Bean 10
Chem 3332

Chapter 22: Alpha Substitutions and Condensations of Enols and Enolate Ions

Review: So far – 2 reaction pathways for carbonyl compounds:

1. Nucleophilic Addition (aldehydes and ketones)
2. Nucleophilic Acyl Substitution (carboxylic acids and derivatives)

In these pathways, a nucleophile attacks the electrophilic carbonyl carbon.

Ch. 22 introduces a third pathway – many reactions, but only one new process (some reactions combine this new process with the old processes)

3. Alpha carbon reactions:
   a. alpha – substitutions
   b. condensations

In these pathways, a carbonyl compound is the <u>nucleophile</u>!

HOW?

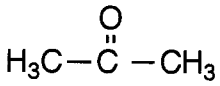
A carbonyl compound can become a nucleophile because its alpha hydrogens are slightly acidic – can be deprotonated by strong bases.

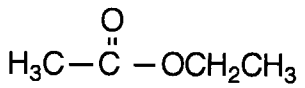
<u>Alpha Carbon Reactions:</u>

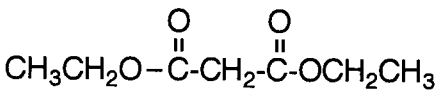
I. Alpha Substitutions
   A. alpha-halogenation of ketones and carboxylic acids
   B. alkylation of enolate anions of ketones and esters (and nitriles)
   C. alkylation of enamines (Stork)
   D. alkylation of beta-dicarbonyl compounds (malonic and acetoacetic ester syn.)

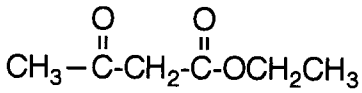
II. Condensation Reactions
   A. aldol condensation
   B. mixed aldol
   C. intramolecular aldol
   D. claisen condensation
   E. mixed claisen
   F. intramolecular claisen
   G. Michael reaction
   H. Robinson annulation

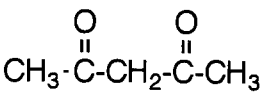
ACIDITY OF CARBONYL COMPOUNDS





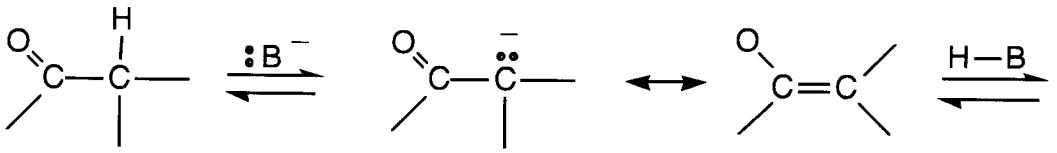




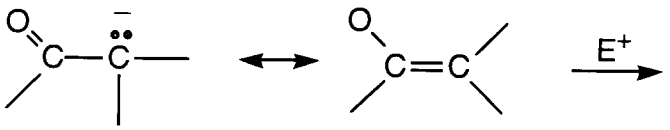


KETO - ENOL TAUTOMERIZATION

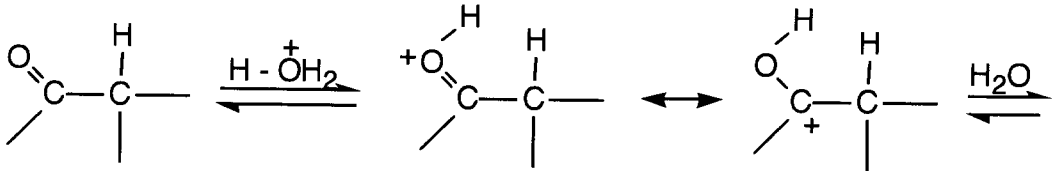
Base - catalyzed:



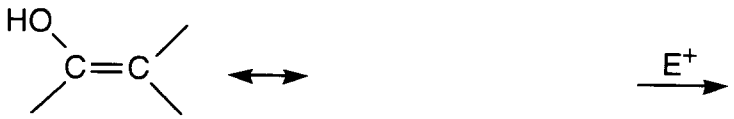
If E^+ is present



Acid Catalyzed:

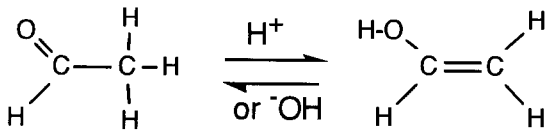


If E^+ is present



We first encountered keto - enol tautomerization in the hydration of alkynes. Which is the major tautomer at EQ?

