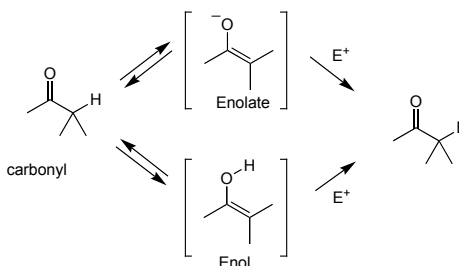
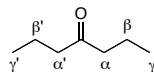


Chapter 20: Enols and Enolates



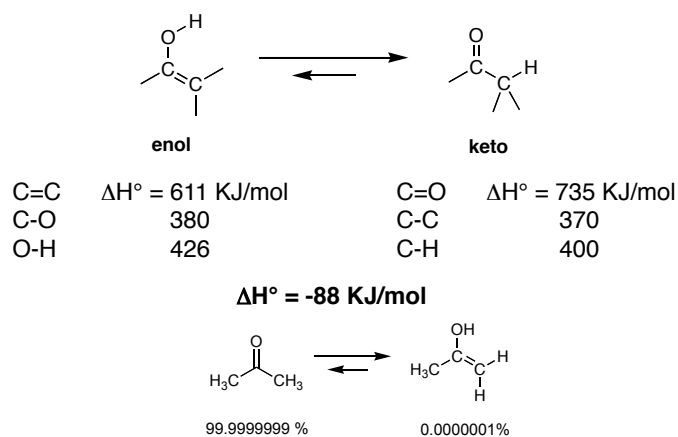
20.1: Enol Content and Enolization



188

Tautomers: isomers, usually related by a proton transfer, that are in equilibrium.

Keto-enol tautomeric equilibrium lies heavily in favor of the keto form (see Table 20.1, p. 821).



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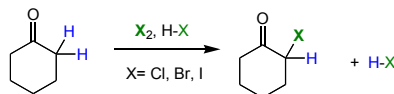
Enolization is acid- and base-catalyzed (p. 823):

Base-catalyzed mechanism:

Acid-catalyzed mechanism:

190

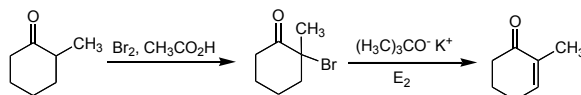
α-Halogenation of Aldehydes and Ketones - α-proton of aldehydes and ketones can be replaced with a -Cl, -Br, or -I (-X) with Cl₂, Br₂, or I₂, (X₂) respectively. The reaction proceeds through an enol.



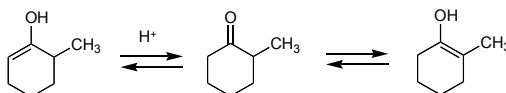
Rate = k [ketone/aldehyde] [H⁺]
rate dependent on enol formation and not [X₂]

α,β-unsaturated ketones and aldehydes:

α-bromination followed by elimination

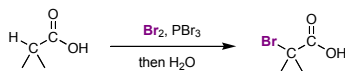


Why is one enol favored over the other?



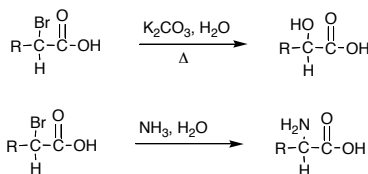
191

Hell-Volhard-Zelinsky Reaction – α-halogenation of carboxylic acids:



Mechanism of α-halogenation goes through an acid bromide intermediate. An acid bromide enolizes more readily than a carboxylic acid. Mechanism is analogous to the α-halogenation of aldehydes and ketones

The α-halo carboxylic acid can undergo substitution to give α-hydroxy and α-amino acids.

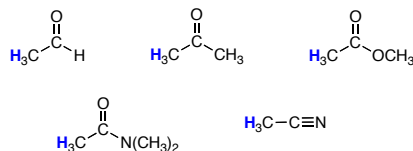


192

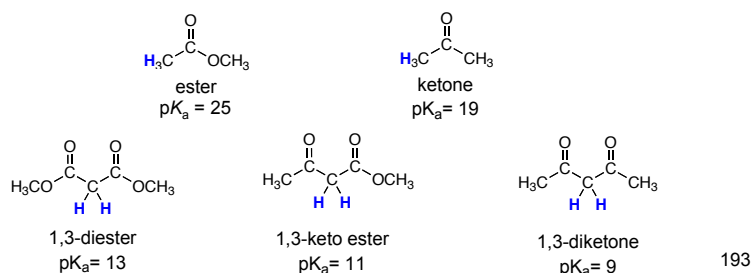
20.2: Enolates

Typical pK_a 's of the α -protons carbonyl compounds
(Table 20.1, p. 825):

