Essentials of Oxidation, Reduction and C-C Bond Formation
Application in Organic Synthesis
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Lecture -07
Mechanistic and Stereochemical Aspects of Mislow-Evans Rearrangement and Synthetic Applications

Hello everyone I hope that you had a chance to go through the last class where we discussed sulfoxide sulfenate rearrangement which is also known as Mislow-Evans rearrangement. It is a concerted process which involves 2,3 sigmatropic rearrangement.

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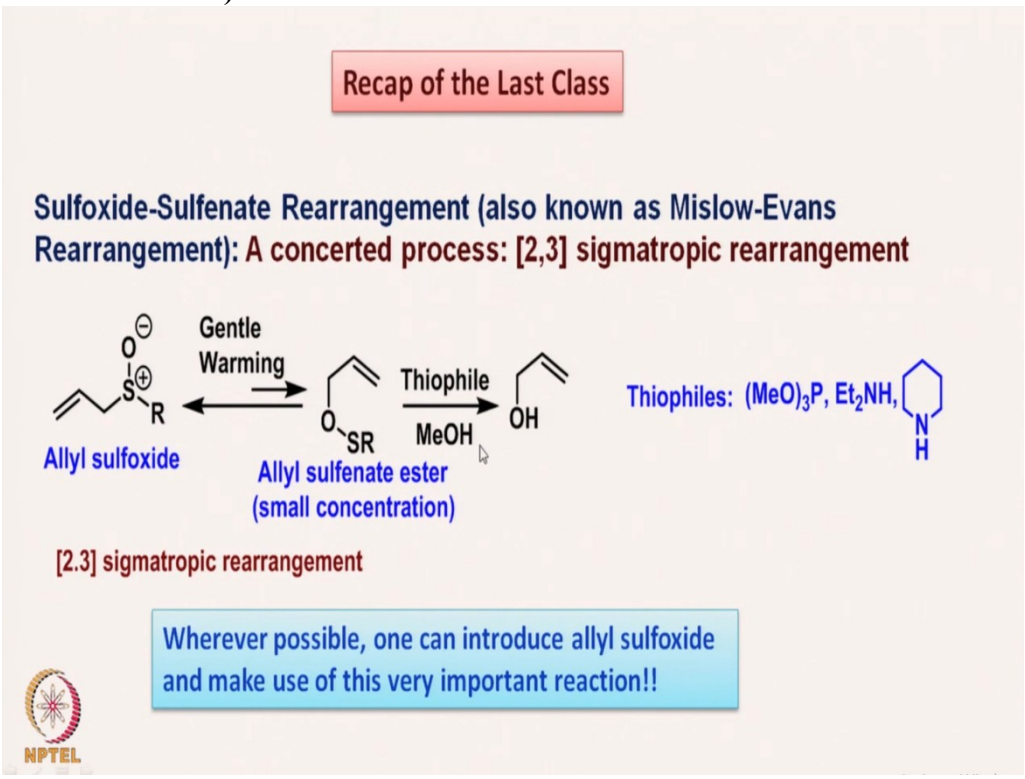

Just to look at it once more we are talking about this sulfoxide which is an allyl sulfoxide that means it is having a double bond here and then there is a sulfoxide which upon gentle warming gives allyl sulfenate ester. So this is basically these two species are in equilibrium with each other and they exist the equilibrium exists mostly on the allylic sulfoxide side. Because oxygen sulphur bond in allyl sulfenate ester is relatively weak.

And when this equilibrium exists to some extent on this side and if during the reaction a thiophile such as trimethylphosphite, diethylamine or say a secondary amine like piperidine is added. Then there is cleavage of oxygen sulfur bond and alloys alcohol is released. Now this is an interesting reaction because as I discussed last time that you can make an ion next to the sulfoxide and react with an electrophile to form the carbon-carbon bond and then if you perform

this reaction you will get an allyl alcohol which is having that substituent which we had introduced earlier next to the sulfoxide that means at this carbon there will be a substituent.

So basically one can introduce allyl sulfoxide in many different ways and alkylate it next to the sulfoxide and make use of this very important reaction in many synthetic endeavors. So first we would look at the mechanism of this reaction, as I mentioned the last time that this sulfoxide, allyl sulfoxide with this negatively charged oxygen here attacks onto this carbon here and this double bond moves and the carbon sulfur bond here breaks to form this allyl sulfenate ester.

