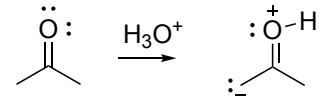
Chapter 22: Carbonyl Alpha Substitution Reactions

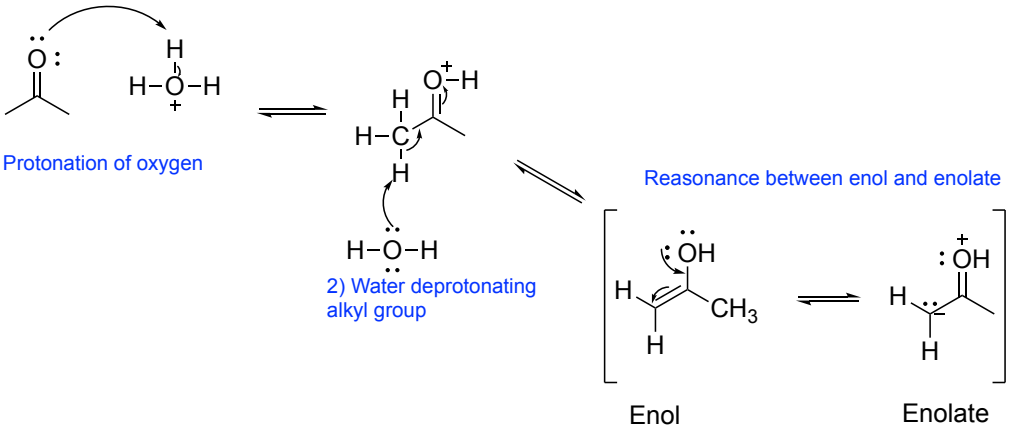
Formation of Enolate

Acid Catalyzed

Overall Reaction:

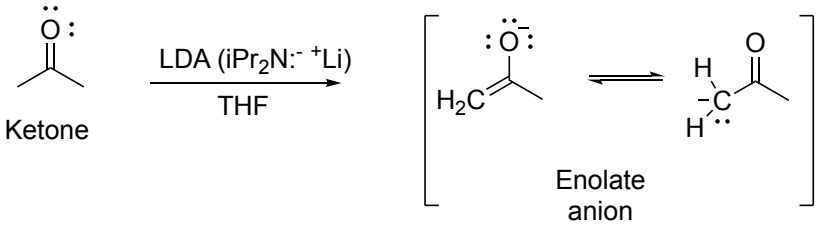


Mechanism:

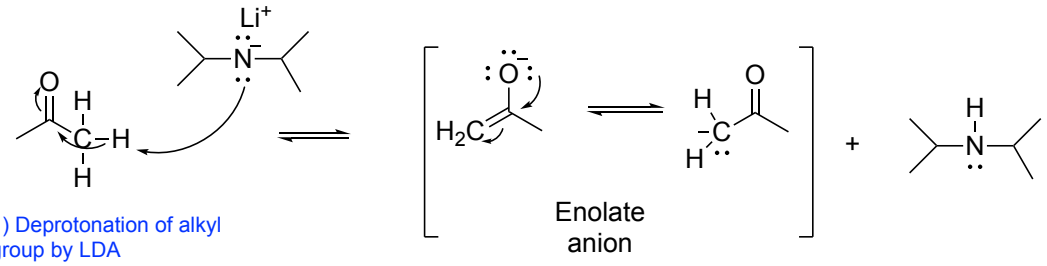


Base Catalyzed

Overall Reaction:



Mechanism:



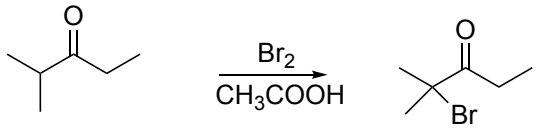
Resonance of the enolate anion

Alpha Substitution Reaction: Halogenation of Aldehydes and Ketones

Acid Catalyzed

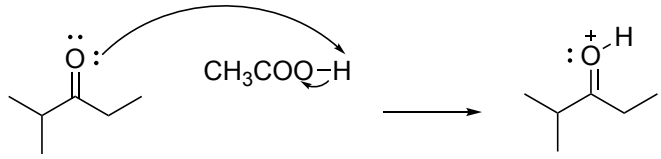
- Notes:
  - Can react with Cl_2, Br_2, I_2 in acidic conditions (normally acetic acid, CH_3COOH)
  - Will yield a monohalogenation at the most substituted carbon

