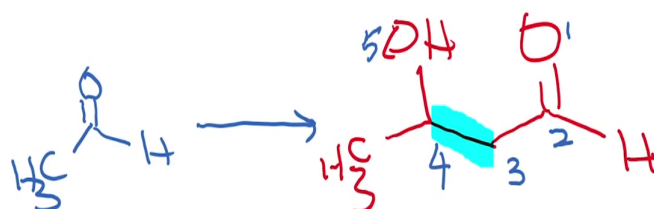


Introductory Organic Chemistry II
Professor Dr. Harinath Chakrapani
Indian Institute of Science Education and Research, Pune
Module 06
Lecture 41
Aldol and related Reactions

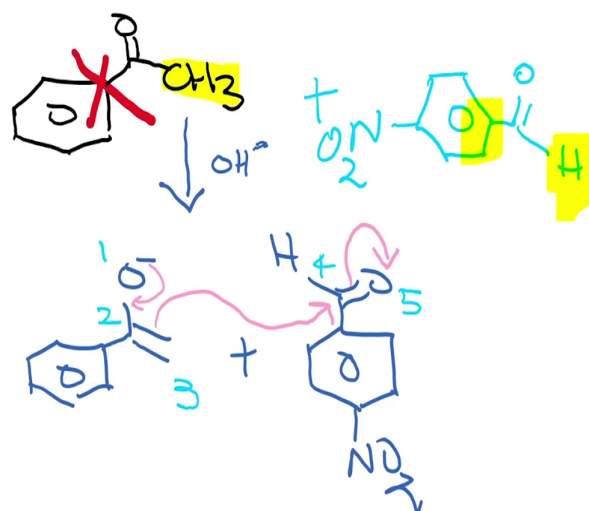
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So now, in the last lecture, we were looking at the aldol reaction of a ketone with itself. So, the example that we can look at is acetaldehyde reacting with itself to give you a new product, which would be the aldol as shown here. And so, the important point here to note is the connection that is being made between this 2, 3, 4, and 5. So, the bond that we are looking at is this carbon-carbon bond between carbon 3 and carbon 4.

So, that is why this is pretty straightforward in our understanding. But now, in this lecture, what we will look at is the concept of cross condensations, so here, what you are seeing is that partner A reacts with itself, so an aldehyde reacts with itself to give you the aldol product. Now, what if we have A and B and can we do aldol reactions with this? So, these are known as cross-condensation reactions. And in this lecture, we will look at some examples of this.

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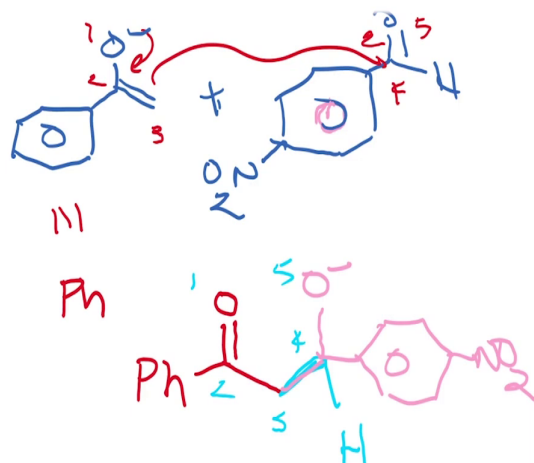


So now, let us take a simple example here. Now, I am just going to start with something like acetophenone. So now, if I take acetophenone, so if I look at this ketone here, we will straightaway see that the enolate can be formed over here, but the enolate sort of this not possible in this position, correct? So, therefore, this has one enolizable hydrogen, okay. Now, of course, as we know, it can react with itself and give you the aldol product.

But you can also react it with an electrophile that is more reactive. So, for example, such as this. So, let us say we start with this 4-nitro benzaldehyde. And I just want to point out here that this hydrogen is an aldehydic hydrogen and so, this is also not enolizable. And clearly, there is no hydrogen here to enolize. So therefore, when I mix these two reagents together, the only enolizable hydrogen in the presence of a base is this.

