

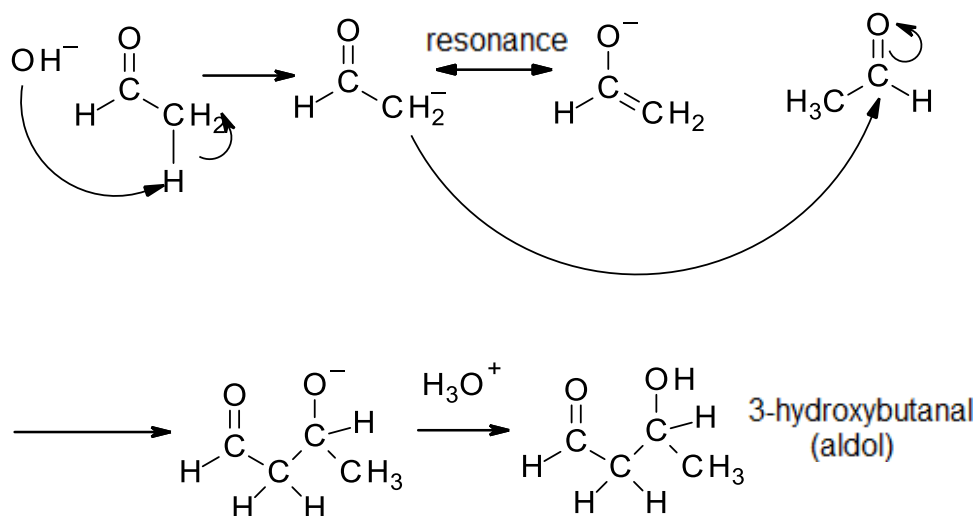
Ch 23 Carbonyl Condensations

Mechanism

- The first part is an alpha substitution, where the deprotonated α C is the Nu and a δ^+ carbon (generally a carbonyl) on another molecule is the E+.
- If the other molecule's carbonyl has no LG, the reaction proceeds as Nu addition.
- If the carbonyl does have an LG, the reaction proceeds as Nu substitution.
- If the carbonyl is conjugated with C=C, the reaction proceeds as conjugate addition.
- The reactions begin with a base removing the α H to create the enolate. The enolate is the Nu that adds to the second molecule, which is the E+.

Aldol Reaction

- Two aldehyde or ketone molecules combine to form a β -hydroxy carbonyl.
- The enolate is created from an aldehyde or ketone by adding a base (NaOH or NaOEt), which removes an α H, creating an enolate.
- The enolate's α C adds to the carbonyl C of another molecule. Typically, the reaction is with an identical molecule, but not necessarily.
- Since no LG is involved, the carbonyl Π bond cannot reform.
- Instead, the O is protonated by adding acid, as in Nu addition.
- The product is a β -hydroxy aldehyde or ketone.
- Reaction is rapid, but reversible. It is favored by equilibrium for ketones and α -substituted aldehydes (R_2CHCHO).
- The reverse reaction occurs in reverse order after the base removes the hydroxyl H. This allows the carbonyl to reform with the enolate as the LG.