Overall Reaction:

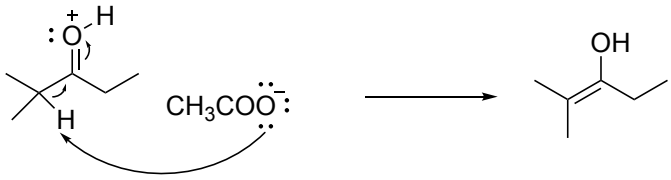


Mechanism:

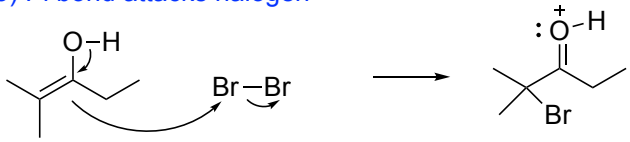
1) Protonation of oxygen by acetic acid



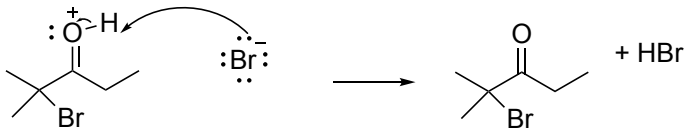
2) Deprotonation of most substituted carbon



3) Pi bond attacks halogen



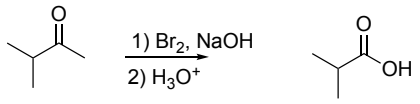
4) Conjugate base deprotonates protonated alkoxide



Base Induced (Haloform)

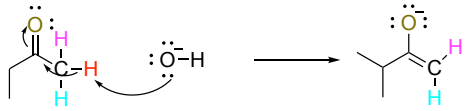
- Notes:
  - Can react with Cl_2, Br_2, I_2 in basic conditions (normally sodium hydroxide)
  - Will yield a multi halogenation at the least substituted carbon
  - Can test for a methyl ketone if treated with acidic workup and will turn into carboxylic acid

Overall Reaction:

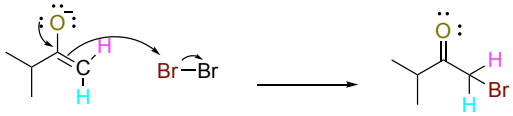


Mechanism:

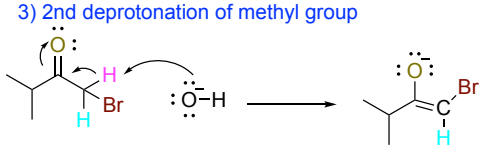
1) 1st deprotonation of methyl group



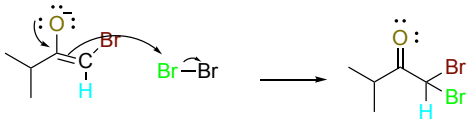
2) 1st pi bond attack of bromine



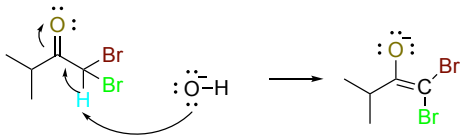
3) 2nd deprotonation of methyl group



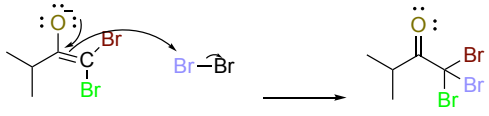
4) 2nd pi bond attack of bromine



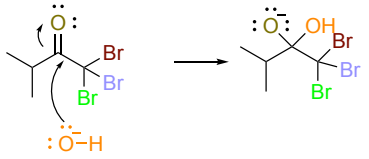
5) 3rd deprotonation of methyl group



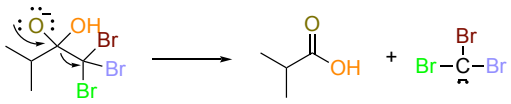
6) 3rd pi bond attack of bromine



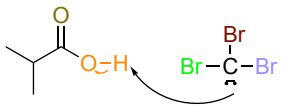
7) Nucleophilic attack of carbonyl by hydroxide