So, what we can expect as the first intermediate in the reaction is this enolate and the coupling partner for the electrophile that is shown here is this, and now, when the reaction actually happens, you can see that this enolate reacts in the following manner, it goes attacks the carbonyl. And now, the carbonyl can open up. And so again, just to be consistent, let us keep the same numbering sequence. So, this is 1, 2, 3, 4, and 5, so I am just going to draw this once again in the next page in a fresh page, so that we understand this better.

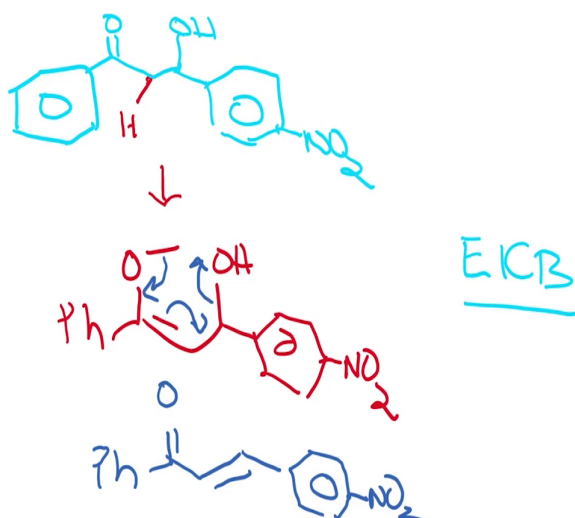
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So, the enolate, we are looking at is this and the aldehyde that we are going to react it with is this. So, we will very soon discuss few aspects of this reaction. But you can clearly see here that for example, that the aldehyde is quite reactive in this case, and therefore, the reaction goes forward. So, let us look at the numbering again. So, this is 1, 2, 3, 4, and 5. So, I am just going to call this as Ph, and so this becomes Ph CO, this ketone is restored.

And now there is a new bond between this and this. So, I am just going to draw this in a different colour, so that you can clearly see it. This is O⁻ and this is a 4-Nitrophenyl, and this is hydrogen. So, this is the kind of reaction that can occur. Now, the question here, again let me just complete the numbering, so that we can go forward with this reaction; 1, 2, 3, 4, and 5. So, now you can propose a reaction, this aldol product can pick up a proton.

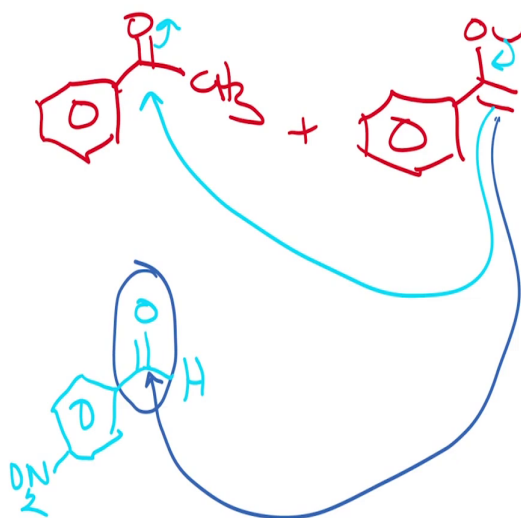
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And so, the proton that you can pick up is shown here. So, C double bond O OH, so you still have some base floating around in the reaction. So, you can propose that this can form the enolate, O minus OH, and the remaining structure remains the same. So, this is the enolate and this is the enolizable hydrogen. And so, you can form the enolate.

And we have already discussed this in the previous lecture that you can have what is known as the E1cB reaction, which is E1 conjugate base reaction, where this comes in here, this goes here, and you can kick out the hydroxide ion. So, the final product that you would get in this case would be PhC(=O)CH=CH(p-C₆H₄NO₂). So, now, the yields are pretty good in this reaction, I do not have a number here, but usually you get this is in excess of 80 percent. So, the question here is, why does not the ketone react with itself?

