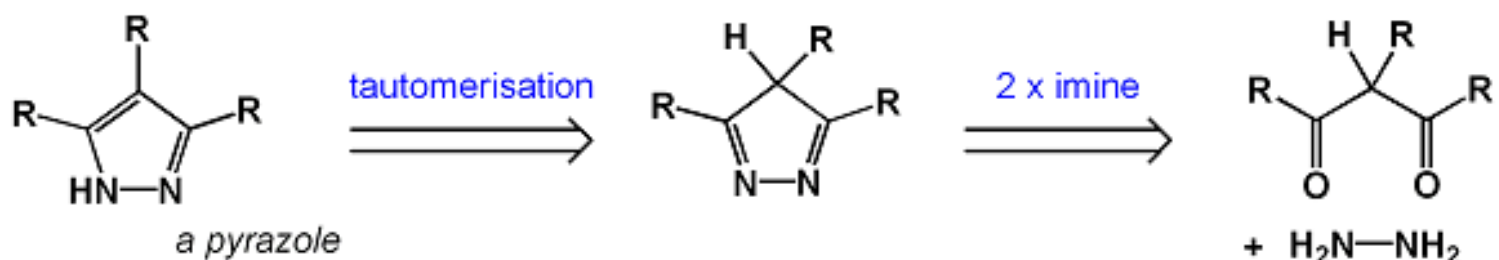
How would you make this pyrrole?



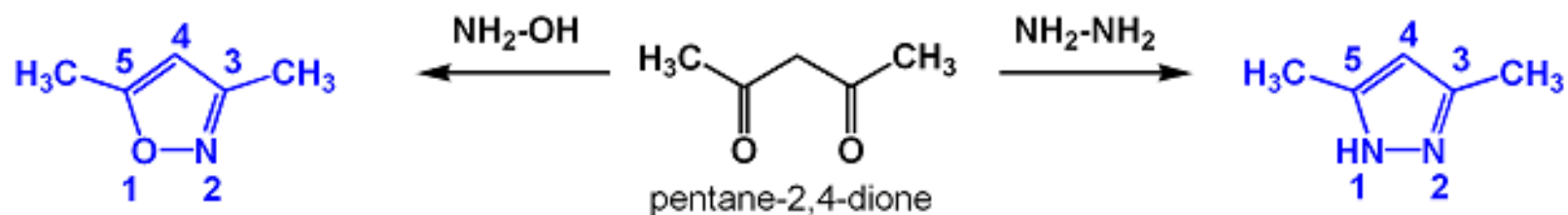
Heterocycles from 1,3-dicarbonyls: isoxazoles and pyrazoles

