Essentials of Oxidation, Reduction and C-C Bond Formation. Application in Organic Synthesis

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Lecture - 49

Bellus-Claisen Rearrangement, Aza-Claisen Rearrangement, Thia- Claisen Rearrangement, Chen-Mapp Rearrangement and Their Synthetic Applications

Hello everyone, I would like to welcome you all for today’s lecture. First we would like to look at briefly what we did last time and then we proceed further. So in the last class, we looked at some aspects of Claisen rearrangement and we looked at the mechanism of the Claisen rearrangement, which is 3,3-sigmatropic rearrangement.

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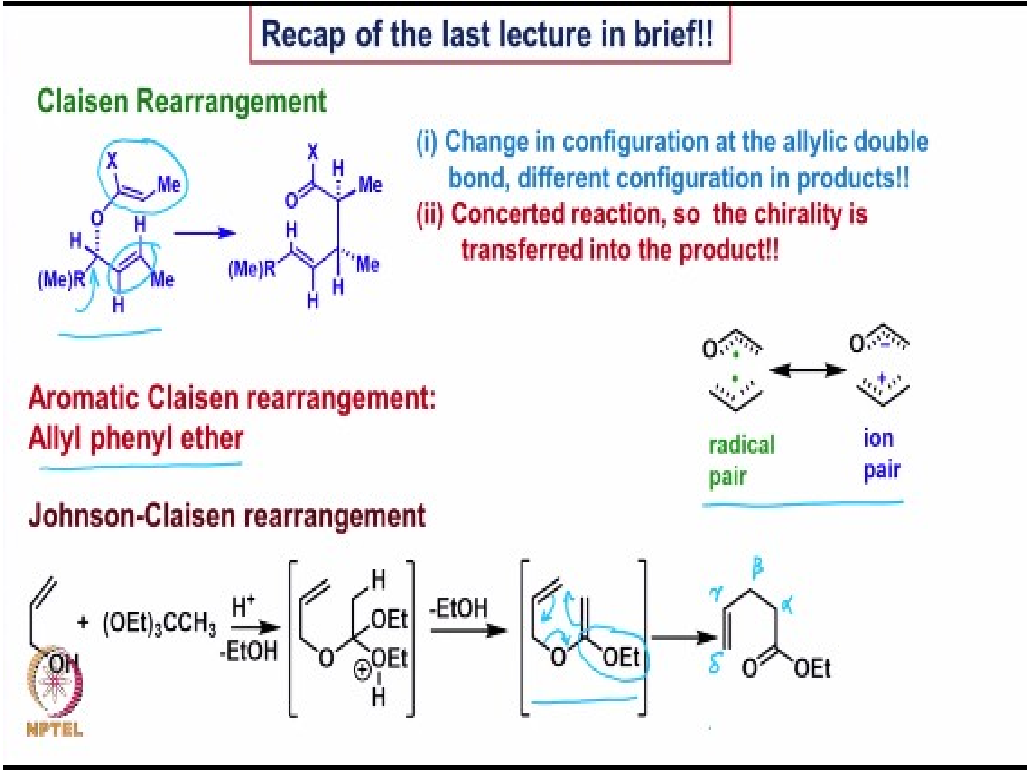

Recap of the last lecture in brief!!

Claisen Rearrangement

(i) Change in configuration at the allylic double bond, different configuration in products!!

(ii) Concerted reaction, so the chirality is transferred into the product!!

Aromatic Claisen rearrangement: Allyl phenyl ether

radical pair

ion pair

Johnson-Claisen rearrangement

So what we looked at it is, if we have well substituted molecules like this, which are allyl vinyl ethers and if we keep the geometry of the double bond fixed here and make a change here that means allylic double bond. So we will get different products with different configuration. And obviously, if there is an asymmetric center here, and if that is a molecule which is a chiral molecule, then the chirality gets transferred, because it is a concerted reaction.

So these aspects we saw and of course, we looked at how the products change based on the change in configuration of the allylic double bond or even vinylic ether double bond, if we keep the other double bond fix. So if one of the double bonds is fixed, the other double bond can be changed and accordingly, the different products with different configurations come.

Then we also look at the aromatic Claisen rearrangement where allyl phenyl ether were allowed to kind of react in a similar fashion where the double bond, one of the double bonds of the allyl phenyl ether was actually an aromatic part of it. We also looked at the mechanism part of it and especially from this toluene point of view, that if we have polar solvents or hydrogen bonding kind of solvents such as ethanol, water, etc, the reaction rate is enhanced.

And that is mainly because of the possibility of such type of intermediates or particularly the ion pair type of intermediate that is a slightly charged intermediate and therefore the reaction is much better in such solvents. Then towards the end, we also saw the variation of Claisen rearrangement, which is Johnson-Claisen rearrangement.

