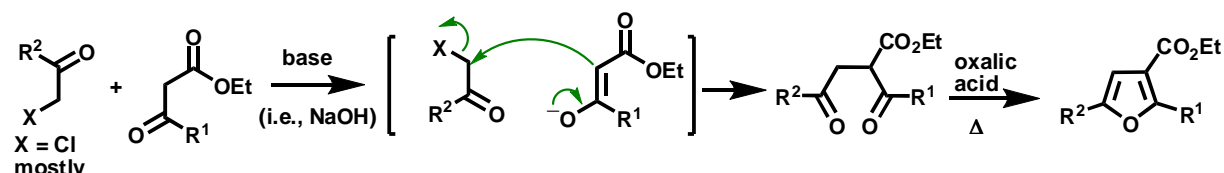
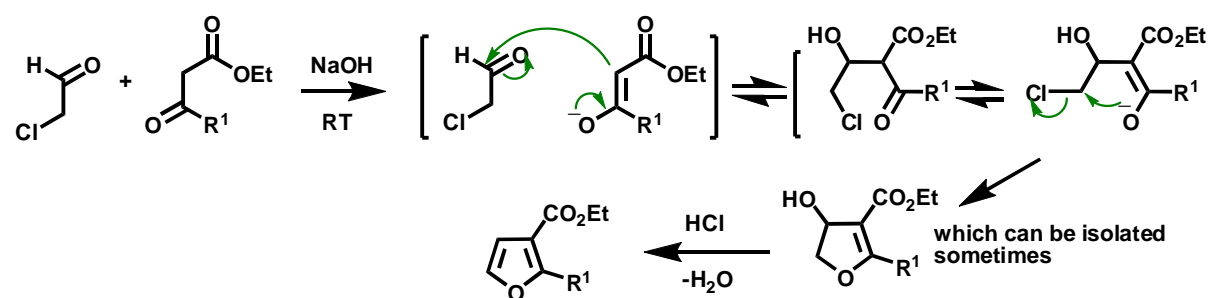


## From $\alpha$ -Heteroatom Substituted Carbonyls and $\beta$ -Keto Esters

**Furans** – In the presence of base,  $\beta$ -keto esters react with  $\alpha$ -halo ketones and aldehydes (usually the chlorides). With ketones, the predominant mode of attack is at the carbon bearing the leaving group, to give a 1,4-dicarbonyl bearing a C-2 ester function. In the presence of acid, these cyclize (and yes, this could easily be called a Paal-Knorr) to give furans with a C-3 ester function.

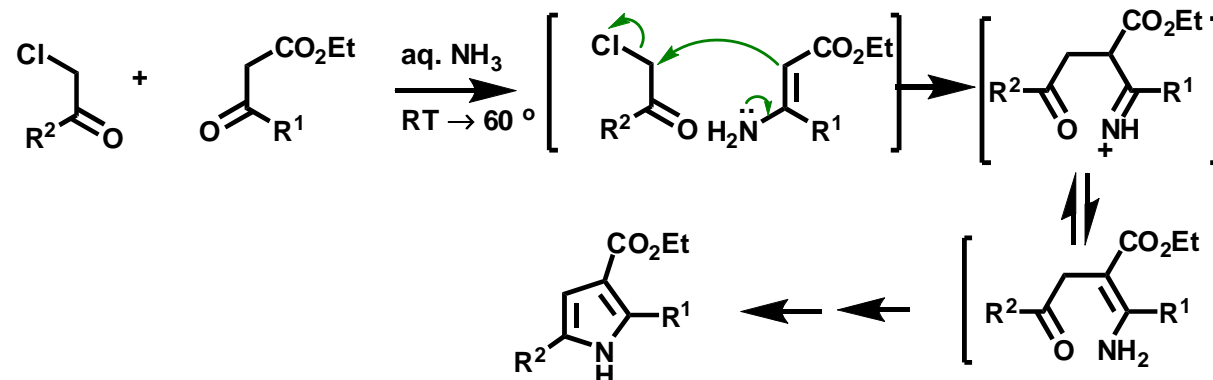


In the carbonyl under attack is an aldehyde, the process predominantly occurs slightly differently, attacking the aldehyde first in an aldol type process. The aldol adduct then undergoes O-alkylation of the  $\beta$ -keto ester function with the carbon bearing the leaving group, which after acid induced elimination gives the furan. So the distinction in terms of product is where any R groups would end up.

