Introductory Organic Chemistry
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Lecture - 49
Ethers and Epoxides Part-1

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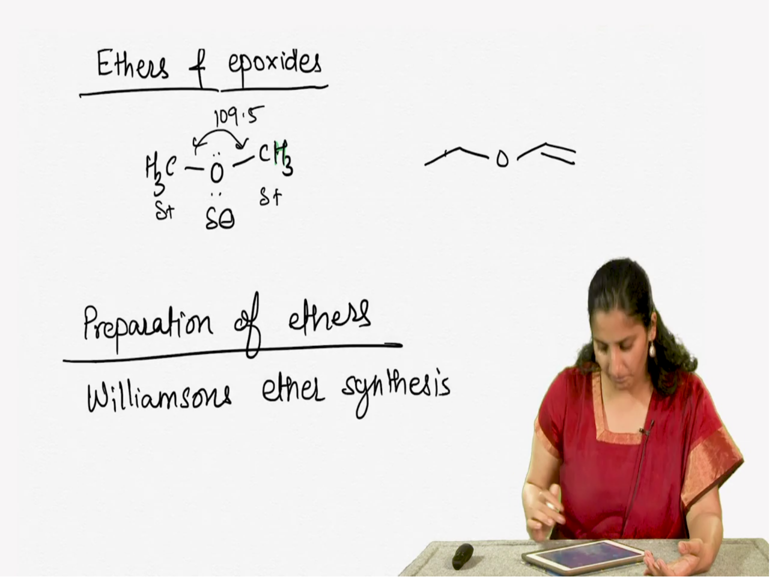

Today, we are going to talk about Ethers and Epoxides. Ethers are molecules in which an atom of oxygen is bonded to two carbon atoms. So, something like dimethyl ether, which is one of the simplest ethers that is possible, is where the oxygen is attached to 2 sp^3 hybridized carbons. Now, it may not be necessary that the oxygen is always attached to sp^3 hybridized carbons. In fact, it is possible that the oxygen is attached to sp^2 hybridized carbon.

So, for example, here we have ethyl vinyl ether which is this, in which one of the carbons is sp^2 hybridized and the other one is sp^3 hybridized. And as long as the oxygen is kind of sandwiched between these two carbon atoms, the compound can be called as an ether compound.

If we think about the bond angle in the case of ethers, the bond angle is very close to 109.5 degrees in the first case. So, C-O-C bond angle in ethers is typically 109 of course, depending on the geometry of the molecule it will change in; especially, when we talk about epoxides which are special kind of ethers the bond angle changes significantly, but we will get to epoxides later.

First let us look at a couple of properties of ethers and a couple of reactions of ethers. So, ethers are in general polar molecules, because oxygen is pulling electrons from both the carbons. So, the oxygen bears a partial negative; whereas, the carbons are both going to bear a partial positive, although it is not going to be a really distinct polar molecule as in the case of alcohols.

So, in the case of alcohols, the OH bond made it really polar, because the oxygen was highly negative and the hydrogen was highly positive really creating that polarity in the molecule. In this case, ethers are polar molecules; however, there are only weak dipole-dipole interactions that are existing between 2 ether molecules.

In the case of alcohols again going back, we saw that they have hydrogen bonding present. In the case of ethers, since there is no hydrogen present that can hydrogen bond. Why am I saying this, because if you think of this hydrogen for example, this hydrogen or the hydrogen on the alkyl groups are not really hydrogens capable of doing hydrogen bonding, because they are not the hydrogens that are attached to some electronegative atom, right. So, in the case of ethers, we see no hydrogen bonding and we see very weak dipole-dipole interactions, where in the delta plus charge on one carbon gets attracted towards delta negative charge on the oxygen of some other ether molecule.

So, this lack of hydrogen bonding really results into the lower boiling point of most ethers. In fact, ethers or some of the organic solvents, where the boiling points are really low. So, they are preferred for procedure such as extraction, wherein we are extracting natural products or we are extracting a compound of interest from the natural product or from animal or plant sources. Wherein, it’s easier to evaporate the solvent later on and what remains behind is the compound of interest. In such procedures ethers are used particularly because they are so easily evaporable and thus the boiling points of most ethers are much lower as compared to alcohols of similar molecular weight.

Now, the other property of ethers that results from this lack of hydrogen bonding is that they are not very miscible with water. If you think of alcohols ethanol, methanol, lower molecular weight alcohols of course, are miscible with water and compared to those ethers or not, that is because of this lack of hydrogen bonding. Ethers are generally used as industrial solvents and many organic synthesis reactions actually use ethers as a solvent and we are going to look at the reason why when we go over the reactions of ethers.

