# Introductory Organic Chemistry
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## Lecture - 47
## Alcohols Part - 2

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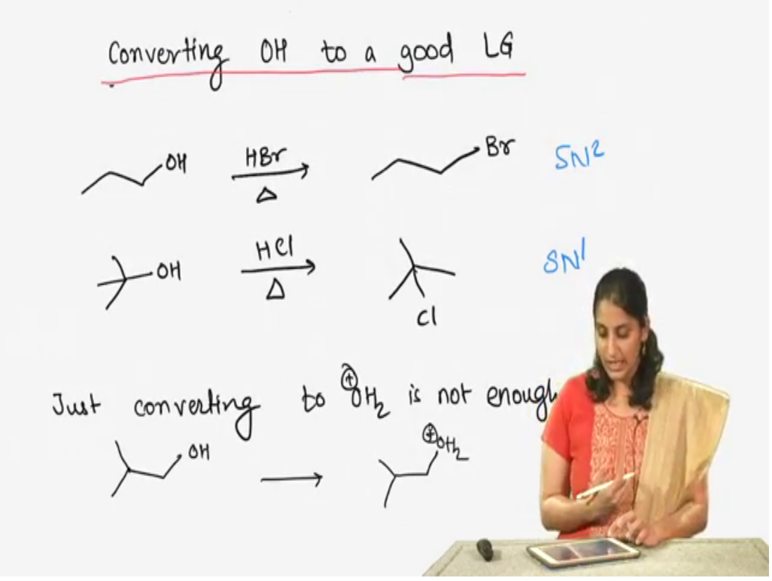

Hello. We have looked at some of the ways of converting the bad leaving group of an alcohol, that is, OH into a good leaving group. We have seen methods with heating with acid such as HBr, HCl, HI wherein the primary alcohols will react via $S_N2$ mechanism whereas, the tertiary alcohols will prefer reacting via $S_N1$ mechanism to create the corresponding alkyl halides, right. Now, this is one of the good ways to convert an OH to $OH_2^+$ which is a good leaving group which is then replaced by the incoming nucleophile in the reaction.

Now, one of the things that I want to mention is that just converting OH to $OH_2^+$ is not enough.

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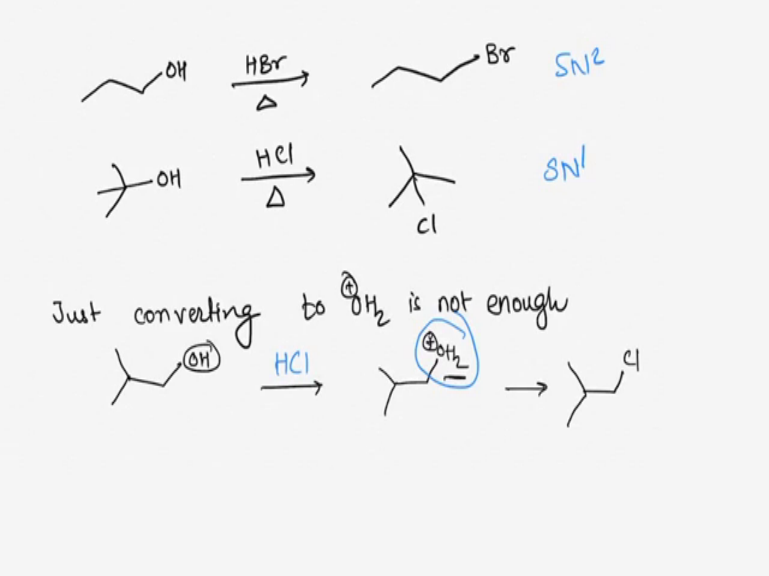

So, for example, here is the most common mistakes that I have seen in organic chemistry while students write their answers is that let's say that we have this alcohol here and we wish to do an E2 reaction on this compound such that I want to kick off this OH as a leaving group. However, this will not undergo E2 reaction right away because the incoming base instead of attacking the beta hydrogen will attack the alcohol hydrogen, right. Instead what we wish to do is we wish to convert it to a good leaving group and then perform the corresponding E2 reaction.

Now, most students would do something like this is they would convert this OH to $OH_2^+$ via reaction with a strong acid, right, but just converting it to $OH_2^+$ does not help. It needs to form the corresponding chloride and then you can do the E2 reaction. Most students think that converting OH to $OH_2^+$ is already made it into a good leaving group and then they attack it with a base. But think about it, as you attack it with a base the base is going to just grab the most acidic hydrogen.

And, in this case the most acidic hydrogen is that of the hydronium ion, right. So, in this case the base instead of attacking the beta hydrogen again would just deprotonate that $OH_2^+$. So, that's why we have to convert it all the way to alkyl halide and then do the corresponding chemistry that we want to do, okay.

