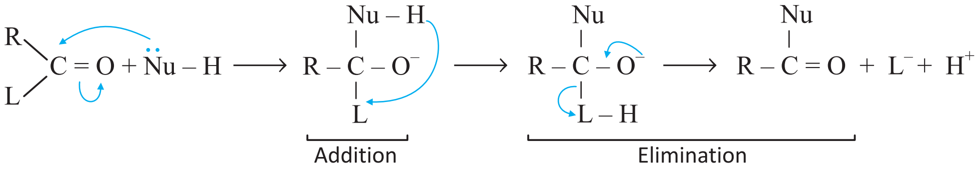
FUNCTIONAL DERIVATIVES OF ACIDS

Section - 3

Carboxylic acids form esters, acid halides, amides and acid anhydrides as a functional derivatives. All these derivatives have a carbonyl group and yield carboxylic acids on hydrolysis. Among these derivatives, acyl chlorides are the most reactive towards nucleophilic substitution reactions (also known as acyl substitution) and amides are least reactive.



On whole the reaction is Nucleophillic substitution where $L : -Cl,\ -NH_2,\ RO-,\ RCOO-$ (Leaving groups)

- The weaker is the base, the better is the leaving group. The basic nature of the above groups is in the order:

  $Cl^- < RCOO^- < OH^- < RO^- < NH_2^-$

  (Conjugate base of weaker acid is stronger and vice-versa. $HCl > RCOOH > H_2O > ROH > NH_3$)
  acid strength

- This means the leaving tendency of the groups is in order : $NH_2^- < RO^- < OH^- < RCOO^- < Cl^-$. Hence the reactivity of the acids and their derivatives follows the order : $RCOCl > (RCO)_2O > RCOOH > RCOOR > RCONH_2$

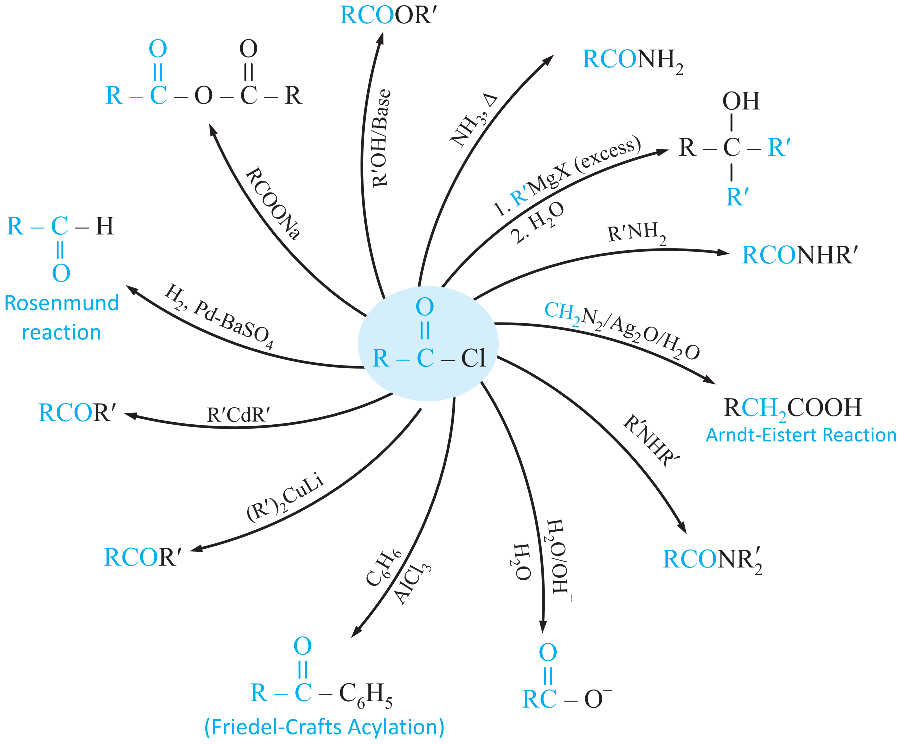
Acid Chlorides :

Preparation :

$$RCOOH + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl\uparrow$$

$$RCOOH + SOCl_2 \longrightarrow RCOCl + SO_2 + HCl$$

Reactions :

