

Active Methylene Compounds

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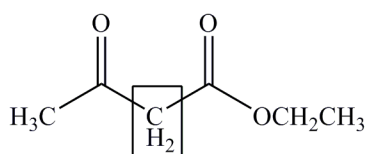
Introduction

The hydrogens in methane practically do not exhibit acidic character. However when two of the hydrogens are replaced by electron withdrawing groups, the rest of the hydrogens become acidic in nature. The electron withdrawing groups present on both sides attract the electron towards themselves and thus weaken the $-CH$ bond of methylene. Thus hydrogen atom can dissociate to give a stable anion. This same phenomena applies to EAA, the two hydrogen atoms bonded to methylene group become acidic and reactive due to two electron withdrawing functional groups i.e. acetyl and ester attached to methylene carbon.

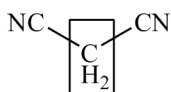
Thus methylene group attached to two electron withdrawing functional groups is termed as reactive methylene group.

Some examples of compounds containing reactive methylene group are given below.

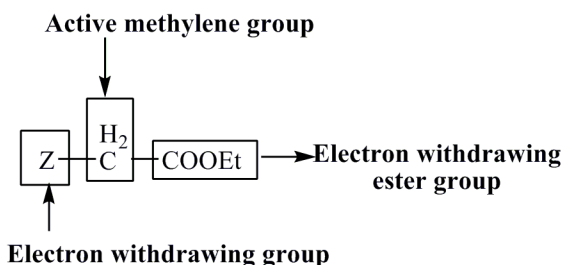
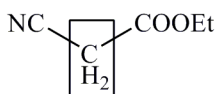
(1) Ethyl acetoacetate (Ethyl 3-oxo-butanoate)



(2) Malonic ester (Diethyl malonate)



(3) Cyanoacetic ester (Ethyl cyanoacetate)



Examples of Electron withdrawing group are;

$-\text{COCH}_3$ (Acetyl)

$-\text{COOEt}$ (Ester)

$-\text{CN}$ (Cyano)

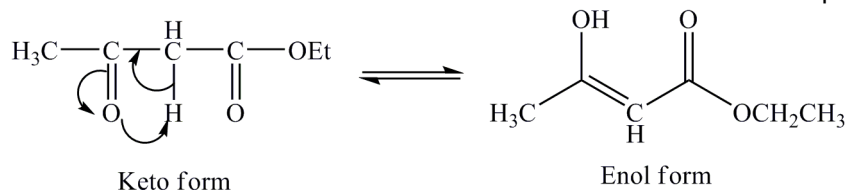
$-\text{NO}_2$ (Nitro)

Characteristics of Tautomerism

- (1) When two structural isomers are mutually interconvertible and exist in dynamic equilibrium, they are called "TAUTOMERS".
- (2) Tautomers are discrete chemical entities, capable of isolation under suitable conditions.
- (3) Tautomers differ from each other in stability. The less stable form is called labile form. The relative proportion of two forms in a tautomeric mixture varies from compound to compound and also with temperature, solvent etc. Tautomeric transformations are also catalyzed by acids and bases.
- (4) Tautomers exist in dynamic equilibrium. Their separation can be achieved only by special methods.

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.



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

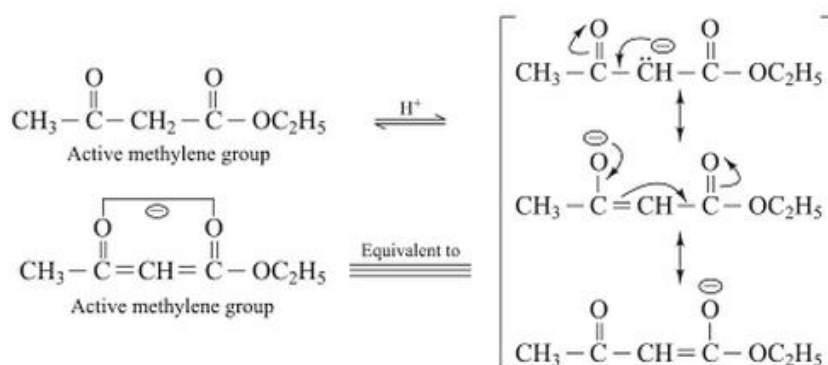
Difference Between Tautomerism And Resonance

As a matter of fact there is no point of similarity between tautomerism and resonance. The former is the phenomenon describing the dynamic equilibrium between isomers whereas the latter is a concept for representing structure of molecules. Some of the important differences have been pointed out below:

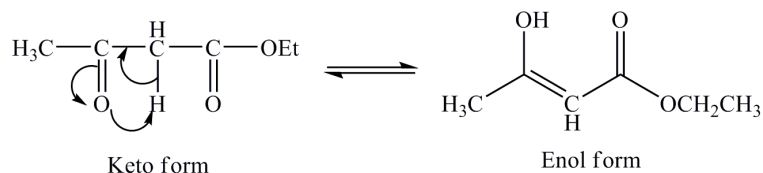
- (1) Tautomerism involves tautomers which have real existence whereas the resonance involves contributing structures which are hypothetical and do not exist.
- (2) Tautomerism involves the migration of atoms whereas for resonance to occur all the atoms must occupy the same position in all the contributing structures. Contributing structures differ from each other in the placement of electrons only.
- (3) The tautomers are in dynamic equilibrium. Since the contributing structures in resonance are hypothetical hence no such equilibrium is possible.
- (4) The resonance involves shortening of single bond lengths and lengthening of double bond lengths but this is not so in tautomerism.
- (5) The resonance lowers the energy of real molecule (i.e. stabilizes it) but this does not happen in tautomerism.
- (6) The molecule should be planar for resonance to occur while it is not necessary in tautomerism.
- (7) All the molecules of compound exhibiting resonance have the same structure, regardless of the fact whether that can be represented or not, whereas compounds exhibiting tautomerism have two or more types of molecules present as equilibrium mixture.
- (8) The tautomerism is shown by placing reversible arrows (\rightleftharpoons sign of equilibrium) between tautomers whereas resonance is depicted by placing double headed arrow (\longleftrightarrow) between contributing structures.

Acidic nature of methylene group

- » Methylene group in EAA is flanked by two electron withdrawing groups, viz, an acetyl group and an ester group. The hydrogens of this methylene group are ionisable due to the electron withdrawing effect of the surrounding groups. Also the negative ion obtained after losing the proton gets stabilized due to resonance as shown hereunder.



EAA offers a classical and most thoroughly investigated example of keto-enol tautomerism.

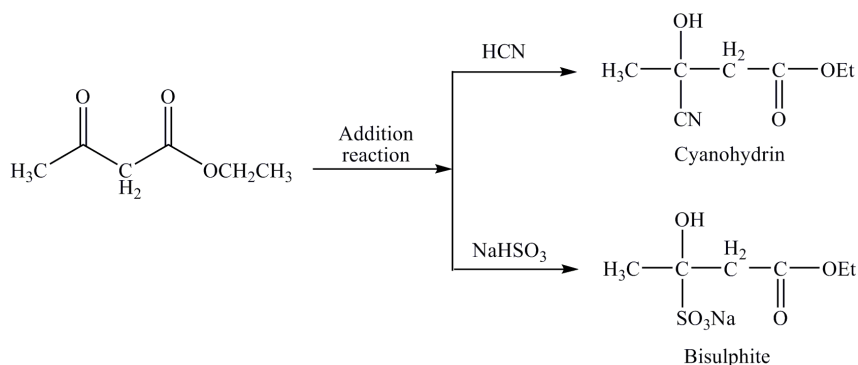


This compound was first prepared by **Geuther** who assigned it the enol structure, while **Frankland** and **Duppa** showed that EAA had keto structure. The presence of each of the keto and enol forms in EAA was supported by two sets of reactions.