8a

Retrosynthetic analysis



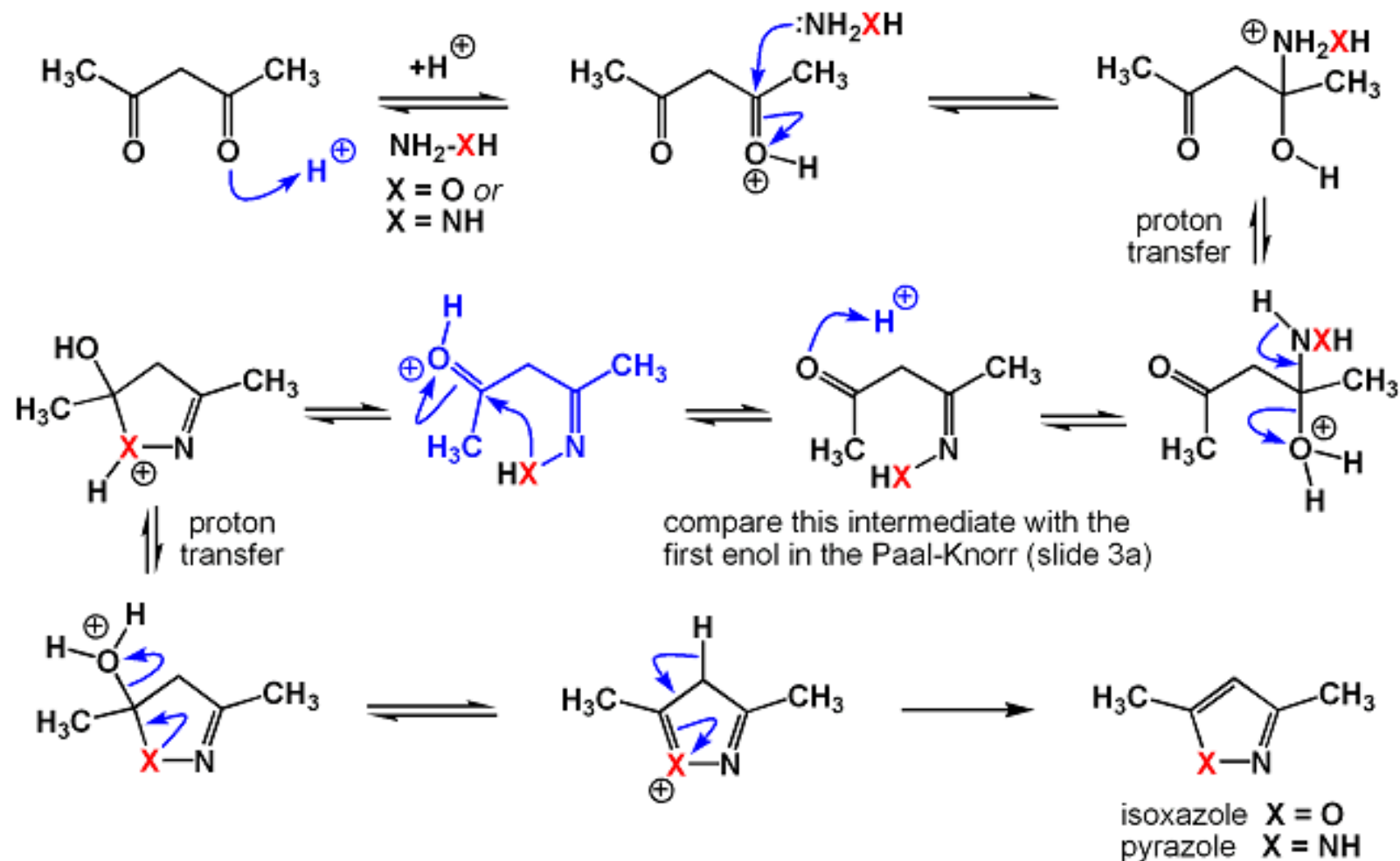
Synthesis of 3,5-dimethylisoxazole and 3,5-dimethylpyrazole from pentane-2,4-dione



Mechanism for isoxazole / pyrazole synthesis

8b

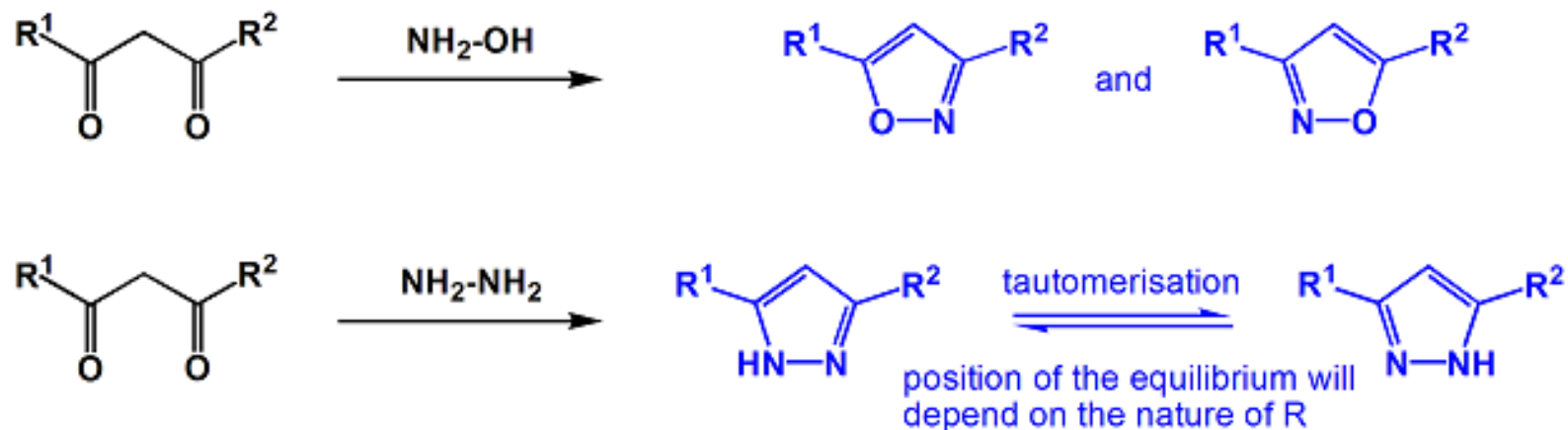
The chemistry involved here is very similar to the Paal-Knorr pyrrole synthesis.



