

Chemistry

B.Sc. Sixth Sem.

ORGANIC SYNTHESIS VIA

ENOLATES

(Unit-1)

LECTURE - 1

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Organic synthesis via Enolates

- *Topics to be studied:*
 - ❖ Active methylene group and active methylene compounds.
 - ❖ Enols and Enolate ions
 - ❖ Enolisation :Acid catalysed and base catalysed enolisation
 - ❖ Ethyl aceto acetate
 - ❖ Claisen Condensation
 - ❖ Keto – Enol tautomerism
 - ❖ Synthetic Applications

Active methylene group and compounds

What do you mean by *active methylene* group?
Give its General Formula.

A methylene (-CH₂-) group which is located between two electron withdrawing groups.

General Formula:



Z and Z' are electron withdrawing
same or different groups

- A methylene group ($-\text{CH}_2$) which is attached from both sides by electron withdrawing groups (e.g. $-\text{CHO}$, $>\text{C}=\text{O}$, $-\text{COOH}$, $-\text{COOR}$, $-\text{CN}$, $-\text{X}$ etc.) is called active methylene group.

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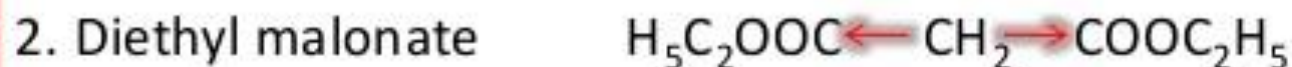
- A methylene group ($-\text{CH}_2$) which is attached from

What do you mean by *active methylene compounds*?

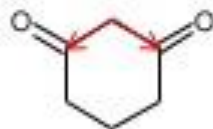
Give their examples.

Compounds containing active methylene group are active methylene compounds.

Examples :



5. 1,3-Cyclohexadione



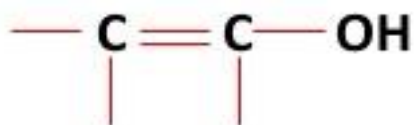
★ In our syllabus we have to study only the first and second example.

Enols and Enolate ions

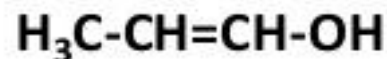
What are enols and enolate ions?

Enols :

Compounds containing hydroxy group directly attached to a c=c bond.

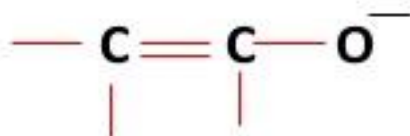


e.g.

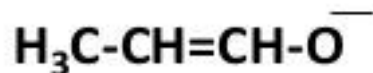


Enolate ions:

Anions of enols are called as enolate ions



e.g.



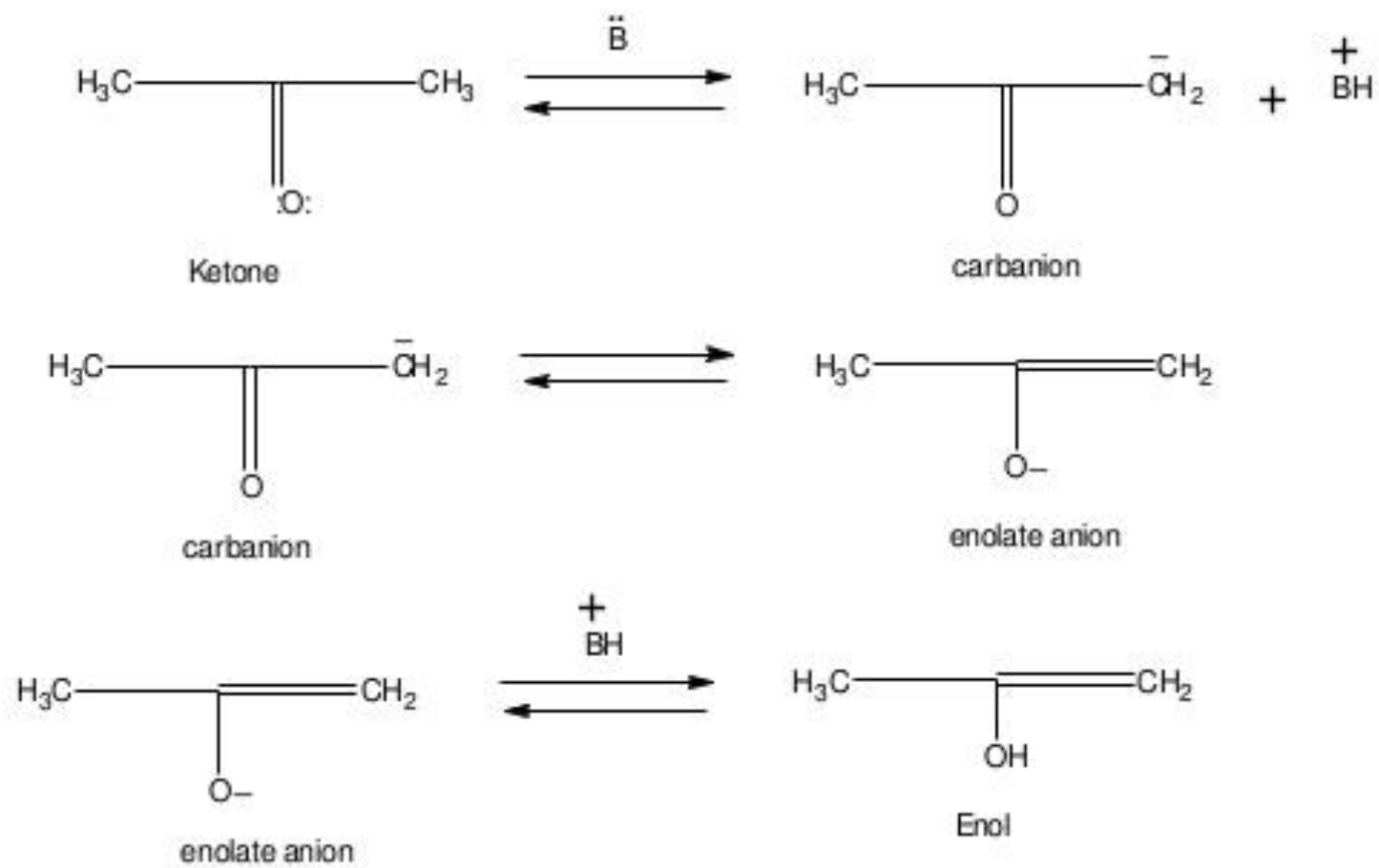
Enolisation

The conversion of a ketone into an enol is known as enolisation.