Example:

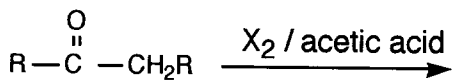


Are Chapter 22 reactions important?

I. Alpha - Substitution

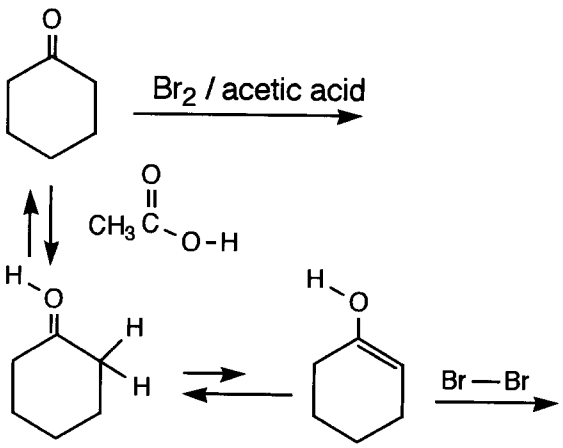
A. Alpha Halogenation of Ketones

1. acidic conditions

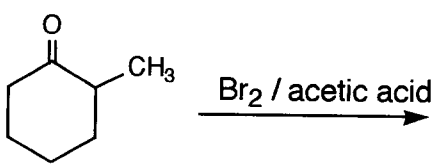


Example:

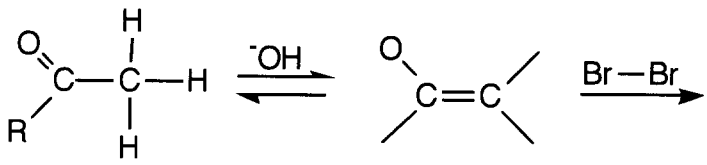
a.



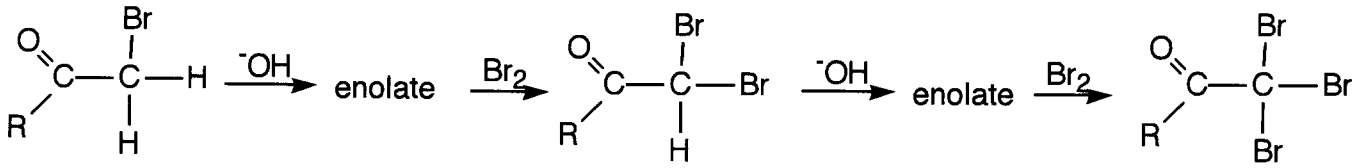
b.



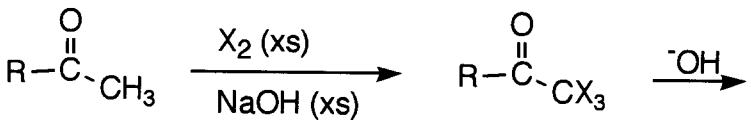
2. basic conditions



Base promoted halogenation cannot be used to form mono-brominated product:



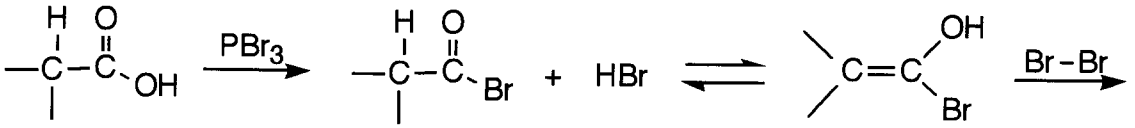
Haloform Reaction:

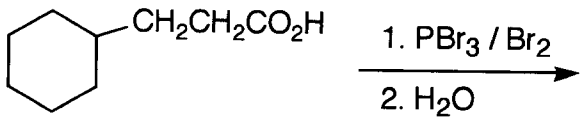


B. Alpha - Bromination of Carboxylic Acids (Hell - Volhard - Zelinsky)

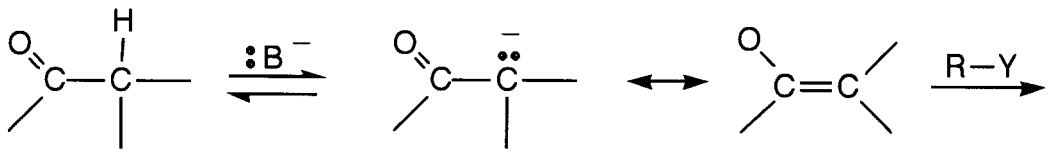
Carboxylic acids do not enolize under acidic or basic conditions.