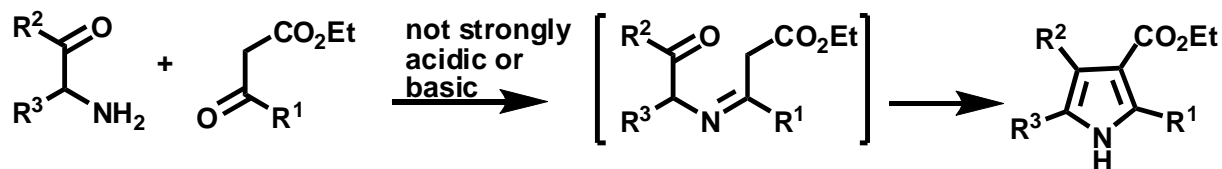


This class of furan syntheses despite its similarity to the ones discussed before, is known as the **Feist-Benary synthesis**.

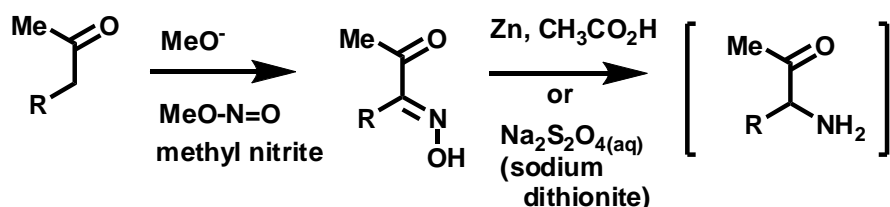
**Pyrrrole** – Once again, the presence of an amine, usually ammonia itself, during this type of process, allows for the synthesis of pyrroles. The ammonia additionally serves as the base (as ammonium hydroxide). Despite the great similarity to the reaction above, this is commonly known as the **Hantzsch pyrrole synthesis**.



A complementary approach to pyrroles is available if one starts with an  $\alpha$ -amino ketone rather than an  $\alpha$ -halo ketone. Since the amino function ends up forming the N- atom of the pyrrole, the regiochemistry is reversed.



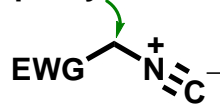
There is an issue with this synthesis, though, in that the  $\alpha$ -amino ketone is often not a stable compound. As a result, it is common to make a stable oxime derivative, and then reductively generate the  $\alpha$ -amino ketone *in situ*.