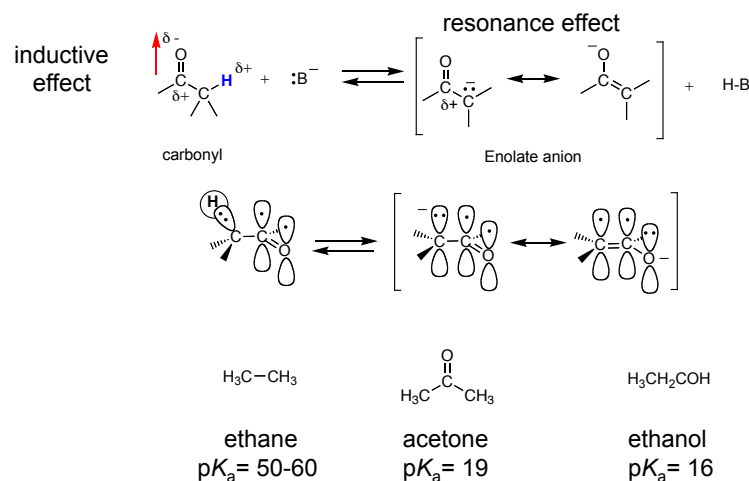
aldehydes	17
ketones	19
esters	25
amides	30
nitriles	25

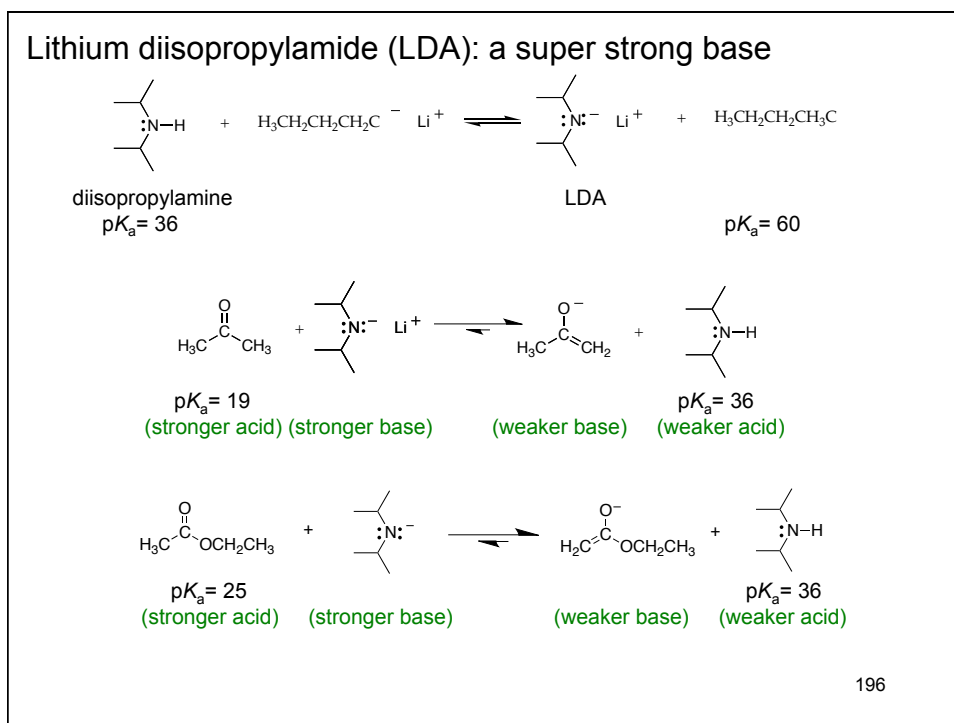
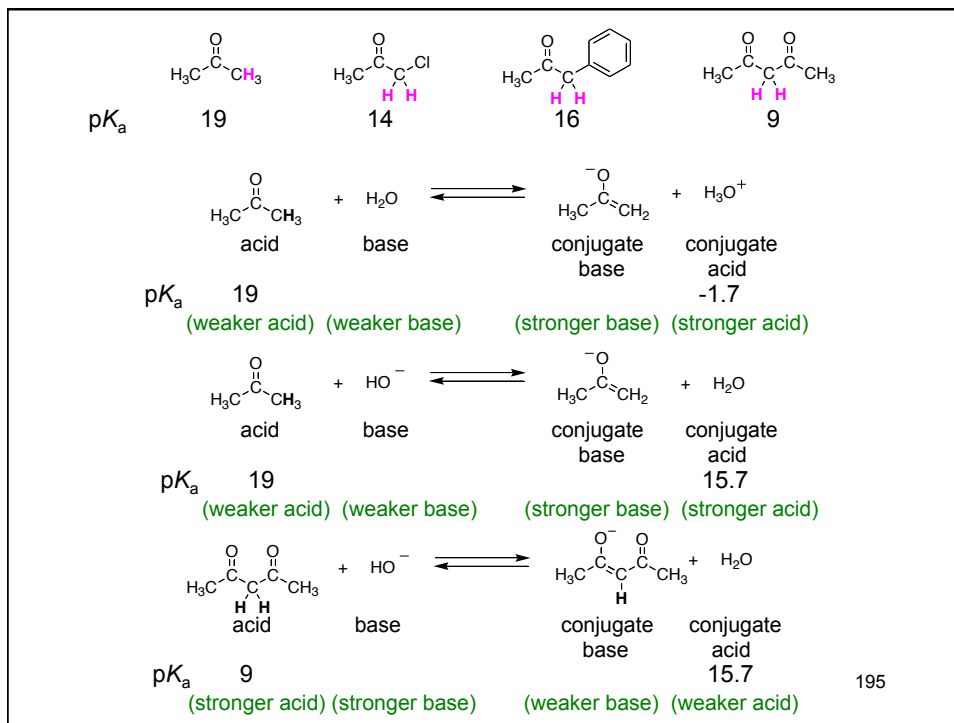