Usually this is a reversible tautomerization but it can be irreversible.

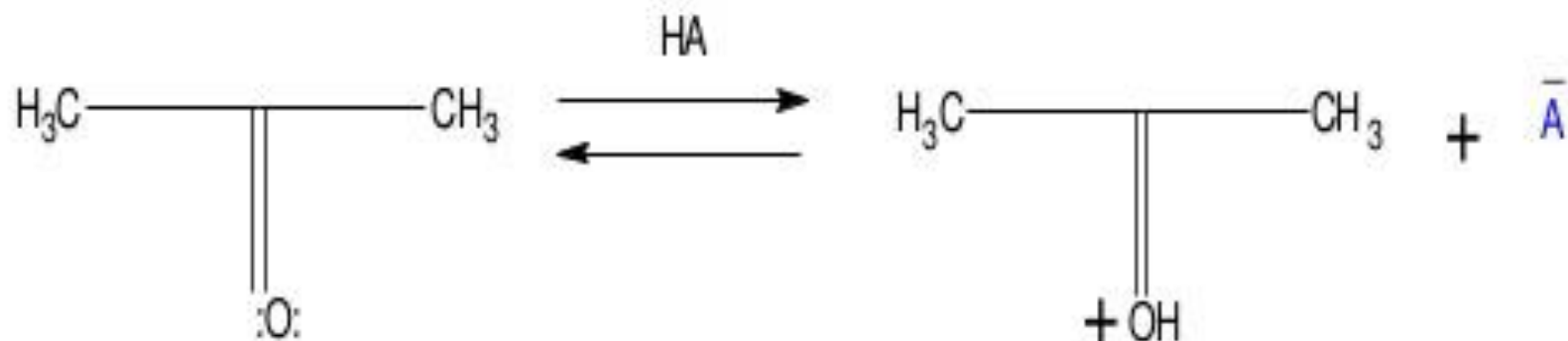
Mechanism of enolisation

1. Base catalysed

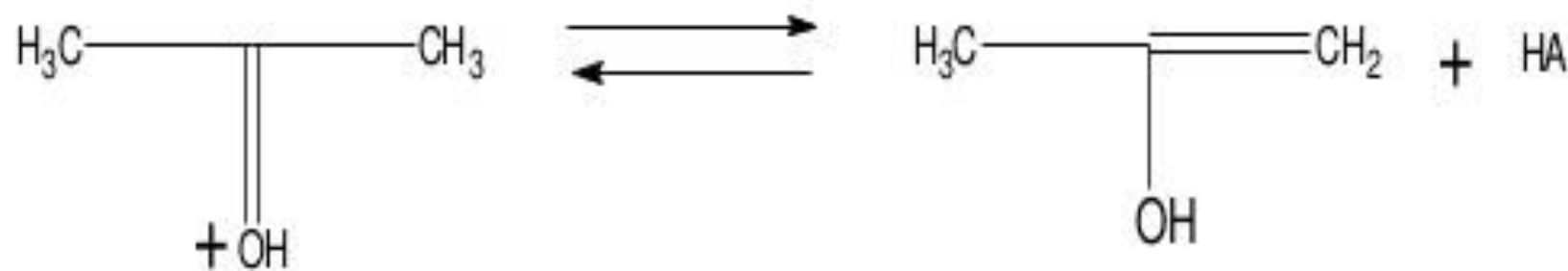


Mechanism of enolisation

2. Acid catalysed



Ketone

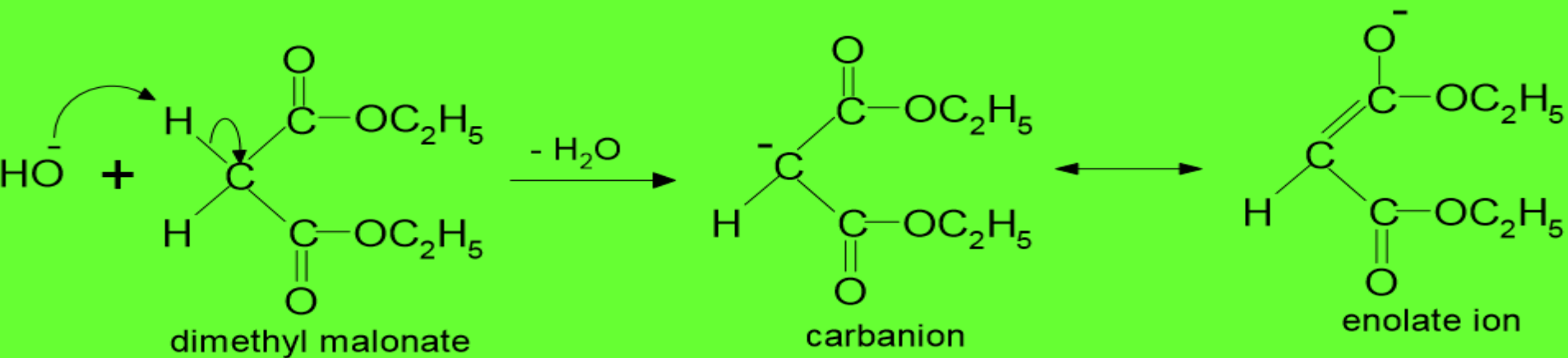


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Before we further move to next topic we should revise

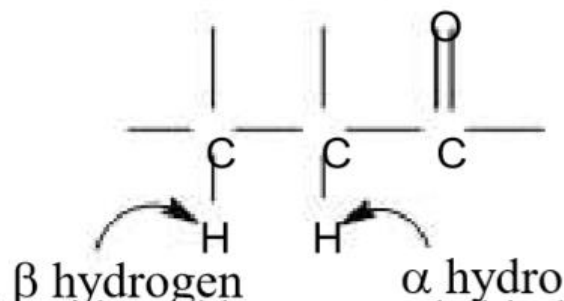
Acidity of α -hydrogen

- The hydrogen atoms of active methylene group are **acidic in nature**.
- The compounds containing active methylene group when treated with base, loses hydrogen atoms to form **carbanion**.
- This carbanion is stabilized by another resonating structure called as **enolate ion**.

