CARBONYL COMPOUNDS

PART-28, PPT-28, SEM-3

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Robinson Annulation Reaction

The Robinson annulation is a chemical reaction used in organic chemistry for ring formation. It was discovered by Robert Robinson in 1935 as a method to create a six membered ring by forming three new carbon-carbon bonds. In one useful variation of the Michael reaction is that the addition product (Michael adduct) of the reaction showed the potentiality to undergo base catalysed intramolecular aldol condensation that closes a ring. This sequence of tandem Michael reaction – aldol condensation leading to ring closure is an example of the Robinson Annulation.

Robinson annulation reaction as it stands now, comprises three steps, (i) Michael condensation, (ii) intramolecular aldol condensation of the Michael condensation product and (iii) dehydration of the aldol condensation product. Since these stepwise reactions generate ring systems, the term 'annulation' (meaning: *furnished with or composed of rings*) is used. The method uses a ketone, in general and an *α,β*-unsaturated ketone, such as, methyl vinyl ketone to form an *α,β*-unsaturated ketone moiety (-C=C-CO-) in a cyclohexane ring by a Michael addition followed by an aldol condensation. This procedure is one of the key methods to form fused ring systems. A few examples are given in Figure 1.

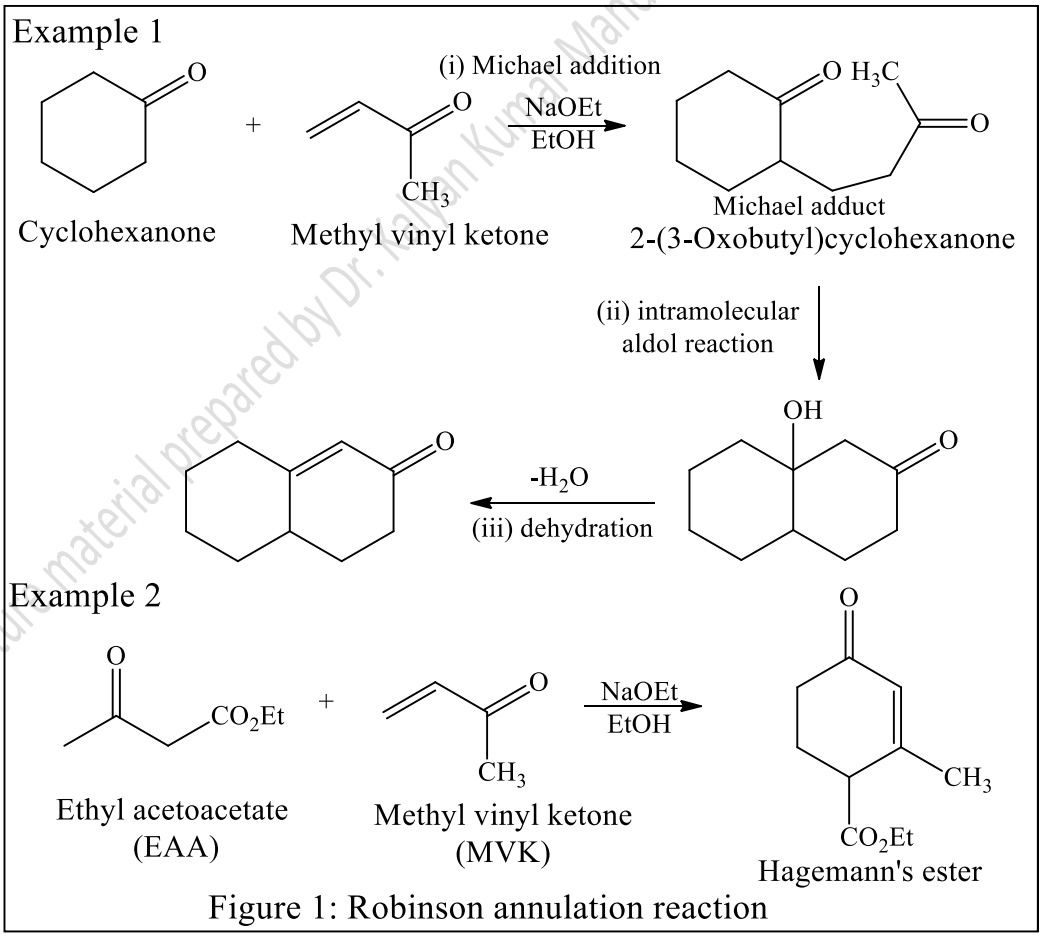

Figure 1: Robinson annulation reaction

Features of Robinson Annulation Reaction

1. It is a combination of Michael addition, intramolecular aldol condensation and dehydration.
2. The reaction can be both acid or base catalyzed, but normally the reaction is carried out under basic conditions.
3. Reaction can be done as one-pot process but the yield is poor. Best result is obtained when the Michael adduct is isolated and then separately subjected to aldol condensation.
4. In case of choice, the Michael addition occurs at the most substituted α-position unless severe steric interference dictates otherwise. One interesting example is shown in Figure 2.
5. This reaction generates more than one stereogenic centres and therefore, can have many stereoisomers.

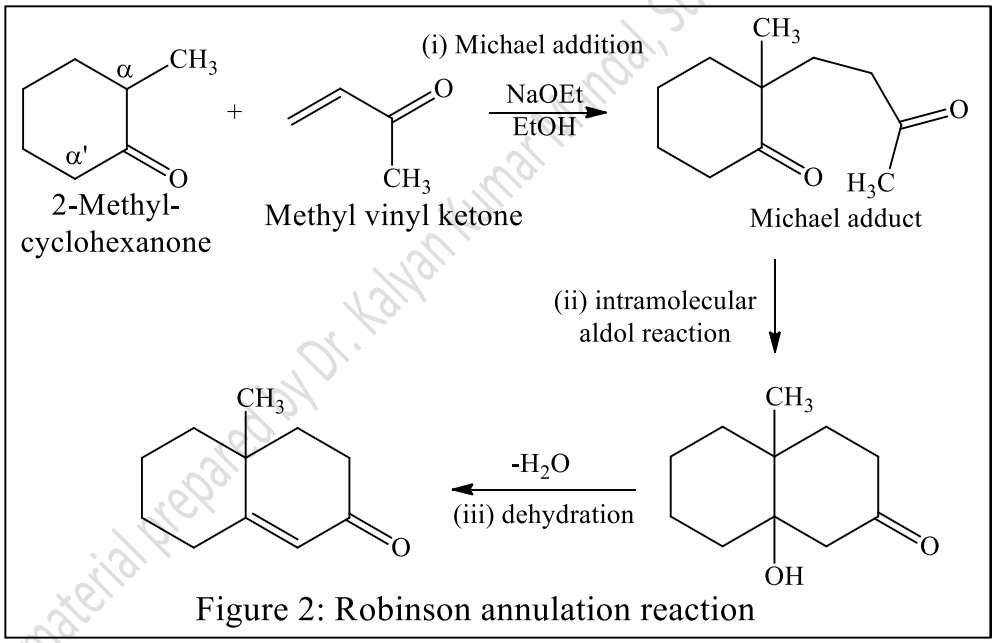

Figure 2: Robinson annulation reaction

Here reaction starts at the more substituted α-position instead of the less substituted α'-position. The product formation involves deprotonation of the less acidic proton.