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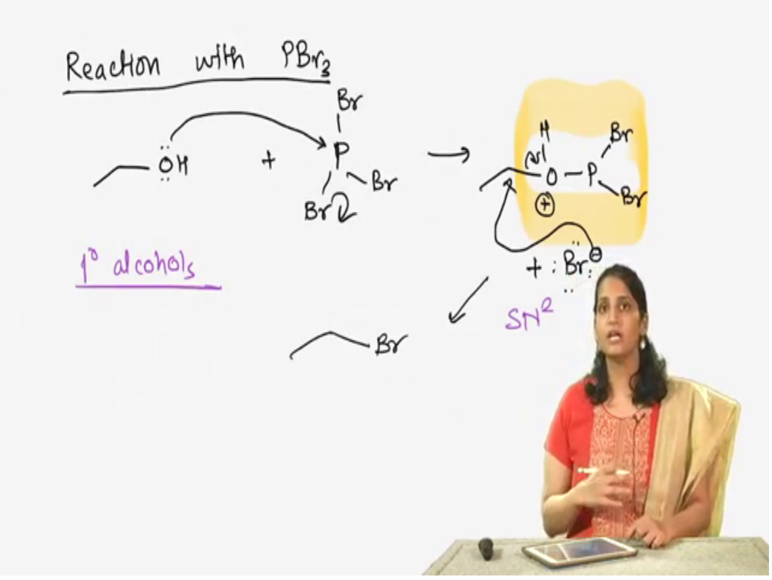

Now, let's look at some other ways which will help us convert the bad leaving group OH into a good leaving group. One of the reactions is reaction with phosphorous tribromide, okay; PBr$_3$ or phosphorus tribromide. Now, reaction with PBr$_3$ is mainly used to convert the bad leaving group OH of primary alcohols to the corresponding good leaving group that is the bromide, okay.

So now, let us look at a reaction between ethanol and PBr$_3$ and let's understand the mechanism, okay. So, in the first step what happens is this oxygen here is going to attack the phosphorus and kick off one of the bromides really creating a protonated dibromo phosphate group, okay. So, what do I mean by that? It's going to form, so, a protonated dibromo phosphate group is formed, okay, plus Br$^-$, right and in the next step this Br$^-$ that left is going to come back attack and kick off this leaving group.

Now, one thing to pay attention to is that this protonated dibromo phosphate group has now become a good leaving group because it's going to leave as a neutral molecule and what we form here is a bromide, right. Now, this reaction where the bromide attacks is an S$_N$2 reaction and that's why we use this kind of PBr$_3$ method only on primary alcohols because if it was a secondary alcohol or a tertiary alcohol then the attack becomes more and more difficult. In fact, tertiary alcohols will not allow that bromide to attack from the backside and convert the second step of the reaction. So, thus we use this PBr$_3$ method only for primary alcohols.

Okay, then what are some of the other methods that we use for secondary or tertiary alcohols? One of the most widely used reagents for conversion of primary or secondary alcohols to corresponding chloro alkanes is thionyl chloride or $SOCl_2$.

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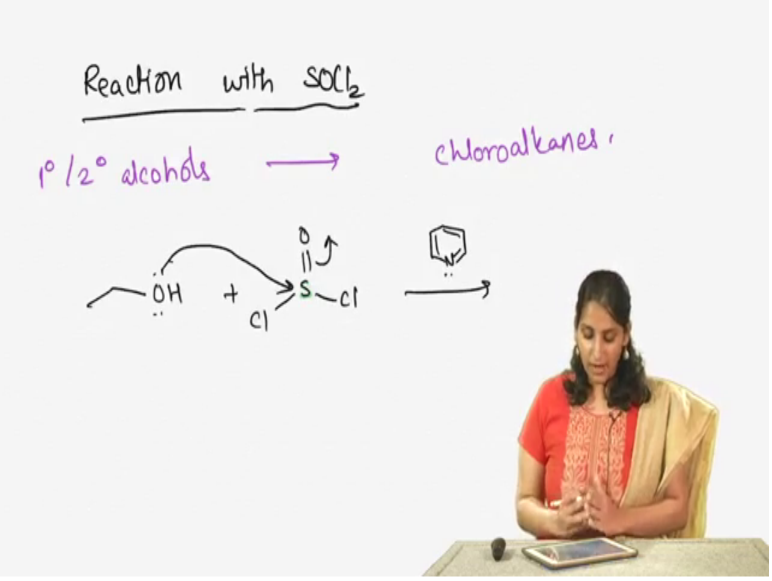

So, the next reaction that we are going to see is reaction with $SOCl_2$ and this is used for mainly primary and secondary alcohols to convert them to corresponding chloro alkanes, okay. So, now, let us look at this reaction. So, when we do this kind of reaction with $SOCl_2$ we also use some kind of a base typically it is pyridine which is used in order to do an acid-base reaction which is required in the course of the mechanism.

