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

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Lecture-03
Sulfur based Oxidations and Pummerer Rearrangement

Hello and welcome you all to today's lecture, I hope you had the opportunity to go through what I discussed in the last class related to the introduction to organic synthesis etc. Now we will have a brief recap of the last lecture where we discussed sulfur based oxidations.

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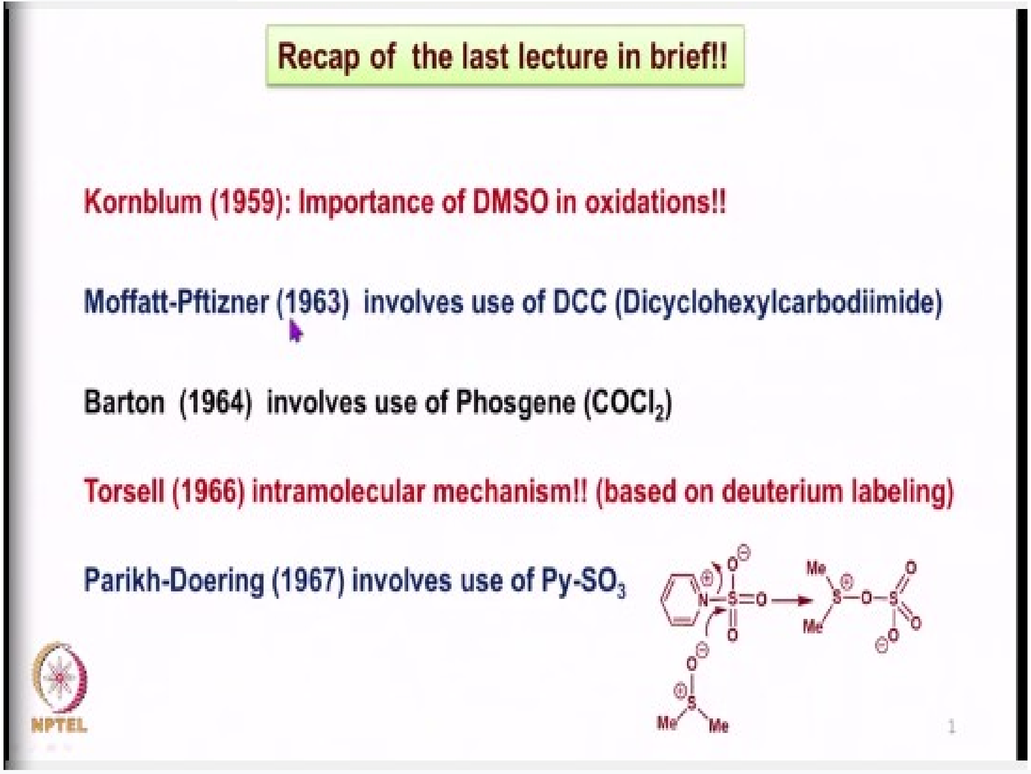

Recap of the last lecture in brief!!

Kornblum (1959): Importance of DMSO in oxidations!!

Moffatt-Pftizner (1963) involves use of DCC (Dicyclohexylcarbodiimide)

Barton (1964) involves use of Phosgene ($COCl_2$)

Torsell (1966) intramolecular mechanism!! (based on deuterium labeling)

Parikh-Doering (1967) involves use of Py-SO_3

Starting with Kornblum oxidation where we saw the importance of DMSO in oxidation. We discussed in this oxidation the activation of halides or tosylate with DMSO eventually leading to the oxidation and forming carbonyl compounds. And of course we discussed some mechanism. Now then we also discussed Mofffatt-Pftizner oxidation which involved the use of dicyclohexylcarbodiimide which activated DMSO and allowed the formation of an intermediate that reacts with the alcohol and eventually leads to the formation of the carbonyl compound.

As an extension of this particular concept Barton used phosgene to activate DMSO and then oxidation of alcohols were discussed by us. Of course we saw that the phosgene being very low boiling compound and not easy to handle was of course a drawback. Now all these cases what was the mechanism that was basically reported by Torsell which allowed through deuterium labeling to confirm that the reaction proceeds for an intramolecular mechanism.

And not an intermolecular mechanism something we had discussed at the beginning of the course where we discussed in the first lecture the mechanism of the oxidation based on chromium. Now Parikh and Doering then reported activation of DMSO using a complex of this type which is called as pyridine sulfur trioxide complex, where the sulfur species here acts as an electrophile to activate DMSO to form this intermediate and that allows oxidation to take place.

