CHEM 330

Topics Discussed on Sept. 21

Principle: a successful cross-Claisen reaction requires the preformed enolate to react with an ester-like agent that:

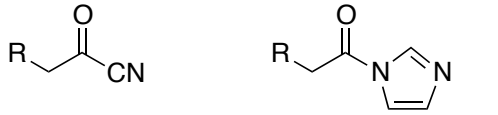
a. reacts with the enolate at a much faster rate (= is much more electrophilic) than an ordinary ester;

b. reacts with the enolate at a rate that is much faster than that of proton exchange;

c. forms a product of addition that (i) either releases a poorly basic fragment incapable of inducing reversibility, or (ii) is relatively stable and unravels to the ultimate 1,3-dicarbonyl only during the final aqueous workup

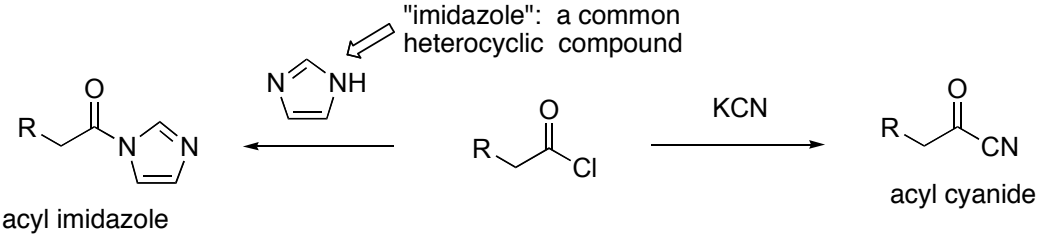
Unsuitability (with a few exceptions) of acid chlorides and anhydrides in cross-Claisen condensations (reasons to be discussed later)

Acyl cyanides and *N*-acyl imidazoles (= acyl imidazoles, acid imidazolides) as useful "ester surrogates" in cross-Claisen condensations:



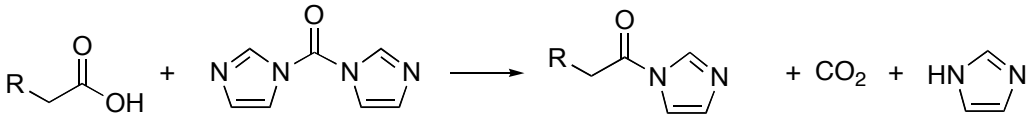
an acyl cyanide an *N*-acylimidazole

Facile preparation acyl imidazolides and acyl cyanides from acid chlorides:

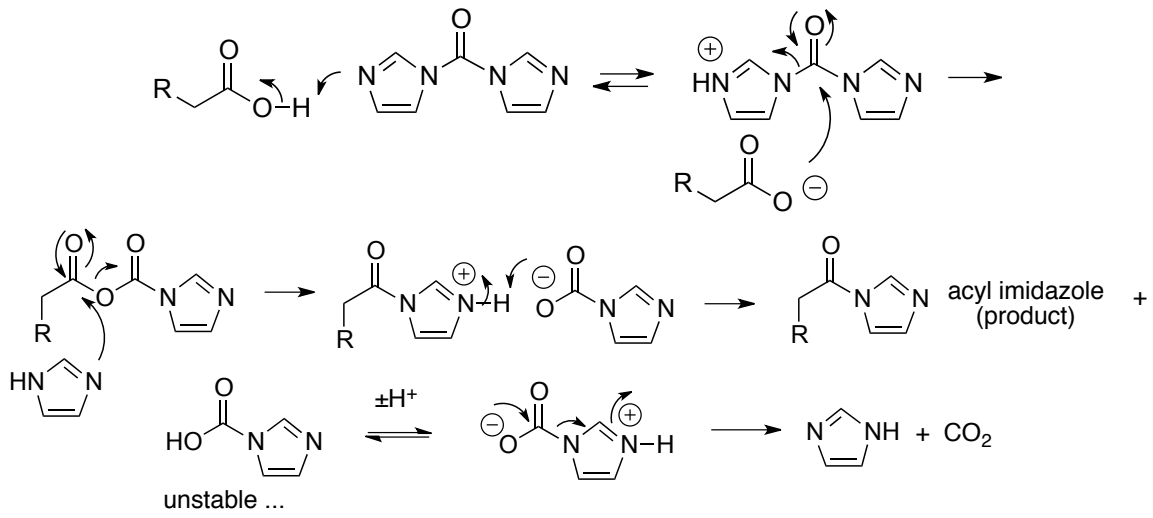


Hazardous nature of acyl cyanides (release of exceedingly toxic HCN)

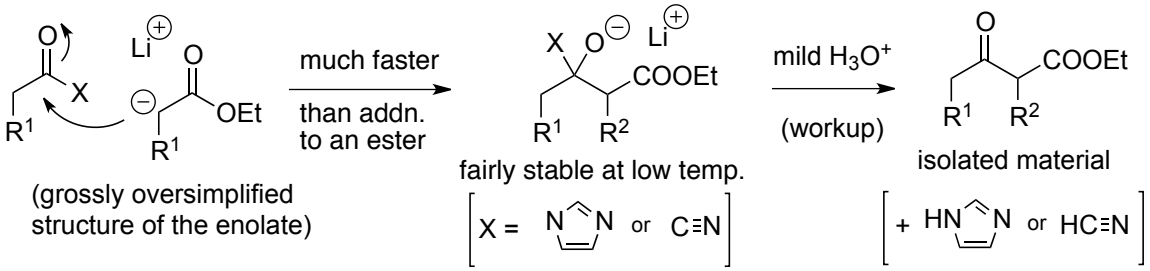
Direct formation of acid imidazolides from carboxylic acids and carbonyldiimidazole ("CDI", Staab reagent):



