

Subject	Chemistry
Paper No and Title	9: Organic Chemistry- III (Reaction Mechanism-II)
Module No and Title	19: Perkin and Knoevenagel condensation
Module Tag	CHE_P9_M19

Principal Investigator		Co- Principal Investigator and Technical Coordinator
Prof A.K.Bakhshi Sir Shankar Lal Professor, Department of Chemistry University of Delhi		Dr Vimal Rarh Deputy Director, Centre for e-Learning and Assistant Professor, Department of Chemistry, SGTB Khalsa College, University of Delhi <i>Specialised in : e-Learning and Educational Technologies</i>
Paper Coordinator	Content Writer	Reviewer
Prof Diwan S Rawat Department of Chemistry University of Delhi	Dr. Vimal Rarh Dr. Archana Milhotra Asst Professor Deshbandhu College University of Delhi	Prof. H. G. Krishnamurty Professor Emeritus Dept. of Chemistry University of Delhi
Anchor Institute : SGTB Khalsa College, University of Delhi		

TABLE OF CONTENTS

1. Learning Outcomes
2. Introduction
3. Perkin Condensation
 - 3.1 Acid anhydride and its enolate ion
 - 3.2 Perkin reaction and mechanism
4. Knoevenagel Condensation
 - 4.1 Knowing 1, 3 dicarbonyl compounds
 - 4.2 Reaction and mechanism
 - 4.3 The Doebner Modification
 - 4.4 Applications
 - 4.5 Recent advances in Knoevenagel condensation
5. Summary

1. Learning Outcomes

After studying this module, you shall be able to

- Know about Perkin reaction and Knoevenagel reactions
- Learn about what happens when the salt of the carboxylic acid acts as a base and a nucleophile in Perkin reaction mechanism
- Identify how Knoevenagel reaction can be treated like a crossed aldol reaction
- Evaluate the steps in the mechanism of Knoevenagel reaction
- Analyse the recent advancements in Knoevenagel reaction

2. Introduction

You are already familiar with the Aldol condensation where an enolisable aldehyde (or a ketone) i.e., having α -hydrogen atom, is reacted with base or acid, they condense to give rise to β – hydroxy-aldehydes (or β – hydroxy-ketones) known as aldols.

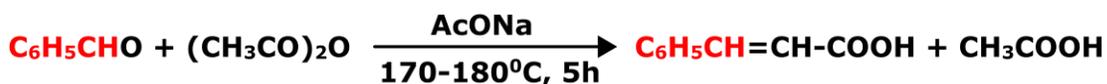
In the presence of the base, α -carbanion is formed which attacks as nucleophile on another molecule of aldehyde/ ketone resulting in the condensation of two molecules and giving rise to an alkoxide ion which takes proton from the medium to form aldol.

In a very analogous manner, Knoevenagel condensation and Perkin condensation also takes place. In other words, one can say that both Knoevenagel and Perkin condensation are modification to the aldol condensation. In aldol condensation, two carbonyl compounds are condensed. If we wish to condense one carbonyl compound with another active methylene compounds, it is the case of Knoevenagel condensation. If we wish to condense aromatic carbonyl compound with acid anhydride, it is the case of Perkin condensation. Let us study about them one by one.

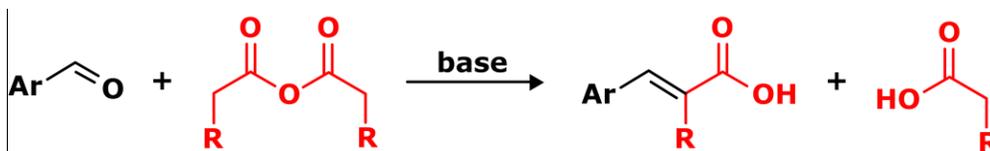
3. Perkin Condensation

The *Perkin reaction* is also analogous to aldol condensation. It was given by William Henry Perkin and is used to make α,β -unsaturated aromatic acid, commonly known as cinnamic acids.

In aldol condensation, two aldehyde (or ketone molecules are condensed with the help of base like NaOH. In this case, an aromatic aldehyde is condensed with an acid anhydride with the help of a suitable base.

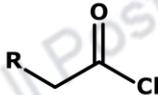
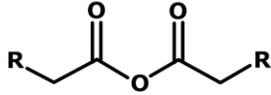
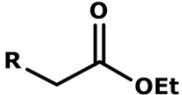
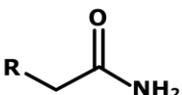


When an aromatic aldehyde is treated with an acid anhydride, in the presence of an alkali salt of the same carboxylic acid from which acid anhydride is made, the product formed is an α,β -unsaturated aromatic acid. The alkali salt of the carboxylic acid acts as the base here to abstract the proton to generate α -carbanion.