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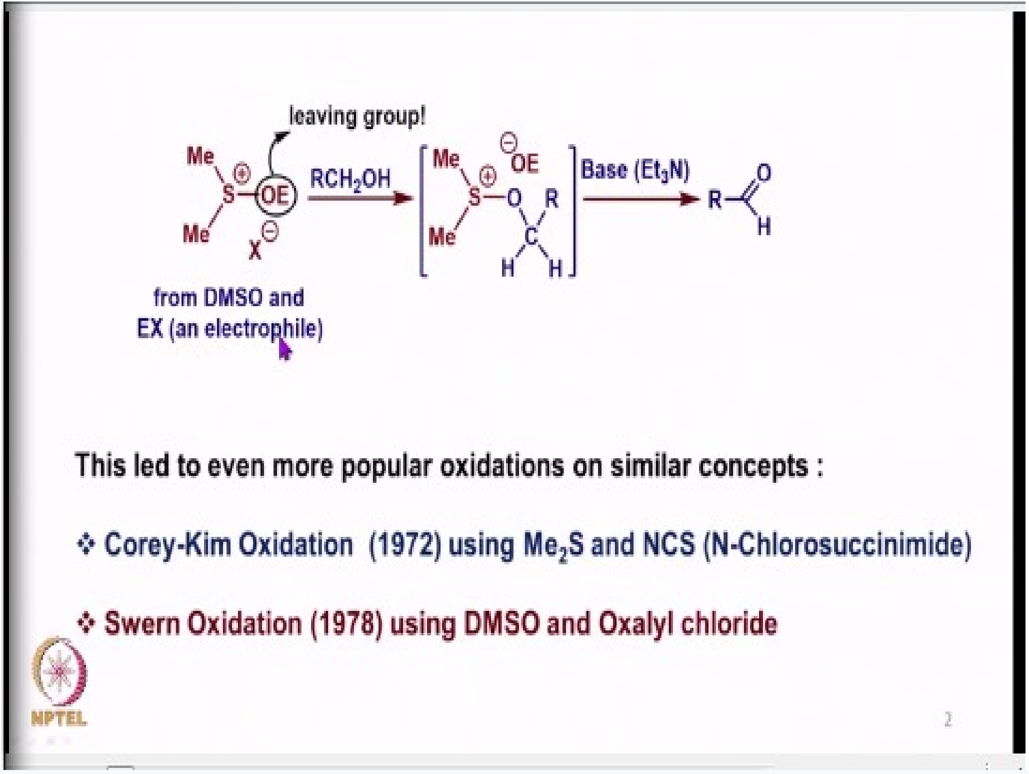

leaving group!

from DMSO and EX (an electrophile)

This led to even more popular oxidations on similar concepts :

- Corey-Kim Oxidation (1972) using Me_2S and NCS (N-Chlorosuccinimide)
- Swern Oxidation (1978) using DMSO and Oxalyl chloride

So, basically what we had discussed was that DMSO is activated by an electrophile whether it is a DCC or whether it is phosgene or whether it is pyridine sulfur trioxide. To form an intermediate of this kind where the oxygen of the DMSO is basically reacting with the electrophile to form a leaving group and so alcohol then reacts with the sulfur here. And this leaving group goes off to form this intermediate which then upon reaction with triethylamine as a base leads to the formation of aldehyde.

As we discussed and as confirmed by the Torsell studies that the hydrogen from the methyl group gets first removed as a proton and generate an anion which then intramolecularly picks up this hydrogen and then the oxidation takes place. Now these types of studies have led to even more popular oxidations on similar concepts. Now today we will discuss these oxidations the first one is Corey-Kim oxidation that was developed in 1972 where they used dimethyl sulphide and N-chlorosuccinimide as a reagent combination to give something similar type of species.

And therefore conceptually it is very similar to what we have discussed so far. And then Swern oxidation which is a very popular oxidation, it was reported in 1978 where Swern used DMSO and Oxalyl chloride to activate DMSO. And leads to the same kind of intermediate and similar type of oxidation but of course this is more popular for reasons that I will discuss today.

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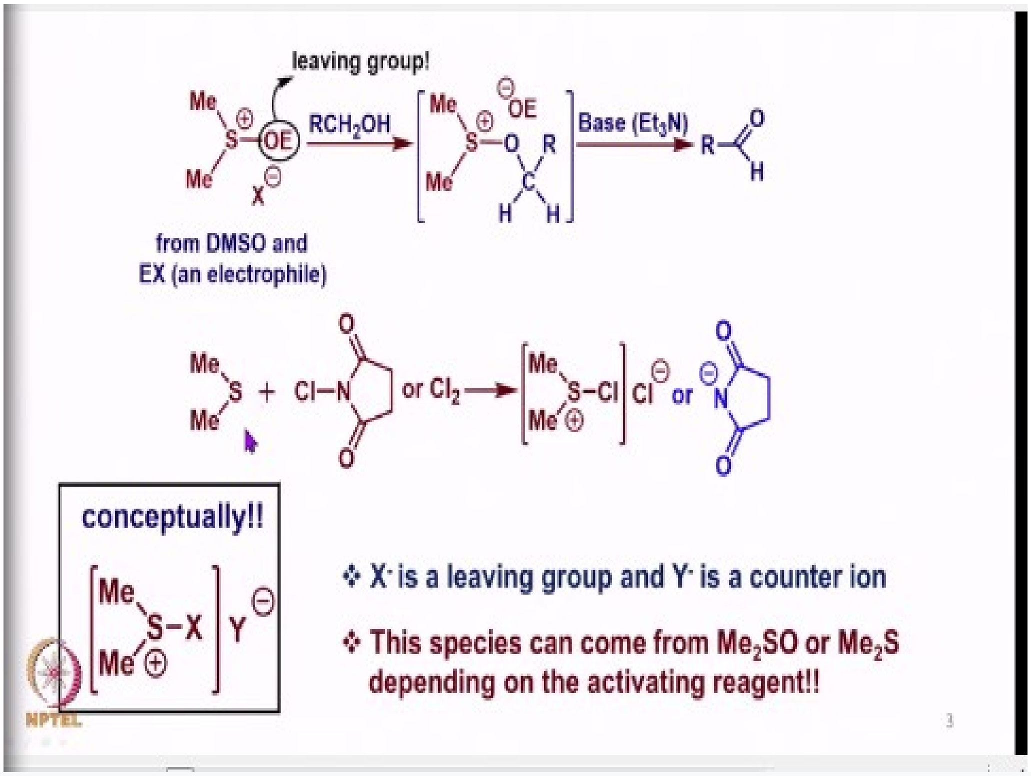

- ❖ X^- is a leaving group and Y^- is a counter ion
- ❖ This species can come from Me_2SO or Me_2S depending on the activating reagent!!

