Subject	Chemistry
Paper No and Title	9: Organic Chemistry-III (Reaction Mechanism-2)
Module No and Title	20: Claisen condensation and Mannich reaction
Module Tag	CHE_P9_M20

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 *Specialised in : e-Learning and Educational Technologies*
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. Claisen Condensation

    3.1 Claisen ester condensation

    3.2 The Mixed Claisen Condensation

    3.3 The Dieckmann reaction

    3.4 Crossed Claisen Condensation

4. The Mannich Reaction

    4.2 Mechanism of Mannich Reaction

    4.3 Asymmetric Mannich reactions

    4.4 Illustrations and Applications

5. Summary

1. Learning Outcomes

After studying this module, you shall be able to

- Know about the basics of Claisen condensation and Mannich reaction.
- Identify the major product formed in crossed Claisen condensation and Dieckmann reaction.
- Evaluate and apply mechanistic details of Claisen, Dieckmann condensations and Mannich reaction.
- Know the applications of Claisen, Dieckamann and Mannich reaction.

2. Introduction

In the previous modules we have studied how the aldol condensation provides an excellent way for making new C-C bond and joins two molecules or moieties which are aldehydes and/or ketones having α-hydrogen in them, by using base like NaOH. Here, if you recall, the base OH^- abstracted the α-hydrogen and gave rise to α-carbanion which attacks as a nucleophile to other aldehyde or ketone. The question now comes to our mind is that In a similar manner if we wish to join two ester molecules how could it be done ? If we take ester and add NaOH as base to generate α-carbanion, its hydrolysis will occur rather than generating α-carbanion. The answer to this is that if sodium alkoxide is used, it will not affect the ester functional group and yet generate the required α-carbanion. This is what is done in claisen condensation whereby esters are condensed to give rise to β-keto-esters as condensation product.

We can very well say that claisen condensation is nothing but aldol applied to esters . We shall study the claisen condensation in detail in this module. When claisen condensation is done with diesters, it leads to cyclic β-keto-esters and this is known as Dieckmann condensation.

Another challenge comes when we have to join formaldehyde with any other aldehyde or ketone through mixed aldol condensation.

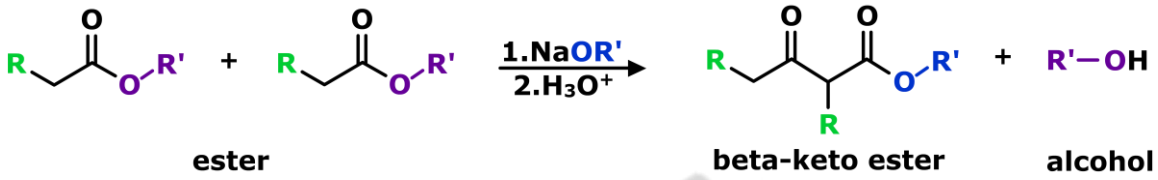
At first, formaldehyde (methanal, $CH_2{=}O$) seems to be the ideal electrophilic partner in a mixed aldol reaction as it cannot enolize. Aldehydes are more electrophilic than ketones. But, the problem is that it is too reactive. It tends to react more than once and to give extra unwanted reactions like from Cannnizzaro reaction, etc.

One way of carrying out the addition of formaldehyde to an aldehyde or ketone is the Mannich reaction. The reaction involves an enolizable aldehyde or ketone, a secondary amine, formaldehyde as its aqueous solution, and catalytic HCl. The product is a β-amino-ketone known as a Mannich base. We shall study about Mannich reaction also in detail in this module.

3. Claisen Condensation

The General Reaction:

Named after Rainer Ludwig Claisen, the Claisen condensation is a carbon–carbon bond forming reaction that occurs between two esters in the presence of a sodium alkoxide as base, resulting in a β-keto ester.



ester

This reaction can be considered as aldol reaction applied to esters. But rather than using hydroxide ion as base to generate the α-carbanion, alkoxide ion is used as the base. You are already aware that esters would hydrolyse if hydroxide ion is used. Hence the appropriate base to generate the α-carbanion is alkoxide ion.

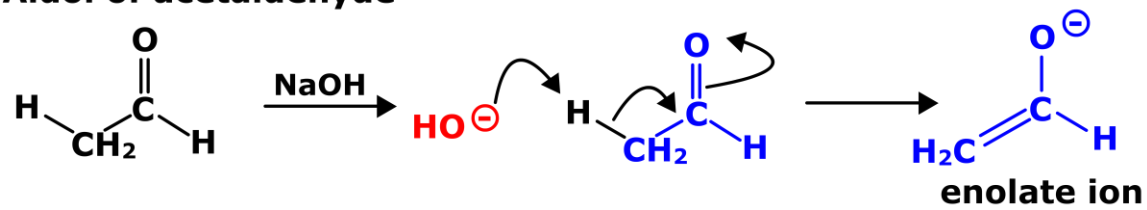
For example,

When ethyl acetate reacts sodium ethoxide, ethyl acetoacetate is obtained as depicted below:

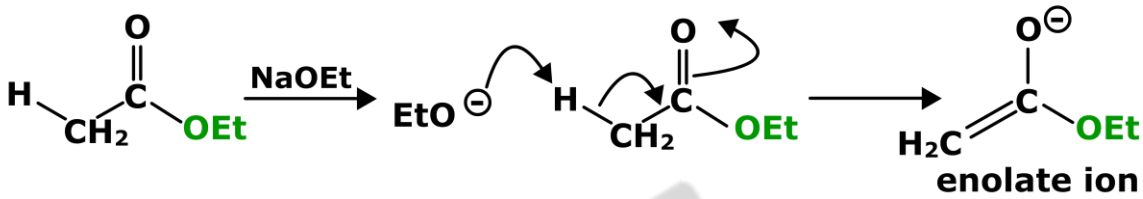
Let us try to understand the mechanism of this reaction by comparing it with aldol reaction of acetaldehyde.

The first step in both is the formation of enolate ion via the abstarction of α-carbanion. From acetaldehyde, the abstraction is done by OH^- as base, while in case of ethyl acetate, ethoxide ion abstracts the α-hydrogen to generate the enolate ion.