And specifically I mentioned many times that if we take an allyl alcohol and react it with triethyl orthoacetate under acidic conditions and heat it then we get an intermediate of this type. This intermediate as you can see has the all the elements of the Claisen rearrangement except that we have an extra O ethyl group here. And that is exactly what allows the reaction to occur and to form what we called it as that alpha, beta, gamma, delta.

So gamma, delta unsaturated ester. So if we start with allyl alcohol and perform Johnson-Claisen rearrangement we get the gamma delta unsaturated ester. And we also took some examples of the application in organic synthesis.

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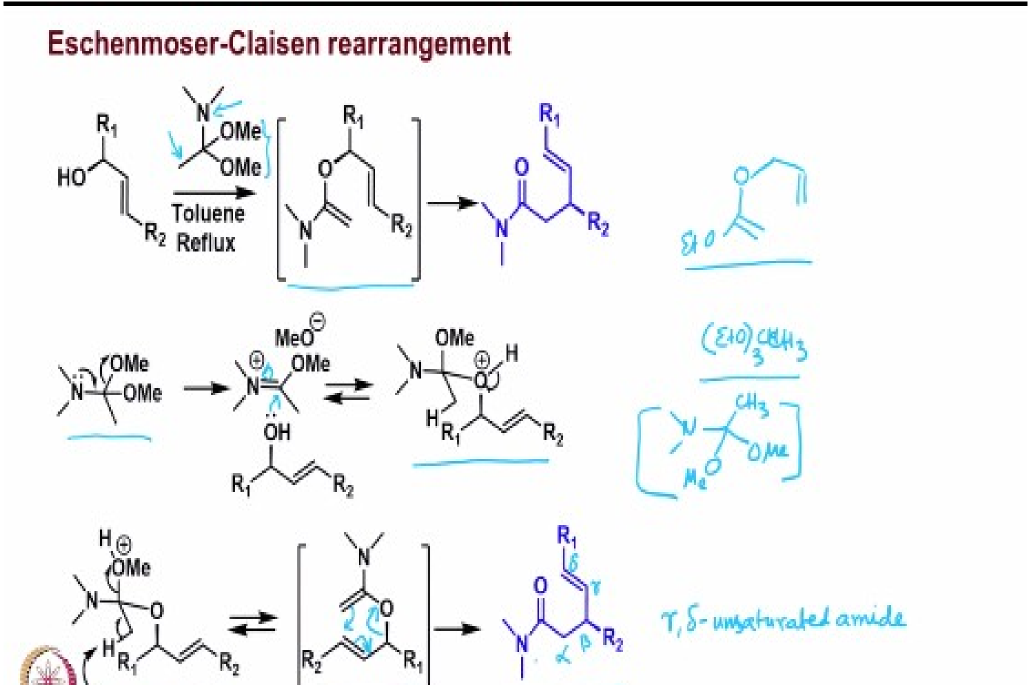

Eschenmoser-Claisen rearrangement

Now towards the end then we saw the Eschenmoser-Claisen rearrangement. If you look at the intermediate, this is the intermediate that is the intermediate which we can compare it with Johnson-Claisen rearrangement. Johnson-Claisen rearrangement intermediate was something of this sort, where we had the ethoxy group. And this is what led to the formation of gamma delta unsaturated ester.

And for this purpose what we had used was triethyl orthoacetate. And here what we are using it is here actually there should be a CH_3. So this is what we had used last time. And what here is being used is two methoxys and a NN dimethyl group and a methyl group here. So it is exactly same as more or less like this except that we have nitrogen here. And of course a methyl group is there as expected.

And you have two methoxys instead of two ethoxy. It does not really matter whether it is two methoxy or two ethoxy. So this is the reagent which is used in here. And we saw the mechanism of it last time that this is what cleaves off and then of course, the attachment of this pair of electron takes place on to the carbon atom here. And the positive charge gets neutralized to form this intermediate, which is what is this one here.

And that loses a proton to form this intermediate of this kind, which of course, upon rearrangement then goes to this. Now we can see here that you have alpha, beta, gamma and delta. But it is gamma, delta unsaturated amide. It is a tertiary amide. So you have a gamma, delta unsaturated amide. So what is the difference? The difference is that of course, is that we have a possibility of reducing this amide to form the corresponding amine.

And of course, we can also hydrolyze it and get the same ester or acid whatever we want it. But main thing is here that we can get the corresponding amine with this particular variation. And it is not really done under acidic conditions, it is just a reflux in toluene.