Now once again we look at what is this conceptual similarity between the oxidation of DMSO type and Corey-Kim type of oxidation is. In Corey-Kim type of oxidation of course we see that there is a dimethyl sulfide that gets activated by N-chlorosuccinimide or chlorine where sulfur makes a sulfur chlorine bond. And we get this species with a chloride ion or this succinimide ion as counter ion, so and then the oxidation occurs.

So, as you can see that there is a conceptual similarity between these two. This is the DMSO species which is activated by an electrophile where OE is leaving group. And here directly the divalent sulfur leads to a species similar to this where there is a leaving group. So, conceptually they are like this that you have an electrophilic sulfur species having a leaving group like X here and of course having a counter ion. Now this species can come from DMSO or DMS that is a dimethyl sulphide depending on what the activating agent is.

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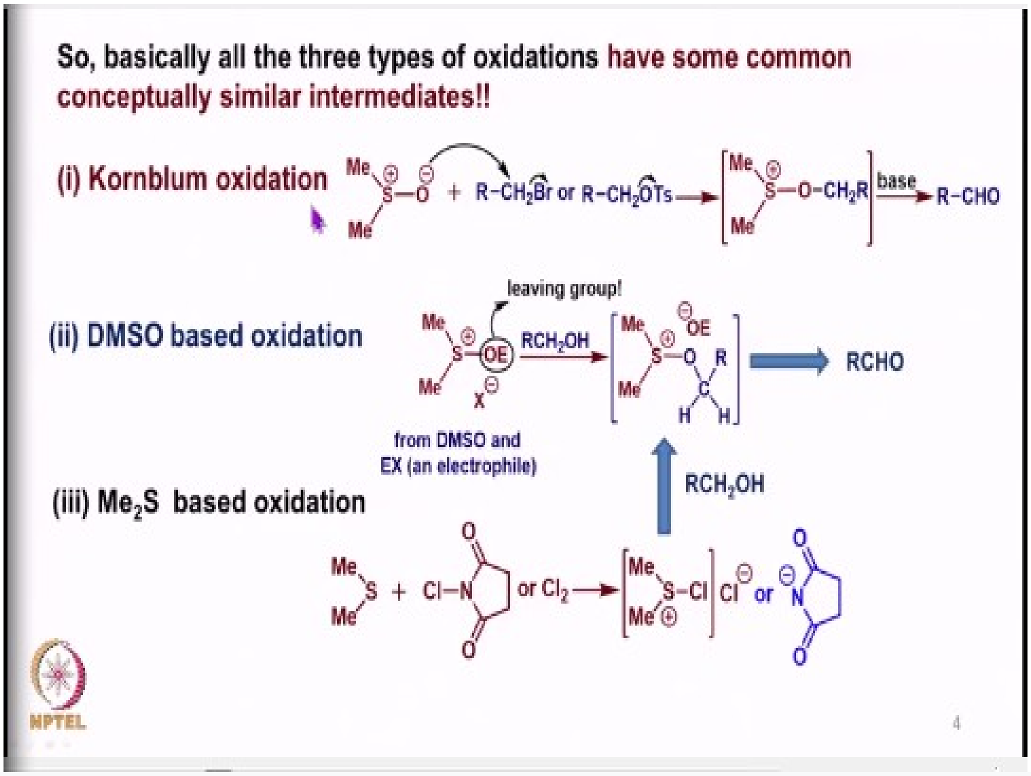

So, basically all the three types of oxidations have some common conceptually similar intermediates!!

(i) Kornblum oxidation

(ii) DMSO based oxidation

(iii) Me_2S based oxidation

Now look at it very carefully then it looks that they are basically conceptually having a similar type of intermediates. In Kornblum oxidation as we saw the DMSO interacts with halide or tosylate and give this intermediate directly and we are not reacting with an alcohol. But we are reacting with a halide or a tosylate which could be a derivative of an alcohol and we get an immediate like this which of course leads to the formation of aldehyde.

In the DMSO based oxidation what we have seen the DMSO then gets activated by the electrophile to form the species to which alcohol reacts to form similar type of species which is formed here by the reaction of DMSO with the halide or tosylate, and then of course rest of the things are similar. In the case of DMS based oxidation what we have seen is that we get similar type of intermediate like here which then react with an alcohol to form similar type of intermediate as Kornblum type of oxidation which then eventually leads to the aldehyde. So, this is the similarity between the 3 types of oxidation.