The allyl sulfenate ester can also be prepared from allyl alcohol upon treatment with RS Cl. For example, we will look at that part a little bit later.

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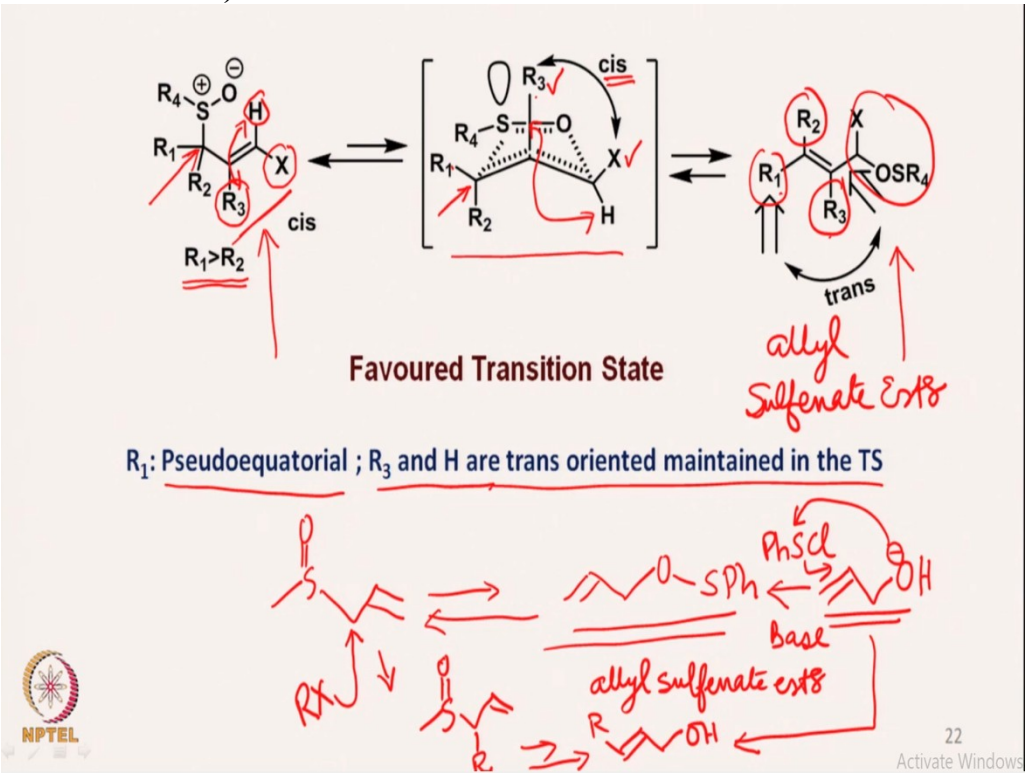

Now look at the mechanism of this reaction as I have indicated earlier that we take allyl sulfoxide, now in this particular example what we have done is to take this allyl sulfoxide in which there is a substituent X here, which is cis to this substituent R_3 and then we have two substituents here R_1 and R_2 next to the sulfoxide where R_1 is larger than the R_2 for example. Now in the equilibrium that exists between the allyl sulfoxide which is this allyl sulfoxide and the allyl sulfenate ester there is an equilibrium that is existing.

Now during the process during the transition state, what is going to happen is going to form a five member transition state is oxygen 1, sulphur 2, this carbon 3, this carbon 4 and this carbon 5. This is what is the 5 member transition state, now as you can see in the transition state that the geometry between the X here and the R_3 is on maintained as cis this is what is assist to each other. This is what was present here as cis to each other here it is maintained.

Because there is no reason for it to undergo any change, now this particular carbon atom here has adopts a particular orientation in such a fashion that R_1 group which is the larger group remains in a kind of pseudo equatorial position. So R_1 is in a pseudo-equatorial position and R_3 and H, now since R_3 and X are cis to each other. So R_3 and hydrogen are trans to each other, so R_3 and hydrogen are trans to each other which is maintained in the transition state.

