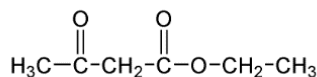


UNIT II

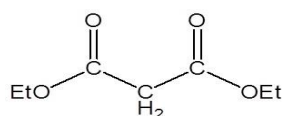
Organic Synthesis via Enolates

Active methylene Compounds

- When a methylene group (-CH₂-) is placed between two strongly electron withdrawing groups such as C=O, C≡N groups, the hydrogen atoms linked to the carbon become acidic and reactive.
- Such a methylene group is called as the reactive methylene group and the compounds containing reactive methylene group are called reactive methylene compounds.
- Some important compounds containing reactive methylene group are as shown:

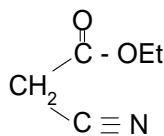


Acetoacetic ester



Malonic Ester

Et = -CH₂CH₃

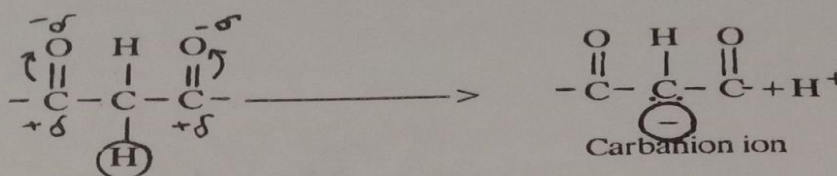


Cyanoacetic ester

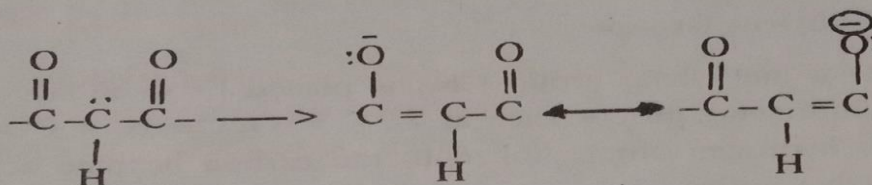
- In these compounds, ester group is the common electron withdrawing group along with other group like C=O, CN (Cyanide group) etc

Acidity of α hydrogen:

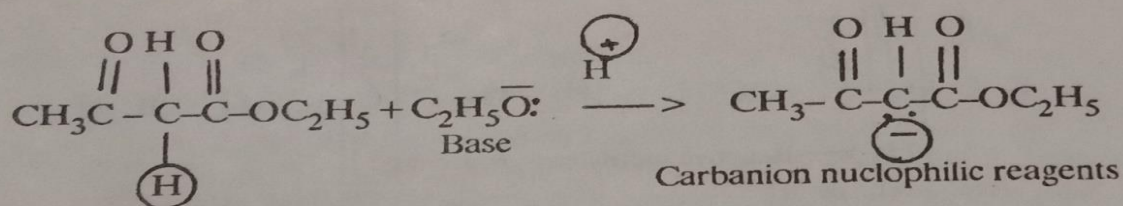
- Due to the presence of electron withdrawing groups on both sides, the methylene carbon becomes electron deficient.
- This results in the weakening of the C-H bond and thus the hydrogen tends to get liberated as a proton i.e. it shows marked acidic character or it becomes reactive as shown.



Again the carbanion ion thus formed is stabilised by resonance as shown.



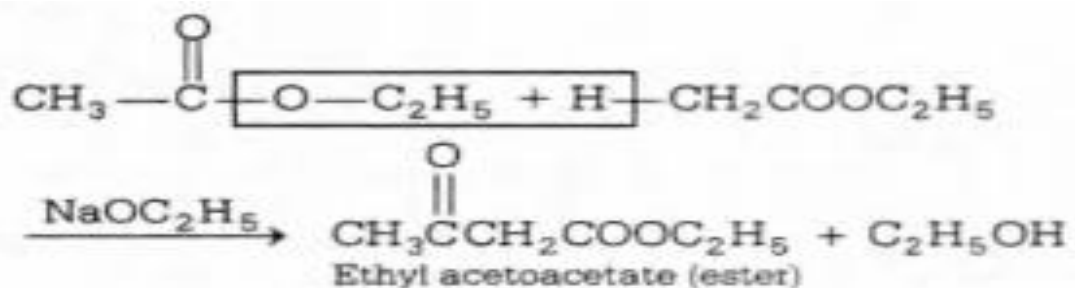
Reactive methylene compounds in presence of a base, give carbanion easily and the carbanion thus formed function as strong nucleophilic reagent and give a number of S_N2 type reactions



Hence reactive methylene compounds which cannot be prepared easily are prepared through these compounds.

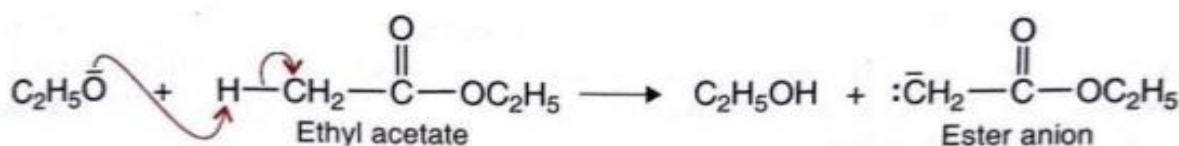
Synthesis of ethyl acetoacetate by Claisen Condensation:

- Ethyl acetoacetate is the ethyl ester of acetoacetic acid ($\text{CH}_3\text{COCH}_2\text{COOH}$) and is widely used as a starting material for the synthesis of a variety of ketones and acids.
- It can be prepared by Claisen condensation of ethyl acetate.
- The condensation of two molecules of an ester (e.g. ethyl acetate), under the influence of sodium or sodium ethoxide, is termed Claisen condensation and is one of the best methods for preparing beta-ketonic esters like ethyl acetoacetate.
- Two molecules of ethyl acetate condense in the presence of sodium ethoxide to produce ethyl acetoacetate. Claisen condensation may also be brought about by sodamide or triphenylmethylsodium etc.

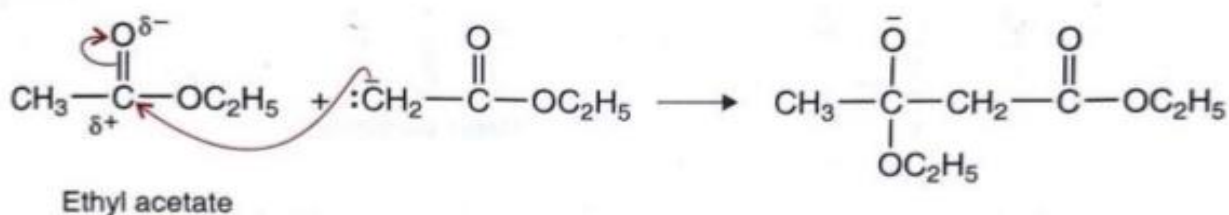


Mechanism:-

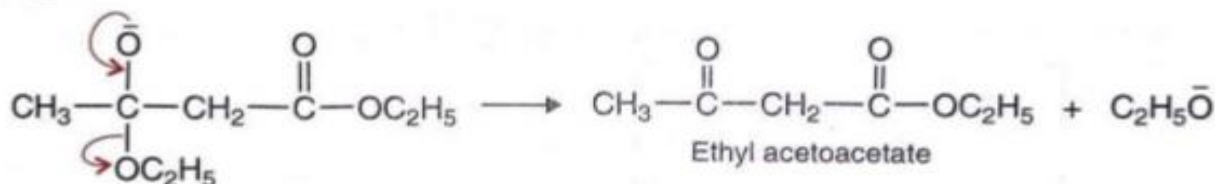
Step 1.



