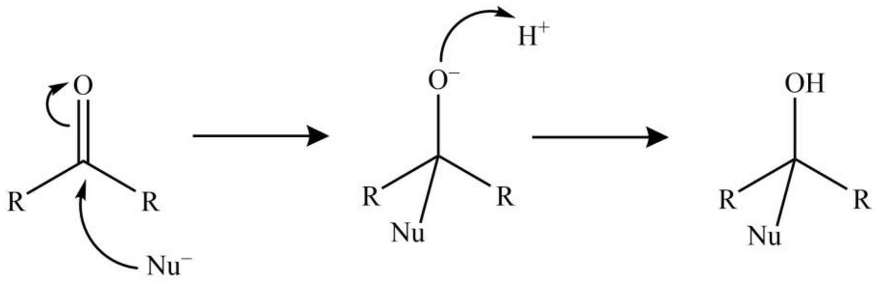
CHAPTER 12

Addition to Carbon-Hetero Multiple Bonds

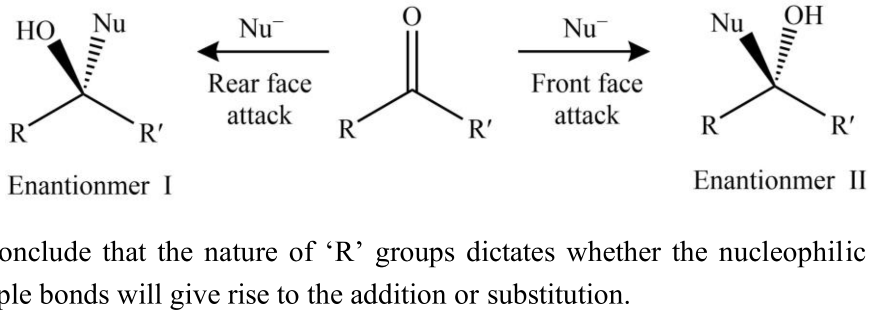
❖ Mechanism of Metal Hydride Reduction of Saturated and Unsaturated Carbonyl Compounds, Acids, Esters and Nitriles

Unlike the nucleophilic addition to carbon-carbon multiple bonds, the nucleophilic addition to carbon-heteroatom multiple bonds is much simpler to study as there is no regiochemical preference (i.e., the orientation of unsymmetrical addition) in most of the cases. For instance, consider >C=O, −C≡N, and −C=N types of bonds which are extremely polar (great difference in electronegativity of participating atoms); so the carbon atoms bear a partial positive charge which makes the molecule an electrophile and the carbon atom as the electrophilic center; and therefore, the electrophilic species of the attacking reagent always goes to the oxygen or nitrogen whereas the nucleophilic part of the reagent attacks at the carbon.



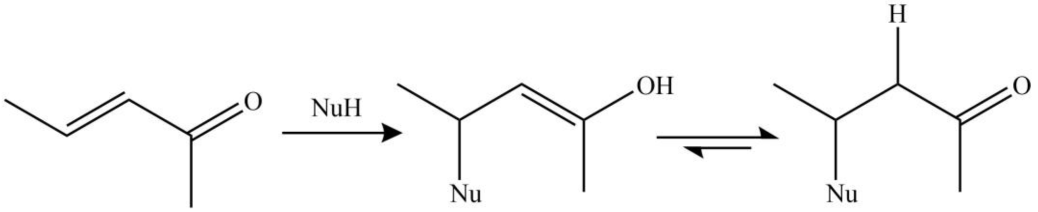
The reaction given above is also called a 1, 2-type nucleophilic addition, and a racemic mixture will be obtained if the alkyl substituents are different.

Furthermore, it is obvious that the first step is just the same as the first step of nucleophilic displacement at a carbonyl's C atom; nevertheless, the latter case rarely takes place because R groups (H and carbon groups like alkyl aryl, etc.) are extremely poor leaving groups supporting the former case (i.e., addition). The acyl substitution dominates in the case of carboxylic acid derivatives (like amides or acid chlorides) because of the presence of 'relatively' good leaving groups like NH_2, OR, Cl, etc.

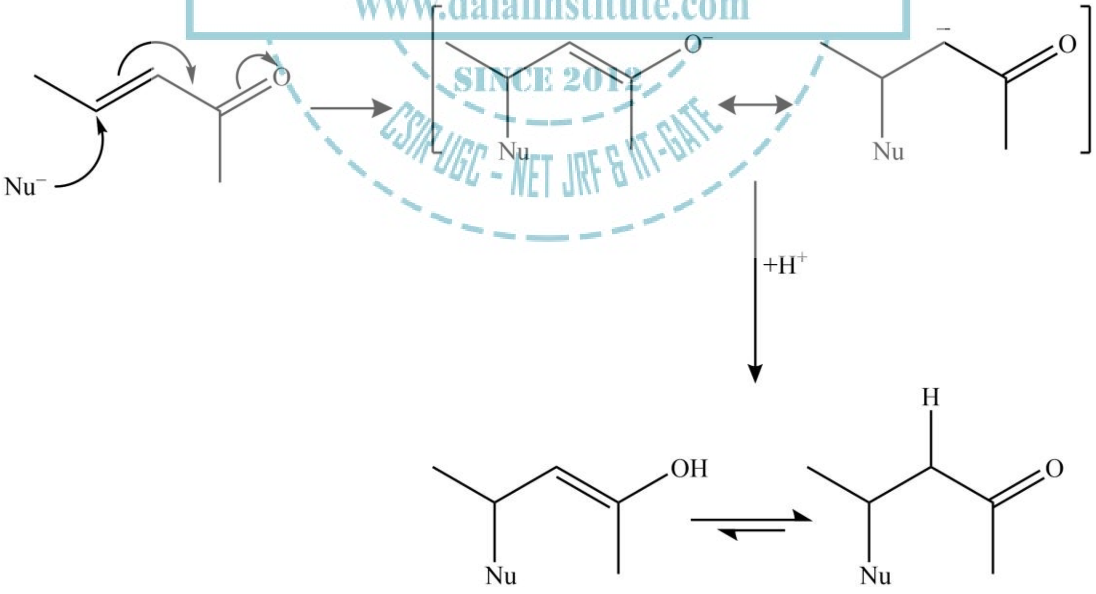


Hence, we can conclude that the nature of 'R' groups dictates whether the nucleophilic attack at carbon-heteroatom multiple bonds will give rise to the addition or substitution.

Until now we have discussed the basic ideas of addition to simple (i.e., non-conjugated) carbon-heteroatom multiple bonds; however, some systems do have unsaturation at least at α- and β-carbon. The nucleophilic addition in such cases is called conjugate addition and is different from ordinary nucleophilic additions to carbon-hetero bonds (i.e., 1, 2-nucleophilic additions) due to far separated attacking sites (i.e., 1, 4-nucleophilic additions). It is also important to recall the fact that normal alkenes neither show 1, 2- nor 1, 4-reactivity (possible only via activation by special substituents) due to lack of polarity.



The mechanism of conjugate addition can be understood by taking the example of an α, β-unsaturated carbonyl compound like cyclohexenone, where it can be showed that the β-position is an electrophilic site that can react with a nucleophile (from resonance structures). After the nucleophilic attack, the negative charge of the nucleophilic part of the attacking reagent is now distributed via resonance in α-carbon carbanion and alkoxide anion. Finally, the protonation results in a saturated carbonyl compound via keto-enol tautomerism (the equilibrium lies toward the keto form because it is more stable than the enol form due to a stronger C=O bond than C=C bond). Also, another electrophile will replace the proton if the reaction further proceeds via vicinal difunctionalization.

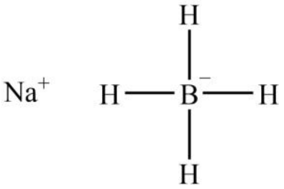


In this section, we will study the mechanism of a special type of addition to the carbon-heteroatom multiple bonds where the reduction of saturated and unsaturated carbonyl compounds (aldehydes, ketones, and acyl halides), acids, esters, and nitriles is carried out using metal hydrides.

➢ *Metal Hydride Reduction of Saturated Carbonyl Compounds*

Many metal hydrides can be used to reduce the saturated carbonyl compounds like aldehydes, ketones, and acid halides.

1. Reduction by Sodium Borohydride: The sodium borohydride ($NaBH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced in the course of reaction because of the polar nature of the metal-hydrogen bond.

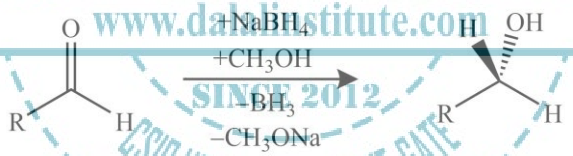


Sodium Borohydride

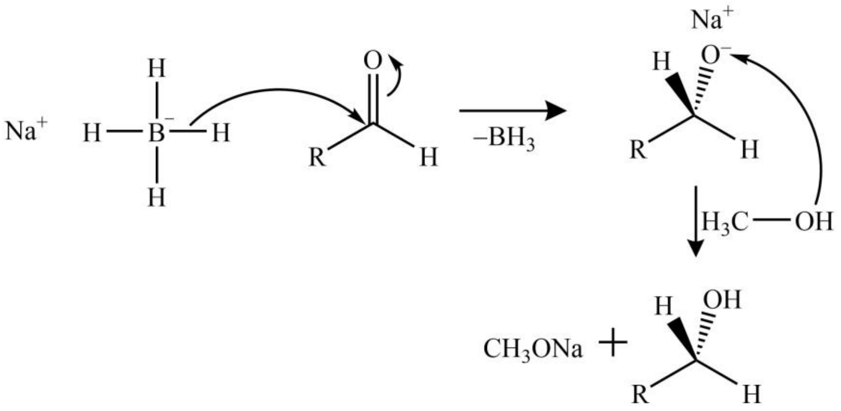
The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to a reduced product.

i) Reduction of aldehydes by $NaBH_4$:

The hydride anion's addition to aldehyde results in an alkoxide anion, which in turn, gives rise to primary (1°) alcohols on protonation.

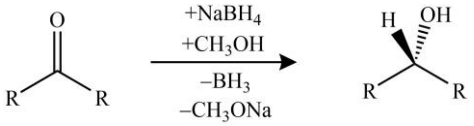


The mechanism for the aldehydic reduction by metal hydride involves the nucleophilic addition of the hydride ion to the carbonyl carbon. In many cases, the Na^+ ion activates the carbonyl group by attaching itself to the oxygen atom, which in turn, will raise the electrophilic character of the C=O group.

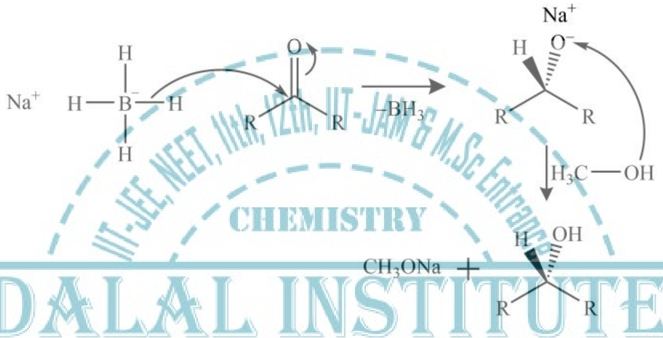


ii) Reduction of ketones by $NaBH_4$*:*

The hydride anion's addition to ketone results in an alkoxide anion which in turn gives rise to secondary (2º) alcohols on protonation.

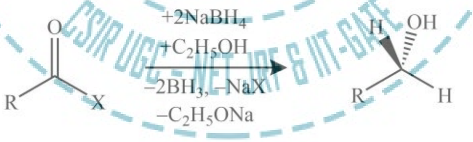


The mechanism for the ketone reduction by metal hydride involves the nucleophilic addition of the hydride ion to the carbonyl carbon. In many cases, the Na^+ activates the carbonyl group by attaching itself to the oxygen atom, which in turn, will raise the electrophilic character of the C=O group.

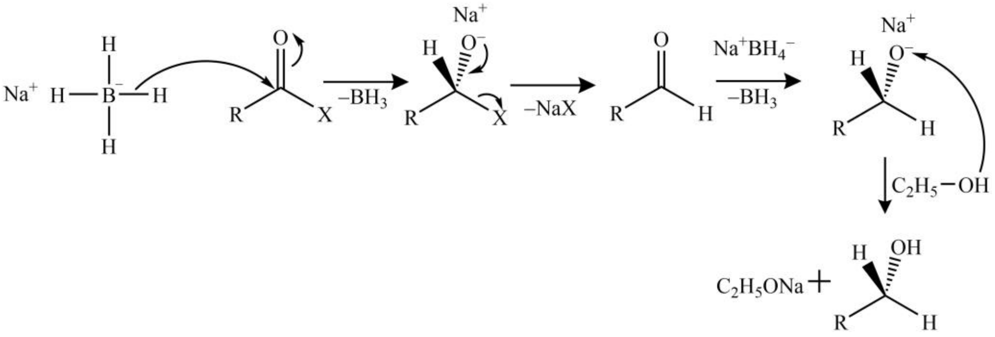


iii) Reduction of acyl halides by $NaBH_4$*:*

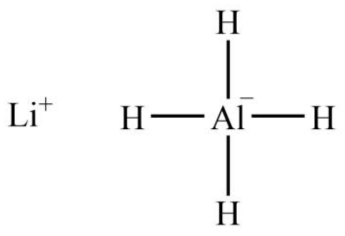
Two subsequent additions of hydride anions to acyl halides result in a sodium alkoxide anion which in turn gives rise to primary (1º) alcohols on protonation.



The mechanism for the acyl halides' reduction by metal hydrides involves the nucleophilic addition of the hydride ion to the carbonyl carbon. In many cases, the Na^+ activates the carbonyl group by attaching itself to the oxygen atom, which in turn, will raise the electrophilic character of the C=O group.



2. Reduction by Lithium aluminium hydride: The lithium aluminium hydride ($LiAlH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced in the course of reaction because of the polar nature of the metal-hydrogen bond.

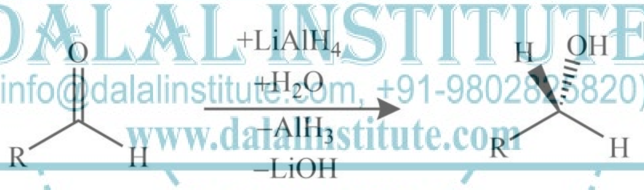


Lithium aluminium hydride

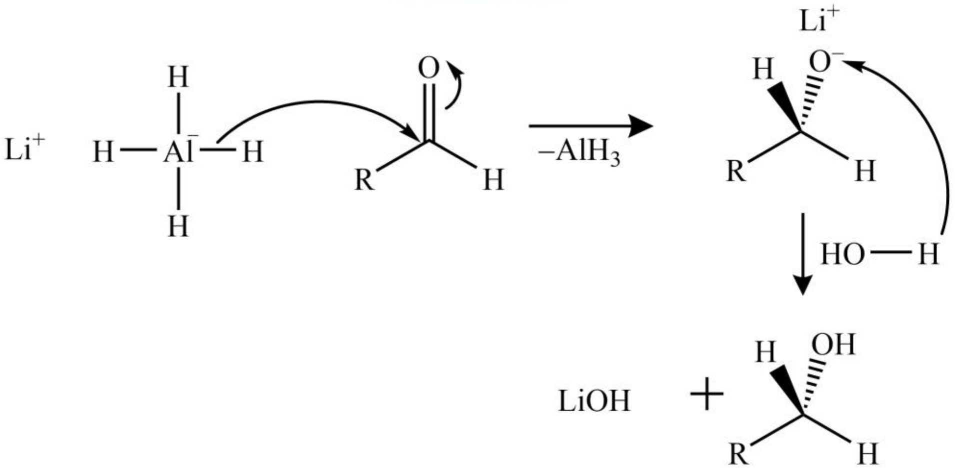
The hydride anion's addition to carbonyl compound results in a lithium alkoxide anion which in turn gives rise to a reduced product.

i) Reduction of aldehydes by $LiAlH_4$:

The hydride anion's addition to aldehyde results in an alkoxide anion which in turn gives rise to primary (1°) alcohols on protonation.

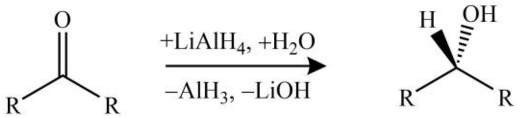


The mechanism for the aldehydic reduction by metal hydride involves the nucleophilic addition of the hydride ion to the carbonyl carbon. In many cases, the Li^+ activates the carbonyl group by attaching itself to the oxygen atom, which in turn, will raise the electrophilic character of the C=O group.

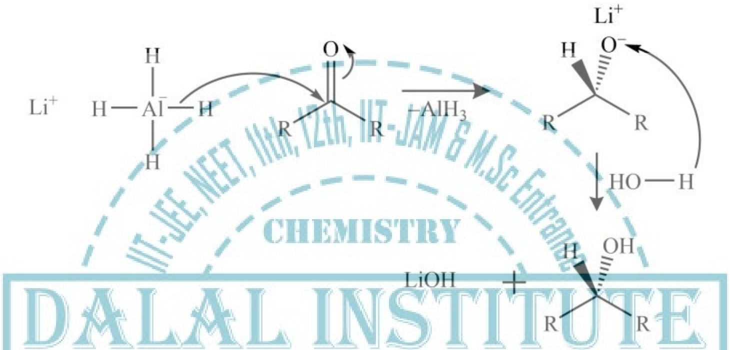


ii) Reduction of ketones by $LiAlH_4$:

The hydride anion's addition to ketone results in an alkoxide anion which in turn gives rise to secondary (2º) alcohols on protonation.

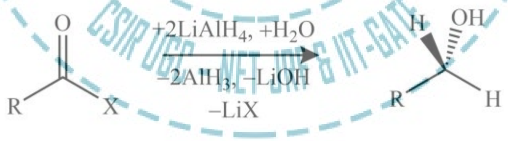


The mechanism for the ketone reduction by metal hydride involves the nucleophilic addition of the hydride ion to the carbonyl carbon. In many cases, the Li^+ activates the carbonyl group by attaching itself to the oxygen atom, which in turn, will raise the electrophilic character of the C=O group.

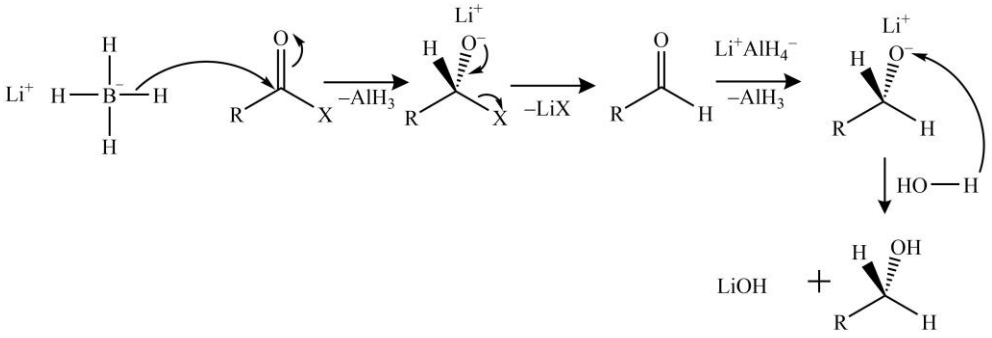


iii) Reduction of acyl halides by $LiAlH_4$:

Two subsequent additions of hydride anions to acyl halides results in an alkoxide anion which in turn gives rise to primary (1º) alcohols on protonation.



The mechanism for the acyl halides' reduction by metal hydride involves the nucleophilic addition of the hydride ion to the carbonyl carbon. In many cases, the Li^+ activates the carbonyl group by attaching itself to the oxygen atom, which in turn, will raise the electrophilic character of the C=O group.



➢ *Metal Hydride Reduction of Unsaturated Carbonyl Compounds*

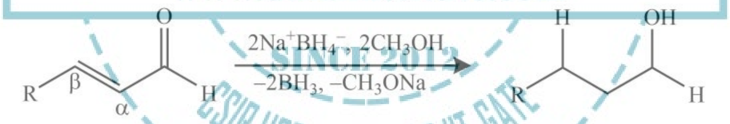
Many metal hydrides can be used to reduce the unsaturated carbonyl compounds like α, β-unsaturated aldehydes, ketones, and acid halides.

1. Reduction by Sodium Borohydride: It is well-known fact that isolated C=C bond cannot be reduced either by $LiAlH_4$ or by $NaBH_4$. However, if this C=C is in conjugation with C=O (i.e., conjugated aldehyde, ketones, or acid chlorides), the substrate can act as an electrophile via at the β-carbon or via the carbon of the carbonyl group. Now since the β-carbon is a "soft" electrophilic site, it will prefer to react with "soft" nucleophile like $NaBH_4$; whereas the carbonyl's carbon is a relatively "hard" electrophilic site, it will prefer to react with "hard" nucleophile like $LiAlH_4$ (HSAB Principle). Nevertheless, after the reduction of the C=C bond, the saturated aldehyde will also get reduced to the alcohol by $NaBH_4$ in the next step. Conversely, $LiAlH_4$ will show a 1, 2-addition, leaving an isolated C=C double bond unaltered.

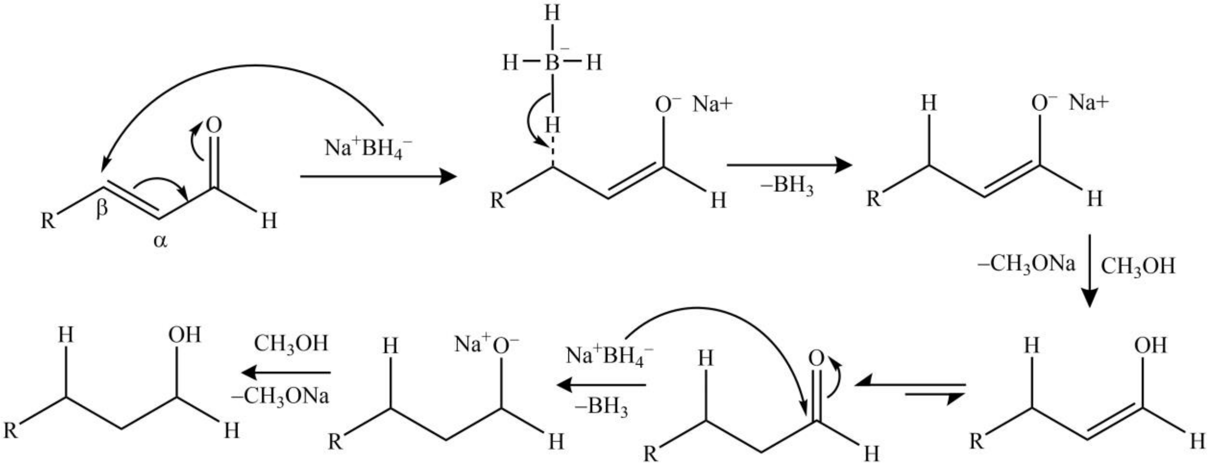
The hydride anion's addition to unsaturated carbonyl compound results in an alkoxide anion which in turn gives rise to a reduced product.

i) Reduction of α, β-unsaturated aldehydes by $NaBH_4$:

The hydride anion's addition to the α, β-unsaturated aldehyde results in an alkoxide anion which in turn gives rise to primary (1°) alcohols on protonation.