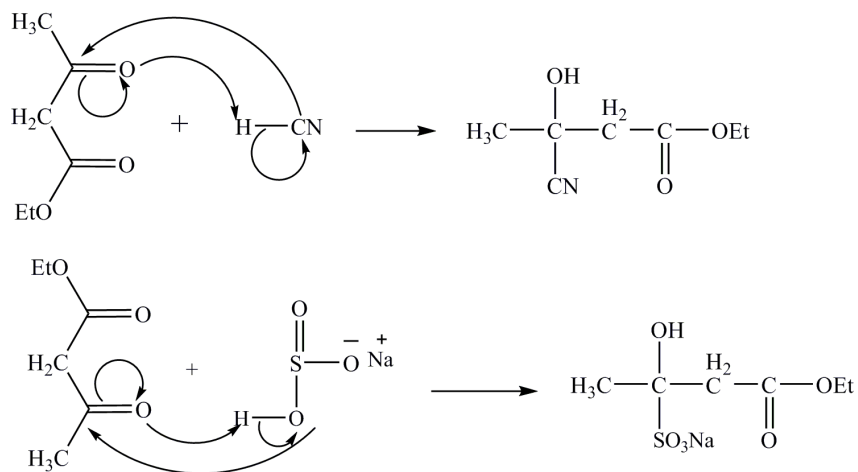
(A) Reactions supporting Keto form (Evidences in favour of Frankland and Duppa formula):

(1) EAA forms addition products with HCN and NaHSO₃, indicating presence of carbonyl (>C=O) group.

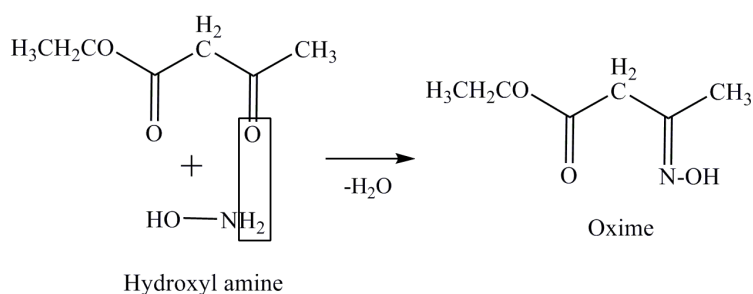
Reaction

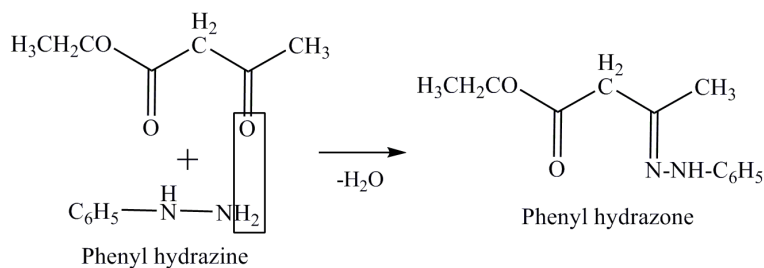


Mechanism

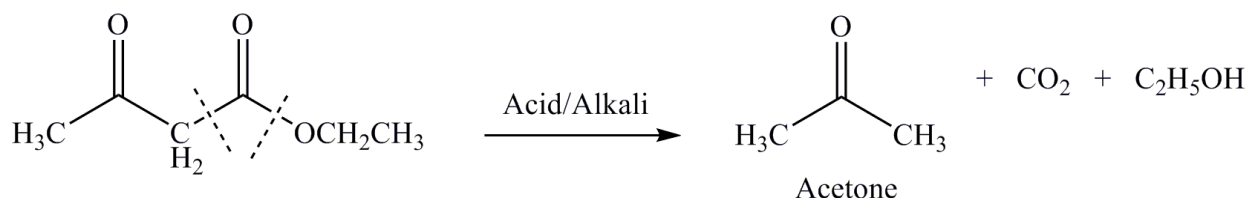


(2) It reacts with hydroxylamine (NH₂OH) and phenyl hydrazine (PhNHNH₂) to form oxime and phenyl hydrazone respectively. Formation of oxime and hydrazone is characteristic of compounds containing ketone group. This reaction indicates presence of keto group in EAA.

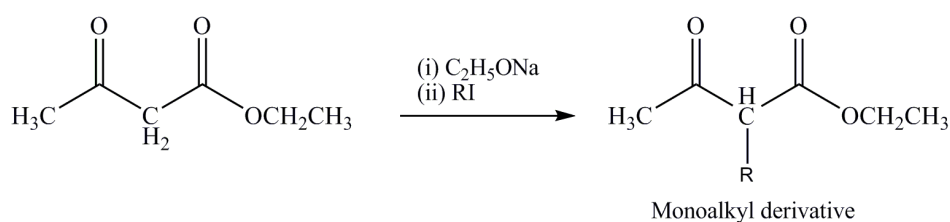




(3) EAA is hydrolysed to acetone when treated with dilute acid or alkali, which indicates presence of $-\text{CH}_2-$ group.



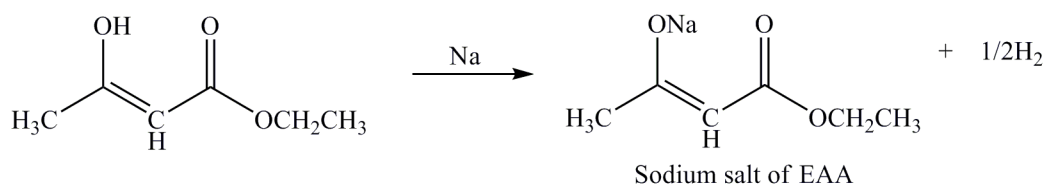
(4) It forms mono and dialkyl derivative indicating the presence of active methylene group.



All the above reactions indicate that EAA exists in KETO form.

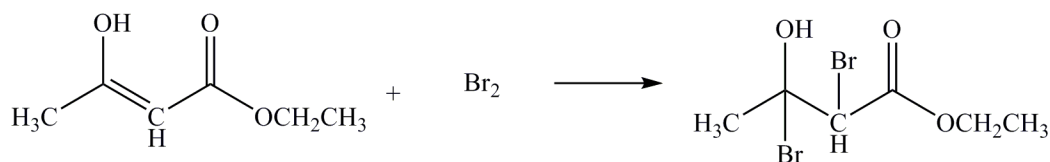
(B) Reactions supporting enol form (Evidences in favour of Geuther formula):

(1) With metallic sodium, EAA forms the sodium derivative along with the evolution of hydrogen gas, which indicates presence of hydroxyl group in EAA.

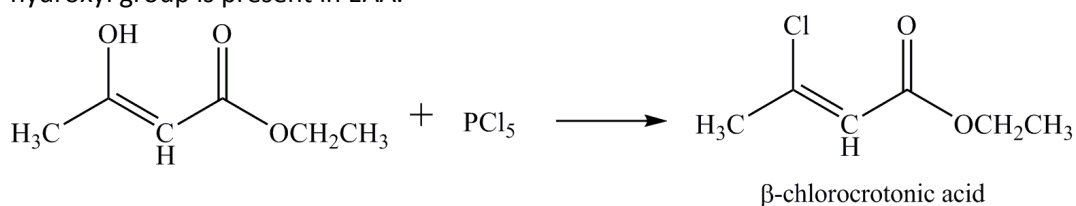


(2) It produces reddish violet color with FeCl_3 solution. This points to the presence of $\text{C}=\text{C}-\text{OH}$.

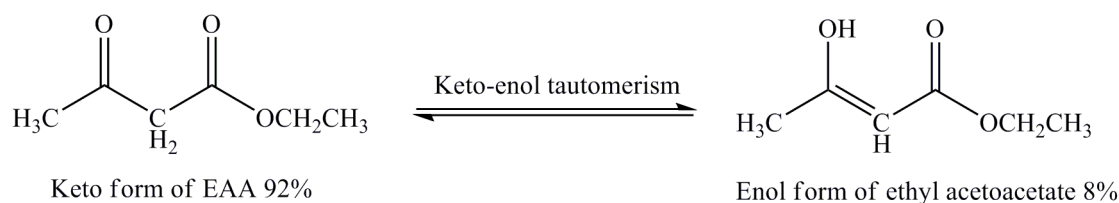
(3) It discharges the color of ethanolic Br_2 solution giving addition reaction, which shows presence of olefinic double bond.



