CARBONYL COMPOUNDS

PART-27, PPT-27, SEM-3

CONTENTS

- Additions of Enolates: Michael Reaction
- Michael Retrogression Reaction: Reversal of Michael Reaction
- Abnormal of Michael Reaction
- Problems

Dr. Kalyan Kumar Mandal
Associate Professor
St. Paul's C. M. College
Kolkata

Additions of Enolates: Michael Reaction

The conjugate addition of stabilized carbon nucleophile to an olefinic or acetylenic unsaturation of *α,β*-unsaturated carbonyl compounds, esters, nitriles, etc., leading to the formation of a new carbon-carbon bond is called Michael condensation (Figure 1).

The usual sources of stabilized carbon nucleophiles are compounds containing active methylene group like acetylacetone, ethyl acetoacetate, diethyl malonate, ethyl cyanoacetate, nitroalkanes, etc. The condensation is carried out in the presence of a base, e.g., sodium ethoxide, or secondary amines.

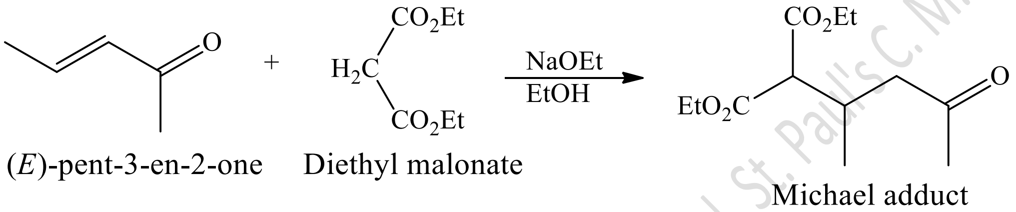

Figure 1: Michael condensation

The final products are usually called Michael adducts. The compound from which the carbanion is generated is called the *Michael donor* and the *α,β*-unsaturated carbonyl compound is called the *Michael acceptor*. The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an *α,β*-unsaturated carbonyl compound containing an electron withdrawing group. This is one of the most useful methods for the formation of C–C bonds.

As originally defined by Arthur Michael (1887), the reaction is the addition of an enolate of a ketone or aldehyde to an *α,β*-unsaturated carbonyl compound at the *β* carbon. A newer definition, proposed by Kohler, is the 1,4-addition of a doubly stabilized carbon nucleophile to an *α,β*-unsaturated carbonyl compound. The resulting product contains a highly useful 1,5-dioxygenated pattern.

Salient Features of Michael Reaction

1. The carbon-nucleophile (Michael donor) can be obtained by the abstraction of proton from compounds having >CH-activated compounds like *β*-dicarbonyl compounds. Best Michael donors are those where a methylene ($-CH_2-$) or methine (>CH-) group is flanked by two strongly electron withdrawing groups, like -CO-, -CN, $-CO_2Et$, etc.

2. Mild reaction conditions are generally used in the Michael reaction as all the reactants and products are carbonyl compounds and additional unwanted side reactions such as reverse Michael addition, aldol condensation or Claisen condensation may occur in presence of stronger bases.

3. Depending on the acidity of the active hydrogen in the donor molecule, less active bases like NEt_3, piperidine, pyridine, potassium hydroxide or benzyltrimethylammonium hydroxide (Triton B) can also be used.

4. In case of strong bases like NaOEt, *t*-BuOk, sodium hydride, or a metal amide, etc., a small amount (0.1-0.3 equivalent) of the base is used in the reaction. In addition to that a low reaction temperature (25 °C or less) and short reaction times are employed to minimize side reactions.

   If one equivalent of base is used then the product can form a new carbanion, if acidic hydrogen is present, that may lead to many side reactions.

5. The reaction can be carried out in both protic and aprotic solvents. Water and alcohol are normal protic solvents that are used. The reaction is generally performed in presence of a protic solvent (e.g., water or alcohol) in order to minimize further transformation of the initially formed Michael adduct.

6. Many molecules can also undergo intramolecular Michael reaction.

7. The reaction can be highly diastereoselective when both the Michael donor and acceptor have defined stereochemistry.

8. The Michael addition is an important atom-economical method for enantioselective and diastereoselective C–C bond formation. A classical tandem sequence of Michael and aldol additions is the Robinson annulation.

