1. Carbanions I

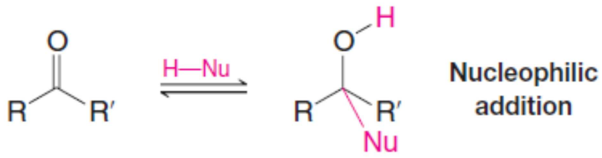
1.1 Introduction

Carbanions are negatively charged ions in which one of its carbon atoms possess three bonds and an unshared pair of electrons, sp^3 hybridized, have pyramidal structures, forms by heterolysis cleavage of covalent bond in organic compounds in presence strong base . The negative charge gives good nucleophilic properties to the unit that can be used in the formation of new carbon bonds. Carbanions thus act as nucleophile.

Presence withdrawing groups caused delocalized the negative charge and stabilized the carbanion by Inductive Effects .

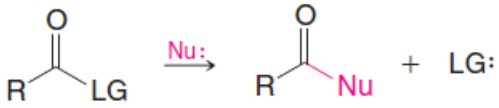
While presence donating groups attachment at carbanion localized the negative charge which caused destabilized the carbanion.

We saw how aldehydes and ketones can undergo nucleophilic addition at their carbonyl groups. For example:



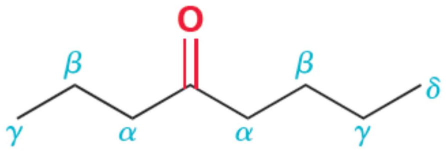
H-Nu = H-OH, H-OR, H-CN, ...etc.

And substitution could occur at a carbonyl group if a suitable leaving group is present. This type of reaction is called acyl substitution For example:



H-Nu =-OH, -OR, -Cl, $-NH_2$, … etc

Reactions can also occur at the α carbon to the carbonyl group, Greek letters are used to describe the proximity of each carbon atom to the carbonyl group.

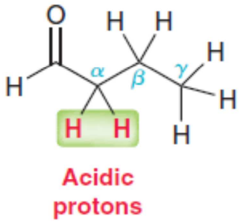


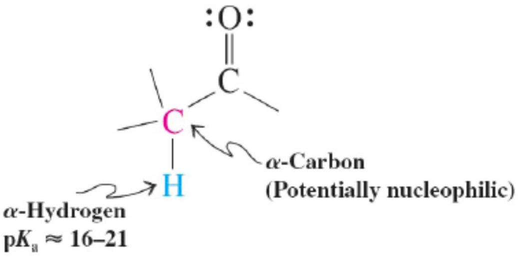
1.2 Acidity of Aldehydes and Ketones: Enolate Ions

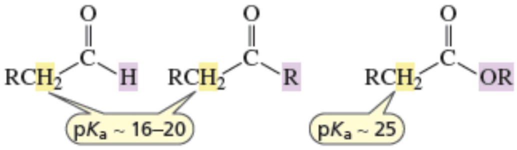
Acidity of α-hydrogens:

A hydrogen bonded to carbon adjacent to a carbonyl carbon is much more acidic than hydrogens bonded to other carbons. For example, the pKa for dissociation of an α-hydrogen from an aldehyde or a ketone ranges from 16 to 20, and the pKa for dissociation of an α-hydrogen from an ester is about 25.

A compound that contains a relatively acidic hydrogen bonded to carbon is called a carbon acid.

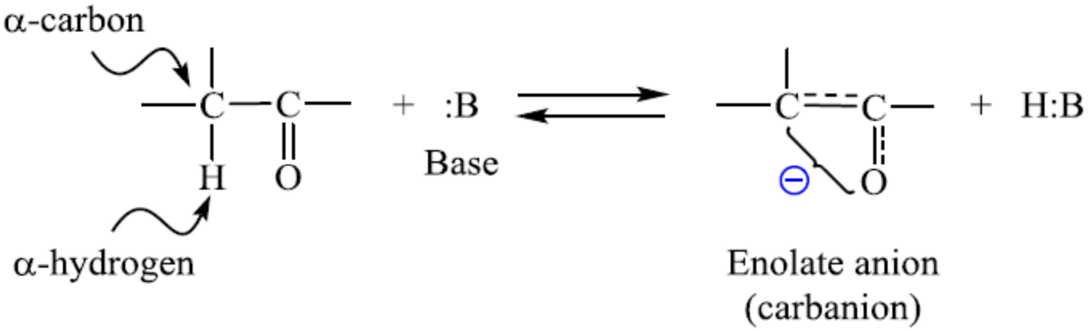




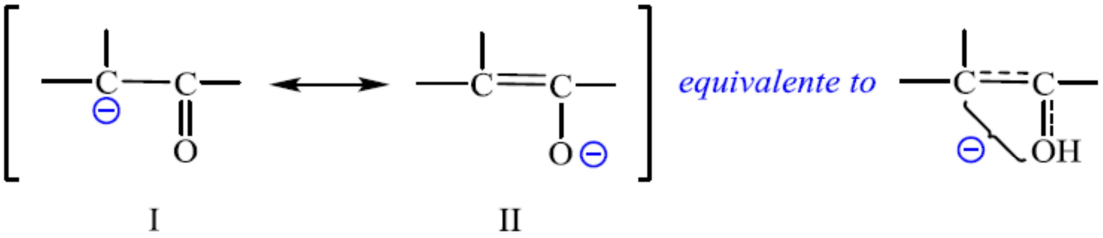


The carbonyl group strengthens the acidity of the hydrogen atoms attached to the α-carbon and, since it act as an electron withdrawing group due to the presence of a highly electronegative oxygen atom.

Thus, the presence of a base with a carbonyl compound that possesses an α-hydrogen will lead to ionization of the latter as the following:



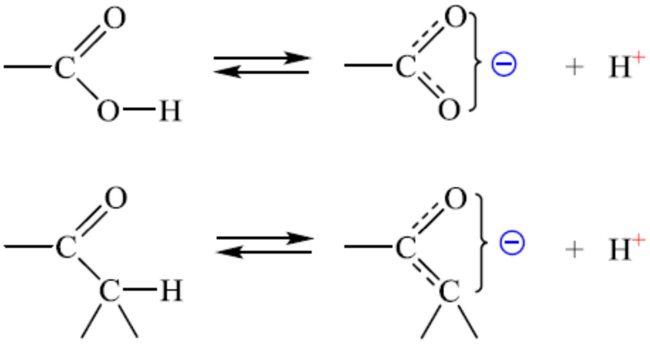
This carbanion is a resonance hybrid of two structures (I and II):



Resonance is possible only through participation by the carbonyl group. Resonance of this kind is not possible for carbanions formed by ionization of β-hydrogens, γ-hydrogens, etc., from saturated carbonyl compounds.

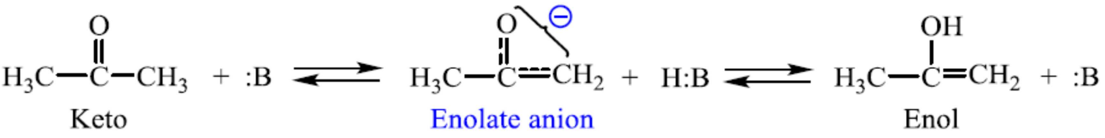
Hydroxide ion is the most common base that used in these reactions and in some cases strong bases can be used like aluminum tertiary butoxide.

The carbonyl group affect on the acidity of α-hydrogen in the same way that it affects on the acidity of the carboxylic acids by accommodate the negative charge of the anion as the following:



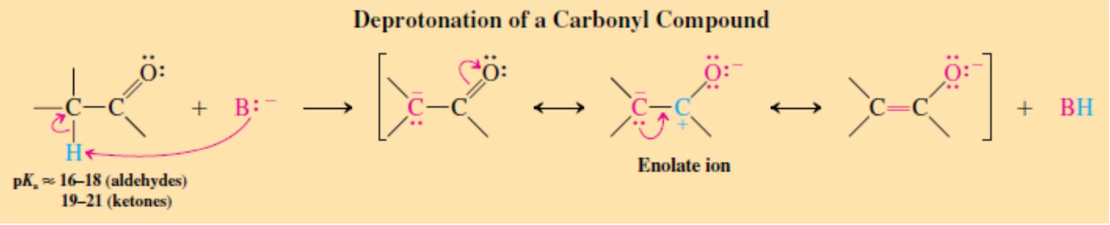
In spite of the fact that the α-hydrogen of an aldehyde or ketone are very weak acidic compared with carboxylic acids, but they are acidic enough to be abstracted by a base to generate carbanions.