(4) On treatment with phosphorous pentachloride (PCl_5), it forms ethyl ester of β -chlorocrotonic acid. PCl_5 is used for the conversion of hydroxyl group into chloro functionality. Hence it has been again proved from this reaction that hydroxyl group is present in EAA.



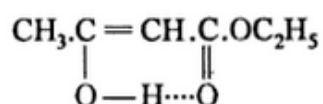
Thus the structure of EAA remained a point of discussion until 1910. The controversy was resolved by Knorr in 1911 when he succeeded in isolating both tautomers in pure form and showed that the two forms are readily interconvertible.



Knorr (1911), who succeeded in isolating both forms. He cooled a solution of EAA in light petrol to -78°C , and obtained crystals which melted at -39°C . This substance gave no coloration with -78°C and did not combine with bromine, and was therefore the pure ketone form corresponding to Frankland-Duppa formula.

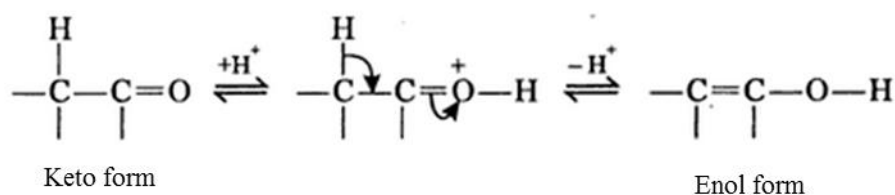
Knorr then suspended the sodium derivative of EAA in light petrol to -78°C , and treated this suspension with just enough HCl to decompose the sodium salt. He now obtained a product which did not crystallise, but set to a glassy solid when cooled. This substance gave an intense coloration with -78°C , and was therefore the pure hydroxy form corresponding to Geuther formula.

The stability of enol form is ascribed to the formation of intramolecular hydrogen bonding.

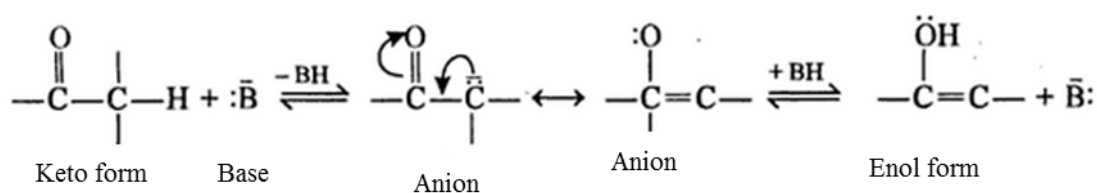


Acids and bases catalyze the interconversion of tautomeric forms and the mechanism for acid and base catalyzed transformation may be written as follows:

Acid catalyzed tautomeric transformation



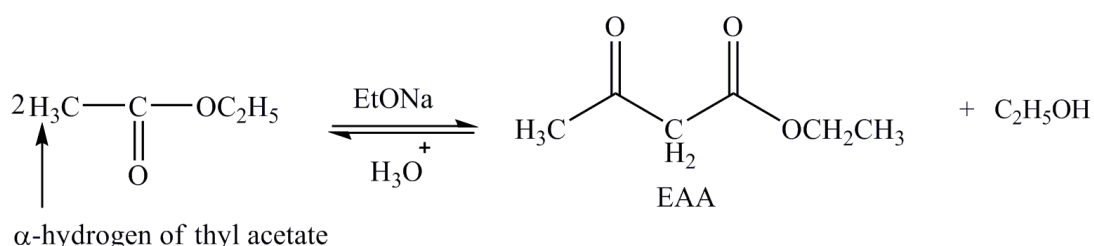
Base catalyzed tautomeric transformation



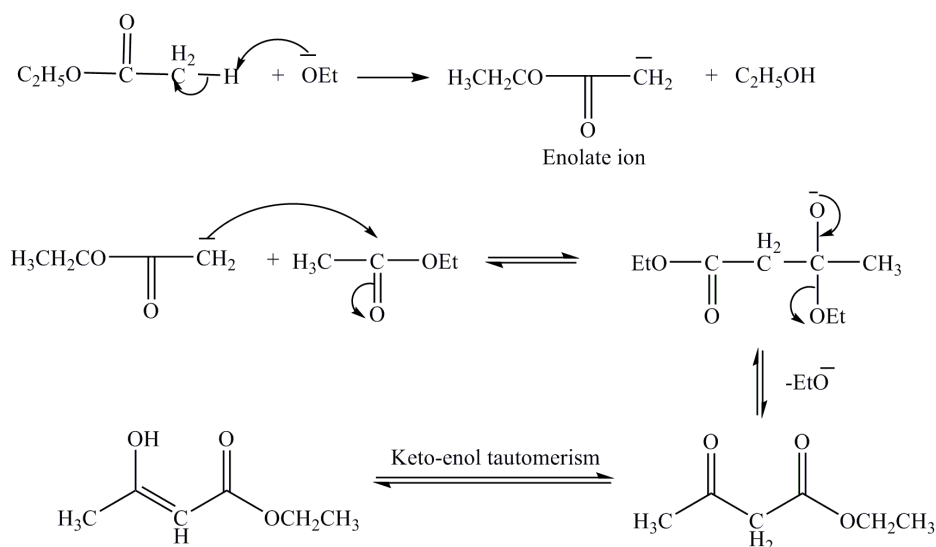
(C) Proof for structure of EAA by Claisen Condensation

Base catalyzed condensation of an ester containing an α -hydrogen atom with a molecule of the same ester or a different one to give β -keto ester is known as Claisen condensation.

Reaction



The generally accepted mechanism for the Claisen condensation is shown here.



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.

Physical Properties of EAA

- (1) Ethyl acetoacetate is colorless liquid and has fruity odour.
- (2) Boiling point is 181°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 color with FeCl_3 .