Now, let us go over some of the reactions to make ethers and this will be kind of revision of some of the reactions that we have seen before. So, one of the good ways to make an ether is a synthesis called as Williamson's ether synthesis. Although the name is quite fancy, the reaction is really S_N2 reaction. So, Williamson ether synthesis really involves nucleophilic attack on an alkyl halide and the nucleophile in this case is an alkoxide.

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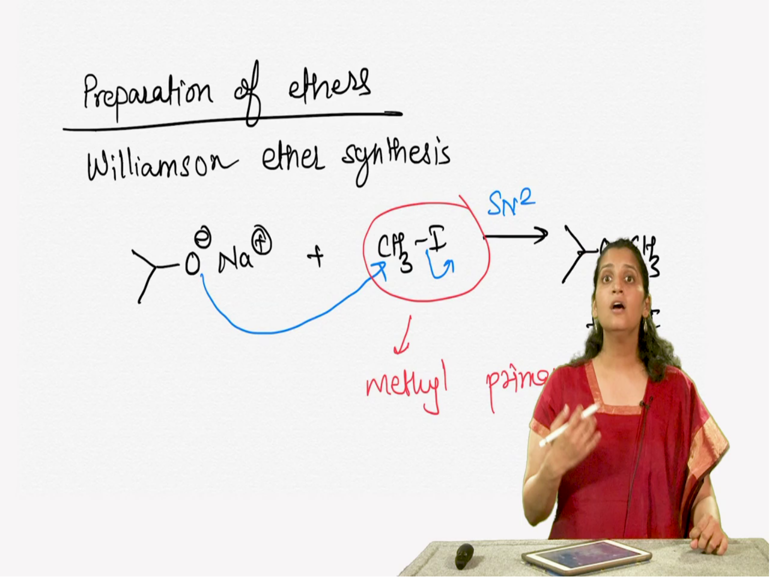

Preparation of ethers

Williamson ether synthesis

So, if I take an alkoxide and reacted with an alkyl halide, what you can really see or imagine here is that I have a methyl alkyl halide and an alkoxide. It's a good nucleophile so, what can happen is S_N2 type of chemistry where the oxygen with its lone pair is going to attack the carbon, kickoff the leaving group and really do S_N2 reaction to form the final product which is an ether, right. This is isopropyl methyl ether and the byproduct will be sodium iodide.

Now, when we are designing Williamson's ether synthesis, we have to pay attention to the fact that we are doing an S_N2 reaction. So, we have to control our reactants such that we have to minimize the competing reaction, which is the beta elimination reaction and kind of favor this nucleophilic substitution reaction such that we produce the ether in excess, right.

So, what are the ways in which we can facilitate the production of this final product with the highest yield? So, one of the things we have to remember that since it's S_N2 reaction, the alkyl halide that we use has to be either methyl or primary such that, it allows for the substitution product to form in excess. If it is a secondary carbon then, it may really result into formation of the elimination product in excess and will not favor the production of ether.

And as you can imagine for a tertiary alkyl halide this particular reaction will fail altogether, because tertiary alkyl halide will not perform S_N2 reaction, right. Similarly, the alkoxide here has to be such that it will prefer forming a substitution reaction.

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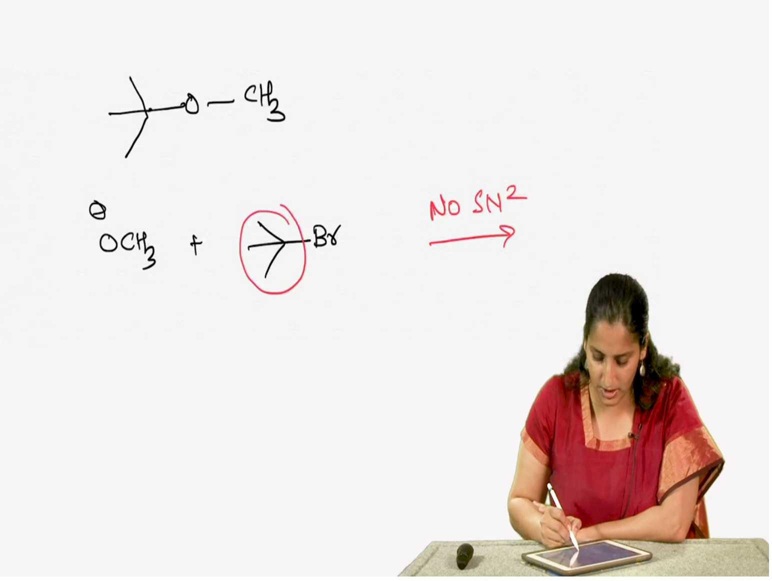

So, for example, if my aim is to make tertiary butyl methyl ether, then I cannot start with methoxide and attack it on tertiary butyl bromide, because this kind of reaction mechanism will fail, this will not do S_N2 reaction, right, because this is a tertiary alkyl halide. And so, for the formation of this methyl tertiary butyl ether or MTBE, what you need to really do is? We need to start with tertiary butoxide and react it with methyl bromide and then this S_N2 reaction will be highly favored resulting into the product that we really see.