So, let's take ethanol and let's react it with $SOCl_2$ in presence of a nitrogen based base. So, this could be pyridine, this could be any kind of amine, okay. Now, one of the steps the first steps of the reaction involves such that the oxygen attacks here and kicks open the sulfur-oxygen double bond. Now, this kind of mechanism is somewhat unseen for us till now. So, I don't want to ponder over the mechanism much, but what I want to mention is that the bond comes back and kicks off a chloride, right, in order to form this molecule, okay.

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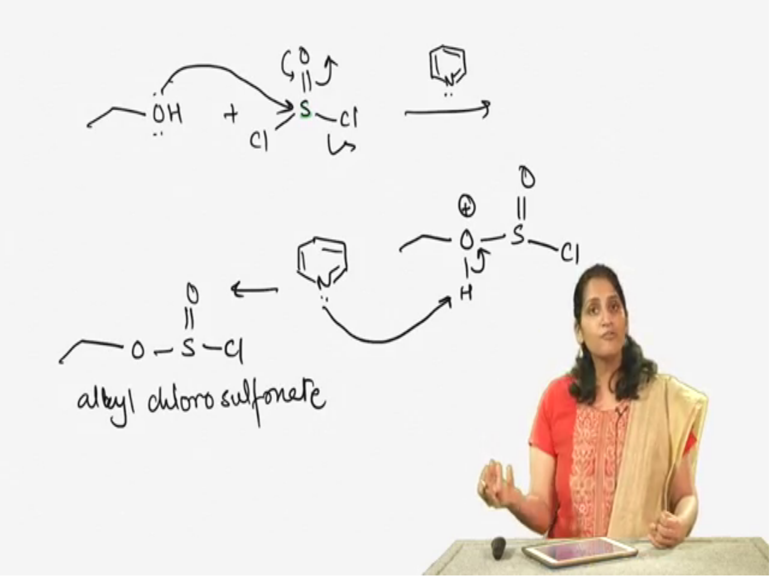

Now, as you can see the protonated alcohol here will react with the pyridine to form the product of the first step, okay. So, this is an alkyl chloro sulfonate, okay. Now, it is important to remember that the role of pyridine here is mainly to act as a base. Many a times you would also see that some textbooks would show the attack of pyridine on that alcohol and really creating an alkoxide to begin with which then reacts with thionyl chloride.

But, one thing to remember is that the reaction between alcohol and the corresponding pyridine is not very much forward driven. In fact, if you look at the pKa values you will see that the K equilibrium for this reaction is very-very low. So, the production of the corresponding alkoxide is very minimal; although it is minimal the amount of the alkoxide that is formed even a slight or a very small amount can act as a catalyst. So, that’s why pyridine here will act mainly as a base, but it will also act as a catalyst kind of driving the reaction forward, okay.

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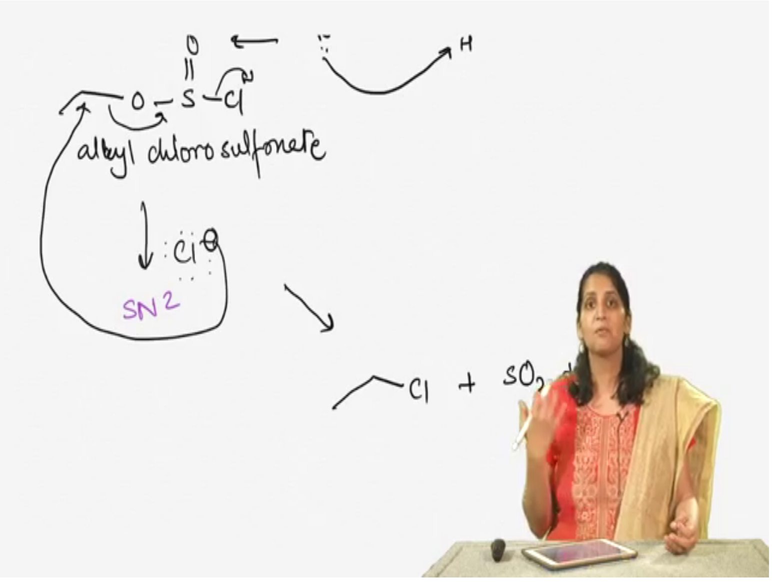

Now, let's proceed to the next step. Now, in the second step this alkyl chloro sulfonate if you see the chloro sulfonate group it has become a good leaving group and in the second step the chlorine that left in the first step will come back, attack this carbon and kick off the corresponding leaving group. Now, this leaving group does not leave just like this what in fact, it leaves as is $SO_2$ and HCl, okay. So, what in fact, it leaves as it leaves to form $SO_2$ as one of the byproducts and the chloride will then react with hydrogen again to form HCl as the other by product, okay.

