Introduction to Organic Chemistry II
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Lecture 31
Tutorial - 4

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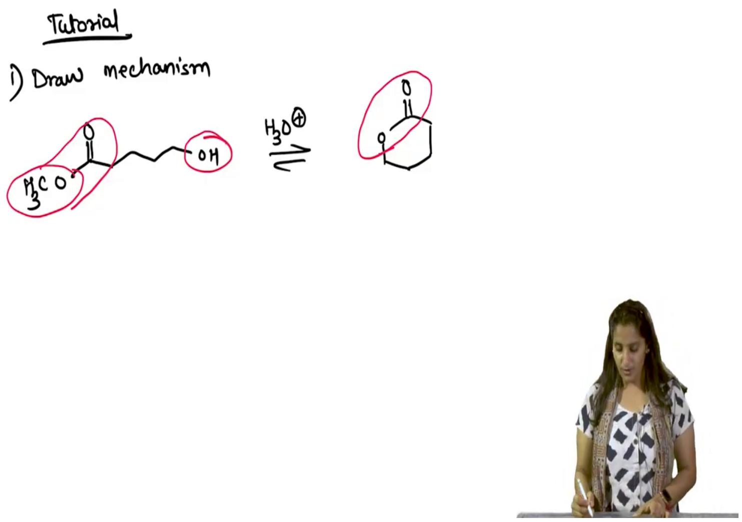
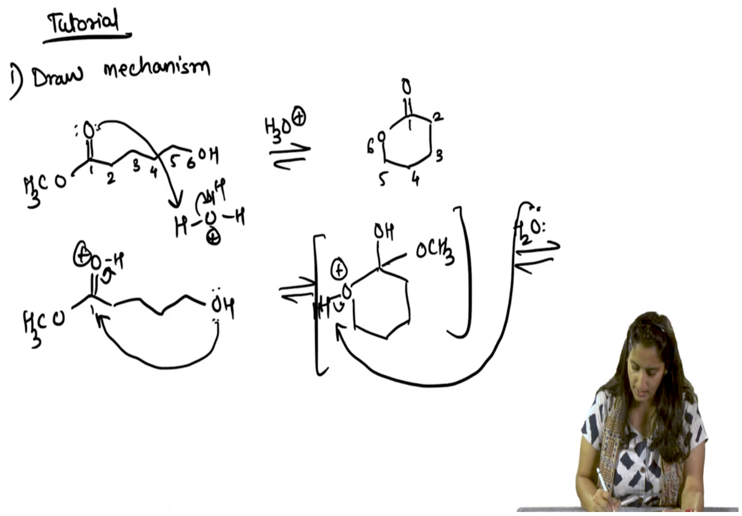


Tutorial

1) Draw mechanism



Tutorial

1) Draw mechanism

So, let us start doing this week's tutorial, and the tutorial for this week is based on the carboxylic acid and their derivatives. And there are some questions from alcohols also but let us start from the question number one. So, the first question is drawing the mechanism of this particular reaction. And as we can see we have a starting ester and we have an alcohol group here.

So, this ester functionality all the way, and the alcohol here they are together forming a new kind of ester. So, in the formation we have again, esterification happening, and this is really trans-esterification reaction, meaning we start from one ester and then we end up with another ester.

The other thing to look at this reaction and realize is that we had an open chain compound which was really a big compound. Now, it has formed a ring structure so it has to do an intra molecular reaction wherein the alcohol from the same molecule comes in to form that 6-membered ring.

Now, how do we go about writing the mechanism for this one? So, let us start. In the first step, remember we are in acidic medium, so in acidic medium you cannot have species like OH^-, that is given. So, the only base that we have here is going to be water, as our base and acid is going to be H^+ or H_3O^+, you can write it that way as well.

So, let us start with H_3O^+ as our acid. And remember that all the other oxygens are going to get protonated and they are going to get deprotonated too, depending on the pH of the medium and how much acidic is the medium, depending on that you are going to have protonation and deprotonation happening in the reaction mixture.

So, in the first step we are going to protonate this. Now, remember that we want to form this 6-membered ring and whenever we are writing a mechanism, it is always good to write down the numbers on your molecule. So, if I see that, I see 1, 2, 3, 4, 5 and 6, sixth is the oxygen which is going to come and attack on carbon number 1. And that is my carbon number 1, here.