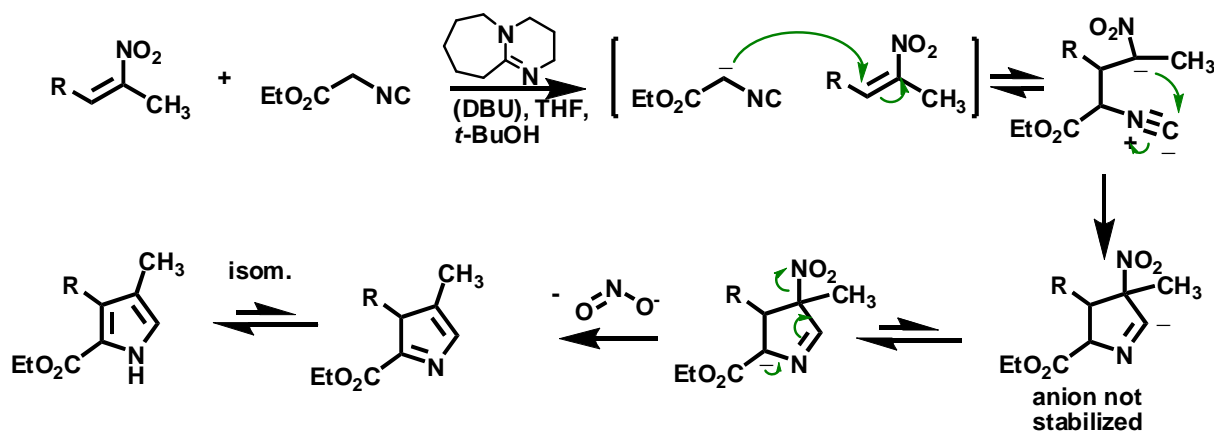
### Special Methods for pyrroles

There are several methods of heterocycle ring synthesis specific for pyrroles that are not readily applicable to the other  $\pi$ -excessive heterocycles, and which we will discuss here. One of these uses an isocyanide along with a leaving group that can also serve as a leaving group. In part this works due to the fact that an isocyanide is an anion stabilizing group not quite as good as an ester (about 3  $pK_a$  units less stabilizing) but about as good as a sulfoxide. As a result an isocyanide with another anion stabilizing group is pretty acid as C-H acids go. The process is based on a Michael type (conjugate) addition, and then ring closing onto the carbon atom of the isocyanide.

pretty acidic H's

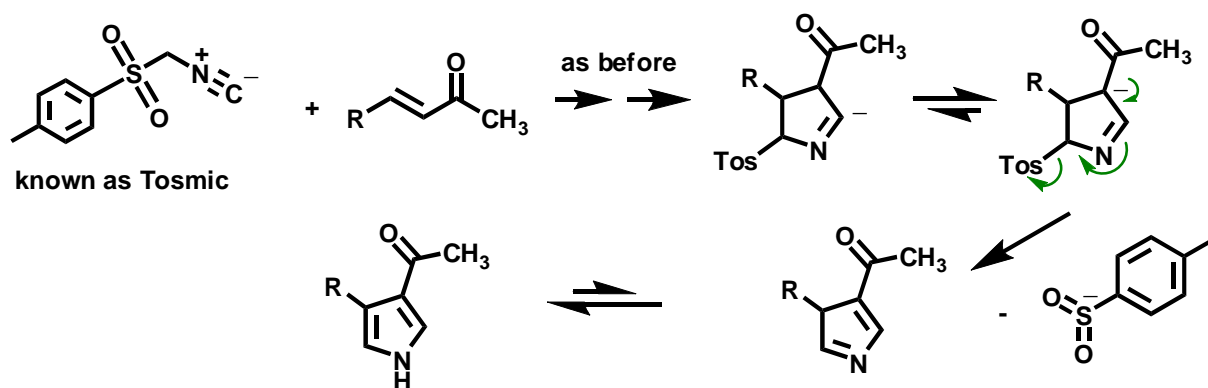


So, for example, if one reacts an ester substituted isocyanate with an unsaturated nitroalkene...

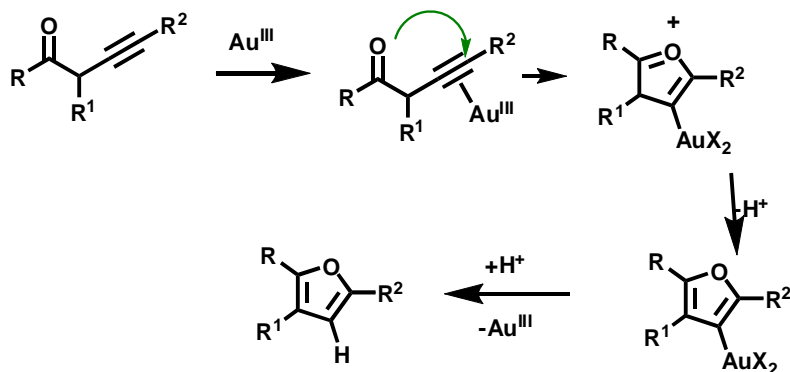


This is called the **Barton-Zard synthesis**.