So, this will form the corresponding products. Now, $SO_2$ being a gas is a very good leaving group. So, that's why this reaction proceeds with very good yields to form the corresponding chloro alkane. One thing to remember is that this second step where the chlorine attacks on that carbon is an $S_N2$ step. So, again we cannot do a tertiary alcohol and convert a tertiary alcohol using $SOCl_2$ because that second step of $S_N2$ will not be facilitated by a tertiary alcohol.

Now, another way to convert the bad leaving group of an OH to a good leaving group is a reaction with sulfonyl chloride to form something called as alkyl sulfonates and alkyl sulfonates, the sulfonates are very good leaving groups, okay.

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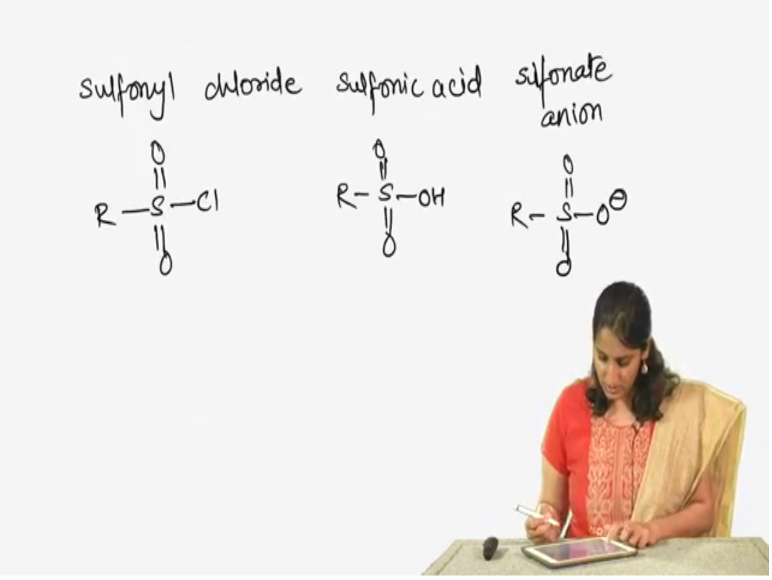

So, let me just go over the corresponding terminologies. A sulfonyl chloride is a molecule that looks like this, okay; whereas, a sulfonic acid which is a very strong acid you might have heard about this, is a molecule that looks like this. Now what we are going to be looking at is a sulfonate anion and the corresponding sulfonate anion will look like this, right. And, I just wanted to introduce these functional groups because we are going to be using them in the reaction with sulfonyl chlorides to form good leaving groups from alcohol. So, now, let's look at the reactions with sulfonyl chlorides, okay.

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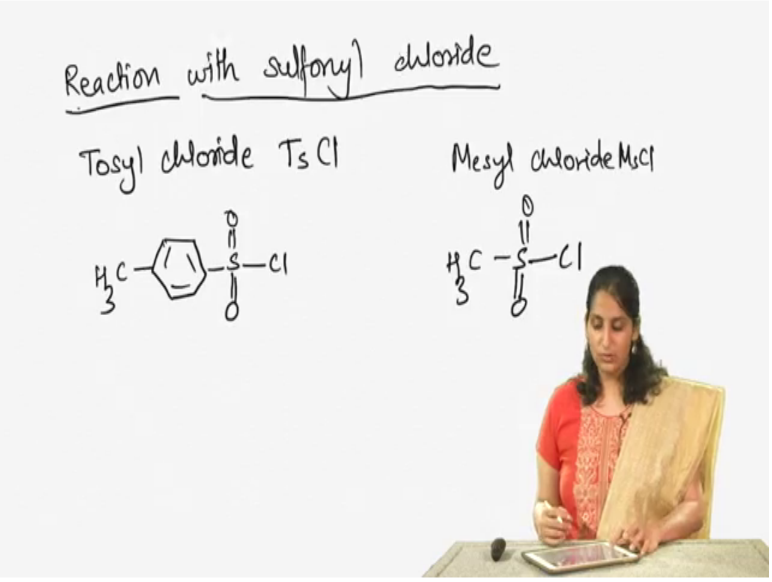

So, two of the most commonly used sulfonyl chlorides are one is para-toluene sulfonyl chloride, also called as tosyl chloride, okay. So, you will see it being written as tosyl chloride or even TsCl, okay; it's even abbreviated as TsCl. Let me draw the structure of para-toluene sulfonyl chloride here, okay. So, that is para-toluene sulfonyl chloride. Either this is used or the other most common used, the sulfonyl chloride is mesyl chloride, MsCl and the corresponding structure is this one, okay. So, it has a methyl group attached to the sulfur.