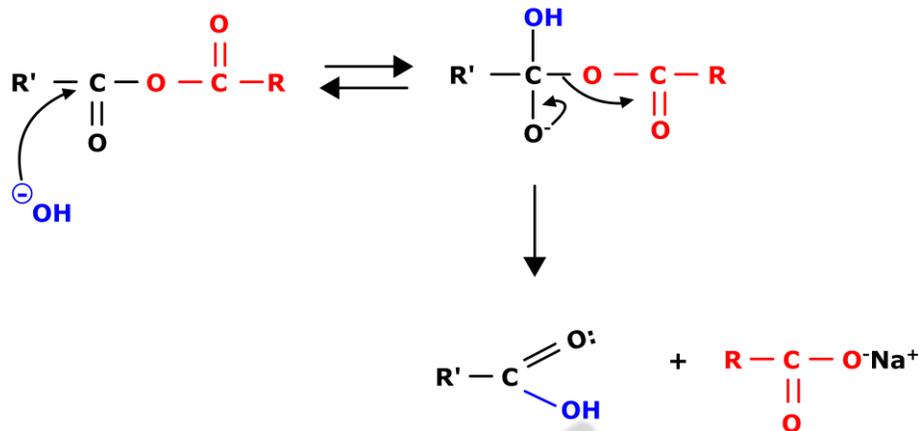


3.1 Acid anhydride and its enolate ion

In the aldol condensation, the base used to generate the enolate ion was NaOH or KOH. But these cannot be used when we have to generate enolate ion from acid anhydrides. This is can be understood as follows. The order of reactivity for enolization of acid derivatives is the same as the order of reactivity towards their nucleophilic attack as given below.

Enolate formation and electrophilic reactivity of acid derivatives			
Electrophilic reactivity	Derivative	Structure	Reactivity towards enolate formation
very high	acid chloride		very high
high	anhydride		high
low	ester		low
very low	amide		very low

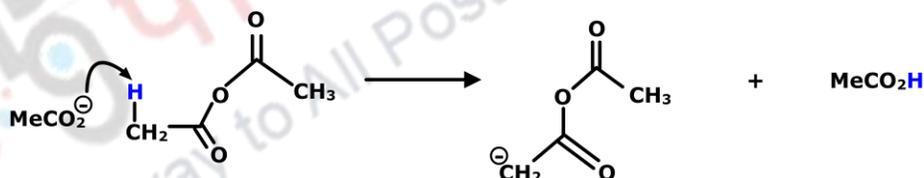
It can be seen that the acid anhydrides are quite reactive towards both. So one has to use a mild base which even if attacks as a nucleophile does not have any impact on the anhydride functional group. If the strong bases like NaOH are used, they hydrolyse the anhydride giving rise to salt of carboxylic acid and we won't be able to generate the enolate ion from it.



The sodium salt of carboxylic acid can act as a base or as a nucleophile.

- **As base:** When it attacks as a base on acid anhydride, it abstracts its acidic proton at alpha position. Note that the alpha hydrogen atoms are made acidic due to electron withdrawing nature of anhydride group.

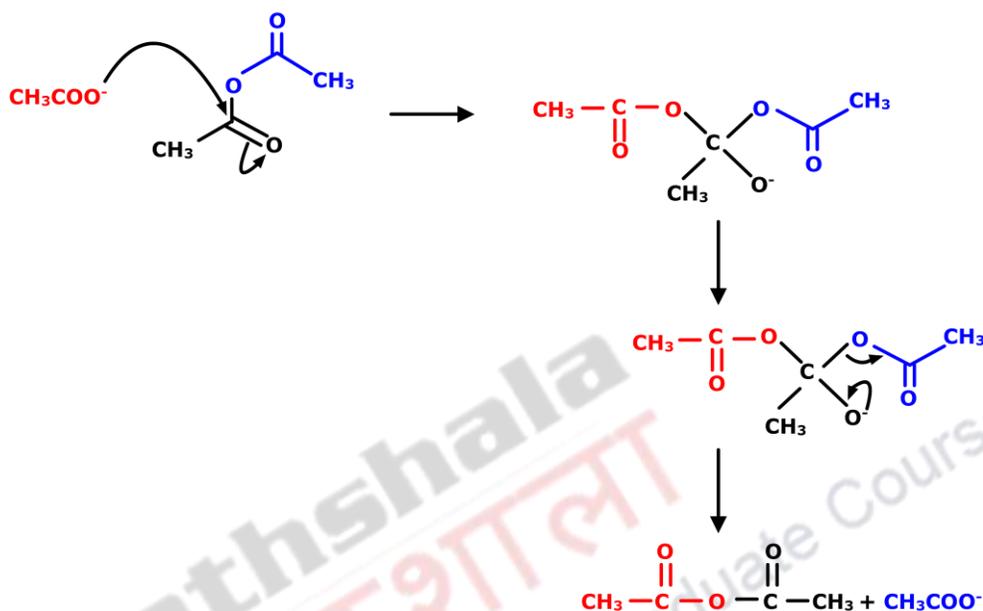
If CH_3COO^- acts as a base



- **As nucleophile:**

When it attacks as a nucleophile on electrophilic carbon of the acid anhydride, there is no harm on the anhydride functional group, simply regenerating the anhydride. It is because the same group is attacking and same is leaving (in case such reaction occurs).