Mechanism of Michael Reaction

In the Michael reaction the base is regenerated, therefore only a catalytic amount of it is sufficient. Although the reaction is reversible, it goes to completion because the addition to the double bond is thermodynamically favourable. The doubly activated methylene compound which serves as the source of the carbanion is called the *Michael donor*, while the *α*,*β*-unsaturated carbonyl compound which adds the carbanion is known as the *Michael acceptor*.

Ionic mechanism of Michael addition is shown in Figure 2 taking diethyl malonate as Michael donor and mesityl oxide as Michael acceptor. In the reaction mechanism, the anion of diethyl malonate acts as the nucleophile (Michael donor).

Deprotonation of diethyl malonate (I) by base leads to carbanion (II) which is stabilized by its electron-withdrawing groups. This nucleophile (enolate ion) reacts with the electrophilic alkene (*β*-carbon to an *α*,*β*-unsaturated carbonyl compound) of the Michael acceptor (here, mesityl oxide, III) to form a new enolate ion (IV) in a conjugate addition reaction (1,4-addition).

Proton abstraction from protonated base (or solvent) by the enolate ion (IV) leads to an enol (V) which tautomerizes to the corresponding ketone, the Michael adduct (VI) in the final step.

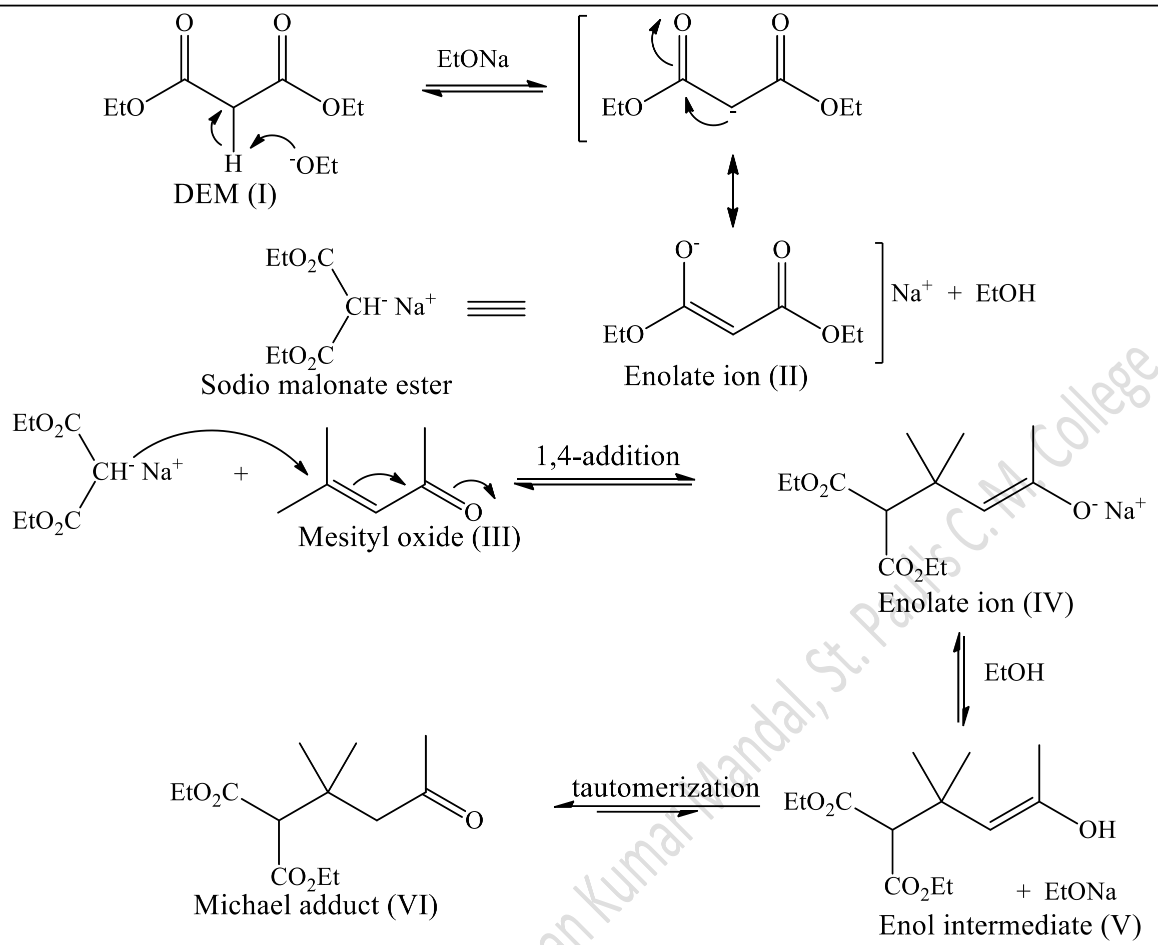

Figure 2: Mechanism of Michael reaction

The course of the reaction is dominated by orbital, rather than electrostatic, considerations. The HOMO of stabilized enolates has a large coefficient on the central carbon atom while the LUMO of many α,β-unsaturated carbonyl compounds has a large coefficient on the β-carbon. Thus, both reactants can be considered soft. These polarized frontier orbitals are of comparable energy, and react efficiently to form a new carbon-carbon bond.