Now, let us look at the reaction of an alcohol with tosyl chloride and let us look at how the reaction proceeds.

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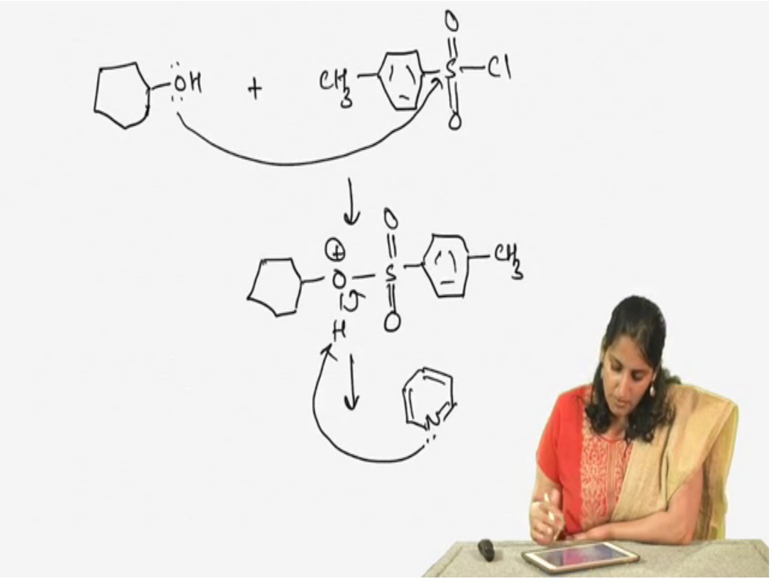

So, I am going to take cyclohexanol and I am going to react it with para-toluene sulfonyl chloride. Again, the first step I want to not elaborate much because the first steps mechanism is something that we have not seen till now. But, what you can imagine is that the lone pair of oxygen will go and attack here and kick open that sulfur-oxygen double bond and in turn later kick off that chlorine to form something like this.

Again, when we go over the reaction mechanisms of carbonyl compounds that time these kind of mechanisms would be clear to you, but for now you can imagine that the production of the following compound takes place and in this case also it is required that we add a good base such as pyridine into the reaction mixture. Now, the role of pyridine again here would be to grab that proton and make this compound stable.

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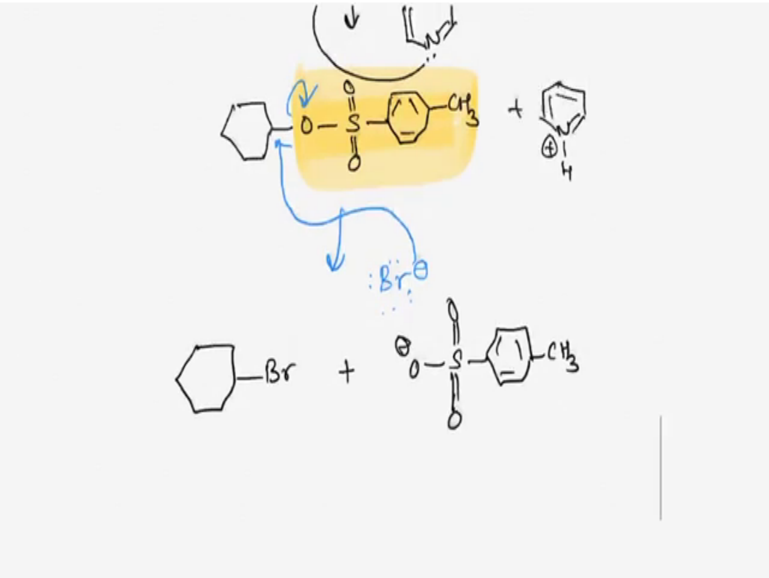

And, if you look at this particular compound here now the one that we have formed is such that now that alcohol is converted to a good leaving group. Why is this a good leaving group? So, when the good leaving group that we are currently talking about is in fact, this one, right and if you remember this sulfonate anion that we talked about, remember the sulfonate anion is quite stable because this has good number of resonance structures and I can draw as many resonance structures, there are 3 oxygen atoms, and you can draw the corresponding number of resonance structures such that the negative charge can resonate between those oxygens and the more the number of resonance structures the more stable is the molecule, right.

