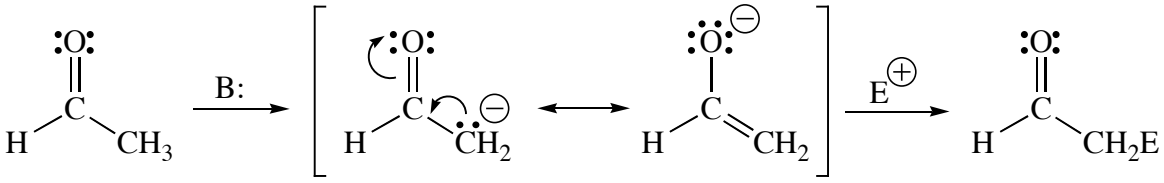
Lecture Notes
Chem 51C
S. King

Chapter 24 Carbonyl Condensation Reactions

I. Reaction of Enols & Enolates with Other Carbonyls

Enols and enolates are electron rich nucleophiles that react with a number of different electrophiles:



$E^{\oplus}$ =

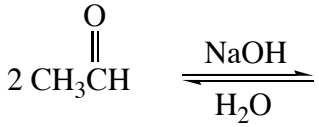
Q: **What if the electrophile was another carbonyl compound?**
A:

Enol or Enolate + Aldehyde or Ketone:

Enolate + Ester:

A. Aldol Addition & Aldol Condensation

1. Base Catalyzed



What's going on here?

In base the enolate ion is the nucleophile:

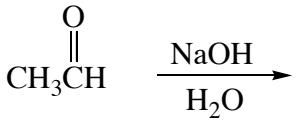
Complete Mechanism:

NOTE: ***HO^- is a leaving group!*** Conjugation makes the double bond particularly stable. This allows hydroxide to be removed in a very exothermic reaction.

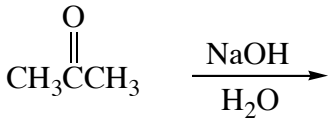
Special Points about the Aldol Condensation:

a. An aldol reaction is an equilibrium process, and the concentration of the aldol product at equilibrium depends on the substrate used:

With aldehydes, the aldol product is favored.



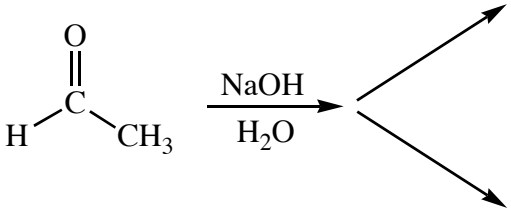
With ketones, reactants are favored.



- The equilibrium must be driven to get the reaction to go to completion. Both reactions can be forced to completion by dehydration (the exothermic dehydration drives the aldol equilibrium to the right).

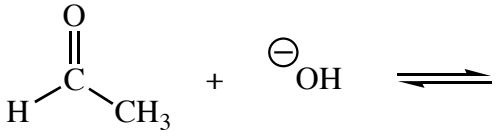
Q: Why exothermic?
A:

b. The conditions for the aldol reaction are the same as for hydrate formation. Why doesn't hydration happen instead?



- Hydration does occur, but the reaction is reversible. Formation of the hydrate is not favored at equilibrium.

c. Look @ pK_a's for the enolate ion formation in the above reaction:



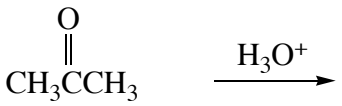
***<u>The equilibrium mixture contains only a small fraction of the enolate ion</u>!!!

Q: How can this reaction occur?

A: Even though the equilibrium concentration of the enolate ion may be small, it still serves as a useful reactive intermediate. Once the enolate reacts with an electrophile (other than a proton), it is removed from the equilibrium. Eventually, all of the carbonyl compound reacts *via* a low concentration of the enolate ion.

2. Acid Catalyzed

The acid catalyzed aldol goes all the way to the dehydrated product and you can't isolate the addition product.