Mechanism of Robinson Annulation Reaction

The mechanism of the reaction begins with the nucleophilic attack by the Michael donor, obtained from the ketone in presence of a base, in a Michael reaction on a β-carbon of the α,β-unsaturated carbonyl system to produce the intermediate Michael adduct.

- Subsequent aldol type ring closure leads to the keto alcohol, which is then followed by dehydration to produce the annulation product.
- In the Michael reaction, the ketone is deprotonated by a base (NaOEt) to form an enolate nucleophile which attacks the electron acceptor (Michael acceptor). This acceptor is generally an *α*,*β*-unsaturated ketone. In the example shown in Figure 2, regioselectivity is dictated by the formation of the thermodynamic enolate. The mechanism of the reaction is illustrated in Figure 3.

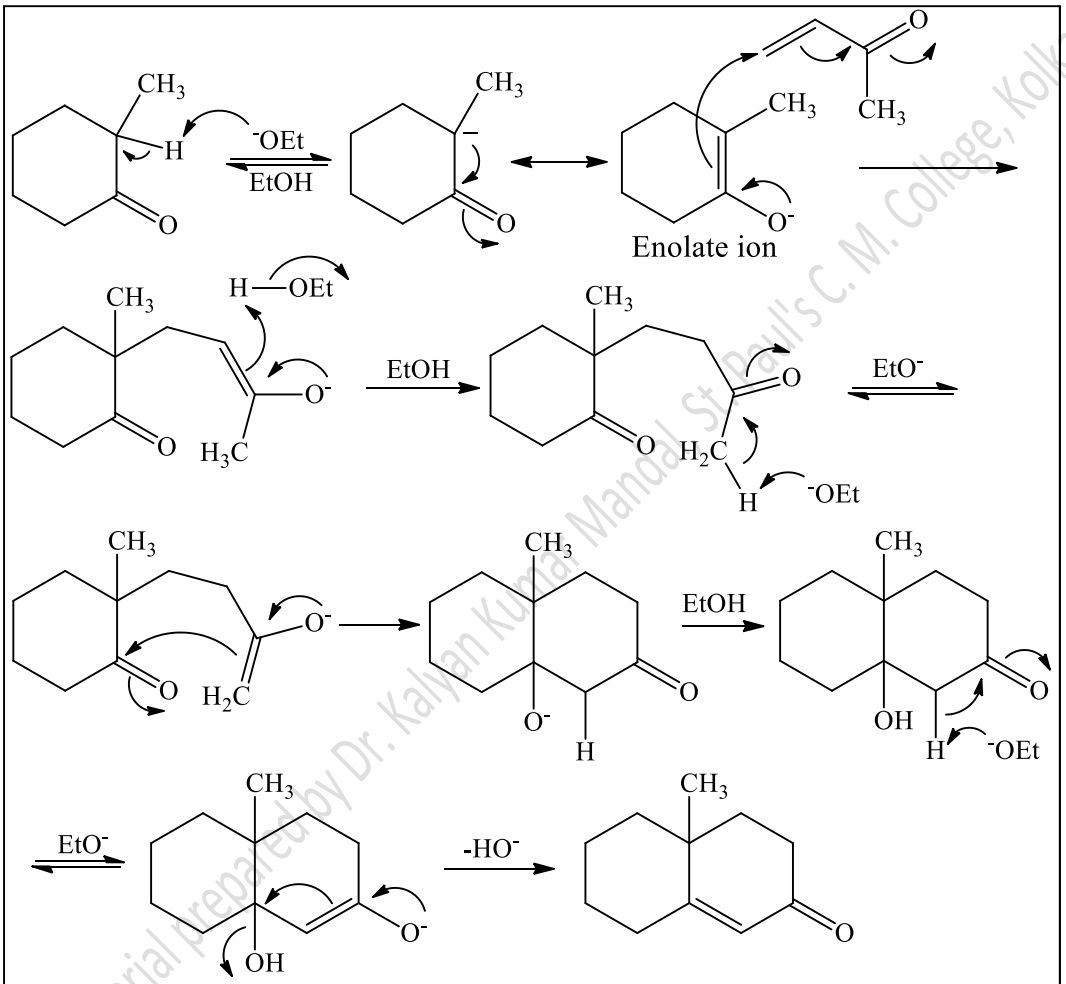

Figure 3: Mechanism of Robinson annulation reaction

Alternatively, the regioselectivity in Robinson annulation reaction is often controlled by using a *β*-diketone or *β*-ketoester as the enolate component, since deprotonation at the carbon flanked by the carbonyl groups is strongly favored. The intramolecular aldol condensation then takes place in such a way that installs the six-membered ring. In the final product, the three carbon atoms of the *α*,*β*-unsaturated system and the carbon *α* to its carbonyl group make up the four-carbon bridge of the newly installed ring.

In order to avoid a reaction between the original enolate and the cyclohexanone product, the initial Michael adduct is often isolated first and then cyclized to give the desired product in a separate step.

Synthesis of Hagemann's Ester

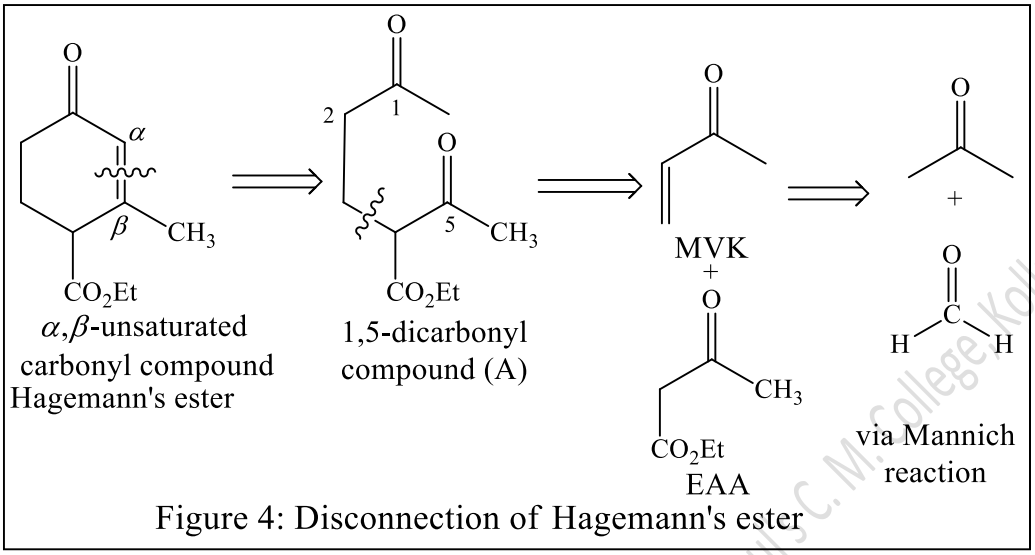

Figure 4: Disconnection of Hagemann's ester

There is a problem during cyclization of the 1,5-dicarbonyl compound (A; Figure 4) for the preparation of Hagemann's ester. This is because during aldol condensation with the unsymmetrical 1,5-dicarbonyl compound (A), there is a possibility of formation of a mixture of products by at least two different cyclisation routes as shown n Figure 5.

