

## Unit 3. Reactions of Carbonyl Compounds

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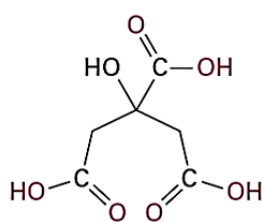
### Learning outcome:

- predict the major organic product of nucleophilic addition reactions to aldehydes and ketones and contrast the mechanisms and products produced with the use of hydride reducing agents, organometallic reagents, Wittig reagents, primary and secondary amines, and alcohols as nucleophiles in these reactions.
- predict the major organic product of nucleophilic acyl substitution reactions of carboxylic acid derivatives and use a series of these reactions to interconvert between carboxylic acids, acid chlorides, anhydrides, esters, and amides.
- utilize the mechanism of enolate formation to predict the products of reactions involving  $\alpha$ -substitution of a carbonyl group and propose synthetic schemes that utilize  $\alpha$ -substitution followed by subsequent decarboxylation.
- Understand and describe carbonyl condensation reactions including aldol, Claisen, Dieckmann and Michael reactions

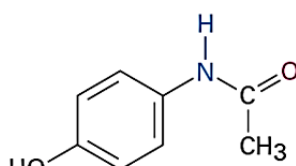
- predict the major organic products of aldol, crossed aldol, and intramolecular aldol reactions
- show the mechanistic similarities between various name reactions such as the Dieckmann cyclizations, Robinson annulations, Michael additions, Claisen condensations, and other enol-based condensations.

## Carbonyl Compounds

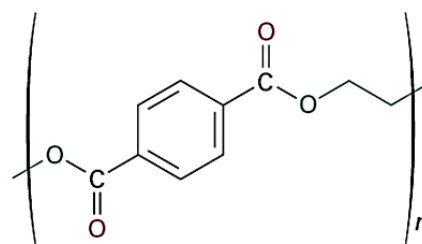
Carbonyl compounds having carbonyl group ( $>C=O$ ) are abundant in nature. They play important roles in biological processes as hormones, proteins, carbohydrates, enzymes and nucleic acids. The carbonyl group is also present in many vitamins, amino acids, drugs, flavorings, plastics, fabrics etc. In addition, carbonyl compounds are also used as solvent and reagents in syntheses in various industries. For example, citric acid is found in citrus fruits; acetaminophen, an active ingredient in analgesic medicines; Dacron, the polyester material used in textile industry.



**Citric acid**  
(a carboxylic acid)

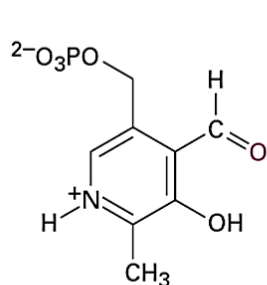


**Acetaminophen**  
(an amide)

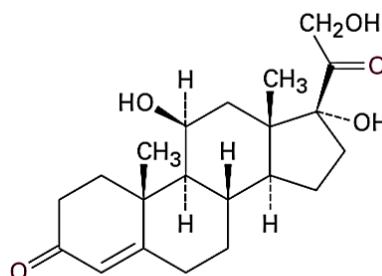


**Dacron**  
(a polyester)

The aldehyde pyridoxal phosphate, a coenzyme is involved in a large number of metabolic reactions; the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.



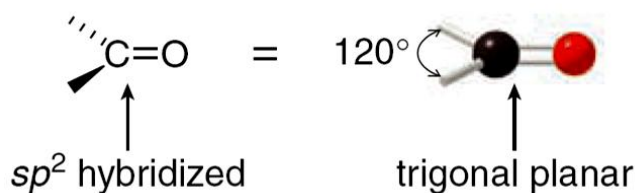
**Pyridoxal  
phosphate (PLP)**



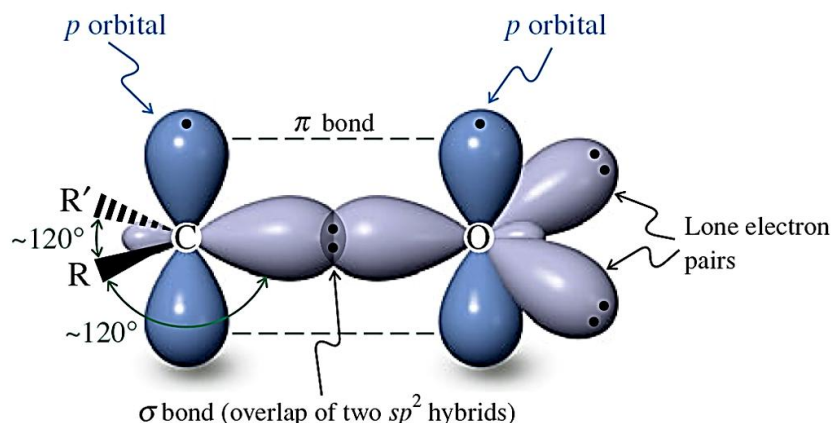
**Hydrocortisone**

### Structure of carbonyl compounds:

In carbonyl compounds, carbon is attached to oxygen with double bond and with other two substituents by single bond. In these compounds, the carbon and oxygen are  $sp^2$  hybridized making trigonal planar structure with bond angles of approximately  $120^\circ$ .

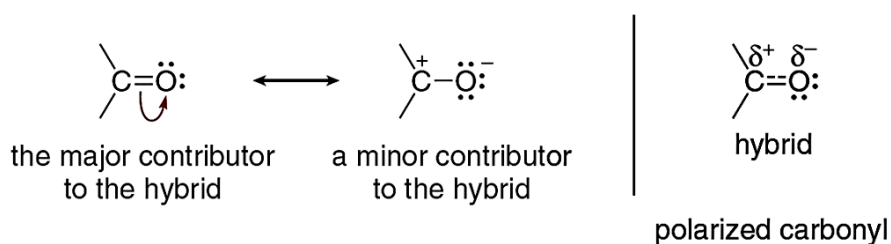


One of the  $sp^2$  hybrid orbitals of carbon overlaps with  $sp^2$  hybrid orbital of oxygen ( $sp^2-sp^2$  overlap) making a  $\sigma$ -bond, and other two  $sp^2$  orbitals of carbon overlaps with  $sp^3$  hybrid orbitals of other two substituent's atoms except in aldehyde where one of the  $sp^2$  orbital of carbon overlaps with s orbital of hydrogen. The two remaining  $sp^2$  orbitals of oxygen contain nonbonding pairs of electrons. The  $p$  orbitals on carbon and oxygen overlap to form a carbon-oxygen  $\pi$ -bond.

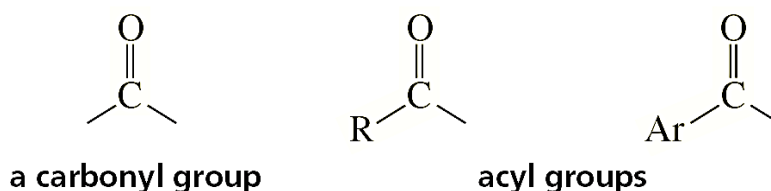


### Chemical reactions:

Oxygen is more electronegative than carbon; therefore, a carbon-oxygen double bond is polar. The carbonyl carbon carries a partial positive charge, is an electrophilic site, and reacts with nucleophile. While oxygen bearing a partial negative charge is nucleophilic site, and reacts with electrophile. The carbonyl carbon act as a Lewis acid and the carbonyl oxygen acts as a Lewis base.



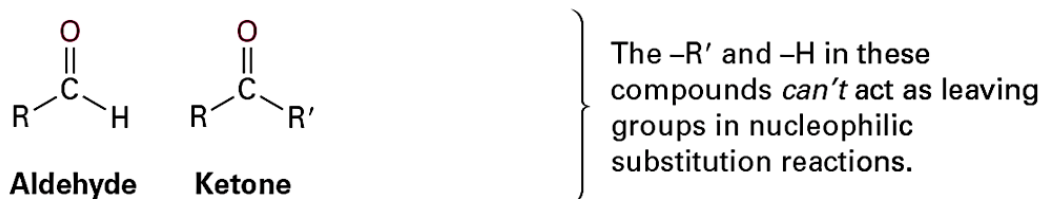
Carbonyl group attached with alkyl or aryl group is called **acyl group**.



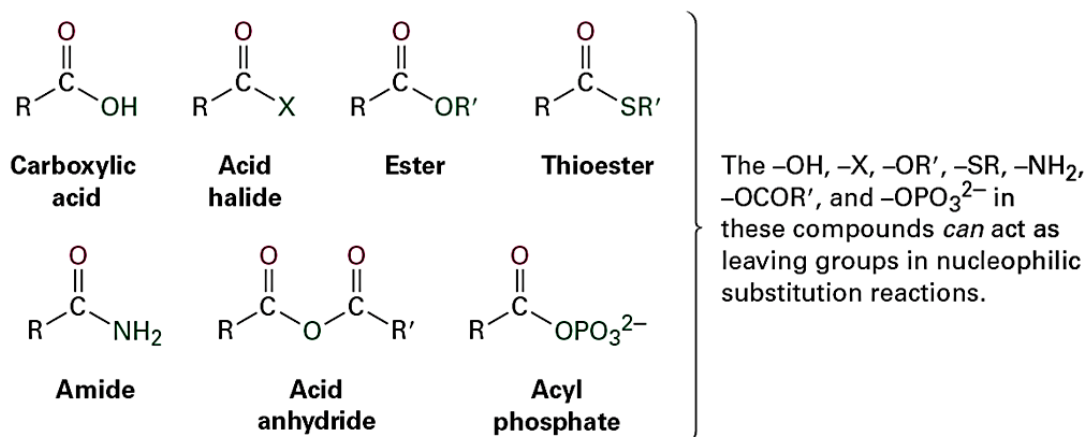
The carbonyl compounds can be classified in two categories on the basis of chemical reactions they undergo:

- (i) Compounds in which the acyl group is attached with a group that cannot be readily replaced by another group (a nucleophile). For example, aldehydes and ketones, in

which the  $-H$  and alkyl or aryl groups are not good leaving groups to be replaced by a nucleophile.



- (ii) Compounds in which the acyl group is bonded to an electronegative atom (oxygen, sulphur, nitrogen, halogen) that can stabilize the negative charge and therefore can act as a leaving group in a nucleophilic substitution reaction. These compounds are also called carboxylic acid derivatives.



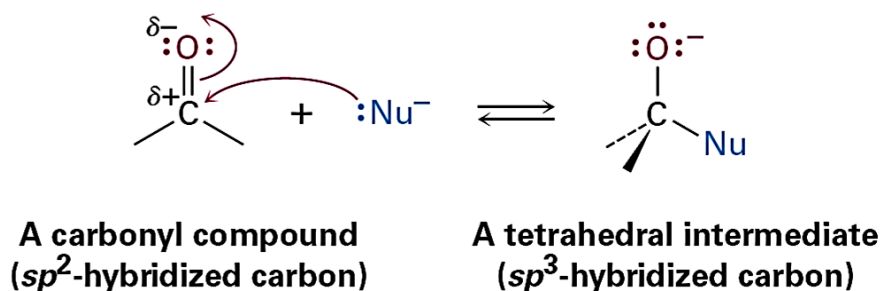
Therefore, aldehydes and ketones undergo nucleophilic addition reactions, while carboxylic acid derivatives (acid halides, esters, thioester, amides, and acid anhydrides) undergo nucleophilic substitution reactions.

### 3.1. Addition Reactions

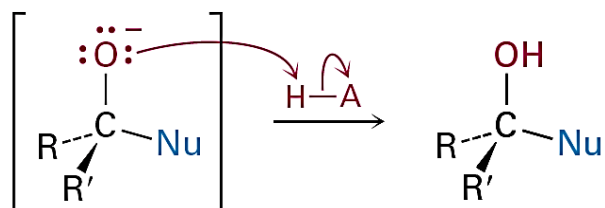
The most common reactions of aldehydes and ketones are nucleophilic addition reactions, in which a nucleophile adds to the electrophilic carbon of carbonyl group, which changes the hybridization of the carbonyl carbon from  $sp^2$  to  $sp^3$ . The electrons of the  $\pi$ -bond of carbonyl group are forced out to the oxygen atom to form an alkoxide anion, which is protonated by water or another proton donor to give addition product.

#### Mechanism:

*Step 1:* Addition of nucleophile to electron deficient carbon.

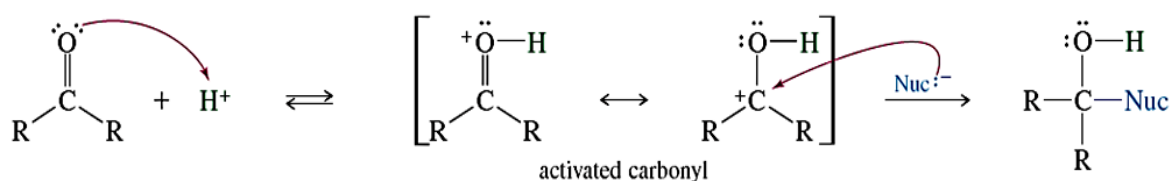


Step 2: Protonation of negatively charged oxygen by water (or another proton source).



The net result is that the  $\pi$  bond is broken, two new  $\sigma$  bonds are formed, and H and Nu are added across the  $\pi$  bond.

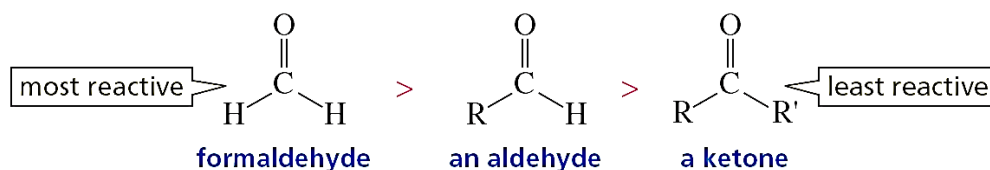
In case of weak nucleophile or neutral nucleophile, such as water and alcohol, however, the nucleophilic addition undergoes in presence of an acid. In this case, the carbonyl group is first protonated followed by the addition of the weak nucleophile. Protonation of carbonyl oxygen results to change the partial positive charge to full positive charge on carbonyl carbon making it more electrophilic which can easily react with weak nucleophile.



Thus, there are two types of mechanism:

- (i) **Nucleophilic attack followed by protonation:** This type of mechanism takes place with strong nucleophile. The reaction undergoes in neutral or alkaline medium.
- (ii) **Protonation followed by nucleophilic attack:** This type of mechanism is observed when the nucleophile is weak. The reaction requires acid catalyst for protonation.

The aldehydes are more reactive than ketones towards nucleophilic addition reactions. The order of reactivity may be generalized as:

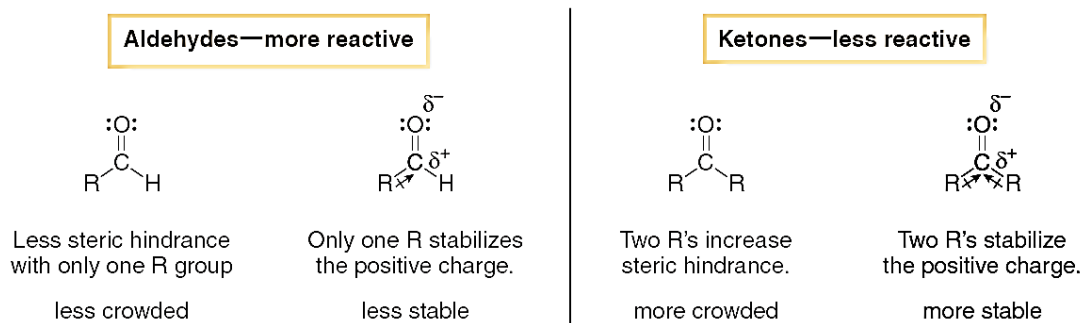


This low reactivity of ketones is due to inductive effect as well as steric hindrance.

**Inductive Effect:** As the carbonyl carbon is electrophilic in nature, greater the positive charge on this, greater is the reactivity towards nucleophilic addition reactions. Because alkyl group exhibits +I (electron donating) effect, more the number of alkyl groups attached to the carbonyl carbon, lesser is the positive charge on carbon and lesser will be the reactivity towards nucleophilic addition reactions.

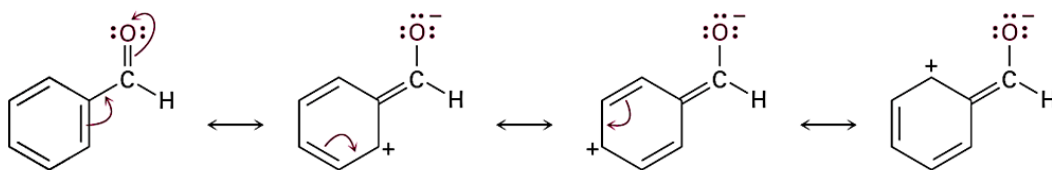
On the other hand, electron-withdrawing substituents (e.g.,  $-\text{CF}_3$  or  $-\text{CCl}_3$  groups) cause the carbonyl carbon to be more positive causing the addition reaction to be more favourable.

**Steric hindrance:** Two alkyl groups in ketones make the carbonyl carbon more crowded and thus hinders the approach of nucleophilic reagent, which decreases the reactivity of ketones as compared to aldehydes.



- The two R groups bonded to the ketone carbonyl group make it more crowded, so nucleophilic attack is more difficult.
- The two electron-donor R groups stabilize the partial charge on the carbonyl carbon of a ketone, making it more stable and less reactive.

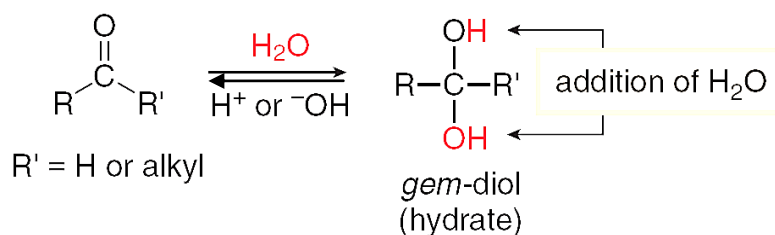
Further, aromatic aldehydes, e.g. benzaldehyde, are less reactive than aliphatic aldehydes in nucleophilic addition reactions because the electron-donating resonance effect of the aromatic ring makes the carbonyl group less electrophilic.



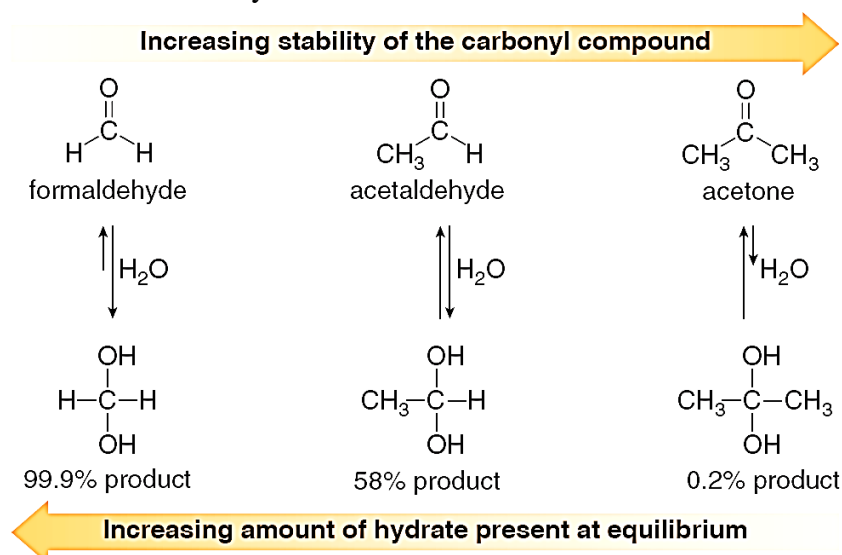
The nucleophilic addition reactions of aldehydes and ketones can be exemplified as under:

### 3.1.1. Hydrate Formation:

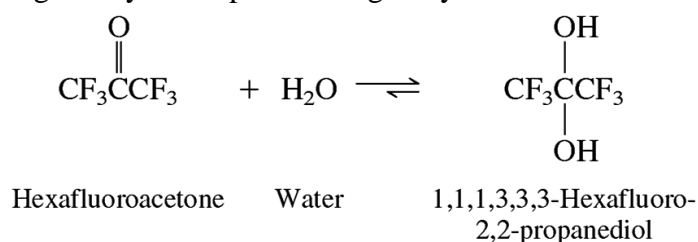
Aldehydes and ketones react with water in presence of acid or base to produce 1,2-diols, or *gem*-diols which are commonly known as hydrates. The reaction is reversible; the hydrates can eliminate water to regenerate an aldehyde or ketone.



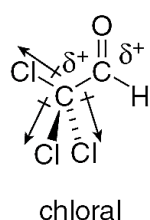
The yield of hydrates depends on the relative stabilities of the starting material (i.e. carbonyl compound) and the product (i.e. hydrate). Less stable carbonyl compounds favor the hydrate product while the more stable carbonyl compounds favor the starting material. As discussed earlier that the alkyl groups stabilize a carbonyl group, the hydrates of aldehydes are more stable than hydrates of ketones; increasing the number of alkyl groups on the carbonyl carbon increases the stability of carbonyl compounds and decreases the amount of hydrate formation.



Further, the electron-donating groups near carbonyl carbon stabilize the carbonyl group and decrease the amount of hydrate at equilibrium, while electro-withdrawing groups near carbonyl carbon destabilize the carbonyl group and favor the hydrate formation. For example, in contrast to the almost negligible hydration of acetone, hexafluoroacetone gives hydrated product in good yield.



Similarly, when acetaldehyde gives only 58% hydrated product at equilibrium, chloral (trichloroacetaldehyde) forms a large amount of hydrate at equilibrium.



Having two similar charges ( $\delta^+$ ) on adjacent atoms destabilizes the carbonyl group.

A less stable carbonyl compound means more hydrate at equilibrium.

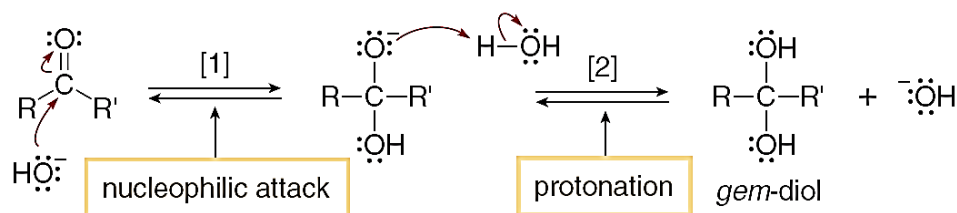
### Mechanism:

The nucleophilic addition of water to an aldehyde or ketone undergoes slowly in neutral conditions but it can be catalyzed either by base or acid.