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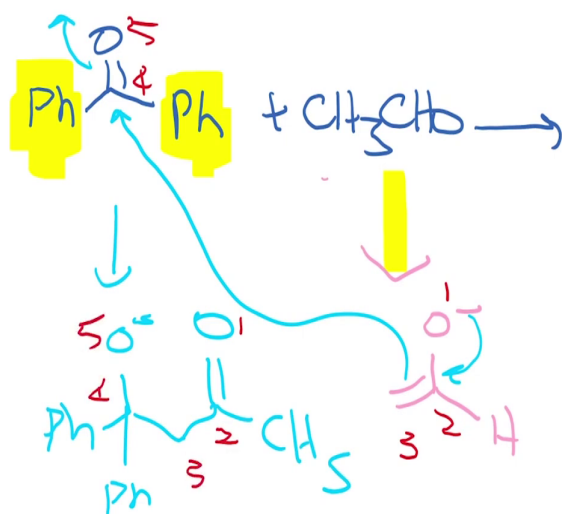


So, this ketone, that is shown here, CH₃, of course, it can react with itself, that is this enolate that is formed, can react with the ketone. But we know that between aldehydes and ketones, aldehydes are clearly better electrophiles. And also notice in the example that we have shown here, we have taken a substrate reactant that is extremely reactive.

So, you also have a strong electron withdrawing group over here, the nitro group. So, that is just going to pull electrons from this carbonyl. And it is going to make this centre even more reactive. So, the enolate, once it is produced has a choice of reacting with this ketone, or it can react with this aldehyde.

And between the two systems, we already know very well, that the aldehyde is substantially more reactive. And so, this is going to result in the formation of the cross-condensation product. So, this is one way in which we can do cross condensations. Let me just quickly write out another example. And then we can move on to the next topic, or summarize this topic.

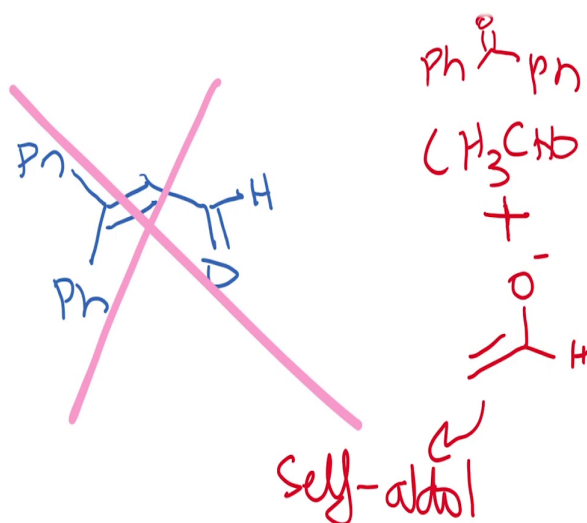
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So, the next example that I am going to look at is Ph C=O Ph + acetaldehyde. And so, if you imagine this has got two different partners, so here is there is no enolizable hydrogen, there is no enolizable hydrogen. So, the aldehyde is also not enolizable. Only, this is enolizable.

So, the first step is fairly straightforward, which is that you produce this enolate. Now, what you can propose is that this enolate attacks here and produces this product. And so, the product that you can expect would be, okay, so let me just do the numbering once again, this is 1, this is 2, this is 3, this is carbon number 4, and this is carbon number 5. So, let me just reiterate that 1, 2, 3, 4, 5.

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So, by extending the logic, further, the product that we would get would be $(\text{Ph})_2\text{C}=\text{CHCHO}$, once it undergoes the E1cB reaction, you will get this as the product. So, this is a fairly straightforward argument except that this is not the product that is formed. So, what happens is actually the acetaldehyde reacts with itself and it gives you the self-aldol product. So, this is the reaction that would occur and you get the self-aldol product.

Now, what is the rationale for this, the rationale for this is that once an enolate is produced, the enolate reacts with the most reactive electrophile and between the aldehyde here and the ketone, which is $\text{Ph C}=\text{O Ph}$, between these two, the aldehyde is clearly more reactive and so, when given a choice the enolate is going to react with itself and give you the product.