So, when we have an electrophilic center like that, the oxygen is going to come, attack here and open it up. What do we form here? We have this O^+H and on this carbon, we have the OCH_3 which still has not left. Now, we are in acidic medium so as I said our base that we have with us is this water molecule so it is going to come attack and deprotonate that oxygen.

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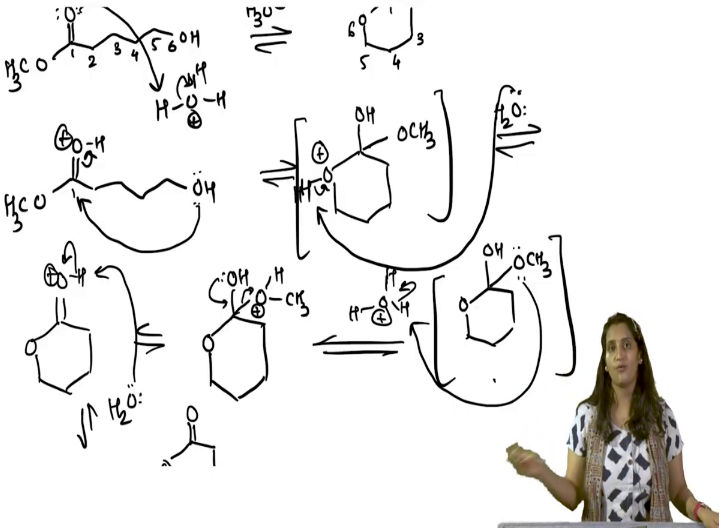

So, that is our intermediate right there, tetrahedral intermediate. And now we have to kick out one of the things, and the leaving group in this case is going to be OCH_3. But we cannot kick it out just like that because we are in acidic medium. So, what we are going to do is, we are going to first make it into a good leaving group, and that becomes our good leaving group here.

So, what do we form here? We have now methanol as our leaving group. That is a better leaving group in the case of acidic medium. So, now we have is, this comes in, we kick that out, reforming, what do we have here? This and then water comes along reforming our product.

And you can try writing the backward mechanism for this also. Again, as I said due to the principle of microscopic reversibility you will see that the same intermediates happen as you try to go backwards. You will have to do different steps, that is, you know addition of methanol instead of removal of methanol but overall it is going to look like, the reaction followed the same path going forward and backward.

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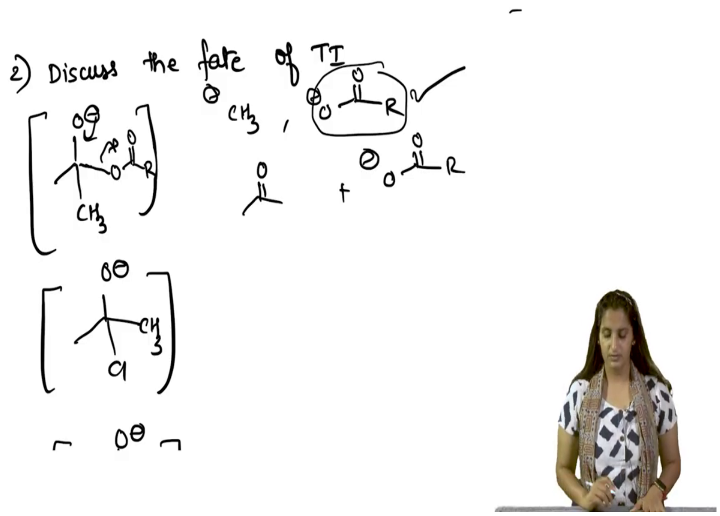

So, that was our question number 1, that is the mechanism. Let us try to solve question number 2, which is discuss the fate of the tetrahedral intermediates that are formed here. Let us start solving our question number 2. So, that is, discuss the fate of the tetrahedral intermediate in this case. Now, in each case they have given us a tetrahedral intermediate, now they want us to discuss what will happen, whether it will collapse and if it collapses to reform the carbonyl bond, whether, which of the leaving groups will leave.

So, now if in the case of first one if this tetrahedral intermediate collapse, we have two options. We have either CH_3^- leaving, or we have this particular group, which is a deprotonated carboxylic acid leaving. Now, between these two, remember this is a much stable molecule because it has a resonance structure, and is resonance stabilized, we also know the corresponding pKaH is 5, whereas for CH_3^- the pKaH is 50. So, there is a lot of difference. This is going to be our leaving group. So, this collapse to kick out this, reforming the ketone, and the conjugate base of a carboxylic acid.

