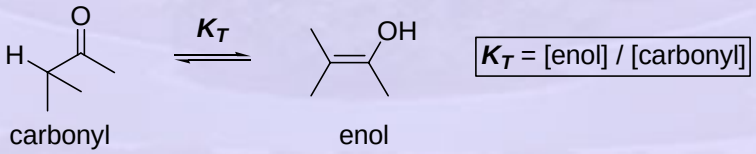
Chemistry of Carbanions

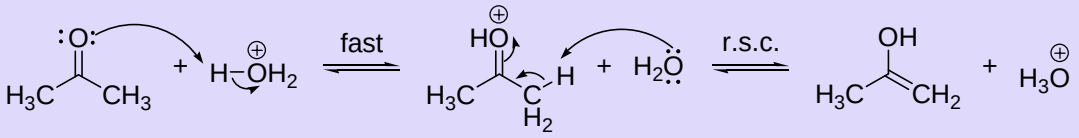
Formation of C-C bond is fundamental to organic synthesis. From about ten petrochemical products which are abundantly available – what we call as natural feedstock – today, we are able to make millions of compounds ranging from drugs to dyes. This advancement was possible largely due to development of organic chemistry – and in particular the ability of the synthetic chemists to modify structures via newer C-C bond formations. The majority of these reactions involve the carbanion intermediates. We are all familiar with the factors which stabilize the carbanions. In this part, we are going to be focusing on one of the most versatile carbanion intermediate namely the enolate, with their utility in various C-C bond formations being central issue in our discussion.

Enols and Enolate Anions:

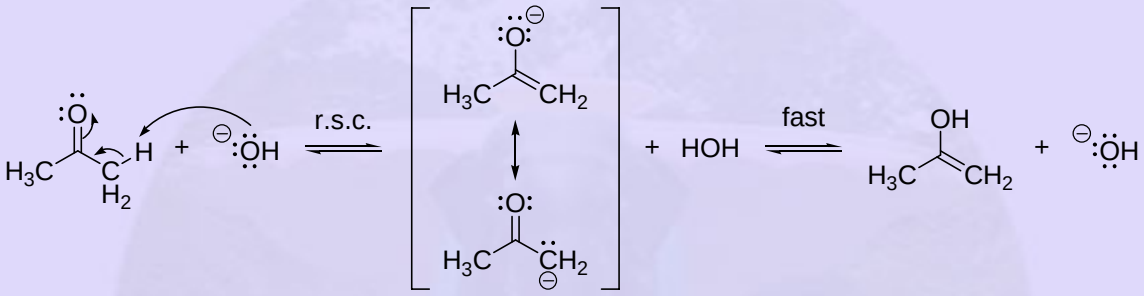
The process whereby a hydrogen atom attached to the α-carbon atom of a carbonyl compound (the α-hydrogen atom) moves to the carbonyl oxygen atom is known as enolization or keto-enol tautomerism. The isomeric carbonyl and enol structures are tautomers. The extent of enolization is dependent on the acidity of the a-proton – more acidic the a-proton, the more probable the enolization and hence the equilibrium constant for tautomerism K_T will be higher. Normally, the carbonyl form is favoured, however structural factors can significantly affect K_T.



The interconversion between the keto and enol form is catalyzed by both acid and the base. In aqueous acid, rapid protonation of carbonyl group occurs first, which is followed by removal of α-proton by water in the rate controlling step leading to the enol.

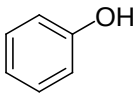
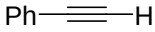
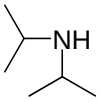
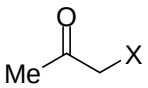
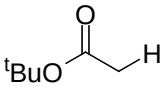


Under basic condition, abstraction of the α-hydrogen atom is the initial rate-controlling step. Proton abstraction from solvent completes the enolization process.

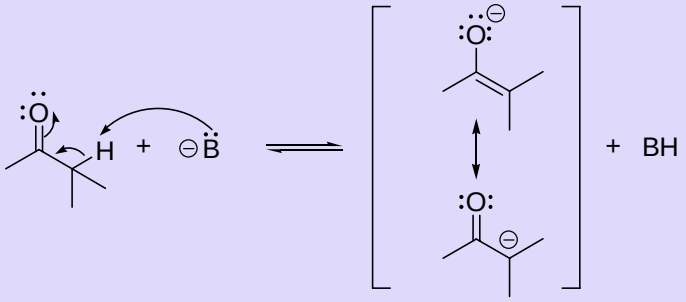


As can be seen, these processes are essentially acid-base reactions and involve equilibriums.

Carbonyl compounds are considerably more acidic (we are obviously referring to Bronsted acidity) than their hydrocarbon analogs (see table 1). Enolate anion is the conjugate base of a carbonyl compound and is resonance stabilized. It can also act as a nucleophile – this in fact is the basis of their reactivity in variety of reactions ranging from alkylation, aldol reactions to more complex iodoform reactions. A general idea of pK_a values of various carbon acids will help us in understanding these reactions better and will also allow us to decide what base could be used for deprotonation of a given proton under certain conditions.