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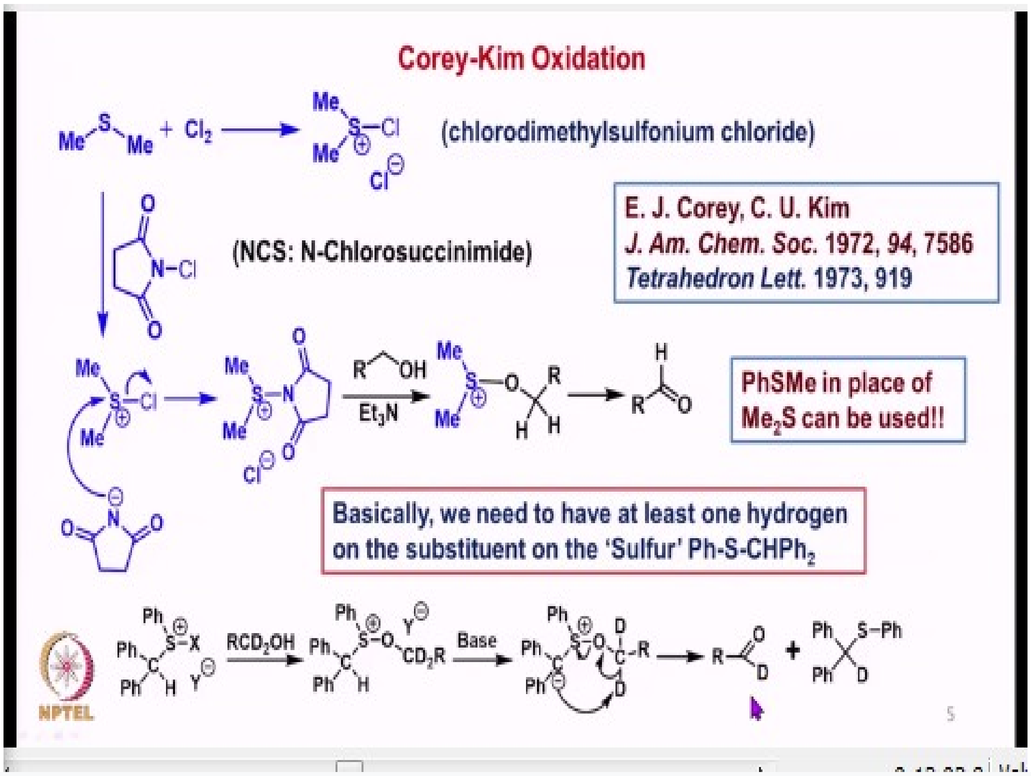

Corey-Kim Oxidation

(chlorodimethylsulfonium chloride)

(NCS: N-Chlorosuccinimide)

E. J. Corey, C. U. Kim
J. Am. Chem. Soc. 1972, *94*, 7586
Tetrahedron Lett. 1973, 919

PhSMe in place of Me_2S can be used!!

Basically, we need to have at least one hydrogen on the substituent on the 'Sulfur' Ph-S-$CHPh_2$

So, today we will look at little more carefully the Corey-Kim oxidation, what he is done is to react a dimethyl sulphide with chlorine to form this chlorodimethylsulfonium chloride or it is reacted with N-chlorosuccinimide to form this particular intermediate, which then reacts with the succinimide ion to form another sulfonium ion intermediate to this particular sulfonium ion intermediate or to this particular sulfonium ion intermediate which is chlorodimethylsulfonium chloride, the alcohol attacks.

And then this particular intermediate is formed, the kind of intermediate that we have seen in earlier oxidations. Then of course the treatment of this intermediate with a base like triethylamine leads to the formation of the corresponding aldehyde or carbonyl compounds, the kind of alcohol that we start with. Say for example if you start with the primary alcohol then we get aldehyde, if we start with the secondary alcohol then we get the ketone.

In place of dimethyl sulphide we can also use thioanisole that means basically what we need is a divalent sulphide, this has been published by Corey and Kim in 1972 and 73 and that is how it is called as Corey-Kim oxidation. So, basically what we need is to have at least one hydrogen on the substituent on the sulfur. Like for example this, this is a divalent sulfur compound in which there is one hydrogen on the carbon.

So, if we activate this divalent sulfur compound with any electrophile like chlorine or N-chlorosuccinimide. Then we will get an intermediate of this kind to which if we react with a alcohol like this as specifically taken this deuterated alcohol to distinguish between this hydrogen or deuterium from this particular hydrogen. So, we get this intermediate to which when base is allowed to react, then this particular proton will be picked up based on the mechanism that we have discussed earlier.

And then the intramolecular abstraction of the proton, in this particular case it will be deuterium which will then lead to the formation of the corresponding deuterated aldehyde. And of course as we can see that it would lead to the formation of this diphenylsulfide containing a deuterium here. Because now what has come out is of course a deuterium from here to here and of course this sulfur oxygen bond has broken therefore we get this particular sulfide. So, this is how the Corey-Kim oxidation takes place.