Aldol of acetaldehyde



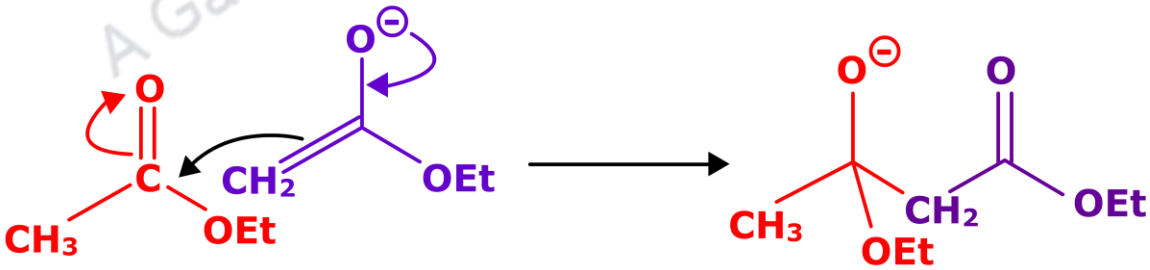
Aldol of ethyl acetate



The next step in both cases is nucleophilic attack by the enolate ion on unenolized carbonyl compound. In aldol reaction of acetaldehyde, the enolate ion attacks as nucleophile to another molecule of the carbonyl compound at the carbonyl carbon. In the claisen reaction, there is a similar attack of enolate ion of ethyl acetate to the carbonyl carbon of ester group of unionised ethyl acetate.

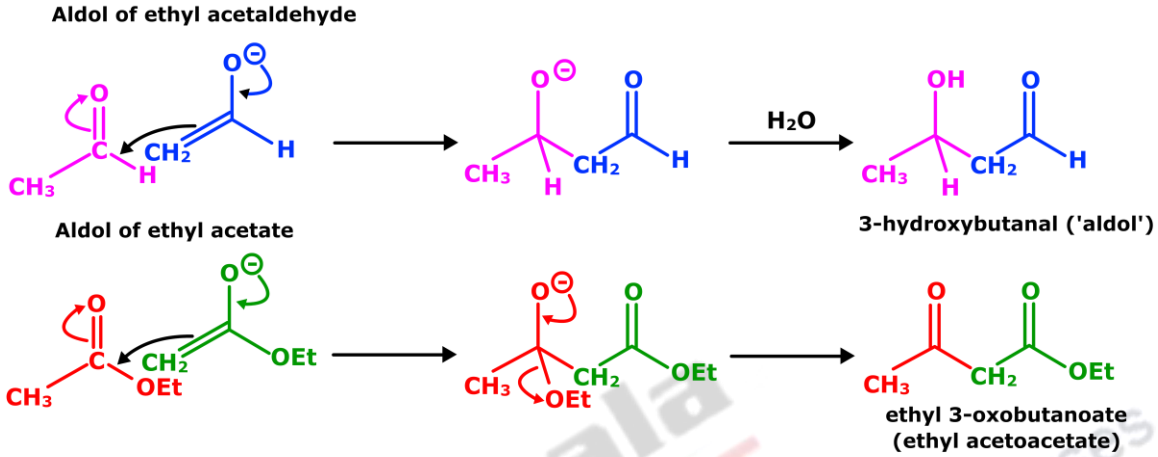
Aldol of ethyl acetaldehyde

Aldol of ethyl acetate



After nucleophilic attack, the Claisen condensation and the aldol addition differ in their mechanism. In the aldol addition, the negatively charged oxygen obtains a proton from the solvent and leads to product**.** On the other hand in the Claisen condensation, the negatively charged oxygen reforms the carbon–oxygen double bond and expels the alkoxy group which is a

good leaving group. Thus, the Claisen condensation is a nucleophilic substitution reaction, whereas the aldol addition is an addition reaction.

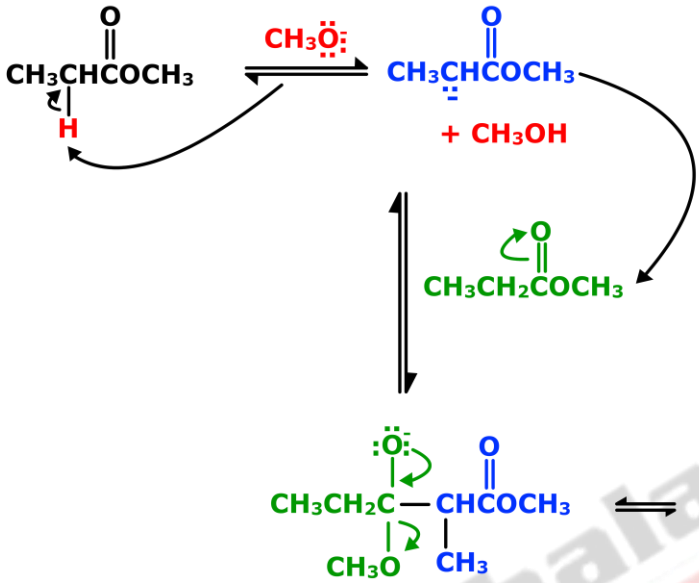


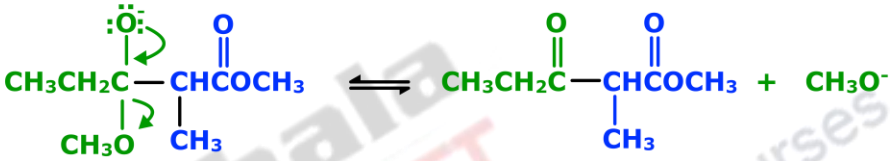
Even though the last step is different, the two products are quite similar. Both are dimers of the original two-carbon chain and both have carbonyl groups at the end of the chain and oxygen substituents at position three. The two reactions obviously belong to the same family as is evident by their similar mechanisms.

Note that in the claisen reaction, the alkoxide ion used as base must be same as that of the alohol part of the ester. Else, it may lead to mixture of products through trans-esterification reaction as well.

