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

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Lecture-04
Further Aspects of Sulfur and Selenium Based Oxidations

Hello everyone, I welcome you all to today's lecture, I am sure you must have gone through the last lecture but we will have a brief recap of the last lecture today before we start the further aspects of oxidation.

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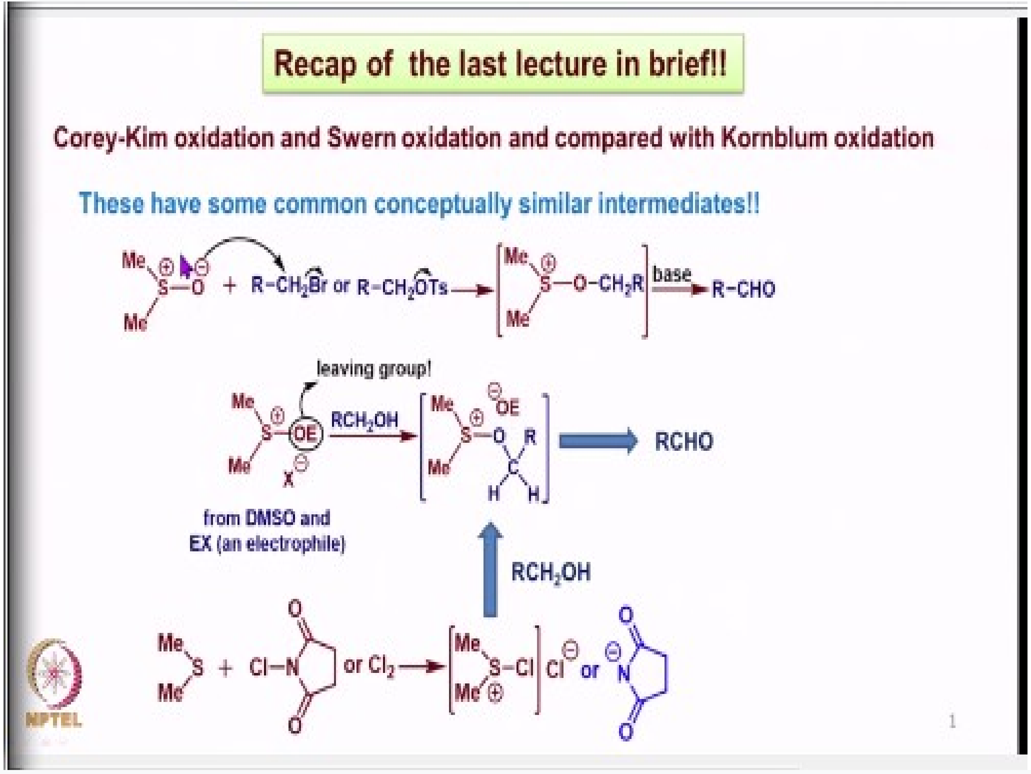

Recap of the last lecture in brief!!

Corey-Kim oxidation and Swern oxidation and compared with Kornblum oxidation

These have some common conceptually similar intermediates!!

What we discussed last time was in detail the Corey-Kim oxidation and Swern oxidation and compared with Kornblum type of oxidations. As we discussed these 3 types of oxidations have some common intermediates which are conceptually very similar. For example in the Komblum oxidation we reacted DMSO with halide or tosylate and not with alcohols. But it gave an intermediate of this type which upon reaction with the base led to the formation of the aldehyde or ketone as the case maybe.

So, basically we do not react with alcohols but we react with alcohol derivatives such as bromide or tosylate. Then of course we took DMSO based oxidations different kinds of course and then we saw the similarity in which DMSO was activated by an electrophile to form a species of this kind which has a sulfonium ion species and a leaving group. This leaving group is formed because oxygen of the DMSO reacts with the electrophile.

So, we have to choose appropriate electrophile such that the OE becomes a nice leaving group. Then the alcohol reacts to form this intermediate which is similar to the intermediate of Kornblum type oxidation. So, conceptually these 2 are similar which of course leads in a similar fashion to the aldehyde. Finally we saw that in Corey Kim oxidation when dimethyl sulphide is reacted with N-chlorosuccinimide or chlorine.

It leads to an intermediate of this kind which of course as we saw that we can compare it with this type of intermediate. And since we have a leaving group on sulphur similar to what we had here but here we had from DMSO and here it is from the dimethyl sulphide. Now this reacts with alcohol to form an intermediate of this type which is similar to the Kornblum oxidation type intermediate.

So, now what we have is the formation of these aldehydes via conceptually similar sulfonium salts or intermediates which are basically conceptually similar to each other.

