Mechanisms and Uses of Aldol Condensations

Tom Crowley

Missouri Western State University

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Dr. Steven P. Lorimor

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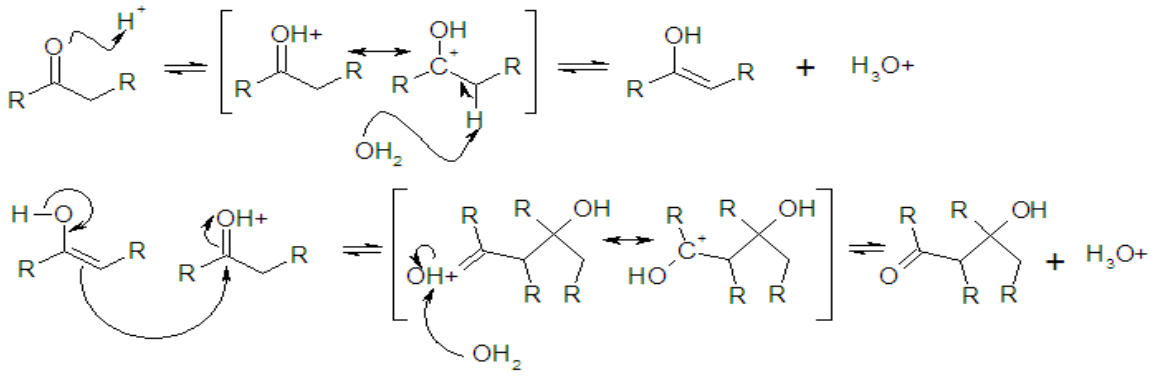
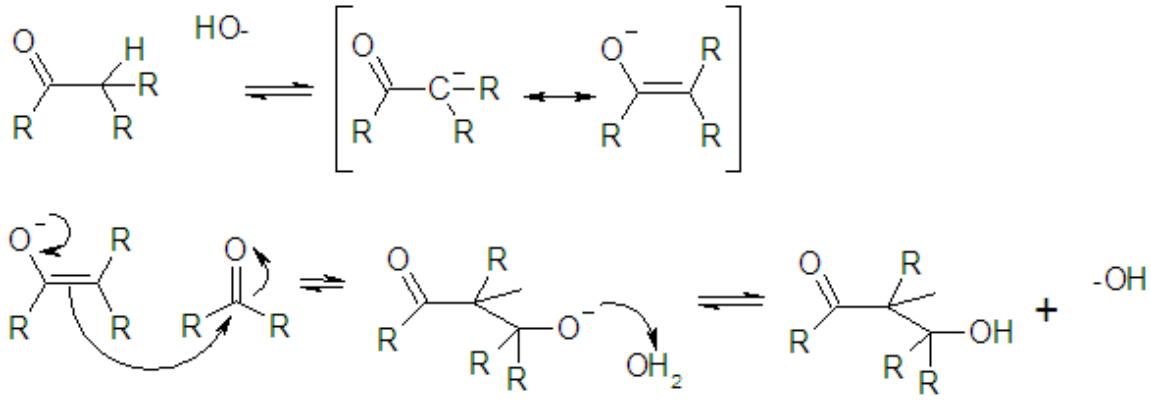
Aldol condensations form a very important class of reactions in organic synthesis. The reaction was discovered independently by Charles-Adolph Wurtz and Alexander Porfyrevich Borodin in 1872. The name aldol was chosen because the product of an aldol condensation often contains an aldehyde and an alcohol group. Aldol condensations are extremely important in pharmaceuticals, used in the production of Lipitor, the immunosuppressant FK506, tetracycline antibiotics, and the antifungal agent Amphotericin B. Aldol condensations are also very important in biological processes, the breakdown of glucose in cells through glycolysis uses enzyme catalyzed aldol reactions.[1]

In general, an aldol condensation is the attack of a nucleophile on a carbonyl to make a β-hydroxy ketone or aldehyde. Usually the nucleophile is an enolate of an aldehyde or ketone that attacks another molecule of the aldehyde or ketone. The aldol condensation can be catalyzed by either an acidic or basic solution. The mechanism for the aldol condensation is as follows:[2]