With the example shown in Figure 2, after the Michael condensation has occurred, it is followed by an internal Claisen condensation if excess base is used. The cyclic compound thus obtained on hydrolysis followed by decarboxylation leads to the formation of dimedone. The formation of dimedone from the Michael condensation adduct is illustrated in Figure 3.

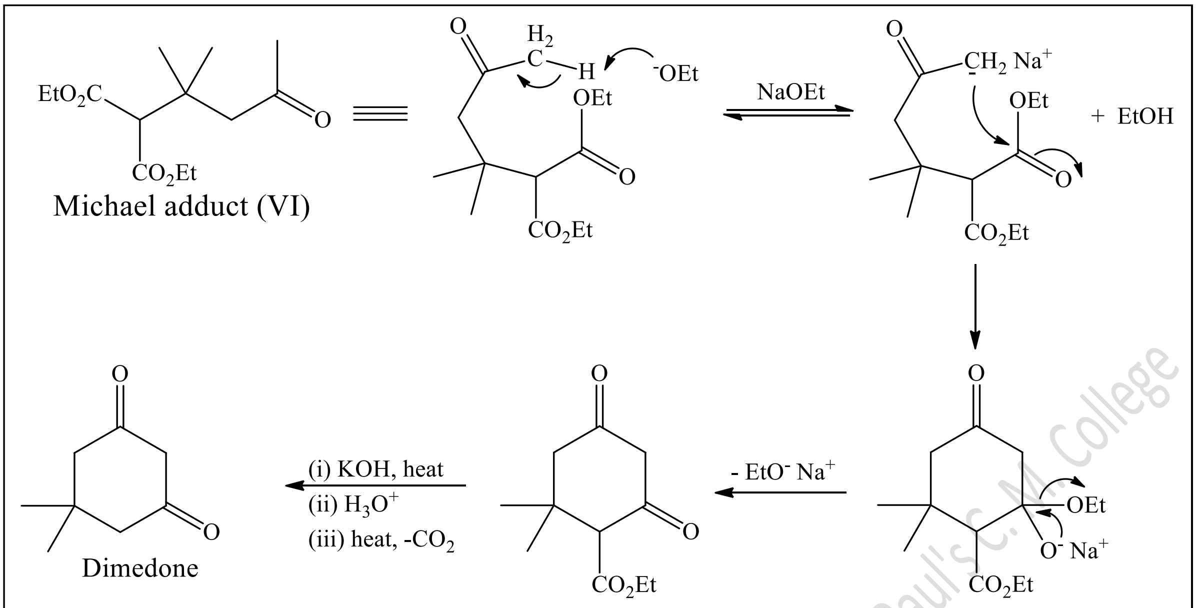

Figure 3: Mechanism for the formation of dimedone

To prepare Michael addition compound, more than one combination of donor and acceptor can sometimes be used. But to carryout the reaction in milder condition, that pair is recommended in which the donor molecule can easily form the resonance stabilized carbanion.

The keto ester Ph-CO-CH_2-CH(Ph)-CH(CO_2Et)$_2$ can be synthesized from Ph-CH=CH-CO-Ph and CH_2(CO_2Et)$_2$ (diethyl malonate) or from Ph-CH(CO_2Et)$_2$ and Ph-CO-CH_3 (acetophenone). However, first combination is better because CH_2(CO_2Et)$_2$ (pK_a ~ 14) can form the carbanion more easily compared to $PhCOCH_3$ (pK_a ~ 16). This result is illustrated in Figure 4.

