Enolate Anions and Enamines

Chapter 19

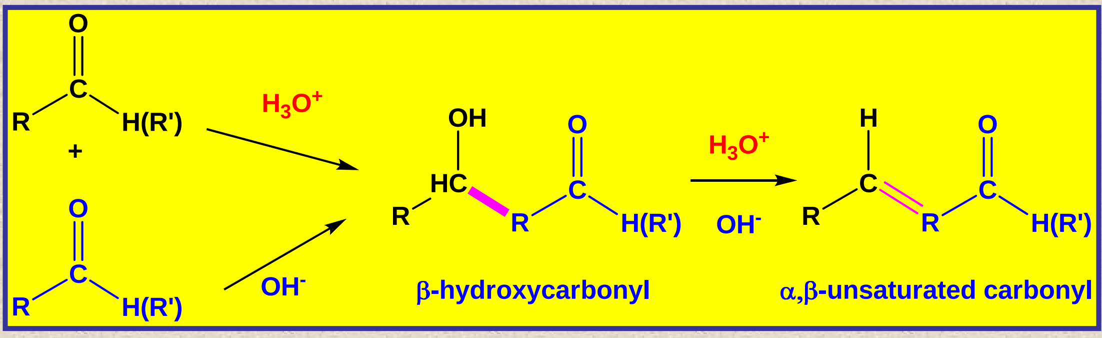
The Aldol Reaction

- The most important reaction of enolate anions is nucleophilic addition to the carbonyl group of another molecule of the same or different compound
  - although these reactions may be catalyzed by either acid or base, base catalysis is more common
  - **The reaction results in a new C—C bond**

The Aldol Reaction

The **product of an aldol** reaction is

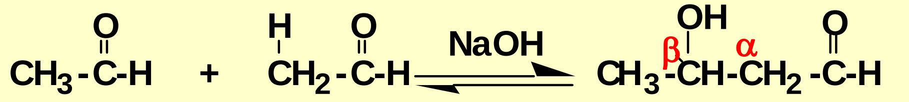
– a β-hydroxyaldehyde or a β-hydroxyketone



Frequently, there is a second, dehydration step

The Aldol Reaction

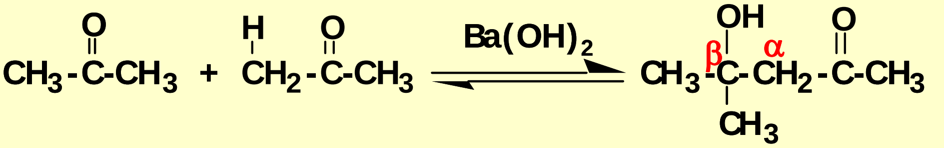
- The **product of an aldol** reaction is
  - a β-hydroxyaldehyde



$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + \overset{H}{\overset{|}{CH_2}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}H \xrightleftharpoons{NaOH} CH_3\text{-}\overset{\beta}{\overset{OH}{\overset{|}{CH}}}\text{-}\overset{\alpha}{CH_2}\text{-}\overset{O}{\overset{\|}{C}}\text{-}H$$

Acetaldehyde Acetaldehyde 3-Hydroxybutanal (a β-hydroxyaldehyde; racemic)

- or a β-hydroxyketone



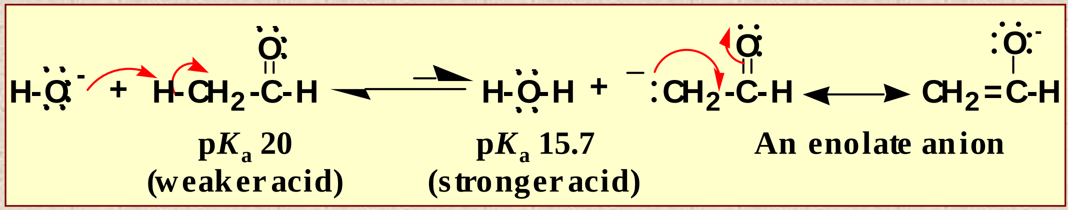
$$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 + \overset{H}{\overset{|}{CH_2}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \xrightleftharpoons{Ba(OH)_2} CH_3\text{-}\overset{\beta}{\overset{OH}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}}\text{-}\overset{\alpha}{CH_2}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$$

Acetone Acetone 4-Hydroxy-4-methyl-2-pentanone (a β-hydroxyketone)

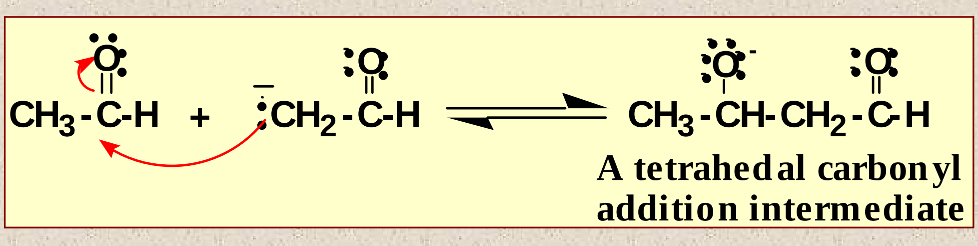
The Aldol Reaction

- **Base-catalyzed aldol reaction**

Step 1: formation of a resonance-stabilized enolate anion



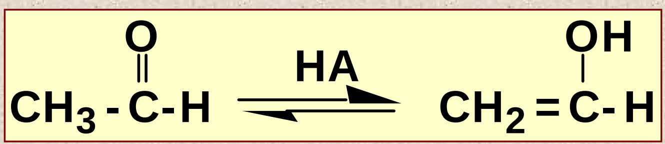
Step 2: carbonyl addition gives a TCAI



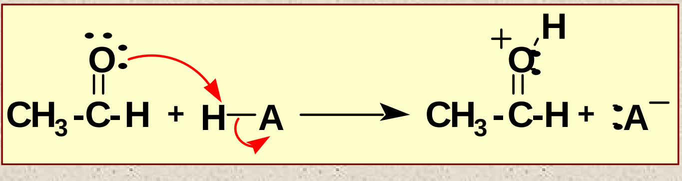
Step 3: proton transfer to O^- completes the aldol reaction

The Aldol Reaction-Acidic

- **Acid-catalyzed aldol reaction**
  - Step 1: acid-catalyzed equilibration of keto and enol forms

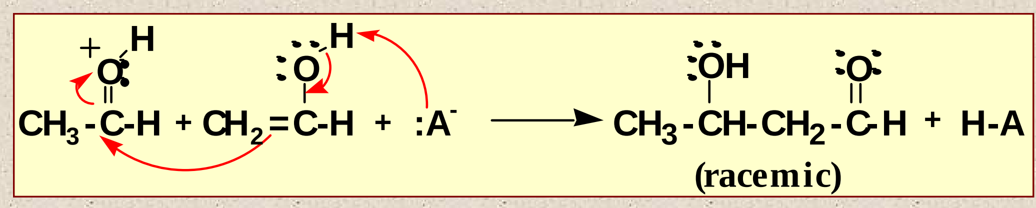


  - Step 2: proton transfer from HA to the carbonyl group of a second molecule of aldehyde or ketone



The Aldol Reaction-acidic

- Step 3: attack of the enol of one molecule on the protonated carbonyl group of another molecule
- Step 4: proton transfer to A^- completes the reaction



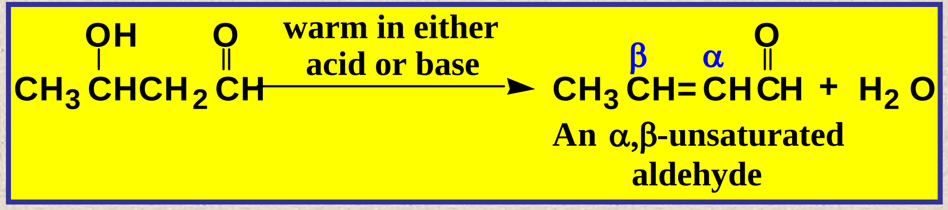
$CH_3\text{-}\overset{\overset{+}{O}H}{\overset{\|}{C}}\text{-}H + CH_2{=}\overset{\ddot{O}H}{\overset{|}{C}}\text{-}H + :A^- \longrightarrow CH_3\text{-}\overset{\ddot{O}H}{\overset{|}{C}H}\text{-}CH_2\text{-}\overset{\ddot{O}}{\overset{\|}{C}}\text{-}H + H\text{-}A$

(racemic)

(Steps 3 & 4 are combined here)

The Aldol Products-H_2O

- aldol products are very easily dehydrated to α,β-unsaturated aldehydes or ketones



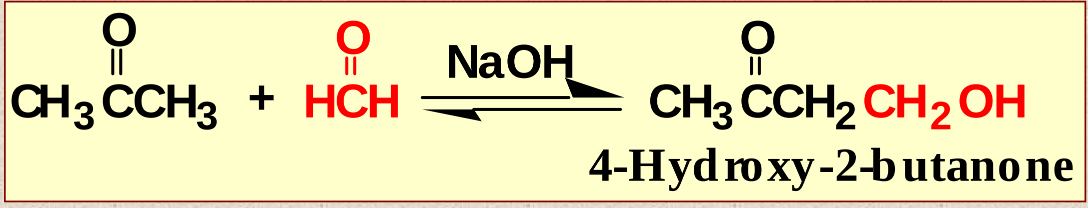
$CH_3\overset{OH}{\overset{|}{C}H}CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[\text{acid or base}]{\text{warm in either}} CH_3\overset{\beta}{C}H{=}\overset{\alpha}{C}H\overset{O}{\overset{\|}{C}}H + H_2O$

An α,β-unsaturated aldehyde

- aldol reactions are reversible and often little aldol present at equilibrium
- K_{eq} for dehydration is generally large
- if reaction conditions bring about dehydration, good yields of product can be obtained

Crossed Aldol Reaction

In a crossed aldol reaction, one kind of molecule provides the enolate anion and another kind provides the carbonyl group