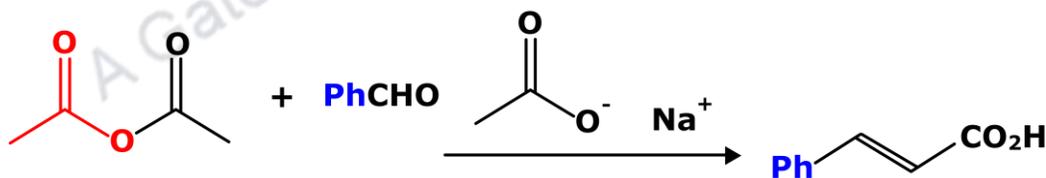
If CH_3COO^- acts as a nucleophile



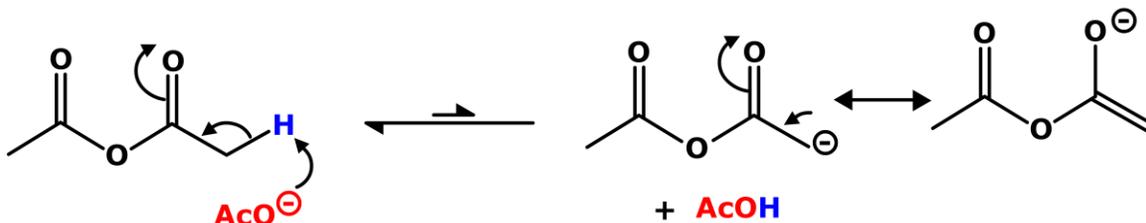
Using alkali salt of same acid as the anhydride is appropriate to generate the enolate ion with no harm on the anhydride.

3.2 Perkin Reaction and Mechanism

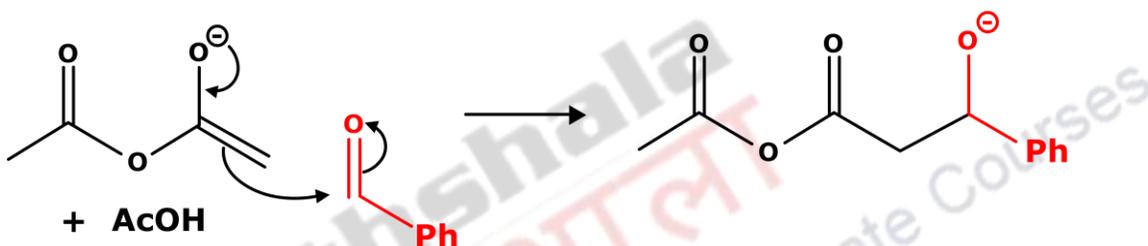
To understand the mechanism of Perkin reaction, let us consider the reaction of acetic anhydride with benzaldehyde in the presence of sodium acetate to produce cinnamic acid.



Step 1: The acetate ion acts as a base and abstracts the alpha hydrogen of the acetic anhydride molecule giving rise to its enolate ion which is resonance stabilised.

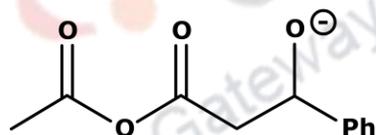


Step 2: The low equilibrium concentration of the enolate attacks as a nucleophile on the electrophilic carbonyl carbon of the benzaldehyde molecules. This results in the formation of a new carbon-carbon bond between the two molecules.



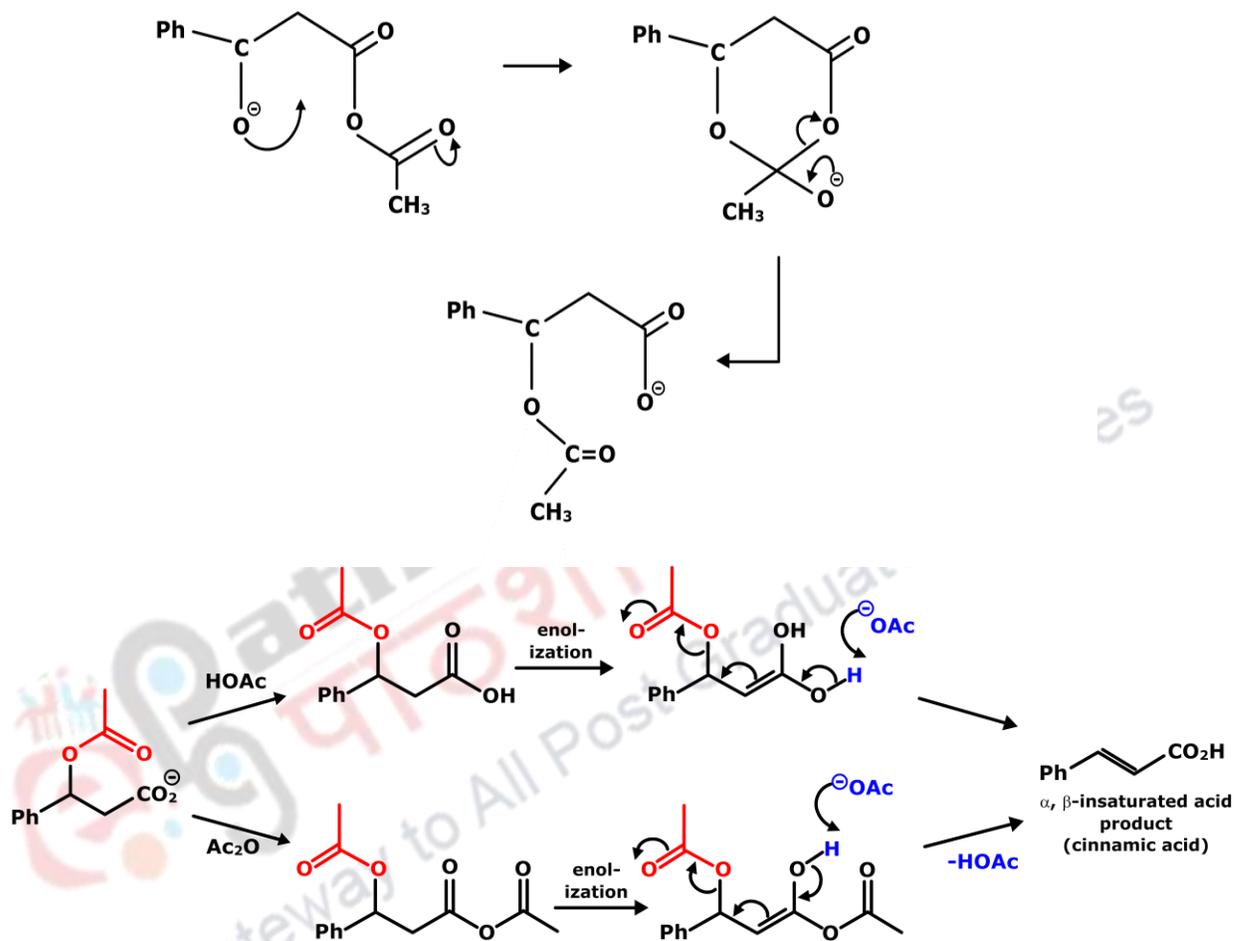
Notice that so far, the reaction is a normal aldol reaction, but something different happens as the reaction proceeds.