Isoxazoles and pyrazoles: Unsymmetrical 1,3-diketones

9a

The reaction of unsymmetrical 1,3-diketones with hydroxylamine (NH_2OH) *may* lead to mixtures of isoxazoles, but with hydrazine (NH_2NH_2) this is not an issue as the two "products" are in fact tautomers.



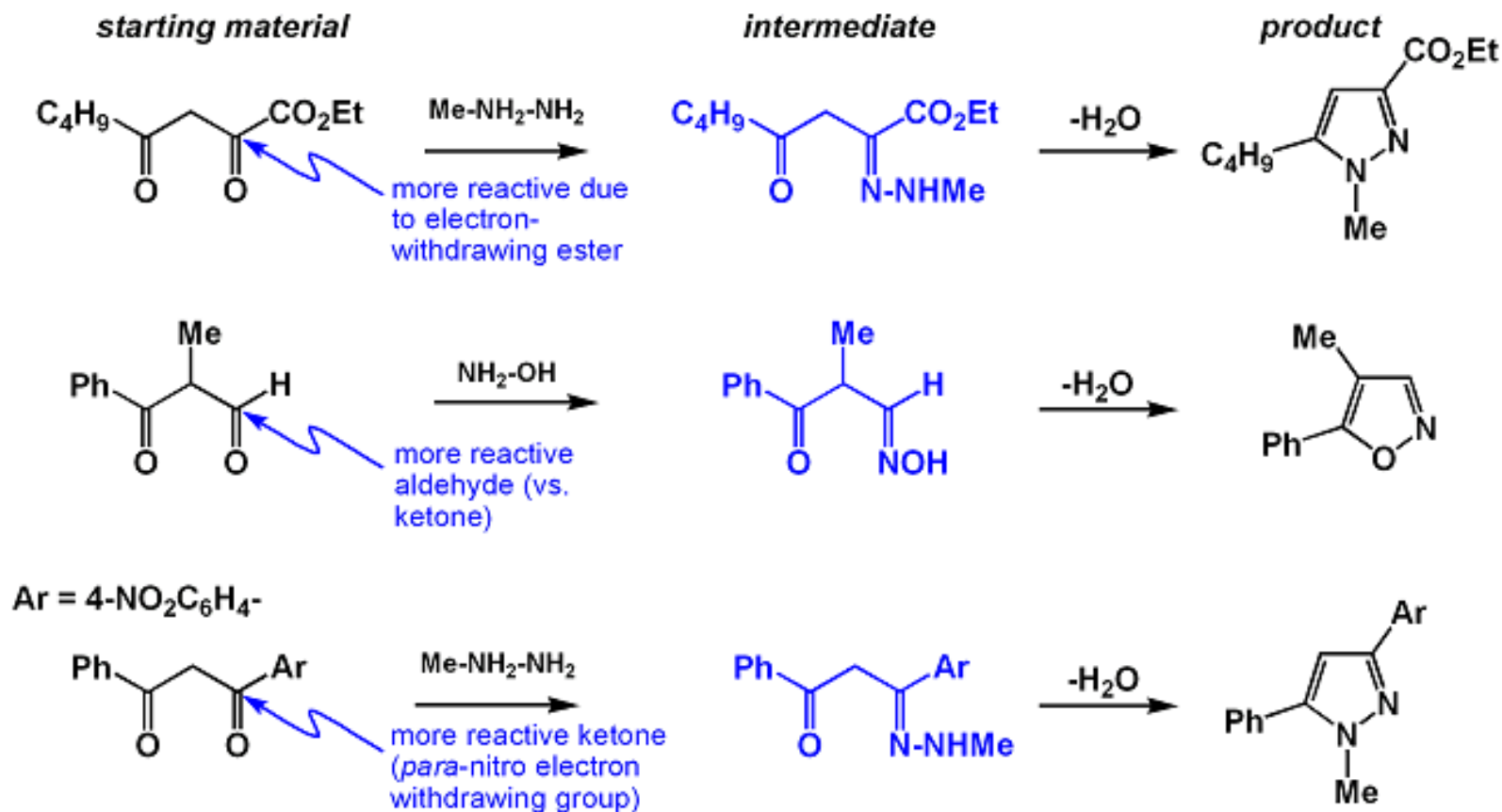
N-alkyl or aryl substituted hydrazines can give two products which *cannot* tautomerise, and so the same question of selectivity seen with hydroxylamine arises (above).