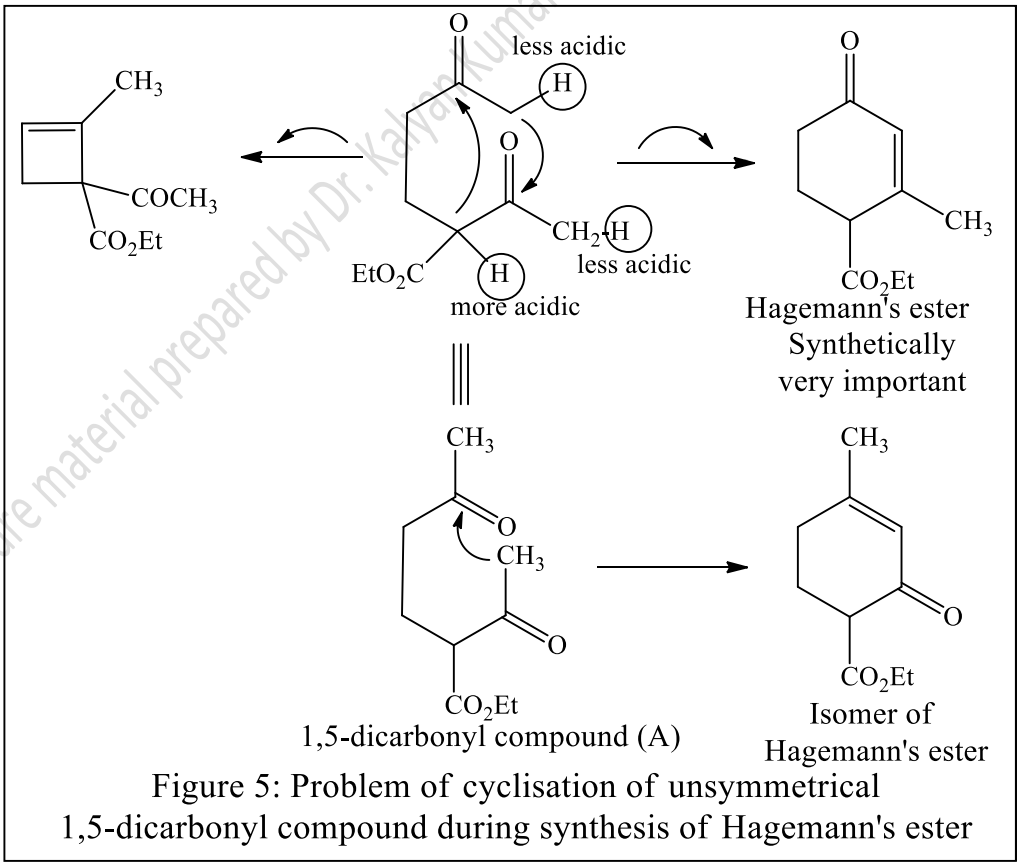

Figure 5: Problem of cyclisation of unsymmetrical 1,5-dicarbonyl compound during synthesis of Hagemann's ester

Originally Hagemann's ester is synthesized via Robinson annulation reaction by using a mixture of ethyl acetoacetate (2 equivalents) and formaldehyde (1 equivalent) instead of using of 1 equivalent of each of methyl vinyl ketone and ethyl acetoacetate. Under this condition a symmetrical 1,5-dicarbonyl compound (B) is prepared which cyclizes unambiguously to Hagemann's ester. The disconnection and the synthesis of this ester are illustrated in Figures 6 and 7, respectively.