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Cross aldol

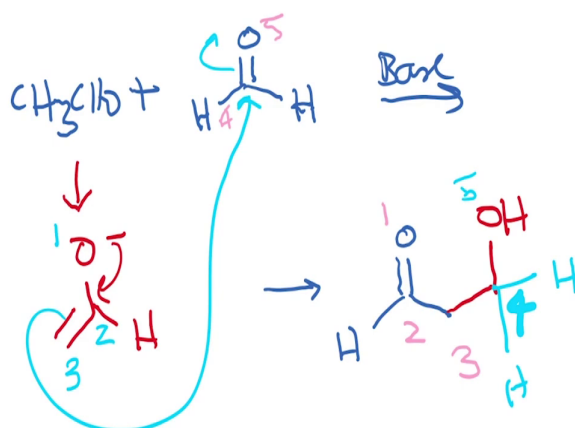
① one partner only enolizes

② other partner more reactive

So, therefore, in order to sort of generalize this concept, what we need to understand is the following. So, in order for cross-aldol to occur, what we would need is point number one would be one partner only enolizes. So, this is obvious because, if you have both partners enolizing then you have a problem of generating multiple enolates. And number two point would be that the other partner must be more reactive.

So, what we mean by this is that if the ketone is being enolized, then the other partner should be more reactive, in which case it must be likely, be an aldehyde or a ketone with an electron withdrawing group or something that favours the formation of the cross-aldol product. Otherwise, you would get self-condensation as the major product. So, next we will look at some further aldol reactions.

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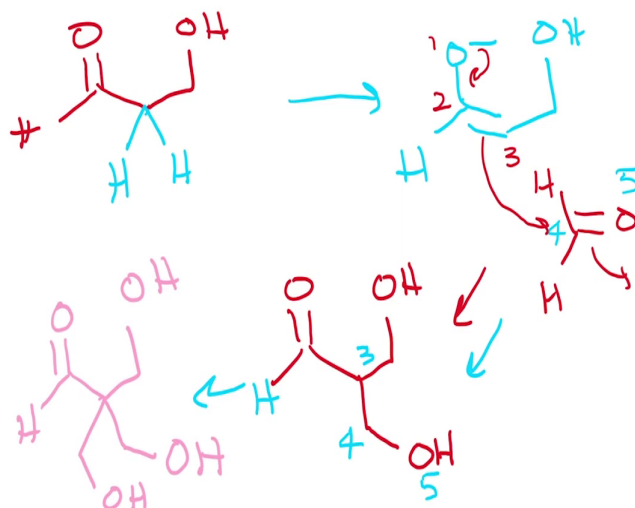
So, now, let us look at another important aldehyde that we have all encountered previously, which is formaldehyde. So, formaldehyde is nothing but a carbonyl flanked by two hydrogens. So, when I react this with acetaldehyde for example, in the presence of a base. Now, what we would expect here clearly is that again I know, once we have cross-aldol reaction such as this, or a potential cross-aldol reaction such as this, we need to look for enolizable hydrogens.

So, this hydrogen is not enolizable, this hydrogen is not enolizable. So, this aldehydic hydrogen is also not enolizable. So, the only enolizable hydrogen here is this in the acetaldehyde. So now, let us say that this undergoes enolization and it forms this enolate. So far, there is nothing major to discuss. Now, once this enolate is produced, this enolate can now react. And we know that between formaldehyde and acetaldehyde, acetaldehyde is more reactive.

And so, we are going to end up attacking here and producing this aldol product. So, let me just draw out this product here, so that you understand the chemistry. So, I am just going to flip this carbon to the other side just so that it is easy for us to understand this. Now, this is the aldehyde, so this is 1, 2, 3, and this is carbon number 4, and oxygen is number 5. So, we keep the same numbering 1, 2, 3, and here is the formaldehyde part, which is number 4, and number 5. So far, there is no problem and you have a hydrogen here and a hydrogen here.

So, under normal circumstances, what you would expect is that this is going to give you the aldol product. However, since it is difficult for us to control the amount of base that is added in these reactions, you also have the possibility of the second enolate that can be formed. And so, that enolate that is going to be produced, I am just going to draw it out separately in the next page.