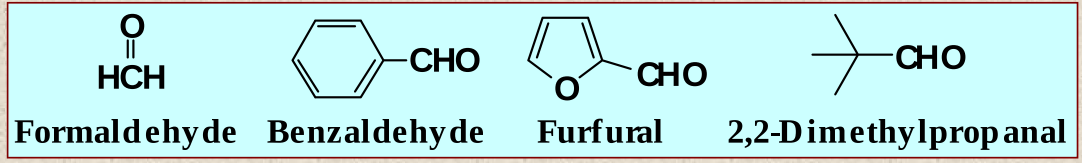
$$CH_3\overset{O}{C}CH_3 + H\overset{O}{C}H \xrightleftharpoons{NaOH} CH_3\overset{O}{C}CH_2CH_2OH$$

4-Hydroxy-2-butanone

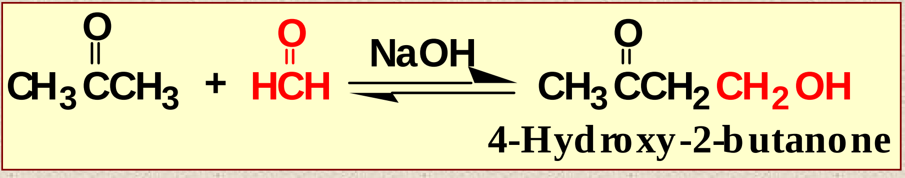
Crossed Aldol Reaction

Crossed aldol reactions are successful if:

1. one of the reactants has no α-hydrogen and, therefore, cannot form an enolate anion and
2. the other reactant has a more reactive carbonyl group, namely an aldehyde



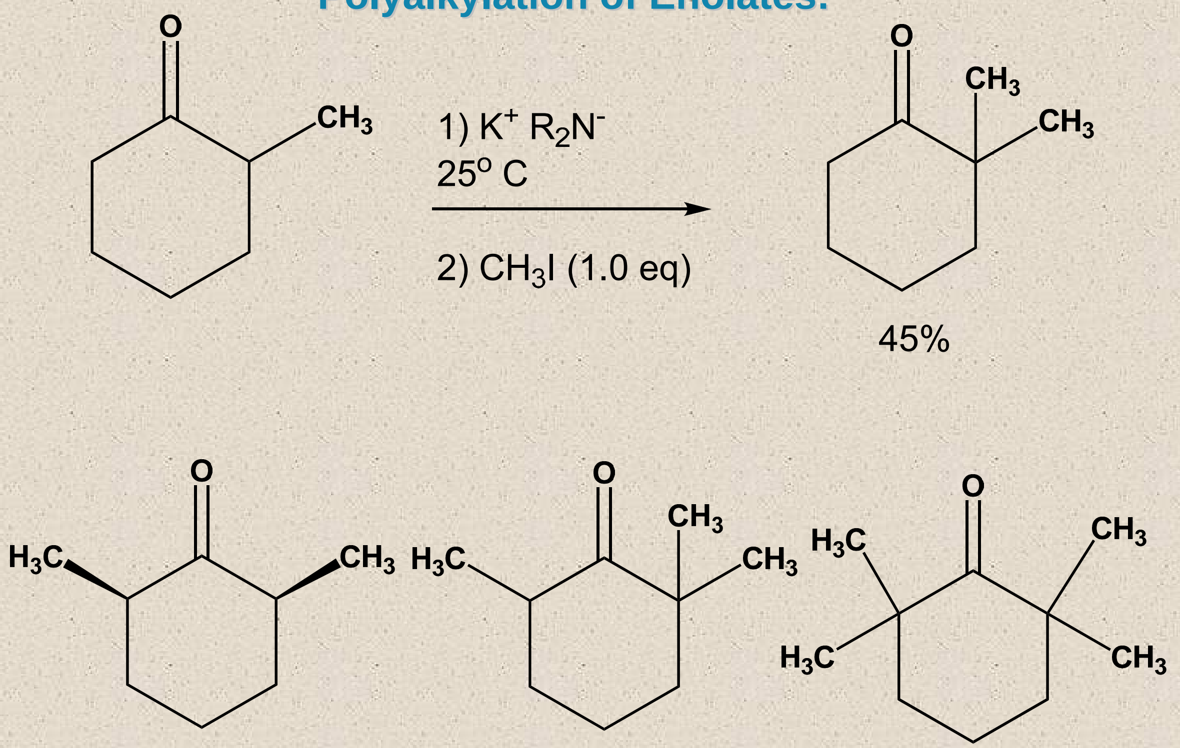
Formaldehyde Benzaldehyde Furfural 2,2-Dimethylpropanal



$$CH_3\overset{O}{C}CH_3 + H\overset{O}{C}H \xrightleftharpoons{NaOH} CH_3\overset{O}{C}CH_2CH_2OH$$

4-Hydroxy-2-butanone

Polyalkylation of Enolates:



1) $K^+ R_2N^-$
25° C

2) CH_3I (1.0 eq)

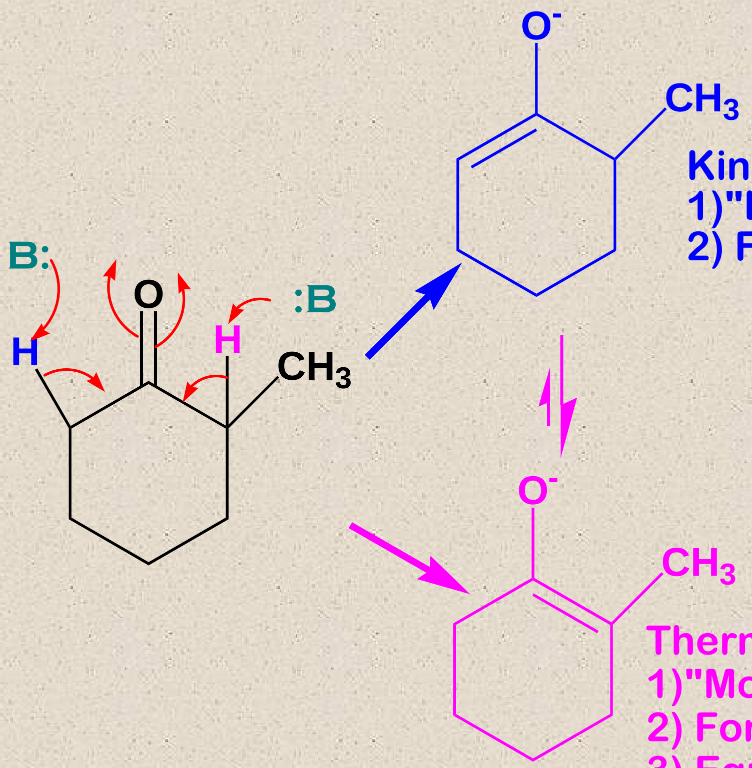
45%

10%

17%

3%

KINETIC VS THERMODYNAMIC ENOLATES



Kinetic Enolate
1)"Less" Stable
2) Form with LDA

Thermodynamic Enolate
1)"More" Stable
2) Form with OH^- or OR^-
3) Equilibrating conditions

Crossed Enolate Reactions using LDA

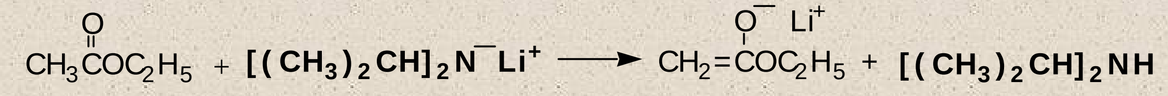
- With a strong enough base, enolate anion formation can be driven to completion.
- The base most commonly used for this purpose is lithium diisopropylamide, LDA.
- LDA is prepared by dissolving diisopropylamine in THF and treating the solution with butyllithium.

$$[(CH_3)_2CH]_2NH + CH_3(CH_2)_3Li \longrightarrow [(CH_3)_2CH]_2N^{-}Li^{+} + CH_3(CH_2)_2CH_3$$

Diisopropylamine **(pK_a 40** **(stronger acid)**	**Butyllithium** **(stronger base)**	**Lithium diisopropylamde** **(weaker base)**	**Butane** **pK_a 50** **(weaker acid)**

Crossed Enolate Reactions using LDA

- Using a molar equivalent of LDA converts an aldehyde, ketone, or ester completely to its corresponding enolate anion.

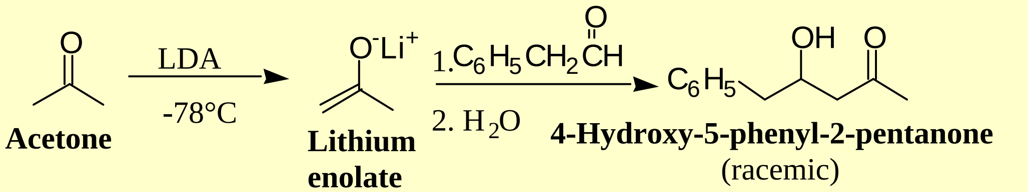


$$CH_3\overset{O}{\overset{\|}{C}}OC_2H_5 + [(CH_3)_2CH]_2N^{-}Li^{+} \longrightarrow CH_2{=}\overset{O^{-}\ Li^{+}}{\overset{|}{C}}OC_2H_5 + [(CH_3)_2CH]_2NH$$

Ethyl acetate **pK_a 23** **(stronger acid)**	**Lithium** **diisopropylamide** **(stronger base)**	**Lithium enolate** **(weaker base)**	**Diisopropylamine** **pK_a40** **(weaker acid)**

Crossed Enolate Reactions using LDA

- The crossed aldol reaction between acetone and an aldehyde can be carried out successfully by adding acetone to one equivalent of LDA to preform its enolate anion:



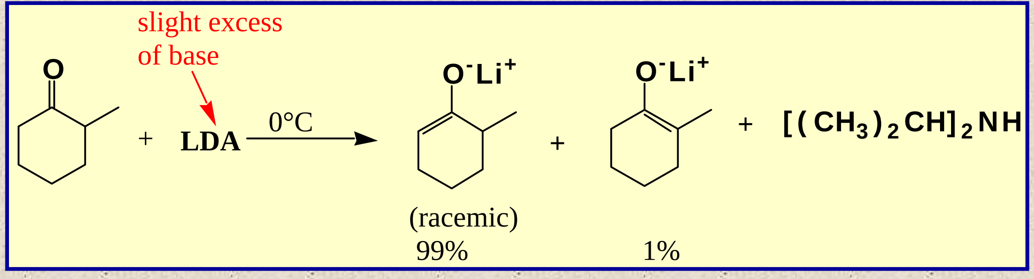
- which is then treated with the aldehyde.