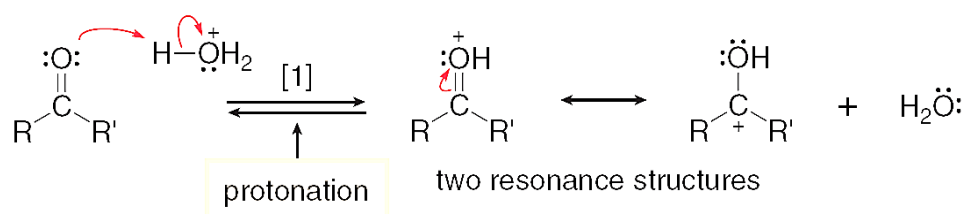
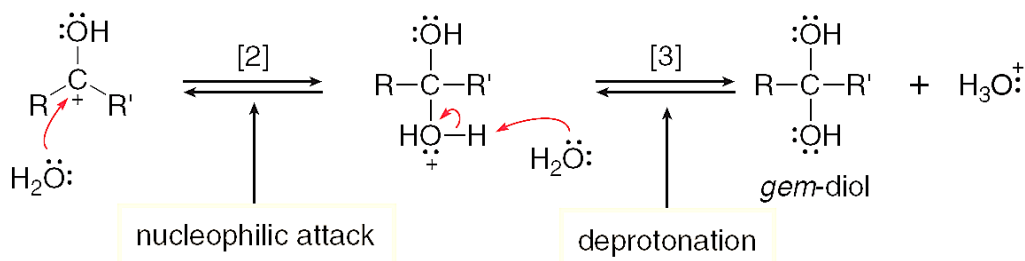


**Base-catalyzed mechanism:**

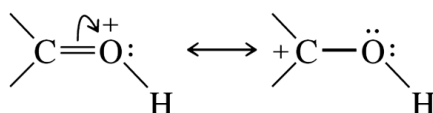
The base-catalyzed reaction is a two step process – attack of nucleophile on carbonyl carbon followed by protonation of alkoxide. The basic catalyst converts water to  $\text{OH}^-$  (hydroxide ion) which is much more reactive than a water molecule. The  $\text{OH}^-$  attacks on electrophilic carbon of carbonyl group to give an intermediate, an alkoxide ion by cleaving the  $\pi$ -bond, and moving an electron pair onto oxygen. This is rate determining step. Protonation of the alkoxide ion by water then yields a neutral addition product (i.e. hydrate) plus regenerates the catalyst ( $\text{OH}^-$ ).

**Acid-catalyzed mechanism:**

Acid-catalyzed hydration of carbonyl compounds is three step processes. In the first step, the carbonyl oxygen is protonated by acid ( $\text{H}_3\text{O}^+$ ), making the carbon more strongly electrophilic. In the second step, the neutral nucleophile ( $\text{H}_2\text{O}$ ) adds to the electrophilic carbon of carbonyl compounds. In the last step, water abstract a proton from the intermediate, giving the neutral hydrate and regenerating the acid catalyst ( $\text{H}_3\text{O}^+$ ). The first and last steps are rapid while the second step is slow rate determining step.

**Step 1: Protonation of carbonyl group.****Step 2 and 3: Nucleophilic attack of water and deprotonation.**

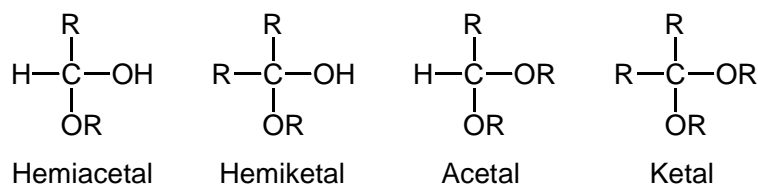
Water being weak nucleophile is less reactive for nucleophilic attack at carbonyl carbon. The acid catalyst activates the carbonyl group towards nucleophilic addition by protonation; the protonated carbonyl has a greater degree of carbocation character (more electron-deficient) than an unprotonated carbonyl.



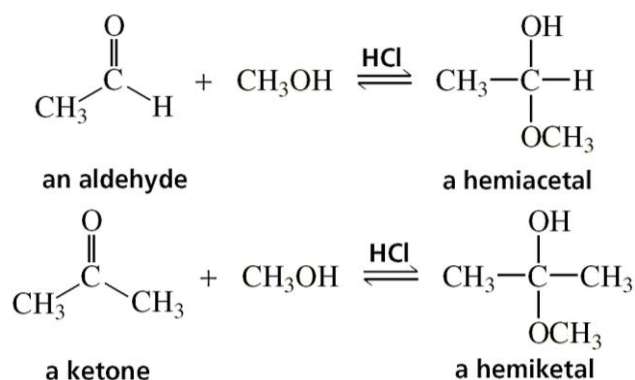
Thus, protonation of oxygen makes the carbonyl carbon of an aldehyde or a ketone much more electrophilic that can be attacked even by a weak nucleophile (i.e. water).

### 3.1.2. Hemiacetals and hemiketals formation:

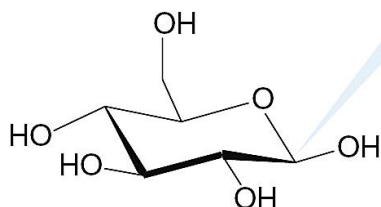
Monoalkylated derivatives of hydrates of aldehydes and ketones are called hemiacetals and hemiketals, respectively, while dialkylated derivatives of hydrates of aldehydes and ketones are called acetals and ketals, respectively. In other words, when –OH and –OR groups are attached to the same carbon, they are called hemiacetals and hemiketals depending upon the nature of other two substituents - if both the substituents are alkyl groups, it is called hemiketal, and if one substituent is alkyl group and other is hydrogen, it is called hemiacetal.



Addition of alcohols (weak nucleophile) to aldehydes and ketones takes place in presence of acid to give hemiacetals and hemiketals, respectively.



Most open-chain hemiacetals are not sufficiently stable to allow their isolation. Cyclic hemiacetals with five- or six-membered rings, however, are usually much more stable. For example, simple sugars like glucose mostly exist in a cyclic hemiacetal form.



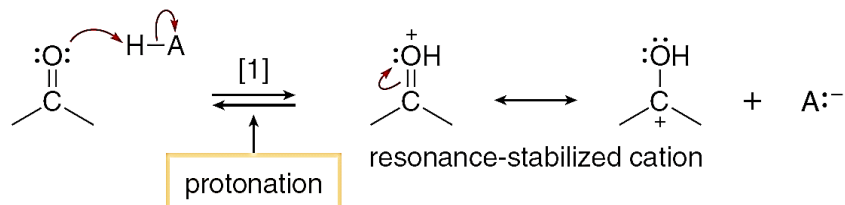
**Hemiacetal: OH and OR groups bonded to the same carbon**

#### Mechanism:

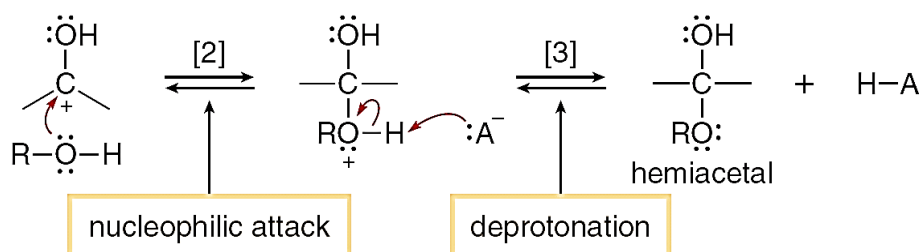
The mechanism of hemiacetal and hemiketal formation is analogous to the hydration of aldehydes and ketones in presence of acid. This is three step processes. In the first step, the acid protonates the carbonyl oxygen to produce resonance-stabilized cation

intermediate; this reaction increases the electrophilicity of carbonyl carbon. In the second step, the alcohol, a weak nucleophile, through its lone pair attacks on electrophilic carbon of the carbonyl group, which shifts the positive charge from carbonyl carbon to the nucleophile. In the last step, loss of proton yields a neutral hemiacetal (or hemiketal).

**Step 1: Protonation of carbonyl oxygen.**

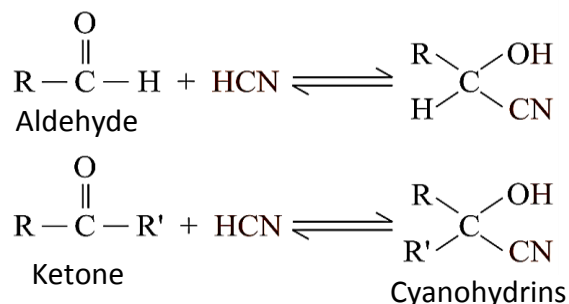


**Step 2 and 3: Nucleophilic attack and deprotonation.**



### 3.1.3. Cyanohydrin formation:

The carbonyl compounds react with HCN to form addition products that are called cyanohydrins. In cyanohydrins, the  $\text{-OH}$  and  $\text{-CN}$  are attached at the same carbon. Addition of HCN proceeds by way of cyanide ion. As HCN is very weak acid, the concentration of cyanide ion in aqueous HCN is too low for cyanohydrin formation to proceed at a reasonable rate. For this reason, cyanohydrin formation is generally carried out by dissolving NaCN or KCN in water and adjusting the pH of the solution to approximately 10.0, giving a solution in which HCN and cyanide ion ( $\text{CN}^-$ ) are present in comparable concentrations.



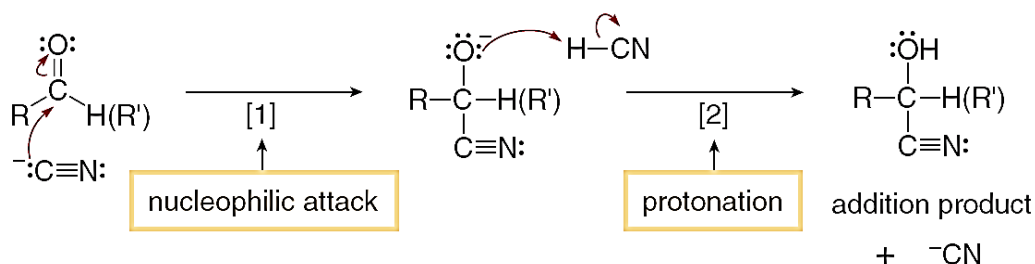
The cyanohydrin addition is reversible reaction. The position of equilibrium favours cyanohydrin formation for aldehydes and most aliphatic ketones. However, for many aryl ketones and sterically hindered aliphatic ketones the position of equilibrium favours starting materials.

**Mechanism:**

Addition of HCN to carbonyl compounds is two step processes – nucleophilic attack followed by protonation.

**Step 1: Attack of nucleophile (CN<sup>-</sup>) on carbonyl carbon.** Cyanide ion (CN<sup>-</sup>) is a very strong nucleophile. It attacks on the carbonyl carbon to form a new carbon-carbon bond with cleavage of  $\pi$ -bond of carbonyl group.

**Step 2: Addition of proton.** Alkoxide ion formed in first step abstract a proton from HCN producing the cyanohydrins and generating a new cyanide ion (CN<sup>-</sup>).

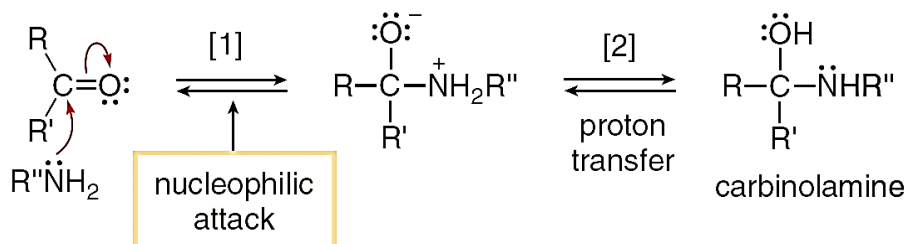


### 3.1.4. Carbinolamines

Ammonia, primary aliphatic amines ( $\text{RNH}_2$ ), and primary aromatic amines ( $\text{ArNH}_2$ ) react with carbonyl compounds to give an addition product called carbinolamine. Carbinolamines are not stable; therefore, undergo dehydration to yield an **imine**.

#### Mechanism:

Nucleophilic attack of ammonia or primary amine by its lone pair of electrons on carbonyl carbon leads to a dipolar tetrahedral intermediate; the oxygen carries negative charge and nitrogen carries positive charge. A proton transfer from nitrogen to oxygen yields a neutral carbinolamine.

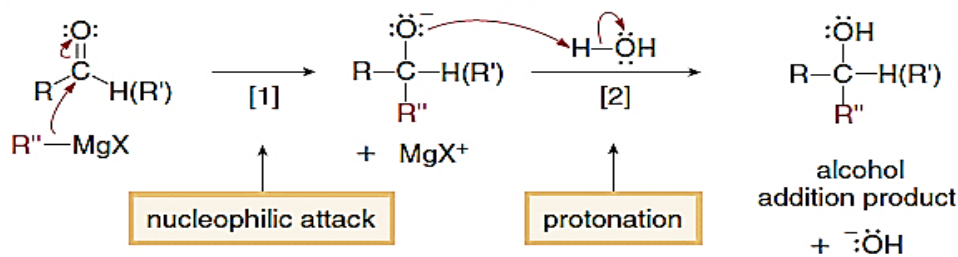


Formation of imine from carbinolamine is elimination reaction, which will be discussed later in addition-elimination reactions.

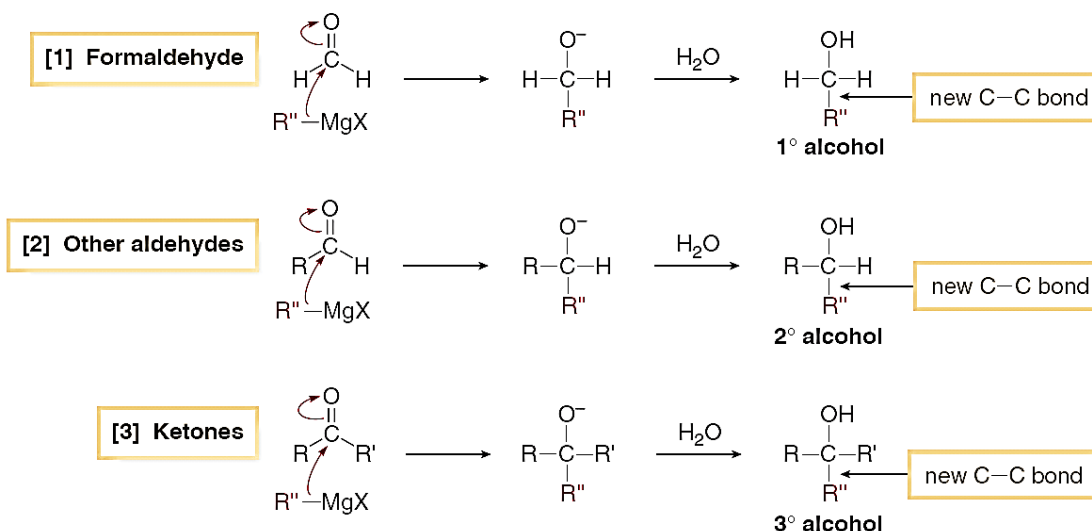
### 3.1.5. Addition of Grignard Reagents

Because of the electronegativity difference between carbon and magnesium, the carbon-magnesium bond of Grignard reagent is polar with carbon bearing a partial negative charge and magnesium bearing a partial positive charge. Therefore, the alkyl group of Grignard reagent behaves as a nucleophile and adds to the carbonyl carbon of aldehyde or ketone to form a tetrahedral addition product, in which alkoxide ion is complexed with magnesium ion. Hydrolysis of the complex with an aqueous acid

provides alcohol. Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.



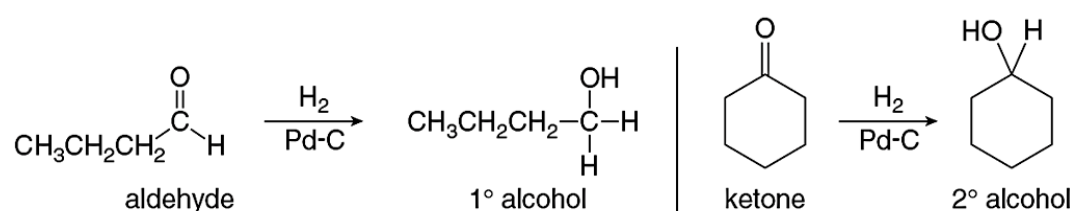
Thus, reaction of Grignard reagent with formaldehyde, other aldehydes and ketone followed by hydrolysis produces primary, secondary and tertiary alcohol, respectively.



Like cyanohydrins formation, addition of a Grignard reagent to a carbonyl compound also leads to the formation of a new C-C bond. Grignard reaction is more versatile – In case of cyanohydrins formation, only one carbon is added to the molecule while with Grignard reagent a variety of structures can be produced because both the structure of the carbonyl compound and the structure of the Grignard reagent can be varied. A Grignard reagent can be prepared by adding an alkyl halide to magnesium shavings in diethyl ether.

### 3.1.6. Addition of Hydrogen

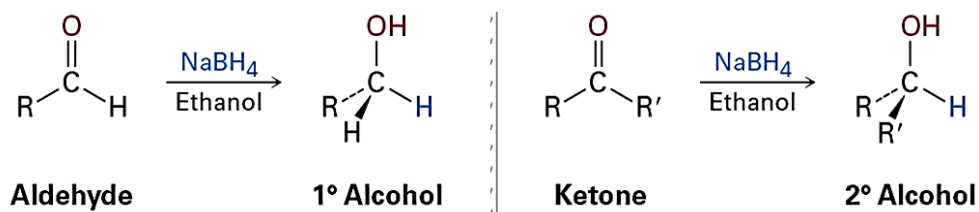
Aldehyde and ketone are reduced to 1° and 2° alcohols, respectively, by using hydrogen in the presence of a transition metal catalyst, most commonly finely divided platinum or nickel. Pd-C, Rh or Raney nickel is also used for hydrogenation of ketones and aldehydes. Reductions are generally carried out at temperatures from 25 to 100°C and at pressures of hydrogen from 1 to 5 atm.



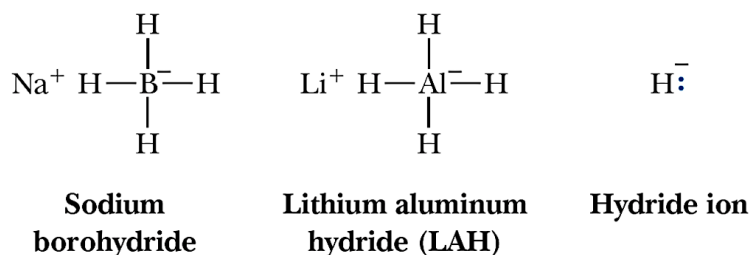
Catalytic reduction of aldehydes and ketones is simple to carry out, yields are generally very high, and isolation of the final product is very easy. However, a disadvantage is that some other functional groups are also reduced under these conditions, for example, carbon-carbon double and triple bonds.

### 3.1.7. Hydride Additions (lithium-aluminum hydride and sodium-borohydride)

Lithium aluminum hydride ( $\text{LiAlH}_4$ ) and sodium borohydride ( $\text{NaBH}_4$ ) are the most common reducing agents to reduce aldehydes and ketones to primary and secondary alcohols, respectively.



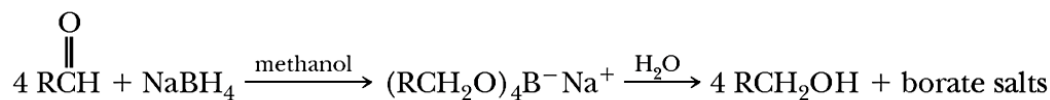
These compounds act as donor of hydride ion, a powerful nucleophile for nucleophilic addition reactions.



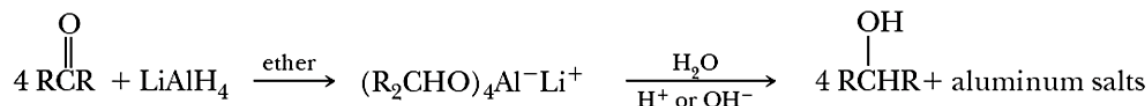
Lithium aluminum hydride is a very powerful reducing agent; it reduces not only the carbonyl groups of aldehydes and ketones rapidly but also those of carboxylic acids and their functional derivatives. Sodium borohydride is a less reactive and, therefore, a much more selective reagent, reducing only aldehydes and ketones; not a sufficiently strong hydride donor to reduce the less reactive (compared with aldehydes and ketones) esters, amides, and carboxylic acids. Neither reagent reduces alkenes or alkynes.

	<u>Reagent</u>	<u>Starting Material</u>		<u>Product</u>
Strong reagent	$\text{LiAlH}_4$	$\text{RCHO}$	→	$\text{RCH}_2\text{OH}$
		$\text{R}_2\text{CO}$	→	$\text{R}_2\text{CHOH}$
		$\text{RCOOH}$	→	$\text{RCH}_2\text{OH}$
		$\text{RCOOR}'$	→	$\text{RCH}_2\text{OH}$
		$\text{RCOCl}$	→	$\text{RCH}_2\text{OH}$
		$\text{RCONH}_2$	→	$\text{RCH}_2\text{NH}_2$
Mild reagent	$\text{NaBH}_4$	$\text{RCHO}$	→	$\text{RCH}_2\text{OH}$
		$\text{R}_2\text{CO}$	→	$\text{R}_2\text{CHOH}$
		$\text{RCOCl}$	→	$\text{RCH}_2\text{OH}$

One mole of sodium borohydride or lithium aluminium hydride reduces four moles of aldehyde or ketone.