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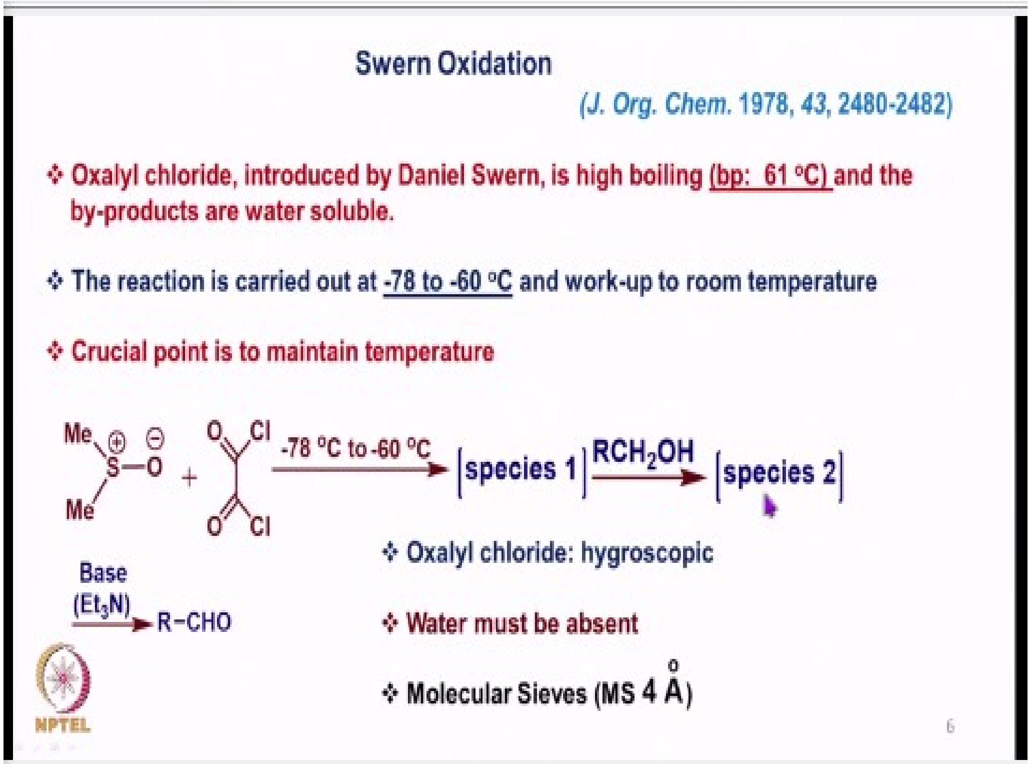

Swern Oxidation

(J. Org. Chem. 1978, *43*, 2480-2482)

- Oxalyl chloride, introduced by Daniel Swern, is high boiling (bp: 61 °C) and the by-products are water soluble.
- The reaction is carried out at -78 to -60 °C and work-up to room temperature
- Crucial point is to maintain temperature

$$\mathrm{Me_2S^{+}{-}O^{-}} + \mathrm{(COCl)_2} \xrightarrow{-78\ ^{\circ}C\ to\ -60\ ^{\circ}C} [\text{species 1}] \xrightarrow{RCH_2OH} [\text{species 2}] \xrightarrow[(Et_3N)]{Base} R{-}CHO$$

- Oxalyl chloride: hygroscopic
- Water must be absent
- Molecular Sieves (MS 4 Å)

Now we look at the Swern oxidation, where oxalyl chloride is used to activate DMSO. The oxalyl chloride has a high boiling point like 61 degrees and the byproducts are water soluble. The reaction was reported in 1978, the reaction is carried out at -78 to -60 degrees and then work up is done at a room temperature. The crucial point is of course to maintain the temperature when DMSO reacts with the oxalyl chloride at - 78 degrees.

And slowly it is brought to - 60 degrees then we get a species 1, and this species 1 then reacts with the alcohol to form a species 2. Then that species reacts with triethylamine to form the corresponding aldehyde. Now one of the problems that is faced here is that oxalyl chloride is hygroscopic. And therefore water must be absent and in order to make sure that water is not present in the reaction medium, molecular sieves are used to remove water. So, basically the conditions require that we have to be very careful to remove water and also we have to maintain the temperature because of mechanistic implications that we will discuss now.

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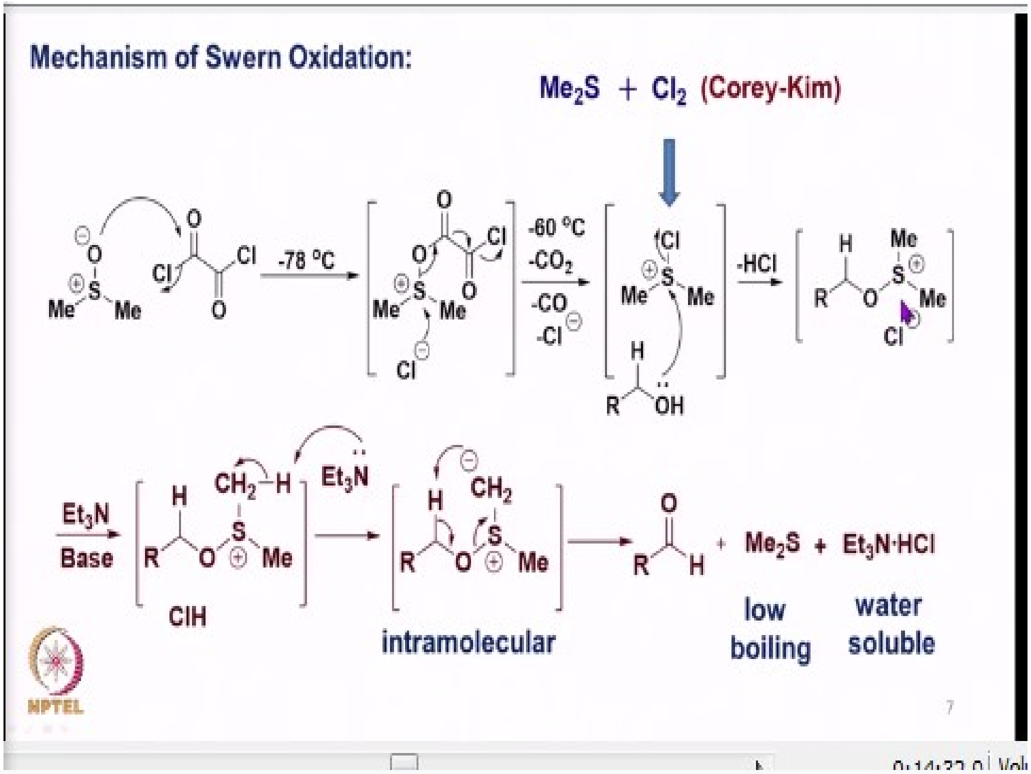