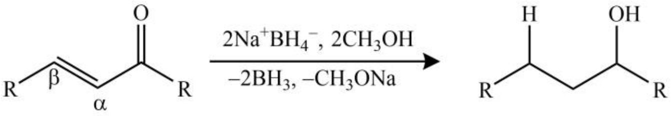


The mechanism for the aldehydic reduction by metal hydride that involves the 1, 4-nucleophilic addition of the hydride ion followed by a 1-2-addition to the carbonyl carbon is given below.

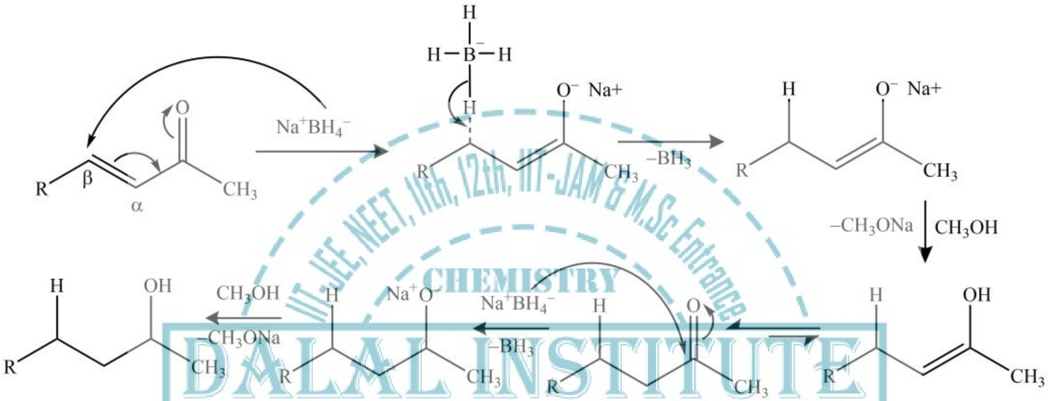


ii) Reduction of α, β-unsaturated ketones by NaBH₄:

The hydride anion's addition to α, β-unsaturated ketone results in an alkoxide anion which in turn gives rise to secondary (2º) alcohols on protonation.

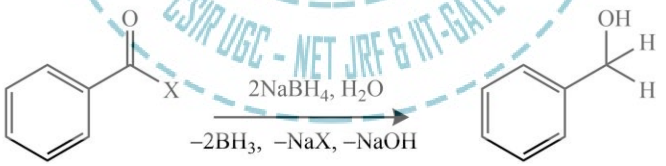


The mechanism for the ketone reduction by metal hydride that involves the 1, 4-nucleophilic addition of the hydride ion, followed by a 1, 2-addition to the carbonyl carbon is given below.

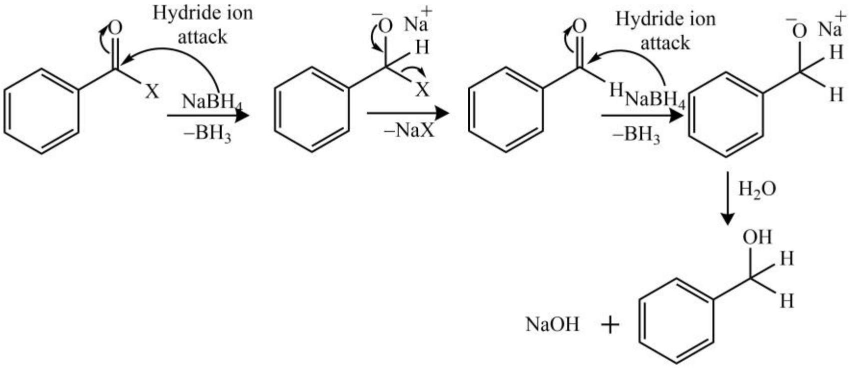


iii) Reduction of α, β-unsaturated acyl halides by NaBH₄:

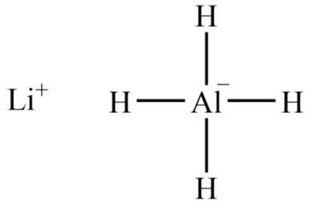
Although it seems like an easy task, there are no reports of NaBH₄-catalyzed 1, 4-addition to acyl halides (with reasonable yield). Nevertheless, 1, 2-adducts for benzoyl chloride have been obtained.



The mechanism for the transformation of benzoyl chloride to benzyl alcohol via NaBH₄ is given below.



2. Reduction by Lithium aluminium hydride: Since the carbonyl's carbon is a relatively "hard" electrophilic site, it will prefer to react with "hard" nucleophile like $LiAlH_4$ (HSAB Principle). Hence, unlike $NaBH_4$, $LiAlH_4$ will show a 1, 2-addition, leaving an isolated double bond unaltered.



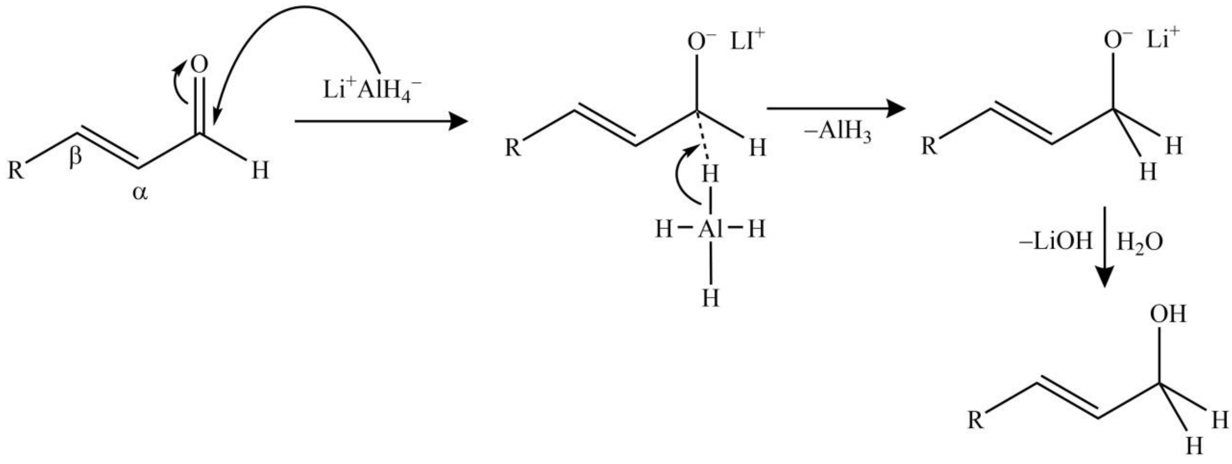
Lithium aluminium hydride

The hydride anion's addition to carbonyl compound results in a lithium alkoxide anion which in turn gives rise to a reduced product.

i) Reduction of α, β-unsaturated aldehydes by $LiAlH_4$:

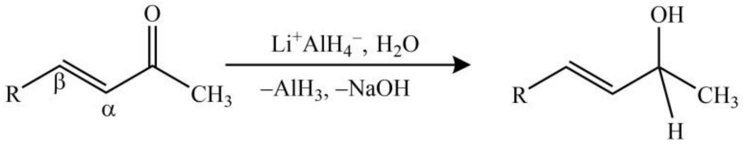
The hydride anion's addition to α, β-unsaturated aldehyde results in an alkoxide anion which in turn gives rise to primary (1°) alcohols on protonation.

The mechanism for the α, β-unsaturated aldehydic reduction by metal hydride involves 1, 2-nucleophilic addition of the hydride ion to the carbonyl carbon as shown below. Furthermore, it is also worthy to note that conjugate addition in product might also be obtained alongside with very small yield.

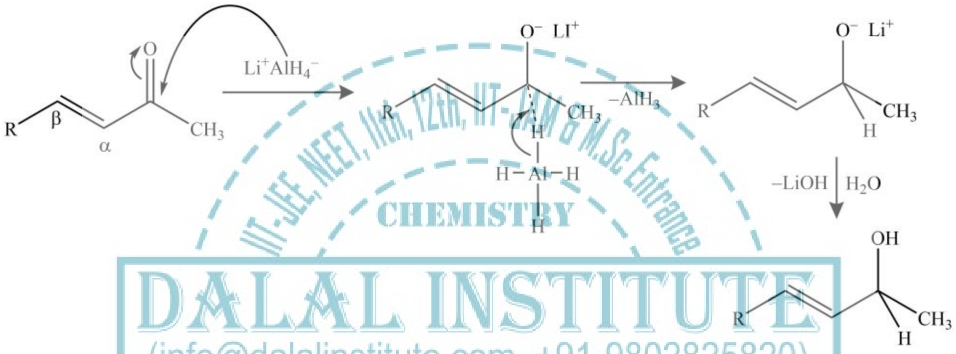


ii) Reduction of α, β-unsaturated ketones by $LiAlH_4$:

The hydride anion's addition to ketone results in an alkoxide anion which in turn gives rise to secondary (2º) alcohols on protonation.

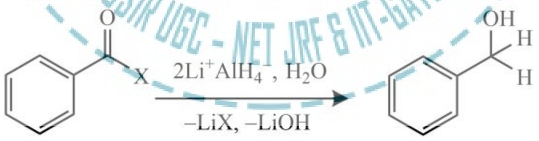


The mechanism for the α, β-unsaturated ketonic reduction by metal hydride involves 1, 2-nucleophilic addition of the hydride ion to the carbonyl carbon as shown below. Furthermore, it is also worthy to note that conjugate addition in product might also be obtained alongside with very small yield.

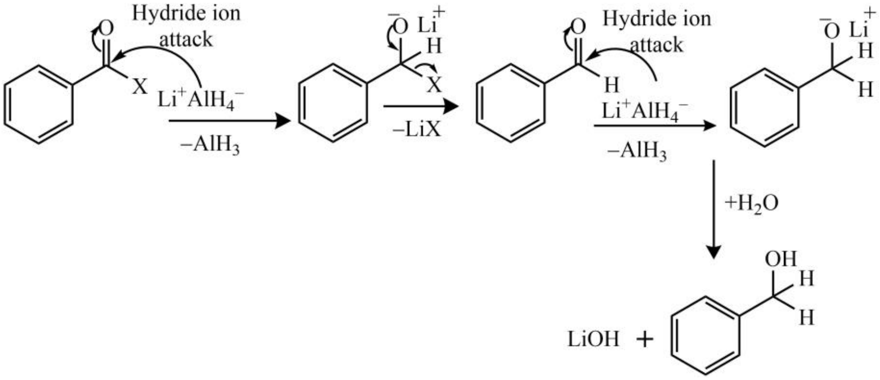


iii) Reduction of α, β-unsaturated acyl halides by $LiAlH_4$:

The hydride anion's addition to ketone or aldehyde results in an alkoxide anion which in turn gives rise to primary (1º) alcohols on protonation.



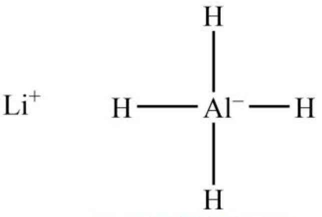
The mechanism for the transformation of benzoyl chloride to benzyl alcohol via $LiAlH_4$ is given below.



➢ *Metal Hydride Reduction of Acids*

Many metal hydrides can be used to reduce the saturated and unsaturated carbonyl compounds like carboxylic acid.

1. Reduction by lithium aluminium hydride: The lithium aluminium hydride ($LiAlH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced in the course of reaction because of the polar nature of the metal-hydrogen bond.

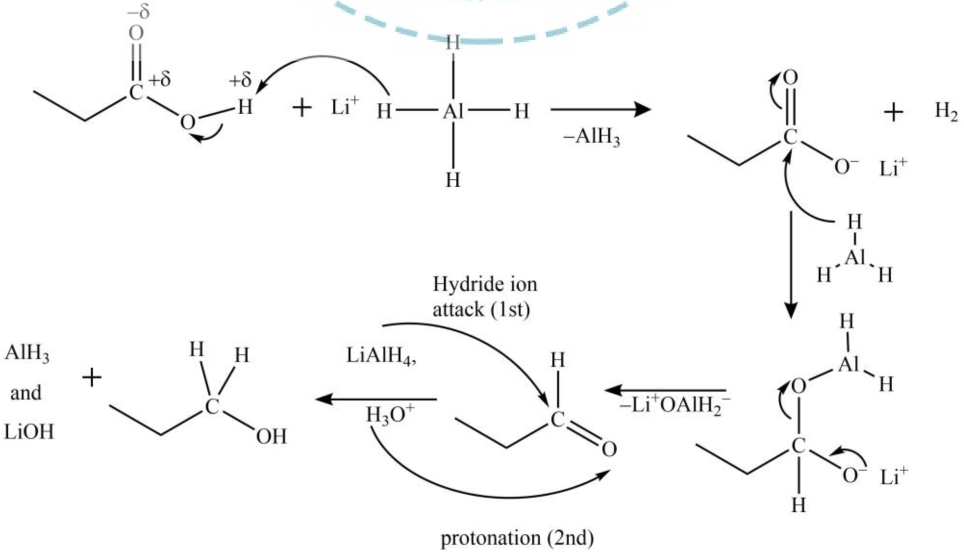


Lithium aluminium hydride

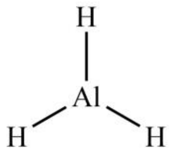
The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to a reduced product.

The hydride anion's attack on carboxylic acid results in a carboxylate anion, which in turn, is attacked by AlH_3 to yield aldehyde. This aldehyde then gives rise to primary (1°) alcohols after 1, 2-addition.

The mechanism for the carboxylic acid's reduction by metal hydride (by LiAlH4 in this case) to give primary alcohols is given below.



2. Reduction by aluminium hydride: The aluminum hydride, i.e., AlH_3, is one of the most common types of electrophilic addition for the reduction of carboxylic acid because simple borohydride cannot reduce carboxylic acids.

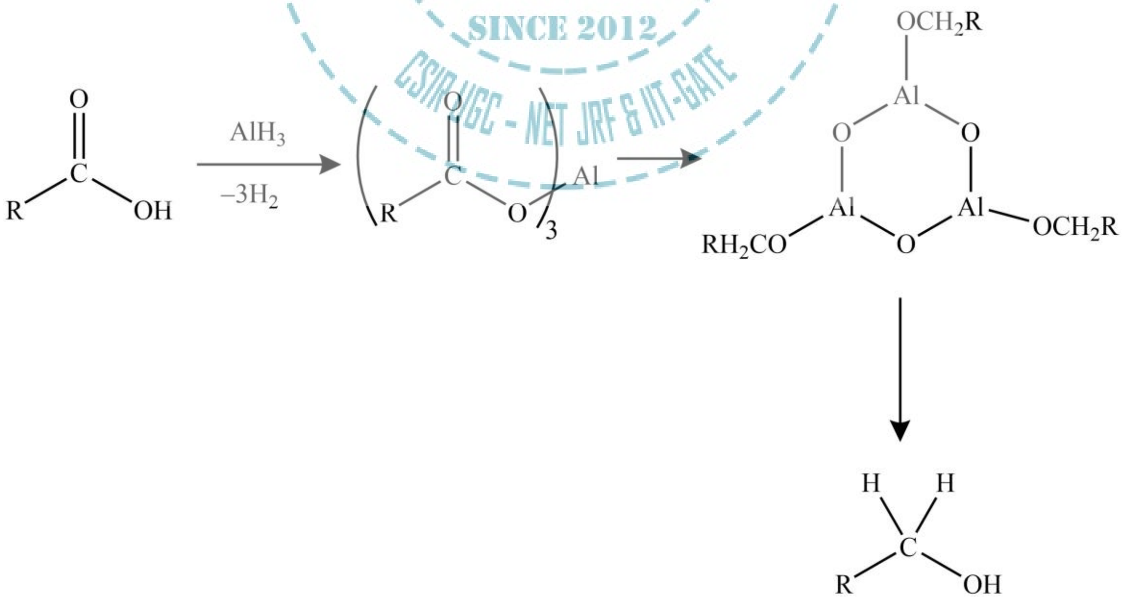


Aluminium hydride

In some cases, the reactivity of aluminium hydride is like lithium aluminium hydride; whereas sometimes it acts as borane (BH_3).

The hydride anion's addition to carboxylic acid results in a complex series of transition states which in turn gives rise to primary (1°) alcohols on protonation.

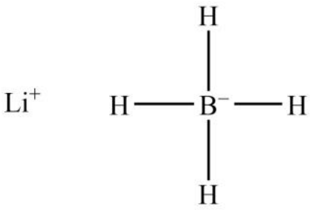
The mechanism responsible for the reduction of carboxylic acids by aluminium hydride involves the following steps.



➢ *Metal Hydride Reduction of Esters*

Metal hydrides like lithium borohydride and lithium aluminium hydride can be used to reduce the carbonyl compounds like esters.

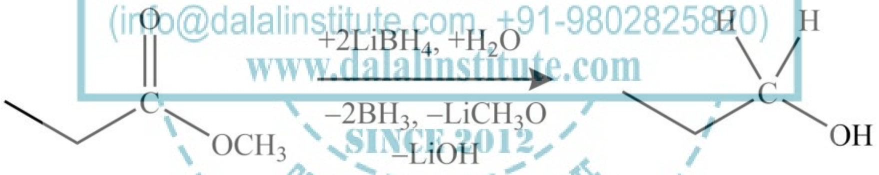
1. Reduction by lithium Borohydride: The lithium borohydride ($LiBH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during reaction because of the polar nature of the metal-hydrogen bond.



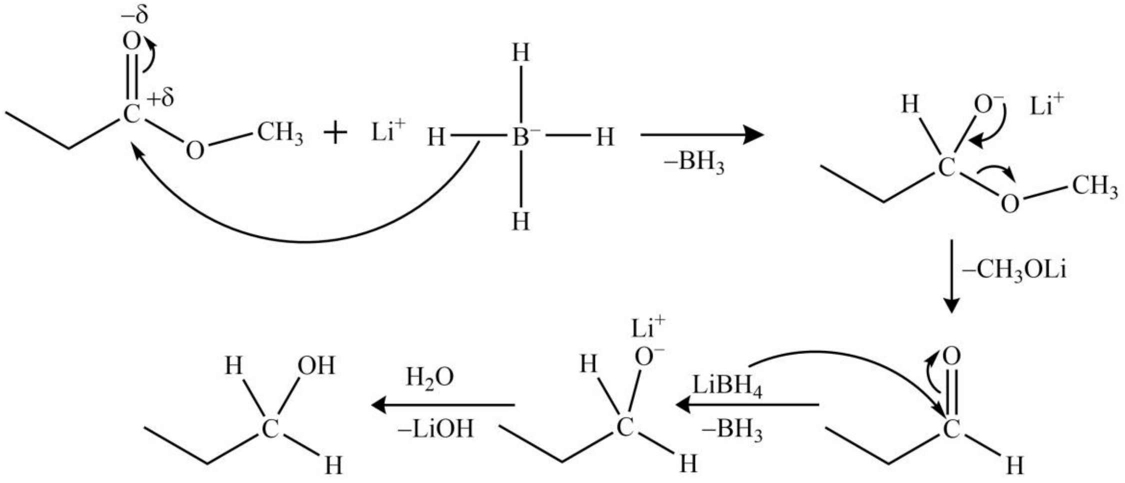
Lithium borohydride

The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to the reduced product.

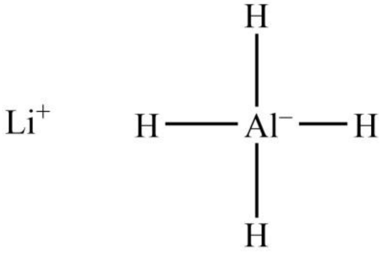
Two subsequent hydride anions' additions to ester result in an alkoxide anion which in turn gives rise to primary (1°) alcohols on protonation.



The mechanism for the ester reduction by metal hydride ($LiBH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbonyl carbon is given below.



2. Reduction by Lithium aluminium hydride: The lithium aluminium hydride ($LiAlH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during reaction because of the polar nature of the metal-hydrogen bond.

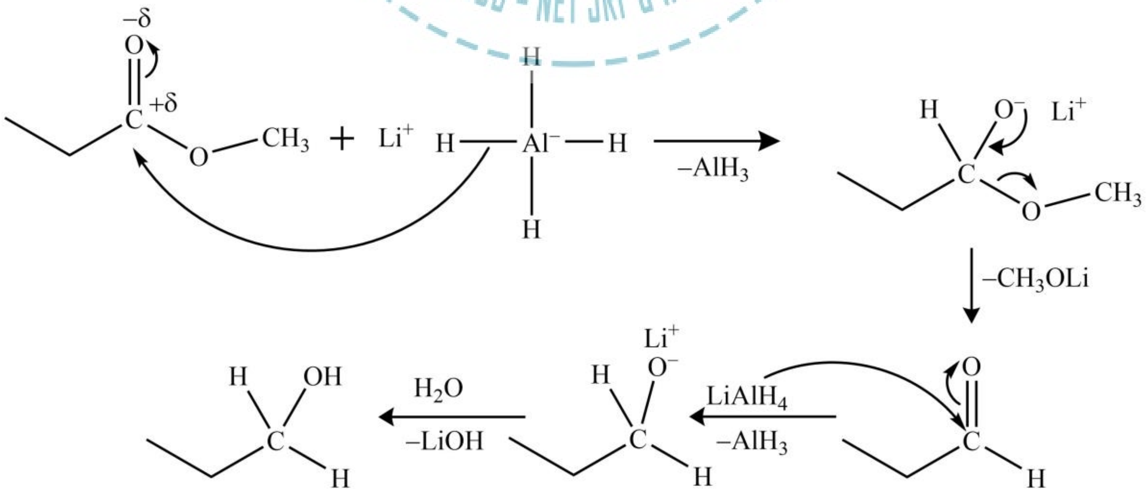


Lithium aluminium hydride

The hydride anion's addition to carbonyl compound results in an alkoxide anion which in turn gives rise to the reduced product.

Two subsequent hydride anions' additions to ester result in an alkoxide anion which in turn gives rise to primary (1º) alcohols on protonation.

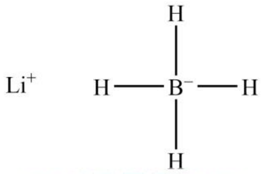
The mechanism for the ester reduction by metal hydride ($LiAlH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbonyl carbon is given below.



➢ *Metal Hydride Reduction of Nitriles*

The nitriles' reduction may simply be defined as the chemical transformation in which a nitrile is reduced to either an aldehyde or an amine by the use of a suitable reagent. Many metal hydrides can be used to reduce the nitrile compounds to amines but $LiBH_4$ and $LiAlH_4$ are most common.

1. Reduction by lithium borohydride: The lithium borohydride ($LiBH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during the reaction because of the polar nature of the metal-hydrogen bond.