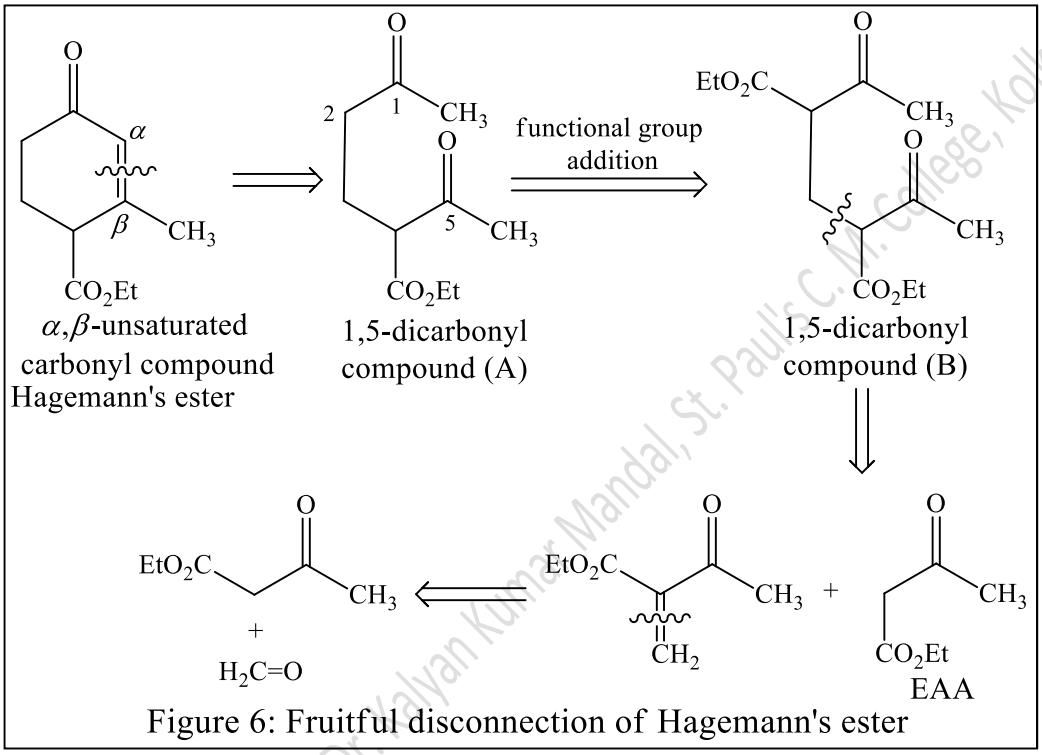

Figure 6: Fruitful disconnection of Hagemann's ester

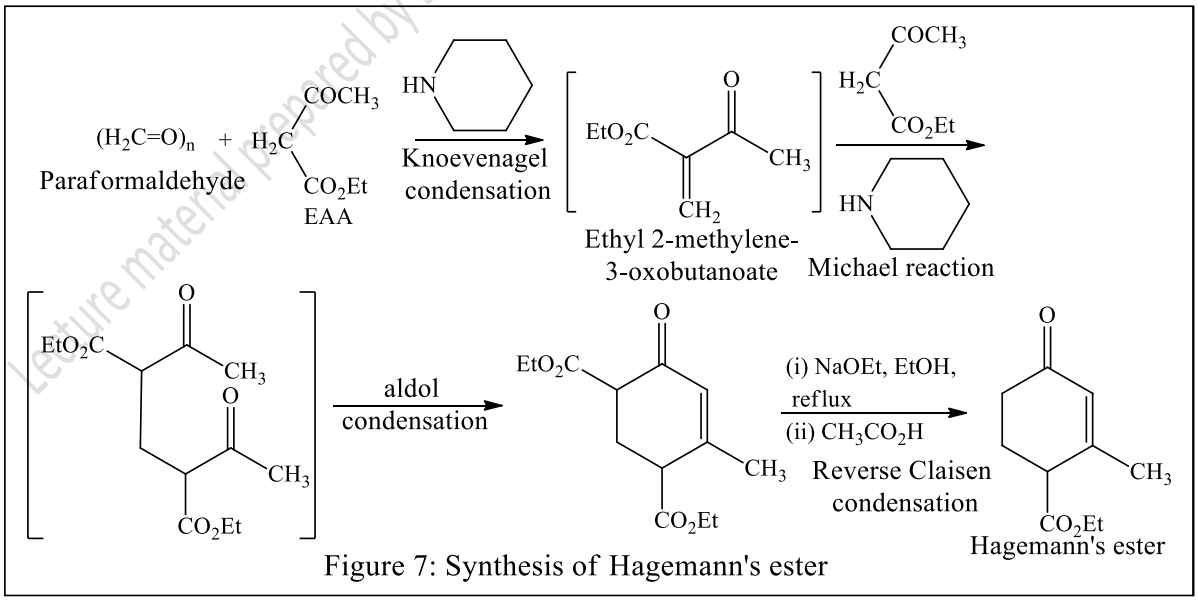

Figure 7: Synthesis of Hagemann's ester

Synthesis of 3-Ethyl-3-methylcyclohexanone

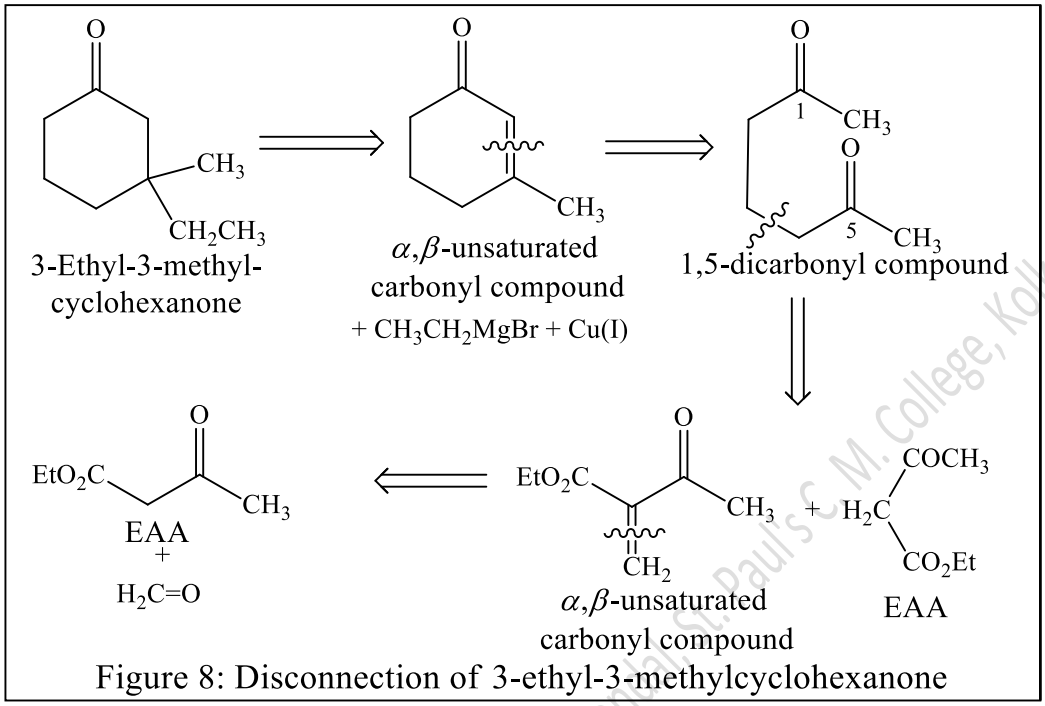

Figure 8: Disconnection of 3-ethyl-3-methylcyclohexanone

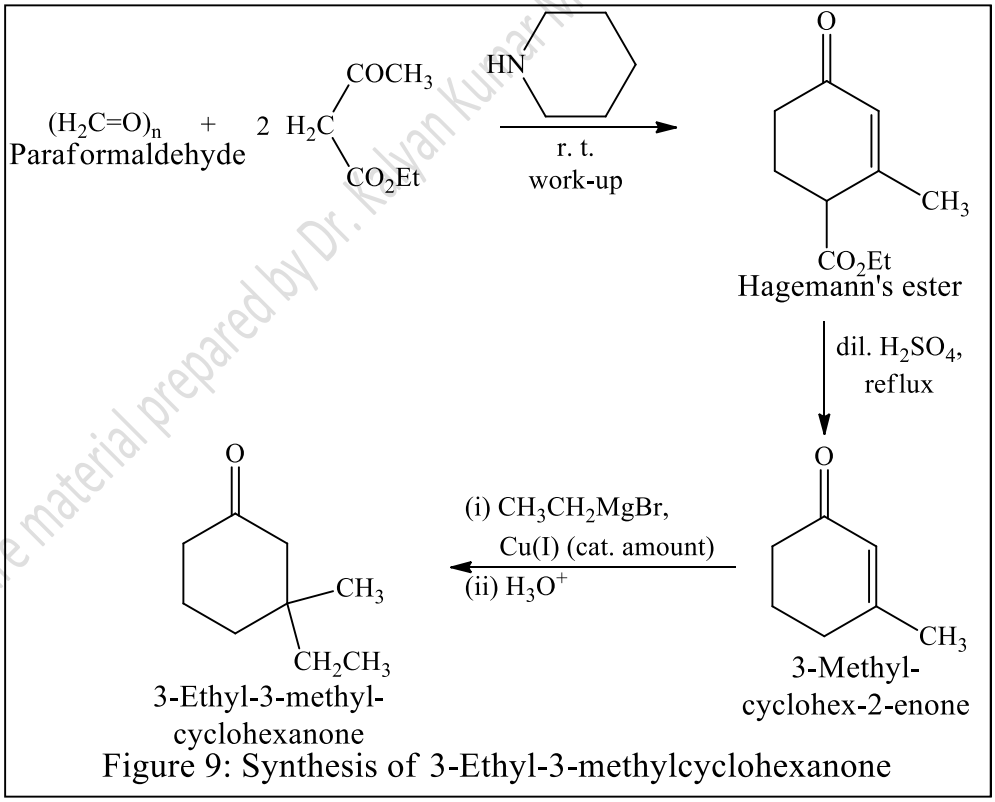

Figure 9: Synthesis of 3-Ethyl-3-methylcyclohexanone

Synthesis of *ortho*-Fused Bicyclic α,β-Unsaturated Ketone

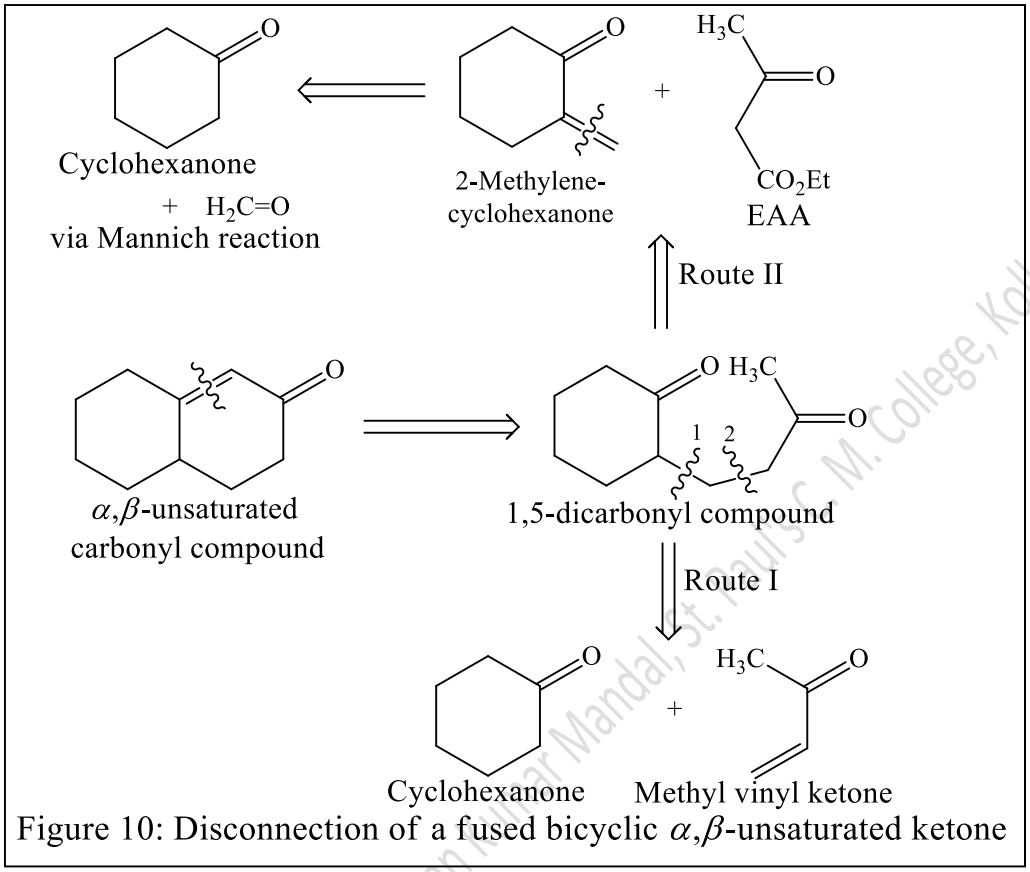

Figure 10: Disconnection of a fused bicyclic α,β-unsaturated ketone

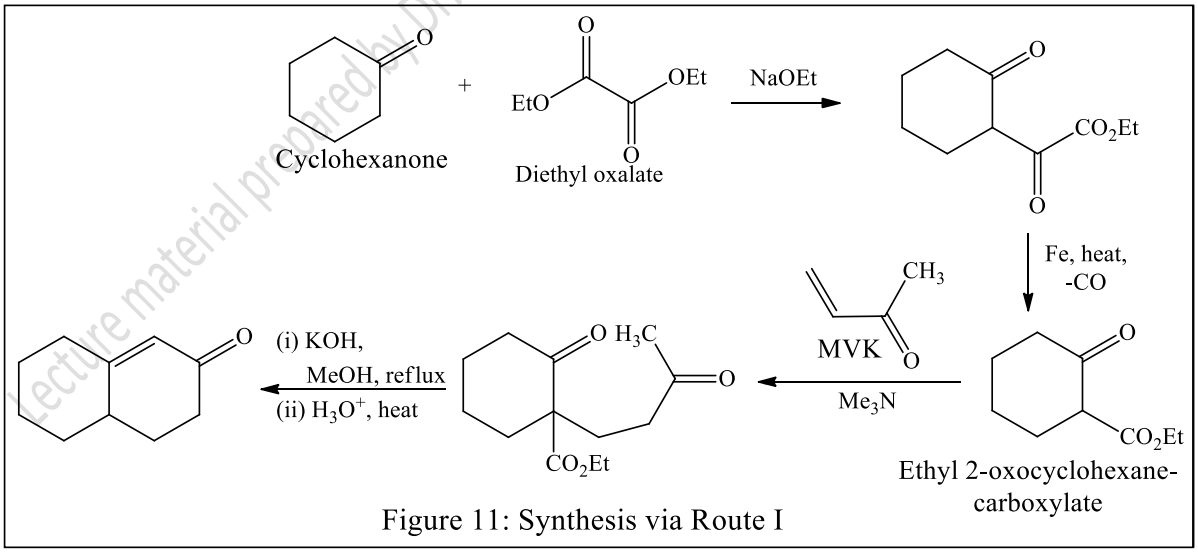

Figure 11: Synthesis via Route I

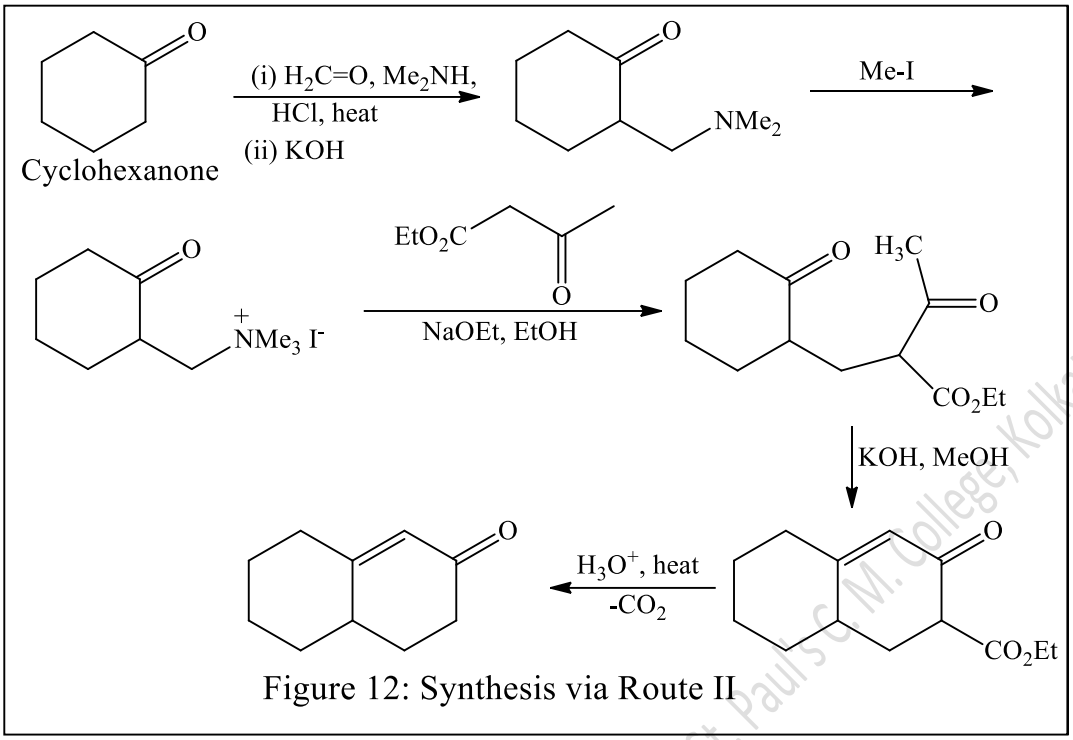

Figure 12: Synthesis via Route II

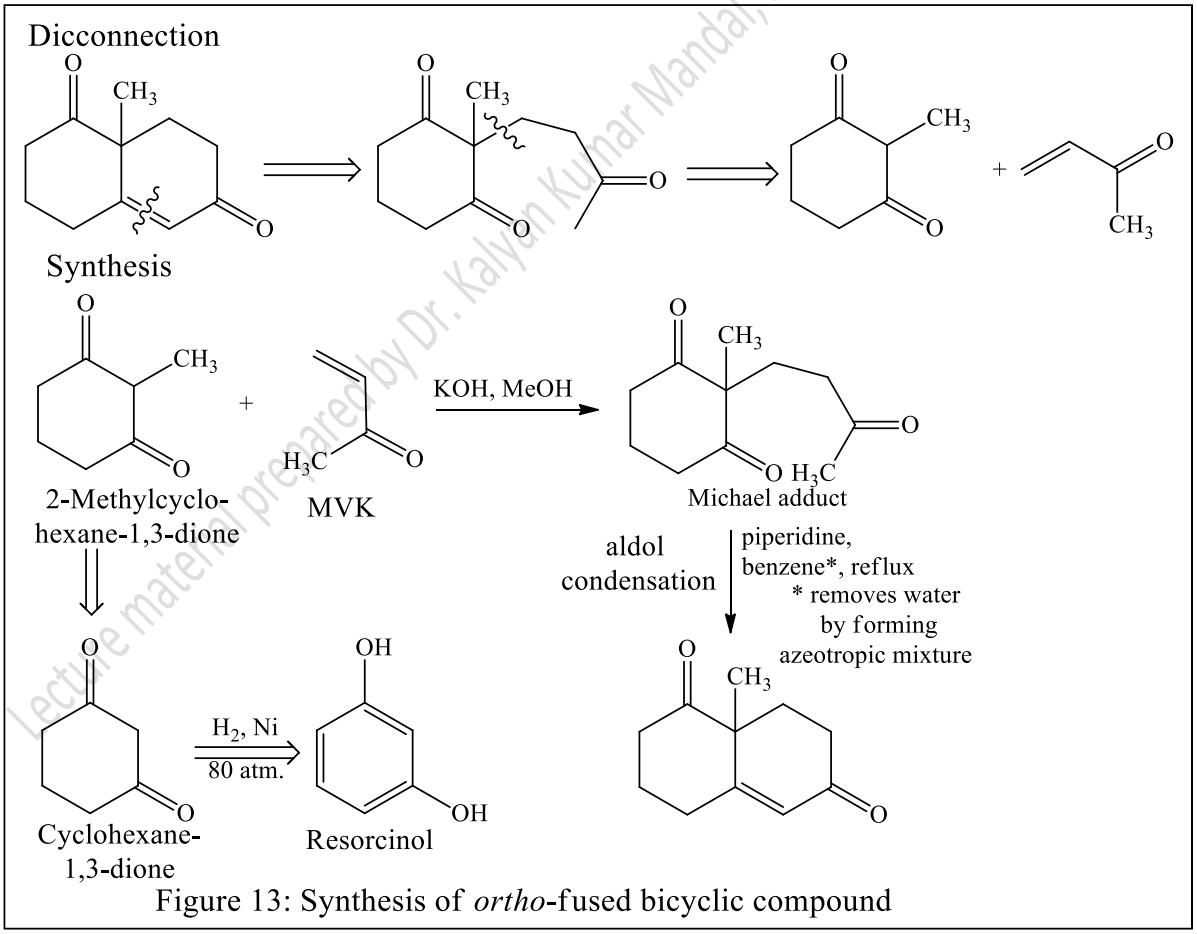