Step 2.



Step 3.



Following steps are involved in the above mechanism:

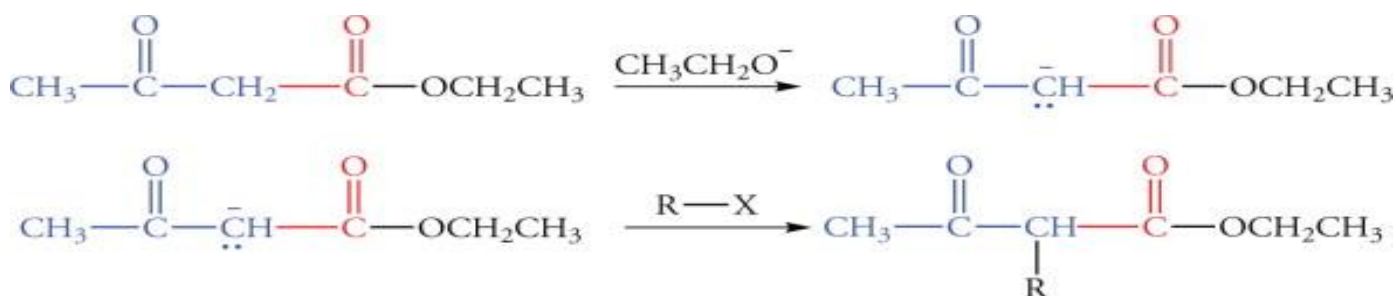
Step 1: Removal of an α -hydrogen by base gives resonance stabilized anion

Step 2: Formation of new bond between enolate i.e. nucleophile and carbonyl carbon of another molecule of ethyl acetate.

Step 3: Breaking of bond to give stable molecule of EAA.

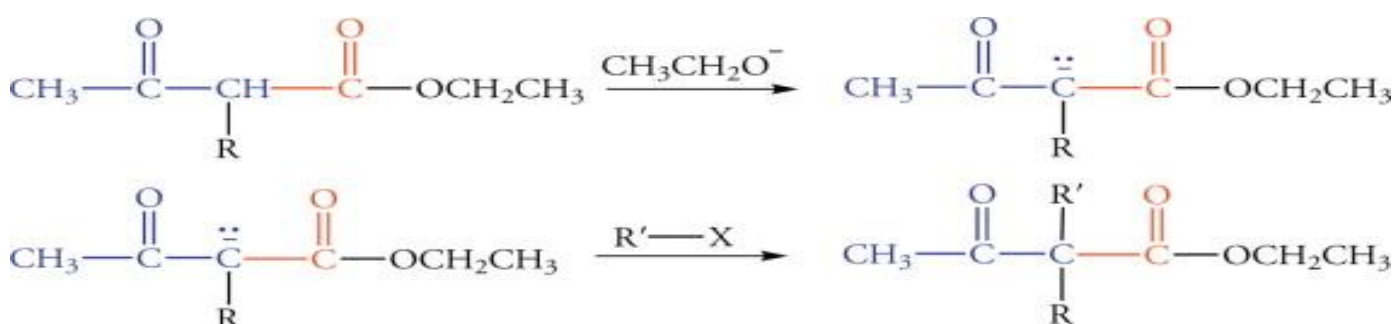
Synthetic uses of Ethyl Acetoacetate

- Acetoacetic ester reacts with base to form a carbanion. The carbanion reacts with alkyl halide (Nucleophilic Substitution reaction) and forms mono alkyl derivative of acetoacetic ester.



Monoalkyl derivative

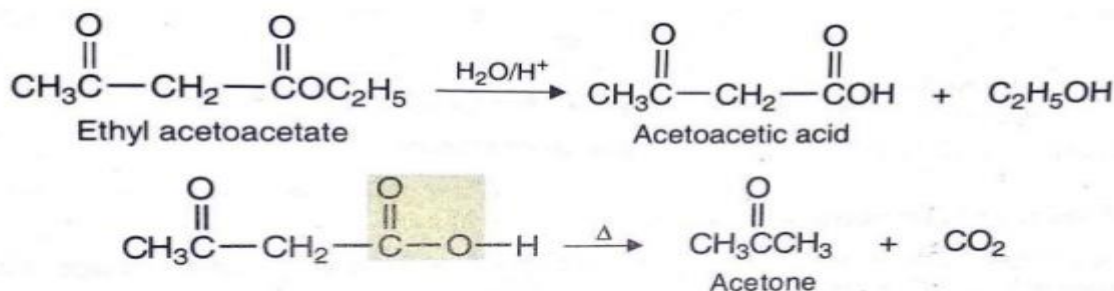
- The above sequence of reactions can be repeated to give a dialkyl derivative of acetoacetic ester.



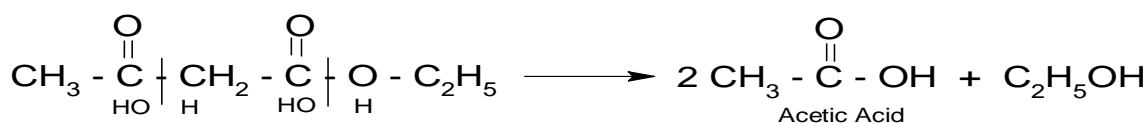
Dialkyl derivative

- **Acetoacetic ester and its alkyl derivatives can undergo two types of hydrolysis with potassium hydroxide:**

(a) **Ketonic hydrolysis:** It is so called because **a ketone is the chief product**. It is carried out by boiling with dilute aqueous or ethanolic potassium hydroxide solution, e.g.,



(b) **Acid hydrolysis:** It is so called because an **acid is the chief product**, is carried out by boiling with concentrated ethanolic potassium hydroxide solution, e.g.,

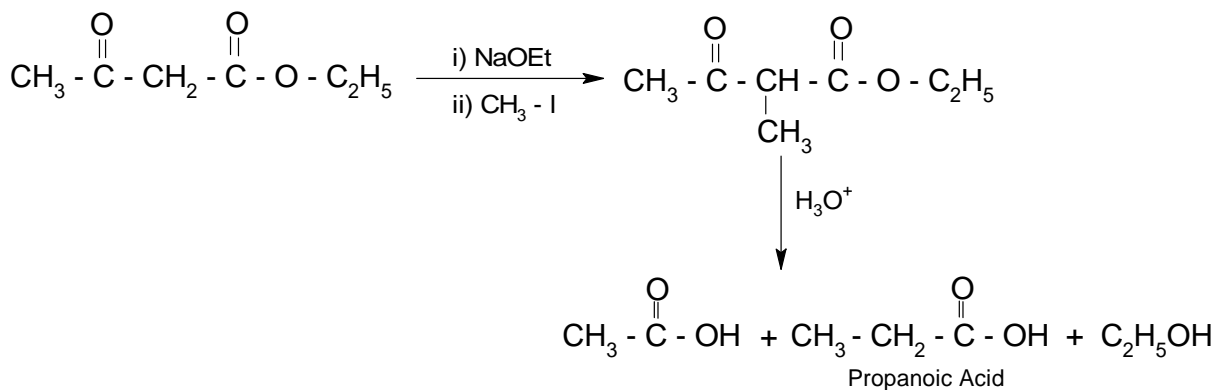


- These alkylation reactions followed by ketonic hydrolysis or acidic hydrolysis are used for the synthesis of various ketones and acids.