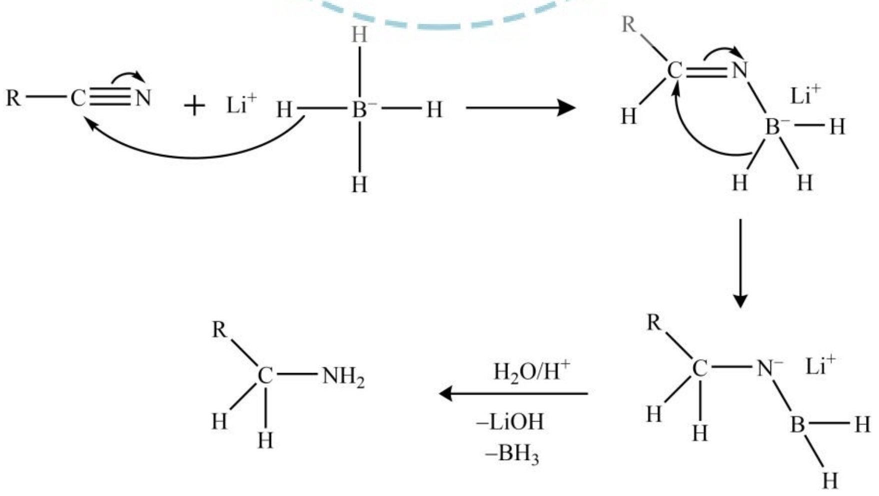
Lithium borohydride

The hydride anion's addition to nitrile compounds results in an anion which in turn gives rise to a reduced product.

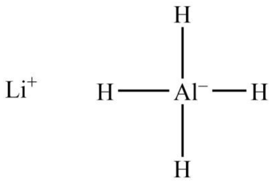
Two subsequent additions of hydride anions to the carbon-nitrogen bond result in a lithium salt which in turn gives rise to primary (1°) amines on protonation.

$$R-C\equiv N \xrightarrow[-BH_3]{LiBH_4/\,H_2O/\,H^+} R-CH_2-NH_2 + LiOH$$

The mechanism for the nitriles' reduction by metal hydride ($LiBH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbon-nitrogen bond is given below.



2. Reduction by Lithium aluminium hydride: The lithium aluminium hydride ($LiAlH_4$) is one of the most common sources of the hydride nucleophile. The hydride anion is produced during reaction because of the polar nature of the metal-hydrogen bond.

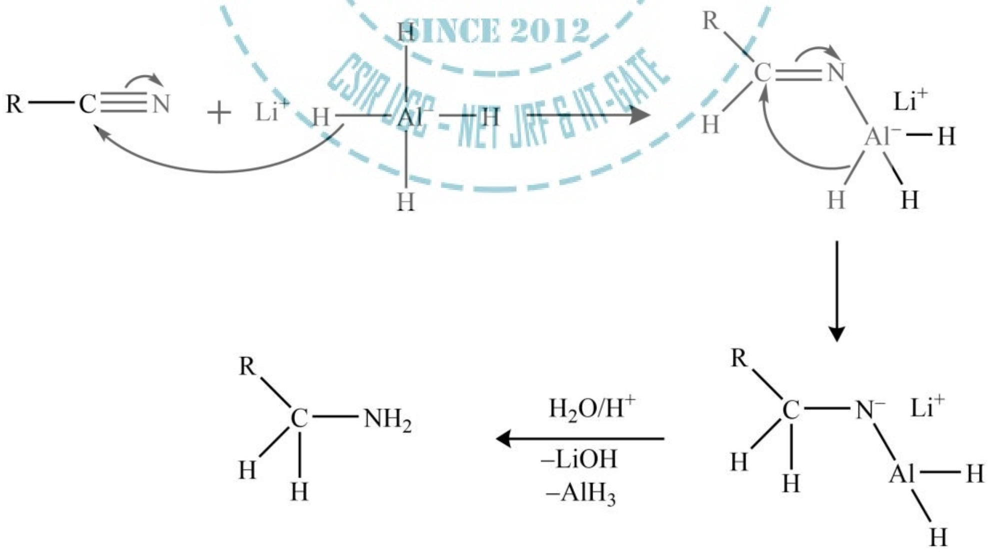


Lithium aluminium hydride

The hydride anion's addition to nitrile compounds results in an anion which in turn gives rise to a reduced product.

Two subsequent additions of hydride anions to the carbon-nitrogen bond result in a lithium salt which in turn gives rise to primary (1°) amines on protonation.

The mechanism for the nitriles' reduction by metal hydride ($LiAlH_4$ in this case) that involves the nucleophilic addition of the hydride ion to the carbon-nitrogen bond is given below.

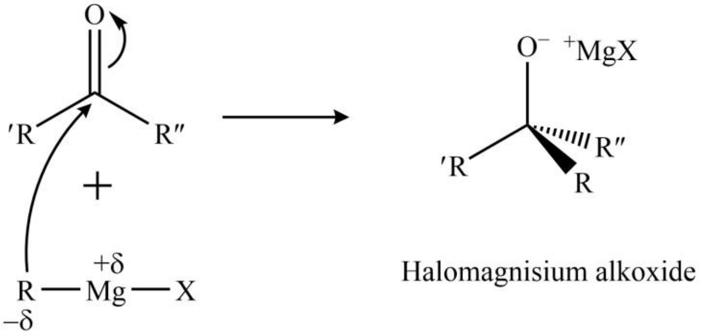


❖ Addition of Grignard Reagents, Organozinc and Organolithium Reagents to Carbonyl and Unsaturated Carbonyl Compounds

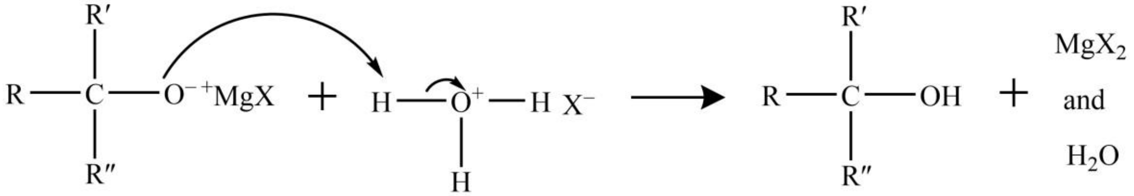
As far as the addition to carbon-heteroatom multiple bonds is concerned, three organometallic reagents are much more important than the others; organomagnesium (Grignard reagents), organozinc, and oreganolithium compounds. In this section, we will discuss the addition of these three types of reagents to carbonyl and unsaturated carbonyl compounds.

➢ *Addition of Grignard Reagents to Carbonyl and Unsaturated Carbonyl Compounds*

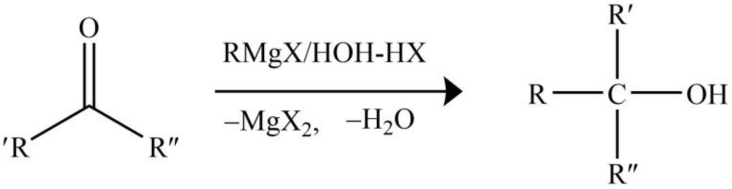
The typical addition mode of organomagnesium compounds (Grignard reagent) to common carbonyl compounds like ketone and aldehydes is given below.



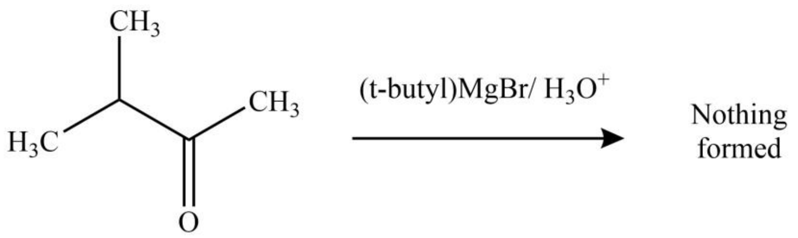
The halomagnesium alkoxide thus formed can react with H_2O (when an HX type mineral acid is available) to result in alcohols; which in turn, could be susceptible to dehydration (acid-catalyzed) if it is tertiary-type. To stop the alcohol's dehydration, we need to add some ammonium chloride (NH_4Cl) to the water so that because its acidic character can be employed to transform ROMgX to ROH.

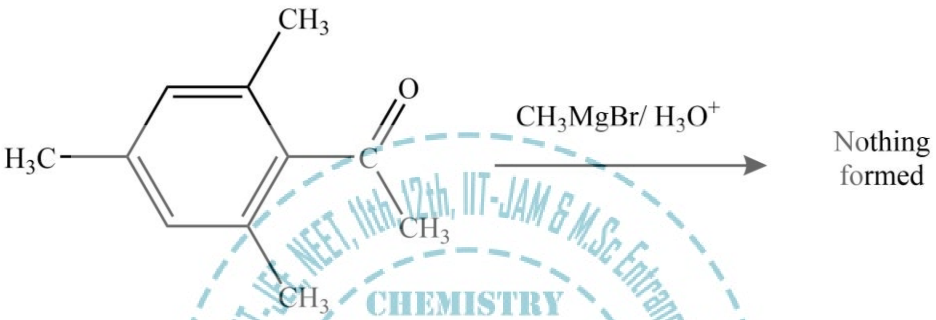


or

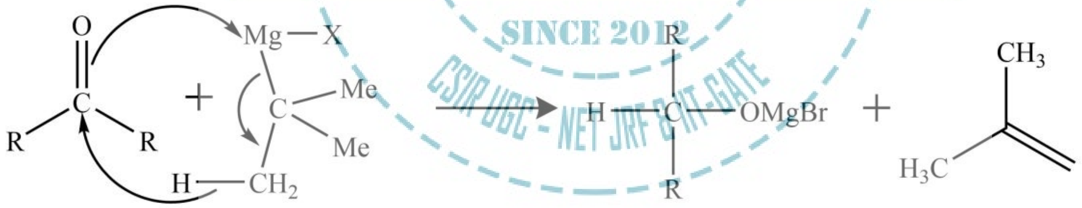


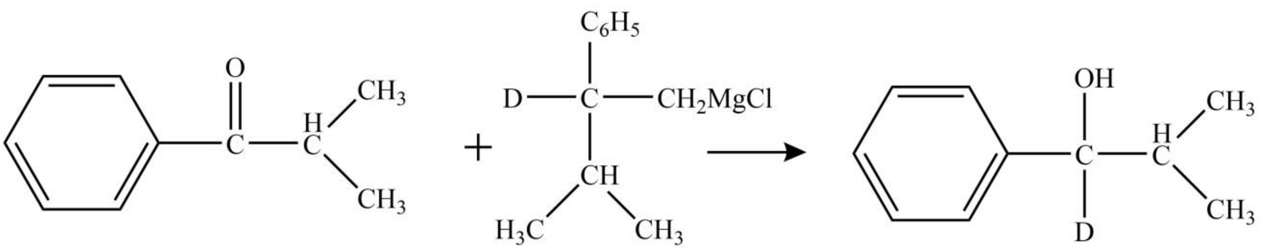
It is also worthy to note that bulky groups in the keto group, or in the reagent itself, greatly affect the nucleophilic addition in a negative way, or gets completely prohibited in some cases.



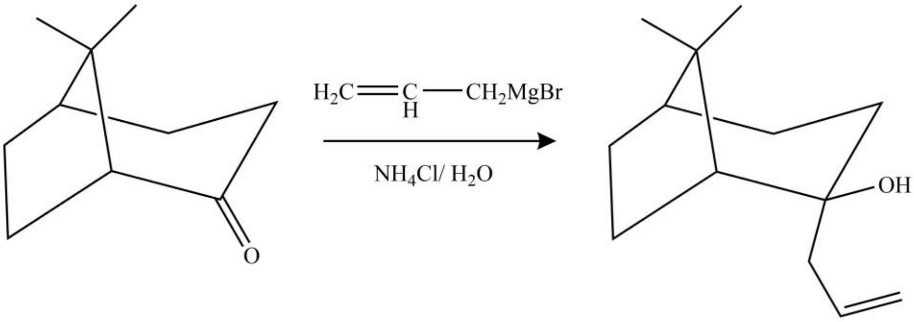


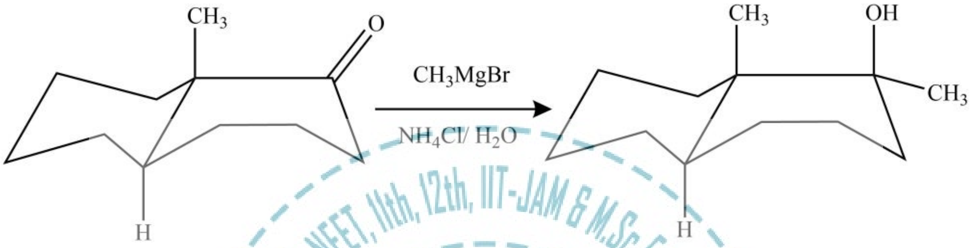
However, if a β-hydrogen is present in the bulky group of Grignard reagent, the transfer of hydride ion can result in the reduction of even highly hindered ketones. Moreover, if this is carried out via chiral Grignard reagent, the resulting product will also become optically active proving that the transfer of hydride ion does take place via the generation of cyclic transition state having six members.



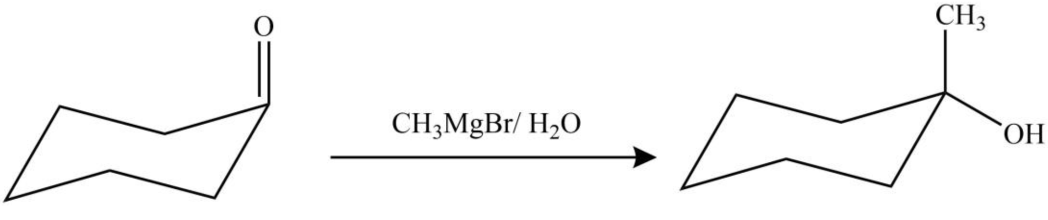


Also, if the Grignard addition takes place in cyclic ketones, the nucleophilic attack will happen from the carbonyl's face with less steric hindrance.

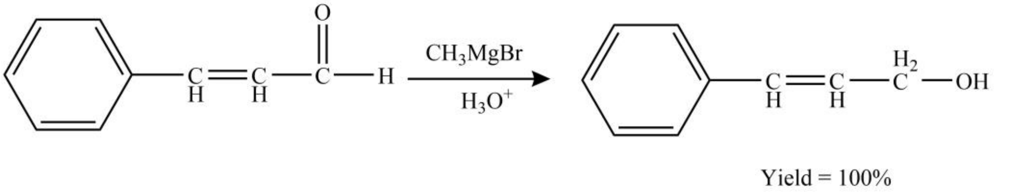


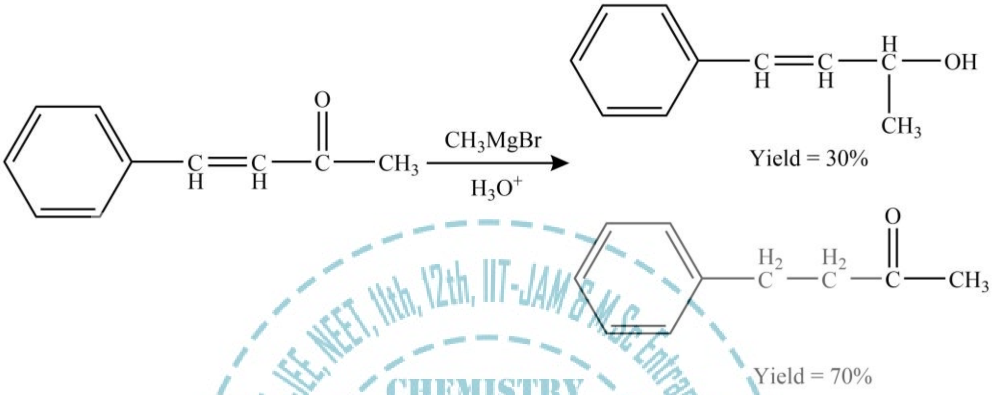


Since the organomagnesium reagent moves towards the substrate from a less hindered end, the final products' nature is also a function of the Grignard reagent used as it will push the hydroxy group to the axial site. On the other hand, a less bulky R (in comparison to OH) will make the hydroxy group occupy an equatorial site.

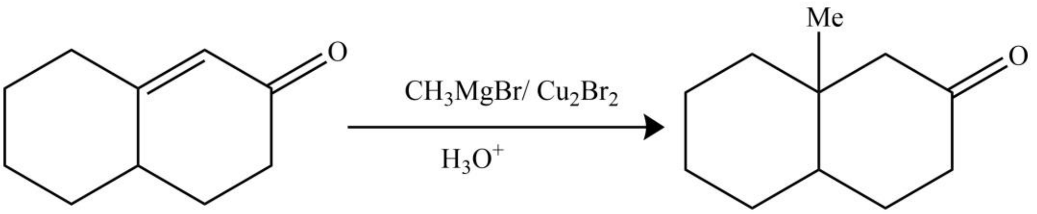


On a final note, if the aldehyde or the ketone used is α-, β-unsaturated, the nucleophilic addition of Grignard reagents becomes must faster and effective than normal carbonyl compounds, yielding 1, 4- and 1, 2-adddition products simultaneously. Moreover, these α-, β-unsaturated ketone and aldehydes give 1, 4- and 1, 2- adducts as the major products, respectively.





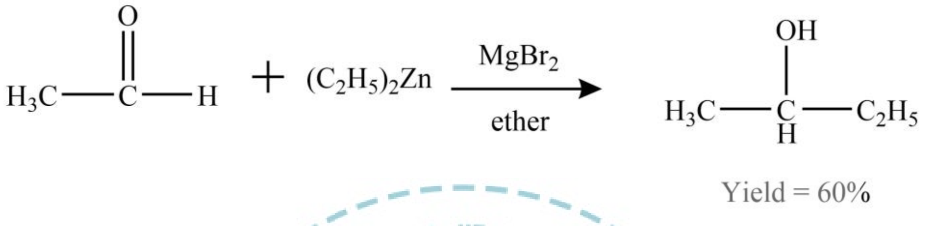
Nevertheless, it should also be noted that only 1, 4-adduct will be obtained if the addition over ketone is carried out in the presence of Cu_2Br_2.



Since the Grignard reagents are very strong bases, they are not suitable to act as nucleophiles with substrate containing acidic hydrogens. In other words, Grignard reagents will act as a base and will abstract the acidic hydrogen instead of participating as a nucleophile to attack the carbonyl group.

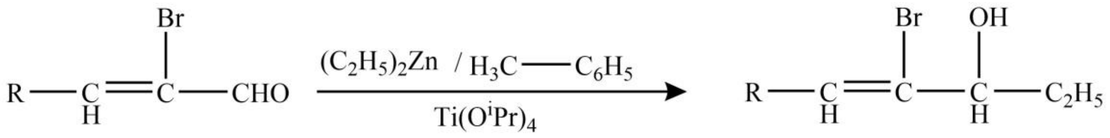
- ***Addition of Organozinc Reagents to Carbonyl and Unsaturated Carbonyl Compounds***

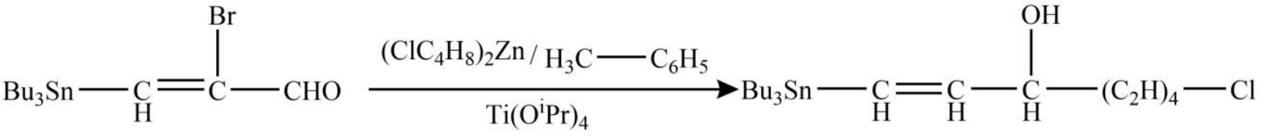
The rate of reaction for carbonyl compounds with dialkylzinc reagents is quite slow. It has also been observed that the rate for higher dialkylzinc is even lesser than lower dialkylzinc reagents. For instance, the reaction of diethylzinc with acetaldehyde takes hours for completion whereas the higher homologs may even take weeks. Nevertheless, allylzinc reagents show greater reactivity towards nucleophilic addition than normal dialkylzinc systems. Furthermore, the metal halide Lewis acids have been shown to enhance the rate of addition via dialkylzinc reagents.



The heteroatom's presence at the α-site (relative to CO group) has also been found to be supportive of nucleophilic addition organozinc reagents.

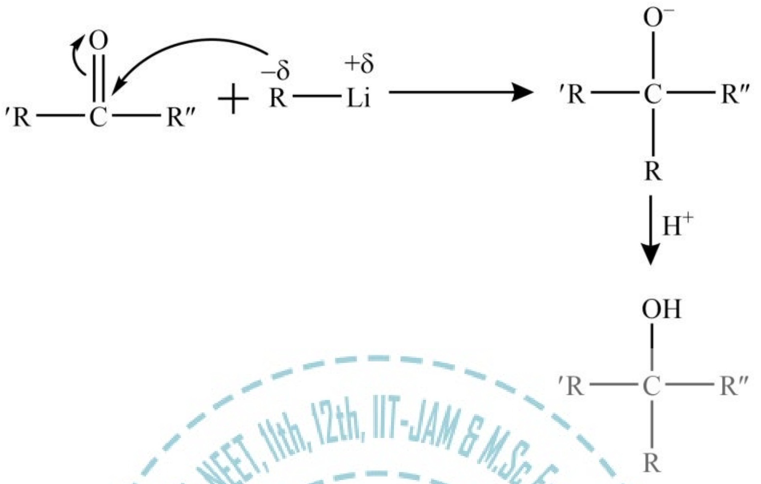
On a final note, it has also been proved that many titanium catalysts are supportive of the reactivity of organozinc reagents, specially $TiCl_4$ and $Ti(O^iPr)_4$.





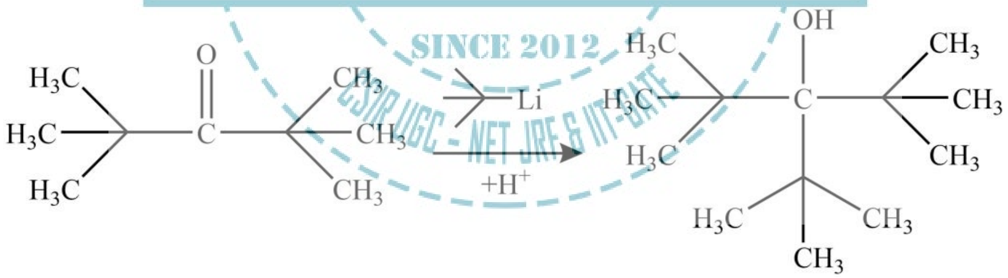
➢ *Addition of Organolithium Reagents to Carbonyl and Unsaturated Carbonyl Compounds*

Organolithium reagents react with organic carbonyl derivatives to generate lithium alkoxide, which in turn gives rise to alcohols upon hydrolysis.

