

First Year Organic Chemistry



THE CHEMISTRY OF THE CARBONYL GROUP: CORE CARBONYL CHEMISTRY

Professor Tim Donohoe

8 lectures, HT, weeks 1-4, 2016

Wednesday at 9am; Friday at 10am (Dyson Perrins)

Handout B

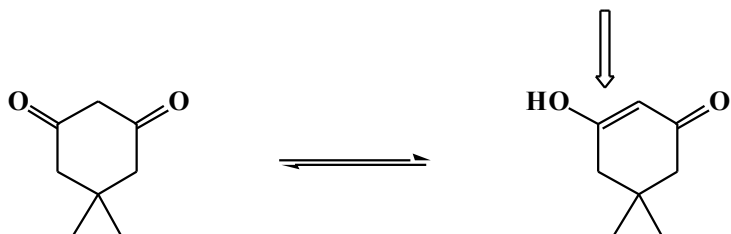


You will be able to download copies of the handouts from this course at <http://donohoe.chem.ox.ac.uk/Teaching/Teaching.htm> as well as through Weblearn

4) Enolisation of carbonyl compounds

A) keto-enol tautomerism

If one looks at the NMR spectrum of dimedone, it contains peaks for TWO different compounds.



The two forms of dimedone are known as the **keto** and

They are known as TAUTOMERS (isomers that are interchangeable via the transfer of a proton):

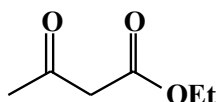
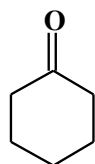
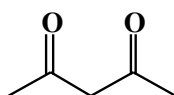
and the process of exchange between them is called

However, if we look at the NMR spectra of simple aldehydes and ketones they have

% enol in neat liquid



% enol in neat liquid



If we look at the bond strengths, we can see why

Sum (KJmol⁻¹)

Keto (C-H) (C=O)

Enol (O-H) (C=C)

Clearly, the presence of extra conjugation in the enol form is enough



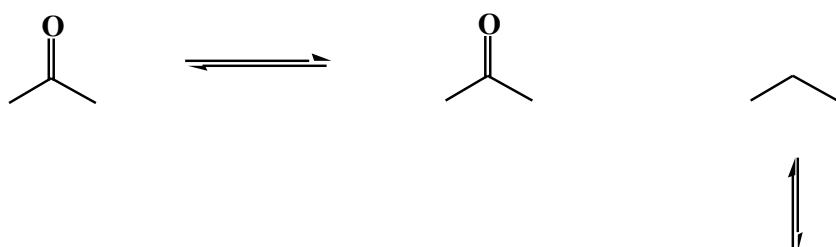
Another factor

There is another way that we can detect the presence of enols in aldehydes and ketones.

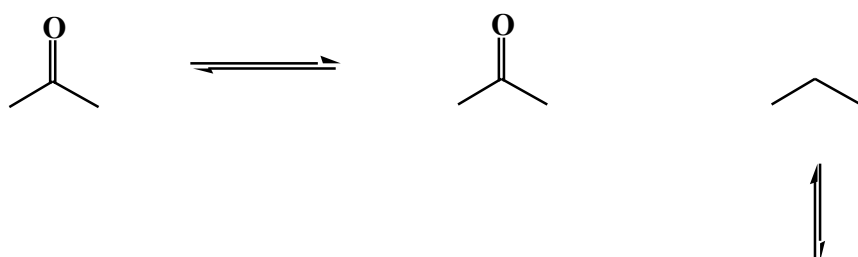
When acetone is dissolved in D_2O it becomes CD_3COCD_3 over a long period of time: moreover, this reaction is catalysed by both

This process occurs through

IN BASE



IN ACID



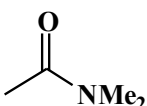
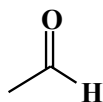
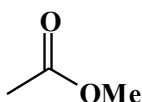
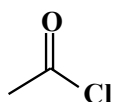
Q. What would happen to $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_2\text{Ph}$ in D_2O with cat. H^+ ?

Think of a carbonyl compound that exists in 100% enol form?

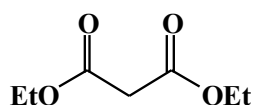
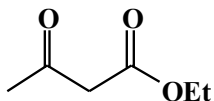
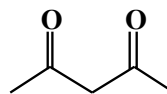
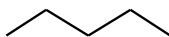
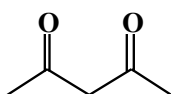
Remember that the acid (or base) speeds up the rate at which the reaction proceeds ie equilibrium is reached, it does NOT

ENOLATES

You have just seen that protons adjacent to a carbonyl are acidic: quantify this property by



Obviously, two carbonyl groups in a 1-3 array activate the protons in between even more. This manifests itself as a much lower pKa.



For a comprehensive collection of pKa values see:

<http://www.chem.wisc.edu/areas/reich/pkatable/index.htm>

As well as exchange at the alpha position, another (usually undesirable) consequence of enolisation



The more acidic the protons, the easier

B) enols and enolates as nucleophiles

You should be familiar with the notion of alkenes acting as nucleophiles (using their relatively high energy, polarisable π -bonds-

