

CHEM 322 Organic Chemistry II - Professor Kathleen V. Kilway
"Organic Chemistry" by Maitland Jones, 3rd edition

Chapter 17: 1, 3, 4, 5, 10, 11, 13, 14, 17, 18, 22, 23, 25, 27, 34, 35, 37, 39, 41, 42, 44, 48, 54, 56, 61, 63.

Chapter 17- Carbonyl Chemistry 2: Reactions at the α -Position

Section 17.1

I. Preview

A- Chemistry at the α -carbon.

- 1- Aldehyde/ketone becomes the Nucleophile.
- 2- Acidic conditions - the enol is formed.
- 3- Basic conditions - the enolate is formed.

B- Essential Skills

- 1- Practice enol and enolate formation.
- 2- Central reaction in this chapter is the aldol reaction.
- 3- It is important to understand this reaction because most of the other condensation reactions are related to this one.

C- Important Details

- 1- β -hydroxy carbonyl compound is the intermediate in the aldol reaction.
- 2- It eliminates H₂O to form an α,β -unsaturated carbonyl compound.
- 3- "Always try the Michael first." p. 897

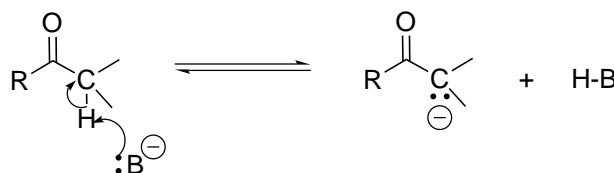
Section 17.2

II. Aldehydes and Ketones are Weak Brønsted Acids

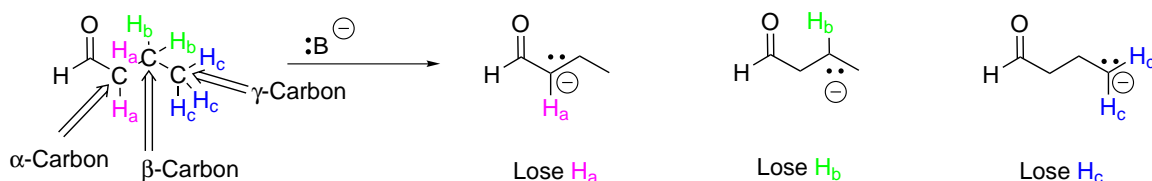
A- Carbonyl compounds as proton donors.

- 1- Carbonyl compounds that have hydrogen at the α -carbon are weak acids.

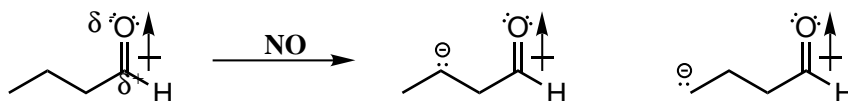
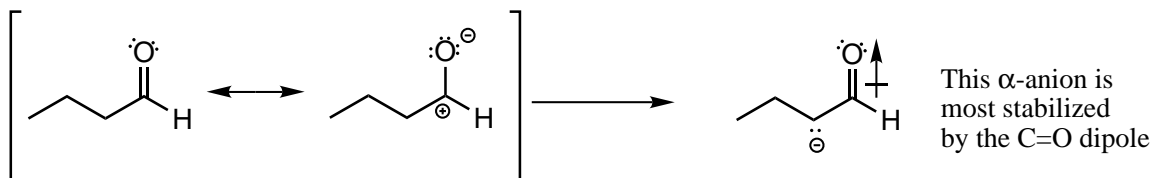
$pK_a = 15-20$



a- They have pK_a s in the high teens, $pK_a = 15-20$.

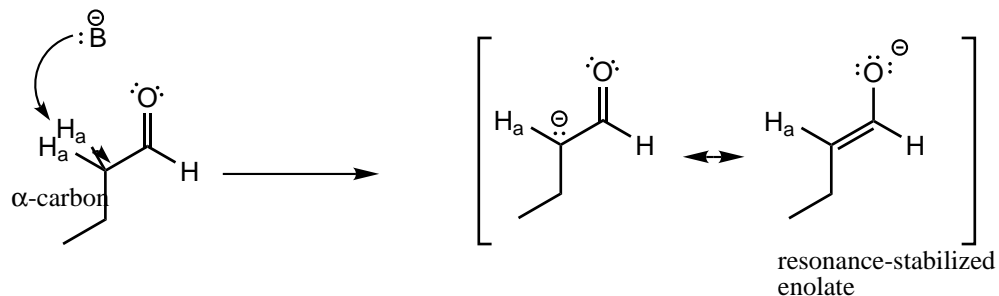


b- Loss of the α -hydrogen gives a more stable anion than loss of β - or γ -hydrogen.



i- The C=O dipole is stabilizing to loss of the α -hydrogen.

ii- It is also resonance-stabilized.

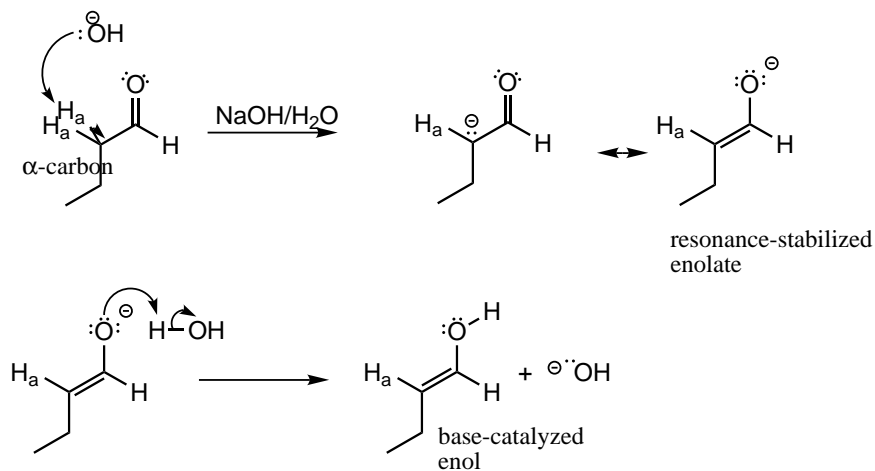


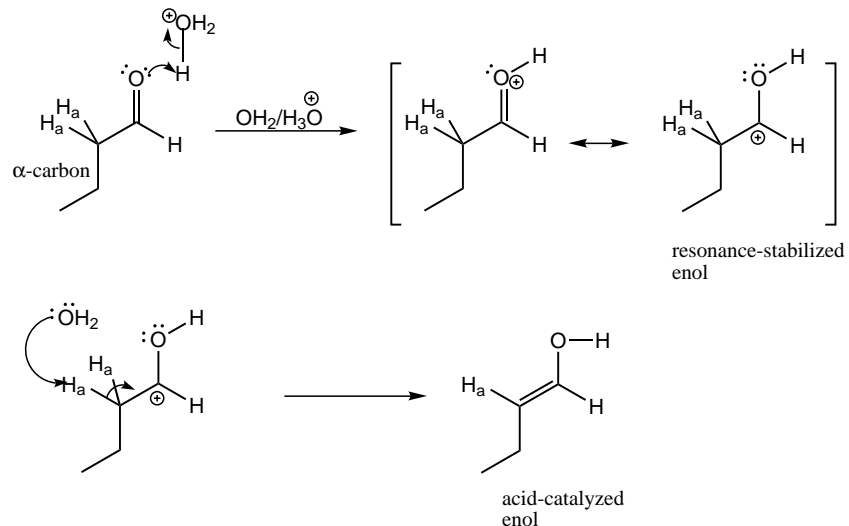
2- The new resonance-stabilized species is called an **enolate**.

a- There are two ways to protonate an enolate anion.

i- If it reprotonates at carbon, the original carbonyl is regenerated.