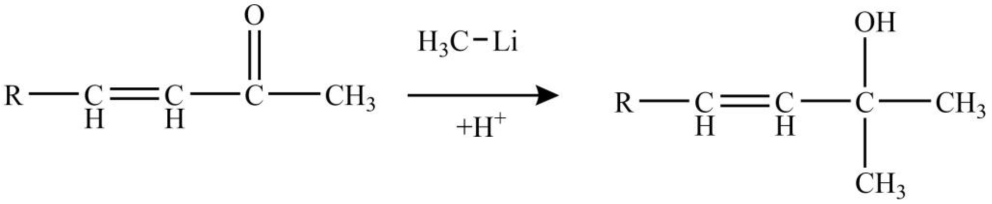


Sometimes a bioproduct via the α-deprotonation can also be obtained because besides being a nucleophilic attacker, organolithium is a powerful base too.

Furthermore, it is also worthy to note that organolithium reagents are better than their organomagnesium counterparts; and therefore, some highly hindered carbonyls (who were unable to react at all with Grignard reagents) can also be used as a substrate to produces quite stable products.



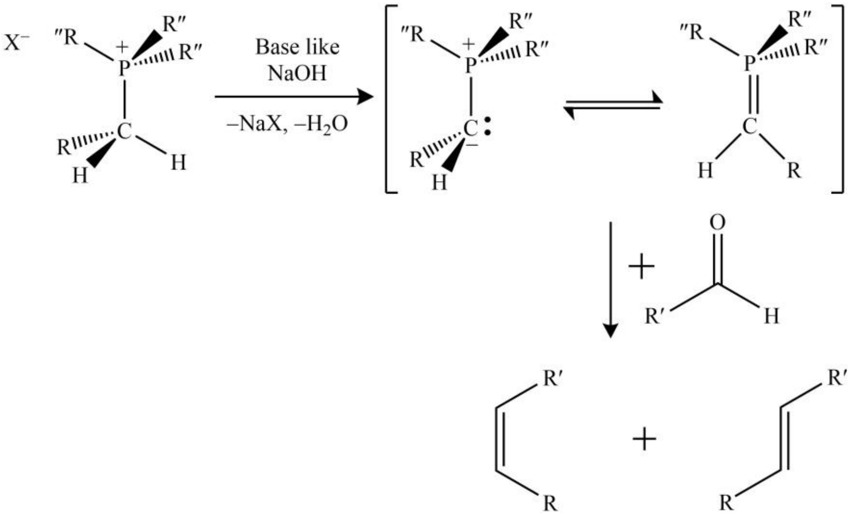
On a final note, the conjugated addition doesn't happen in the case of organolithium, leaving 1, 2-adducts as the only products.



❖ Wittig Reaction

The Wittig olefination (or Wittig reaction) may simply be defined as a chemical transformation where a ketone or aldehyde reacts with a triphenyl phosphonium ylide (Wittig reagent).

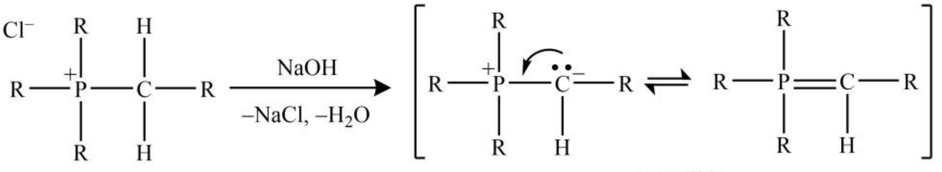
The conversion of aldehydes and ketones to alkenes is one of the most common uses of Wittig reactions. Usually, the Wittig reaction is employed to add a methylene group using $Ph_3P{=}CH_2$ (methylenetriphenylphosphorane or Wittig reagent). The importance of Wittig reaction can be imagined by the fact that George Wittig, who invented this reaction, was awarded the Nobel prize in 1979 for the same work.



With help of Wittig reagent, a camphor-like ketone, which has a very much sterically hindered carbon, can also be transformed into its methylene derivative. Now before we proceed further to study different aspects of Wittig reaction, we need to first know what a Wittig reagent actually is and how does it behave around different kinds of substrates.

➢ *The Wittig Reagent (An Organophosphorus Ylide)*

The Wittig reagent is a ylide, and a ylide may be defined as a compound with opposite charges on adjacent atoms both of which have complete octets. These ylides are obtained as the zwitterionic conjugate bases of the cationic part of phosphonium salts.



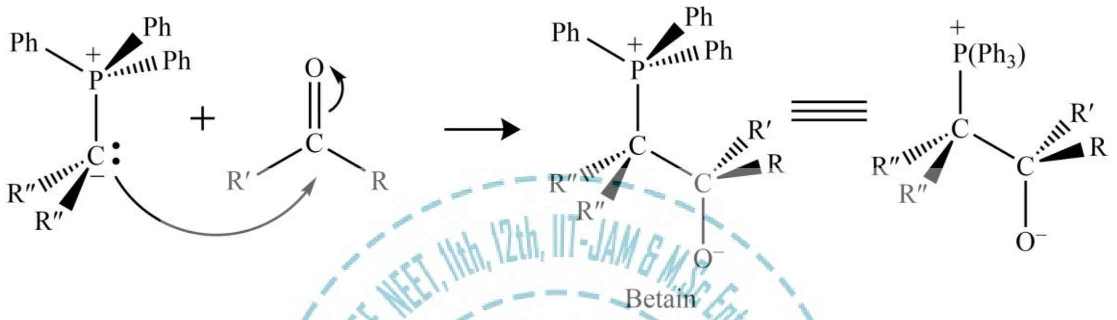
An Ylide

Since these ylides are stabilized by $p\pi$-$d\pi$ bonding, the carbanions adjacent to the phosphonium centers also get stability benefits from the same. It is also obvious that the phosphorus's ability to hold more than eight valence electrons permits for a resonance structure with double-bonded; and therefore, enhances the stability.

➢ *Mechanism of Wittig Reaction*

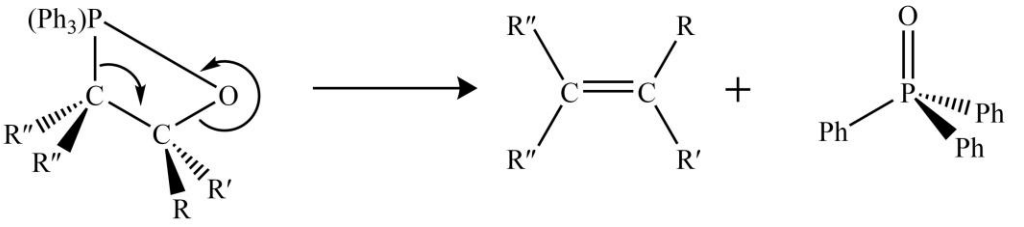
The NMR studies have confirmed the formation of two intermediates after the generation of the first carbon-carbon bond during the Wittig reaction, the betaine (a dipolar species) and oxaphosphatane (a four-membered heterocyclic structure). The final product will be obtained by the cleavage of oxaphosphatane to alkene and phosphine oxide which is irreversible and exothermic in nature. Precisely, the mechanism can primarily be divided into three steps as given below.

1. Nucleophilic attack on the carbonyl:



2. Formation of four-membered ring:

3. Generation of the alkene:

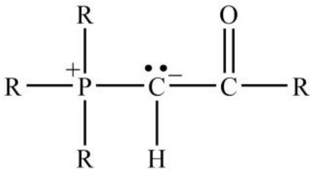


Oxaphosphatane

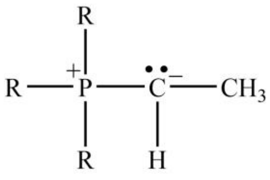
A major benefit of the alkene synthesis via Wittig's route is that, unlike alcohol dehydration, the site of the double bond is fixed absolutely.

➢ *Stereochemistry of Wittig Reaction*

In the case of aldehydes, the geometry around double bonds can easily be predicted by analyzing the ylide's nature. With unstable ylides (R_3 = alkyl), (Z)-alkenes are formed with reasonable to very high selectivity. With stable ylides (R_3 = ester or ketone), (E)-alkenes are formed with a very high magnitude of selectivity. The selectivity ratio (E/Z) is usually very poor with semi-stabilized ylides (R_3 = aryl).



will give E-alkene

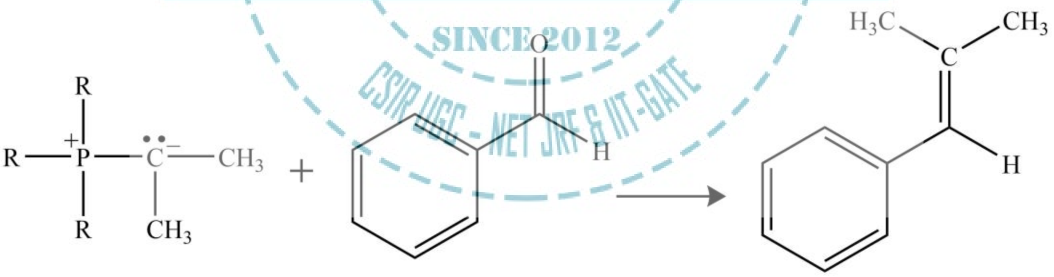


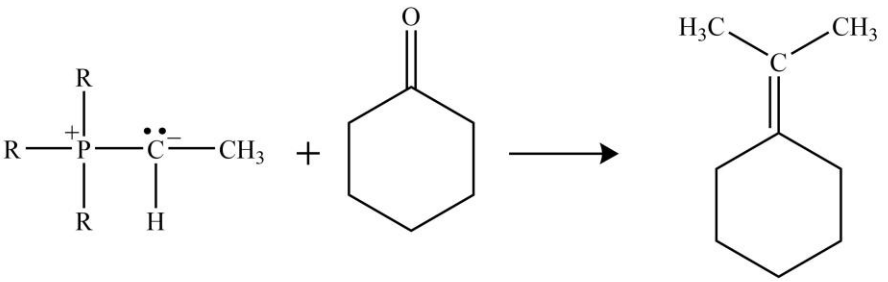
will give Z-alkene

If we want to get (E)-alkene but from a destabilized ylide, the Schlosser modification of the Wittig reaction can be employed. Otherwise, the (E)-alkene selectively can also be obtained via Julia olefination and its different variants. Since the (E)-enoate (α, β-unsaturated ester) are prepared via Horner-Wadsworth-Emmons reaction, the same can be used as a substitute for the Wittig reaction. On a final note, the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction can be used to get (Z)-enoate.

➢ *Examples of Wittig Reaction*

Some of the most common examples of organic chemical transformation via Wittig reagent are given below.



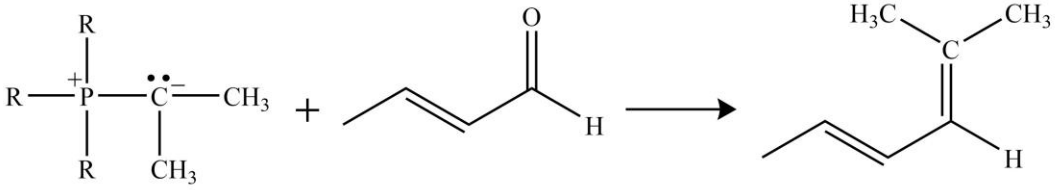


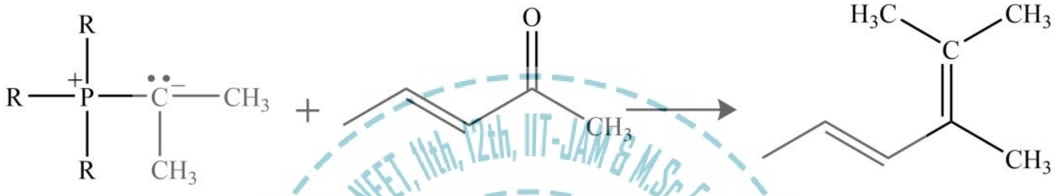
It has been observed that the Wittig reagents usually tolerate carbonyl compounds with numerous types of functional groups like OH, OR, epoxide, aromatic nitro, and ester groups.

➢ *Applications of Wittig Reaction*

Some of the most common applications of organic chemical transformation via Wittig reagent are given below.

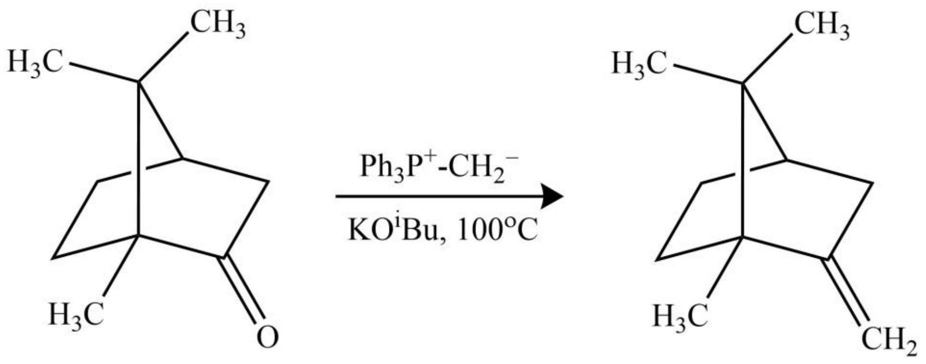
1. The conversion of aldehydes and ketones to alkenes is one of the most common uses of Wittig reactions.





2. The Schlosser modification Wittig reaction can be used to get allylic alcohols by the reaction of the betaine ylide with a secondary aldehyde.

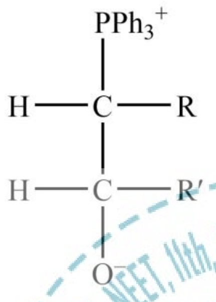
3. Even a sterically hindered ketone such as camphor can be converted to its methylene derivative.



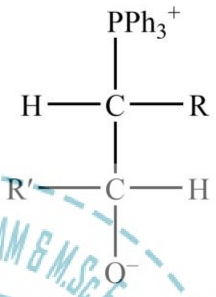
➢ *Limitations of the Wittig reaction*

Some of the most common limitations of organic chemical transformation via Wittig reagent are given below.

1. The Wittig reaction proceeds mainly via the erythro betaine intermediate that gives rise to the Z-alkene, which is problematic if the E-isomer is the desired product. This limitation can be overcome by converting the erythro betaine into threo betaine using phenyllithium at low temperature which can afford to yield the E-alkene (Schlosser modification).

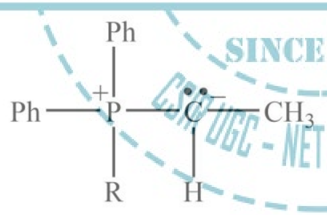


erythro betain
(gives Z-alkene)

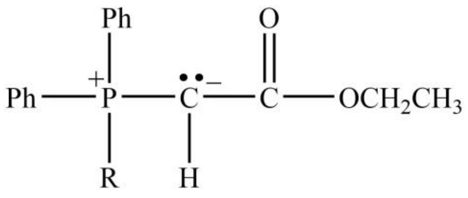


threo betain
(gives E-alkene)

2. The yield given by conventional Wittig reaction is very low when a sterically hindered ketone is used, and the rate of transformation was also found to be very small. This is especially true for stabilized ylides. This limitation can be overcome by using a phosphonate ester (Horner-Wadsworth-Emmons reaction).



Non-stablized ylide



Stablized ylide

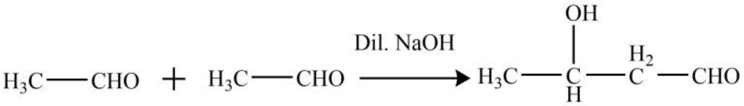
❖ Mechanism of Condensation Reactions Involving Enolates: Aldol, Knoevenagel, Claisen, Mannich, Benzoin, Perkin and Stobbe Reactions

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*

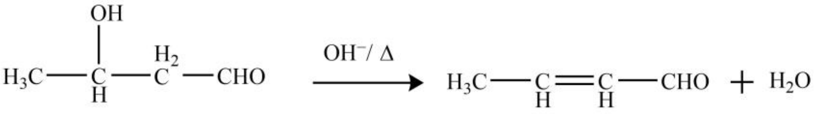
The aldol condensation may simply be defined as a condensation reaction in organic chemistry where an enol or an enolate ion reacts with a carbonyl compound to give a β-hydroxyaldehyde or β-hydroxyketone (an aldol addition), followed by the dehydration to form a conjugated enone.

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



$$H_3C-CHO + H_3C-CHO \xrightarrow{\text{Dil. NaOH}} H_3C-CH(OH)-CH_2-CHO$$

Aldol addition (first part)



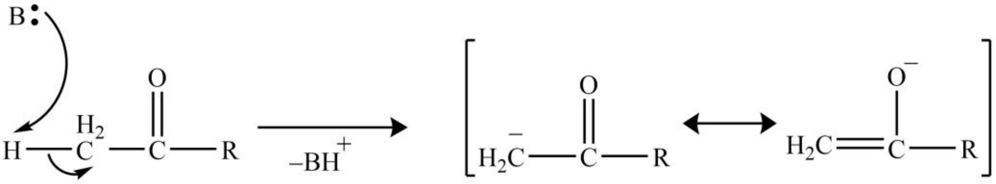
$$H_3C-CH(OH)-CH_2-CHO \xrightarrow{OH^-/\Delta} H_3C-CH=CH-CHO + H_2O$$

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).

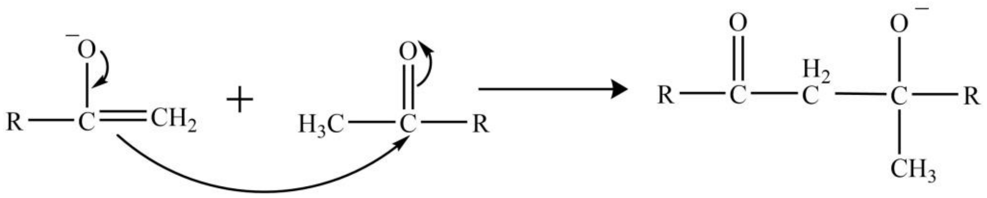
The dehydration of aldol product can occur via two pathways; a strong base like NaOH deprotonates the aldol product to an enolate, which then eliminates via the E_1CB route, whereas the second pathway for dehydration needs acid catalyzation for the enol mechanism. The dehydration part may also take place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

i) Step 1:



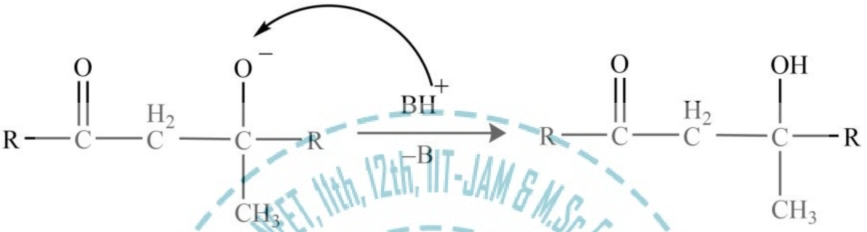
Enolate ion

ii) Step 2:



Alkoxide ion

iii) Step 3:

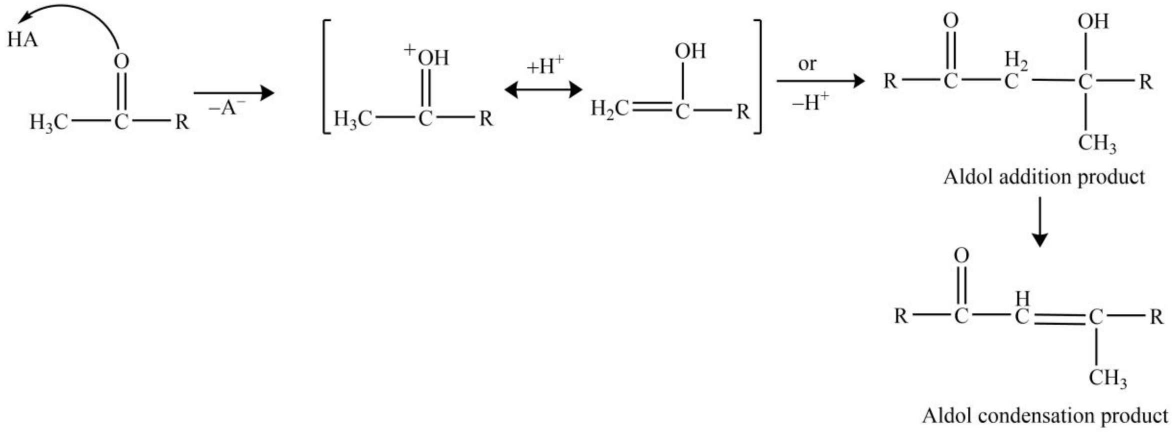


iii) Step 4:

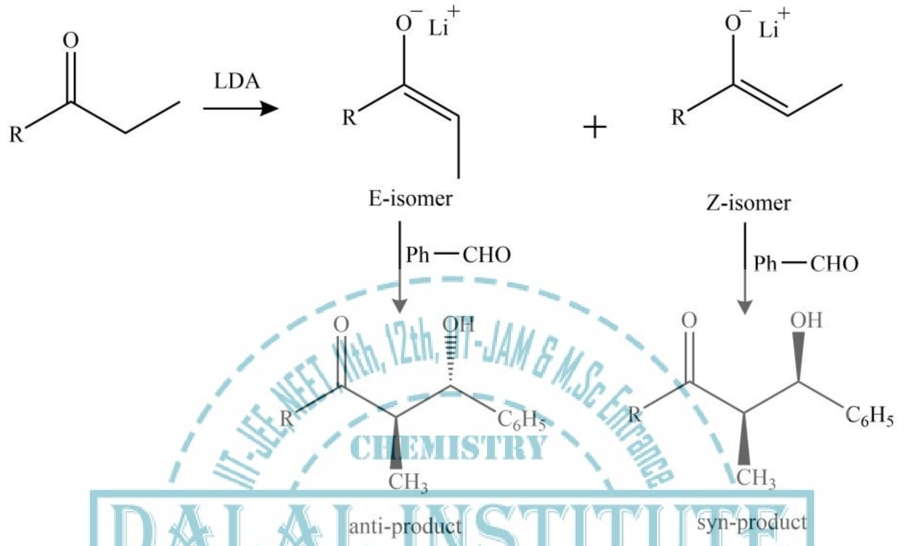
Aldol condensation product

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

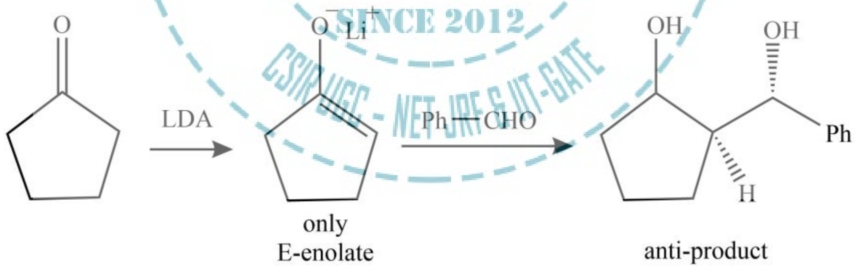
For the acid-catalyzed mechanism, the enol form acts as the nucleophile rather than electrophile, which is obviously triggered by the protonation of oxygen.