Crossed Enolate Reactions using LDA

- For ketones with two sets of nonequivalent α-hydrogens, is formation of the enolate anion regioselective?
  - The answer is that a high degree of regioselectivity exists and that it depends on experimental conditions.

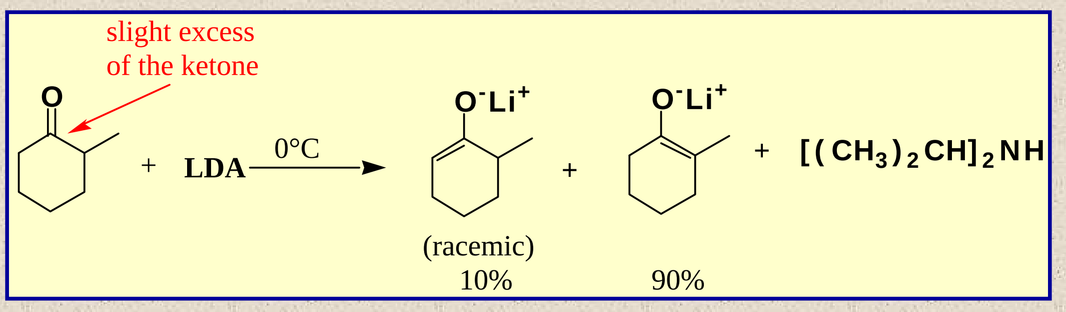
Crossed Enolate Reactions using LDA

– When 2-methylcyclohexanone is treated with a slight excess of LDA, the enolate is almost entirely the less substituted enolate anion.



Crossed Enolate Reactions using LDA

- When 2-methylcyclohexanone is treated with LDA under conditions in which the ketone is in slight excess, the product is richer in the more substituted enolate.

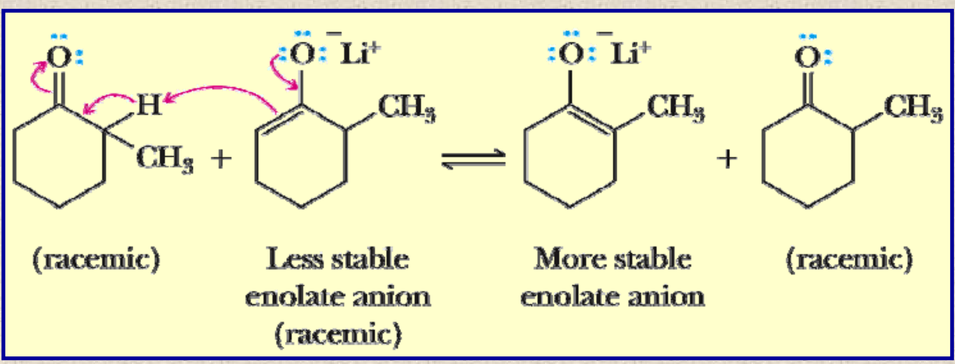


Crossed Enolate Reactions using LDA

- The most important factor determining the composition of the enolate anion mixture is whether the reaction is under kinetic (rate) or thermodynamic (equilibrium) control.
- **Thermodynamic Control**: Experimental conditions that permit establishment of equilibrium between two or more products of a reaction. The composition of the mixture is determined by the relative stabilities of the products.

Crossed Enolate Reactions using LDA

- Equilibrium among enolate anions is established when the ketone is in slight excess, a condition under which it is possible for proton-transfer reactions to occur between an enolate anion and an α-hydrogen of an unreacted ketone. Thus, equilibrium is established between alternative enolate anions.



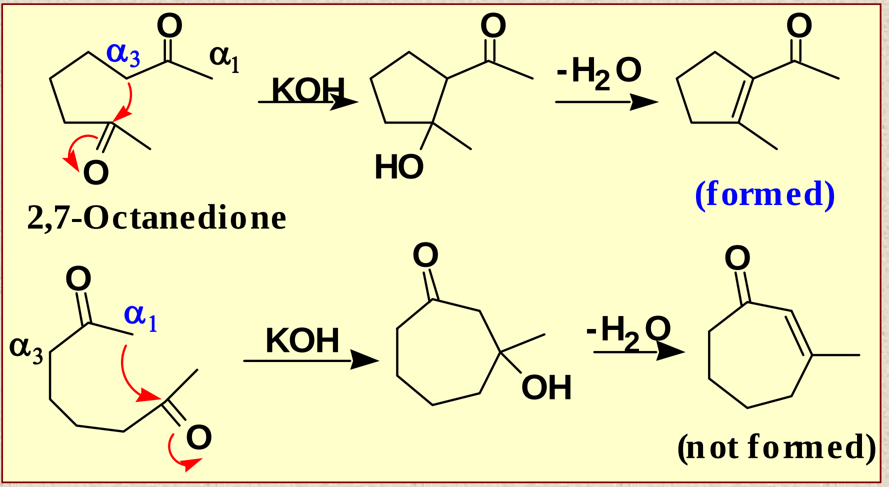
Crossed Enolate Reactions using LDA

- **Kinetic control:** Experimental conditions under which the composition of the product mixture is determined by the relative rates of formation of each product.
  - In the case of enolate anion formation, kinetic control refers to the relative rate of removal of alternative α-hydrogens.
  - With the use of a bulky base, the less hindered hydrogen is removed more rapidly, and the major product is the less substituted enolate anion.
  - No equilibrium among alternative structures is set up.

Intramolecular Aldol Reactions

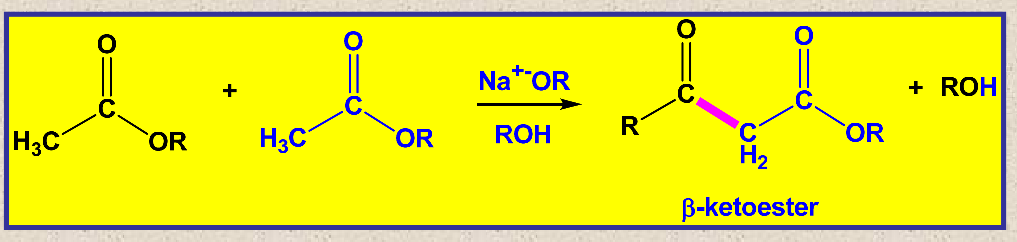
intramolecular aldol reactions are most successful for formation of five- and six-membered rings

consider 2,7-octadione, which has two α-carbons

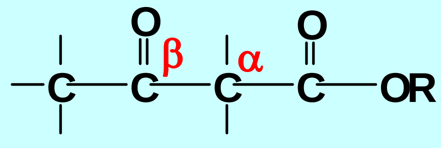


Claisen Condensation

- Esters also form enolate anions which participate in nucleophilic acyl substitution



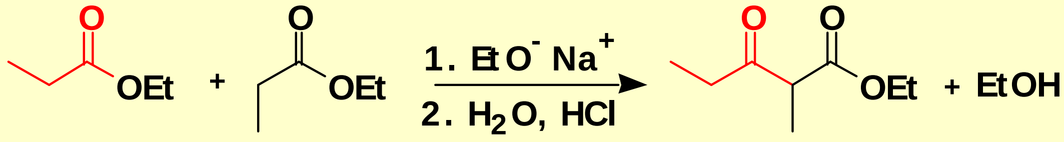
the product of a Claisen condensation is a β-ketoester:



A β-ketoester

Claisen Condensation

– Claisen condensation of ethyl propanoate gives this β-ketoester



Ethyl propanoate

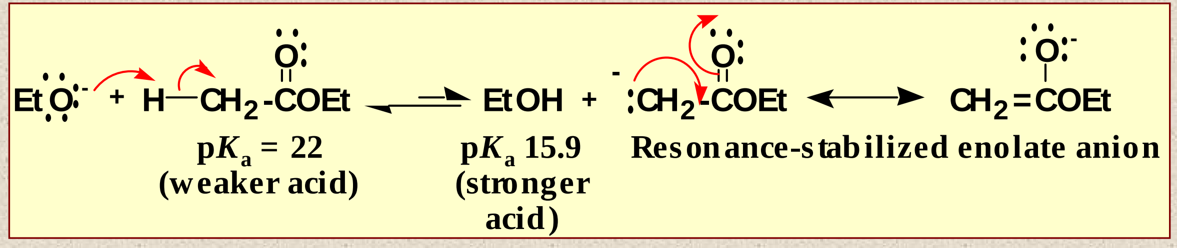
Ethyl propanoate

Ethyl 2-methyl-3-oxopentanoate (racemic)

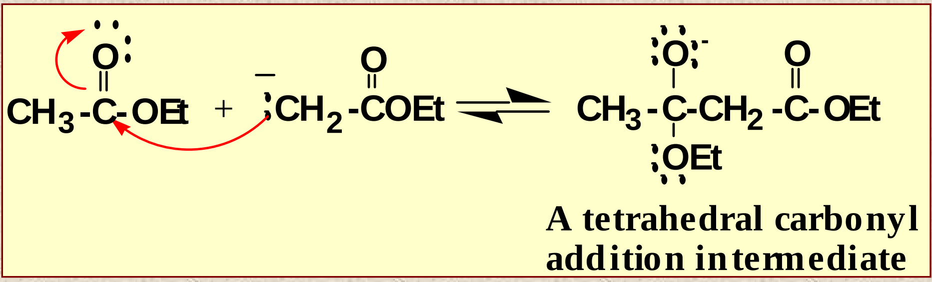
Nota bene: the base should be the alkoxide of the ester group (This will overcome trans-esterification.)