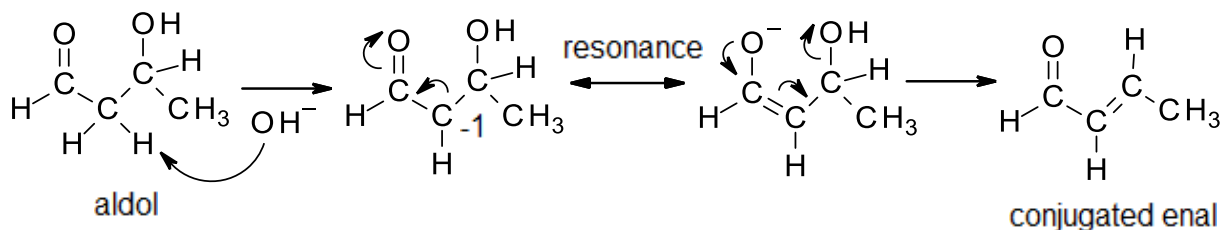


Condensation vs. α -Substitution

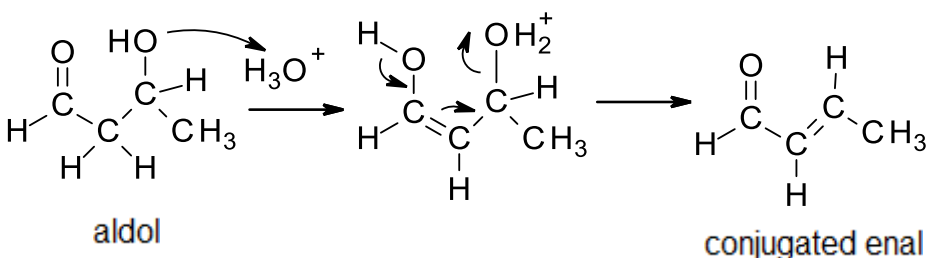
- Both reactions are similar in that they start with a base creating an enolate.
- Condensations occur at warm temperatures with only a catalytic amount of base.
- An α -substitution uses a full equivalent of base to create the enolate over dry ice ($-78^\circ C$), the alkyl halide is added immediately after creating the enolate.

Dehydration of Aldols

- The β -hydroxyl can be removed along with an α H to create a Π bond. The result is a conjugated enone (or enal).
- This also drives the aldol reaction's equilibrium towards the products.
- The dehydration can be catalyzed either by acid or base, along with mild heating.
- The base-catalyzed reaction starts with the base removing the α H to create an enolate, where the α C has a lone pair and a negative charge. The β -OH leaves as the α C's lone pair forms the α - β Π bond.



- The acid-catalyzed reaction starts with the acid protonating both the β -OH, as well as rearranging the carbonyl and α C into an enol. As H_2O leaves the β C, the carbonyl Π bond reforms, and the α - β Π bond forms.

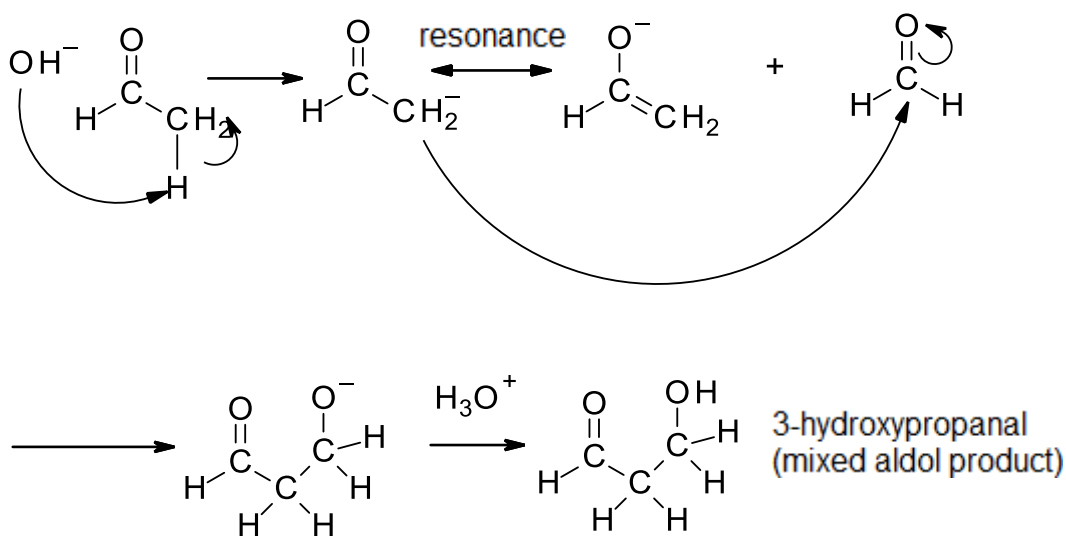


Synthesis with Aldols

- Chemists use the retrosynthetic method to determine how to perform a synthesis, essentially working backward from product to reactants to determine how the product can be created.
- Larger aldehydes and alcohols can be synthesized from smaller aldehydes by using the aldol reaction.