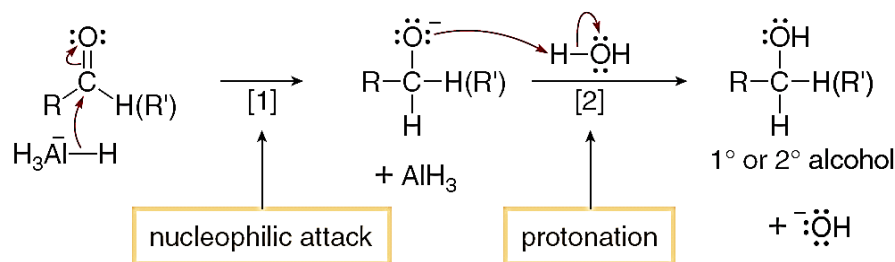
A tetraalkyl borate



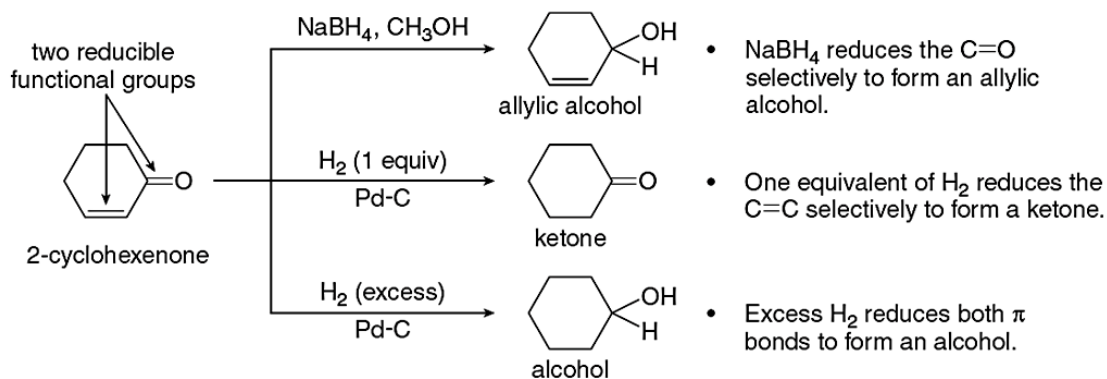
A tetraalkyl aluminate

### Mechanism:

The mechanism of hydride ion reduction is analogous to the base-catalyzed nucleophilic addition reaction i.e. nucleophilic attack followed by protonation.  $\text{LiAlH}_4$  and  $\text{NaBH}_4$  donate hydride ion nucleophile ( $\text{H}^-$ ) to carbonyl carbon to produce alkoxide ion intermediate, which is protonated by addition of aqueous acid to give alcohol. The reaction is effectively irreversible because the reverse process would require expulsion of a very poor leaving group.



When a compound contains both a carbonyl group and a carbon-carbon double bond, selective reduction of one functional group can be achieved by proper choice of reagent. For example, 2-cyclohexenone, a compound that contains both a carbon-carbon double bond and a carbonyl group, can be reduced to three different compounds—an allylic alcohol, a carbonyl compound, or an alcohol—depending on the reagent.



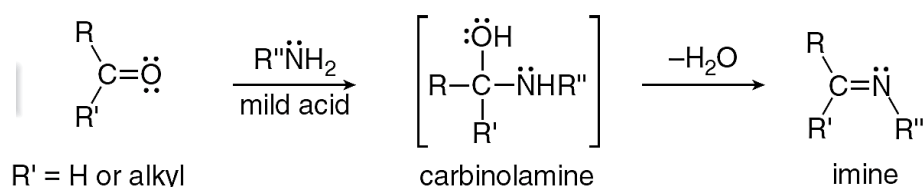
## 3.2. Addition-Elimination Reactions

### 3.2.1. Imines and related compounds:

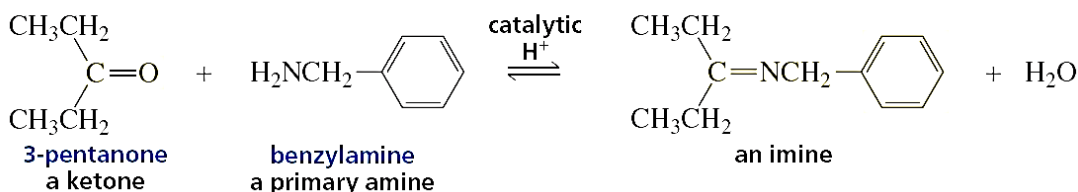
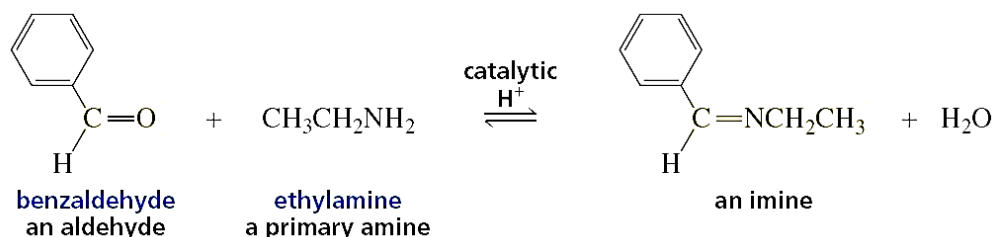
Ammonia derivatives react with aldehydes and ketones to first form addition product, which eliminates water to produce imine, often called ‘Schiff’s base’. Imines are nitrogen analogues of ketones and aldehydes with a carbon–nitrogen double bond in place of the carbonyl group.

#### Reaction with primary amine (formation of Schiff’s base):

As discussed earlier, nucleophilic addition of primary amines to aldehydes and ketones results in the formation of carbinolamine which is converted to imine on water elimination.



The reaction undergoes in acidic medium, however, the reaction rate decreases in very high acidic medium due to protonation of amine ( $\text{RNH}_2 + \text{H}^+ \rightarrow \text{RNH}_3^+$ ), which is no longer a nucleophile.



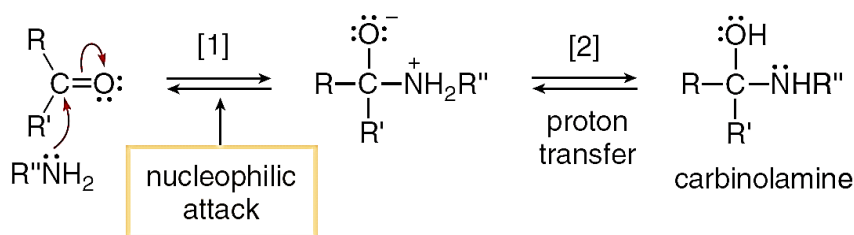
Thus, the final result of the reaction is the replacement of  $\text{C}=\text{O}$  with  $\text{C}=\text{NR}$ .

#### Mechanism:

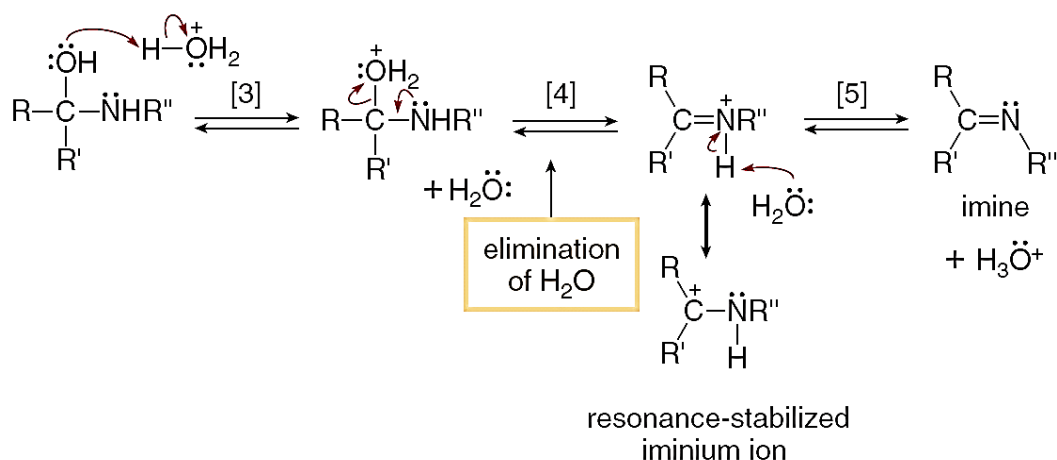
Imines are formed in a reversible, acid-catalyzed process. The reaction can be divided into two parts – first addition and then elimination.

**Part 1: Nucleophilic addition of amine to form carbinolamine.** Nucleophilic attack of amine on carbonyl carbon followed by proton transfer results in the formation of unstable carbinolamine.



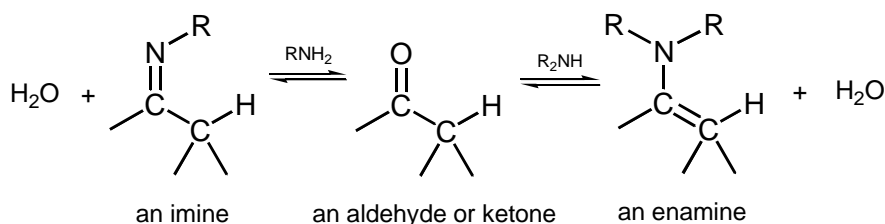


**Part 2: Elimination of water to form imine.** Carbinolamine is protonated at oxygen to make it a good leaving group, leading to the loss of water, which results in the formation of resonance-stabilized iminium ion. Loss of proton from iminium ion forms imine.

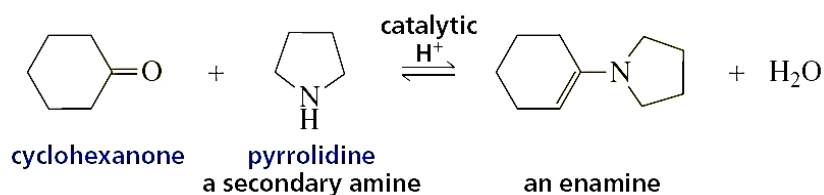
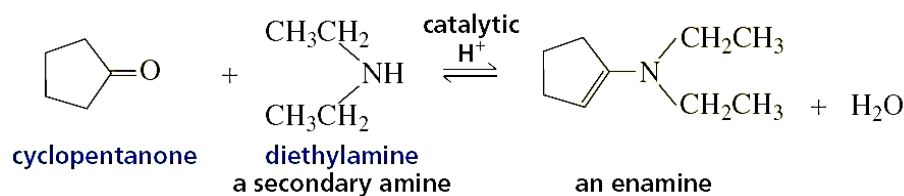


### Reaction with secondary amines:

Addition of primary amines to aldehydes and ketones yields **imines** ( $R_2C=NR$ ), while secondary amines yield **enamines**,  $R_2N-CR=CR_2$  (ene + amine = unsaturated amine).



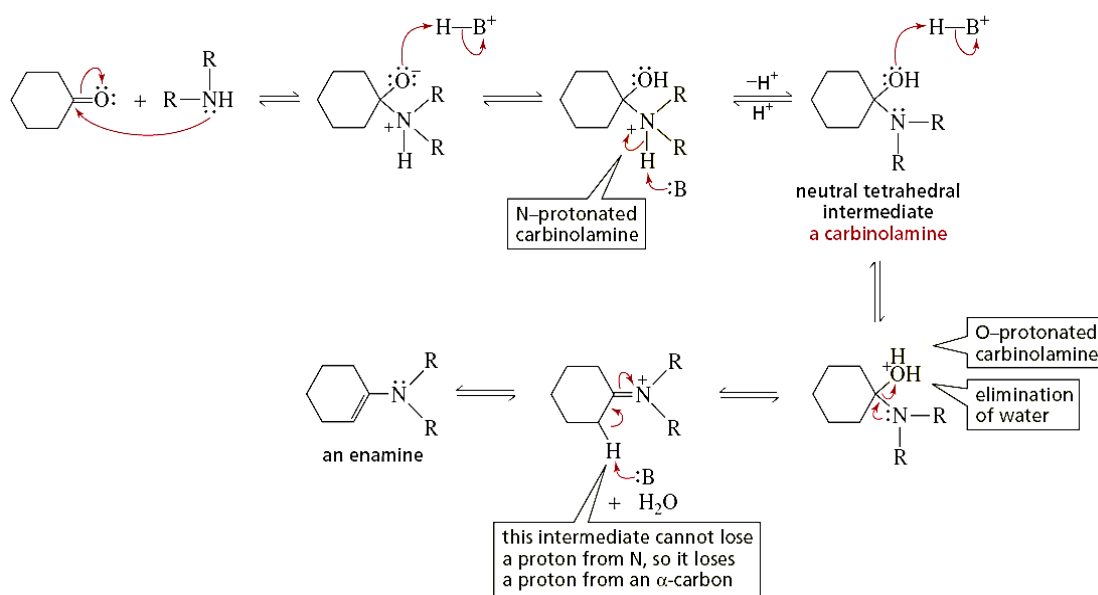
For example:



Imine formation and enamine formation appear different because one leads to a product with a C=N bond and the other leads to a product with a C=C. However the mechanisms are same. Like imine formation, the enamine formation also undergoes in mild acidic conditions.

### Mechanism:

The mechanism for enamine formation is exactly the same as that for imine formation except the last step, involving loss of proton. In case of reaction with primary amine, the protonated imine loses a proton from nitrogen in the last step of the reaction, forming a neutral imine. However, when the amine is secondary, the positively charged nitrogen doesn't carry any hydrogen bonded to it. Therefore, a proton is removed from the  $\alpha$ -carbon to get a stable neutral molecule, an enamine.

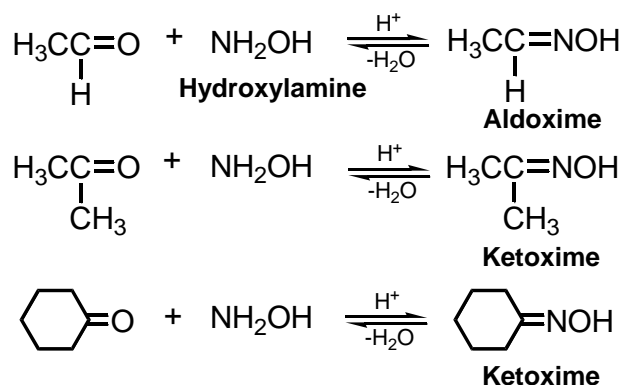


Tertiary amines do not form stable addition products with aldehydes and ketones because, on forming the tetrahedral intermediate (carbinolamine), the resulting formal positive charge cannot be neutralized by loss of a proton.

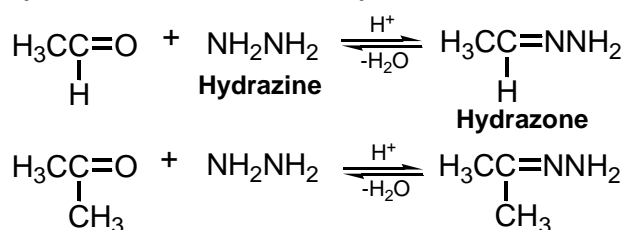
### Formation of imine derivatives:

Compounds such as, hydroxylamine ( $NH_2OH$ ), hydrazine ( $NH_2NH_2$ ), semicarbazide ( $NH_2NHCONH_2$ ) all have an  $-NH_2$  group as primary amines have, therefore they all react with aldehydes and ketones like primary amines to produce imine derivatives (oxime, hydrazone and semicarbazone, respectively). Similarly, phenyl-substituted hydrazines give phenylhydrazones.

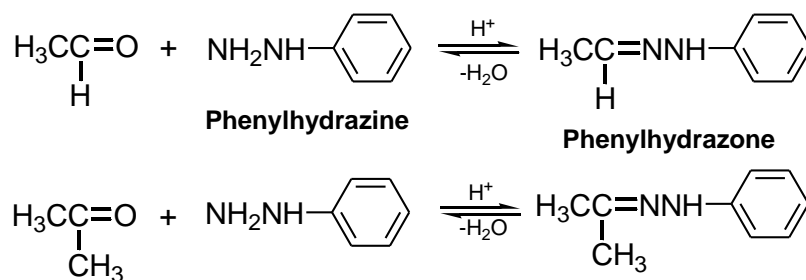
#### (i) Reaction with Hydroxylamine (formation of oxime):



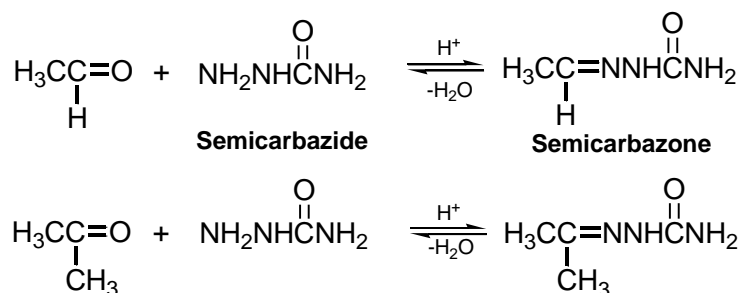
## (ii) Reaction with Hydrazine (formation of hydrazone):



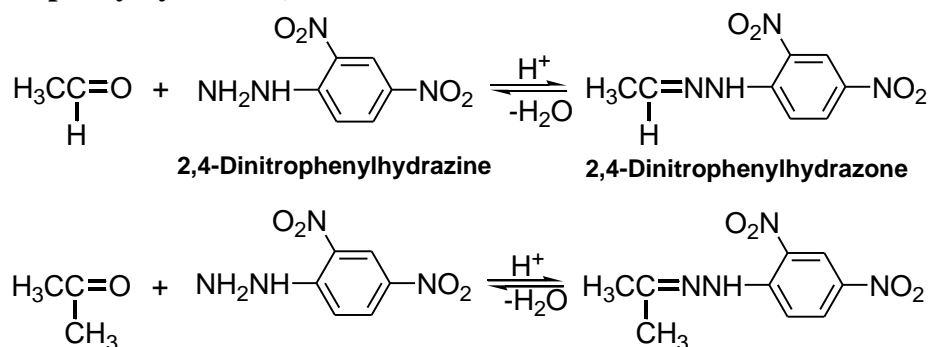
## (iii) Reaction with phenylhydrazine (formation of phenylhydrazone):



## (iv) Reaction with semicarbazide (formation of semicarbazone):



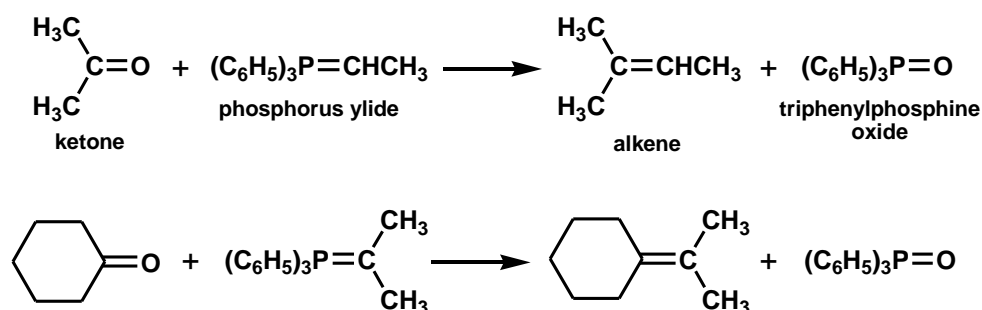
## (v) Reaction with 2,4-dinitrophenylhydrazine (formation of 2,4-dinitrophenylhydrazone):



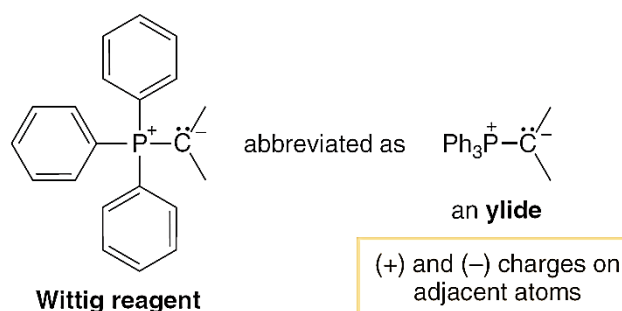
### 3.2.2. Wittig reaction:

In Wittig reaction, an aldehyde or ketone reacts with a phosphorus ylide to yield an alkene in which the oxygen atom of the carbonyl reactant is replaced by the  $=CR_2$  of the ylide. This is very useful reaction for the synthesis of alkenes as there is no ambiguity in the position of double bond, which is a great advantage over most other alkene syntheses. The reaction may be carried out in a number of different solvents such as tetrahydrofuran (THF) or dimethylsulfoxide (DMSO).

Different alkylhalides can be used to prepare phosphorus ylides, which on the reaction with carbonyl compounds result in the formation of various alkenes. Yields are generally highest with aldehydes that have the least hindered carbonyl group, and are lower with ketones in which the carbonyl group is more hindered.

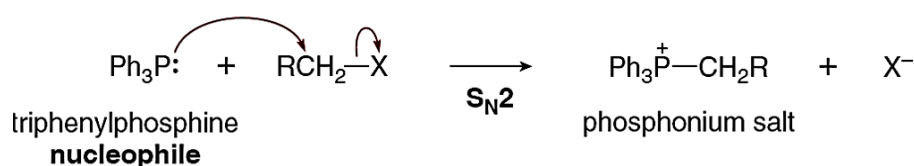


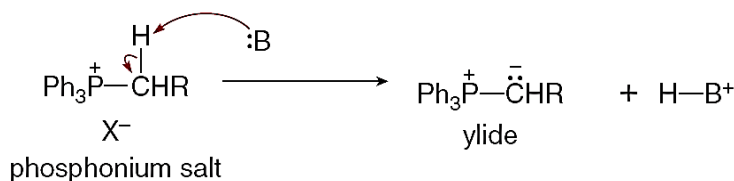
Ylide is a molecule with no net charge but with negative charge on carbon atom adjacent to a positively charged heteroatom. A typical Wittig reagent has a phosphorus atom bonded to three phenyl groups, plus another alkyl group that bears a negative charge and thus serves as nucleophilic centre. Phosphorus ylides are also called phosphoranes.



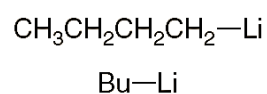
Wittig reagent is prepared by the nucleophilic attack ( $S_N2$ ) of triphenylphosphene ( $\text{Ph}_3\text{P}:$ ) on alkyl halide to form triphenylphosphonium salt followed by the removal of proton from the carbon atom bonded to phosphorus by using a strong base like alkoxides, sodium hydride, or butyl lithium ( $\text{BuLi}$ ).

#### Step 1:



**Step 2:**

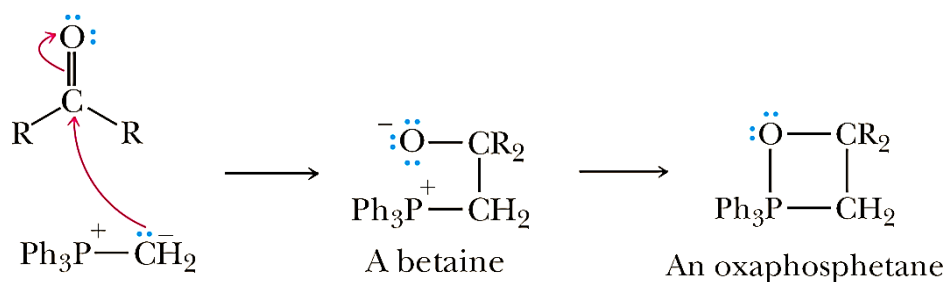
Typical strong base:



As the reaction undergoes by  $\text{S}_{\text{N}}2$  mechanism, yield is better in case of unhindered primary halides; yield is poor with secondary halides.