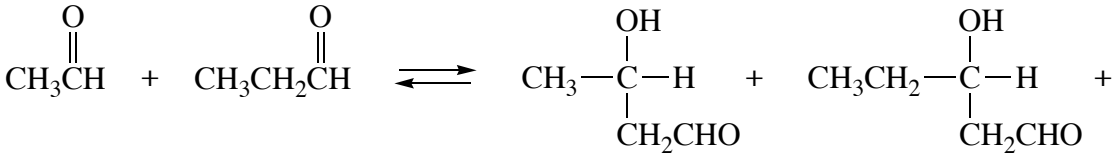
Mechanism:

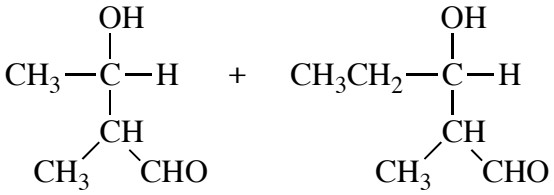
In acid the enol is the nucleophile:

3. Crossed Aldol Reactions

When the enolate of one aldehyde or ketone adds to the carbonyl group of a different aldehyde or ketone, a **mixed** or **crossed aldol product** is obtained. The compounds to be used in a crossed aldol reaction must be selected ***very carefully***, or a mixture of several products will be formed.

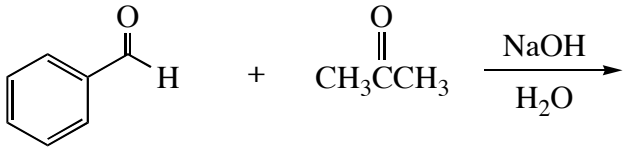
A bad example:





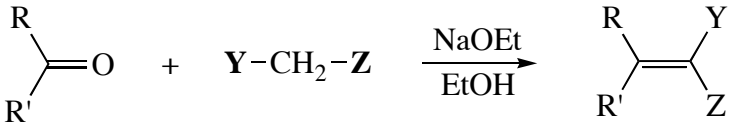
Way around this:

a. Choose the reagents so that one of the participants has no α-hydrogens (only one enolate can be formed).



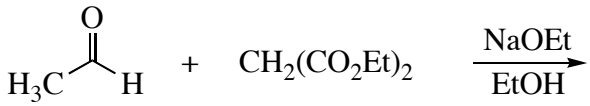
- In this example, you don't even need to heat the reaction to get dehydration to occur because the double bond is conjugated with carbonyl *and* the aromatic ring!
- Once the enolate of acetone is formed, it will more readily add to benzaldehyde than another molecule of acetone.

b. Choose the reagents so that one of the participants has especially acidic α-hydrogens.



Y, **Z** = CO_2Et, CHO, COR, CN, NO_2

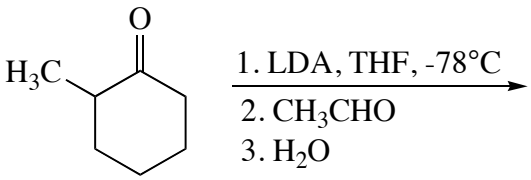
Example:



c. Use directed aldol addition.

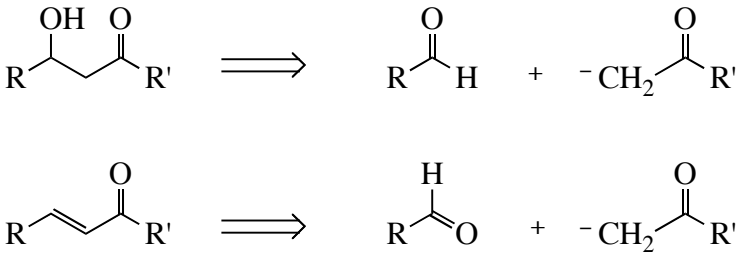
Steps:

1. Prepare the enolate of one carbonyl with LDA
2. Add the second carbonyl (*the electrophile*) to this enolate



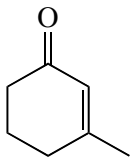
4. Synthesis with the Aldol Condensation

☛ **Key Structural feature to look for in synthesis:**



Example 1:

Determine whether the following α,β-unsaturated ketone can be prepared by an aldol condensation:

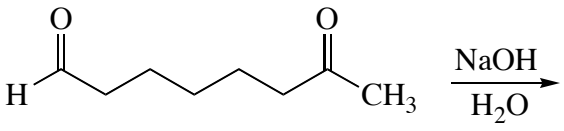


Is this feasible? Will you only get one product?

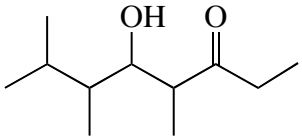
☛ ***General Rule:*** If a 5 or 6 membered ring can be formed, the cyclization will occur readily.

Look at all the possible enolates:

Example 2: Predict the major product in the following reaction:

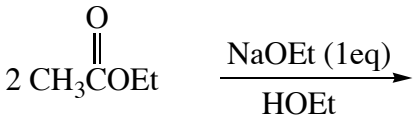


Example 3: (*from a recent midterm*) Show the two organic starting materials that would be used to synthesize the following ketone by a crossed-aldol reaction.