Synthesis of Different Michael Adduct

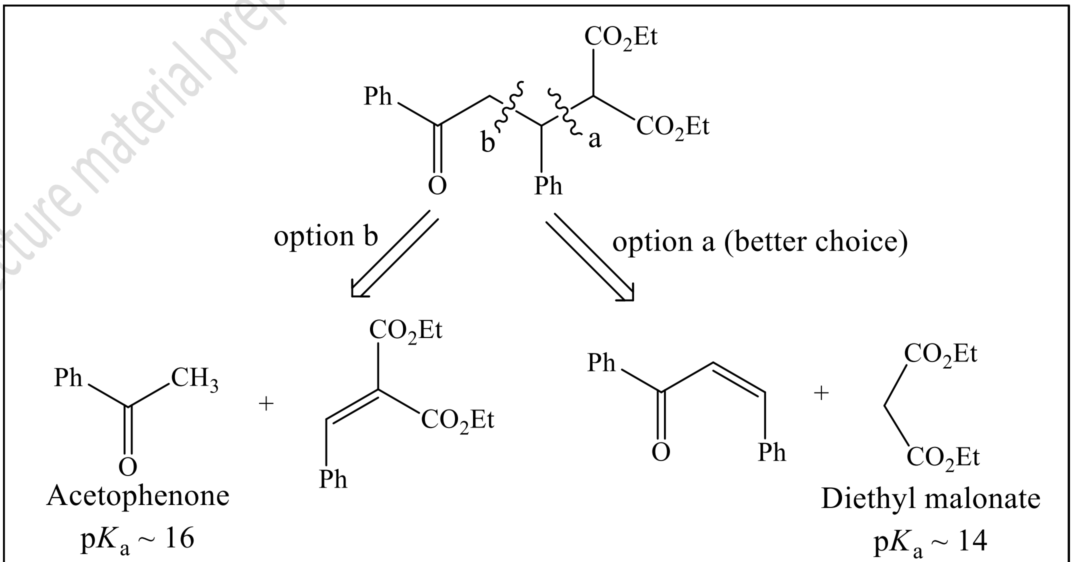

Figure 4: Choice of starting materials in forming the Michael adduct

Formation of anion from DEM can be accomplished with a weaker base while formation of enolate from acetophenone will require the use of a stronger base. Thus (a) needs a less vigorous condition.