Acidity of 1,3-dicarbonyl compounds

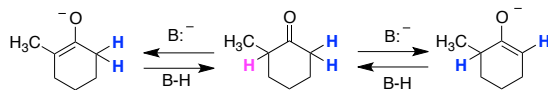


The inductive effect of the carbonyl causes the α -protons to be more acidic. The negative charge of the enolate ion (the conjugate base of the carbonyl compound) is stabilized by resonance delocalization. The pK_a of the α -protons of aldehydes and ketones is in the range of 16-20





Enolate Regiochemistry – deprotonation of unsymmetrical ketones.



More substituted enolate:
thermodynamically more stable

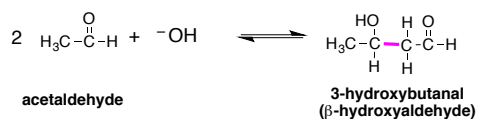
Less substituted enolate:
less hindered, formed
faster kinetically

The more substituted (*thermodynamic*) enolate is formed under reversible conditions ($t\text{BuO}^- \text{K}^+$, $t\text{BuOH}$).

The less substituted (*kinetic*) enolate is formed under irreversible conditions (LDA, THF, -78°C).

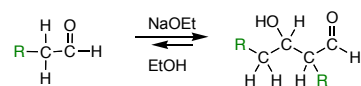
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20.3: The Aldol Condensation – An enolate of one carbonyl (nucleophile) reacts with the carbonyl carbon (electrophile) of a second carbonyl compound resulting in the formation of a new C–C bond. Mechanism of the base-catalyzed aldol reaction (Mechanism 20.2, p. 828):

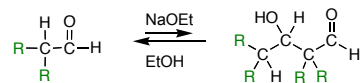


The position of the equilibrium for the aldol reaction is highly dependent on the reaction conditions, substrates, and steric considerations of the aldol product. Low temperature tends to favor the aldol product.

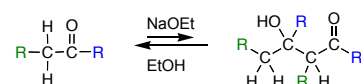
198



aldol reactions involving α -monosubstituted aldehydes are generally favorable



aldol reactions involving α,α -disubstituted aldehydes are generally unfavorable



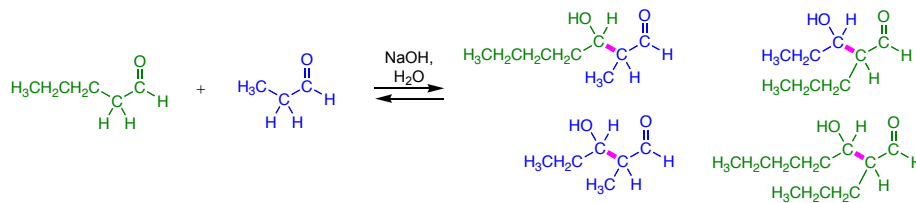
aldol reactions involving ketones are generally unfavorable

The aldol product can undergo acid- or base-catalyzed dehydration to an α,β -unsaturated carbonyl. The dehydration is essentially irreversible. The dehydration is favored at higher temperatures. (mechanism, p. 829)

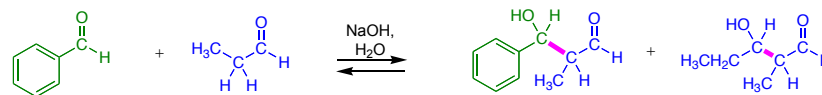
199

20.4: Mixed and Directed Aldol Reactions –

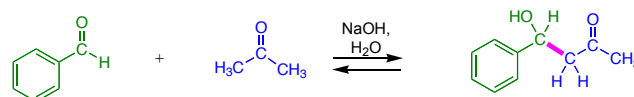
Mixed aldol reaction between two different carbonyl compounds – four possible products (not very useful)