Enols and enolates are simply electron-rich alkenes and so react rapidly

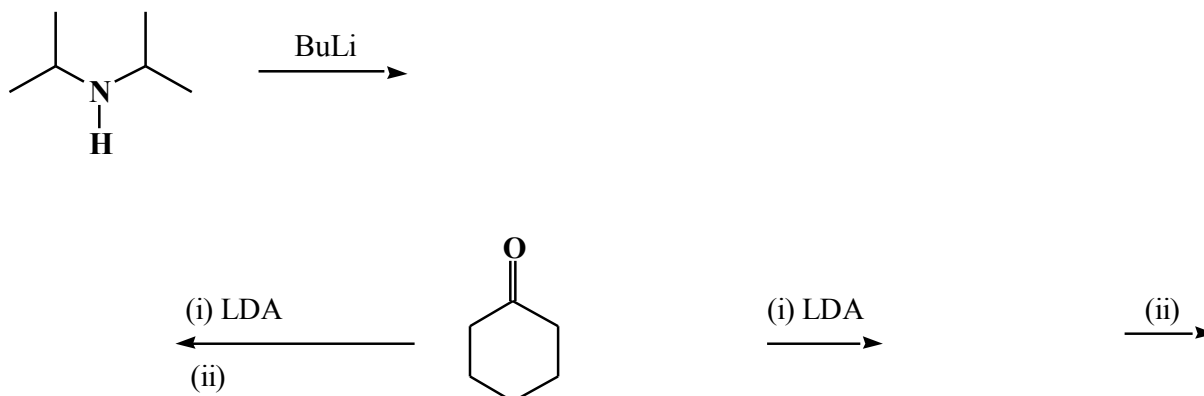


With the exception of highly reactive, charged, electrophiles,

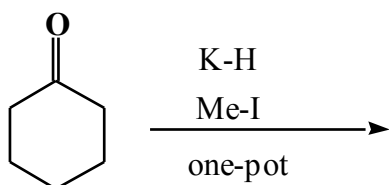
Simple reactions of enols and enolates

1) alkylation

For simple ketones it is best to use a strong base such as LDA at low temp.



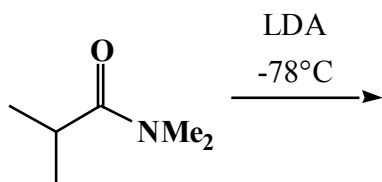
Using an excess of base and alkylating agent it is possible to over-alkylate



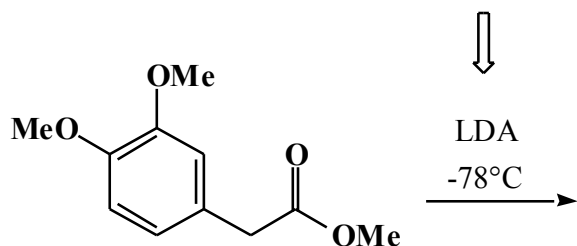
Note: there are problems with the alkylation of enolates derived from aldehydes.



But, esters, acids and amides can all be alkylated successfully using these conditions.



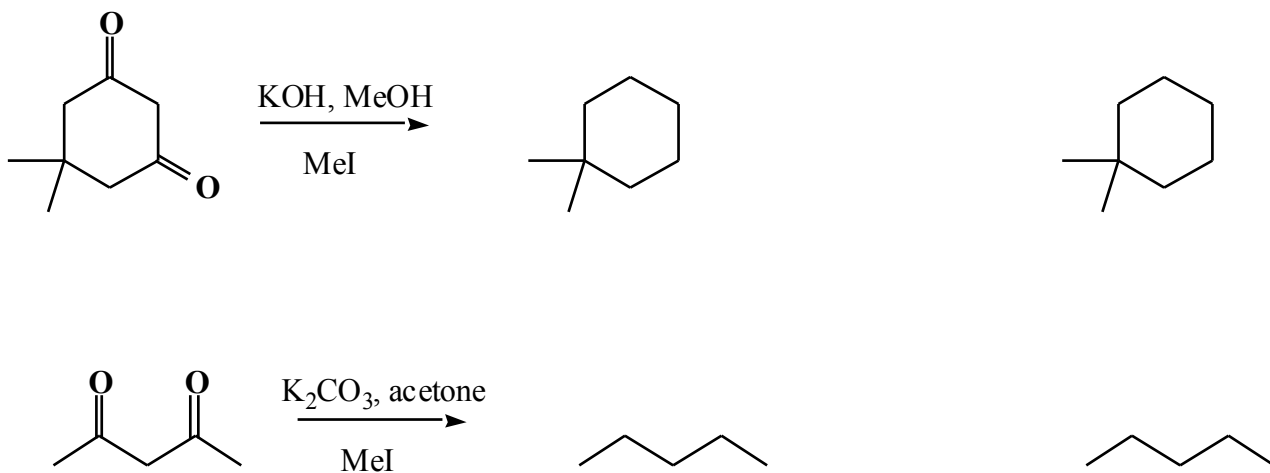
key step in the synthesis
of verapamil (angina)



Remember that TWO equivalents of base are required to alkylate carboxylic acids:



It is fair to say that the above conditions are not easy to replicate on a large scale. Remember that if a CH is flanked by TWO carbonyl groups then it is much more acidic: here alkylation doesn't need such a strong base.



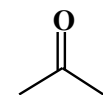
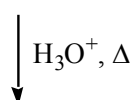
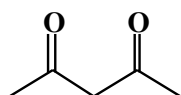
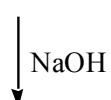
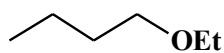
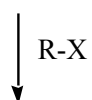
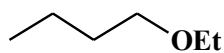
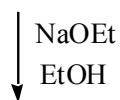
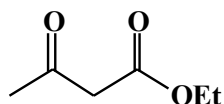
With respect to synthesis, the two most important β -dicarbonyl compounds are



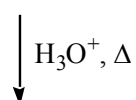
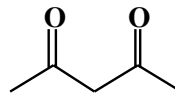
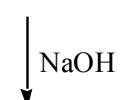
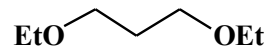
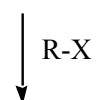
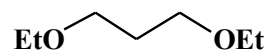
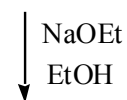
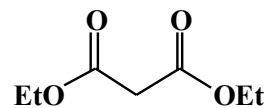
Both of these are easily alkylated under mild conditions.