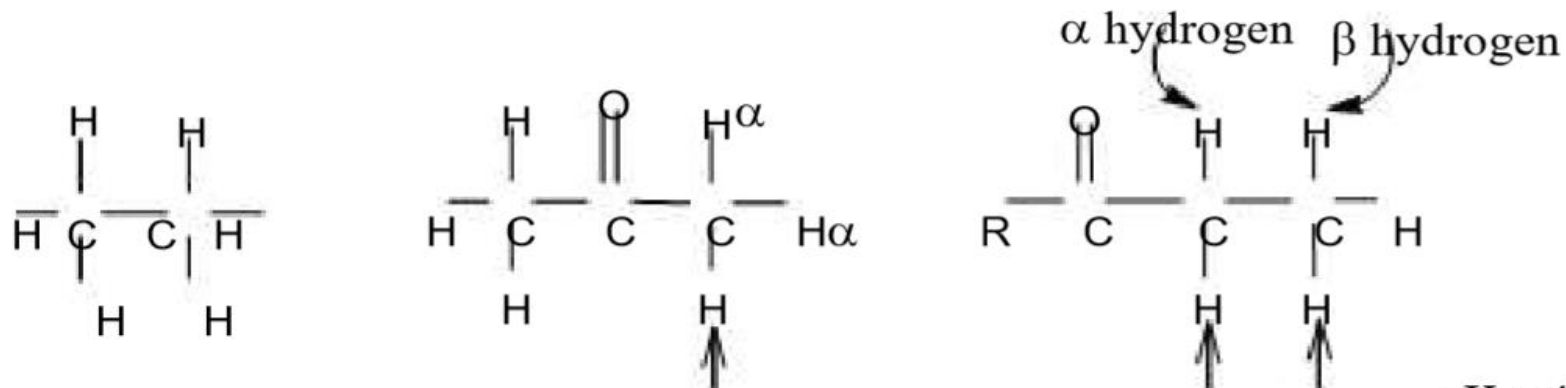


1. Acidity of α hydrogens:

The α (alpha) - hydrogen is the hydrogen atom that is bound to the carbon (called as α - carbon atom) adjacent to the carbonyl carbon. The next carbon is the β -carbon and the hydrogen atoms attached to it are called as β -hydrogen atoms and so on.



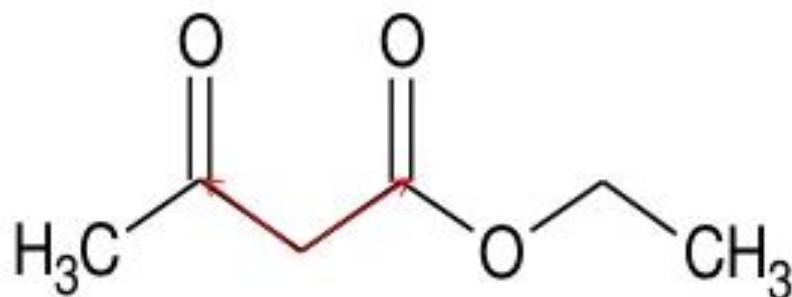
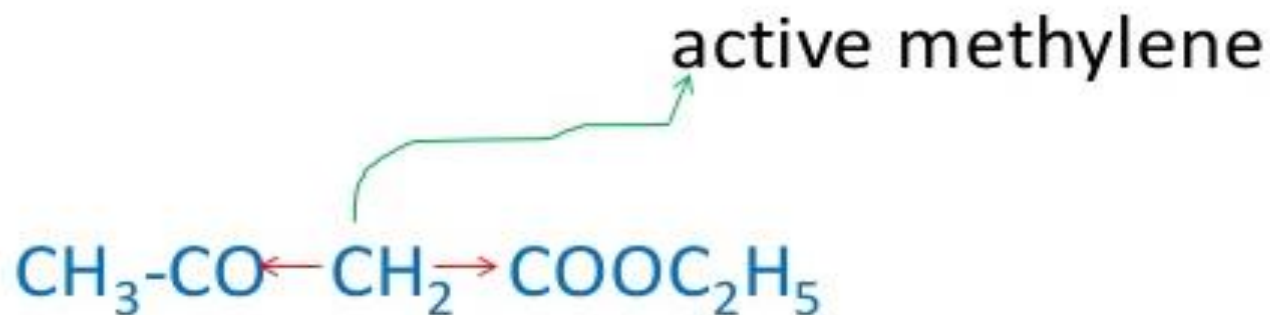
Aldehydes and ketones are weak acids and have remarkably low pK_a values (between 15 and 20). Hence, they may act as a Bronsted acid in an acid-base reaction with a strong base. But, aldehydes and ketones are much stronger acids **than** alkanes. Due to the only minor difference in electronegativity between hydrogen and carbon, C-H bonds in alkanes are hardly polarized. Thus, hydrogens of alkanes are in fact not acidic. The pK_a values of alkanes are around 50.



The acidity of α -hydrogens of aldehydes and ketones is much less than carboxylic acids, which have pK_a values around 3 to 4. $pK_a=4$

Ethyl aceto acetate

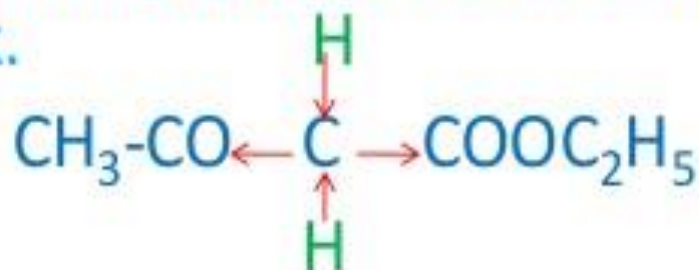
Structure:



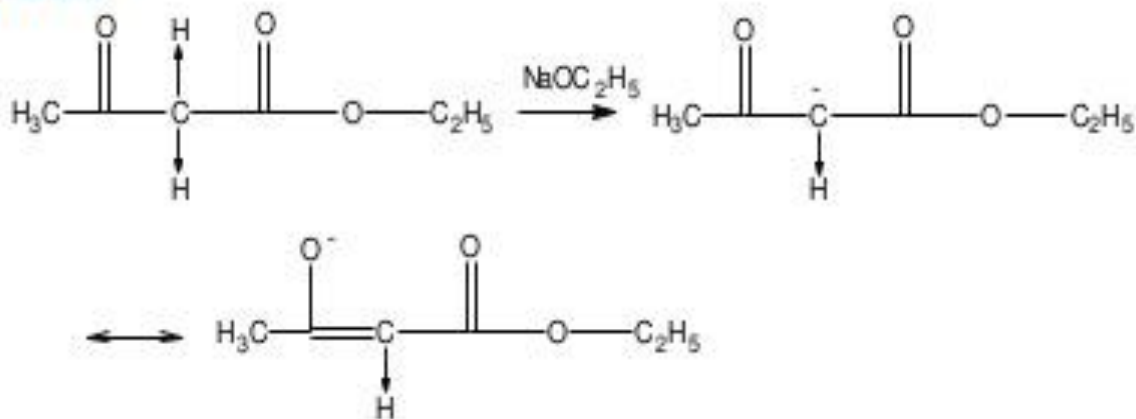
Why is methylene group in EAA reactive?