Convert to acid bromide first.

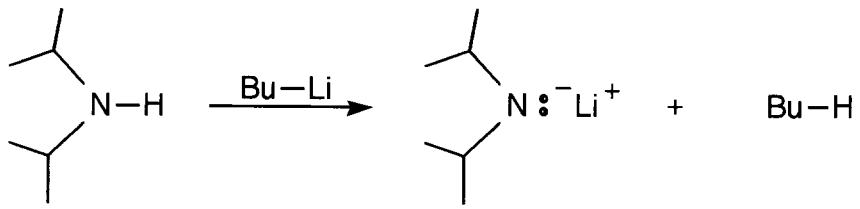




C. Alkylation of ketones and esters (and nitriles)

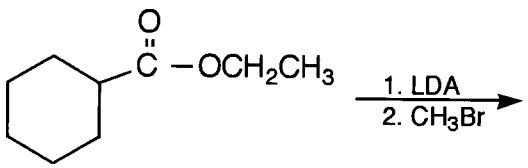


- α-hydrogens of ketones (pK_a = 19-20) and esters (pK_a = 24) are only weakly acidic
- if base used is hydroxide EQ lies far to keto tautomer, so enolate anion is produced slowly
- problem: hydroxide attacks R-Y
- solution: use stronger base that gives 100 % enolate



Examples:

a. $H_3C-\overset{O}{\overset{\|}{C}}-CH_3$ $\xrightarrow[2.\ CH_3CH_2Br]{1.\ LDA}$

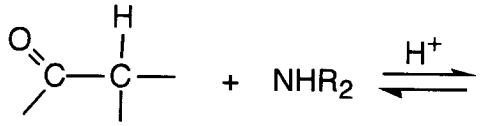
b. 

c. $CH_3CH_2\text{-}C\equiv N$ $\xrightarrow[2.\ CH_3Br]{1.\ LDA}$

d. 

D. Alkylation of Enamine

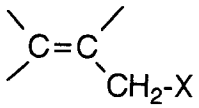
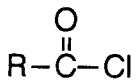
Review:



Enamine is similar to enolate anion:

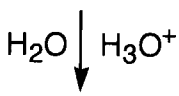
Stork Synthesis: enamine serves as Nu in the formation of alpha substituted aldehydes and ketones

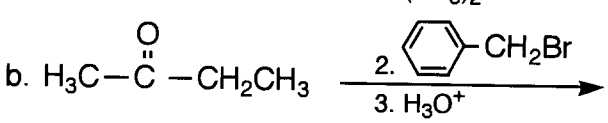
1. form enamine
2. add R - Y
3. hydrolysis

R - Y = $Ph-CH_2-X$  $R-X$ 

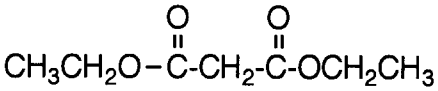
Examples:

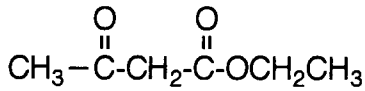
a. 

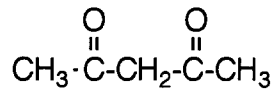


b. 

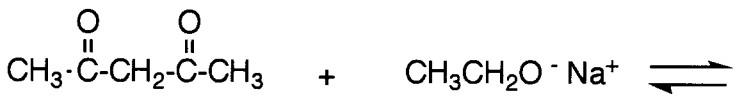
E. Alkylation of Βετα - Dicarbonyl Compounds



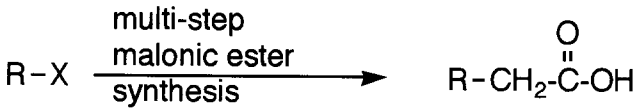




- more acidic than mono carbonyl compounds (and γ, δ, etc, dicarbonyl cpds.)
- do not need LDA to obtain a good yield of enolate ion



1. Malonic Ester Synthesis: a sesuence of reactions that converts an alkyl halide to an α-substituted (or disubstituted) acetic acid