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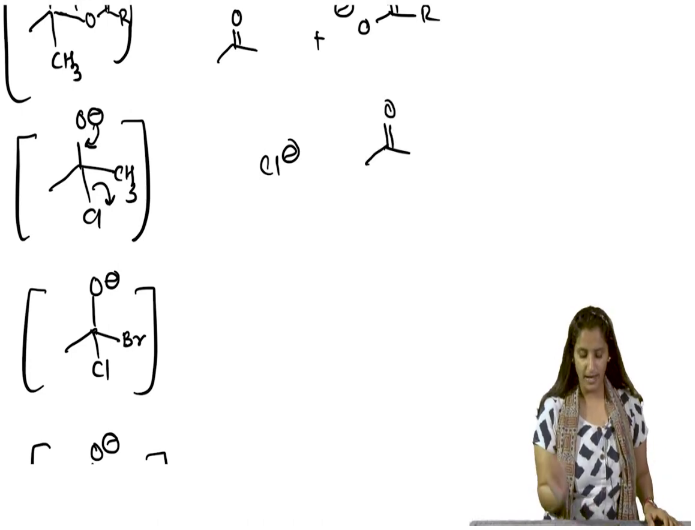

Now, for the next one, it is very clear you have a chlorine, you have a methyl. Between chlorine and methyl, chlorine is going to be the more stable leaving group because when it leaves you form a chloride ion. So, it is going to be a wonderful leaving group. So, you are going to reform the ketone and kick out the chlorine.

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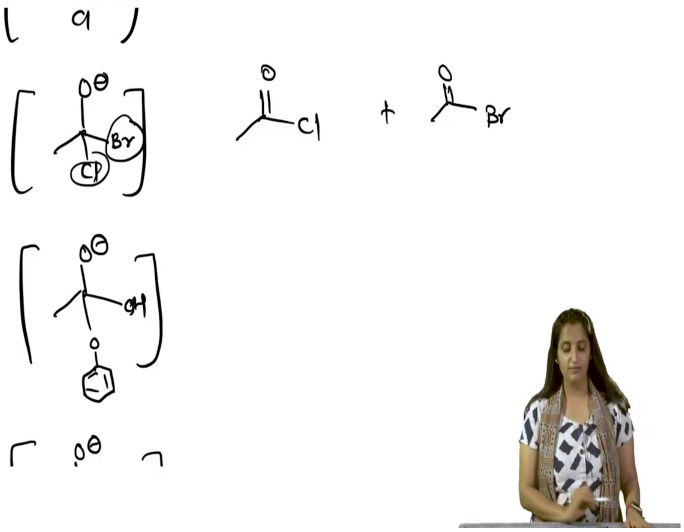

Now, the next one is a little tricky. You have bromine and chlorine as leaving groups. Between bromine and chlorine, bromine is a better leaving group than chlorine because bromine is going to leave as Br$^-$. Br$^-$ is more stable than chloride because bromides have a bigger size, they can stabilize the charge. Although, under reaction conditions both of them are going to pretty much behave very similarly.

So, it is very difficult to really selectively only kick out the bromine. You are going to have a mixture formed here. So, maybe you will form more of the acid chloride, and less of the acid bromide, but, depending on the reaction conditions of course, but more likely you are going to form a mixture and both of them are going to equally good leaving groups, I would call them under reaction conditions.

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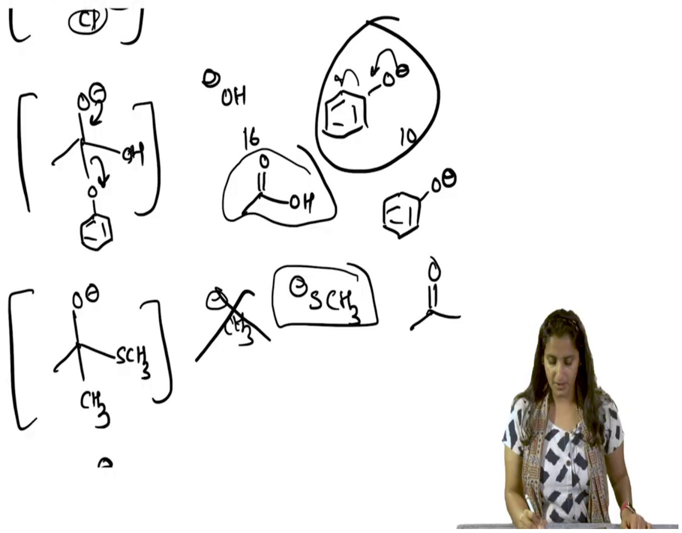