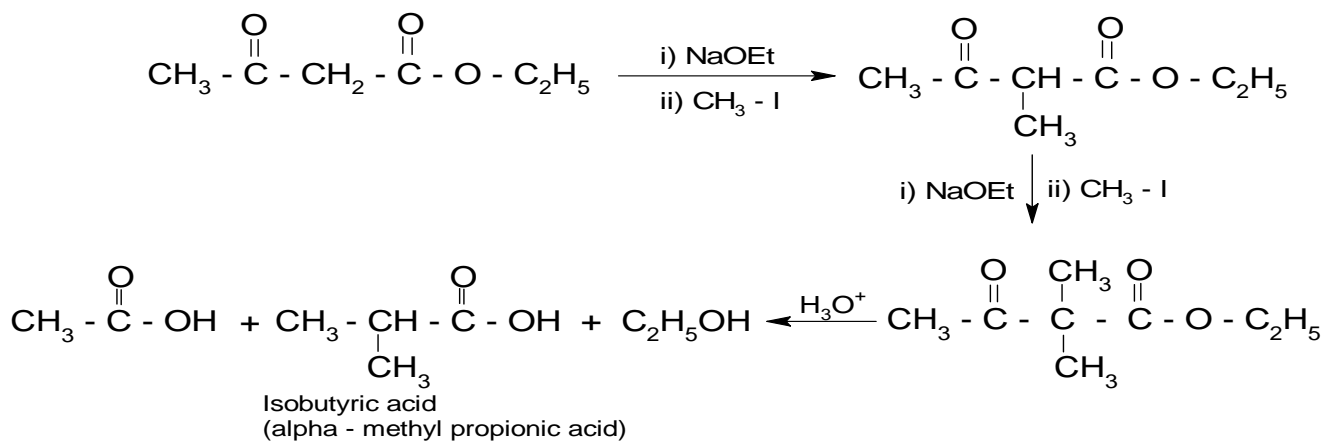
(1) Synthesis of monocarboxylic acids

EAA on acid hydrolysis gives acetic acid. The monoalkyl and dialkyl derivatives of EAA on acid hydrolysis yields corresponding higher mono carboxylic and substituted monocarboxylic acids respectively. For example;

Synthesis of propanoic acid:

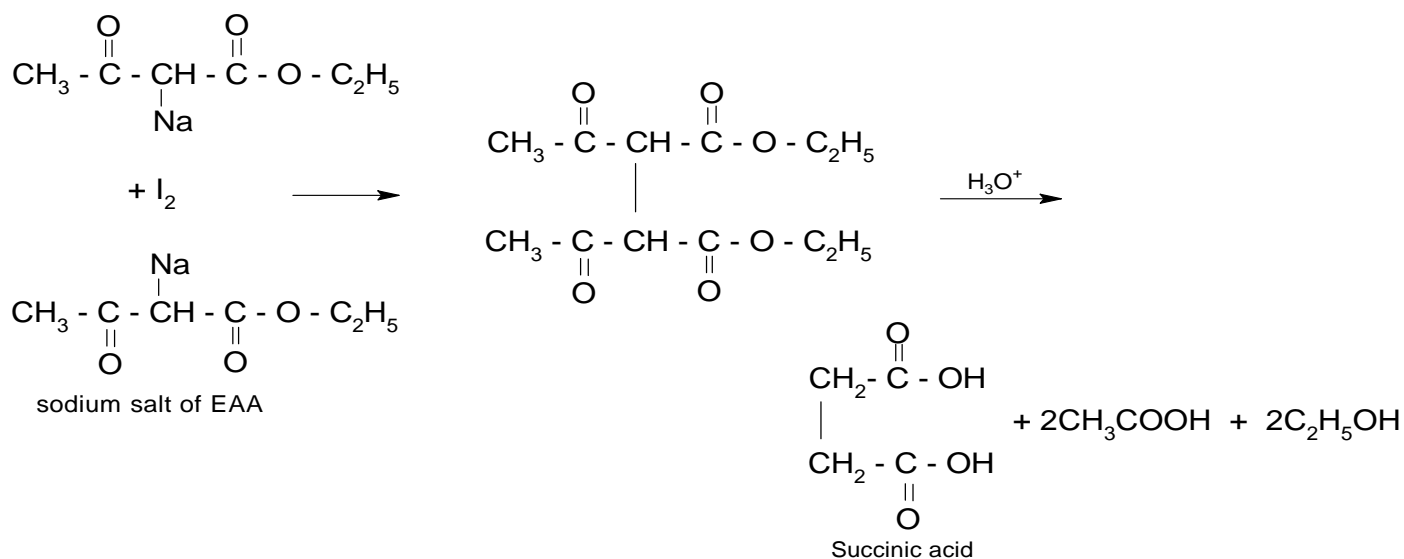


Synthesis of Isobutyric acid:



(2) Synthesis of dicarboxylic acids: -

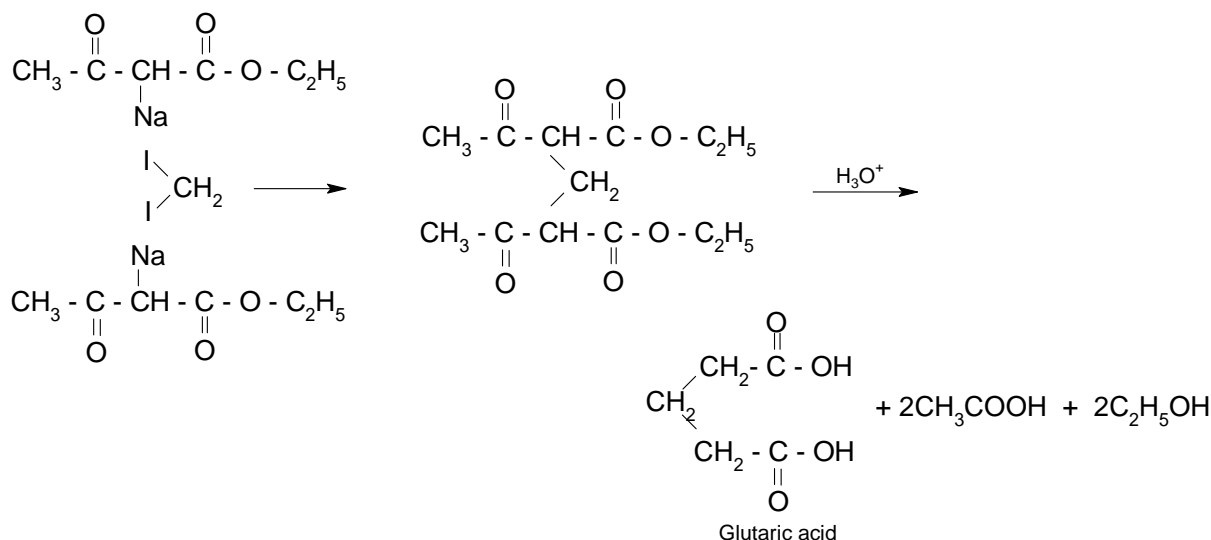
Synthesis of Succinic acid: -



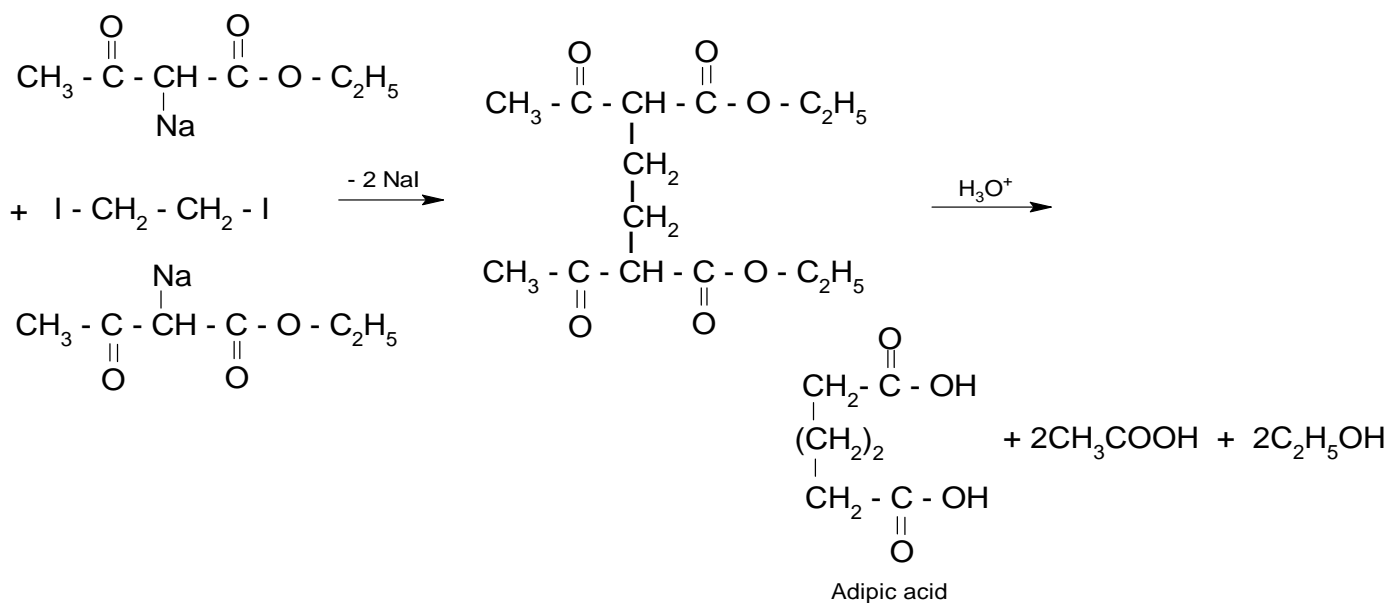
(3) Preparation of Higher Dicarboxylic acids

Higher dicarboxylic acids such as glutaric acid, adipic acid, are prepared by reaction of two moles of the sodium salt of EAA with dihaloalkanes (having halogen at the terminal carbons) followed by acid hydrolysis. This is shown in the following reaction.

Synthesis of Glutaric acid:-

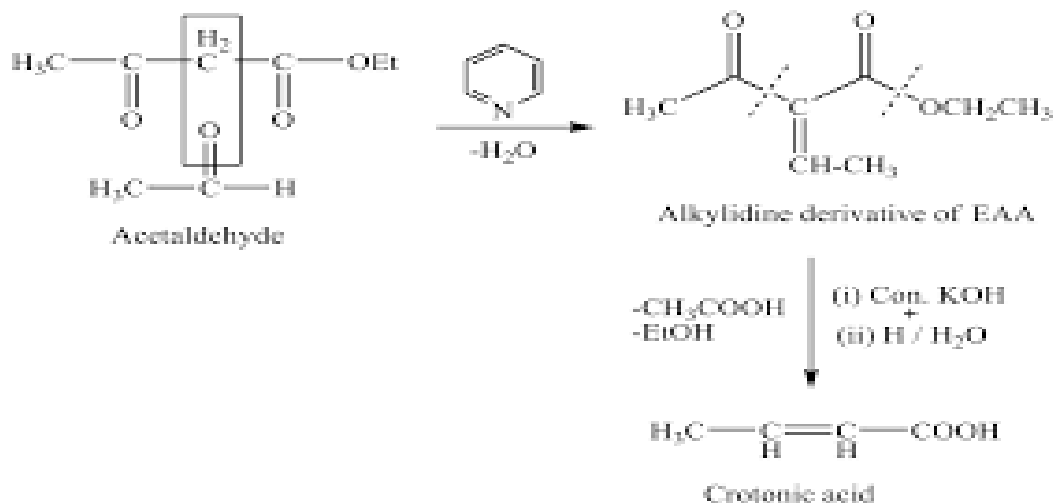


Synthesis of Adipic acid (Hexanedioic acid)



(4) Synthesis of unsaturated compounds: -

Synthesis of crotonic acid

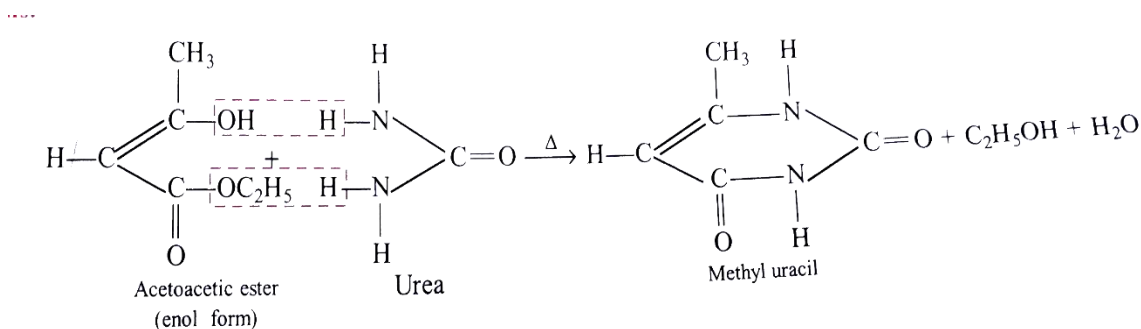


Synthesis of cinnamic acid

With Benzaldehyde, Acetoacetic ester gives Cinnamic Acid ($\text{C}_6\text{H}_5 - \text{CH} = \text{CH} - \text{COOH}$)