Examples of isoxazoles and pyrazoles made from unsymmetrical 1,3-diketones

9b

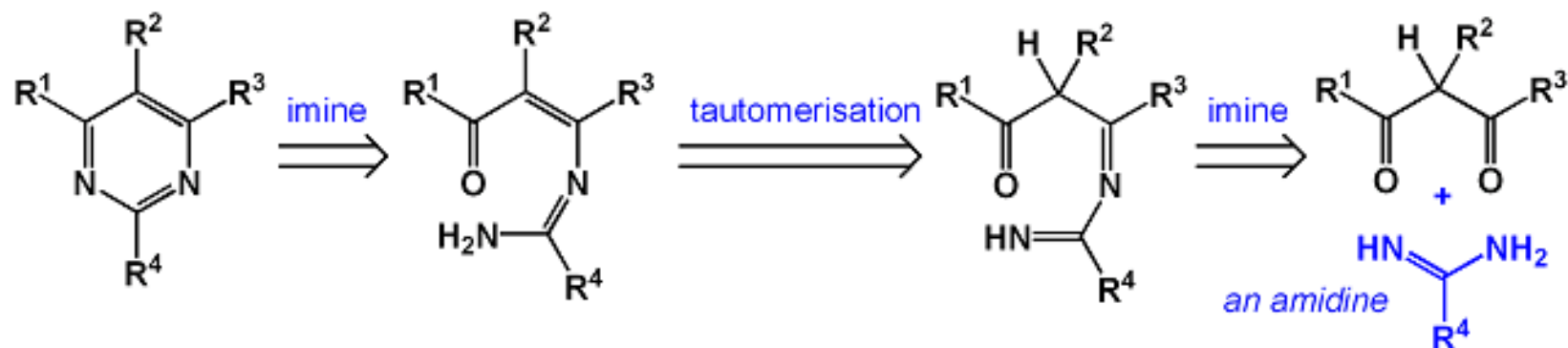
The reaction of unsymmetrical 1,3 diketones *may however* lead to *single isoxzoles or pyrazoles* if one carbonyl group is more reactive than the other.



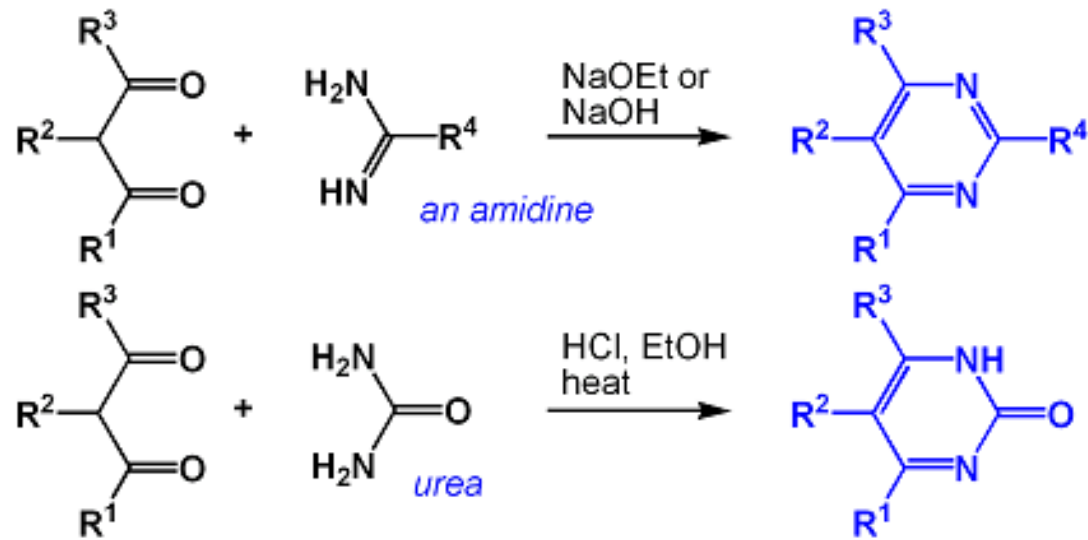
Synthesis of pyrimidines and 2-pyrimidones from 1,3-diketones