Now, in the next one, you have OH which is going to leave as hydroxide as a leaving group or you have phenoxide as the leaving group. Phenoxide has a corresponding pKaH of 10, hydroxide has a corresponding pKaH of 16. We know phenoxide is a better leaving group because this is resonance stabilized. So, you have a lot of resonance structure into the ring.

And thus, what we are going to see is, you are going to form, reform the carboxylic acid, and you are going to form the corresponding phenoxide as a leaving group. In fact, instead of the phenol, people try to use para-nitrophenol because para-nitrophenol is even more acidic than phenol. So, as a result of which para-nitro phenoxide is going to be much more better leaving group than phenoxide itself. And that is why you are going to see this particular carboxylic acid formed.

Let us move to the next one. Now, you have methyl as a leaving group, very bad leaving group, it is not going to leave. But the other leaving group possibility is this SCH_3^-. So, thioxide is a wonderful leaving group because this is going to have a pKaH very close to 7 to 9, so that is a wonderful leaving group. Sulphur because of its big size can really stabilize that negative charge better, and thus you are going to have that being kicked out reforming your ketone.

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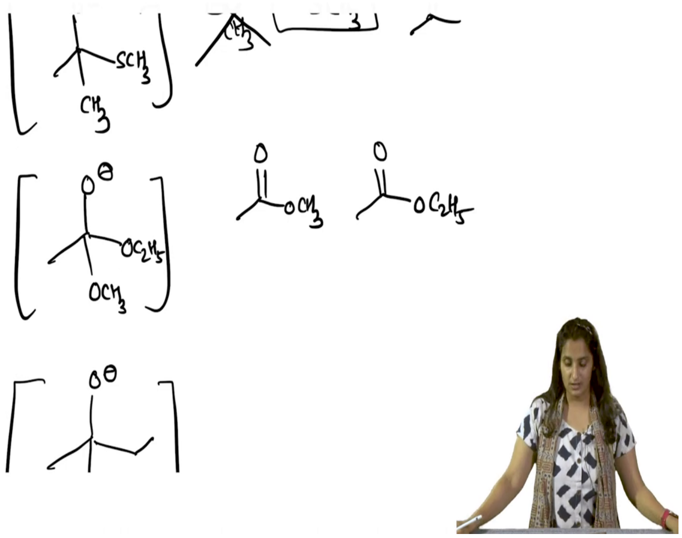

The next one, you have ethoxide versus methoxide as a leaving group. So, ideally, you would say that, you know, kind of between the both of them there is a pKa difference a little bit, but under reaction conditions you are going to form a mixture, it is very difficult to selectively kick out one of these two and only form a particular product.

So, for this one, because both of them have the corresponding pKaH very similar to 16, so one is 16 and I think one is 15 point something, so that is why you are going to form either this or this. Both of these are going to form as a mixture at the end of the reaction.

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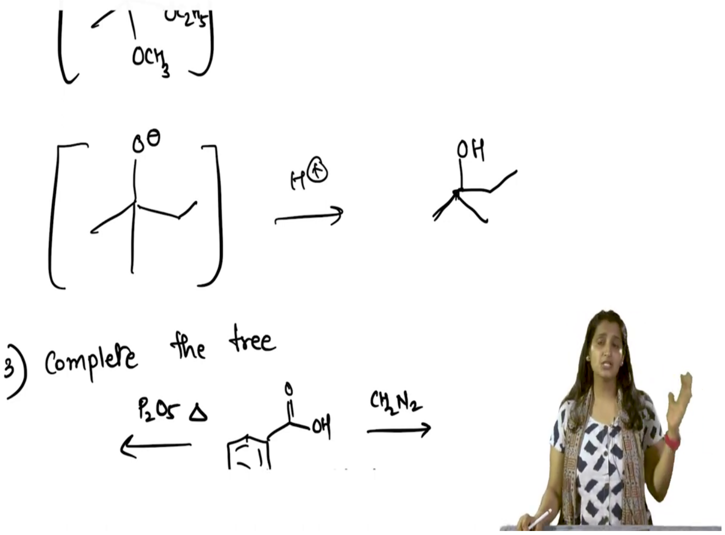

