Hello everybody, my name is Doctor Richa Sardessai and I'm affiliated to the Saint Joseph Vaz College Cortalim.
Today we're going to be studying the reaction and the mechanism of the Knoevenagel condensation. This module is a part of the Bachelor of Science program in chemistry for third years. Semester 6. The course code is CHC110 and the course title is organic chemistry and section A.
The title of the unit is, Unit 1 name reactions and rearrangements and the module name is reaction and mechanism Knoevenagel condensation. At the end of this module, the student will understand, the scope of enolate chemistry, learn the mechanism of Knoevenagel reaction and gain knowledge of the applications of Knoevenagel reaction. This module is broadly divided into 4 sections.

The first is the chemistry of active methylene groups. Second is Knoevenagel reaction nd its mechanism.
3rd is the Doebner modification, and finally we will be looking into the application of Knoevenagel reaction.
As an introduction, first let us understand the chemistry of active methylene groups. In a normal hydrocarbon, the methylene group, which is flanked by two alkyl groups, hardly shows any substantial difference in the acidity of the hydrogen. However, once we replace the alkyl groups by any electron withdrawing groups, then the acidity of the hydrogen is greatly increased.
Due to this increase in acidity, the hydrogen becomes extremely labile and is readily picked up by a base and causes it to react to different types of electrophilic centers, giving an array of different products.
Hence this is an efficient synthetic methodology. The electron withdrawing groups can be of different types, like. Aldehyde, ketone carboxylic acid carboxylic esters, the cyano group, the Nitro group,
the sulfoxide, sulfone's or sulfate esters, or any other such group. The reactivity of the active methylene group is responsible for a number of named reactions like Perkin reaction, Stobbe reaction, aldol reaction, Darzen’s glycidic Ester condensation and of course now vinegar reaction. The Knoevenagel reaction was first discovered by Emil Knoevenagel.

It is a type of carbon carbon bond forming reaction. Emil Knoevenagel published his work in Chemische Berichte in 1894.

He observed that the reaction of formaldehyde with diethyl malonate in the presence of diethyl amine as a catalyst formed a bis adduct. A couple of years later he reacted benzaldehyde with acetoacetate ester under two different set of conditions.
The first was reacting it with two moles of acetoacetate ester in piperidine at 20 degrees Celsius to give bis adduct. However, when he reacted benzaldehyde with one mole of acid acetate ester at zero degrees Celsius in piperidine, an alpha beta unsaturated product was observed. Essentially, Knoevenagel reaction is a condensation of aldehydes and ketones usually not containing an alpha hydrogen with compounds containing active methylene group to form alpha beta unsaturated compounds. The catalysts usually used are fading, piperidine or diethylamine. The general reaction shown here is the. Carbonyl compound reacting with an active methylene group in the presence of base.

However, the most common active within group used for Knoevenagel condensation is the diethylmalonate whose mechanism we're going to be seeing soon. Now coming to the mechanism of the

Knoevenagel condensation. The first step is that the base picks up the acidic hydrogen of diethylmalonate to generate a Carbanion and a protonated base. This carbonanion then reacts with an electrophilic centre of a carbonyl group to generate an oxyanion .This oxyanion then undergoes a proton transfer from the protonated base to generate an alcohol. It is pertinent to mention here that the diethyl malonate consists of two. Active hydrogens or Two acidic hydrogens. The second acidic hydrogen can also be picked up by the base, which in fact it does to generate a carbon-carbon double bond by the elimination of the hydroxide ion. In the Doebner modification of Knoevenagel reaction. The malonic acid is used as the active methylene compound and is treated with aldehyde in the presence of base. The advantage of this modification is that alpha, beta unsaturated carboxylic acids can directly be generated by using this method. Now let us come to the application of Knoevenagel reaction. Benzaldehyde when treated with diethyl malonate in the presence of base generates this alpha beta unsaturated compound which on hydrolysis generates the alpha beta unsaturated acid, which is called as cinnamic acid.
Cyclohexanone Reacts with Meldrum's acid in the presence of base to give an Alpha beta unsaturated product. In both these cases we observe simple carbonyl compounds, react with active methylene groups to give a carbon carbon double bond. However the application of Knoevenagel reaction is quite wide.

For example, the para chlorobenzaldehyde reacts with this compound to generate Lumifantrine. Lumifantrine is a component of the drug coartem. Along with Artemether it shows antimalarial activity. Additionally Salicylaldehyde also reacts with diethylmalonate to generate. Ethyl coumarin three carboxylate. Both of these compounds have significant biological activity.

Hence, Knoevenagel reaction has been shown in different types of synthetic methodology's to generate compounds which have either biological activity. Or synthetic application.

The Hantzsch pyridine, synthesis, the Gewald reaction, and the Feist–Benary furan synthesis all contain another Knoevenagel reaction step. Finally the Knoevenagel or condensation is an important tool for synthetic transformation and hence is used for carbon carbon bond formation. The mechanism of the Knoevenagel reaction includes the formation of the enolate followed by addition to a carbonyl compound to give an alpha beta unsaturated compound. The Doebner modification of Knoevenagel reaction uses the malonic acid as the source of the active methylene group to directly give the alpha beta unsaturated compound. The Knoevenagel reaction finds a lot of applications in the synthesis of important chemical intermediates pharmaceuticals, polymers, drugs, cosmetics and perfumes. If you wish to learn more about this module, you may refer to these references. Thank you.