Step 3: Next step is an intramolecular acylation, whereby the alkoxide ion attacks to the other end acyl group and abstracts it, resulting in carboxylate ion at one end and acylated hydroxyl at the other end.



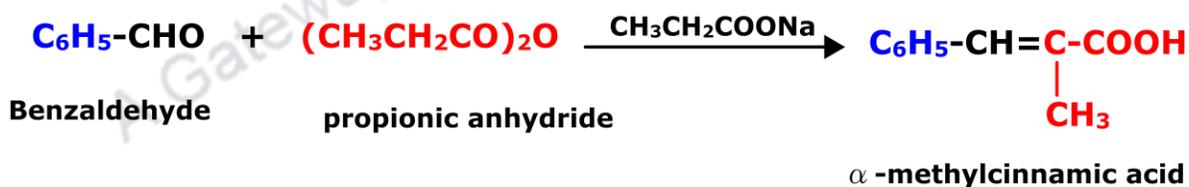
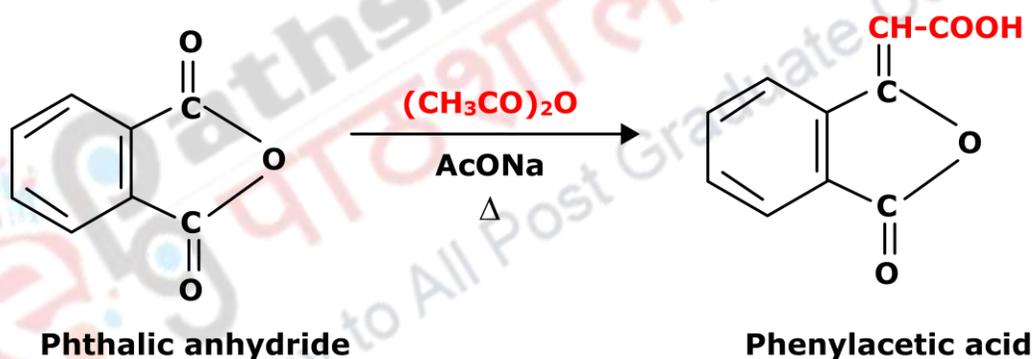
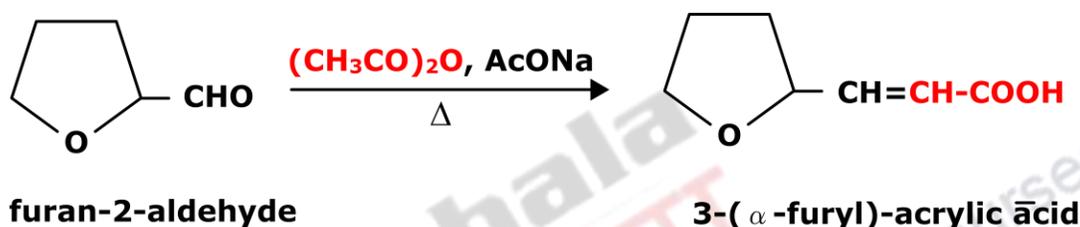
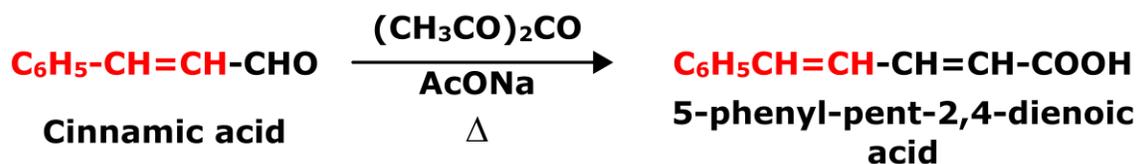
Step 4: In the next step, acetic acid is eliminated giving rise to cinnamic acid, an α,β -unsaturated acid. Acetate is a better leaving group than hydroxide, hence this step is much more favourable than the usual dehydration at the end of an aldol condensation. Elimination of acetic acid may occur either from the carboxylic acid itself or from the mixed anhydride formed from one more

molecule of the acetic anhydride.