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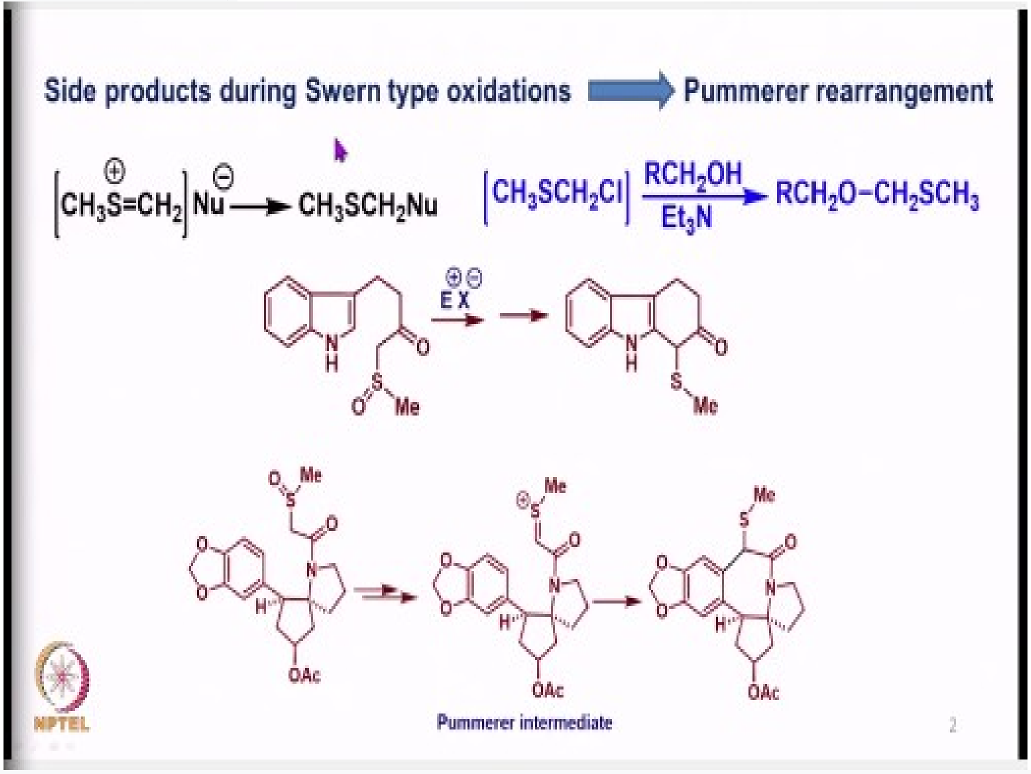

Side products during Swern type oxidations → Pummerer rearrangement

$[CH_3\overset{\oplus}{S}=CH_2]\overset{\ominus}{Nu} \rightarrow CH_3SCH_2Nu$

$[CH_3SCH_2Cl] \xrightarrow[Et_3N]{RCH_2OH} RCH_2O-CH_2SCH_3$

Pummerer intermediate

We also saw various kinds of side products that form during Swern type oxidations arising out of what is called as Pummerer rearrangement, so I discussed what was the Pummerer rearrangement. But in context with the oxidations involving DMSO and an electrophilic species we saw that an intermediate of this type which has a sulfonium ion and a double bond and a leaving group which can act as a nucleophile.

And then of course that can react to form this alpha functionalized sulphide which is also basically a Pummerer intermediate or Pummerer type of intermediate. Now in the Swern oxidation as we saw that we get alpha chloro sulphide which is a Pummerer type of intermediate. Either this directly reacts with alcohol to form this as a by-product or the alcohol can directly react with this sulfonium ion species arising before this chloro species is formed.

And then this alcohol reaction with this sulfonium ion species can lead to this by-product. In either case Pummerer type of intermediate is first formed, which is this kind of intermediate or this kind of species. Then we also saw that if we take an indole based molecule like this and react with an electrophile through the Pummerer intermediate when the reaction proceeds. It allows the carbon-carbon bond formation to take place here to form this particular final product.

Now today we look at another example where the Pummerer rearrangement has been carried out and the Pummerer intermediate trapped in intramolecular fashion. For example if we take a case like this which is similar to this but somewhat more complicated having a spiro system here. So, as you can see here that we have this part here which can be activated with an electrophile leading to the formation of the Pummerer intermediate of this kind as we discussed last time.

And then this undergoes cyclization on this particular position because this oxygen can give electron density and activate the para position which leads to the formation of the carbon-carbon bond here and eventually to this particular product. So, this is another application of the Pummerer type of intermediates to be trapped in an intramolecular fashion to lead to useful products.

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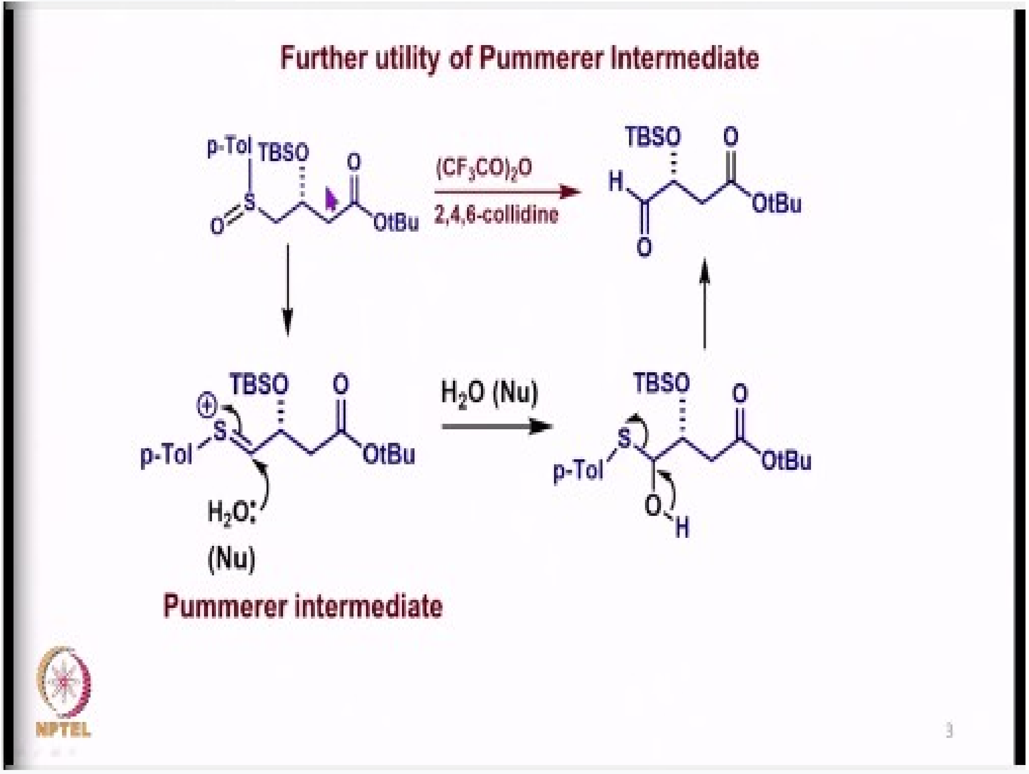

Further utility of Pummerer Intermediate

Now further utility of the Pummerer intermediate has also been reported in the literature. If we start with a molecule like this which of course one can take as a optically active molecule but now it has a sulfoxide. Now this sulfoxide when it is treated with tri fluoro acetic anhydride in the presence of a base like 2, 4, 6 collidine, then what is obtained is eventually this particular aldehyde.