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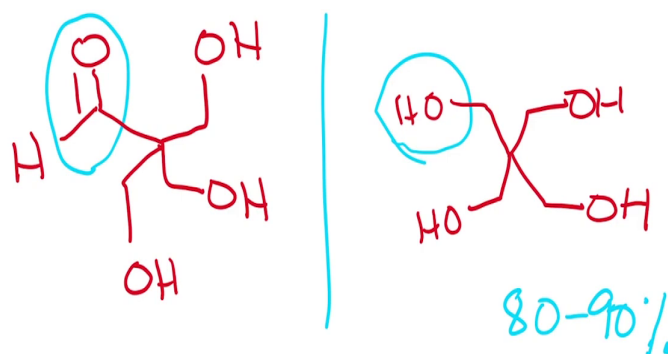
And so, this enolate is derived from acetaldehyde. So, you have this OH, and you know this is the enolate, this is the enolizable hydrogen and in the presence of the base you could form O⁻ and hydrogen over here. So, this again, we have already looked at previously. Now, the only situation here is that under normal circumstances, this would undergo E1cB reaction and give you the product, but since formaldehyde is so reactive in this case, that it promotes the second addition in this situation.

So, what happens is that you get this and the product that is formed is this C double bond O, the OH is already here. Now, there is a second addition of an alcohol, of a CH₂OH. So, again, just to keep the numbering consistent. So, this is 1, 2, 3, 4. And this was for the previous addition. Now, for this addition, this is 1, 2, and 3, and this would be 4, and this would be 5. So, this is the bond between carbon 3 and carbon 4, and this would be carbon 5.

So, I am just skipping the step of undergoing protonation but you will first form the alkoxide which is then going to pick up a proton. So, subsequently this can happen once again. And

the product that you can expect is this, $\text{CHOC}(\text{CH}_2\text{OH})_3$. So, again keep in mind that formaldehyde is quite reactive and therefore this kind of reaction is favoured.

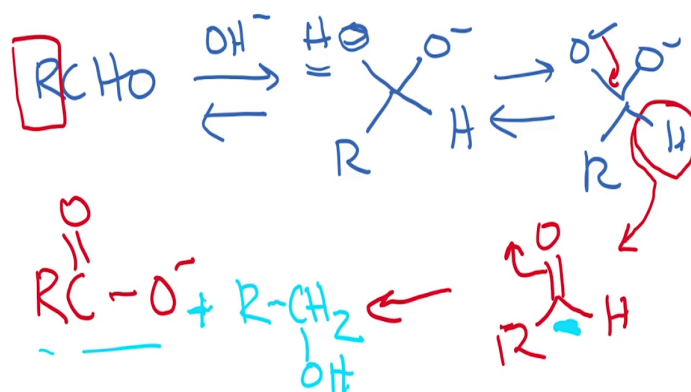
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Now, the twist in the tail is that what we would expect as the product is this CHOC(CH₂OH)₃, but actually the product that is isolated is this C(CH₂OH)₄. So, now, this is the product, but you get this in between 80 and 90 percent yield. So, that is quite a large yield of the reaction. So, what is going on here is that, just to understand here these three CH₂OH are also preserved here. And one of these aldehydes is now undergoing a reduction to form the alcohol.

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Cannizzaro



So, I think many of you would be very familiar with this reaction known as the Cannizzaro reaction, I think you must have studied this in your 11th or 12th. But this is the reaction that

we are familiar with aldehydes, so when you have an aldehyde RCHO , and what can happen is that, you have the $\text{RCHO}^-(\text{OH})$ in the presence of a base you get addition of hydroxide ion to give you this kind of a product.