Because :

1. Inductive effect: CH_2 group is located between two electron withdrawing groups (-I effect). hence two C-H bonds are weak.



2. Resonance effect : Base abstracts proton from methylene group to form a carbanion which is stabilised by resonance.



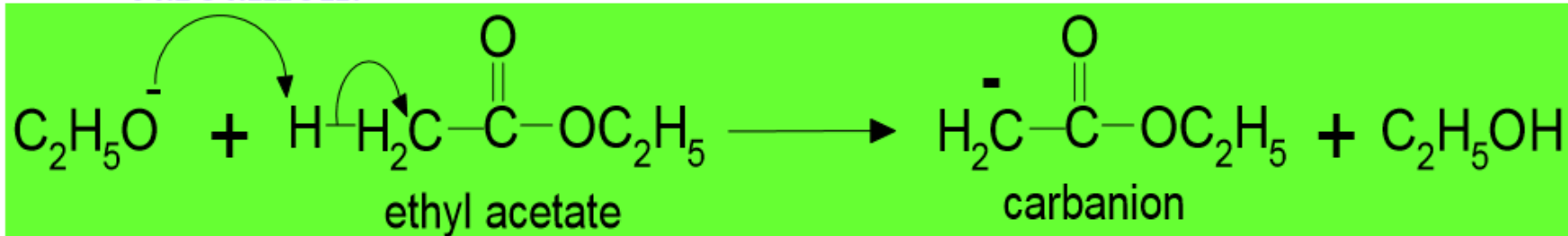
Synthesis of Ethyl acetoacetate

Claisen condensation

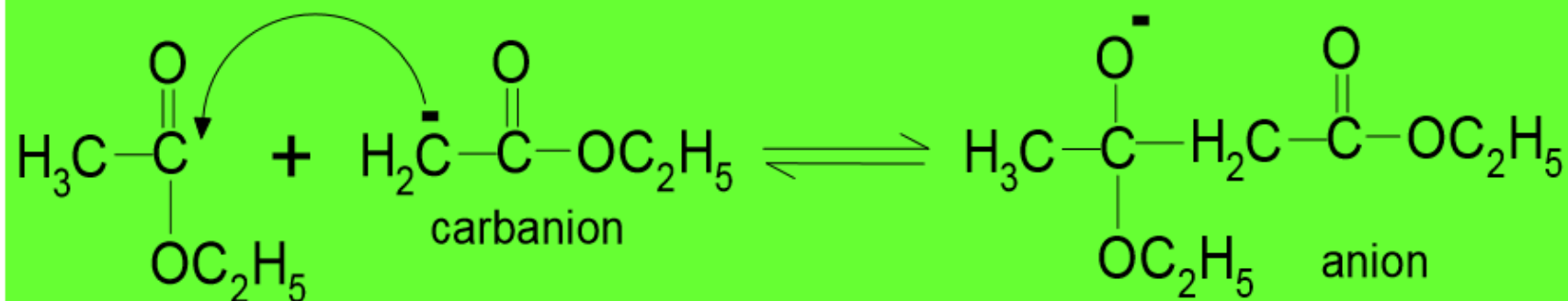
Ethyl acetate undergoes self condensation in the presence of strong base like sodium ethoxide to give ethyl aceto acetate.



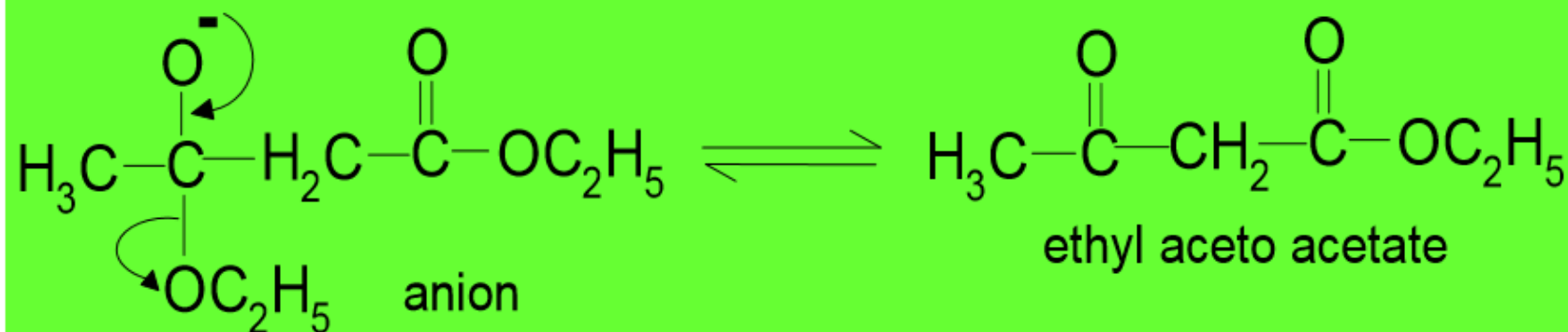
- This base catalyzed condensation of ester containing α -hydrogen atom is called Claisen condensation.
- **Mechanism:** It involves following steps.
 - a) Base abstract α - H atom from ethyl acetate to form carbanion.



- b. This carbanion attacks on carbonyl carbon of another ethyl acetate molecule to form anion.

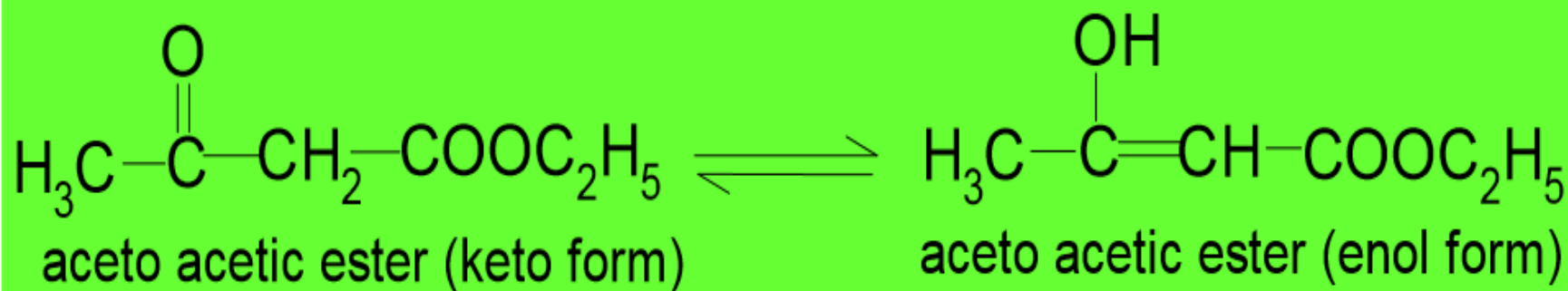


- c. This anion loses ethoxide ion to form ethyl aceto acetate.