If the EWG on the isocyanate is a sulfone, it's no longer the Michael acceptor that must have the leaving groups (since  $R-SO_2^-$ ) is a leaving group. This approach to pyrroles is called the **van Leusen synthesis**.



There are many, many newer syntheses of such heterocycles, which cannot be covered here. Particularly trendy are  $Au^I$  or  $Au^{III}$  catalyzed isomerizations of alkynes or allenes, i.e.,...



i.e., Dembinski, R. *Org. Lett.* **2007**, *9*, 1175.

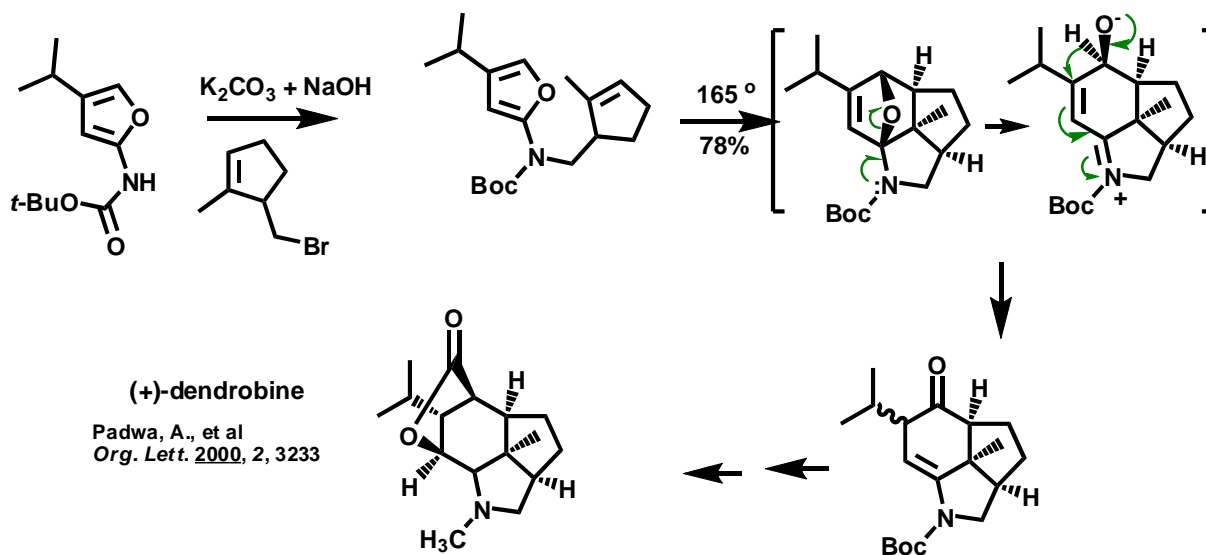
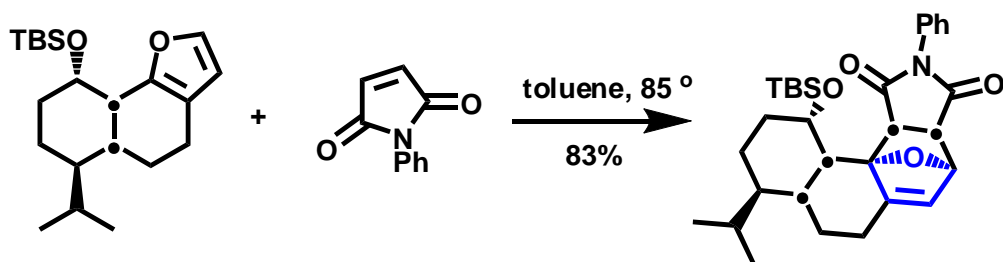
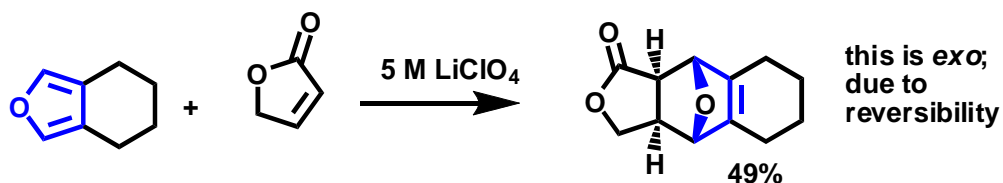
For pyrroles, see Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260; Dake, G. *J. Org. Chem.* **2006**, *71*, 4525.