Now this aldehyde has come from this particular part here that is CH $_2$SO para tolyl. That means the sulfoxide part sulfoxide and methyl part here. So, now what happens is when tri fluoro acetic anhydride reacts with the sulfoxide the Pummerer intermediate is formed which is of this type. Now as we have seen in earlier cases that the nucleophile attacks on to this carbon. Now if it so happens that nucleophile is water, then of course we get an intermediate of this type which is not a stable intermediate.

As you can see it is basically a hemithioacetal, so this hemi thioacetal then undergoes a cleavage and leads to the formation of the corresponding aldehyde. So, basically it is a very easy conversion that if one takes the corresponding sulfide here and oxidizes to the corresponding sulfoxide. Then you can straight away go to the formation of the corresponding aldehyde, so this is an interesting utility of the Pummerer intermediate trapping.

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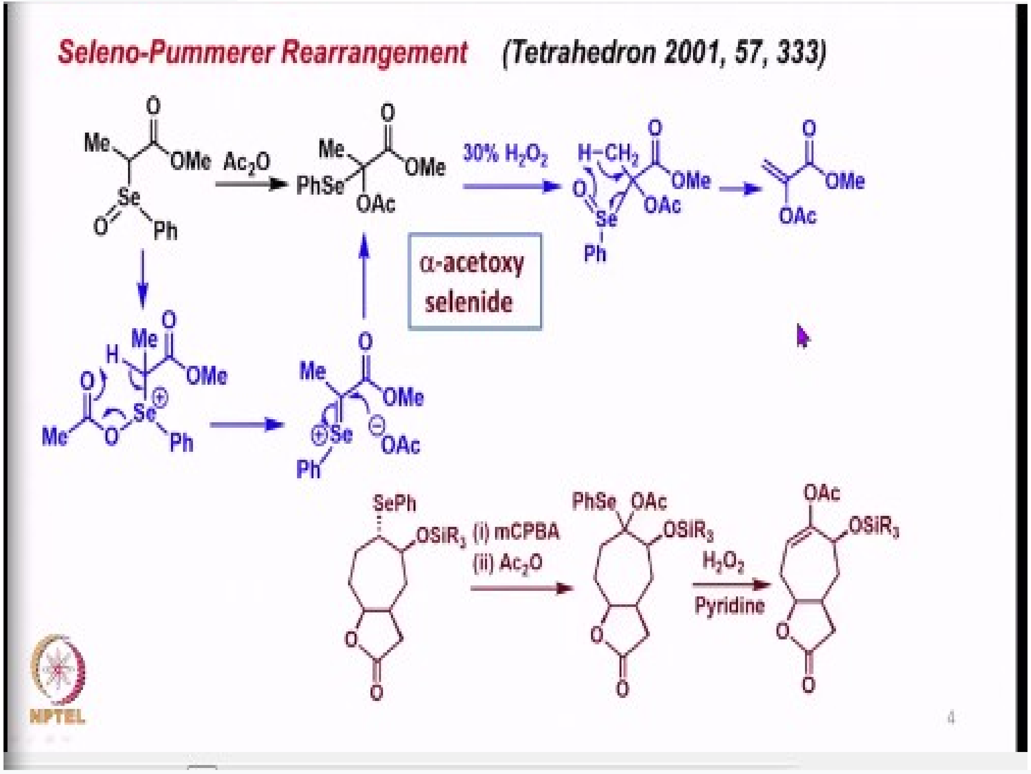

Seleno-Pummerer Rearrangement (*Tetrahedron 2001, 57, 333*)

α-acetoxy selenide

Now there is also something called as a seleno Pummerer rearrangement just the way as sulfides can be converted to sulfoxides. And Pummerer rearrangement can be carried out if we have one hydrogen alpha to it. Similarly if we take a selenoxide of this kind and if we treat with acetic anhydride then we can have an alpha acetoxy selenide because selenides are also important intermediates.

Now what happens is that if we somehow get this particular alpha acetoxy selenide, then if we allow the oxidation of selenide to selenoxide to take place say in the presence of 30% hydrogen peroxide. Then it can allow an elimination of this kind involving a 5 member transition state to form the double bond like this. And this is of course a very important intermediate for number of reasons, now how does the reaction occur?

Of course in a similar fashion as we discussed earlier, first sulfoxide base, Pummerer rearrangement that selenoxide reacts with acetic anhydride to form the oxygen carbon bond, which then undergoes elimination to form this particular ionic intermediate to which the acetate ion attacks onto the carbon to form this alpha acetoxy selenide, very similar to what we discussed for sulfoxide based rearrangement.

Now if we take an example of this kind then we see that if we oxidize this selenide to selenoxide followed by reaction with acetic anhydride. Then similar to this we can get alpha acetoxy selenide which upon reaction with hydrogen peroxide in the presence of pyridine, pyridine basically to takes care of the acid. Then what we see is an elimination towards this side leading to this particular product and this product can be very useful for a number of different synthetic operations.