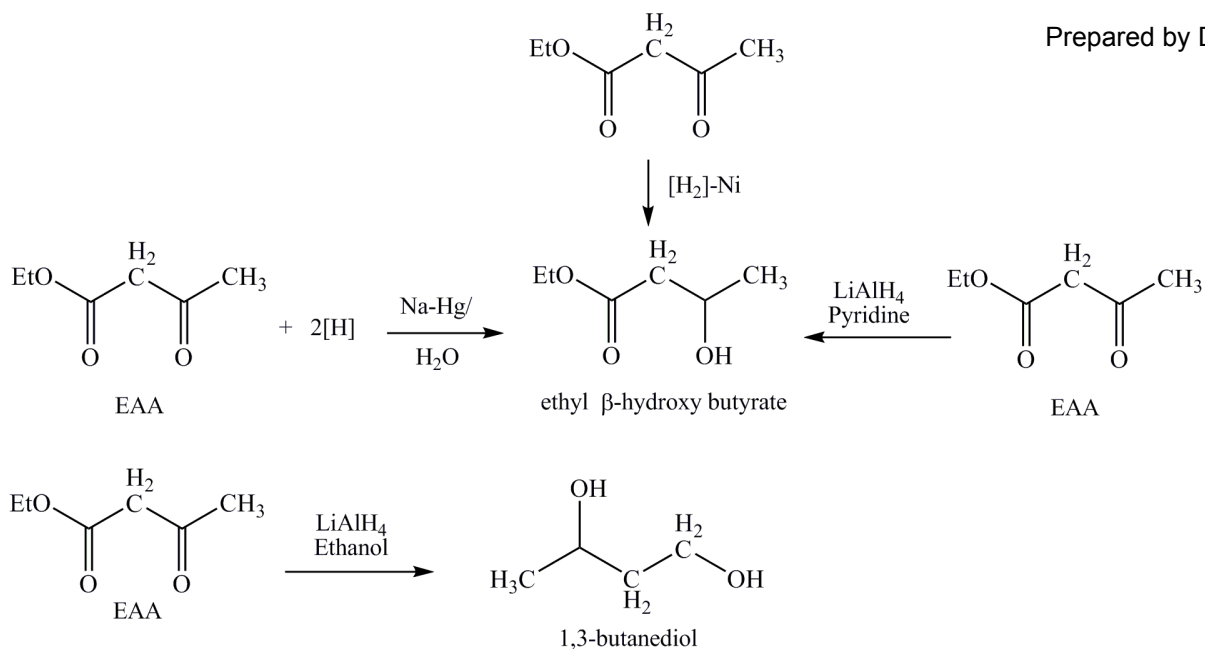
Chemical properties of EAA

(A) Reactions due to Keto form

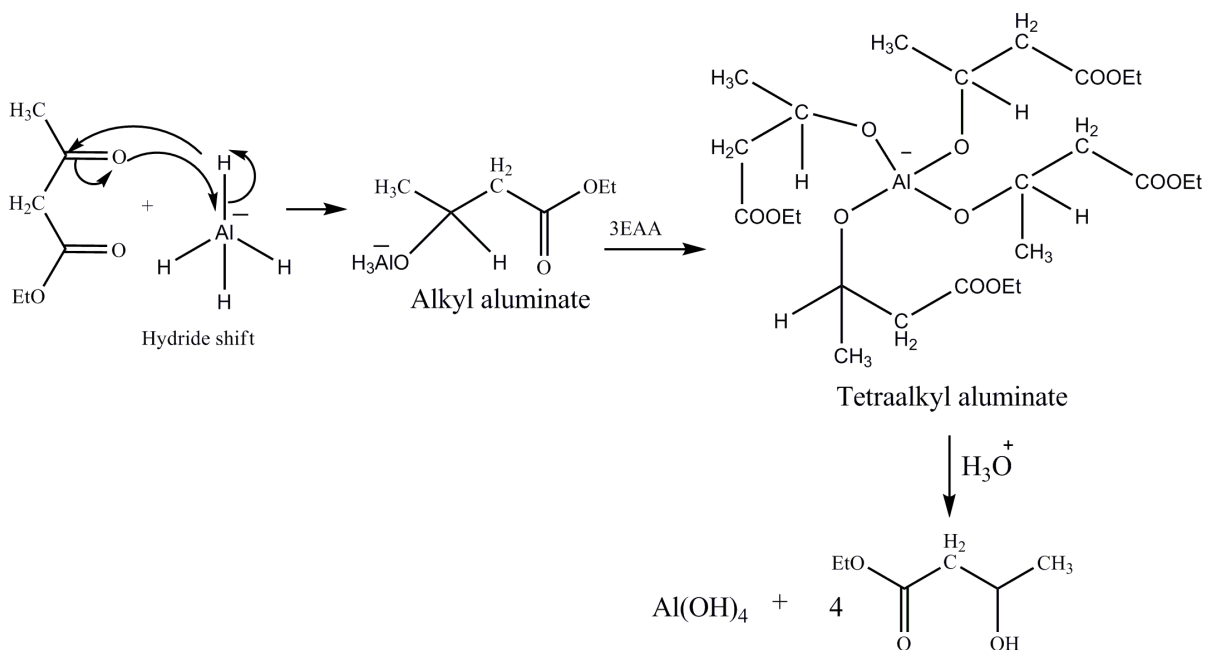
(1) Reduction

EAA on reduction with Na-Hg amalgam OR LiAlH_4 in presence of pyridine gives ethyl β -hydroxy butyrate, whereas in presence of LiAlH_4 and ethanol the product of reaction is 1,3-butanediol.

Mechanism of reduction using LiAlH_4 in presence of pyridine as solvent is given below. Due to higher reactivity of LiAlH_4 , reduction is carried out in aprotic solvents (in the absence of a proton source). The neutral AlH_3 binds to the negative oxygen atom of EAA forming an alkyl aluminate, which can be performed three additional times producing a tetra-alkyl aluminate. This complex is then hydrolyzed in a separate step to yield the final alcohol. This reaction involves hydride shift (transfer of negative hydrogen) from LiAlH_4 to carbonyl carbon of EAA.

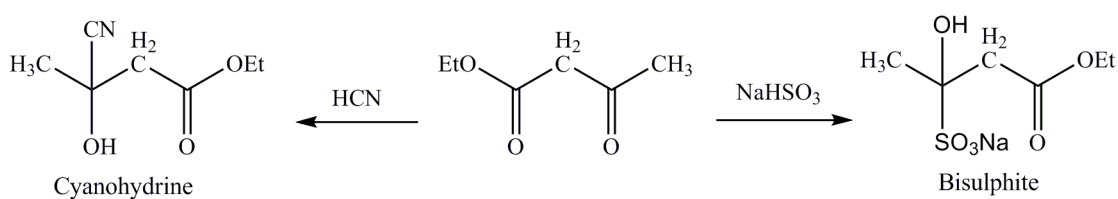


Mechanism



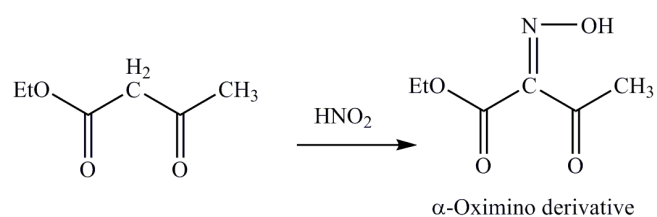
(2) Addition reaction

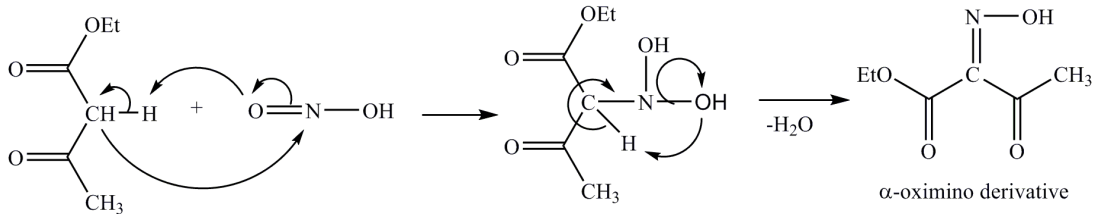
For mechanism refer reaction (1) under the heading reactions supporting Keto form.



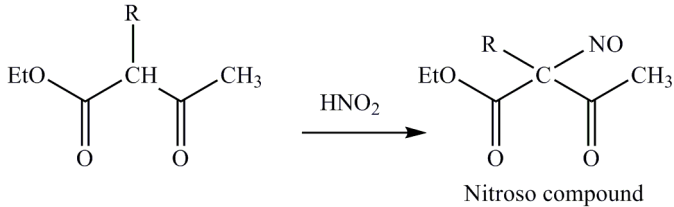
(3) Reaction with nitrous acid: EAA on reaction with nitrous acid gives α-oximino derivative.