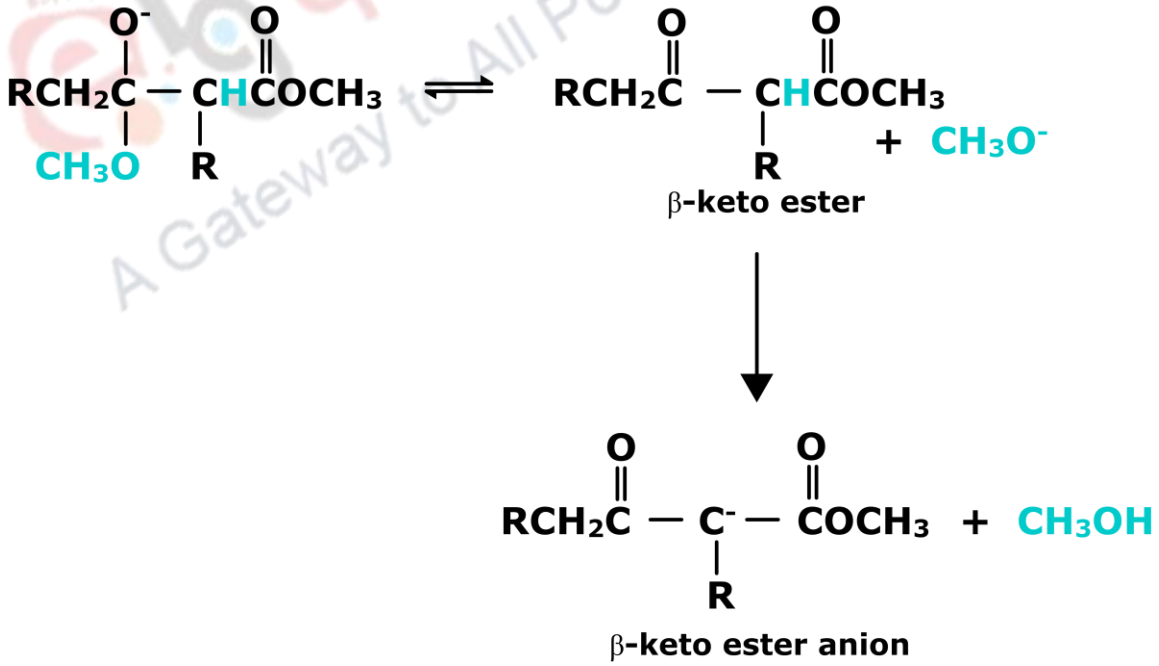
Another example and its mechanism

Claisen ester condensation of methylpropanoate :



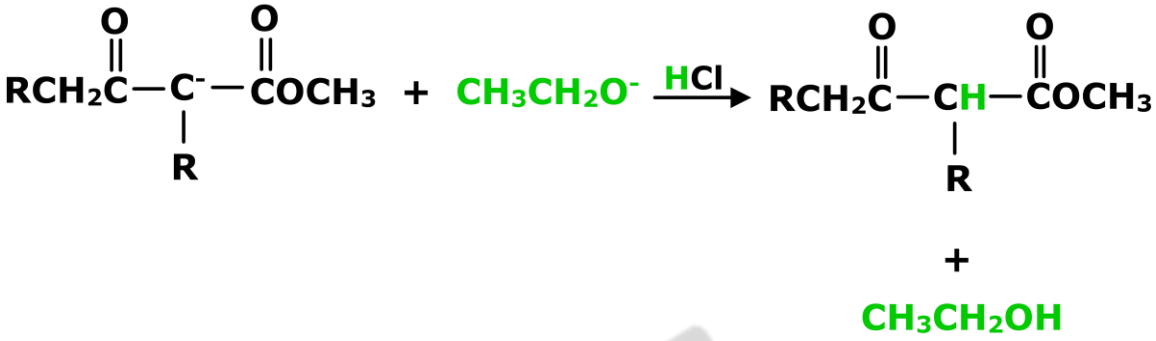


Expulsion of the alkoxide ion is reversible because the alkoxide ion can readily reform the tetrahedral intermediate by reacting with the β-keto ester. The condensation reaction can be driven to completion, however, if a proton is removed from the β-keto ester. Removing a proton prevents the reverse reaction from occurring, because the negatively charged alkoxide ion will not react with the negatively charged β-keto ester anion. It is easy to remove a proton from the β-keto ester because its central α-carbon is flanked by two carbonyl groups, making its α-hydrogen much more acidic than the α-hydrogens of the ester starting material.

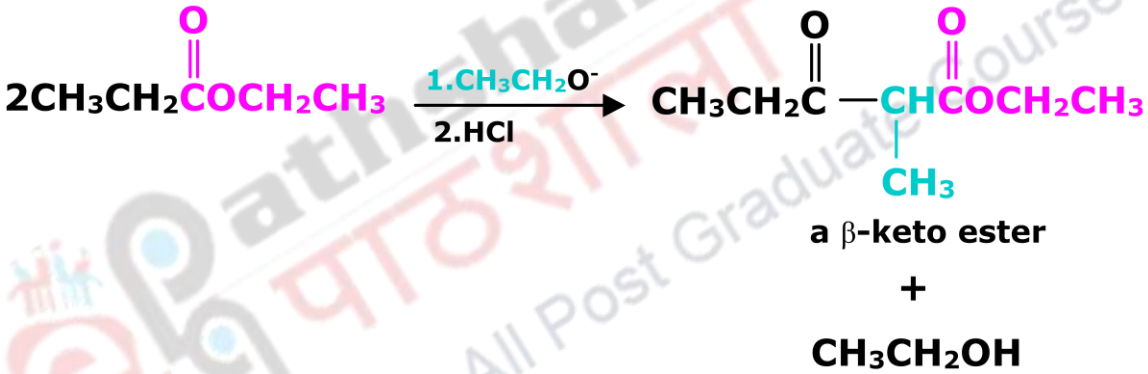


CHEMISTRY	Paper 9: Organic Chemistry-III (Reaction Mechanism-2)
	Module No. 20: Claisen condensation and Mannich reaction

Consequently, a successful Claisen condensation requires an ester with two α-hydrogens and an equivalent amount of base rather than a catalytic amount of base. When the reaction has been completed, addition of acid to the reaction mixture reprotonates the β-keto ester anion. Any remaining alkoxide ion that could cause the reaction to reverse would also be protonated.



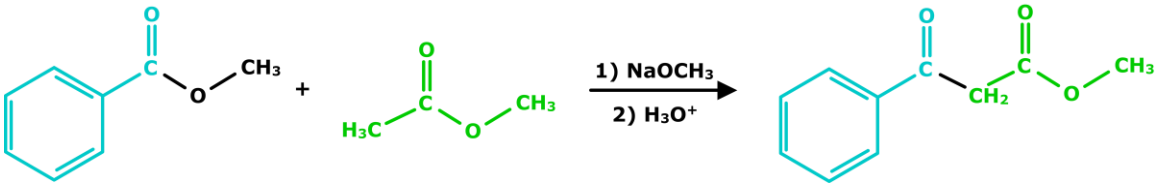
Another example:



a β-keto ester

3.4 Crossed Claisen Condensation

Claisen condensations between different ester reactants are called crossed Claisen reactions. Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures. Because of this most crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogen.



3.5 Applications of Claisen Condensation

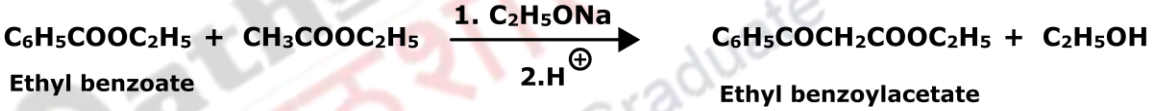
Simple and crossed Claisen condensations have been extensively used in the synthesis of a wide variety of organic compunds, e.g., vitamins, sex hormones, alkaloids, terpenes, flavones, etc. Crossed Claisen condensations between two different esters (both having α-hydrogens) have little synthetic value, for a mixture of four products are obtained. However, if one of the esters has no α-hydrogen, it acts as a carbanion acceptor and the self condensation of the other ester is minimized. Commonly used esters with no α-hydrogen are: ethyl benzoate, ethyl formate, ethyl oxalate, ethyl carbonate, etc. These estres are good carbanion acceptors.