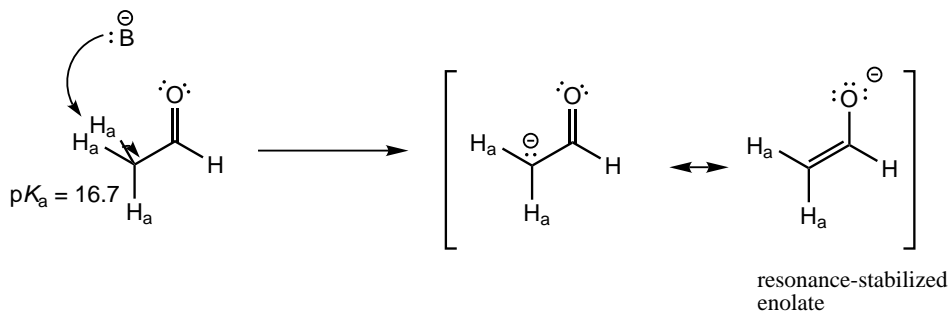
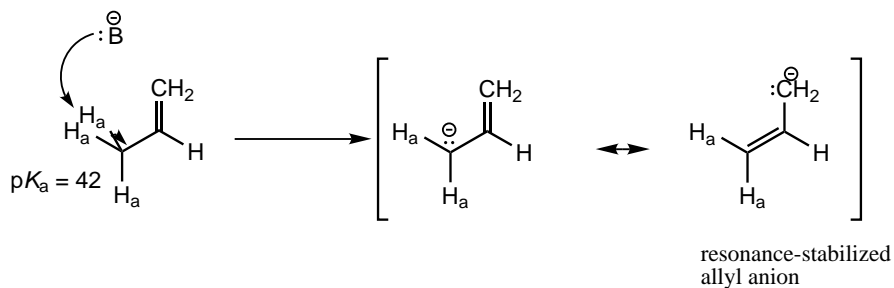
ii- If it protonates at oxygen, the **enol** is formed.



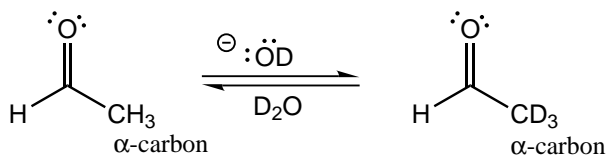


3- There is stabilization of the enolate because:

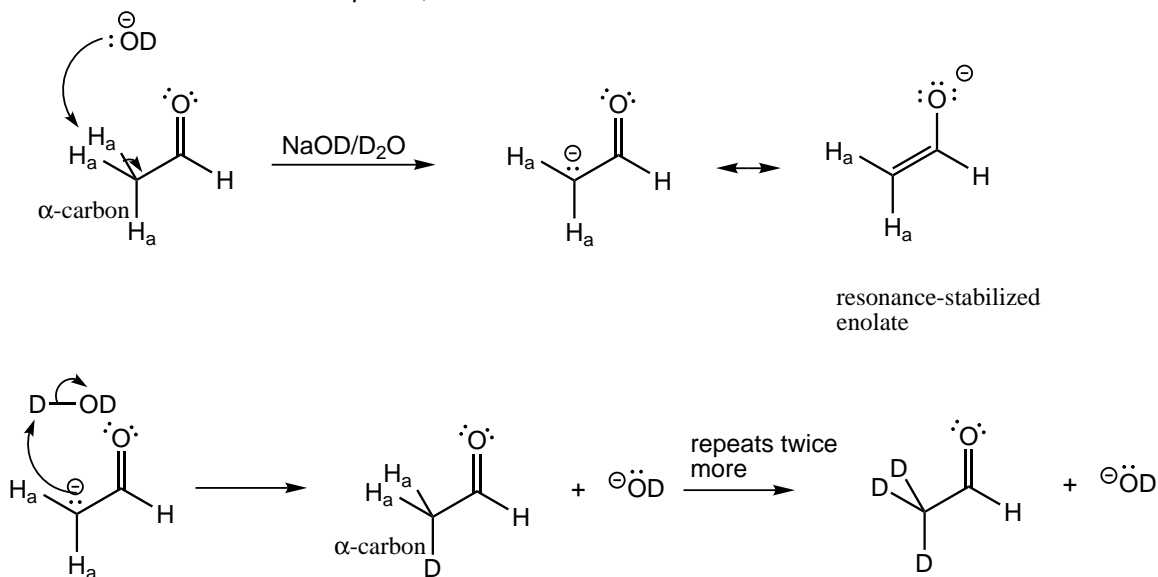
- a- Three $2p$ orbitals form an allyl-like system. (See Chapter 112, p 583.)
- b- Two π electrons are found in the lowest bonding molecular orbital and two are in the nonbonding orbital.
- c- The enolate is less symmetrical than an allyl system because of oxygen. (Fig. 17.7)
 - i- This promotes acidity at the α -carbon.
 - ii- The pK_a of acetaldehyde is 16.5, but the pK_a of propene is 42.



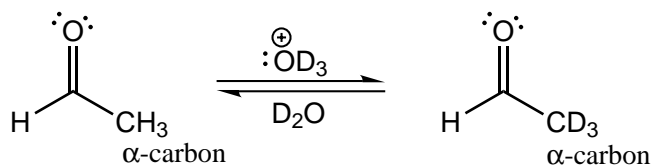
- 4- Exchange reactions with deuterium show how the mechanism works.
 a- The enolate is formed when the three α -hydrogens of acetaldehyde are removed by base (^-OD) and exchanged for deuterium.



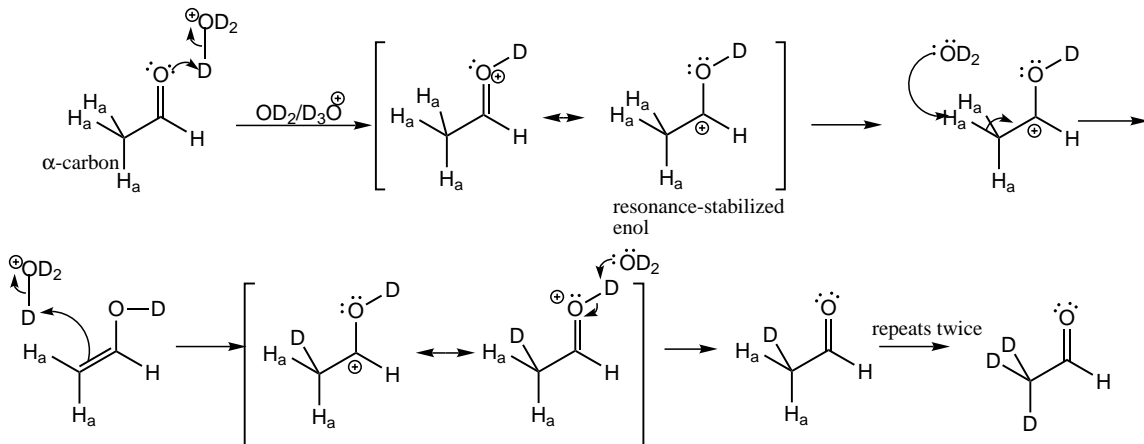
- i- It is an equilibrium reaction.
 ii- It is endothermic for acetaldehyde. (It wants to revert to starting material.)
 iii- It is a catalytic process, that is, the catalyst (^-OD) is regenerated. (Fig. 17.10 and 17.11, p 902)



- b- The three α -hydrogens of acetaldehyde can also be exchanged for deuterium in acid.