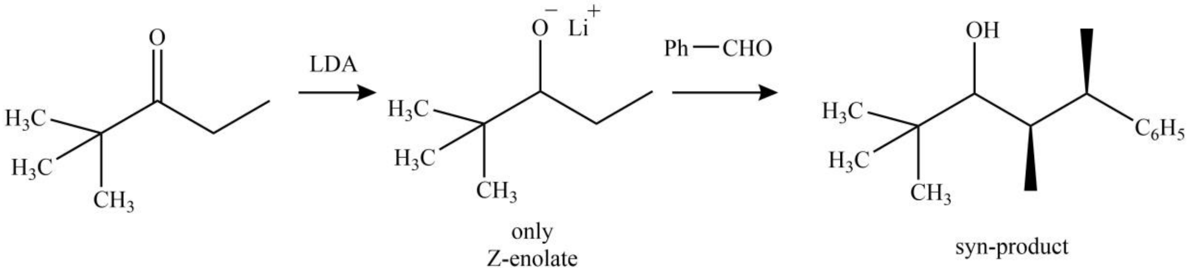
Stereochemistry of aldol condensation: Two stereoisomers will be obtained if enolate-yielding ketones are unsymmetrical. Consequently, syn- and anti-isomers will be formed from the condensation between aldehyde and ketonic enolate. It has also been observed that syn-isomer is generally the major product 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.

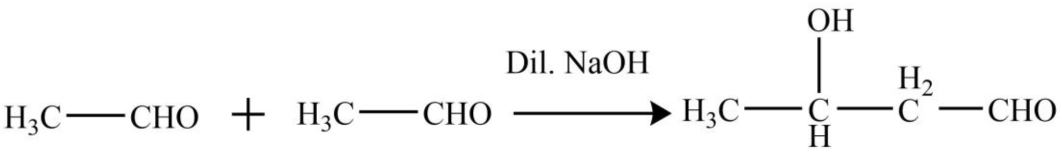


Ketones with very bulky group can only react Z-enolate giving exclusively syn product; consider the reaction between tertiary butyl ketone and benzaldehyde.



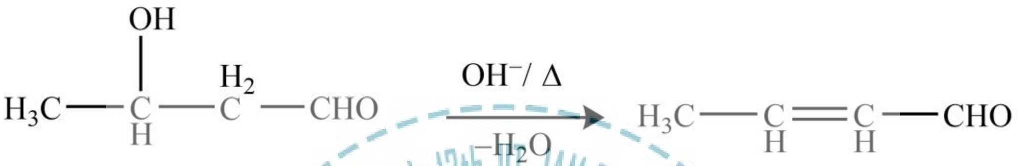
Examples of aldol condensation: Some of the most common examples of organic chemical transformation involving aldol condensation are given below.

i) The aldol addition of acetaldehydes followed by dehydration.



$$H_3C{-}CHO + H_3C{-}CHO \xrightarrow{\text{Dil. NaOH}} H_3C{-}\overset{OH}{\underset{H}{C}}{-}\overset{H_2}{C}{-}CHO$$

Aldol addition (first part)



$$H_3C{-}\overset{OH}{\underset{H}{C}}{-}\overset{H_2}{C}{-}CHO \xrightarrow[-H_2O]{OH^-/\Delta} H_3C{-}\underset{H}{C}{=}\underset{H}{C}{-}CHO$$

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.

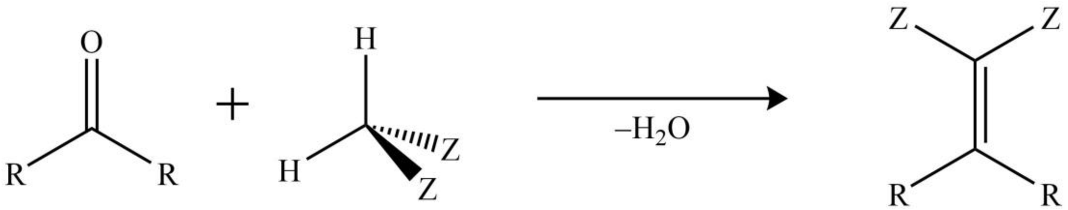
ii) Aldol condensation reactions are also taught in organic chemistry at the university-level as they can illustrate important reaction mechanisms. In other words, it includes the nucleophilic addition of an enolate to an aldehyde to give or "aldol" (aldehyde + alcohol) or a β-hydroxy ketone.

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.

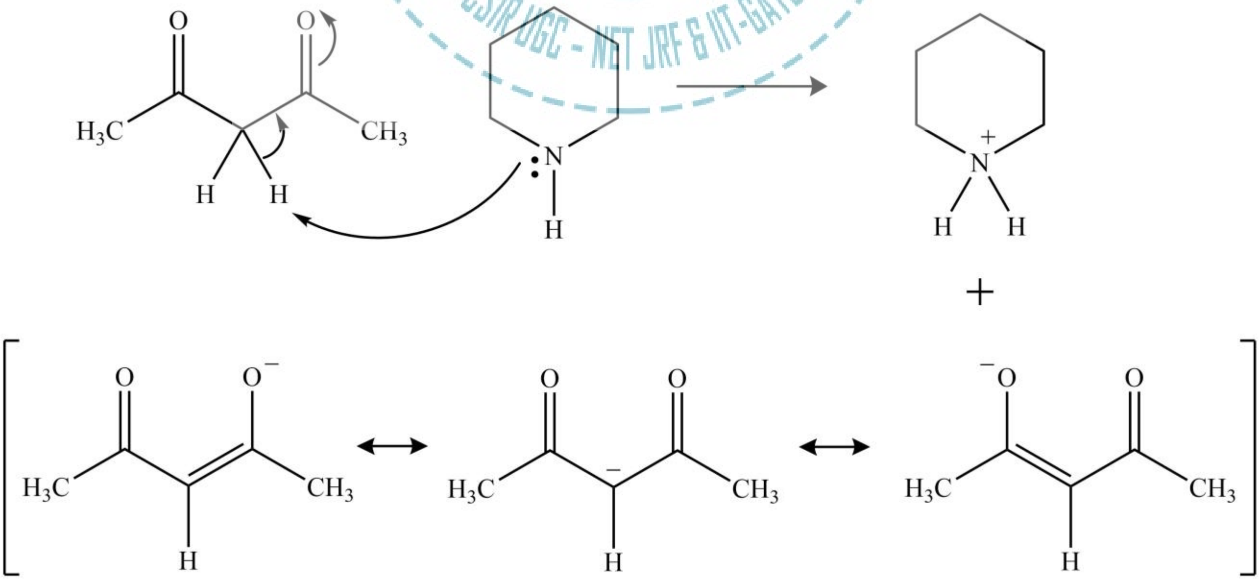
This reaction is a modification to aldol condensation and was invented by a German chemist Emil Knoevenagel; and therefore, is also named after him.



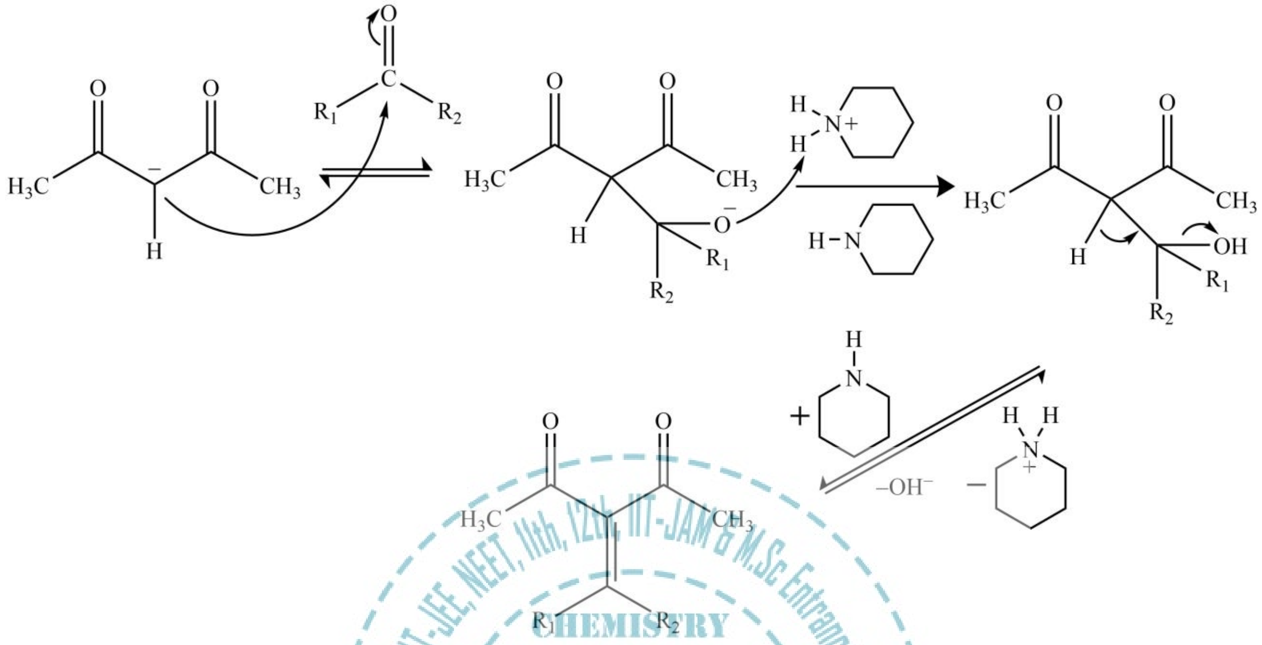
Where the carbonyl group is a ketone or an aldehyde and Z–CH_2–Z is the active methylene group. The catalyst used in this reaction is typically a weakly basic amine. Furthermore, it is also worthy to note that the active hydrogen component can also be of Z–CHR–Z or Z–CHR_1R_2 form, where Z is an electron-withdrawing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



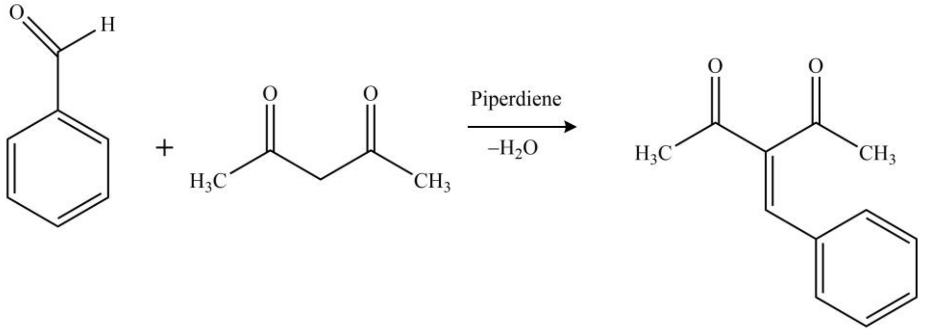
i) Step 2:



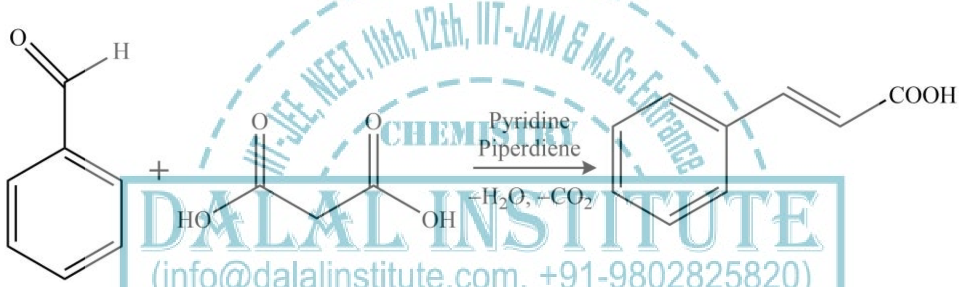
Stereochemistry of Knoevenagel condensation: In most of the Knoevenagel condensation reactions, both cis and trans isomers are formed guided by mainly steric and mode of attack.

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

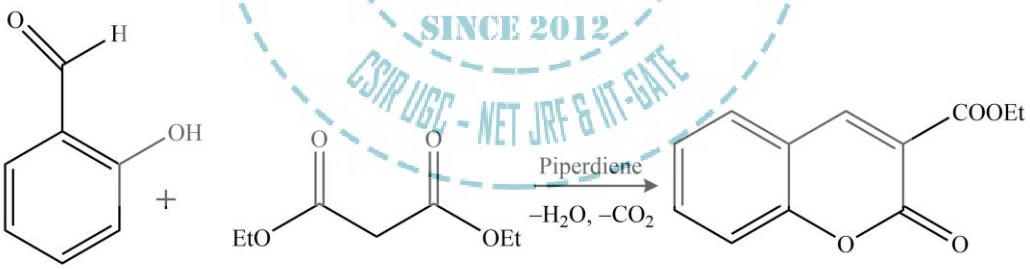
1. The reaction between benzaldehyde and acetylacetone.



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).

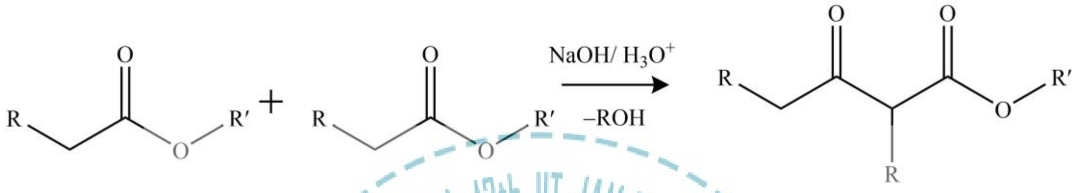
2. A Knoevenagel condensation reaction is confirmed in the reaction of thiobarbituric acid with 2-methoxybenzaldehyde in C_2H_5OH using piperidine as a basic assistant, yielding subsequent formation of a charge-transfer complex molecule.

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*

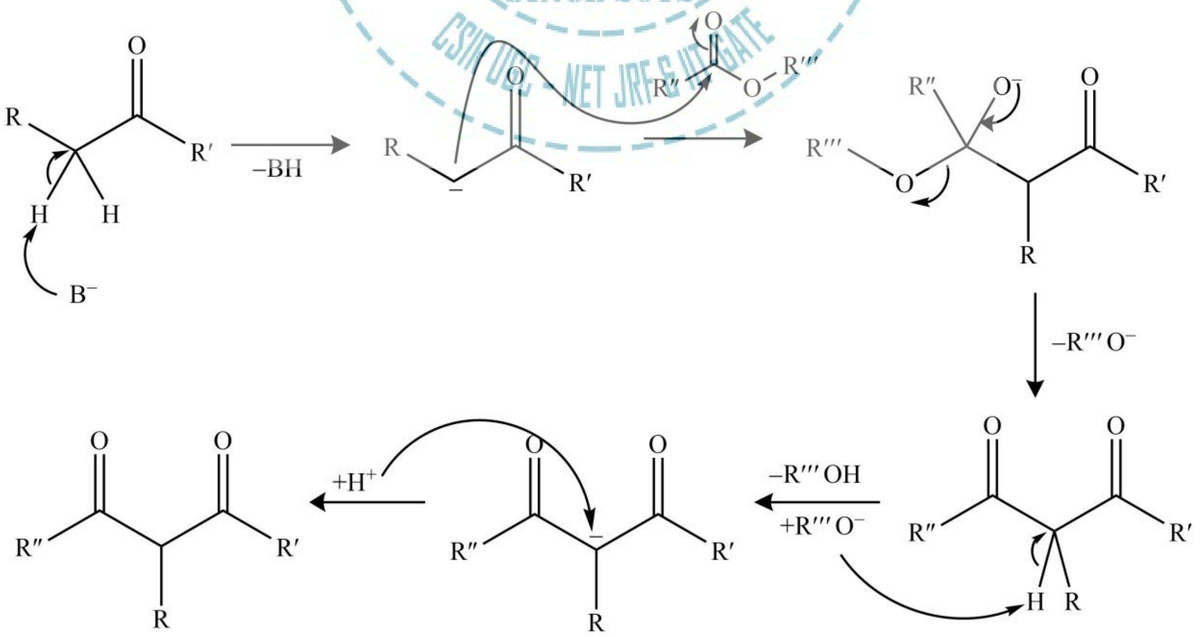
The Claisen condensation may simply be defined as a chemical reaction giving carbon-carbon bond between two esters or one ester and another carbonyl compound in the availability of a strong base, resulting in a β-diketone or a β-keto ester.

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.

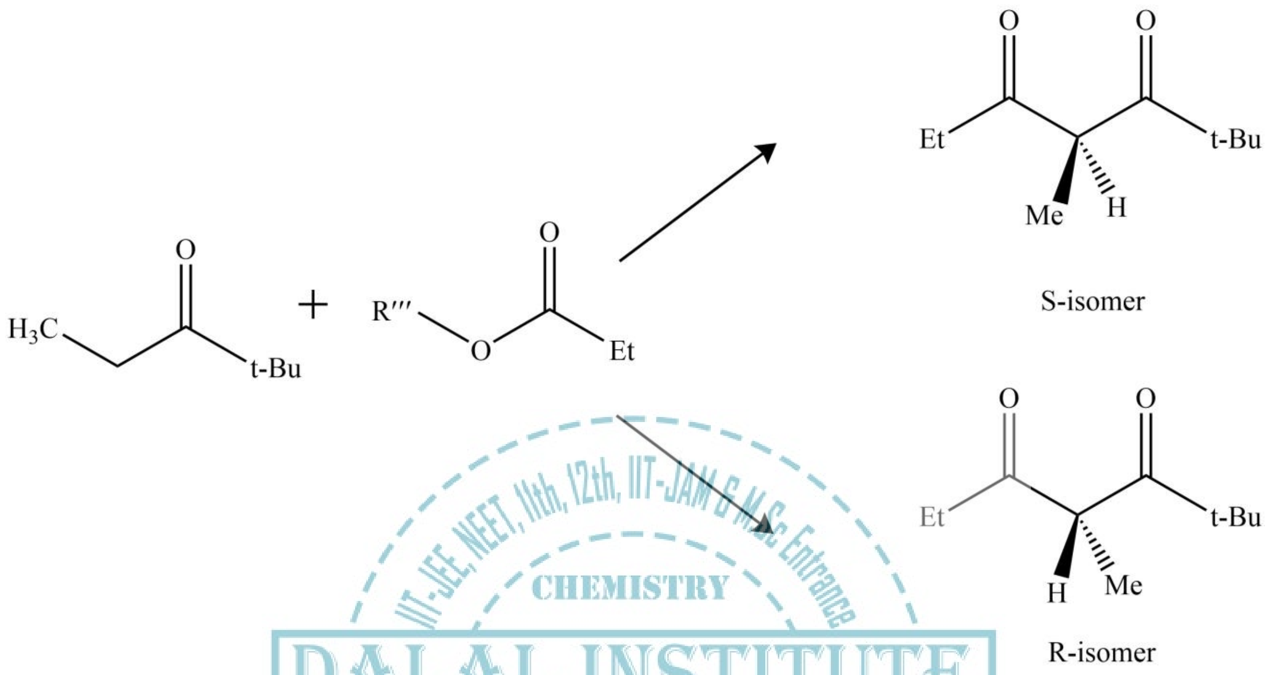


It is obvious that the molecule eliminated in this 'modified aldol condensation' is not water but alcohol. Now depending upon various enolizable and nonenolizable carbonyl compounds, many types of Claisen condensations can be obtained.

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).

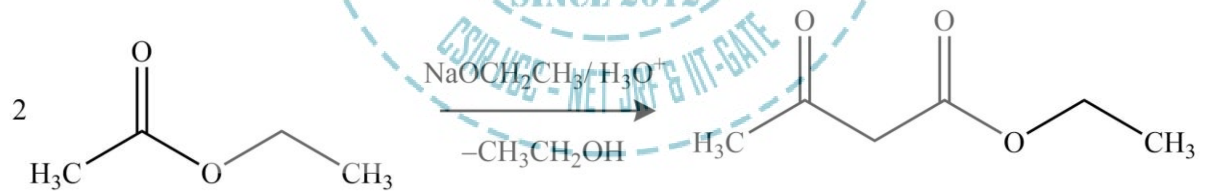


Stereochemistry of Claisen condensation: In the case of different R groups (R‴ ≠ R′), the Claisen condensation will give rise to chiral β-diketones or β-diketoesters as shown below.

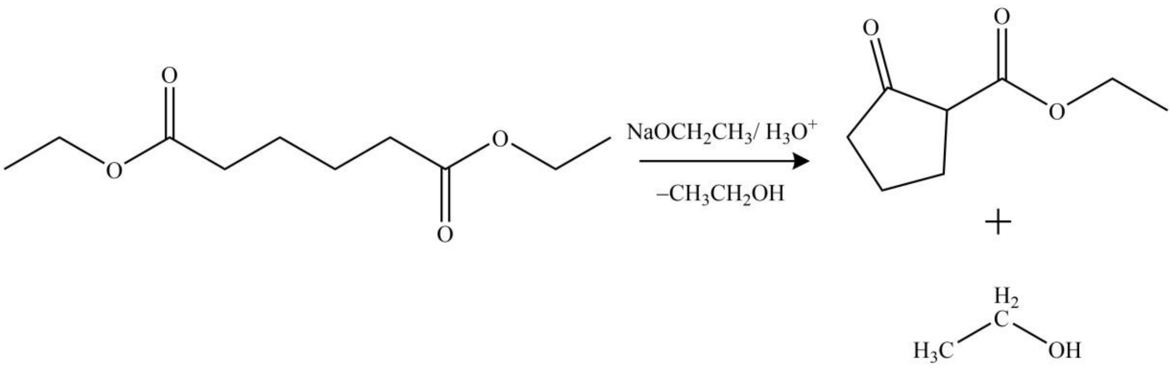


Examples of Claisen condensation: Some of the most common examples of organic chemical transformations involving Claisen condensation are given below.

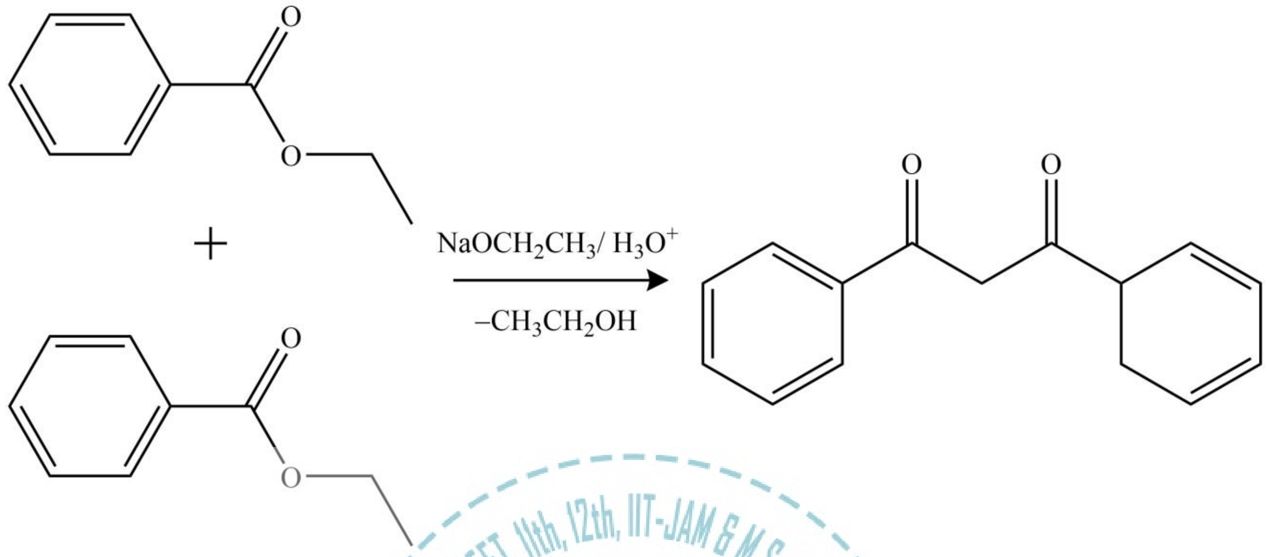
1. The condensation reaction of ethyl acetate.