This is what is here R_3 and H they are trans to each other which results in the formation of this allyl sulfenate ester and in this allyl sulfenate ester as one can see that the R_2 here and R_3 are trans to each other and therefore R_1 and the remaining group is also trans to each other. That is exactly what we are getting it from here the R_1 is cis to R_3, R_1 is trans to the remaining part of it here and therefore R_2 and R_3 they remain trans to each other.

So it is a concerted process and it allows this allyl sulfenate ester to form readily. Now as I mentioned earlier that you can make allyl sulfoxide which can this is allyl sulfoxide and this is in equilibrium, mainly in this sulfenate ester. Now as we said earlier that we can make anion here and introduce an alkyl group or any group. So, essentially what it means that this compound which can easily come from allyl alcohol upon treatment with phenyl SCl and say any base.

So the base will take up the proton from here and the anion here will attack on to this sulfur to form this allyl sulfenate ester. So you can start with an allyl alcohol make the alpha sulfenate ester which can undergo rearrangement to form this allyl sulfoxide. Then you can introduce here an RX that is R group here which can give an R substitution here and of course then we can carry out further reactions to form say R here and OH here, so this kind of reactions can be converted.

So basically what I wanted to show that this allyl sulfoxide can be converted this allyl alcohol can be converted to this substituted allyl alcohol why are these sulfoxide sulfenate rearrangement.

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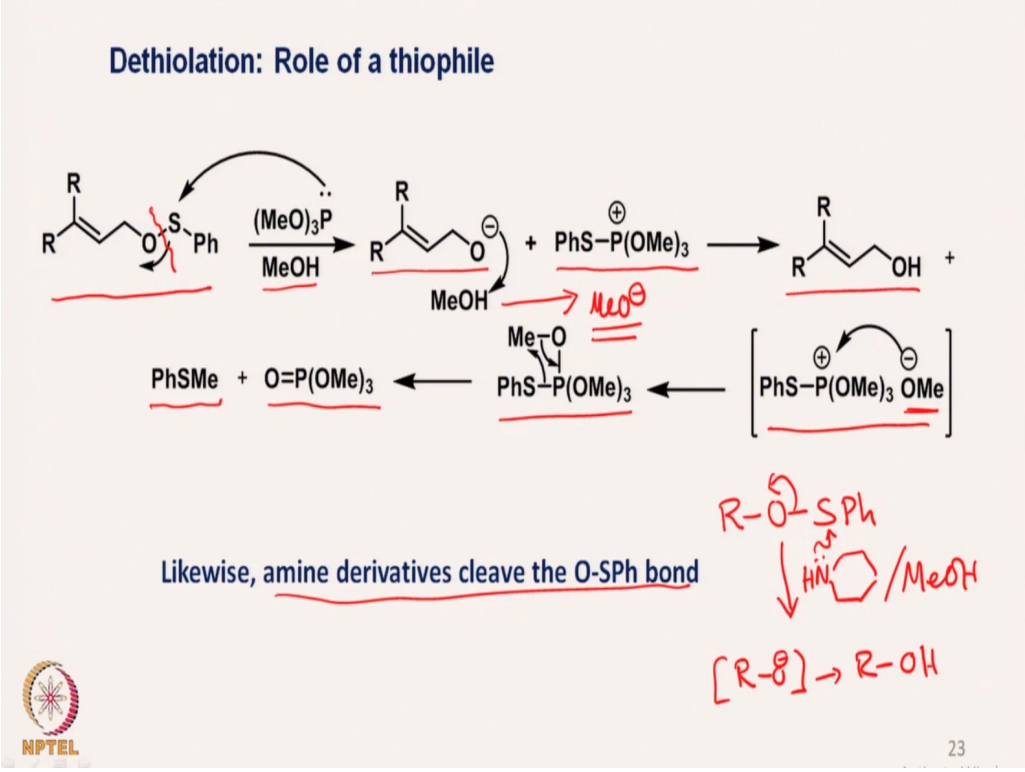

Now the dethiolation occurs by using trimethyl phosphite which is a very useful thiophile, so when the allyl sulfenate ester is formed the trimethyl phosphite attacks with the lone pair of electron to the sulfur oxygen bond here to the sulfur atom to break the carbon sulfur oxygen bond here. So what is happening is that when trimethyl phosphide attacks onto the sulfur this oxygen comes out with a negative charge and this is what is formed and of course you generate a species like this.