***Note:* Carbanions that stabilized by carbonyl carbon is known as enolate anion, since the formed anion is not only in the keto form, but also in the enol form:**



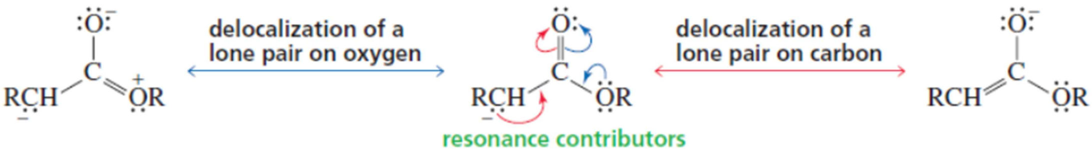
Why are aldehydes and ketones relatively acidic?

We know that acid strength is enhanced by stabilization of the conjugate base. In the enolate ion, the inductive effect of the positively polarized carbonyl carbon strongly stabilizes the negative charge at the α -position. Aldehydes are stronger acids than ketones because their carbonyl carbon bears a larger partial positive charge. Further strong stabilization is provided by delocalization of charge onto the electronegative oxygen.



Why aldehydes and ketones are more acidic than esters ?

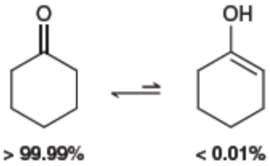
The electrons left behind when an α-hydrogen is removed from an ester are not as readily delocalized onto the carbonyl oxygen as are the electrons left behind when an α-hydrogen is removed from an aldehyde or a ketone. Because a lone pair on the oxygen of the OR group of the ester can also be delocalized onto the carbonyl oxygen, the two pairs of electrons compete for delocalization onto oxygen:



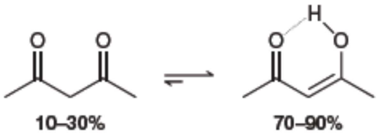
The keto and enol forms of carbonyl compounds are constitutional isomers, but of a special type. Because they are easily interconverted by proton transfers in the presence of an acid or base,

- Interconvertible keto and enol forms are called tautomers, and their interconversion is called tautomerization.

In general, the position of equilibrium will significantly favor the ketone, as seen in the following example:



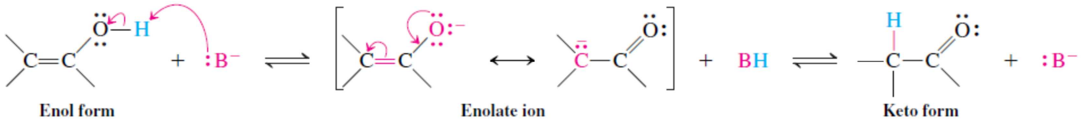
In some cases, the enol tautomer is stabilized and exhibits a more substantial presence at equilibrium. Consider, for example, the enol form of a beta-diketone, such as 2,4-pentanedione.



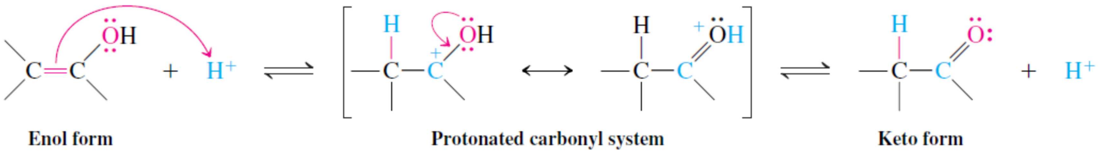
The equilibrium depend on the solvent that is used, but the enol generally dominates. Because :
(1) The enol has a conjugated π system, which is a stabilizing factor, and (2) the enol can form an intramolecular H-bonding interaction. Both of these factors serve to stabilize the enol.

An enol equilibrates with its keto form in acidic or basic solution

Base-Catalyzed Enol–Keto Equilibration



Acid-Catalyzed Enol–Keto Equilibration



1.3 Reactions involving carbanions:

The carbanions are highly basic, exceedingly reactive particles. In their reactions they behave as we would expect: as nucleophiles.

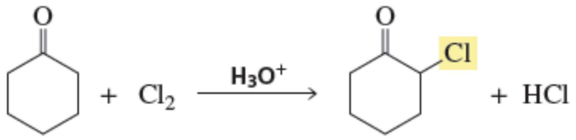
As nucleophiles, carbanions can attack carbon and, in doing so, form carbon-carbon bonds.

1.3.1 Halogenation of ketones:

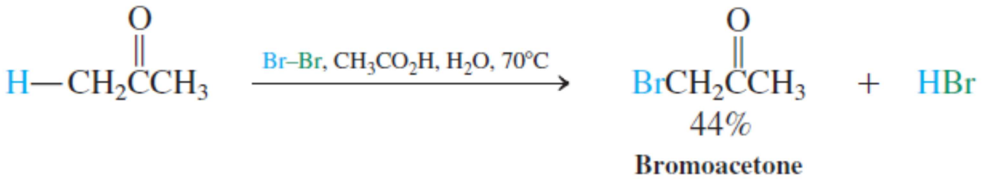
Ketones that contain α-hydrogen can be halogenated at α-carbon, since the reaction of an aldehyde or ketone with halogen (Cl2, Br2, I2 but not F2) will afford the α-halo product. The reaction proceeded in either basic ro acidic medium.

a) Acid-Catalyzed -Halogenation of Ketones

In the presence of acid, halogenation usually stops after the first halogen has been introduced, as shown in the following example.



Cyclohexanone 2-chlorocyclohexanone (65%)



$$H{-}CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{Br{-}Br,\ CH_3CO_2H,\ H_2O,\ 70°C} BrCH_2\overset{O}{\overset{\|}{C}}CH_3 + HBr$$

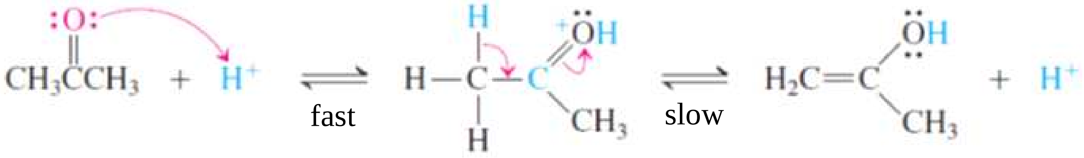
44%

Bromoacetone

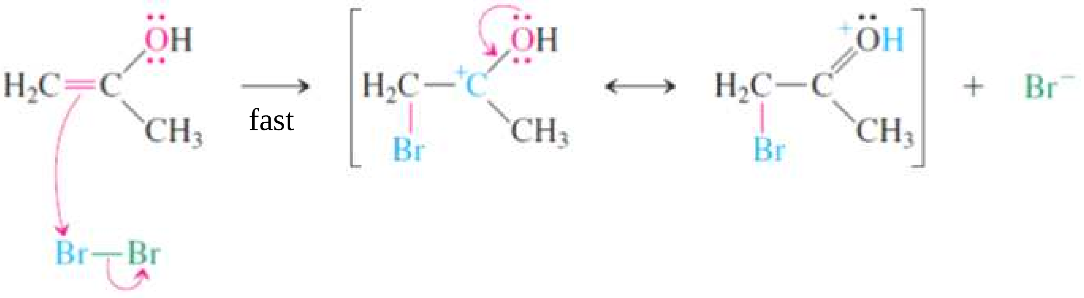
The rate-determining reaction here is the formation of the enol, which involves two steps: rapid, reversible protonation (step 1) of the carbonyl oxygen, followed by the slow loss of an α-hydrogen. Once formed, the enol reacts rapidly with halogen (step2):

Mechanism of the Acid-Catalyzed Bromination of Acetone

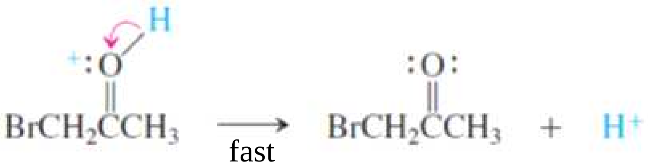
Step 1. Enolization *(rate determining)*



Step 2. Halogen attack



Step 3. Deprotonation



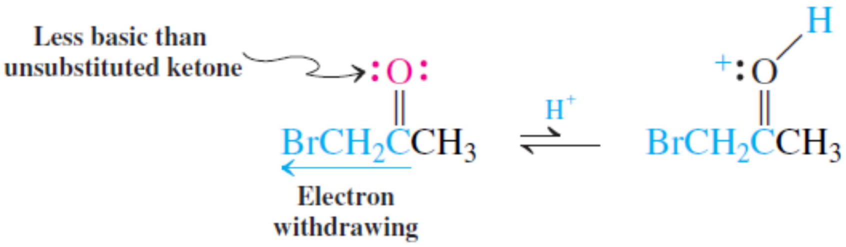
Evidence for the mechanism includes the observation that acid-catalyzed halogenations show second-order kinetics, the reaction rate depends on the concentration of acetone and the acid, but is independent on bromine concentration. and follow the rate law:

$$\text{Reaction rate} = k\,[\text{Ketone}]\,[\text{H}^+]$$

Why is further halogenation retarded ?

The electron-withdrawing power of the halogen makes protonation, the initial step in enolization, *more difficult* than in the original carbonyl compound.

Halogenation Slows Down Enolization



b) Base-promoted halogenations of ketones:

Acetone reacts with bromine to form bromoacetone; the reaction accelerated by base (e.g. hydroxide ion, acetate ion, etc.).

$$CH_3COCH_3 + Br_2 + \underset{\text{Base}}{:B^-} \longrightarrow CH_3COCH_2Br + Br^- + H{:}B$$

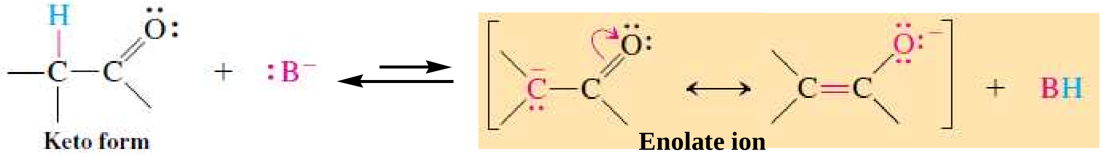
Kinetic study of the reaction shows that the reaction rate depends on the concentration of acetone and the base, but is independent on bromine concentration.

$$\text{rate} = k\,[\text{acetone}][{:}B]$$

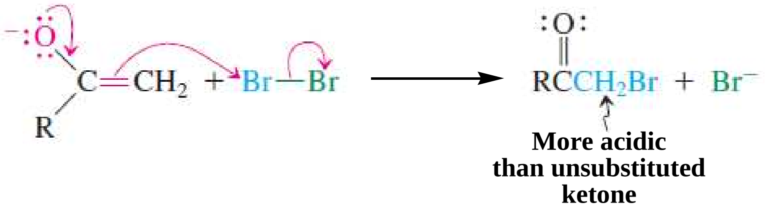
Base-mediated halogenation is entirely different. It proceeds instead by the formation of an enolate ion, which then attacks the halogen. Here the reaction continues until it *completely* halogenates the same α-carbon, leaving unreacted starting material (when insufficient halogen is employed).

Mechanism of the base-Catalyzed Bromination of Acetone

Step 1. Deprotonation of the a carbon forms the enolate ion



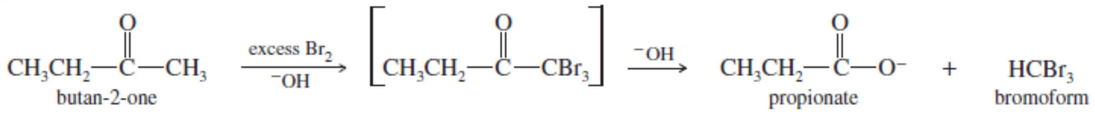
Step 2. The enolate ion attacks the electrophilic halogen.



The base abstract a proton slowly (step1) from acetone to form carbanion, which then react with bromine to give bromoacetone (step 2).
Step 1 (generation of carbanion) is the rate determining step (r.d.s).

Why is base-catalyzed halogenation so difficult to stop at the stage of mono halogenation?
The electron-withdrawing power of the halogen increases the acidity of the remaining α-hydrogens, accelerating further enolate formation and hence further halogenation.

Example:



Note:

a- *The rate of iodination of acetone is the same with bromination, and this indicates that the reaction is independent on the halogen concentration.*

b- *Halogenation can be done with other halogenating agents like sulfuryl chloride*(SO_2Cl_2) *or cupric chloride*($CuCl_2$) *for chlorination and N-bromosuccinimide for bromination.*

1.3.2 Aldol Condensation

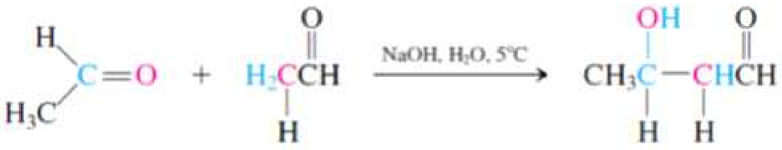
Under the influence of dilute base or dilute acid, two molecules of an aldehyde or a ketone (that contain α-hydrogen) may combine to form a β-hydroxyaldehyde or β-hydroxyketone, the common name *aldol* (from *ald*ehyde alcoh*ol*).This reaction is called the **aldol additions**.

In every case the product results from addition of one molecule of aldehyde (or ketone) to a second molecule in such a way"that the α -carbon of the first becomes attached to the carbonyl carbon of the second.

Under more severe conditions (higher base or acid concentration, or heat, or both), the product of aldol addition undergoes a dehydration reaction (loses H_2O). The overall reaction is called an **aldol condensation**, forms a *new carbon-carbon double bond*.

The term *condensation* is used to refer to any reaction in which two molecules undergo addition accompanied by the loss of a small molecule such as water, carbon dioxide, or nitrogen gas. In the case of aldol condensations, water is the small molecule that is lost, to give α,*β*-unsaturated carbonyl compound (enal or enone).

For examples:

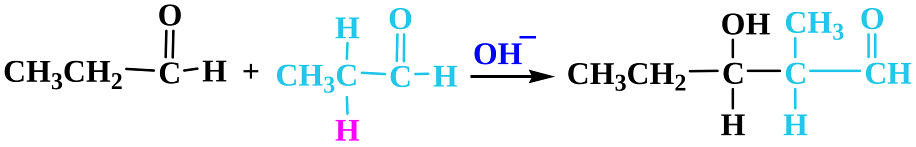


2 moles of acetaldehyde

3-Hydroxybutanal

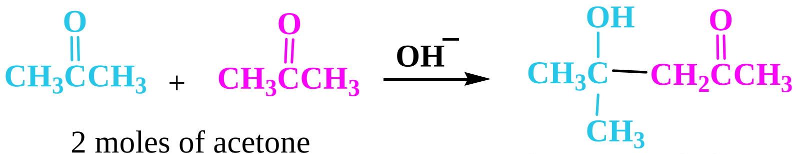
β-Hydroxybutyraldehyde

formed as a racemic mixture



$$CH_3CH_2-\overset{O}{\overset{\|}{C}}-H + CH_3\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}}-H \xrightarrow{OH^-} CH_3CH_2-\overset{OH}{\underset{H}{C}}-\overset{CH_3}{\underset{H}{C}}-\overset{O}{\overset{\|}{C}H}$$

2 moles of propionaldehyde β-hydroxy-α-methylvaleraldehyde (3-hydroxy-2-methylpentanal)



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + CH_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{OH^-} CH_3\overset{OH}{\underset{CH_3}{C}}-CH_2\overset{O}{\overset{\|}{C}}CH_3$$

2 moles of acetone 4-Hydroxy-4-methyl-2-pentanone

Note: If the aldehyde or ketone doesn't contain α-hydrogen, a simple aldol condensation cannot take place like:

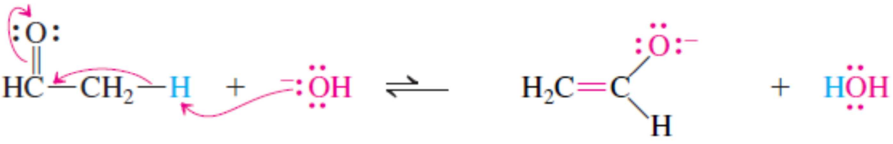
Benzaldehyde	PhCHO or ArCHO	no α-hydrogen
Formaldehyde	HCHO	
2,2-Dimethylpropionaldehyde	$(CH_3)_3CCHO$	
Benzophenone	PhCOPh or ArCOAr	
Tri-substituted ketone	$ArCOCR_3$	

a) Base-Catalyzed Aldol Condensations

Under basic conditions, the aldol condensation occurs by a nucleophilic addition of the enolate ion (a strong nucleophile) to a carbonyl group. Protonation gives the aldol product.

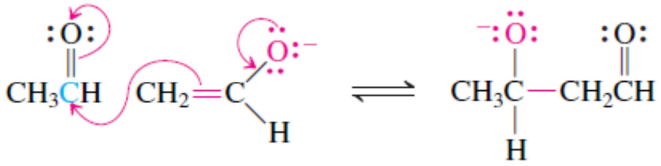
Mechanism of Aldol Formation

STEP 1. Enolate generation



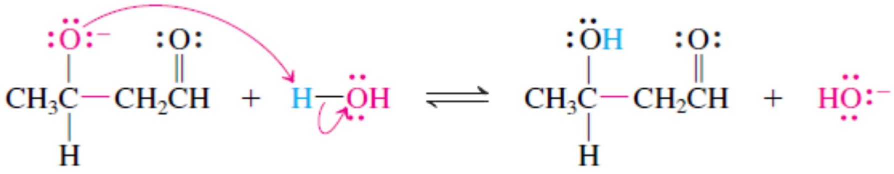
Small equilibrium concentration of enolate(I)

STEP 2. Nucleophilic attack



(II)

STEP 3. Protonation



50–60%

3-Hydroxybutanal (III)
(Aldol)

In step1, Hydroxide ion abstract a hydrogen ion from the α-carbon to form carbanion (I),which attacks carbonyl group in step2 to form ion (II). In step3, ion (II) an alkoxide, abstracts a hydrogen ion from water to form β-hydroxyaldehyde (III) and regenerate the hydroxide ion.

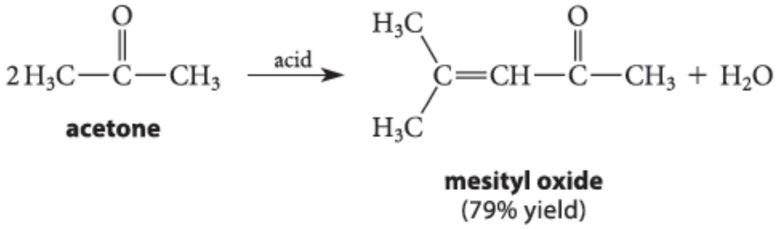
Illustrate these steps for:
(a) propionaldehyde (b) phenylacetaldehyde
(c) acetophenone (d) cyclohexanone .

Note: *The carbonyl group plays two roles in this reaction:*

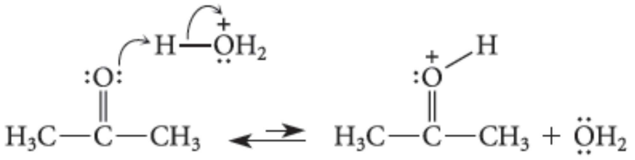
1. *It provides the unsaturated linkage at which the addition occurs (step 2).*
2. *It makes the α-hydrogen acidic enough for carbanion formation (step 1) to take place.*

b)Acid-Catalyzed Aldol Condensations

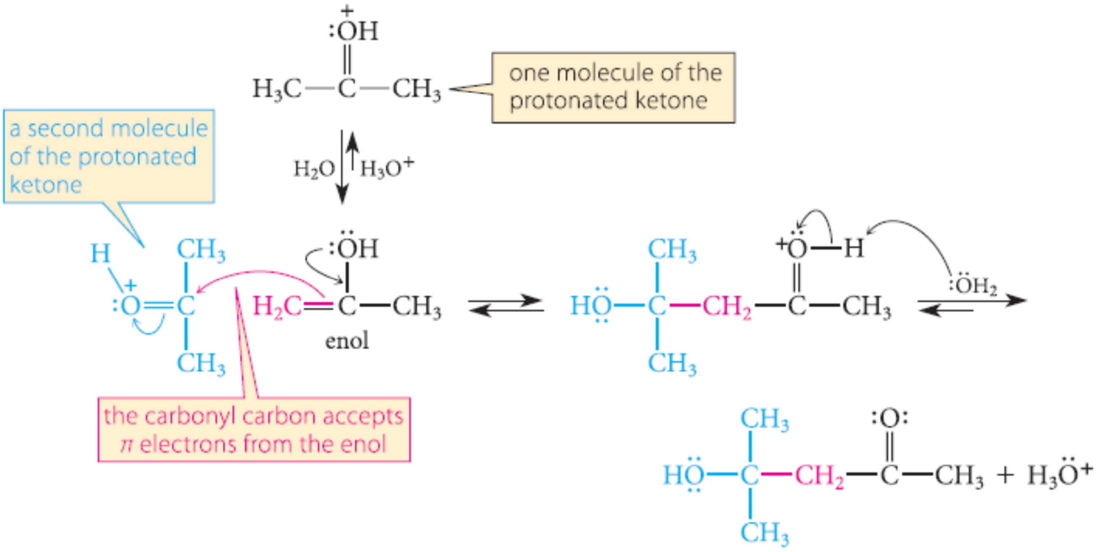
Acid-catalyzed aldol condensations, generally give α,*β*-unsaturated carbonyl compounds as products; addition products cannot be isolated.



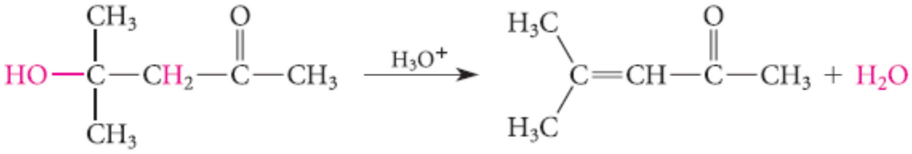
In acid-catalyzed aldol condensations, the conjugate acid of the aldehyde or ketone is a key reactive intermediate.



This protonated ketone plays two roles. First, it serves as a source of the *enol*. Second, the protonated ketone is the electrophilic species in the reaction. It reacts as an electrophile with the *π* electrons of the enol to give the conjugate acid of the addition product:



The loss of a proton gives the *β*-hydroxy ketone product. Under the acidic conditions, this material spontaneously undergoes acid-catalyzed dehydration to give an α,*β*-unsaturated carbonyl compound:



Let’s contrast the species involved in the acid- and base-catalyzed aldol reactions.

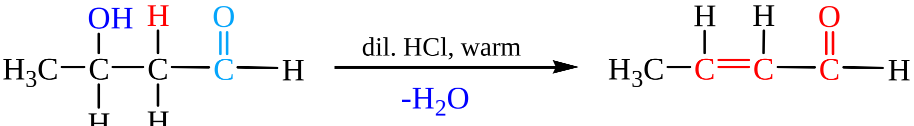
Reaction	***Nucleophile***	***Electrophile***
Base-catalyzed aldol reaction	enolate ion	neutral carbonyl compound
Acid-catalyzed aldol condensation	enol	protonated carbonyl compound

1.3.2.1 Dehydration of the Aldol Product

The β-hydroxyaldehydes or β-hydroxyketones that formed from aldol condensation are very easily dehydrated either by heating the basic solution of reaction or by a separate acid catalyzed reaction (which is the general procedure to prepare alkenes from alcohols).

Dehydration of aldol products will give compounds that have the carbon-carbon double bond between α- and β- carbon atoms in conjugation with the carbonyl group which is called α,β-unsaturated carbonyl compounds.

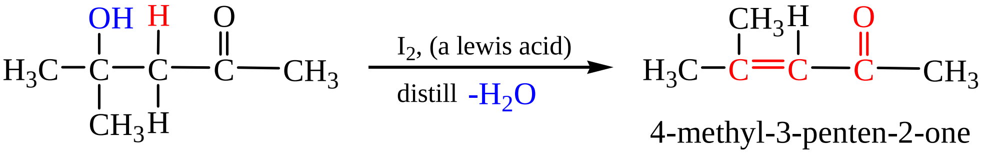
For example:



$H_3C-CH(OH)-CH_2-CHO \xrightarrow[-H_2O]{\text{dil. HCl, warm}} H_3C-CH=CH-CHO$

3-Hydroxy-2-Butanal **(Aldol)**

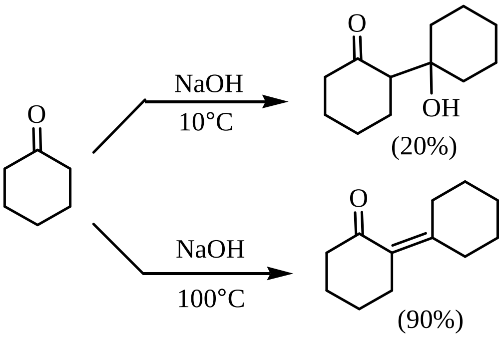
2-Butenal (**Crotonaldehyde**)



$H_3C-C(OH)(CH_3)-CH_2-CO-CH_3 \xrightarrow[\text{distill } -H_2O]{I_2\text{, (a lewis acid)}} H_3C-C(CH_3)=CH-CO-CH_3$

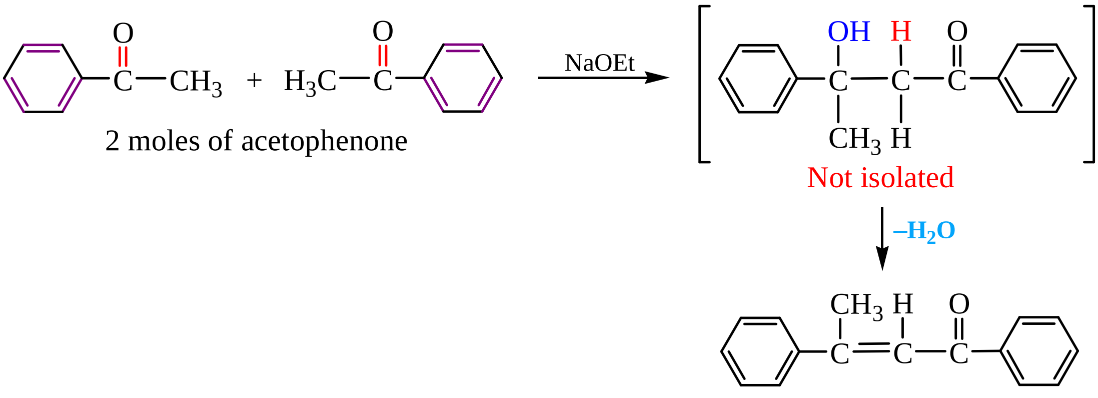
4-Hydroxy-4-methyl-2-pentanone

4-methyl-3-penten-2-one (**Mesityl oxide**)



When the α,β-unsaturated carbonyl compound is further conjugated (π system) with a carbon–carbon double bond or a benzene ring, **elimination of H_2O is spontaneous** and the β-hydroxy carbonyl compound cannot be isolated.

For example:



2 moles of acetophenone

Not isolated

1,3-Diphenyl-2-buten-1-one

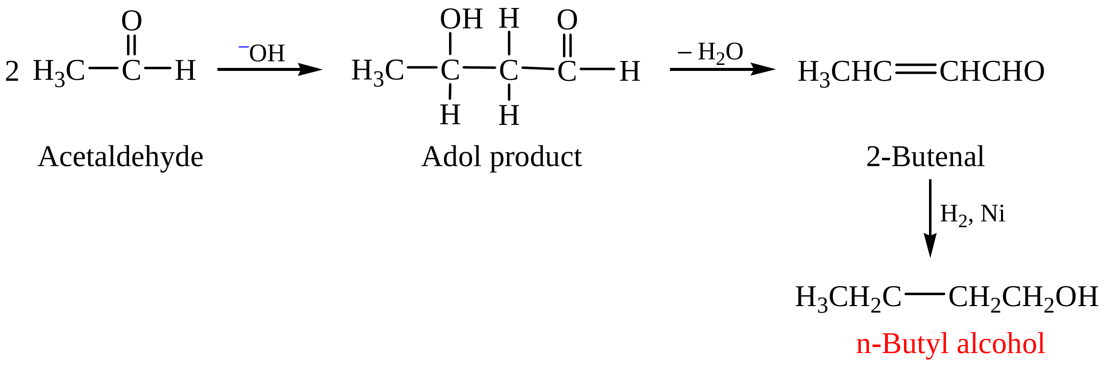
1.3.2.2 Use of aldol condensation in synthesis:

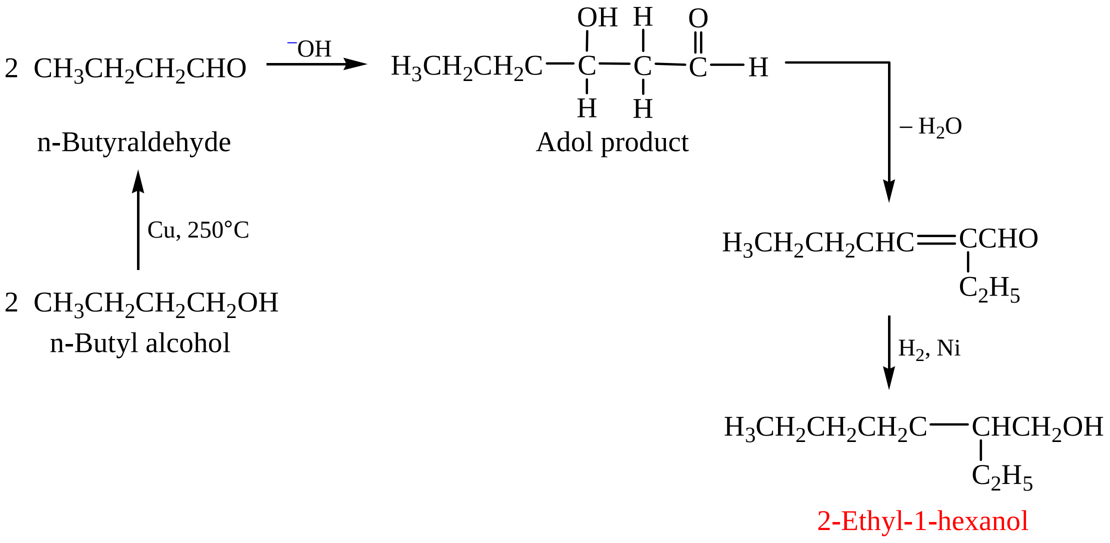
Aldol condensation products can be used in the synthesis of a wide variety of organic compounds through their different reactions. For example:

1- Dehydration of aldol products will produce α,β-unsaturated carbonyl compounds (discussed previously).

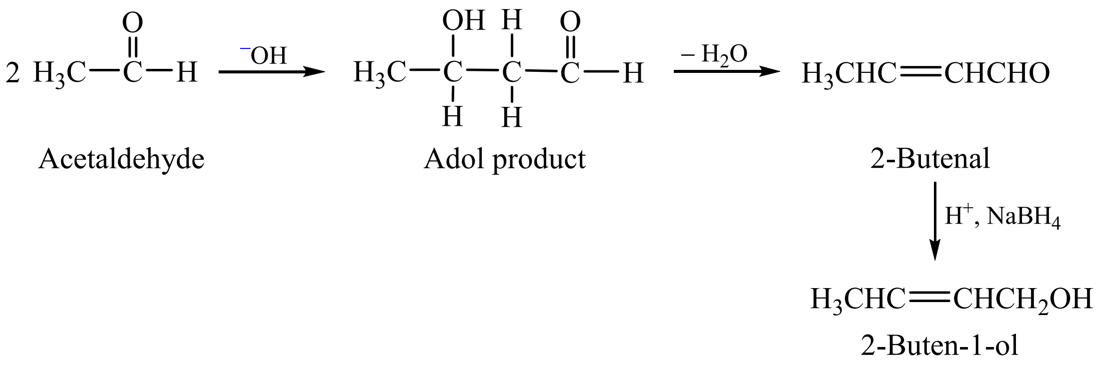
2- Catalytic hydrogenation of α,β-unsaturated carbonyl compounds yields saturated alcohols, since addition of hydrogen occurring both at carbon-carbon and carbon-oxygen double bonds.

e.g.: n-Butyl alcohol and 2-Ethyl-1-hexanol are both prepared on an industrial scale as the following:





Synthesis of unsaturated alcohols by the use of a reagent that reduce only the carbonyl group and leaves the carbon-carbon double bond intact (chemoselective reagent) like sodium borohydride $NaBH_4$

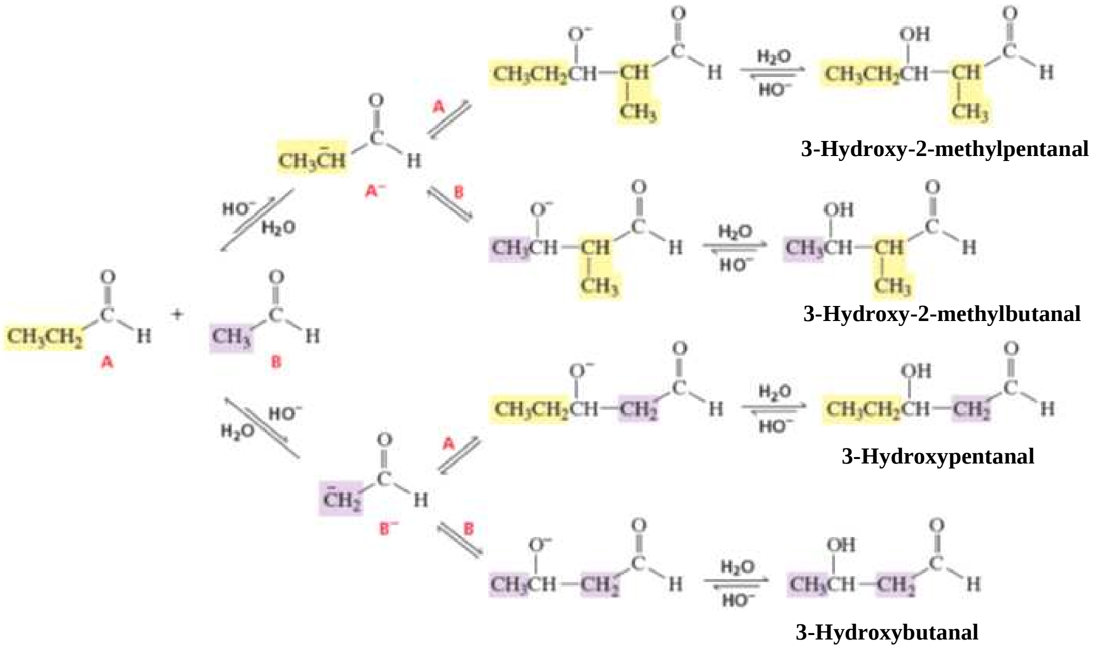


Note: *Chemoselective reagent, A reagent that, in performing its particular job, selectively attacks one of several different functional groups.*

1.3.2.3 Crossed aldol condensation:

An aldol condensation between two different carbonyl compounds is called crossed aldol condensation in which at least one of them have an α-hydrogen. A mixture of four possible products may be obtained.

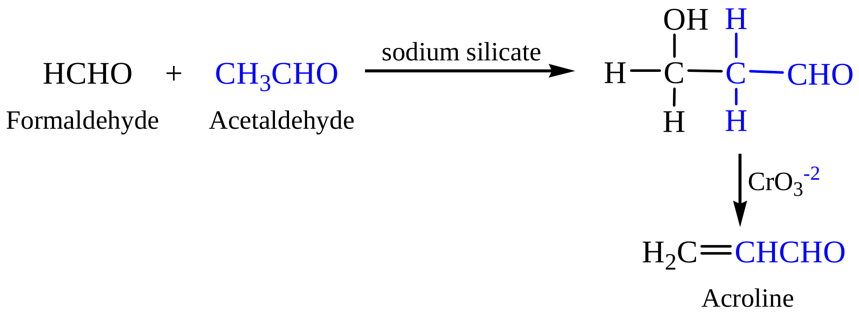
For example:



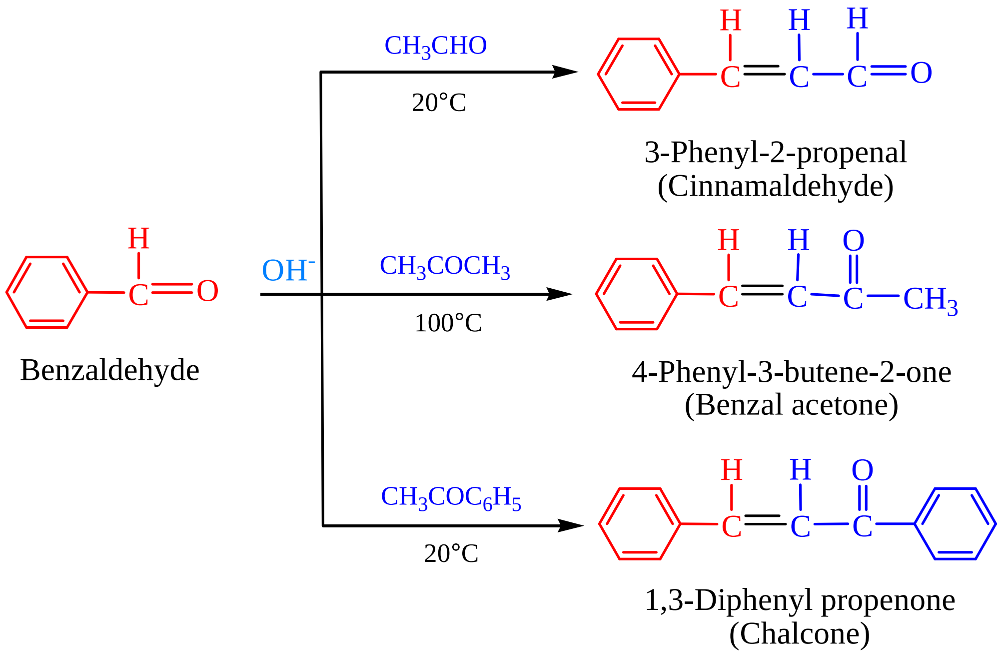
Under certain conditions, a good yield of single product can be obtained from crossed aldol condensation:

a) One reactant contains no α-hydrogen and therefore is incapable of condensing with itself (e.g. aromatic aldehydes or formaldehyde).
b) This reactant is mixed with the catalyst; and then
c) A carbonyl compound that contains α-hydrogen is added slowly to this mixture.

e.g.



$$\underset{\text{Formaldehyde}}{HCHO} + \underset{\text{Acetaldehyde}}{CH_3CHO} \xrightarrow{\text{sodium silicate}} H-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-CHO \xrightarrow{CrO_3^{-2}} \underset{\text{Acroline}}{H_2C=CHCHO}$$



Benzaldehyde

3-Phenyl-2-propenal
(Cinnamaldehyde)

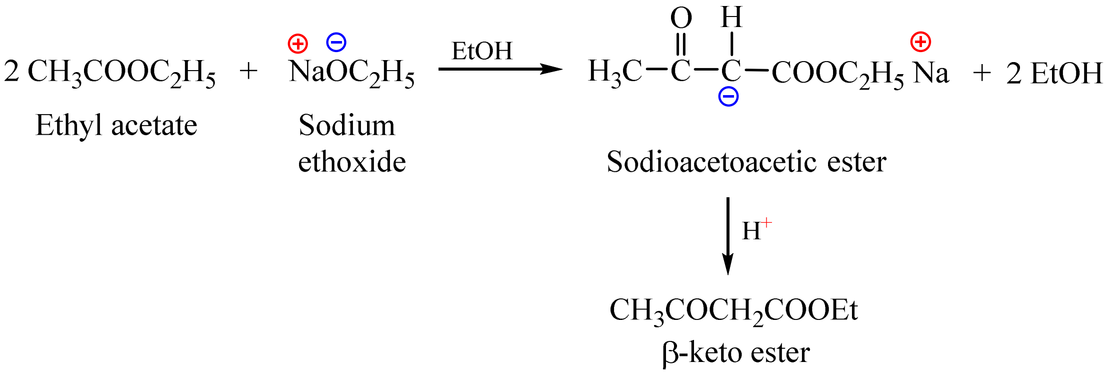
4-Phenyl-3-butene-2-one
(Benzal acetone)

1,3-Diphenyl propenone
(Chalcone)

1.3.3 Claisen condensation (formation of β-keto esters):

Aliphatic esters that contain at least one α-hydrogen undergoes condensation reaction in the presence of sodium ethoxide (as a base) to produce β-keto esters.

The typical example for this reaction is the formation of ethyl acetoacetate from ethyl acetate.



$$2\,CH_3COOC_2H_5 + \overset{\oplus}{Na}\overset{\ominus}{O}C_2H_5 \xrightarrow{EtOH} H_3C-\overset{O}{\overset{\|}{C}}-\underset{\ominus}{\overset{H}{\overset{|}{C}}}-COOC_2H_5\,\overset{\oplus}{Na} + 2\,EtOH$$

Ethyl acetate Sodium ethoxide Sodioacetoacetic ester

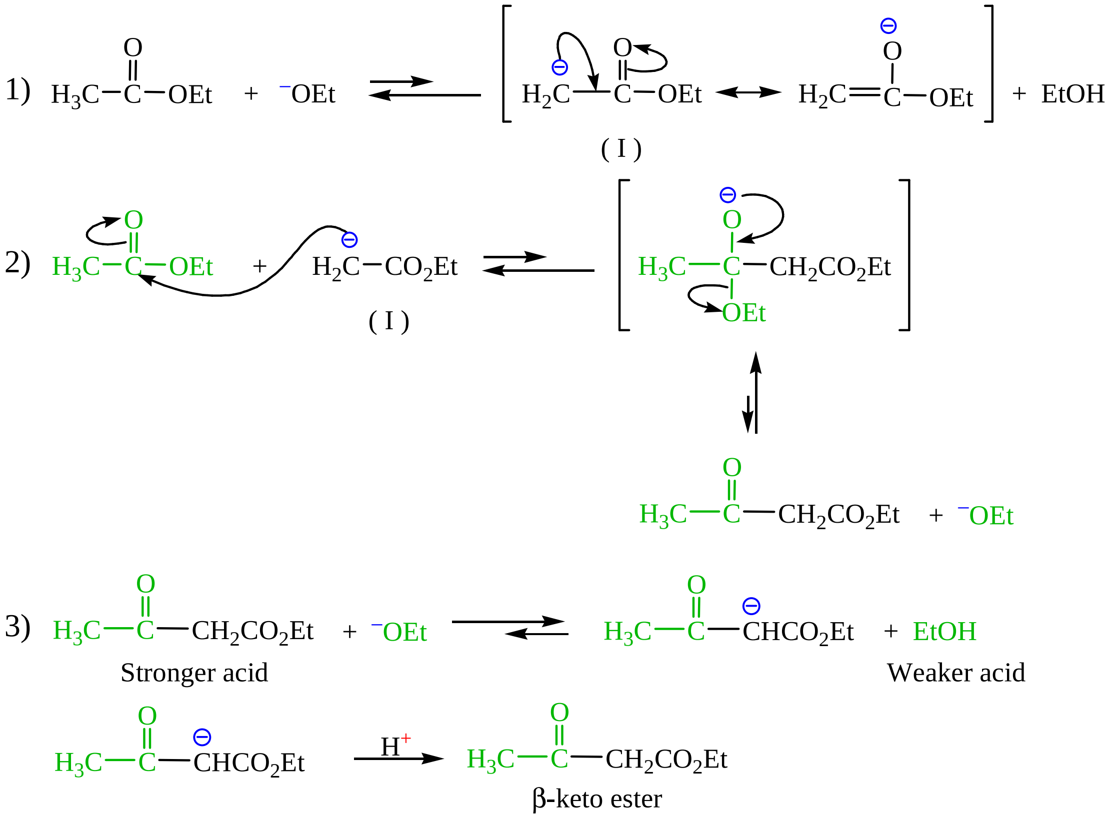
$$\downarrow H^+$$

$$CH_3COCH_2COOEt$$

β-keto ester

An α-hydrogen in an ester is less acidic than those in aldehydes or ketones (due to the interaction between oxygen atoms in the ester group), however the ethoxide ion is basic enough to abstract this proton and convert the ester (partially) to carbanion (enolate).

The generally accepted mechanism for this reaction involves the following steps:

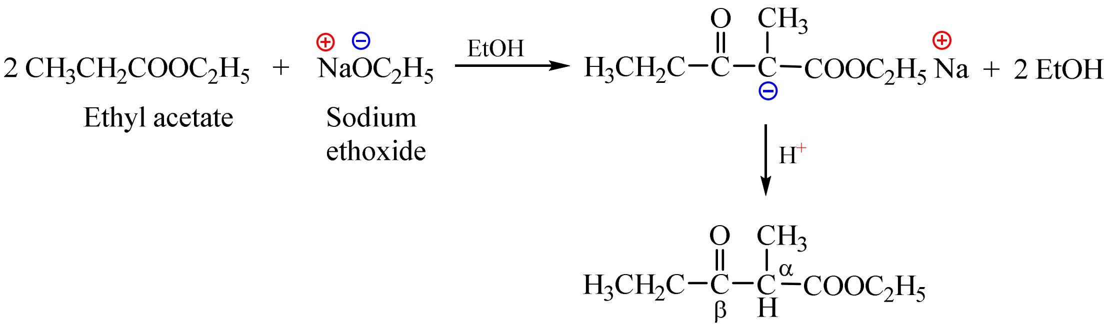


Ethoxide ion abstract a hydrogen from the α-carbon of the ester to form carbanion I (step1). The nucleophilic carbanion I attacks the carbonyl carbon of a second molecule of ester forming a tetrahedral intermediate to displace ethoxide ion and yield the keto ester (step2). The β-keto ester that formed in step 2 react with the ethoxide ion and form the sodium salt of the ester (sodioacetoacetic ester). So, to obtain the final product the resulting mixture must be acidified.

Like the aldol condensation, the reaction involves nucleophilic attack of a carbanion on an electron deficient carbonyl carbon.

In aldol condensation, nucleophilic attack leads to addition (the typical reaction of aldehydes & ketones).

In Claisen condensation, nucleophilic attack leads to substitution (the typical reaction of acyl compounds).



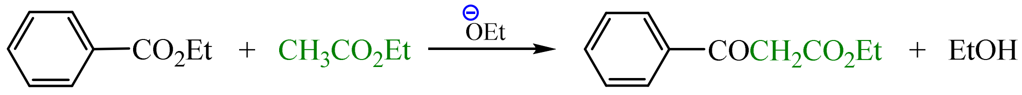
Ethyl-3-oxo-2-methylpentanoate
Ethyl-α-methyl-β-ketovalerate

1.3.3.1 Crossed Claisen condensation:

Like crossed aldol condensation, a crossed Claisen condensation useful only when one of the reactant has no α-hydrogen and thus incapable of undergoing self-condensation.

e.g.

1)

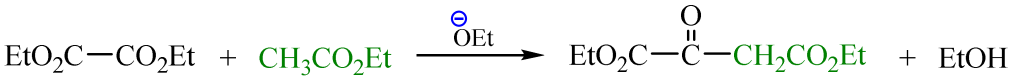


Ethyl benzoate Ethyl acetate Ethyl benzoyl acetate

2) $HCO_2Et + CH_3CO_2Et \xrightarrow{^{\ominus}OEt} HCOCH_2CO_2Et + EtOH$

Ethyl formate Ethyl acetate Ethyl frormylaceate

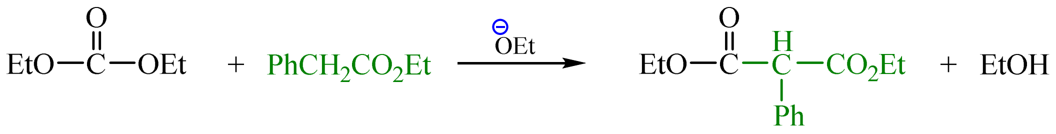
3)



$EtO_2C-CO_2Et + CH_3CO_2Et \xrightarrow{^{\ominus}OEt} EtO_2C-\overset{O}{\overset{\|}{C}}-CH_2CO_2Et + EtOH$

Ethyl oxalate Ethyl acetate Ethyl oxaloacetate

4)



$EtO-\overset{O}{\overset{\|}{C}}-OEt + PhCH_2CO_2Et \xrightarrow{^{\ominus}OEt} EtO-\overset{O}{\overset{\|}{C}}-\underset{Ph}{\underset{|}{\overset{H}{C}}}-CO_2Et + EtOH$

Ethyl carbonate Ethyl phenylacetate Ethyl phenylmalontate

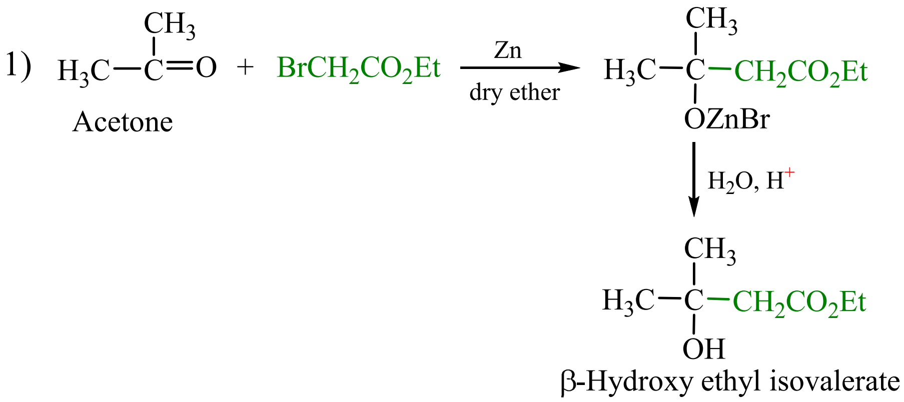
1.3.4 Reactions related to aldol condensation:

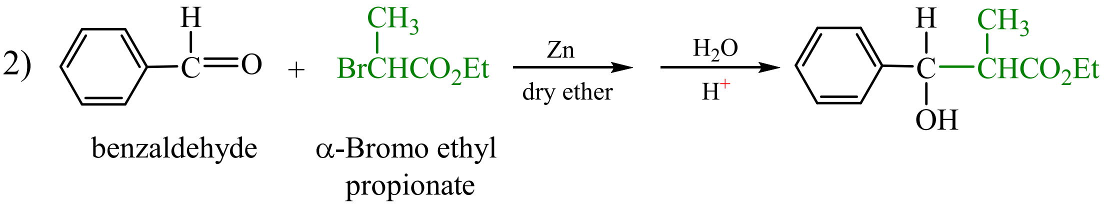
A large number of condensations that are closely related to the aldol condensation. Closer examination shows that these reactions involve attack of a carbanion on a carbonyl group. In each case the carbanion is generated by the abstraction of α-hydrogen by a base like sodium hydroxide, sodium ethoxide, sodium acetate or amines; on the other hand the carbonyl compound could be aldehyde, ketone, anhydride or ester.

1.3.4.1 Reformatsky reaction: Preparation of β-hydroxy esters

As we learned previously, carbanions can be produced by the abstraction of α-H from aldehydes, ketones or esters by the action of a base. These intermediates (carbanions) can be also produced by the reaction of alkyl halide with zinc metal to form organometallic compounds (e.g. Grignard reagent RMgX). The formation and subsequent reaction of the organozinc compound is similar to the formation and reaction of a Grignard reagent. Zinc is used in place of magnesium simply because the organozinc compounds are less reactive than Grignard reagents; they do not react with the ester function but only with the aldehyde or ketone.

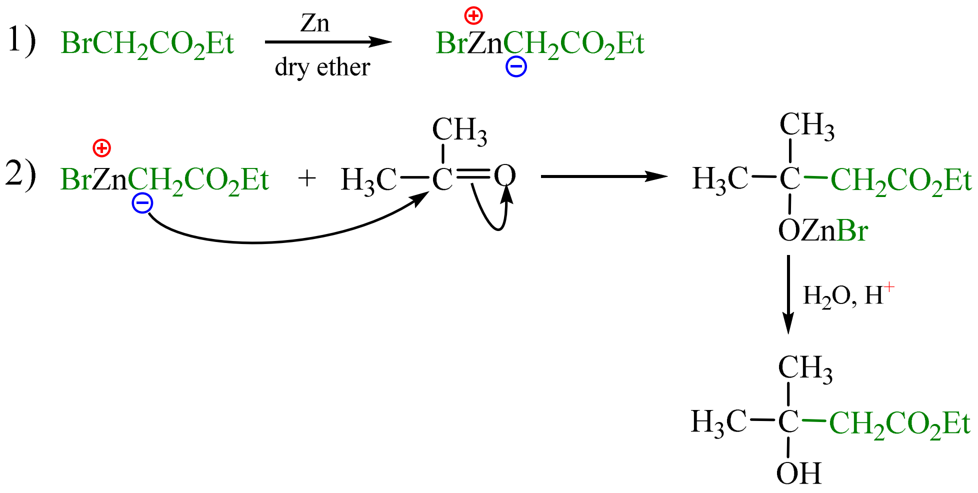
This concept can be applied on esters, since the reaction of α-bromoester with zinc in the presence of aldehyde or ketone will produce β-hydroxy ester.





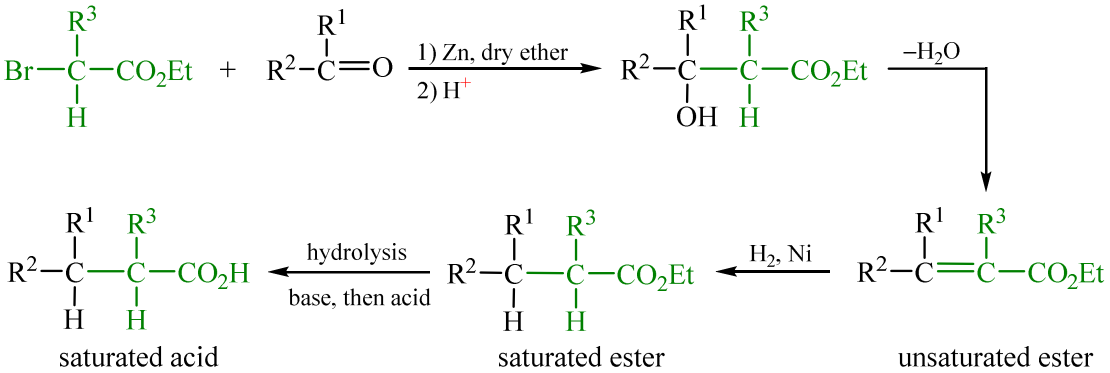
The reaction proceeded through a mechanism in which the α-bromo ester reacts with zinc metal in dry ether to give the organo metallic intermediate which used directly and react with the carbonyl compound (aldehyde or ketone) to give the ordinary addition product that on hydrolysis produce the final product.

mechanism:



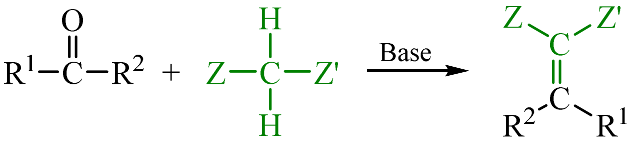
Compounds like α-halo nitrile (RX-CH-CN), α-halo-N,N-disubstituted amide and γ-halo vinyl ester have also been used.

β-Hydroxy acids or their esters can loss water molecule to give α,β-unsaturated acids or esters which can be reduced to their corresponding saturated acids or esters, furthermore hydrolysis of esters produces their acids.



1.3.4.2 The Knoevenagel condensation:

This type of condensation involve the reaction between aldehydes or ketones (that contain no α-hydrogen) with compounds of the type Z-CH_2-Z or ZCHRZ' in the presence of suitable base to form the olefins as the following equation:



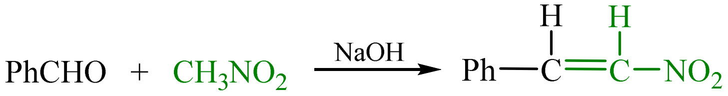
Z and Z' may be: (CHO, COR, COOR, CN, NO_2, SOR, SO_2R or SO_2OR).

Furthermore, other compounds that have α-hydrogen can be used like chloroform, 2-methyl pyridine, cyclopentadiene, -----etc.

For example:

1) 

$$PhCHO + CH_3COCH_2CO_2Et \xrightarrow{Et_3N} Ph-\overset{H}{C}=\overset{COCH_3}{C}-CO_2Et$$

2) 

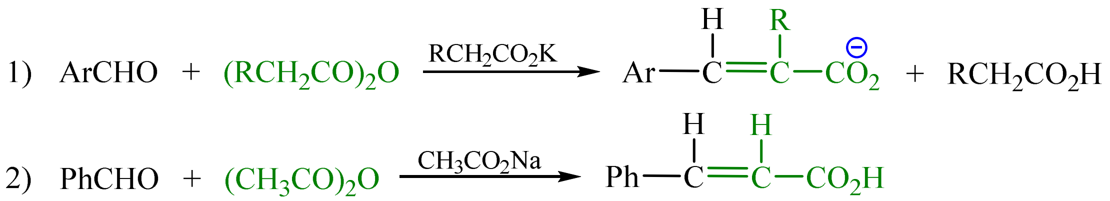
$$PhCHO + CH_3NO_2 \xrightarrow{NaOH} Ph-\overset{H}{C}=\overset{H}{C}-NO_2$$

1.3.4.3 Perkin reaction:

The reaction of aromatic aldehydes with anhydrides is called Perkin reaction. The product structure depends on the anhydride, since the use of an anhydride that has two α-hydrogens will produce olefin as a main product. On the other hand the salt of β-hydroxy acids can be isolated in the case of the use of an anhydride that contain one α-hydrogen like $(R_2CHCO)_2O$ since there is no possibility to eliminate water molecule.

The base that used in this reaction is the sodium or potassium salt of the carboxylic acid that the anhydride is derived from.

e.g. :



$$1)\ ArCHO + (RCH_2CO)_2O \xrightarrow{RCH_2CO_2K} Ar-\overset{H}{C}=\overset{R}{C}-CO_2^{\ominus} + RCH_2CO_2H$$

$$2)\ PhCHO + (CH_3CO)_2O \xrightarrow{CH_3CO_2Na} Ph-\overset{H}{C}=\overset{H}{C}-CO_2H$$

1.3.4.4 Cope reaction:

In this reaction, cyclohexanone react with ethyl cyanoacetate in the presence of ammonium acetate as a base, and benzene as a solvent.