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

Prof. Dr. Yashwant D. Vankar
Retired from Department of Chemistry
Indian Institute of Technology-Kanpur

Lecture-02
Sulphur Based Oxidation of Alcohols

Hello everyone, I would like to welcome you all for today's lecture, we will briefly look at what we discussed last time, we started looking at the oxidation of alcohols using chromic acid and we considered the possibility of abstraction of hydrogen from the intermediate that is involving chromium based intermediate either in an intermolecular fashion such as this.

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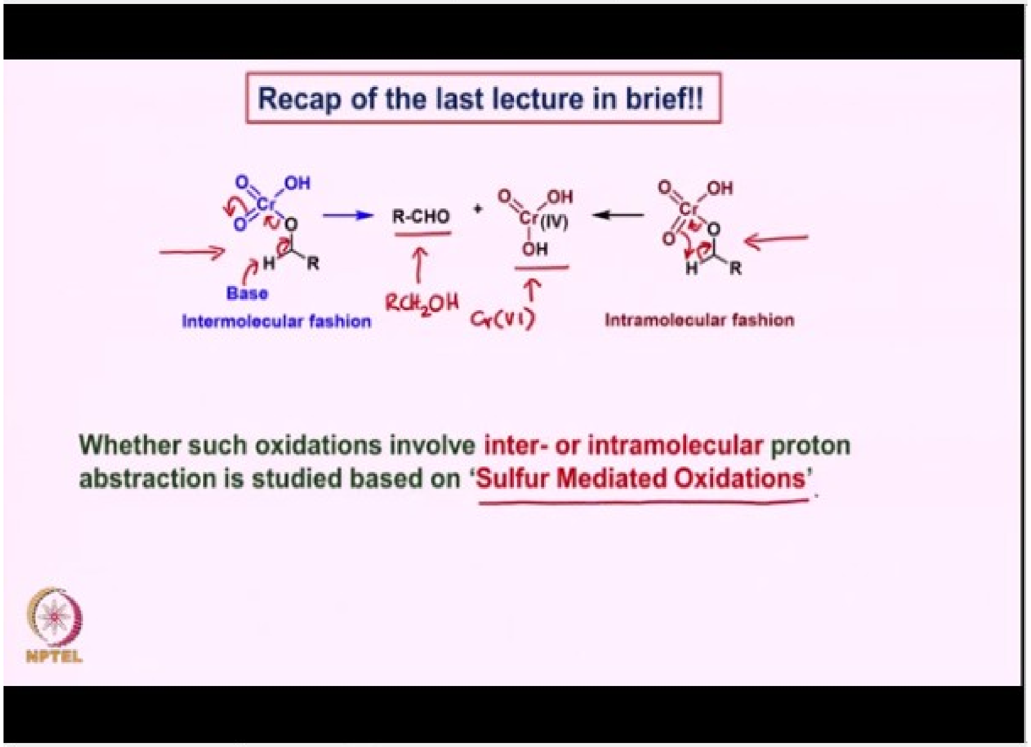

Recap of the last lecture in brief!!

Whether such oxidations involve inter- or intramolecular proton abstraction is studied based on 'Sulfur Mediated Oxidations'.

So, the base picks up the proton from here in an intermolecular fashion and then the oxidation occurs in this fashion. This was one possibility that we considered after the alcohol reacts with the chromic acid and it forms this intermediate Alternatively, the same intermediate can also undergo an intramolecular proton abstraction and that can happen in this fashion.

So, that the same intermediate that is formed. So, from chromium VI we started and we get chromium IVas one of the intermediates and of course, the aldehyde comes from the corresponding alcohol. So, this is what we discussed last time. Now, the abstraction of proton in an inter molecular or intra molecular fashion is something that we need to establish, it is very difficult to do that with chromium based intermediates because, the reactions are very fast and it is very difficult to carry out such reactions.

But whether such oxidations involve intermolecular or intramolecular proton abstraction has been studied using a sulfur mediated oxidations.