Aldehydes with no α -protons can only act as the electrophile

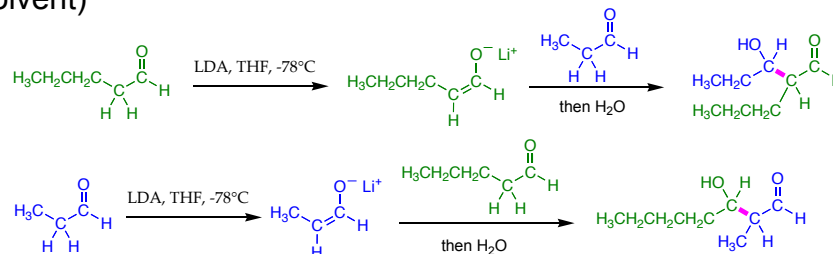


Preferred reactivity

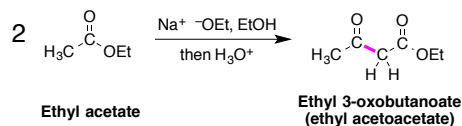


200

Directed aldol reaction – Discrete generation of an enolate with lithium diisopropyl amide (LDA) under aprotic conditions (THF as solvent)



20.5: Acylation of Enolates: The Claisen Condensation Reaction. Base-promoted condensation of two esters to give a β -keto-ester product

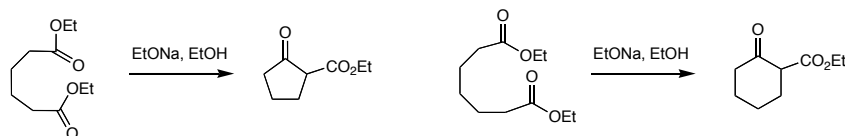


201

The mechanism of the Claisen condensation (Mechanism 20.3, p. 834) is a base promoted nucleophilic acyl substitution of an ester by an ester enolate and is related to the mechanism of the aldol reaction.

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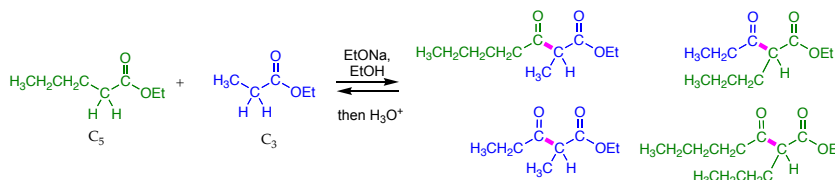
The Dieckmann Cyclization: An intramolecular Claisen Condensation. The Dieckmann Cyclization works best with 1,6-diester, to give a 5-membered cyclic β -keto ester product, and 1,7-diester to give 6-membered cyclic β -keto ester product.



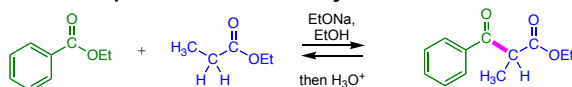
Mechanism: same as the Claisen Condensation

203

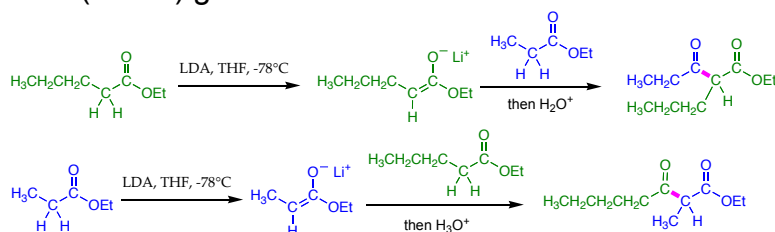
Mixed Claisen Condensations. Similar restrictions as the mixed aldol condensation. Four possible products:



Esters with no α -protons can only act as the electrophile

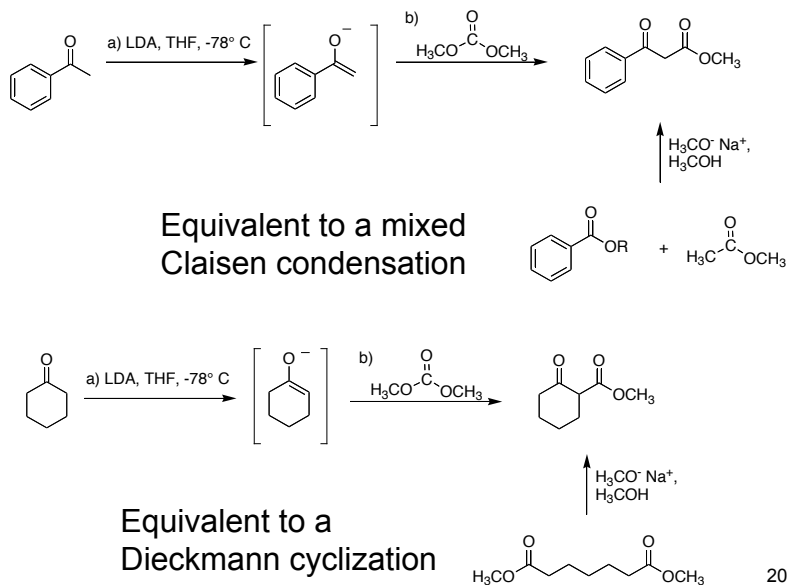


Discrete (*in situ*) generation of an ester enolate with LDA



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Acylation of Ketones with Esters. An alternative to the Claisen condensations and Dieckmann cyclization.