From either of these two routes, the unsaturated acid is formed in a single step with the anhydride assisting the intermediate steps.

Examples:



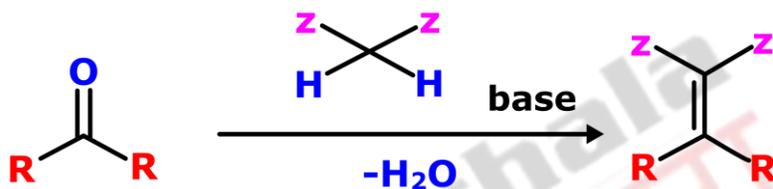
4. Knoevenagel Condensation

Emil Knoevenagel in the 1890's gave the classic organic synthesis named as Knoevenagel Condensation Reaction. It is a modified Aldol Condensation.

Knoevenagel condensation is a nucleophilic addition of an active hydrogen containing compound to a carbonyl group. This is followed by a dehydration reaction in which a molecule of water is eliminated. The product formed is α, β - conjugated enone.

The active hydrogen containing compounds are mostly the ones which contain two electron withdrawing groups joined to a methylene group. These electron-withdrawing groups make the hydrogen atoms of the methylene group acidic which can be easily removed by using appropriate base. Hence these hydrogen atoms are referred as active hydrogen atoms.

The general equation for Knoevenagel reaction is:

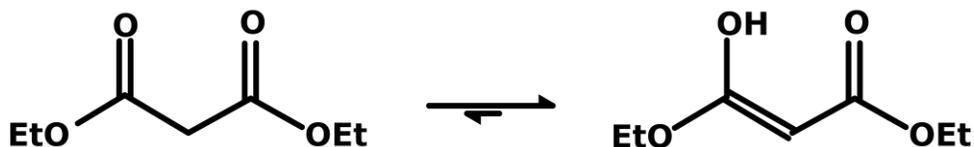


In the general reaction depicted above, the carbonyl group can be either an aldehyde or a ketone. The base used is usually an amine. Z is an electron-withdrawing group. Some examples of active hydrogen containing compounds used are diethyl malonate, Meldrum's acid, ethyl acetoacetate, which are strong enough to enable deprotonation to produce the enolate ion in the presence of a mild base. On the contrary, if strong base is used, self-condensation of the aldehyde or ketone takes place. Hence mild base is used for generation of the carbanion and not strong base. Let us try to know more about the active hydrogen containing compounds and their enolisation, especially the 1,3 – dicarbonyl compounds and ethylacetoacetate.

4.1 Active hydrogen containing compounds

You are already aware that 1,3 dicarbonyl compounds and ethyl acetoacetate are largely enolized under normal conditions due to tautomerisation. So why don't the enolised molecules immediately undergo aldol type reaction with themselves without adding any base? This happens because:

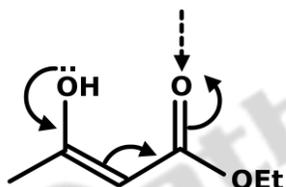
- The enols are very stable due to conjugation with the carbonyl of ester group



**diethyl malonate
(diethyl propanediote)**

- The carbonyl group in the unenolized fraction is of poorly electrophilic ester group and ketone groups. The carbonyl group of ester functionality of the enolised fraction is not electrophilic because of conjugation.

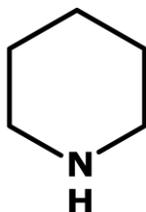
electrons are fed into this
carbonyl group making
it less electrophilic



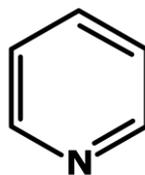
When a simple carbonyl compound is treated with acid or base as catalyst, there is a small proportion of reactive enol or enolate in the presence of large amounts of unenolized electrophile and hence an Aldol reaction (self-condensation) occurs. On the other hand, with 1,3-dicarbonyl compounds there is a small proportion of less reactive unenolized form in the presence of large amounts of stable (and hence unreactive) enolised form. Hence, no aldol type reaction occurs.

4.2 Knoevenagel Reaction and its Mechanism

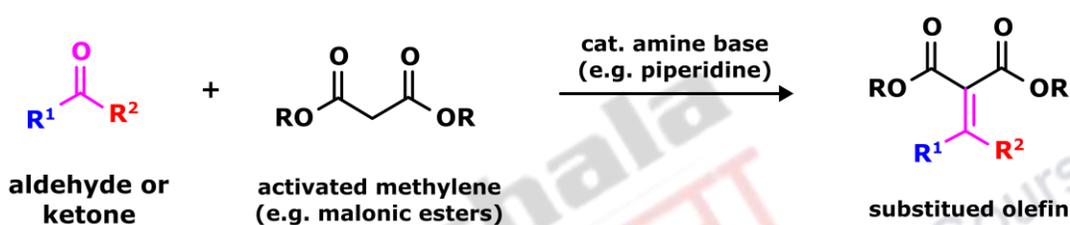
Knoevenagel reaction can be treated like a crossed aldol reaction. To carry out the Knoevenagel reaction, electrophilic carbonyl compound such as an aldehyde or ketone is treated with active hydrogen containing compound (or active methylene compound, e.g., malonic esters) in the presence of basic mixture of piperidine and pyridine.