Keto-Enol Tautomerism

- Ethyl aceto acetate exists as an equilibrium mixture of two **functional forms** as keto and enol. These two forms are constantly interconvert into one another.
- This phenomenon in which two structural isomers spontaneously interconvert and exist in dynamic equilibrium is called **tautomerism**.

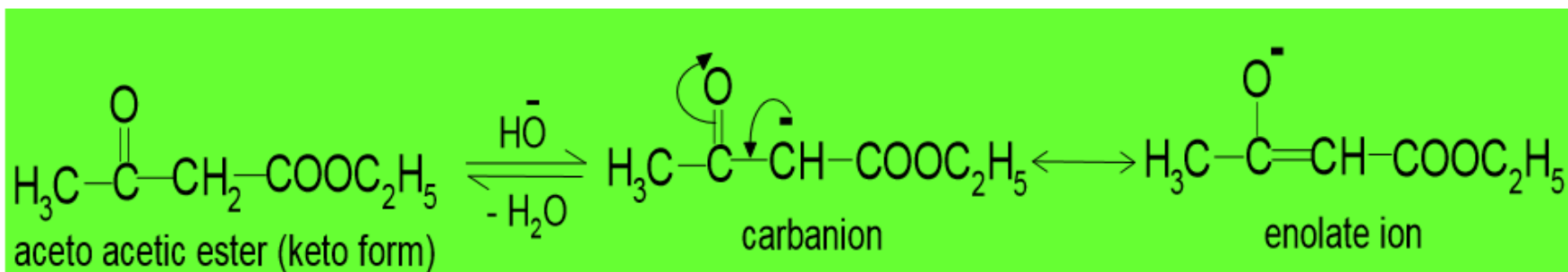


- The tautomer which containing carbonyl group is called **keto form** while other tautomer which containing hydroxyl group attached to double bonded carbon is called **enol form**.

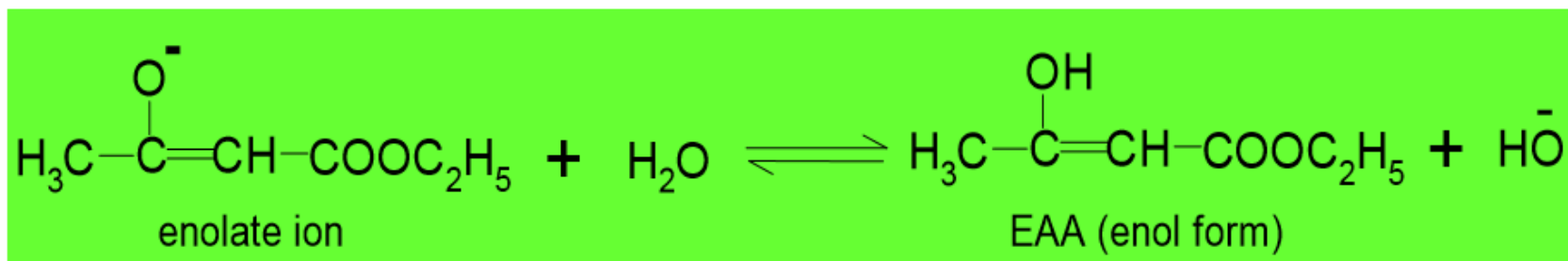
- **Mechanism:** Keto and enol forms are isomers which are easily interconvertible in presence of small amount of acid or base.

A. Base Catalyzed Keto-Enol Tautomerism:

- In first step, Base abstract proton from EAA to form **carbanion** which is resonance stabilized.

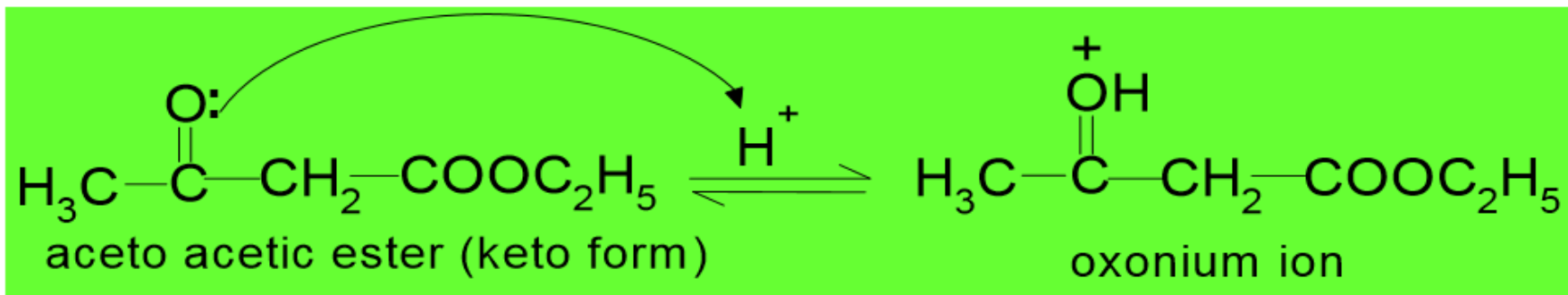


- In second step, enolate ion takes proton from water molecule to form **enol** form of EAA.

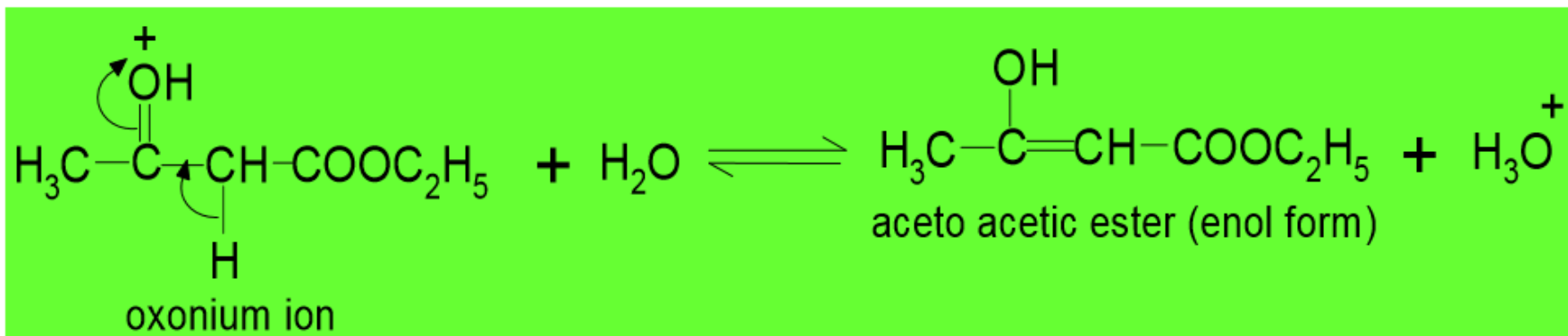


B. Acid Catalyzed Keto-Enol Tautomerism

- In first step, carbonyl oxygen takes proton from acid to form **oxonium ion**.