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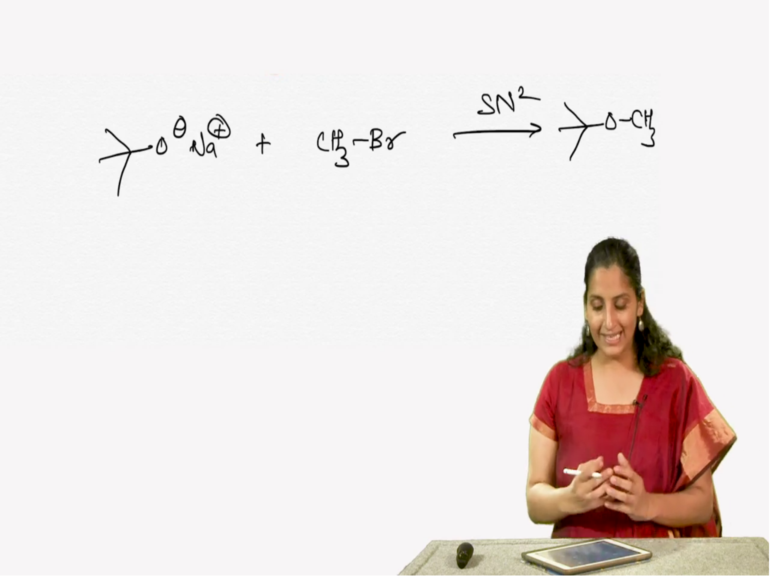

So, when designing the Williamsons ether synthesis, we have to pay attention to the final product and design it accordingly. The other way to synthesize an ether, and this is one of the most commercially available pathway to ethers or industrial scale pathway to ethers is actually acid catalyzed dehydration of primary alcohols.

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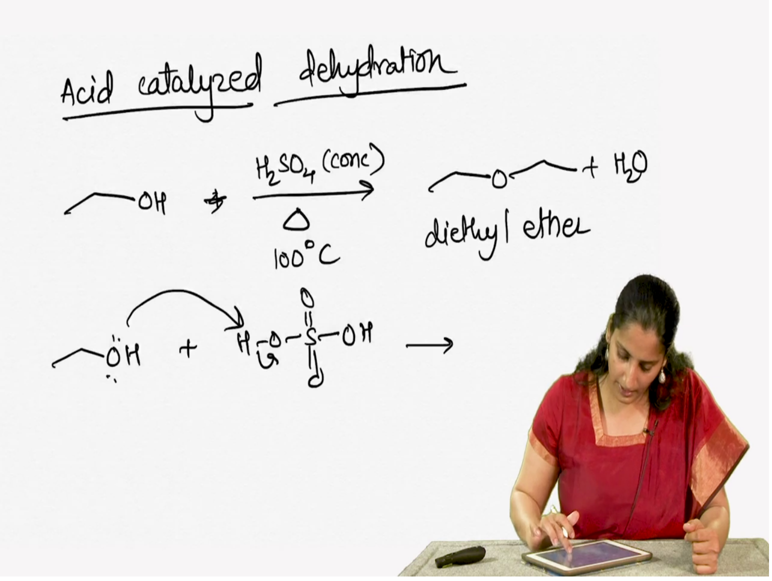

So, let’s take a primary alcohol and let’s perform the acid catalyzed dehydration to really form the ether. So, in this case, we are going to put it in H_2SO_4 concentrated and heat it up at around 100 degree centigrade or more than 100 degree centigrade. And what it does is, it results into the formation of corresponding diethyl ether.

So, how does this reaction take place? Can you imagine? Of course, this is similar to a reaction of alcohols we have seen before, wherein in the presence of an acid, the first step is the alcohol gets protonated, because alcohols are weak bases. So, they can attack strong acids and get protonated.