Probable mechanism of the above reaction:



General mechanism for the reaction of an enolate with an acyl cyanide or an acyl imidazole (same as for the standard Claisen reaction):



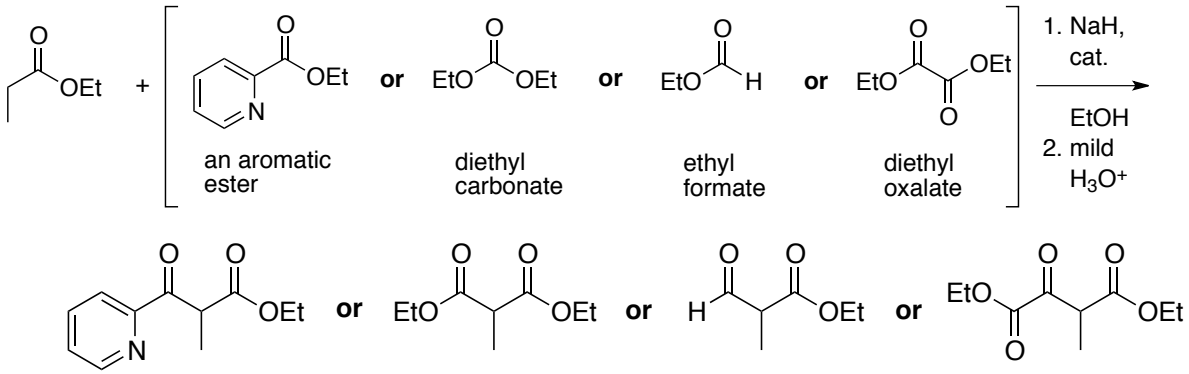
Principle: the successful cross-Claisen condensation of the type shown above take place so that:

> (i) no opportunity exists for thermodynamic equilibration of the initial product mixture (= no proton exchanges), and
>
> (ii) the ***rate*** at which a particular product forms is much faster than that at which other products might form – regardless of relative thermodynamic stability
>
> a reaction occurring under such conditions is said to proceed under **kinetic control**

Special cases of successful cross-Claisen condensations occurring under conditions of thermodynamic control (reversibility of all steps – except the final deprotonation of, e.g, EtOH with NaH)

Case a (important): condensation of an enolizable ester with a non-enolizable one; e.g., Ar-COOEt ("Ar" = aryl group, such as a benzene ring, a pyridine, …), EtOCOOEt (diethyl carbonate), EtO-CHO (ethyl formate), EtOOC-COOEt (diethyl oxalate)...

Example: products from the reaction of ethyl propionate, with the above esters:

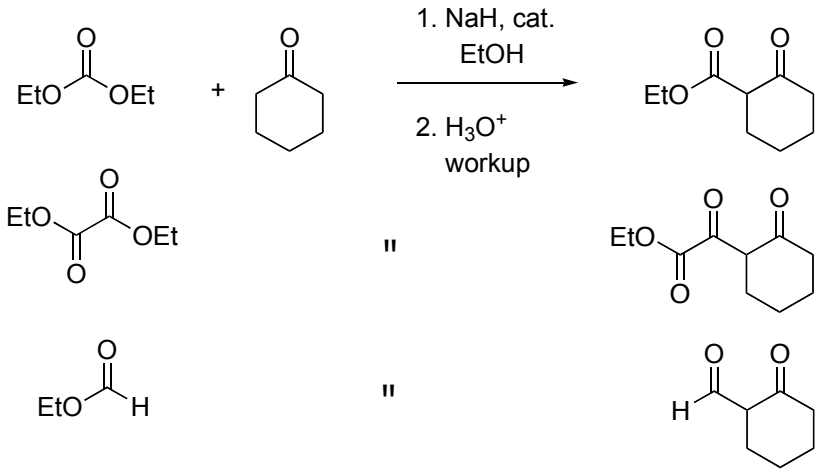


Minimizing the self-condensation of the enolizable ester: slow addition thereof to a mixture of NaH/EtOH and non-enolizable ester:

> Under these conditions, the instant concentration of the enolizable ester in the medium is so low that the self-condensation becomes statistically improbable.

The products of the above cross-Claisen reactions as valuable building blocks for the synthesis of various medicinal agents

Important use of carbonate, oxalate, and formate esters in "Claisen-like" condensations involving enolates of ketones, e.g., cyclohexanone:



Reminder: 1,3-dicarbonyl compounds of the type shown above exist in equilibrium with their enol tautomers, which may become the major species at equilibrium

The above cross-Claisen products as valuable building blocks for the synthesis of medicines and of other compounds of biomedical relevance (examples to be provided later)