Figure 13: Synthesis of *ortho*-fused bicyclic compound

Stetter Reaction: Utilizing Michael Addition in Synthesising 1,4-Dicarbonyls

The Stetter reaction is an important reaction used in organic chemistry to form carbon-carbon bonds through a 1,4-addition reaction utilizing a nucleophilic catalyst. While the related 1,2-addition reaction, the benzoin condensation, was known since the 1830s, the Stetter reaction was reported in 1973 by Dr. Hermann Stetter. The reaction provides synthetically useful 1,4-dicarbonyl compounds and related derivatives from aldehydes and Michael acceptors. Unlike 1,3-dicarbonyls, which are easily accessed through the Claisen condensation, or 1,5-dicarbonyls, which are commonly made using a Michael reaction, 1,4-dicarbonyls are challenging substrates to synthesize.

Traditionally utilized catalysts for the Stetter reaction are thiazolium salts and cyanide anion. The Stetter reaction is an example of umpolung chemistry, as the inherent polarity of the aldehyde is reversed by the addition of the catalyst to the aldehyde, rendering the carbon centre nucleophilic rather than electrophilic.

The cyanide ion catalysis is restricted to aromatic aldehydes because use of aliphatic aldehydes triggers undesired Aldol reactions. The slatter reaction using aldehydes are shown in Figure 14. For aliphatic substrates, thiazolium catalysis is the best. It is to be noted that Ronald Breslow first proposed the mechanism of thiazolium ion catalysis in Benzoin Condensation (1958).