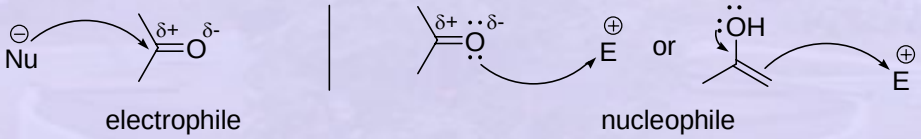
<table>
<tr><th>Acid</th><th>pKa</th></tr>
<tr><td>H_2O</td><td>14 or 15.7 depending on source slight variation in numbers possible</td></tr>
<tr><td>CH_3OH</td><td>~16</td></tr>
<tr><td>HCl</td><td>-8</td></tr>
<tr><td>  </td><td>9.95</td></tr>
<tr><td>CH_3CO_2H</td><td>4.76</td></tr>
<tr><td>CH_4</td><td>48</td></tr>
<tr><td>$H_2C{=}CH\ CH_3$</td><td>43</td></tr>
<tr><td>  </td><td>23</td></tr>
<tr><td>  </td><td>15</td></tr>
<tr><td>H_2</td><td>~36</td></tr>
<tr><td>  </td><td>36(in THF)</td></tr>
<tr><td>NH_3</td><td>38</td></tr>
<tr><td>  </td><td>X
<table><tr><td>H</td><td>26.5</td></tr><tr><td>Ph</td><td>19.8</td></tr><tr><td>COCH3</td><td>9</td></tr></table></td></tr>
<tr><td>  </td><td>24.5</td></tr>
</table>

e.g. One can use $^{i}Pr_2N^-$ (pKa of conjugate acid ~ 36) for deprotonation of CH_3COCH_3 (pKa = 26.5) in such a way that equilibrium will be almost exclusively towards enolate. (We call this as deprotonation under kinetic conditions.)



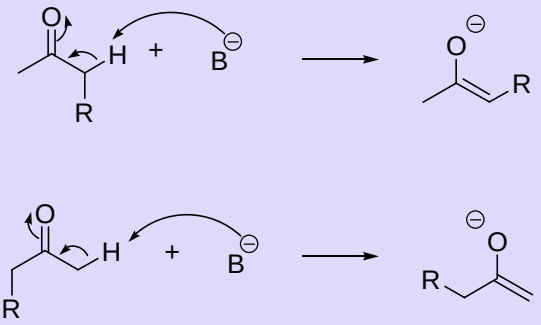
There is one more factor that we need to keep in mind before we go further. Look at the table – can we use BuLi or MeLi i.e. Bu^- or CH_3^- to deprotonate acetone? Ideally speaking, yes, provided we take only basicity into account. pKa of conjugate acid is more than that of the proton to be abstracted. However, one more aspect we have to worry about is the nucleophilicity – MeLi or BuLi are also good nucleophiles like Grignard reagents. So they are not typically used for deprotonation but rather non-nucleophilic, bulky LDA (lithium diisopropylamide) or LiHMDS (lithium hexamethyldisilazide) are used more often.

One has to look at C=O as well. Due to the polarization of C=O bond, it can act as an electrophile at carbon centre or as a nucleophile (or base) through oxygen or α-carbon centre (of the enol form).

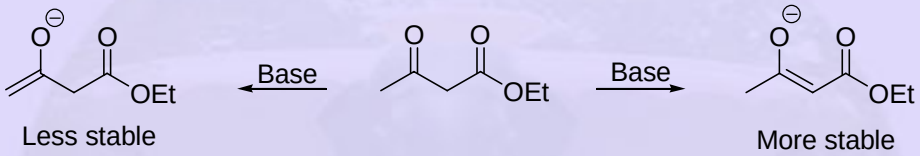


Kinetic and Thermodynamic Enolates:

Generation of enolates of ketones is at times challenging because they pose a problem in regioselectivity – ketones can have enolizable protons on both sides of the carbonyl groups. The problem is not so much when one side of the ketone does not have the enolizable proton (e.g. acetophenone) or the ketone is symmetrical (e.g. 3-pentanone). The real issue is with the unsymmetrical ketones where enolizable protons are present on either side. For successful reactions, we need to control which side enolate is formed.

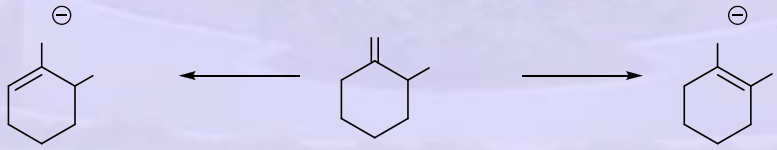


If one of the two protons is significantly more acidic, the selective enolate formation is straight forward. E.g. in the case of ethyl acetoacetate, there are two types of enolizable protons. However, only one of the two protons is deprotonated first. This is an example of thermodynamic control: only the more stable of the two possible enolates is formed.



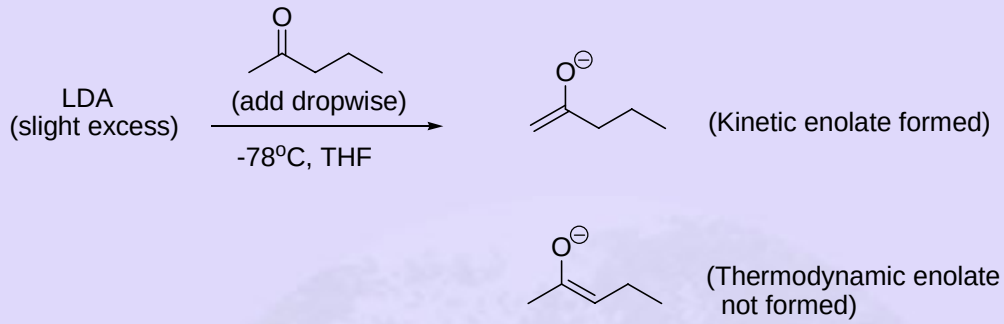
Less stable More stable

This principle can be extended further where the difference in the acidity of the protons on either side is not as pronounced. Take example of 2-methyl cyclohexanone. There are two enolates which are possible as shown. Now enols and enolates are alkenes and hence the more substituted it is, the more stable it will be. So, when equilibration is possible, the more stable enolate will form. This is possible if a proton source is available, in this case a slight excess of ketone itself can act as a source of proton.