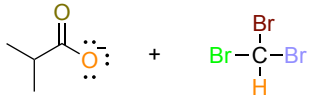
8) Tribromide group leaves



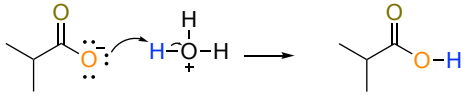
9) Carbanion deprotonates carboxylic acid



10) Carboxylate anion forms



11) Acid workup reforms carboxyl group



Alkylation of the Alpha Position

Malonic Ester Synthesis:

- Purpose: to prepare a carboxylic acid from an alkyl halide and add carbons to the carbon chain

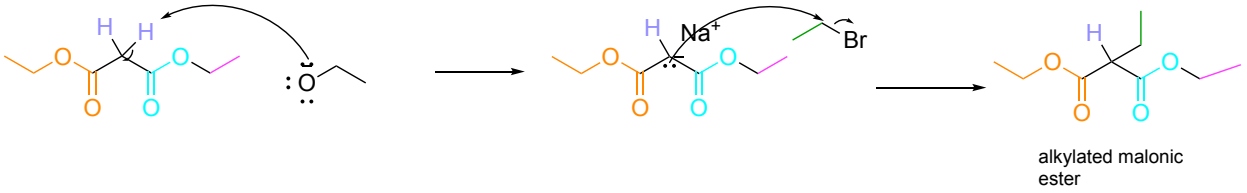
Overall Reaction:



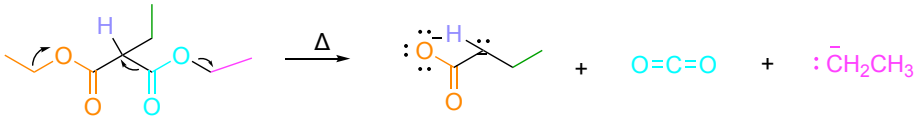
Mechanism:

1) Deprotonation of alpha carbon

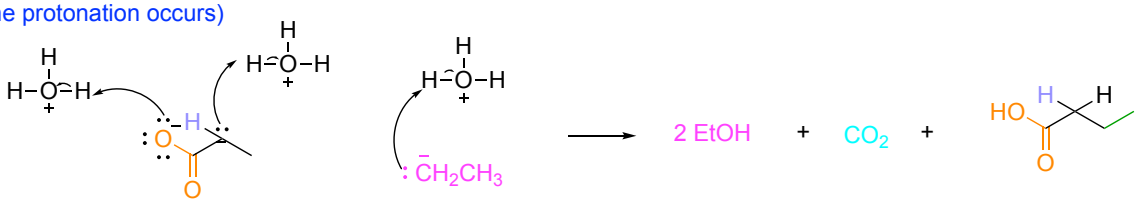
2) Nucleophilic attack by the carbanion to the primary alkyl halide



3) Decarboxylation due to heat



4) Protonation via an acid. (Steps 3 and 4 occur simultaneously, just wanted to give a more clear depiction of how the protonation occurs)