Ketones are generally more acidic than esters and the arte of their base catayzed condensation (aldol) is very slow. Hence, ketones serve as nucleophiles in mixed Claisen condensation to give a large variety of products.

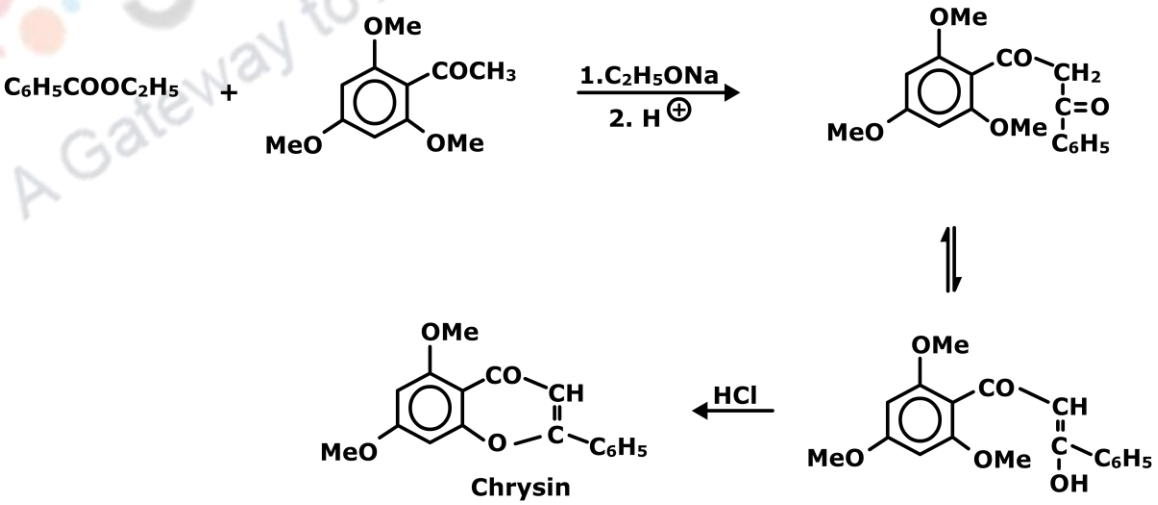
Some of the examples of crossed Claisen condensation and thir applications are discussed here:

1. **Condensation with ethyl benzoate**

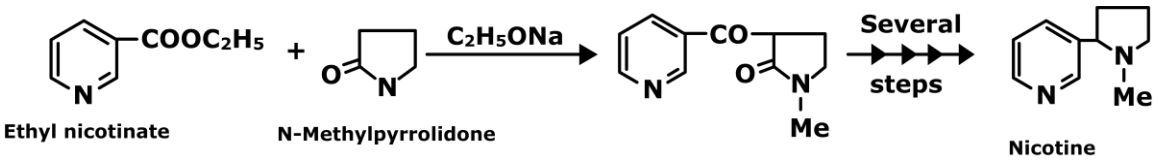
(a.)



(b.) Synthesis of flavones (Chrysin):

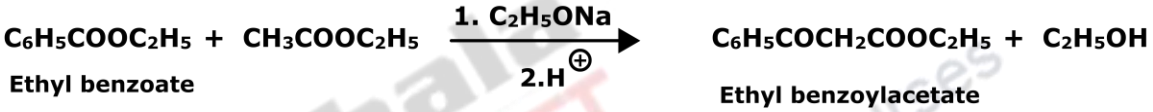


(c.) Synthesis of nicotine from ethyl nicotinate:

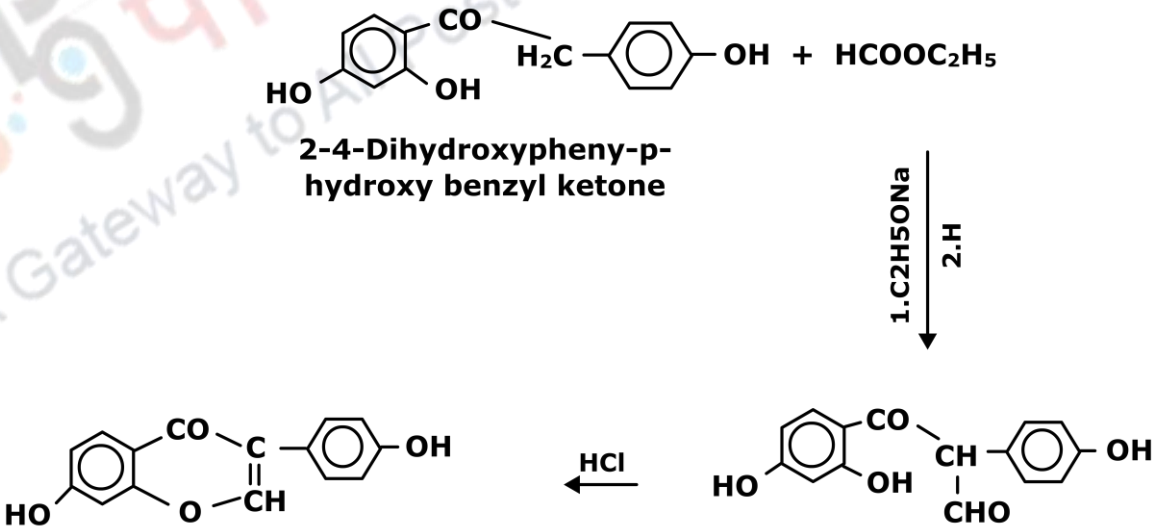


2. Condensation with ethyl formate

(a.) Formylation: The reaction is utilized for formylation during the synthesis of various natural products, e.g., equilenine, thiamine (Vitamin B1), isoflavones, etc.



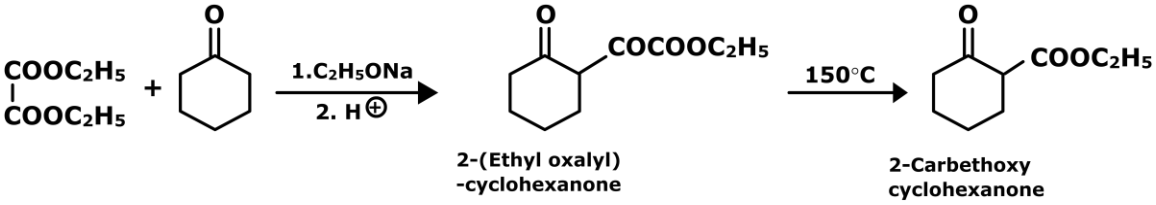
(b.) Synthesis of daidzein (isoflavone):