Now with we have in the reaction medium methanol as a solvent methanol is a solvent, so the negatively charged oxygen then takes up the proton from the methanol and becomes allyl alcohol and then what is released is this phosphorus sulphur bonded species where there is a tri-methyl phosphite species is present as a phosphonium ion and methoxide ion comes from the methanol.

So this methoxide this particular removal gives this and of course you get from here you will get methanol as methoxide ion. This is the methoxide ion that is present here and this attacks on to the positively charged phosphorus to form this intermediate and this intermediate, now as you can see that there is three methoxy groups attached to the phosphorus and the fourth methoxy group which has come from methanol is something that one can write like this.

Which undergoes a decomposition to form trimethyl phosphate here and of course a thioanisole. So this is the mechanism for the dethiolation of allyl sulfenate ester using trimethyl phosphite as a thiophile. On the other hand amine derivatives will straight away cleave the oxygen sulfur bond that means if you have here say R-O-S phenyl and you have say you have a nitrogen containing thiophile and of course methanol as a solvent.

Then this lone pair of electron can directly attack then it can go to this O^- here which eventually will give the corresponding R-OH. So this is how the thiophiles react with allyl sulfenate esters

and cleave the oxygen sulfur bond. So whenever such a reaction is being done that means allyl sulfoxide to allyl sulfenate rearrangement you use any of the thiophiles and that allows the cleavage or shifting of the equilibrium to the right side.

Now there are several very interesting examples in the literature. For example, as I have mentioned earlier that the formation of allyl sulfenate ester occurs upon treatment of allyl alcohol with phenyl SCl triethyl amine.

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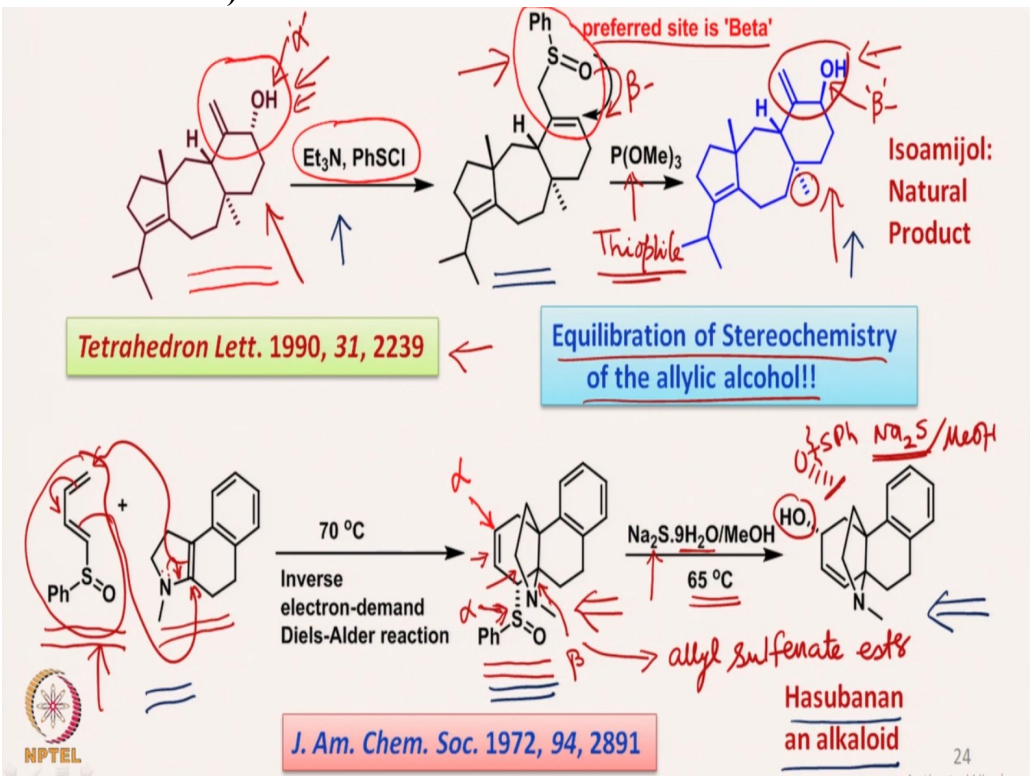