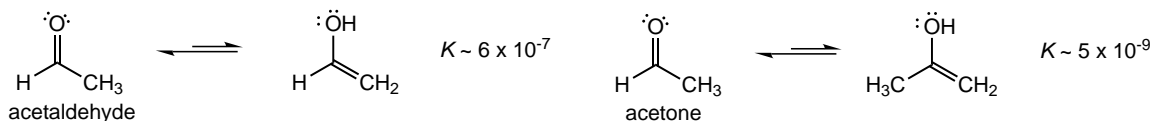
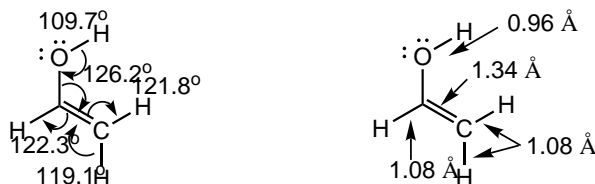
- i- Instead of deprotonating the α -hydrogen and forming enolate, oxygen is protonated and the neutral enol is formed.
 ii- It is also an equilibrium reaction and eventually the α -hydrogens will be replaced with deuterium and the catalyst will be regenerated.



5- Simple aldehydes and ketones prefer their carbonyl forms to their enol forms.

a- K_{eq} for acetaldehyde is $\sim 5 \times 10^{-6}$.

b- K_{eq} for acetone is $\sim 6 \times 10^{-8}$.



c- Aldehydes are found in enol form a little more than ketones because the extra methyl group stabilizes the keto form of ketones.

6- However, β -dicarbonyl compounds (1,3-dicarbonyls) prefer their enol forms, with K_{eq} in the range of 0.1 - 3.2.

a- They have increased stability over the simple aldehydes and ketones.

i- An intramolecular hydrogen bond can be formed.

ii- The enol form provides conjugation between $\text{C}=\text{C}$ and the $\text{C}=\text{O}$ groups.

b- Cyclohexadienone (1,3-cyclohexadienone) also prefers its aromatic enol form.

i- Formation of the aromatic phenol is extremely energetically favorable.

ii- The reaction has a K_{eq} of $>10^{13}$.

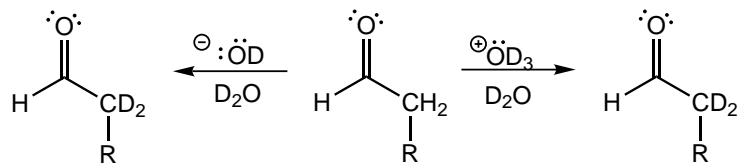
Section 17.3

II. Reactions of Enols and Enolates

A- Exchange Reactions

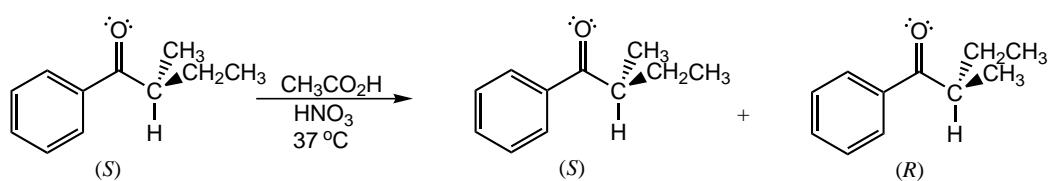
1- Hydrogens in α -position can be exchanged for deuterium in acid or base.

2- See Figure 17.12, p 903.



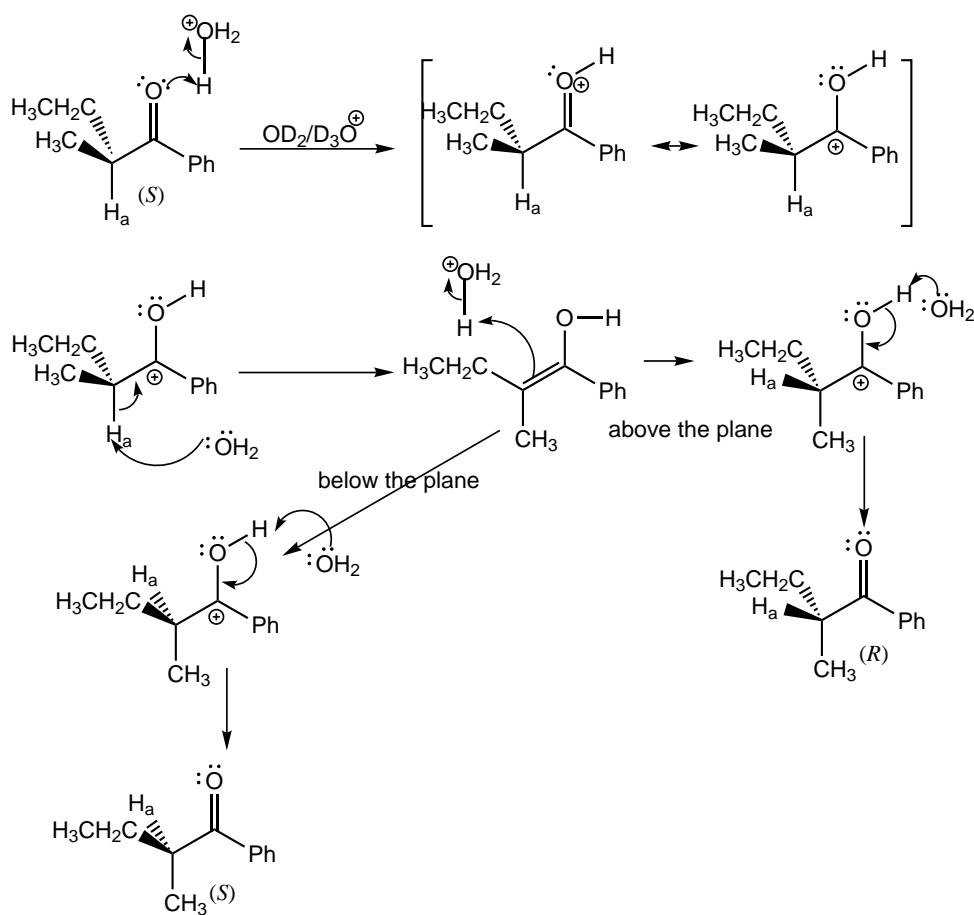
B- Racemization

1- If there is an α -hydrogen on a stereogenic carbon, loss of optical activity (racemization) occurs.



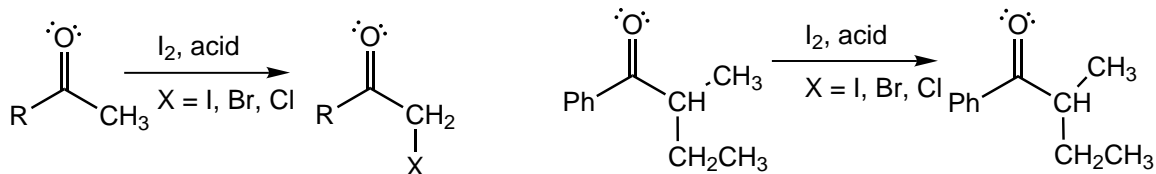
also happens in base

2- The mechanism proceeds through a planar intermediate. (Fig. 17.26 and 17.27, p 909)



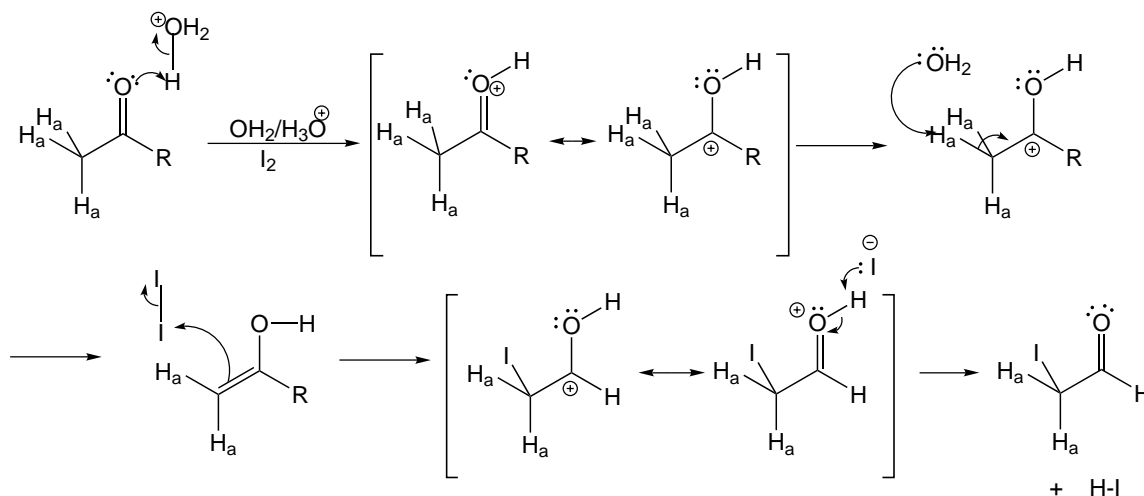
C- Halogenation in the α -Position

1- In acid, adding X_2 ($X = I, Cl$ or Br) to a ketone with an α -hydrogen replaces one of the methyl hydrogens with the halogen.