Let us go and have a look at the next one. Now, the next one here, they are all alkyl groups, so that is, really no way for this particular tetrahedral intermediate to collapse and thus as a result of which more likely it will grab a proton from the solvent, it will grab a proton from one of the reagents and it is going to form an alcohol at the end. And the reason is that alkyl groups are very, very bad leaving groups. The corresponding pKaH is close to 50, terrible leaving groups.

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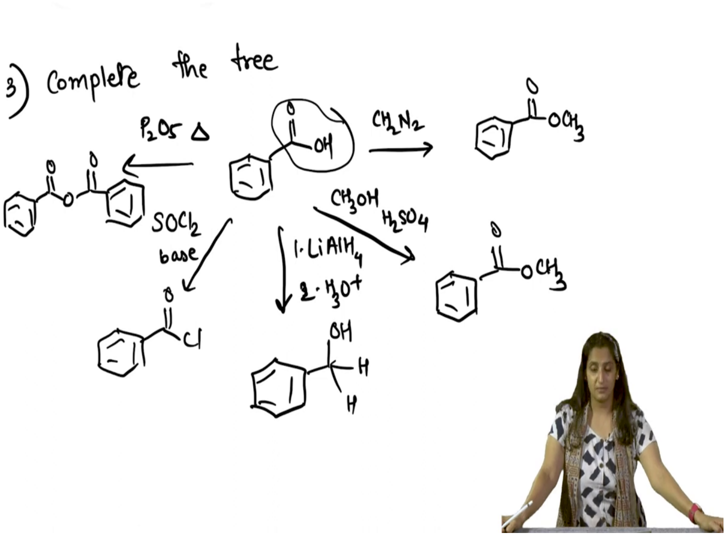

Now, the next question is, complete the reaction tree here. So, very simple reactions of carboxylic acids. I just thought of adding them here as a revision. So, you have a carboxylic acid and with diazomethane it is going to form the corresponding methyl ester. So, diazomethane is a wonderful reagent, very clean reagent. You get only one product very often because you have a wonderful, wonderful leaving group that is, the methyl ester.

Then with methanol and H_2SO_4, so these are the reaction conditions. So, acid, alcohol and mineral acid, this is Fischer esterification, so for Fischer esterification we are going to see a nice ester formation. Then we have $LiAlH_4$ and H_3O^+, so what are we going to have? We are going to have a complete reduction. And remember $LiAlH_4$ will not reduce the benzene ring.

So, it is going to reduce this carboxylic acid into the alcohol and the second step is always followed by H_3O^+, because you are going to have to hydrolyze that O^- that forms. So, that is how the step is written for reduction. First, we do the reduction, then H_3O^+.

With $SOCl_2$ and base, the carboxylic acid is going to form acid chloride, and with P_2O_5 and heat the carboxylic acid is going to form acid anhydride. So, that is the reaction tree, that is what we have completed. I just thought of adding this question here just to revise various reactions of carboxylic acids, different reactions that we have seen in this particular chapter. Let us go ahead.

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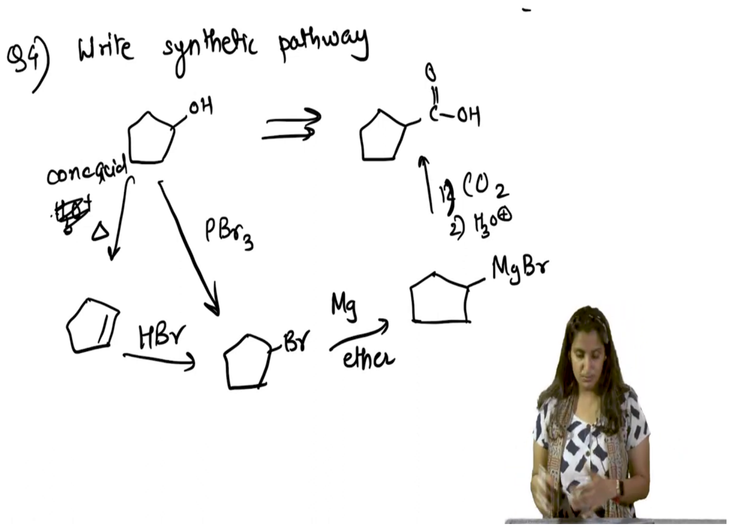