Reaction



Mechanism

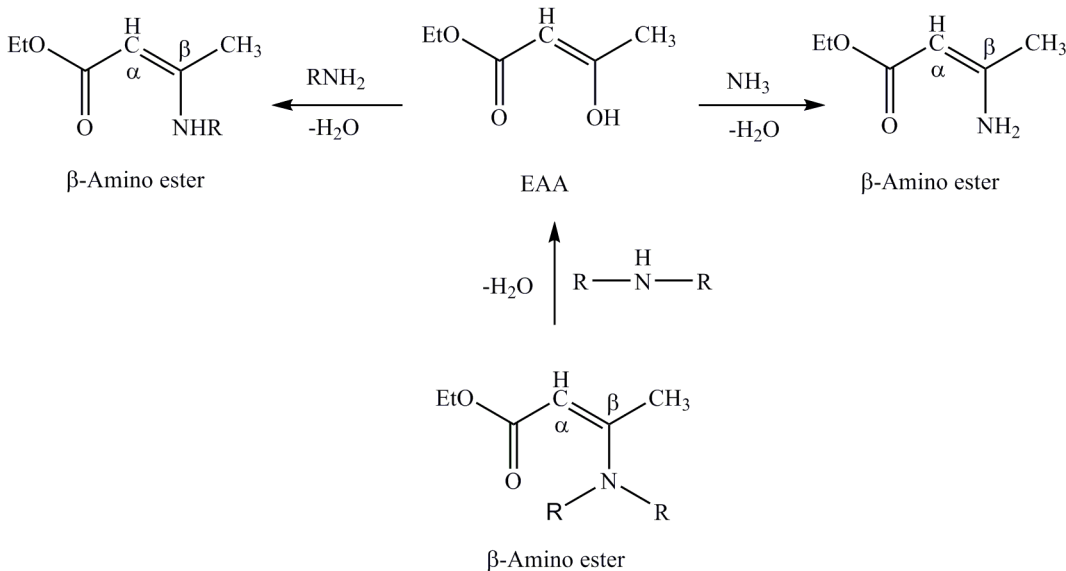
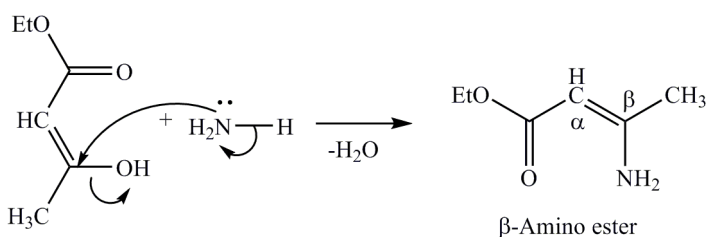
When alkyl group is attached with reactive methylene group, then it gives nitroso compound on reaction with nitrous acid, which on hydrolysis gives acetic acid and oximino compound.

**(4) Reaction with phenyl hydrazine and hydrazine hydrate**

Refer reaction (2) under the heading evidences in favour of Frankland-Duppa formula.

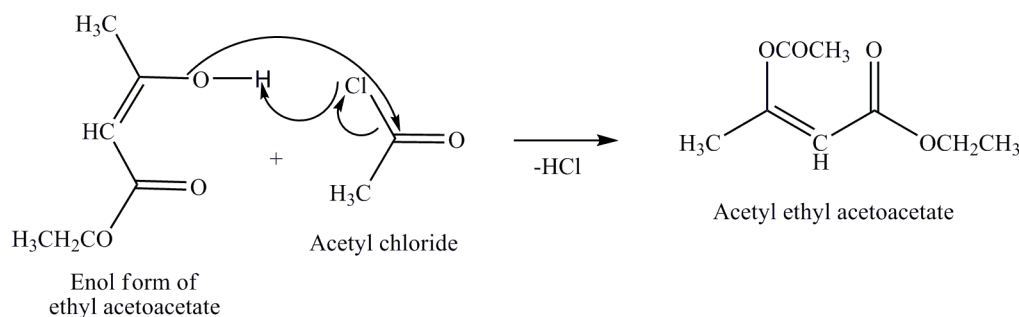
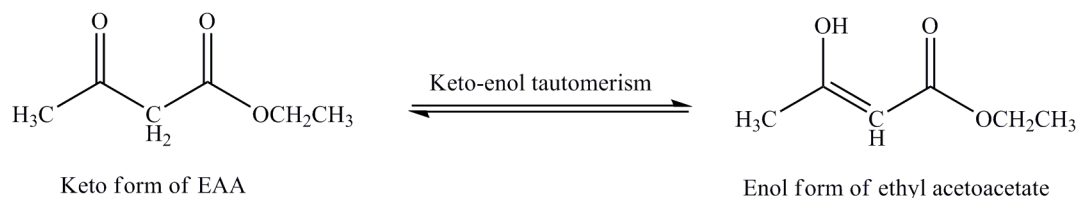
(B) Reactions that EAA undergo due to presence of Enolic group**(1) Reaction with Ammonia and 1^o amine/2^o amine**

EAA on treatment with **ammonia** or **1^o amine** or **2^o amine** gives β -amino crotonic ester by removal of water molecule. Mechanism of this reaction is illustrated by taking example of ammonia.

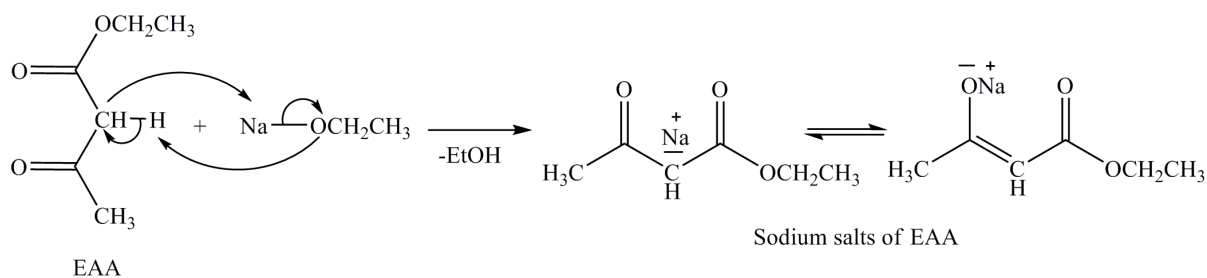
Reaction**Mechanism**

(2) Reaction with acetyl chloride

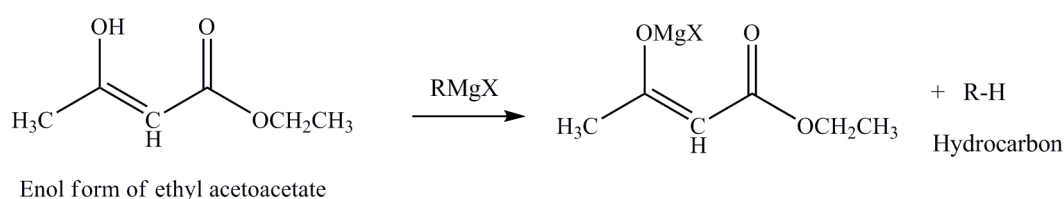
EAA in benzene is treated with acetyl chloride to form O-acetyl derivative of enolic form of EAA. This reaction is an example of electrophilic substitution reaction.

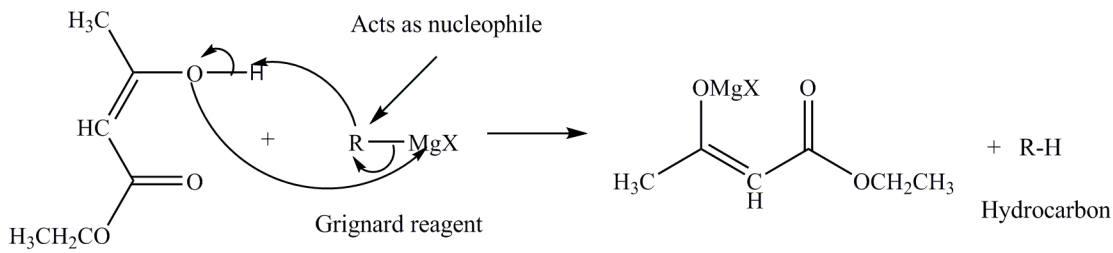
Reaction**Mechanism****(3) Reaction with base**

In the presence of base like sodium ethoxide, EAA loses a proton to form corresponding sodium salt. The carbanion thus formed is stabilized through resonance.