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.

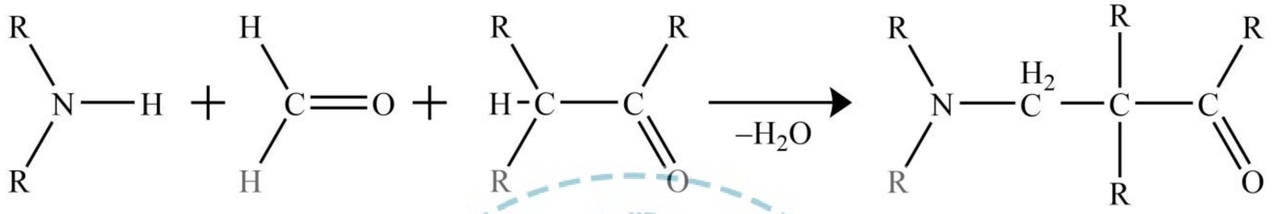
2. Crossed Claisen condensation reaction between two different esters (both are having α-H) have little to no synthetic impoartance, and we will obtain an a mixture of four products. Nevertheless, if no α-hydrogen are available in one of the esters, it will act as a acceptor for carbanion and the self-condensation 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*

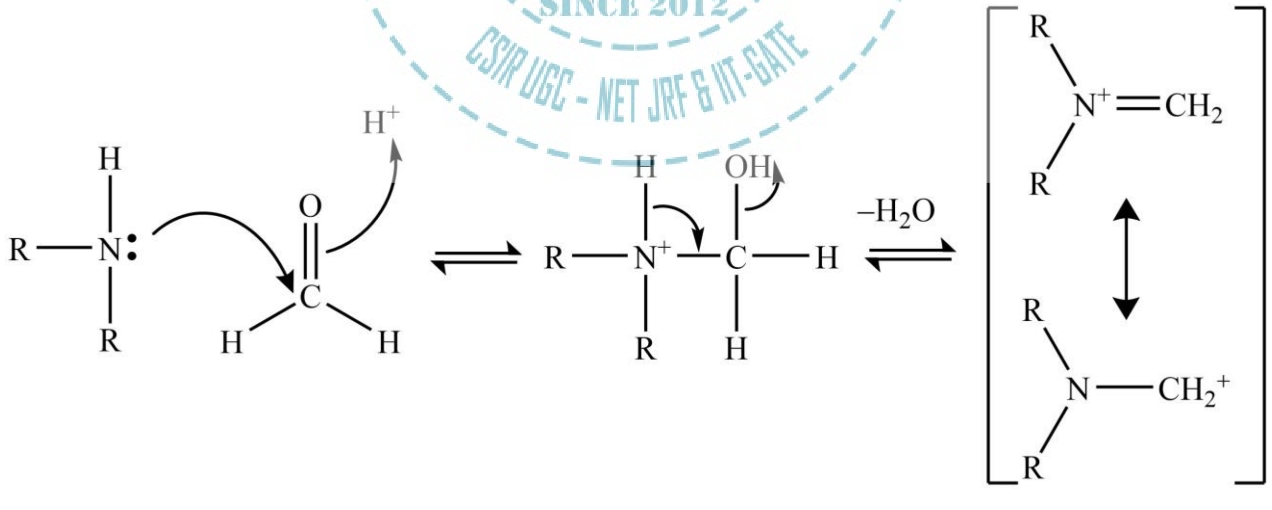
The Mannich condensation may simply be defined as an organic chemical transformation where a carbonyl functional group's neighboring proton (acidic in nature) undergoes amino alkylation by formaldehyde and ammonia (or a secondary, or primary amine), giving rise to a β-amino-carbonyl compound called Mannich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

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



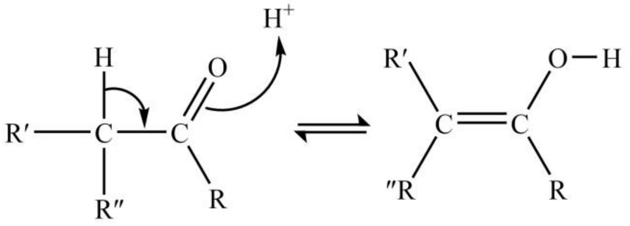
The Mannich condensation is a case of nucleophilic addition of an amine to a carbonyl group trailed by the dehydration to yield a Schiff base, which in turn, reacts in an electrophilic addition mode with a compound containing acidic hydrogen (next step).

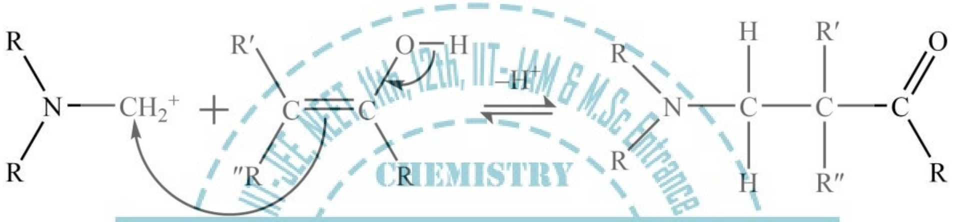
Mechanism of Mannich condensation: The Mannich condensation's mechanism begins with the generation of an iminium ion from the formaldehyde and the amine used. The protonated oxygen is highly acidic with a pKa value of −2. The reaction will be stopped when the carbonyl gets deprotonated by amine base; 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.



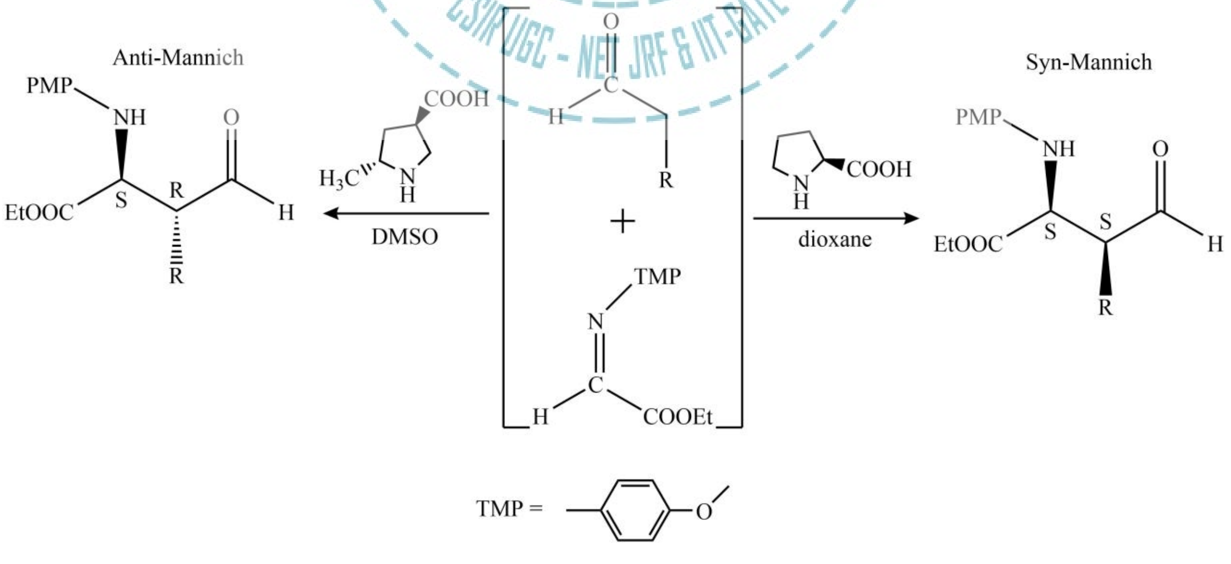
iminium ion

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.





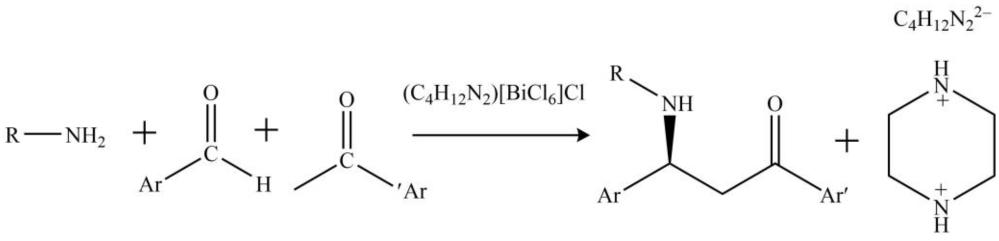
Stereochemistry of Mannich condensation: Asymmetric Mannich reactions have also been studied in the recent era. It has been observed that if two prochiral centers are present in an appropriately functionalized ethylene bridge of Mannich adduct, two diastereomeric pairs of enantiomers are obtained. One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



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

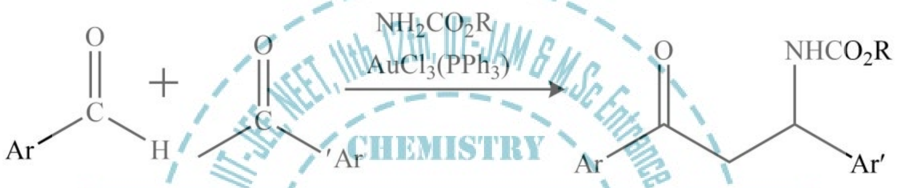
Examples of Mannich condensation: Some of the most common examples of organic chemical transformation Mannich condensation are given below.

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



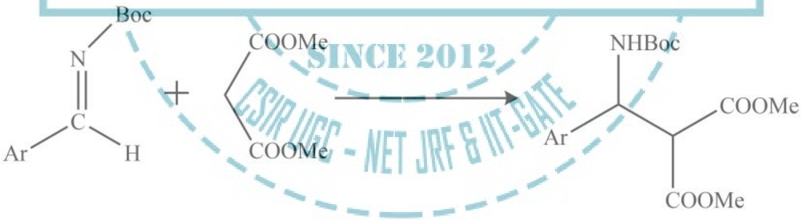
R = Ar, Bu

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.

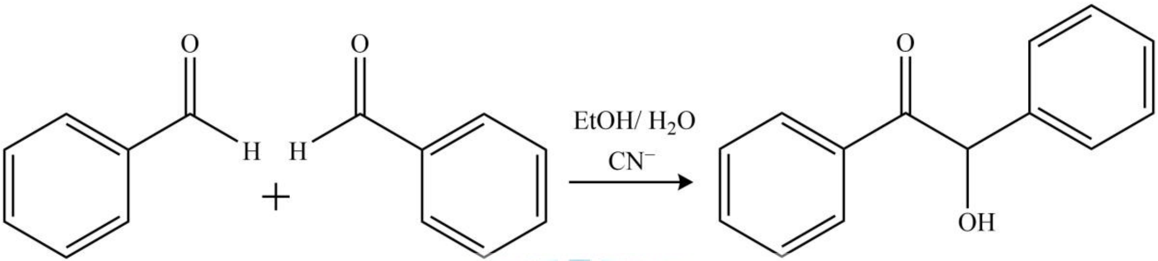
3. Many detergents and soaps are synathesized via Mannich condensation which find applications in cleaning industry, epoxy coatings, and automotive fuel treatments.

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).

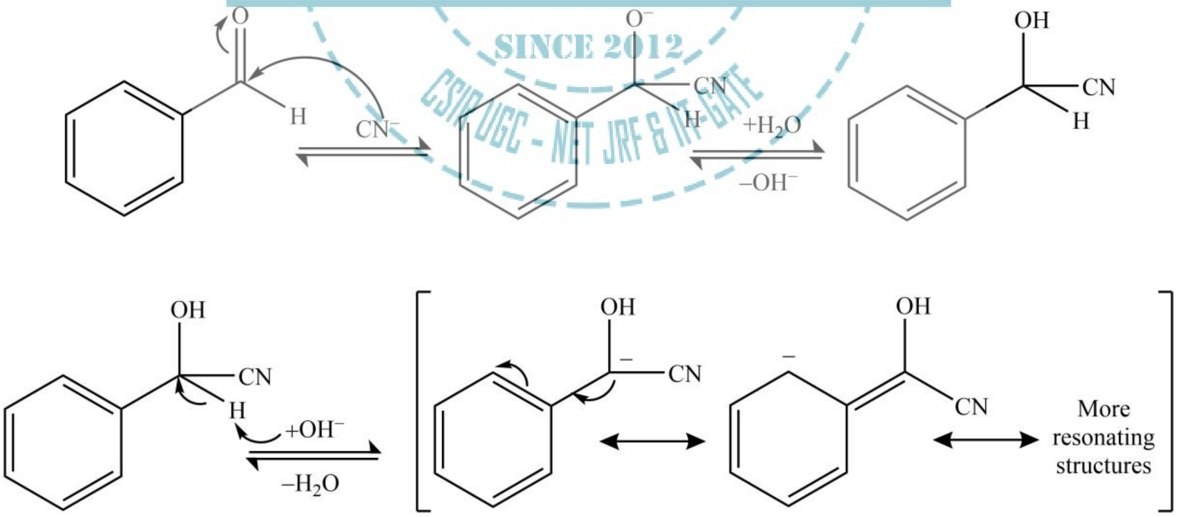
➢ *Benzoin Condensation*

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.

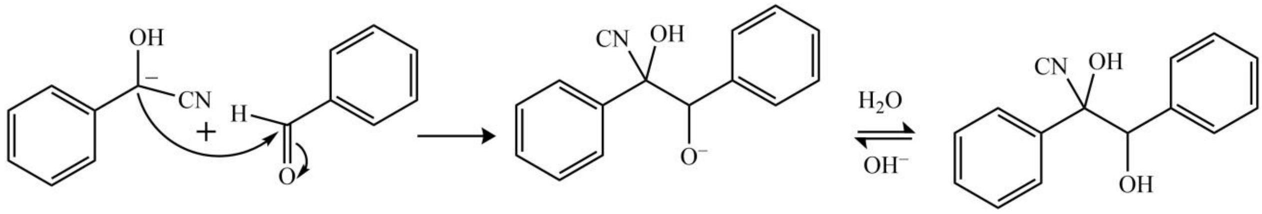


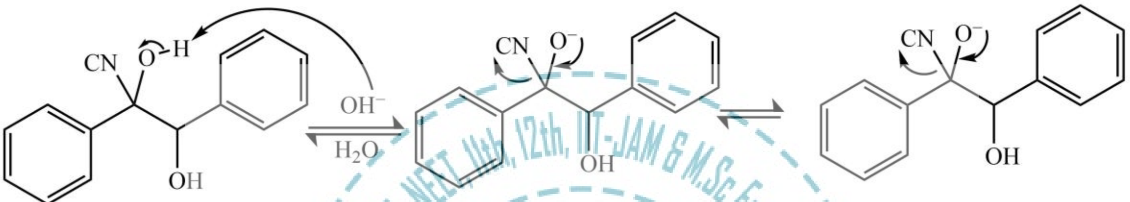
Mechanism of benzoin condensation: The benzoin condensation is catalyzed by nucleophiles like N-heterocyclic carbene or cyanides. A. J. Lapworth proposed a mechanism in 1903 which says that the cyanide anion from sodium cyanide reacts with the given aldehyde via nucleophilic addition (first step); followed 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.



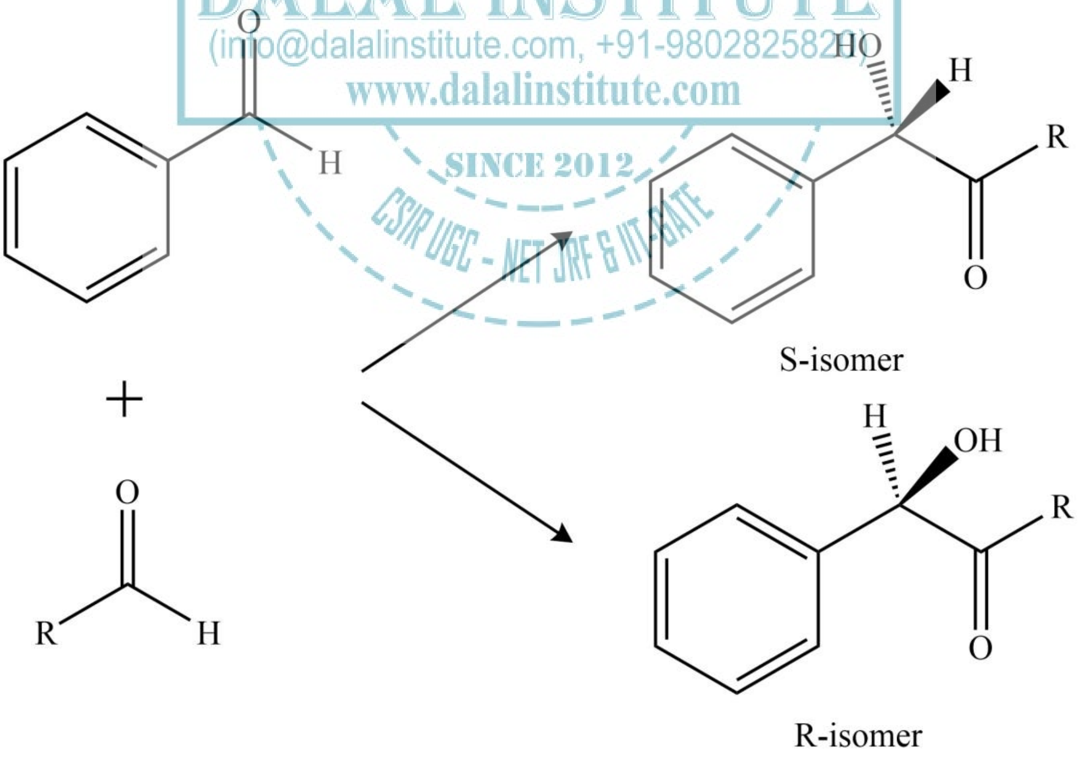
By looking at the mechanism, it can clearly be seen that one aldehyde accepts a proton whereas the other one donates a proton. Although most of the aldehydes are capable of donating as well accepting proton (like benzaldehyde); some aldehydes like 4-dimethylaminobenzaldehyde can only donate protons.

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



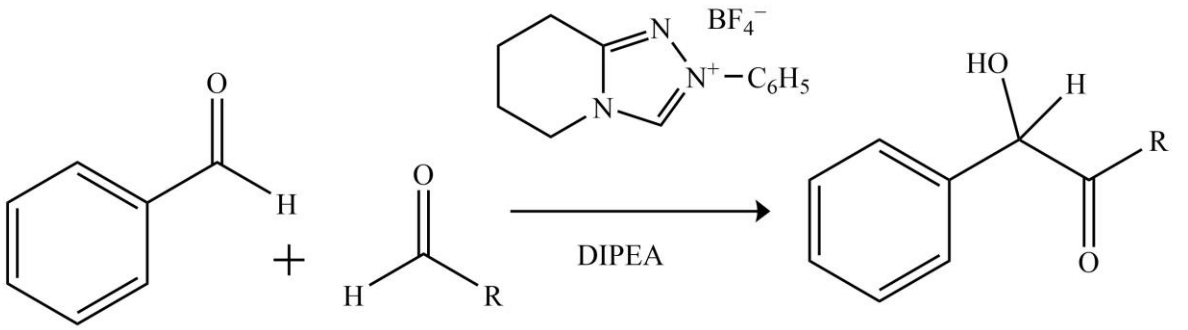


Stereochemistry of benzoin condensation: If participating aldehydes are different in benzoin condensation reactions, the final product will exist as an enantiomeric pair.



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.

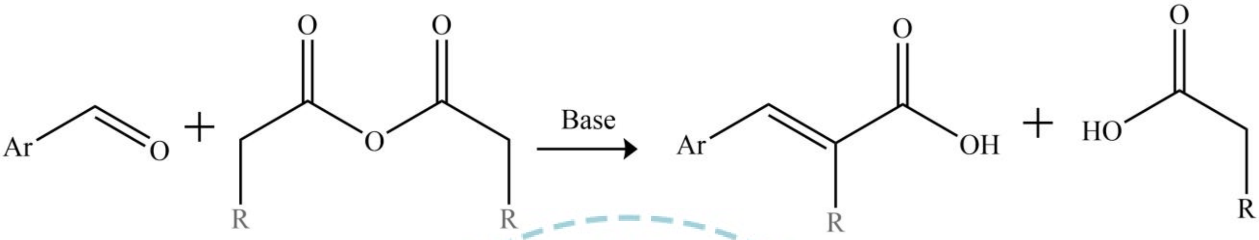
3. The asymmetric version of benzoin condensation has been carried out by using chiral triazolium and thiazolium salts; triazolium salts yielded higher enantiomeric excess in comparison to thiazolium salts.

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*

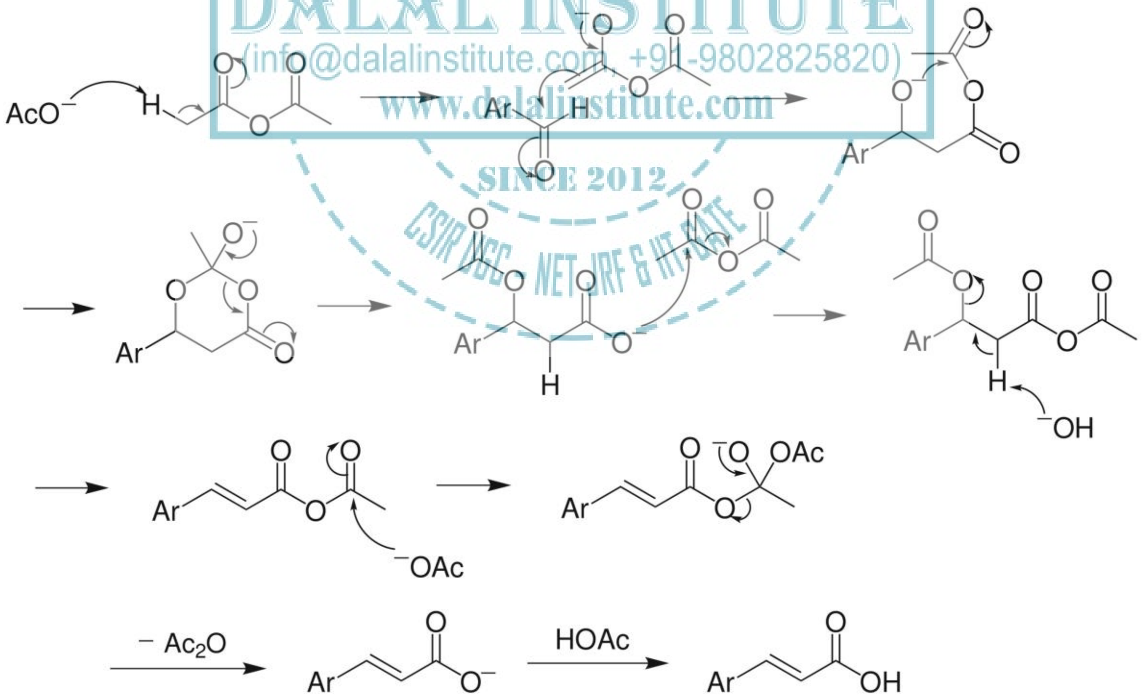
The Perkin condensation may simply be defined as an organic transformation where an α, β-unsaturated aromatic acid is obtained by the aldol condensation of an acid anhydride and an aromatic aldehyde, in the availability of an alkali salt (acting as a base catalyst) of the acid.