The next one is, write the synthetic pathway. So, herein we have the starting material, and we have to form the product, which is on the right-hand side. Now, to think about it, always compare the starting material and the end product. So, in the starting material I have 5 carbons, in the end product I have 6 carbons. Starting material is an alcohol, I need to end up with a carboxylic acid. So, all of these things you need to think before you start doing any retrosynthesis problem. This is a very easy retrosynthesis problem, we have included here.

Now, in order to add a carboxylic acid and also add a carbon functionality we know one reaction that works, which is reacting a Grignard and carbon dioxide. So, if we take CO_2, and if we start from the corresponding Grignard and react it with carbon dioxide in the first step and in the second step as H_3O^+, we are going to form the corresponding acid.

So, we need to form the Grignard. Now, the problem is converting an alcohol directly to a Grignard. It is not going to happen. So, we need to think of something that will form the Grignard. So, we also know how to form these Grignard's. We know that magnesium and ether, when kind of put it under anhydrous conditions, if we stir our alkyl bromides we can get there.

Now, how do I convert from here to here? So, this is a secondary alcohol, so it is possible to convert it to a bromide using PBr_3. Now, there are other ways to do this. We can either, first of all do dehydration, so H_3O^+ and heat, or concentrated acid and heat, sorry, let us do concentrated acid and heat. We form the corresponding alkene, and with that alkene we can add HBr to that in the second step to get to the bromide. So, that is the possible reaction pathway to get from this starting material to this product. Let us go ahead.

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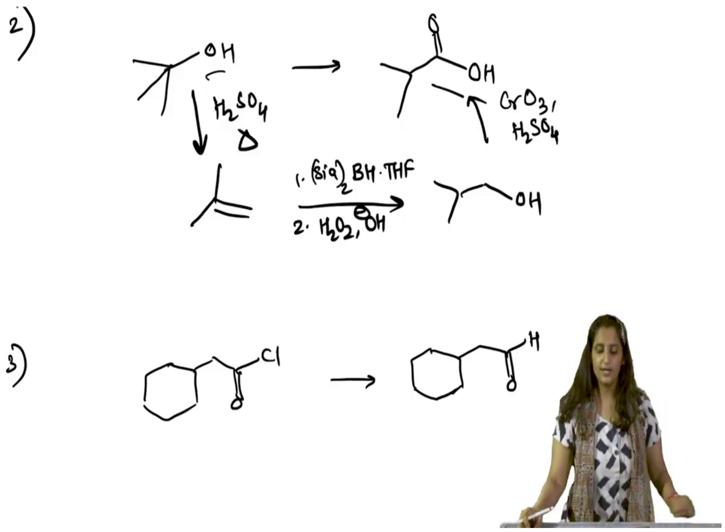

For the second one, what do we again observe? We have a starting material as alcohol, end product as acid. Although the number of carbon here now stays the same so I cannot use the method that I was using which was Grignard and CO_2 addition to form this. Now, to get here what we need to do is, I know that carboxylic acid can be formed if I can start from the corresponding alcohol. Simply, Jones reagent, CrO_3, H_2SO_4, or we can use $KMnO_4$, or some kind of oxidizing agent is going to give me starting from the alcohol, primary alcohol is going to give me a carboxylic acid.

So, now to get to this carboxylic acid we have formed the alcohol, but how do I convert this alcohol over here? In order to do that, we will do the same stuff again. We will try to create the alkene, and then from alkene to alcohol is easier. How do I do that? So, if I have this alkene, and I need to make the corresponding alcohol? I need to add the OH on the less substituted carbon. So, I need to do hydroboration and oxidation.

So, in the first step, we will do the hydroboration and then oxidation to form the corresponding alcohol. To get from this tertiary alcohol to this alkene, we can simply put it in H_2SO_4 and heat. Let us go ahead for the next question.