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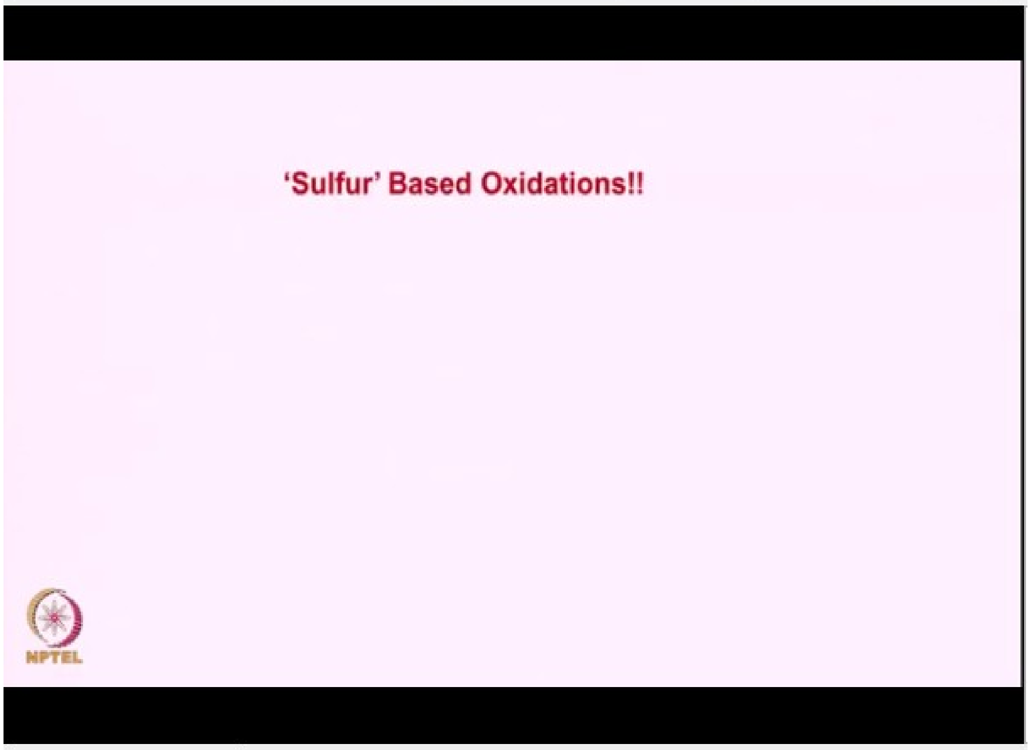

‘Sulfur’ Based Oxidations!!

Now, we look at sulfur mediated oxidations and one of the most important and very popular oxidations involving sulfur based intermediates is swern oxidation.

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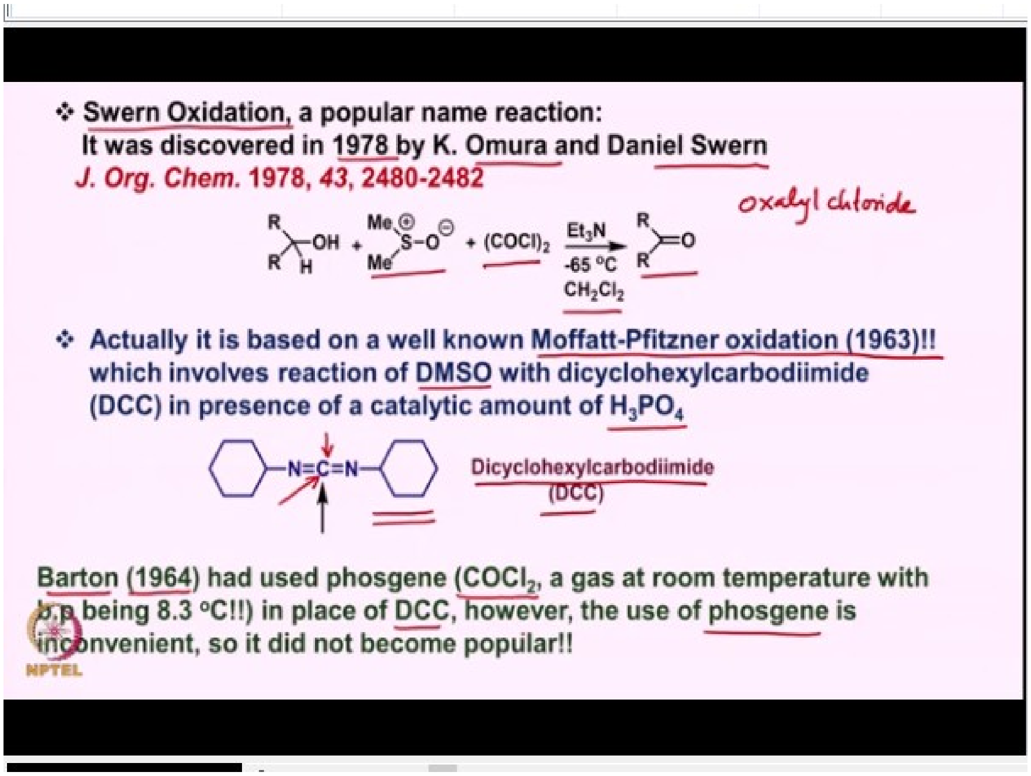