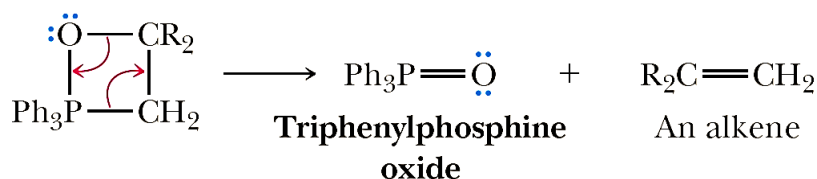
**Mechanism of Wittig reaction:**

**Step 1: Addition of ylide with carbonyl compounds.** Nucleophilic attack of negatively charged carbon of the ylide on the carbonyl carbon forms a dipolar intermediate called a **betaine**. As phosphorus and oxygen make a strong bond, the attraction of opposite charges in betaine promotes the fast formation of a four-membered **oxaphosphetane** ring (*oxa* = oxygen; *phosph* = phosphorus; *it* = four-membered ring; *ane* = carbon-carbon single bond).



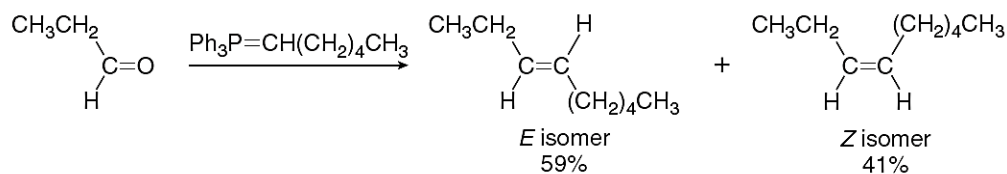
In some case, depending on the structure of the reactants and the experimental conditions, the oxaphosphetane ring may be formed directly by a cycloaddition, like Diels-Alder reaction, rather than via a betaine.

**Step 2: Decomposition of oxaphosphetane.** Oxaphosphetane decomposes to give triphenylphosphine oxide and an alkene. The driving force for a Wittig reaction is the formation of the very strong phosphorus-oxygen bond in triphenylphosphine oxide.



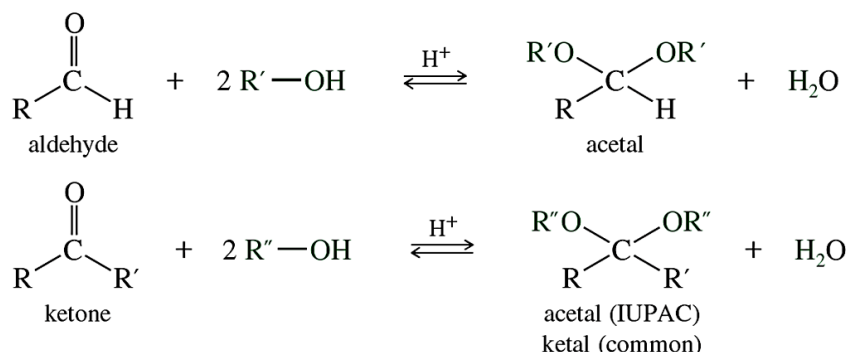
A number of primary, secondary, and allylic halides can be used to prepare phosphorus ylides, which on the reaction with a wide variety of carbonyl compounds result in the formation of various alkenes. Yields are generally highest with aldehydes that have the least hindered carbonyl group, and are lower with ketones in which the carbonyl group is more hindered.

Wittig reaction has one limitation that sometimes (not always) a mixture of stereoisomers (*E*- and *Z*-isomers) is formed. For example, reaction of propanal with Wittig reagent yields *E*- and *Z*- isomers.



### 3.2.3. Acetal formation:

As described earlier, the nucleophilic acyl addition of a molecule of alcohol to aldehydes and ketones produces hemiacetals and hemiketals, respectively. Addition of another molecule of alcohol to aldehydes and ketones with the elimination of water gives acetals and ketals, respectively. Acetals and ketals are comparatively more stable than hemiacetals and hemiketals, and can be isolated in good yield under the proper conditions.



#### Mechanism:

The formation of acetal can be divided in two parts:

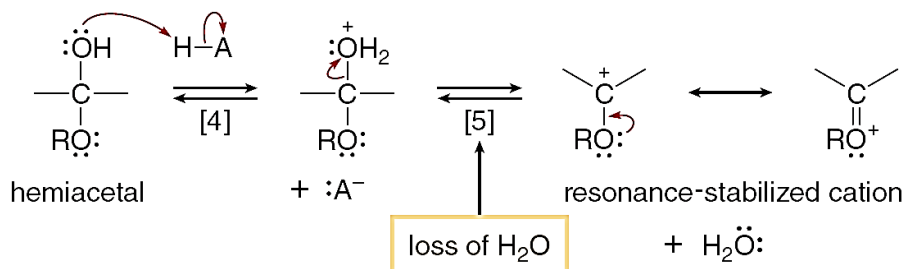
- (i) Addition of a molecule of alcohol to carbonyl compounds to give hemiacetals.
- (ii) Conversion of hemiacetals to acetals by  $\text{S}_{\text{N}}1$  substitution.

The formation of hemiacetals (Step 1-3) has already been described earlier. Now we will discuss only the second part.

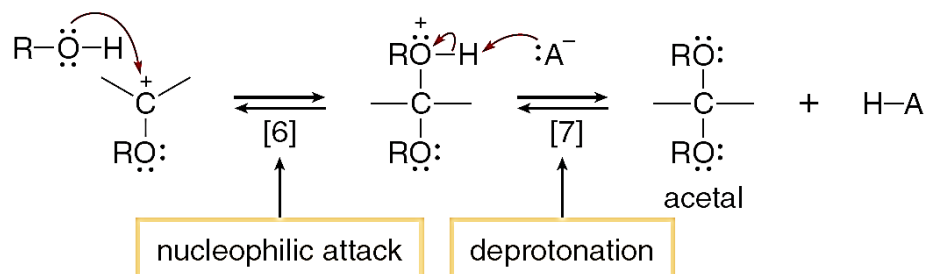
#### Conversion of hemiacetals to acetal:

The reaction is catalyzed by an acid and carried out in two stages – elimination of water from hemiacetal followed by nucleophilic substitution.

**Steps 4 and 5: Elimination of water.** The  $-\text{OH}$  group in the hemiacetal is protonated by the acid to make it a good leaving group ( $\text{H}_2\text{O}$ ). Loss of water generates a resonance-stabilized cation.



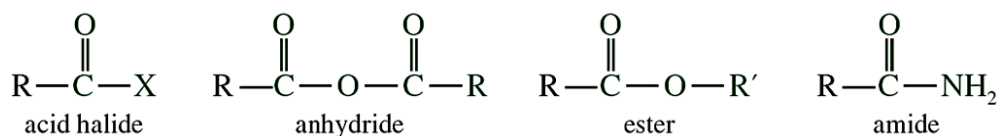
**Steps 6 and 7: Nucleophilic attack of alcohol and deprotonation.** The nucleophilic attack of second molecule of alcohol on electron-deficient carbon of resonance-stabilized cation followed by proton loss produces acetal with the regeneration of acid catalyst.



All the steps in acetal formation are reversible. The equilibrium may be shifted to the right by removing the water from the reaction mixture, while the reverse reaction i.e. hydrolysis of acetals is favored by treating the acetal with a large excess of aqueous acid to drive the equilibrium to the left. The acetal formation (as a protecting group) and its hydrolysis (after completing the desired reaction) are very useful in organic synthesis.

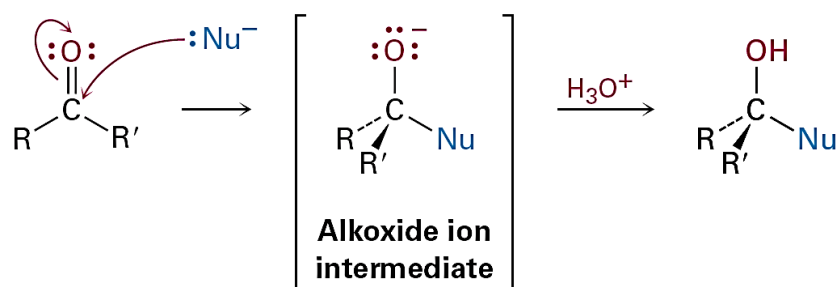
### Reactions of carboxylic acids and their derivatives

As discussed in the beginning that there are two types of carbonyl compounds. One in which the acyl group is attached with  $-H$ , alkyl or aryl group; these groups cannot be replaced by another nucleophile. These compounds undergo nucleophilic acyl substitution reactions. Aldehydes and ketones belong to this class. Another type of carbonyl compounds are where the acyl carbon is attached with electronegative atom (oxygen, halogens, nitrogen, sulphur) e.g. carboxylic acids, acid halides, amides, esters, anhydrides.

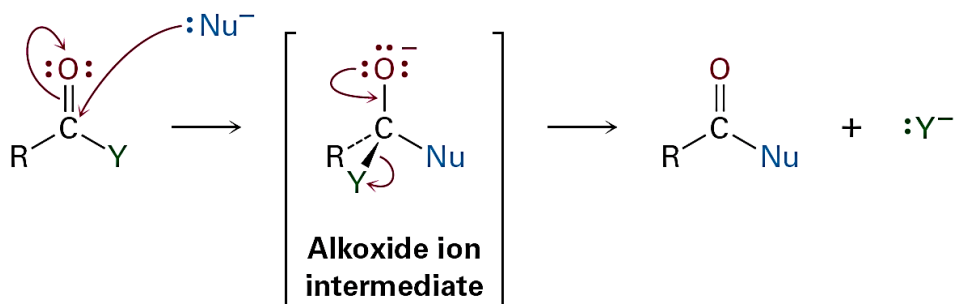


In these compounds the group attached with carbonyl carbon can easily be substituted by other nucleophile as they are good leaving groups or may be converted to good leaving groups by protonation. Therefore, these compounds undergo nucleophilic substitution reactions via addition-elimination mechanism.

#### **(a) Aldehyde or ketone: Nucleophilic addition**



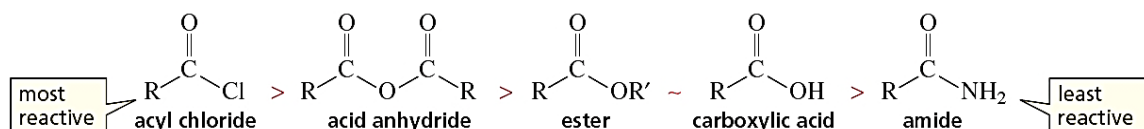
**(b) Carboxylic acid derivatives: Nucleophilic acyl substitution**



Till now we have discussed about the reactions of aldehydes and ketones. Now we will discuss about the reactions of carboxylic acid derivatives.

**Relative reactivities of carboxylic acid derivatives:**

Acid derivatives differ greatly in their reactivity toward nucleophilic acyl substitution. For example, acetyl chloride reacts with water in a violently exothermic reaction, while acetamide is stable in boiling water. Acetamide is hydrolyzed only by boiling it in strong acid or base for several hours. The order of reactivity of acid derivatives can be summarized as follows:

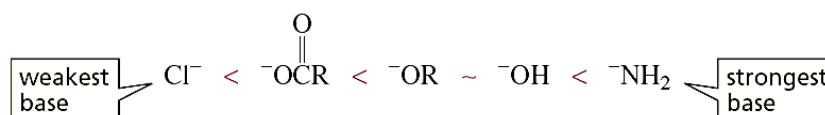


Acid halides (or acyl halides) are most reactive while amides are least reactive for nucleophilic substitution reactions. Based on this order of reactivity, more reactive acyl compounds (acid chlorides and anhydrides) can be converted to less reactive ones (carboxylic acids, esters, and amides). The reverse is not possible by direct reaction.

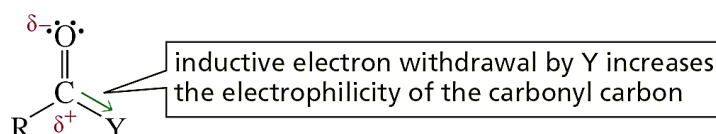
Factors affecting the reactivity of these groups:

- (i) **Leaving group:** *The weaker the base, the better it is as a leaving group.* Because a weak base does not share its electrons as well as a strong base does, a weaker base forms a weaker bond and therefore, can easily be broken. Thus, the most electronegative group is weakest base. A compound having better leaving group will be more reactive. In other words, a compound having most electronegative group attached to carbonyl carbon will be most reactive for nucleophilic substitution.

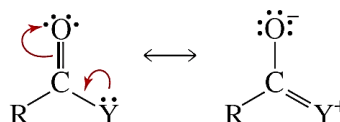




- (ii) **Inductive effect:** The electronegative group attached to the carbonyl carbon withdraws electrons and thus make the carbonyl carbon more electrophilic to be attacked by a nucleophile easily. Hence, more electronegative group attached to the acyl group, more reactive the compound is for nucleophilic reactions.

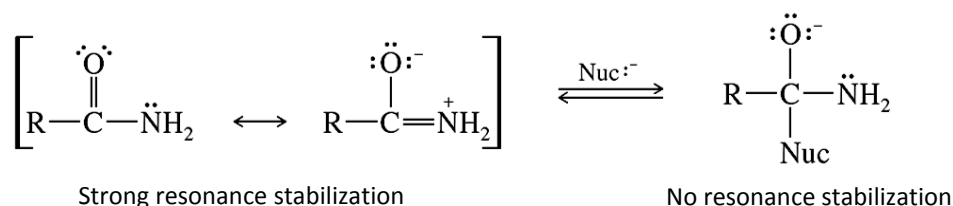


- (iii) **Resonance stabilization:** A compound that is stabilized more by resonance structures is less reactive and the compound that is less stabilized is more reactive.



resonance contributors of a carboxylic acid or carboxylic acid derivative

The resonating structure having positive charge on most electronegative atom contributes least to the resonance stabilization. Therefore, the positive charge on chlorine atom in acid chloride is least contributing to the resonance stabilization than the positive charge on relatively less electronegative oxygen in carboxylic acids, acid anhydride and esters, and further less electronegative nitrogen in amides. Therefore, amides are resonance-stabilized more than other acid derivatives and the stabilization is lost after nucleophilic attack. Hence, acid amides are least reactive and halides are most reactive.

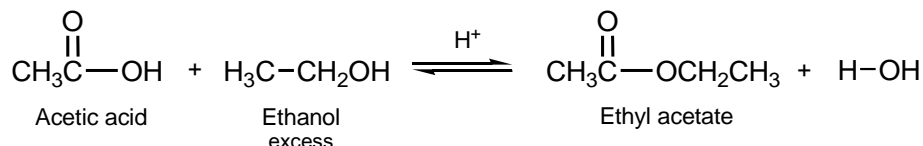


The acid halides and acid anhydride are so reactive that no catalyst is required to convert them to other acid derivatives. However, in case of esters and amides, acid or base catalyst is required to facilitate the reaction. Acid halides and acid anhydrides are so reactive that they not found in nature; they react with water so rapidly that they can't exist for long in living organism while esters and amides are quite common in nature.

### 3.2.4. Esterification and ester hydrolysis

#### Esterification

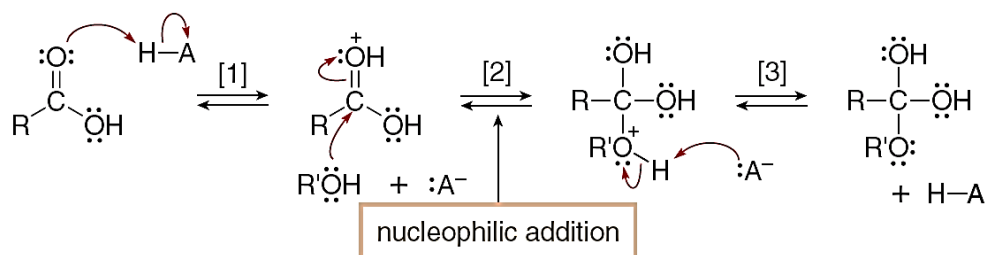
Nucleophilic acyl substitution reaction of carboxylic acids with alcohols in acidic medium results in the formation of esters. The process is called **Fischer esterification reaction**. During the reaction water is eliminated, in which  $\text{-OH}$  comes from the carboxylic acid and  $\text{-H}$  comes from the alcohol. The reaction is reversible, so excess alcohol is used to drive the reaction towards products side.



### Mechanism:

Esterification is another example of addition-elimination reaction. The mechanism is analogous to acetal formation can be divided in two parts. First part is the addition of nucleophile (i.e. alcohol) to the carboxylic acid to form tetrahedral molecule of ester hydrate. Second part is elimination of leaving group (i.e. water) from ester hydrate to produce ester.

#### Part 1: Addition of nucleophile $\text{R}'\text{OH}$ .

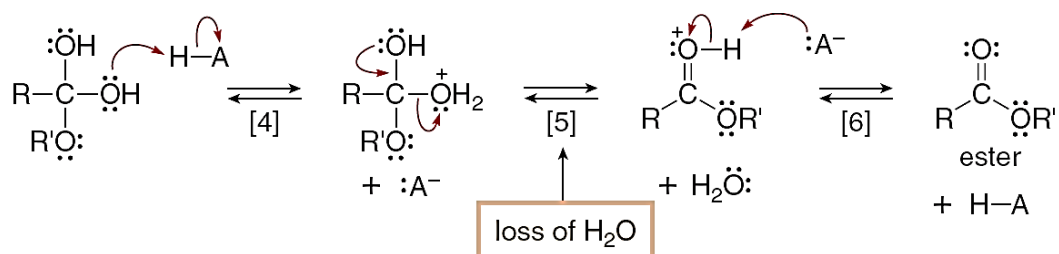


**Step 1 : Protonation of carboxylic acid.** As ethanol is weak nucleophile, the reaction is carried out in presence of acid. The acid catalyst protonates the carbonyl oxygen of carboxylic acid, which enhances the electrophilicity of carbonyl carbon.

**Step 2: Nucleophilic attack of alcohol on carbonyl carbon.** Nucleophilic addition of alcohol ( $\text{R}'\text{OH}$ ) forms tetrahedral intermediate.

**Step 3: Deprotonation.** A loss of proton from the tetrahedral intermediate generates a neutral addition product (ester hydrate) like hemiacetal.

#### Part 2: Elimination of leaving group (water).



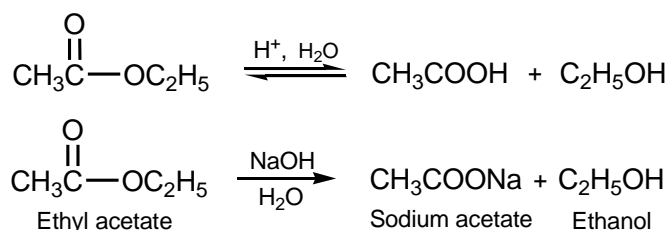
**Step 4: Protonation of  $\text{-OH}$  group.** The protonation of an  $\text{-OH}$  group in ester hydrate forms a good leaving group.

**Step 5: Elimination of leaving group.** A molecule of water is eliminated and protonated ester is formed.

**Step 6: Loss of proton.** A loss of proton makes the final product i.e. ester.

## Ester Hydrolysis

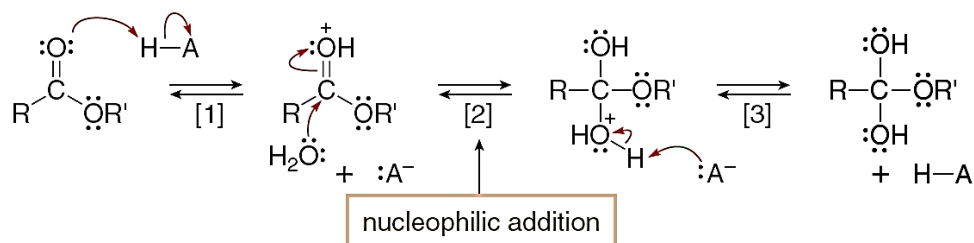
The reverse reaction of esterification is hydrolysis is driven towards the product side by using a large excess of water. Esters are hydrolyzed very slowly at neutral pH, even when heated to reflux. Hydrolysis may be carried out either in acidic or alkaline medium unlike esterification which is catalyzed only by acids, not by base. Acid-catalysed hydrolysis is reversible, while base-catalyzed hydrolysis is irreversible reaction.



### Mechanism of acid-catalyzed hydrolysis:

The acid-catalyzed hydrolysis is just reverse of Fischer esterification. Esterification was started with addition of water and completed with elimination of water. Ester hydrolysis starts with addition of water and finishes with elimination of alcohol.

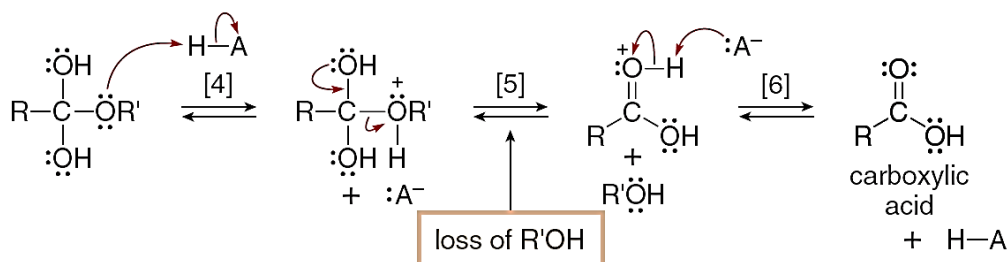
**Step 1: Protonation.** Let us start from the last step of esterification that is loss of proton to make ester. Here, in hydrolysis, this will be the first step i.e. carbonyl oxygen will be protonated which makes the carbonyl carbon more electrophilic.



**Step 2: Nucleophilic addition of water.** Step 5 in esterification was removal of water, so in hydrolysis it is addition of water.

**Step 3: Loss of proton.** Step 4 in esterification was protonation of -OH group to make it better leaving group. Here, in hydrolysis, it is removal of proton to make a neutral tetrahedral molecule i.e. hydrate of ester.