Now compare a situation where we use a strong, bulky base such as LDA. LDA is too hindered and attacks the least hindered C-H bond α to the carbonyl group. It also prefers to attack more acidic C-H bond and C-H bond on less substituted carbons are indeed more acidic. Also, the statistic helps with more protons present on the less substituted carbon atom. These factors combine and ensure that we form the less substituted enolate as the major product provided we do not allow the equilibrium to be attained which will lead to the formation of more stable enolate. This can be accomplished by controlling a

few things - temperature is typically maintained at -78°C, the reaction times are typically short and using excess of base compared to ketone at all the time which can be easily achieved by adding ketone drop-wise to the base. This enolate which is formed faster is kinetic enolate.

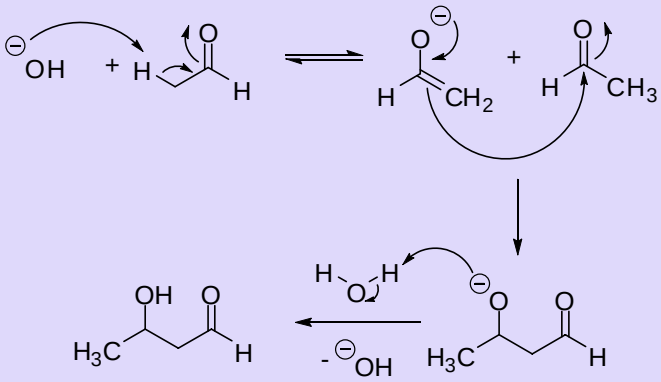


Reactions of enolates:

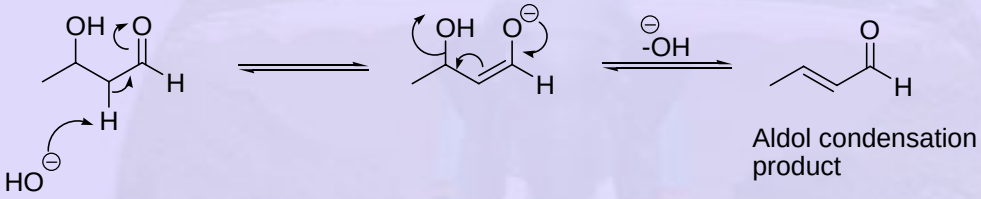
Enolates are nucleophiles and thus can be reacted with a variety of electophiles. Depending on the type electrophile used we have different classes of reactions. Some of the reactions that we are going to be discussing are (i) aldol reaction (ii) Claisen condensation (iii) Diekman cyclization (iv) alkylation of enolates (active methylene compounds) (v) Michael addition and (vi) Robinsons annelation.

(i) Aldol Reaction:

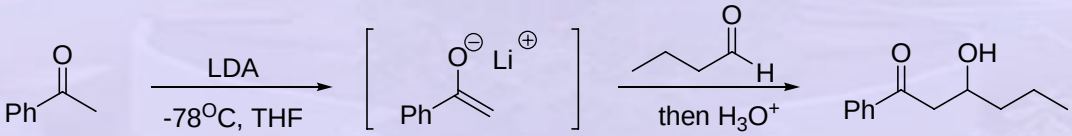
Consider the reaction of acetaldehyde with a base like NaOH. As we have discussed earlier, under basic condition we'll form enolates. Based on the pKa whoever, you'll realize that formation of enolate is not going to be complete (hydroxide is not strong enough base to ensure complete deprotonation) and the equilibrium would largely be towards the aldehyde and sodium hydroxide. Thus, only a small amount of the nucleophilic enolate is formed. The enolate thus formed will react with the acetaldehyde molecule which is not enolized to form the alkoxide. This alkoxide will be protonated by the water which was initially formed in the first step. The product of this step is a compound which contains an aldehyde ('ald') as well as a hydroxyl ('ol') group whose common name is 'aldol'. The name aldol however is used for the whole class of reactions involving an enolate and a carbonyl compound. Notice that the base catalyst (hydroxide ion) is regenerated in the last step, so this indeed is a catalytic process.



