Quadrant II – Notes

Programme: Bachelor of Science (Third Year)

Subject: Chemistry

Course Code: CHC 110

Course Title: Organic chemistry

Unit: Unit II – Section A : Chemistry of Enolates

Module Name: Claisen condensation for the preparation of Ethyl acetoacetate (Reaction and Mechanism). Keto-enol tautomerism in Ethyl acetoacetate.

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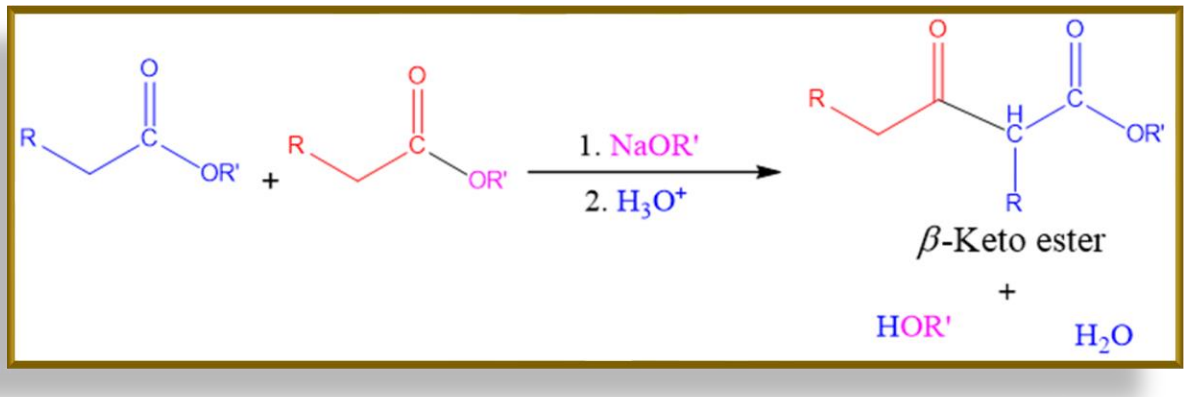
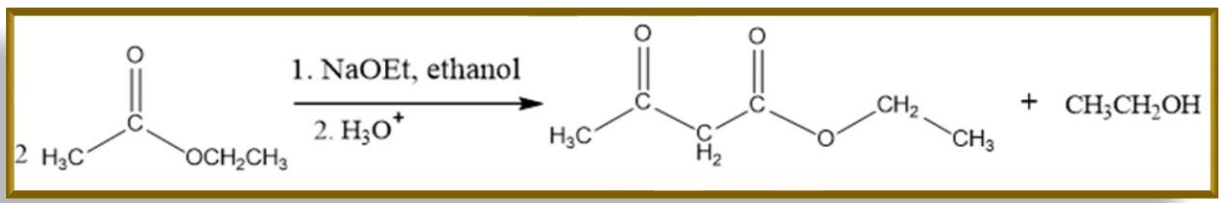
Claisen condensation: The base catalysed condensation of an ester containing an α hydrogen atom, with a molecule of the same ester or a different ester to give a β-keto ester. This reaction involves a new C-C bond formation.