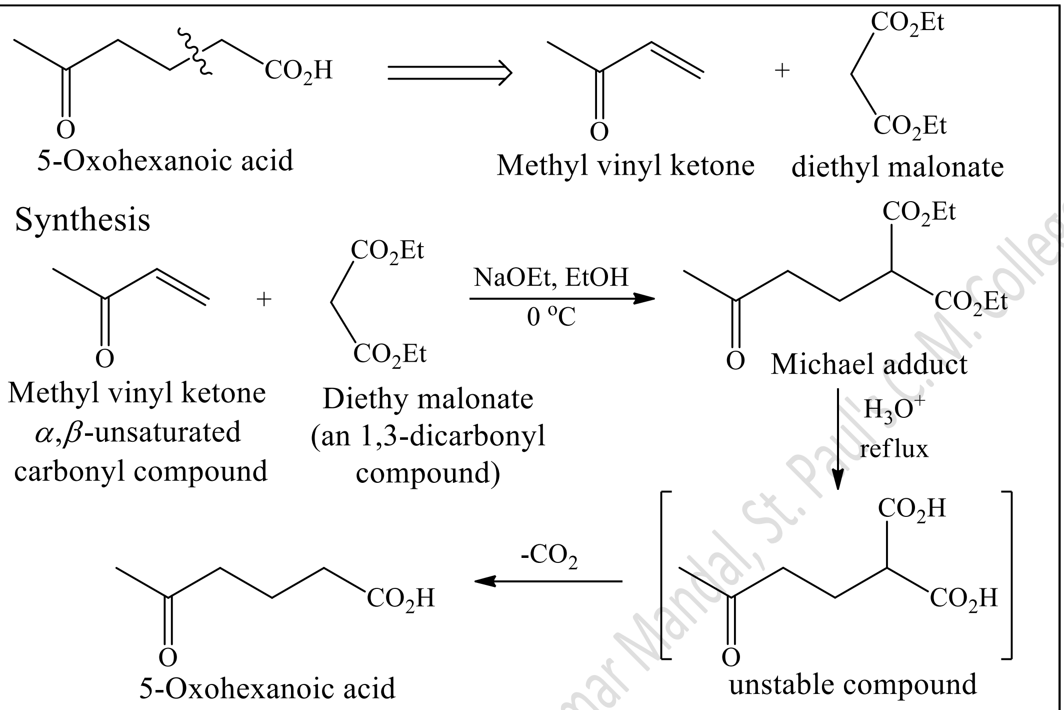

Figure 5: Synthesis of 5-oxopentanoic acid using Michael condensation

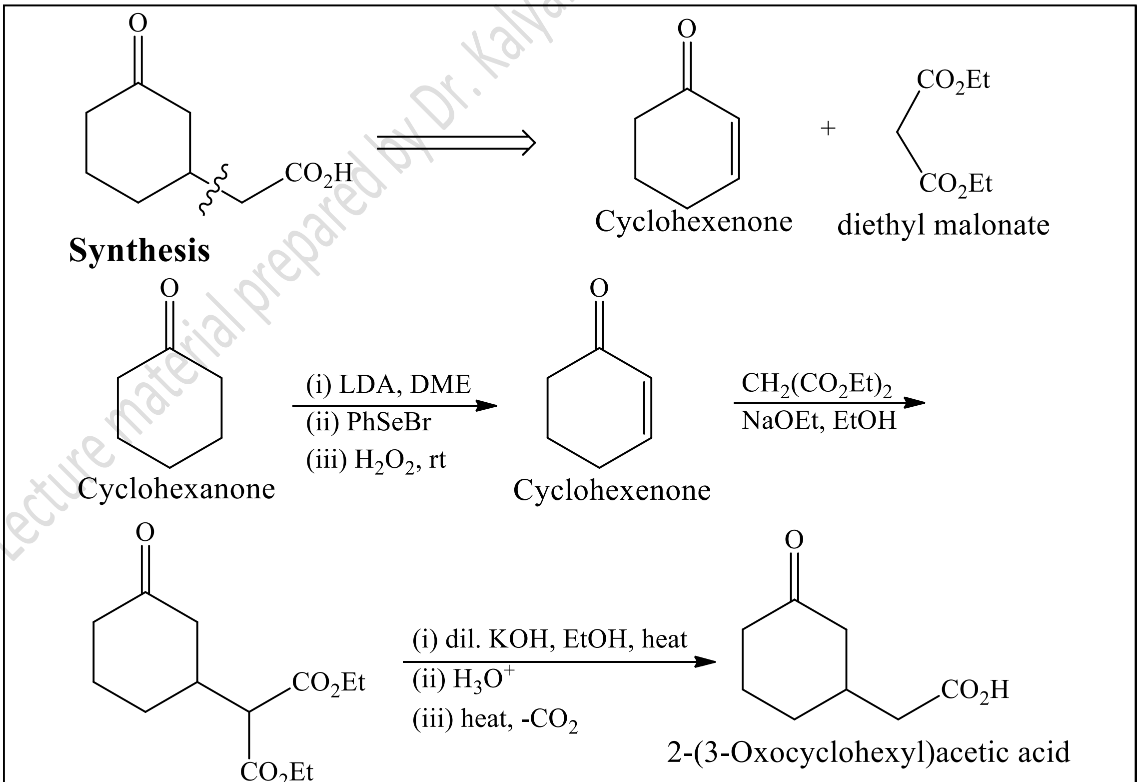

Figure 6: Synthesis of 1,5-dicarbonyl compound using Michael condensation

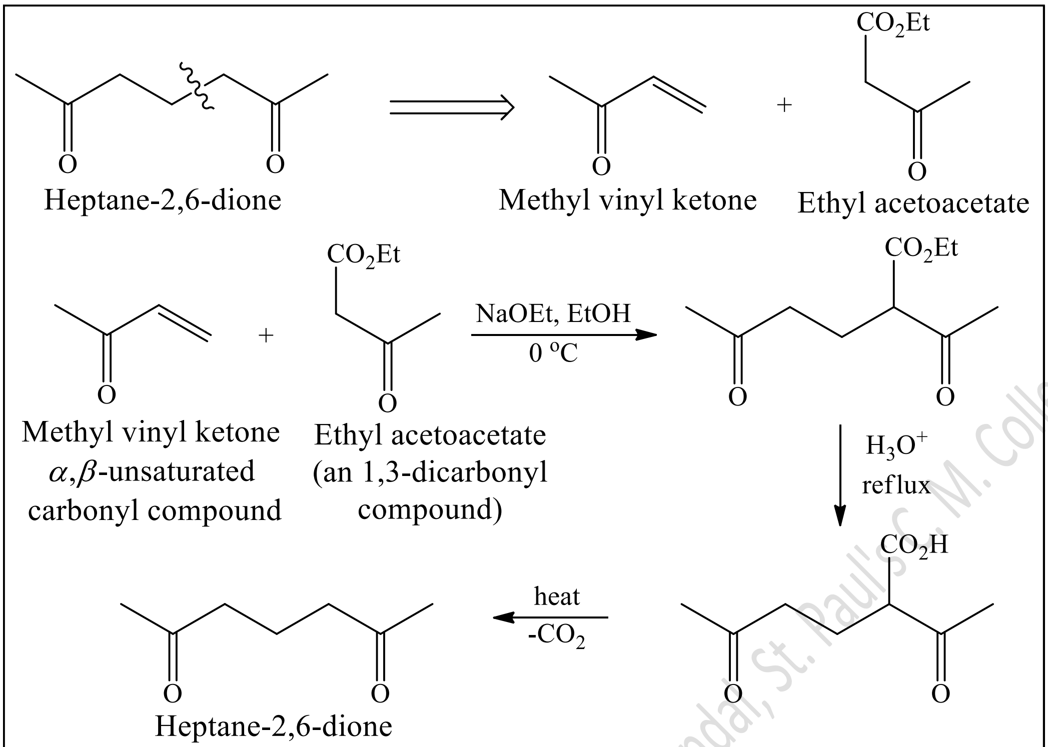

Figure 7: Synthesis of heptane-2,6-dione using Michael condensation

Michael *Retrogression* Reaction: Reversal of Michael

Michael condensation is reversible. Thus, a Michael retrogression, i.e., reversal, may occur to produce compounds different from the starting materials, e.g., starting with benzylidenemalonic ester and ethyl acetoacetate in the presence of a large amount of sodium ethoxide results in a mixture containing the reactants (1 & 2), the Michael condensation product (5), and benzylidene-acetoacetate (3) and malonic ester (4) (produced by retrogression). If the reaction is carried out with the last two compounds as starting materials, the same mixture is obtained as shown in Figure 8.

The use of a full equivalent of base, elevated reaction temperatures and long reaction time frequently promote reversal of Michael reaction (called a retrograde Michael reaction) or further transformations of the initial product, as the Michael addition product is forced to stay in the equilibrium mixture.