10a

Retrosynthetic analysis reveals that pyrimidines can be made from an amidine and 1,3-diketones



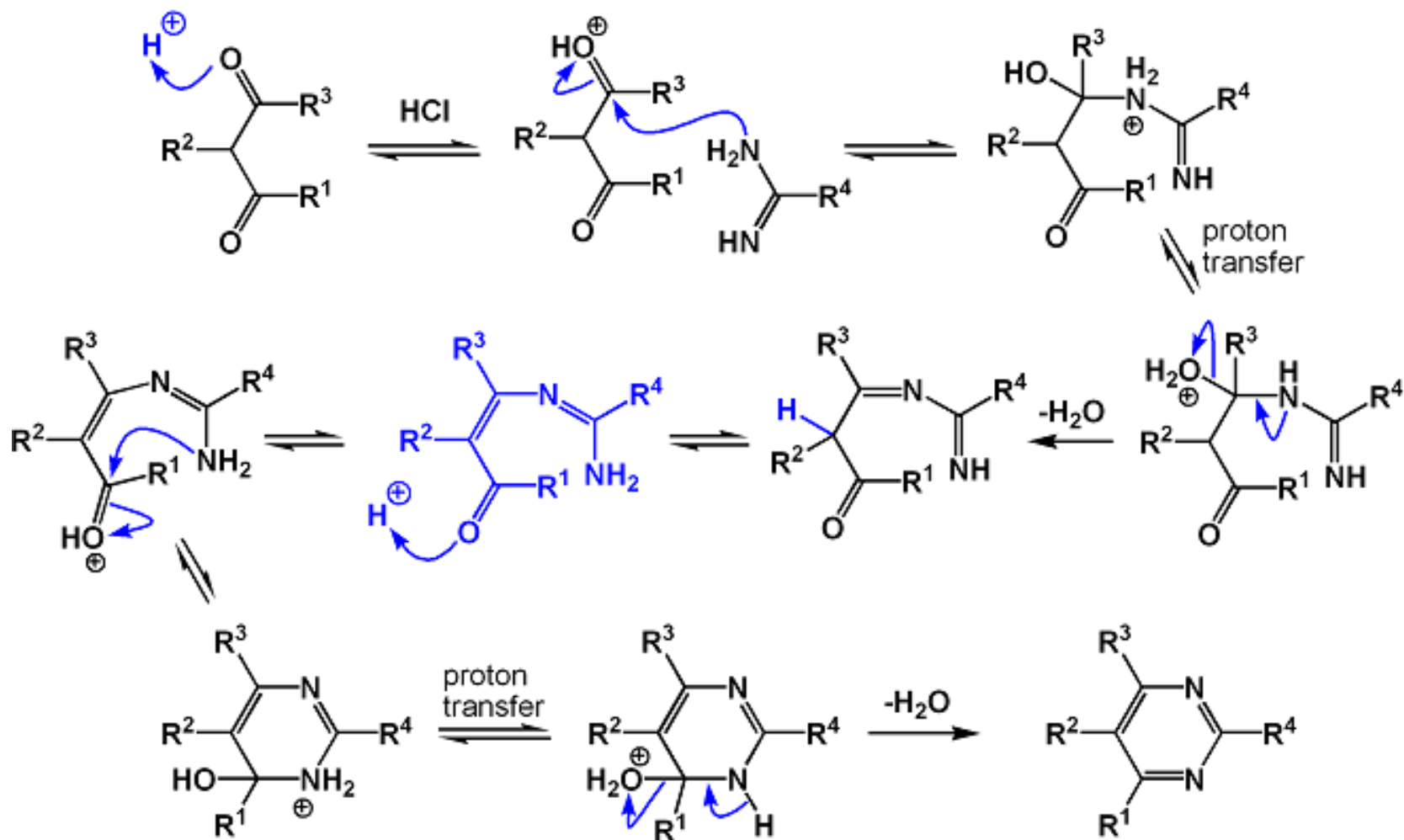
Reactions are normally conducted with acid or base catalysis, eg:



Analogous reactions can be conducted with urea, thiourea and guanidine.