- In second step, oxonium ion loses proton to form **enol form**.



Synthetic applications of EAA

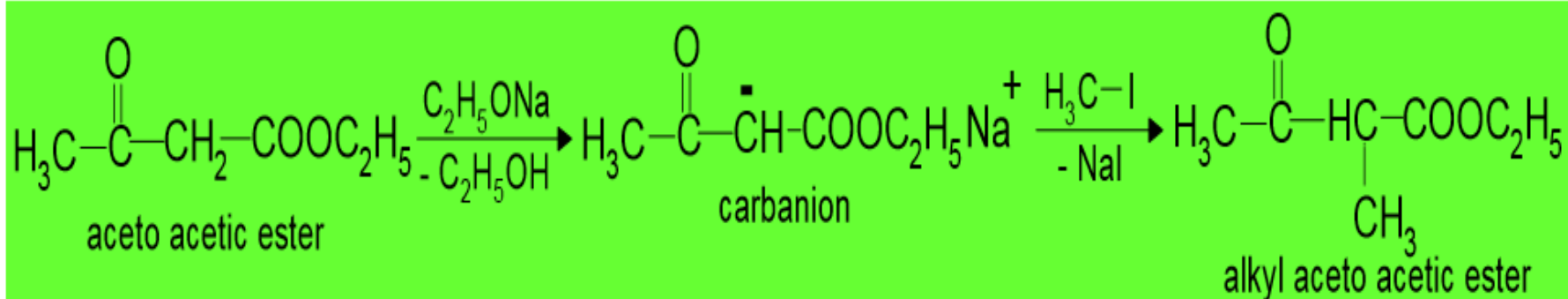
Syntheses of various carboxylic acids and methyl ketones.

Common steps involved :

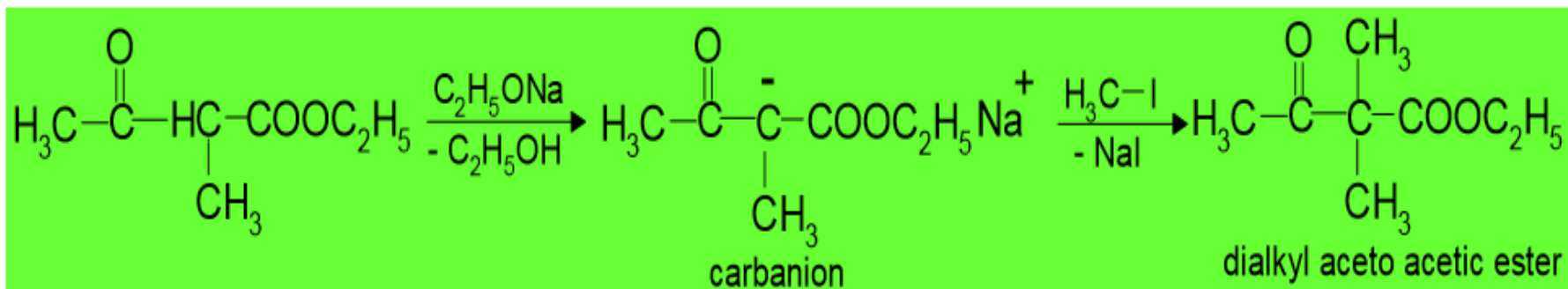
1. Na-salt formation: Reaction with Na-alkoxide, one or both alpha hydrogen atoms get replaced by Na.
2. Alkylation : reaction of Na-salt of EAA with RX to form mono or dialkylated EAA.
3. Hydrolysis : Depending on nature of product desired one of the following procedures is used
 - i) **Ketonic hydrolysis** : Alkylated EAA is heated with dil. alkali or acid. Hydrolysis yields ketone as the product.
 - ii) **Acid hydrolysis** : Alkylated EAA is heated with con. NaOH followed by acidification. Hydrolysis yields carboxylic acid as the product.

1. Synthesis of alkyl aceto acetic ester:-

- Aceto acetic ester when treated with sodium ethoxide gives carbanion which on further treatment with alkyl halide gives corresponding **alkyl derivative**.

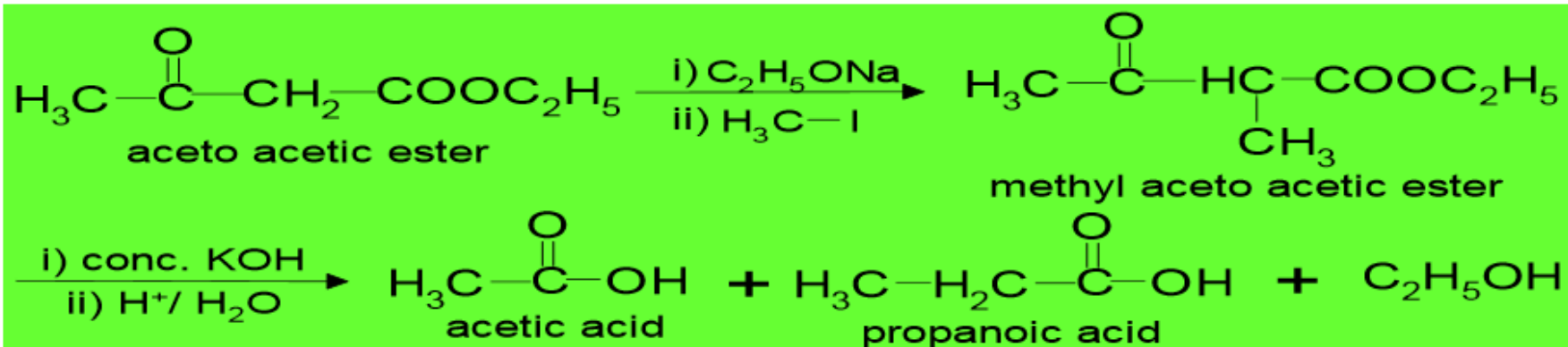


- This alkyl aceto acetic ester again on treatment with sodium ethoxide followed by reaction with alkyl halide gives **dialkyl aceto acetic ester**.

