SEM-III, CORE COURSE-7

ORGANIC CHEMISTRY-3

TOPIC: CARBONYL AND RELATED COMPOUNDS

SUB-TOPIC: CONDENSATIONS-II (PPT-8)

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

• CLAISEN-ESTER CONDENSATION

• DIECKMANN CONDENSATION
CLAISEN CONDENSATION

• Self condensation of two molecules of an ester containing α-hydrogen atom promoted by a base such as sodium ethoxide in presence of ethanol, leads to the formation of a β-keto ester is known as Claisen condensation.

• The Claisen condensation may also take place between an ester and a ketone to form a 1,3-diketone.
FACTS

• The base catalyst, ethoxide ion (EtO\(^-\)), in Claisen condensation is introduced by adding just over one mole of sodium plus just a little EtOH to generate an initial small concentration of NaOEt. Further EtOH is generated in step-I, which yields further NaOEt with sodium and the concentration of ethoxide ion (EtO\(^-\)) is thereby maintained.

• When Claisen condensation is carried out with a mixture of two different esters, each of which possesses an α-hydrogen atom, a mixture of four possible products is generally obtained and the reaction is seldom useful synthetically.

• The mechanism of the Claisen condensation is the ordinary tetrahedral mechanism, with one molecule of ester being converted to a nucleophile by the base and the other serving as the substrate.
MECHANISM

STEP-I: Formation of the enolate ion

EtO⁻ + H₂C=O⁻ → EtO⁻ + H₂C=O⁻ + EtOH

Ethyl acetate

STEP-II: Reaction of the enolate ion with the un-enolised ester

O⁻ + H₂C=O⁻ → O⁻ + H₂C=O⁻ + EtOH

Ethyl acetoacetate

STEP-III: Reversible formation of the enolate ion of ethyl acetoacetate

O⁻ + H₂C=O⁻ → O⁻ + H₂C=O⁻ + EtOH

Ethyl acetoacetate

STEP-IV: Acidification leading to the formation of ethyl acetoacetate

CH₃CO₂H + O⁻ → CH₃CO₂⁻ + O⁻ + EtOH

Ethyl acetoacetate
EVIDENCE IN SUPPORT OF THE MECHANISM

1. Compounds containing an active methylene group undergo deuterium exchange with sodium ethoxide in the presence of EtOD. This can be explained by the reversible formation of a carbanion.

\[
\text{carbanion} \quad \text{enolate ion}
\]

2. Optically active esters of the type R\(^1\)R\(^2\)CHCO\(_2\)Et are racemised by the ethoxide ion. This result also indicates the formation of a resonance stabilised carbanion which is expected to be racemised.
POSITION OF EQUILIBRIUM

Since this condensation is reversible, what factors favour shifting of the overall equilibrium to the right?

- Ethanol ($pK_a$ 15.9) is a stronger acid than ethyl acetate ($pK_a$ 25.0), consequently the equilibrium of the first stage lies on the left. However, ethyl acetoacetate ($pK_a$ 10.68) is a stronger acid than ethanol. Thus the former is present mainly as its anion, i.e., conjugate base, in the last stage of the condensation and so the equilibrium lies largely on the right. In this way, the ethyl acetoacetate anion is removed from the reaction and so the overall equilibrium is displaced to the right.

- This argument is supported by the fact that ethyl isobutyrate ($\text{Me}_2\text{CHCO}_2\text{Et}$) does not undergo the Claisen condensation in presence of sodium ethoxide.
When the original ester has two alkyl substituents on the α-carbon atom e.g., with Me₂CHCO₂Et, the β-keto ester that would be produced, Me₂CHCOCMe₂CO₂Et, does not contain an active α-hydrogen atom and consequently the formation of the stable enolate of the product is no longer possible. Hence, for ethyl isobutyrate, the overall equilibrium lies almost completely on the left and this reaction does not go well under the normal equilibrating conditions (EtONa in EtOH).
SELF-CONDENSATION OF ETHYL ISOBUTYRATE