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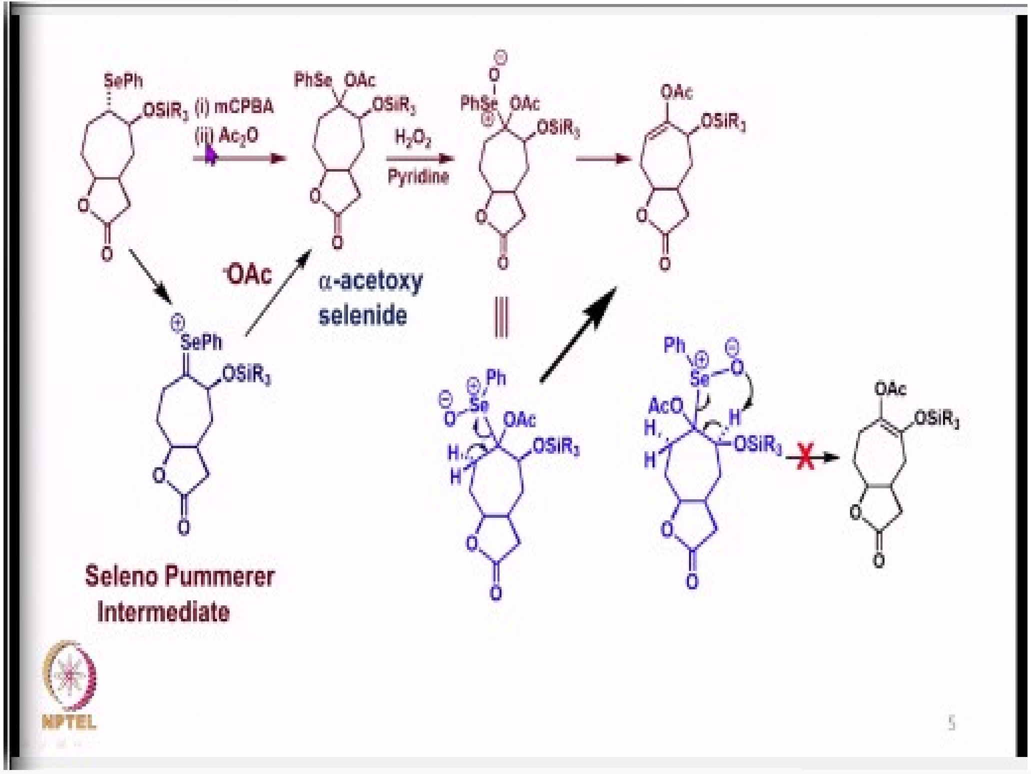

Now we have to look at it how does this reaction occur? Of course as we saw that meta chlorobenzoic acid will first convert the selenide to selenoxide. And when selenoxide reacts with acetic anhydride then of course we will get this seleno Pummerer intermediate which upon reaction with the nucleophile present in the reaction medium. That the acetate ion would lead to acetoxy selenide.

Of course this acetoxide selenide then upon oxidation with hydrogen peroxide lead to the formation of the selenoxide. Now this selenoxide as we discussed leads to this particular product with an elimination on the left hand side. Now if we look at this it is particular compound here, we can write the structure in this particular fashion, where we have shown clearly the two hydrogens on the left hand side.

Now this selenide here has alpha configuration and when the Pummerer rearrangement takes place and if it proceeds via this seleno Pummerer intermediate, then obviously we have lost the stereochemistry here. So, this acetate can either attack from alpha side or beta side, that means it can be a mixture of alpha or beta selenide, that means this carbon selenium bond can be either alpha or beta.

So, now if we make the selenoxide, and for this elimination to occur we need a 5 member transition state where oxygen takes up the proton form here and then of course this carbon selenium bond gets cleaved. So, whether this is alpha or beta for both the compounds we have the two hydrogens which are available here because such a 5 membered transition state requires the atoms to be in the same plane.

That means if this carbon selenium bond is alpha, then it is much easier for this transition state to form in which this also is alpha. That means alpha hydrogen is abstracted when this carbon selenium bond is also alpha oriented. And of course when it is beta oriented then this particular proton will be eliminated but in both the cases we will get the same product. That means elimination on the left hand side is more facile because there are two different types of hydrogens available.

And therefore irrespective of the carbon selenium bond stereochemistry elimination will give the same product. On the other hand we consider why the elimination did not take place on the right side. Now if the right side, now as we see here that carbon hydrogen bond is alpha oriented. So, if carbon selenium bond is alpha oriented then of course elimination should give this product but generally we do not see any such product form, here or in many cases.

And the reason for that is that when this oxygen is approaching the hydrogen which is now attached to the same carbon as $OSiR_3$. Basically what is happening is the electrons on the oxygen are coming very close to the oxygen electrons here and of course there also will be steric repulsion. So, base electronic as well as steric factors do not permit or do not easily allow the elimination to occur on the right side and thus this product is not formed and what we get generally is this product.
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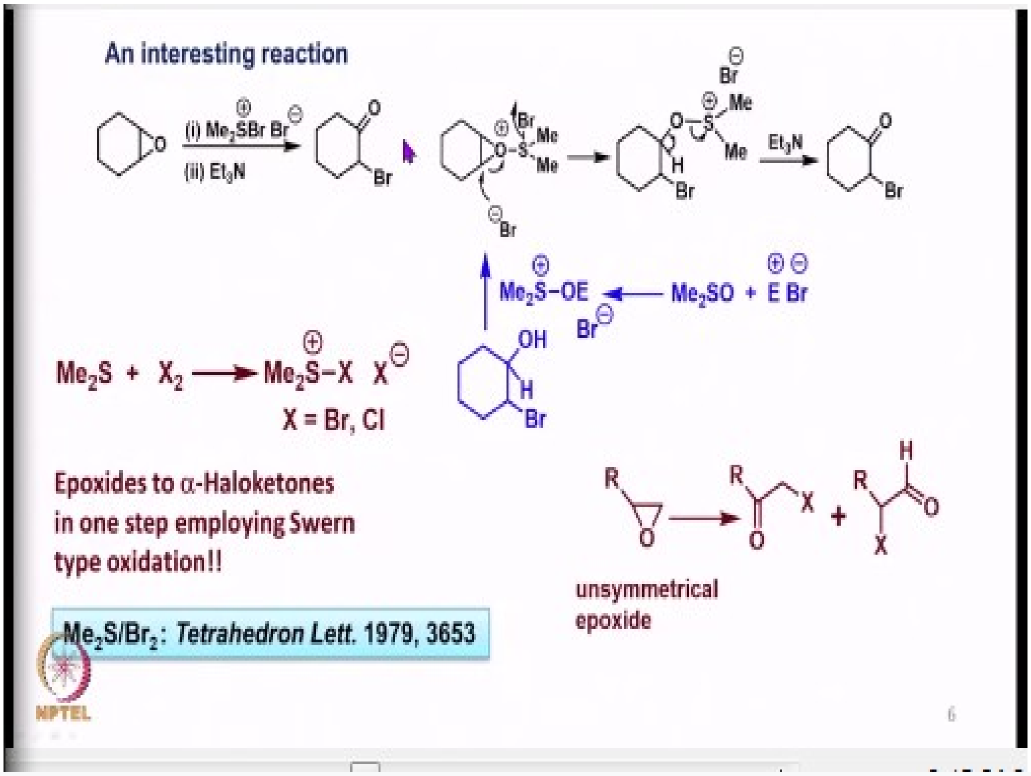