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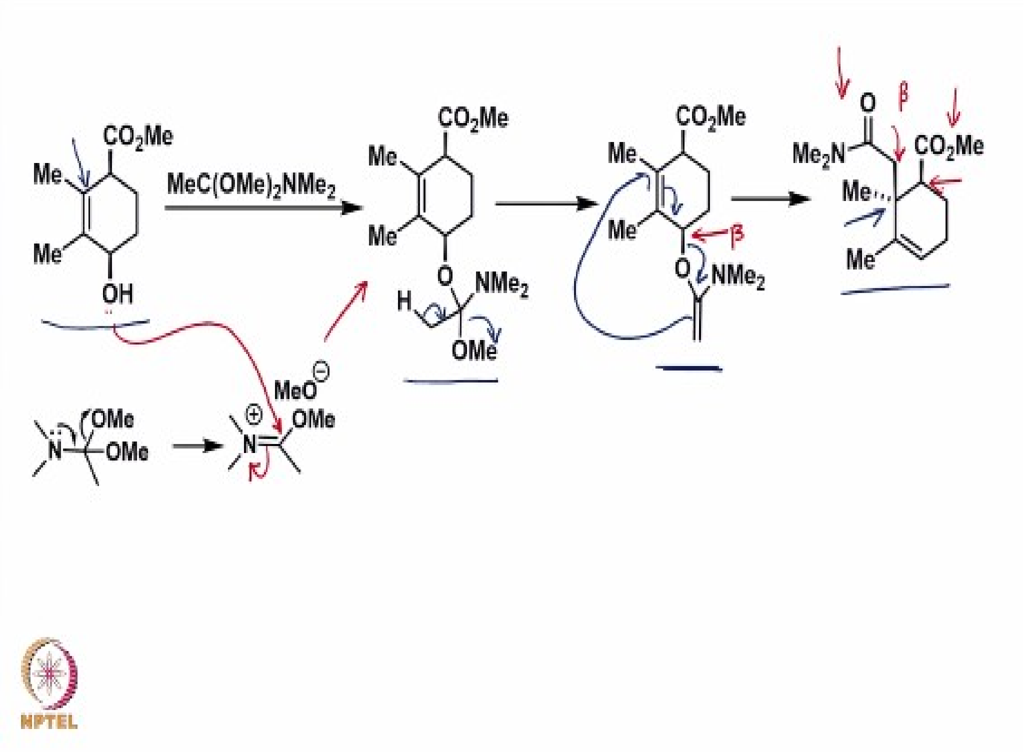

One of the applications of this Eschenmoser-Claisen rearrangement is the conversion of this type of molecules where we have a double bond at this particular position and if this is the intermediate that can form upon reaction with the reagent that we employ in Eschenmoser-

Claisen rearrangement. Then that undergoes elimination to form this intermediate and that undergoes rearrangement.

Obviously, it is going to be from this side. It is going to be here and then here and then here. So this is how it happens and we get this particularly molecule which is a quaternary carbon containing this amide group here and as you can see that the geometry of the particular this group here is beta oriented and in the product also it is beta oriented. So the chirality is retained in these products.

So it is very clear that the reaction is occurring by the reaction of this alcohol on to this particular double imonium ion and of course, you get the product which is like this. So this is a beautiful application of the Eschenmoser's recommendation. Now what can be done is of course, is you have a very nice amide group here and you have an ester group here and both of them are beta oriented.

Of course, if one wants one can do the epimerization here and convert this into alpha orientation or whichever way one wants to manipulate the molecule according to requirement from the synthesis point of view.

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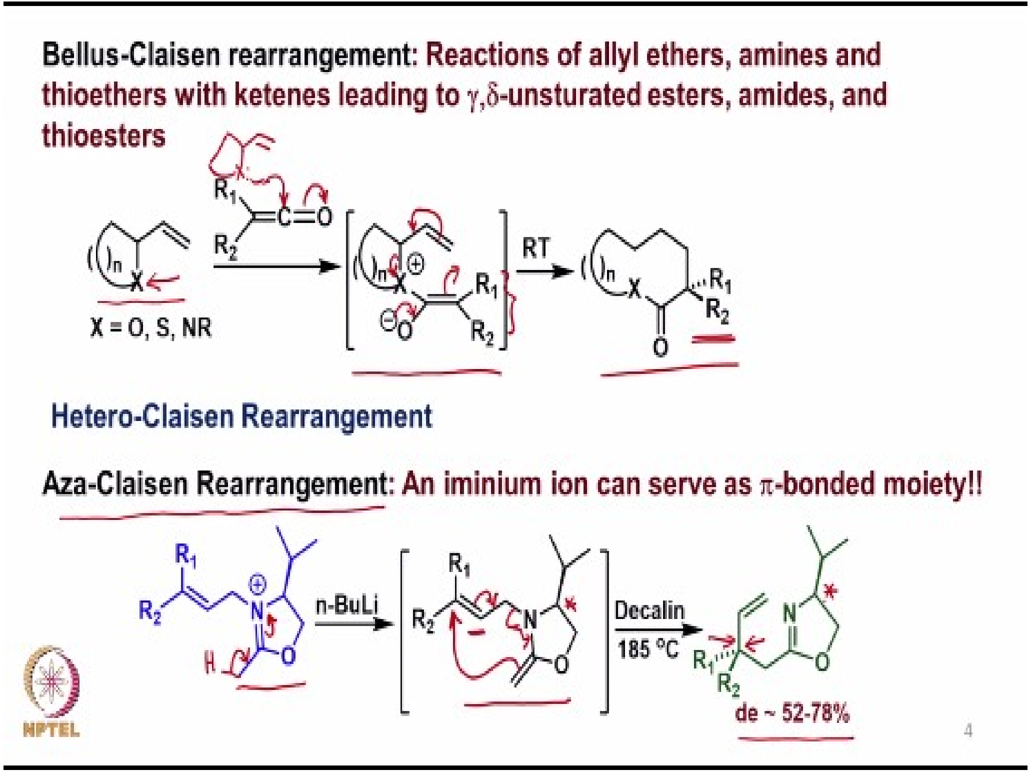