(5) Synthesis of cyclic compounds: -

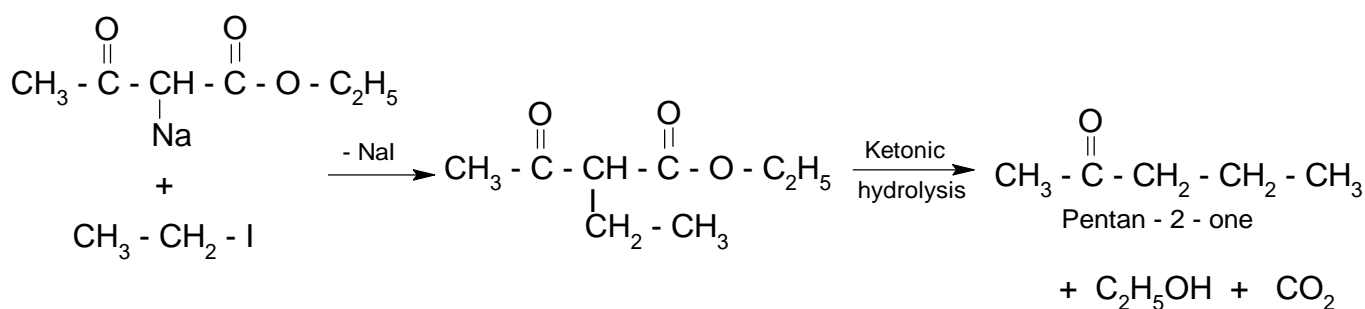
Enolic form of ethyl acetoacetate condenses with urea to form 4 – methyl uracil



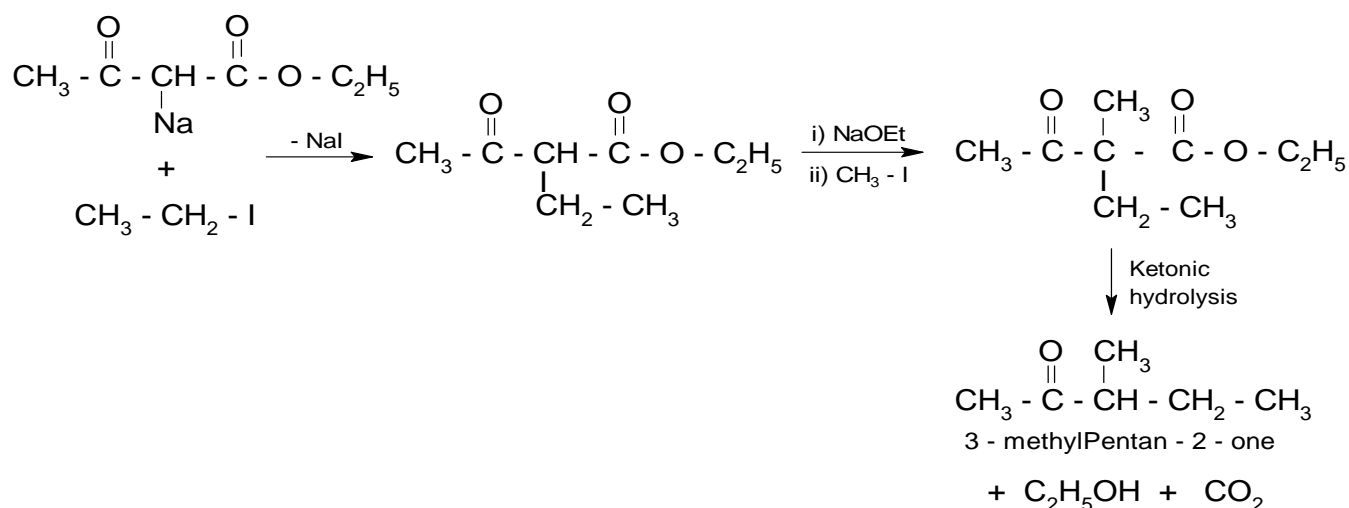
(6) Synthesis of Ketones:

Mono and dialkyl derivatives of EAA on ketone hydrolysis give higher ketones

Synthesis of pentan – 2 – one

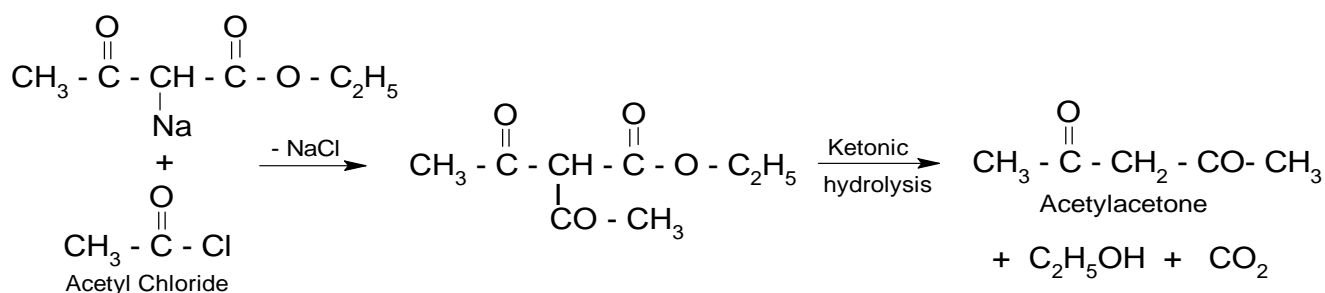


Synthesis of 3 – methyl pentan – 2 – one:



(7) Synthesis of diketones:

Synthesis of acetylacetone:

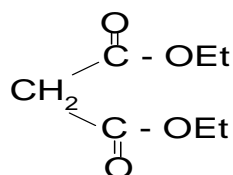


Physical Properties of EAA:

- (1) Ethyl acetoacetate is colourless liquid and has fruity odour.
- (2) Boiling point is 181⁰ C
- (3) Sparingly soluble in water but readily soluble in ethanol, ether and most organic solvents.
- (4) Neutral to litmus.
- (5) Soluble in dilute NaOH and it is enol form which dissolves to give Na-salt.
- (6) Refractive index is 1.4232.
- (7) Gives reddish violate colour with FeCl₃

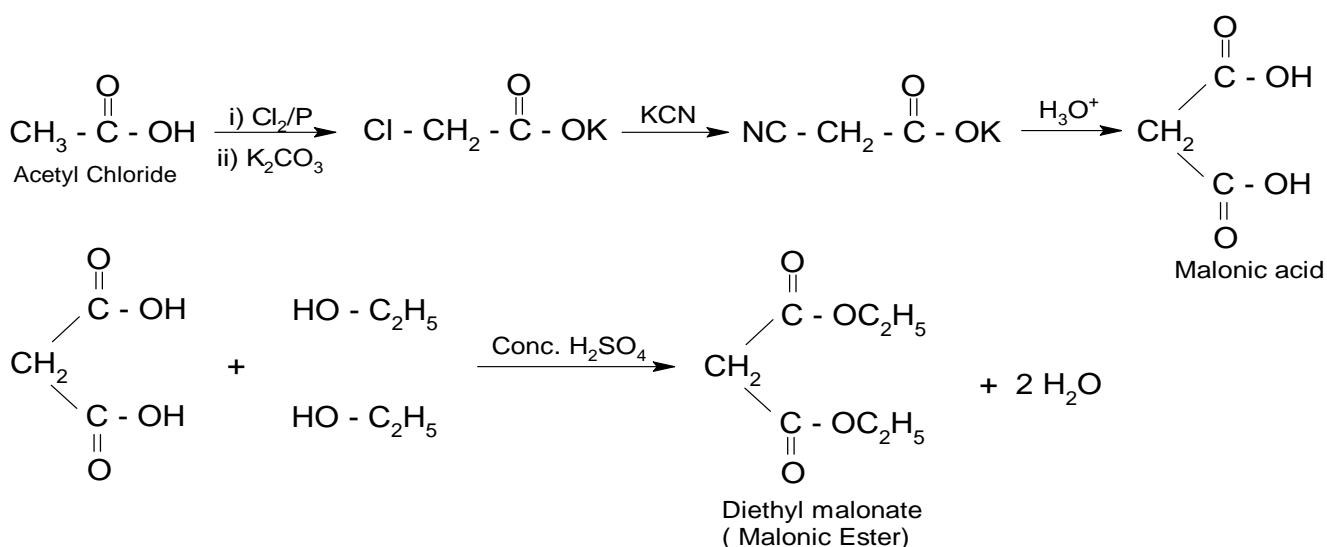
Malonic Ester (Diethyl Malonate)