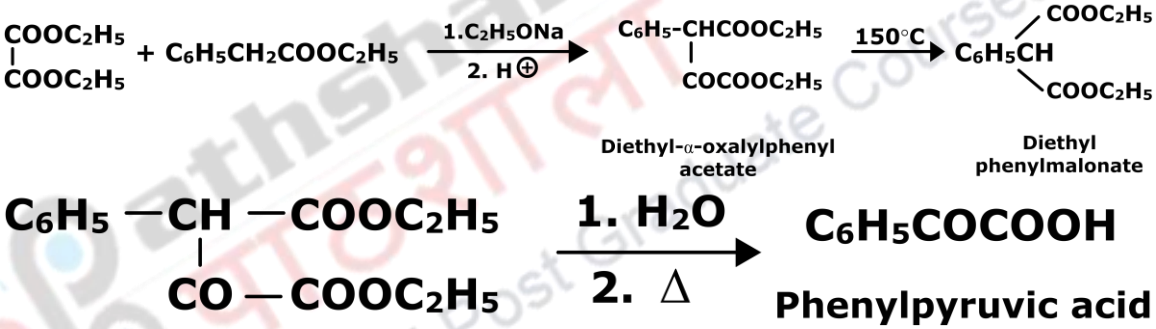
(c.) **Daidzein(isoflavone)**

3. **Condensation with diethyl oxalate: (i.)** Ketones and esters condense with diethyl oxalate to give oxalyl derivatives which have synthetic utility. Since they loose carbon monoxide on heating to give malonic ester derivatives, which maybe used for prepararion of aryl-substituted dibasic acid derivatives and α-keto acids.

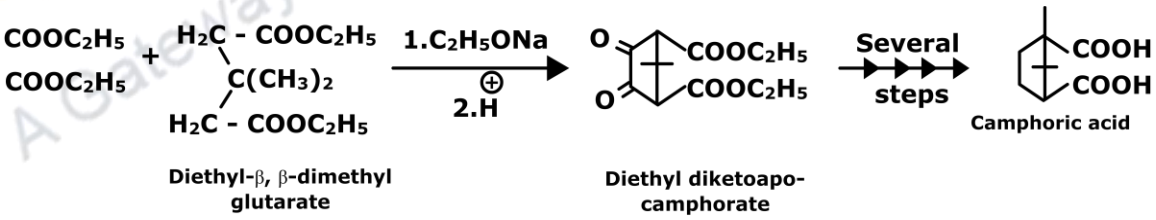
(a.)



(b.) Phenyl substituted malonic ester has important synthetic applications, e.g., phenobarbitone may be prepared. Diethyl-α-oxalyl phenyl acetate on hydrolysis and heating gives α-keto acids.



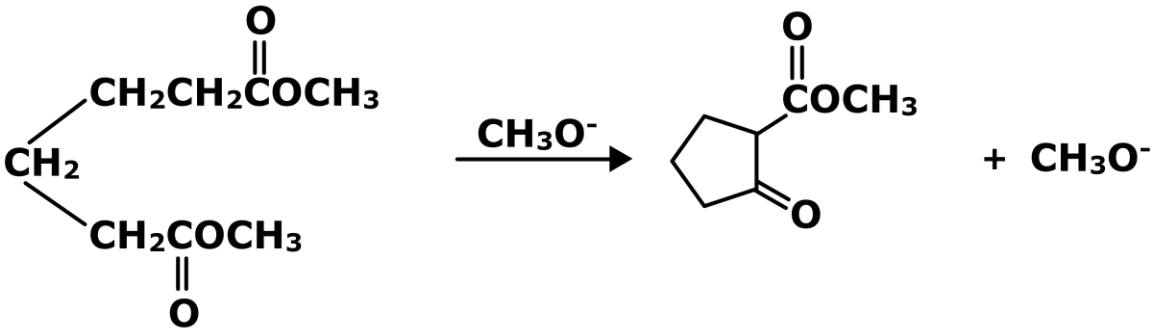
(ii.) Camphoric acid may be synthsised:



The Dieckmann reaction

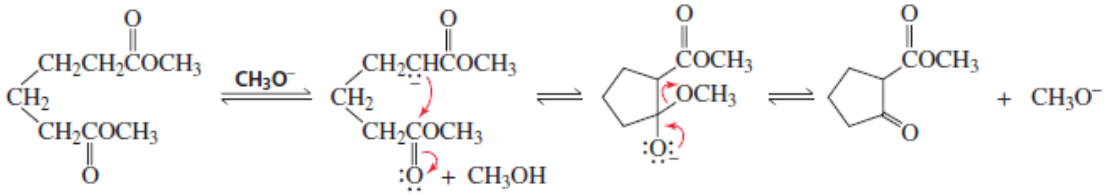
The addition of alkoxide base to a 1,6-diester causes the diester to undergo an intramolecular Claisen condensation, thereby forming a five-membered ring ester. An intramolecular Claisen condensation is called a Dieckmann condensation.

Example: Cyclization of the dimethyl ester of adipic acid (dimethyl hexanedioate).

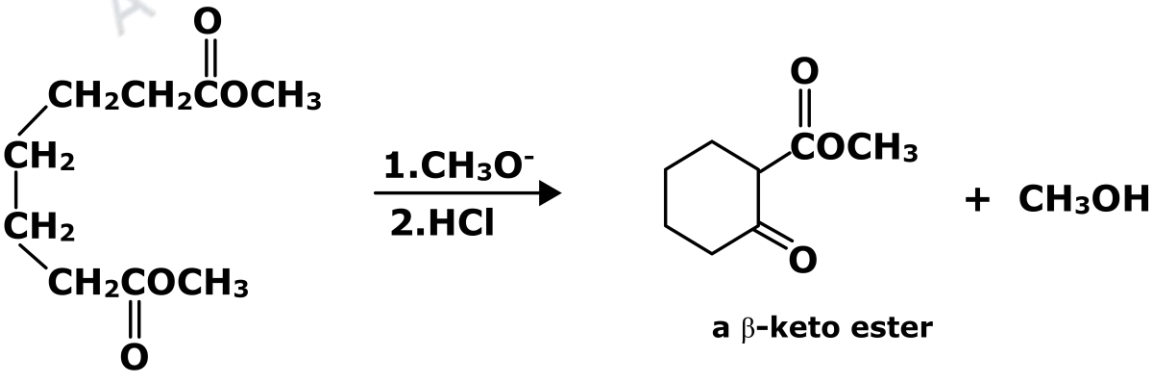


Mechanism

The mechanism of the Dieckmann condensation is the same as the mechanism of the Claisen condensation. The only difference between the two reactions is that the attacking enolate and the carbonyl group undergoing nucleophilic attack are in different molecules in the Claisen condensation, but are in the same molecule in the Dieckmann condensation. The Dieckmann condensation, like the Claisen condensation, is driven to completion by carrying out the reaction with enough base to remove a proton from the ester product. When the reaction is over, acid is added to reprotonate the condensation product.