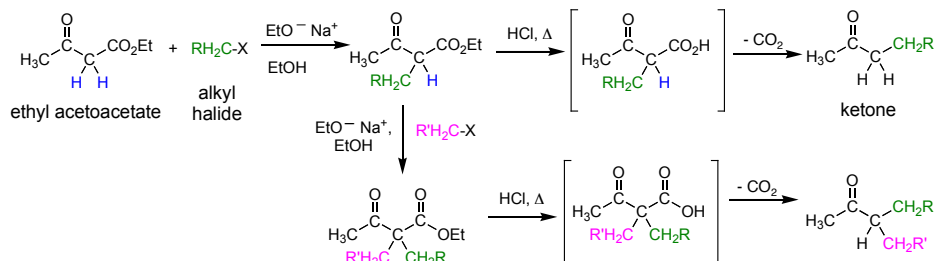


20.6: Alkylation of Enolates: The Acetoacetic Ester and Malonic Ester Syntheses – enolate anions of aldehydes, ketones, and esters can react with other electrophiles such as alkyl halides and tosylates to form a new C-C bonds. The alkylation reaction is an $\text{S}_{\text{N}}2$ reaction.

Reaction works best with the discrete generation of the enolate by LDA in THF, then the addition of the alkyl halide

206

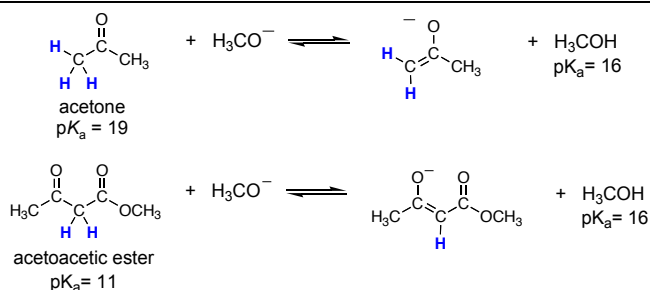
Acetoacetic Ester Synthesis: The anion of ethyl acetoacetate can be alkylated using an alkyl halide (S_N2). The product, a β -keto ester, is then hydrolyzed to the β -keto acid and decarboxylated to the ketone. (Ch. 18.16).



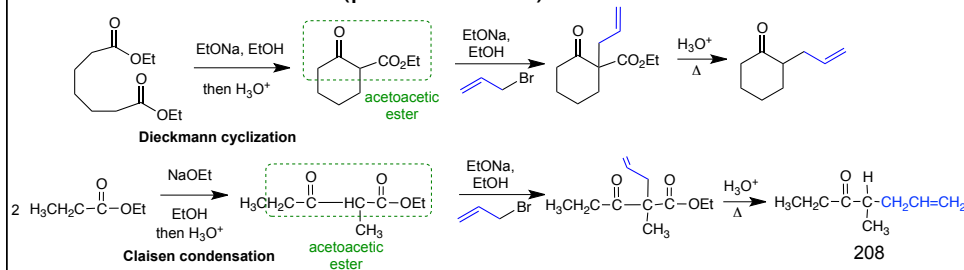
An acetoacetic ester can undergo one or two alkylations to give an α -substituted or α,α -disubstituted acetoacetic ester