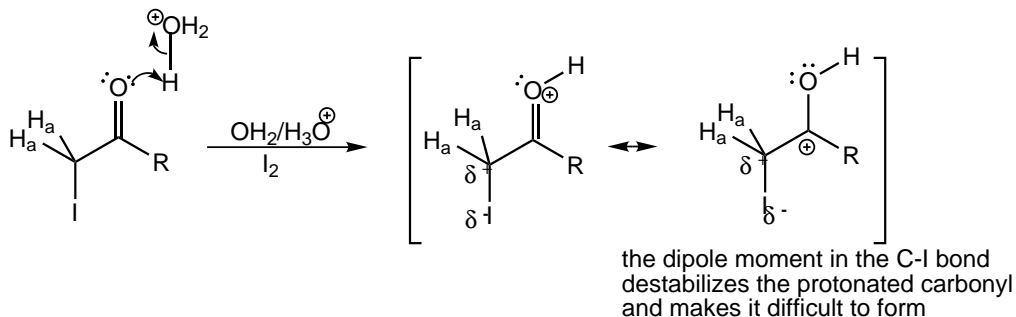
a- This only happens once in acid.

b- When the halogen adds to the α -position of the enol, the first step in enol formation is disfavored.

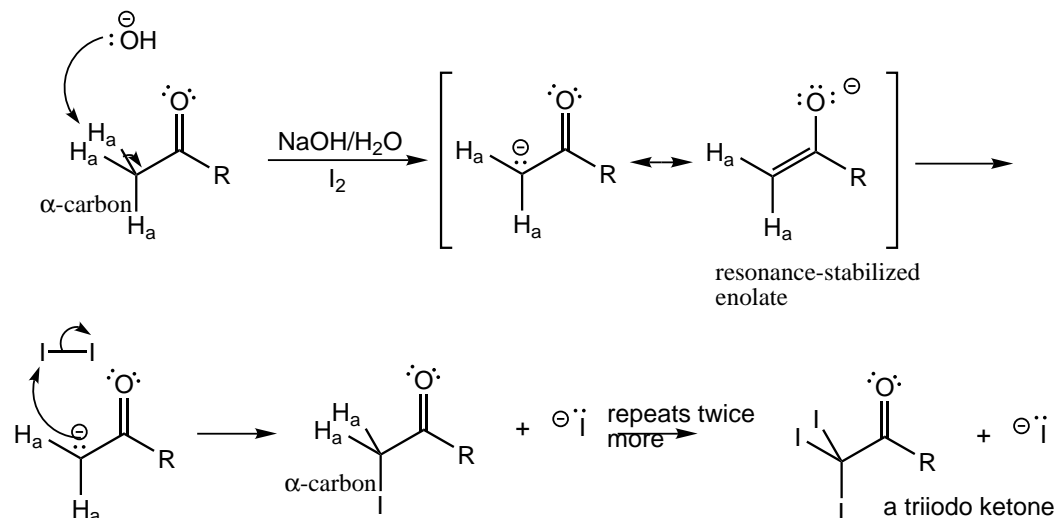


i- The halogen inductively withdraws electrons.

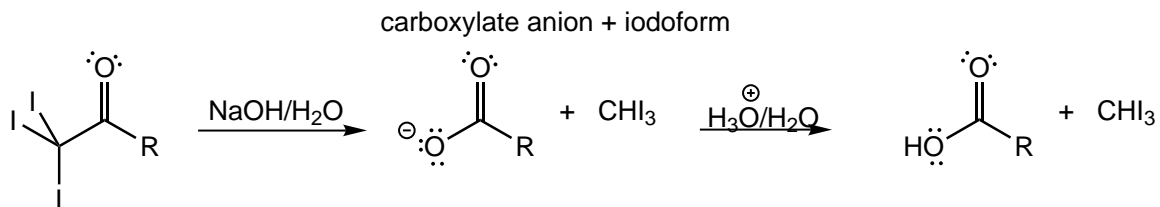
ii- There is a dipole in the C-I bond, which destabilizes the protonated carbonyl. (Fig. 17.31, p 911)



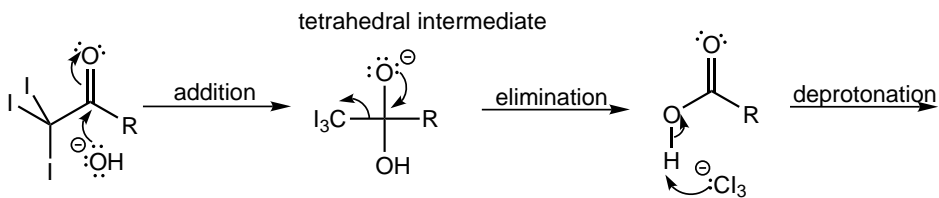
- 2- In base, the reaction goes on to replace all α -hydrogens with the halogen.
 a- The enolate, which has a negative charge on the α -carbon, is the intermediate.



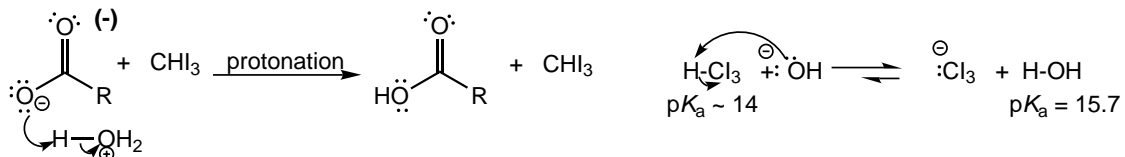
- i- The inductive effect of the halogen favors formation of the halogenated enolate.
 ii- The dipole of the C-I bond now stabilizes the intermediate resonance forms.
 b- If there are three α -hydrogens, they are all replaced by the halogen, which goes on further in the **haloform reaction**.



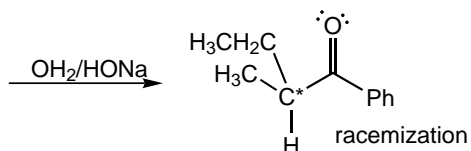
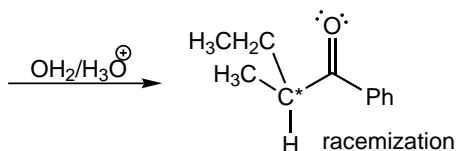
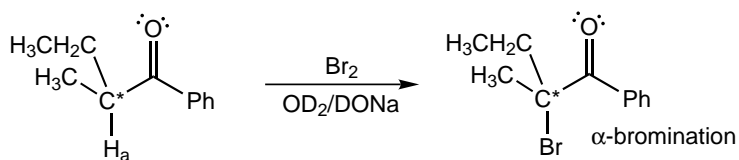
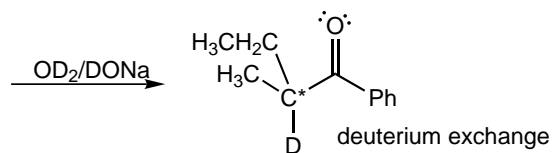
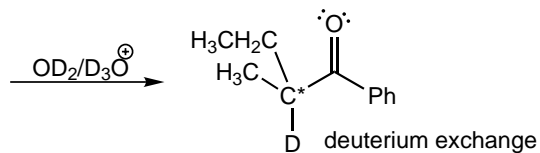
- i- First step is addition of hydroxide to the carbonyl group, giving a tetrahedral intermediate.
 ii- Then CX_3 is lost in the elimination step.
 iii- The CX_3 deprotonates the hydroxyl group to give the haloform.
 iv- Adding acid in the final step gives the carboxylic acid.