Claisen Condensation

Step 1: formation of an enolate anion

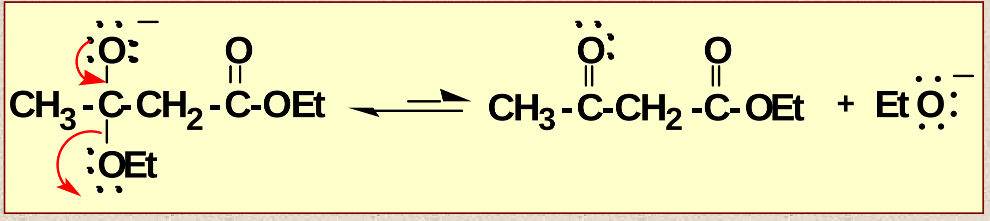


Step 2: attack of the enolate anion on a carbonyl carbon gives a TCAI

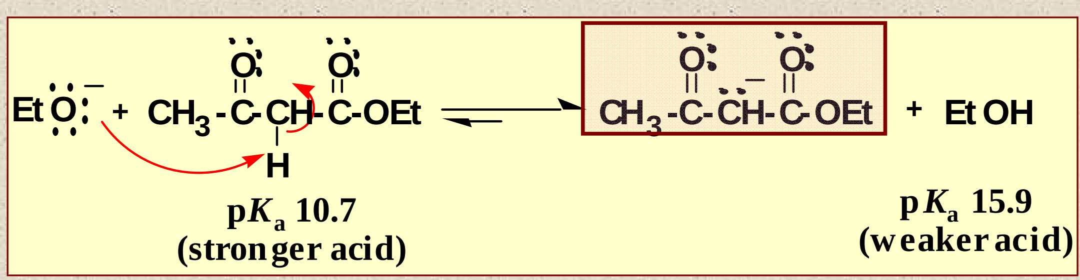


Claisen Condensation

Step 3: collapse of the TCAI gives a β-ketoester and an alkoxide ion:



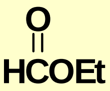
Step 4: an acid-base reaction drives the reaction to completion:



Crossed Claisen Condensations

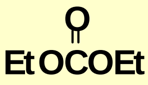
Crossed Claisen condensations between two different esters, each with α-hydrogens, give mixtures of products and are not useful

- crossed Claisen condensations are useful, if there is an appreciable difference in reactivity between the two esters; when one of them has no α-hydrogens



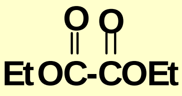
$H\overset{O}{\overset{\|}{C}}OEt$

Ethyl formate



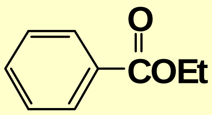
$EtO\overset{O}{\overset{\|}{C}}OEt$

Diethyl carbonate



$EtO\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}OEt$

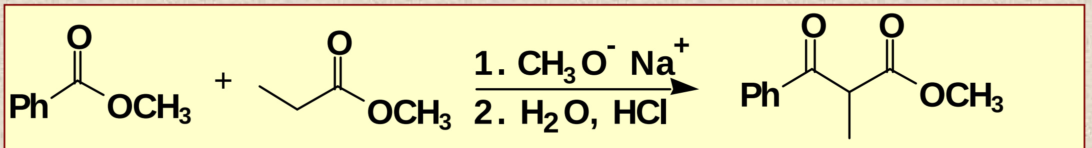
Diethyl ethanedioate (Diethyl oxalate)



Ethyl benzoate

Crossed Claisen Condensations

- the ester with no α-hydrogens is generally used in excess



Methyl benzoate

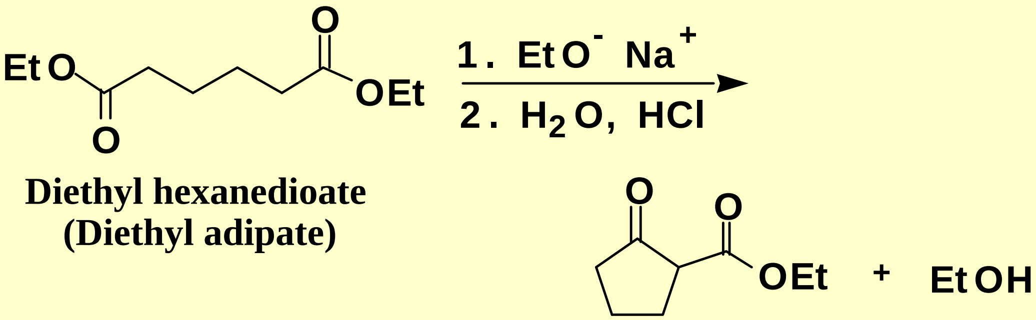
Methyl propanoate

Methyl 2-methyl-3-oxo-3-phenylpropanoate (racemic)

Only this enolate can be formed

Dieckman Condensation

- An intramolecular Claisen condensation



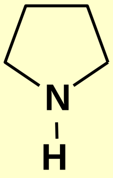
Diethyl hexanedioate
(Diethyl adipate)

Ethyl 2-oxocyclo-
pentanecarboxylate

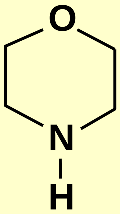
Enamines

Enamines are formed by the reaction of a **2° amine with the carbonyl group of an aldehyde or ketone**

the 2° amines most commonly used to prepare enamines are pyrrolidine and morpholine:

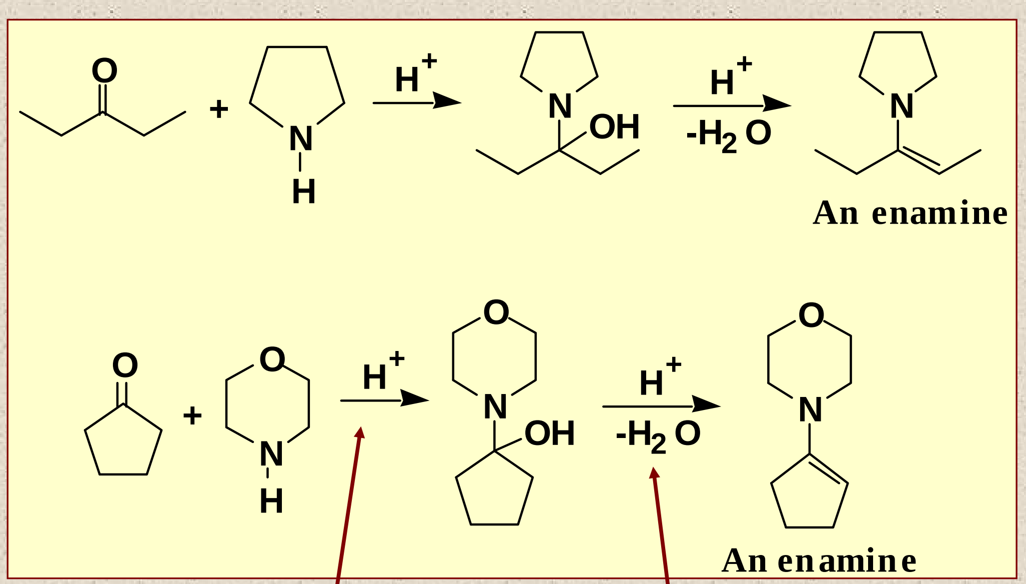


Pyrrolidine



M orpholine

Preparation of Enamines



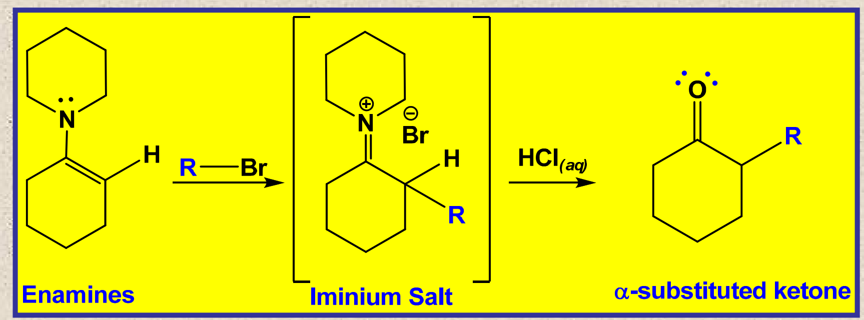
Acid catalyst is usually TsOH; azeotropic removal of H_2O.

See Chapter 16 for details

Enamines-Alkylation

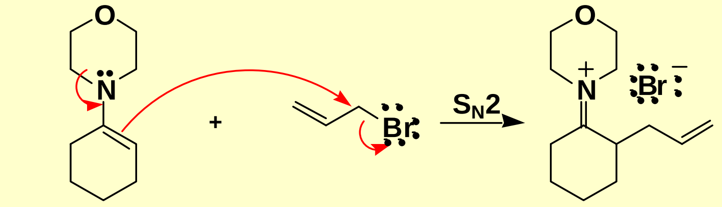
The value of enamines is that the β-carbon is nucleophilic (**same C that was α to carbonyl**)

- – enamines undergo S_N2 reactions with methyl and 1° haloalkanes, α-haloketones, and α-haloesters



Enamines-Alkylation

treatment of the enamine with 1 eq of an alkylating agent gives an iminium halide:

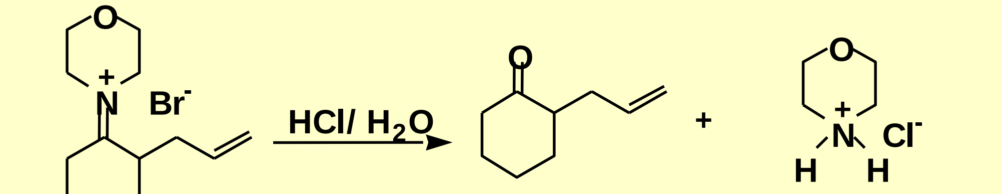


The morpholine enamine of cyclohexanone

3-Bromopropene (Allyl bromide)

An iminium bromide (racemic)

hydrolysis of the iminium halide (salt) gives the alkylated aldehyde or ketone:

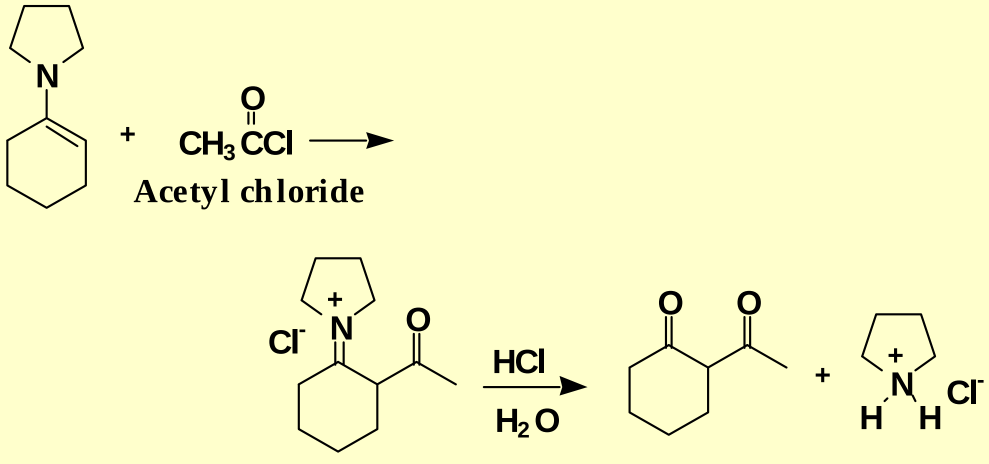


2-Allylcyclohexanone

Morpholinium chloride

Enamines-Acylation

enamines undergo acylation when treated with acid chlorides and acid anhydrides



Acetyl chloride

An iminium chloride (racemic)

2-Acetylcyclohexanone (racemic)

Synthetic Advantages of Enamines vs Enolates

1) Avoids proton transfer.