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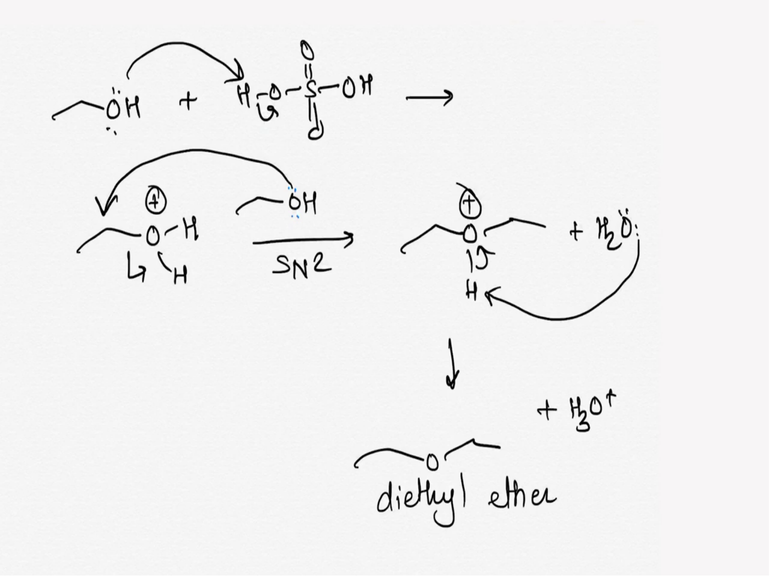

And in the first step, we form this hydronium ion. And then what happens is another molecule of ethanol is going to come and with the lone pair of this oxygen it’s going to attack this carbon and kick out water as a leaving group. So, this is again S_N2 mechanism and what we form here is the protonated ether as an intermediate step. Which of course, will be later deprotonated forming the final product which is diethyl ether.

So, moral of the story is this reaction will work well for primary alcohols, but may not really work well for secondary or tertiary alcohols especially because it cannot do S_N2 reaction. So, that’s why industrially you will see that the ethers that are produced via this method are mainly started from primary alcohols.

In the case of tertiary alcohols the reaction will work, but it will follow S_N1 pathway. And especially when it comes to S_N1 pathways since you are creating the carbocation, it is susceptible to rearrangement. So, industrially, this kind of reactions are more favored for a primary alcohol.

Another way of creating ethers is something that we have seen in the chapter of alkenes.

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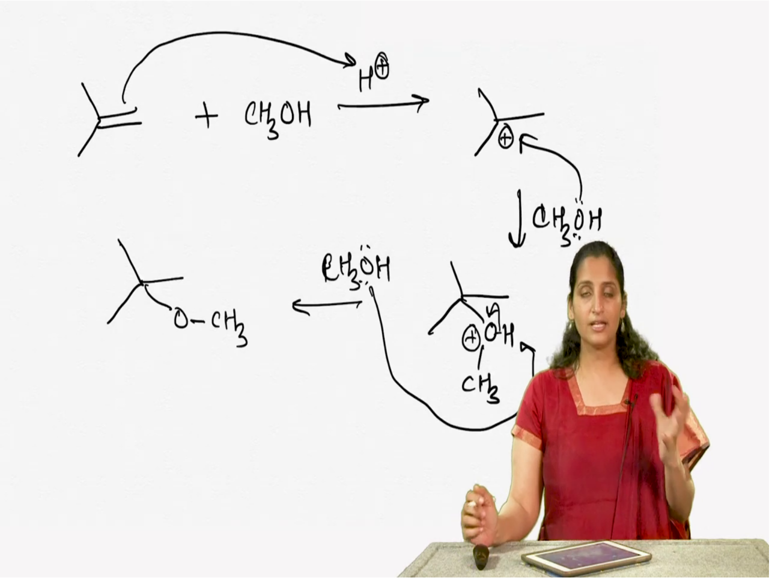

So, let’s take an alkene and let’s react it with an alcohol under acidic conditions. So, I am going to just say H^+. Now in the first step as you can imagine the double bond will attack the proton and in fact, the methanol can also get protonated, but the protonated methanol is also a great acid for the alkene to attack on.

So, the first step really results into the formation of a carbocation and we will form the more stable tertiary carbocation here, which will later be attacked by a molecule of methanol, right. And of course, the reaction will proceed forward, where in one more molecule of methanol will come along and form the final ether.

So, this reaction is nothing but electrophilic addition of methanol on the corresponding carbon-carbon double bond. In fact, one of the reactions that we have seen for alkenes which was oxymercuration; if instead of water, if we use any alcohol as the solvent for that reaction then instead of forming an alcohol at the end of oxymercuration reaction we actually end up with an ether. So, most of the reactions that we have seen where an alcohol results as the end product, if we change the solvent from water to methanol or ethanol or any low molecular weight alcohol, it actually changes to the formation of ether.