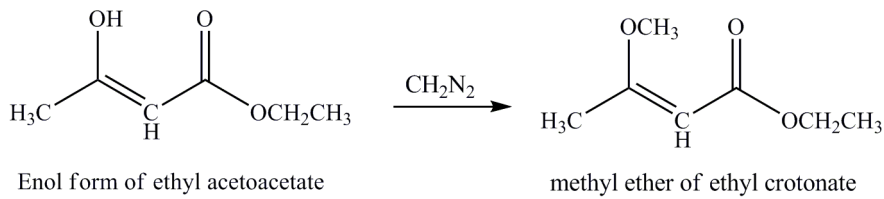
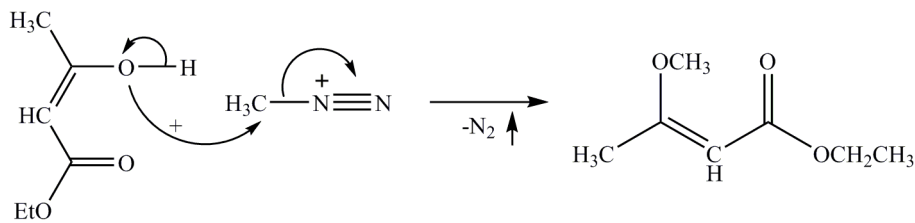
**(4) Reaction with Grignard reagent**

Reaction with Grignard reagent results in formation of its corresponding hydrocarbon derivative as the hydroxy group in enol form acts as source of active hydrogen.

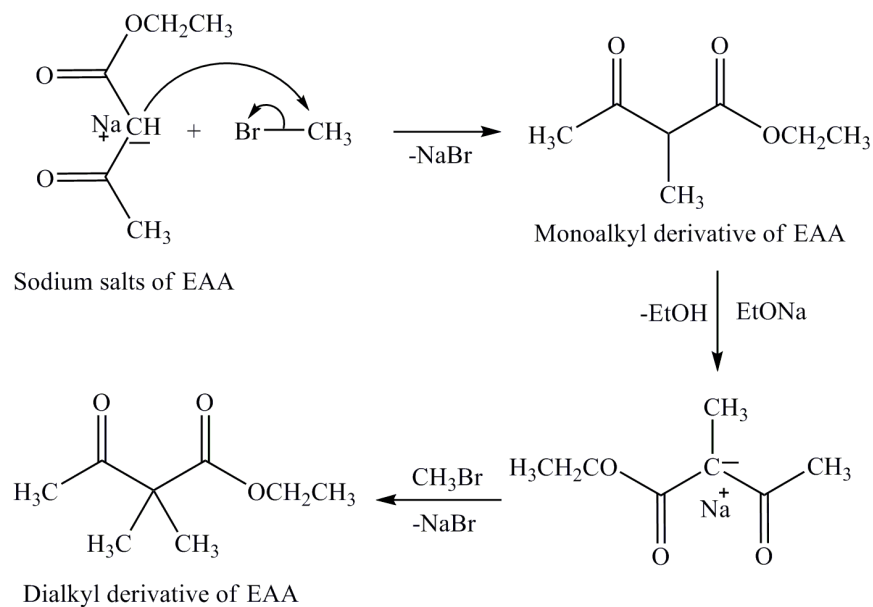
Reaction

Mechanism**(5) Reaction with Diazomethane**

Reaction with diazomethane forms methyl ether of ethyl crotonate.

Reaction**Mechanism****(C) Reactions of synthetic importance****(1) Reaction with Haloalkanes**

The sodium salt of EAA reacts with 1° and 2° haloalkanes to form corresponding alkyl derivatives. The reaction can be used to prepare both monoalkyl as well as dialkyl derivatives of EAA.



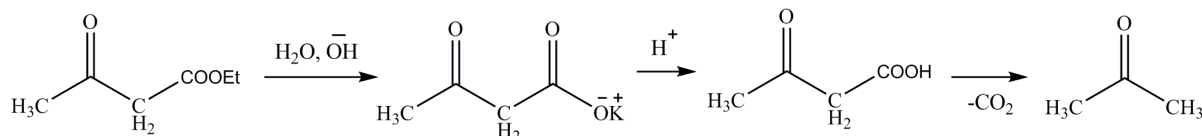
Both the hydrogens of methylene group cannot be replaced in a single step simultaneously by the base. Thus to prepare dialkyl derivative, alkyl groups are introduced one at a time. In case two different alkyl groups are to be introduced, the larger group is introduced first due to steric reasons.

(2) Hydrolysis of EAA

In presence of KOH, the hydrolysis of EAA may occur in two ways either ketone or carboxylic acid as the final product. Based on the product obtained, the hydrolysis can be categorized as ketonic hydrolysis and acid hydrolysis.

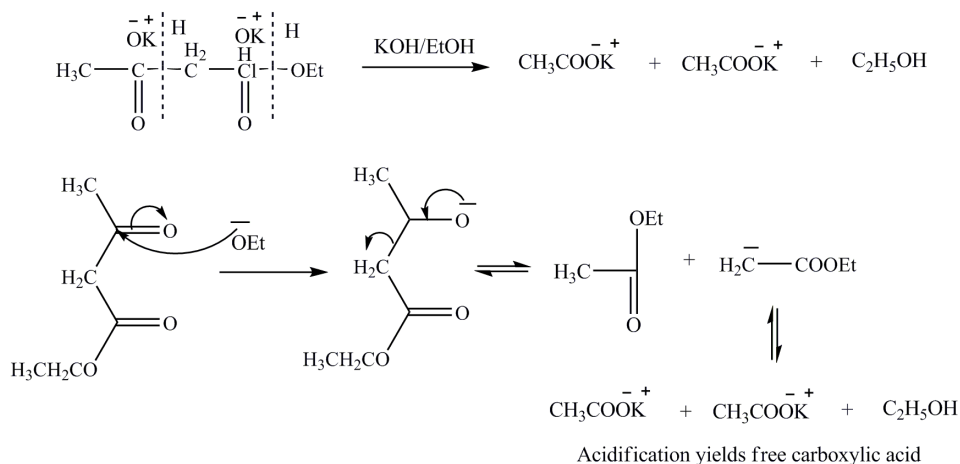
Ketonic hydrolysis

Heating EAA with dilute solution of aqueous or ethanolic KOH results in the formation of β -keto acid. This acid on heating undergoes decarboxylation (removal of CO_2) to yield ketone as the final product.



Acid hydrolysis

Heating EAA with concentrated solution of ethanolic KOH results in the formation of potassium salt of acetic acid. This acidification gives free acetic acid as the final product. It is to be noted that in various synthetic strategies from EAA, involving acid hydrolysis, the EAA contributes two carbon units to the product.



Applications

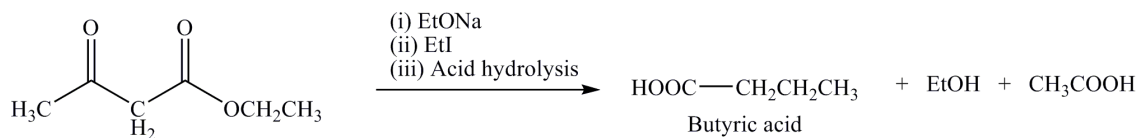
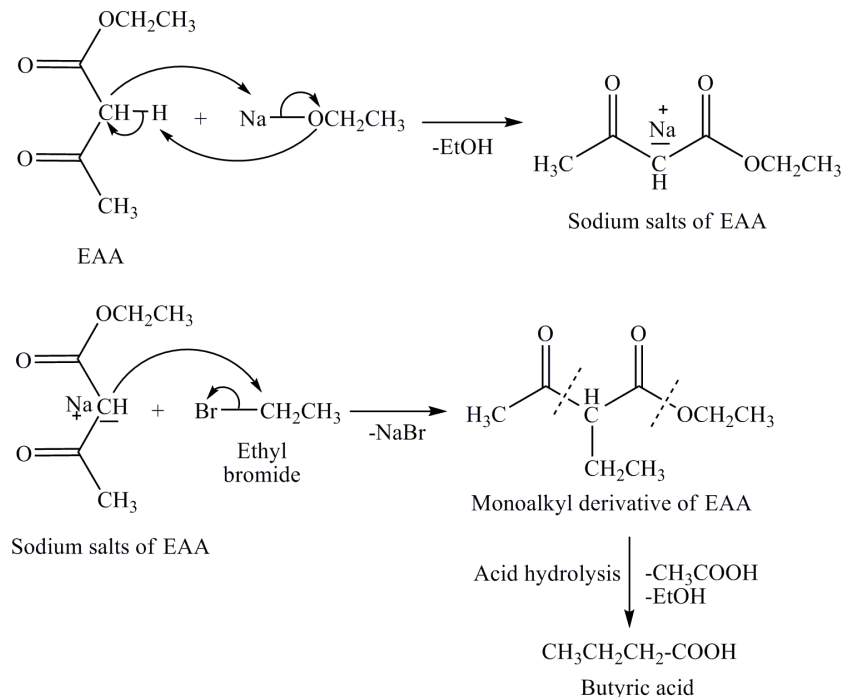
EAA and its alkyl derivatives react with a number of other reagents to yield different functional group derivatives. Some examples of their use in the synthesis of functional group derivatives are mentioned here.