### (Non-Traditional) Reactions of $\pi$ -Excessive Heterocycles

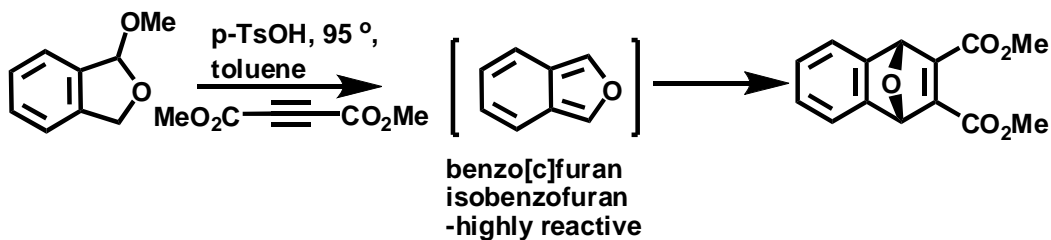
For a review, see Wright, D. L. *Progress in Heterocyclic Chemistry* **2005**, *17*, 1.

This is dominated by furan chemistry, because of the limited aromaticity of it relative to the other heterocycles.

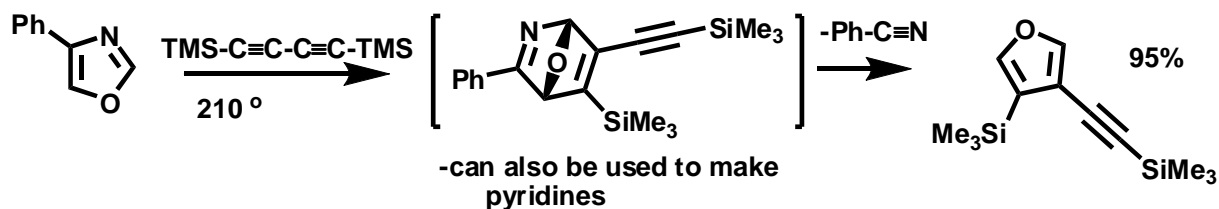
The **Diels-Alder** reaction chemistry of furan is extensive, as it really acts a somewhat electron rich dienes. It follows (kinetically) the endo rule when possible, but furan Diels-Alders are highly reversible; as a result, it is nearly as common to isolate exo products (or mixtures). Some examples...



One class of furans, namely isobenzofurans, are unstable intermediates (unless substituted with large groups) that are used heavily for constructing new benzocyclohexene or arene ring systems.