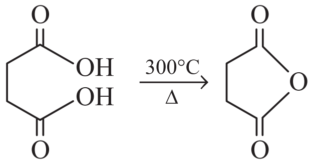


Acid Anhydrides :

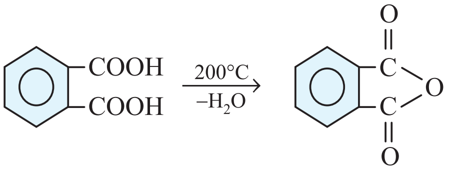
Preparation :

$$2RCOOH \xrightarrow[\Delta]{P_2O_5} (RCO)_2O$$

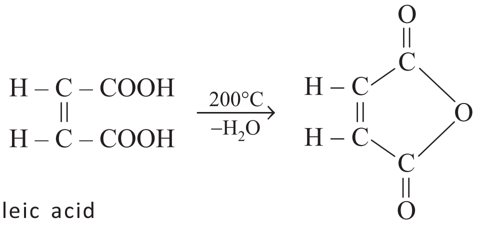
$$RCOOH + R'COCl \xrightarrow{\text{Pyridine}} R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R'$$



Succinic anhydride



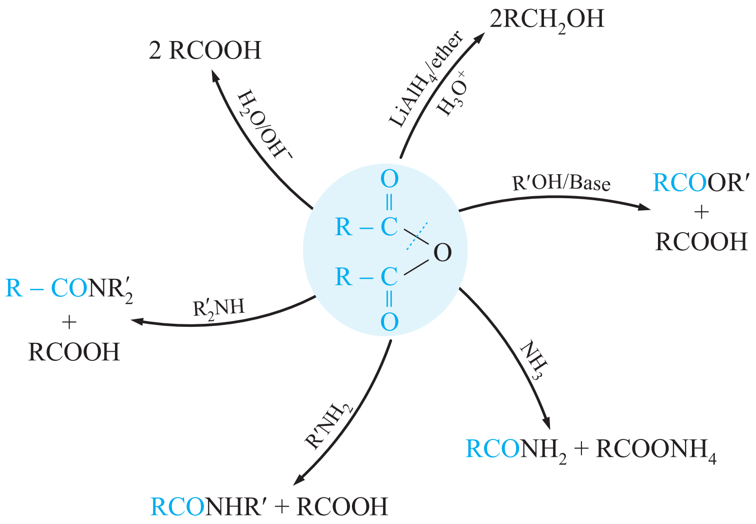
Phthalic anhydride



Maleic anhydride

cis-maleic acid

Reactions :



Note : The anhydrides having 'α' hydrogen reacts with benzaldehyde to form Cinnamic acid and its derivatives. (*Perkin Reaction*)

Amides :

The amides include alkanamides, substituted amides and formamides.

$RCONH_2$	$RCONHR$	$RCONR_2$
1° amides	2° amides	3° amides
Alkanamides	N-Alkyl Alkanamides	N, N-Dialkyl Alkanamides
$HCONH_2$	$HCONHR$	$HCONR_2$
Formamide (1°)	N-Alkyl Formamide (2°)	N, N-Dialkyl Formamide (3°)

Preparation : $RCOOH + NH_3 \longrightarrow RCOONH_4 \xrightarrow{\Delta} RCONH_2$

$$RCOOH + PCl_5 \longrightarrow RCOCl \xrightarrow{NH_3} RCONH_2$$

$$RCOCl \xrightarrow{RNH_2} RCONHR$$

$$RCOCl \xrightarrow{R_2NH} RCONR_2$$

Reactions :

➤ Hydrolysis :

$$\left[\begin{array}{l} RCONH_2 + H_2O \xrightarrow{H_2SO_4} RCOOH + NH_3\uparrow \\ RCONH_2 + NaOH \xrightarrow{H_2O} RCOONa + NH_3\uparrow \end{array}\right.$$

1° amides

This is typical of 1° amides to give off NH_3.

$$\underset{\text{2° amides}}{RCONHR + H_2O} \xrightarrow{H^+} RCOOH + \underset{\text{1° amine}}{RNH_2}$$

$$\underset{\text{3° amides}}{RCONR_2 + H_2O} \xrightarrow{H^+} RCOOH + \underset{\text{2° amine}}{R_2NH}$$

➤ Dehydration :

$$RCONH_2 \xrightarrow[\Delta]{P_4O_{10}} RC \equiv N + H_2O$$

$$RCONH_2 + HNO_2 \longrightarrow RCOOH + N_2 + H_2O$$

1° Amides behave differently with nitrous acid, giving off N_2.