EAA is an important tool to yield various types of organic reagents. Its importance is based on the presence of active methylene group and the ability of it to undergo ketonic or acidic hydrolysis. Due to the acidic nature of methylene hydrogen, it forms salt with sodium ethoxide (base). This salt acts as a nucleophile which can take part in S_N reaction.

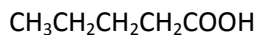
(1) Synthesis of monocarboxylic acids

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

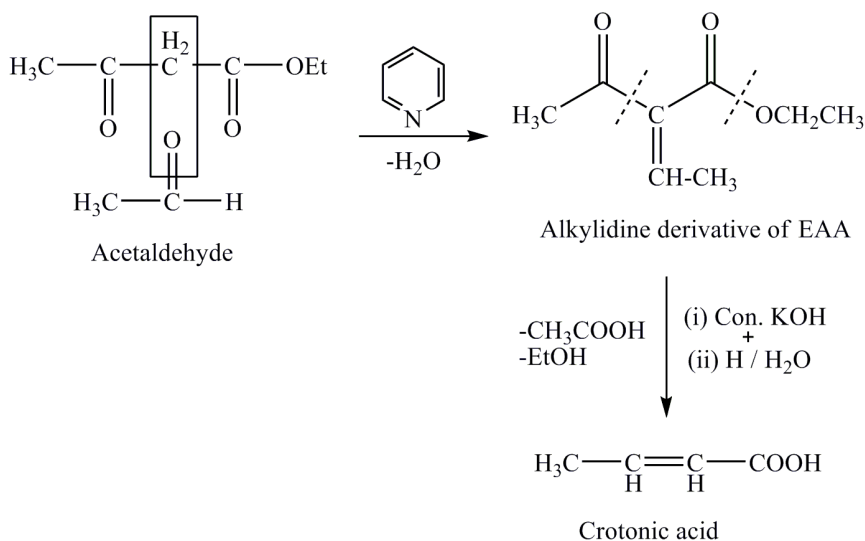
» Preparation of Butyric acid and Valeric acids

Reaction**Mechanism**

The structure of Valeric acid is given below.



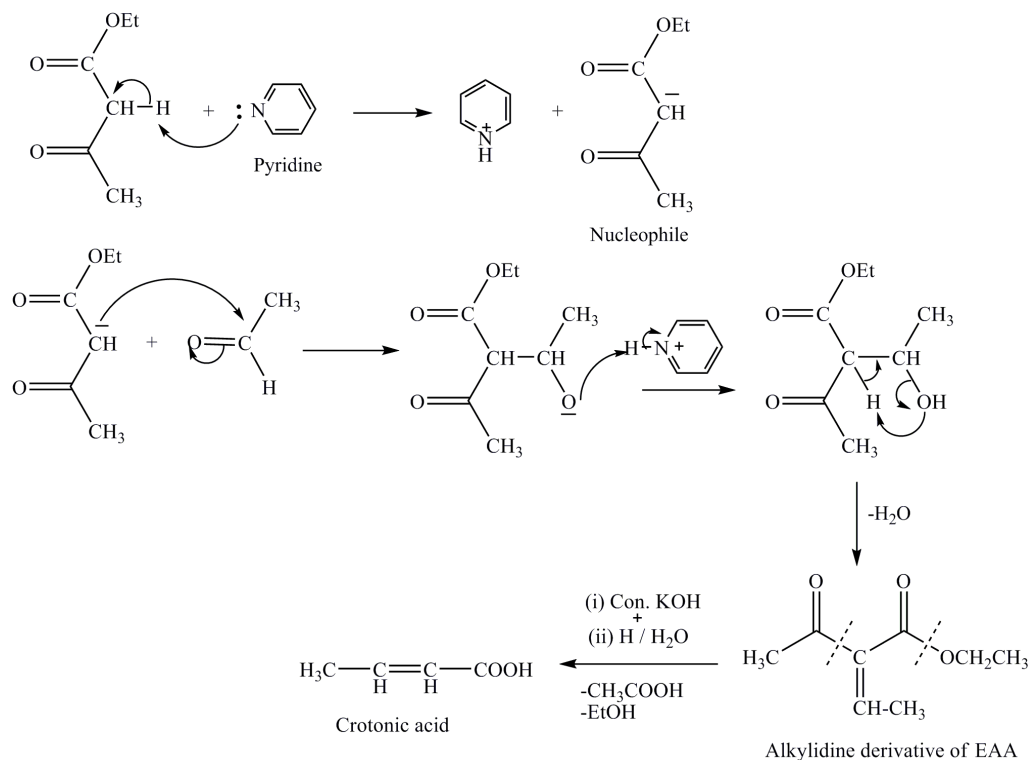
In above reaction if propyl bromide is taken instead of ethyl bromide then the product of reaction is Valeric acid.

(2) Preparation of crotonic acid (α,β -unsaturated acid)-Knoengel condensation**Reaction**

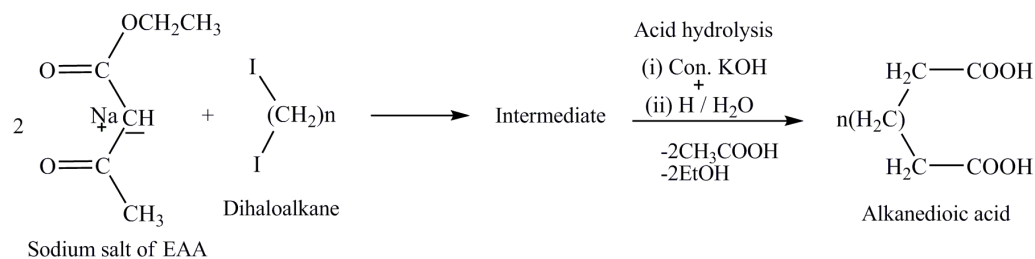
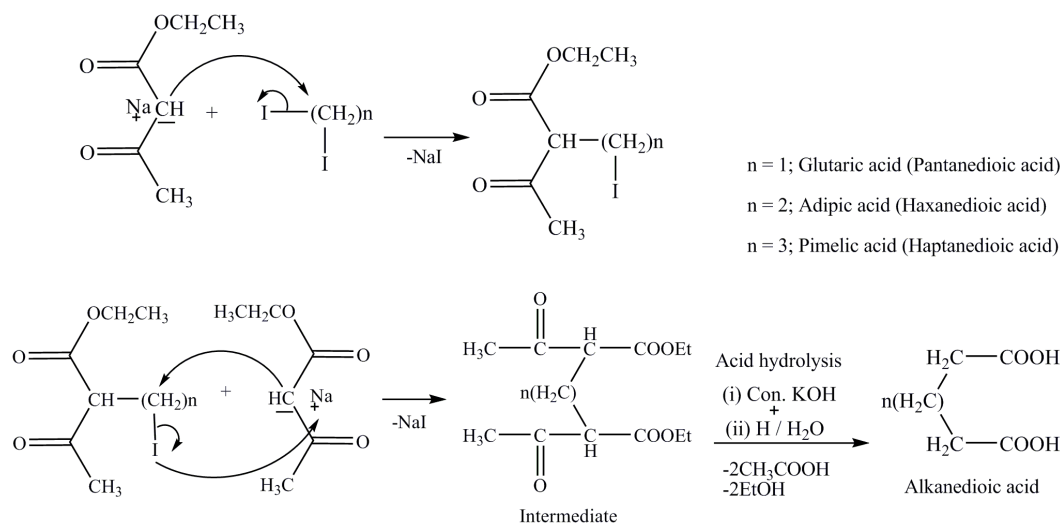
Knoengel condensation is the reaction of an aldehydes or ketone with an active methylene group containing compound in presence of weak base. The product is conjugated due to loss of water molecule after addition of the active methylene compound to the carbonyl group. Weaker bases are used to avoid side reaction of the aldehydes and ketones, such as the aldol condensation.