Another example: A six-membered ring β-keto ester is formed from a Dieckmann condensation of a 1,7-diester.



a 1,7-dieter

a β-keto ester

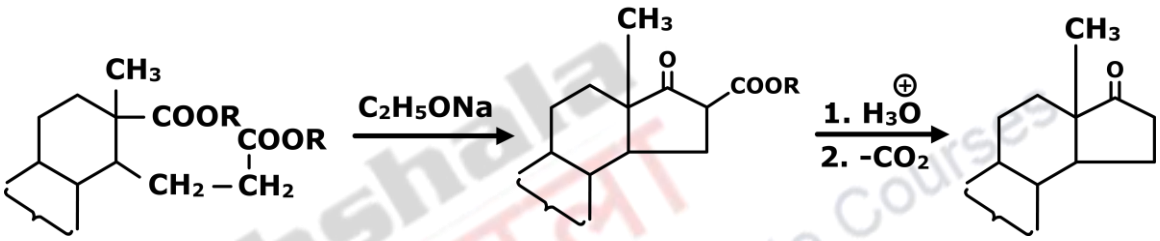
3.3.1 Applications of Dieckmann Reaction

The reaction affords a useful route for the synthesis of cyclopentanone and cyclohexanone derivatives. Some examples are given for illustartion here:

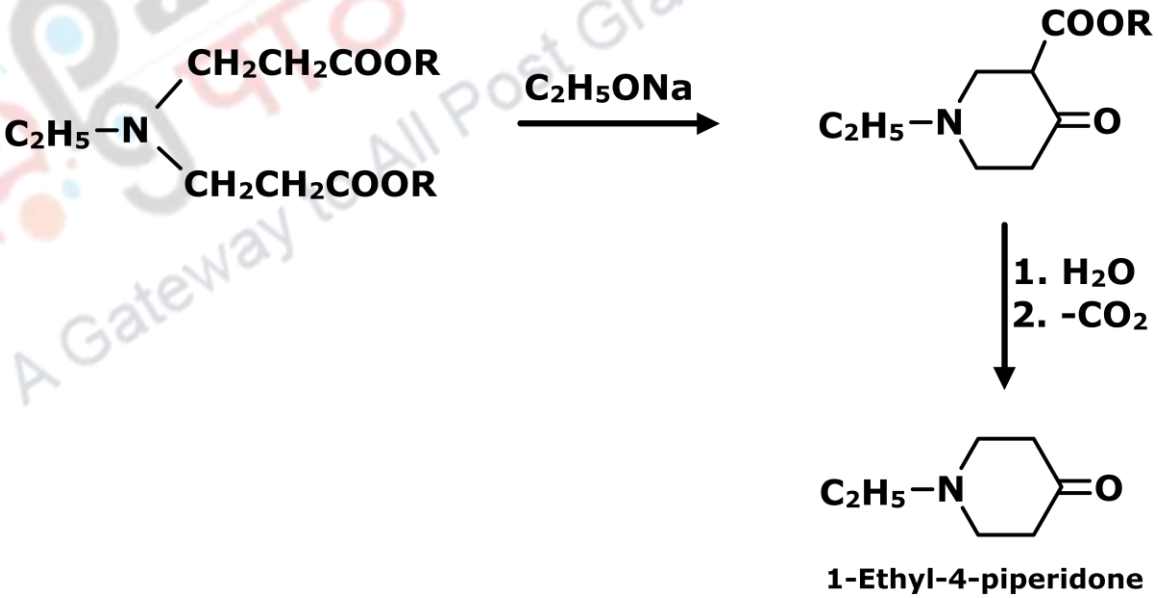
1. The reaction has been used to build up five or six membered rings in the synthesis of various natural products. The general process is given below:

Synthesis of steroids

1. **Preparation of heterocyclic ketoesters**

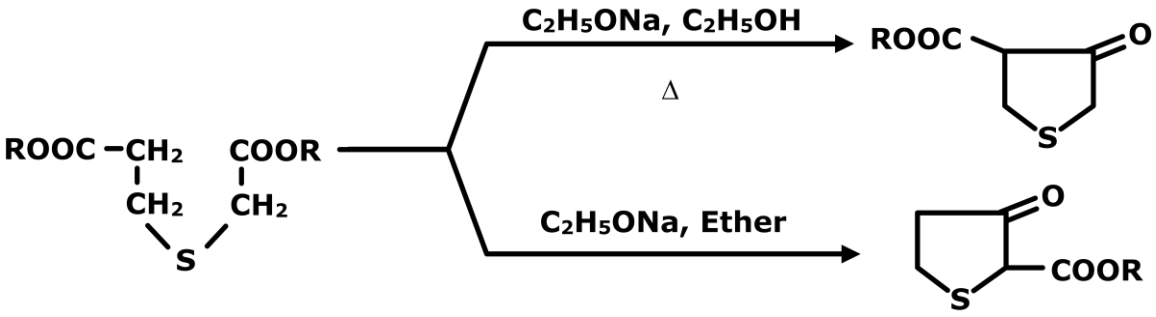


a. **Piperidone derivative:**

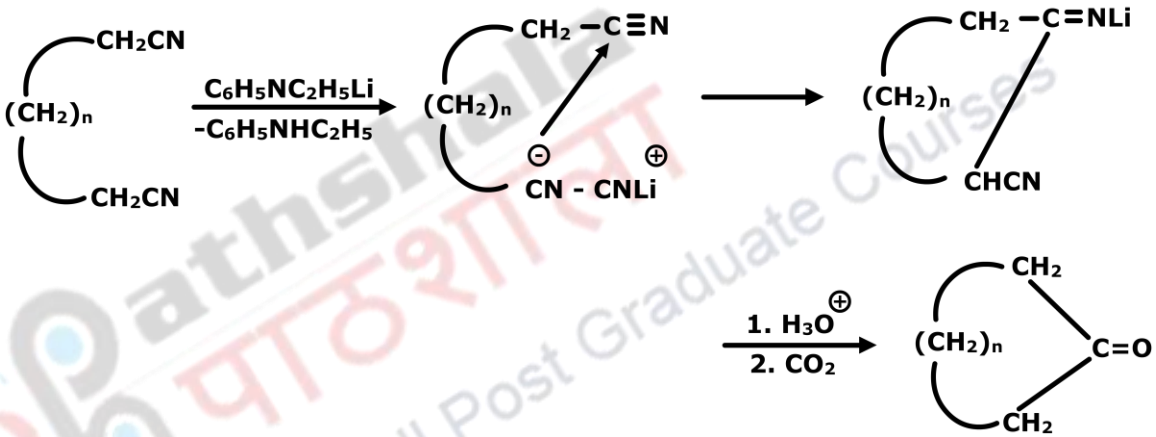


1-Ethyl-4-piperidone

b. **Thiophene derivatives**- Depending on the conditions of the reaction, two isomers are obtained.