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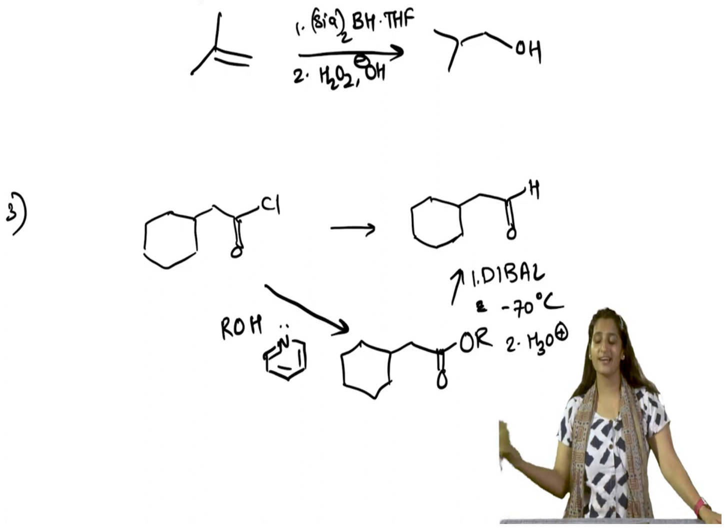

Now, we have acid chloride, and the end product is an aldehyde. Again, various ways to do that. So, remember that we know various ways to form aldehydes. So, one of the ways is to start from an alcohol and then we can use a milder oxidizing agent. The oxidizing agent in this case will be PCC, pyridinium chlorochromate, and that is going to form an aldehyde.

So, to get from acid chloride to the corresponding alcohol, it is very easy. We can first convert it to an acid, reduce it all the way and then get to the aldehyde. So, it is kind of a long way. So, instead of that what we can do is, we can start from an ester, any ester for that matter, and we can use DIBAL as our reagent, and the main condition that we have is, it has to be done at a really -70 °C or -78 °C to make sure that the aldehyde does not get converted to the alcohol. So, that is the first step. Second step is hydrolysis, and that is how we form esters to aldehydes. Now, from acid chlorides to esters, we know ways to form that. We can just simply react it with ROH and pyridine.

Now, remember, you can really use any alcohol here because it does not matter what the intermediate ester is. You are only interested in the starting material and the end product. So, pretty much most of the regular esters or simple esters would work here.

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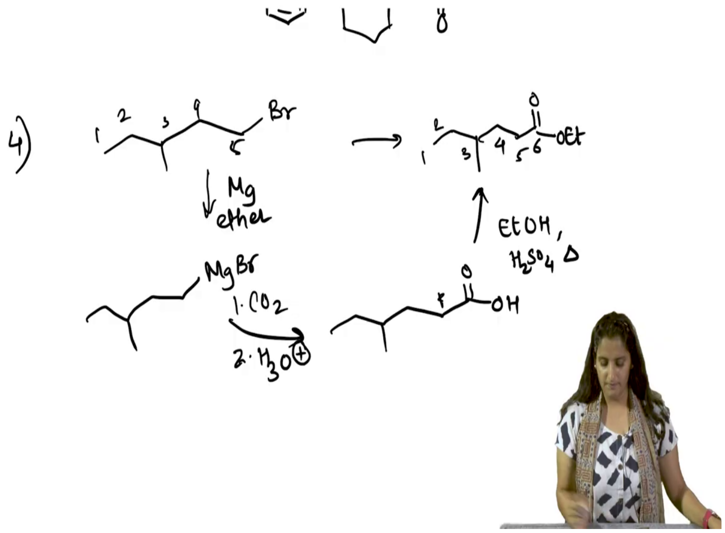

So, now let us look at this one next problem. How many carbons do we have? We have 1, 2, 3, 4, 5; 1, 2, 3, 4, 5, 6, good. So, now we have one more carbon added to start with. The other thing is that we have a starting bromide, which is very good because I know that if I have a bromide and if I make a Grignard, and react it with carbon dioxide I end up adding a carboxylic acid and, but the end product is not carboxylic acid, the end product is an ester. So, first we need to form the corresponding acid. So, in order to get here I am going to start from this acid and I am going to add ethanol and H_2SO_4 and heat it together to form the ester.

Now, from here to here, as I said, it is very easy. First, we form the Grignard. Remember, you can always think of an alternative way to get this synthesis done. There is more than one way for us to do this. So, what we are going to do is, we are going to start from here and then with CO_2 as the first step and the second step as H_3O^+, that is it. That is our synthesis right there.