➤ Hoffmann's Rearrangement :

$$RCONH_2 + 4\,NaOH + Br_2 \longrightarrow RNH_2 + 2\,NaBr + Na_2CO_3 + 2\,H_2O$$

Note : N-alkyl substituted amides do not give this reaction. Only 1° amides give this reaction.

The mechanism of this reaction is important and is covered in next chapter.

➤ Reduction :

$$\underset{1°}{RCONH_2} \xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4/\text{ether}} RCH_2NH_2 \quad \text{(1° amine)}$$

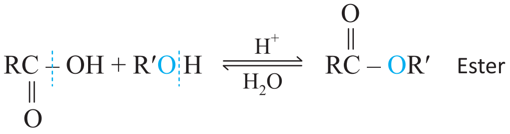
$$\underset{2°}{RCONHR} \xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4/\text{ether}} RCH_2NHR \quad \text{(2° amines)}$$

$$\underset{3°}{RCONR_2} \xrightarrow[\text{2. } H_3O^+]{\text{1. } LiAlH_4/\text{ether}} RCH_2-NR_2 \quad \text{(3° amines)}$$

Esters :

Preparation :

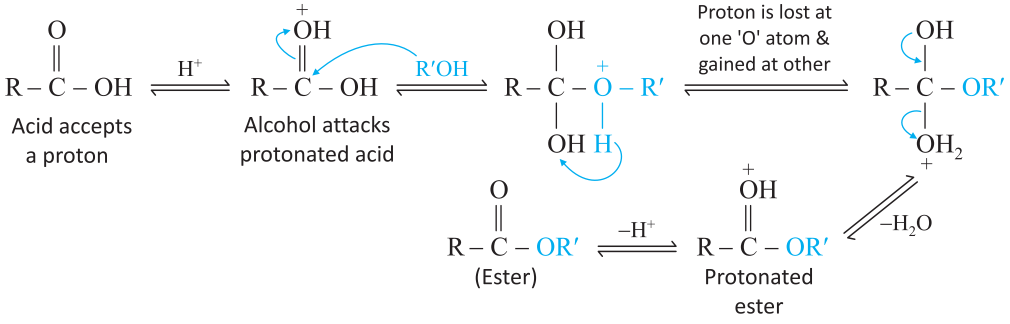
The esters are formed by the reaction between an acid, RCOOH and an alcohol by warming with mineral acid, H⁺ in a reaction called as Fisher Esterification.



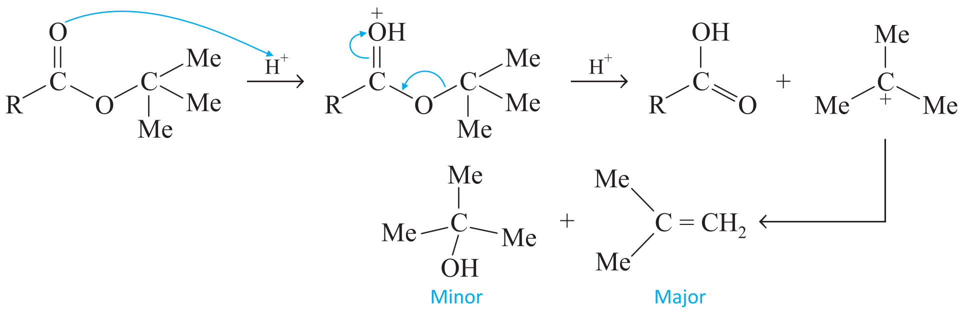
$$\underset{\underset{O}{\|}}{RC} \vdots OH + R'O \vdots H \underset{H_2O}{\overset{H^+}{\rightleftharpoons}} \overset{\overset{O}{\|}}{RC} - OR' \quad \text{Ester}$$

Mechanism :

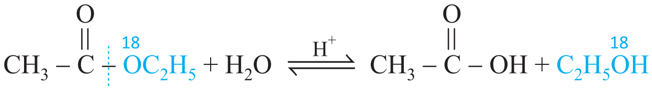
Esterification : (Acid catalysed) $RCOOH + R'OH \overset{H^+}{\rightleftharpoons} RCOOR' + H_2O$



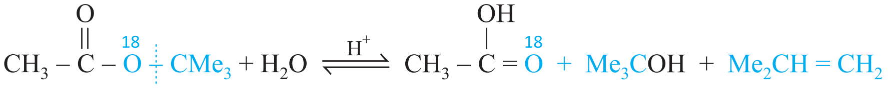
- On reversing the direction, we get mechanism of hydrolysis of ester.
- If R′ is tertiary, then during hydrolysis of ester, the cleavage occurs at O – C-alkyl bond to give an alkene and an alcohol.