And, thus the following leaving group that we have created has now become a good leaving group; the sulfonate anion is a good leaving group. So, I can take this particular compound which is cyclohexyl para-toluene sulfonate, right and I can react it with any nucleophile of my choice. So, the second step here is such that I can take a nucleophile of my choice; so, let's take bromine as the nucleophile and the bromine here can do a reaction such that $S_N2$ type of reaction, such that you can attack on that carbon and kick it off as a leaving group really creating a good leaving group which is your sulfonate anion, right and the corresponding alkyl bromine.

One of the really key features that we want to focus on is this first step when the oxygen's lone pairs attacked on this sulfur the carbon-oxygen bond did not really take part in the reaction it was the oxygen that was attacking the sulfur, but the C-O bond does not get affected in the reaction and as a result if this particular carbon is a chiral carbon such that it bears a chiral center, the stereochemistry of that carbon does not get affected as the reaction's first step happens, okay. And, this is very important because what you will see is that it allows you to do some reactions that thionyl chloride would not have allowed. So, I am going to go over one such example in next few minutes.

The other advantage of using sulfonate esters is that a hydroxyl group which is a very poor leaving group it can be converted to a tosylate or a mesylate and you know both are really good leaving groups which can be readily displaced by various nucleophilic substitution reactions. So, you will see that amongst all the reactions that are used to convert the bad leaving group OH to a good leaving group, use of these sulfonate esters is one of the main key reactions that chemists like to use.

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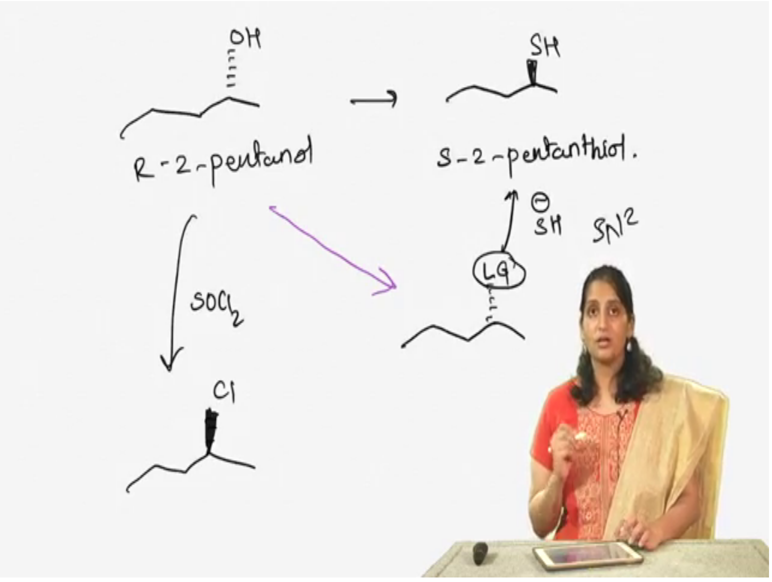

Now, I want to go over one example; herein I have R-2-pentanol with me and I want to convert it to S-2-pentanethiol, right. So, this has to be converted to the corresponding S-2-pentanethiol, okay. Now, of course, I will have to do a reaction such that I convert that OH from a bad leaving group to a good leaving group and once it is converted to a good leaving group the corresponding nucleophile $SH^-$ can come and attack in an $S_N2$ fashion, right.

So, I know a reaction such that a good leaving group here. So, I am just writing LG as a leaving group; a good leaving group in this particular situation can be replaced with $SH^-$ in an $S_N2$ kind of chemistry. Now, the question is how do I make that OH from a bad leaving group to a good leaving group, but still keep the chirality of the carbon the same?

Now, remember if I do a reaction with $SOCl_2$, right, I will create the corresponding chloride, but the chloride will have this particular stereochemistry. Why? Because the second step of reaction with $SOCl_2$ is when the chloride will attack from the backside and will kick off the leaving group, right. And thus the formation of the chloride will be opposite to that of the OH, right and in fact, although chlorine is a good leaving group the orientation or the stereochemistry is not like I wanted it to be and so, it would be beneficial to use either tosyl chloride or mesyl chloride over here.

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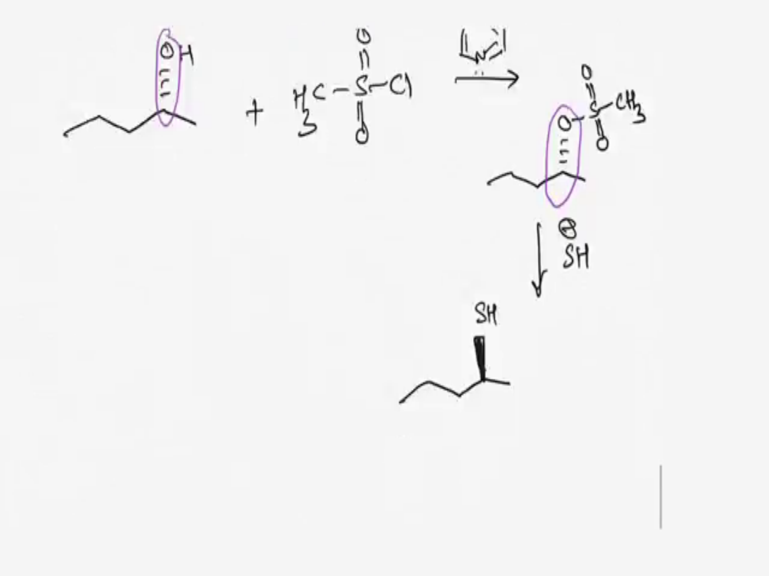