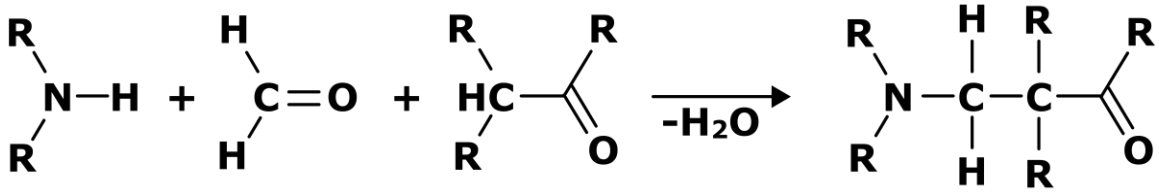
2. **Extension of the reaction:** Zeiglar applied Dieckmann reaction on dinitrides to obtain large size rings using lithium ethyl anilideand high dilution technique.



4. Mannich Reaction

The General Reaction:

Named after chemist Carl Mannich, it is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound also known as a Mannich base.

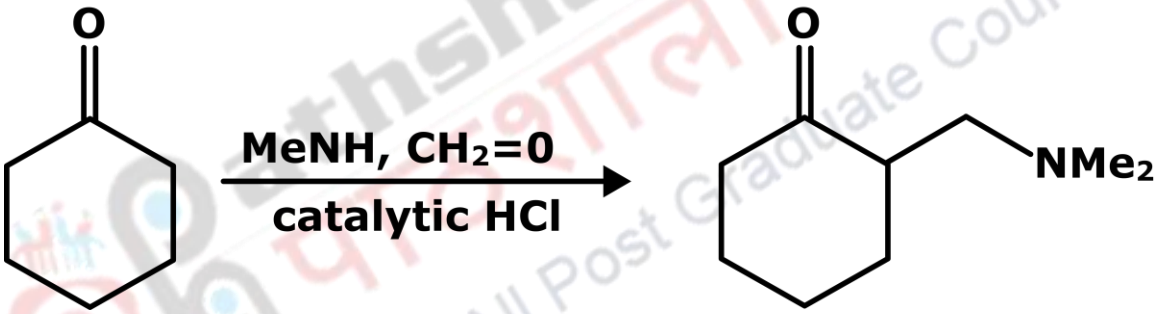


It is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton. The Mannich reaction is a condensation reaction.

In this reaction, primary or secondary amines or ammonia, are used for the activation of formaldehyde. Tertiary amines lack an N–H proton to form the intermediate enamine. α-CH acidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocycles such as furan, pyrrole, and thiophene. Indole is a particularly active substrate; the reaction provides gramine derivatives**.**

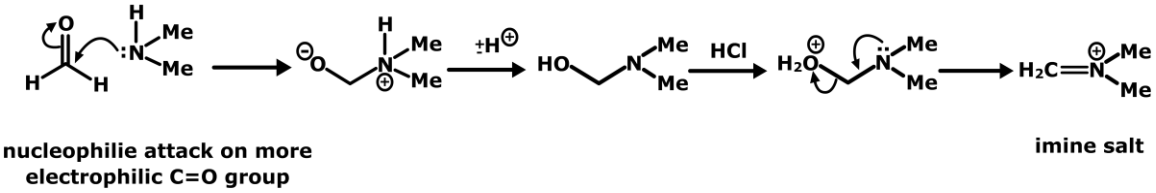
Example:

The reaction of cyclohexanone, dimethylamine and formaldehyde as its aqueous solution, in the presence of catalytic HCl gives rise to an amino-ketone.

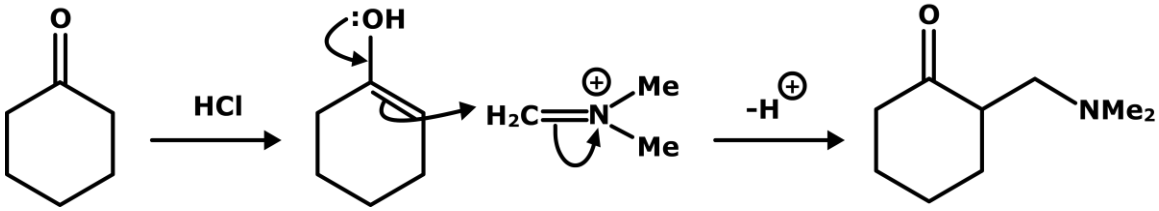


Mechanism

- The mechanism involves the preliminary formation of an imine salt from the amine and formaldehyde.
- The amine is nucleophilic and attacks the more electrophilic of the two carbonyl compounds available. That is, of course, formaldehyde. No acid is needed for this addition step, but acid-catalysed dehydration of the addition product gives the imine salt.
- In the normal Mannich reaction, this is just an intermediate but it is quite stable and the corresponding iodide is sold as 'Eschenmoser's salt' for use in Mannich reactions.



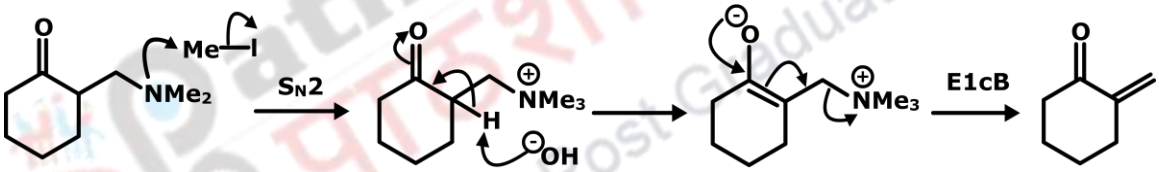
- The electrophilic salt can now add to the enol (we are in acid solution) of the ketone to give the product of the reaction, an amine sometimes called a Mannich base.



By using this reaction, we can add one molecule of formaldehyde to carbonyl compounds. Note that the product is not actually an aldol product. However it remains a very important reaction.

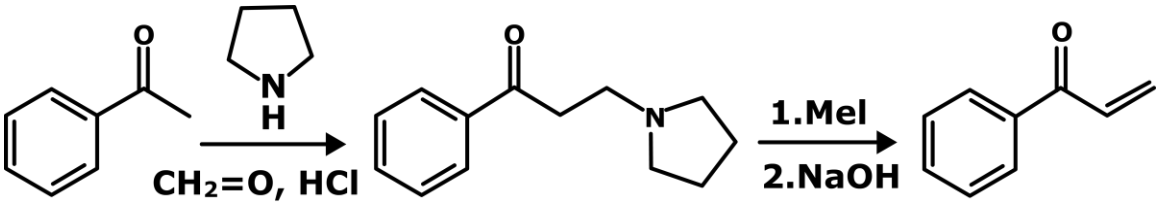
- It is a simple way to make amino-ketones and many drug molecules belong to this class.
- The Mannich products can be converted to enones.