Mechanism of Swern Oxidation:

So, now you can see that in the mechanism of Swern oxidation the DMSO reacts with oxalyl chloride in this particular fashion to form oxygen carbon bond at - 78 degrees to lead to the formation of this intermediate in which chloride ion attacks on to the sulfur and carbon dioxide, carbon monoxides and of course chloride ion are released to form this intermediate onto which the alcohol attacks, and then upon the loss of hydrochloric acid this intermediate is formed.

Now this particular intermediate as you can see coming from DMSO oxalyl chloride is similar to the intermediate that comes from dimethyl sulfide and chlorine as reported by Corey-Kim. Then of course triethylamine picks up the proton from here, forming an intermediate of this kind which then in an intramolecular fashion leads to the elimination of this oxygen sulfur bond. And of course we get the corresponding aldehyde and dimethyl sulphide which is low boiling.

And then of course triethylamine hydrochloride which is water soluble. So, as you can see that we have the low boiling carbon dioxide, carbon monoxide and of course we have water soluble triethylamine hydrochloride. So, we can easily work up this reaction and get essentially pure aldehyde or a ketone from the reaction.

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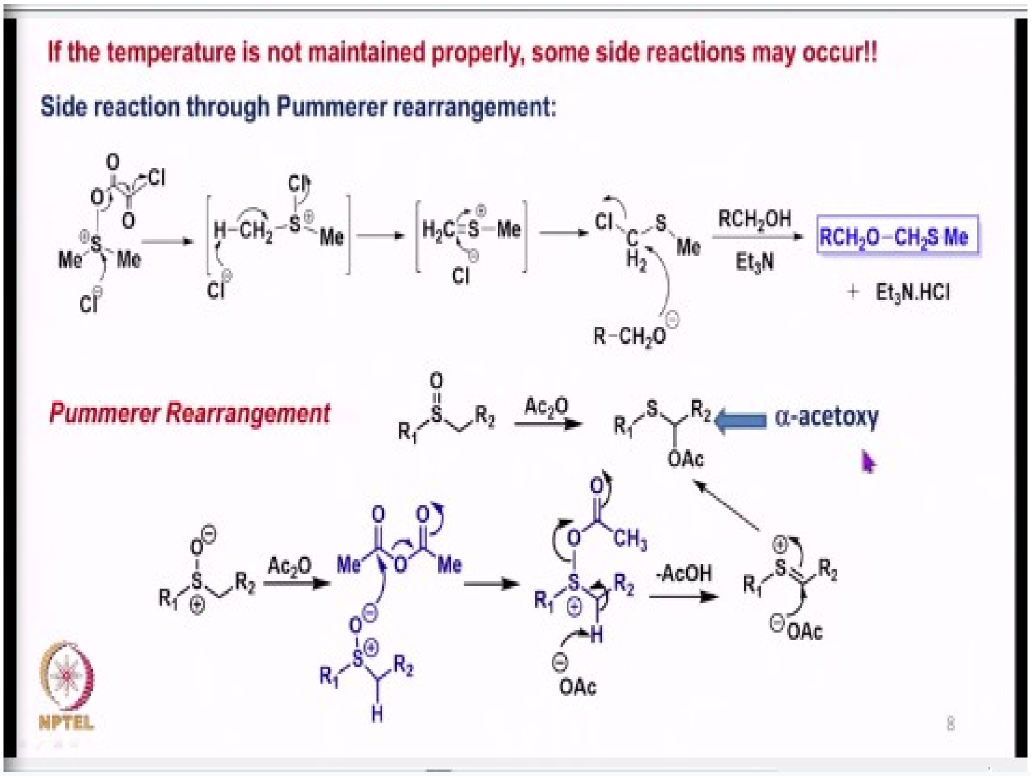

If the temperature is not maintained properly, some side reactions may occur!!

Side reaction through Pummerer rearrangement:

Pummerer Rearrangement

Now if the temperature is not maintained properly then some side reactions may occur. The side reactions are through a rearrangement called as Pummerer rearrangement. Now if you recall this is the first intermediate that forms when DMSO reacts with oxalyl chloride. And then of course as we discussed the chloride ion attacks onto the sulfur and of course we get this intermediate which is similar to the intermediate that Corey-Kim reported.

Now what can happen is instead of alcohol attacking onto this particular sulfur, chlorine as a chloride ion can pick up a hydrogen from here. And this type of elimination occurs leading to the formation of this sulfonium salt in which now the chloride ion attacks onto the carbon, forming this species to which then alcohol can attack directly and form this type of sulfur intermediate. This can also form directly from this species here. So, instead of chlorine attacking as a chloride ion onto this carbon of the alcohol can directly attack onto this carbon to form this sulfur intermediate.