An interesting reaction

$Me_2S + X_2 \longrightarrow \overset{\oplus}{Me_2S}-X\ X^{\ominus}$

X = Br, Cl

Epoxides to α-Haloketones in one step employing Swern type oxidation!!

Me_2S/Br_2: *Tetrahedron Lett.* 1979, 3653

unsymmetrical epoxide

Now there is an interesting reaction on the usage of this sulfur based reagents for the conversion of epoxide to alpha haloketones and it is published in 1979. It is a very interesting reaction, so I thought that it would be worth discussing it here. So, how it is happening is that if take epoxide and directly convert to the corresponding alpha bromoketone in one step using this reagent. So, basically this reagent which is used here is nothing but a combination of dimethyl sulphide and bromine and this forms a yellow, orangish yellow kind of solid of this type.

Of course we can also take dimethyl sulfide and react with chlorine instead of bromine, then of course we will get the corresponding chlorides, that of course is not as stable as this. However whether we take chlorine or bromine, if we have a species like this and if we react with epoxide, we get the corresponding alpha haloketone. So, basically it is a reaction or conversion of epoxides to alpha haloketones.

In one step, employing Swern type oxidation, so I will discuss that how it is Swern type oxidation? Now when this epoxide comes in contact with this sulfonium bromide, then you have oxygen sulfur bond and then of course you will generate a positive charge on the oxygen. So, the nucleophile Br - opens the epoxide to form an intermediate of this kind. Because now Br will be gone as a Br ion and of course we will get carbon bromine bond here and this intermediate.

Now this particular part of the intermediate is similar to Swern type of intermediate that is the intermediate form in Swern type oxidation. And therefore if we use tri ethylamine in the reaction then of course it will pick up a proton from the methyl and then the anion will pick up a proton next to the oxygen. And oxidation as we have discussed would take place in an intra molecular fashion to form this alpha bromoketone, as you can imagine that if we take corresponding bromohydrin.

And then if we react with Swern type of oxidation or DMSO based oxidation where DMSO is activated with electrophile to form this intermediate and then of course basically doing the oxidation only of alcohol to ketone. But this is already having a bromine, what we are starting here is a different reaction. We are starting with an epoxide and converting in one step to the corresponding alpha bromoketone.

Of course if we start with an unsymmetrical epoxide of this kind, then it is difficult to predict where the nucleophile will attack after the oxygen has been activated by sulfur, it could be on this or on this position depending on that we will get a mixture of products. So, this is one of the problems of one of the things that one has to consider when we utilize this particular oxidation to form alpha haloketones from epoxide.

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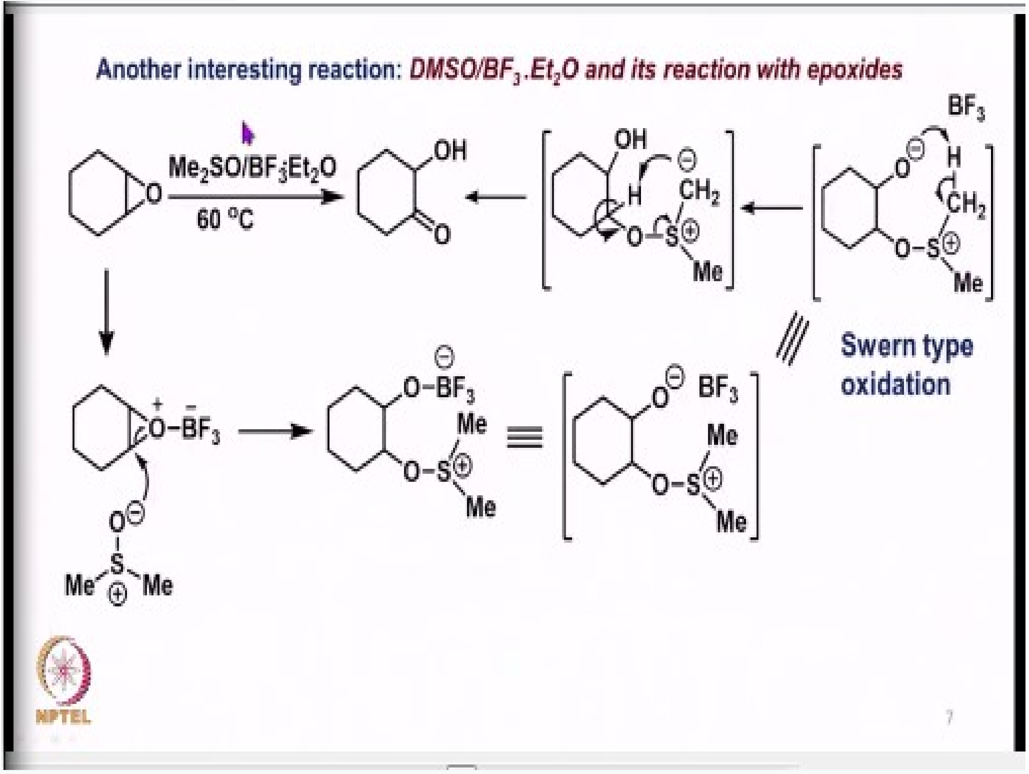