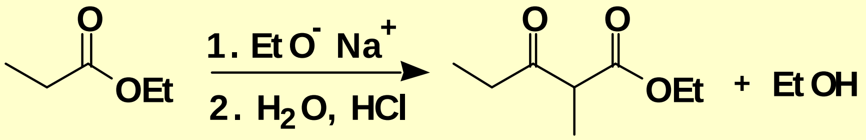
2) Regiochemistry of alkylation can be controlled. (For un-symmetric ketones)

3) Avoids polyalkylation.

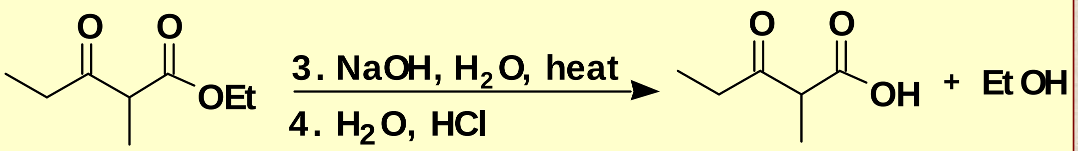
4) Avoids O-alkylation.

Claisen condensations as routes to ketones

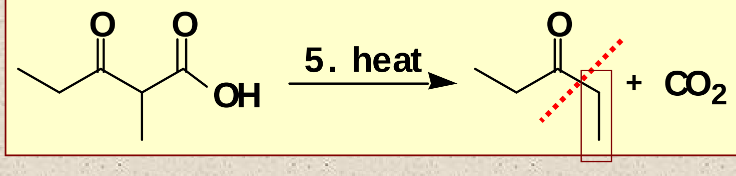
Reactions 1 & 2: Claisen condensation followed by acidification



Reactions 3 & 4: Saponification and acidification



Reaction 5: thermal decarboxylation



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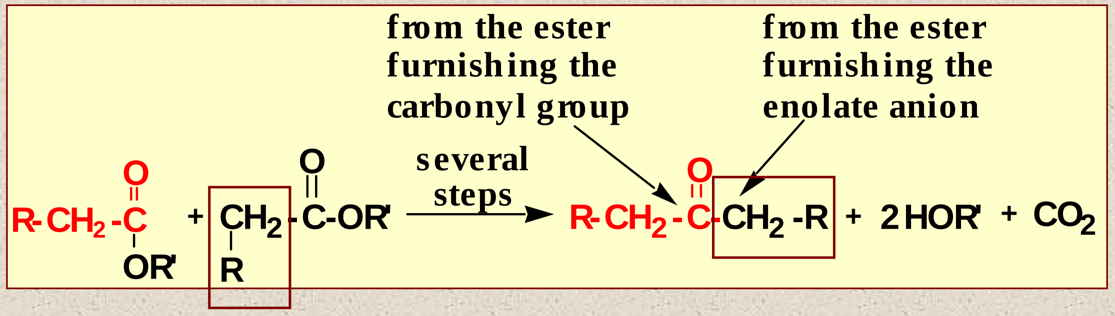
Claisen condensations as routes to ketones

The result of Claisen condensation, saponification, acidification, and decarboxylation is a ketone:



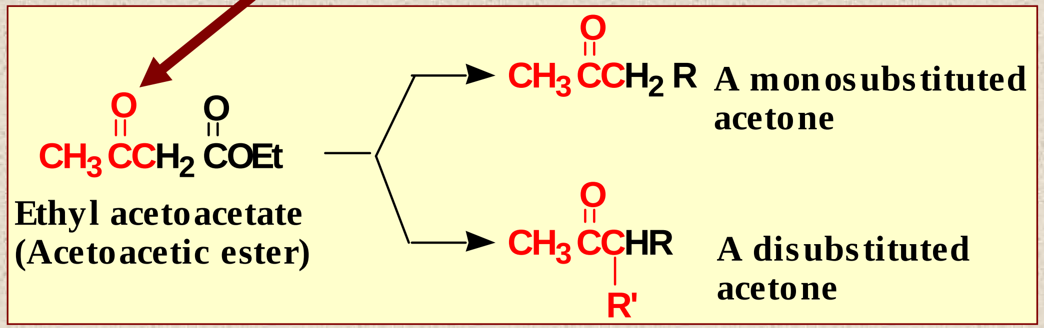
$$R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{\underset{OR'}{C}} + \boxed{\underset{R}{CH_2}}\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR' \xrightarrow{\text{several steps}} R\text{-}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}\boxed{CH_2\text{-}R} + 2\,HOR' + CO_2$$

from the ester furnishing the carbonyl group

from the ester furnishing the enolate anion

Acetoacetic Ester Synthesis

The acetoacetic ester (AAE) synthesis is useful for the preparation of mono- and disubstituted acetones of the following types



$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}OEt$$

Ethyl acetoacetate
(Acetoacetic ester)

$$CH_3\overset{\overset{O}{\|}}{C}CH_2R$$

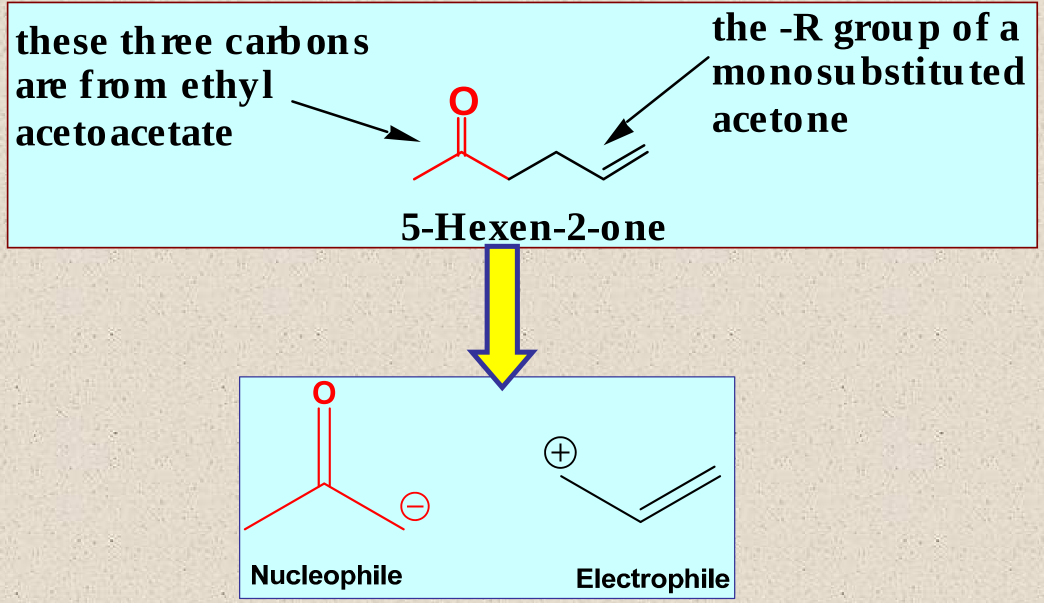
A monosubstituted acetone

$$CH_3\overset{\overset{O}{\|}}{C}\underset{R'}{CH}R$$

A disubstituted acetone

Acetoacetic Ester Synthesis

– consider the AAE synthesis of this target molecule, which is a monosubstituted acetone



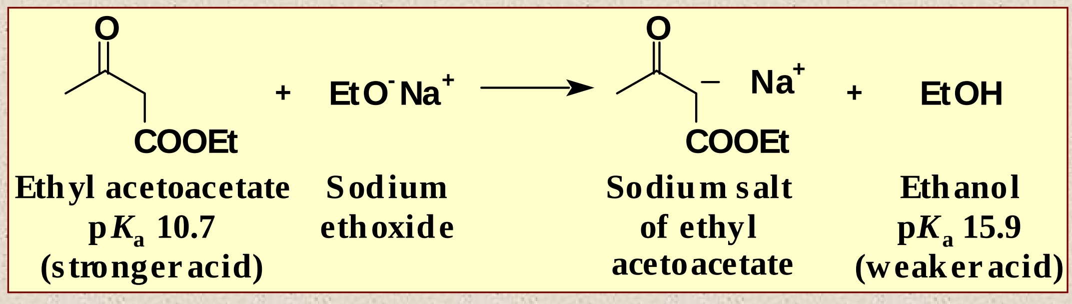
these three carbons are from ethyl acetoacetate

the -R group of a monosubstituted acetone

5-Hexen-2-one

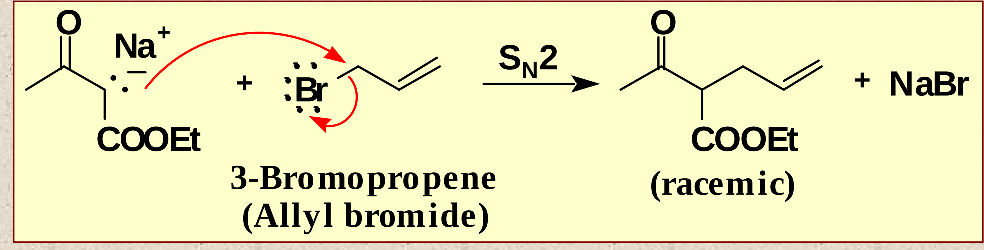
Acetoacetic Ester Synthesis

– Step 1: formation of the enolate anion of AAE



Ethyl acetoacetate pK_a 10.7 (stronger acid)	Sodium ethoxide	Sodium salt of ethyl acetoacetate	Ethanol pK_a 15.9 (weaker acid)