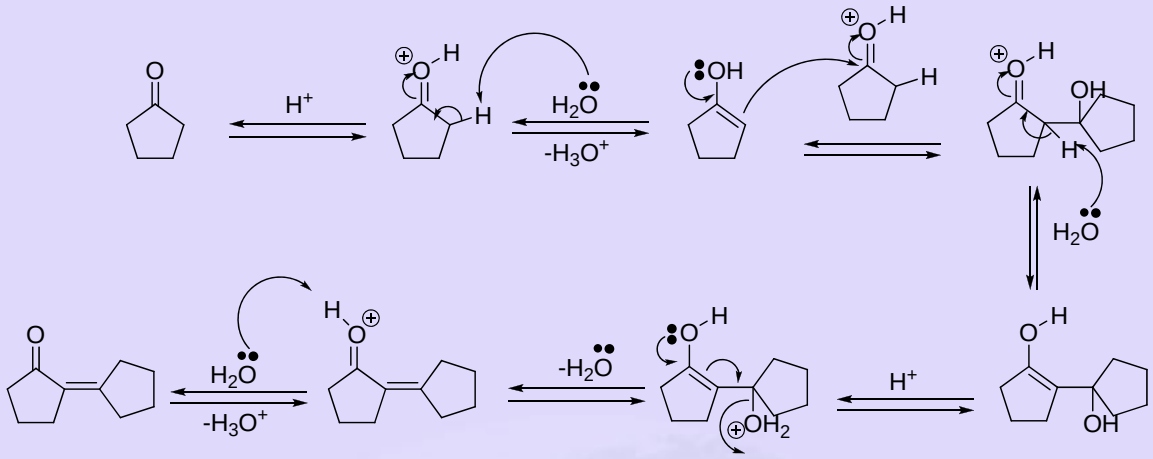
In general, in these reactions the concentration of base has to be controlled. With higher concentration, dehydration of aldol products occurs rather readily due to the formation of stable conjugated unsaturated carbonyl compounds. This elimination is an example of a typical E1cB reaction.



One of the ways to ensure that the aldol product rather than aldol condensation product is obtained is to use kinetic conditions discussed earlier for carrying out aldol reaction.

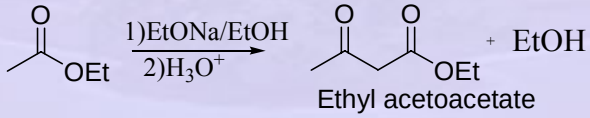


The aldol reaction could be catalyzed under acidic conditions as well. However, under these conditions typically aldol condensation product is obtained i.e. the dehydration of initial aldol product takes place rapidly. For mechanistic discussion, let's consider example of cyclopentanone with an acid. In acidic medium, the ketone tautomerizes to its enol form. The enols are much less nucleophilic than the enolates. However, protonation of carbonyl oxygen makes it better acceptor (electrophile) than the unprotonated ketone! The reaction is thus acid catalyzed.

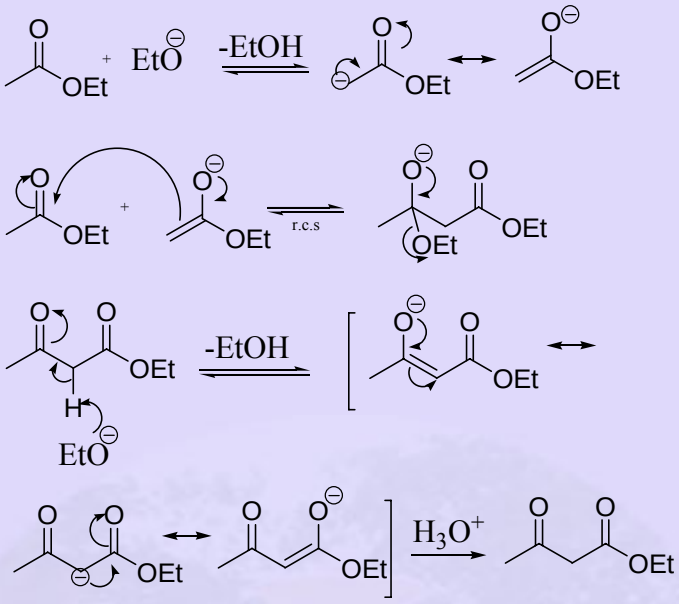


(ii) Claisen condensation or reaction:

The enolate generation and further reactions are not limited to ketones and aldehydes. Even protons α to the ester functional group are acidic enough and can be deprotonated with base to form enolates. These enolates are nucleophilic and can react with a variety of electrophiles. Incidently, the carbonyl of ester can itself act as an electrophile. Thus, ethyl acetate when reacted with sodium ethoxide leads to the formation of a β-keto ester, namely ethyl acetoacetate.



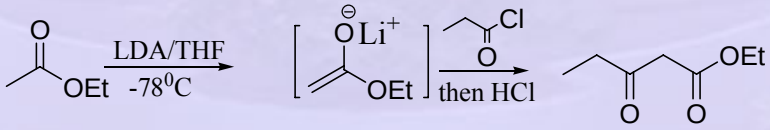
This reaction is known as Claisen reaction or Claisen condensation. The Claisen condensation involves a series of equilibria.



All the equilibria are shifted towards the product because the stability of the anion of the ethyl acetoacetate which itself is obtained by acidifying the reaction.

Another way to shift the equilibrium to right is to distill off the alcohol by-product as it is formed.

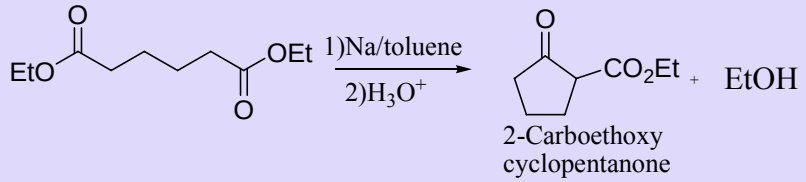
Formation of the enolate in a separate initial step of the reaction by using a strong base and then reacting with an acyl chloride also improves the yield of the β-keto esters.