Another interesting reaction: *DMSO/BF$_3$.Et$_2$O and its reaction with epoxides*

Now there is another interesting reaction with DMSO BF$_3$ etherate with epoxide. So, if you take an epoxide and react with DMSO in the presence of BF$_3$ etherate at 60 degrees we get the corresponding alpha hydroxy ketone. This also has somewhat similar type of oxidation as Swern type of oxidation but slightly differently. So, we can imagine that DMSO reacts with the epoxide, after the epoxide has been activated by BF$_3$ etherate.

The DMSO would open the epoxide in this fashion leading to the formation of this ionic intermediate, which can be written up like this where BF$_3$ then comes off. Now we can think that, we have the intra molecular proton abstraction by this way to form the anion at the carbon. Basically this and this is similar where we have expanded the methyl group to show that the O - will pick up the hydrogen from here.

It can also happen that this hydrogen is picked up by another such species in an intermolecular fashion. Essentially leading to formation of this anion, and then this anion will undergo intra molecular proton abstraction. Similar to the Swern type of oxidation and then eventually lead to the formation of the alpha hydroxy ketone. So, this is an interesting reaction which is of course a very unique type of reaction and has been reported in the literature. And which is somewhat similar to the DMSO based oxidations involving the similar type of intermediates as shown here.

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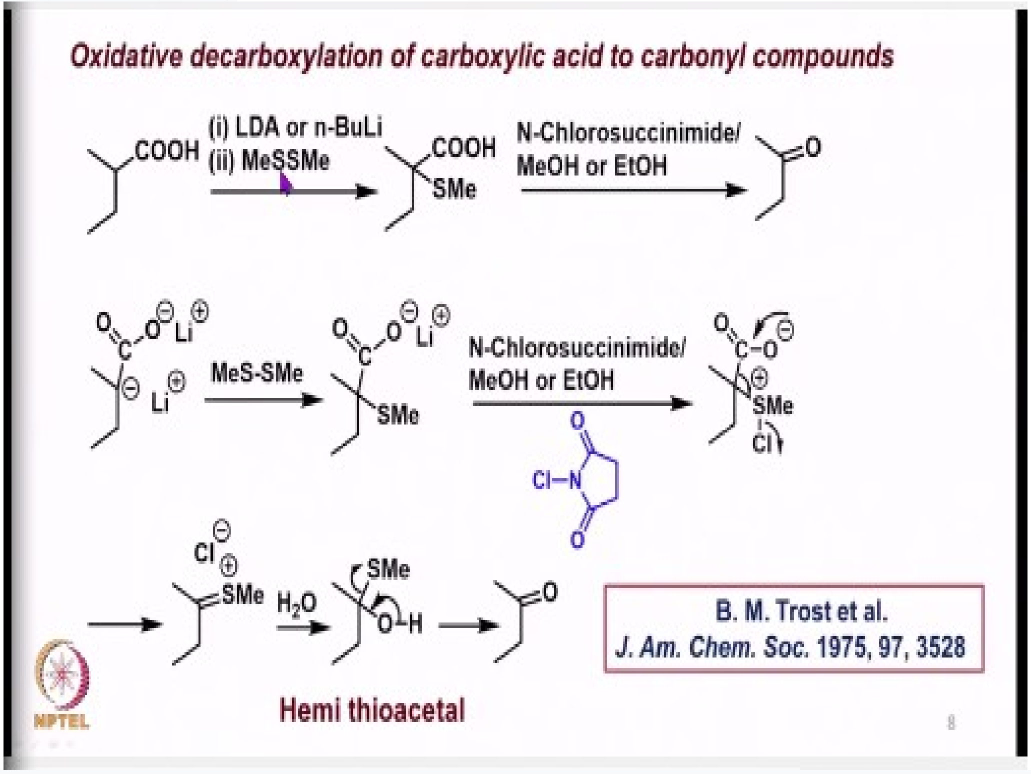

Oxidative decarboxylation of carboxylic acid to carbonyl compounds

Hemi thioacetal

B. M. Trost et al.
J. Am. Chem. Soc. 1975, 97, 3528

Now there is another interesting reaction which is also involving oxidative type of interesting transformations. And it is also by using sulfur based chemistry and similar type of sulfonium intermediates. This involves oxidative decarboxylation of carboxylic acids to carbonyl compounds. That means basically we are starting with this carboxylic acid and eventually converting into the corresponding ketone, what is required is?

And this is reported by B. M. Trost several years ago, is we start with the carboxylic acid and react with the base like LDA lithium diisopropylamide or butyl lithium and a disulfide like di-methyl disulfide. Then what happens is of course we get alpha functionalized carboxylic acid which then reacts with N- chlorosuccinimide to form this, how does this reaction occur? The reaction with base yields this di anion because this will be picked up first and also this will be picked up.

Now this anion or this di anion then reacts with dimethyl disulfide to form this carbon sulfur bond here because this is more stable than this. And therefore this is less reactive than this anion therefore this carbon sulfur bond forms. Now this activation of this particular species with N-chlorosuccinimide in methanol of water, it forms this particular intermediate. Because now sulfur will react with N- chlorosuccinimide to form this sulfonium ion species, which then now as you can see here is a leaving group.

In earlier cases we had seen that the alcohol reacts onto the sulfur directly. But now here there is no nucleophile present and therefore decarboxylation occurs, cleaving this carbon-carbon bond and followed by expulsion of the chloride ion to generate this intermediate. If this intermediate is formed then of course water can react during the workup and what we can get is this hemithioacetal which then cleaves and leads to the formation of the corresponding ketone.