– Step 2: alkylation with allyl bromide

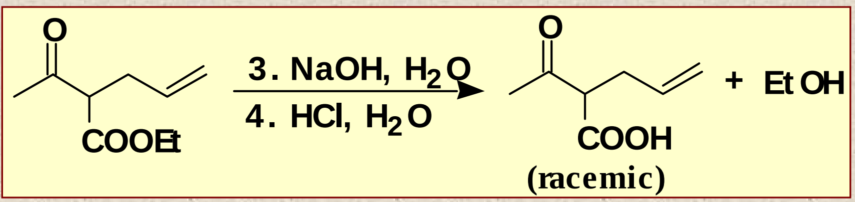


3-Bromopropene
(Allyl bromide)

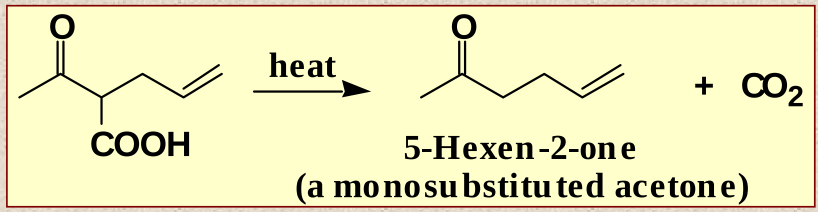
(racemic)

Acetoacetic Ester Synthesis

– Steps 3 & 4 saponification followed by acidification

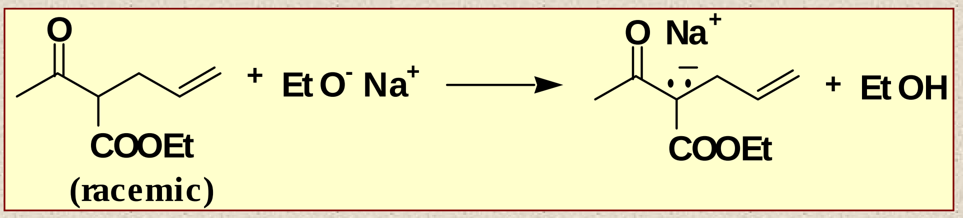


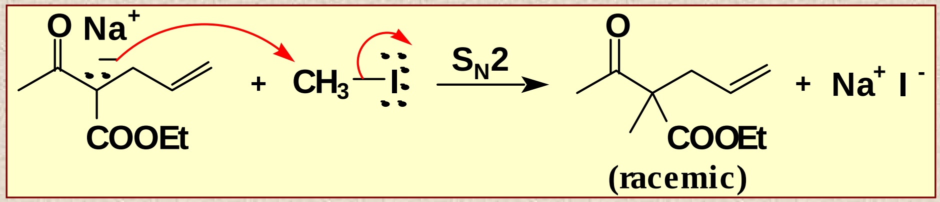
– Step 5: thermal decarboxylation

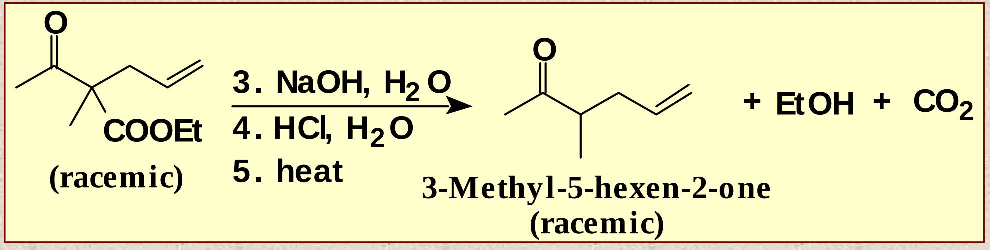


Acetoacetic Ester Synthesis

– to prepare a **disubstituted acetone**, treat the monoalkylated AAE with a second mole of base, etc







Acetoacetic Ester Synthesis

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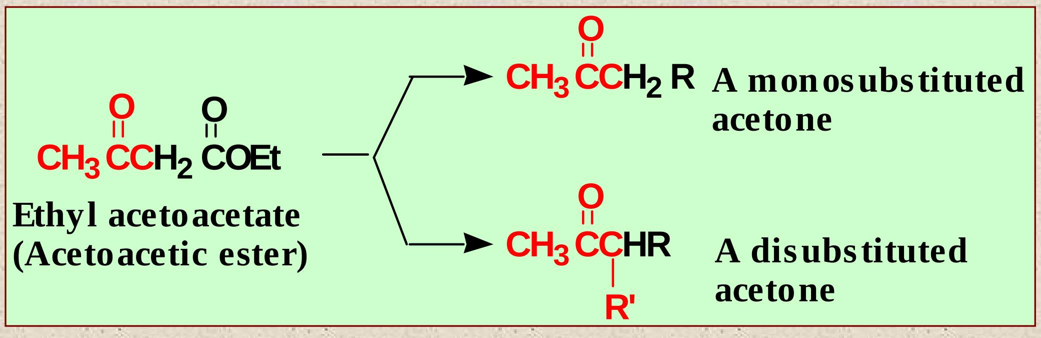
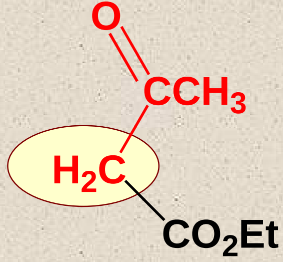
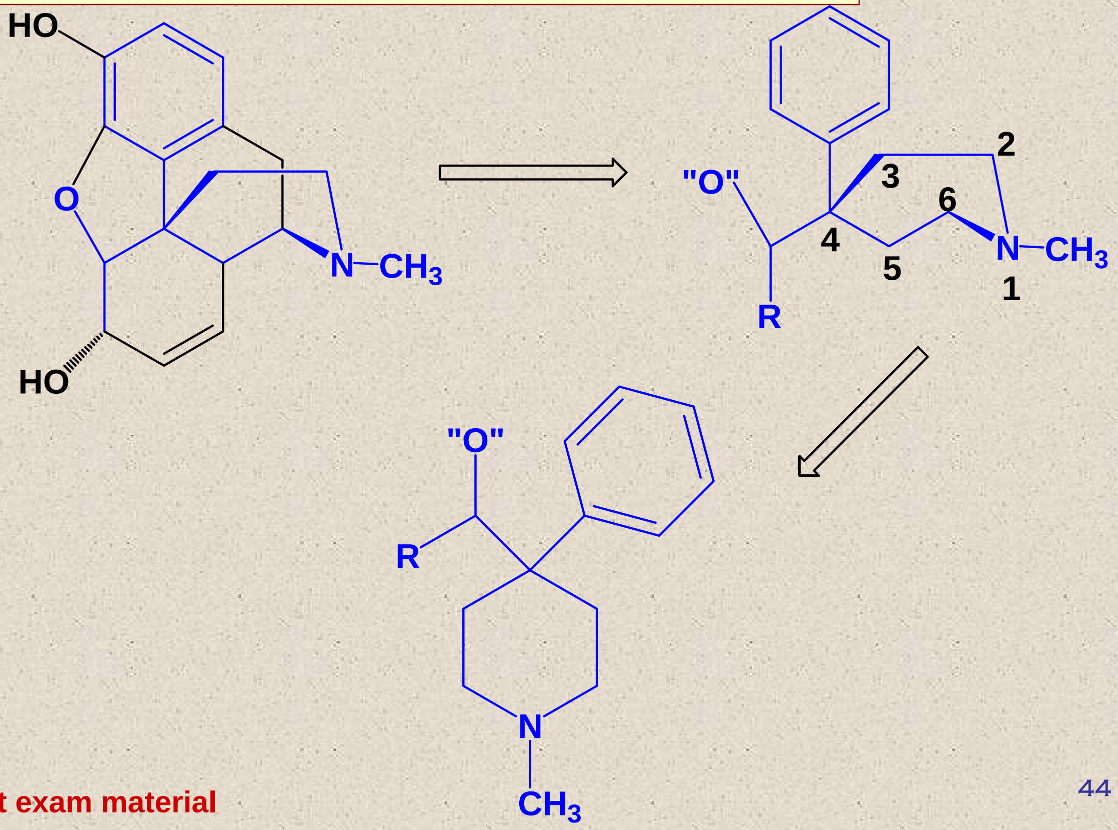


These types of reactions involve active (i.e. acidic) methylene units as the nucleophilic component.