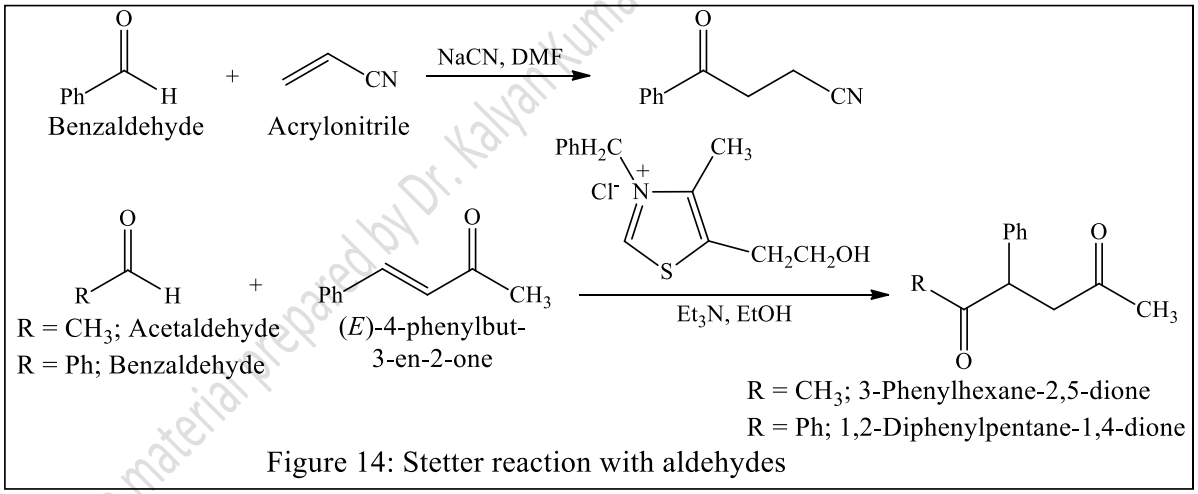

Figure 14: Stetter reaction with aldehydes

Scope of Stetter Reaction

The Stetter reaction produces classically difficult to access 1,4-dicarbonyl compounds and related derivatives. The traditional Stetter reaction is working on a wide variety of substrates. Aromatic aldehydes, heteroaromatic aldehydes, and benzoins can all be used as acyl anion precursors with thiazolium salt and cyanide catalysts. However, aliphatic aldehydes can only be utilized if a thiazolium salt is used as a catalyst, as they undergo aldol condensation side reaction when a cyanide catalyst is used. In addition, α,β-unsaturated esters, ketones,

nitriles, nitro compounds, and aldehydes are all appropriate Michael acceptors with either catalyst.

Synthesis of 1,4-Dicarbonyl Compounds

Synthesising an 1,4-dicarbonyl compound is difficult, because it involves using at least one illogical synthon. This fact is described by considering the retrosynthetic analysis of an 1,4-dicarbonyl compound as illustrated in Figure 15.

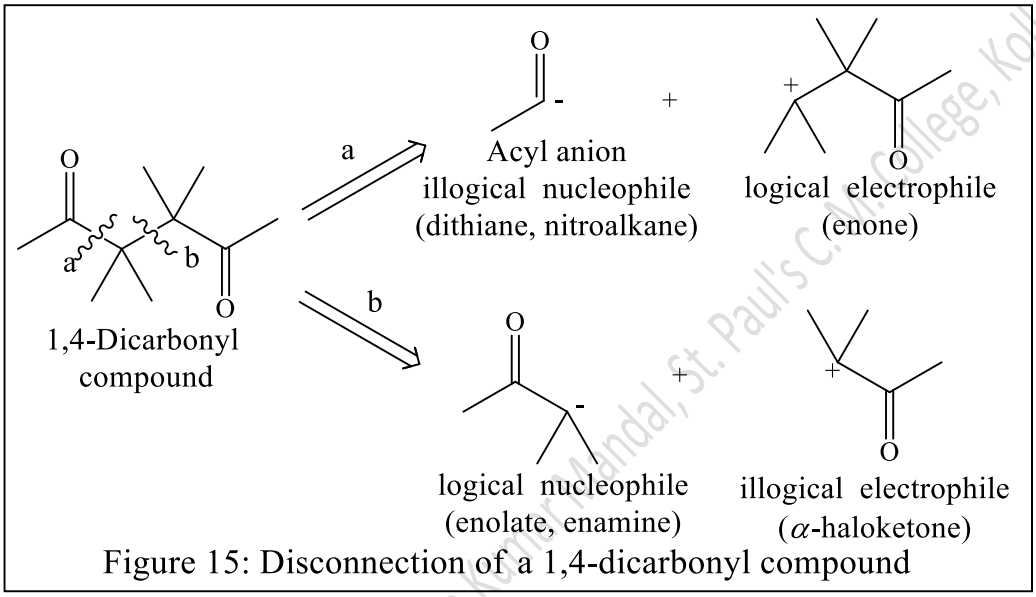

Figure 15: Disconnection of a 1,4-dicarbonyl compound

Mechanism of Stetter Reaction

As the Stetter reaction is an example of umpolung chemistry, the aldehyde is converted from an electrophile to a nucleophile under the reaction conditions. This is accomplished by activation from some catalyst - either cyanide (CN^-) or thiazolium salt. For the use of either catalyst, the mechanism is very similar; the only difference is that with thiazolium salts, the catalyst must be deprotonated first to form the active catalytic species.

The active catalyst can be described as the combination of two contributing resonance forms – an ylide or a carbene, both of which exhibit the nucleophilic character at carbon. The thiazolium ylide or CN^- can then add into the aldehyde substrate, forming a cyanohydrin in the case of CN^- or the Breslow intermediate in the case of thiazolium salt. The formation of Breslow intermediate is shown in Figure 16.