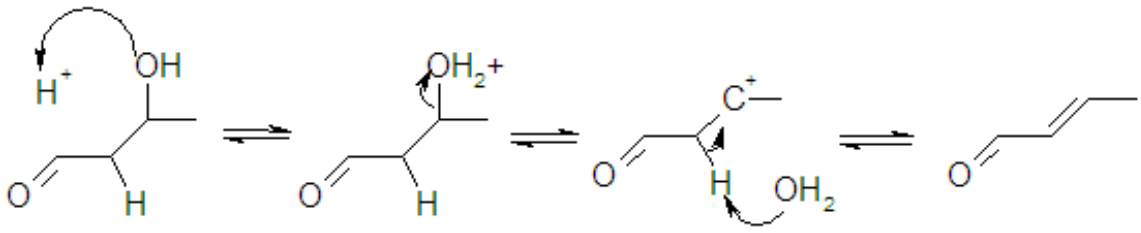
Acid catalyzed aldol condensation



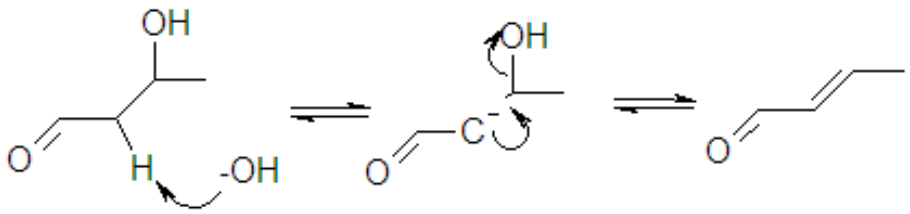
Base catalyzed aldol condensation.

Ketones are harder to use in aldol condensations, they usually produce much smaller yields than aldehydes. [2]

Aldol condensations are reversible, forming equilibria. To drive an aldol reaction to completion, dehydration is used to remove the aldol product from the reaction. The dehydration can also be carried out by acidic or basic solutions. Prior to the development of the Wittig reaction, an aldol condensation followed by dehydration was the best way to link two molecules by a carbon-carbon double bond. It is still often the simplest and cheapest way.[2]



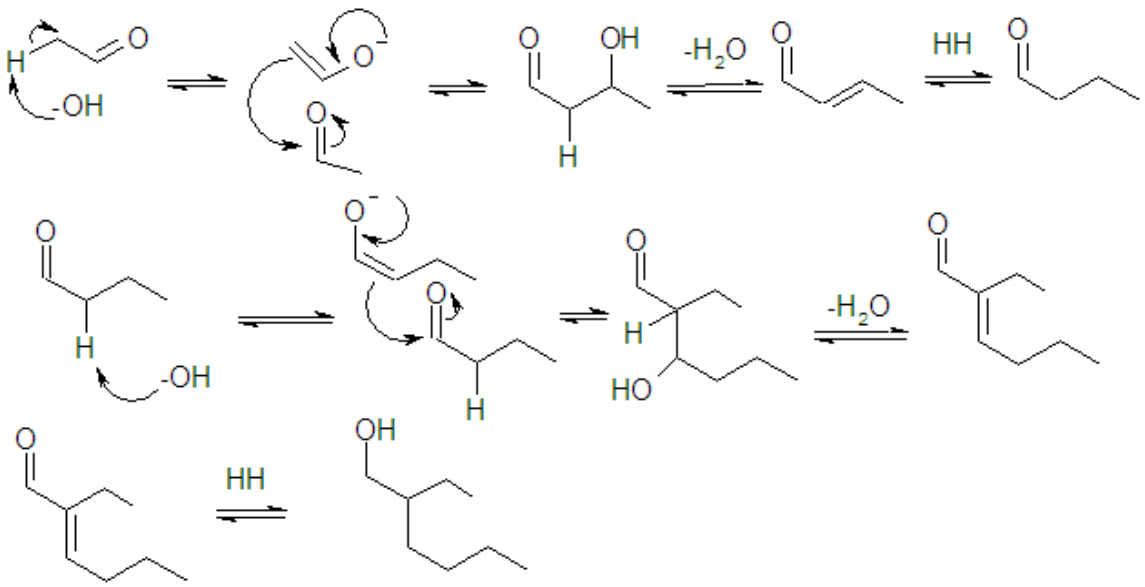
Acid catalyzed dehydration.



Base catalyzed dehydration.