How would you perform this crossed-aldol reaction to obtain the product selectively? Show synthesis below:

B. **The Claisen Condensation** (enolate + ester):

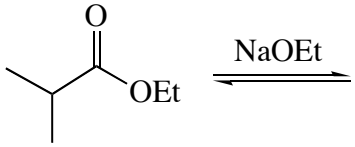


Mechanism:

<u>Important points</u>:

- Reaction is an equilibrium process and is thus reversible. Because of this, ***the Claisen condensation does not give a good yield of the β-ketoester unless the product is converted to its enolate in the basic reaction mixture***. The intermediate simply undergoes the reverse reaction and decomposes to give the starting enolate and ester.

If there are no α-hydrogens to deprotonate, *then* the reaction won't go!

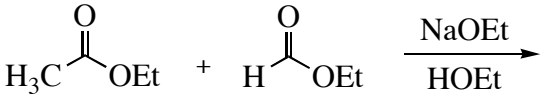


1. Crossed Claisen Condensation

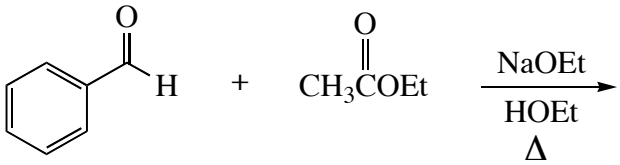
Like the aldol reaction, Claisen Condensations can be done with two different esters, but the compounds must be chosen carefully

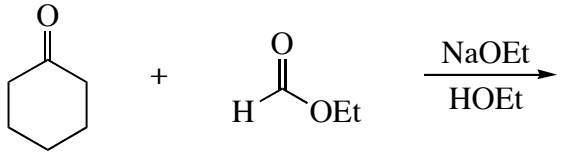
Ways to do this:

a. Choose the reagents so that one of the participants is especially reactive or has no α-hydrogens (only one enolate can be formed).



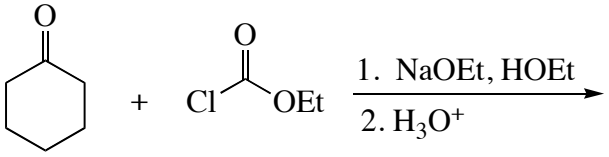
b. Aldehydes or ketones can also be condensed with esters. If addition to an ester is desired, the ester should be especially reactive.





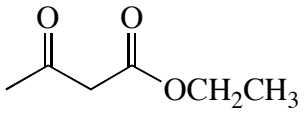
c. β-Dicarbonyls can be prepared by reacting an enolate with ethyl-chloroformate or diethylcarbonate

ethyl chloroformate *diethyl carbonate*



2. Synthesis with Claisen Condensation

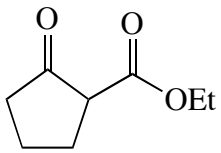
☛ **Key Structural feature:**



Steps:

1. Start counting from ester
2. Break the α,β-bond
3. Add –OEt to the β-position
4. Put (–)–charge in the α-position

Synthesis: Target molecule:



A UNIFIED LOOK AT CONDENSATION REACTIONS:

We've seen examples of condensations using:

- Aldehydes and Aldehydes
- Aldehydes and Ketones
- Esters and Esters
- Esters and Aldehydes or Ketones

A large variety of reactions are possible between enolate ions and compounds containing carbonyl groups. **How do you decide the type of reaction that will occur**???

This decision can be made by considering four questions:

1. Is there an enolizable hydrogen atom in one or both of the reactants? (Include H's alpha to carbonyl, nitrile, nitro, or cyano groups.)

2. Is there a carbonyl that can be attacked by the enolate?

Keep in mind reactivity:

3. Is the carbonyl in the same molecule as the enolate?

5 or 6 membered rings form easily.

4. Is the carbonyl carbon attached to a good leaving group?

L.G. present? It will be lost in going to the product.

∴ A Claisen-type Condensation will occur.

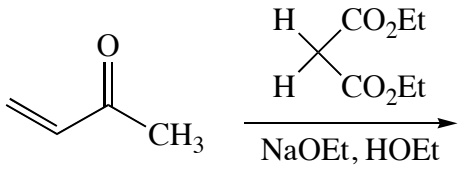
L.G. absent? The product will be a β-hydroxy carbonyl compound or its dehydration reaction.