carboxylate anion



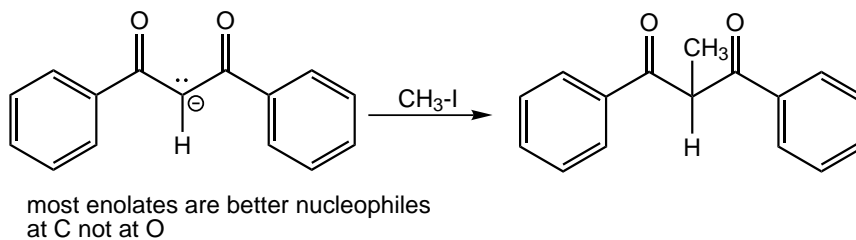
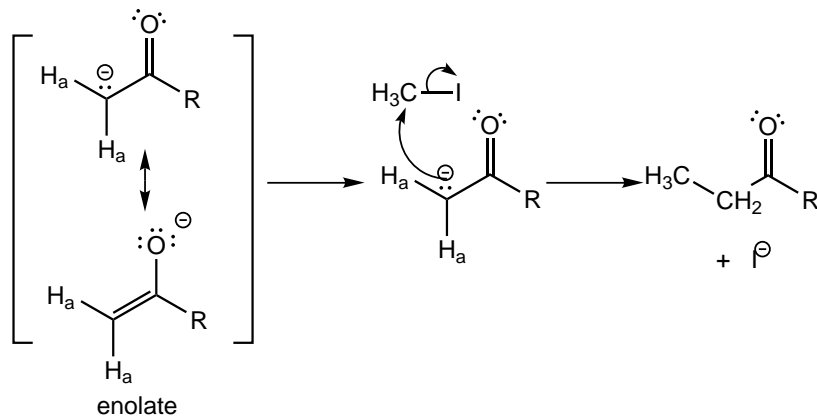
- c- Using I_2 in this reaction gives a yellow solid, a positive test for methyl ketones.
- 3- Summary of reactions at α -positions, and prototypes for future reactions:
- Deuterium exchange.
 - Halogenation at α -position.
 - Racemization.



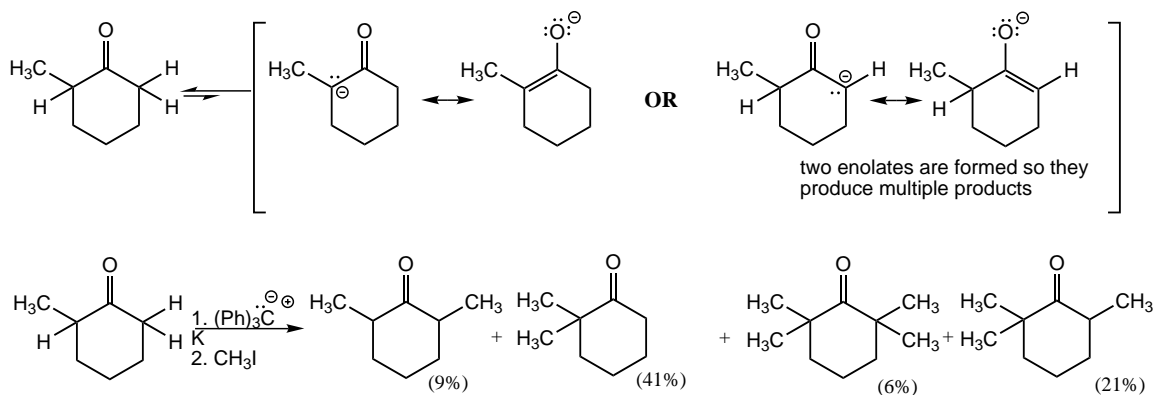
D- Alkylation Reactions

1- Enolates are better nucleophiles at carbon than at oxygen.

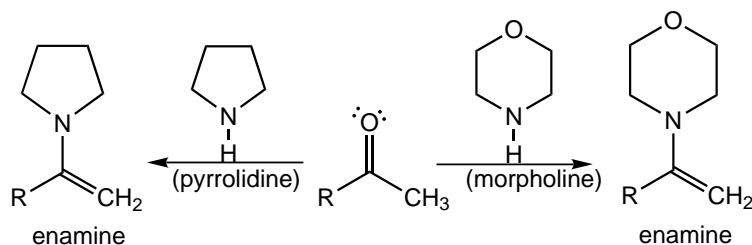
a- Enolates can be used as nucleophiles in S_N2 displacements to alkylate the α -position.



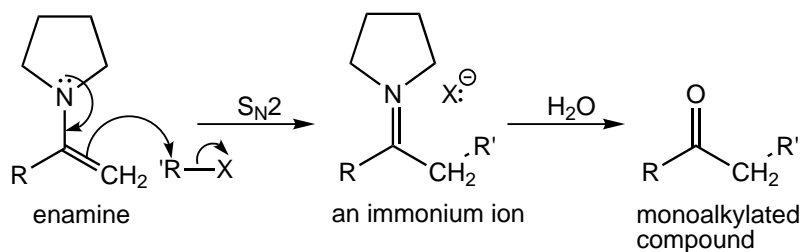
b- There can be more than one alkylation of ketones if there is more than one α -hydrogen.



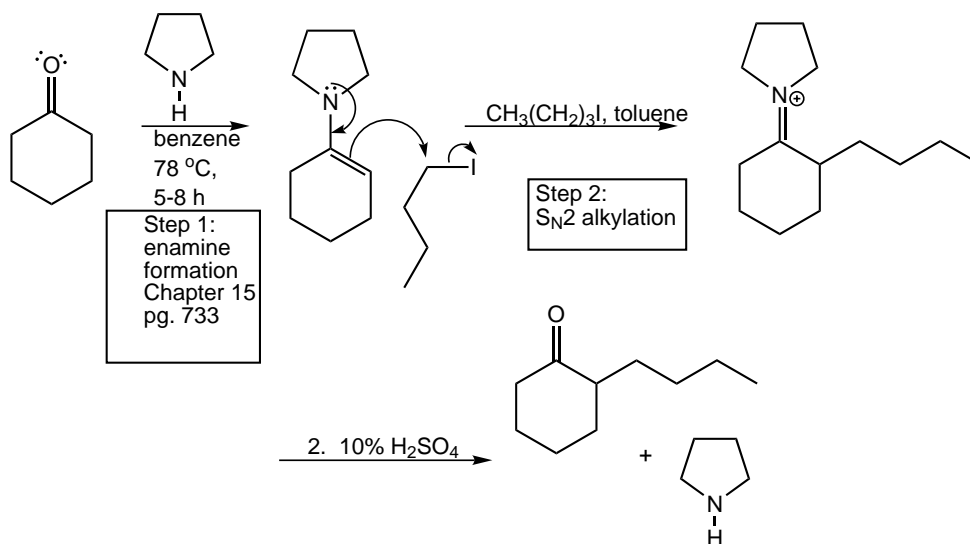
- c- Using a strong base that is a poor nucleophile can help.
- Sodium hydride is effective.
 - Lithium diisopropylamide (LDA)** also works well.
- 2- Secondary amines can be used to form an enamine from the carbonyl group.
- This minimizes over alkylation.
 - Although not completely free of problems, it works relatively well.



- i- First convert the ketone to an enamine.



- ii- Alkylate the enamine (at α -position).