**Step 4: Protonation of -OR group.** The -OR group of ester is protonated to make it a better leaving group that is reverse of step 3 in esterification.



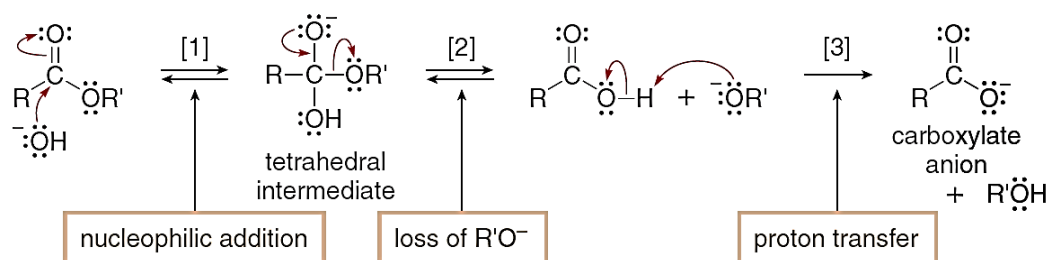
**Step 5: Removal of leaving group (ROH).** The removal of leaving group (i.e. alcohol, ROH) produces protonated carboxylic acid.

**Step 6: Removal of proton.** Removal of proton forms carboxylic acid.

### Mechanism of base-catalyzed ester hydrolysis

Hydrolysis of ester in alkaline medium is called **saponification**. Base-catalyzed ester hydrolysis is simple three step process. First two steps are reversible while the last step is irreversible.

**Step 1: Attack of nucleophile.**  $\text{OH}^-$  being a strong nucleophile attacks on carbonyl carbon and forms tetrahedral intermediate.



**Step 2: Removal of leaving group  $\text{OR}$ .** Elimination of leaving group i.e  $\text{OR}$  produces carboxylic acid and alkoxide ion.

**Step 3: Exchange of proton.** Alkoxide ion ( $\text{OR}$ ) is a strong base. Abstract of a proton from carboxylic acid by alkoxide ion produces resonance stabilized carboxylate ion and alcohol. Once carboxylate ion is formed, it can be protonated with strong acid to form neutral carboxylic acid.

There are two major differences between hydrolysis of esters in aqueous acid and aqueous base.

- In case of ester hydrolysis in aqueous acid, only catalytic amount of acid is required. While for hydrolysis in aqueous base, base is required in stoichiometric amounts because it is a reactant, not a catalyst.
- Hydrolysis of an ester in aqueous acid is reversible, but hydrolysis in aqueous base is irreversible because a carboxylate anion being negatively charged cannot react with a nucleophile ( $\text{ROH}$ ).

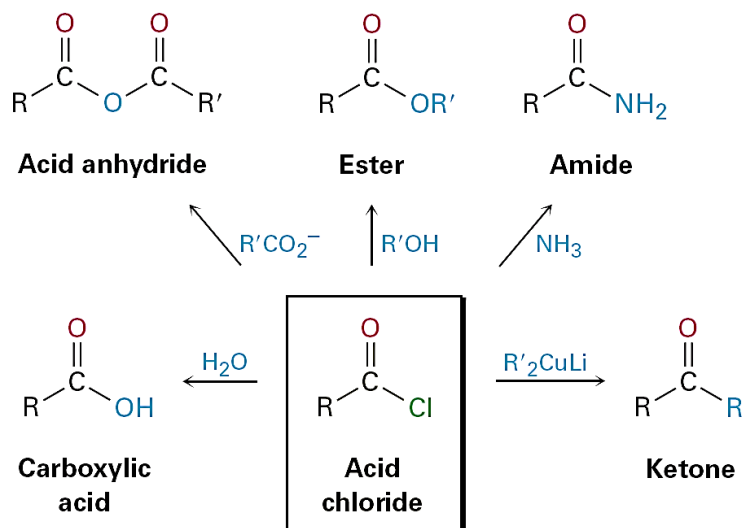
### 3.2.5. Reactions of acid chlorides

Acid chlorides are most reactive among all acid derivatives because of highly electronegative chlorine atom attached to carbonyl carbon, which enhances the electrophilic character of carbonyl carbon and thus can readily be attacked by a nucleophile. Chloride ion being a good leaving group further increases the rate of nucleophilic reaction.

The reaction of acid chloride with water, carboxylic acid, alcohol, and ammonia or amines results in the replacement of  $\text{Cl}$  group of acid chloride by  $\text{OH}$ ,  $\text{OCOR}$ ,  $\text{OR}$ ,

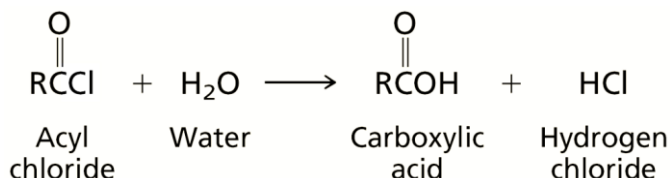
or  $-\text{NH}_2$  (or  $-\text{NHR}$ , or  $-\text{NR}_2$ ) to yield carboxylic acid, acid anhydride, ester, and amides respectively.

Acid chlorides are very reactive and they do not require acid or base as catalyst, however, a weak base like pyridine is added to remove  $\text{HCl}$  when it is formed in the reactions as by-product.

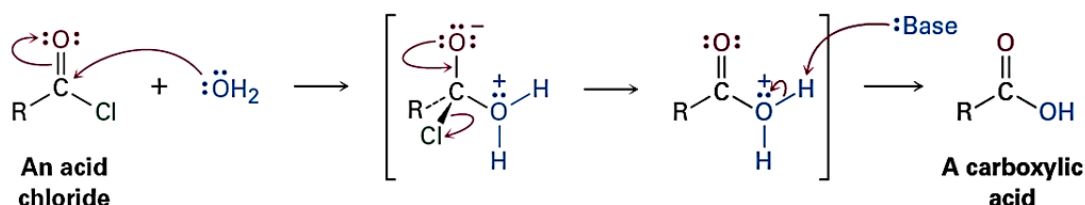


### Reaction with water (formation of carboxylic acids):

The reaction of acid chlorides with water, that is called hydrolysis, forms carboxylic acids along with  $\text{HCl}$  as a by-product. A base such as pyridine is added in the reaction mixture to remove  $\text{HCl}$  to avoid side reactions.

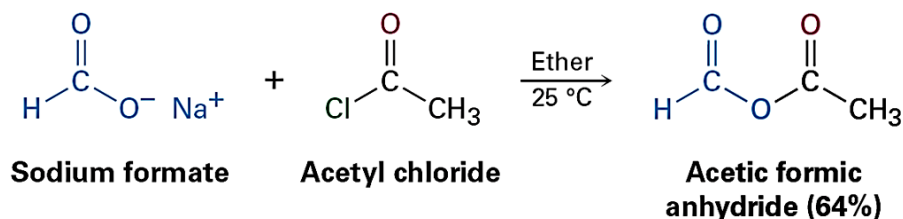


**Mechanism:** This is typical addition-elimination reaction which starts with the nucleophilic attack of water on the carbonyl carbon to produce tetrahedral intermediate. Removal of  $\text{Cl}^-$  as leaving group followed by loss of a proton from tetrahedral intermediate gives the final product, carboxylic acid.

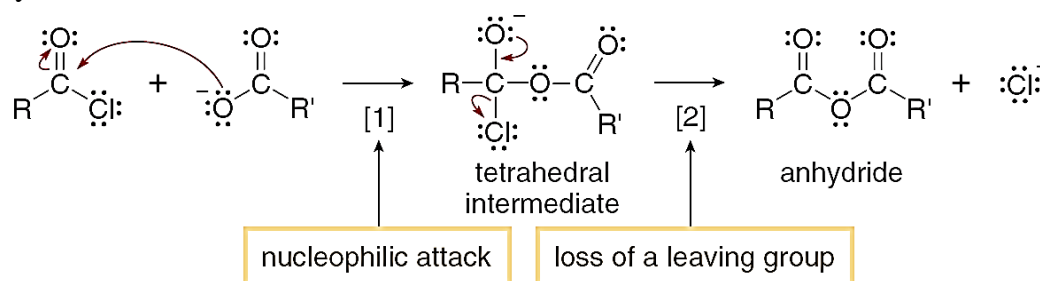


### Reaction with carboxylic acids (formation of anhydrides):

Acid chlorides react with carboxylic acids (or its salts) and produce anhydrides. The reaction can be used for the preparation of both symmetrical and asymmetrical anhydrides.

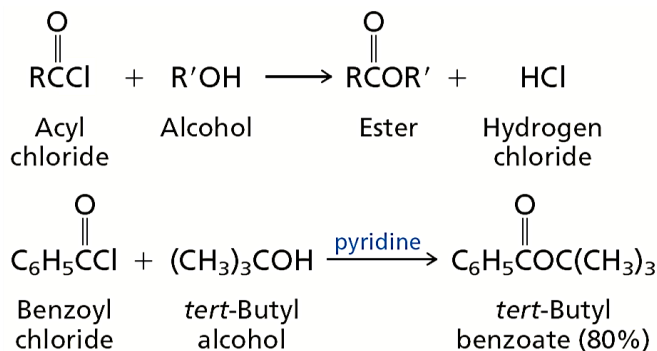


The mechanism of the reaction is same as mentioned above in hydrolysis. The oxygen atom of the acid attacks the strongly electrophilic carbonyl group of the acid chloride to form a tetrahedral intermediate. Loss of chloride ion (leaving group) gives the anhydride.



#### Reaction with alcohol (formation of esters):

Acid chlorides react rapidly with alcohols to form esters. The reaction is highly exothermic. Acid chlorides are powerful dehydrating agents; therefore, the temperature of the reaction should be kept low to avoid dehydration of the alcohol.



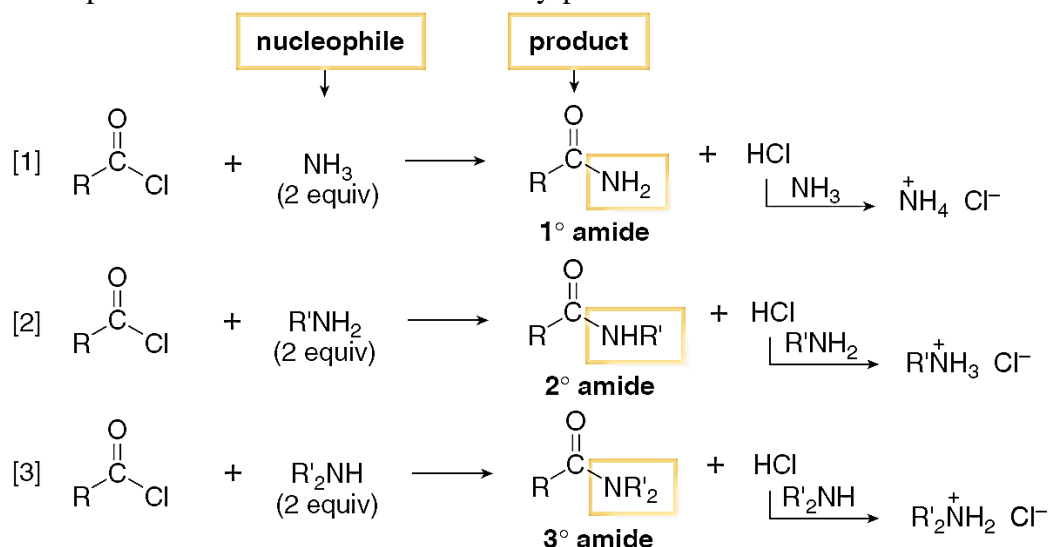
Bulky groups on either of the reactants retard the reaction rate because of steric hindrance. The order of reactivity among alcohols is

Primary > secondary > tertiary

Mechanism of the reaction is same as in hydration. Alcohol attacks the carbonyl carbon to produce tetrahedral intermediate, which on elimination of leaving group (chloride group) followed by loss of a proton gives final product – ester.

#### Reaction with ammonia and amines (formation of amides):

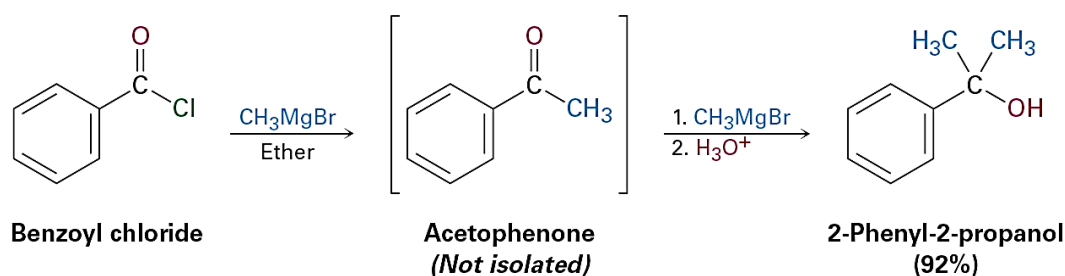
Acid halides react readily with ammonia and 1° and 2° amines to form 1°, 2°, and 3° amides, respectively. The reaction utilizes two equivalents of  $\text{NH}_3$  or amine – one acts as nucleophile while other reacts with HCl by-product to form an ammonium salt.



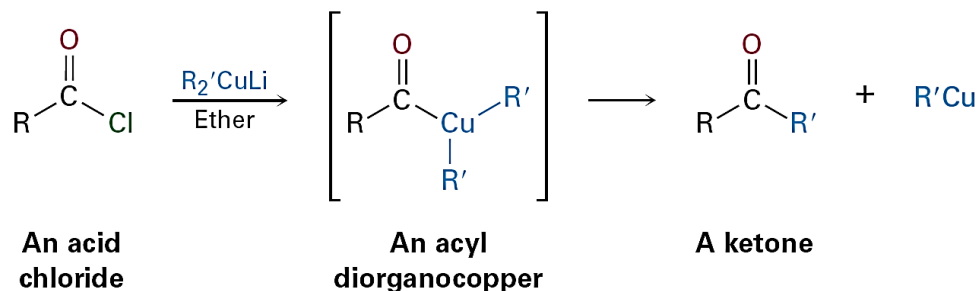
The reaction follows the same addition-elimination mechanism with the nucleophilic attack of ammonia or amines to carbonyl group followed by elimination of leaving group and a proton to produce final product – amides. As amines are quite basic, they react with HCl by-product to form ammonium salts.

#### Reaction with Grignard reagent (formation of alcohol):

Grignard reagent ( $\text{RMgX}$ ) attacks the carbonyl group of acid chlorides to make the corresponding ketones. However, these ketone products are further attacked by Grignard reagent to give alkoxides, which are converted to tertiary alcohols on protonation.



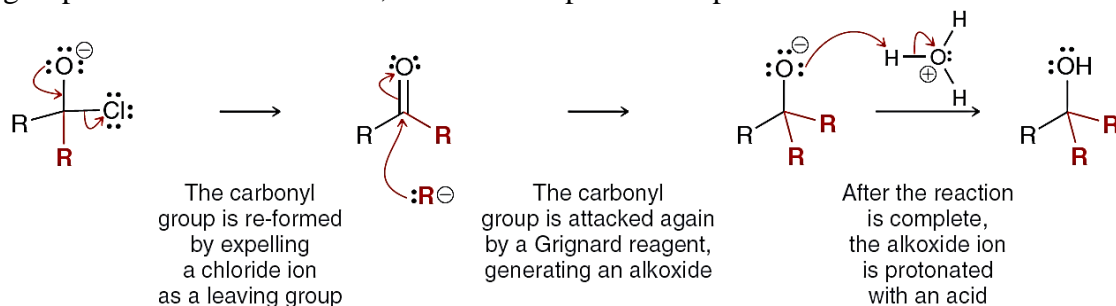
The reaction can be restricted up to the formation of ketone by using selective reagent like lithium dialkyl cuprate,  $\text{R}_2\text{CuLi}$  (**Gilman reagent**).  $\text{R}_2\text{CuLi}$  reagent (Gilman reagent) reacts only with reactive acid chlorides; they do not react with aldehyde, ketones, esters, amides, or acid anhydrides.



The reaction is carried out at  $-78^\circ\text{C}$  in ether solution and the yield is often excellent.

#### Mechanism:

The mechanism involves the nucleophilic attack of Grignard reagent at carbonyl carbon of acid chloride, which is followed by a loss of leaving group ( $\text{Cl}^-$ ) to reform the carbonyl function. These two steps produce a ketone, which is attacked by another molecule of Grignard reagent to give alkoxide ion. The alkoxide ion does not have any group to eliminate. Therefore, addition of a proton completes the reaction.



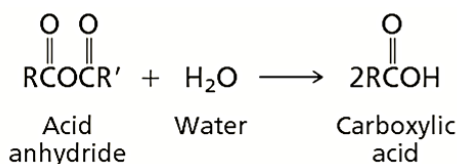
Esters react with Grignard reagent in the same way; the only difference is that the leaving group is alkoxide in case of ester. Formate esters give secondary alcohols and other esters yield tertiary alcohols.

### 3.2.6. Reactions of acid anhydrides

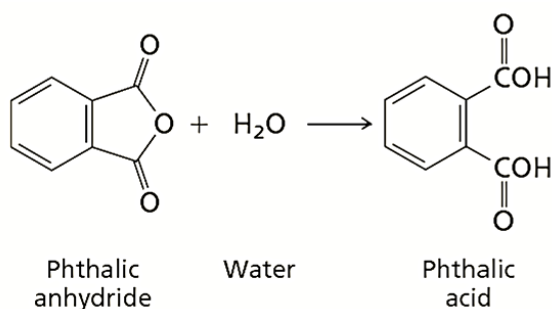
Acid anhydrides are comparatively weaker than acid chlorides; they can be readily converted to carboxylic acids, esters, and amides but not to acyl chlorides. The reaction mechanisms for all reactions are same as described earlier in case of hydration of acid chloride. Acid anhydride contains two carbonyl groups – one serves as electrophilic centre and other becomes part of leaving group.

#### Reaction with water (formation of carboxylic acids):

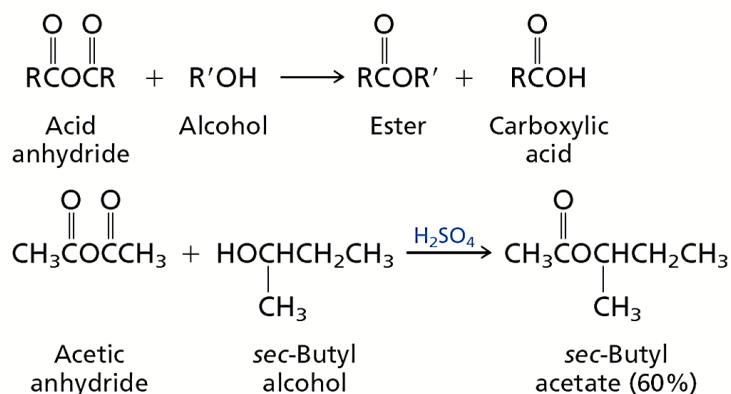
Hydrolysis of acid anhydride with water generates two molecules of carboxylic acids. Cyclic anhydrides are converted to dicarboxylic acids on hydrolysis. The reaction undergoes without any acid or base as a catalyst like in case of acid chlorides.



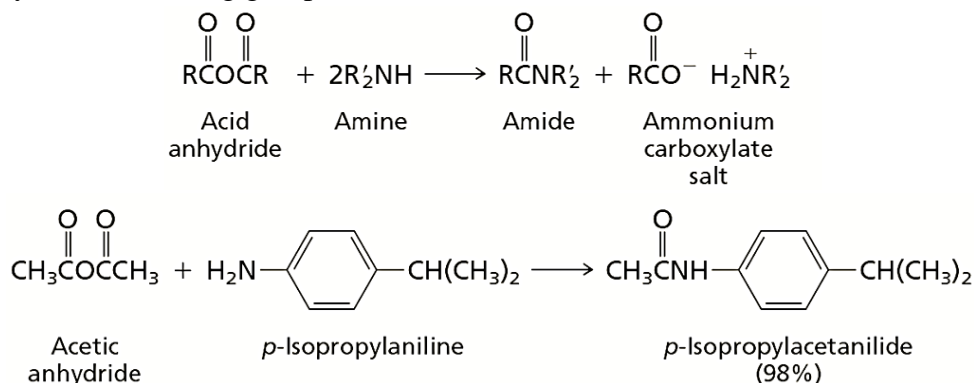



**Reaction with alcohol (formation of esters):**

An acid anhydride reacts with alcohol to form an ester. One of the carbonyl group becomes part of the ester and other is expelled as leaving group which is converted to acid on abstraction of a proton during reaction. Thus a molecule of carboxylic acid (or a carboxylate salt) is always formed as a by-product.


**Reaction with ammonia and amines (formation of amides):**

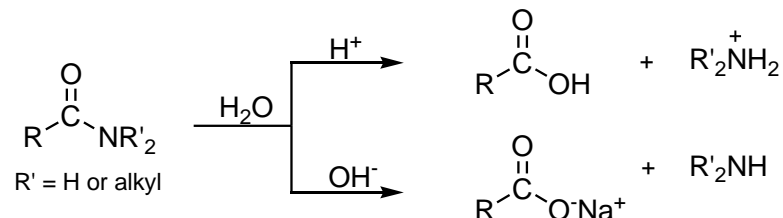
Acid anhydride reacts quickly with ammonia, primary and secondary amines to give primary, secondary and tertiary amides respectively. As in case of acid chlorides, two equivalents of ammonia or amines are required – one becomes the part of amides and other reacts with the proton produced in the reaction and forms salt with the carboxylate ion (leaving group).


**Reaction with Grignard Reagent (formation of alcohol):**

Acid anhydride reacts with Grignard reagent and produce tertiary alcohol analogous to the reaction of acid chloride. The only difference is the identity of leaving group i.e. carboxylate ion here.

### 3.2.7. Reactions of amides

As Amides have the poorest leaving group of all the carboxylic acid derivatives, they are least reactive acid derivatives. They react with water and alcohol only on heating in presence of strong acids or bases and produce carboxylic acids and amine.