Acetoacetic Ester Synthesis

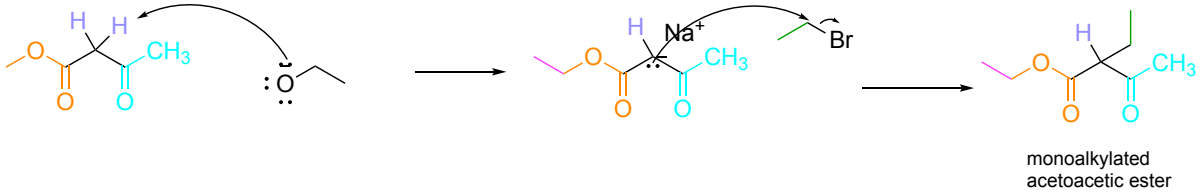
- Purpose: to prepare a methyl ketone from an alkyl halide and add carbons to the carbon chain

Overall Reaction:

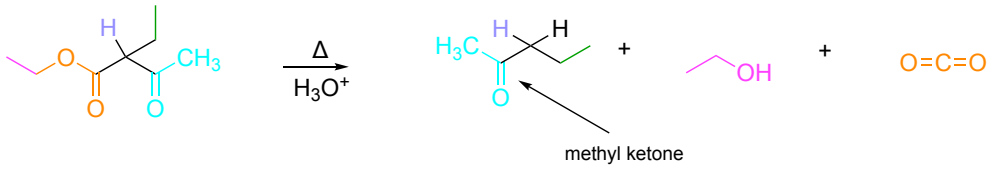


Mechanism:

2) Nucleophilic attack by the carbanion to the primary alkyl halide



3) Decarboxylation due to heat and protonation due to acidic conditions

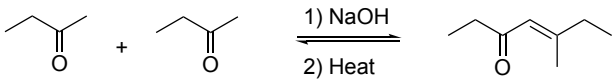


Chapter 23: Carbonyl Condensation Reactions

Aldol Condensation: Self Condensation:

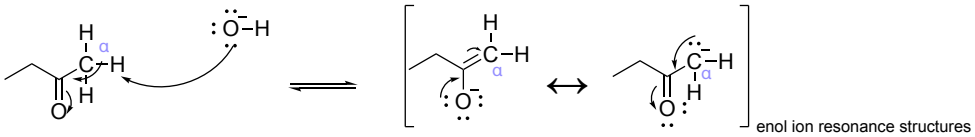
- Starting Materials: One alpha carbon provided by an aldehyde/ ketone acting as the (enolate component) donor. The other aldehyde/ ketone provides the carbonyl carbon acting as the (carboxylic component) acceptor.
- Catalyzed by: NaOH
- Product: B-Hydroxy aldehyde/ketone AKA aldol
- What is an aldol? There is a carbonyl (either from a ketone or aldehyde), in the alpha position is a carbon, in the beta position is a carbon bonded to a hydroxyl group

Overall Reaction:

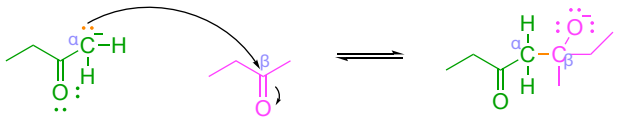


Mechanism:

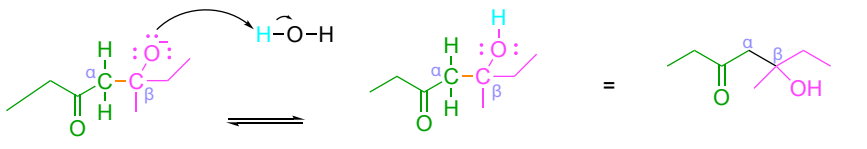
1) Formation of the the enol ion: Deprotonation of methyl α carbon



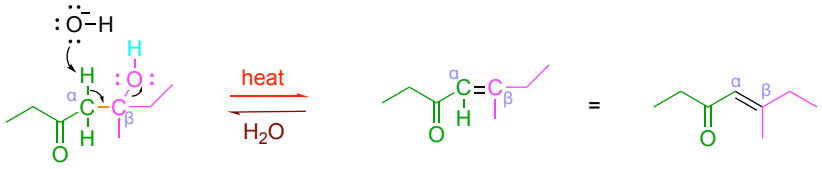
2) Carbanion enolate nucleophillic attack of carbonyl carbon (β carbon)