Bellus-Claisen rearrangement: Reactions of allyl ethers, amines and thioethers with ketenes leading to γ,δ-unsturated esters, amides, and thioesters

X = O, S, NR

Hetero-Claisen Rearrangement

Aza-Claisen Rearrangement: An iminium ion can serve as π-bonded moiety!!

de ~ 52-78%

Now there is another rearrangement which is called as Bellus-Claisen rearrangement and that is reaction of allyl ethers of this kind, ally ethers or allyl amines or allyl thioethers. That means, this X can be either oxygen, sulfur or nitrogen. When this is reacted with a ketene then what happens is that the lone pair of electrons on the allylic ether or amine or thioether and interacts it onto this here.

And clearly this moves out here. So what you have is a possibility of X group here reacting with a lone pair of electron coming on reaction like this. And this is what is formed here. And once that is formed now one can see it very clearly that what you have is your 1, 2, 3, 4, 5 and 6. And this undergoes the rearrangement as expected and you have the ring expansion and forming this kind of product.

It is obvious that the geometry of this group here would affect the stereochemistry of the asymmetric center that is being created. But interestingly this reaction occurs at room temperature as you can see, because there is a very strong driving force for the double bond to move because there is a negative charge here. At the same time there is a driving force for cleaving the carbon X bond which is positively charged.

So the reaction requires not very high temperature and the reaction occurs at room temperature. So this is what is a variation of the Claisen rearrangement which is called as Bellus-Claisen rearrangement. Now there is also an Aza-Claisen rearrangement, which is kind of an iminium ion can serve as a pi bonded moiety. Like for example, if you have a methyl group here attached to this iminium ion here, then of course we can deprotonate that.

So there is a hydrogen here. If hydrogen is deprotonated by butyllithium, then of course we can generate this type of intermediate here. And this type of intermediate is now well suited as you can see it is an enamine kind of thing with an oxygen also being here and then that undergoes a rearrangement.

So essentially the all these reactions are nothing but an arrangement of atoms in such a fashion that you have a possibility of 3,3-sigmatropic rearrangements where one can put a hetero atoms of different kind and make the reaction work. Now here it requires high temperature because it does not have similar situation as we saw in the Bellus-Claisen rearrangement. So it is a slightly different.

However, of course depending on the stereochemistry of the double bond here, we are going to look at the possibility of getting different absolute configurations at the center in case the cis or trans double bond. If the, of course this reaction is not a chiral reaction, but we are only talking about the geometry based rearrangement to get to this product.

Of course if this happens to be a chiral center, then of course we are not going to talk about the absolute configuration in terms of this one. Because now that will be a kind of diastereoselective reaction. And of course, if this influences the geometry of this one, then of course we can look at. And that is the reason why the diastereoselectivity comes into the range of 52 to 78% if this happens to be a stereo defined center.