∴ An Aldol-type reaction will occur

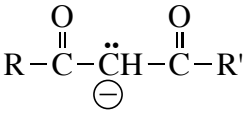
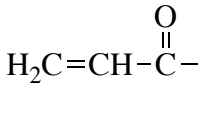
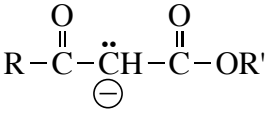
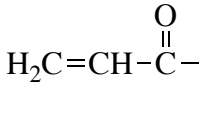
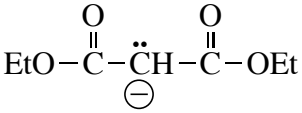
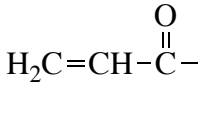
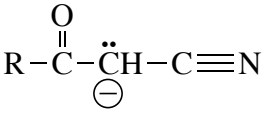
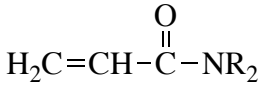
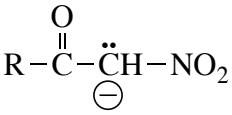
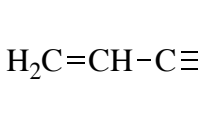
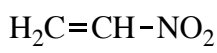
Best way to learn this is to Practice, Practice, Practice!!!

II. Alkylation of the β-Carbon: The Michael Reaction

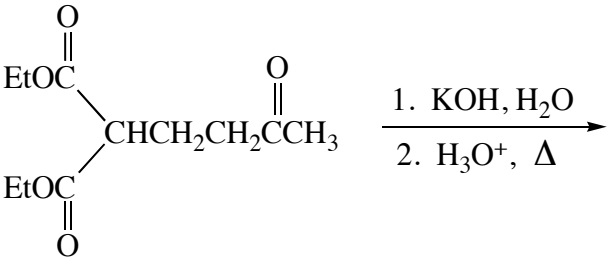
The addition of an enolate to the double bond of an α,β-unsaturated carbonyl compound is called a **Michael Reaction**. This reaction works especially well when the enolate is a stabilized enolate *(formed from a β-dicarbonyl compound)*.



- The electrophile (the α,β-unsaturated carbonyl) accepts a pair of electrons. It is the **Michael acceptor**. The attacking nucleophile donates a pair of electrons. It is called the **Michael donor**.
- The product of the addition of an enolate anion to an α,β-unsaturated carbonyl compound is a **1,5-dicarbonyl compound**. Some of the more common Michael donors and acceptors are shown on the next page.

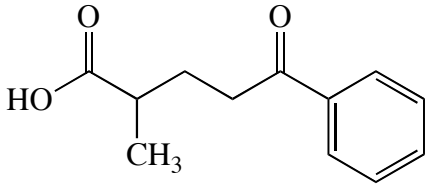
Michael donors		Michael acceptors	
	β-diketone		conjugated aldehyde
	β-keto ester		conjugated ketone
	malonic ester		conjugated ester
	β-keto nitrile		conjugated amide
	α-nitro ketone		conjugated nitrile
			nitroethylene

The product of the Michael Reaction may be treated *like any other substituted malonic ester*. Hydrolysis of the ester and decarboxylation leads to a δ-keto acid (1,5 dicarbonyl).



A. The Michael Addition in Synthesis: Retrosynthetic Analysis

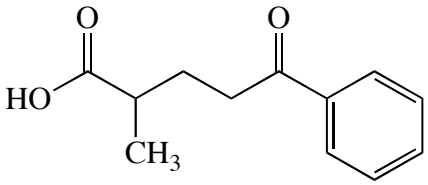
Example: Provide a synthesis of the following compound using a Michael Reaction, using the route that would give the best yield.

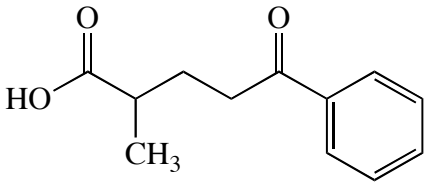


Steps:

1. Break β–γ-bond
2. Put a double bond in the α,β position
3. Put a (–) charge in the γ-position

Two ways to break:

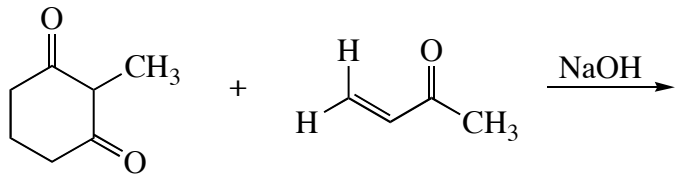




Synthesis using Strategy A:

III. The Robinson Annulation: Michael Reaction Followed by Aldol

The product of a Michael Reaction, a 1,5 dicarbonyl, is often ideally suited to under-go an intramolecular aldol condensation. In fact, if the Michael addition takes place under strongly basic conditions, the 1,5-dicarbonyl is not isolated. It undergoes a spontaneous intramolecular aldol condensation, with dehydration, to give a new 6-membered ring. This is known as a Robinson Annulation.