When a very strong base such as the triphenylmethyl sodium, \( \text{Ph}_3\text{C}^-\text{Na}^+ \) (\( \text{pK}_a \) of \( \text{Ph}_3\text{CH} \approx 33 \)) is used, then the equilibrium of the first stage with ethyl isobutyrate lies large on the right and the Claisen condensation will proceed. Triphenylmethyl carbanion is a strong enough base to convert an ester entirely into its enolate. Reaction of the enolate with a second molecule of ester then gives the \( \beta \)-keto ester and the position of the equilibrium of the last stage will no longer matter.
Self-Condensation of Mono-substituted Acetates

- Self-condensation of simple mono substituted acetates $RCH_2CO_2Et$ works well under the conditions (EtONa in EtOH). The enolate anion is formed first in low concentration which remains in equilibrium with the un-enolised ester. It then carries out a nucleophilic attack on the more abundant un-enolized ester molecules.

- These steps are all unfavourable equilibria and on their own, would give very little product. However, the reaction works because the equilibrium is driven over by the essentially irreversible formation of a stable, delocalized enolate from the product. Finally, the reaction is worked up in acid and the $\beta$ keto-ester product is formed.
The Claisen ester condensation compared to the Aldol Reaction

• The treatment of acetaldehyde with base led initially to the formation of an enolate anion and then to the aldol reaction. On the other hand, treatment of ethyl acetate with base gives the corresponding enolate anion and finally ethyl acetoacetate.

• To start with, there is hardly any difference. In case of Claisen condensation, an ethoxide ion is used as base rather than the hydroxide ion, as hydroxide would hydrolyse the ester, but otherwise the first steps are very similar.
The next step in both cases is the nucleophilic attack by the enolate ion on an unenolized carbonyl compound. The concentration of enolate is low and each enolate ion is surrounded by unenolized aldehyde or ester molecules, so this reaction is to be expected.

Only now does something different happen. The aldehyde dimer simply captures a proton from the solvent to give an aldol product. The adduct from the ester has a leaving group, EtO⁻, thus instead of adding a hydrogen atom, EtO⁻ is lost to yield a β-keto ester.

The Claisen condensation is, thus, considered as a nucleophilic substitution at the carbonyl group passing through the formation of the tetrahedral intermediate.
• 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.

• In both the reactions, the base concentration is not high enough to transform the carbonyl/ester compound entirely into the corresponding enolate. Only a small equilibrium concentration is produced, which reacts with the carbonyl/ester electrophile.

• The aldol reaction often works best when there is an extra driving force to push it across-dehydration to an enone. Similarly, the ester dimerization works best when the product reacts with the ethoxide ion to give a stable enolate ion.
CROSSED CLAISEN CONDENSATION

• When Claisen condensation is carried out with a mixture of two different esters, each of which possesses an α-hydrogen atom, a mixture of all four possible products is usually obtained, e.g., with ethyl acetate and ethyl propionate:

\[
\begin{align*}
2 \text{CH}_3\text{CO}_2\text{Et} & \xrightarrow[\text{NaOEt}, \text{EtOH}]{} \text{CH}_3\text{COCH}_2\text{CO}_2\text{Et} + \text{EtOH} \\
2 \text{CH}_3\text{CH}_2\text{CO}_2\text{Et} & \xrightarrow[\text{NaOEt}, \text{EtOH}]{} \text{CH}_3\text{CH}_2\text{COCH(CH}_3\text{)CO}_2\text{Et} + \text{EtOH} \\
\text{CH}_3\text{CO}_2\text{Et} + \text{CH}_3\text{CH}_2\text{CO}_2\text{Et} & \xrightarrow[\text{NaOEt}, \text{EtOH}]{} \text{CH}_3\text{COCH(CH}_3\text{)CO}_2\text{Et} + \text{EtOH} \\
\text{CH}_3\text{CH}_2\text{CO}_2\text{Et} + \text{CH}_3\text{CO}_2\text{Et} & \xrightarrow[\text{NaOEt}, \text{EtOH}]{} \text{CH}_3\text{CH}_2\text{COCH}_2\text{CO}_2\text{Et} + \text{EtOH}
\end{align*}
\]

Question: Explain the formation of the possible products mechanistically in the above "Mixed" Claisen condensation. Explain, also, the utility of the reaction.
CROSSED CLAISEN CONDENSATION