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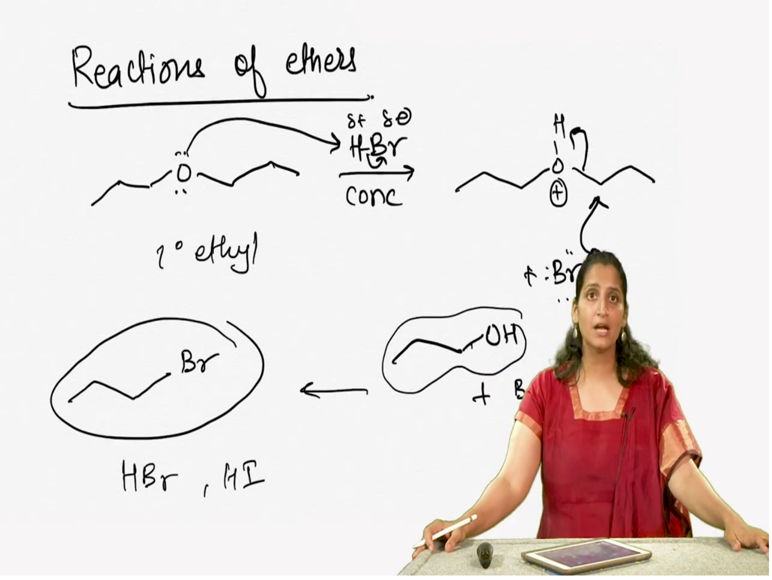

Now, let us look at the reactions of ethers. Now, ethers are very similar to hydrocarbons actually when it comes to their reactivity. They do not react a whole lot and they do not react especially with oxidizing agents; they are stable towards even really strong bases and exceptions to this are some of the really reactive ethers. But most ethers for that matter will not react with most weak acids or even strong bases, oxidizing agents and so, what happens is, Ethers are actually great solvents. Because they are good at solubilizing various compounds and they do not really take part in the chemical reaction, you will see that ethers are one of the most excellent solvents to carry out many organic reactions. So, one of the main use of ethers is actually their use as a solvent.

However, there are a few reactions of ether and these are the reactions with really strong acids. So, if you take any dialkyl ether and if we put it in a really strong or concentrated hydroiodic acid or hydrobromic acid, then what happens is, the ether is going to cleave or the ether is going to split into two parts and that reaction is called as cleavage of dialkyl ethers. And in fact, let's look at one of the reactions. I am going to take propyl-propyl ether or Dipropyl ether and we are going to react it with concentrated HBr, okay.

So, now, let's try to predict what this reaction will result into? One of the ways to think about is that where is the nucleophile and where is the electrophile? Now, the nucleophile here is going to be the oxygen because, the oxygen has electrons, it's going to be attracted towards a positive charge and the positive charge that is present here is on the hydrogen.

So, the first step of course, will be such that the ether gets protonated and this kind of acid base reaction is one of the main fastest happening reactions in organic chemistry as we have seen in the chapters of acids and bases. So, in the first step we are going to form this protonated ether. Now, bromide is going to be leaving as a leaving group in this reaction. Now, what happens is, the bromide is going to come back and attack here and kick it out as a leaving group, okay.

What happens next is that you have now formed bromopropane and propanol, but if you really think about it, you are in concentrated HBr solution and we have just seen a reaction wherein the alcohols in presence of concentrated HBr also result into formation of the corresponding alkyl bromides. So, in all the final product that will be isolated from this reaction is bromopropane. So, when we are using really concentrated solutions like these, what happens is you end up with the formation of the corresponding haloalkane as the final product.

Now, HBr and HI will do this kind of chemistry wherein they split the ethers into two parts and convert it to the corresponding haloalkanes; whereas, HCl is not really effective for such kind of reaction, the reason being that chloride is not a great nucleophile especially in water as compared to bromide or iodide, that we have seen. Because of the big size of bromide or the big size of iodide, they are really great nucleophiles, because they have that polarizability property. And as compared to that chloride does not effectively attack in the nucleophilic reaction. So, what we see is that HBr and HI are great acids for this kind of reaction.

Now, this was for a primary ether in the sense that both the carbons attached to the oxygen were primary carbons, but if we look at a tertiary or an allylic or a benzylic ether, then the reaction mechanism changes.