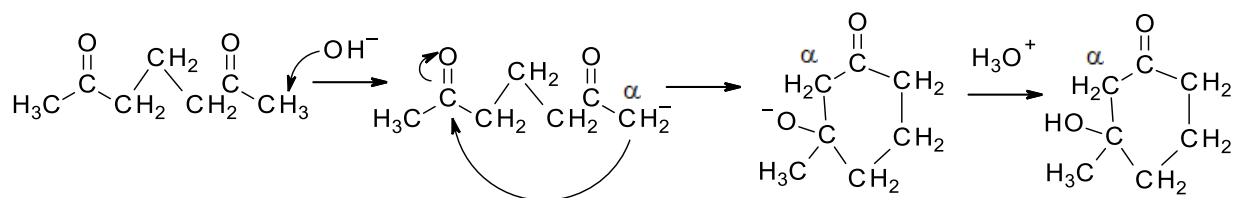
Mixed Aldol Reactions

- If two different aldehydes are mixed together, then four different aldol products (two mixed and two unmixed) can potentially be created together. That would be a mess.
- The process can result in only one product if one of the two aldehydes does not have an α H. If there is no H, that aldehyde cannot form an enolate, and would function only as the carbonyl E^+ . Formaldehyde (CH_2O) and benzaldehyde ($PhCHO$) have no α H, and are also good E^+ 's because they are sterically unhindered.
- It also helps if the carbonyl that forms the enolate is more acidic, such as acetoacetate ester.



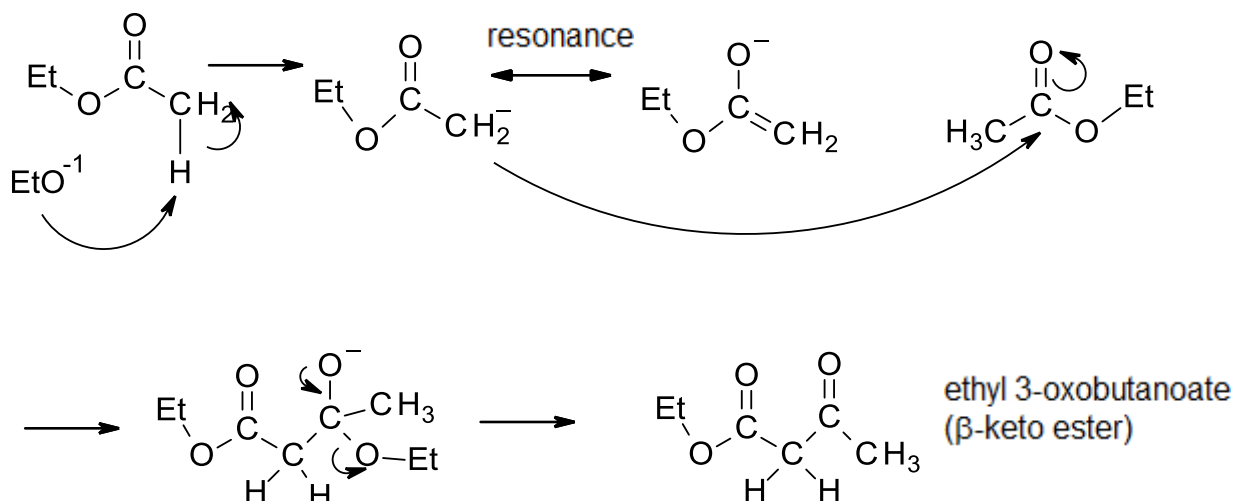
Intramolecular Aldol

- A molecule that has two carbonyls can form a cyclic enone from an aldol reaction if the product contains a stable ring with 5 or 6 atoms, such as with hexanedial and 2,6-heptanedione (below).