- Observe the position of $\overset{18}{O}$ in the products as shown below :



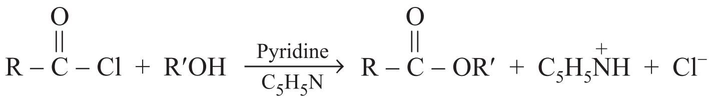
$$CH_3-\overset{\overset{O}{\|}}{C} \vdots \overset{18}{O}C_2H_5 + H_2O \overset{H^+}{\rightleftharpoons} CH_3-\overset{\overset{O}{\|}}{C}-OH + C_2H_5\overset{18}{O}H$$



$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{18}{O} \vdots CMe_3 + H_2O \overset{H^+}{\rightleftharpoons} CH_3-\overset{\overset{OH}{|}}{C}=\overset{18}{O} + Me_3COH + Me_2CH=CH_2$$

Note : Since a tetrahedral intermediate occupies more space than a planar carbonyl group, we would expect the rate of this reaction to be retarded when bulky reactants are used. When the esterification of acetic acid was compared with that of 2, 2-dimethylpropanoic acid, $(CH_3)_3-C-COOH$, the relatively small methyl group of acetic acid is replaced by a larger tert-butyl group, and the bulkier acid reacted fifty times slower than acetic acid. Similarly, increasing the size of the alcohol reactant results in a similar rate reduction.

In its formation, steric factor is most important both in acids and alcohols. If acid chlorides or acid anhydrides are esterified with alcohols, it is considered as the better method, as it is not reversible.

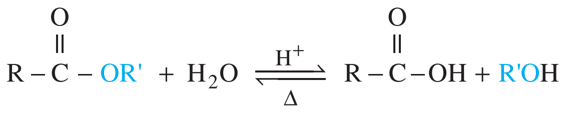


$$R-\overset{\overset{O}{\parallel}}{C}-Cl + R'OH \xrightarrow[C_5H_5N]{\text{Pyridine}} R-\overset{\overset{O}{\parallel}}{C}-OR' + C_5H_5\overset{+}{N}H + Cl^-$$

$$(RCO)_2O \xrightarrow{R'OH} RCOOR'$$

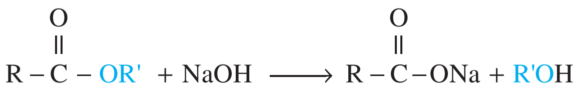
Reactions :

Hydrolysis :



$$R-\overset{\overset{O}{\parallel}}{C}-OR' + H_2O \xrightleftharpoons[\Delta]{H^+} R-\overset{\overset{O}{\parallel}}{C}-OH + R'OH$$

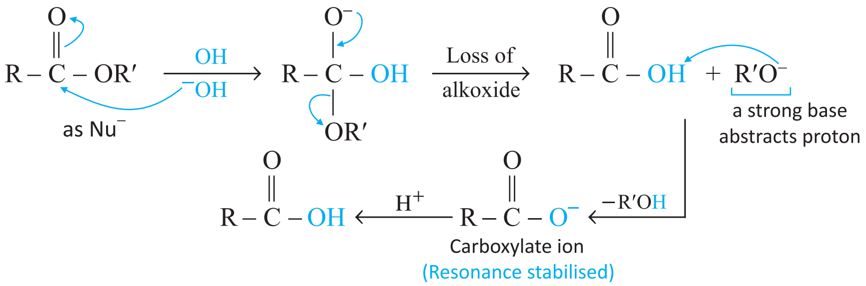
[The mechanism is simply the reverse of esterification done earlier.]