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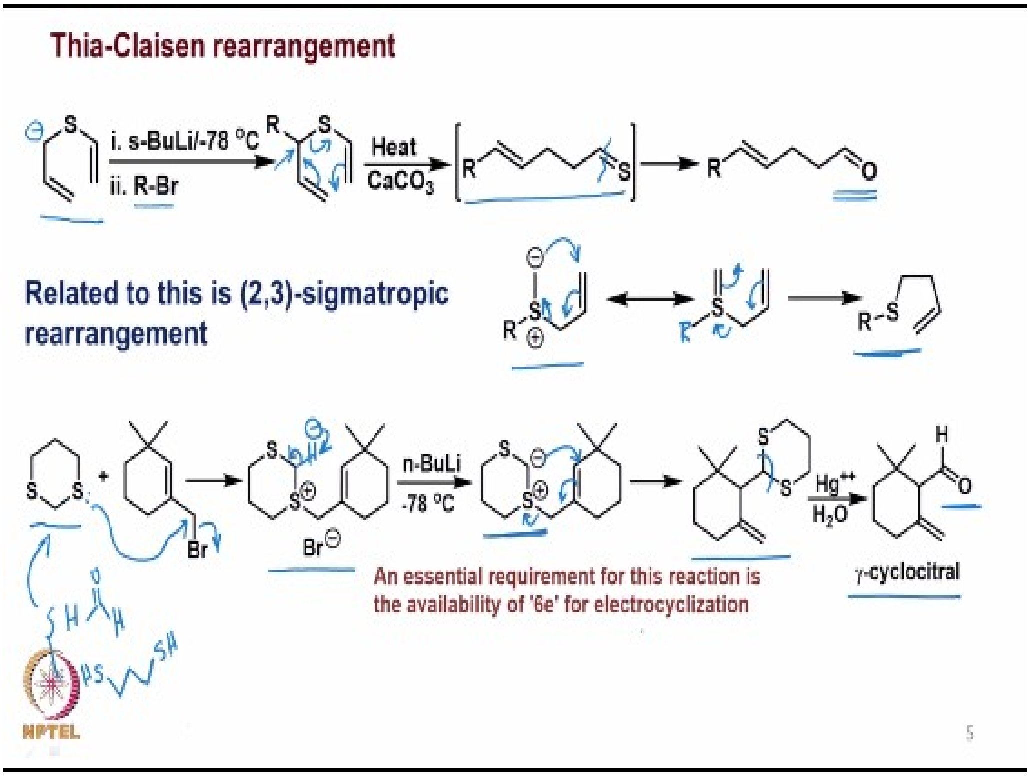

Thia-Claisen rearrangement

Related to this is (2,3)-sigmatropic rearrangement

An essential requirement for this reaction is the availability of '6e' for electrocyclization

Now we have Thia-Claisen rearrangement where instead of Aza-Claisen rearrangement if we have a thia molecule, something of this kind here then what is going to happen is we will have possibility of deprotonating proton from here and then if we react with R-Br then we can introduce here an R group an alkyl group or any such a carbon-carbon bonded species.

And when this is heated with calcium carbonate, then of course you have this Thia-Claisen rearrangement and we can get a molecule of this kind which during the workup will get hydrolyzed and the corresponding aldehyde would form. Now this is somewhat related to 2,3-sigmatropic rearrangement of this kind, where we have such possibility. It is just to indicate that such a thing can happen.

And of course, one can get if we have R group here. So it is related to this particular kind of rearrangement. Now what is the utility of these kind of reactions. And the interesting reactions of this kind are in the synthesis of for example gamma cyclocitral. Now here if we start with a 1,3-dithiene which is basically a protected formaldehyde, if we take formaldehyde and protect it with thiol which is dithiol.

So if we can take something of this type, then we can react them together to form this intermediate. And this is a commercially available substrate where if we react with allyl bromide, which is a very easy substrate, so then you have a lone pair of electron attacking on to this particular carbon. And this carbon-bromine bond breaks to form this sulfonium bromide where there is already a double bond.

Now if we make a anion from this particular substrate by reacting with butyllithium, then we expect that this particular hydrogen will be picked up and what we will get is this kind of anion.

And this anion can undergo the rearrangement and as we discussed above is the 2,3-sigmatropic rearrangement kind of thing as we discussed it here.

Similar reactions would occur here and to form this particular rearranged dithiane here. This is a rearranged dithiane which can be cleaved hydrolytically at this particular position and we can get the corresponding aldehyde here. So this is essentially this reaction or this reaction here requires that there should be availability of six electrons for electrocyclization. Its kind of electrocyclization here and of course the reaction is concerted reaction.