The base catalyzed dehydration works because the loss of the hydroxide ion is highly exothermic in this case, producing a conjugated system, and a more stable molecule.[2]

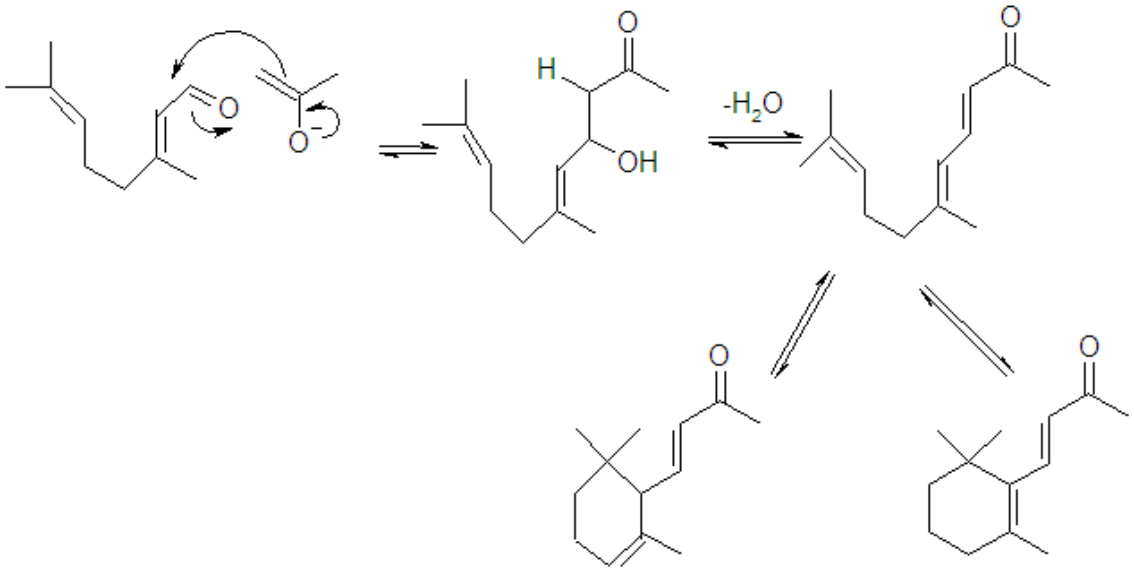
2-ethyl-hexanol is a molecule used in the production of plasticizers and sun blocks. Industrial production of 2-ethyl-hexanol uses aldol condensations of ethanal using this mechanism:[3]



The simplest aldol condensations use one type of aldehyde or ketone. However, it is possible to use more than one type of molecule. This is called a crossed aldol condensation. If not planned properly, four aldol products may be formed. Since a carbonyl needs α- protons to make an enolate, crossed aldol condensations often use a molecule without α- protons as the electrophile. The carbonyl with α- protons is then

added slowly to reaction vessel so that the enolate attacks the electrophile in excess, helping to control the reaction.[2]

An example of a crossed aldol condensation is the industrial synthesis of α and β-ionone from citral and acetone. α-ionone is used in perfumes as a violet aroma, and β-ionone is used in the synthesis of vitamin A. Both are used as artificial berry flavors. The production of these compounds follows this mechanism:[3]



α-ionone β-ionone

The aldol condensation creates two new stereogenic centers on a molecule, so an uncontrolled reaction can produce four stereoisomers. This is often random, because the enolate ion is planar, and attacks a planar carbonyl, making two tetrahedral atoms. A common way to control aldol condensation stereocenters is to use s-proline as a catalyst. The proline forms a complex with the carbonyl, and the enolate attacks stereospecifically. The exact mechanism is not precisely known, but kinetic studies show that only one molecule of proline is involved in the transition state. This is supported because the

enantiomeric excess is constant as proline concentration is changed, suggesting that the previously assumed two proline model was wrong.[4]

Kinetic studies of aldol condensations show that the aldol condensation is a two step mechanism. If the reaction took place in one step, then the rate would be proportional to the square of the aldehyde concentration, but it is only proportional to the first power of the aldehyde concentration. The rate law for aldol condensations fits this equation[6]:

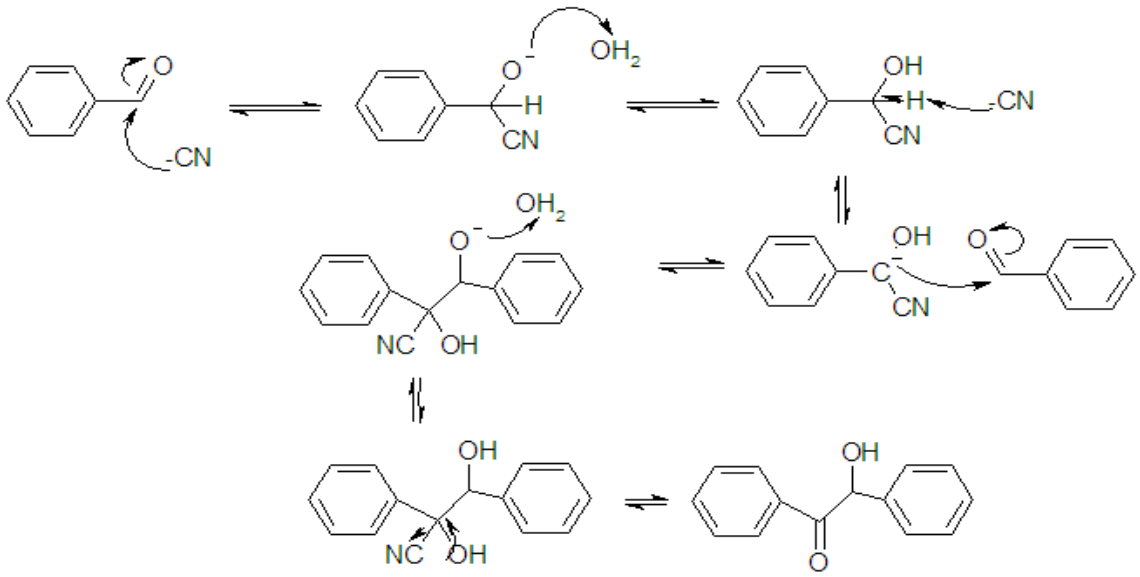
$$rate = kK_{eq}\frac{[enolate][B][carbonyl]}{[BH]}$$

[Enolate] is the concentration of the aldehyde that can be enolized, [carbonyl] is the concentration of the aldehyde that can be attacked, and [B] is the base in the reaction. If the base is the conjugate base of the solvent, then the [BH] term in the denominator drops out.

When the reaction is carried out in heavy water, the product contains no deuterium. This implies that enolization is slower than the attack on the carbonyl, since the only way for a deuterium to appear on the final product is the reversal of the enolization.[5] When the reaction is carried out with low concentrations of the attackable aldehyde, attack of the aldehyde is less likely, so destruction of the enolate becomes more significant and deuterium exchange can occur[6].

One notable exception to normal aldol condensations is the benzoin condensation. The aldehyde proton on benzaldehyde is not acidic enough to be removed by hydroxide, alkoxide, carboxylate ions, or amines. The base most often used is the cyanide ion, even though it is a weaker base than others. The cyanide adds to the carbonyl, producing a

cyanohydrin intermediate. This makes the proton acidic enough to be abstracted. The benzoin condensation proceeds through this mechanism[5]:

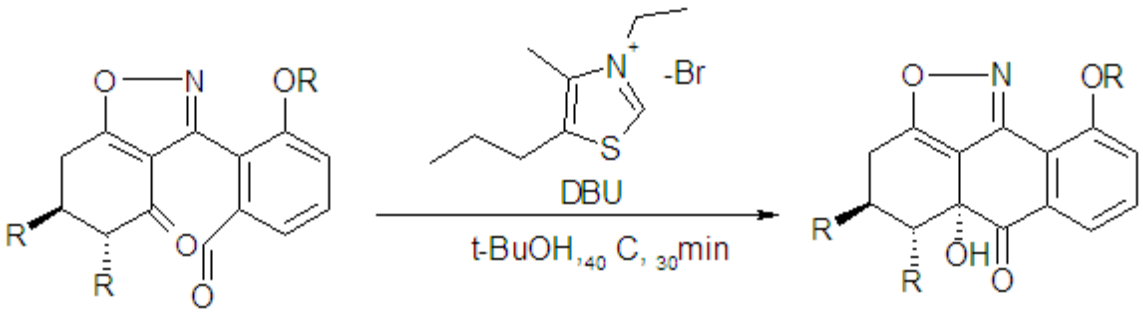


The rate of the benzoin condensation follows this equation:

$$rate = k[Benzaldehyde]^2[CN^-]$$

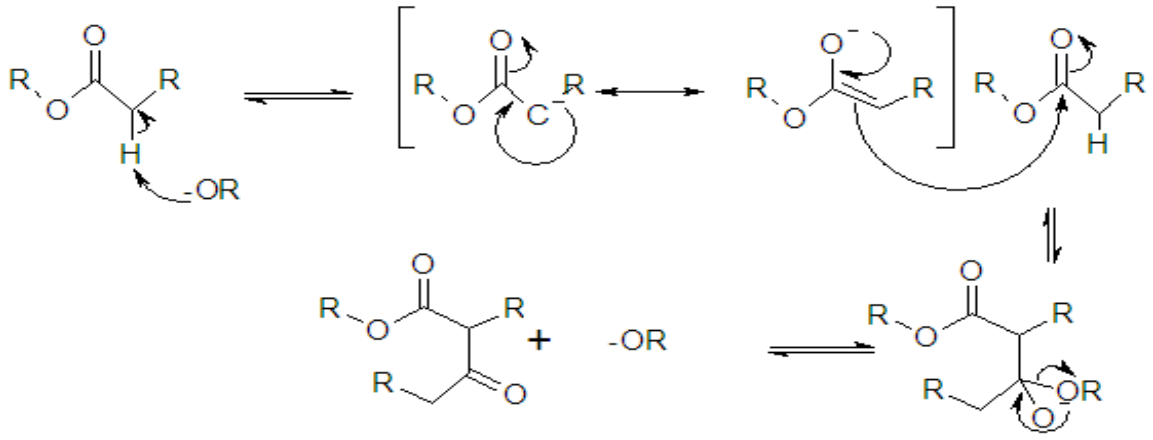
Because the rate is proportional to the square of the benzaldehyde concentration, the rate determining step must involve two molecules of the benzaldehyde. The rate determining step must be the carbanion attack on the carbonyl. Once the benzaldehyde molecules are bonded, the cyanide can be easily removed. Because benzaldehyde is an aromatic molecule, it is affected by electron donating and withdrawing groups. p-dimethylaniline benzaldehyde will not work in this reaction because the dimethylaniline group donates electrons to the carbonyl group, decreasing its ability to attract electrons. Groups that strongly attract electrons are also incompatible with this reaction, because the negative charge is pulled away from the carbanion, making it too weak to attack the other benzaldehyde.[6]

It is possible to use an internal benzoin condensation between two benzaldehyde groups on the same molecule. This can be done with an isoxazole using a thiazolium salt as a catalyst, DBU as the base, and tert-butanol as the solvent. This can be used to produce stereodefined preanthroquinones.[7]



Another way to control the stereochemistry of benzaldehyde condensations is through enzymatic methods. The enzymes benzaldehyde lyase and benzoyl formate decarboxylase both catalyze benzoin condensations with enantiopure products. The enzymes produced R enantiomers with an enantiomeric excess of greater than 99%.[8]

Another modification of the aldol condensation is the Claisen condensation. The α-protons of an ester are acidic, with pK_as around 24. Esters are not as acidic as aldehydes or ketones, which have pK_as around 20, but can still be deprotonated by weak bases to make enolate ions. The enolate ion can then attack the carbonyl on another ester, making a β-ketoester. The mechanism is as follows[2]:



β-ketoesters have pK_as around 11, making them highly acidic and easily deprotonated, since the negative charge is delocalized over both carbonyls. Since deprotonation is strongly exothermic, so it is used to drive the reaction to completion. The deprotonation means that this is not base catalyzed, because one equivalent of base is consumed, it's known as base promoted.[2]