So, I am going to draw a reaction with mesyl chloride and pyridine. In the first step, I am going to convert it to the corresponding sulfonate ester and the key to this reaction is that to see that the stereochemistry at this center does not change as we use sulfonate esters. Once we are done with that then we can do a reaction with $SH^-$ to form the corresponding S-2-pentanethiol, right. So, it is important to choose the method wisely depending on what is the requirement, okay.

Now, I want to kind of go back and look at one of the reactions that we have seen for formation of an alcohol.

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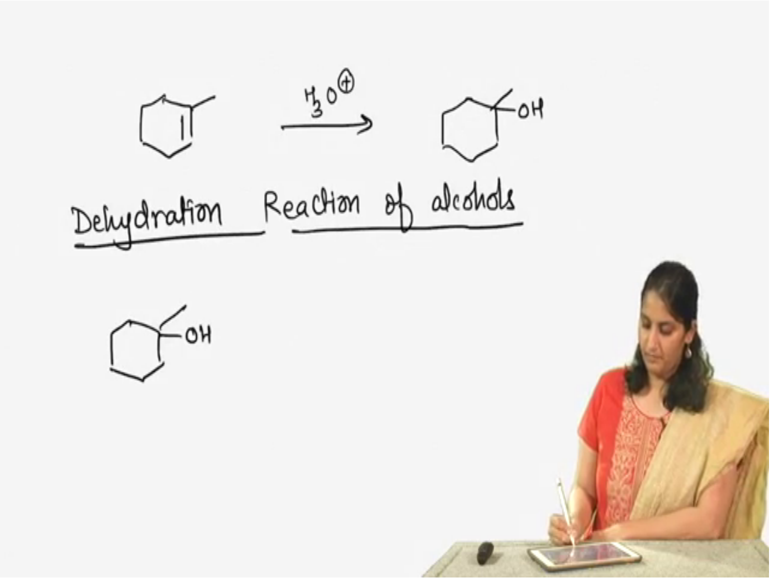

Let’s take an alkene and in presence of $H_3O^+$ we have said that it can form the corresponding alcohol, right. So, this is in fact, 1-methylcyclohexene and when it reacts with $H_3O^+$, it forms the corresponding tertiary alcohol. Now, I want to go over one of a very related reaction which is a dehydration reaction. So, in fact, this was a hydration reaction where we have added water, now, we are going to look at a reaction where we will dehydrate that alcohol to remove water molecule from that molecule, right.

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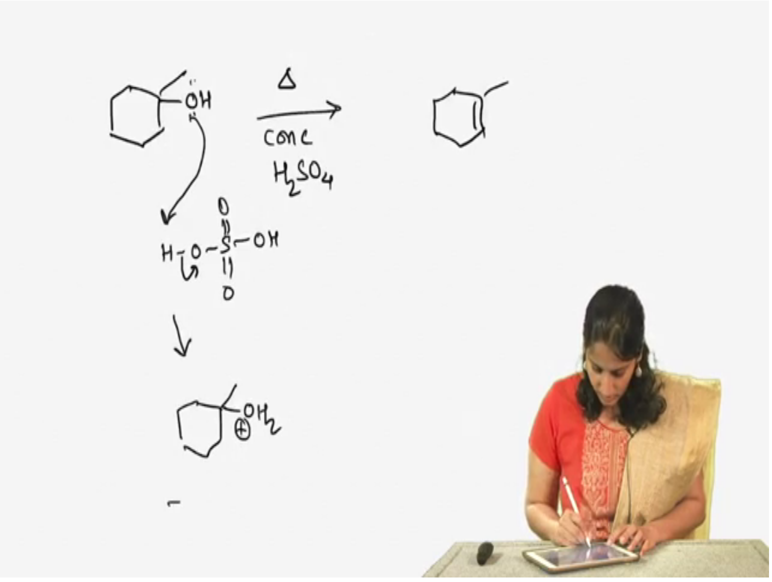

So, now, we will go over the dehydration chemistry, okay. Now, the reaction that we will see is dehydration reactions of alcohols and this is in fact, against the hydration reaction and so, I have taken 1-methylcyclohexanol and I am going to heat it with concentrated $H_2SO_4$ to give you 1-methylcyclohexene, okay. So, now, think about what could be the first step of the reaction and this is in fact, how I want students to really look at reaction mechanisms is to not really memorize them, but to think about what could happen if these two things are placed together.