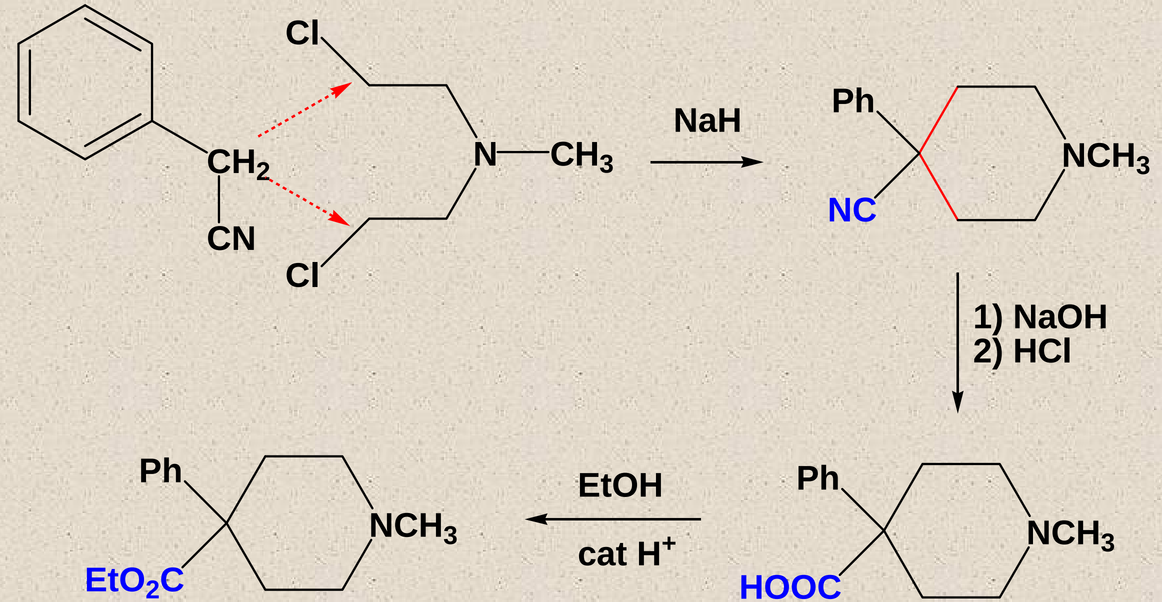


Application: Synthesis of 4,4-Disubstituted Piperidines



Not exam material

Application: Synthesis of 4,4-Disubstituted Piperidines



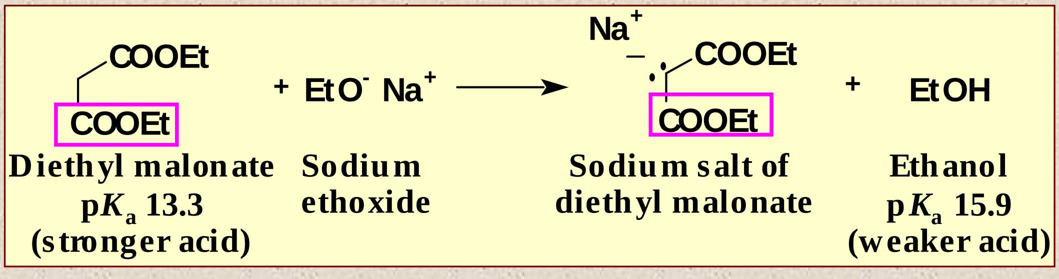
Meperidine

Demerol ®

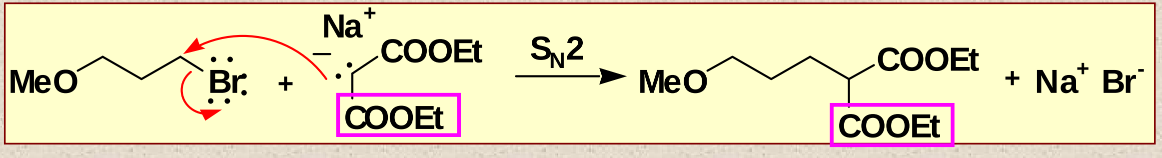
Not exam material

Malonic Ester Synthesis

- treat malonic ester with an alkali metal alkoxide

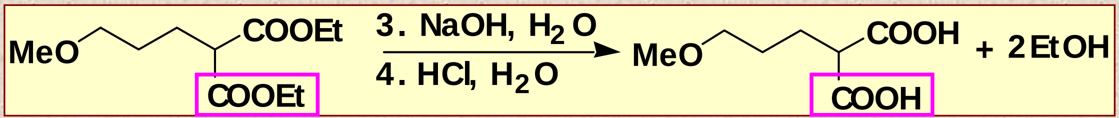


- alkylate with 1-bromo-3-methoxy propane

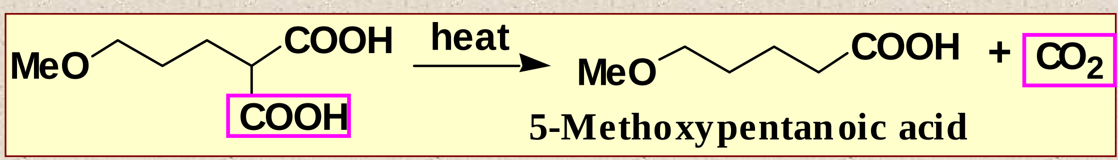


Malonic Ester Synthesis

– saponify and acidify



– decarboxylation

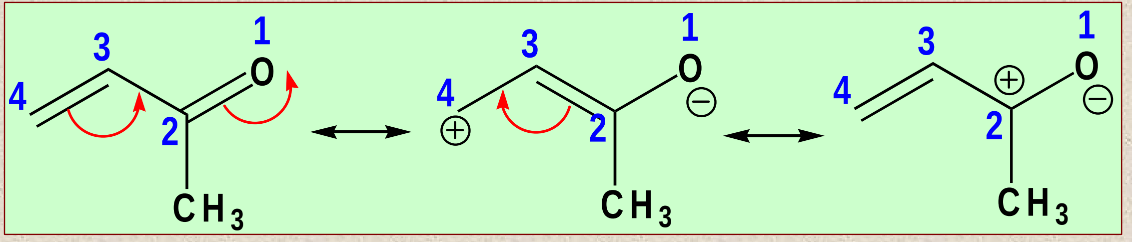


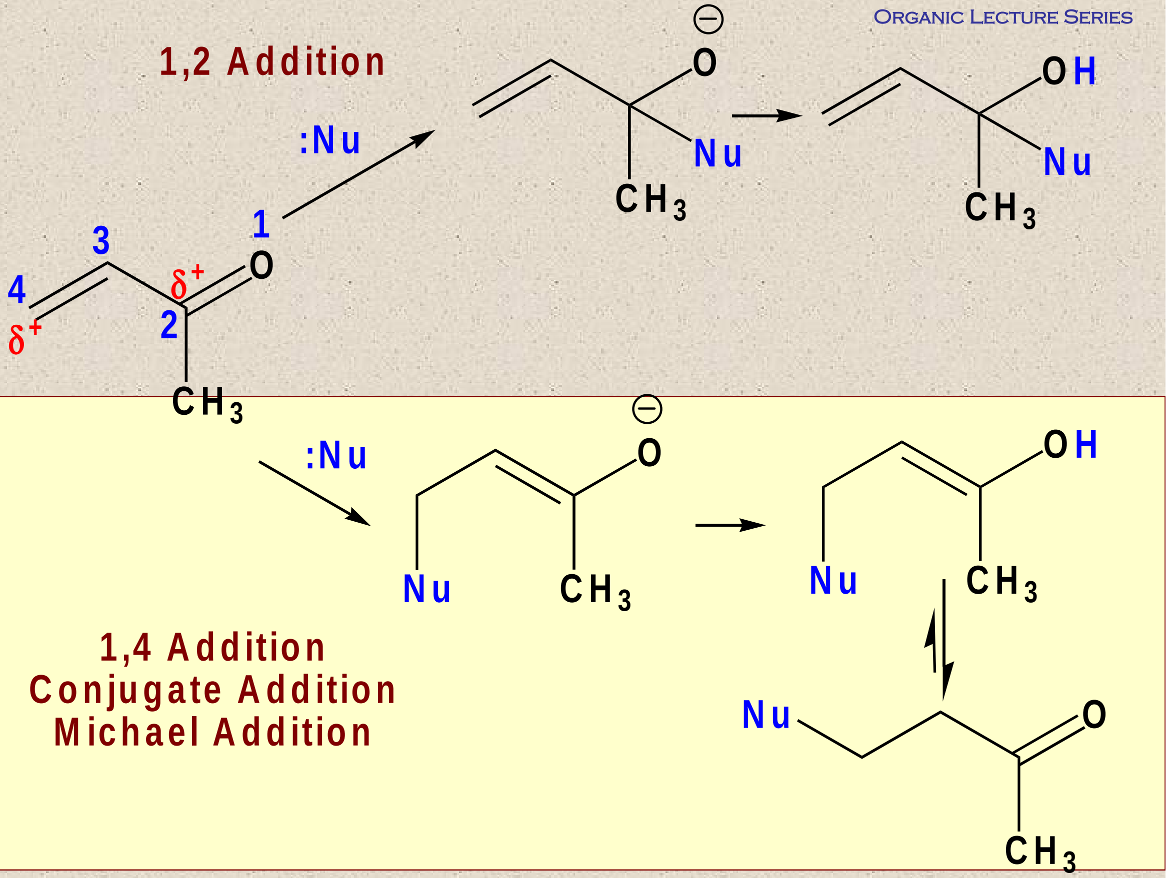
5-Methoxypentanoic acid

Addition to α,β-unsaturated Carbonyls

When the carbonyl group is conjugated with an alkene, the two groups can act in tandem to expand synthetic utility.