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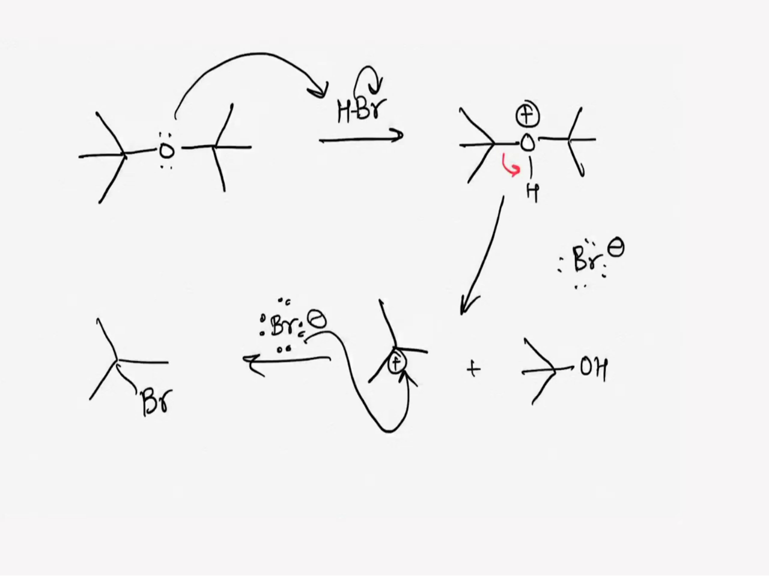

So, what we can now do is the reaction. If I take this ether and I react it with HBr, again the first step will be protonating the oxygen, right creating the first step of the synthesis, which is an acid-base step. Now, the bromide cannot really come and attack because, the bromide has to attack in an S_N2 manner. What we have are two tertiary carbons? So, the bromide cannot attack in an S_N2 manner.

In fact, what happens next is you have an S_N1 like reaction, where in one of the tertiary butyl carbocations will be formed and you are going to have the alcohol as a leaving group. And then, the bromide will attack forming the final product which is tertiary butyl bromide and tertiary butanol.

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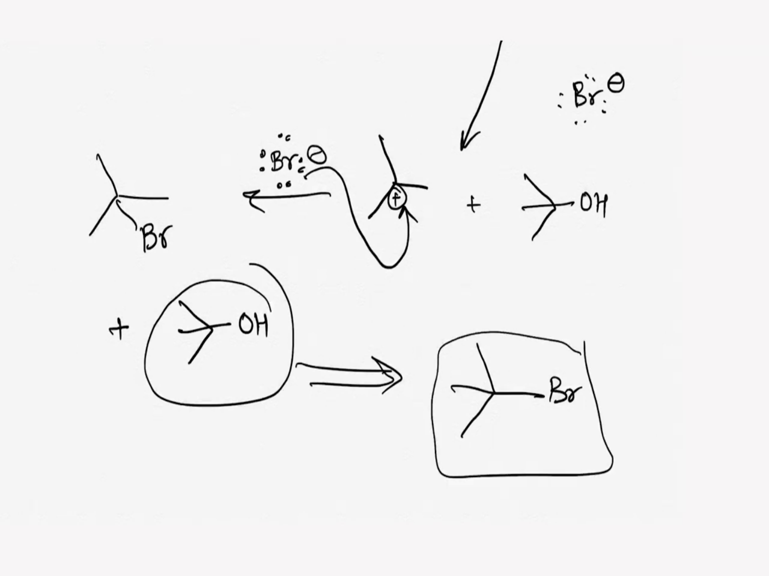

But of course, if you keep on doing this reaction, then the tertiary butanol will also over time convert to tertiary butyl bromide. So, it all depends on how concentrated the HBr is as well as what is the reaction temperature, but at higher temperature and concentrated HBr conditions, you will form the corresponding tertiary butyl bromide in excess. So, that was the reactions of ether that I wanted to discuss.

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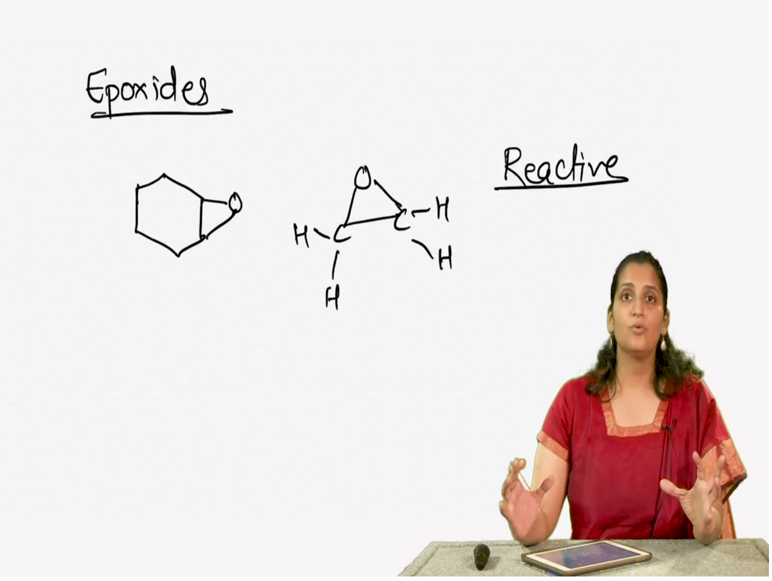