So for example, in this particular example which is an allyl alcohol part here and if it is treated with triethylamine phenylSCl what directly is shown is this allyl sulfoxide. So in the earlier case that I showed just now was that;

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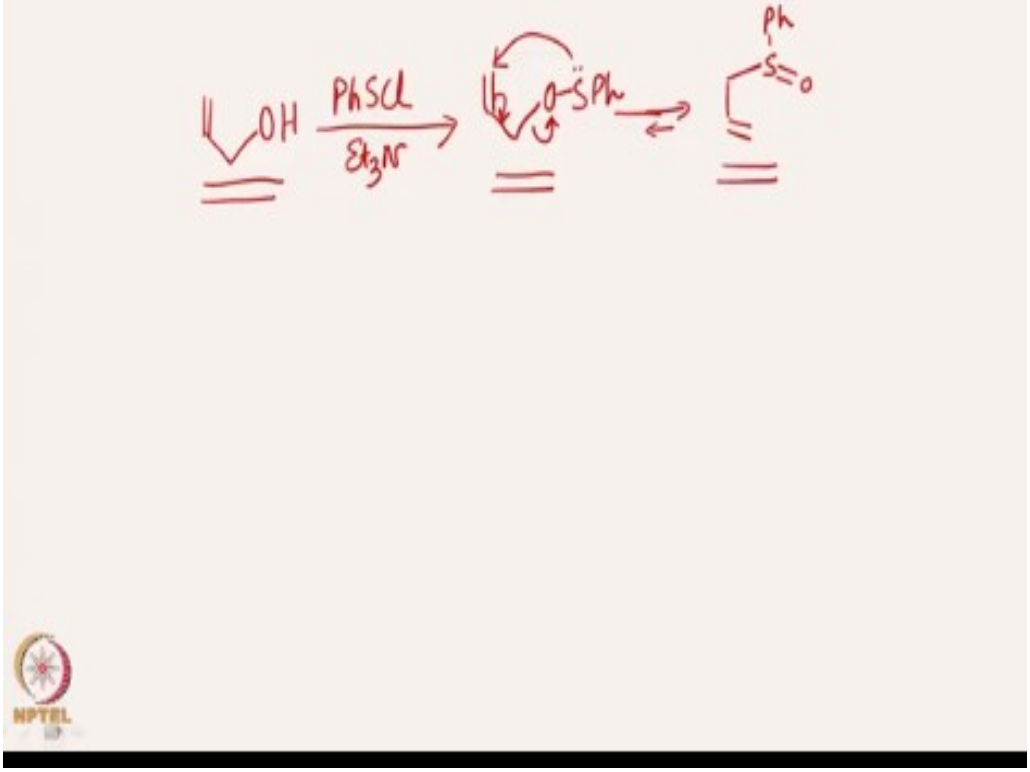

You have allyl alcohol and when it is treated with in the presence of triethylamine that is phenylS Cl and triethylamine one can get OS phenyl and this is in this will be in equilibrium more on this side. So you have a lone pair of electron coming here and this is what is happening to form here something like this. So you have starting with an allyl alcohol you are getting an allyl sulfenate ester which is in equilibrium with allyl sulfoxide.

Now this is what this is what we have seen in this particular case that this allyl alcohol here, this alcohol here is converted to the allyl sulfoxide by the way I have shown the mechanism on the previous slide. Now this of course upon treatment with the thiophile present in the reaction medium, then allows the cleavage of the allyl sulfenate ester which will result from this particular allyl sulfoxide.

Now you would be surprised to see that this is an allyl alcohol and this is also an allyl alcohol there is nothing change nothing difference here between these two paths here. The only difference that you can see is the stereochemistry here. The stereochemistry of the hydroxy group is beta here beta oriented where here it is and it is alpha oriented. Now that means what we have done is essentially an epimerization of this molecule here to this molecule here.