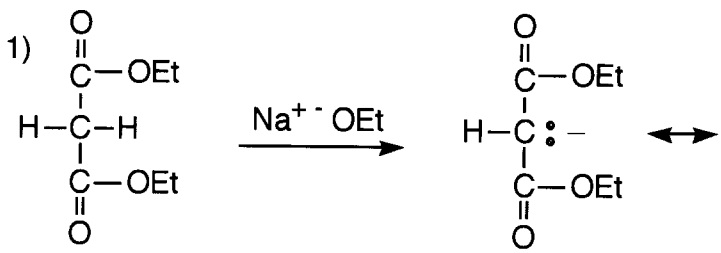


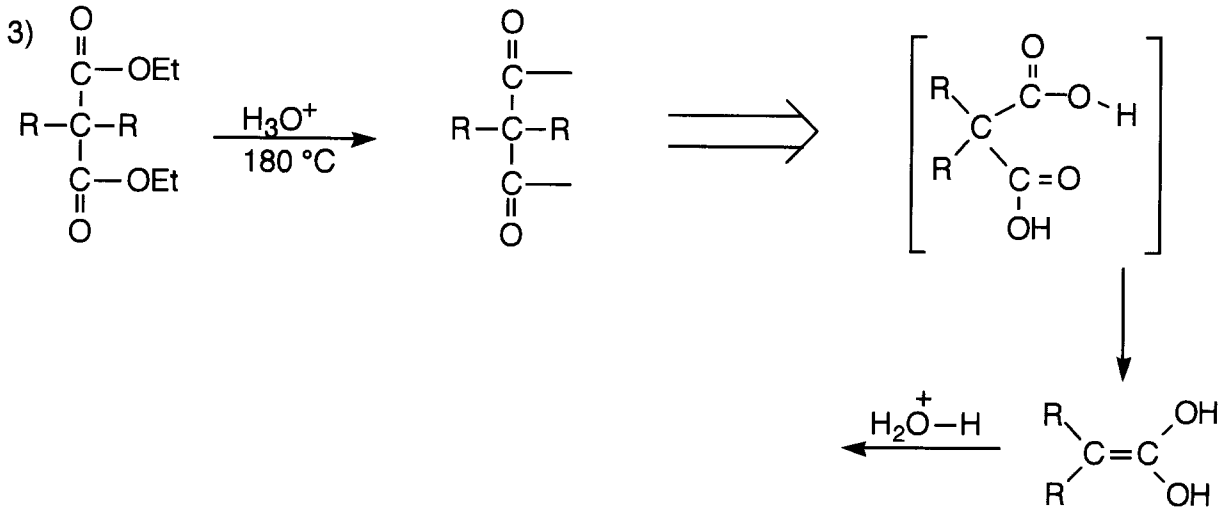
a malonic ester

Steps:

1) treat malonic ester with base to form enolate ion
2) alkylate (add R-X)
3) hydrolyze/decarboxylate

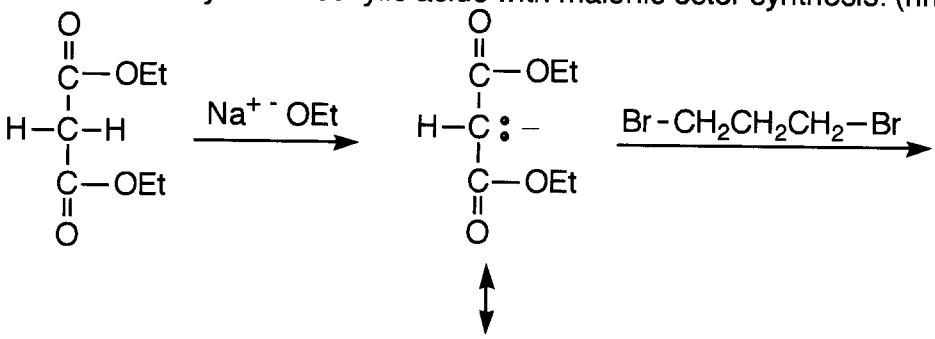
Mechanism:



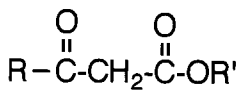
3) 

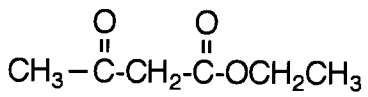
Example:

Formation of cyclic carboxylic acids with malonic ester synthesis: (ring size 3 - 6)