- **Swern Oxidation, a popular name reaction:**
  It was discovered in 1978 by K. Omura and Daniel Swern
  J. Org. Chem. **1978, *43*, 2480-2482**

- **Actually it is based on a well known Moffatt-Pfitzner oxidation (1963)!! which involves reaction of DMSO with dicyclohexylcarbodiimide (DCC) in presence of a catalytic amount of H_3PO_4**

Dicyclohexylcarbodiimide (DCC)

Barton (1964) had used phosgene ($COCl_2$, a gas at room temperature with b.p being 8.3 °C!!) in place of DCC, however, the use of phosgene is inconvenient, so it did not become popular!!

So, in the swern oxidation, what has been reported is that the DMSO that is dimethyl sulfoxide reacts with oxalyl chloride, this is the acid halide from oxalic acid. So, it is called as oxalyl chloride, oxalyl chloride reacts with DMSO at low temperature to form certain intermediate which then reacts with the alcohol in the presence of trimethylamine at - 65 degrees in dichloromethane at solvent.

And eventually leads to the formation of the ketone. Now, this was reported in 1978 by Swern and of course, his collaborator Omura. So, this is what is a popularly known as Swern oxidation. Now, this oxidation is actually based on a well known oxidation called Moffatt-Pfitzner oxidation which were discovered in 1963, which involved reaction of DMSO. So, all of them are based on DMSO based oxidations.

And they react with dicyclohexylcarbodiimide. This is the structure of dicyclohexylcarbodiimide. As you can see, that the carbon atom here is flanked basically by 2 nitrogens by double bonds and therefore, this particular carbon atom is highly electrophilic particularly, under the presence of catalytic amount of an acid such as phosphoric acid. Now, this was discovered in 1963.

Based on this, the oxidations of alcohols were reported. And subsequently, in 1964, Barton reported the use of phosgene, which is a gas at room temperature with a boiling point being 8.3 degrees centigrade in place of DCC. However, the use of phosgene is not very convenient and therefore, it did not become very popular, this reaction, but the Moffitt-Pfitzner oxidation was actually carried out by a lot of people in their oxidation endeavours.

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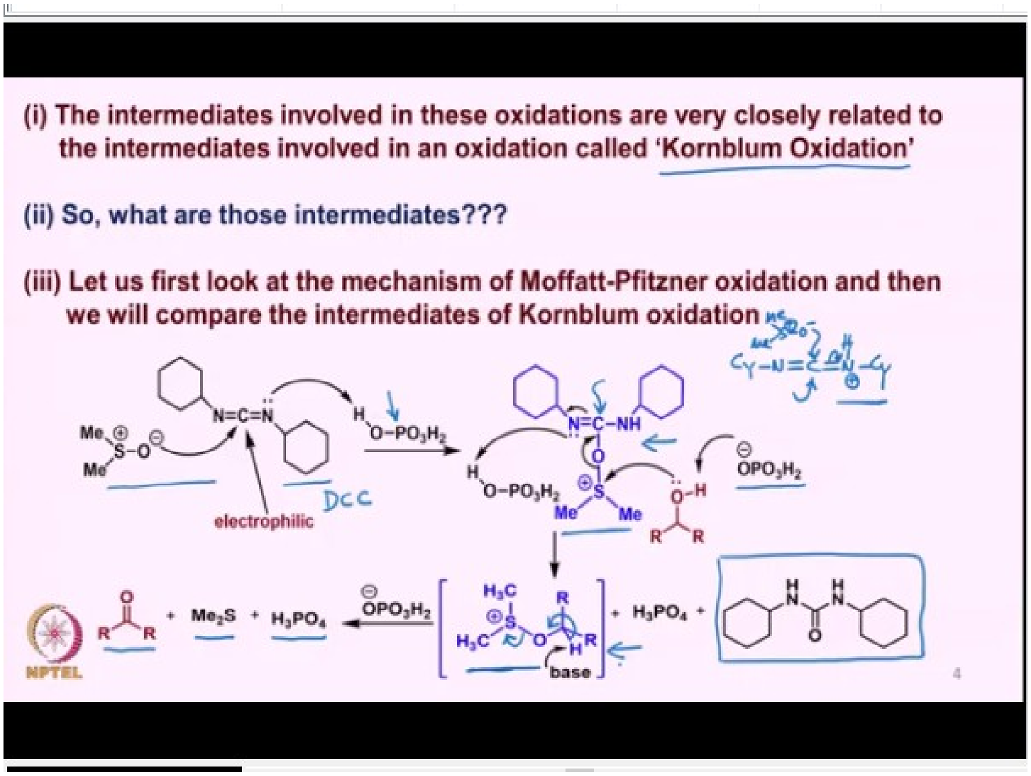