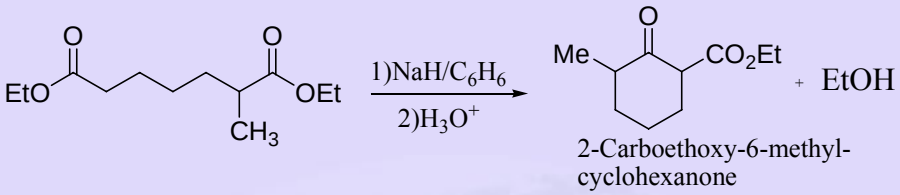


This by far is much better method especially for preparing products of mixed ester condensation which typically yields a mixture of products.

iii) Dieckmann Reaction

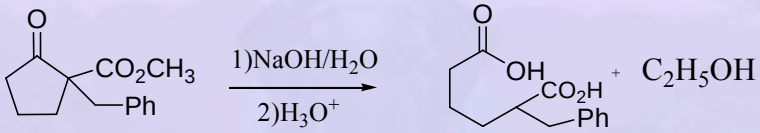
The intra-molecular condensation of diesters leading to the formation of cyclic β-keto esters is known as Dieckmann reaction. This reaction is mechanistically similar to Claisen reaction and is particularly useful in the formation of five and six-membered rings.

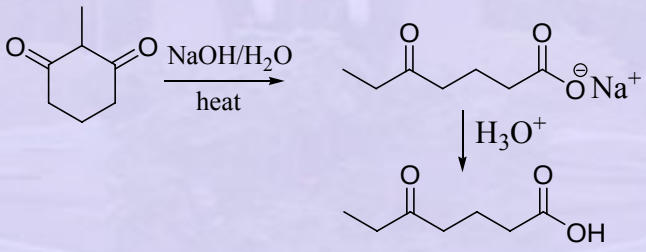




Note: It is important to remember that just like aldol reaction Claisen reaction and Dieckmann reaction are reversible.

E.g.

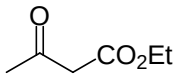
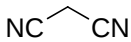
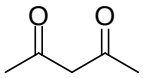
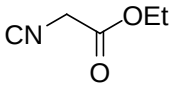




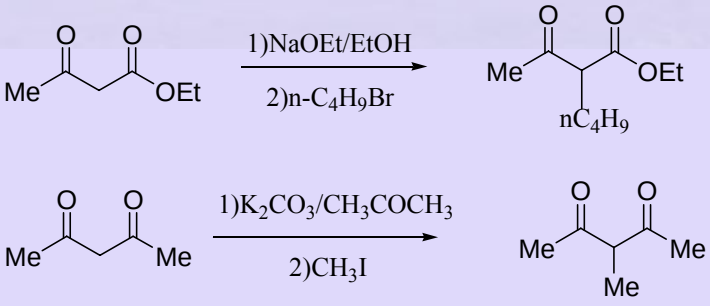
iv) Alkylation of enolates:

The enolates of aldehydes, ketones and esters typically undergo condensation reactions as they also contain an electrophilic carbonyl group. Formation of the enolate anion is much more facile when two adjacent groups can stabilize the negative charge. These types of compounds are often referred to as active methylene compounds – they posses pKa values less than those of water and alcohols (see table 2).

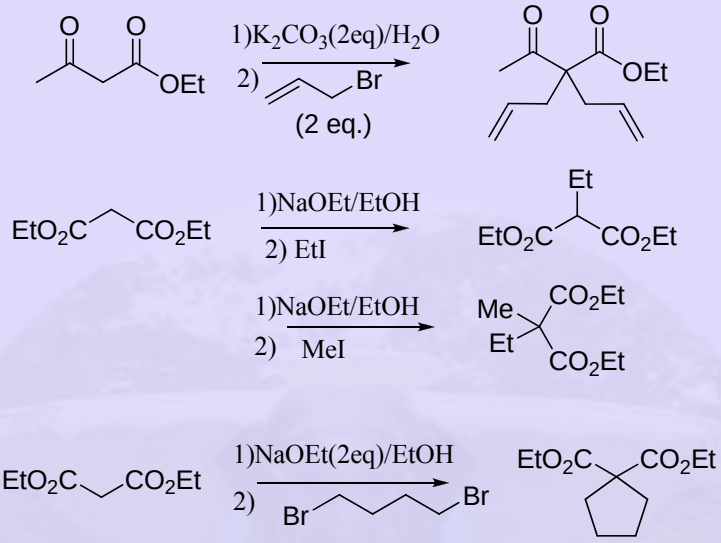
Table 2: pKa's of active methylene compounds

Substrate	pKa
$CH_2(CO_2Et_2)$	13
	11
	11
	9
	9

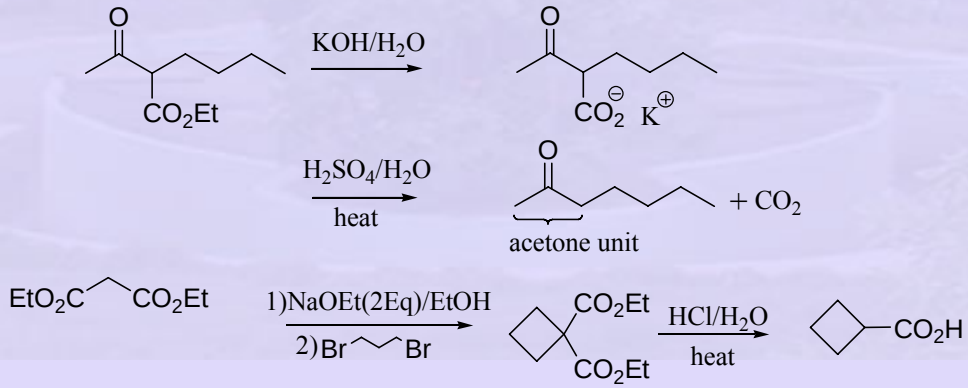
The enolates generated from these active methylene compounds are very nucleophilic and can be readily alkylated with a wide range of alkyl halides (electrophiles).