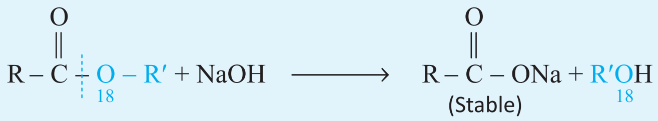
$$R-\overset{\overset{O}{\parallel}}{C}-OR' + NaOH \longrightarrow R-\overset{\overset{O}{\parallel}}{C}-ONa + R'OH$$

Mechanism

Hydrolysis of esters (Base catalysed) :



Note : ➤ Base catalysed hydrolysis is not reversible as carboxylate ion formed is resonance stabilised.

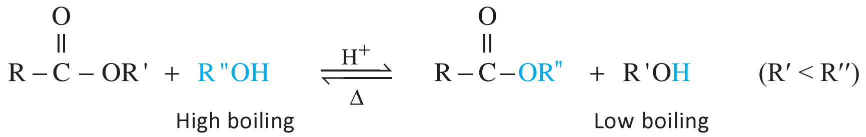


$$R-\overset{\overset{O}{\parallel}}{C}\,\vdots\,\underset{18}{O}-R' + NaOH \longrightarrow \underset{\text{(Stable)}}{R-\overset{\overset{O}{\parallel}}{C}-ONa} + R'\underset{18}{O}H$$

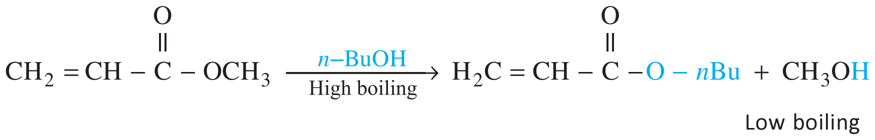
➤ The mechanism of esterification and hydrolysis of esters is also known as **Acyl-O cleavage** reaction mechanism.

Trans-esterification :

Trans-esterification is the process of exchanging the alkoxy group of an ester compound by another alcohol. These reactions are often catalyzed by the addition of an acid or base.



$$R-\overset{\overset{O}{\parallel}}{C}-OR' + \underset{\text{High boiling}}{R''OH} \xrightleftharpoons[\Delta]{H^+} R-\overset{\overset{O}{\parallel}}{C}-OR'' + \underset{\text{Low boiling}}{R'OH} \qquad (R' < R'')$$



$$\text{e.g.,}\quad CH_2=CH-\overset{\overset{O}{\parallel}}{C}-OCH_3 \xrightarrow[\text{High boiling}]{n\text{–}BuOH} H_2C=CH-\overset{\overset{O}{\parallel}}{C}-O-nBu + \underset{\text{Low boiling}}{CH_3OH}$$

Saponification :

Saponification is the hydrolysis of an ester under basic conditions to form an alcohol and the salt of the acid. Saponification is commonly used to refer to the reaction of a metallic alkali (base) with a fat or oil to form soap. Saponifiable substances are those that can be converted into soap.

$$\underset{\text{Fatty acids}}{R-COOR'} \xrightarrow[H_2O]{NaOH} \underset{\substack{\text{Carboxylate}\\\text{(Soap)}}}{RCO\bar{O}Na^+} + \underset{\text{Alcohol}}{R'OH}$$

Reduction :

Esters are reduced by $LiAlH_4$ in presence of ethers to a mixture of alcohols.

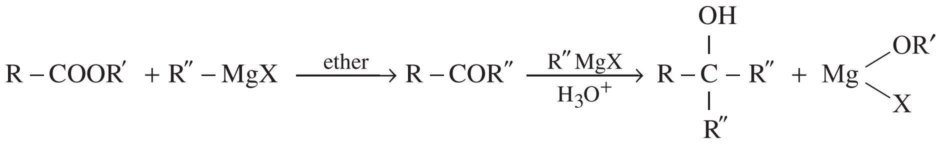
$$R-COOR' \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4/\text{ether}} RCH_2OH + R'OH$$

Conversion to Amides :

$$RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH$$

$$RCOOR' + R''NH_2 \longrightarrow RCONHR'' + R'OH$$

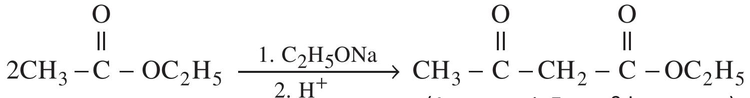
With Grignard Reagent :



$$R-COOR' + R''-MgX \xrightarrow{\text{ether}} R-COR'' \xrightarrow[H_3O^+]{R''MgX} R-\overset{\overset{OH}{|}}{\underset{\underset{R''}{|}}{C}}-R'' + Mg\begin{matrix}OR'\\X\end{matrix}$$