- Diethyl malonate is an important synthetic reagent and is simply called as malonic ester.
- It is a diethyl ester of malonic acid
- It is a reactive methylene compound where the methylene group is placed between two $\text{C}_2\text{H}_5\text{COO}$ groups



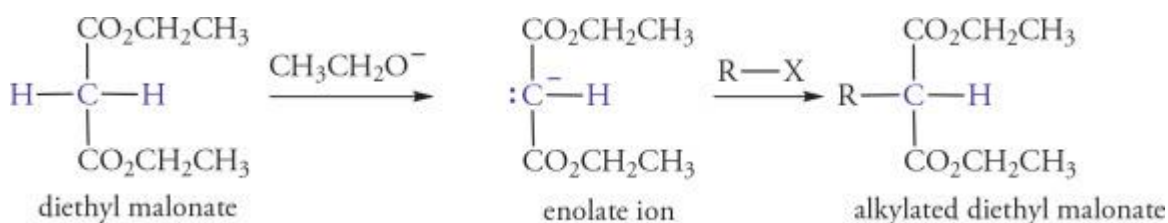
Method of preparation: -

- Monochloro acetic acid obtained by chlorination of acetic acid on treatment with K_2CO_3 gives potassium chloroacetate.
- This on heating with KCN gives pot.
- Cyanoacetate which on acidic hydrolysis gives malonic acid.
- Malonic acid on esterification with ethyl alcohol gives malonic ester.

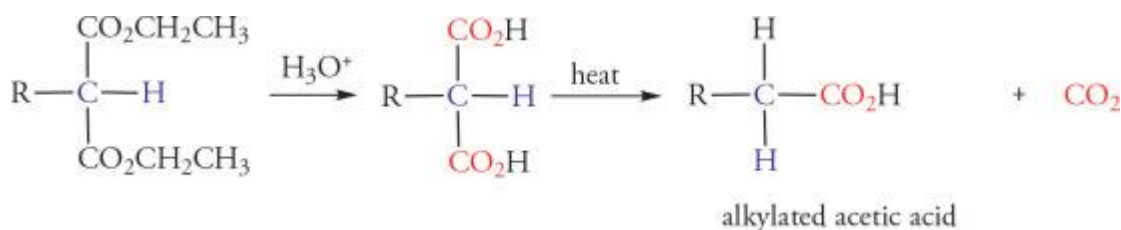


Chemical Properties:

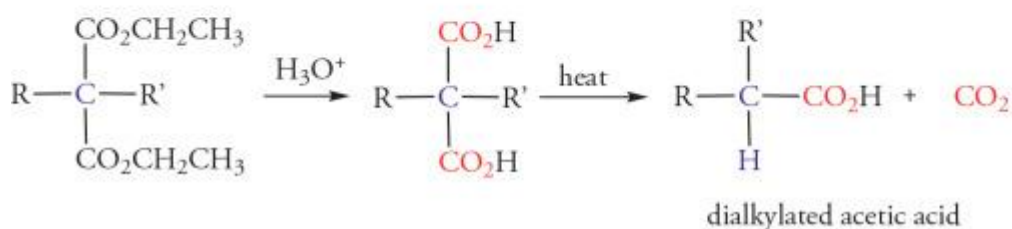
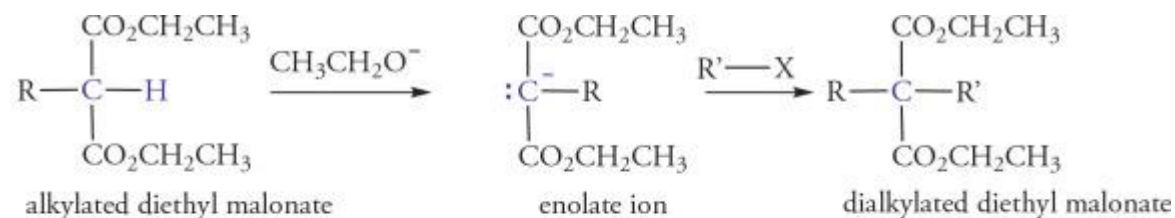
Malonic ester contains reactive methylene group. It reacts with $\text{C}_2\text{H}_5\text{ONa}$ and forms sodio derivative which then reacts with alkyl halide and form monoalkyl derivative



Acid catalyzed [hydrolysis](#) of the alkylated product yields a [malonic acid](#) that decarboxylates when heated and gives substituted acetic acid



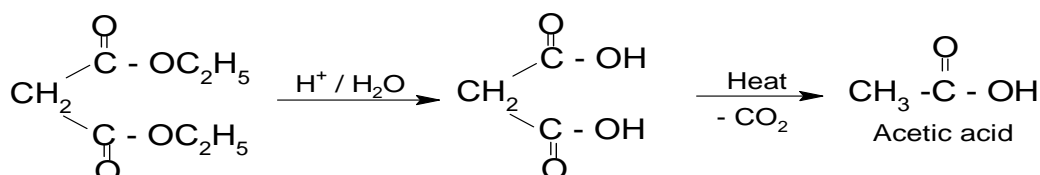
More complicated structures can be prepared by the malonate ester synthesis. It is possible to introduce a second [alkyl group](#) by repeating the steps outlined above using either the same alkyl group or a different one.