When two acidic hydrogen atoms are present on the same carbon atom, mono- and dialkylation are both possible. The product obtained is a simple function of quantities of the reactants used. Dialkylation or successive mono-alkylation with two different alkylating reagents is possible.

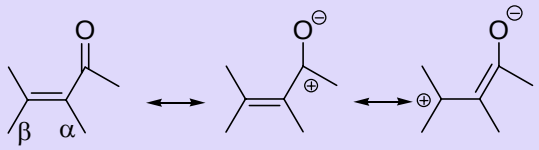


β-keto eaters undergo decarboxylation via the corresponding β-keto acid which greatly enhances their utility in organic synthesis. The product after decarboxylation is essentially similar to the one obtained on corresponding ketone enolate alkylation.



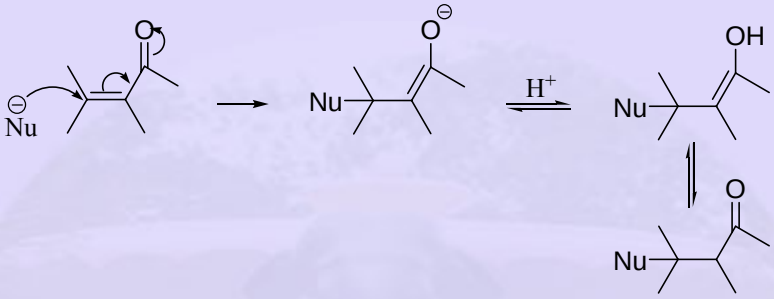
v) Michael Reaction

Olefins on their own are not very good partners in reactions with nucleophiles i.e., they are not very good acceptors. But when conjugated with electron withdrawing groups such as aldehydes, ketones, esters, amides, nitriles, etc., olefins undergo addition of nucleophiles rather easily.

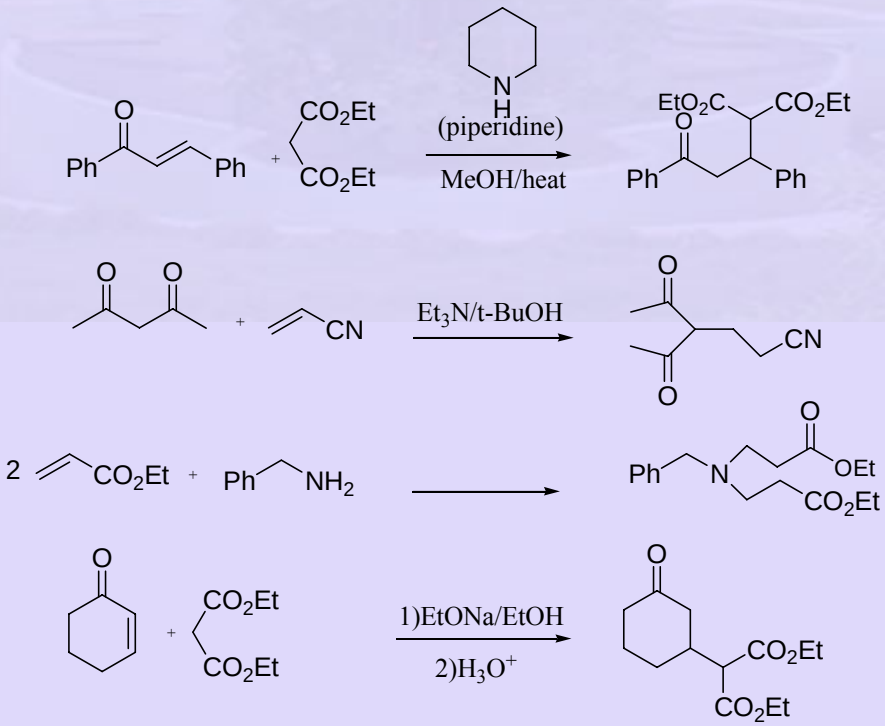


(The resonance structures of α, β-unsaturated carbonyl compounds)

A look at resonance structures of this type of compounds quickly reveals the fact that the β-carbon is electron deficient and can be attacked by the nucleophile. When addition of nucleophiles proceeds with such a mode, it is commonly referred to as 1,4-addition.