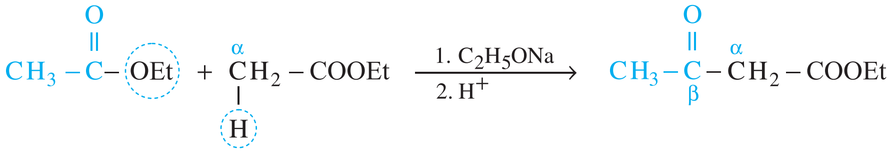
Claisen Condensation :

When two moles of an ester having an α-hydrogen condense in presence of base, ethoxide followed by acidification gives β-keto ester, the reaction is known as Claisen Condensation. For example consider ethyl acetate, $CH_3COOC_2H_5$.



$$2CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow[2.\ H^+]{1.\ C_2H_5ONa} CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

(Acetoacetic Ester-β-keto-ester)

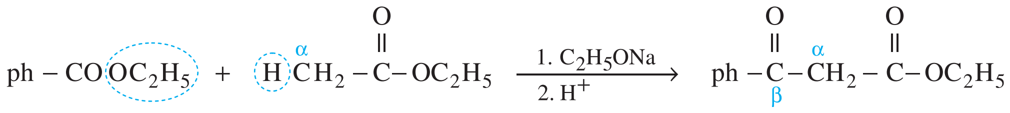


$$CH_3-\overset{\overset{O}{\|}}{C}-OEt + \overset{\alpha}{C}\underset{\underset{H}{|}}{H_2}-COOEt \xrightarrow[2.\ H^+]{1.\ C_2H_5ONa} CH_3-\underset{\beta}{\overset{\overset{O}{\|}}{C}}-\overset{\alpha}{C}H_2-COOEt$$

Note : One ester molecule loses an α-hydrogen to form enolate type of anion and then it attacks the other ester molecule in a nucleophillic substitution reaction. The other ester loses an alkoxide ion to form a condensation product.

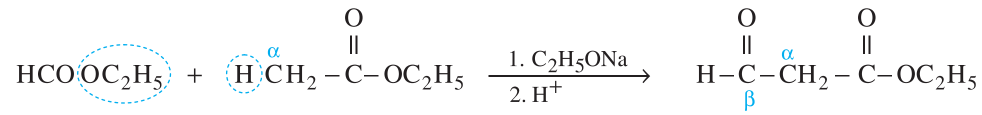
Cross Claisen Condensation :

Esters with no α-H (such as benzoate and formates) give cross-Claisen condensation with an ester having α-H.



$$ph-COOC_2H_5 + H\overset{\alpha}{C}H_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow[2.\ H^+]{1.\ C_2H_5ONa} ph-\underset{\beta}{\overset{\overset{O}{\|}}{C}}-\overset{\alpha}{C}H_2-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

(ester with no α - H) (ester with α - H)

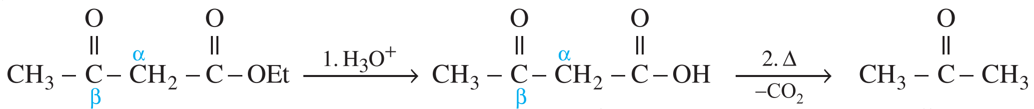


$$HCO\,OC_2H_5 + H\,\overset{\alpha}{C}H_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow[2.\ H^+]{1.\ C_2H_5ONa} H-\underset{\beta}{\overset{\overset{O}{\|}}{C}}-\overset{\alpha}{C}H_2-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

(ester with no α - H) (ester with α - H)

β-keto Ester Synthesis :