Synthesis of pyrimidines: mechanism

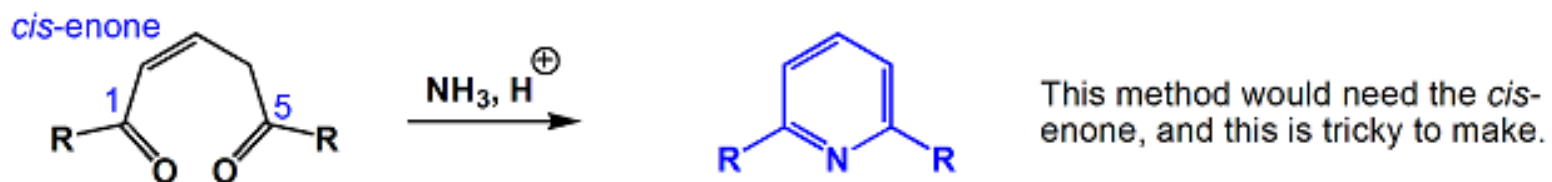
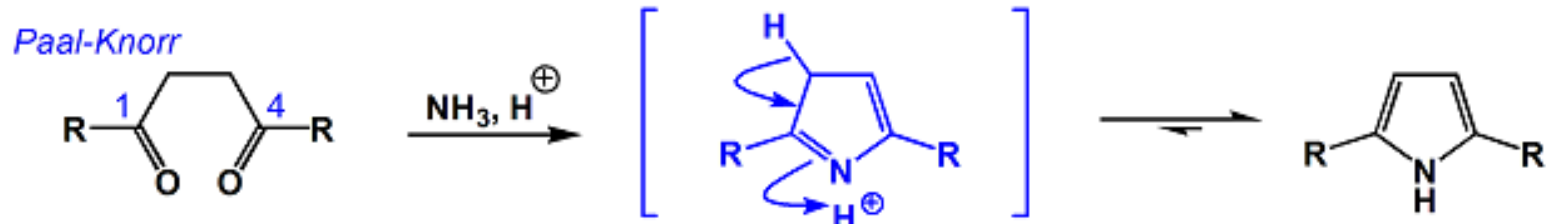
10b



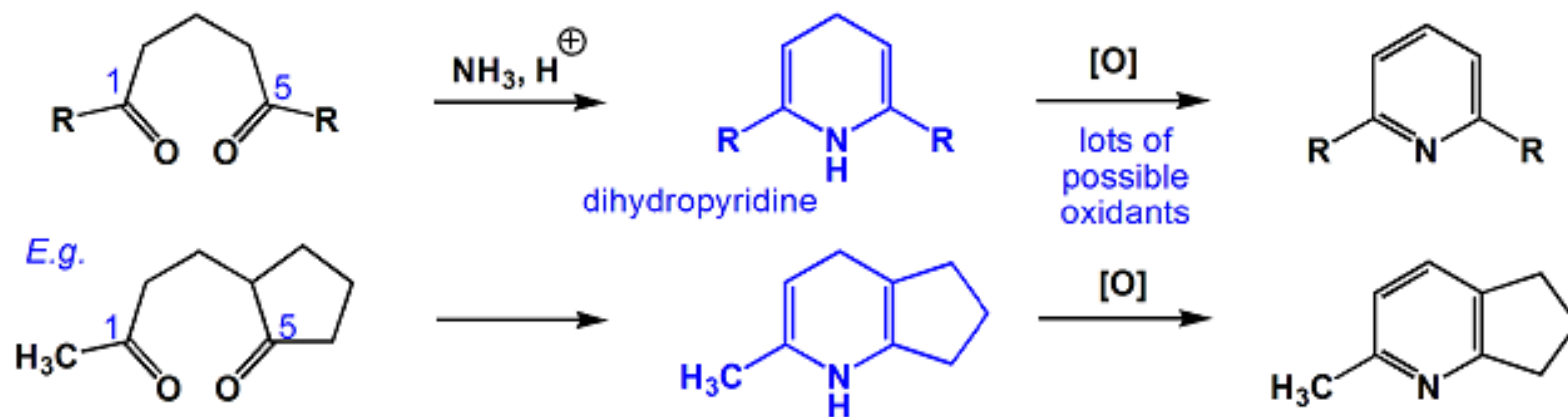
Synthesis of pyridines from 1,5-dicarbonyls

11b

Can the Paal-Knorr pyrrole synthesis be adapted to use a 1,5 dicarbonyl to make a pyridine?