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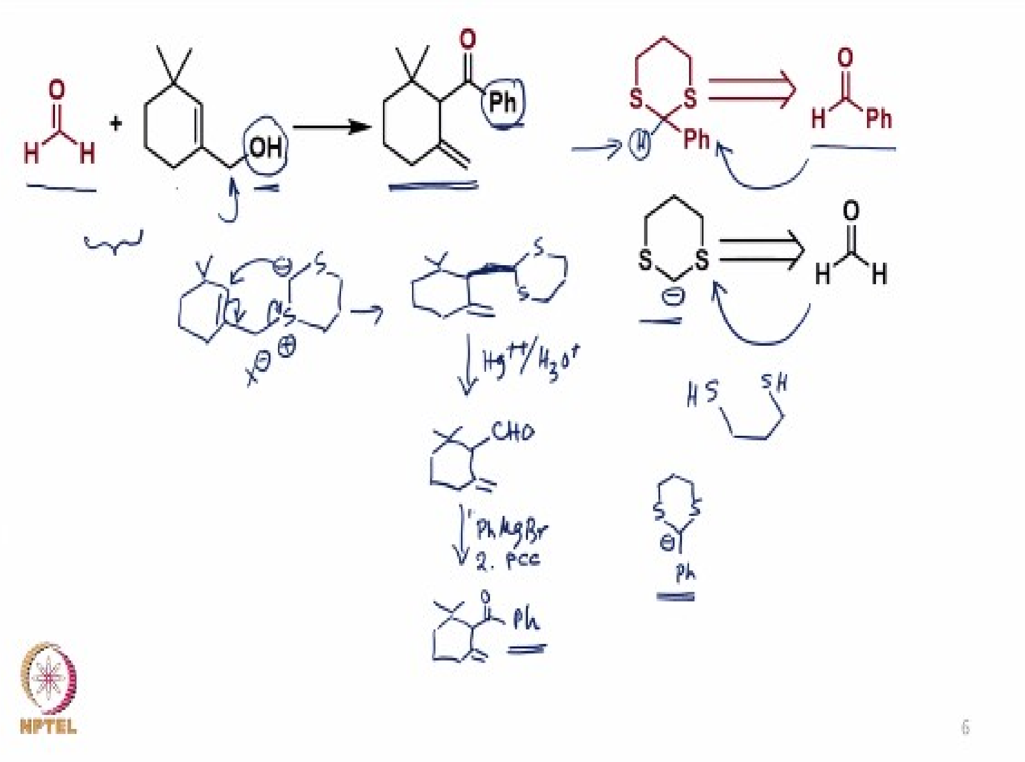

Now if we try to look at the variations in terms of the application of such reactions in organic synthesis, what can be done? For example, if we say that okay we want to convert and a formaldehyde into this kind of substrate. Now this substrate, if we look at the previous example that we took, we had here hydrogen here. But we started with the corresponding bromide and we started with a dithiane here.

So we have to recognize that whether we start with the corresponding bromide here or whether we start with alcohol. So it is very clear that we have to convert the alcohol into a leaving group and therefore, it could be bromide or it could be mesylate or it could be to tosylate. But at the same time in order to make a nucleophilic attack on to this carbon atom, while we are thinking of converting this into a leaving group, we also have to make sure that we generate an equivalent of the dithiane.

That is this particular dithiane anion we have to make it. And therefore we had to convert this into this. So in an examination point of view, if this particular reaction is given where this is to be formed, then obviously one should also think about how a phenyl group is going to come. So from phenyl point of view, one can think about it this that we can start with the benzaldehyde and then we carry out the same reaction and we can probably make it easily with the same thiol, dithiol.

That means, we take this kind of dithiol. So if we have this dithiol, so then we will make 1, 2, 3, 4, 5 and the carbon number there 6. So we can make a six-membered such substrate. And of course, then we can remove this particular proton by butyllithium and we can generate the corresponding species which you will be having phenyl ring here. So one can have a nucleophile of this kind.

So either we have that as one of the possibilities that we can consider or we can think about such a possibility. And later on, after we have got the formyl group here then we can do by reaction with phenyl magnesium bromide. So let us go with this. So we can convert this by appropriately converting into a bromine as a leaving group, a dithiane as a group here.

Then of course, we can get the corresponding this substrate here. And then we have a positive charge here and we put here X-. X- could be a bromide or could be a tosylate or whatever. And now if we carry out the reaction here, then of course, we have such a possibility. And then we can convert this product into. Then the formyl group here, which we discussed with Hg++ and H_3O+ water.

And then of course we can get the corresponding aldehyde here. There should be, directly there should be a carbon atom here. So we should get aldehyde here. And once we have got the aldehyde here, then we can carry out phenyl magnesium bromide reaction. And of course, then followed by oxidation, any oxidation like for example PCC. We do the oxidation here.

Then what we will get is corresponding CO phenyl. So this is how the reaction can be done. On the other hand, we can directly start with this particular substrate. So we will always have a phenyl group here and then you can we do not have to do this extra step here. So either we do the extra step to start with or we do the extra step later on.

So this is how the application of such molecules can be expected to be looked at in the synthesis of different kinds of molecules and of course also from the examination point of view. Now how do how does the hydrolysis occur? How does the hydrolysis of this dithiane based molecule once we have activated the anion next with sulfur, this is what it is.