piperidine
pK_{aH} 11



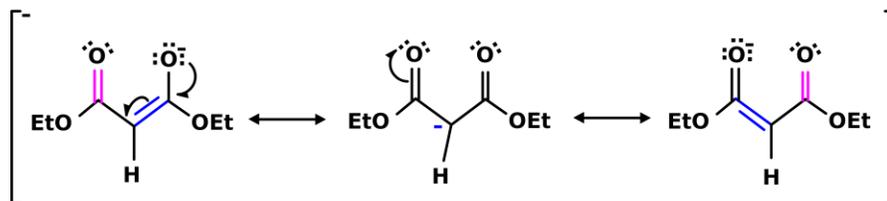
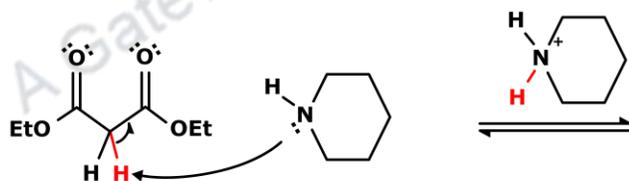
pyridine
pK_{aH} 5.5



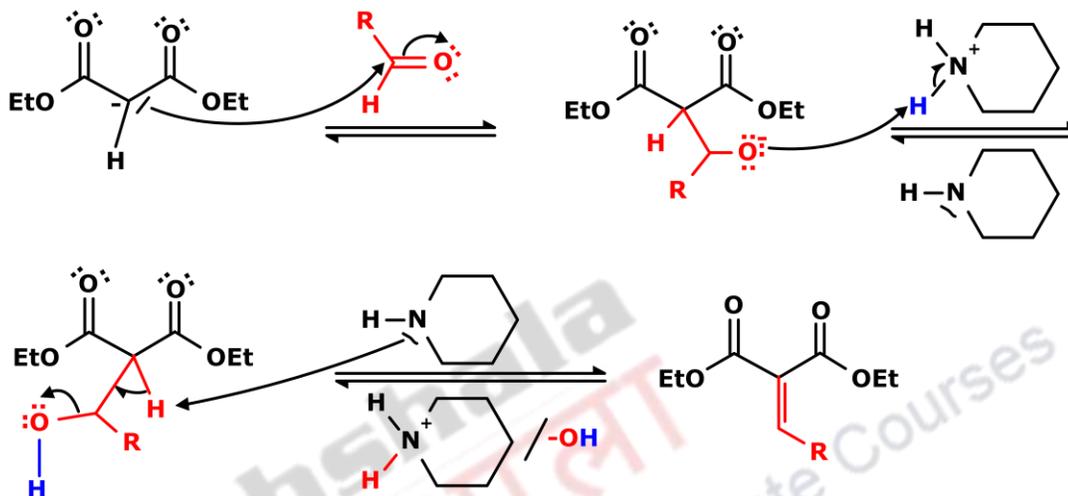
Mechanism

The mechanism is very similar to aldol condensation where a carbanion is generated which attacks as nucleophile on the electrophilic centre of the other molecule leading to condensation.

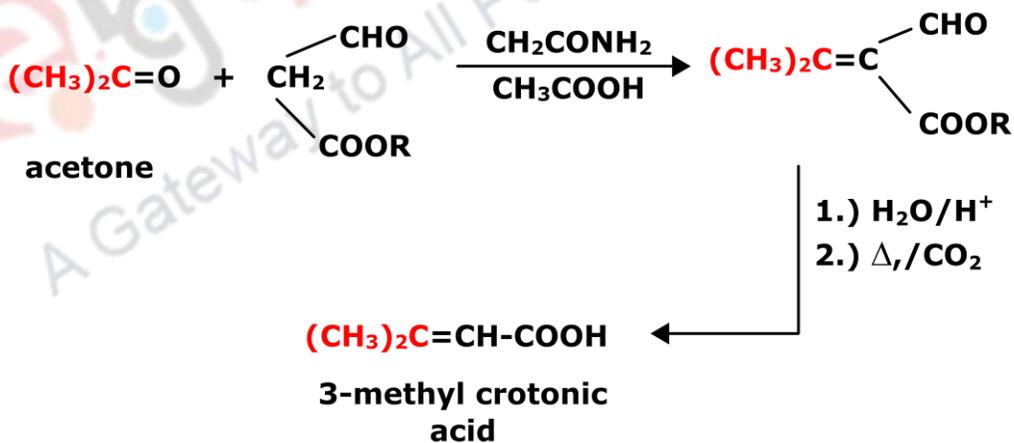
- **Step 1:** Deprotonation of the activated methylene by the base (piperidine) to give a carbanion which is resonance stabilized via enolate ion.



- This enolate ion attacks as nucleophile via the carbon of carbanion on the carbonyl carbon of the aldehyde (or ketone). Unlike aldol, the resulting intermediate rather than taking proton undergoes base-induced elimination.