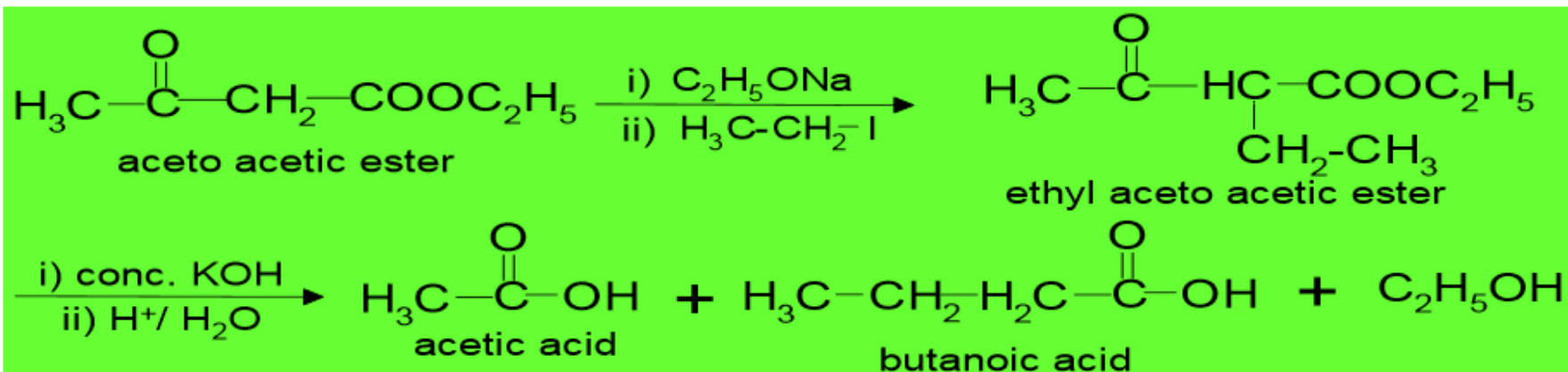


2. **Synthesis of Mono-carboxylic acid:** - Higher carboxylic acids prepared by alkylating EAA followed by hydrolysis.

- EAA when treated with sodium ethoxide and methyl iodide gives methyl EAA which on further hydrolysis gives **propanoic acid**.

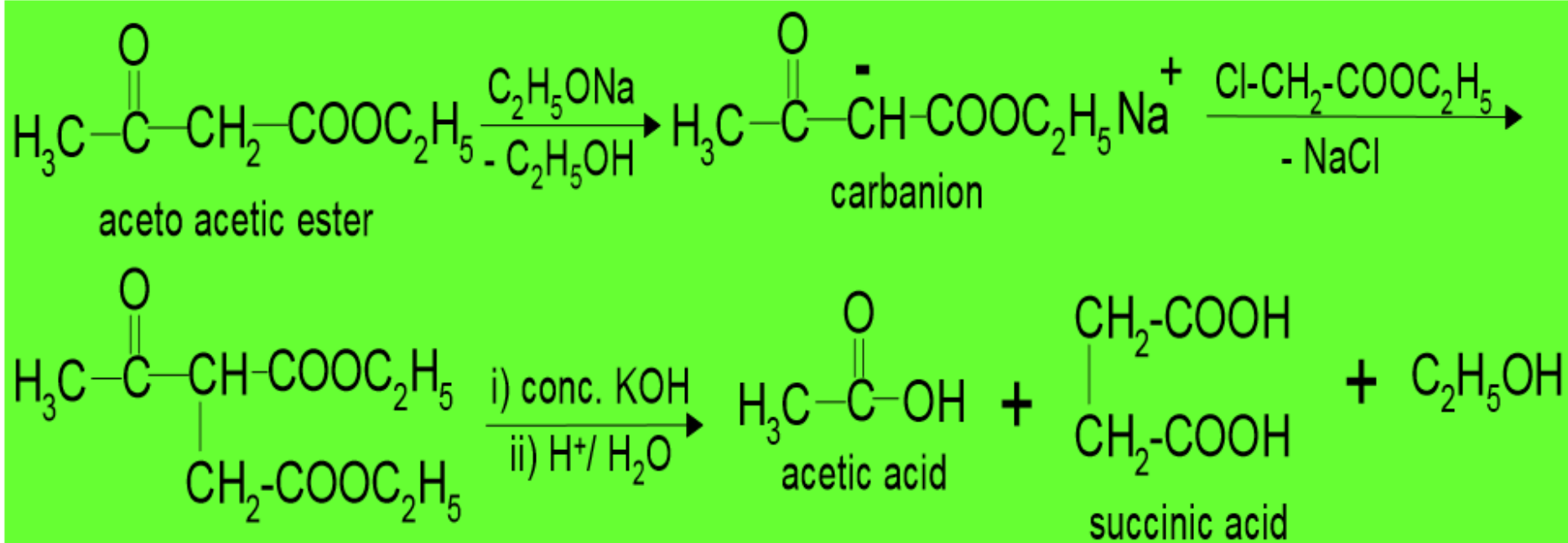


- EAA when treated with sodium ethoxide and ethyl iodide gives ethyl EAA which on further hydrolysis gives **butanoic acid**.