- iii- The carbonyl is regenerated through a final hydrolysis step. (Fig. 17.47, p 920)

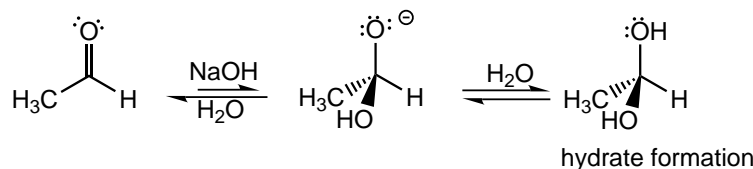
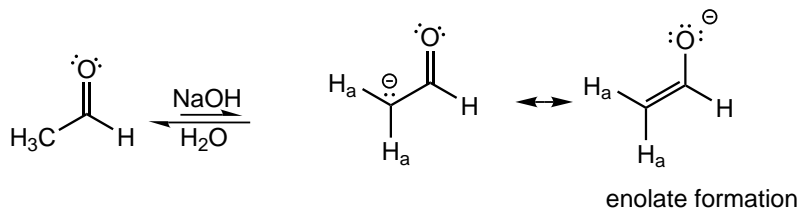
Section 17.4

IV. Condensation Reactions of Carbonyl Compounds: The Aldol Condensation

A- Enols and enolates are nucleophilic and react with Lewis acidic carbonyl groups.

1- Acetaldehyde can react with hydroxide to form the hydrate, or the enolate.

a- Hydrate formation does not give an isolable product.

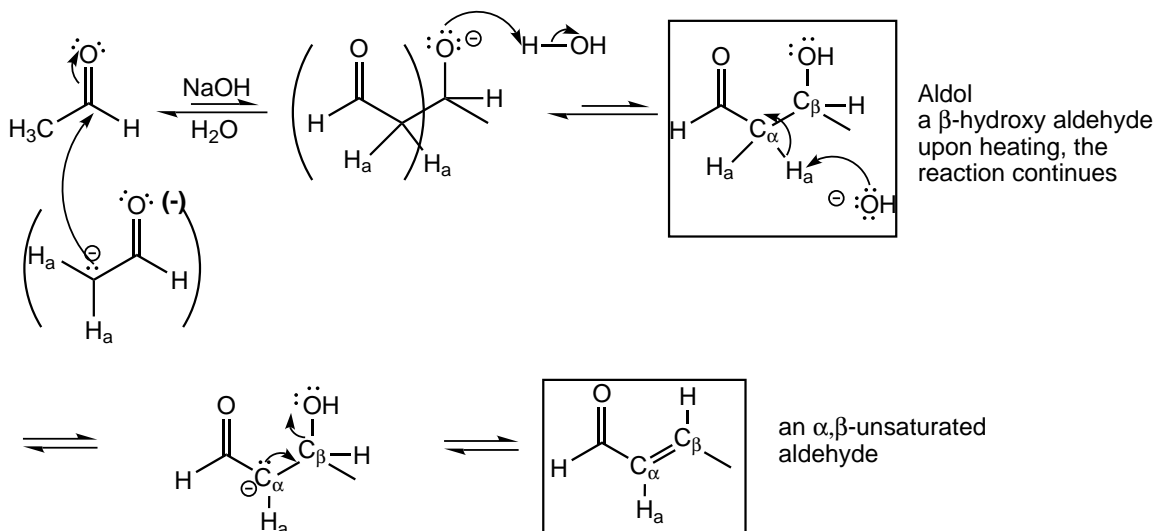


b- But the enolate can be used in a reaction called the **aldol condensation**. (Fig. 17.53, p 923)

i- Step 1: formation of enolate.

ii- Step 2: the enolate is a nucleophile and can add to the carbonyl group of acetaldehyde in S_N2 fashion.

iii- Step 3: protonation of oxygen gives a β -hydroxy carbonyl compound, and the catalyst (OH^-) is regenerated.



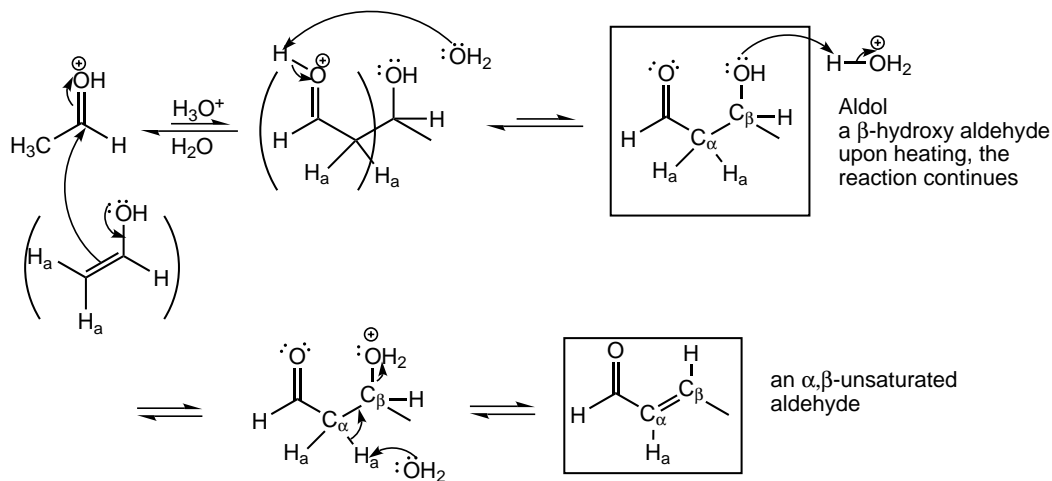
2- In acid, the catalyst is H_3O^+ .

a- The enol is weakly nucleophilic.

b- The protonated carbonyl group is a good Lewis acid.

i- Step 1: formation of enol.

- ii- Step 2: the C=C of the enol adds to a protonated carbonyl group.
 iii- Step 3: oxygen is deprotonated to give the β -hydroxy carbonyl compound, and the catalyst (H_3O^+) is regenerated. (Fig. 17.54, p 925)

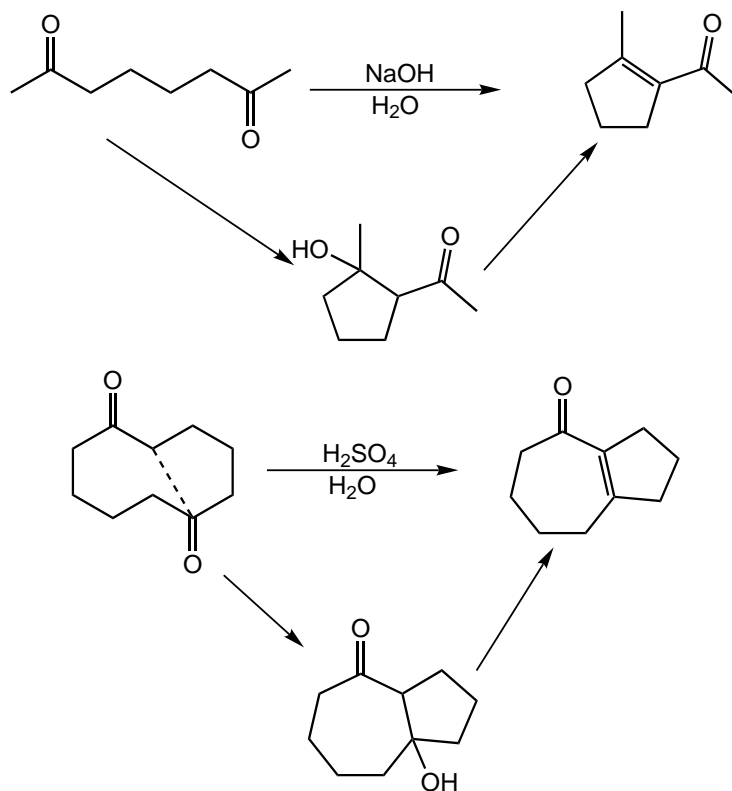


- 3- Both acid- and base-catalyzed aldol condensations give the β -hydroxy product.
- 4- In acid the β -hydroxy carbonyl compound can be dehydrated to the α,β -unsaturated aldehyde or ketone.
 - a- The hydroxy group can be protonated.
 - b- Water is a good leaving group.
- 5- The dehydration reaction is harder in base because hydroxide is a poor leaving group.
 - a- It can still be accomplished at a relatively high temperature.
 - b- The mechanism is the E1cB reaction. (Fig. 17.55, p 924)
- 6- Aldol condensation is an equilibrium reaction.
 - a- Like hydration, the aldol product is not usually favored at equilibrium.
 - b- If $\text{Ba}(\text{OH})_2$ is used, the reaction equilibrium lies to the right to give product.