- The Crossed Claisen reaction can be synthetically very useful if one of the ester partners has enolisable α-hydrogens and the other does not (e.g., esters of formic acid, aromatic esters, oxalic esters, etc.). The esters without α-hydrogen atom act only as a carbanion acceptor.
- Ethyl carbonate also does not contain any α-hydrogen atoms and is very useful for introducing a carbethoxy group into compounds with an active methylene group.
- If ketones or nitriles are used as the donor in this condensation reaction, a β-diketone or a β-ketonitrile is obtained respectively.

\[
\begin{align*}
\text{HCO}_2\text{Et} & + \text{CH}_3\text{CO}_2\text{Et} \quad \text{NaOEt} \quad \text{EtOH} \quad \rightarrow \quad \text{HCOCH}_2\text{CO}_2\text{Et} & + \text{EtOH} \\
\text{PhCOOEt} & + \text{CH}_3\text{CO}_2\text{Et} \quad \text{NaOEt} \quad \text{EtOH} \quad \rightarrow \quad \text{PhCOCH}_2\text{CO}_2\text{Et} & + \text{EtOH} \\
(\text{CO}_2\text{Et})_2 & + \text{CH}_3\text{COOEt} \quad \text{NaOEt} \quad \text{EtOH} \quad \rightarrow \quad \text{EtO}_2\text{C}\text{C}\text{OCH}_2\text{CO}_2\text{Et} & + \text{EtOH} \\
(\text{EtO})_2\text{CO} & + \text{CH}_3\text{COOEt} \quad \text{NaOEt} \quad \text{EtOH} \quad \rightarrow \quad \text{EtO}_2\text{CCH}_2\text{CO}_2\text{Et} & + \text{EtOH}
\end{align*}
\]
Intramolecular Claisen Condensation
Dieckmann Condensation

- When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester. This intramolecular version of the Claisen ester condensation is known as the Dieckmann condensation. This cyclisation reaction is most successful for the formation of 5-, 6-, and 7-membered cyclic β-keto esters from the esters of adipic, pimelic or suberic acids respectively with sodium ethoxide.
- As all these esters are symmetrical, it doesn’t matter which ester group forms the enolate anion as they are the same.
- Though the keto ester is the final product in this reaction, yet subsequent acid or base catalysed hydrolysis followed by decarboxylation leads to the formation of the corresponding cyclic ketone.

![Chemical structure](image)
MECHANISM

Diethyl adipate

EtO⁻ + H → CO₂Et

EtO⁻ + OEt → CO₂Et

EtO⁻ + EtOH → CO₂Et

HCl ↔ H₂O

O

CO₂Et

H

CO₂Et

HCl → H₂O

(i) NaOH solution (20%) reflux

(ii) Dilute HCl to acidify

β-Keto acid

heat

- CO₂

Cyclopentanone
EVIDENCE IN FAVOUR OF FORMATION OF THE ENOLATE ION

The enolate ion formed under the reaction conditions can be demonstrated by trapping the enolate ion with an alkyl halide before work-up.

\[
\text{Diethyl adipate} \xrightarrow{\text{NaOEt, EtOH}} \text{Enolate ion} \xrightarrow{\text{MeI}} \text{Ethyl 1-methyl-2-oxocyclopentane carboxylate}
\]

Home-work:

\[
\text{(H}_2\text{C})_5\text{CO}_2\text{Et} \xrightarrow{\text{i} \text{NaOEt/EtOH}} \xrightarrow{\text{H}_3\text{O}^+ \text{ii}} \text{A}
\]

\[
\text{(H}_2\text{C})_6\text{CO}_2\text{Et} \xrightarrow{\text{i} \text{NaOEt/EtOH}} \xrightarrow{\text{H}_3\text{O}^+ \text{ii}} \text{B}
\]

Diethyl pimelate

Diethyl suberate

Home-Work: Explain the order of reactivity (decreases from 1 to 4) of the given compounds towards nucleophiles in connection with Crossed Claisen condensation:

1. Diethyl oxalate  
2. Ethyl formate  
3. Diethyl carbonate  
4. Ethyl benzoate

Identify the products, A and B. Give plausible mechanism for their formation.