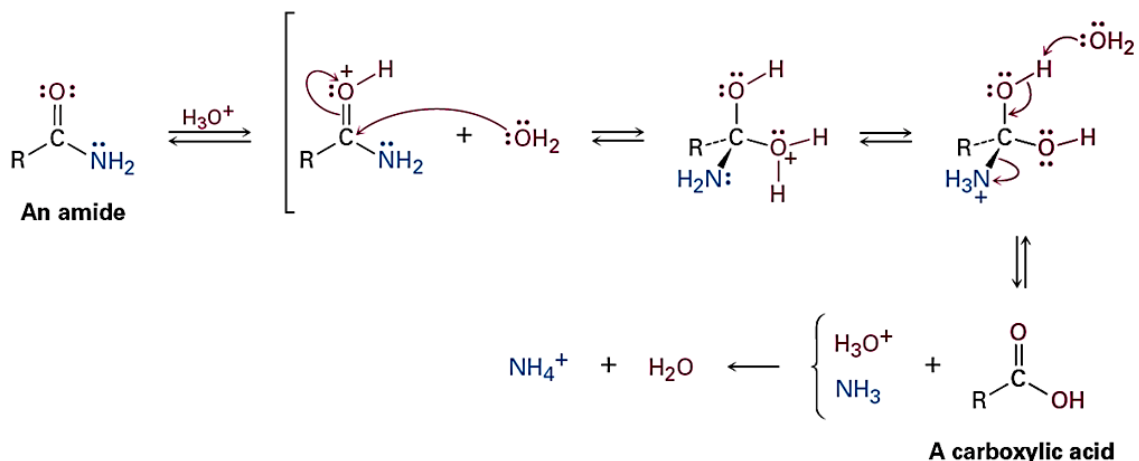


In acidic conditions, the amine by-product is protonated as an ammonium ion, while in base, carboxylic acid is deprotonated and forms a salt. In both cases, the reaction is irreversible.

#### Mechanism:

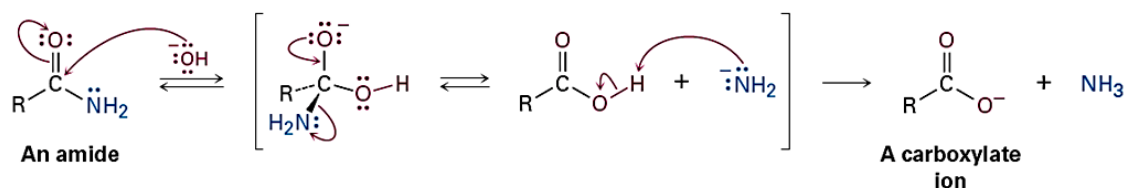
##### (i) Acid-catalyzed:

The mechanism of amide hydrolysis in acid is exactly the same as the mechanism of ester hydrolysis in acid except that the leaving group is different.



##### (ii) Base catalyzed:

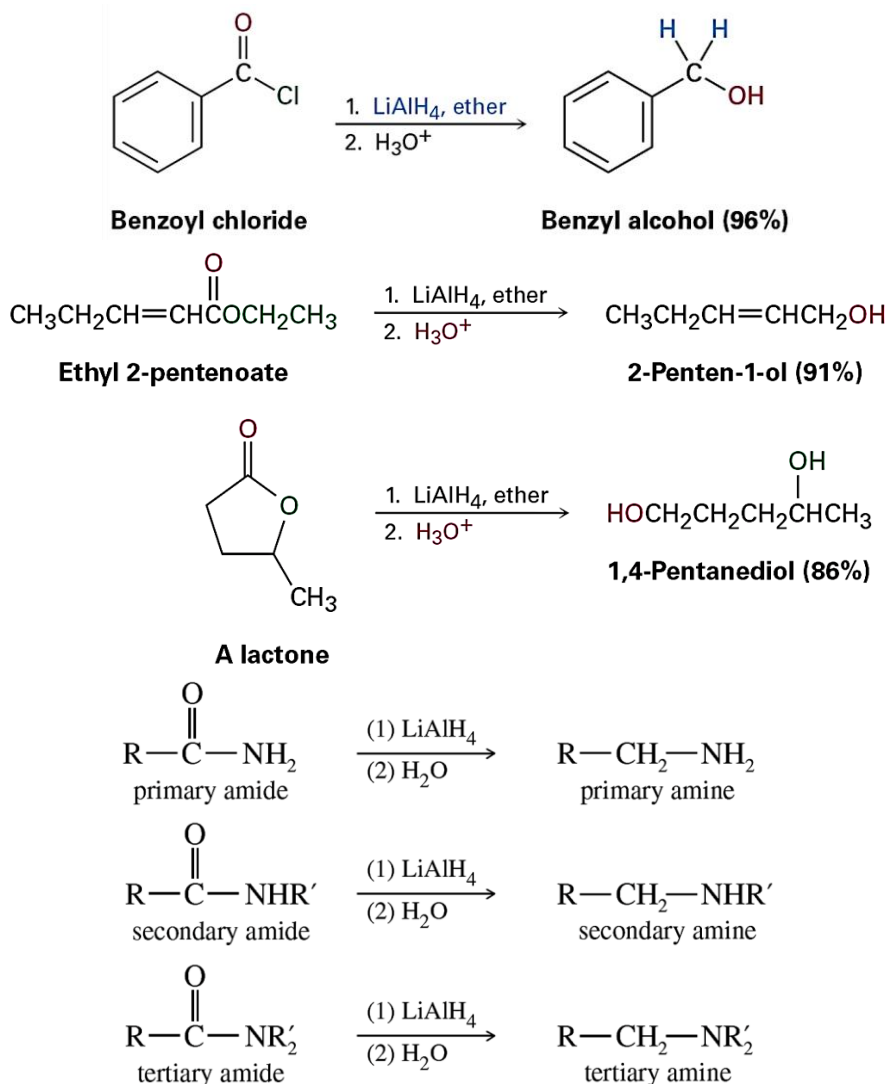
The hydrolysis of amides in presence of a base is initiated by nucleophilic attack of  $\text{OH}^-$  on the carbonyl carbon followed by elimination of leaving group ( $\text{NH}_2$ ), which resulted in the formation of carboxylic acid and amide ion. These steps are reversible. The equilibrium is shifted towards product side by the exchange of proton from carboxylic acid to amide ion to make carboxylate ion.



### 3.2.8. Reductions of acid derivative

Acid chlorides are very reactive; therefore they can be reduced to primary alcohols either by catalytic hydrogenation,  $\text{NaBH}_4$  or  $\text{LiAlH}_4$ . Other acid derivatives being less

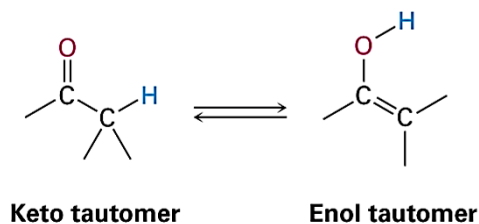
reactive can only be reduced by  $\text{LiAlH}_4$ , a strong reducing agent; acid anhydride, carboxylic acids and esters give primary alcohols, while amides produce amines.



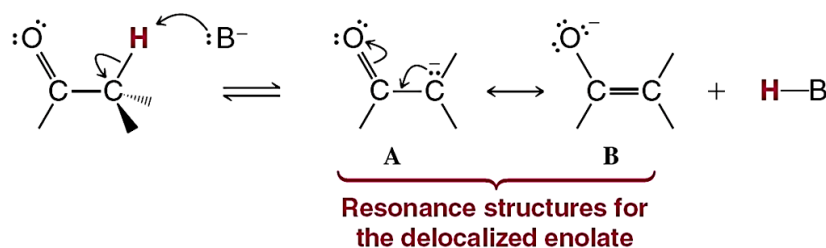
These reactions and their mechanisms will be discussed in detail in Unit 4.

### 3.3. Enolization-Ketonization reactions

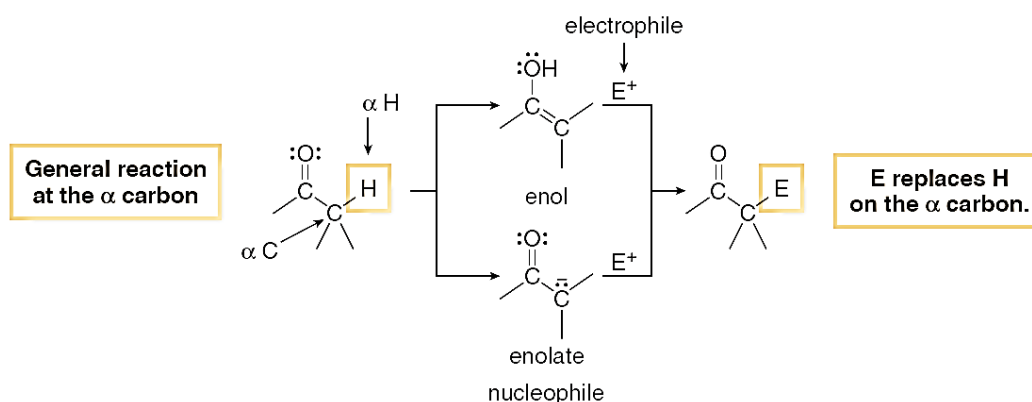
The reactions discussed so far involve carbonyl group ( $>\text{C}=\text{O}$ ) as the reactive centre. Carbon (s) adjacent to  $>\text{C}=\text{O}$  group, known as  $\alpha$ -carbon and hydrogens attached to  $\alpha$ -carbons known as  $\alpha$ -hydrogens, also participate in some significant reactions. The aldehydes and ketones containing atleast one  $\alpha$ -hydrogen exhibit keto-enol tautomerism; therefore the reaction involving  $\alpha$ -hydrogen in aldehydes and ketones are called enolization-ketonization reactions.



Due to electron-withdrawing nature of  $>\text{C}=\text{O}$  group,  $\alpha$ -hydrogen in aldehydes and ketones is acidic in nature and can easily be abstracted by a strong base resulting in the formation of resonance-stabilized enolate ion.



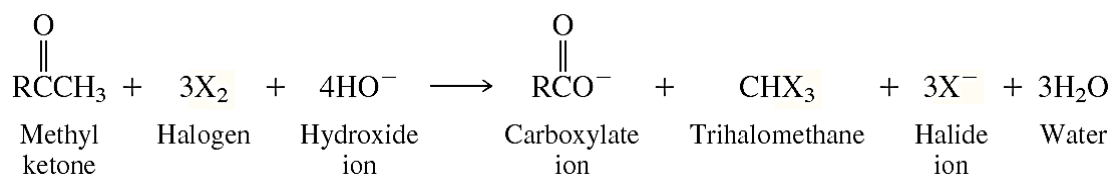
Addition of a proton to structure 'A' above gives keto form while addition of proton to structure 'B' gives enol form. Because of the formation of carbanion ion at  $\alpha$ -position, substitution by an electrophile takes place at  $\alpha$ -position.



Formation of enol is catalyzed either by acid or base while the formation of enolate is catalyzed by strong base. Enolates are more useful than enols because (i) enolates possess a full negative charge and are therefore more reactive than enols and (ii) enolates can be isolated and stored for short periods of time, unlike enols, which cannot be isolated or stored. Therefore, more of the reactions, we will discuss here, will be with enolates.

### 3.3.1. Haloform Reaction of Methyl Ketones

Aldehyde (only acetaldehyde) and ketones containing methyl group attached to carbonyl group ( $\text{CH}_3\text{CO}-$ ) react with a halogen in presence of alkali; the reaction with excess halogen and excess base ended with multiple halogenations at  $\alpha$ -carbon to form haloform ( $\text{CHX}_3$ ) and sodium salt of carboxylic acid. Thus chlorine, bromine, and iodine produce chloroform ( $\text{CHCl}_3$ ), bromoform ( $\text{CHBr}_3$ ), and iodoform ( $\text{CHI}_3$ ), respectively. Iodoform is yellow crystalline solid with sharp melting point; therefore, the reaction is used for qualitative test for detection of  $\text{CH}_3\text{CO}-$  group in organic compounds. Bromoform and chloroform are liquids.

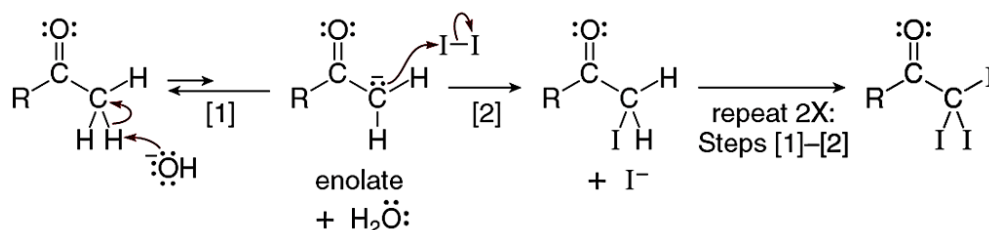


**Mechanism:**

The mechanism of haloform (for example iodoform) reaction can be divided into two parts.

**Part 1: Conversion of  $-\text{CH}_3$  to  $-\text{CI}_3$** 

**Step 1: Abstraction of  $\alpha$ -hydrogen by base (formation of carbanion).**  $\alpha$ -hydrogens of carbonyl compounds are acidic in nature because of electronegative behavior of carbonyl group; therefore, it can easily be abstracted by a base.

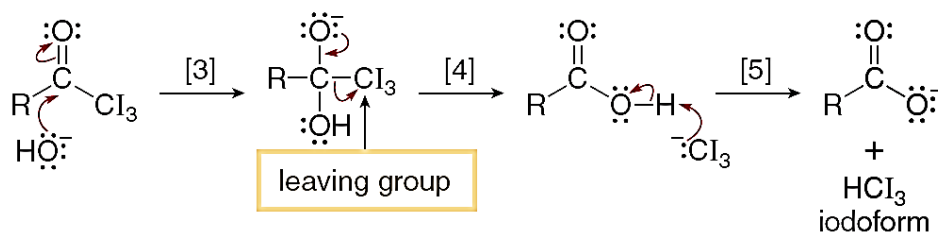


**Step 2: Reaction of carbanion with iodine (formation of  $\alpha$ -iodocarbonyl compound).** Carbanion reacts with iodine to form a substituted product in which a hydrogen atom is replaced by iodine.

**Repetition of Step 1 and 2: Formation of triiodocarbonyl compound.** The introduction of iodine (an electronegative species) at  $\alpha$ -carbon further increases the acidic character of  $\alpha$ -hydrogens and their abstraction by base occurs more readily. Therefore, the reaction does not stop after monosubstitution, rather it goes on till all the three hydrogens are replaced by iodine and triiodocarbonyl compound is formed.

**Part 2: Cleavage of carbon-carbon bond (Formation of iodoform)**

**Step 3: Nucleophilic attack of  $^-\text{OH}$  on carbonyl carbon.**  $^-\text{OH}$  attacks the carbonyl group as in typical nucleophilic addition reactions to form tetrahedral intermediate ion.



**Step 4: Elimination of leaving group (cleavage of carbon-carbon bond).**  $^-\text{CI}_3$  (with three electro-withdrawing groups) serves as a good leaving group and is eliminated with the cleavage of carbon-carbon bond to form carboxylic acid and  $^-\text{CI}_3$ .

**Step 5: Proton exchange (formation of iodoform).** Proton transfer from carboxylic acid to  $^-\text{CI}_3$  results in the formation of iodoform ( $\text{CHI}_3$ ) and resonance stabilized carboxylate ion which makes salt with the base.

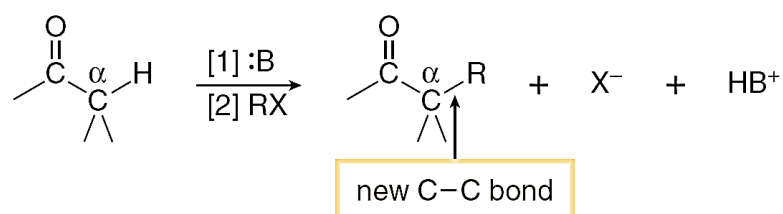
**Note:** The iodoform reaction undergoes with following compounds:

- (i) Ethanol – the only primary alcohol that gives iodoform reaction.

- (ii) All secondary alcohols with  $\text{CH}_3\text{CH}(\text{OH})$ - group. This group is first oxidized by sodium hypiodite,  $\text{NaOI}$  (from  $\text{I}_2 + \text{NaOH}$ ) to ketone and then undergoes iodoform reaction.
- (iii) Acetaldehyde – the only aldehyde that has  $\text{CH}_3\text{CO}$ - group.
- (iv) All aliphatic and aromatic methyl ketones with  $\text{CH}_3\text{CO}$ - group.

### 3.3.2. Alkylations at the $\alpha$ -Carbon

Carbonyl compounds react with alkyl halide in presence of strong base (like LDA) through enolate formation. Abstraction of hydrogen from the  $\alpha$ -position of carbonyl compounds generates enolates which as a nucleophile reacts with the electrophilic carbon of alkyl halides in an  $\text{S}_{\text{N}}2$  reaction displacing the leaving group by the backside attack; it results in the alkylation at  $\alpha$ -carbon of carbonyl compounds. The reaction is useful as a new C–C bond is formed.



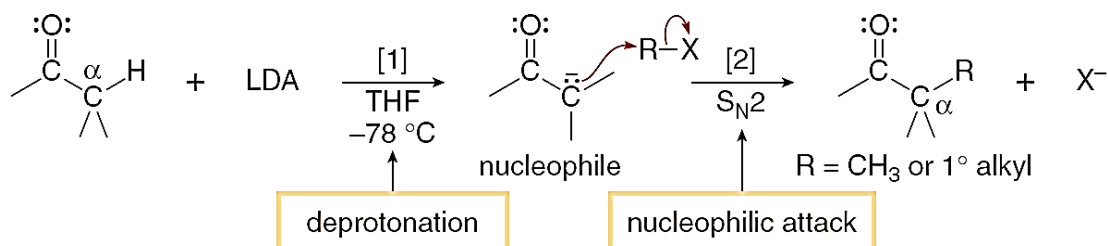
As the reaction follows  $\text{S}_{\text{N}}2$  mechanism, it undergoes successfully with unhindered halides like primary alkyl, primary benzylic or primary allylic halides. Hindered alkyl halides and those with halogens bonded to  $sp^2$  hybridized carbons do not undergo substitution. Ketones and ester can be alkylated by this method, however, aldehydes give poor yield because aldol condensation competes with alkylation.

Typical bases such as sodium hydroxide or an alkoxide ion cannot be used to form enolates for alkylation because these strongly nucleophilic bases compete with enolates and give side reactions with alkyl halide. Lithium diisopropylamide (LDA) avoids these side reactions because LDA being very bulky base is a poor nucleophile, so it generally does not react with the alkyl halide.

#### Mechanism:

The alkylation reaction undergoes through two step process:

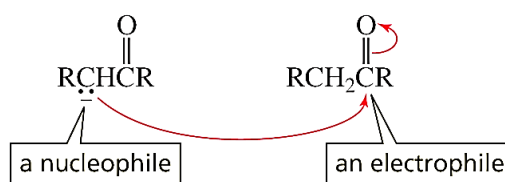
**Step 1: Deprotonation at  $\alpha$ -carbon (formation of enolate).** A strong non-nucleophilic base like LDA abstracts a proton from  $\alpha$ -carbon of carbonyl compound to generate an enolate. Low temperature ( $-78^\circ\text{C}$ ) is used for the reaction.



**Step 2: Nucleophilic attack on alkyl halide (formation of alkylated product).** The nucleophilic enolate attacks from the backside of the alkyl halide, displacing the halide (a good leaving group) and producing the alkylate product by an  $S_N2$  reaction.

### 3.3.3. Aldol and Related Condensation reactions

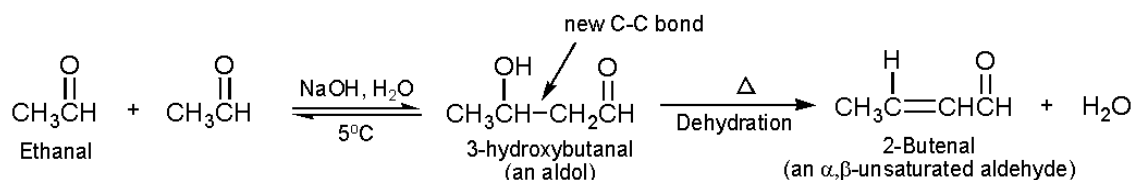
As we have seen so far that carbonyl group behaves as an electrophile in presence of an electron rich reagent, however, in  $\alpha$ -substitution reactions, carbonyl compounds behaves as a nucleophile when it is converted to an enolate ion. In carbonyl condensation reaction, carbonyl compounds behave both as an electrophile and as a nucleophile – one molecule behaves as an electrophile while other serves as a nucleophile.



Depending on the starting material four types of addition or condensation reactions are observed with enolates.

#### Aldol condensation:

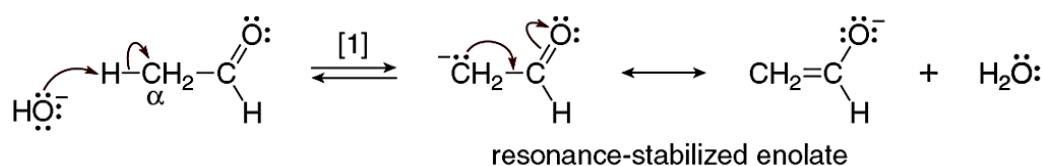
Two molecules of aldehydes containing  $\alpha$ -hydrogen undergo addition reaction in the presence of a base to form  $\beta$ -hydroxy aldehydes, known as aldol (*ald* = aldehydes, *ol* = alcohol) and the reaction is known as **Aldol addition**. In fact, under the basic reaction conditions,  $\beta$ -hydroxy aldehydes are often not isolated and easily undergo dehydration to give  $\alpha,\beta$ -unsaturated aldehyde; the overall reaction (addition followed by water loss) is called **Aldol condensation**. This is another versatile method to form C–C bond.



The same reaction can also be carried out between two molecules of ketones to form ketol, which on dehydration produces  $\alpha,\beta$ -unsaturated ketone. However, the reaction goes more slowly with ketones because the carbonyl group in ketones is less electrophilic due to electron donating alkyl group attached to it, hence less susceptible to nucleophile attack.

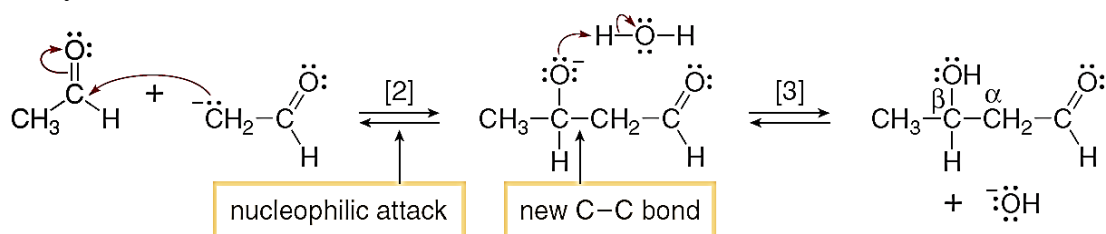
#### Mechanism:

**Step 1: Abstraction of  $\alpha$ -hydrogen by base (Formation of enolate ion).**  $\alpha$ -Hydrogen in carbonyl compounds is acidic because of the electron withdrawing nature of carbonyl group; this  $\alpha$ -hydrogen is abstracted by base to form a resonance-stabilized enolate.