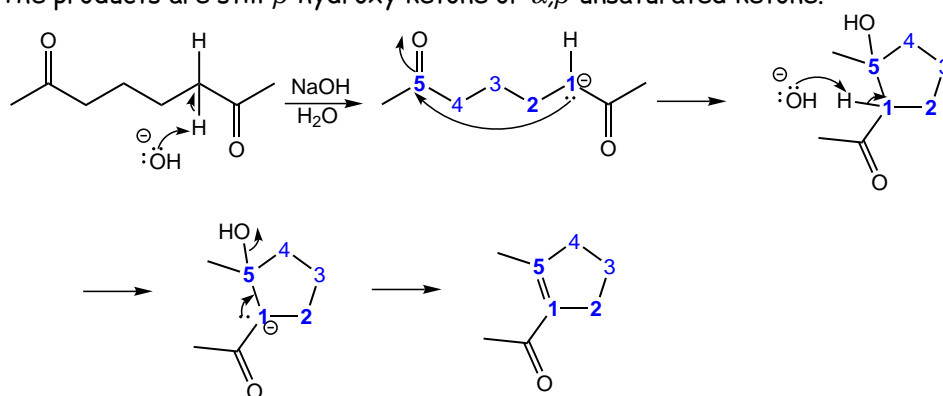
Section 17.5

V. Reactions Related to the Aldol Condensation

A- Intramolecular Aldol Condensations

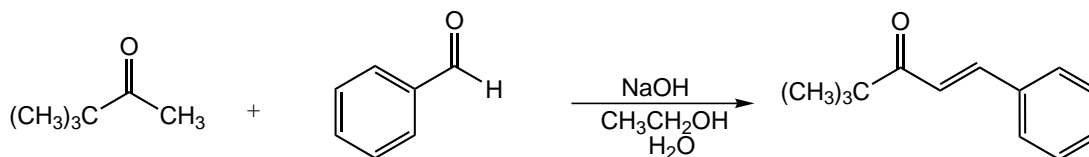


- 1- This happens with both acid- and base-catalyzed reactions.
- 2- The molecule must have an enolizable hydrogen and a carbonyl group.
- 3- Five- or six-membered rings are more favorable.
- 4- The products are still β-hydroxy ketone or α,β-unsaturated ketone.

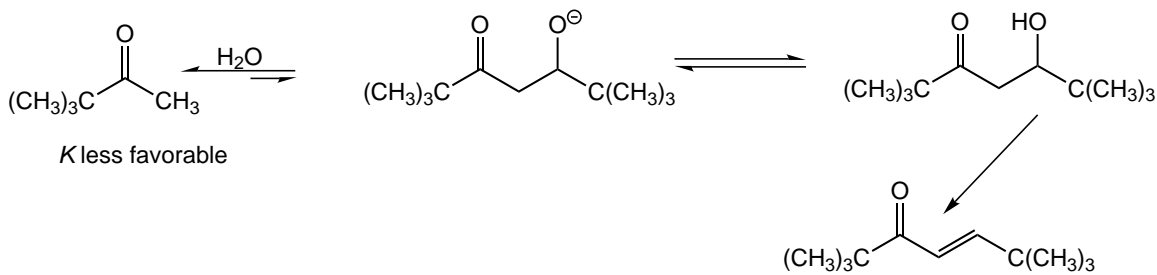


B- Crossed Aldol Condensations

- 1- Aldol condensation between two different carbonyl compounds is called a **crossed aldol condensation**.
- 2- This has the potential of giving a multiplicity of products. (Fig. 17.65, p 934)
- 3- There are ways to make the reaction more specific.
 - a- The **Claisen-Schmidt condensation**.

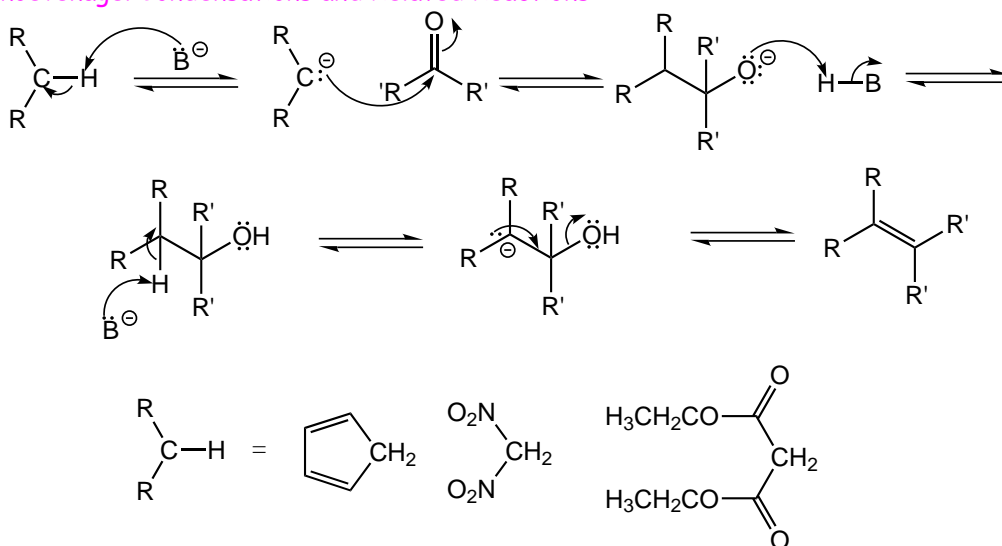


- i- Use an aldehyde for one partner, e.g. benzaldehyde.
- ii- Use a ketone that has hydrogens on only one α -carbon for the other, e.g., *tert*-butyl methyl ketone.

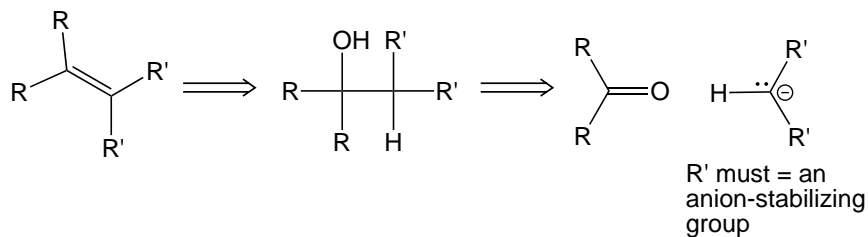
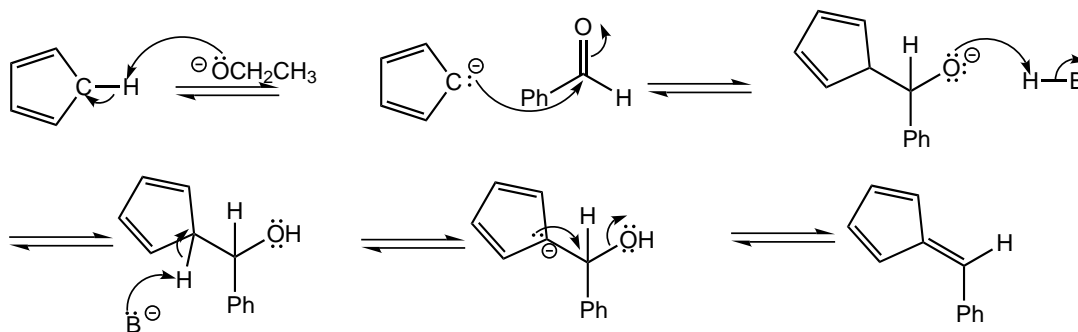


- b- LDA removes a proton from a sterically less hindered position and can be used with certain kinds of molecules.