Now this is basically the side product that can form and this is what is coming due to rearrangement which is very similar to Pummerer arrangement. Now what is Pummerer rearrangement? Pummerer rearrangement is that if you start with a sulfoxide and react with an electrophile like acetic anhydride. Then what we get is basically alpha acetoxy sulphide, like here what we have got is alpha chlorosulfide.

So, if we start with DMSO, then what we have got is alpha chlorosulfide which of course reacts with the alcohol anion in the Swern oxidation because alcohol was present in the reaction medium to form this intermediate. But this particular species is basically due to the rearrangement which is similar to what is called as Pummerer rearrangement. In the Pummerer rearrangement for example here when DMSO reacts with acetic anhydride then O - reacts with the carbon of the acetic anhydride to form this intermediate.

And of course acetate ion will come out. Now just the way as chloride ion has removed the proton from here the acetate ion removes the proton from here. And this acetate ion leaves off, acetic acid comes off and we generate this sulfonium ion intermediate which is what is here. Now acetate attacks onto this to form the alpha acetoxy sulfide, similar to alpha chlorosulfide. So, this is the similarity between the 2 reactions and that happens because if the temperature is not maintained then some of these side reactions can occur.

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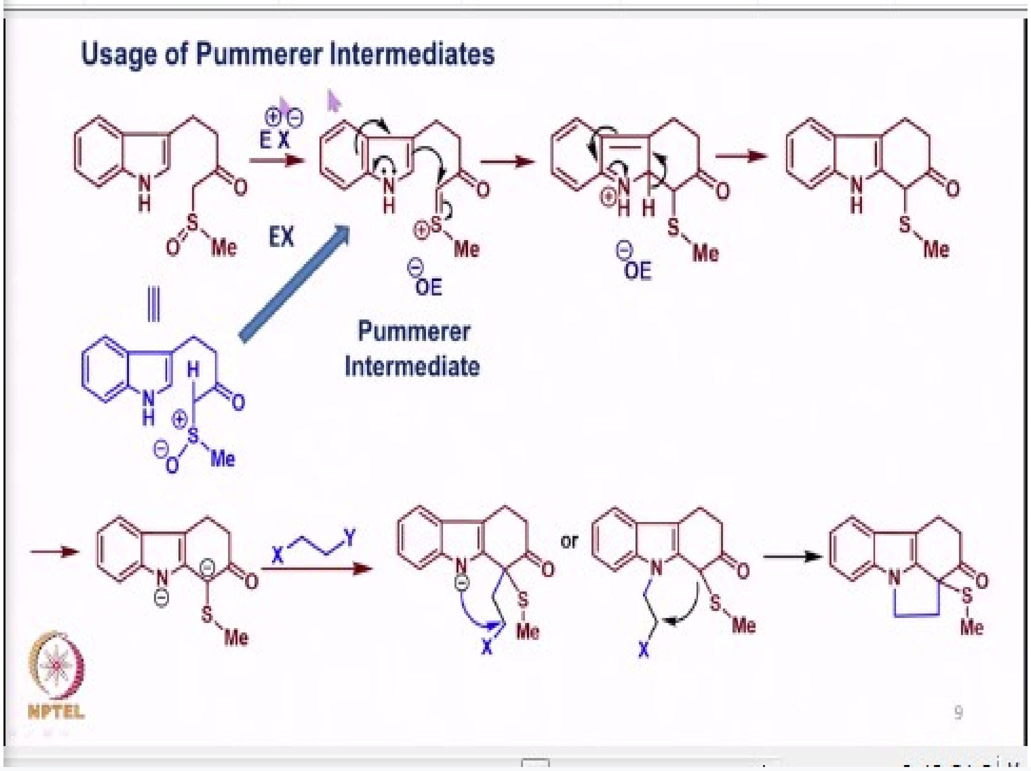

Usage of Pummerer Intermediates

Now there are lot of interesting reactions that have been reported using the positive aspects of the Pummerer rearrangement, in fact Pummerer rearrangement was independently discovered. Now what is happening in the Pummerer rearrangement is of course as we discussed that a sulfonium ion forms form a sulfoxide. So, for example if you start with a sulfoxide like this which has an indole moiety.

Now this side chain which is attached is on the third carbon of the indole and we have sulfoxide and of course a carbonyl group and in between we have 2 hydrogens. So, we can of course write this sulfoxide like this and if we react this with an electrophile like acetic anhydride, trifluoro acetic anhydride or anything of that sort. Then what will happen is that O - will react with the electrophile get activated as a leaving group.

Then of course this proton will fall as we discussed earlier in the Pummerer rearrangement leading to the formation of this sulfonium ion, which is what is a Pummerer type of intermediate. So, now depending on what the electrophile is the counter ion will be, so if we start with acetic anhydride then of course we get the corresponding acetate. Generally we choose in such a reaction the electrophile in which has electron withdrawing group.

So, that this does not become a very good nucleophile, so instead of this nucleophile attacking on to this carbon here. Since this species now is well suited for an intramolecular reaction and therefore the reaction occurs to trap this intermediate this species, where this carbon is now electrophilic and therefore the nucleophilic carbon of the indole then attacks to this leads to the formation of this type of intermediate which then looses a proton to form the indole derivative of this type.