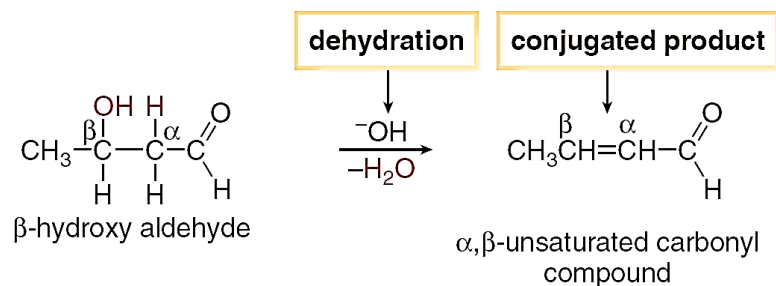
**Step 2: Nucleophilic attack of enolate on the second molecule of aldehydes.**

Nucleophilic attack of enolate (carbanion) on the electrophilic carbonyl carbon of the other molecule of aldehydes results in the formation of new C-C bond; the  $\alpha$ -carbon of one molecule of aldehydes is joined to carbonyl carbon of the other molecule of aldehydes.



**Step 3: Protonation (aldol formation).** Protonation of alkoxide by the solvent (water) produces  $\beta$ -hydroxy aldehydes (an aldol) with the regeneration of the base catalyst.

**Step 4: Dehydration of aldol (formation of  $\alpha,\beta$ -unsaturated aldehyde).** On heating aldol product easily loses water to make  $\alpha,\beta$ -unsaturated aldehydes. The newly formed double bond is in conjugation with carbonyl group, which gives the extra stability to the molecule and hence, favours the reaction equilibrium towards product side. Once the conjugated  $\alpha,\beta$ -unsaturated aldehyde is formed, it is not reconverted to the  $\beta$ -hydroxy aldehyde.



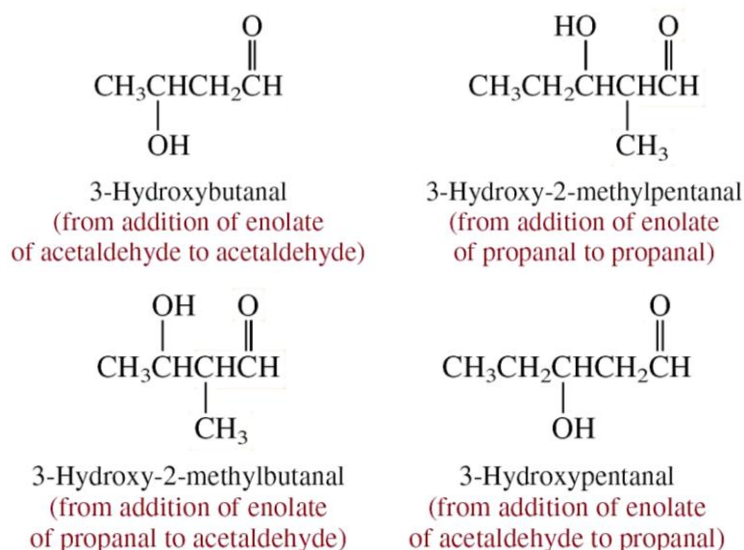
**Mixed aldol condensation or crossed aldol condensation:**

The condensation carried out between two different aldehydes (both containing  $\alpha$ -hydrogen) is called mixed aldol condensation as it produces a mixture of different  $\beta$ -hydroxy aldehydes. For example, condensation between ethanol and propanal forms a mixture of four products:

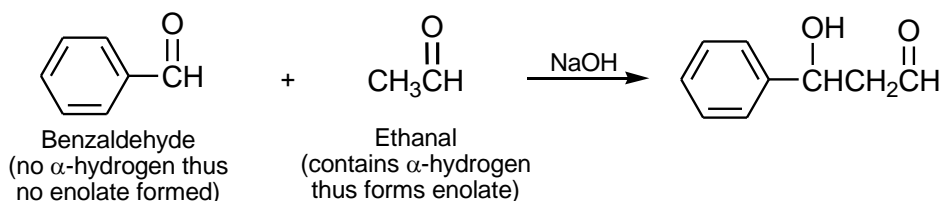
- ✓ 3-hydroxybutanal and 3-hydroxy-2-methylpentanal are formed by self condensation of ethanol and propanal, respectively.
- ✓ 3-hydroxy-2-methylbutanal is formed by the condensation of ethanol with enolate of propanal ( $\text{CH}_3\text{-CH}^-\text{-CHO}$ ). Thus, propanal serves as nucleophile and ethanol carbonyl acts as electrophile.



- ✓ 3-hydroxypentanal is formed by the condensation of propanal with enolate of ethanal ( $\text{CH}_2\text{CHO}$ ); ethanal provides nucleophile while propanal serves as electrophilic centre.



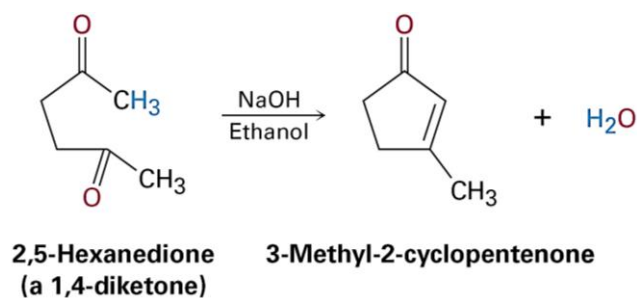
The reaction could be useful when one of the reactants contains  $\alpha$ -hydrogen and other does not have the  $\alpha$ -hydrogen, so that only one reactant can form an enolate and the other will serve as electrophile. For example,



Alternatively, one of the reactants may be an unusually acidic nucleophilic donor such as ethyl acetoacetate, which would generate enolate.

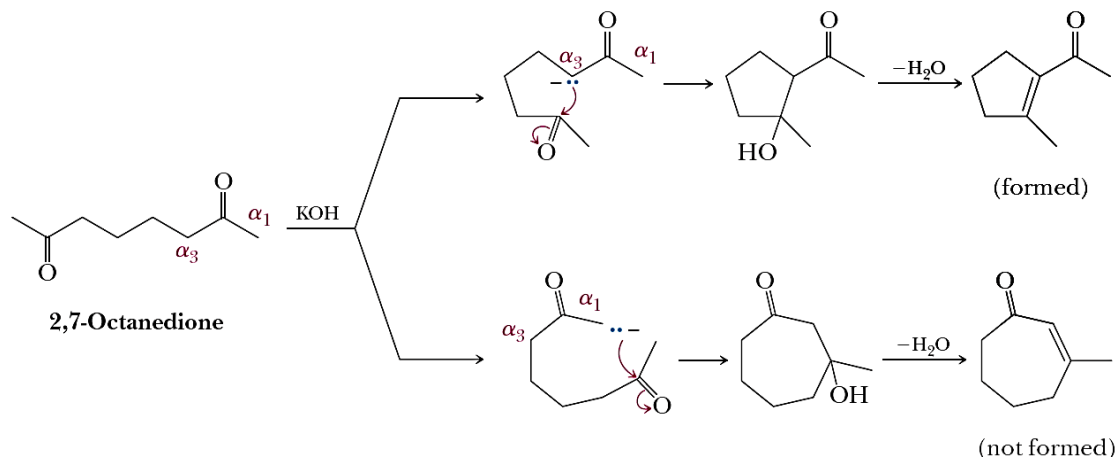
### Intramolecular Aldol condensation:

Compounds containing two carbonyl groups can undergo intramolecular aldol condensation. For example, cyclisation of 2,5-hexanedione takes place when heated in presence of aqueous sodium hydroxide to give 3-methyl-2-cyclopentenone (a five-membered ring compound).



The reaction is particularly useful for the formation of five- or six-membered rings because they are more stable. Rings larger than six and smaller than five are less stable

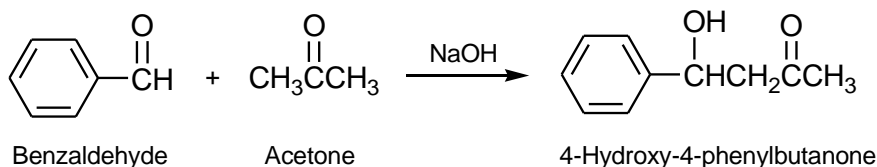
and thus less favored by their energy and entropy. For example, the intramolecular aldol condensation of 2,7-octanedione (a 1,6-diketone) preferentially leads to the formation of a more stable five-membered ring product; not seven-membered ring product.



In general, smaller rings form faster than larger rings because the reacting groups are closer together. However, the formation of three- and four-membered rings is disfavored because of the strain in these rings.

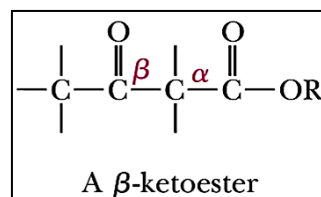
### Claisen-Schmidt condensation

Mixed aldol condensation in which a ketone, having  $\alpha$ -hydrogen, reacts with an aromatic aldehydes (contain no  $\alpha$ -hydrogen) is known as Claisen-Schmidt condensation

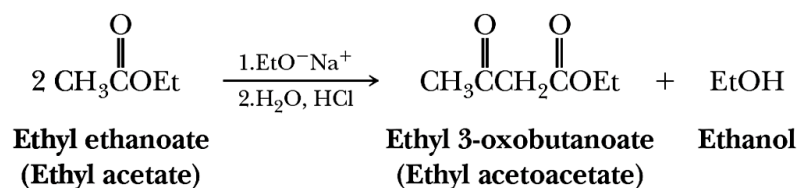


### Claisen condensation

Condensation of two molecules of esters, containing  $\alpha$ -hydrogen, in presence of a base to form  $\beta$ -keto esters is called **Claisen condensation**. The aldol condensation is carried out with aldehydes and/or ketones while Claisen condensation undergoes with **esters**.



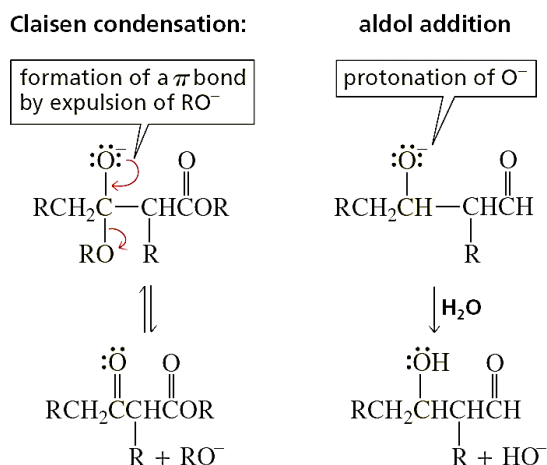
For example: The Claisen condensation of ethyl acetate in presence of sodium ethoxide followed by acidification gives ethyl acetoacetate.



The non-aqueous bases, such as sodium ethoxide in ethanol and sodium methoxide in methanol are generally used in Claisen condensations instead of aqueous bases (like NaOH) because aqueous bases would bring about the hydrolysis of the ester.

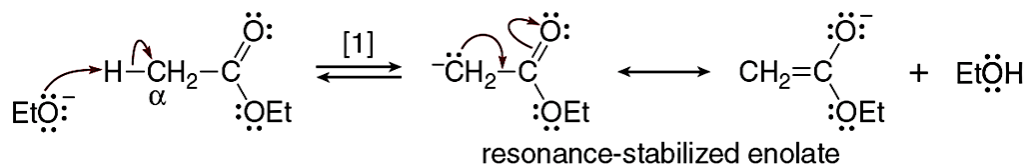
The alkoxide base used to form the enolate should have the same alkyl group as the ester, e.g., ethoxide for an ethyl ester; otherwise **transesterification** may occur.

The first two steps of Claisen condensation are analogous to that of aldol condensation; the enolate of one ester molecule adds to the carbonyl carbon of the other ester molecule. After this addition, the Claisen condensation and the aldol condensation follow different mechanism. In aldol condensation, the negatively charged oxygen is protonated by the solvent; however, in Claisen condensation, alkoxy group is detached as a leaving group and the carbon-oxygen double bond is reformed. Because in esters, the carbon bonded with negatively charged oxygen is also bonded to a group that can be expelled. However, in aldehydes or ketones, the carbon to which the negatively charged oxygen is bonded is not bonded to a group that can be expelled.

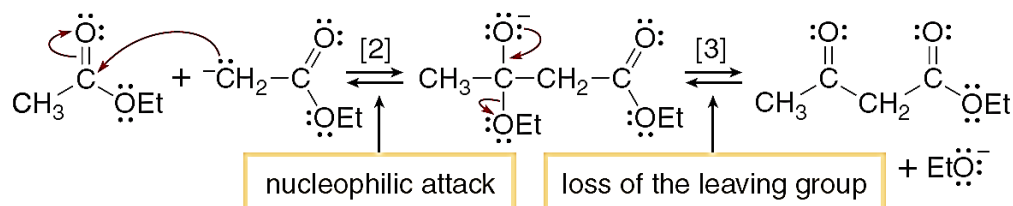


### Mechanism:

**Step 1: Abstraction of  $\alpha$ -hydrogen of ester by base (formation of enolate).** The base abstracts a proton from  $\alpha$ -carbon to form a resonance-stabilized enolate (or carbanion).



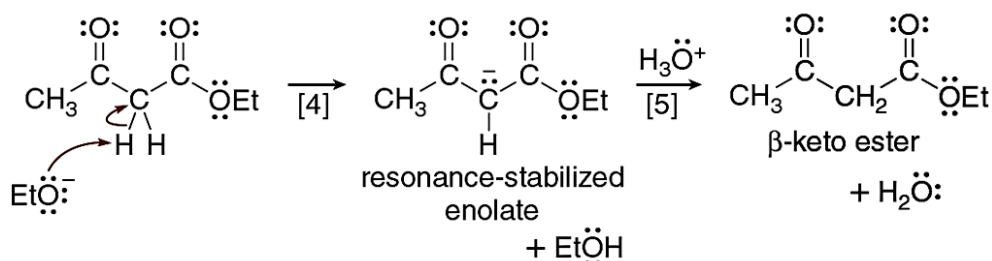
**Step 2: Nucleophilic attack of enolate on the carbonyl carbon of other ester molecule.** The nucleophilic enolate attacks on the carbonyl carbon of other ester molecule which resulted in the formation of new C-C bond; the  $\alpha$ -carbon of one ester molecule is joined to the carbonyl carbon of the other molecule.



**Step 3: Removal of alkoxide ion as leaving group (formation of β-keto ester).**

Unlike aldol condensation, an alkoxide ion is expelled as leaving group and >C=O is reformed, which resulted in the formation of β-keto ester.

**Step 4: Deprotonation.** Ethoxide ion formed in step 3 is a strong enough base to deprotonate β-keto ester. The hydrogens attached to the carbon which is flanked by two carbonyl groups in β-keto ester are very acidic and are easily removed by base to produce resonance-stabilized enolate; it shifts the equilibrium completely to the product side and drive the overall reaction to completion.

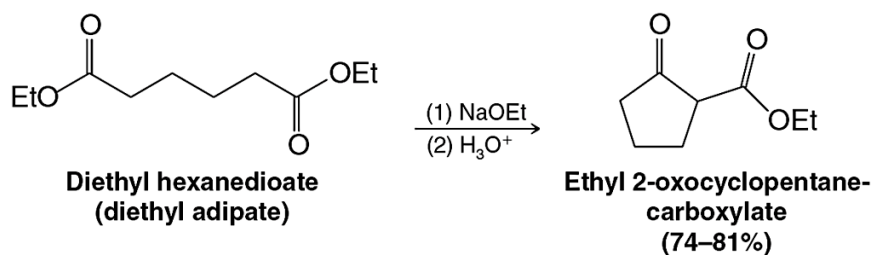


**Step 5: Protonation.** The enolate of β-keto ester is protonated with a strong acid to regenerate the neutral β-keto ester.

The steps 1–3 are reversible, but the removal of proton from β-keto ester forms highly stable enolate which drives the reaction towards right side and finally protonation of this enolate completes the reaction. Because the generation of a resonance-stabilized enolate from the product β-keto ester drives the Claisen condensation, only esters with two or three hydrogens on the α-carbon undergo this reaction; that is, esters must have the general structure CH<sub>3</sub>CO<sub>2</sub>R' or RCH<sub>2</sub>CO<sub>2</sub>R'.

## Dieckmann condensation

An intramolecular Claisen condensation of a diester to give a five- or six-membered ring is named as **Dieckmann condensation**.

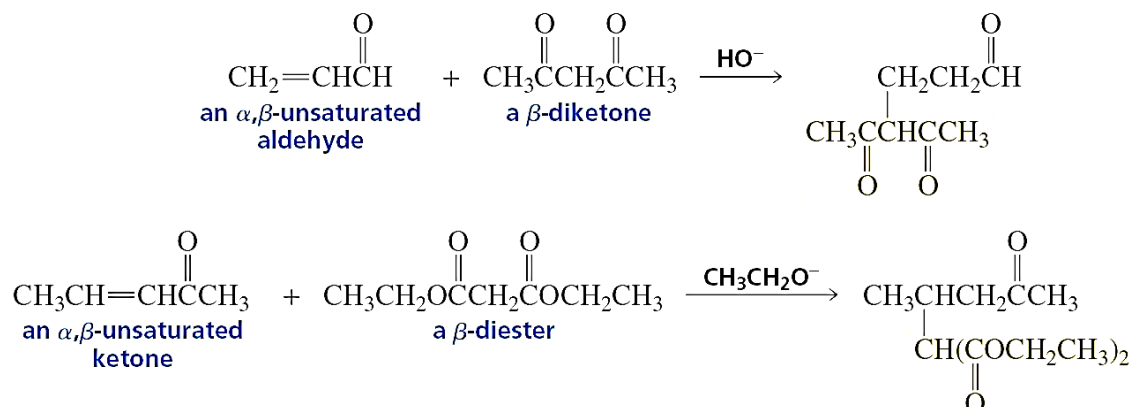


In general, the Dieckmann condensation is useful only for the preparation of five and six-membered rings, which are formed from 1,6-diester and 1,7-diester, respectively.

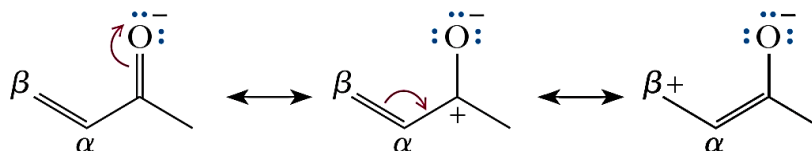
Rings smaller than five, are disfavoured due to angle strain. Rings larger than seven are less favourable as in that case intermolecular condensation begins to compete strongly.

### Michael addition:

The nucleophilic addition of compounds containing reactive methylene group (flanked by two keto groups like malonic ester, ethylacetoacetate,  $\beta$ -diketones, or  $\beta$ -keto nitriles) to  $\alpha,\beta$ -unsaturated carbonyl compounds in presence of base (as catalyst) is known as Michael addition.



In general, C=C bond is difficult to be attacked by a nucleophile, however,  $\beta$ -carbon of  $\alpha,\beta$ -unsaturated carbonyl compounds is activated because of adjacent carbonyl group and can be attacked by a nucleophile as it gets positive charge through resonance.

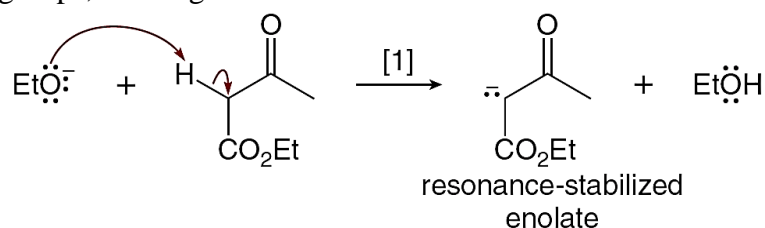


The Michael addition involves conjugate addition (1,4-addition) of a resonance stabilized enolate to  $\beta$ -carbon of  $\alpha,\beta$ -unsaturated carbonyl compounds. The electrophile (the  $\alpha,\beta$ -unsaturated carbonyl compound) accepts a pair of electrons, so it is called the Michael acceptor. The attacking nucleophile donates a pair of electrons, so it is called the Michael donor. A wide variety of compounds can serve as Michael acceptors and donors:

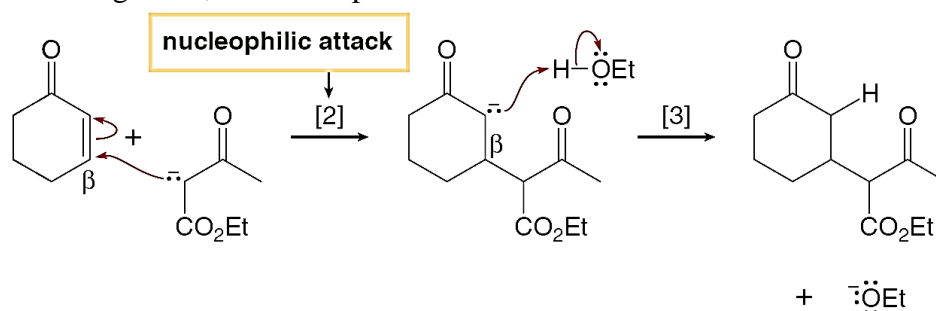
Michael acceptors		Michael donors	
$\text{H}_2\text{C}=\text{CHCHO}$	Propenal	$\text{RCCH}_2\text{CR}'$	$\beta$ -Diketone
$\text{H}_2\text{C}=\text{CHCOCH}_3$	3-Buten-2-one	$\text{RCCH}_2\text{COEt}$	$\beta$ -Keto ester
$\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$	Ethyl propenoate	$\text{EtOOCCH}_2\text{COEt}$	Diethyl malonate
$\text{H}_2\text{C}=\text{CHCONH}_2$	Propenamide	$\text{RCCH}_2\text{C}\equiv\text{N}$	$\beta$ -Keto nitrile
$\text{H}_2\text{C}=\text{CHC}\equiv\text{N}$	Propenenitrile	$\text{RCH}_2\text{NO}_2$	Nitro compound
$\text{H}_2\text{C}=\text{CHNO}_2$	Nitroethylene		

**Mechanism:**

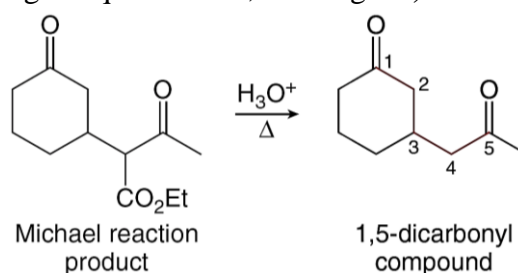
**Step 1: Enolate formation.** Base removes the acidic proton from the carbon flanked by two carbonyl groups, forming the enolate.