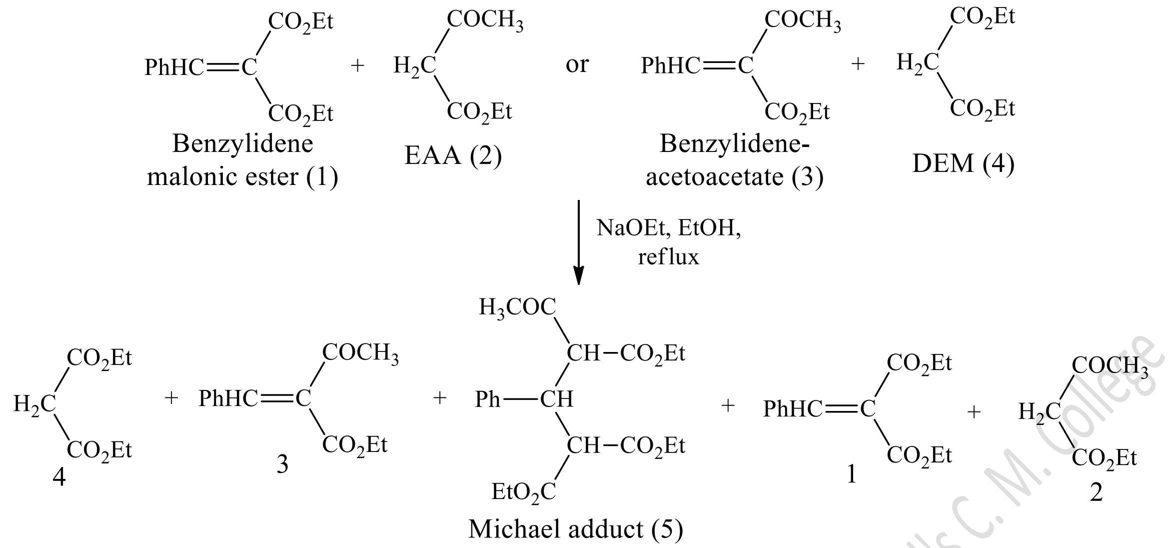

Figure 8: Michael *retrogression* reaction

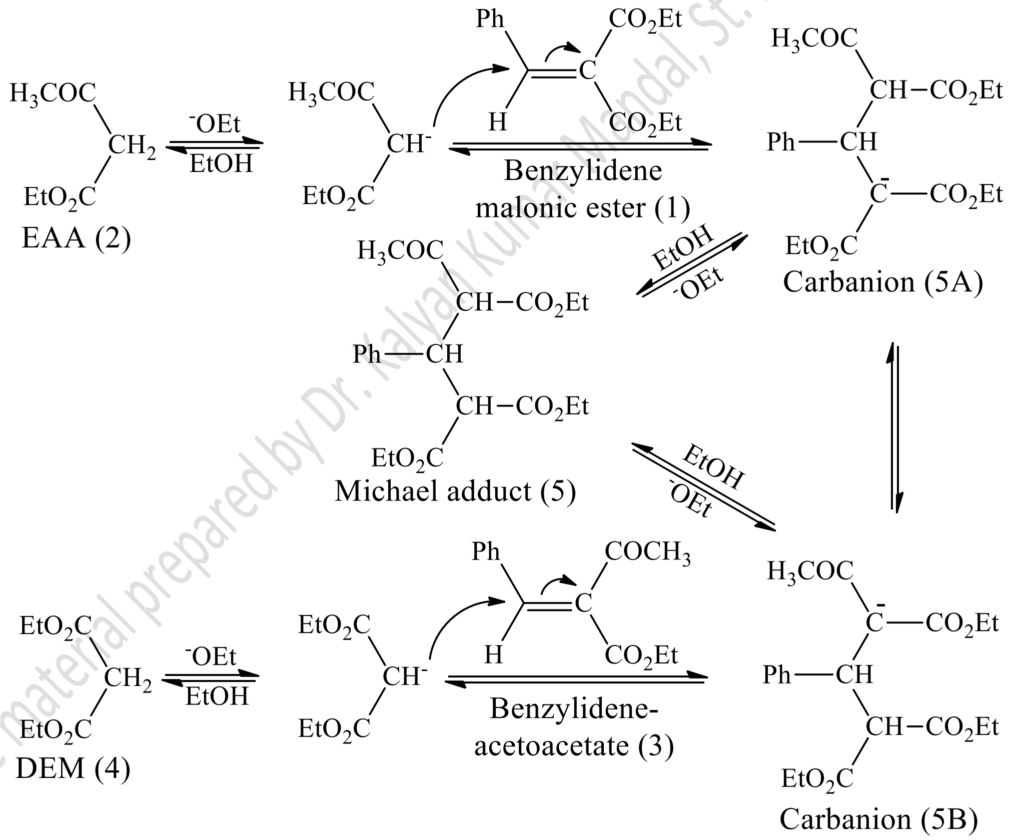

Figure 9: Reversibility of Michael reaction

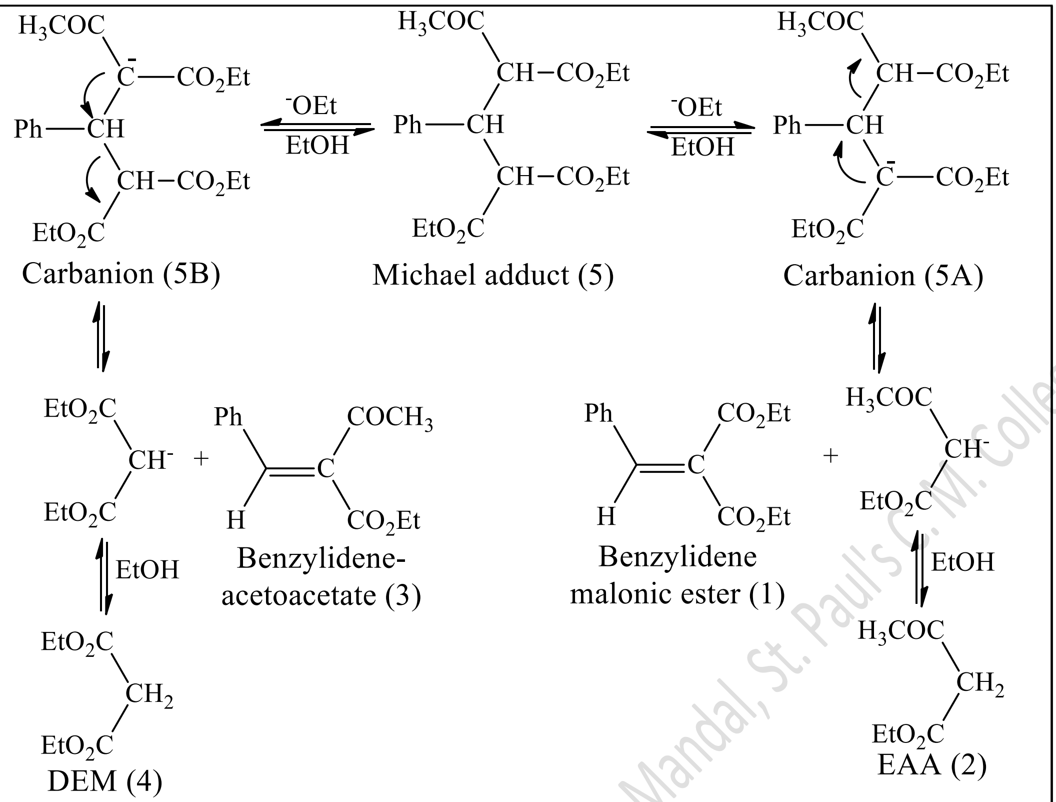

Figure 10: Mechanism of Michael *retrogression* reaction

The transformation, shown in Figure 10, indicates that Michael addition *is reversible* and this retrogression reaction passes through the formation of a carbanion. This reaction is, therefore, considered as an elimination reaction of E_1cB type.