EAA on treatment with acetaldehyde in the presence of pyridine or diethylamine as catalyst gives alkyldine derivative of EAA by Knoengel condensation. This derivative on

hydrolysis gives crotonic acid which is α,β -unsaturated acid. The detailed reaction and mechanism of this reaction is given here.

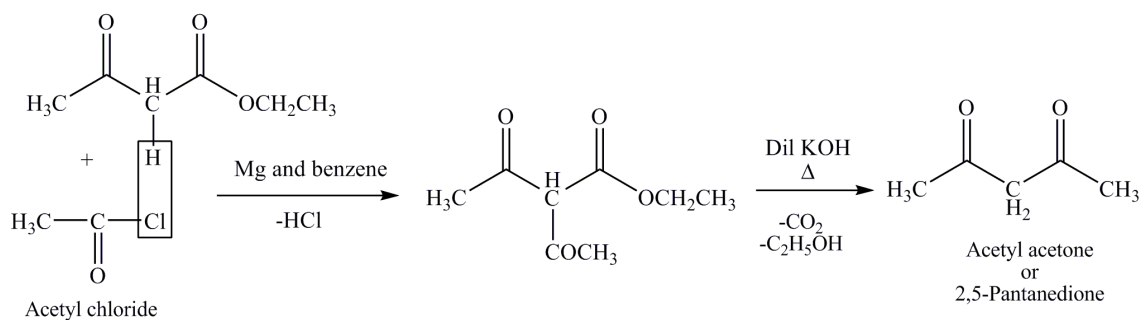
Mechanism**(3) Preparation of Higher Dicarboxylic acids**

Higher dicarboxylic acids such as glutaric acid, adipic acid, pimelic acid, and the like, 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.

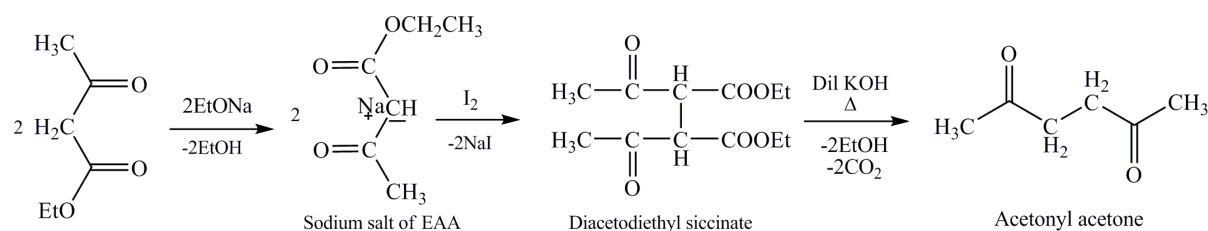
Reaction**Mechanism**

(4) Preparation of Acetyl acetone

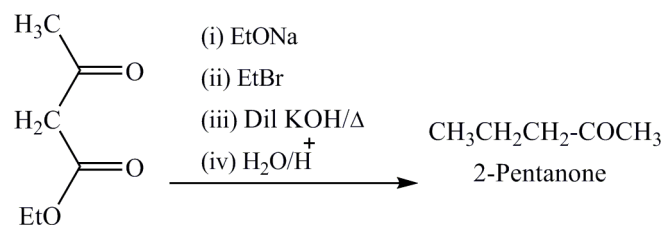
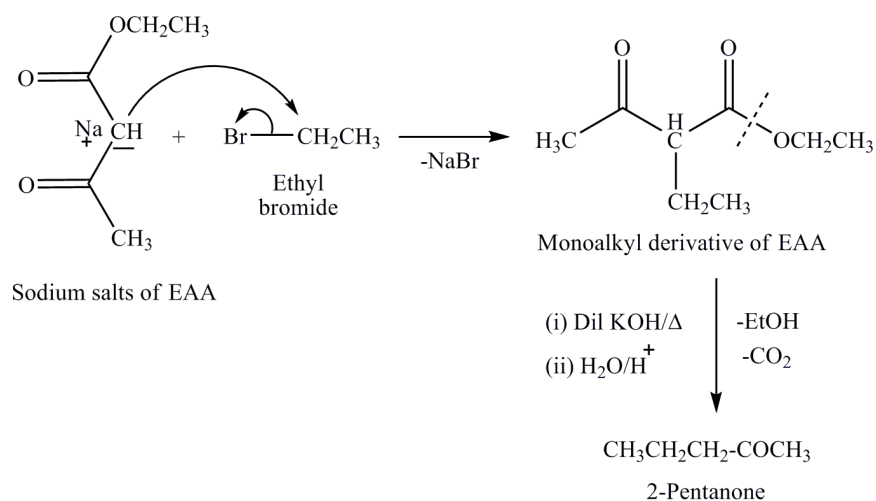
EAA in benzene is treated with acid chloride (R-COCl) in presence of Mg and the resulted product is subjected to hydrolysis to give 1,3-diketone derivative i.e. acetyl acetone.

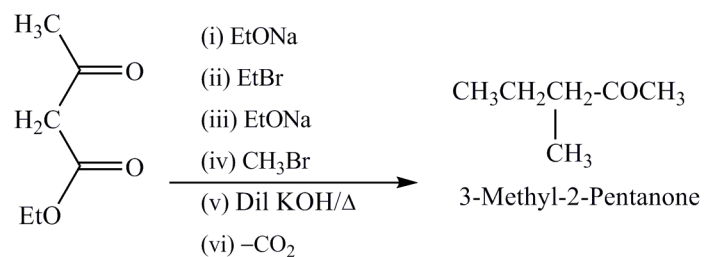
Reaction**(5) Preparation of Acetonyl acetone**

Sodium salt of EAA on reaction with I₂ gives diacetodiethyl succinate, which on hydrolysis followed by decarboxylation gives acetonyl acetone.

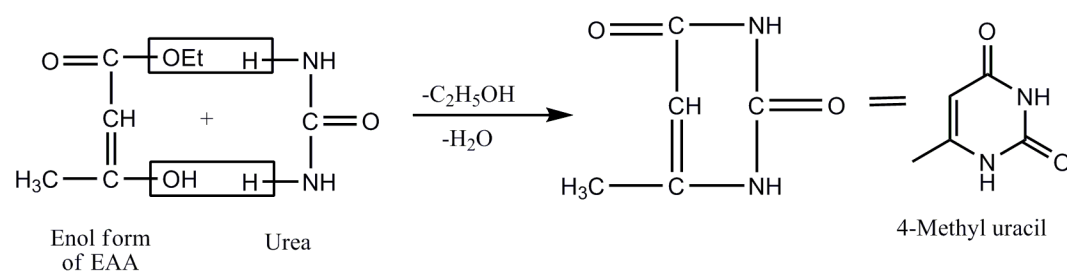
Reaction**(6) Preparation of 2-pentanone**

Sodium salt of EAA on reaction with ethyl bromide gives α-ethyl derivative of EAA. This derivative on hydrolysis gives 2-pentanone.

Reaction**Mechanism**

(7) Preparation of 3-methyl-2-pentanone**Reaction****(8) Preparation of 4-methyl uracil**

EAA reacts with urea in the presence of POCl_3 to form 4-methyl uracil, which is heterocyclic compound.

Reaction**(9) Preparation of 2,5-dimethyl pyrrole**

Pyrrole is five membered heterocyclic compound containing one nitrogen atom. It has been used widely in preparation of medicine in pharma industry.

Reaction