Ester hydrolysis and then heating with acid forms CO₂ (decarboxylation)

ethyl acetoacetate



diethylmalonate

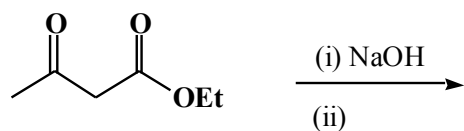
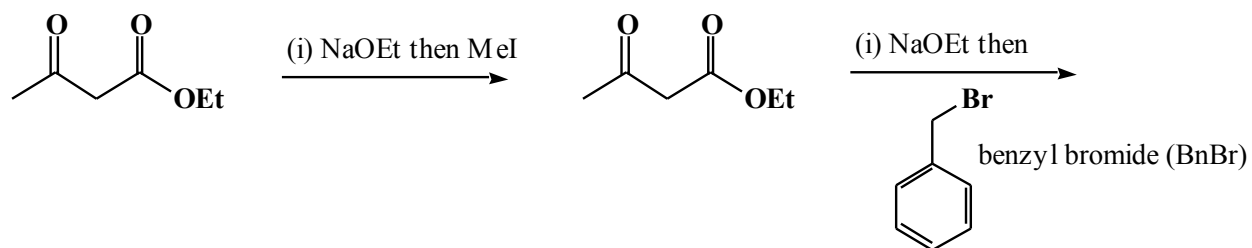


Q. Why use NaOEt here: what about NaOMe?

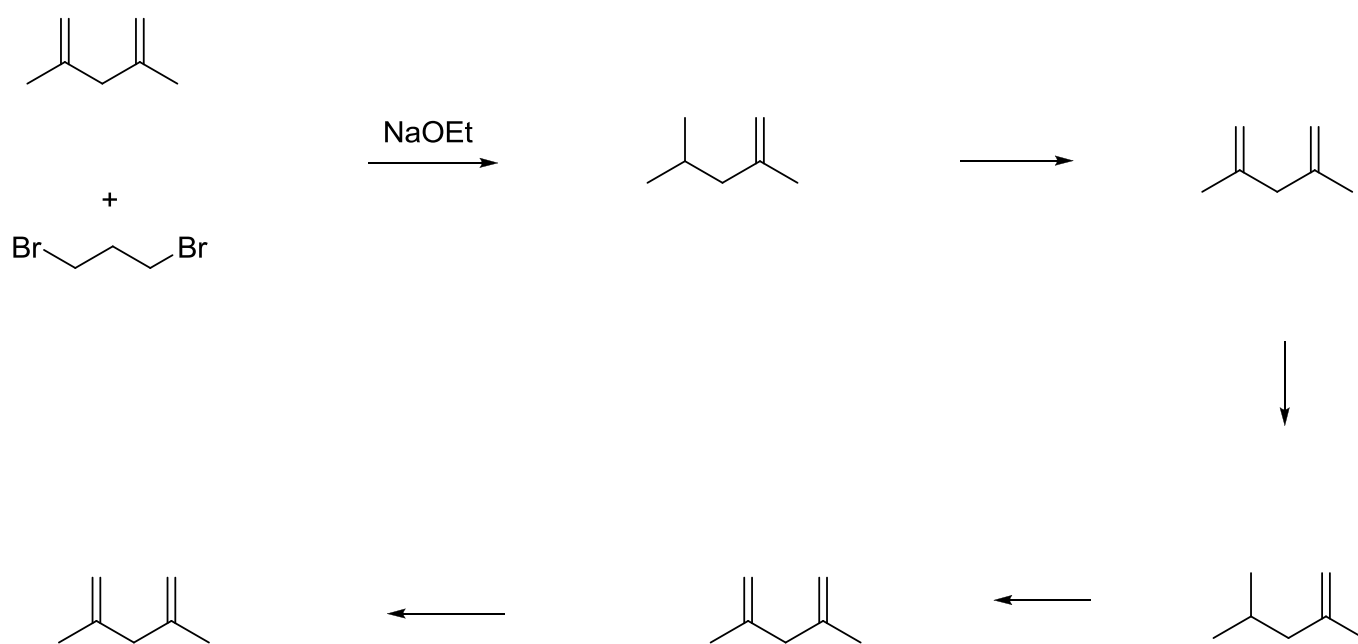
Look at the decarboxylation reaction in more detail.



Also, there is no reason why we cannot alkylate twice:



Or alkylate twice in an intramolecular sense



2) Halogenation

a) Under basic conditions,

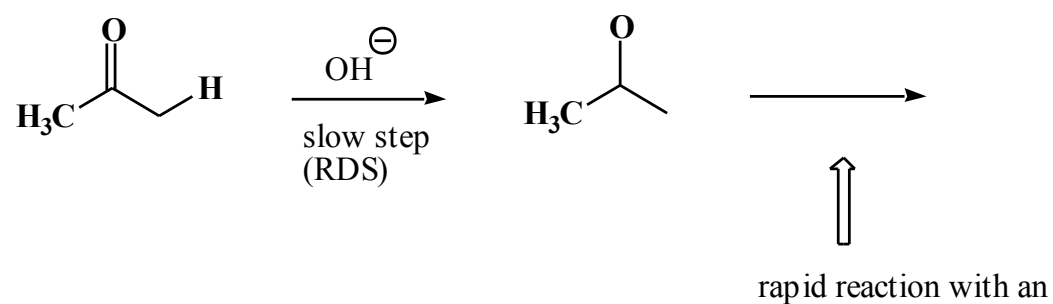
Consider the bromination of acetone with NaOH and Br₂