The most reliable method for making the enone is to alkylate the Mannich base with MeI and then treat the ammonium salt with base. Enolate ion formation leads to an E1cB reaction rather like the dehydration of aldols, but with a better leaving group.



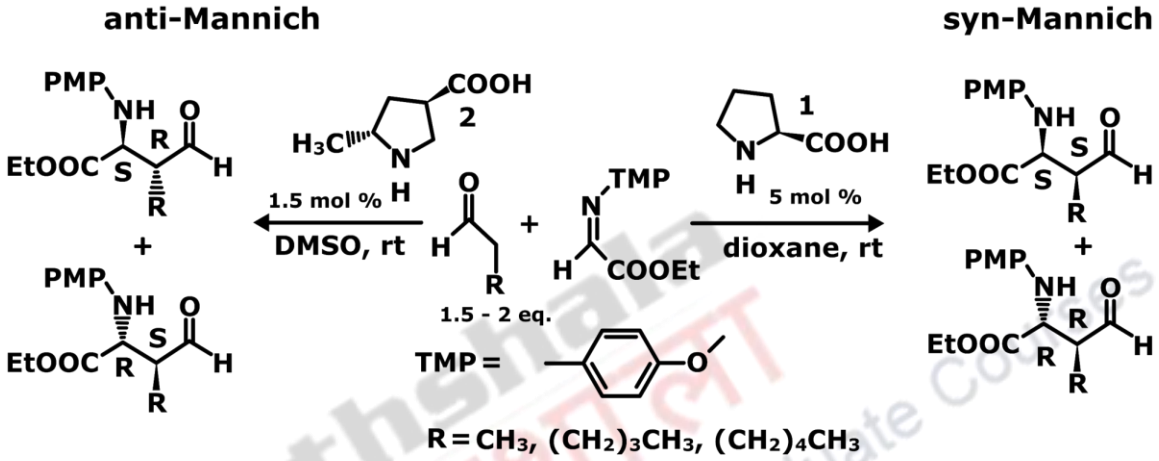
Enones like this, with two hydrogen atoms at the end of the double bond, are called exo-methylene compounds; they are very reactive, and cannot easily be made or stored. They certainly cannot be made by aldol reactions with formaldehyde alone as we have seen. The solution is to make the Mannich base, store that, and then to alkylate and eliminate only when the enone is needed. This is in the Michael reaction.

If the enone is to be obtained as product, the secondary amine does not end up in the molecule so the more convenient (less volatile and less smelly) cyclic amines, pyrrolidine and piperidine, are often used. Enones with monosubstituted double bonds can be made in this way.



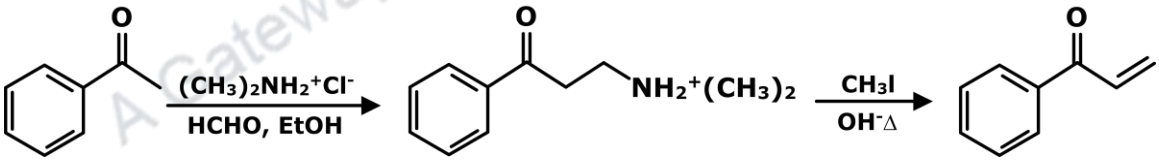
4.3 Asymmetric Mannich Reactions

When properly functionalized the newly formed ethylene bridge in the Mannich adduct has two prochiral centers giving rise to two diastereomeric pairs of enantiomers. The first asymmetric Mannich reaction with an unmodified aldehyde was carried with *(S)*-proline as a naturally occurring chiral catalyst.

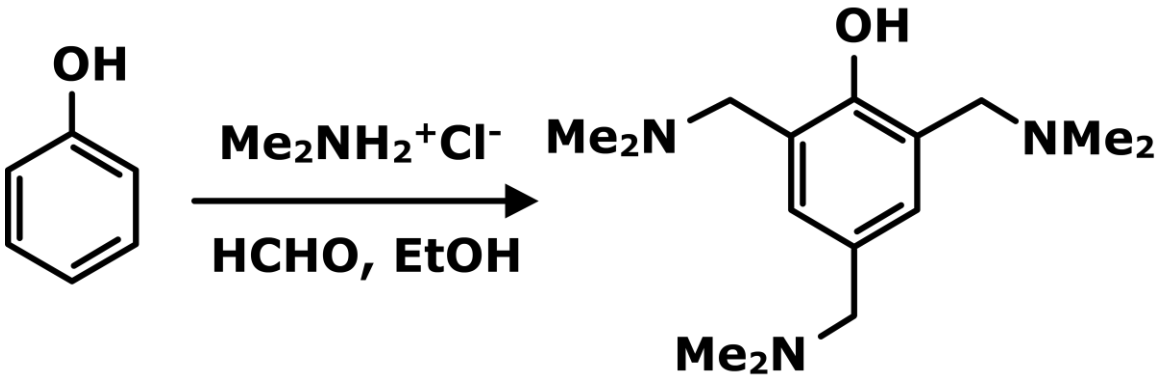


4.4 Illustrations and Applications

- The Mannich reaction of acetophenone with formaldehyde and dimethylaminium chloride in alcohol furnishes the salt of 2-(dimethylamino)-1-phenylethanone, which can be conveniently eliminated to acrylophenone (1-phenylprop-2-en-1-one), an α,β-unsaturated compound by converting it into a quaternary salt and subsequent heating (Hoffman elimination).



- Phenol gives a trisubstituted product in the Mannich reaction.



- The Mannich-Reaction is used in the organic synthesis of natural compounds like peptides, nucleotides, antibiotics, and alkaloids (e.g., tropinone).
- The Mannich reaction is used in the synthesis of medicinal compounds like rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant), tramadol, and tolmetin (anti-inflammatory drug) and azacyclophanes.

5. Summary

- Because esters can contain α-hydrogens they can undergo a condensation reaction similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol, one ester acts as a nucleophile while a second ester acts as the electrophile. During the reaction a new carbon-carbon bond is formed. The product is a β-keto ester.
- A major difference with the aldol reaction is the fact that hydroxide cannot be used as a base. Instead, an alkoxide is used.
- The intramolecular form of the Claisen condensation is the Dieckmann condensation.
- The Mannich reaction is the aminoalkylation reaction, involving the condensation of an enolizable carbonyl compound (α-CH acidic compound) with a nonenolizable aldehyde (like formaldehyde) and ammonia; or a primary or a secondary amine to furnish a β-aminocarbonyl compound, also known as Mannich base.
- Since the β-aminocarbonyl compounds can be conveniently reduced to β- aminoalcohols, which show considerable pharmacological activity, the Mannich reaction plays an important role in pharmaceutical chemistry.