(i) The intermediates involved in these oxidations are very closely related to the intermediates involved in an oxidation called 'Kornblum Oxidation'

(ii) So, what are those intermediates???

(iii) Let us first look at the mechanism of Moffatt-Pfitzner oxidation and then we will compare the intermediates of Kornblum oxidation

Now, the intermediates which are involved in these kinds of oxidations are very closely related to another oxidation known as Kornblum oxidation. So, what are those intermediates? We will look at those intermediates a bit later, but the first let us see how the mechanism of the Moffatt-Pfitzner oxidation and very closely how the Barton oxidation has been also looked at it.

So, as I mentioned, that dicyclohexylcarbodiimide, which is DCC is having 2 nitrogens and one of the nitrogen gets protonated with the phosphoric acid that we use it here and it forms an intermediate or the protonation. So, if we write cyclohexane as CY, then what it would look like it would look something like this and this gets protonated and then you have a positive charge on the nitrogen.

This makes this carbon much more electrophilic than the original DCC because the positive charge here on the nitrogen would like to get neutralized when the alcohol attacks on it. So, if the DMSO attacks on it. So, first DMSO attacks. So, you have a DMSO here, you have methyl here and the methyl here, the DMSO minus attacks onto this carbon, this is how it is shown here.

So, when DMSO attacks onto this carbon, which is now having nitrogen protonated. So, this is the intermediate that is going to come out. This is a very crucial intermediate. And again, now the second nitrogen gets protonated and again forms the same ammonium ion like what we have written here, but now on the other nitrogen and again this carbon becomes very electrophilic.

And at the same time, now, the alcohol reacts on to the sulfur and this carbon oxygen sulfur bond breaks and the new carbon oxygen bond is formed, because the carbon now is electrophilic because of the protonation of the nitrogen here and therefore, what is proposed is that the dihydrogen phosphate ion which comes out after the loss of proton from here, in both the cases the protons are basically lost.

So, you have dihydrogen phosphate and ion that picks up the hydrogen from here that picks up the proton from here and the negative charge of the oxygen from the alcohol then reacts with the sulfur and then this bond breaks. Thereby now the phosphoric acid is again regenerated by the abstraction of this particular proton. And of course, the nucleophilicity of the alcohol becomes larger.

And that leads to this particular intermediate and this intermediate as it was proposed earlier, is that again base which is present in the reaction medium, you have this dihydrogen phosphate and that can pick up a proton from here and then oxidation can occur in this fashion to give the ketone and then as you can see, the dimethyl sulfide goes off and of course, you regenerate the phosphoric acid.

Now, the only thing what happens is that when this dicyclohexylcarbodiimide is protonated and then of course, you lose the oxygen from the DMSO then you form a carbon oxygen double bond and this is what leads to the formation of this dicyclohexylurea, this is a urea having 2 dicyclohexyl parts. So, this is something it is an important by-product, but then this particular by-product does create some problem which we will talk in a minute. But here what I would like to mention is that this particular intermediate which is shown in blue, and another intermediate this as shown in this blue also are very crucial intermediates.