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



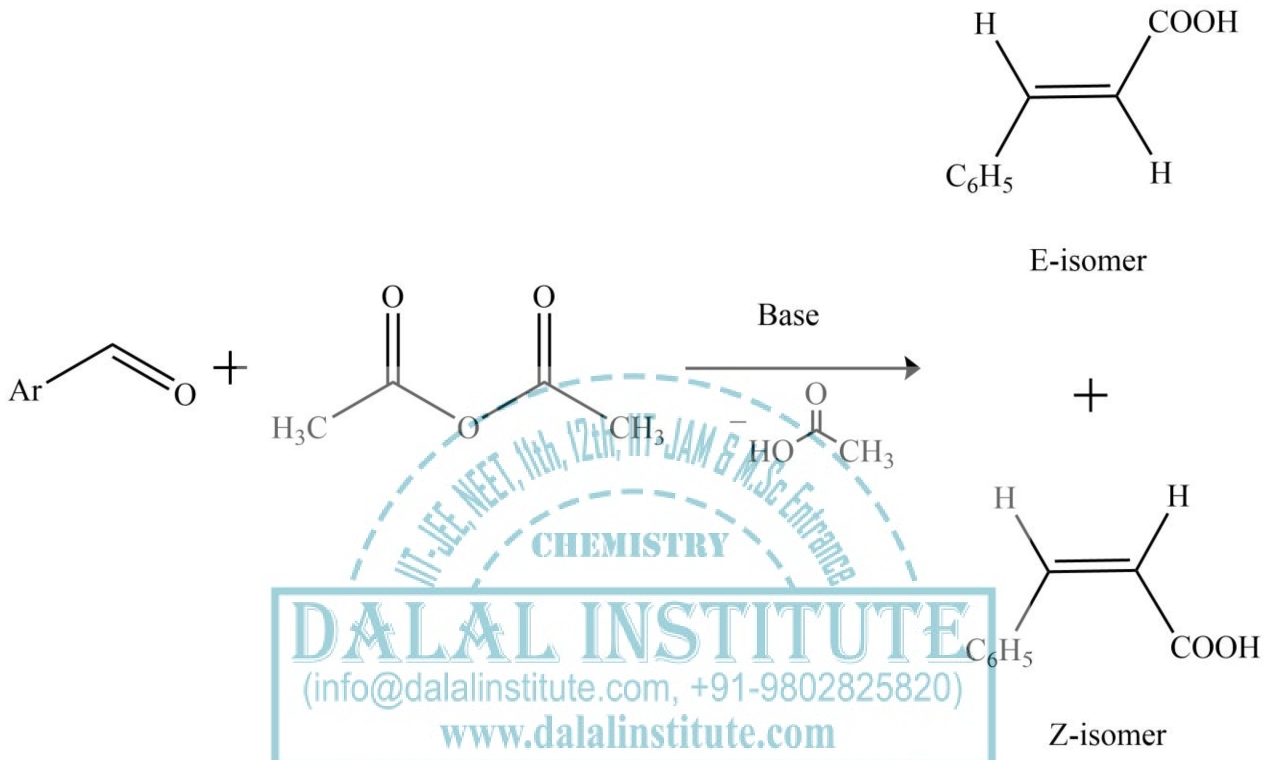
The relative arrangement of the aromatic ring and carboxylic acid in the end product of Perkin condensation can either be Z or E.

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



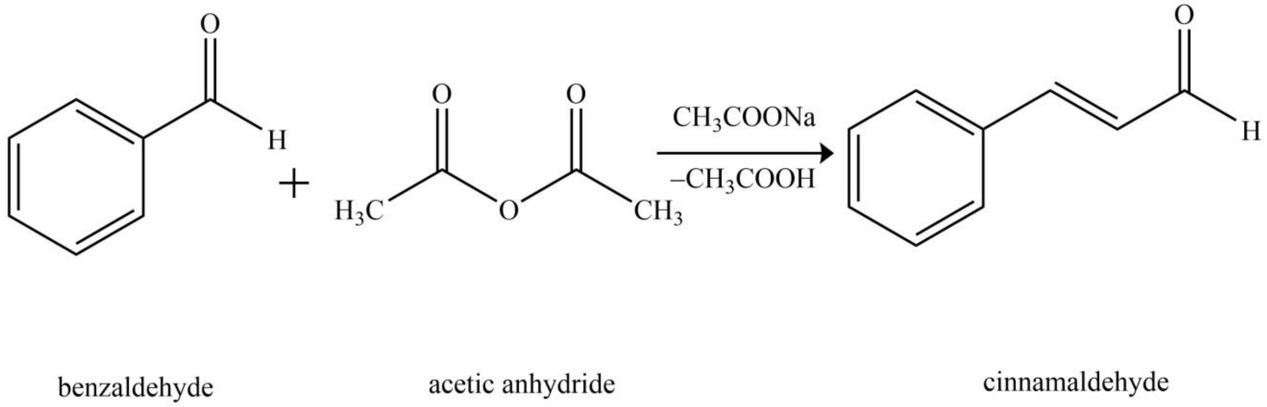
It is also worthy to note that the mechanism given above is not accepted by all of the scientific community; and therefore, many other sorts can also be found in different texts. One of such versions differs in the aspect of decarboxylation without transfer of acetic group.

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).

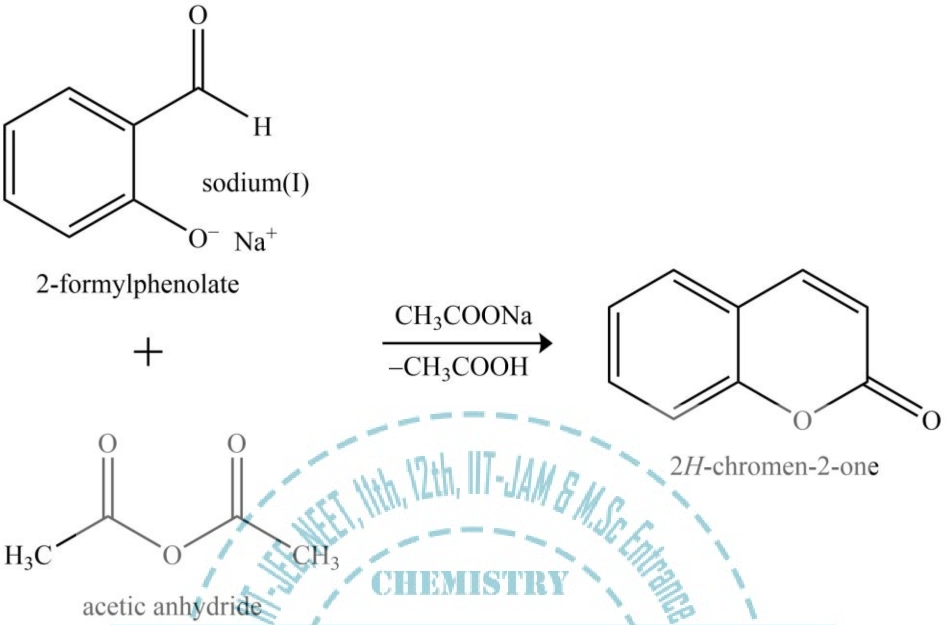


Examples of Perkin condensation: Some of the most common examples of organic chemical transformations involving Perkin condensation are given below.

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



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.

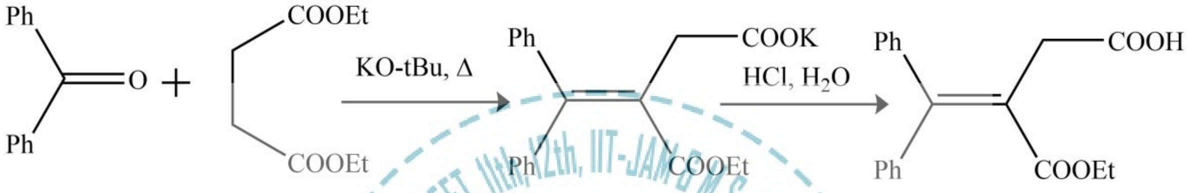
2. Perkin condensation is used to synthesis of ‘coumarin’ which finds uses in medicine, rodenticide precursor, laser dyes, aromatizers, and perfumes.

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*

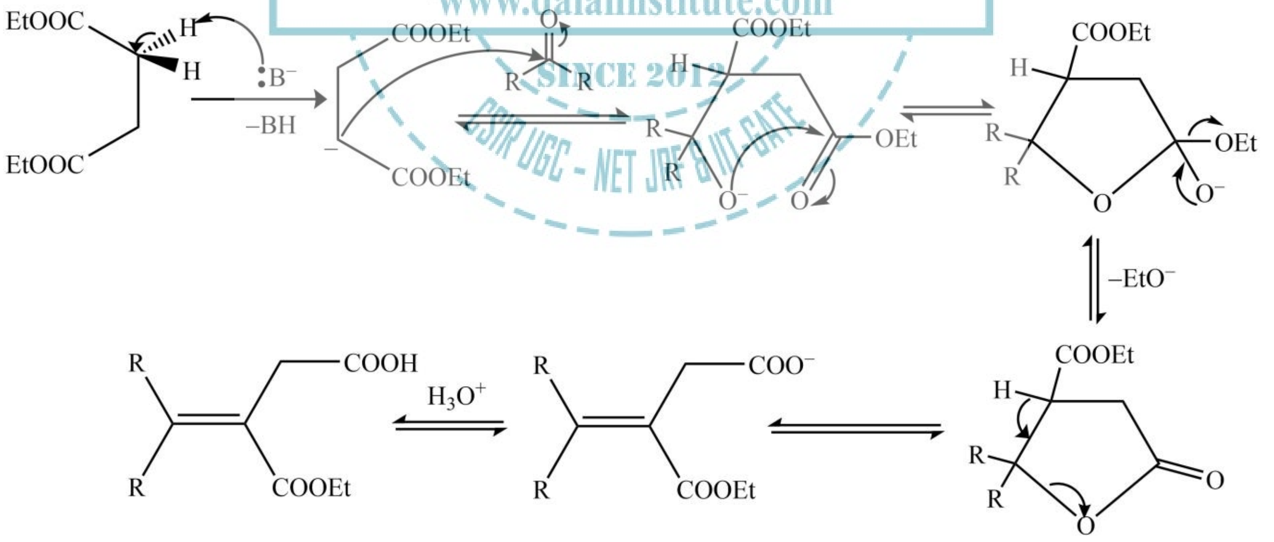
The Stobbe condensation may simply be defined as a modification to Claisen condensation where the diethylesters of succinic acid react with aldehydes (or ketones) to give rise to alkylidene succinic acids or their monoesters in presence of a relatively less strong base.

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.



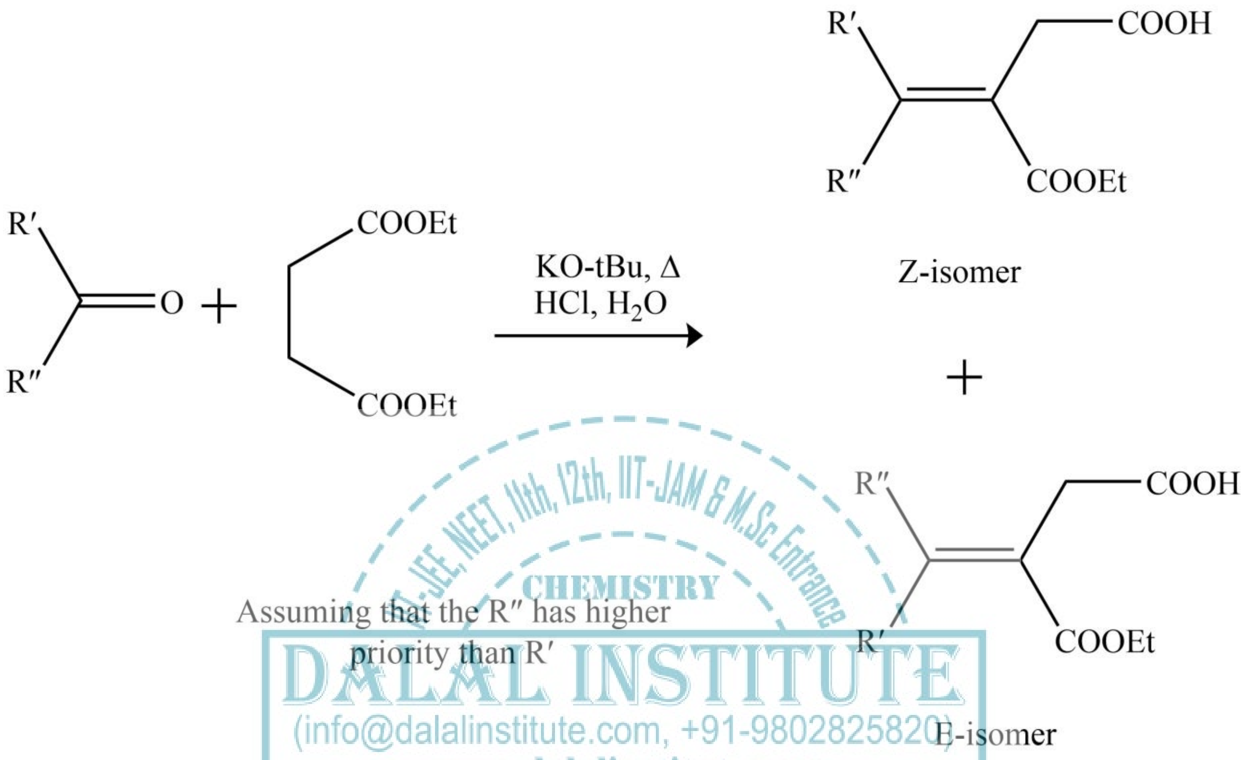
In the later years, Stobbe and his co-workers observed that this is quite common when succinic acid’s esters are treated with aldehyde or ketones.

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.

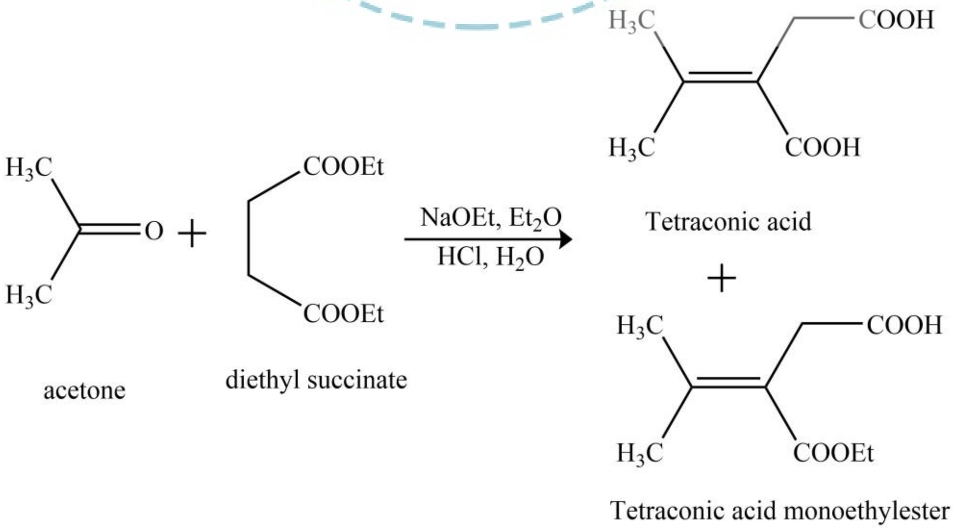
Stereochemistry of Stobbe condensation: Only one alkene stereoisomer will be obtained if symmetrical ketones are used; nevertheless, unsymmetrical ketones will give rise to a mixture of alkene stereoisomers.



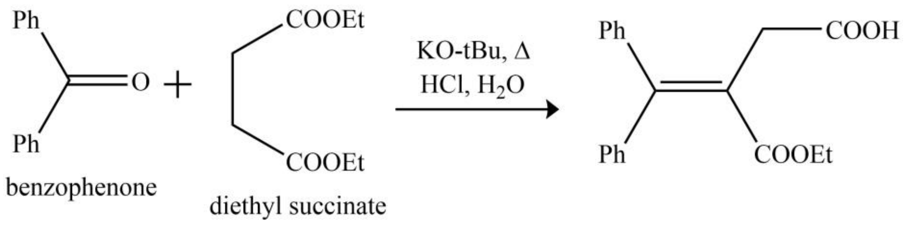
Assuming that the R″ has higher priority than R′

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

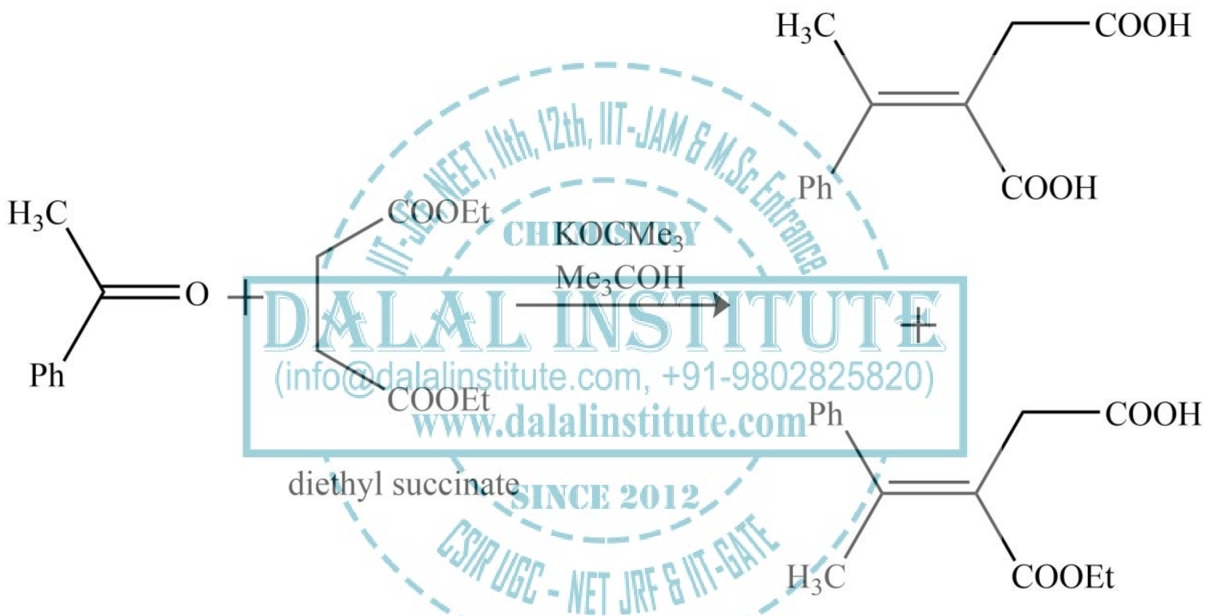
1. One of the most popular examples of Stobbe condensation is the reaction between acetone and diethyl succinate to give tetraconic acid and its monoethyl ester.



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.

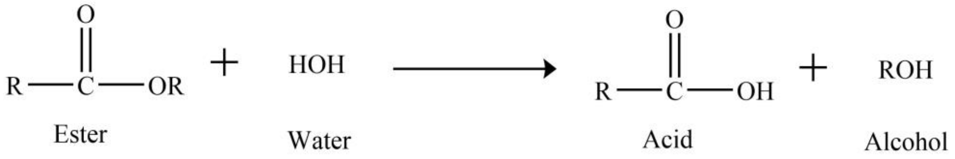
❖ Hydrolysis of Esters and Amides

In this section, we will discuss the mechanism of acid- and base-catalyzed hydrolysis of esters and amides (both are the derivatives of carboxylic acid) in detail.

➢ *Hydrolysis of Esters*

Although the esters are derived from acids, they are generally neutral compounds. In an archetypal ester reaction, the OR group (i.e., alkoxy) of the ester is swapped by another group. One such type of reaction is the ester hydrolysis where the OH group (generated by the water-splitting) replaces the alkoxy group of esters under consideration. The ester hydrolysis can either be catalyzed by an acid or by a base.

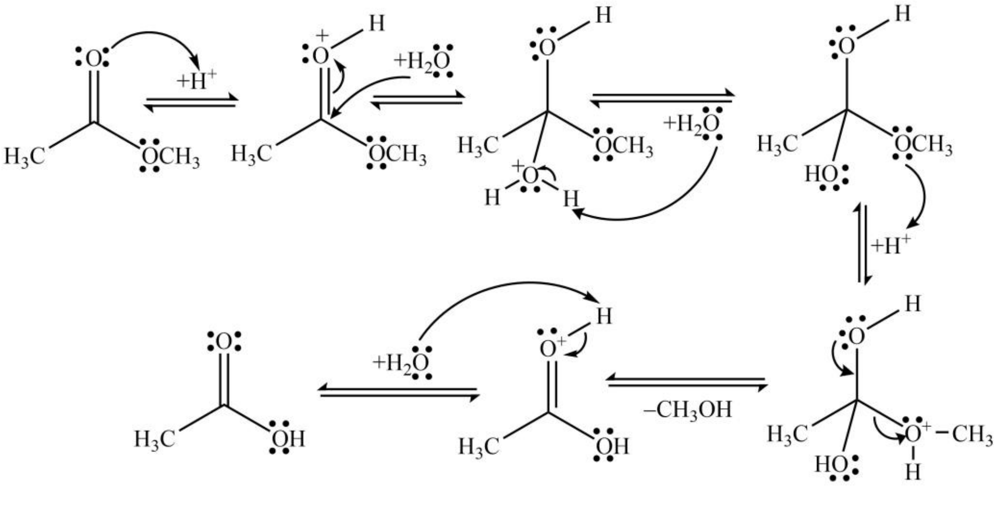
Illustrative Reaction: The typical organic chemical reaction depicting acid hydrolysis of esters is shown below.