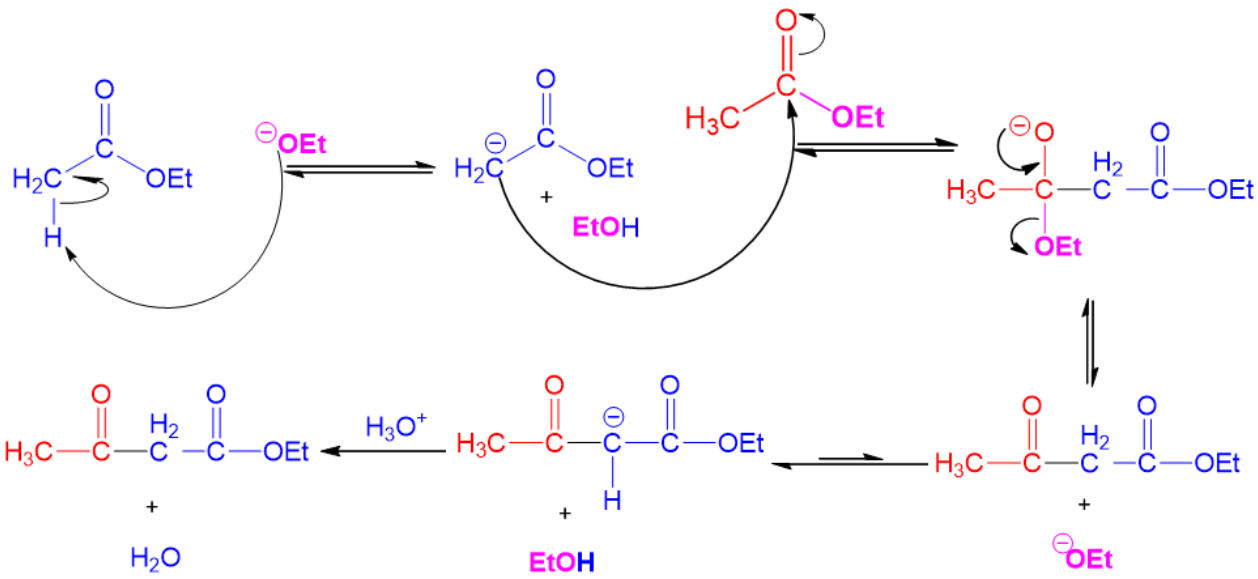


The best example is the preparation of Ethyl acetoacetate *via* the Claisen condensation of ethyl acetate. Two moles of ethyl acetate condense in presence



of base such as sodium ethoxide to give one mole each of ethyl acetoacetate and ethyl alcohol.

Mechanism



Step 1: abstraction of acidic proton from the α carbon atom of ethyl acetate by base to give the corresponding enolate.

Step 2: nucleophilic addition of the ester enolate to the carbonyl group of the second neutral ester giving the anionic form of the tetrahedral intermediate.

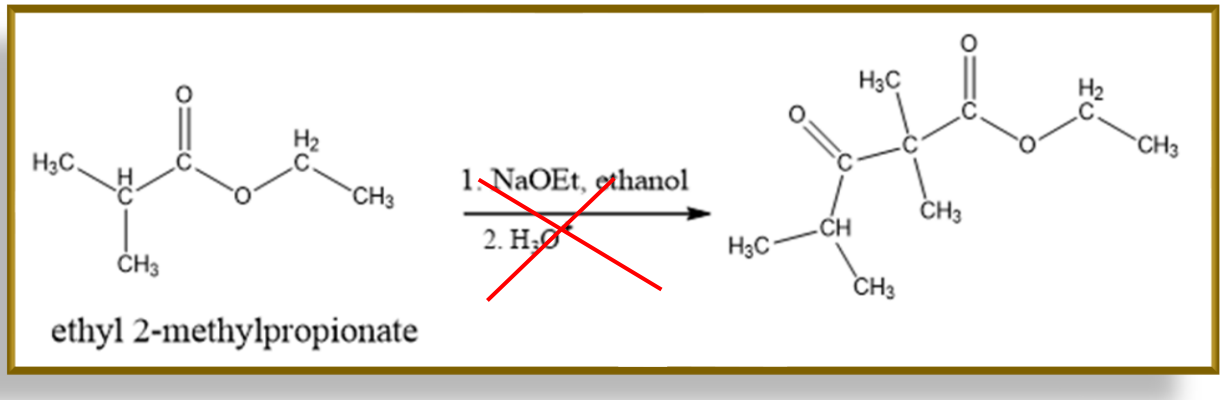
Step 3: dissociation of the unstable tetrahedral intermediate giving β-keto ester product by expelling ethoxide.

Step 4: but the ethoxide ion is basic enough to convert the β-keto ester into its enolate, as the pKa of β-keto ester is approximately 11. Deprotonation of the β-keto ester helps in shifting the equilibrium and driving the reaction to completion.

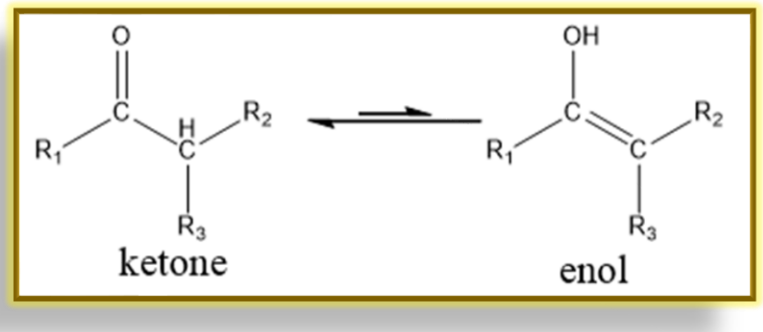
Step 5: protonation by addition of acid in a separate step yields the final product.

All the steps in the mechanism are reversible. Final step i,.e. deprotonation of β-keto ester by alkoxide drives the reaction to completion and the final acid work up results in the β-keto ester product i.e. ethyl acetoacetate.

However equilibrium is unfavourable to reaction when β-keto ester formed does not have acidic proton to form stable anion by deprotonation. For eg. ethyl 2-methylpropionate fails to give the β-keto ester under these conditions.