Experimentally, it has been shown that the rate of reaction

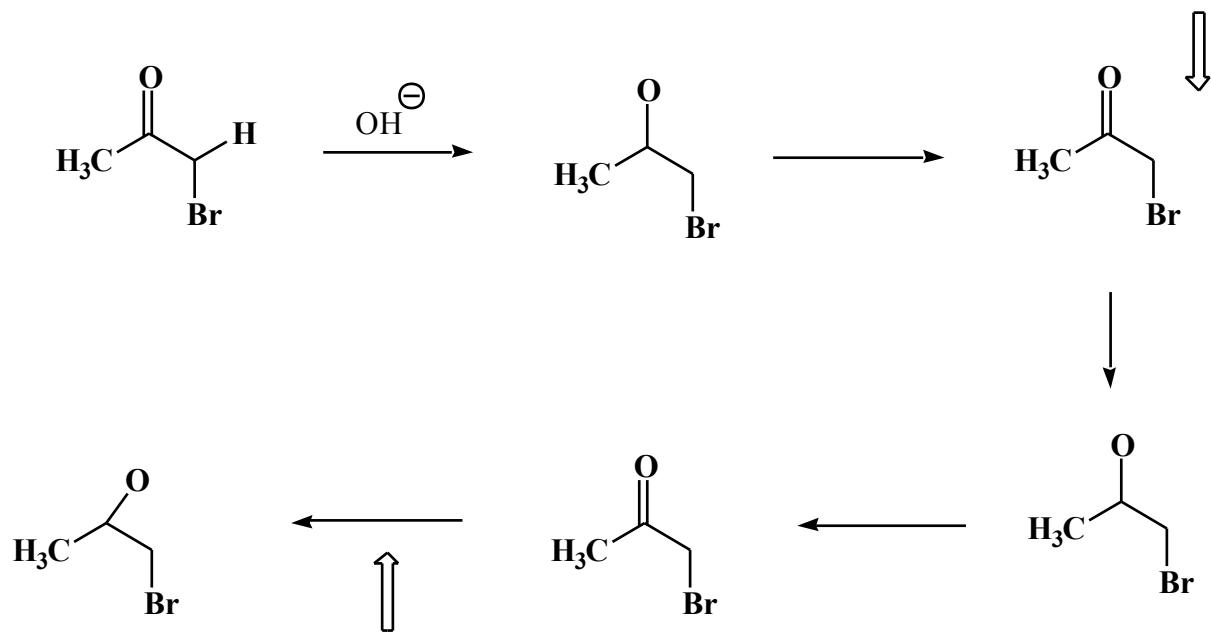
But is **not** related to

Also bromination and iodination proceed at exactly the same rate

The only way to reconcile these observations is with the following mechanism:



Unfortunately, the reaction does not stop here:



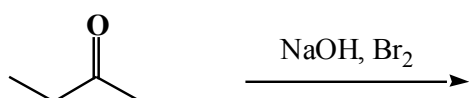
No further deprotonation is possible

the best leaving group is lost

H_2O	15.6
HCBBr_3	9

Known as the bromoform (or iodoform with I_2) reaction.

This reaction is unusual because a carbon-carbon bond is broken; the reaction can be used as a test for methyl ketones.



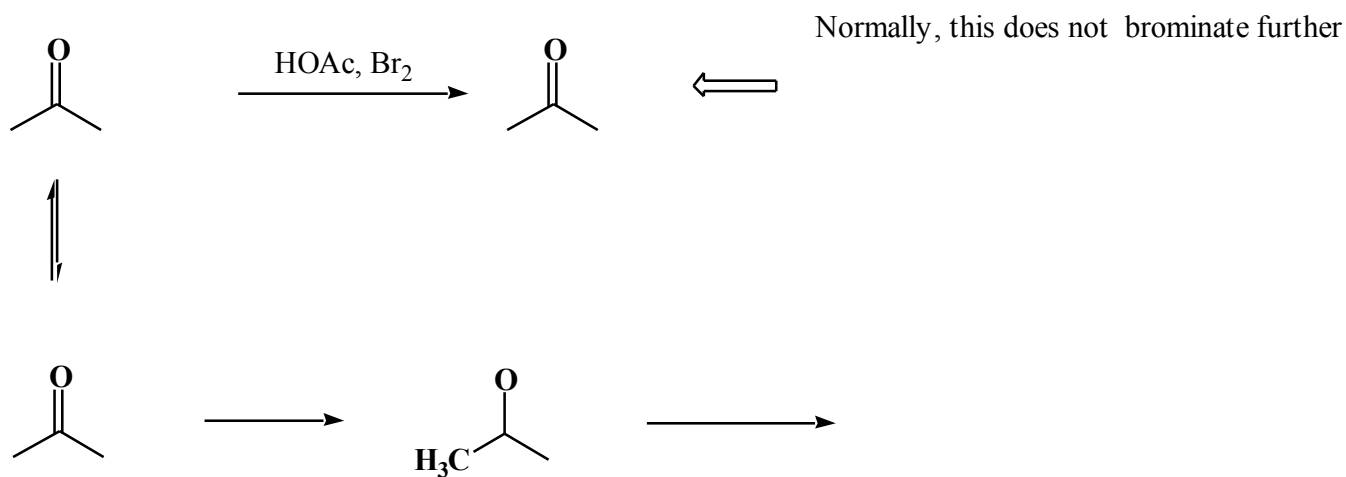
b) Under acidic conditions,

It is also possible to halogenate ketones under acidic conditions; again,

it has been shown that the rate of reaction

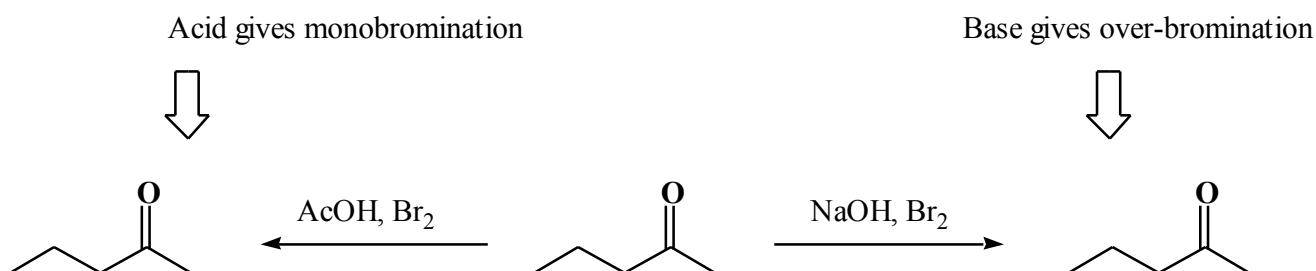
But is **not** related to

So, we need to amend our previous mechanism to accommodate the rate limiting formation of an



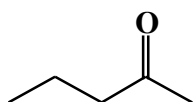
Clearly, for monobromination of aldehydes and ketones, ACID is superior

Compare the bromination of unsymmetrical ketones under the two sets of conditions,

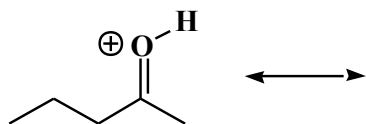


As for **regiochemistry**, consider the product determining step in each case:

In base



In acid

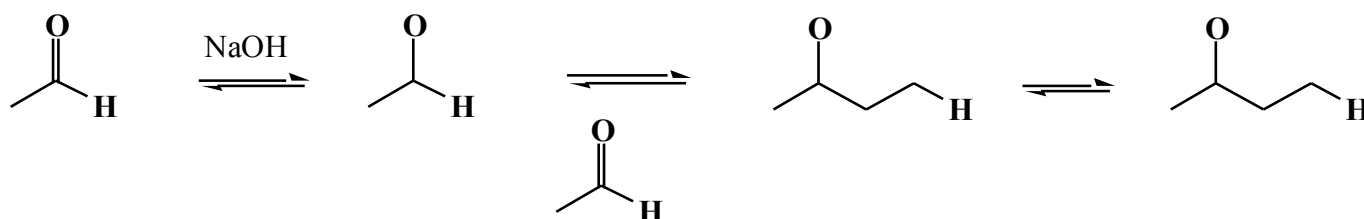


3) Reaction with carbonyl groups

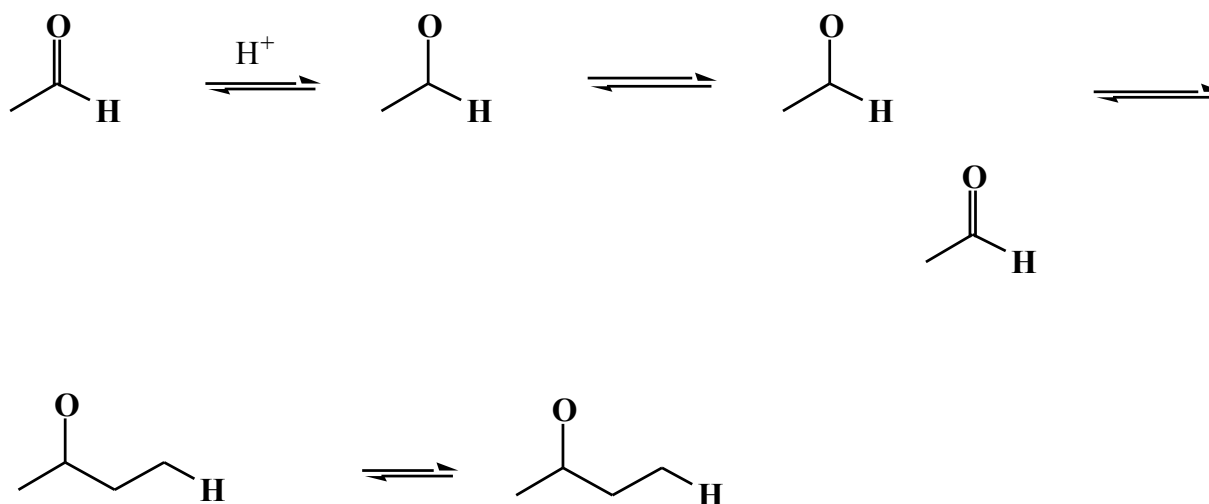
A) reaction with aldehydes and ketones: the aldol reaction

Consider the reaction of an enol or enolate with a carbonyl compound:

With base



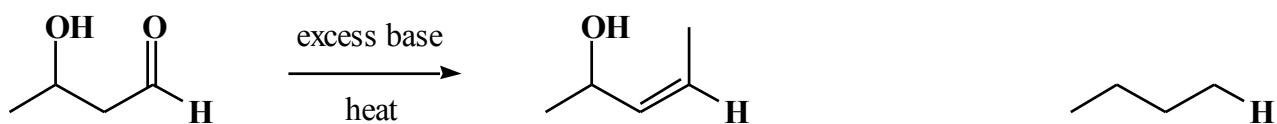
With acid



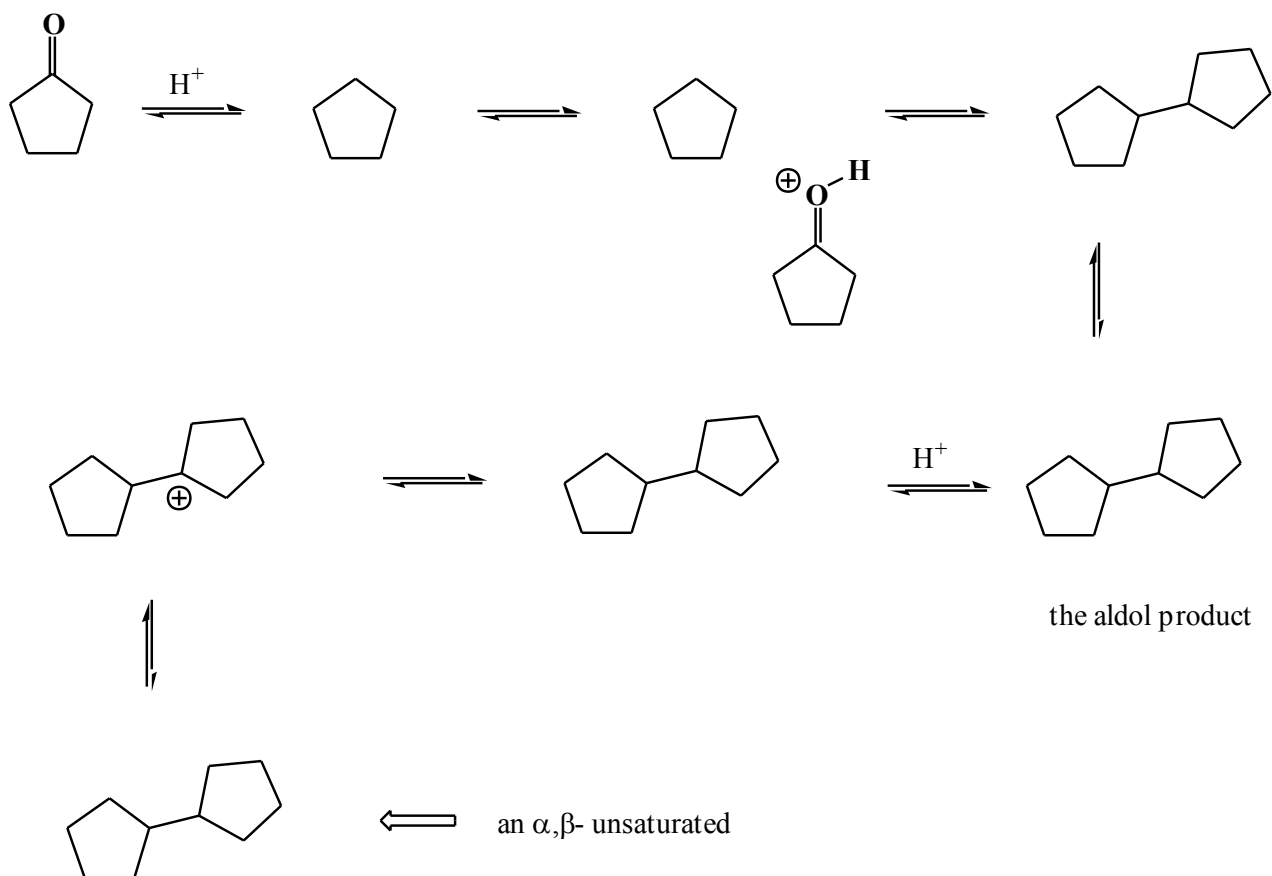
In this case the equilibrium favours the product- but this is not always the case and with acetone, for example, the equilibrium favours the starting materials.