The enolates of acetoacetic esters are synthetic equivalents to ketone enolates

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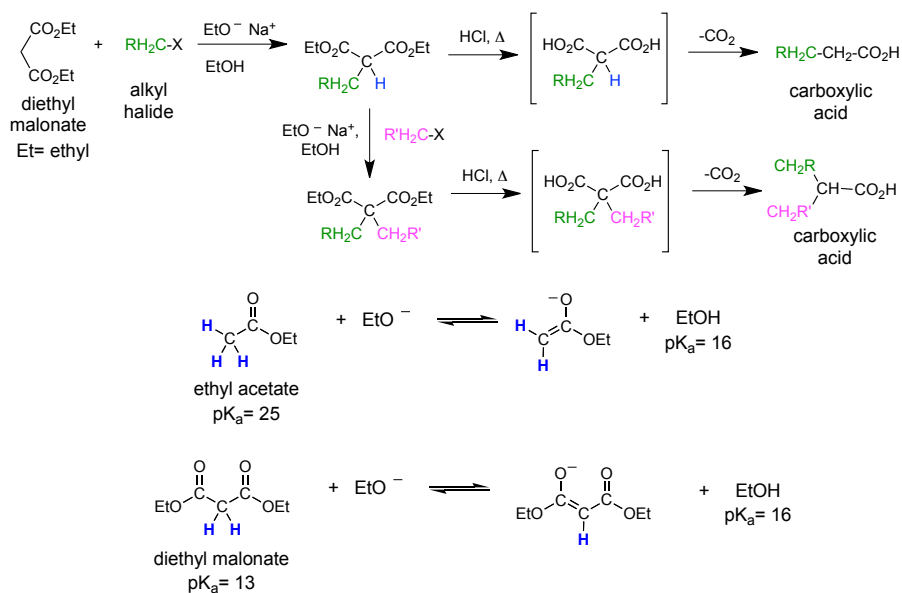


β -Keto esters other than ethyl acetoacetate may be used. The products of a Claisen condensation or Dieckmann cyclization are acetoacetic esters (β -keto esters)



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The Malonic Acid Synthesis:



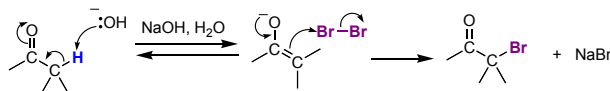
209

Summary:

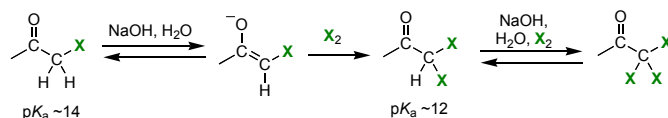
Acetoacetic ester synthesis: equivalent to the alkylation of an ketone (acetone) enolate

Malonic ester synthesis: equivalent to the alkylation of a carboxylic (acetic) acid enolate

20.7: The Haloform Reaction – Carbonyls undergo α -halogenation through base promoted enolate formation (Ch. 20.1).



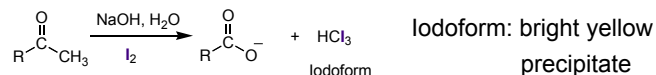
The product is more reactive toward enolization, which results in further α -halogenation of the ketone or aldehyde. For methyl ketone, an α,α,α -trihalomethyl ketone is produced.



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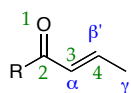
The α,α,α -trihalomethyl ketone reacts with aqueous hydroxide to give the carboxylic acid and haloform (HCX_3) (Mechanism 20.4, p. 842)

Iodoform reaction: chemical tests for a methyl ketone



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20.8: Conjugation Effects in α,β -Unsaturated Aldehydes and Ketones – carbonyls that are conjugated $\text{C}=\text{C}$.



$\text{R} = \text{H}$, α,β -unsaturated aldehyde = enal

$\text{R} \neq \text{H}$, α,β -unsaturated ketone = enone

Conjugation of the $\text{C}=\text{C}$ and $\text{C}=\text{O}$ π -electrons is a stabilizing interaction.

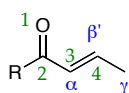
α,β -Unsaturated ketones and aldehydes are prepared by:

- Aldol reactions with dehydration of the aldol
- α -halogenation of a ketone or aldehyde followed by $\text{E}2$ elimination

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1,2 vs 1,4-addition to α,β -unsaturated ketone and aldehydes –

The resonance structures of an α,β -unsaturated ketone or aldehyde suggest two sites for nucleophilic addition; the carbonyl carbon and the β -carbon.



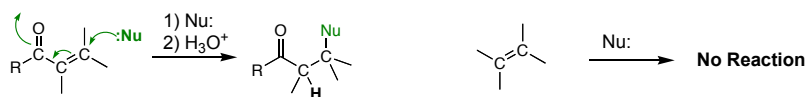
Organolithium reagents, Grignard reagents and LiAlH_4 react with α,β -unsaturated ketone and aldehydes at the carbonyl carbon. This is referred to as *1,2-addition*.

Organocopper reagents, enolates, amines, thiolates, and cyanide react at the β -carbon of α,β -unsaturated ketone and aldehydes. This is referred to a *1,4-addition* or *conjugate addition*.

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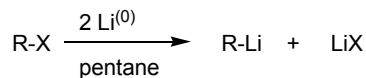
When a reaction can take two possible path, it is said to be under *kinetic control* when the products are reflective of the fastest reaction. The reaction is said to be under *thermodynamic control* when the most stable product is obtained from the reaction. In the case of 1,2- versus 1,4 addition of an α,β -unsaturated carbonyl, 1,2-addition is kinetically favored and 1,4-addition is thermodynamically favored.