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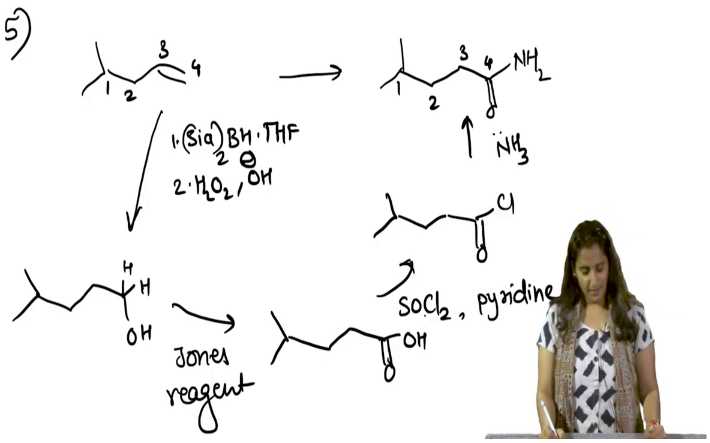

We have one more. Now, this one forms an amide. So, we have a starting alkene, and we are going to end up with an amide. How do we do that? Let us look at it. 1, 2, 3, 4; 1, 2, 3, 4. So, we are not adding a carbon, but we are forming an amide. Now, for amide synthesis, there are various ways of doing it. As we said, one of the good ways to do it is to start from an acid chloride or anhydride and react it with the corresponding amine. In this case, a simple ammonia reaction would do.

So, what I am going to do is retro synthetically we are going to start with an acid chloride and react it with ammonia. How do I form the acid chloride here? I know that I can use an acid with $SOCl_2$ and pyridine. How do I form the acid? Every time think backwards and every time think how do I get to this particular product?

So, I have this acid, what are the ways to get it? I can maybe start from an alcohol here, this is a primary alcohol so if I put it in Jones reagent, something really strong oxidizing agent, $KMnO_4$, or any kind of oxidizing agent, it is going to form that particular alcohol to acid, and then to form this particular alcohol, remember if you do H_3O^+ reaction, or if you do oxymercuration, it is going to form the OH on the more substituted carbon. So, we need to form it on the less substituted carbon. So, we will start with hydroboration, and reduction. So, that is the synthesis question.

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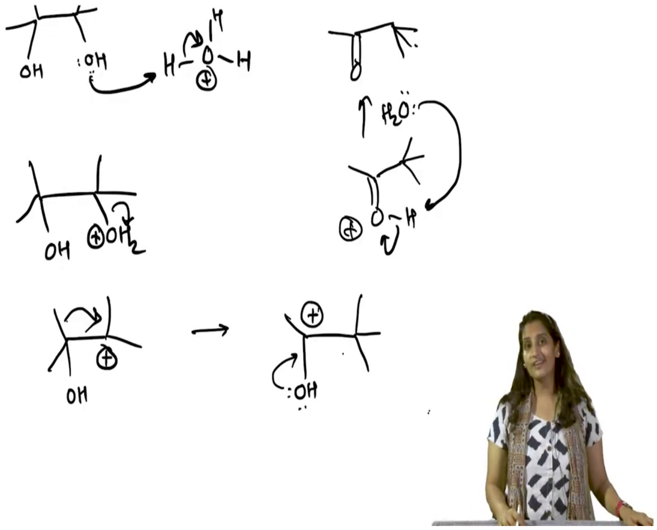

Now, we have one last remaining problem for this particular tutorial, which is a short mechanism problem. So, for this mechanism problem, what we have to do is, we need to think what will be the first step. Now, you have OH groups, which are alcoholic, this is a rather glycol molecule, and a diol, and then you have H_3O^+ present. So, the first step is going to be protonation.

So, in the next step, you have that water leaving as a leaving group because you are forming something very, very stable. It is a tertiary carbocation. Not only tertiary, it is being stabilized. You can do a methyl shift, and the methyl shift is going to be forming this particular carbocation.

Again, why is this more stable? Because this oxygen here can put its electrons down to the positive charge or the electrophilic center here forming a ketone. So, that is a really, really stabilizing interaction. And that is why you see a methyl shift happening, and that is not yet complete. You have a protonated ketone, and then in the final step water is going to come in. Remember, formation of that ketone is really, really stabilizing. So, that is the end product of this particular mechanism. Hope you had fun solving the tutorial. See you next week.