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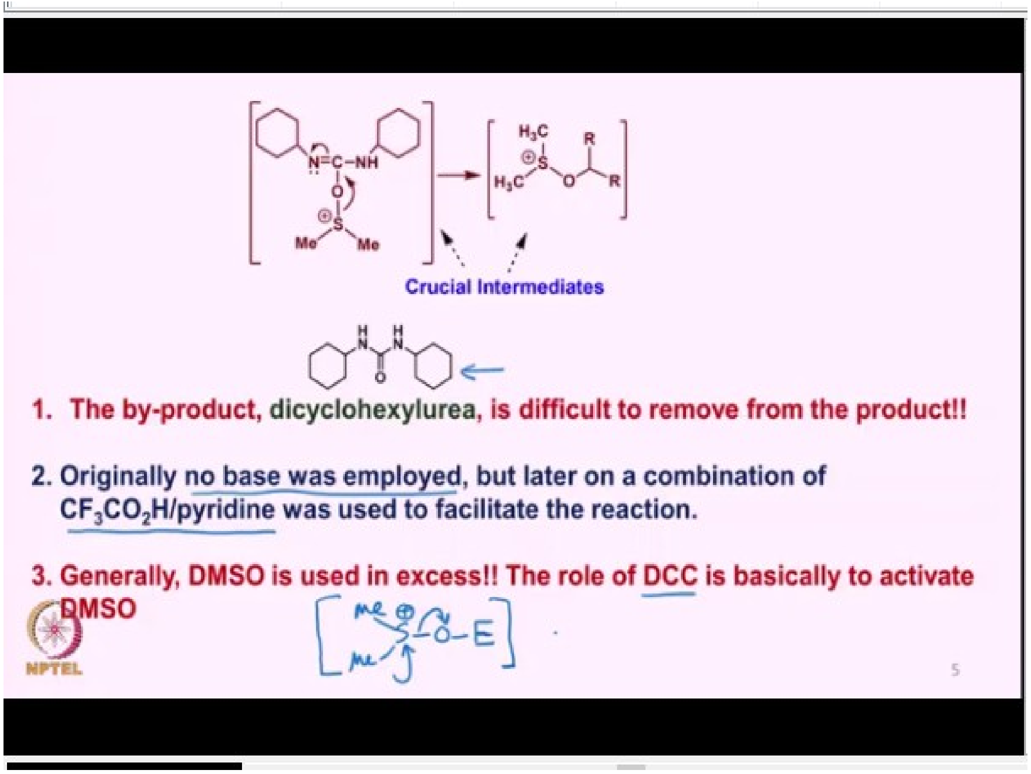

Crucial Intermediates

1. The by-product, dicyclohexylurea, is difficult to remove from the product!!
2. Originally no base was employed, but later on a combination of CF_3CO_2H/pyridine was used to facilitate the reaction.
3. Generally, DMSO is used in excess!! The role of DCC is basically to activate DMSO

Now, as these crucial intermediates and this dicyclohexylurea are the ones which are worth considering. Now what happens during the reaction that this dicyclohexylurea becomes difficult to remove while purification of the ketone is being done. So, many people did not want to prefer to use the dicyclohexylcarbodiimide because of the difficulty in separating dicyclohexylurea.

So, originally there was no base that was used there, therefore, the reaction took a bit longer time. But later on they started using a trichloroacetic acid and pyridine as a combination in which trichloroacetic acid protonates the dicyclohexylcarbodiimide. And of course pyridine acts as a base and does the reaction gets facilitated. In general, the DMSO is used in excess. And of course, as you can see that the main role of the DMSO is of course, to get activated by DCC.

So, the DCC activates the DMSO forming an intermediate of this type where you can say that E is a part of the dicyclohexylcarbodiimide. And therefore, you have a positive charge here, this is the actually role of DMSO. So, the oxygen of the DMSO gets activated by the DCC, and then your alcohol attacks onto this carbon. And this goes as a leaving group, we will look at it these intermediates a little more carefully.