So, this is how a very interesting oxidative decarboxylation of carboxylic acid to carbonyl compound has been reported by Trost.

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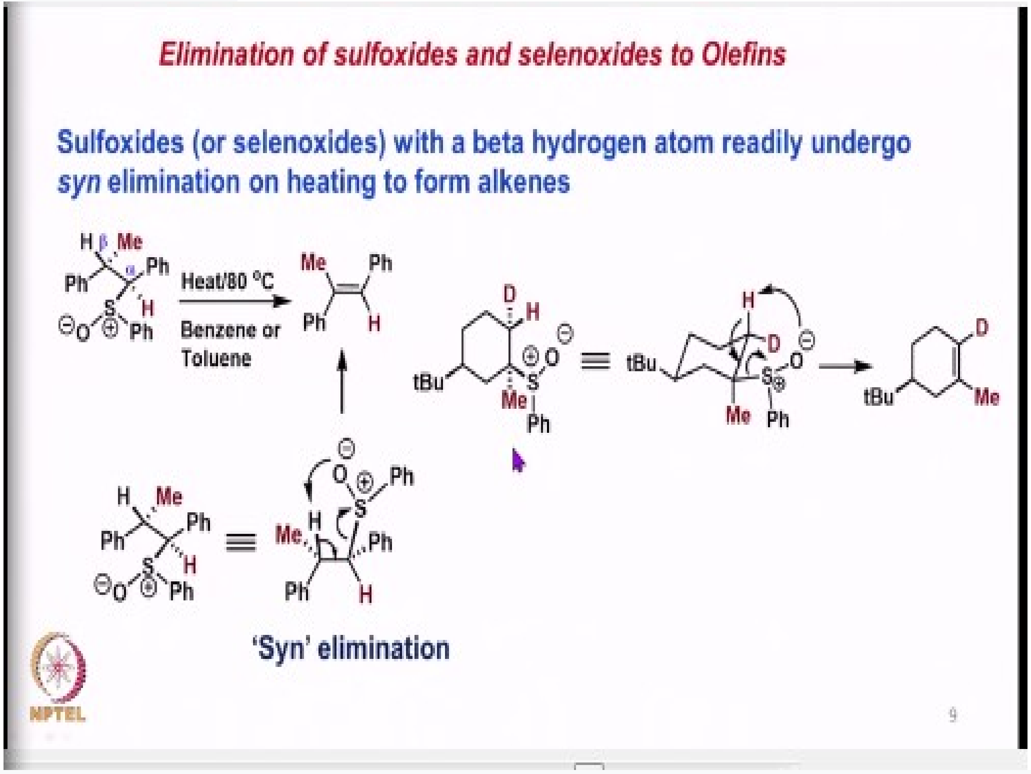

Elimination of sulfoxides and selenoxides to Olefins

Sulfoxides (or selenoxides) with a beta hydrogen atom readily undergo *syn* elimination on heating to form alkenes

'Syn' elimination

Now we discussed the eliminations of selenoxide but we also will now look at the elimination of sulfoxides little more carefully and with the mechanism. Sulfoxides or selenoxides with the beta hydrogen undergo syn elimination on heating to form alkenes. If you take the sulfoxide here with this particular stereo chemical dispositions, then you can see that there is an alpha hydrogen there is also beta hydrogen.

So, if you heat at 80 degrees in benzene or toluene we get this particular product as the final product formed in this reaction. Now what happens is that if we write it in this particular fashion here like what we have done? Now here is basically put it in such a fashion everything is same, so that this carbon hydrogen which is here is beta oriented, this carbon sulfur bond is also beta oriented, that is exactly what we have written it here too, except that it is slightly differently put.

But now this hydrogen this carbon-carbon sulfur and oxygen they are all in one plane and then syn elimination takes place. Because carbon hydrogen and carbon sulfur bonds are in the same direction. This syn elimination leads to the formation of this pair of olefin, now it is a stereo selective elimination. So, that means if we take a sulfoxide of this kind where there is a hydrogen and also deuterium.

If we write the conformation, so the carbon sulfur bond is beta oriented and then the hydrogen which is beta oriented is axial. And deuterium which is alpha oriented is equatorial and of course tertiary butyl which is beta oriented is also equatorial. Now for this elimination to occur obviously carbon sulfur oxygen and this hydrogen carbon they are syn disposed. So, now this syn disposed species then undergo syn elimination to form this particular olefin. So, this is the example of elimination of sulfoxides to olefin.

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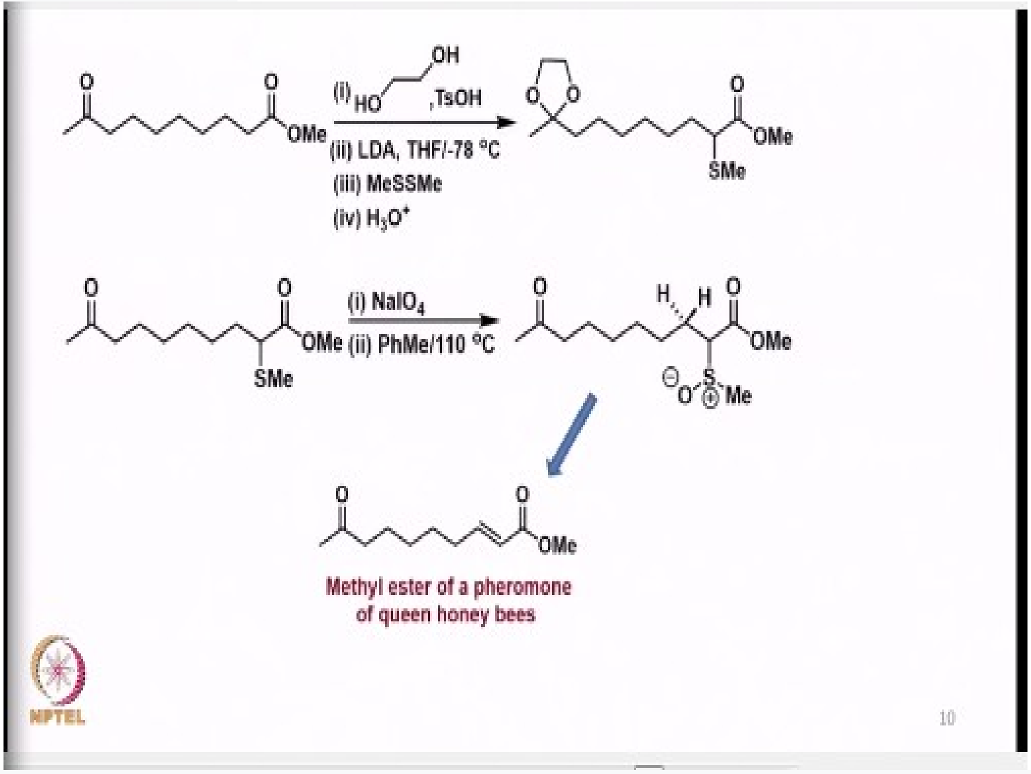