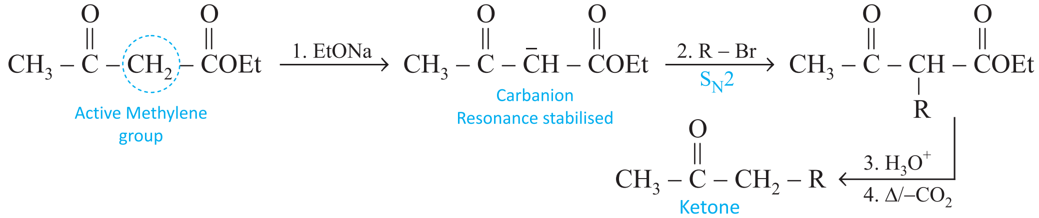
The products of Claisen-condensation, β-keto esters are hydrolysed easily by H_2O/H^+ to give β-keto acids. These can be heated to give off CO_2 to form ketones.



$$CH_3-\underset{\beta}{\overset{\overset{O}{\|}}{C}}-\overset{\alpha}{C}H_2-\overset{\overset{O}{\|}}{C}-OEt \xrightarrow{1.\ H_3O^+} CH_3-\underset{\beta}{\overset{\overset{O}{\|}}{C}}-\overset{\alpha}{C}H_2-\overset{\overset{O}{\|}}{C}-OH \xrightarrow[-CO_2]{2.\ \Delta} CH_3-\overset{\overset{O}{\|}}{C}-CH_3$$

β-keto acid Ketone

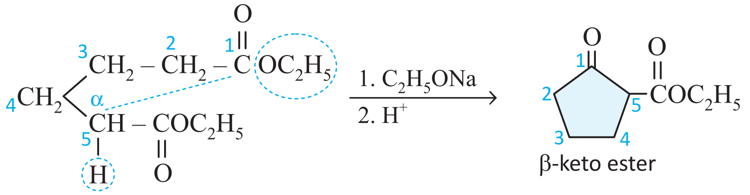
- Note that β-keto ester has an active methylene group. One can synthesize higher ketones using the acidic hydrogen of active methylene group as follows :



$$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}OEt \xrightarrow{1.\ EtONa} CH_3-\overset{\overset{O}{\|}}{C}-\bar{C}H-\overset{\overset{O}{\|}}{C}OEt \xrightarrow[S_N2]{2.\ R-Br} CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{C}H-\overset{\overset{O}{\|}}{C}OEt \xrightarrow[4.\ \Delta/-CO_2]{3.\ H_3O^+} CH_3-\overset{\overset{O}{\|}}{C}-CH_2-R$$

Intramolecular Claisen Condensation (Dieckmann Reaction) :

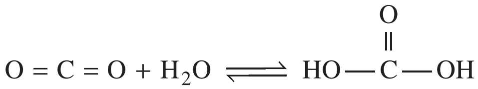
Esters of a dicarboxylic acids undergo an intramolecular Claisen condensation when a five or six-membered ring can be formed. This is referred to as *Dieckmann Reaction or condensation*.



β-keto ester

Carbonic Acid derivatives

Aqueous carbonic acid (CO_2 gas dissolved in H_2O) is unstable and behaves as dibasic acid.

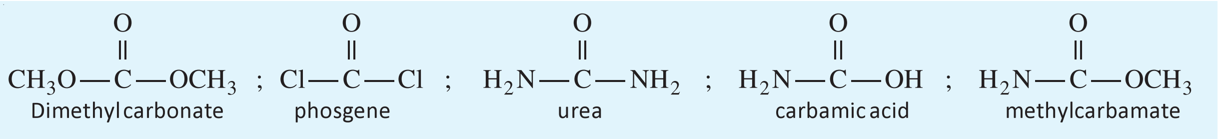


$$O=C=O + H_2O \rightleftharpoons HO-\overset{\overset{O}{\|}}{C}-OH$$

$$H_2CO_3 + H_2O \rightleftharpoons HCO_3^- + H_3O^+$$

$$HCO_3^- + H_2O \rightleftharpoons CO_3^{2-} + H_3O^+$$

Following derivatives of carbonic acid are formed :



$$CH_3O-\overset{\overset{O}{\|}}{C}-OCH_3\ ;\ Cl-\overset{\overset{O}{\|}}{C}-Cl\ ;\ H_2N-\overset{\overset{O}{\|}}{C}-NH_2\ ;\ H_2N-\overset{\overset{O}{\|}}{C}-OH\ ;\ H_2N-\overset{\overset{O}{\|}}{C}-OCH_3$$

Dimethylcarbonate ; phosgene ; urea ; carbamic acid ; methylcarbamate