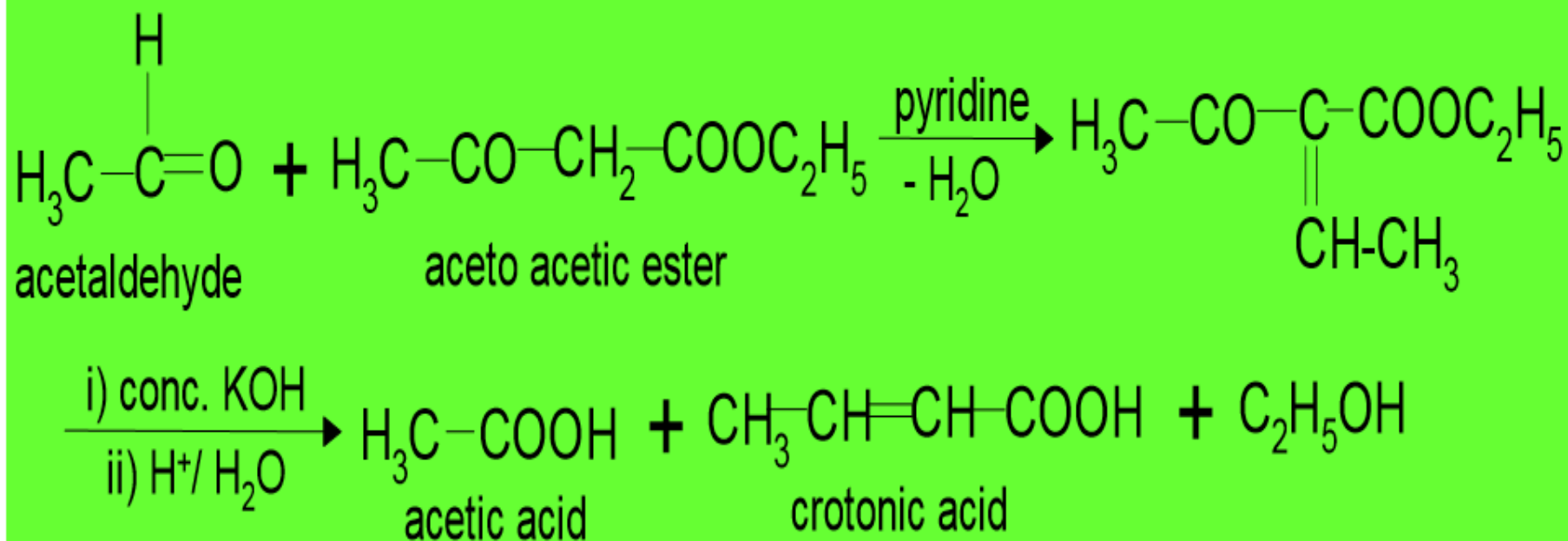
3. Synthesis of Dicarboxylic Acid: -

- Aceto acetic ester on treatment with sodium ethoxide gives carbanion which on condensation with halo ester followed by hydrolysis gives corresponding dicarboxylic acid.
- Aceto acetic ester on treatment with sodium ethoxide gives carbanion which on condensation with ethyl chloro acetate followed by hydrolysis gives succinic acid.



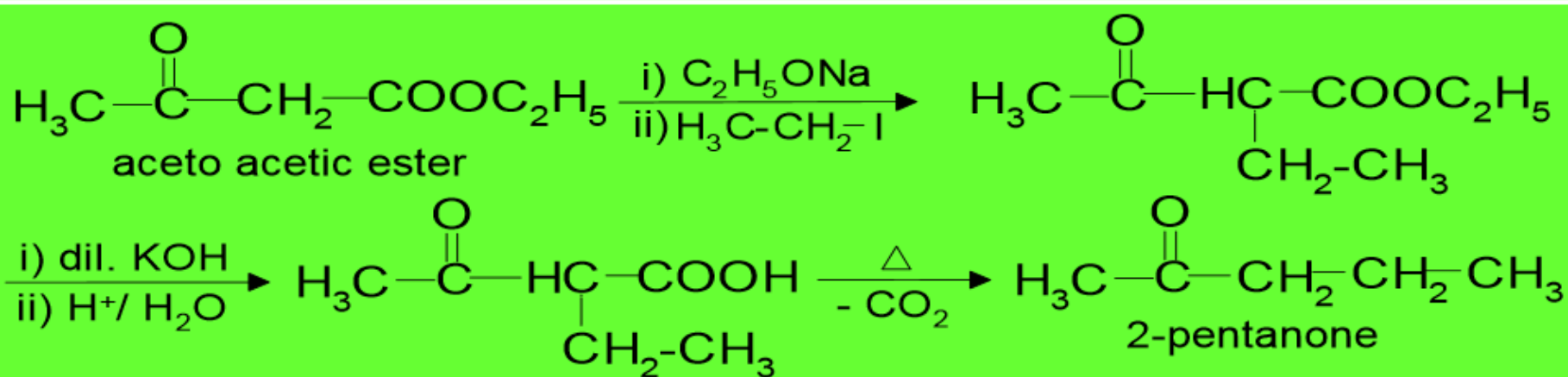
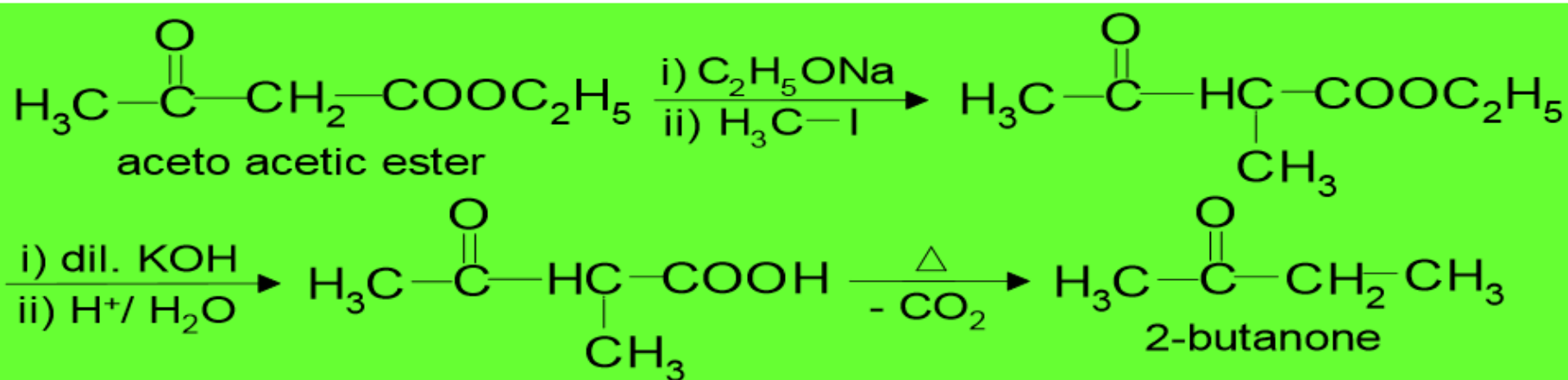
4. Synthesis of unsaturated acid:-

- AAE on condensation with **aldehyde** or **ketone** in presence of base (pyridine) gives intermediate which on further acid hydrolysis gives **α , β -unsaturated acid**.
- AAE on condensation with **acetaldehyde** in presence of base (pyridine) gives intermediate which on further acid hydrolysis gives **crotonic acid**.



5. Synthesis of ketone: -

- AAE on alkylation gives corresponding alkyl aceto acetic acid which on hydrolysis gives corresponding carboxylic acid intermediate. This intermediate carboxylic acid further on decarboxylation gives ketone.



End

of

Lecture - 1