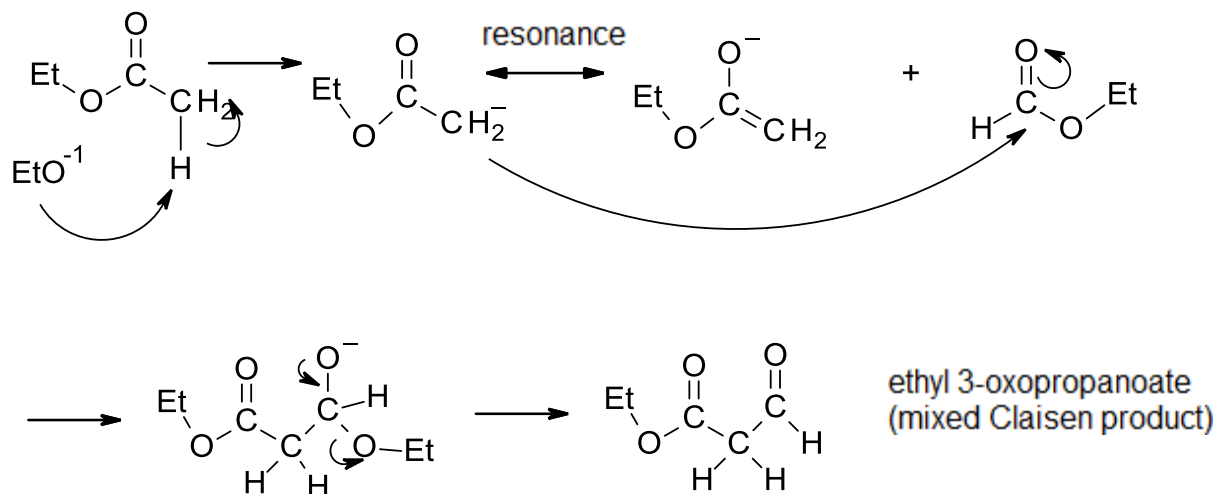
Claisen Condensation

- Two esters combine to form a β -keto ester (like acetoacetate).
- Beginning is similar to aldol, where an alkoxide base (NaOEt) removes an α H and creates an enolate.
- The enolate reacts with the ester carbonyl on another molecule. Typically, it is an identical molecule, but not necessarily.
- The primary difference from aldol is that the ester has an alkoxy group that functions as the LG, so that the Nu acyl substitution occurs.



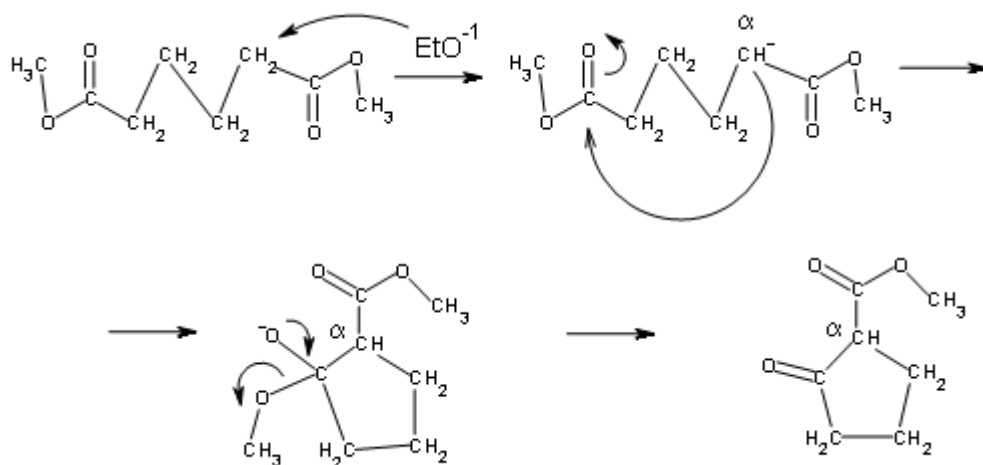
Mixed Claisen Condensations

- Since two different esters mixed together can result in four different products, The mixed reaction can only be successful if one ester has no α H. If there is no α H, that ester cannot form an enolate, and would function only as the carbonyl E^+ .
- Formate (HCOOR), benzoate (PhCOOR), and oxalate ($\text{RCO}_2\text{CO}_2\text{R}$) esters have no α H and work well as electrophiles.