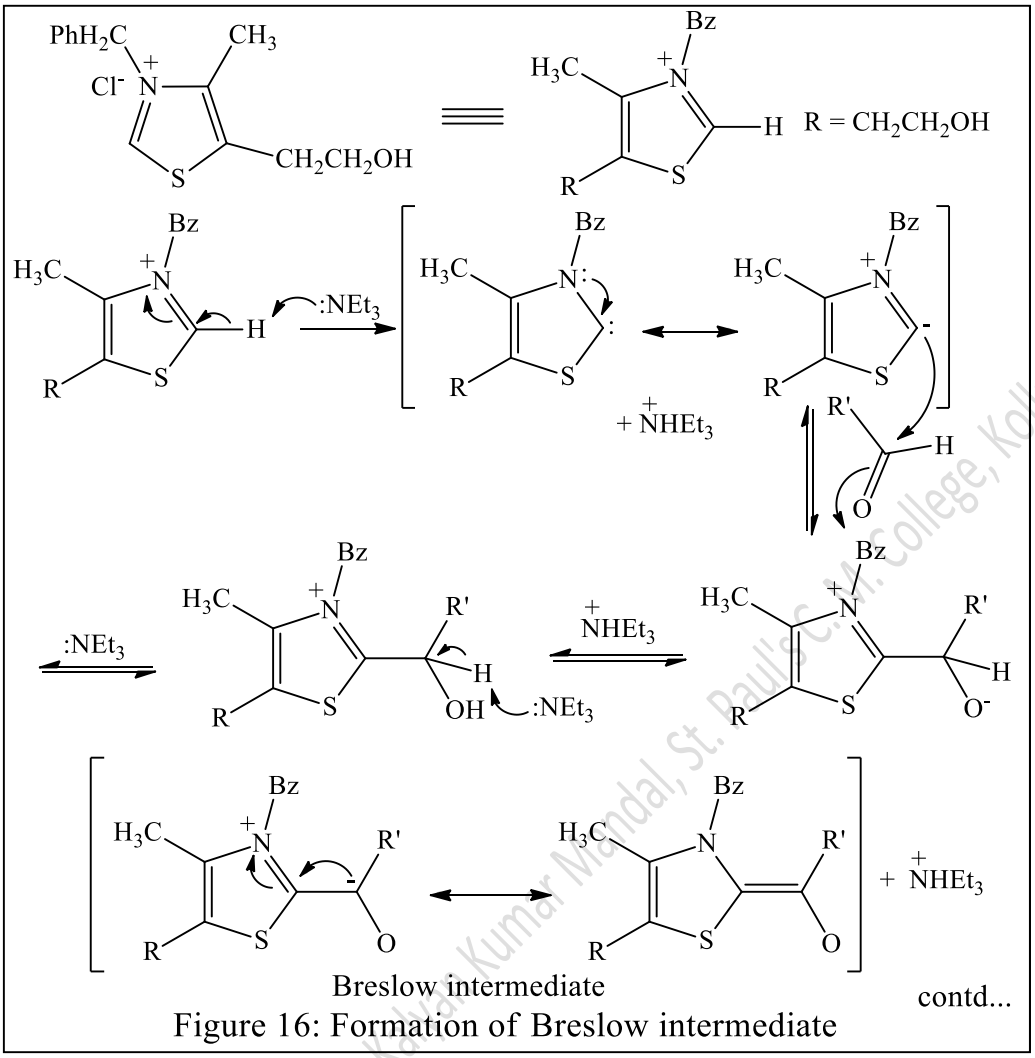

Figure 16: Formation of Breslow intermediate

Once the "nucleophilic aldehyde" synthon is formed, whether as a cyanohydrin or stabilized by a thiazolium ylide, the reaction can proceed down two pathways. The faster pathway is self-condensation with another molecule of aldehyde to give benzoin products. However, benzoin condensation is completely reversible, and therefore does not interfere with product formation in the Stetter reaction.

In fact, benzoins can be used instead of aldehydes as substrates to achieve the same overall Stetter transformation, because benzoins can be restored to their aldehyde precursors under the reaction conditions. The desired pathway toward the Stetter product is the 1,4-addition of the nucleophilic aldehyde to a Michael-type acceptor. After 1,4-addition, the reaction is irreversible and ultimately, the 1,4-dicarbonyl is formed when the catalyst is kicked out to regenerate CN^- or the thiazolium ylide. Mechanism for the formation of 1,4-dicarbonyl compound is shown in Figure 17.

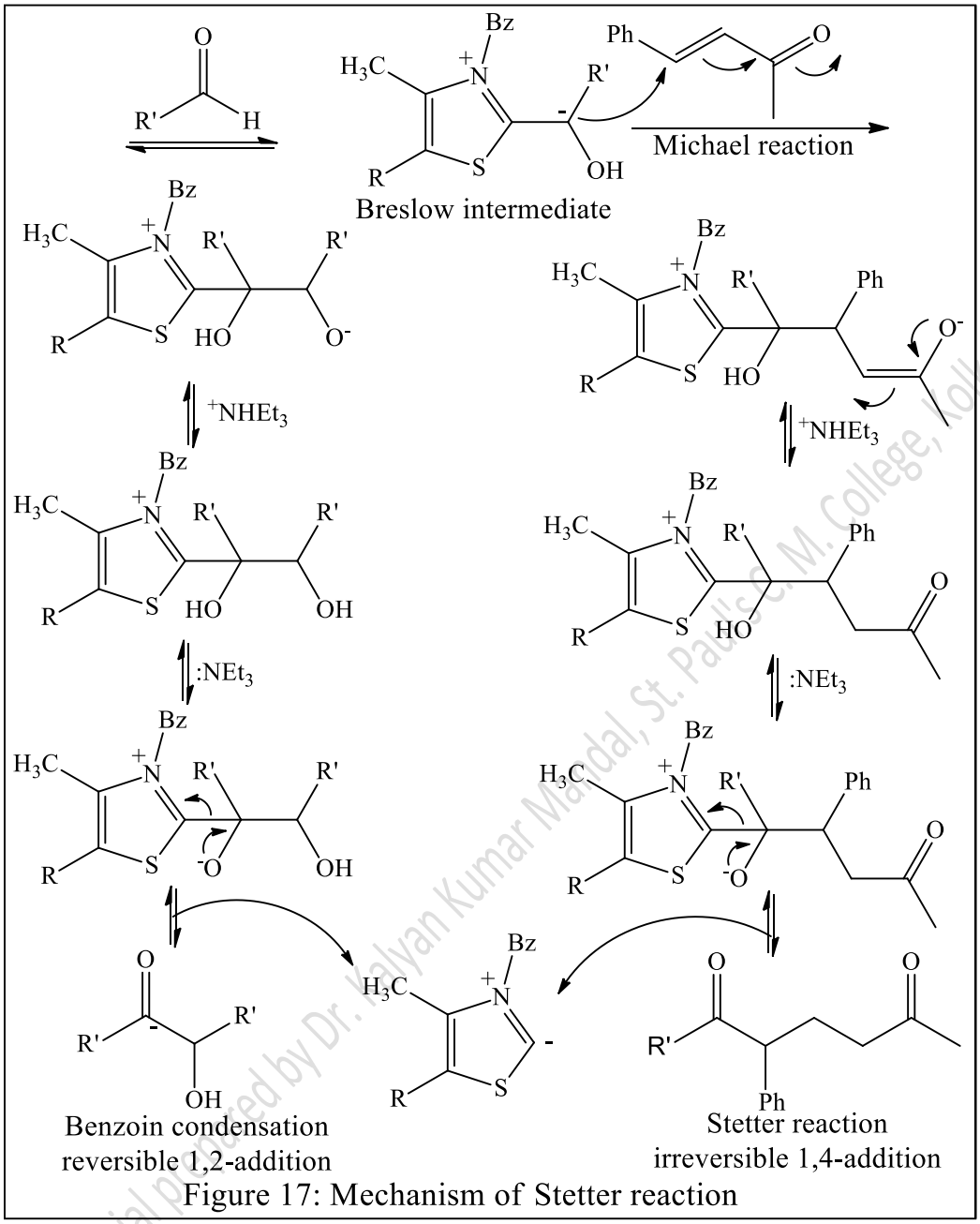

Figure 17: Mechanism of Stetter reaction

Features of Stetter Reaction

- The thiazolium salts are actually precatalysts in Stetter reaction since the added base (e.g., Et_3N, NaOAc) deprotonates the highly acidic C-H bond (pK_a 18) between the nitrogen and sulphur atoms to generate an ylide structure *in situ* (this ylide behaves the same way as cyanide ions do).
- This reaction competes with the benzoin condensation (1,2-addition). However, the benzoin condensation is reversible, and since the Stetter reaction leads to more stable products, the main product will be derived from 1,4-addition.
- Since the mechanism involves the rapid, reversible formation of benzoins from aromatic aldehyde substrates, benzoins can be used instead of the aldehydes (aliphatic aldehydes cannot be replaced with acyloins).