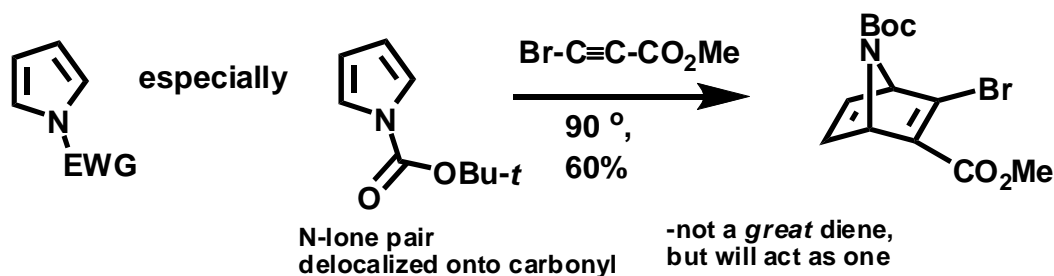


**On Other Systems.** Oxazoles are similarly low aromaticity heterocycles, and so they have comparable reactivity to furans. They may even be used to form furans by a Diels-Alder/retro Diels-Alder process.

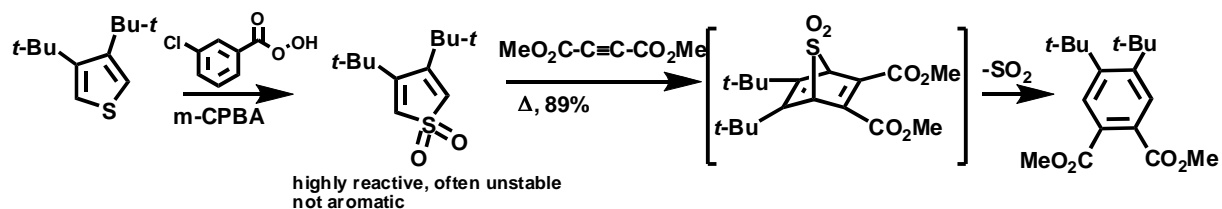


For **thiophenes, pyrroles**, they are not generally reactive in cycloadditions, because the involvement of the lone pair makes them too aromatic to allow the transition state to be accessible energetically. This can be solved in some cases by chemically altering the systems such that the lone pair is 'tied up' otherwise.

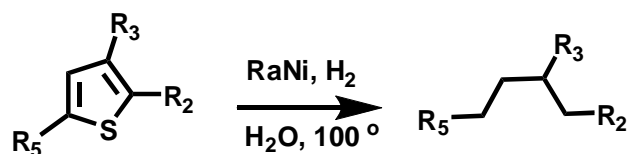
For pyrrole



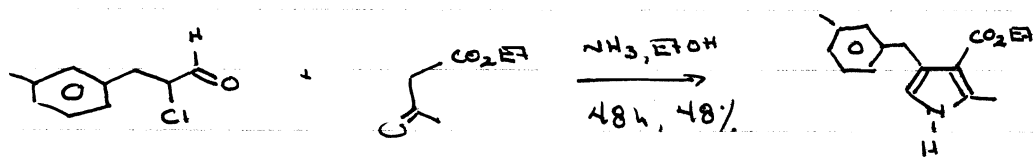
For thiophenes, there are rare cases....but only rare ones.



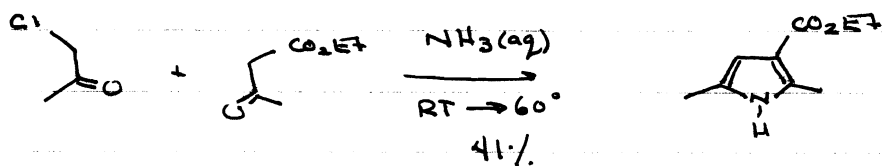
For thiophenes, it is also possible to extrude the sulfur by a hydrogenation/hydrogenolysis combination.