Mechanism:

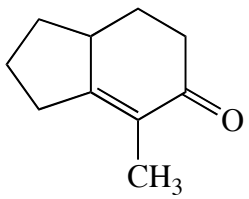
Step 1: Michael Addition

Step 2: Aldol Condensation

A. The Robinson Annulation: Retrosynthetic Analysis

Robinson is: Michael followed by Aldol
Retrosynthesis: Take apart Aldol, then Michael

Example: Provide a synthesis of the following compound using a Robinson Annulation.



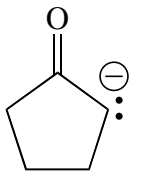
Q: Why won't an unstabilized enolate work?

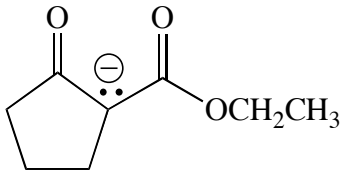
A. The Robinson Annulation involves a Michael reaction. The Michael reaction does not work well with unstabilized enolates. *Why not?*

Go back to page 31 of the notes.

** Remember, the stronger the nucleophile, the more 1,2 addition.

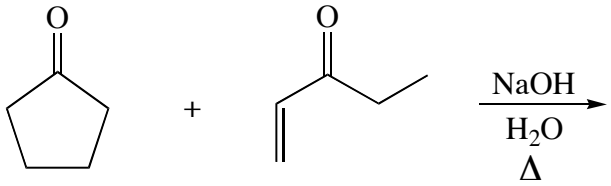
COMPARE:





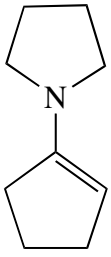
Base strength correlates with nucleophile strength across any row in the periodic table:

CONDITIONS FOR THIS ROBINSON ANNULATION:

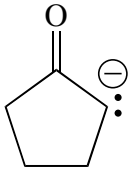


A Great Alternative: Use a Stork Enamine Synthesis!

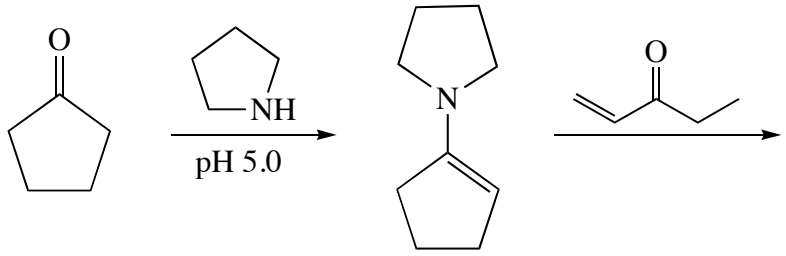
Use:



instead of:



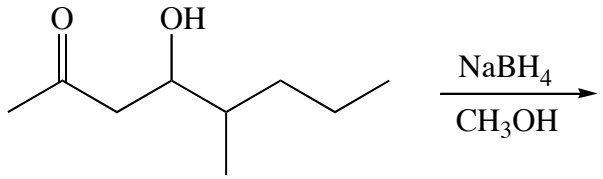
NEW & Improved reaction:



IV. More Organic Synthesis: Looking for Disguised Key Structural Units

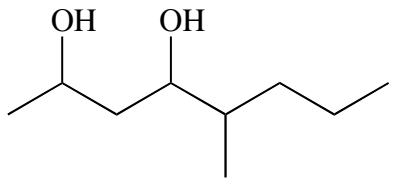
In this chapter we have learned to synthesize β-hydroxycarbonyls, α,β-unsaturated carbonyls, β-ketocarbonyls, and 1,5 dicarbonyls. When a target molecule has these key structural characteristics, it is easy to propose a synthesis by following the retrosynthetic rules outlined in the notes (pg. 110, 115, 120, 122.) If these key structures undergo further reaction, however, the easily identifiable characteristics are disguised, and it can be difficult to recognize the masked structural units.

Example 1:

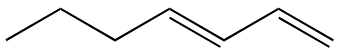


It is helpful to imagine a new target molecule with recognizable structural features, and then determine which reactions will convert the new target molecule into the real target molecule.

Target molecule:



Example 2: Provide a synthesis of the following compound from ketones or aldehydes of 4 or fewer carbons:



Example 3: Provide a synthesis of the following compound from acyclic precursors