Intramolecular Claisen Condensations

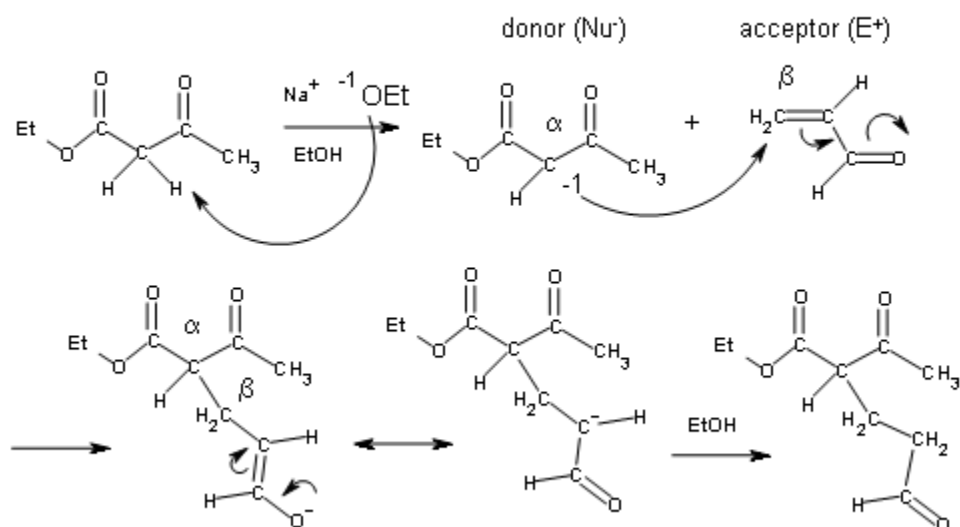
- Also known as Dieckmann Cyclization.
- A diester can form stable ring with 5 or 6 atoms, such as with hexanedioate and heptanedioate esters.
- The ring has the remaining CO_2R on its #1 C and the (oxo) carbonyl on the #2 C.
- Because the product is a β -keto ester (like acetoacetate), it can be used in further α substitutions. As in the previous chapter, base converts the dicarbonyl compound into an enolate, which acts as a Nu in an $\text{S}_{\text{N}}2$ reaction with an alkyl halide. Hydrolysis and decarboxylation can be accomplished as well by heating in acid.



The Michael Reaction

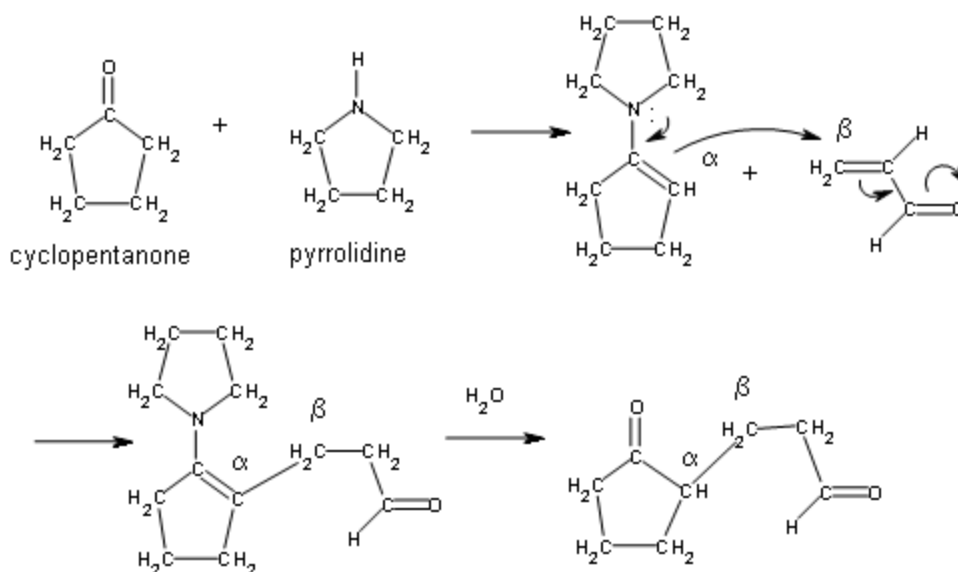
- This reaction also begins with an alkoxide base (NaOEt) removing an α H to create an enolate.
- This reaction is different from aldol and Claisen condensations in that the enolate (donor or Nu^-) adds to the β C of a conjugated enone (acceptor or E^+). This is identical to the conjugated enone addition seen at the end of the aldehydes and ketones chapter.
- The best enolates are from dicarbonyl compounds (like acetoacetate).
- The acceptor can have the $\text{C}=\text{C}$ conjugated with $\text{C}=\text{O}$ (enone, enal, enoate, or enamide), CN (nitrile), or NO_2 (nitroalkene).
- The product is a single, condensed, 1,5-dicarbonyl molecule with the α C from the donor bonded to the β C of the donor.