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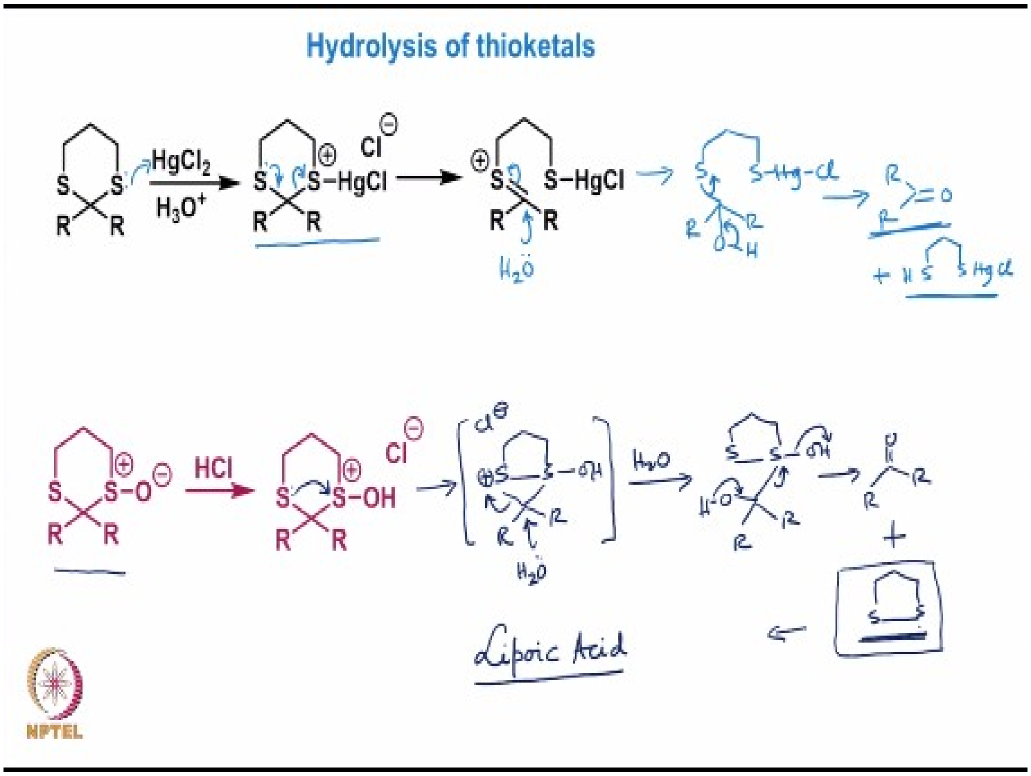

Hydrolysis of thioketals

So what happens is that essentially the one of the lone pair of electrons on this that reacts with the mercury plus and of course, you generate this type of sulfonium ion and then you have a lone pair of electron here that opens up in the here in this fashion and of course you get this intermediate. Now this intermediate is then attacked by water and water attacks and forms a kind of hemithioacetal.

One can tentatively write the structure to be like this. And what you have here is this intermediate which is not stable and then therefore it breaks here to form the ketone. It regenerates the ketone and then of course we will have the thio species which is present here. In most of the cases, this thio species is some sort of thio.

But then which we are not particularly interested in recovering at this stage because we are more interested in the ketone that is formed. However, there have been reports in the literature, where it is possible that if we convert instead of dithiane we take the corresponding sulfoxide. That means, we convert this sulfide into a sulfoxide by oxidation.

And then if we treat with HCl, then what happens is this is the intermediate upon protonation takes place and then this particular lone pair of electron on this actually forms species of something of this kind, where there is a sulfur-sulfur bond which is formed. And of course, you will have this and a positive charge here. And you might say that okay let it be as it is here.

Now this is the one that intermediate then breaks upon hydrolysis and the water then reacts in this fashion here. So you have water reacting in this way to form this intermediate, which would look somewhat like this. And then what you have is a hemiacetal as we discussed earlier time. And of course, this can just simply break off from here and you can generate the ketone.

And then what is observed is of course, that you do get a 5-membered sulfur sulfur containing bond. Now the reason why I have mentioned is that such a reaction where the recovery of the ketone along with the formation of this 5-membered, sulfur-sulfur bond is noticed and that has been utilized in the synthesis of a molecule called lipoic acid.

It is a very important molecule and the synthesis of that in a very nice fashion has been reported by making use of this kind of reaction where the emphasis is not on the ketone, but the emphasis is on the side product which is this dithiane SS bond containing a 5-membered this particular heterocycle moiety. So this is how the reaction of dithianes occur. And the usefulness of this is that, we can do various kinds of sulfur catalyzed Thia-Claisen rearrangement.