Methyl ester of a pheromone of queen honey bees

So, in a similar fashion selenoxides also undergo elimination. Now one of the products that has been utilized is in this particular type of transformation is that we start with this keto ester. Then we can get the corresponding sulfide here by first protecting this ketone as a ketal followed by LDA deprotonation here. And then reaction with dimethyl disulphide then we can remove this ketal from here and then that leads to the formation of this intermediate.

That means this particular intermediate is formed after the third step and the fourth step that is the hydrolysis of this ketal leads to the release of the ketone here. So, that will lead to the formation of this particular thio intermediate. Now if you make the sulfoxide by using sodium metaperiodate and heat it. Then of course via the sulfoxide elimination occurs and of course we get this particular product as the final product which is a basically a pheromone which I discussed earlier in the first lecture, that this is a pheromone of queen honey bees.

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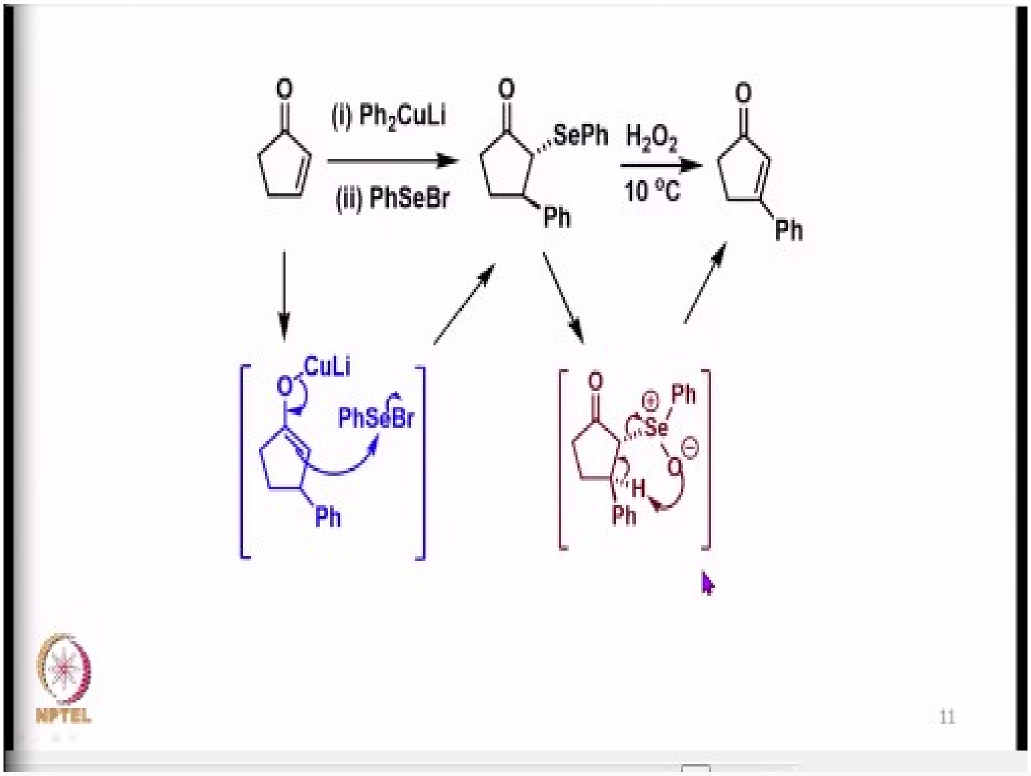

Now we can also carry out another interesting reaction where now we are going to use similar type of selenoxide based elimination. And that is if we take an alpha beta unsaturated ketone of this kind and react with lithium diphenyl cuprate and react with phenyl selenium bromide. Then we get this type of selenium intermediate which upon reaction with hydrogen peroxide leads to the formation of the double bond.

What happens is of course lithium dimethyl cuprate will add in a michael fashion here. And the corresponding enol cuprate then acts as a nucleophile to react with the electrophile that is phenyl SeBr. In this fashion to form this trans intermediate that means this carbon selenium bond will be opposite to the carbon phenyl bond. And if this happens to be a beta bond then of course this will be an alpha bond.

Now this carbon selenium bond which is alpha oriented and the carbon hydrogen bond which is here is also alpha oriented as shown here. Then when hydrogen peroxide is reacted with it, it forms the selenoxide and this selenoxide has a carbon hydrogen bond which is in the same stereo chemical disposition as this cause an selenium bond. And this undergoes syn elimination to form this enone, so this is how if an selenoxide based syn eliminations have been utilize it. So, we will stop it here today and take up some other aspects of this kind of chemistry next time, till then bye.