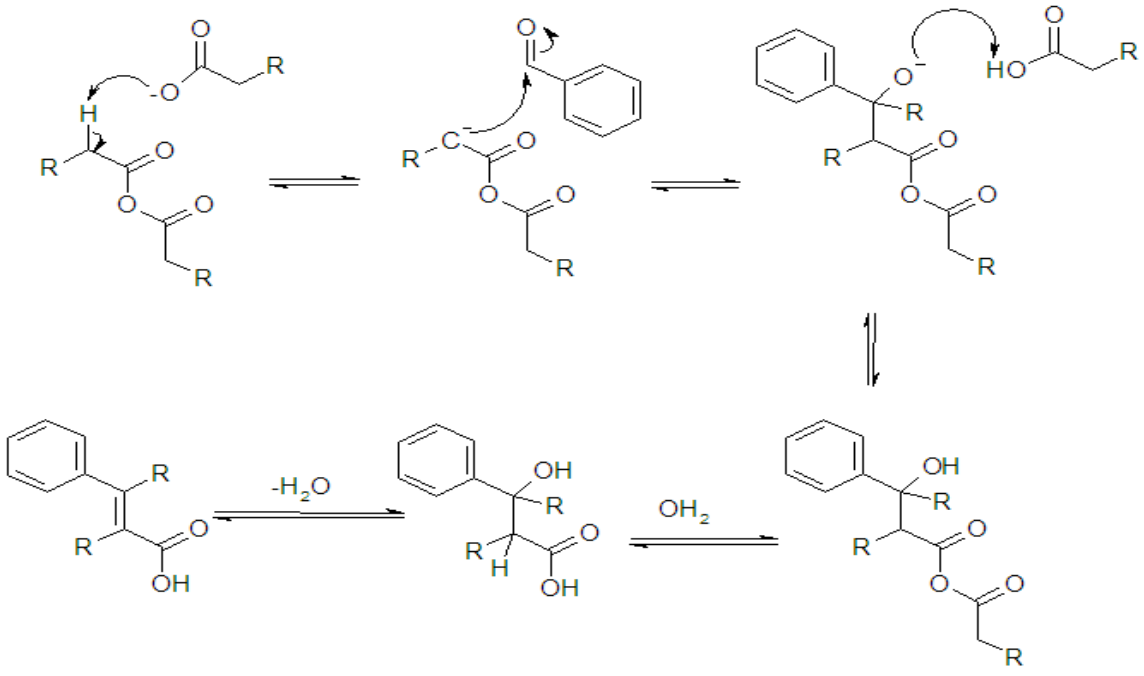
Like aldol condensations, Claisen condensations can be done between different esters. These crossed claisen condensations also make several different products. Again, choosing an ester with no α-protons can help control the reaction. If the difference in the pK_as is large enough, pH can be used to deprotonate just one of the esters.[2]

Crossed Claisen reactions are very important in biological processes. The first step of the citric acid cycle is an enzyme catalyzed condensation of acetyl-CoA, a thioester, with oxaloacetate. The amino acid side chains in the active site hold the substrate molecules in place through hydrogen bonding.[9]

The products of a Claisen condensation can be controlled through the use of esters and acid chlorides. This method has been used to synthesize complex natural products such as cis-jasmone and r-muscone.[10]

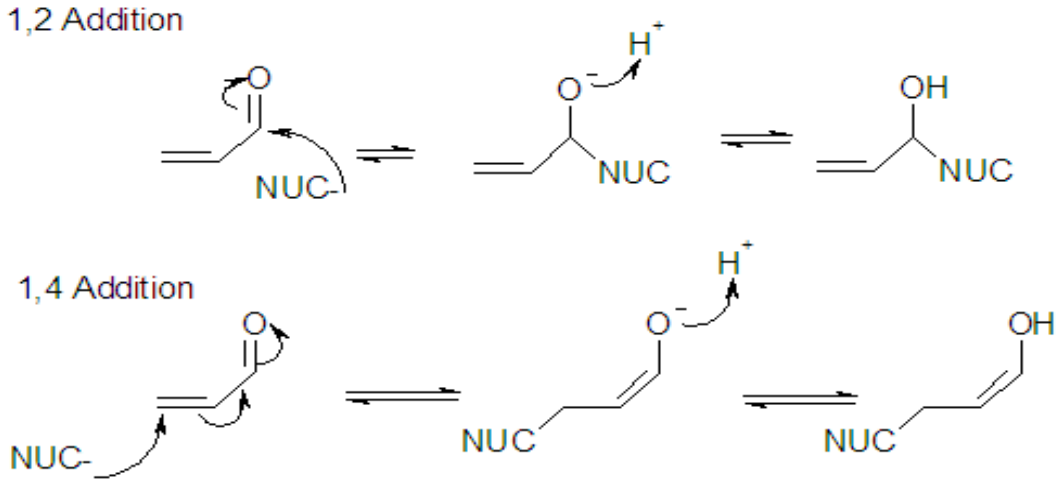
If the claisen concentration is done between the two esters of a diester, it is called a Diekman cyclization. This reaction forms five or six member rings.[2]

A modification of the claisen condensation is the Perkins reaction. In a Perkins reaction, the α-protons of an acid anhydride are deprotonated by a base, usually a salt of the carboxylic acid in the anhydride, then the carbanion attacks the carbonyl of a benzaldehyde to make a cinnamic acid derivative. If the carboxylate in the salt is different from the acid anhydride, the carboxylates will interchange, making a new acid anhydride. Also, if the anhydride is asymmetrical, then two possible products will be made, depending on which side of the molecule attacks. The Perkins reaction follows this mechanism:[5]