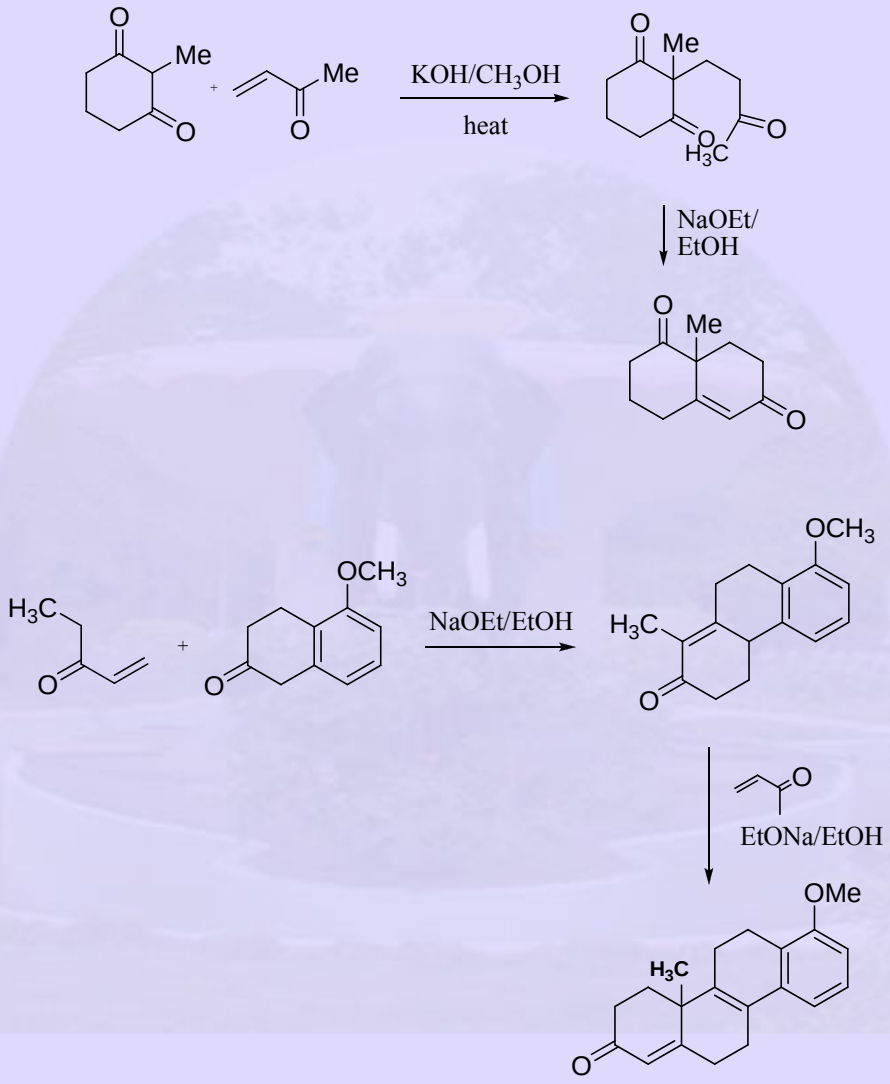


This type of 1,4- or conjugate addition of a carbanion or its equilant to α, β-unsaturated compounds is commonly known as Michael reaction. They are Alkylation reactions in which the conjugated substrate is the alkylating agent.



vi) Robinson annulation:

Conjugate addition is quite useful reaction and can be used in conjunction with an aldol condensation for the formation of cyclic structures. This is known as Robinson annulation.

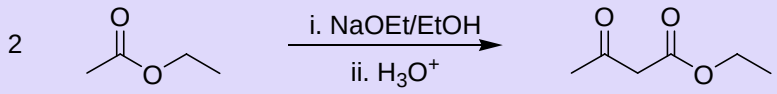


(Suggest a suitable mechanism for the second step!)

Assignment
ENOLATE ANIONS

Suggest a suitable mechanism for the following reactions. Write each step and show the rearrangement clearly by means of arrows.

1.



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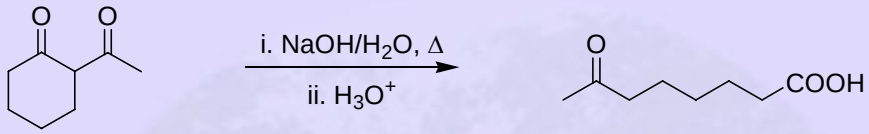

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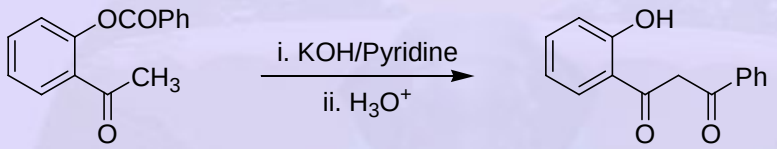

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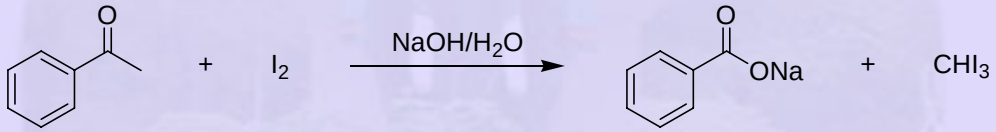

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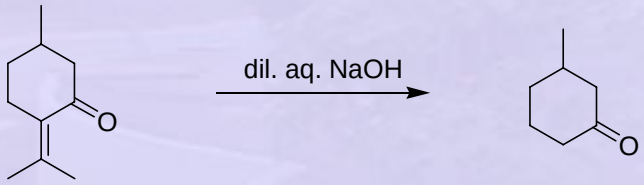