3) Protonation of oxygen anion



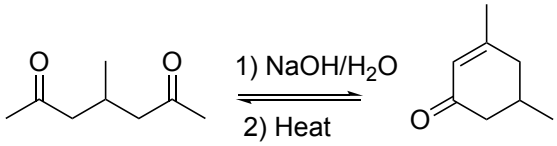
4) Deprotonation of alpha carbon and elimination of β hydroxyl group (elimination of water)



Intramolecular Aldol Condensation

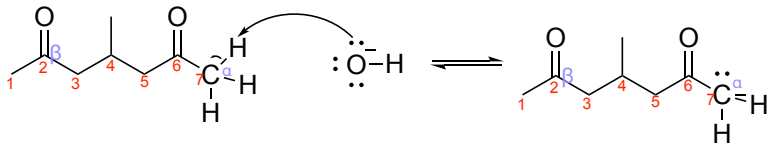
- Same mechanism as above, just starting from a linearized carbon chain to producing a cyclic carbon chain (ring)

Overall Reaction:

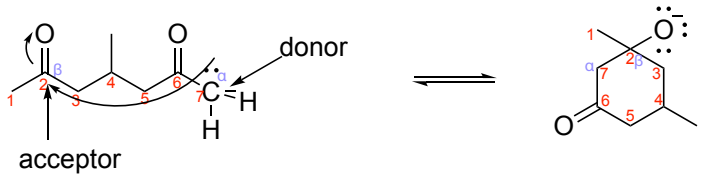


Mechanism:

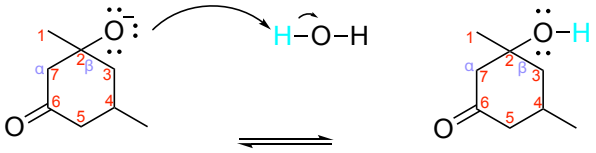
1) Formation of the the enol ion: Deprotonation of methyl α carbon



2) Carbanion enolate nucleophillic attack of carbonyl carbon (β carbon)

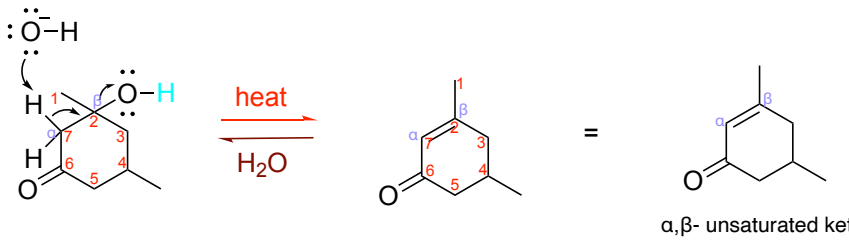


3) Protonation of oxygen anion



β-hydroxy ketone

4) Deprotonation of alpha carbon and elimination of β hydroxyl group (elimination of water)

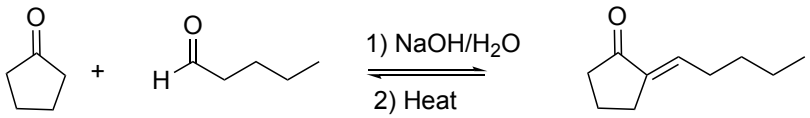


α,β- unsaturated ketone

Mixed/ Crossed Aldol Condensation Reactions

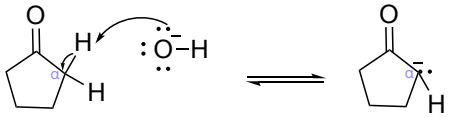
- A reaction between two unique aldehydes, two unique ketones, or one ketone and one aldehyde
- If a ketone is used, the ketone is the enolate donor and the aldehyde is the electrophile
- Will only work if only one of the starting materials does not have an acidic hydrogen

Overall Reaction:

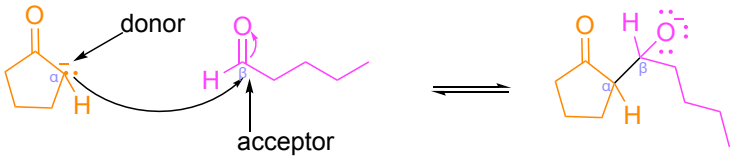


Mechanism:

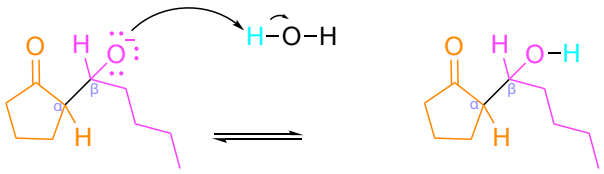
1) Formation of the the enol ion: Deprotonation of methyl α carbon



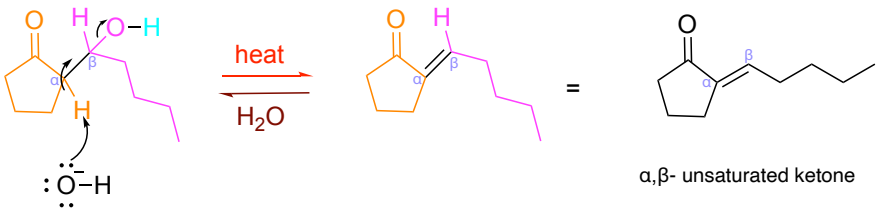
2) Carbanion enolate nucleophillic attack of carbonyl carbon (β carbon)



3) Protonation of oxygen anion



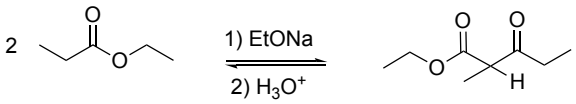
4) Deprotonation of alpha carbon and elimination of β hydroxyl group (elimination of water)



Claisen Condensation

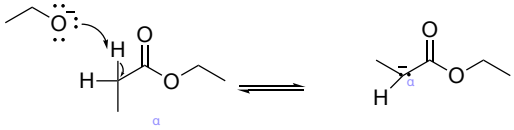
- Reaction between two of the same esters to produce a β-keto ester or a β-diketone
- Base used: a strong base such as NaOEt (cannot use NaOH)
- The starting ester must have two alpha hydrogens because the second deprotonation by the alkoxide is what makes this reaction favorable

Overall Reaction:

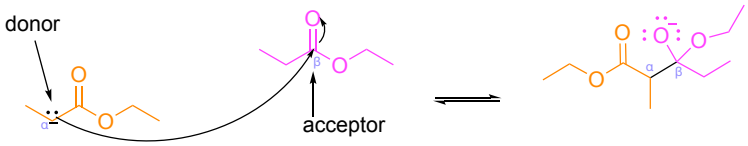


Mechanism:

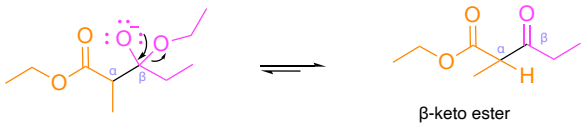
1) Formation of the the enol ion: Deprotonation of α carbon



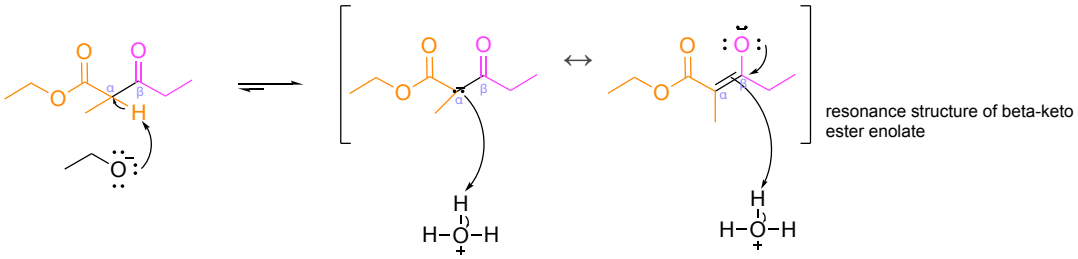
2) Carbanion enolate nucleophillic attack of carbonyl carbon (β carbon)