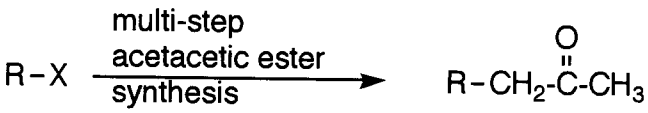


2. Acetoacetic Ester Synthesis: similar to malonic ester synthesis, but uses a beta keto ester rather than a beta diester





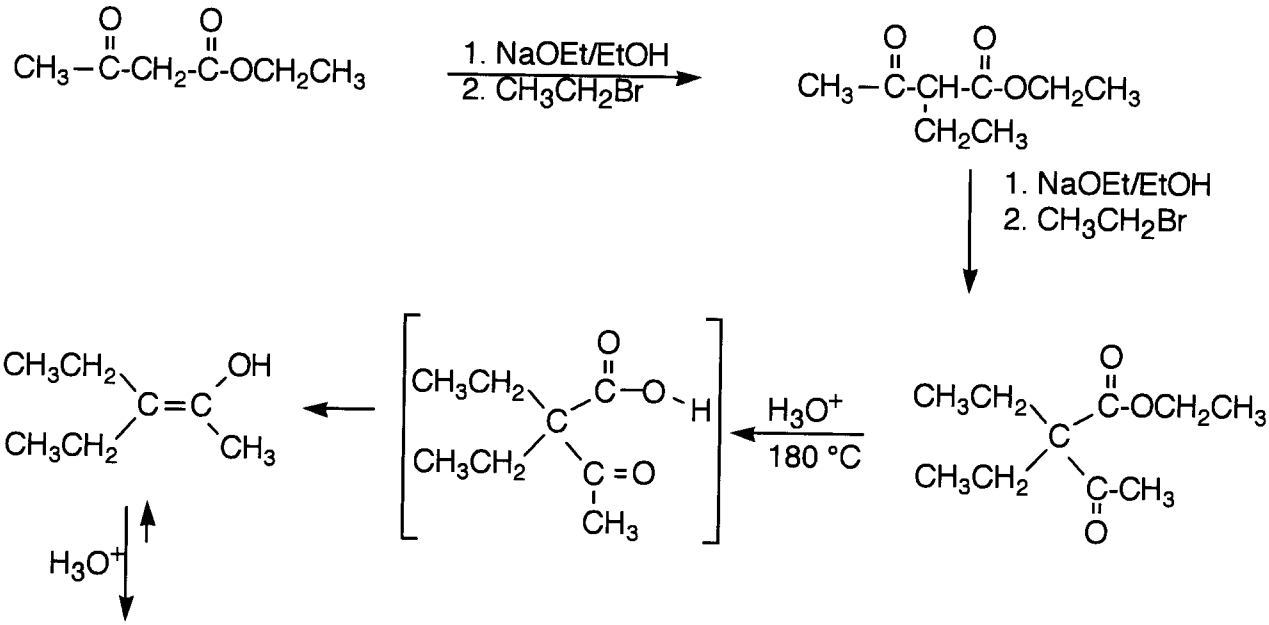
ethyl-3-oxobutanoate
ethyl acetoacetate
acetoacetic ester



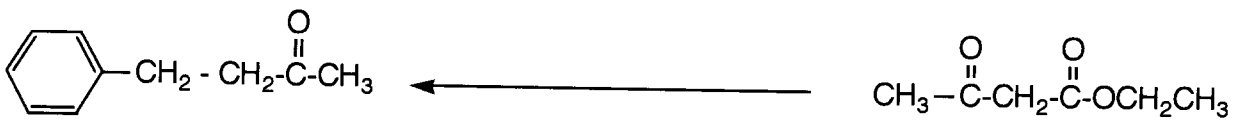
Steps:

1. treat acetoacetic ester with base to form enolate ion
2. alkylate (add R-X)
3. hydrolyze/decarboxylate

Example:



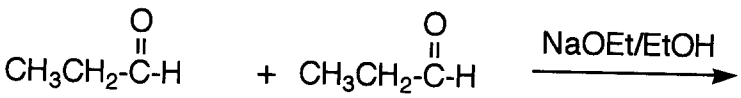
Synthesis Example:



II Condensation Reactions: A combination of the old carbonyl pathways (nucleophilic addition or nucleophilic acyl substitution) with the new pathway (alpha substitution)