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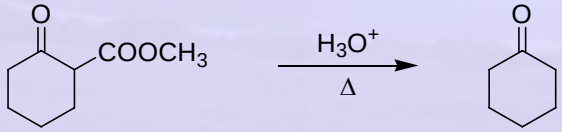
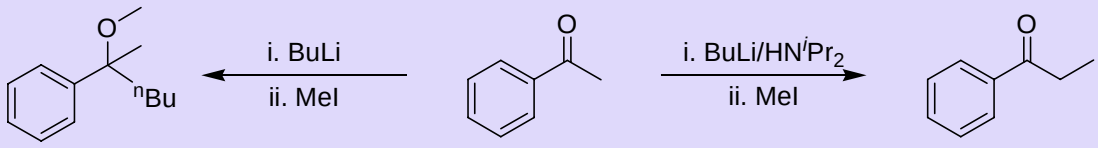
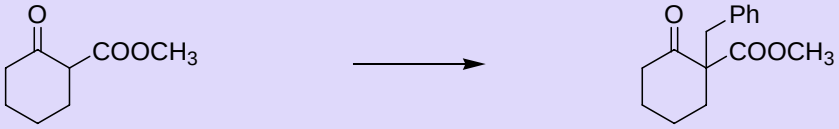
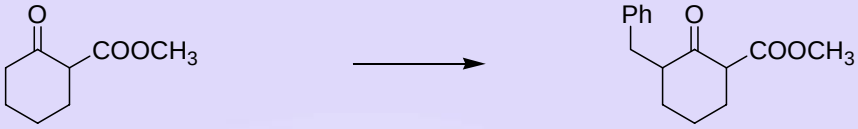


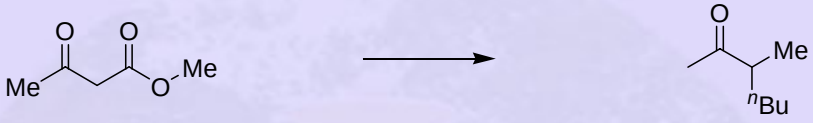
Explain the following observation:



How will you effect the following conversions? Indicate the reagents and reaction conditions clearly.

1. 

2. 

3. 

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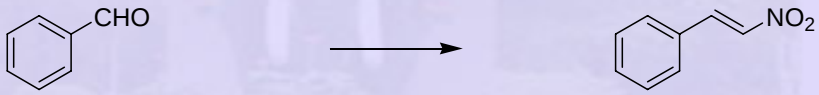
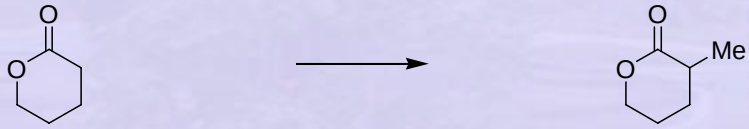
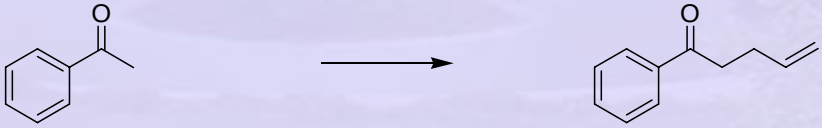
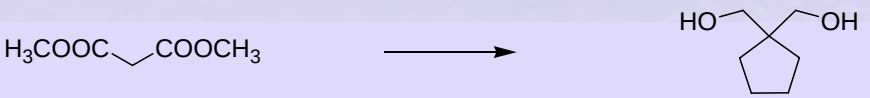
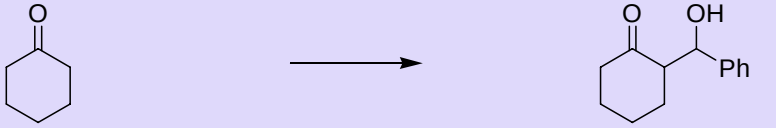
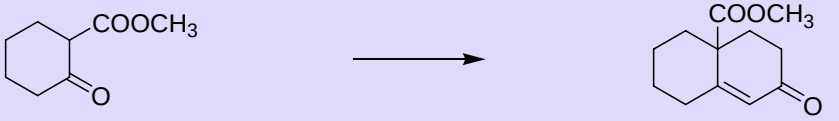
5. 

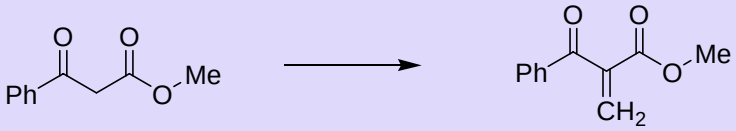
6. 

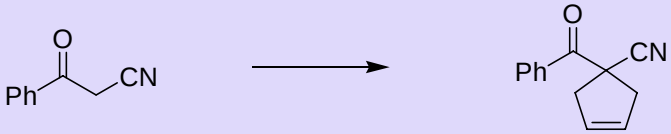
7. 

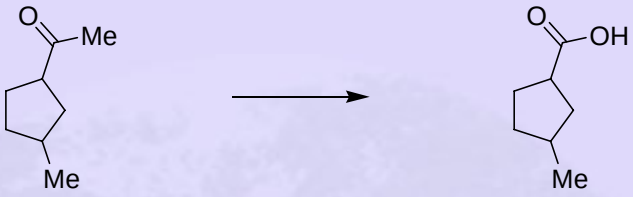
8. 

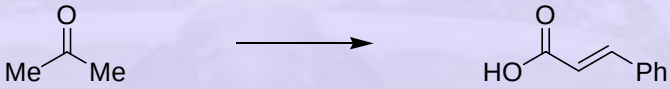
9. 

10. 

11. 

12. 

13. 

14. 

15.