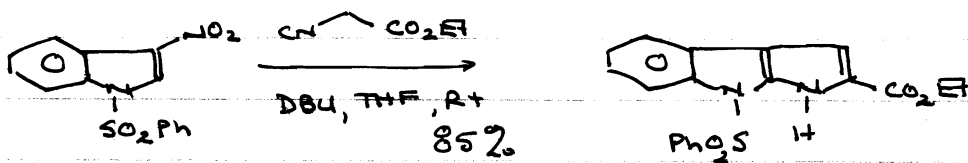
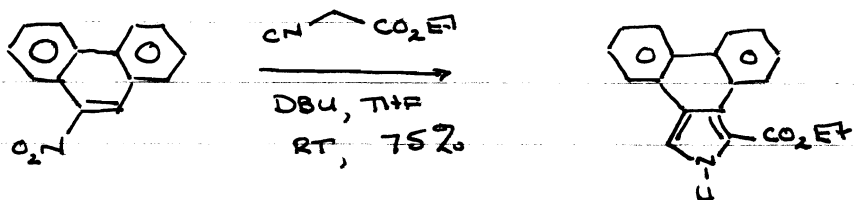
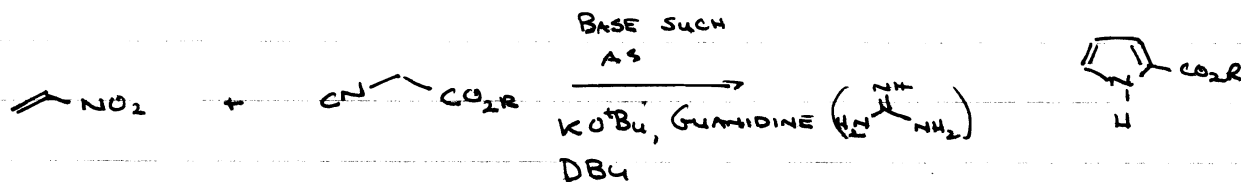
# EXAMPLES HANTZSCH PYRROLE SYNTHESIS



NOTE: CHLORIDE SITE IS ATTACKED FIRST

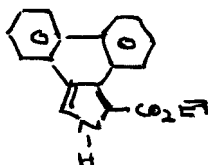
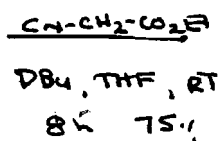
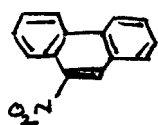


# BARTON ZARD SYNTHESIS

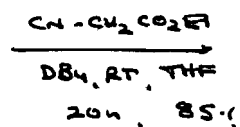
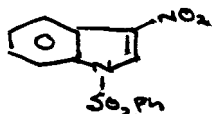


EXAMPLES:

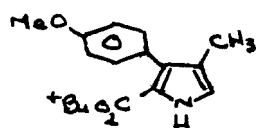
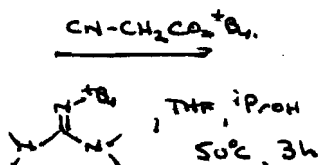
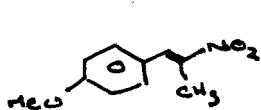
BARTON-ZARD SYNTHESIS



J. Chem. Soc., Perkin Trans 1  
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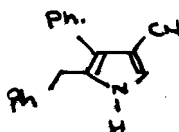
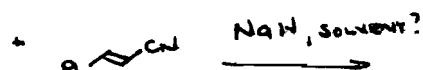
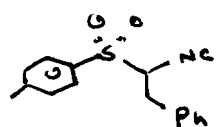
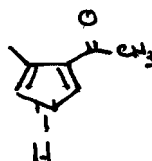
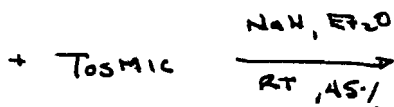
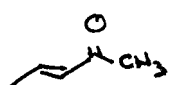
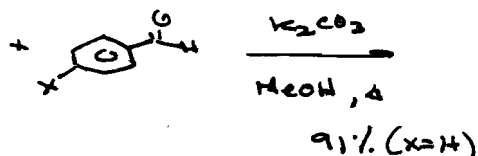
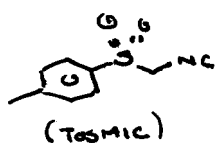


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