So, I have a really concentrated sulfuric acid and we have alcohol present. We have seen that alcohols can really behave as weak acids or weak bases as well. So, in presence of a strong sulfuric acid it's going to behave as a weak base. And, it's going to attack the sulfuric acid. In turn what we will create is this protonated alcohol molecule and the corresponding conjugate base, right. Now, if you think about it you have a good leaving group, you are in acidic medium and you have a good leaving group on a tertiary carbon.

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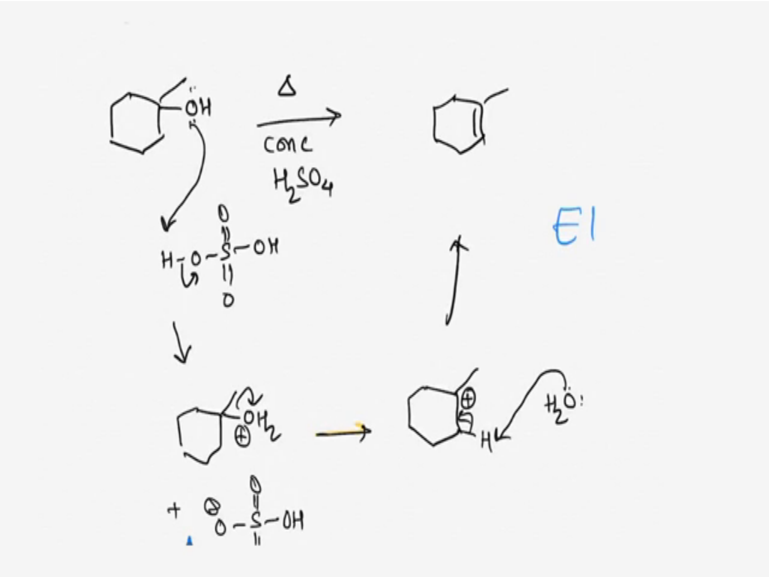

So, what happens next is this good leaving group is going to leave creating a carbocation and it's a tertiary carbocation so, it is stable enough. And, the next step of the reaction would be when a base in the reaction, now in this case we know we have that conjugate base present, but remember a sulfuric acid if it is 85 percent concentrated sulfuric acid it also has water molecules present in it.

So, in the next step water molecule which will act mainly as the base in this case is going to come attack that hydrogen and reform that carbon-carbon double bond, okay. This mechanism if you remember is very similar to elimination unimolecular mechanism, right because you have a good leaving group; the good leaving group leaves forming a carbocation and then a base comes in, grabs the beta hydrogen and forms the carbon-carbon double bond. So, this is E1 mechanism.

And, what you will see is that we have formed the carbon-carbon double bond starting from an alcohol. Now this same reaction could be worked backwards wherein we start from an alkene add $H_3O^+$ and it goes back to form the corresponding alcohol, right. So, depending on what is the concentration of $H_2SO_4$ the reaction could be driven towards one end or the other. If I use very dilute acid then alkenes will react with that dilute acid to give you alcohols; whereas, if you use strong concentrated acids in higher temperatures then the alcohol will get dehydrated to form the corresponding alkene.

Now, if you remember the reaction mechanism of converting an alkene to alcohol and if you see all the intermediates in the reaction, the alkene attacks a proton and forms a carbocation, right and later that carbocation gets attacked by water to form the protonated alcohol molecule which then will form the corresponding alcohol. So, going backwards from an alcohol to alkene, we are seeing the same kind of intermediates; going from alkene to alcohol the intermediates that you see they are the same while going backwards, right. So, in fact, this is called as the 'Principle of Microscopic Reversibility', okay.

So, according to this principle, the sequence of transition states and reactive intermediates, of course that is the mechanism for any reversible reaction, must be the same but in reverse order for the backward reaction as that of for the forward reaction. So, if the forward reaction you are forming intermediates 1, 2, while coming backwards you would form the intermediates in the sequence of 2 and 1, right. So, that is what the principle of microscopic reversibility states.

If we look at this reaction then primary alcohols are difficult to dehydrate. Again, because primary alcohols will require an E2 type of mechanism because they cannot really form a stable carbocation. So, tertiary alcohols can be dehydrated at a very low temperatures even 50 degrees or so, but as we go to secondary or primary alcohols we have to elevate the temperatures of the reactions so that to form the corresponding alkenes.