If these reactions are forced then **elimination** follows the aldol to form

Elimination with base



Elimination with acid

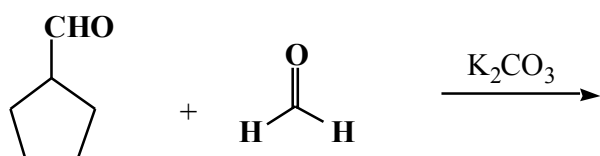


Base catalysed aldol reactions can give either the aldol product or the dehydrated product by an

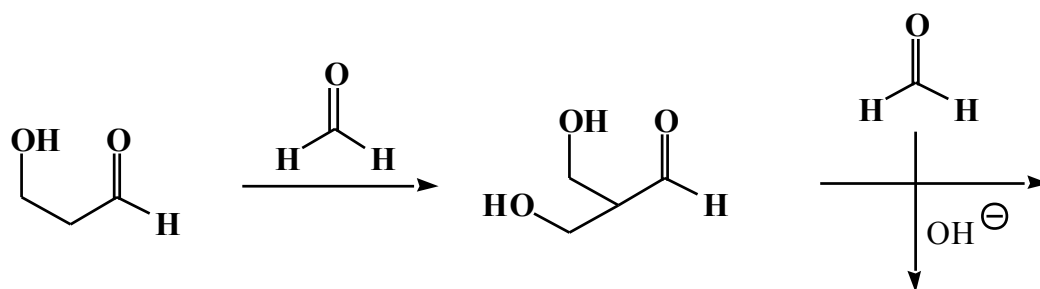
Acid catalysed aldol reactions can give the aldol product but usually give the dehydrated product by an

These are all examples of self condensation, crossed aldol reactions are clearly going to be complicated. For example, reaction of CH_3CHO with $\text{CH}_3\text{CH}_2\text{CHO}$ will result in

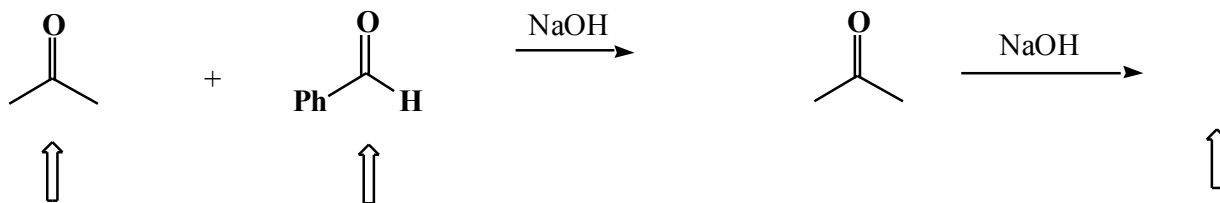
In practice, the crossed aldol reaction only works well when one component cannot form an enol/enolate and is more reactive than the other.



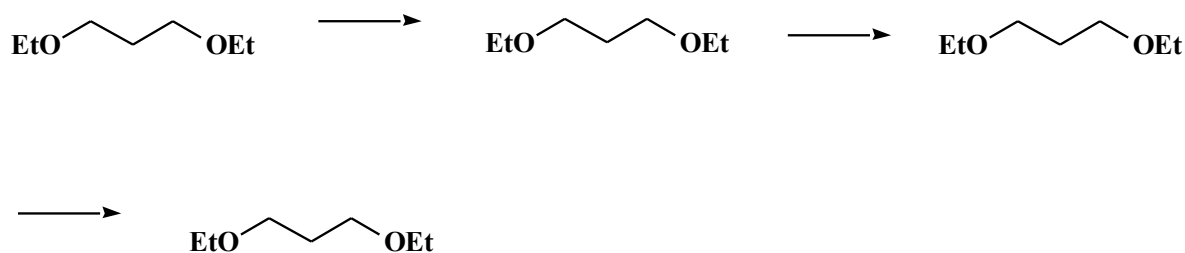
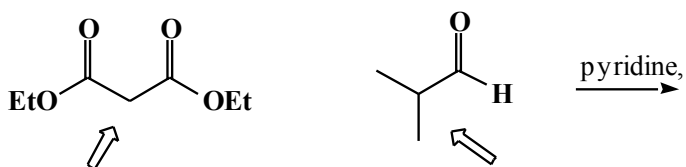
In fact it is difficult to stop this reaction:



Benzaldehyde, PhCHO is also a carbonyl compound that cannot form an enolate; so it is a good partner in the aldol reactions with ketones.