So when this allyl alcohol which is having hydroxyl group in an alpha position becomes allyl sulfenate ester undergoes a rearrangement to the corresponding sulfur oxide and then this sulfoxide again undergoes a rearrangement to allyl sulfenate tester but not the previous allyl sulfenate ester. Now this undergoes rearrangement in such a fashion that the oxygen of the allyl sulfoxide now comes from the beta side, which is the preferred beta side. Why it is preferred?

It is because of this particular methyl group which is alpha and therefore the preferred site is the beta. So essentially this is nothing but an epimerization of one allyl alcohol to another allyl

alcohol via this allyl sulfoxide allyl sulfenate rearrangement or Mislow advanced rearrangement. So this is an equilibration of the stereochemistry of the allylic alcohol. This is a very interesting example which is reported in the literature in 1990.

Now another very interesting application that has been reported in the literature is using allylic sulfoxide or this diene sulfoxide containing diene which is then converted to an allyl sulfoxide by Diels Alder reaction. So this diene which is present in here, if this diene is treated with a dienophile of this type. Now this particular lone pair of electron allows to push the electron density in such a fashion, so that there is a regioselective Diels Alder reaction.

And this is what leads to the formation of this particular intermediate where the sulfoxide group here is coming next to this particular junction here with and the double bond comes in here, this is the double bond. So a diene containing sulfoxide in a particular fashion oriented or situated in a particular fashion allows a regio selective Diels Alder reaction to form this and of course because of this particular this ring is beta oriented sulfoxide is coming in an alpha fashion.

Now when this undergoes allyl sulfoxides are now sulfenate rearrangement because now you have generated an allyl sulfoxide that undergoes allyl sulfoxide sulfenate arrangement and interestingly this sodium sulphide in the presence of water that is hydrated at 65 degrees was used as a thiophile to allow this reaction to take place. That means now this particular substrate will undergo a rearrangement to form allyl sulfenate ester.

And that allyl sulfenate ester that means in place of this it would be O-S phenyl, this is what it will be here and then this is the one that is cleaved by means of sodium sulphide in water and methanol. So basically sulphide ion attacks onto the sulfur here and then oxygen sulfur bond breaks to form the allyl alcohol part. Now since the geometry since the stereochemistry of the carbon sulfur bond here in this particular part carbon sulfur bond which is alpha oriented here particular one the transfer of the oxygen onto this carbon happens from the alpha side.

So this is how an alkaloid which is known as Hasubanan alkaloid that has been synthesized by using this very crucial Diels Alder reaction followed by allyl sulfoxide sulfenate rearrangement to form this alkaloid. Now, so one can generate as I have mentioned just now that one can take the top example shows the allyl alcohol to be converted to the other allyl alcohol with change in stereochemistry via this allyl sulfoxide. Now similarly Diels Alder reaction can be done to form the allyl sulfoxide and then that can be converted to the corresponding allyl alcohol in many in a different way.

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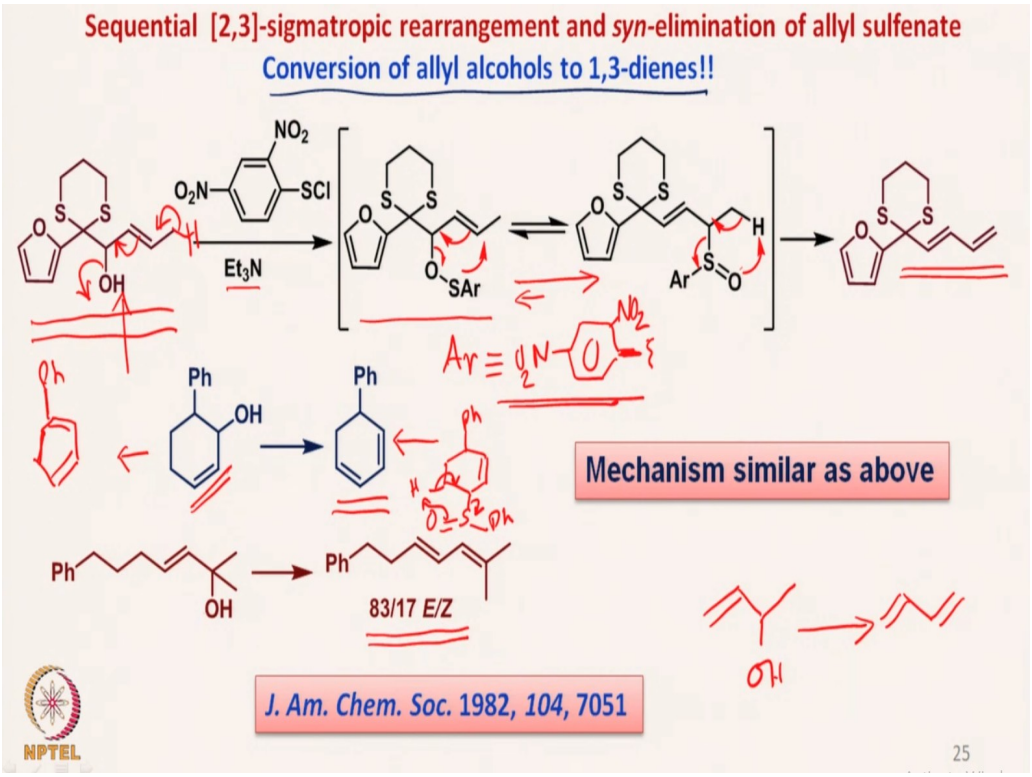