To minimize, Michael retrogression, use of excess of active methylene compound (Michael donor) is recommended.

Abnormal Michael Reaction

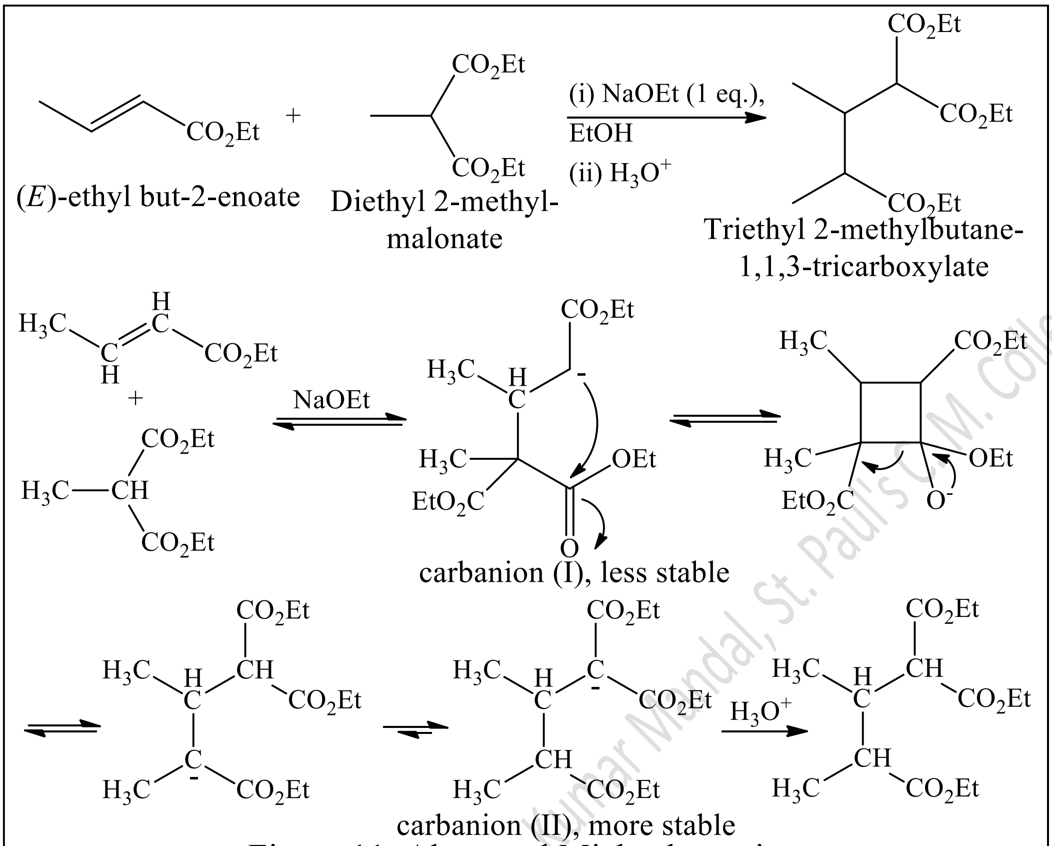

Figure 11: Abnormal Michael reaction

This transformation proceeds as the product is more acidic (i.e. the corresponding anion is more stable) than the initial Michael addition product and the reaction condition is a basic one as a full equivalent of NaOEt is used.

Synthesize the following Compounds Using Michael Condensation as one of the Steps