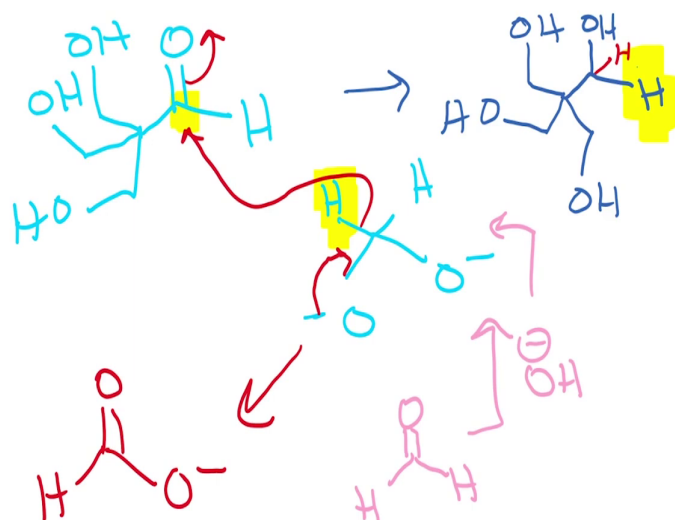
And now, subsequently, this can again lose another, this hydroxyl group can be deprotonated, and you can get this dianion. Now, this dianion, again, so what I neglected to mention is that this R is actually non-enolizable. So, therefore, the addition to the aldehyde is the only reaction that can occur, but this tetrahedral intermediate that is produced is very reactive.

And so, when it collapses, what can happen is that obviously, it cannot kick out O^{2-} , but instead it can kick out hydride. So, when this hydride is kicked out, it actually what it does is, it does not leave as hydride, but it leaves as a hydride that attacks an aldehyde. So, this is the H^- that is going to leave. And so, the product that you are going to get from the first part now is $\text{RC}=\text{O O}^-$, and the product that you get from the reaction with this would be $\text{RCH}_2 \text{OH}$.

So, you can go back and work out the mechanism of this reaction. But so what essentially happens is that with a non-enolizable compound such as formaldehyde, what you expect is that, you get this kind of a reaction where you form this tetrahedral intermediate, and then there is a migration of hydride to the original aldehyde that is formed, and you get a mixture of the carboxylate, as well as the alcohol.

So, therefore, this is not a reduction reaction. But it is a redox neutral reaction, because the aldehyde is now oxidized to the carboxylate or reduced to the alcohol, so you get equal amounts of the carboxylate as well as the alcohol. So, therefore, it is not a reduction or an oxidation reaction, it is a redox neutral reaction. So, now with this background, let us now look at the structure that we drew out in the previous example.

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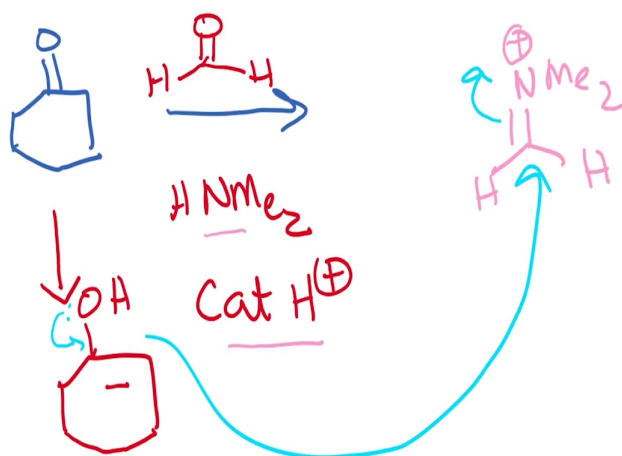
So, I am just drawing it in a slightly different way, so that you understand it better. So, here is the OH, the OH, and the OH, and here is your aldehyde. And what can happen is that your formaldehyde produces this kind of an intermediate and I just describe to you how this kind of an intermediate can be formed from formaldehyde in the presence of addition of hydroxide ion and subsequent deprotonation will give you this product.

Now, carefully see the arrow pushing, so what happens is, this goes here, and this hydride goes over here, and this aldehyde opens up. And so, the product that you get is OH, OH, OH, CH_2OH and CH_2OH , and this hydride is now forming a bond with this carbonyl. And so, I am just going to draw it out in a slightly different colour, so that we can understand it. So, this is the hydride that has come out and this is the OH.