Now there is another very interesting example which is reported in the literature is basically converting allyl alcohols to dienes. So it involves conversion of allyl alcohol to 1, 3 dienes. Now if one looks at the various procedures of converting allyl alcohols to 1, 3 dienes, of course one can straight away, that you can take an allyl alcohol. For example, here and you can carry out some way of dehydration to form this dienes. But this is a straight method if there is no specificity involved in a particular fashion.

But for example, here we have an example of this kind of substrate. Now this substrate can be converted to the allyl sulfenate ester by treating with this sulfenyl chloride in the presence of triethylamine as a base to form OSAr. Ar indicates the aromatic part that is this is basically nothing but this part this is the Ar part and from here we are attaching. So this is the Ar part so this is what allyl sulfenate ester is formed which will be in equilibrium with the allyl sulfoxide like this here like the way the mechanism is shown of course.

It would be more towards this side and less towards this side. Now this can undergo either back towards this or it is suitably placed for the elimination of sulfoxide to form the diene. So you have converted this alcohol here by essentially removing a proton in this way and subsequently accompanied by the loss of OH, this is what eventually that has happened that means there is a loss of proton from here and a loss of hydroxide from here and the diene is formed.

But that has been done by a very interesting way of making this allyl sulfenate ester followed by allyl sulfoxide and which eventually gives this of course you will lose the carbon sulphur bond from here and you have a diene that is formed. In a similar fashion one can start doing in a similar mechanism fashion you can have the conversion of this allyl alcohol to the sulfoxide, that would look like this and when this undergoes elimination here this is formed.

So it is now one can see the difference, now if we simply take this alcohol and allow the dehydration to take place, so the dehydration will give this particular diene whereas if one goes by allyl sulfoxide method we get the diene in this fashion. So there is a very great possibility of manipulating the allyl alcohol part in such a way that one gets the diene in a very specific fashion. In a similar fashion you have this tertiary allyl alcohol that can also be converted to the corresponding diene like this in using this particular strategy.