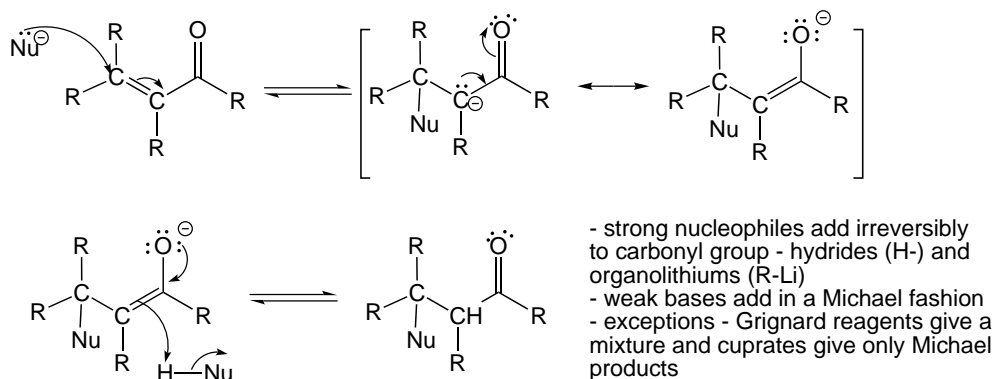
C- Knoevenagel Condensations and Related Reactions



- 1- Some bases can generate many enolates from compounds in Table 17.2, p 937.
 - a- These have anion stabilizing groups.
 - b- The condensation product is formed as the result of the **Knoevenagel condensation**.
- 2- The synthesis of **fulvenes** also involve the addition of a complex anion to a carbonyl group. (Fig. 17.71, p 939)



D- More Related Condensations: The Michael Reaction



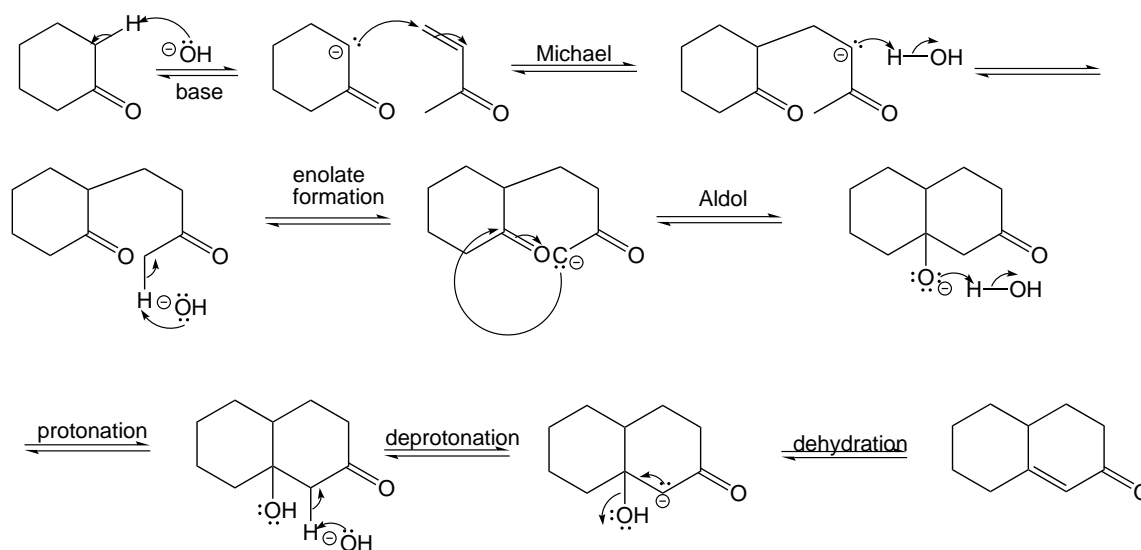
- 1- A nucleophile can add to the C=C bond of an α,β -unsaturated carbonyl compound.
- 2- This is called the **Michael reaction**. (Fig. 17.74, p 940, and 17.75, p 941)

Section 17.6

VI. Problem Solving

A- Condensation Reactions in Combination: Magid's Second Rule

- 1- Condensation reactions are often done in combination.
 - a- A common sequence of reactions uses the Michael followed by an aldol condensation.
 - b- Six-membered rings can be constructed with this sequence in a reaction called the Robinson annulation. (Fig. 17.81, p 945)



- 2- One problem solving technique to try in these problems is called Magid's Second Rule, which states to always try the Michael first.

Section 17.7

VII. Special Topic: Alkylation of Dithianes

A- Thioacetals are also called dithianes.

- 1- They are strong Bronsted Acids.

Section 17.8

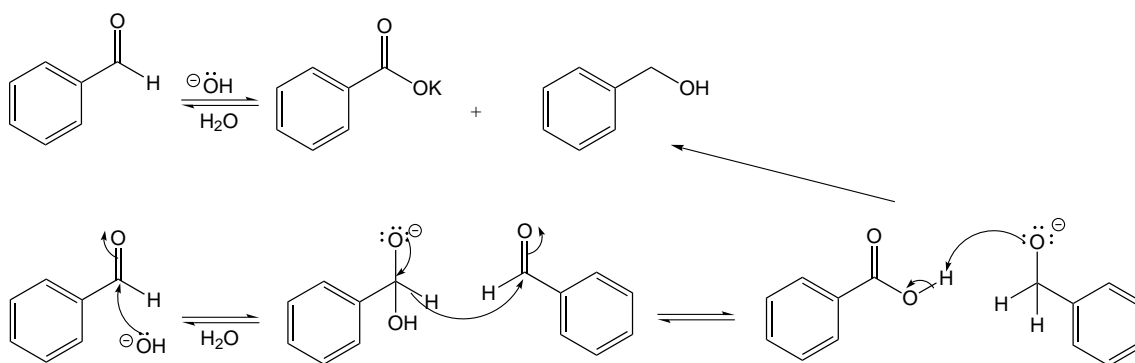
IIX. Special Topic: Amines in Condensation Reactions; The Mannich Reaction

Skip

Section 17.9

IX. Carbonyl Compounds without α -Hydrogens: Magid's Third Rule

A- The Benzoin Condensation



- 1- When a molecule without an α -hydrogen such as benzaldehyde is treated with cyanide, it undergoes a reaction known as the **benzoin condensation**.

- 2- Alkoxides are not good catalysts for this reaction because the anion that is formed is not resonance stabilized.

B- The Cannizzaro Reaction

- 1- If benzaldehyde stands in a strong base such as hydroxide, a redox reaction known as the **Cannizzaro reaction** can occur.

- 2- A hydride shift is involved, but a Lewis acid must be in place to accept it. (Fig. 17.90, p 952)

C- Meerwein-Ponndorf-Verley-Oppenauer Equilibration

Skip.

D- The Bartlett-Condon-Schneider Reaction

Skip.

Section 17.10

X. The Aldol Condensation: Modern Synthesis

A- Reactions with unsymmetrical ketones

- 1- An unsymmetrical ketone can give two different enolates and therefore two different products
 - a- The **kinetic enolate** is less stable, but more easily formed.
 - i- LDA is very effective in forming the kinetic enolate.
 - ii- It is too sterically hindered to access the more hindered α -hydrogen.
 - b- The **thermodynamic enolate** is more stable, but easier to form.
 - i- This more difficult approach works well with B^- .
 - ii- It is not sterically hindered like the LDA. (Fig. 17.104, p 960)
- 2- Enol borinates can also be made
 - a- Using smaller R groups favor the kinetic enolate.
 - b- Larger R groups favor the thermodynamic enolate. (Fig. 17.105, p 960)
- 3- Enolates can exist as E/Z forms.