Now, let us look at some special kind of ethers and these are really epoxides. So, epoxides are cyclic ethers. And I am going to draw some epoxides here, right. And they are cyclic because, you have a 3-membered ring of the epoxide form, such that the oxygen is bonded to two other carbons. And this ring is very close to an equilateral triangle in geometry. So, it has a bond angle of around 60 degree and as you can imagine this is very close to cyclopropane, right. And we had seen that cyclopropane ring because, of its angles being very deviated from 109 degrees makes it really strained and in fact, cyclopropane ring performs reactions in which it opens up to really relieve that angle strain.

And in the case of epoxides as well, you will see reactions which are mainly such that the epoxide ring will pop open and it will release that angle strain because, it wants to achieve that closer to 109.5 degrees as the bond angle. And that makes epoxides as one of the most reactive functional groups as compared to most other ethers or even other functional groups. And so, these are one of the main things that, we want to remember is that they are reactive because, they want to release that angle strain that is present in the molecule.

Let us look at some of the reactions to prepare an epoxide. And in order to show the next reaction, I want to actually go back to one of the reactions of alkenes that we had seen, which was the halohydrin formation.

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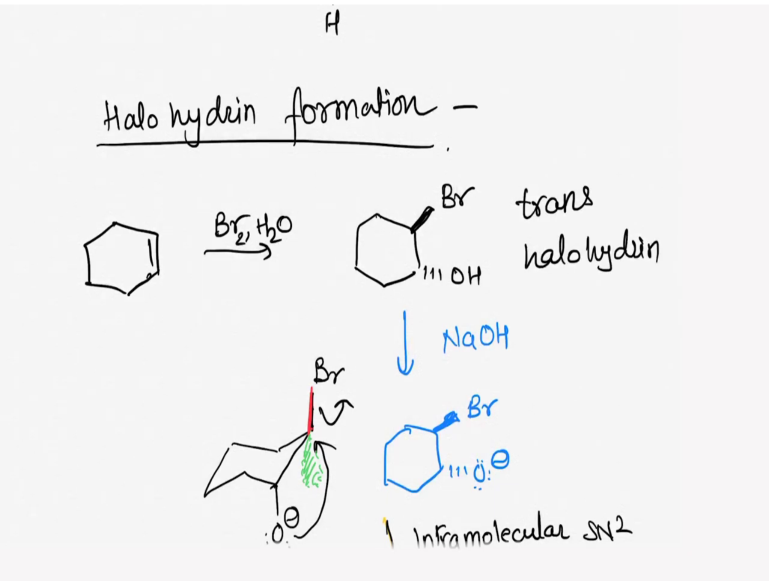

Now, remember the reaction, where we started with an alkene and we reacted with bromine and water to really form halohydrin in which the bromine and the OH were anti to each other. So, that was the product that was formed. Now, starting from the halohydrin or the corresponding halohydrin, we can actually make an epoxide. So, this is done by taking the halohydrin and really reacting it with a strong base.

So, let's take the halohydrin and let's react it with a strong base like NaOH. Now, the base is going to look for the most acidic proton. And in this case it's going to look for that proton on that oxygen, because that is the most acidic proton, and really result into the formation of the corresponding alkoxide, right.

Now, if you see the geometry of this alkoxide and if we draw the chair formation for example, we have the bromine going up and this oxygen going down, right. Because, they are such that one is coming towards you one is going away from you. So, one of the ways to represent it on the chair form is this. Now, what happens is that the oxygen will put its electrons on that carbon and kick out the bromine. So, this is something like an intramolecular S_N2 reaction, right so, what we form here is this.