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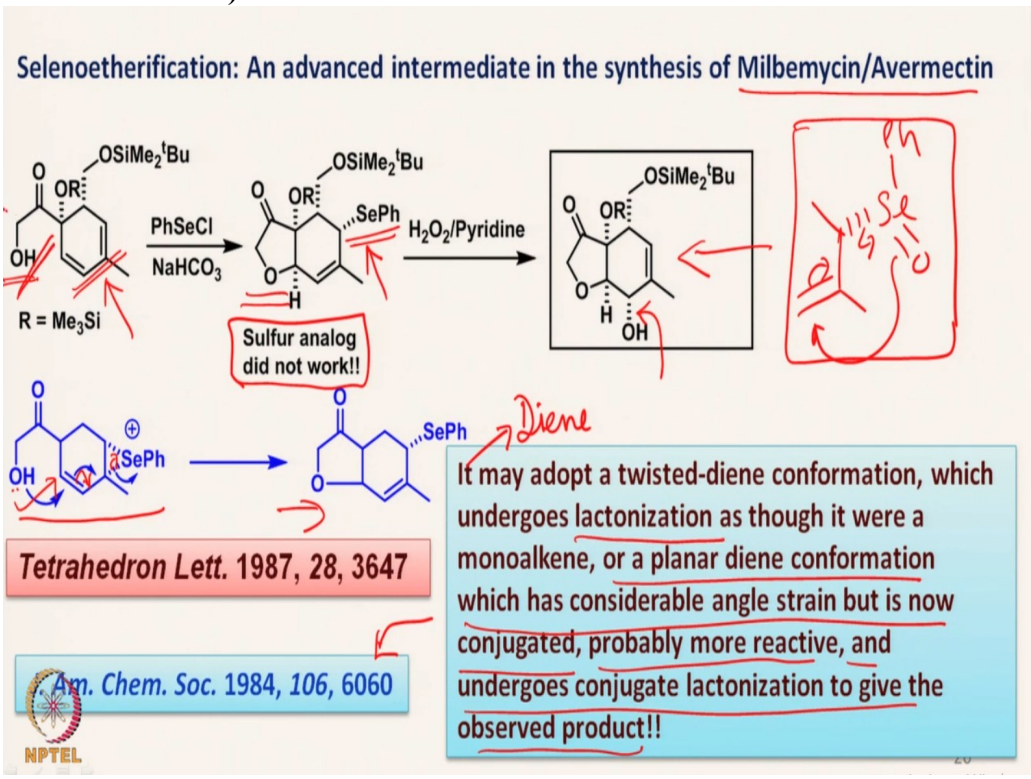

Now there is a very interesting selenoetherification it is used to synthesize an advanced intermediate in the synthesis of natural products called milbemycin / Avermectin. Now what is done here is something that is very interesting, that they start with a diene of this type which has an alcohol here suitably produce alcohol. When this is treated with phenyl saline chloride, now this is an example of not sulfoxide sulfenate rearrangement. But it is of an example of a saline oxide selenate rearrangement.

Now they tried in this paper they have tried to do a sulfoxide based chemistry and they were not successful and therefore they did selenium-based allyl selenoxide, allylic selenate ester based chemistry and they were successful. So sulfur analog did not work and that is the reason why they did the selenium thing. Now what is happening here is that when this diene is taken and treated with phenyl selenyl chloride in the presence of sodium bicarbonate what happens is this cyclization occurs to form a 5 member ring which of course has now selenide here.

Which; upon treatment with hydrogen peroxide forms the corresponding saline oxide that means this is going to form and that undergoes rearrangement to form this allylic alcohol of course via allyl selenate ester. Now interesting thing about this reaction is first of all how this five member ring is formed and for that five member ring formation this is what is supposedly taking place the selenium attaches to the double bond here.

And a three membered selenium intermediate is formed which then has the double bond moving in this direction and this carbon selenium bond breaks and of course subsequently the alcohol attacks onto this to form this particular intermediate. The only question that one can ask at this stage is the stereochemistry of the selenide, now because the selenide is alpha oriented the alcohol is also coming alpha oriented.

Because that is exactly; what is going to happen based on this allyl selenoxide, saline allyl selenate ester rearrangement. So this work is somewhat difficult to explain but according to the publication what they have suggested that this particular diene this it is basically diene may adopt a twisted diene conformation which undergoes lactonization this is the lactonization here as though it were a monoalkene.

That means this diene is not behaving like a diene but is more like a monoalkene or a planar diene conformation which has considerable angle strain but is now conjugated, probably more reactive and undergoes conjugate lactonization to give the observed product. So this five member ring formation is taking place mainly because of the diene that is behaving in a particular fashion.

So we will stop at this stage and we will take some more examples of the reaction this particular reaction for discussing the application of the sulfoxide, sulfenate rearrangement and further reactions. So you can go and look at some of these literature references if it is possible and get more idea about this sulfoxide, sulfenate rearrangement. I mention about this particular example undergoes lactonionization it is quite likely that it is not this hydroxyketone.

But it is actually an acid here, so I will check it on this particular paper and get back to you in the future class to clarify this lactone part of this particular example. So you please go ahead and study what I have told so far and we will see in the next class with some more examples and more applications thank you.