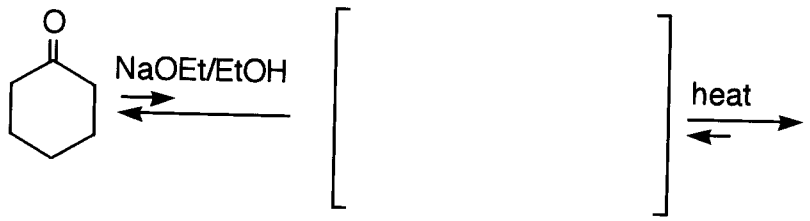
A. Aldol Condensation - for aldehydes and ketones that have alpha hydrogens
- produces a beta hydroxy aldehyde or ketone
- steric factors are important : ketones and alpha disubstituted aldehydes give poor yields
- strength of base used is important, only necessary to convert small % to enolate ion (do not want 100% enolate!)

Example:

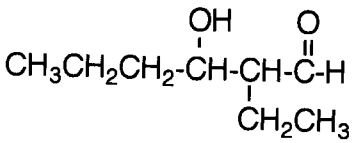


Dehydration of Aldol Products: warming the aldol product readily leads to an alpha, beta unsaturated carbonyl ; with dehydration, most aldehydes and ketones can successfully be used in aldol condensations

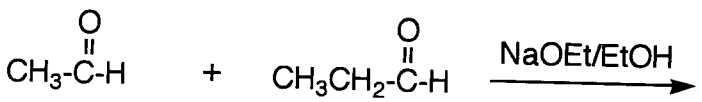
Example:



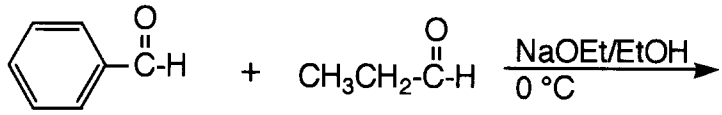
Synthesis Practice: From ethanal synthesize the compound below.



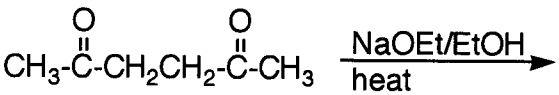
B. Crossed (Mixed) Aldol: condesation between two different aldehydes or ketones
Consider:



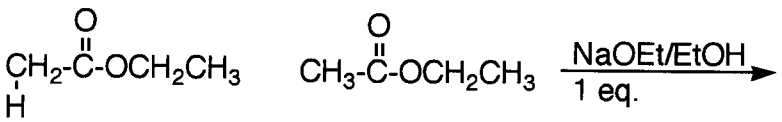
Successful Crossed Aldol: One reactant has NO alpha hydrogens (cannot form enolate)



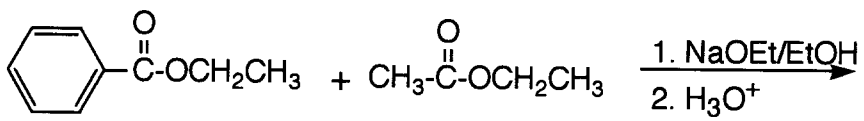
C. Intramolecular Aldol: enolate anion and the carbonyl attacked are in the same molecule; 5 and 6 membered rings readily form

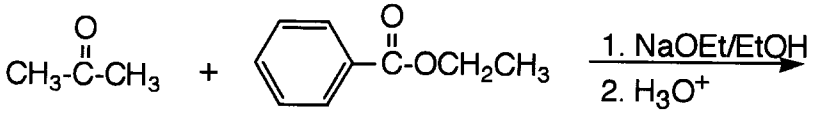


D. Claisen Condensation: Forms beta-keto esters from esters

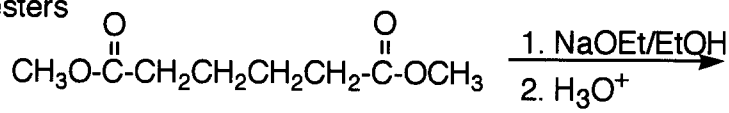


E. Crossed (Mixed) Claisen: one reactant must have no alpha-hydrogens

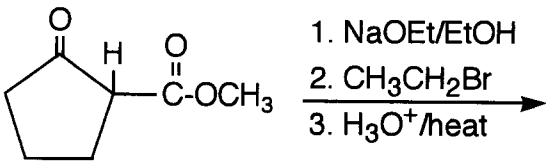
1) 

2) 