**Step 2 & 3: Nucleophilic attack at  $\beta$ -carbon followed by protonation.** The nucleophilic addition of the enolate to the  $\alpha$ -carbon of the  $\alpha,\beta$ -unsaturated carbonyl compound forms a new carbon-carbon bond and a resonance-stabilized enolate, which on protonation gives 1,4-addition product.

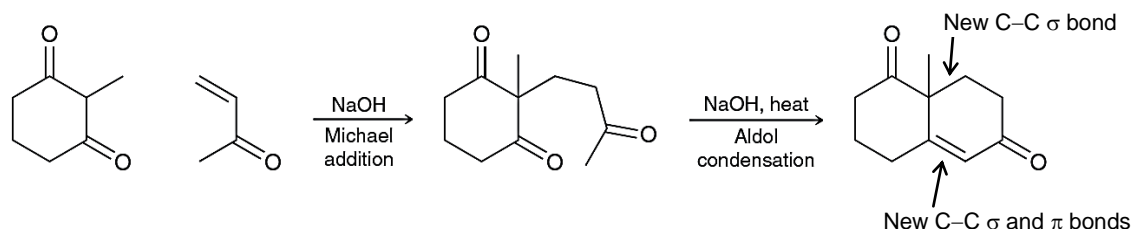


When the product of a Michael reaction is also a  $\beta$ -keto ester, it can be hydrolyzed and decarboxylated by heating in aqueous acid, forming a **1,5-dicarbonyl compound**.



## Robinson annulation:

A ring-forming reaction involving Michael addition followed by intramolecular aldol condensation is called **Robinson annulation** (“Annulation” comes from *annulus*, Latin for “ring”). This reaction results in the formation of 2-cyclohexenone ring with the formation of three new carbon-carbon bonds – two  $\sigma$  bonds and one  $\pi$  bond.



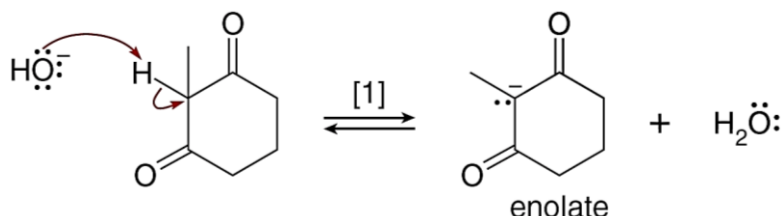
The Robinson annulation is often used for the synthesis of polycyclic compounds.

## Mechanism:

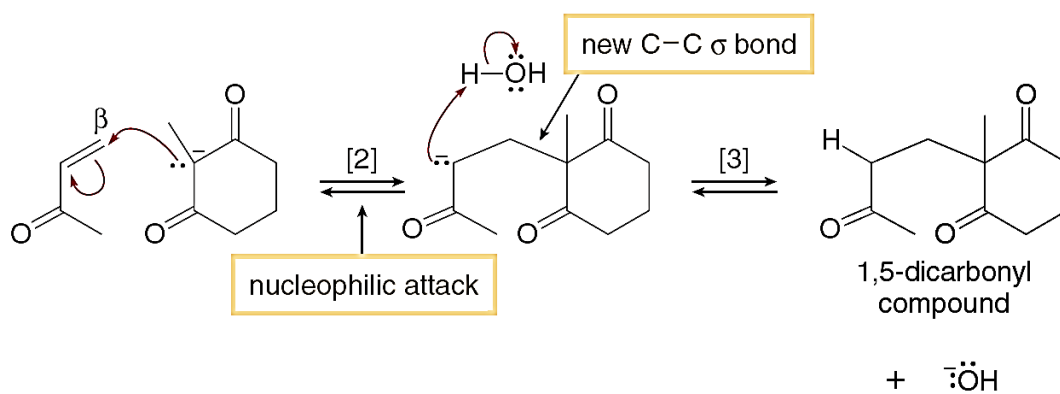
The mechanism of the Robinson annulation consists of two parts: a **Michael addition** to the  $\alpha,\beta$ -unsaturated carbonyl compound to form a 1,5-dicarbonyl compound, followed by an **intramolecular aldol reaction** to form the six-membered ring.

### Part 1: Michael addition.

#### Step 1: Enolate formation

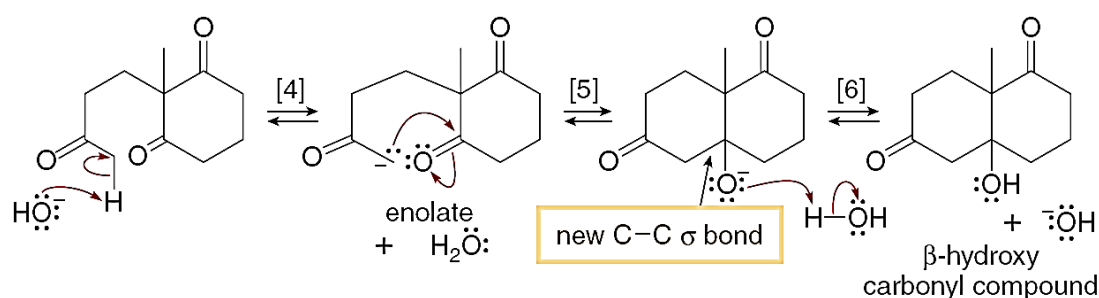


#### Steps 2 and 3: Nucleophilic attack and protonation

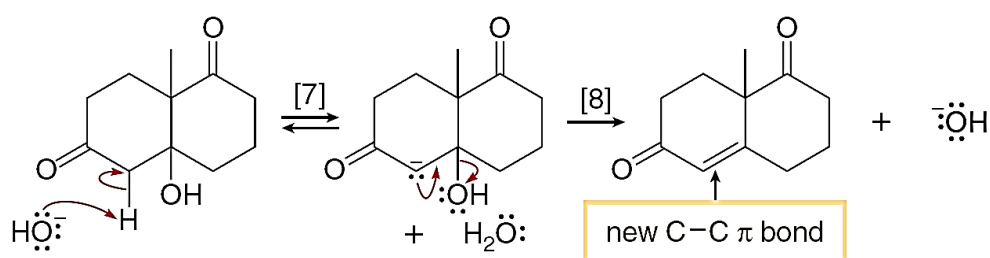


### Part 2: Intramolecular aldol condensation.

#### Steps 4-6: Aldol addition



#### Steps 7 and 8: Dehydration.



### 3.4. Summary

- Carbonyl compounds have carbonyl group ( $>\text{C}=\text{O}$ ) in which carbon is attached with oxygen by double bond, and with two other substituents by single bond. Carbonyl carbon is  $sp^2$  hybridized having trigonal planar structure.
- Based on their reactivities, Carbonyl compounds can be classified into two groups – (i) Class I compounds contain a group that cannot be replaced by another group. Aldehydes and ketones belong to this category; (ii) Class II compound contain a group that can be replaced by another group. Carboxylic acids and its derivatives (amide, acid chloride, acid anhydride, and esters) belong to this category.
- Carbonyl group is polarized with a partial negative charge on oxygen and partial positive charge on carbon. Lewis acids such as proton react at oxygen while nucleophile reacts with carbonyl group at the carbon atom.
- Class I compounds undergo nucleophilic addition, and nucleophilic addition-elimination reactions while class II compounds undergo nucleophilic acyl substitution reactions.
- Many of these reactions form new carbon-carbon bonds, making it a very important class of reactions in organic synthesis.
- Nucleophilic addition reactions of class I (aldehydes and ketones) compounds with  $\text{H}_2\text{O}$ ,  $\text{HCN}$ , and alcohols give hydrates, cyanohydrins and hemiacetals (or hemiketals). Further addition of another molecule of alcohol to hemiacetal (or hemiketal) followed by elimination of water results in the formation of acetals (or ketals). Aldehydes form hemiacetals and acetals while ketones give hemiketals and ketals. Hemiacetals and hemiketals are unstable unless they are making five- or six-membered ring as found in carbohydrates.
- Hemiacetal formation can be catalyzed by either acid or base while acetal formation can be catalyzed only by acid.

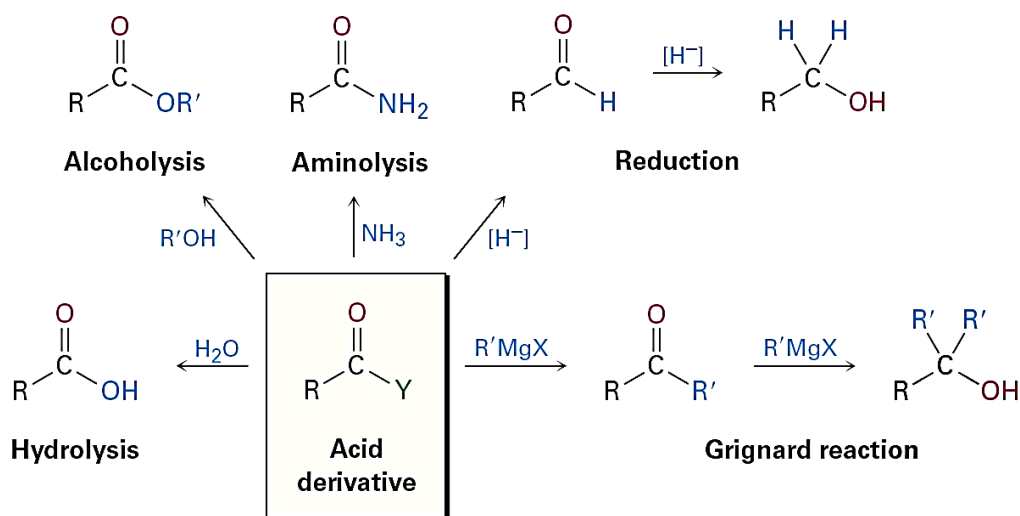


- Addition of ammonia, 1° and 2° amines yield carbinolamines. As two electronegative atoms (oxygen and nitrogen) are attached with the same carbon in carbinolamines, they are unstable, and eliminate water to form imines and enamines. Addition of primary amines to aldehydes and ketones yields imines ( $R_2C=NR$ ), while secondary amines yield enamines ( $R_2N-CR=CR_2$ ).
- Ammonia derivatives like hydroxyl amine, hydrazine, etc. react with aldehydes and ketones to give analogous imine products.
- Addition of Grignard reagent to formaldehyde, other aldehydes and ketones followed by hydrolysis produces 1°, 2°, and 3° alcohols, respectively. This results in the formation of new C–C bond. The reaction is irreversible because carbanions do not function as leaving group.
- Aldehydes and ketones are reduced by catalytic hydrogenation or with metal hydride reducing agents ( $NaBH_4$  or  $LiAlH_4$ ) to primary and secondary alcohols, respectively. Advantage of using metal hydride reducing agent is that carbonyl groups can be reduced without affecting carbon-carbon double or triple bonds. Catalytic hydrogenation reduces both multiple bonds as well as carbonyl groups.
- Metal hydride reductions are not reversible reactions as hydride cannot be removed as leaving group.
- Aldehydes and ketones can be converted to alkene by Wittig reaction, which involves the addition of phosphonium ylides (deprotonated phosphonium salts) to carbonyl group. This also forms new carbon-carbon bond. Both *E*- and *Z*- products are usually formed.
- The mechanism of a Wittig reaction involves  $S_N2$  mechanism to initially form an oxaphosphetane, which rearranges to give the product.
- Aldehydes are more reactive than ketones as a result of steric and electronic effects.
- A general mechanism for nucleophilic addition under basic conditions involve two step:
  - a. Nucleophilic attack at carbonyl carbon
  - b. Protonation at carbonyl oxygenWith strong nucleophile under neutral or alkaline conditions nucleophilic attack is the first step and protonation is the second step. However, in case of weak nucleophile reaction takes place in acidic conditions, and the first step is protonation and the second step is nucleophilic attack.
- Class II compounds (carboxylic acid derivatives – acid chlorides, acid anhydrides, esters, and amides) undergo nucleophilic acyl substitution reaction. Acyl group is a carbonyl group attached to an alkyl or aryl group.
- A nucleophile adds to the electrophilic acyl carbon, breaking  $C=O$   $\pi$  bond to produce a tetrahedral addition intermediate, which collapses by losing a weakest base as leaving group and reform the  $C=O$   $\pi$  bond.
- The stability of carboxylic acid derivatives increases in the order of acid chlorides < acid anhydride < esters < amides. More stable a compound means less reactive it is. Therefore, the reactivity pattern is:

acid chlorides > acid anhydride > esters > amides

Acid chlorides are most reactive and amides are least reactive acid derivatives.

- Carboxylic acids react with alcohol catalyzed by acid to produce esters; the reaction is called Fischer esterification.
- The mechanism of Fischer esterification involves initial protonation of the carbonyl group oxygen, followed by nucleophilic attack of an alcohol on the carbonyl carbon, and then a proton transfer. Loss of water gives the ester.
- The most common reactions of carboxylic acid derivatives are substitution by water to yield an acid (hydrolysis), by an alcohol to yield an ester (alcoholysis), by an amine to yield an amide (aminolysis), by hydride ion to yield an alcohol (reduction), and by an organomagnesium halide to yield an alcohol (Grignard reaction).



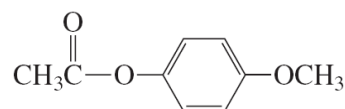
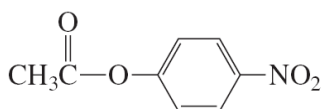
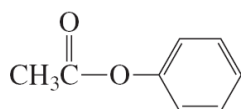
- Acid chlorides and acid anhydride react spontaneously with water called hydrolysis. Hydrolysis of acid chloride yields carboxylic acid and HCl while acid anhydride produces two molecules of carboxylic acid.
- Acid or base catalysis is needed for the hydrolysis of esters and amides but is not required for acid halides and acid anhydrides.
- The role of an acid is to increase the electrophilicity of the carbonyl and to protonate the leaving group in order to facilitate its departure.
- The role of a base is to improve nucleophilicity and to facilitate leaving group departure by creating anionic tetrahedral intermediates.
- Esters are hydrolyzed to produce carboxylic acid and alcohol.
- Mechanism of esters hydrolysis in presence of acid is exactly reverse of Fischer esterification.
- Base catalyzed ester hydrolysis is called saponification.
- Amides are least reactive acid derivatives and react with water under vigorous conditions of heating in presence of strong acid or base; the reaction gives carboxylic acid and amines.
- Acid chlorides react with alcohols to give esters and HCl. When the product ester is acid sensitive, a base such as a tertiary amine is used to neutralize the HCl as it is formed.

- Acid anhydrides react with alcohols to give one molecule of ester and one molecule of carboxylic acid.
- Esters react with alcohols in an acid-catalyzed reaction called **transesterification**, an equilibrium process in which one ester –OR group is exchanged for another.
- Amides are not reactive enough to react with alcohols.
- Acid chlorides react with ammonia, 1°, and 2° amines to form an amide and one equivalent of an ammonium chloride. Two equivalents of ammonia, 1°, and 2° amines is required – one to serve as a nucleophile and the other to serve as a base to react with acid produced.
- Acid anhydrides react with two equivalents of ammonia, 1°, and 2° amines, to form an amide and one equivalent of an ammonium carboxylate salt.
- Esters react slowly with ammonia, 1°, and 2° amines to form an amide and an alcohol.
- Acid chloride, acid anhydride and esters react with two equivalents of Grignard reagent to prepare alcohols with the introduction of two alkyl groups at the same carbon. Formate esters give secondary alcohols while other esters, acid chloride, and acid anhydride produce tertiary alcohol.
- A more selective organometallic reagent like lithium dialkyl cuprate (called Gilman reagent) converts acid chlorides to ketones. It does not react with aldehyde, ketone, acid anhydride, ester, or amide.
- $\text{NaBH}_4$ , a mild reducing agent does not reduce the acid derivatives except acid chloride. Generally  $\text{LiAlH}_4$ , a strong reducing agent is required to reduce acid derivatives. Acid chloride, acid anhydride and esters give alcohols with  $\text{LiAlH}_4$  while amides yield amines.
- Diisobutylaluminum hydride (DIBAL-H), a mild reducing agent is used to convert acid chloride, acid anhydride and esters to aldehydes.
- In the presence of catalytic acid or base, the keto-group of a carbonyl compound tautomerize to enol, and both ketone and enol forms exist in equilibrium.
- When treated with a strong base, the  $\alpha$ -position of the carbonyl compound is deprotonated to produce a resonance-stabilized enolate ion.
- Hydrogens next to the carbonyl group (called  $\alpha$ -hydrogens) are acidic ( $\text{pK}_a$  values in the 21-25 range) because of the electron-withdrawing nature of the carbonyl function and because the enolate ion is resonance stabilized. Aldehydes and ketones ( $\text{pK}_a \sim 16\text{--}20$ ) are more acidic than esters ( $\text{pK}_a \sim 25$ ).  $\beta$ -Diketones ( $\text{pK}_a \sim 9$ ) and  $\beta$ -keto esters ( $\text{pK}_a \sim 11$ ) are even more acidic.
- Therefore,  $\alpha$ -position of a carbonyl compound can serve as a nucleophile that creates new carbon-carbon bonds, making enolate anions important for organic synthesis.
- Aldehydes and ketones react with halogens leading to alpha halogenation; the reaction can be catalyzed either by acids or bases. Under acidic conditions, a halogen replaces one of the  $\alpha$ -hydrogens of the carbonyl compound, whereas under basic conditions, all the  $\alpha$ -hydrogens are replaced by halogens.
- Acid-catalyzed reaction produces acid (e.g. HBr when react with bromine), and is thus autocatalytic.

- Treatment of a methyl ketone with excess base and excess halogen gives trihalo derivative of methyl ketone, which on acid workup results in the formation of carboxylic acid. The reaction is called haloform reaction.
- Many carbonyl compounds, including ketones, esters, and nitriles, can directly be alkylated at  $\alpha$ -position by generating enolate by treatment with LDA followed by reaction with alkyl halides.
- In the **aldol reaction**, enolate anions derived from aldehydes or ketones react with a second molecule of aldehyde or ketone to give a carbonyl addition reaction and create a new carbon-carbon bond. The reaction is base-catalyzed and involves initial deprotonation of the  $\alpha$ -hydrogen to create an enolate anion. The enolate anion being strong nucleophilic attacks on the carbonyl carbon of another aldehyde or ketone molecule giving a carbonyl addition intermediate, which in turn, reacts with water to produce a  $\beta$ -hydroxy aldehyde or ketone product.
- The  $\beta$ -hydroxy aldehyde or ketone products of aldol reactions are easily dehydrated and lose  $\text{H}_2\text{O}$  to give an  $\alpha,\beta$ -unsaturated aldehyde or ketone. The whole reaction then is called Aldol condensation.
- Crossed aldol, or mixed aldol, reactions are aldol reactions that occur between different partners and are only efficient if one partner lacks  $\alpha$ -protons; the more reactive carbonyl (usually an aldehyde) has no  $\alpha$ -hydrogens, so that only the less reactive carbonyl species (usually a ketone) can form the enolate anion.
- Intramolecular aldol reactions show a preference for formation of five- and six-membered rings.
- When an ester is treated with an alkoxide base, a Claisen condensation reaction occurs, and the product is a  $\beta$ -keto ester. The reaction is not catalytic, because the deprotonated  $\beta$ -keto ester product is substantially less basic than the starting  $-\text{OR}$ . Therefore, an amount of base equal to one half equivalent compared to the amount of starting ester is the minimum amount that must be used.
- An intramolecular Claisen condensation, called a Dieckmann cyclization, produces a cyclic,  $\beta$ -keto ester.
- $\alpha,\beta$ -unsaturated aldehydes and ketones are susceptible to nucleophilic attack at the  $\beta$ -position. This reaction is called a conjugate addition, or *1,4-addition*, or a Michael reaction. It takes place with a wide variety of  $\alpha,\beta$ -unsaturated carbonyl compounds (aldehydes, ketones, esters, amides) as well as  $\alpha,\beta$ -unsaturated nitro and nitrile compounds. The nucleophile is called a Michael donor, and the electrophile is called a Michael acceptor.
- A Robinson annulation is a Michael addition followed by an intramolecular aldol and can be used to make cyclic compounds.

### 3.5. Exercise

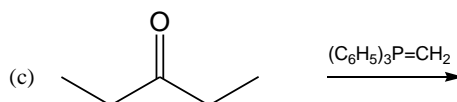
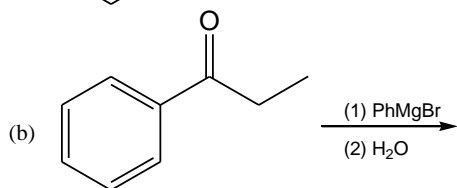
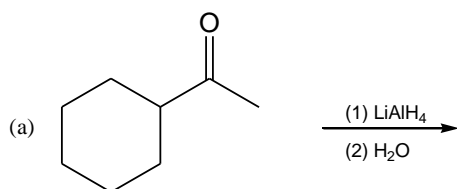
- 3.5.1. List the following esters in order of decreasing reactivity toward hydrolysis:



3.5.2. Using appropriate carbonyl compounds and Grignard reagents, give the synthesis of the following alcohols:

- (a) Butan-1-ol
- (b) 2-Methylpropanol
- (c) Butan-2-ol
- (d) Cyclohexylmethanol
- (e) 3-Methylpentan-3-ol

3.5.3. Predict the major product(s) for each reaction below:



3.5.4. How will you distinguish between the following compounds:

- (a)  $\text{CH}_3\text{CHO}$  and  $\text{CH}_3\text{COCH}_3$
- (b)  $\text{CH}_3\text{CH}_2\text{CHO}$  and  $\text{CH}_3\text{CHO}$
- (c)  $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_3$  and  $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3$

3.5.5. A carbonyl compound in the presence of base results in the formation of crotonaldehyde (But-2-enal). Identify the carbonyl compound, write the name of the reaction, and give its mechanism.