So, I am just going to highlight this. So, this is just the hydride that is added over here, there is already a hydrogen present. So, this is the product which is called Pentaerythritol which is produced in this reaction. Now, let us now complete the other side of this reaction. And if you see here, the product that is formed is formate.

So, when you react acetaldehyde with formaldehyde, the aldol reaction does occur but it subsequently goes forward and gives you the Pentaerythritol as the product. So, one of the messages that we can take from this reaction is that formaldehyde is an extremely reactive partner, and is not really suitable for aldol reactions, if you want to produce the aldol.

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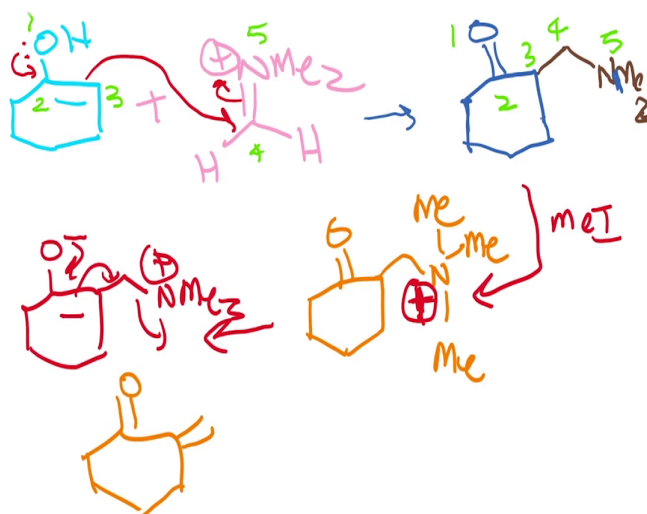


Let us now look at, so, is it impossible to use formaldehyde or to add formaldehyde? And the answer is no. So, what we need to do is, we need to modify the conditions a little bit. And now let us look at those modified conditions. So, I am just going to start with cyclohexanone as the starting material, so instead of using the formaldehyde as the electrophile, what we are going to do is we are going to use formaldehyde, but we are going to use dimethyl amine and we are going to use some catalytic amount of acid.

So, under these conditions, now let us look at what reaction can happen. So, again, in the presence of catalytic hydrogen and dimethylamine, formaldehyde is going to produce $\text{H}_2\text{C}=\text{NMe}_2^+$. So, this is something that we have already looked at in the past that is, if you take an aldehyde and react it with the secondary amine, you get an imine.

Now, this imine is the active electrophile that is produced and also under acidic conditions, you can also imagine that the cyclohexanone will form the enol as shown here. And now, the enol is the reactive partner in the proposed aldol reaction and you get this kind of a reaction. So, the product of this reaction, I am just going to draw it out in the next page.

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So, that reacting partners are the enol from cyclohexanone which you already know the reaction mechanism too and you have $\text{H}_2\text{C}=\text{NMe}_2^+$. So now, the reaction that you are going to look at is this, going to form here and kick this out. So, the product that is going to be formed is C double bond O. Now, let me just number this, so that we can all be on the same page. So, this is 1, 2, 3, 4, 5.

So, again here 1, 2, and now there is a bond between carbon 3 and carbon 4 and there is NMe_2 and there used to be a positive charge, but that positive charges now disappeared. So, this is 3 and this is 4 and this is 5. So, the product that is formed is actually the aldol type product where instead of the alcohol, you have NMe_2 .

Now, in order for us to produce the α, β -unsaturated ketone, what we can do is do a simple addition of methyl iodide in the presence of a mild base, and what you get is the product as shown here, which is C double bond O N Me Me Me, so you get this quaternary ammonium salt.

And what we can expect is this quaternary ammonium salt is quite a good leaving group. And so, since you have added a small amount of base, you may consider the formation of the enolate and NMe_3^+ . And this enolate can now rearrange and kick out trimethylamine and give you the final product. So, this reaction can indeed occur. And what we will do is we will start the next part of this lecture with this and move forward.