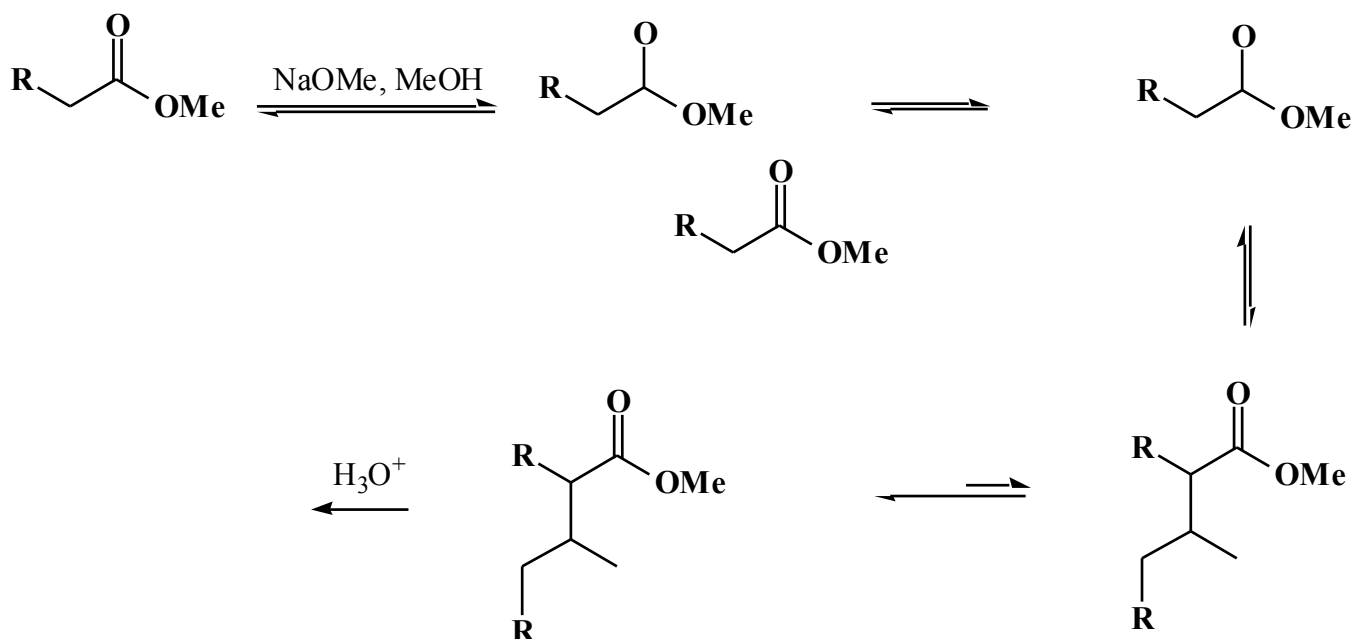


We can easily perform crossed aldol reactions with malonates and do not require a strong base to form an enolate.

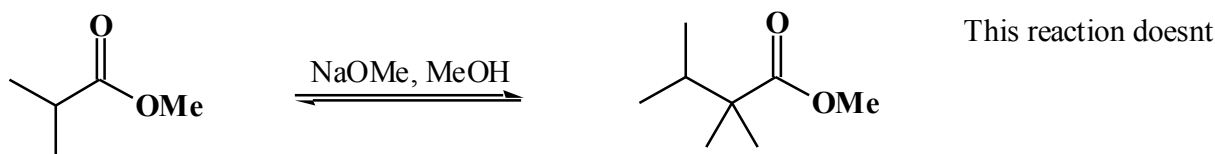


B) reactions of esters: the Claisen reaction

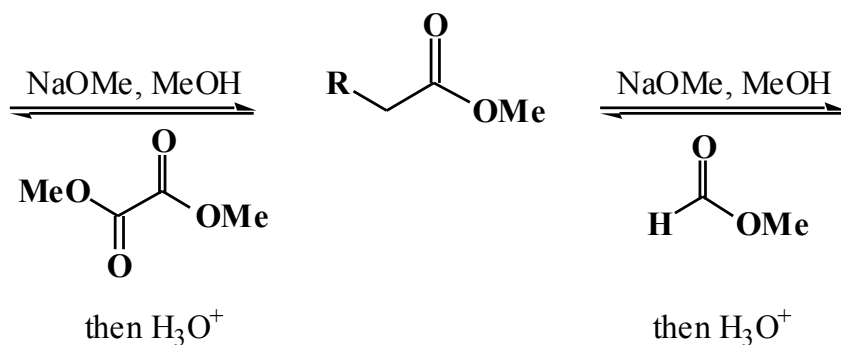
In essence, this is an equilibrium reaction of an ester enolate with the ester starting material.



How do we know that deprotonation drives the equilibrium? Try a Claisen with a disubstituted ester.



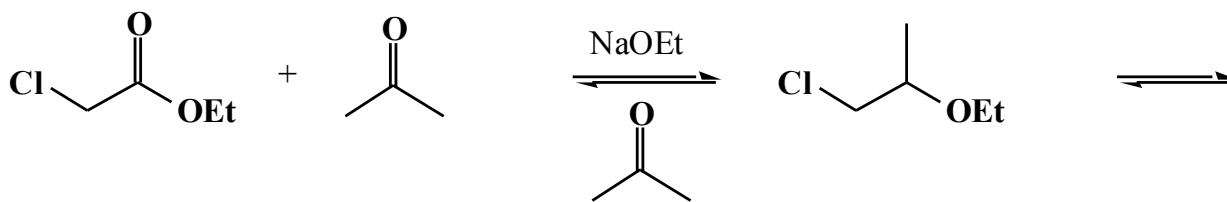
Just like the aldol, crossed Claisen reactions are only viable if one component is more electrophilic than the other AND



C) further reactions of esters: alpha-halo esters

(i) Darzens reaction

Aldehydes and ketones condense with alpha-halo esters in the presence of base. This works well for aromatic aldehydes and ketones and for aliphatic ketones.