Conjugated molecules allow for a further extension of the aldol condensation mechanism. Resonance distributes the partial positive charge of the carbonyl carbon along the conjugated system. Usually, the conjugated system is an α,β-unsaturated carbonyl. If the nucleophile attacks at the carbonyl carbon, it is called 1, 2 addition. If the

nucleophile is added to the β carbon, it is called 1, 4 addition. This is called a Micheal addition, and is described by this mechanism:

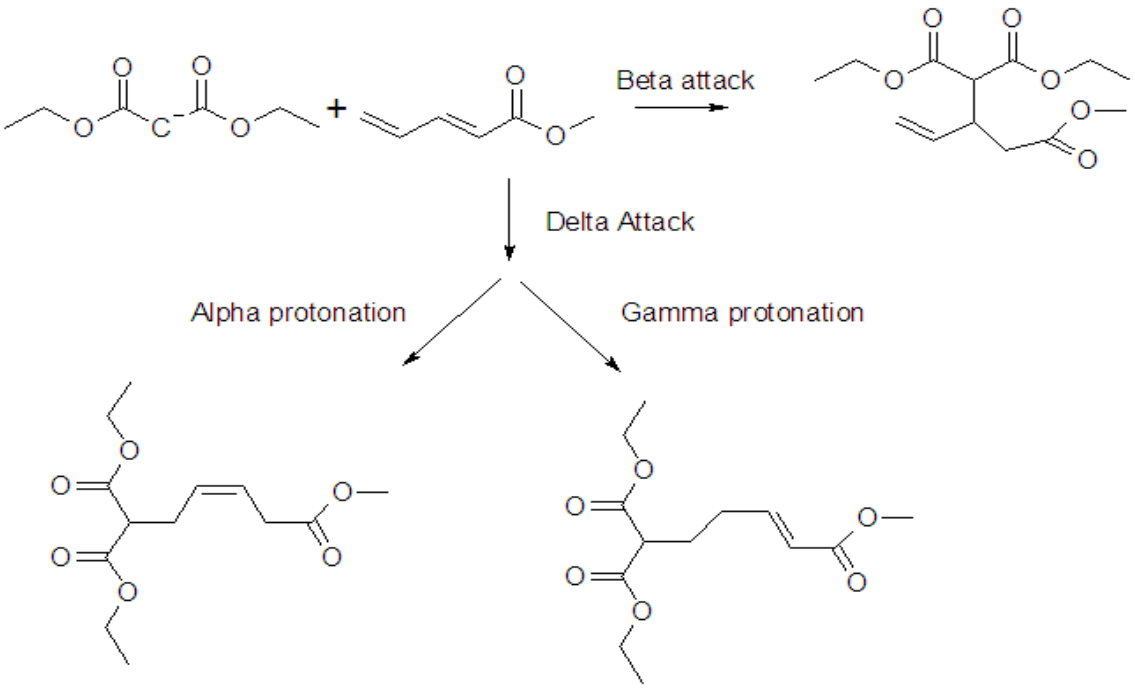


The electrophile is known as a Micheal acceptor, and the nucleophile is known as a Micheal donor. Micheal donors are carbanions stabilized by two strong electron withdrawing groups, such as carbonyl, cyano, and nitro groups.[2] One difference between Micheal additions and standard aldol condensations is that Micheal additions have lightly lower reactivity and are less readily reversible.[5]

The initial product of the Micheal reaction is quickly converted to its keto form, making the overall reaction an ester addition to the carbon-carbon double bond. The rate determining step is the formation of the new carbon-carbon bond.[6]

The maximum yield of this reaction is determined by the basicity of the reaction mixture. Since the product of a Micheal addition is a weaker acid than the reactants, a large excess of base will favor the reactants. A small amount of base is needed to start the reaction, so the concentration of base must be very carefully controlled if any product is to be obtained.[6]

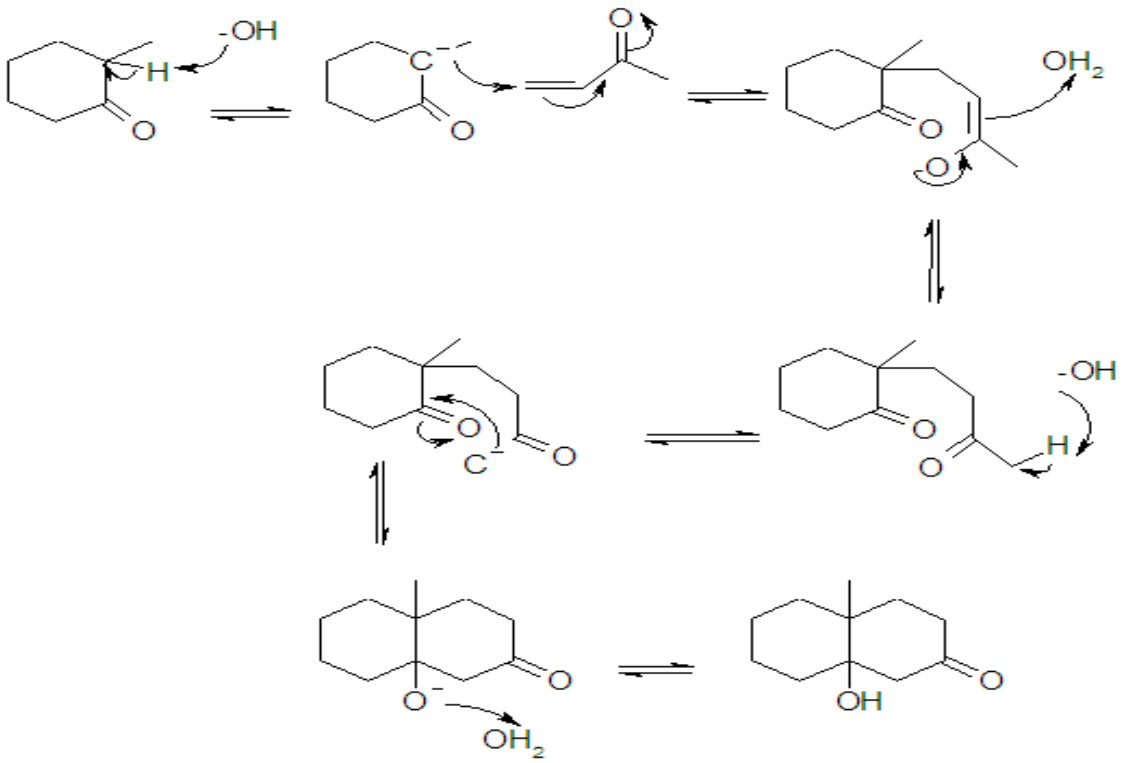
The Micheal reaction is governed by the stability of conjugated systems. If the α and β carbons are both attached to benzene rings, for example, then the Micheal addition will not work, because the doubly aromatic molecule is already too stable to react. If the Micheal acceptor has two or more carbon-carbon double bonds, then a micheal donor can add to several more places on the acceptor. For example, an α,β,γ,δ-unsaturated carbonyl can be attacked by the donor at the β and δ carbons. This yields two products. However, if the donor attacks at the δ carbon, then protonation can occur at either the α or γ carbons, yielding two more possible products, for a total of four products.[6]



The major product is the most stable product. The stability of each molecule is determined by its conjugation. For example, in the above reaction, the major product is made by the donor attacking the δ carbon, then protonation at the γ carbon because that is the only way to retain the conjugated carbonyl system. If a benzene ring had been attached to the δ carbon, then the donor would prefer to attack the β carbon because it would be the only way to preserve the aromatic conjugated system. The

thermodynamically favored product is usually the predominate product because the reaction is allowed to come to equilibrium before being worked up. However, it is possible to isolate the kinetic product, if the reaction is carried out in cold temperatures, and is forced to stop before equilibrium is achieved.[6]

A combination of the Micheal reaction with the standard aldol condensation is the Robinson annulation. Robinson annulations make a six member rings by first adding a ketone enolate to an α,β-unsaturated ketone to produce a δ-diketone. Under strongly acidic conditions, this molecule can undergo a cyclic aldol condensation with itself. This will usually deprotonate, producing a cyclohexanone[2].



The aldol condensation is clearly a very flexible mechanism, capable of joining a wide variety of compounds. Its many forms and alterations make up a large part of organic synthesis, and play a critical role in laboratory, industrial, and biological

processes. Even though this general reaction has been known since the 1870s, it continues to be used extensively. Current research into the aldol condensation continues to make new products in medicine, industry, and new ways to control the stereochemistry and other features of molecules.

Works Cited

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