Mechanism involved: Since the ester hydrolysis can either be catalyzed by an acid or by a base; a brief overview for both kinds must be understood for a better understanding.

i) Acid-catalyzed mechanism of ester hydrolysis:

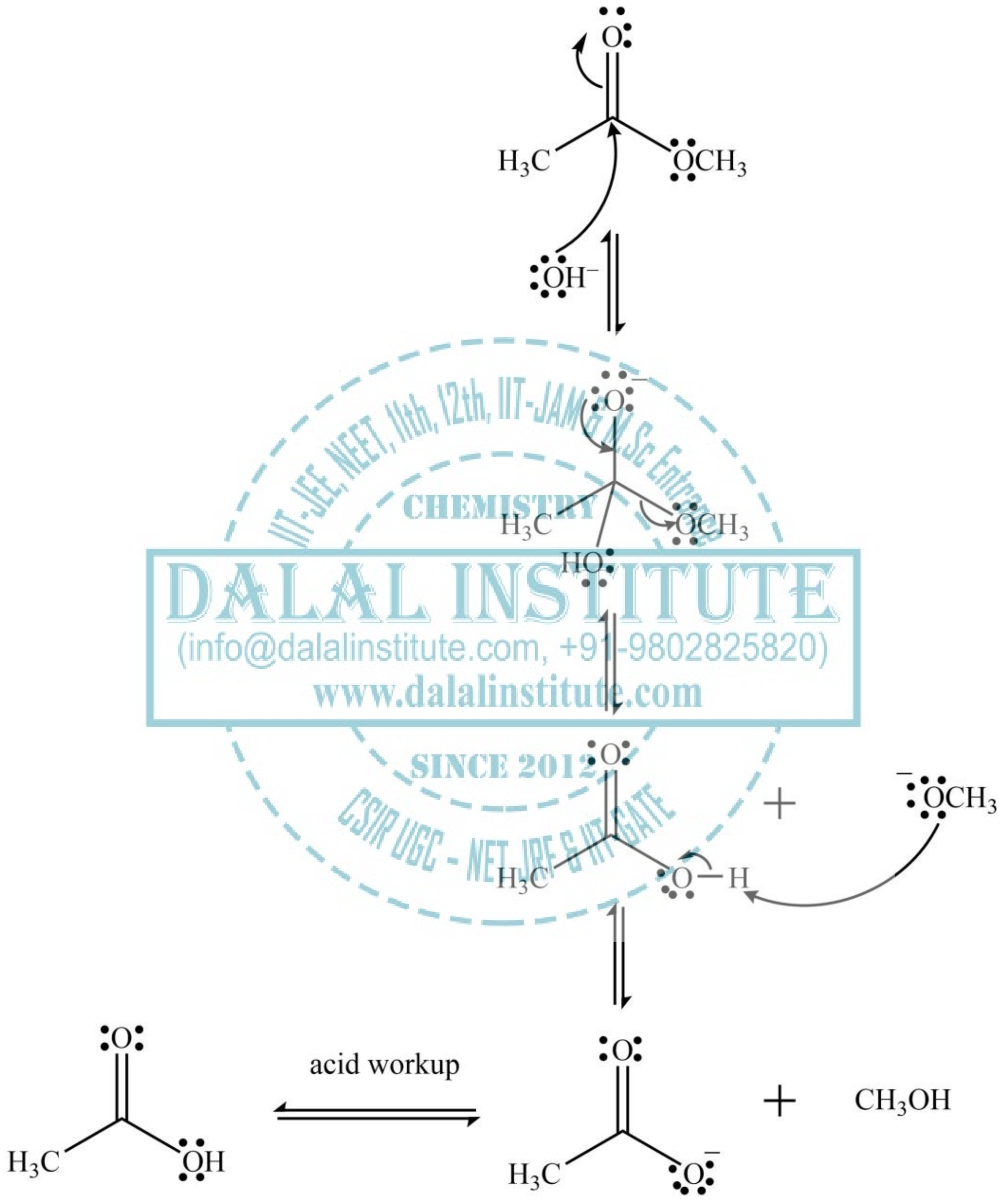
The mechanism for acid-catalyzed ester hydrolysis is a case of 'less reactive system type', and all the steps involved are shown below.



Furthermore, it is also worthy to note that the acidic hydrolysis of esters is just the reverse of esterification where an ester is heated with a large amount of water in the presence of a strongly acidic catalyst. Also, acidic ester hydrolysis is a reversible process and does not complete with 100% yield (like esterification).

ii) Base catalyzed mechanism of ester hydrolysis:

The mechanism for base-catalyzed ester hydrolysis is a case of 'reactive system type', and all the steps involved are shown below.

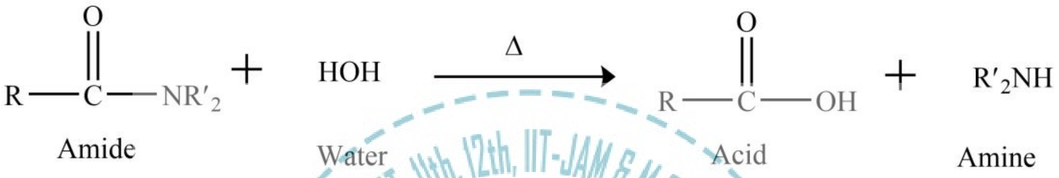


The mechanism given above gives rise to the breakage of the acyl-oxygen bond (second step); and is supported by experimental pieces of evidence through if the compound is isotopically labeled (i.e., ^{18}O). A similar conclusion was drawn if esters of chiral alcohols were used. The base-catalyzed ester hydrolysis is popularly known as the "saponification" process due to its use of soap-synthesis.

➢ *Hydrolysis of Amides*

Amides are derivatives of carboxylic acid where the OH group has been substituted by NR_2, NH_2, NHR, or amine. Since the reaction between an amine and a carboxylic acid giving amide occurs via the release of the water molecule (condensation reaction), the amides' hydrolysis can be labeled as the reverse of condensation reaction as the amine and acid are being reproduced. The amides' hydrolysis isn't easy and requires conditions like the heating of amide with aqueous acid for a long interval of time. Like the hydrolysis of esters, the amide hydrolysis can either be catalyzed by an acid or by a base.

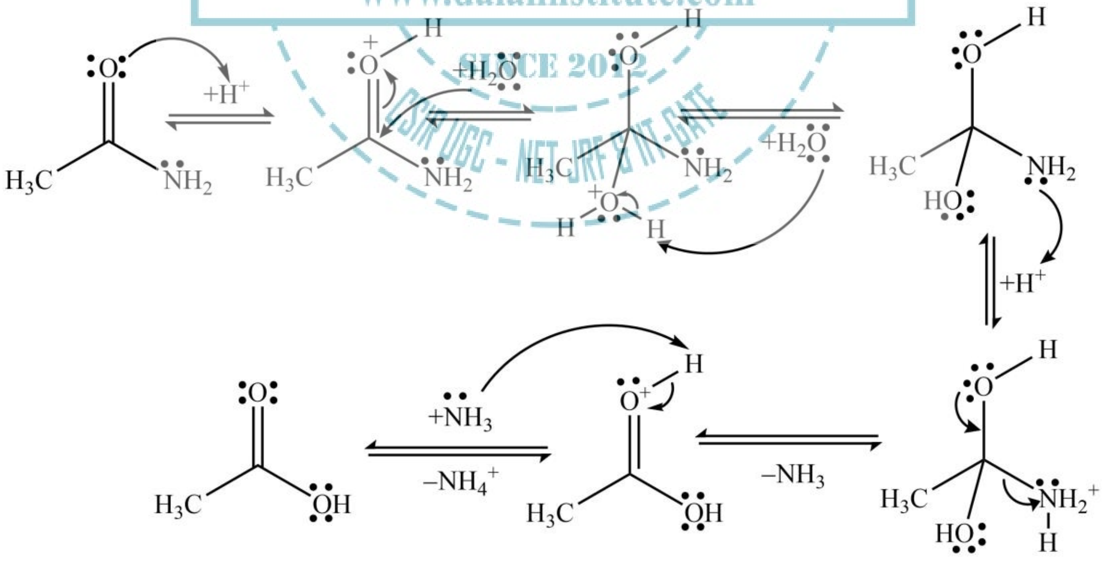
Illustrative Reaction: The typical organic chemical reaction depicting acid hydrolysis of amides is shown below.



Mechanism involved: Since the amide hydrolysis can either be catalyzed by an acid or by a base; a brief overview for both kinds must be discussed for a better understanding.

i) Acid-catalyzed mechanism of amide hydrolysis:

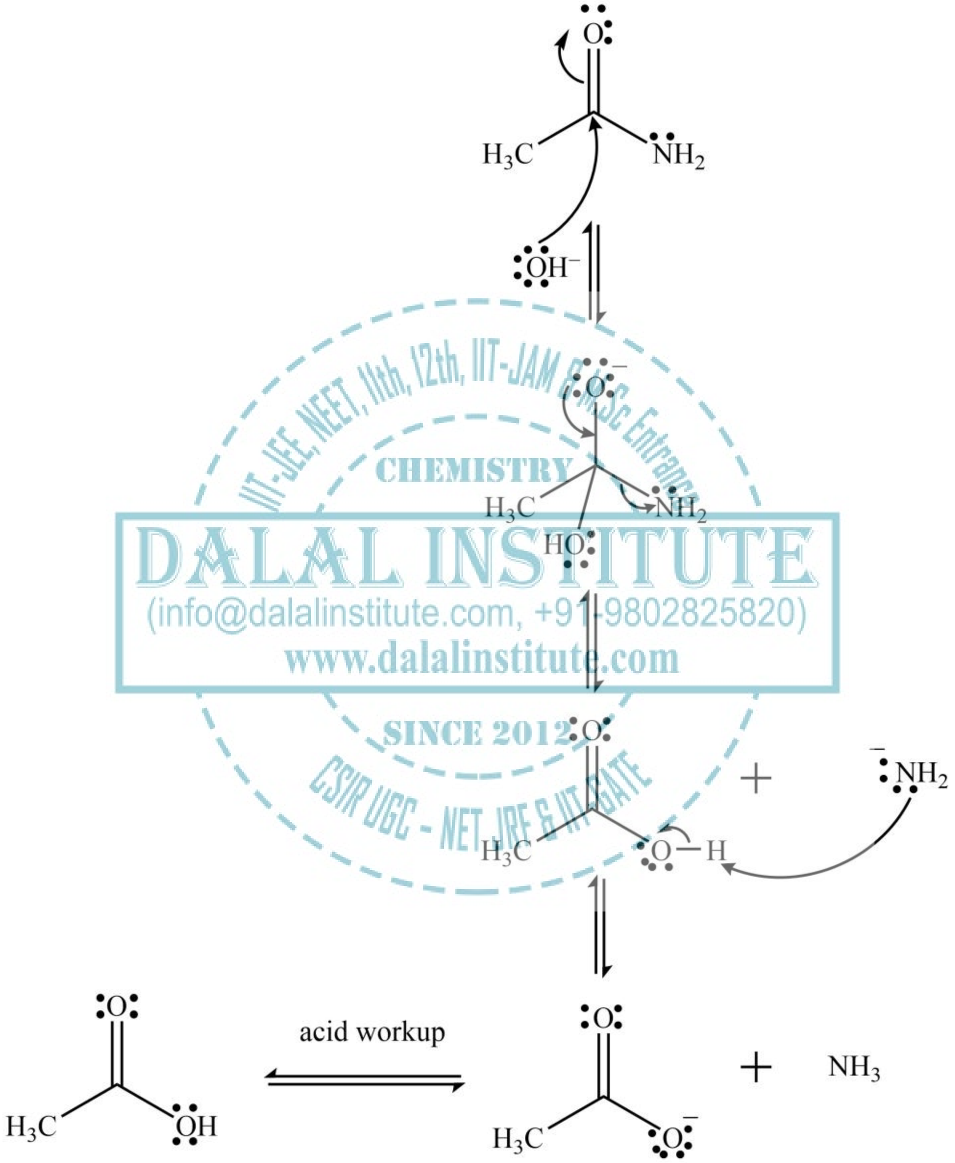
The mechanism for acid catalyzed amide hydrolysis is a case of 'less reactive system type', and all the steps involved are shown below.



It is obvious from the mechanism given above that the acid catalysed amide hydrolysis is quite analogous to the acid catalysed esters' hydrolysis; and proceed via the protonation of the carbonyl group and not the amide one.

ii) Base catalyzed mechanism of amide hydrolysis:

The base-catalyzed amide hydrolysis is extremely difficult to carry out but possible if the amide is heated for a very long span of time. All the steps involved in the base-catalyzed hydrolysis of amide are shown below.



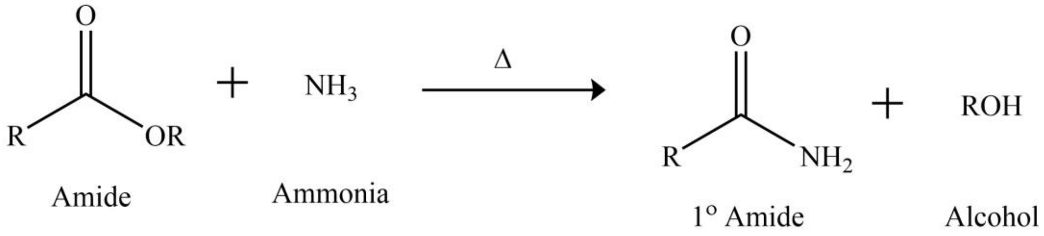
It is obvious that the major problem in the way of substitution to happen is the need for a good leaving group; however, the deprotonated amine so strongly basic that it is almost the opposite of a good leaving group. Consequently, the breaking of amide is proved to be extremely difficult even if we couple very high temperatures with a base like KOH.

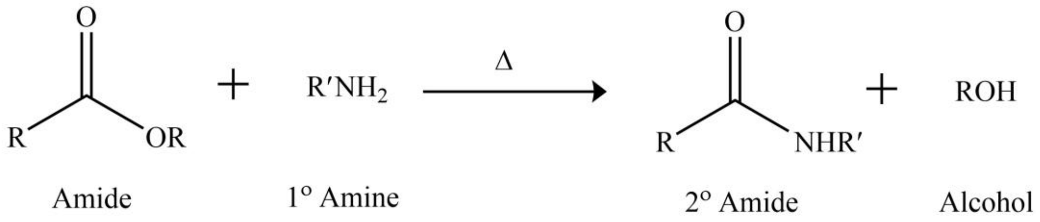
❖ Ammonolysis of Esters

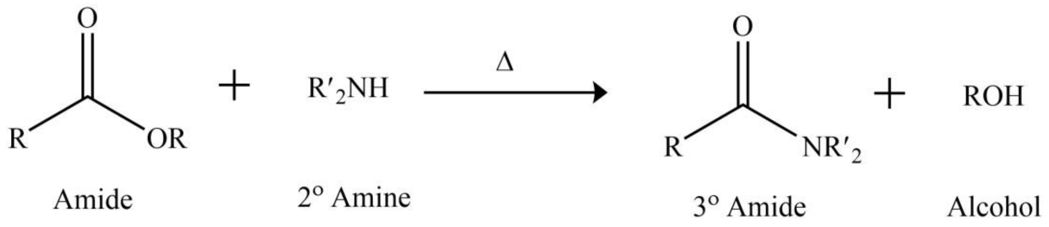
Before we study the ammonolysis of esters, we need to distinguish the term ‘ammonolysis’ from the term ‘aminolysis’ first. The precise definition of ‘ammonolysis’ includes the chemical reactions in which a compound is split into two parts by its reaction with ammonia; however, in broader terms, admins can also be used. On the other hand, the precise definition of ‘aminolysis’ includes the chemical reactions in which a compound is split into two parts by its reaction with amine; nevertheless, in broader terms, ammonia can also be used. Hence, we can conclude that the terms ‘ammonolysis’ and ‘aminolysis’ are pretty much similar not only w.r.t names but also in their approach; and therefore, are used in an exchangeable manner in different textbooks.

➢ *Definition and Examples Reactions of Ammonolysis of Esters*

Now we come to the ‘ammonolysis’ of esters, which popularly means that the esters can be converted into primary, secondary, and tertiary amides (along with alcohols) by treating them with ammonia, primary amines, and secondary amines respectively.



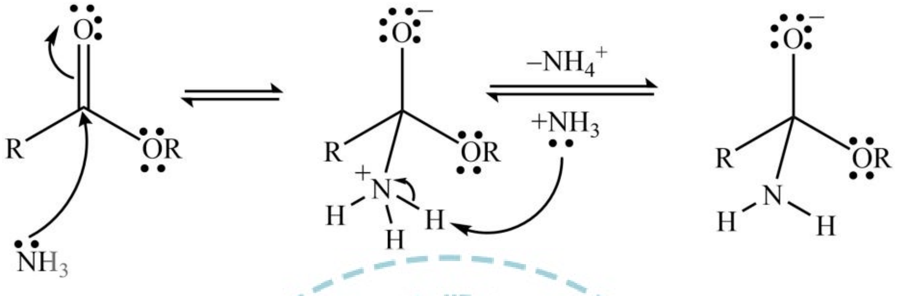




Since the RO^- is a very poor leaving group, the conventional nucleophilic addition-elimination pathway will not be useful as far the practicality is concerned. Hence, unlike the reaction of acyl chlorides with amines, the corresponding nucleophilic addition-elimination in case esters requires much stronger conditions.

- ***Mechanism of Ammonolysis of Esters***

Before we discuss the mechanism of ammonolysis of esters, we understand different outcomes first. Initially, an ammonia molecule (or amine) attacks the carbonyl via nucleophilic addition; whilst a large amount of ammonia still present in the reaction solution, followed by the formation of an anionic tetrahedral intermediate due to deprotonation.



At this point, C=O double bond can only be restored only if either the alkoxy (RO$^-$) or the amide (NH$_2^-$) group is detached. Now although both are very poor leaving groups; the pKa values of alcohol and ammonia suggested that alkoxy groups (RO$^-$) are much weaker bases than ammonia's conjugate base (i.e., NH$_2^-$), and therefore, is a better leaving group. Consequently, the reassortment of the C=O bond will happen via loss of alkoxy group giving rise to an amide product.

However, it is also worthy to note that the relative betterment of alkoxy as a leaving group doesn't make it a good leave group on the absolute scale; and therefore, the ammonolysis of esters isn't a very effective route for the amides' synthesis, indicating acyl chlorides as more suitable substrates.

❖ Problems

Q 1. Discuss the basic mechanism of addition to carbon-heteroatom multiple bonds.

Q 2. What is carbonyl reduction? How $LiAlH_4$ acts differently than $NaBH_4$ in such transformations?

Q 3. Give the mechanism involved in the metal hydride reduction of nitriles.

Q 4. What are Grignard reagents? Explain with a suitable example.

Q 5. State and illustrate the mechanism of the Wittig reaction.

Q 6. Write down the mechanism involved in the Claisen condensation.

Q 7. Illustrate the mechanism of hydrolysis of ester and amides.

Q 8. Define the process of ammonolysis.

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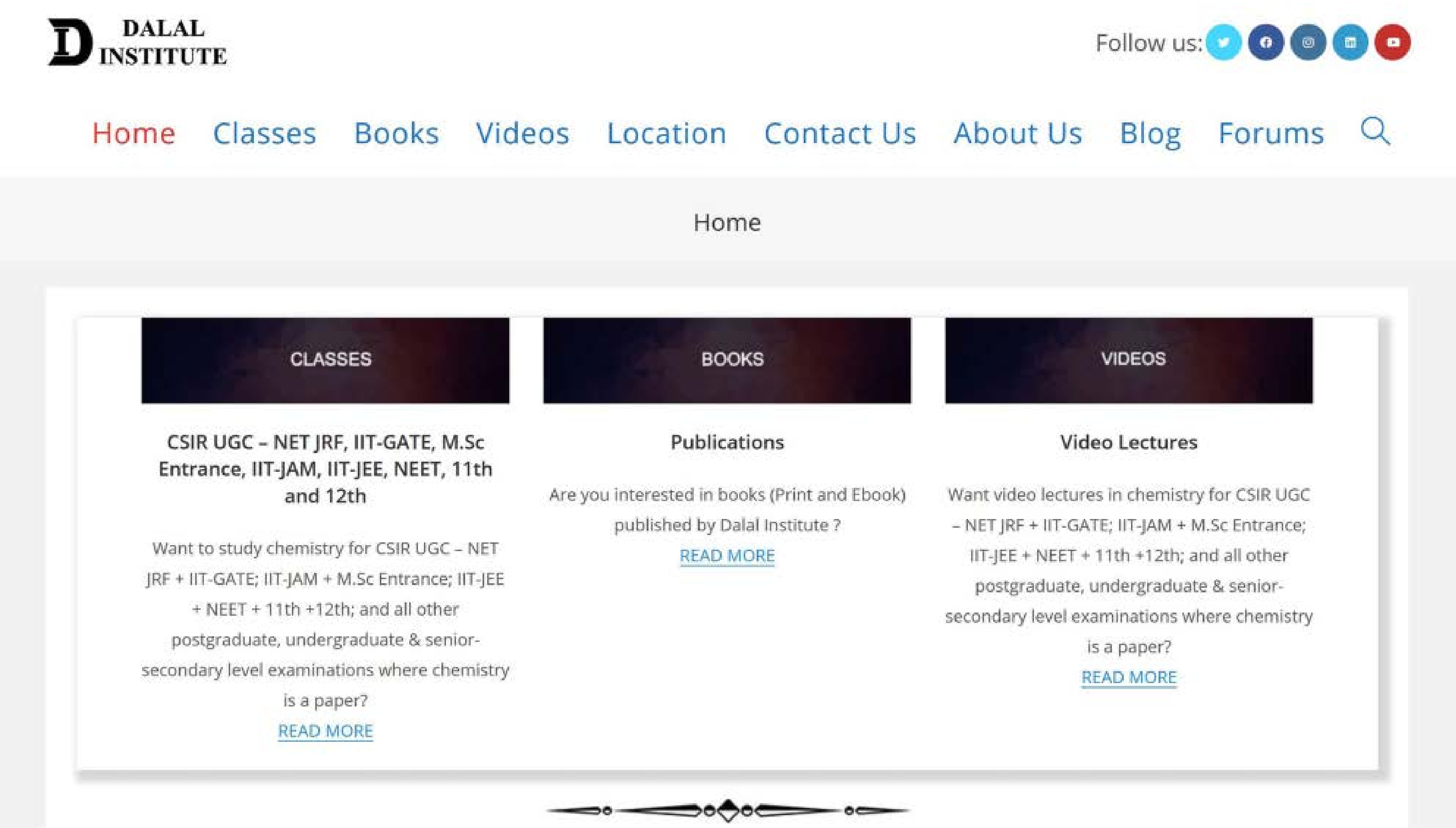

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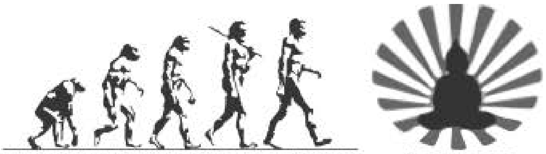

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