(ii) Reformatsky reaction of alpha bromo esters

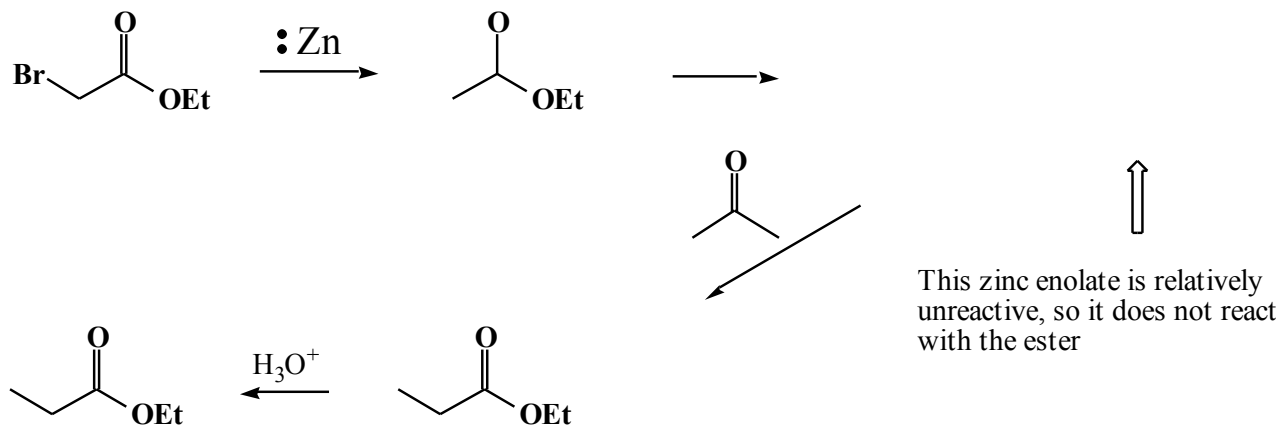
Esters cannot be used in the crossed aldol condensation with aldehydes and ketones because aldehydes and ketones are

(I) More

(II) More

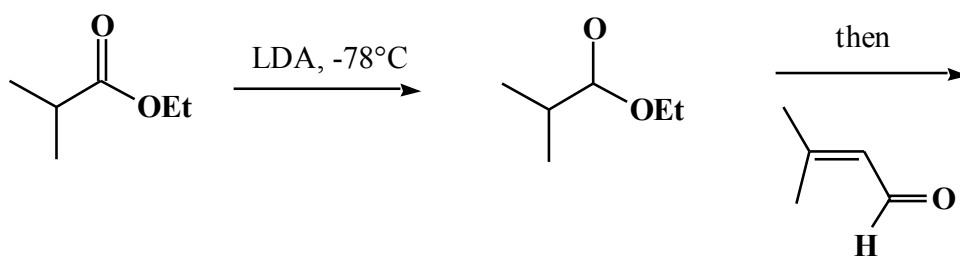
So, the aldehyde (or ketone) would simply

One simple way of making ester enolates that can and do react with aldehydes and ketones is



Note: you cannot make zinc enolates from alpha bromo aldehydes and ketones via this chemistry- the carbonyl starting materials

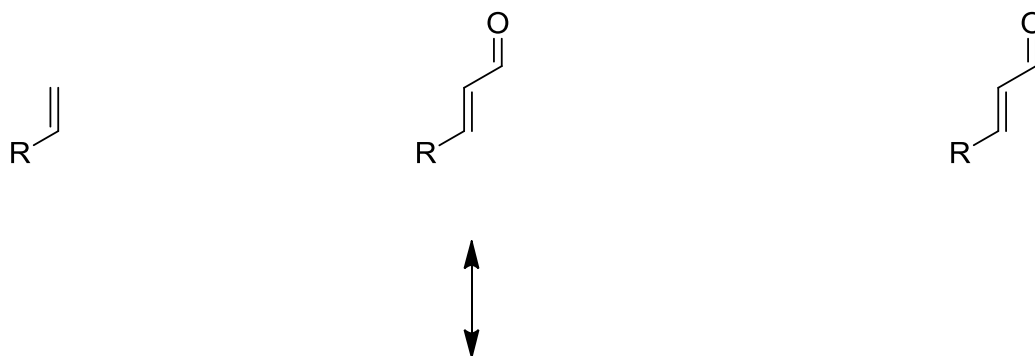
A modern alternative to this involves making the ester enolate with a very strong base (LDA). This means that self condensation is not a problem. Then, in a separate step, add the aldehyde (or ketone) electrophile. The reaction below was a key step in the laboratory synthesis of the natural product himalchene.



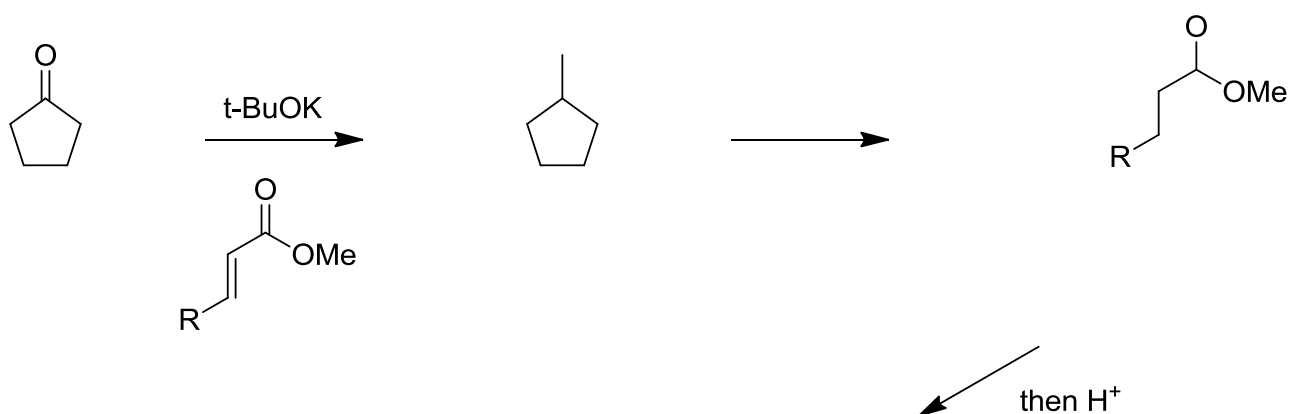
Problems on a large scale

4) α,β -unsaturated carbonyl compounds as electrophiles (C=C bonds)

Earlier, we discussed the fact that delocalisation reduces the electrophilicity of carbonyl groups. By the same token, the alkene is a much worse nucleophile and indeed becomes



Enolates are particularly adept at addition to the beta position of α,β -unsaturated carbonyl compounds, this is known as



The reaction works particularly well when the enolate is easily formed with a weaker base, ie