Malonic ester and its alkyl derivatives are used for the synthesis of number of organic compounds

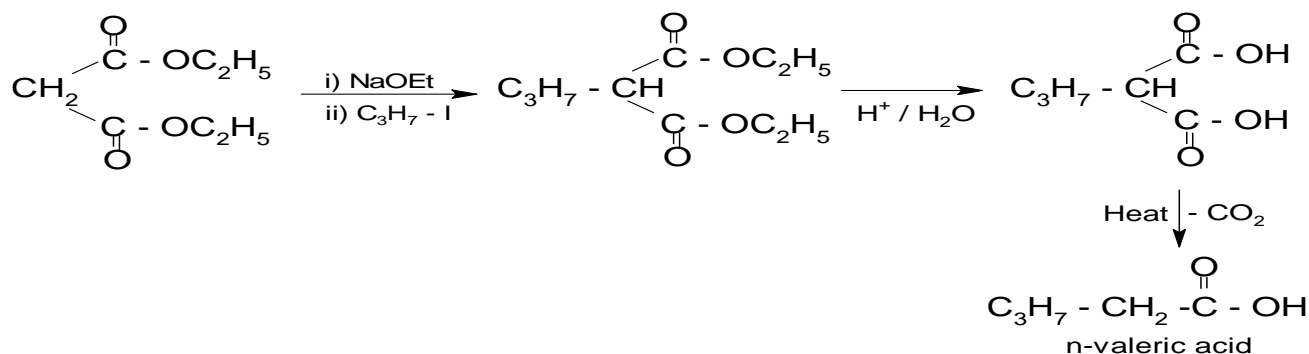
Synthetic applications of malonic ester:

(1) Synthesis of fatty acids (Acetic acid):



(2) Synthesis of higher fatty acids:

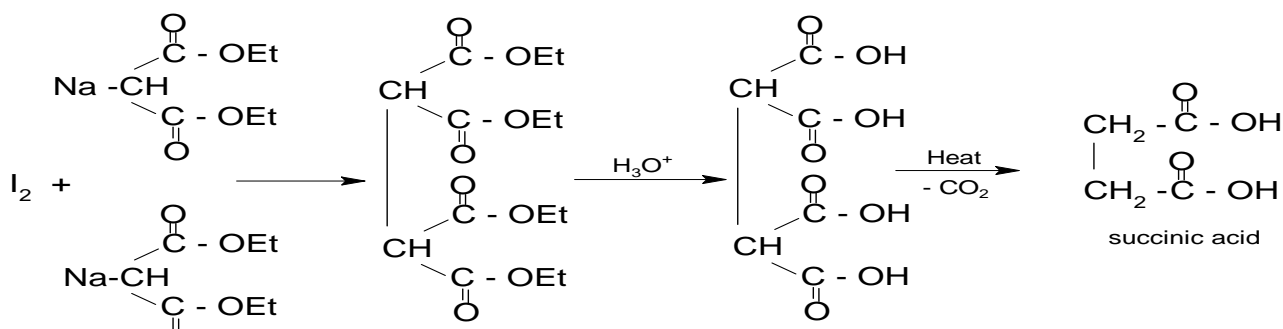
Synthesis of n – valeric acid:



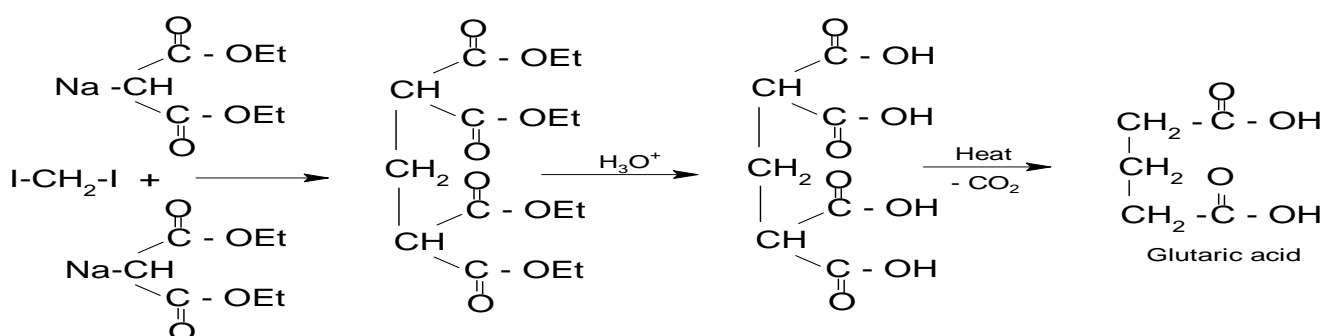
Thus by starting with a suitable monoalkyl or dialkyl derivatives, required fatty acids can be obtained

(3) Synthesis of dicarboxylic acids:

Synthesis of Succinic acid:

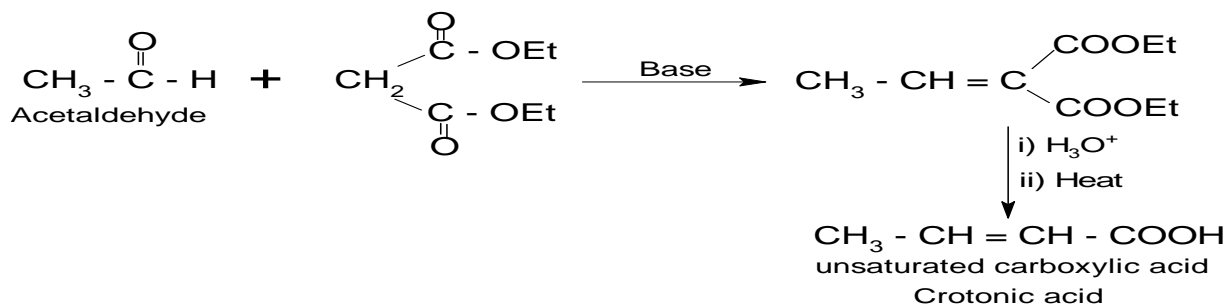
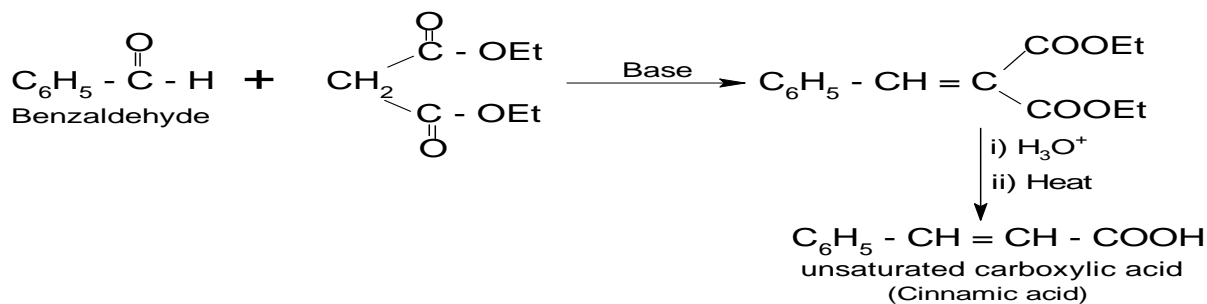


Synthesis of Glutaric acid:



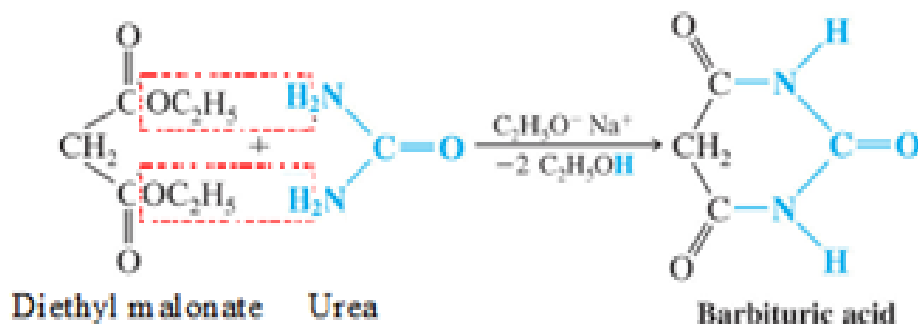
(4) Synthesis of unsaturated acids:

Malonic ester condenses with aldehydes in presence of base to give α,β - unsaturated acids

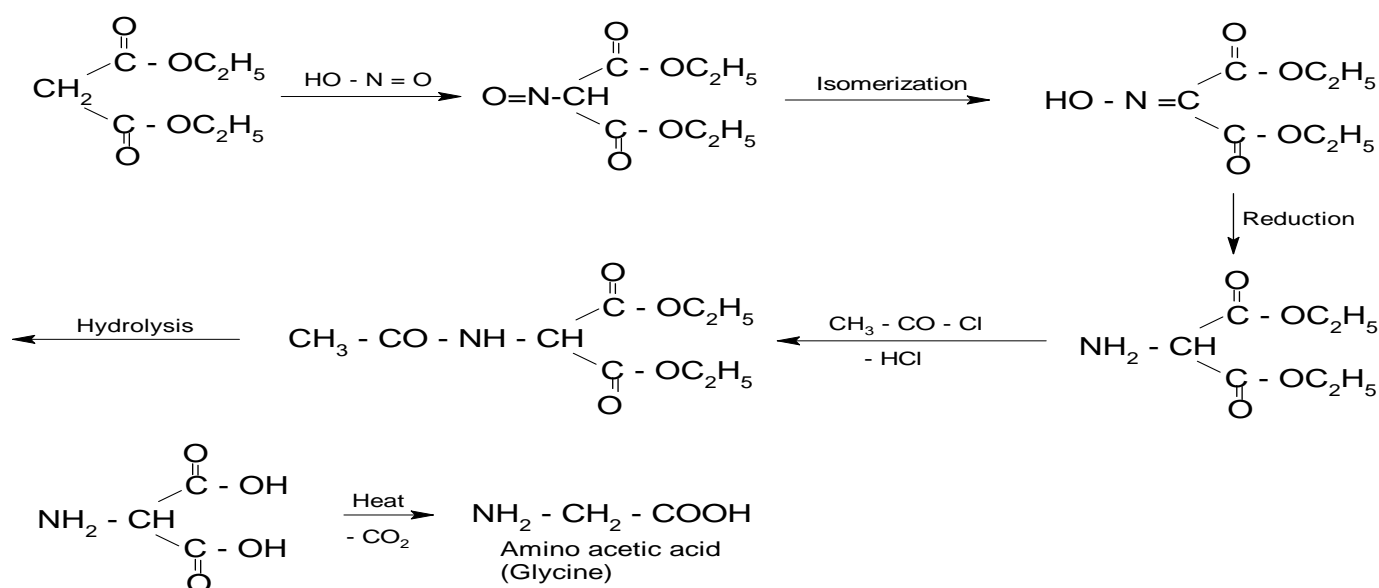


(5) Synthesis of barbituric acid:

Urea condenses with malonic ester and forms malonyl urea (Barbituric acid)

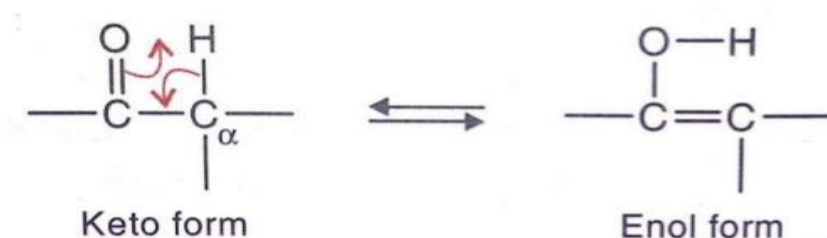


(6) Synthesis of Glycine:



Keto-enol Tautomerism in Ethyl acetoacetate (EAA)

- Aldehydes, ketones and other carbonyl compounds exhibit this special type of tautomerism.
- This type of tautomerism has been observed in EAA.
- It involves migration of proton from α -carbon to carbonyl oxygen by the following mechanism.



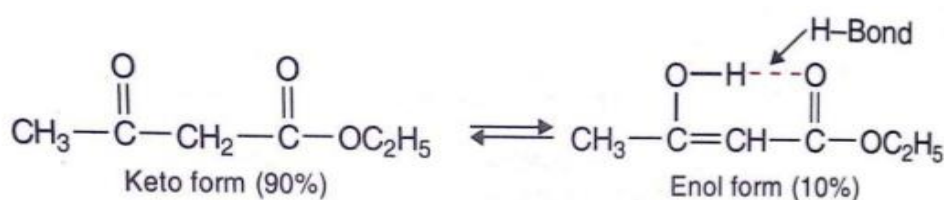
Stability of Keto form:

- The tautomer containing carbonyl group ($>\text{C}=\text{O}$) is designated as keto form, and the other one containing hydroxyl group ($-\text{OH}$) attached to a doubly bonded carbon is referred as enol form.
- This kind of tautomerism is termed as keto-enol tautomerism.

- Due to greater strength of π bond of $C=O$ group as compared to that of $C=C$ group, the keto form is more stable than enol form.
- In simple aldehydes and ketones the amount of enol form is negligible ($<1\%$).
- However, the percentage of enol form increases in case of 1,3 – dicarbonyl compounds. It is because of the formation of intramolecular H – bonding.

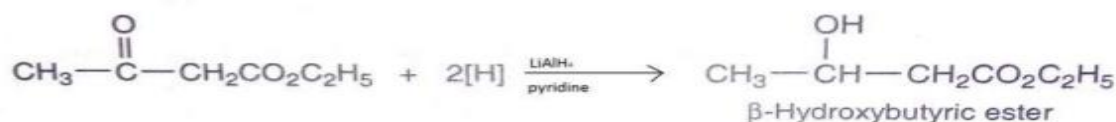


- Ethyl acetoacetate also exist as a tautomeric mixture of keto and enol form.
- The enol form is present in appreciable quantity and the stability of the enol form is said to be due to the intra – molecular hydrogen bonding.



❖ Facts in favor of keto form:

- EAA forms a bisulphite compound with sodium hydrogen sulphite.
- EAA forms a cyanohydrin with hydrogen cyanide.
- EAA forms an oxime with hydroxylamine and phenylhydrazone with phenylhydrazine.
- On reduction with sodium amalgum or by using LiAlH_4 in pyridine, EAA gives β -hydroxybutyric ester containing a secondary alcohol group.



❖ Facts in favor of enol form:

- EAA reacts with sodium metal to form sodium derivative and hydrogen gas is evolved. This indicates the presence of $-\text{OH}$ group.
- EAA forms an acetyl derivative with acetyl chloride which shows the presence of $-\text{OH}$ group.
- When EAA is treated with alcoholic bromine solution, the brown color of the later is discharged. This indicates the presence of $C=C$ bond.
- EAA forms a reddish violet color when treated with FeCl_3 . This indicates the presence of $C=C-\text{OH}$ structural unit as in phenol.