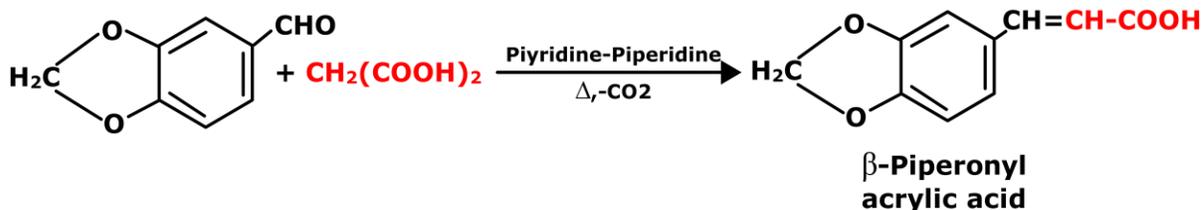
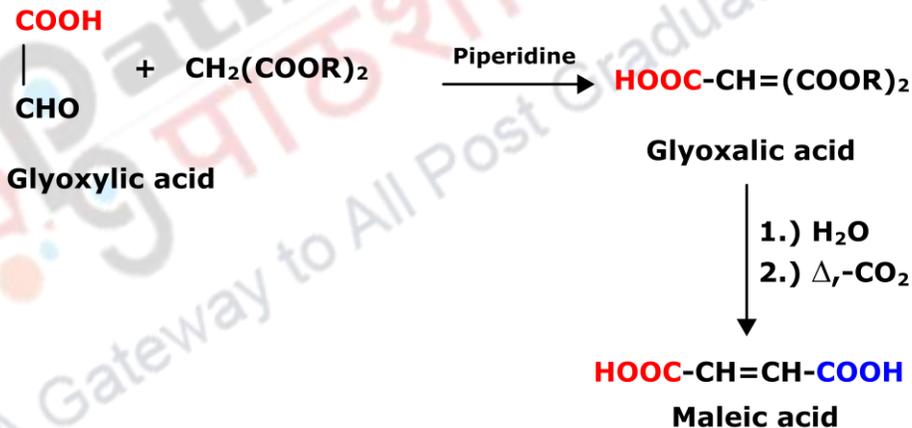
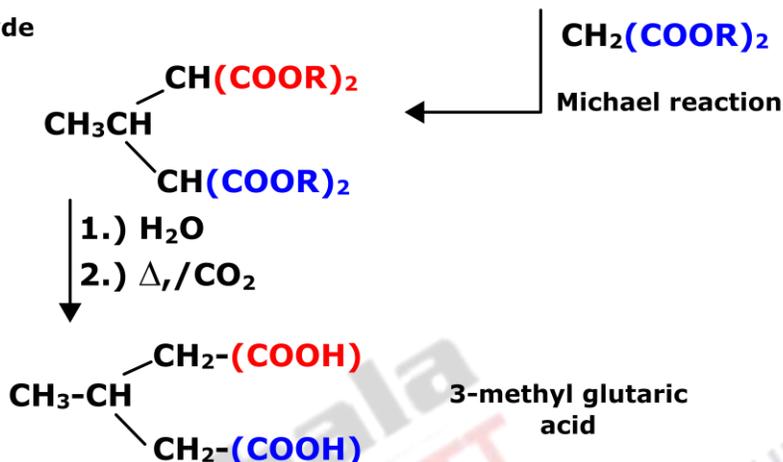


Few examples of Knoevenagel reaction are listed below:



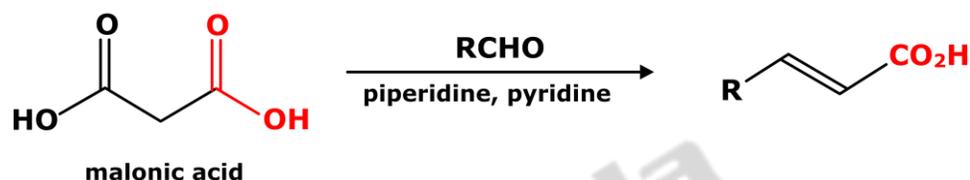


acetaldehyde



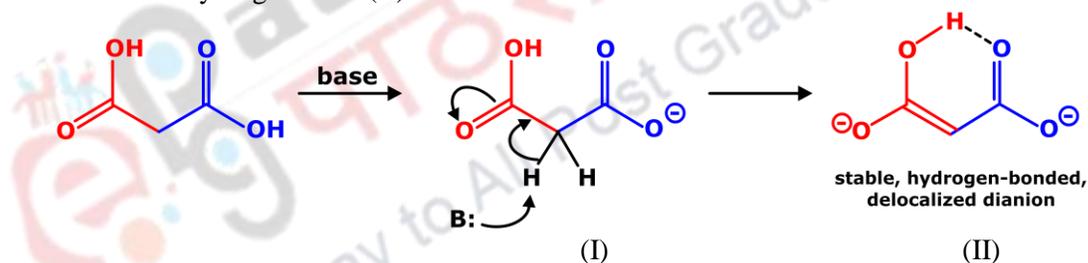
4.3 The Doebner Modification

When malonic acid is used in place of active methylene compounds, and treated with aldehyde in the presence of base, the product formed can lose a molecule of carbon dioxide in a subsequent step. The final product hence obtained is an α, β -unsaturated carboxylic acid. This is called as Doebner modification.