Keto-enol tautomerism in Ethyl acetoacetate



Tautomers are isomers of a compound, whose structures differ in arrangement of atoms, but exist in equilibrium. Ketone & enol differ only in location of a double bond & Hydrogen. Ketone & its corresponding enol are called keto-enol tautomers. Interconversion of these tautomers is called Keto-enol tautomerism.

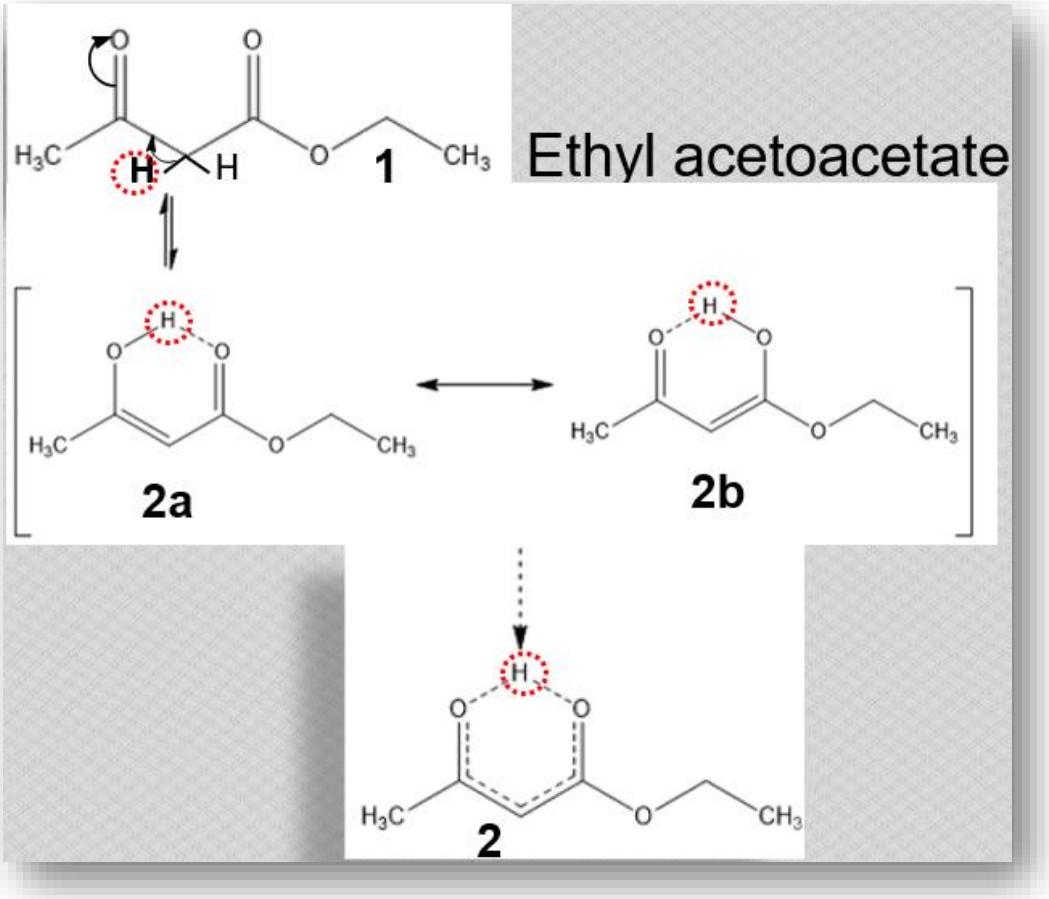
For simple carbonyl compounds under normal conditions, the equilibrium usually strongly favors the more stable, keto tautomer. As compared to the acid catalyzed process, the self-enolization/tautomerization of most ketones is negligible. The Keto form is favored almost exclusively.

β-Dicarbonyl compounds also undergo tautomerization. The α-H, attached to α-C, flanked between the two carbonyl groups is acidic (pKa = 9-13), making ketones readily enolizable. The enol tautomer may predominate at equilibrium.

In case of β-diketones stabilization of enol form arises from stabilization by π-system conjugation & intramolecular Hydrogen bonding.

Ethyl acetoacetate is a β- keto ester, which undergoes self-enolization where the keto form **1** exists in equilibrium with its enol isomer **2a** and **2b**. This process occurs because the α-H, attached to the carbon flanked between the two carbonyl groups is acidic (pKa ~ 11),

Typically, more stable keto form is favoured at room temperature & above.



According to PMR spectroscopy studies, keto tautomer of EAA is the more favourable structure. The substitution of an alkyl group larger than ethyl on the alkoxy end of the acetoacetate molecule results in increased enolization.