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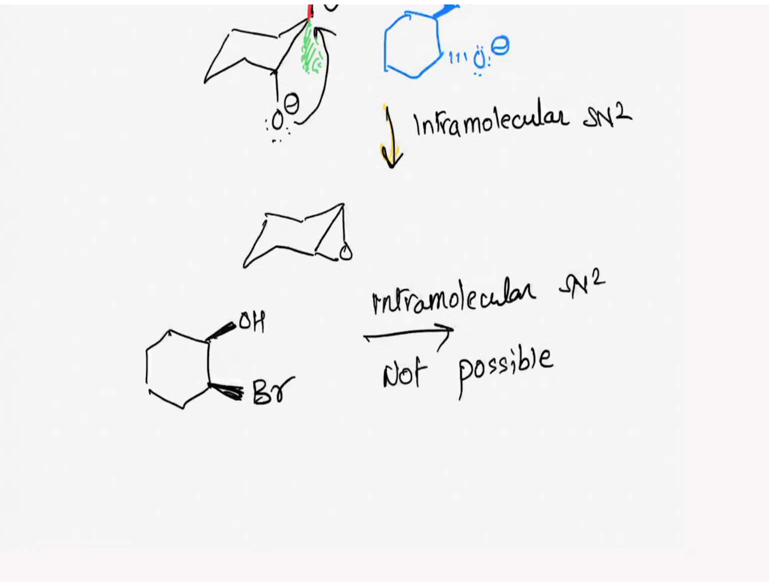

Now, to think about it, intramolecular S_N2 reactions, it is possible for this molecule to undergo such kind of reaction is that because, the electrons of the oxygen are situated such that they can easily donate into the anti-bonding molecular orbital of the carbon-bromine bond.

So, since the bonding molecular orbital is here going towards the bromine, the anti-bonding molecular orbital of the carbon-bromine bond is actually situated right here. And it is easier for the oxygen to put its electrons into that anti-bonding molecular orbital, really breaking the bond between carbon and bromine. So, not all halohydrins can really show this kind of geometry in fact, syn halohydrins, wherein we start with this molecule.

Let's say if both the OH and bromine were coming towards you. Then this molecule will not show intramolecular S_N2 reaction. And that is because, it cannot achieve that conformation where in the oxygen can put electrons in the anti-bonding molecular orbital of the carbon-bromine bond; in none of the chair conformations you can actually see that. And so, it is important that we start with a trans halohydrin.

And if you think about it this follows the rules of S_N2 reaction, where in the nucleophile which is the oxygen is attacking from the backside of the carbon-bromine bond or the carbon-leaving group bond, and really causes the inversion of configuration at the site of substitution. So, this is nothing, but intramolecular S_N2 just that it is happening in the same molecule. So, it looks a little different, but it follows all the rules of S_N2 reaction that we have seen.

And in fact, to think about it in a little different manner this is nothing, but an intramolecular version of the Williamson ether synthesis, because Williamson ether synthesis required you to start with an alkoxide and attack it on an alkyl halide. Just that in this case, it is happening intramolecularly and that's why this can be also called as the different version of Williamson ether synthesis.

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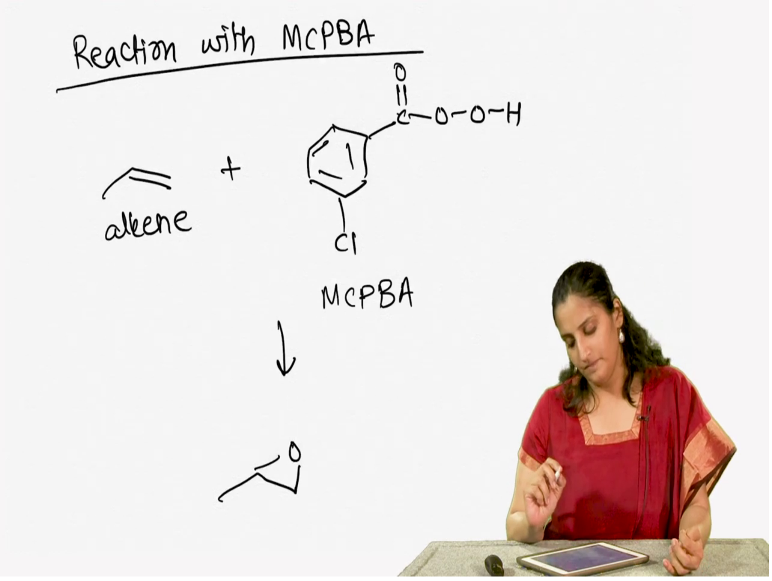

Another reaction to form an epoxide is a reagent called as meta-chloroperbenzoic acid, okay. And this kind of reaction starts with alkenes. So, any alkene can take part in this reaction and reacted with meta-chloroperbenzoic acid. Now, per acids have a functional group of C=OOOH, okay. So, this is MCPBA or meta-chloroperbenzoic acid and when it reacts with an alkene what it results into the formation of is the corresponding epoxide. Now, I don't want to go over the mechanism of this one, but you can remember MCPBA as a reagent to form an epoxide.