Michael reaction



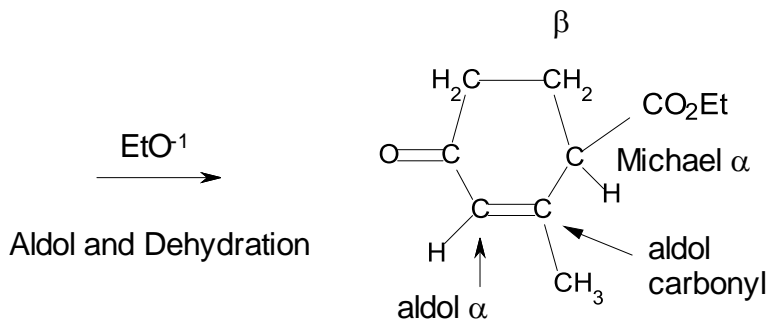
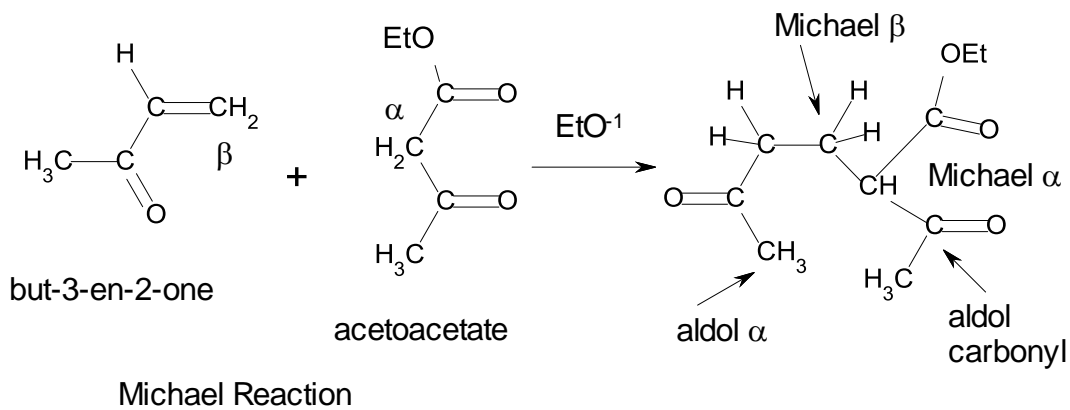
Gilbert Stork Enamine Reaction

- The overall result is identical to the Michael reaction, but using an amine (pyrrolidine) allows a monocarbonyl molecule to become a donor by converting it into an enamine ($\text{C}=\text{C}-\text{N}$).
- The enamine has resonance that is similar to the enolate, allowing the α C to have a lone pair and a negative charge, while the N has a Π bond and a positive charge.
- The enamine adds to the β C of a conjugated enone, and rearranges slightly so that the enone's α C gains an H^+ from the enamine's α C.
- In the final step, water is added to revert the enamine back to a carbonyl.
- The product is a 1,5-dicarbonyl molecule, as in the Michael reaction.



Robinson Annulation

- Annulation means making a ring.
- First, a dicarbonyl compound condenses with an enone in a Michael reaction.
- Then, an aldol reaction (with dehydration) between two carbonyls creates a cyclic enone with a 6-membered ring.



Biological Carbonyl Condensations

- Aldol reactions are common to metabolic pathways. Carbohydrate metabolism, in particular, uses aldolase enzymes (amines) to convert carbonyl compounds into enamines, and the enamines condense with phosphate esters of carbohydrates.
- Claisen reactions occur in fatty-acid biosynthesis where a synthase enzyme (thioester is the acceptor) is added to a malonyl-ACP's decarboxylated enolate. ACP stands for Acyl Carrier Protein and is attached to a sulfur atom that bonds with carbonyls.