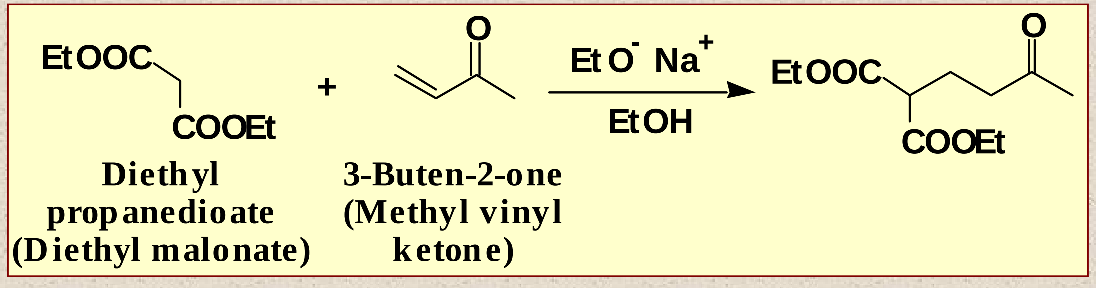
α,β-unsaturated carbonyl compounds can exhibit properties of both the carbonyl and alkene group:





Michael Reaction

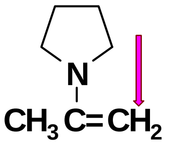
- **Michael reaction:** the nucleophilic addition of an enolate anion to an α,β-unsaturated carbonyl compound (1,4 addition)
  - Example:



Diethyl propanedioate (Diethyl malonate)

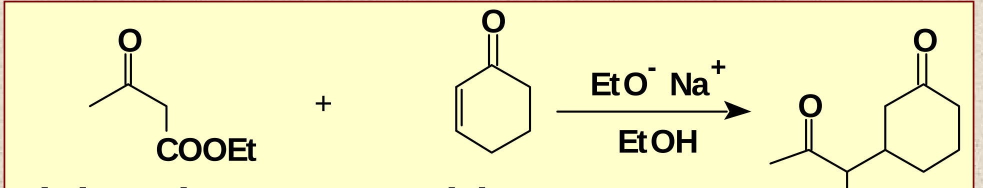
3-Buten-2-one (Methyl vinyl ketone)

Michael Acceptors & Nucleophiles

These Types of α,β-Unsaturated Compounds are Nucleophile Acceptors in Michael Reactions		These Types of Compounds Provide Effective Nucleophiles for Michael Reactions	
$CH_2{=}CH\overset{\overset{O}{\|}}{C}H$	Aldehyde	$CH_3\overset{\overset{O}{\|}}{C}\boxed{CH_2}\overset{\overset{O}{\|}}{C}CH_3$	β-Diketone
$CH_2{=}CH\overset{\overset{O}{\|}}{C}CH_3$	Ketone	$CH_3\overset{\overset{O}{\|}}{C}\boxed{CH_2}\overset{\overset{O}{\|}}{C}OEt$	β-Ketoester
$CH_2{=}CH\overset{\overset{O}{\|}}{C}OEt$	Ester	$CH_3\overset{\overset{O}{\|}}{C}\boxed{CH_2}CN$	β-Ketonitrile
$CH_2{=}CH\overset{\overset{O}{\|}}{C}NH_2$	Amide	$EtO\overset{\overset{O}{\|}}{C}\boxed{CH_2}\overset{\overset{O}{\|}}{C}OEt$	β-Diester
$CH_2{=}CHC{\equiv}N$	Nitrile		Enamine
$CH_2{=}CHNO_2$	Nitro compound		
		NH_3, RNH_2, R_2NH	Amine

Michael Reaction

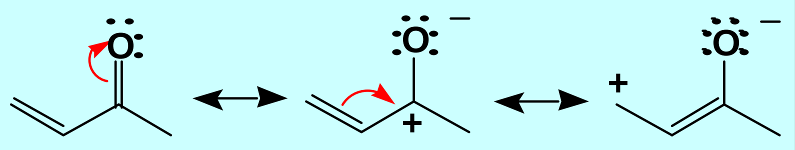
Example:



Ethyl 3-oxobutanoate (Ethyl acetoacetate)

2-Cyclohexenone

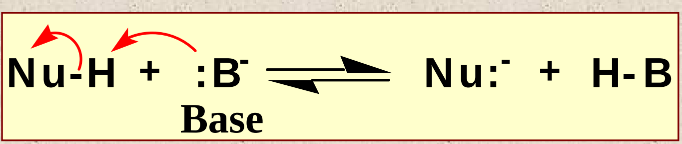
- the double bond of an α,β-unsaturated carbonyl compound is activated for nucleophilic attack:



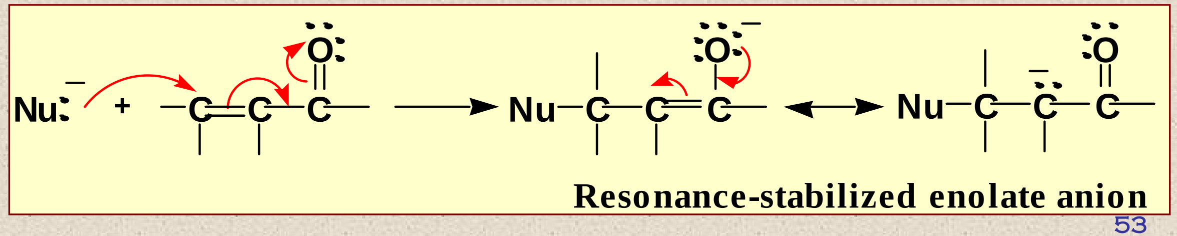
Michael Reaction

- Mechanism

Step 1: proton transfer to the base

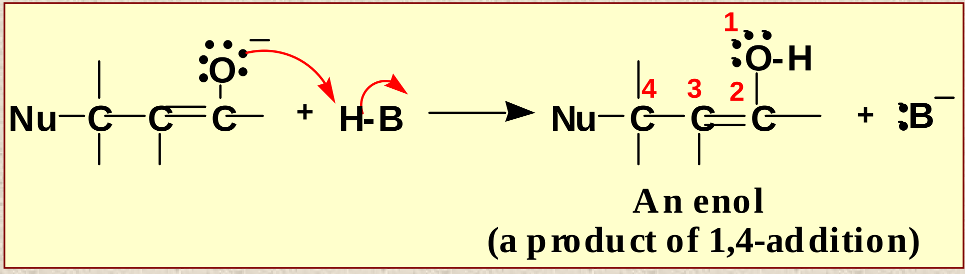


Step 2: addition of Nu:⁻ to the β carbon of the α,β-unsaturated carbonyl compound

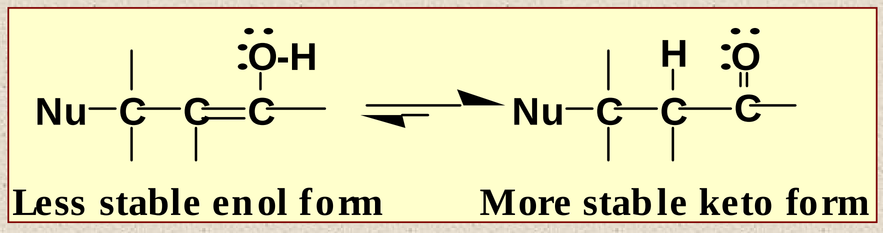


Michael Reaction

Step 3: proton transfer to HB gives an enol



Step 4: tautomerism of the less stable enol form to the more stable keto form

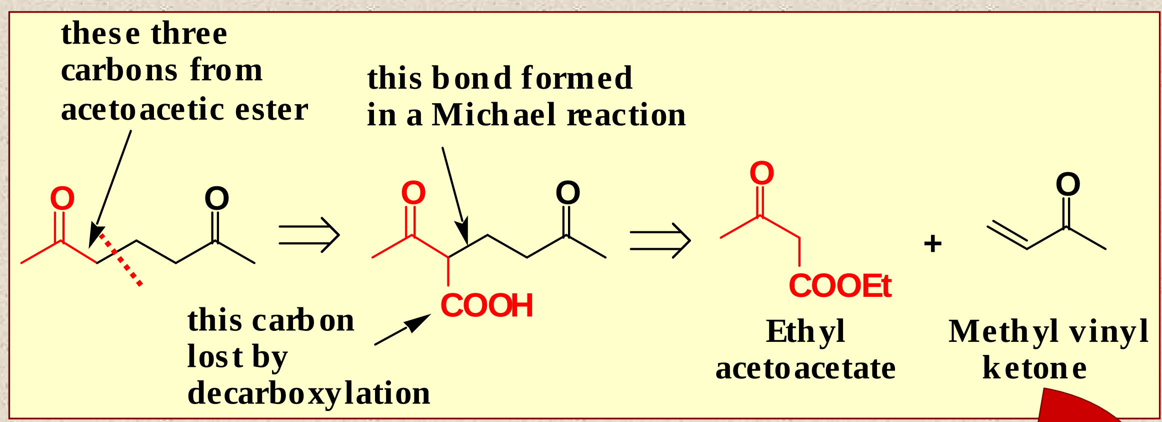


Michael Reaction

A final note about nucleophilic addition to α,β-unsaturated carbonyl compounds:

- ☐ resonance-stabilized enolate anions and enamines are **weak nucleophiles**,
- ☐ react slowly with α,β-unsaturated carbonyl compounds
- ☐ give 1,4-addition products

Retrosynthesis of 2,6-Heptadione



these three carbons from acetoacetic ester

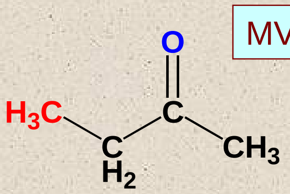
this bond formed in a Michael reaction

this carbon lost by decarboxylation

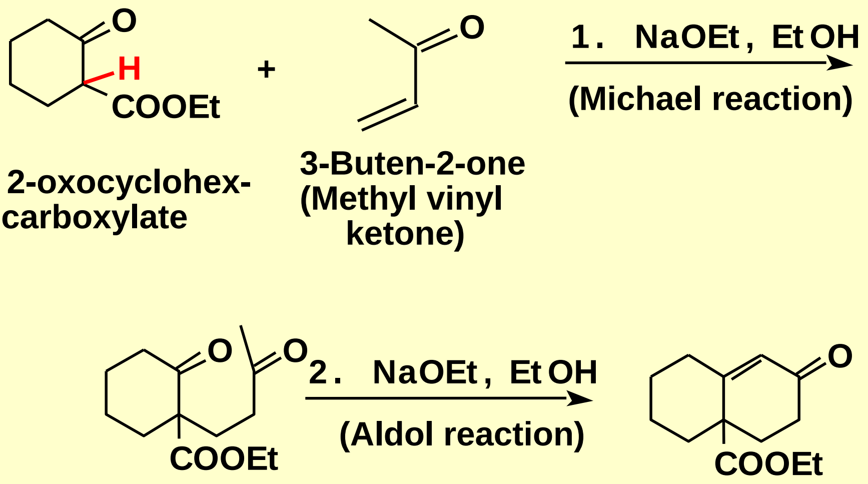
Ethyl acetoacetate

Methyl vinyl ketone

MVK is the reagent to add a 2-oxobutyl side chain



Michael-Aldol in Combination: The Robinson Ring Annulation



Ethyl 2-oxocyclohexanecarboxylate

3-Buten-2-one (Methyl vinyl ketone)