Where, now you can see that there is a new carbon-carbon bond form and a new cyclic ring is attached to the indole. So, we are going through the Pummerer intermediate and making use of this to form this kind of cyclic molecules. Now what can be done with this is that now we have two hydrogens here which are alpha to the carbonyl group. We also have one hydrogen here which is alpha to the carbonyl and of course is also alpha sulfide.

Now this is definitely more acidic proton and of course the hydrogen here on the nitrogen is also acidic. So, if we react this particular species with 2 equivalents of base then we can get this particular di anion, the anion will form on the nitrogen as well as onto this carbon. Now these 2 anions of course can react with a species like this in which there are 2 leaving groups.

So, if we have something like ethylene dibromide for example, then we can get either this reacting first or this anion reacting first. And eventually what will happen is you will have a C-C bond formation here and then followed by that there will be N-C bond. And then of course we can proceed in either way depending on what this particular species is we can of course have substitutions on these carbons then we will get different type of final molecule.

But eventually what will happen is that we will get a ring here of this kind, so we will have not only three rings attached to each other. Now we have 4 rings attached to each other and now we have scope where the chemistry based on this sulfur moiety can be carried out based on this carbonyl can be carried out and various kinds of reactions and various kinds of products can be formed. So, this is an interesting example of the utility of the Pummerer rearrangement product or Pummerer intermediate.

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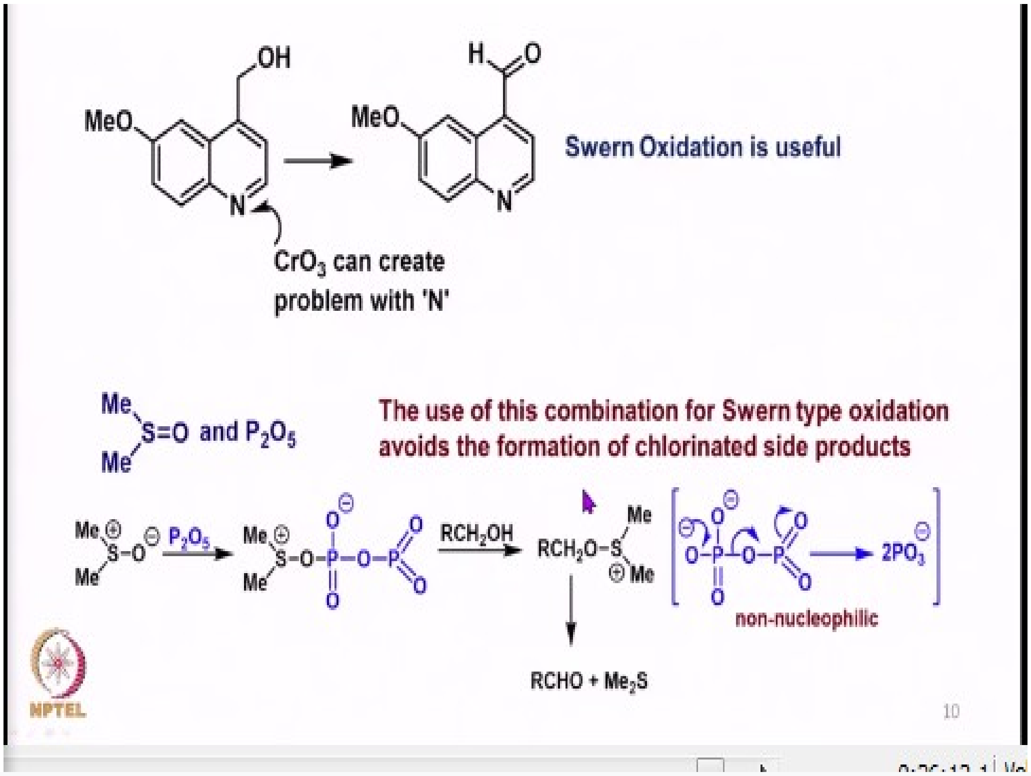

Swern Oxidation is useful

CrO_3 can create problem with 'N'

The use of this combination for Swern type oxidation avoids the formation of chlorinated side products

The Swern type of oxidation can be utilized in the oxidation of this species here, where there is a nitrogen. What is found is that such alcohols, if they are oxidized using chromium trioxide based reagents. Then sometimes there is an oxidation of the nitrogen directly to form the corresponding N oxide and the alcohol is not readily oxidized. In this case says of course one can make use of Swern oxidation.

But in Swern oxidation as we discussed chloride becomes a leaving group, and then chlorine based products are formed as side products. So, in order to avoid the formation of chlorine based side products some people have made use of DMSO P_2O_5 combination which is similar to Swern oxidation. But now does not have a chloride or any such species which can give side products.

So, DMSO reacts with P_2O_5 to form an intermediate of this kind which does not have any kind of anion that can react with the intermediates. And therefore now when alcohol reacts with this intermediate then we get a species like this which is similar to the species that we have seen in Swern oxidation or other oxidations and of course we get the corresponding aldehyde. Now the part which has come out from this sulfur based intermediate is of this type.

And of course this will expel 2 phosphite species and they are of course non nucleophilic. So, therefore this is a very interesting variation of the DMSO based oxidation or Swern type of oxidation and without having any chlorinated by-products. So, we will stop it here and look at the other aspects of oxidations next time, till then take care and study what I have taught today, bye.