3) Elimination of ethoxide

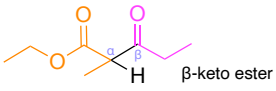


4) Deprotonation of alpha carbon



5) Acid workup

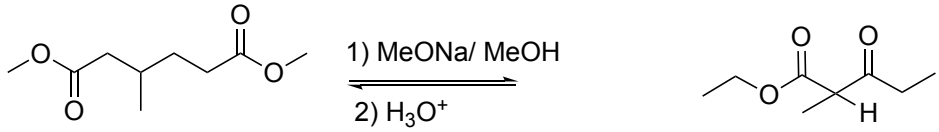
*protonation necessary to drive the equilibrium forward towards β-keto ester



Dieckmann Condensation

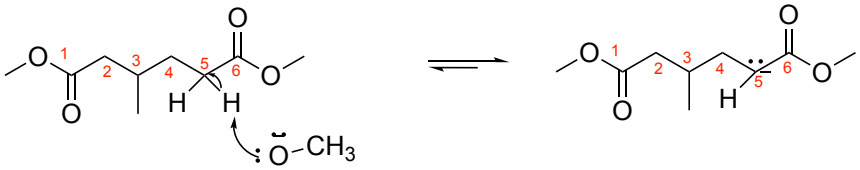
- Similar mechanism to above, but the reaction is an intramolecular reaction, with the starting material as one diester forming a cyclic β-keto ester in basic with a strong base

Overall Reaction:

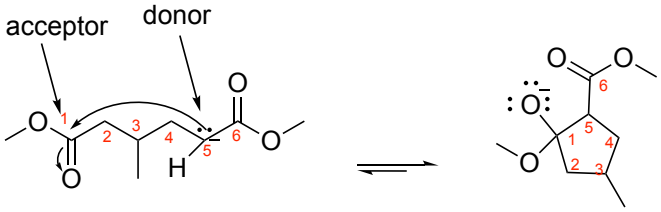


Mechanism:

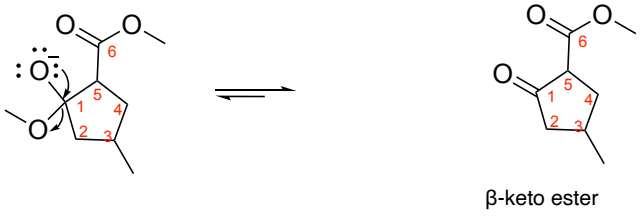
1) Formation of the the enol ion: Deprotonation of α carbon



2) Carbanion enolate nucleophillic attack of carbonyl carbon (β carbon)



3) Elimination of ethoxide

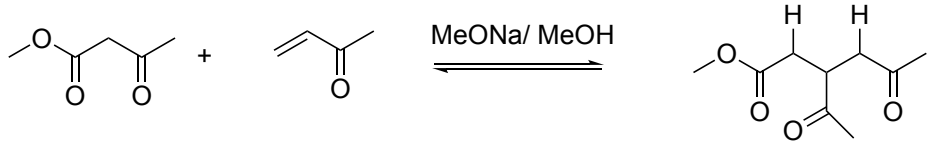


Additions to α, β-Unsaturated Aldehydes and Ketones

Micheal Addition

- A reaction between an α, β-unsaturated carbonyl acceptor (Micheal acceptor) and an enolate ion donor to the β carbon (Micheal donor)
- Examples of Micheal acceptors:
  - Propenal, 3-Buten-2-one, Ethyl propenoate, Propenenitrile , Nitroethylene
- Examples of Micheal donors:
  - β-Diketone, β-Keto ester, Diethyl malonate, β-Keto nitrile, Nitro compound

Overall Reaction:



Mechanism:

