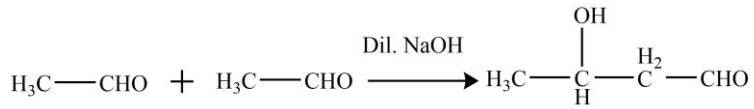
❖ Mechanism of Condensation Reactions Involving Enolates: Aldol, Knoevenagel, Claisen, Mannich, Benzoin, Perkin and Stobbe Reactions

So far we have discussed the structure and reactivity of addition reactions of carbon-heteroatom multiple bonds, now we need to study some of the most important name reactions (Aldol, Knoevenagel, Claisen, Mannich, Benzoin, Perkin, and Stobbe condensations) involving this type of mechanism.

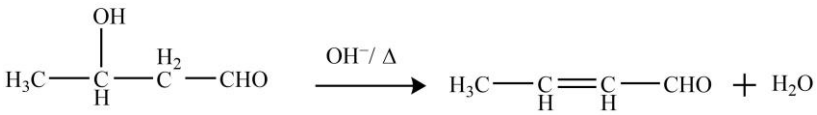
➢ *Aldol Condensation*

The aldol condensation may simply be defined as a condensation reaction in organic chemistry where an enol or an enolate ion reacts with a carbonyl compound to give a β-hydroxyaldehyde or β-hydroxyketone (an aldol addition), followed by the dehydration to form a conjugated enone.

The aldol condensation was invented in 1872 by a French chemist, Charles Wurtz, who first synthesized the β-hydroxy aldehyde using acetaldehyde.



Aldol addition (first part)

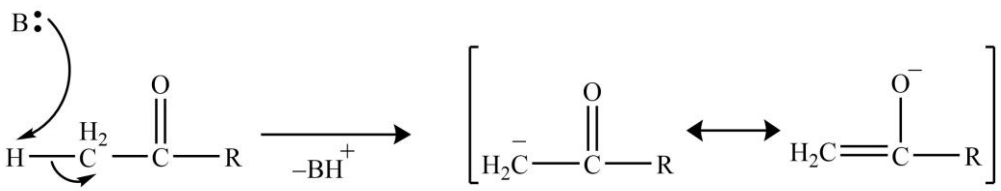


Dehydration of Aldol adduct (second part)

Mechanism of aldol condensation: The mechanism of aldol condensation can be fragmented into two parts; the first part is a simple aldol reaction (including 3 steps), whereas the second part includes the dehydration reaction (1 step i.e., elimination of an alcohol or H_2O molecule).

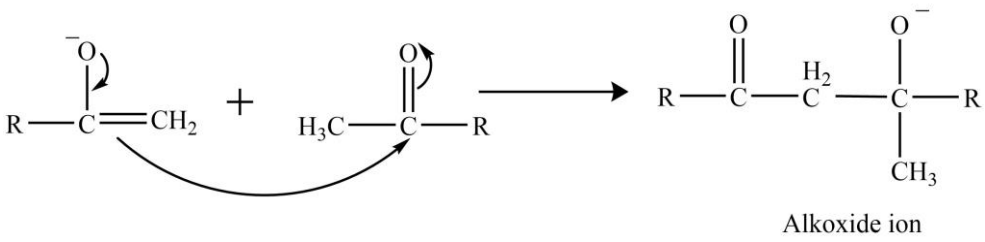
The dehydration of aldol product can occur via two pathways; a strong base like NaOH deprotonates the aldol product to an enolate, which then eliminates via the E_1CB route, whereas the second pathway for dehydration needs acid catalyzation for the enol mechanism. The dehydration part may also take place by decarboxylation if an activated carboxyl group is available. All four steps for aldol condensation are given below.

i) Step 1:

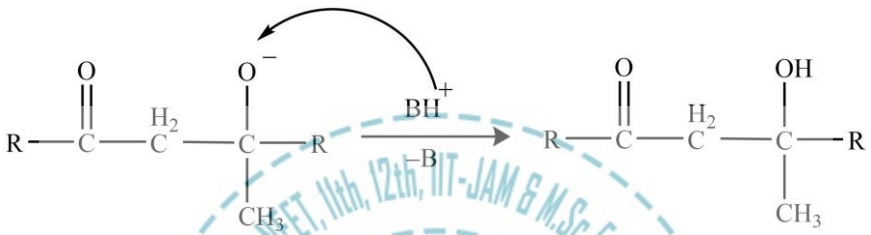


Enolate ion

ii) Step 2:



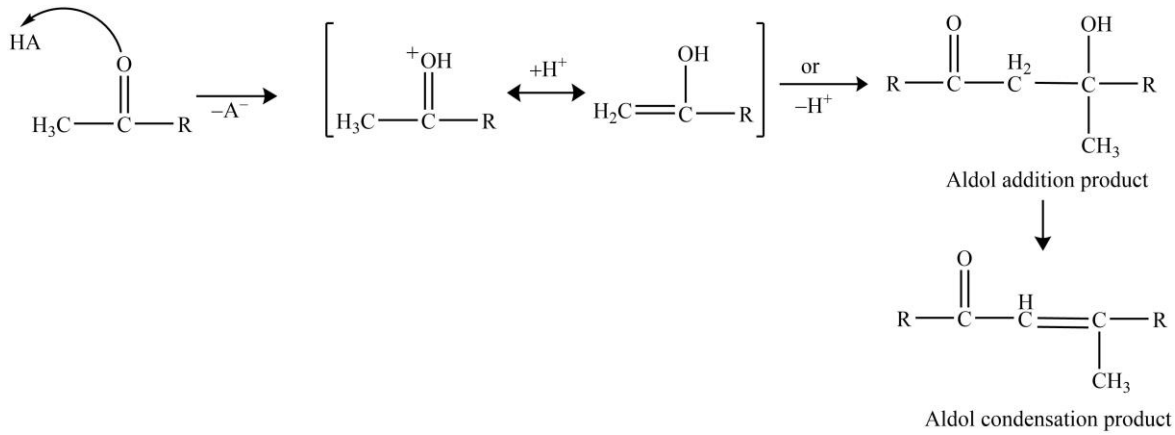
iii) Step 3:



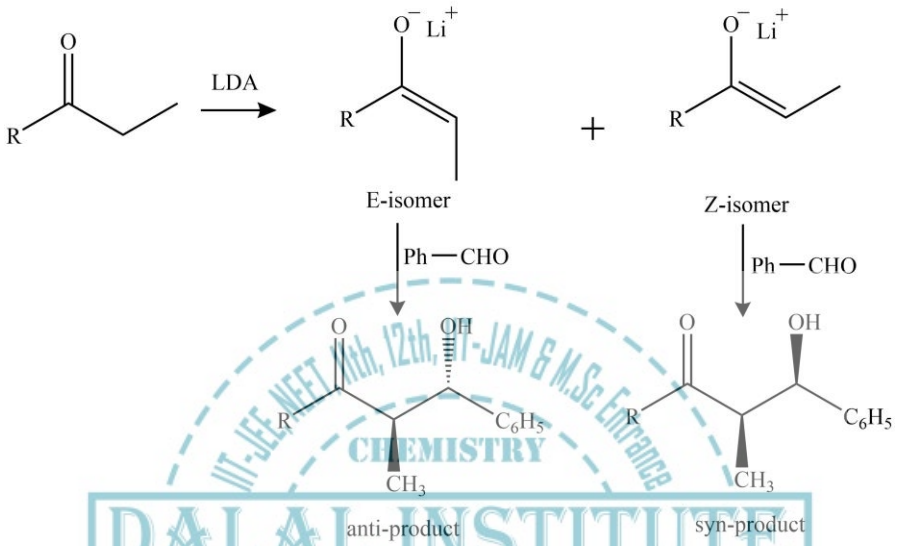
iii) Step 4:

Furthermore, the aldol condensation may also be fine-tuned under kinetic or thermodynamic control for the desired product.

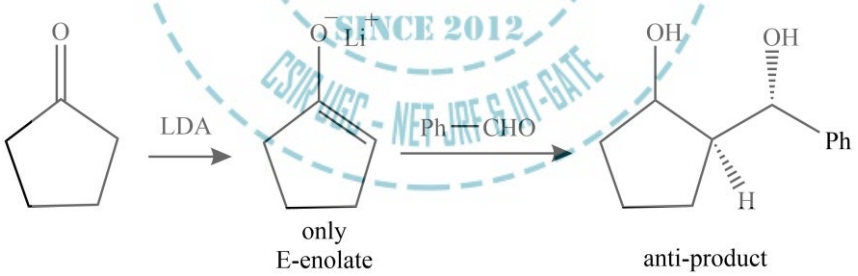
For the acid-catalyzed mechanism, the enol form acts as the nucleophile rather than electrophile, which is obviously triggered by the protonation of oxygen.



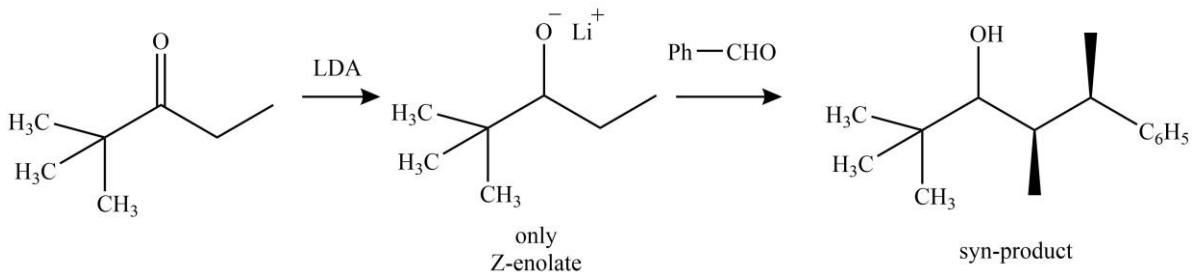
Stereochemistry of aldol condensation: Two stereoisomers will be obtained if enolate-yielding ketones are unsymmetrical. Consequently, syn- and anti-isomers will be formed from the condensation between aldehyde and ketonic enolate. It has also been observed that syn-isomer is generally the major product and ant is minor. Furthermore, the substituted enolate can exist either as Z- or E configuration, the corresponding treatment of aldehyde will give rise to syn- and anti-product.



Since some enolate can only exist as E-configuration, they will exclusively result in the anti-product; for instance, consider the following reaction.

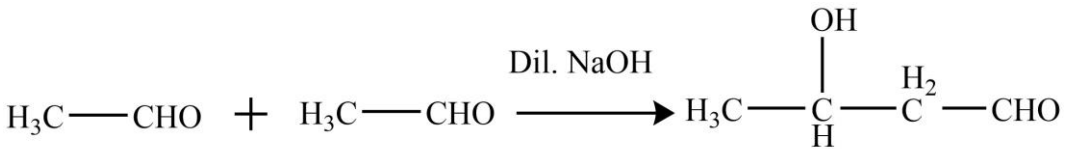


Ketones with very bulky group can only react Z-enolate giving exclusively syn product; consider the reaction between tertiary butyl ketone and benzaldehyde.

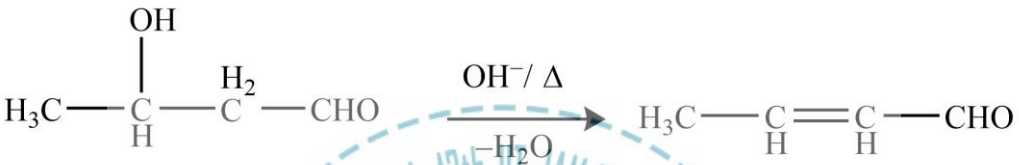


Examples of aldol condensation: Some of the most common examples of organic chemical transformation involving aldol condensation are given below.

i) The aldol addition of acetaldehydes followed by dehydration.



Aldol addition (first part)



Dehydration of Aldol adduct (second part)

ii) The aldol addition of aromatic aldehydes and ketones followed by dehydration.

Applications of aldol condensation: Some of the most common applications of organic chemical transformation involving aldol condensation are given below.

i) The Aldol condensation reactions are vital to the synthesis of many organic compounds as they give a good way to form C−C bonds. For instance, the Robinson annulation involves an aldol condensation; the Wieland-Miescher ketone is a chief reactant for many organic reactions.

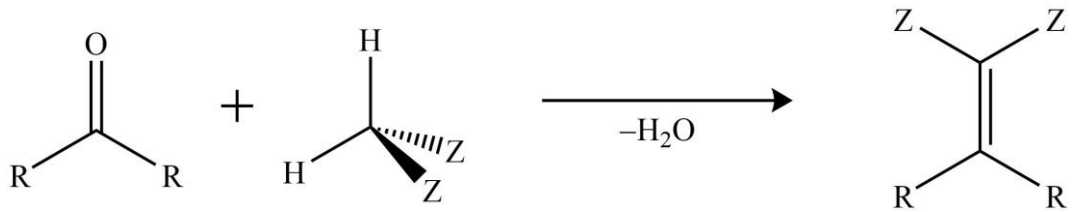
ii) Aldol condensation reactions are also taught in organic chemistry at the university-level as they can illustrate important reaction mechanisms. In other words, it includes the nucleophilic addition of an enolate to an aldehyde to give or "aldol" (aldehyde + alcohol) or a β-hydroxy ketone.

iii) The aldol condensation also finds its applications in the field of biochemistry. Nevertheless, the aldol condensation reactions in such cases are not officially condensation reactions because they don't involve the small molecule's loss.

➢ ***Knoevenagel Condensation***

The Knoevenagel condensation may simply be defined as a nucleophilic addition of an active methylene compound to a carbonyl group followed by the elimination of a water molecule (i.e., dehydration), resulting in an α, β-unsaturated ketone generally.

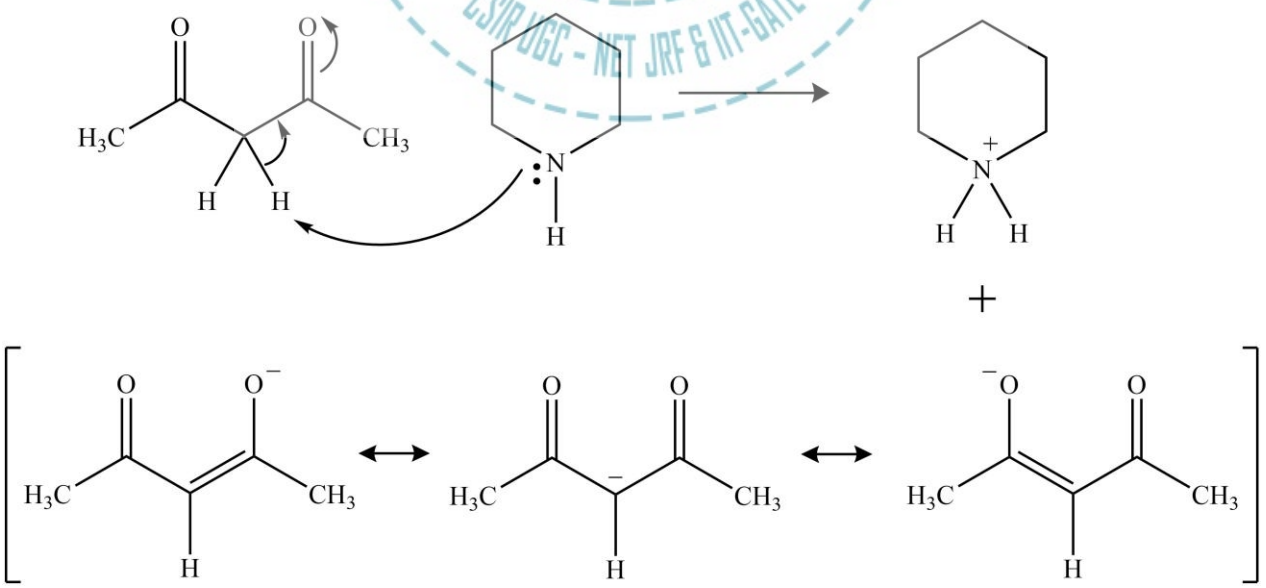
This reaction is a modification to aldol condensation and was invented by a German chemist Emil Knoevenagel; and therefore, is also named after him.



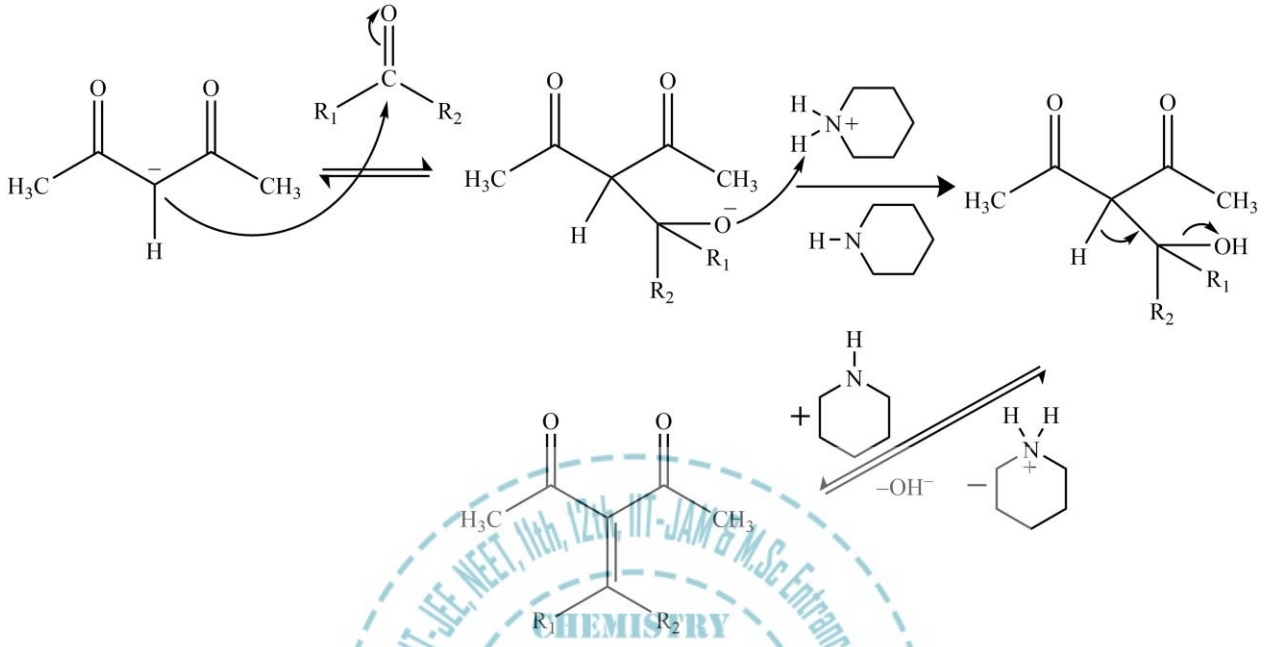
Where the carbonyl group is a ketone or an aldehyde and Z–CH_2–Z is the active methylene group. The catalyst used in this reaction is typically a weakly basic amine. Furthermore, it is also worthy to note that the active hydrogen component can also be of Z–CHR–Z or Z–CHR_1R_2 form, where Z is an electron-withdrawing functional group.

Mechanism of Knoevenagel condensation: The mechanism of Knoevenagel condensation includes two steps where the step includes the deprotonation of methylene by a base to result in a resonance stabilized carbanion. The carbanion formed during the first step acts as a nucleophile, and attacks at the carbon of carbonyl group of the ketone to yield to give aldol addition product followed by dehydration (second step). Both the steps for clear depiction are illustrated below.

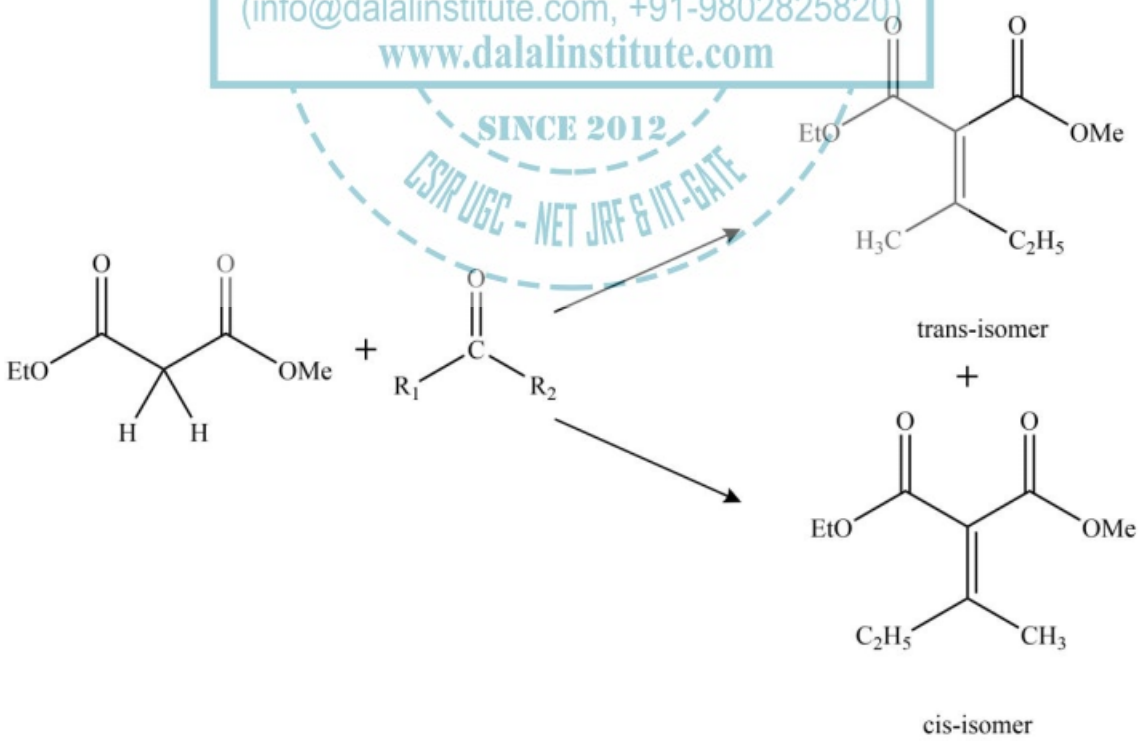
i) Step 1:



i) Step 2:

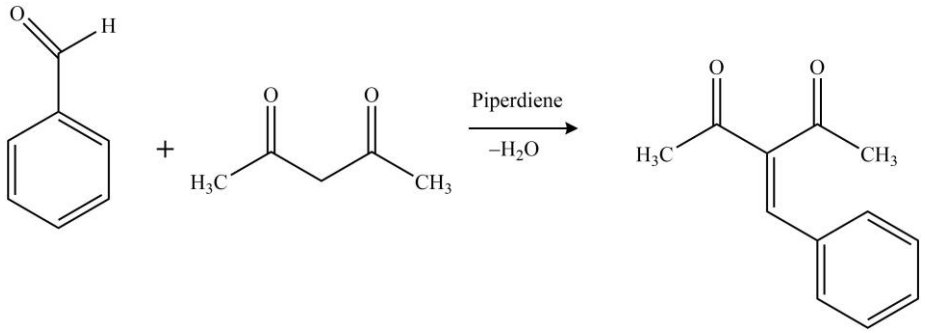


Stereochemistry of Knoevenagel condensation: In most of the Knoevenagel condensation reactions, both cis and trans isomers are formed guided by mainly steric and mode of attack.

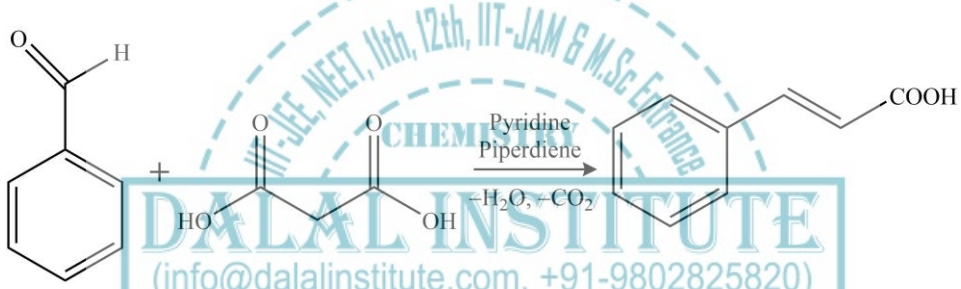


Examples of Knoevenagel condensation: Some of the most common examples of organic chemical transformation Knoevenagel condensation are given below.

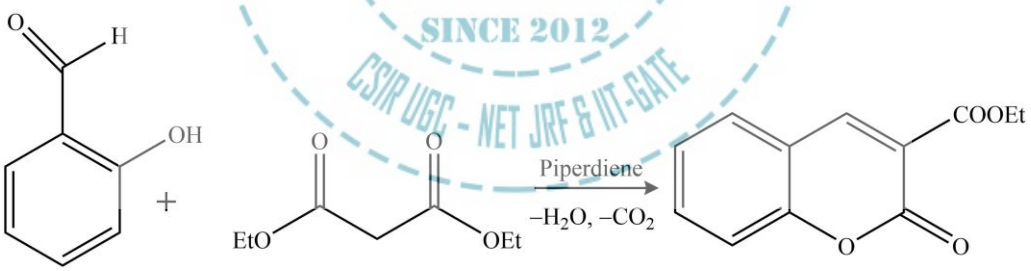
1. The reaction between benzaldehyde and acetylacetone.



2. The reaction between benzaldehyde and malonic acid.



3. The reaction between 2-hydroxybenzaldehyde and diethyl malonate.



Applications of Knoevenagel condensation: Some of the most common applications of organic chemical transformation involving Knoevenagel condensation are given below.

1. The Knoevenagel condensation is the main step in the commercial production of antimalarial drug lumefantrine (a Coartem's component).

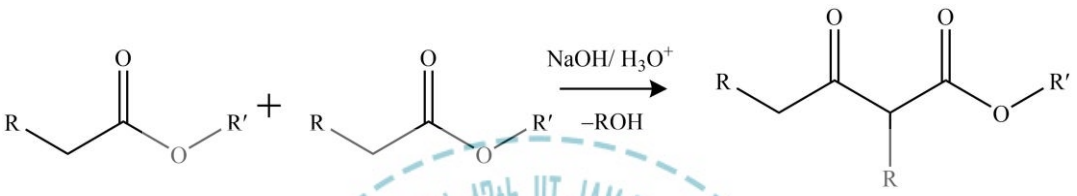
2. A Knoevenagel condensation reaction is confirmed in the reaction of thiobarbituric acid with 2-methoxybenzaldehyde in C_2H_5OH using piperidine as a basic assistant, yielding subsequent formation of a charge-transfer complex molecule.

3. The Knoevenagel condensation is also found in a multicomponent reaction with microwave-assisted synthesis with cyclohexanone, malononitrile, and 3-amino-1,2,4-triazole.

➢ *Claisen Condensation*

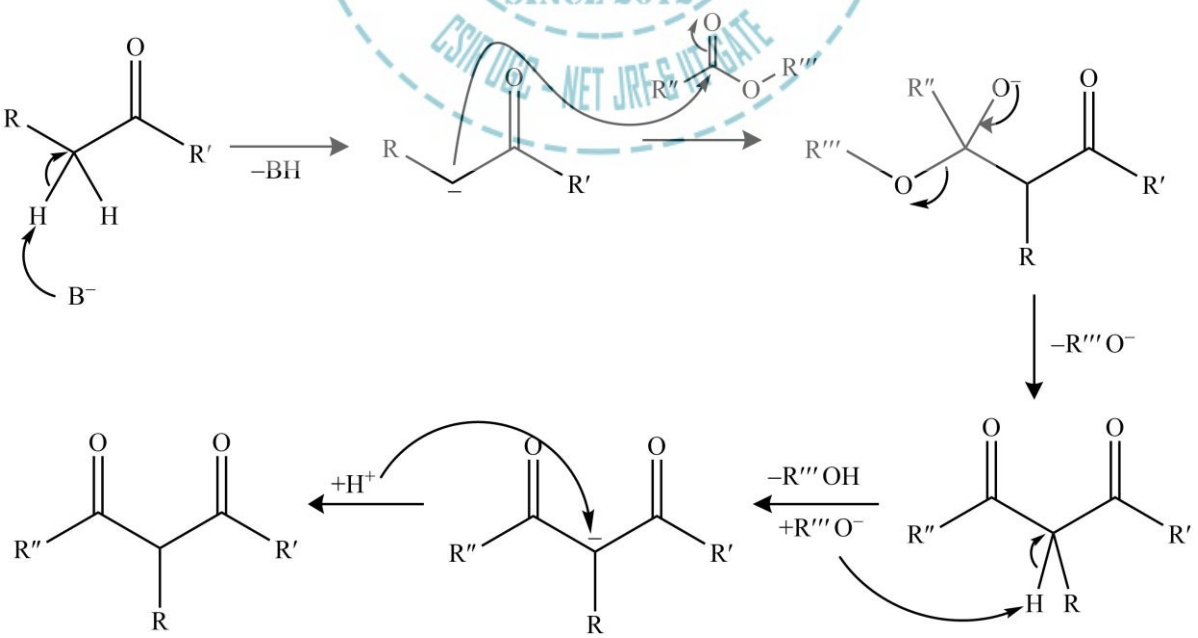
The Claisen condensation may simply be defined as a chemical reaction giving carbon-carbon bond between two esters or one ester and another carbonyl compound in the availability of a strong base, resulting in a β-diketone or a β-keto ester.

This reaction is a modification to aldol condensation and was invented by a German chemist Rainer Ludwig Claisen in 1887; and therefore, it is also named after him. The primary condition for Claisen condensation is that one reagent (at least) must have α-hydrogen so that it can be enolized via deprotonation. A typical Claisen condensation is shown below.

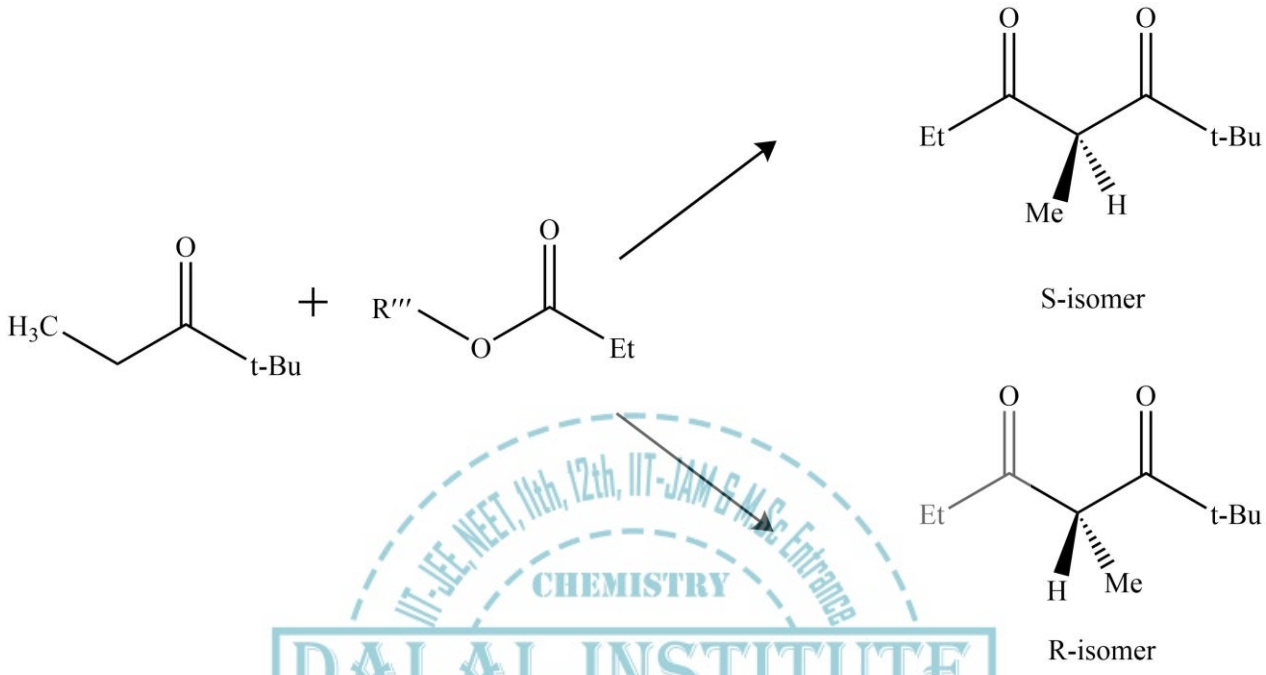


It is obvious that the molecule eliminated in this 'modified aldol condensation' is not water but alcohol. Now depending upon various enolizable and nonenolizable carbonyl compounds, many types of Claisen condensations can be obtained.

Mechanism of Claisen condensation: The mechanism starts with the detachment of α-proton by a strong base giving a resonance stabilized enolate anion. After that, the carbonyl carbon of the second ester is attacked by the enolate anion. The alkoxy anion is then eliminated, and reattached, followed by the elimination of the alcohol molecule. Finally, a proton from aqueous acid is added to neutralize the enolate to give rise to the final product (β-diketone in this case).

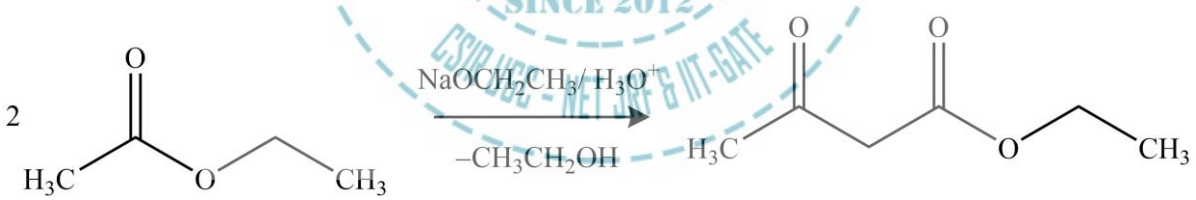


Stereochemistry of Claisen condensation: In the case of different R groups (R‴ ≠ R′), the Claisen condensation will give rise to chiral β-diketones or β-diketoesters as shown below.

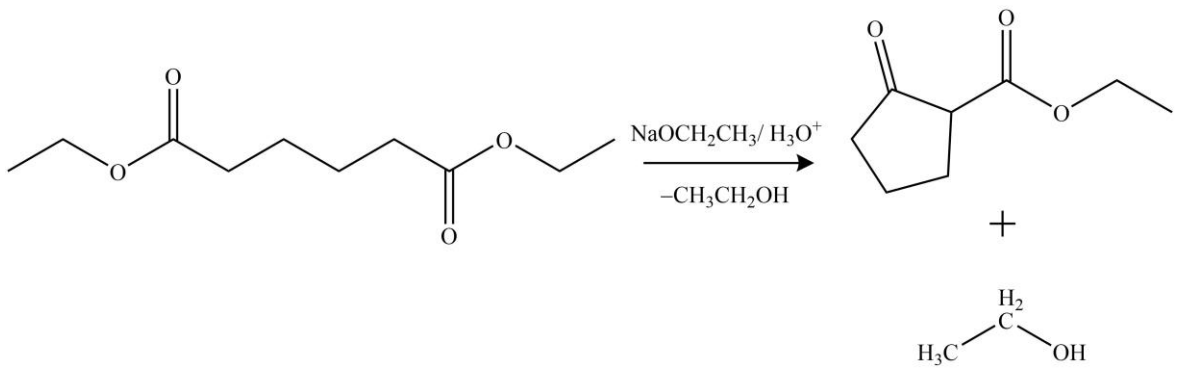


Examples of Claisen condensation: Some of the most common examples of organic chemical transformations involving Claisen condensation are given below.

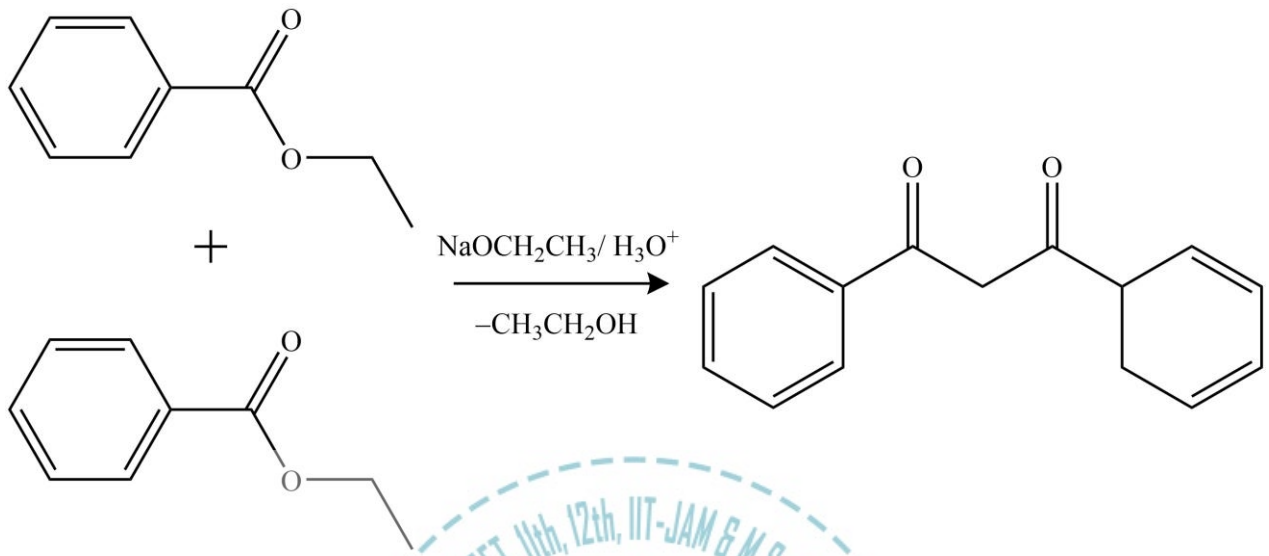
1. The condensation reaction of ethyl acetate.



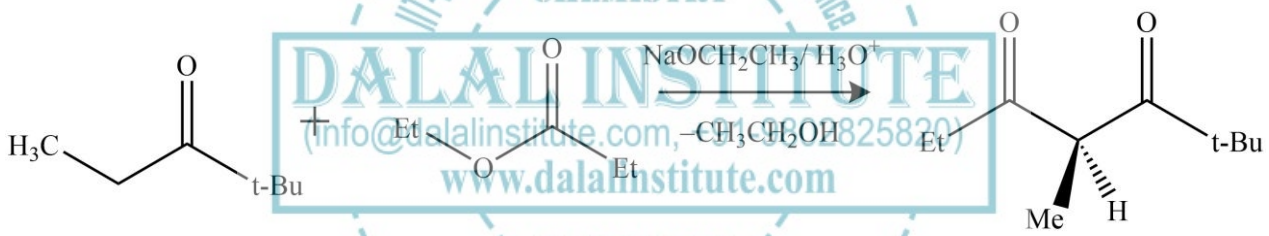
2. The condensation reaction of diethyl adipate.



3. The condensation reaction of ethyl benzoate.



3. The reaction between 2,2-dimethylpentan-3-one and ethyl propionate.



Applications of Claisen condensation: Some of the most common applications of organic chemical transformation involving Claisen condensation are given below.

1. Crossed and simple Claisen condensations have been widely used in the preparation of a huge range of organic compounds, like terpenes, vitamins, flavones, alkaloids, etc.

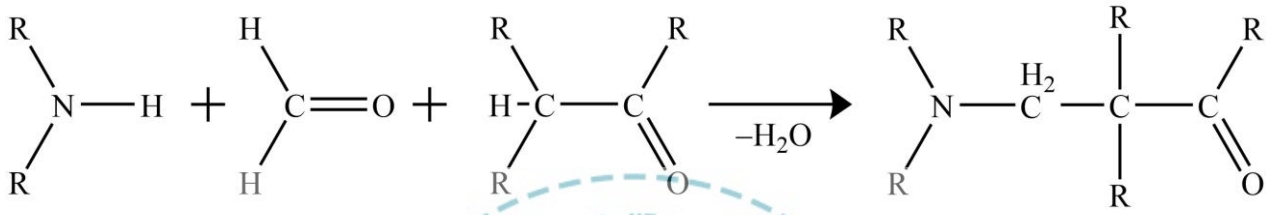
2. Crossed Claisen condensation reaction between two different esters (both are having α-H) have little to no synthetic impoartance, and we will obtain an a mixture of four products. Nevertheless, if no α-hydrogen are available in one of the esters, it will act as a acceptor for carbanion and the self-condensation of the other ester is diminished. Most popularly used esters which have zero α-hydrogen are ethyl formate, ethyl benzoate, ethyl carbonate, ethyl oxalate, etc.

3. Since the esters are generally less acidic than ketones, the rate of their base-catalyzed condensation reaction (aldol-type) is very small; and therefore, the ketone can act as nucleophiles in crossed Claisen condensation reactions to give rise to a huge number of different kinds of products.

➢ *Mannich Condensation*

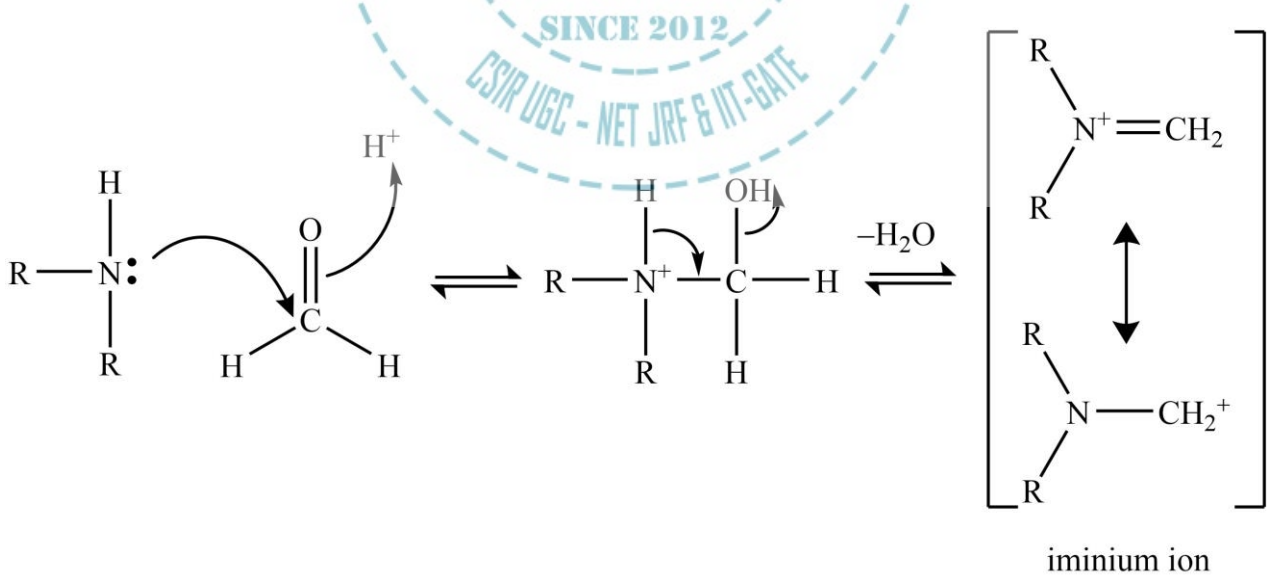
The Mannich condensation may simply be defined as an organic chemical transformation where a carbonyl functional group's neighboring proton (acidic in nature) undergoes amino alkylation by formaldehyde and ammonia (or a secondary, or primary amine), giving rise to a β-amino-carbonyl compound called Mannich base.

This reaction was invented by an eminent German chemist Carl Mannich in 1912; and therefore, is also named after him.



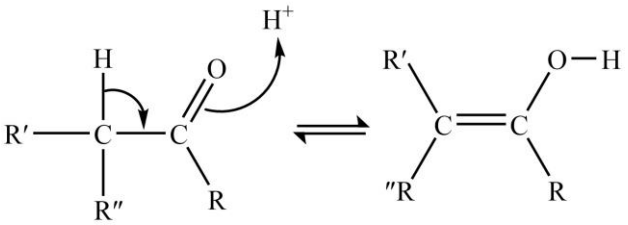
The Mannich condensation is a case of nucleophilic addition of an amine to a carbonyl group trailed by the dehydration to yield a Schiff base, which in turn, reacts in an electrophilic addition mode with a compound containing acidic hydrogen (next step).

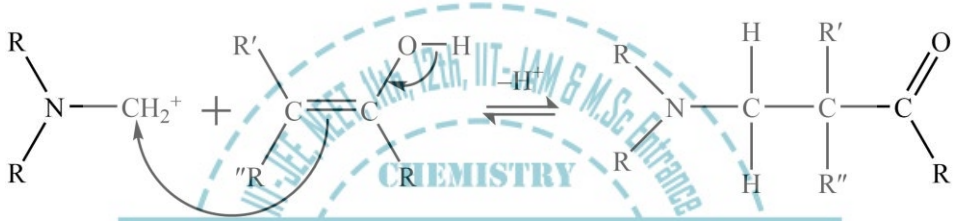
Mechanism of Mannich condensation: The Mannich condensation's mechanism begins with the generation of an iminium ion from the formaldehyde and the amine used. The protonated oxygen is highly acidic with a pKa value of −2. The reaction will be stopped when the carbonyl gets deprotonated by amine base; and therefore, it is necessary to perform at a pH of about 5. Hence, the right pathway should begin with a nucleophilic attack at carbonyl's carbon by the nitrogen atom.



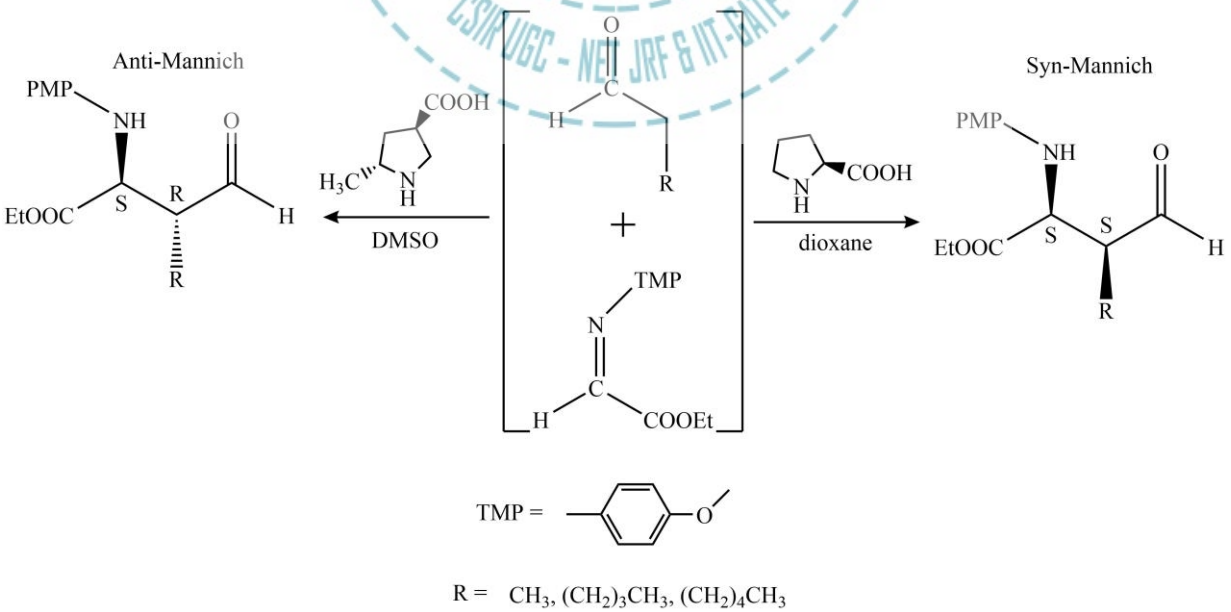
iminium ion

The carbonyl compound like ketone will undergo tautomerization to yield enol form, which can attack the iminium ion afterward. It is also important to note that the enolization and Mannich addition can occur twice with methyl ketones, trailed by an β-elimination to give rise to β-amino enones.





Stereochemistry of Mannich condensation: Asymmetric Mannich reactions have also been studied in the recent era. It has been observed that if two prochiral centers are present in an appropriately functionalized ethylene bridge of Mannich adduct, two diastereomeric pairs of enantiomers are obtained. One of the most commonly reported examples (also first) of asymmetric Mannich reaction was performed using (S)-proline as a naturally occurring chiral catalyst.

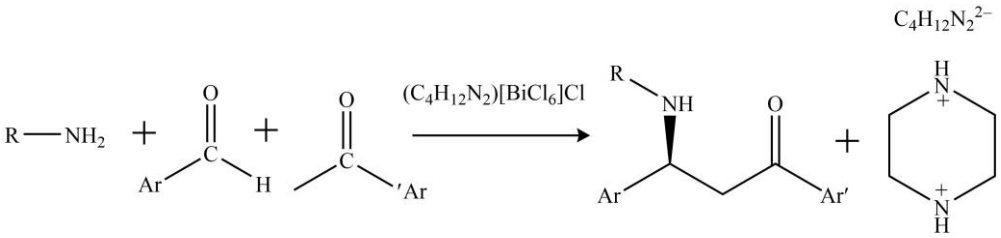


TMP =

R = CH_3, $(CH_2)_3CH_3$, $(CH_2)_4CH_3$

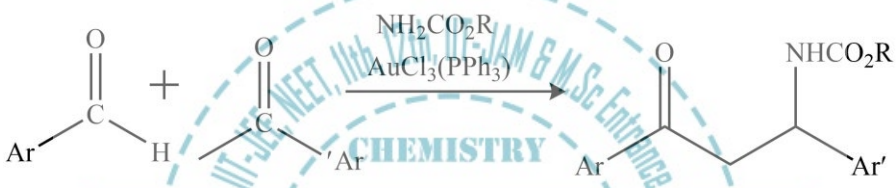
Examples of Mannich condensation: Some of the most common examples of organic chemical transformation Mannich condensation are given below.

1. The reaction between aniline, benzaldehyde, and an aromatic ketone.



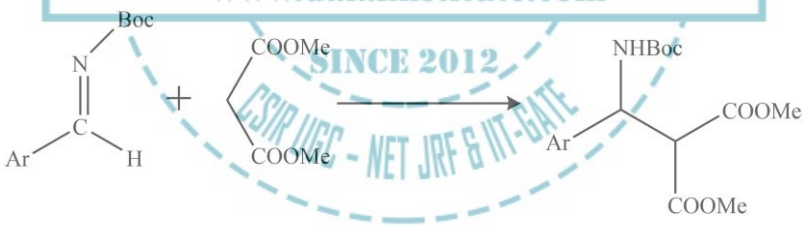
R = Ar, Bu

2. The reaction between amide, benzaldehyde, and an aromatic ketone.



R = Et, Bn

3. Magnesium(II)-Binaphtholate-catalysed condensation reaction with malonates



Applications of Mannich condensation: Some of the most common applications of organic chemical transformation involving Mannich condensation are given below.

1. The Mannich condensation is used in the synthesis of peptides, alkyl amines, antibiotics, nucleotides, alkaloids like tropinone, and many important agrochemicals.

2. Mnay polymers, Formaldehyde tissue crosslinking, catalysts, Pharmaceutical drugs like rolitetracycline (fluoxetine (antidepressant), tolmetin (anti-inflammatory drug), and tramadol are formed via Mannich condensation.

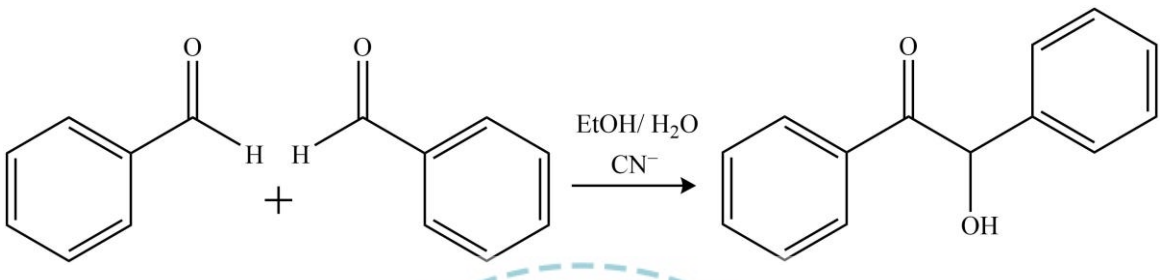
3. Many detergents and soaps are synathesized via Mannich condensation which find applications in cleaning industry, epoxy coatings, and automotive fuel treatments.

4. The thermal decay of Mannich reaction products gives rise to α, β-unsaturated ketones by (e.g. methyl vinyl ketone through 1-diethylamino-butan-3-one).

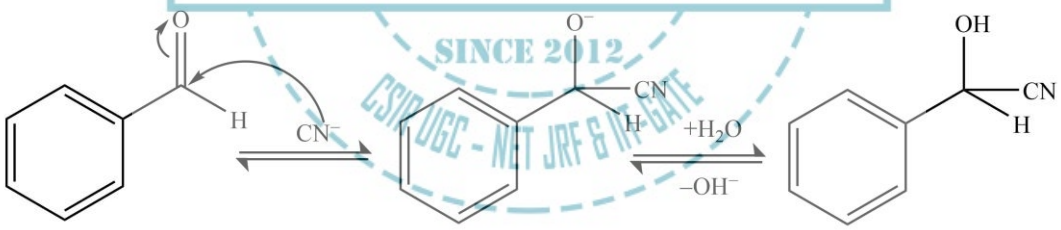
➢ *Benzoin Condensation*

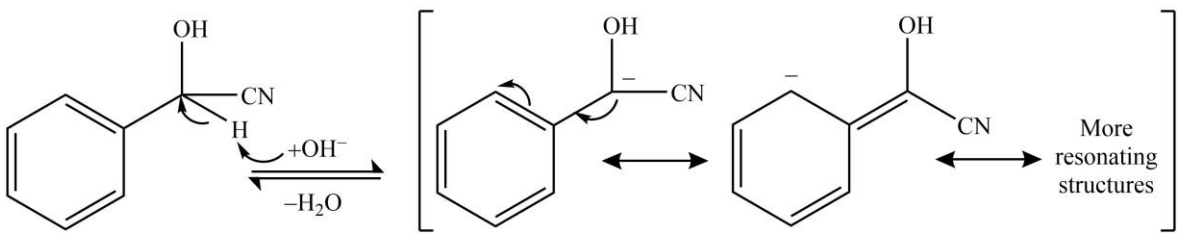
The benzoin condensation may simply be defined as an addition reaction involving two aldehydes (generally aromatic aldehydes or glyoxals) to give rise to an acyloin.

This reaction was invented by two German chemists Justus von Liebig and Friedrich Wohler, and its classic case is the conversion of benzaldehyde to benzoin.



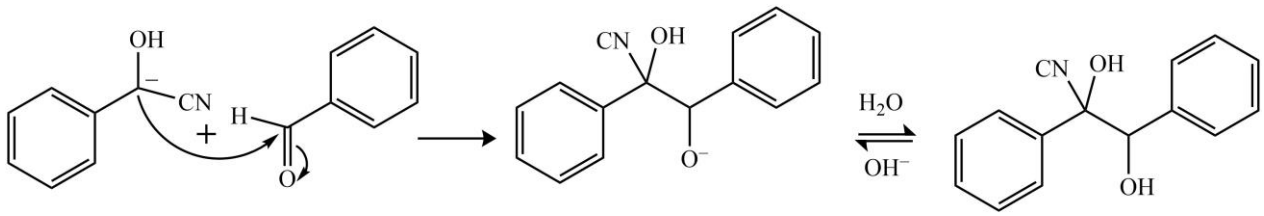
Mechanism of benzoin condensation: The benzoin condensation is catalyzed by nucleophiles like N-heterocyclic carbene or cyanides. A. J. Lapworth proposed a mechanism in 1903 which says that the cyanide anion from sodium cyanide reacts with the given aldehyde via nucleophilic addition (first step); followed by the rearrangement of the intermediate imparting polarity reversal of the carbonyl group, which in turn, attacks another carbonyl group via nucleophilic addition (second step). The benzoin as the final product will be obtained by the proton transfer and cyanide ion's elimination happening afterward. Also, being a reversible transformation, the products' distribution is governed by the comparative thermodynamic stability of the reactants and products.

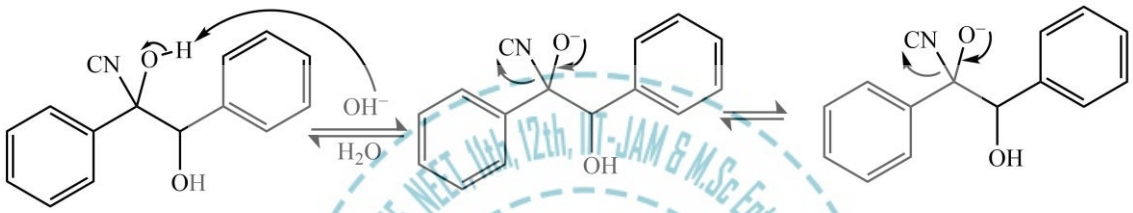




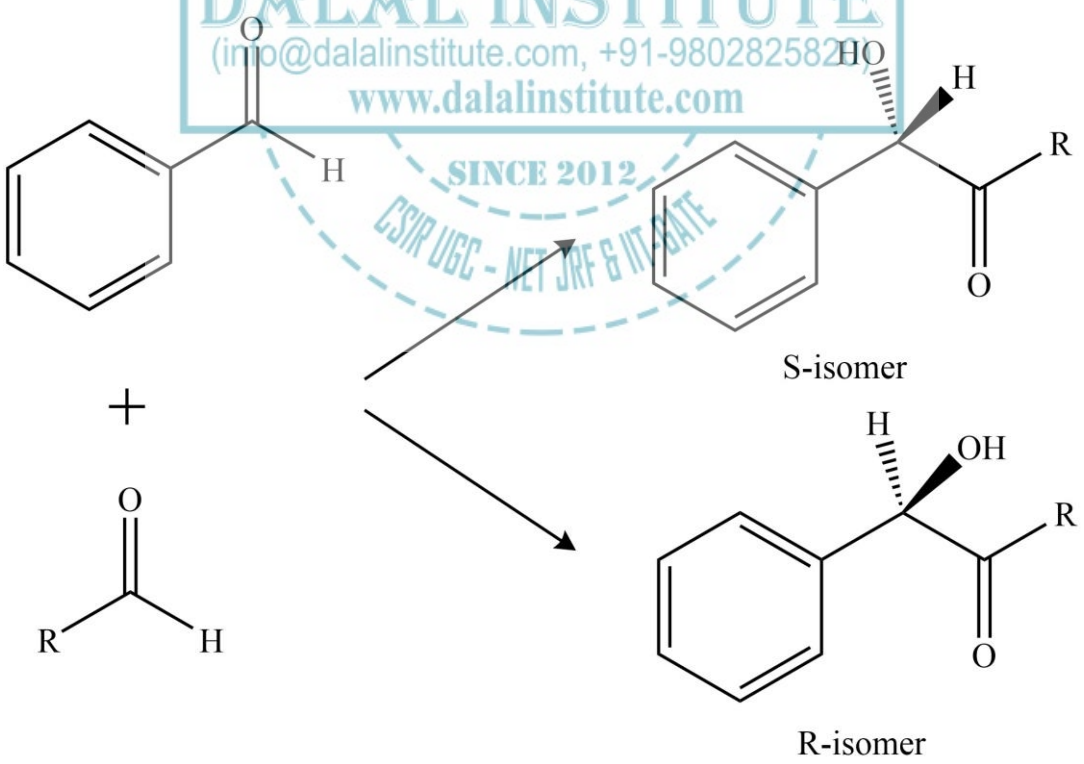
By looking at the mechanism, it can clearly be seen that one aldehyde accepts a proton whereas the other one donates a proton. Although most of the aldehydes are capable of donating as well accepting proton (like benzaldehyde); some aldehydes like 4-dimethylaminobenzaldehyde can only donate protons.

Exploiting this possibility, mixed benzoins can easily be synthesized. Nevertheless, the homo-dimerization should be sidestepped by careful matching of proton donating-accepting aldehydes.



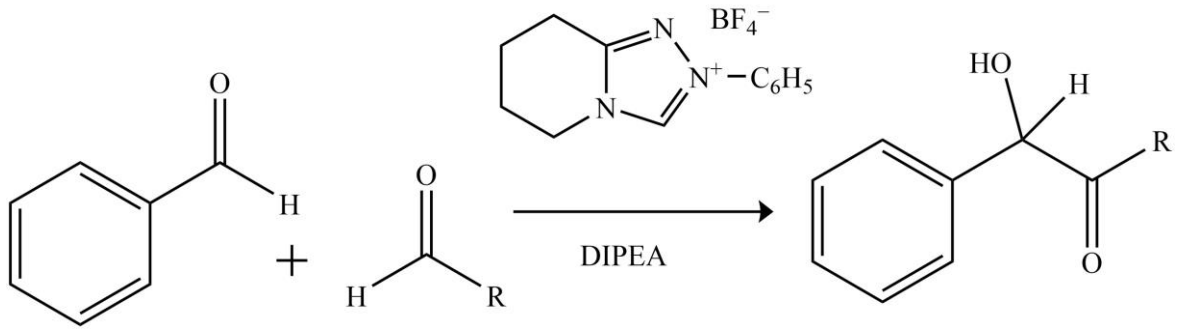


Stereochemistry of benzoin condensation: If participating aldehydes are different in benzoin condensation reactions, the final product will exist as an enantiomeric pair.



Examples of benzoin condensation: Some of the most common examples of organic chemical transformations benzoin condensation are given below.

1. The *n*-heterocyclic carbene-catalyzed cross-benzoin reactions with chemoselective behavior.



2. A regiospecific catalyzed cross silyl benzoin reaction

Applications of benzoin condensation: Some of the most common applications of organic chemical transformation involving benzoin condensation are given below.

1. The benzoin condensation can be extended to aliphatic aldehydes if thiazolium salts are used. The resulting compounds are vital in the heterocyclic synthesis. Also, the 1,4-addition of an aldehyde analogous to an enone is labeled as the Stetter reaction.

2. In biochemical systems, the coenzyme thiamine is accountable for the biosynthesis of acyloin-like compounds via benzoin condensation; and this coenzyme has a thiazolium moiety, which becomes a nucleophilic carbene after deprotonation.

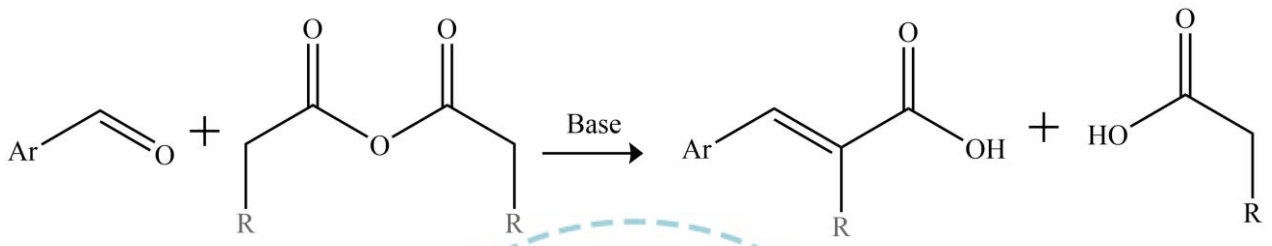
3. The asymmetric version of benzoin condensation has been carried out by using chiral triazolium and thiazolium salts; triazolium salts yielded higher enantiomeric excess in comparison to thiazolium salts.

4. Owing to the thermodynamical control, retro benzoin condensation can be very valuable. If acyloin or benzoin can be prepared by another route, then they can be transformed into ketones via cyanide or thiazolium catalytic use. The mechanism will almost be the same except that it takes place in the backward direction; which in turn, allows ketonic access.

➢ ***Perkin Condensation***

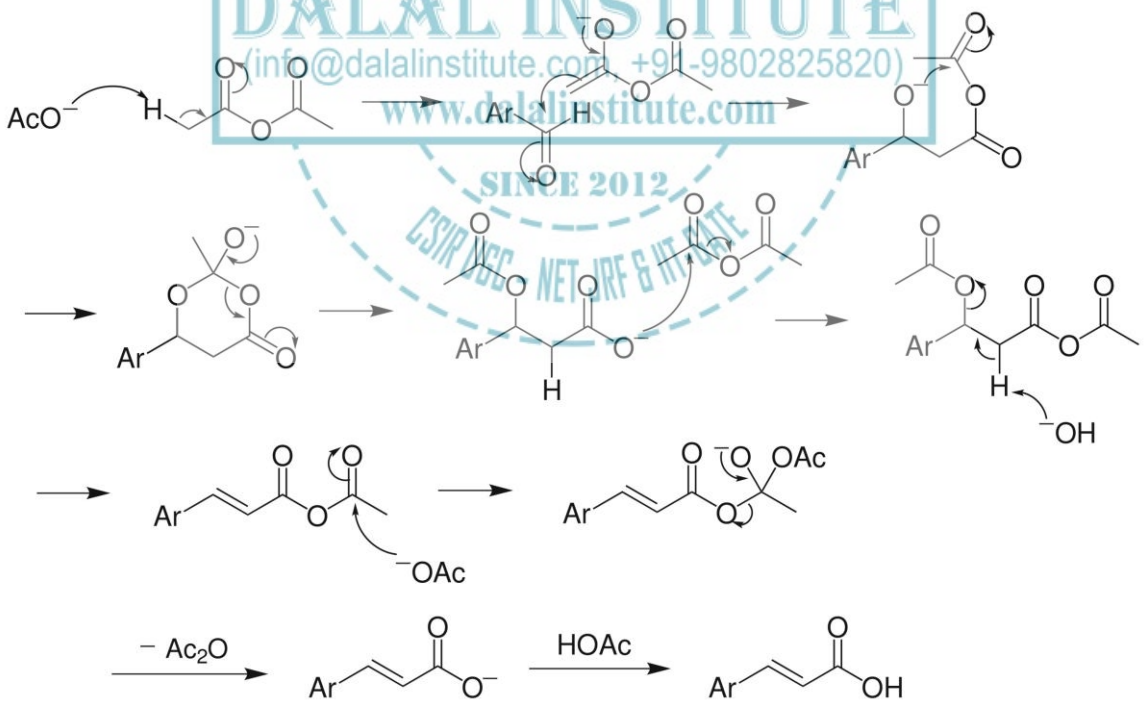
The Perkin condensation may simply be defined as an organic transformation where an α, β-unsaturated aromatic acid is obtained by the aldol condensation of an acid anhydride and an aromatic aldehyde, in the availability of an alkali salt (acting as a base catalyst) of the acid.

This reaction was invented by an English chemist William Henry Perkin to make cinnamic acids; and therefore, is also named after him.



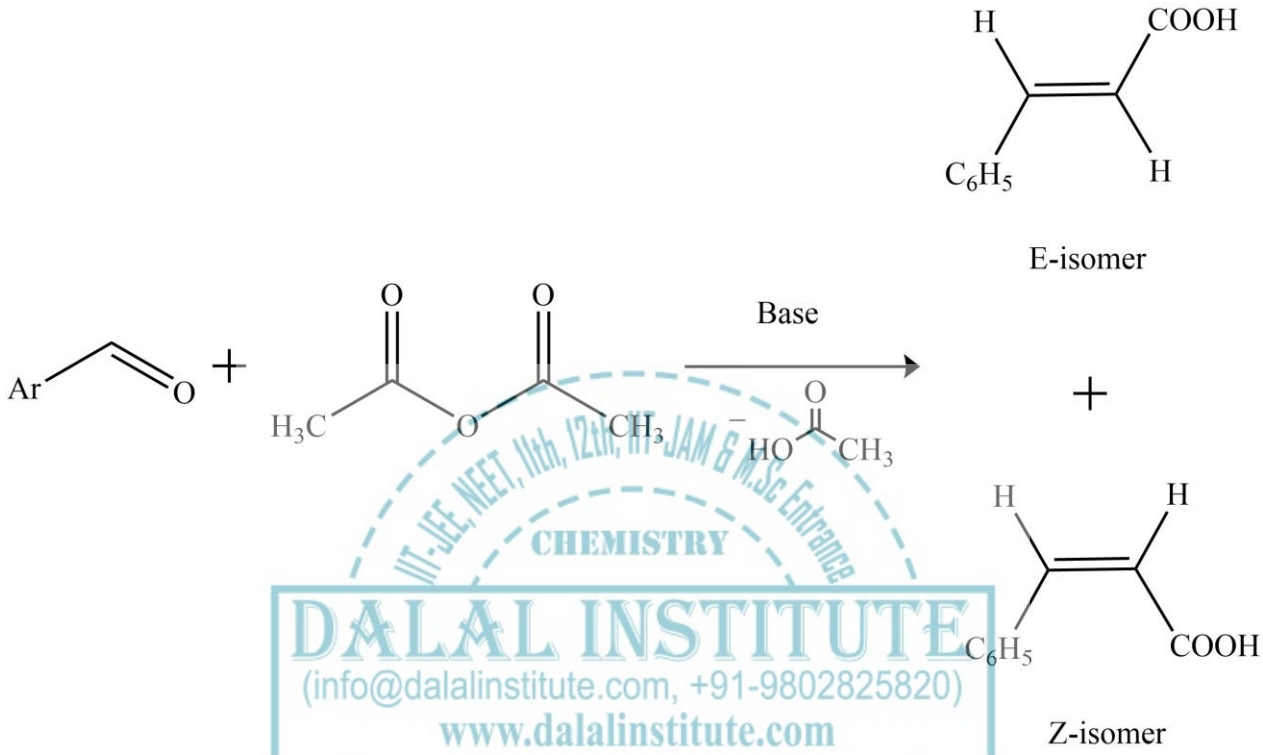
The relative arrangement of the aromatic ring and carboxylic acid in the end product of Perkin condensation can either be Z or E.

Mechanism of Perkin condensation: The most widely accepted mechanism for the Perkin condensation is given below.



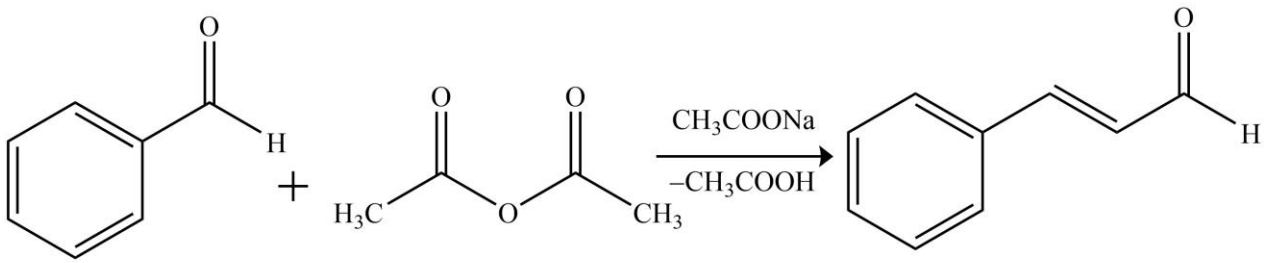
It is also worthy to note that the mechanism given above is not accepted by all of the scientific community; and therefore, many other sorts can also be found in different texts. One of such versions differs in the aspect of decarboxylation without transfer of acetic group.

Stereochemistry of Perkin condensation: In the Perkin condensation, the geometrical arrangement of the aromatic ring and carboxylic acid in the ending product can either be Z- or E-type (although the amount of major and minor will be different).



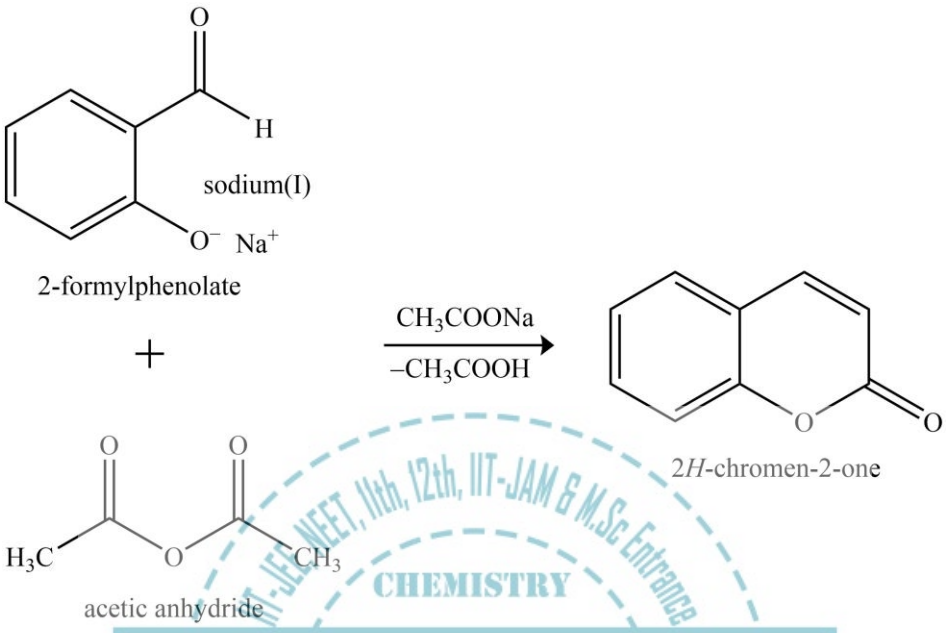
Examples of Perkin condensation: Some of the most common examples of organic chemical transformations involving Perkin condensation are given below.

1. The most popular example of Perkin condensation is the reaction between benzaldehyde and acetic anhydride to give cinnamic acid.



benzaldehyde acetic anhydride cinnamaldehyde

2. The reaction between sodium salt of salicylaldehyde and acetic anhydride to give coumarin is also an example of Perkin condensation.



3. One more example of Perkin condensation includes the generation of coumarin from 2-hydroxybenzaldehyde.

Applications of Perkin condensation: Some of the most common applications of organic chemical transformation involving Perkin condensation are given below.

1. One of the most important applications of Perkin condensation is in the laboratory preparation of the phytoestrogenic stilbene resveratrol.

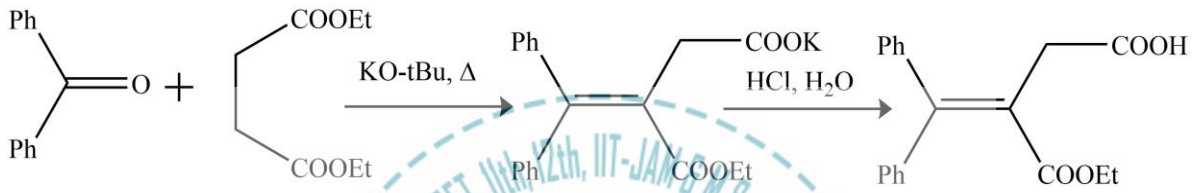
2. Perkin condensation is used to synthesis of 'coumarin' which finds uses in medicine, rodenticide precursor, laser dyes, aromatizers, and perfumes.

3. Perkin condensation is the most popular route for the synthesis of cinnamic acid which is an extremely important compound for synthetic indigo, flavorings, and pharmaceuticals industry.

➢ *Stobbe Condensation*

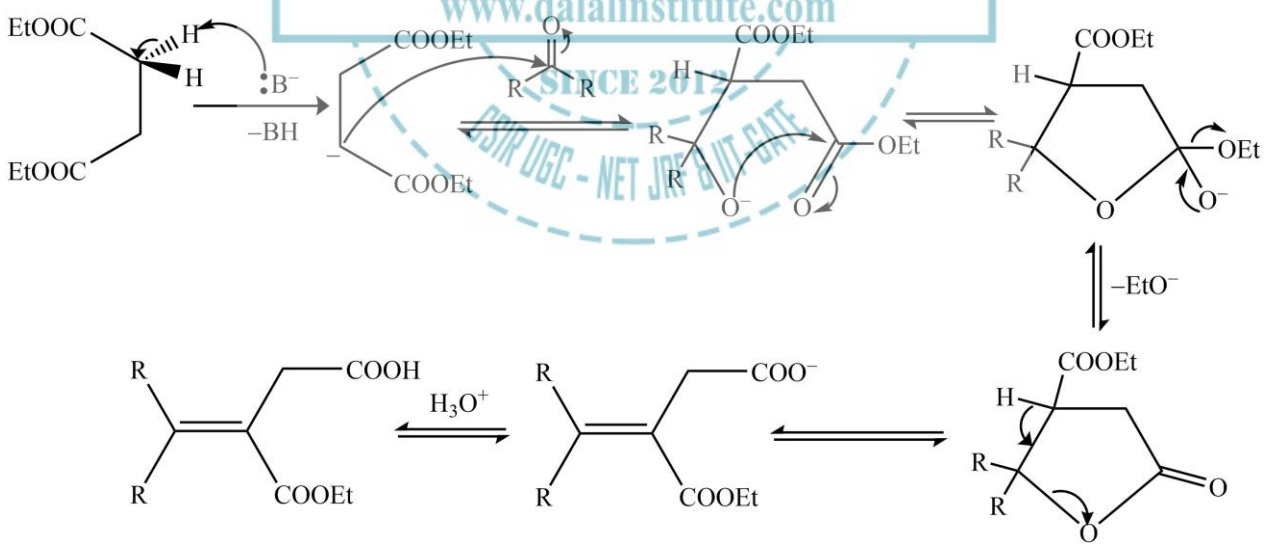
The Stobbe condensation may simply be defined as a modification to Claisen condensation where the diethylesters of succinic acid react with aldehydes (or ketones) to give rise to alkylidene succinic acids or their monoesters in presence of a relatively less strong base.

This reaction is a modification to Claisen condensation and was invented by a German chemist Hans Stobbe; and therefore, is also named after him. The initial reaction was observed in 1893 when H. Stobbe observed that the reaction between acetone and diethyl succinate (in the presence of C_2H_5ONa) yielded an α-, β-unsaturated ester (tetraconic acid) and its monoethyl ester, instead of a 1-, 3-diketone product via normal Claisen condensation.



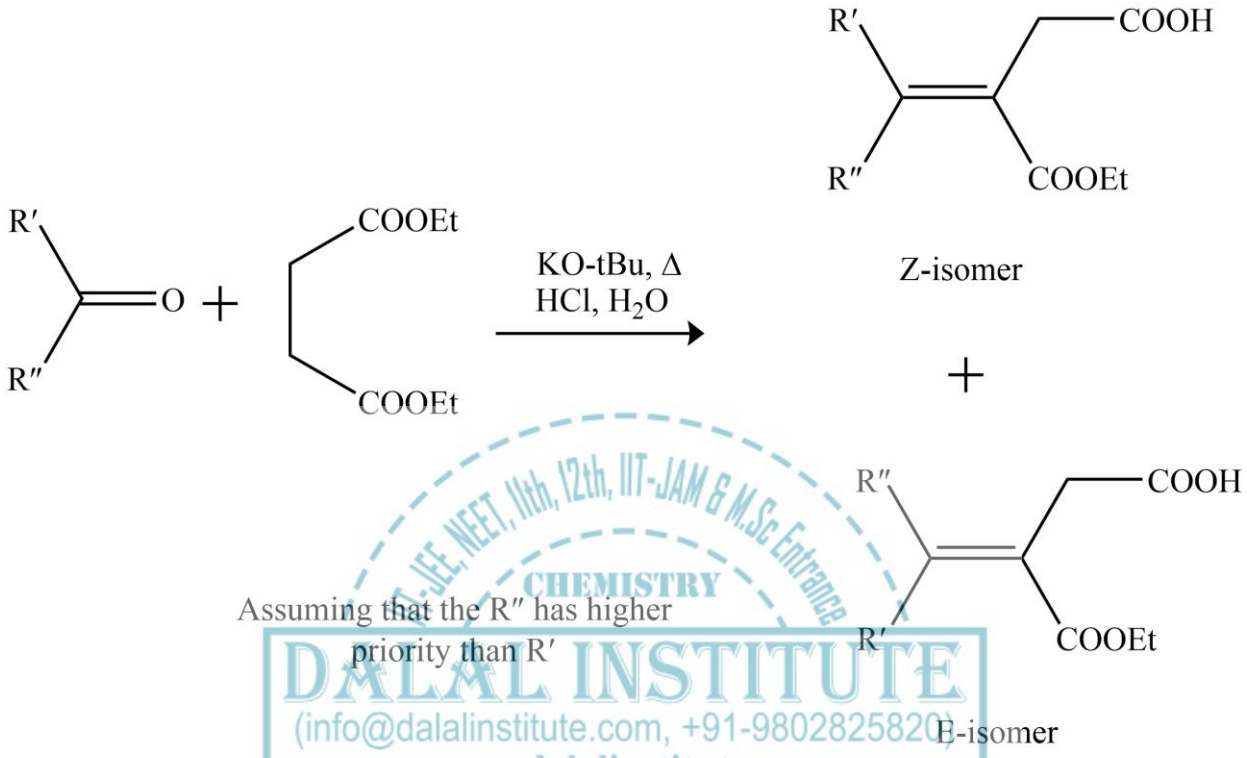
In the later years, Stobbe and his co-workers observed that this is quite common when succinic acid's esters are treated with aldehyde or ketones.

Mechanism of Stobbe condensation: The most widely accepted mechanism for Stobbe condensation that can explain the generation of an ester group, as well as the formation of a carboxylic acid group is a function of a lactone intermediate as shown below.



The carbonyl component isn't restricted in Stobbe condensation; and therefore, it even can have α-hydrogens. Nevertheless, if α-hydrogens are present in the carbonyl component, the double bond migration can trigger the formation of many types of final products.

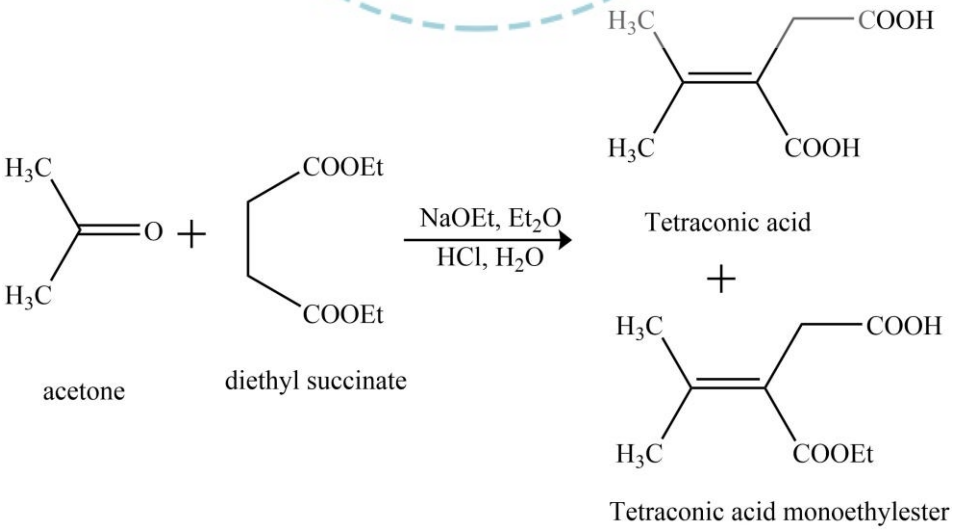
Stereochemistry of Stobbe condensation: Only one alkene stereoisomer will be obtained if symmetrical ketones are used; nevertheless, unsymmetrical ketones will give rise to a mixture of alkene stereoisomers.



Assuming that the R″ has higher priority than R′

Examples of Stobbe condensation: Some of the most common examples of organic chemical transformation Stobbe condensation are given below.

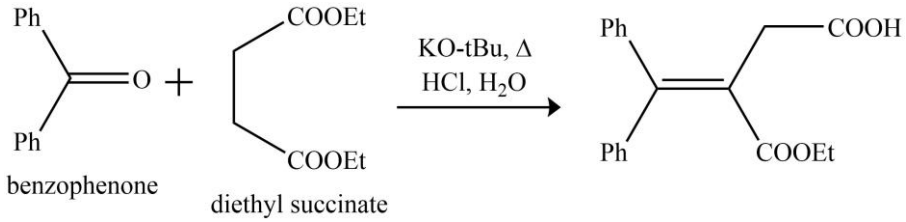
1. One of the most popular examples of Stobbe condensation is the reaction between acetone and diethyl succinate to give tetraconic acid and its monoethyl ester.



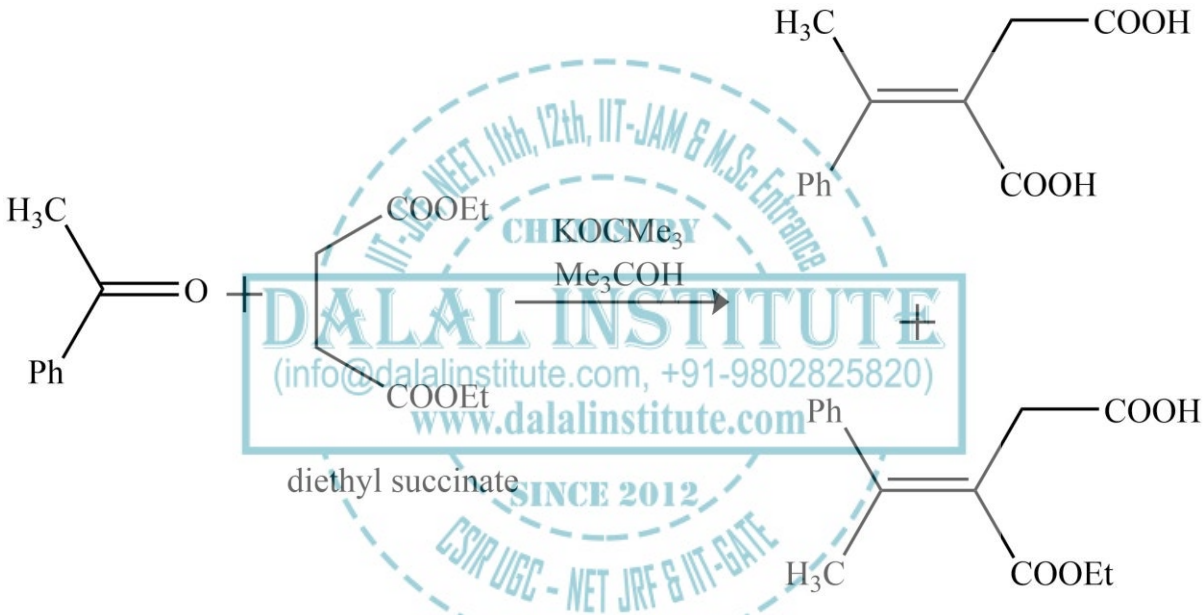
acetone

diethyl succinate

2. The reaction between benzophenone and diethyl succinate to give corresponding monoethyl ester is also an example of Stobbe condensation.



3. One more example of Stobbe condensation includes the generation of acids and monoethyl esters from the reaction between alkyl aryl ketone with diethyl succinate.



Applications of Stobbe condensation: Some of the most common applications of organic chemical transformation involving Stobbe condensation are given below.

1. Stobbe condensation is widely used to synthesize different types of organic acids.

2. one of the major applications of Stobbe condensation is the synthesis of polycyclic ring systems. For instance, the Stobbe products from aryl ketones can give rise to naphthol or indenone derivatives when undergoes dehydration route.

3. Tetralone and phenenthren derivatives can also be obtained using Stobbe condensation.

4. Reinhard Sarges' synthesis of tametraline and synthesis of dimefadane are also based upon the employment of Stobbe condensation in the first step.

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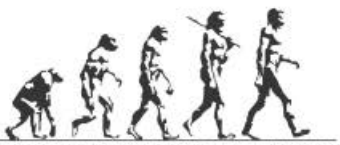

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