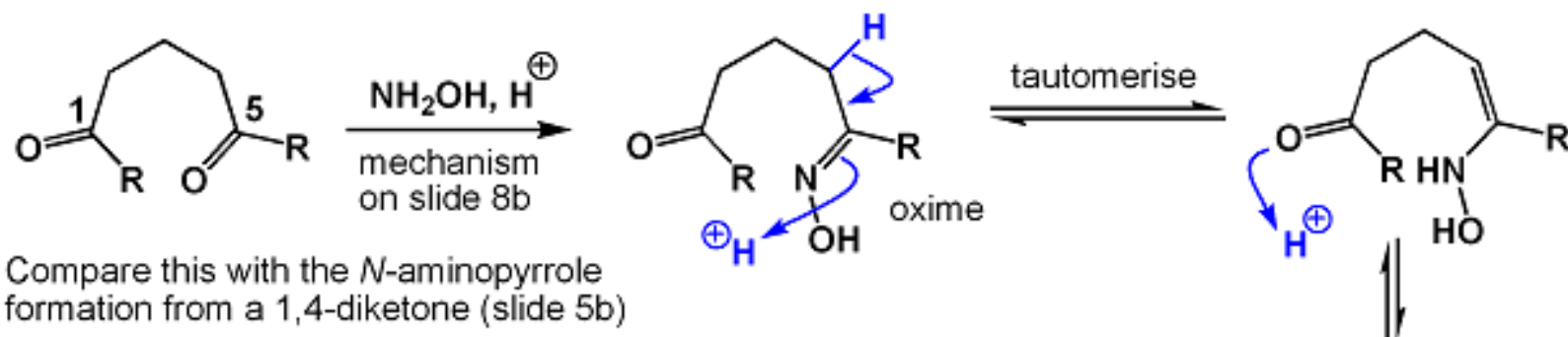
An alternative and easier approach would make a **dihydropyridine**, followed by a separate oxidation (cf. the pyridazine synthesis (slide 4b/5a))



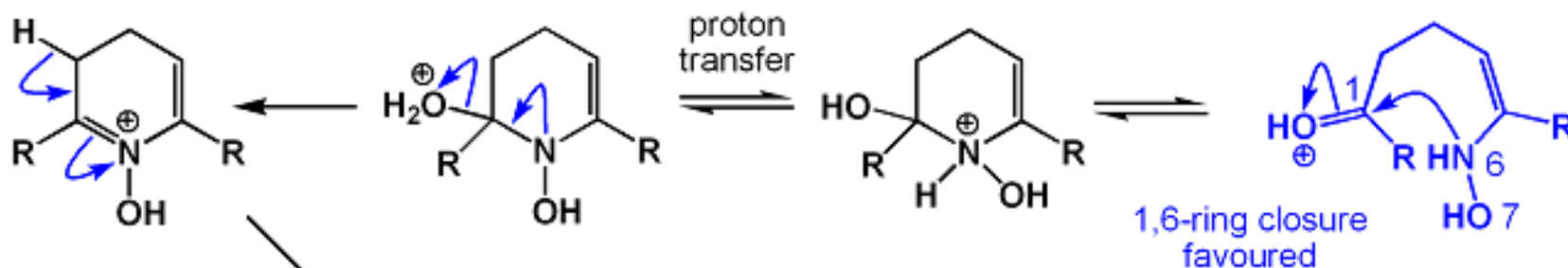
Synthesis of pyridines from 1,5-dicarbonyls

12a

An alternative approach to oxidation of the **dihydropyridine**, is by using hydroxylamine as the source of nitrogen. The *N*-hydroxydihydropyridine can undergo elimination of water to form the pyridine *in situ*.



Compare this with the *N*-aminopyrrole formation from a 1,4-diketone (slide 5b)



Using ammonia in place of hydroxylamine (see slide 11b) would get you to this stage (H in place of OH).