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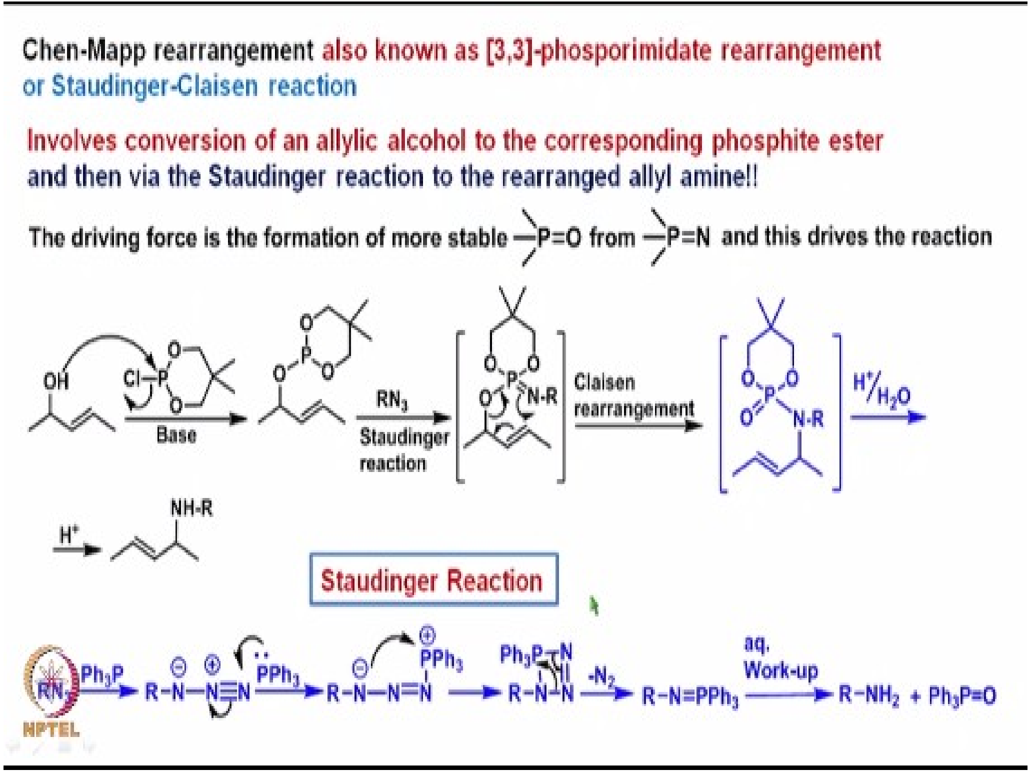

Chen-Mapp rearrangement also known as [3,3]-phosporimidate rearrangement or Staudinger-Claisen reaction

Involves conversion of an allylic alcohol to the corresponding phosphite ester and then via the Staudinger reaction to the rearranged allyl amine!!

The driving force is the formation of more stable —P=O from —P=N and this drives the reaction

Staudinger Reaction

Now we have another rearrangement, which is called as Chen-Mapp rearrangement which is also known as 3,3-phosphorimidate rearrangement or Staudinger-Claisen reaction. It involves conversion of an allylic alcohol to the corresponding phosphite ester. And then via the Staudinger reaction to the rearranged allyl amine. The driving force is the formation of more stable phosphorus oxygen double bond from phosphorus nitrogen double bond and this drives the reaction.

Let us take an example. If we take an allylic alcohol of this kind and react with this chlorophosphite in presence of a base then we get the corresponding phosphite ester like this, which then reacts with an azide like RN$_3$ and forms an intermediate of this particular type via what is called as Staudinger reaction.

And then this undergoes Claisen rearrangement to form this particular type of intermediate in which this phosphorus nitrogen double bond has been converted to the phosphorus oxygen double bond, which is more stable than this particular phosphorus nitrogen double bond. And thus this undergoes acidic hydrolysis to release the corresponding allyl amine. That means this particular bond gets cleaved.

Now what is the Staudinger reaction? The Staudinger reaction is reaction of an azide with trivalent phosphine or phosphite and then that leads to the formation of this kind of intermediate which then leads to another intermediate which is of a 4-member type which looses nitrogen gas to form this nitrogen phosphorus double bond and upon aqueous workup under acidic condition leads to the formation of triphenylphosphine oxide and releases the corresponding amine.

This is exactly what has been utilized in this particular allylic alcohol case. So we have converted the alcohol to the corresponding amine with of course a rearrangement and that involves the movement of the double bond from here to here and formation of a carbon nitrogen bond here. So this is what is known as Chen-Mapp rearrangement.

So we will stop it at this stage and then take up the remaining part of this kind of reactions in the next class. Till then you take care of it and study these reactions carefully. Until then bye. Thank you.