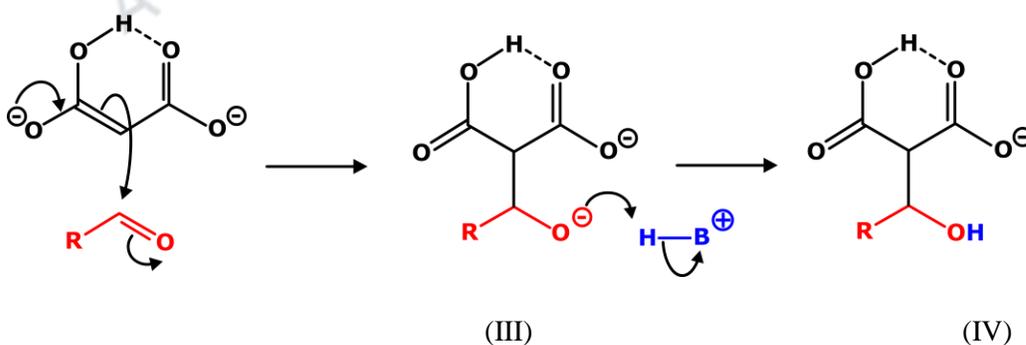


Mechanism:

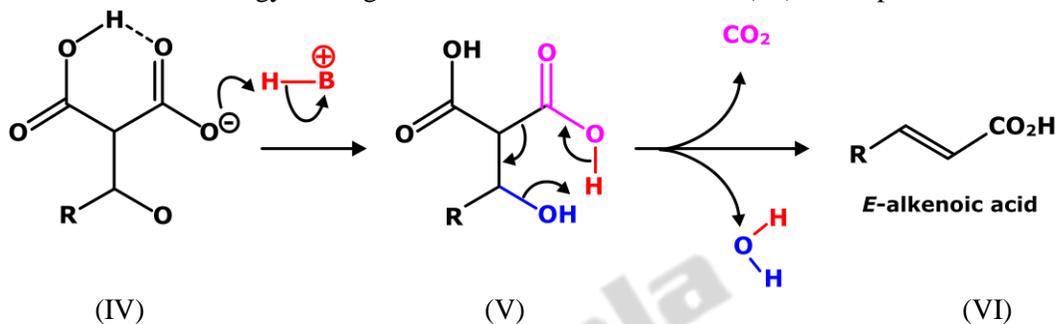
Base abstracts the active methylene hydrogen atom resulting in enolate ion(I). The enolate formed in this case is a dianion and is quite stable due to extensive delocalization and the intramolecular hydrogen bond (II).



The dianion attacks as nucleophile to the electrophilic carbonyl carbon of the aldehyde, and after proton abstraction from the medium (III), the aldol (IV) is formed (monocarboxylate in this basic solution).

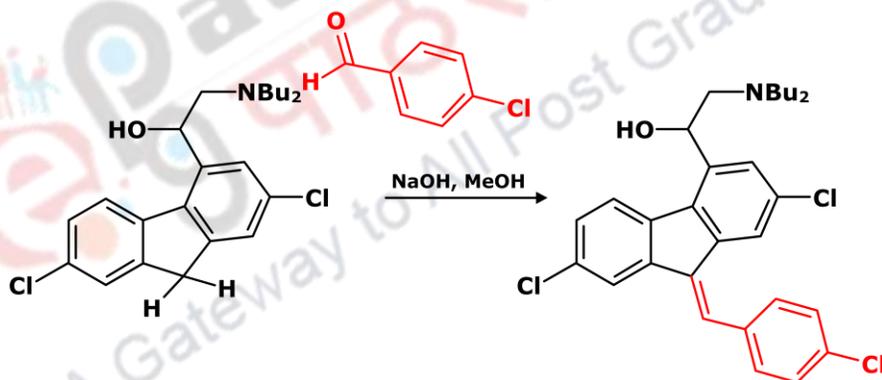


From the aldol (IV), the next step to take place is decarboxylation and dehydration. The decarboxylation and dehydration occurs via a cyclic transition state (V). Note that ideally, CO_2 from any of the two $-\text{COOH}$ groups could happen, which could give either *E* or *Z* double bond in the product. But since the product has *E* (or *trans*) geometry, that transition state is involved which has lower energy leading to more stable *E* alkenoic acid (VI) as the product.



4.4 Applications

In the commercial production, the Knoevenagel condensation is a key step in the production of antimalarial drug lumefantrine (a component of Coartem)



4.5 Recent advances in Knoevenagel condensation

Research is still continuing to explore newer synthetic methods using the Knoevenagel condensation with novel new catalysts and reaction activation. There have been use of microwave and ultrasound irradiated reactions in this context. Many have successfully conducted Knoevenagel reaction with Solvent free conditions. Many chemists have used Solid-phase synthesis and the Photochemical condensation with fruit extracts as catalysts to carry out Knoevenagel condensation.

5. Summary

- The Knoevenagel and Perkin condensation both are modification to aldol condensation.
- The enols of 1,3 dicarbonyl compounds are stable and less electrophilic, therefore they do not undergo self-condensation.
- If an aldehyde or ketone reacts with an activated methylene a substituted olefin is formed in the presence of an amine base which act as a catalyst. This is known as Knoevenagel condensation.
- Reaction undergoing in the presence of carboxylic acid groups, involving in pyridine-induced decarboxylation is known as the Doebener Modification.
- In the Knoevenagel condensation of carbonyl substrates zinc chloride is used with acidic methylene reagents, it does not required any solvent, to produce products of good purity in high yield.
- The Perkin reaction results in the formation of an α,β -unsaturated acids due to reaction of aldehydes with acid anhydrides in presence of base.