NOTE: conjugation to the carbonyl activates the β -carbon toward nucleophilic addition. An isolated $\text{C}=\text{C}$ does not normally react with nucleophiles

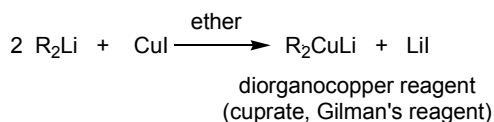


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Preparation of organocopper reagents organocopper reagents(Ch. 14.10)

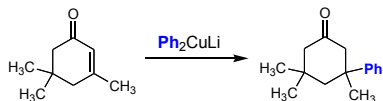
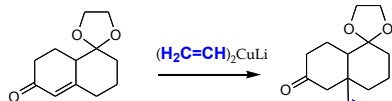
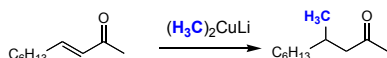


Dialkylcopper lithium: $(\text{H}_3\text{C})_2\text{CuLi}$



Divinylcopper lithium: $(\text{H}_2\text{C}=\text{CH})_2\text{CuLi}$

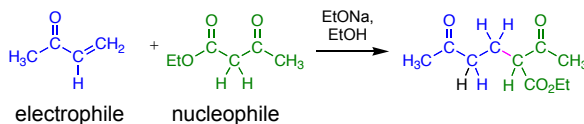
Diaryl copper lithium: Ar_2CuLi



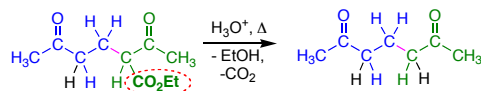
α,β -unsaturated ketones and aldehydes react with diorganocopper reagents to give 1,4-addition products (C-C bond forming reaction)

215

The Michael Reaction –The conjugate addition of a enolate ion to an α,β -unsaturated carbonyl. The Michael reaction works best with enolates of β -dicarbonyls.



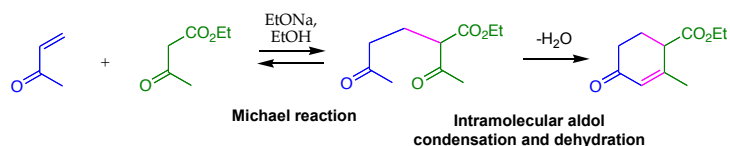
This Michael addition product can be decarboxylated.



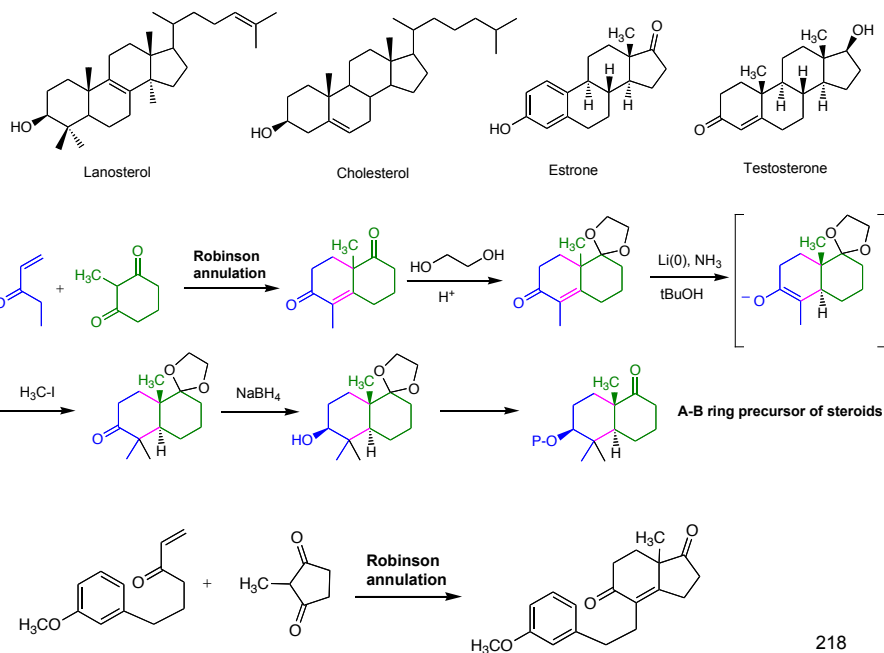
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Robinson Annulation – The product of a Michael reaction is a 1,5-dicarbonyl compound, which can undergo a subsequent intramolecular aldol reaction to give a cyclic α,β -unsaturated ketone or aldehyde.