F. Intramolecular Claisen (Dieckmann Cyclization): similar to intramolecular aldol; forms cyclic beta-keto esters

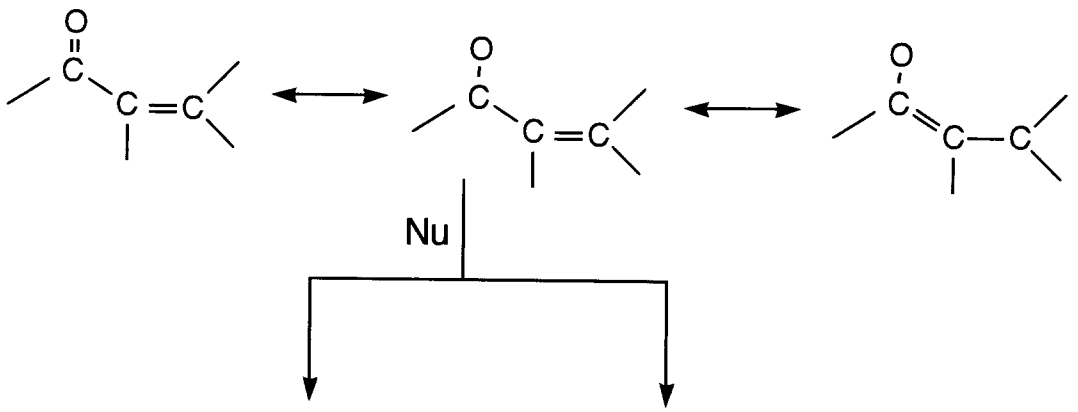


Synthesis of alpha-substituted cyclopentanones and cyclohexanones using Dieckmann followed by acetoacetic ester-like synthesis:



G. The Michael reaction: a conjugate addition to an alpha, beta-unsaturated system (such as an enone); also described as a reaction between a Michael donor and a Michael acceptor (see Table 22-2, page 1046)

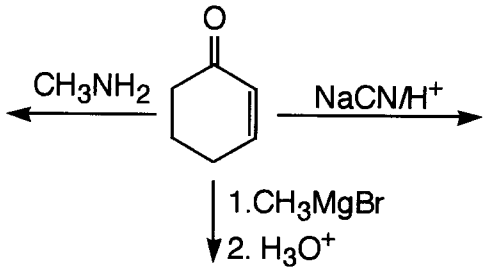
Conjugate addition vs direct addition to an enone:

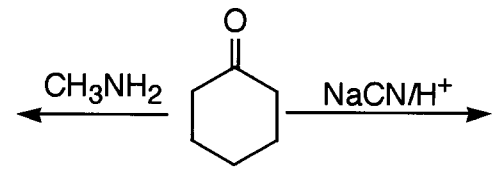


Nucleophiles that give direct addition product:
- Grignard and organolithium reagents
- $LiAlH_4$

Nucleophiles that give conjugate addition product:
- amines
- cyanide anion
- Michael donors listed in Table 22-2

Examples:

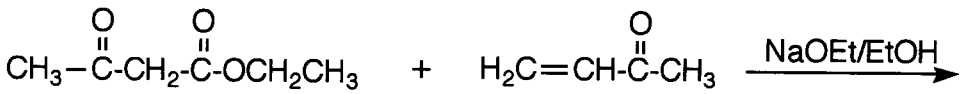




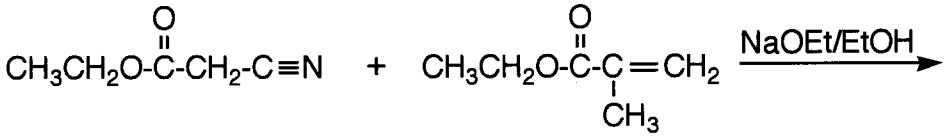
Michael donors: systems that have particularly acidic alpha-hydrogens such as beta-keto esters, beta-diesters, beta-dicarbonyls, beta-keto nitriles, beta-keto nitro

Michael acceptors: alpha, beta unsaturated systems - C=C conjugated with X=Y

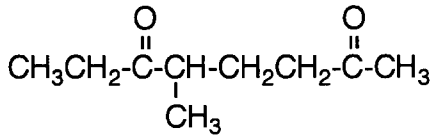
Michael Example and Mechanism:



More Michael Examples:



Synthesize:



H. Robinson Annulation: an important ring forming reaction
2 parts: 1. Michael addition, 2. Intramolecular aldol/dehydration