annulation: to build a ring onto a reaction substrate

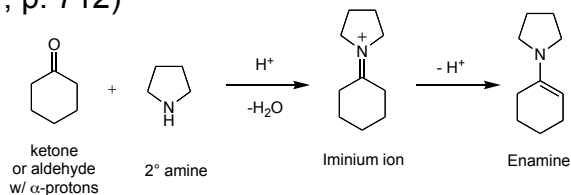


217

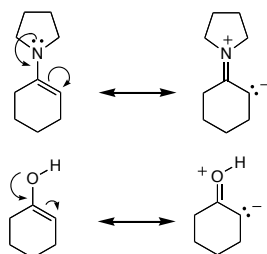


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Synthetic Applications of Enamines (Ch. 21, p.910). Recall that the reaction of a ketone with a 2° amines gives an enamine (Ch. 17.11, p. 712)

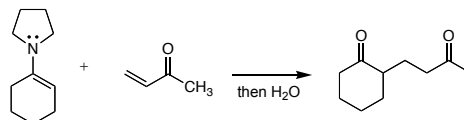


Enamines are reactive equivalents of enols and enolates and can undergo α -substitution reaction with electrophiles. The enamine (iminium ion) is hydrolyzed to the ketone after alkylation.

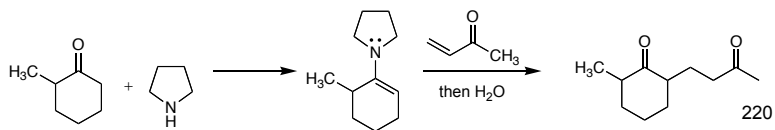


219

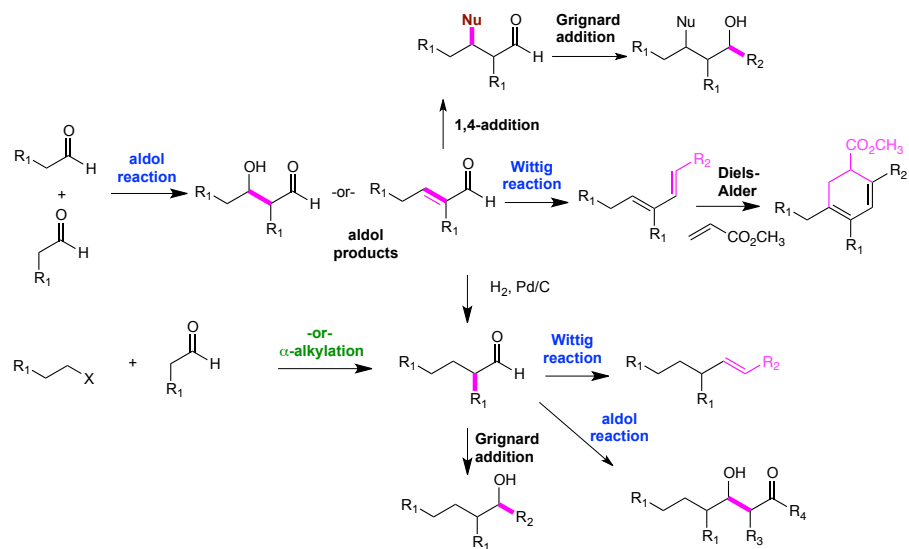
Reaction of enamine with α,β -unsaturated ketones (Michael reaction).



Enamines react on the less hindered side of unsymmetrical ketones

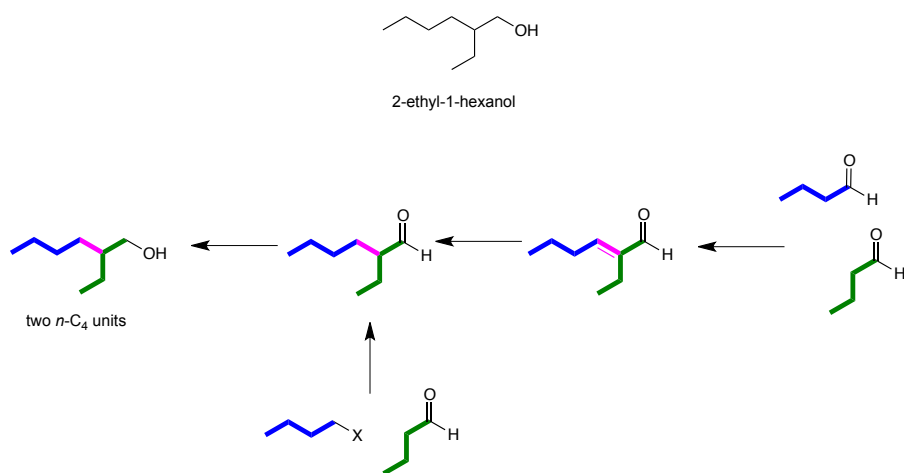


Organic Synthesis



Robert B. Woodward (Harvard): 1965 Nobel Prize in Chemistry
 "for his outstanding achievements in the art of organic synthesis"

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