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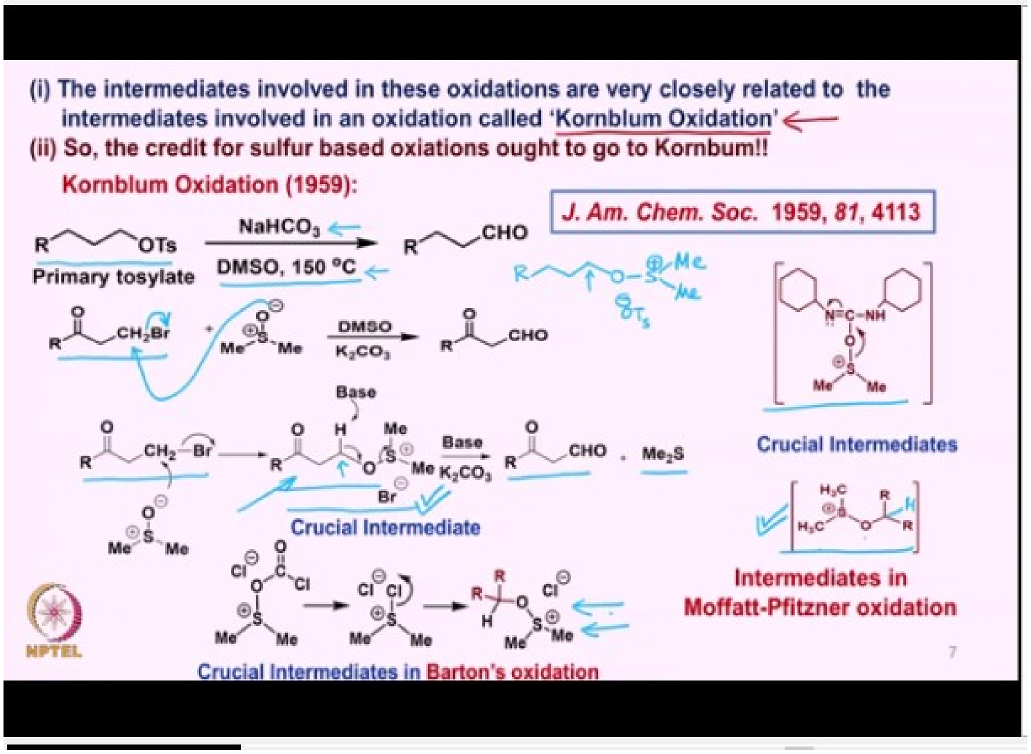

(i) The intermediates involved in these oxidations are very closely related to the intermediates involved in an oxidation called 'Kornblum Oxidation'

(ii) So, the credit for sulfur based oxiations ought to go to Kornbum!!

Kornblum Oxidation (1959):

J. Am. Chem. Soc. 1959, *81*, 4113

And the Bartons oxidation with phosgene is also somewhat similar. So, they your DMSO attacks on phosgene and the phosgene is nothing but this particular compound, where there are 2 chlorines attached to a carbonyl group and this is what is the phosgene and it is acting like an electrophile and DMSO attacks onto this carbon and leading to the formation of this intermediate.

Now, this intermediate of course, these reactions have to be done at low temperature. And once this intermediate forms, it is expected that such an intermediate can lose carbon dioxide and of course chlorine and forming after the loss of carbon dioxide, this intermediate here and this intermediate now has the sulfur as positively charged and there is a leaving group which is a chlorine.

Therefore, the alcohol attacks on to this particular intermediate and leading to another intermediate of this kind. Now, if you look at very carefully, whether you consider this as an intermediate or this as another intermediate and the second intermediate is just. So, this intermediate is very similar to this particular intermediate. And this intermediate is also similar to this intermediate or this intermediate or this intermediate.

Because you have a leaving group on the sulfur, which is connected to the oxygen in this particular case or in this case you have it plugged in as a leaving room. So, both these crucial intermediates, which have been mentioning right from the beginning, whether it is Moffatt-Pfitzner oxidation or the Barton oxidation are similar in nature. Now, if we go back and look at the literature, so, basically these intermediates, which I mentioned as crucial intermediates, of 2 different kinds are essentially related to yet another very important oxidation which was the basis for all the oxidation involving sulfur is known as Kornblum oxidation.

So, it was a Nathan Kornblum, who actually discovered this is in 1959. And this particular oxidation is also based on oxygen, sulfur and of course, all the sulfur based oxidations involving DMSO should definitely give credit to Kornblum. So, what was the Kornblum oxidation? The Kornblum oxidation involved to the reaction of say primary tosylate or a bromide of this kind to start with, of course, the reactions were carried out using very good leaving groups on a primary carbon atom.

The reason was that in these cases the reaction requires the use of DMSO in the presence of a base like sodium bicarbonate at high degrees 150 degrees. So, in these cases, what happens is the DMSO acts like a nucleophile and reacts as say for example here and then SN 2 fashion and leading a to an intermediate of this type here as I have shown it here. And in a similar fashion, if you take it here, then of course, you will have similar intermediate like you have R CH 2 CH 2 CH 2.

And then of course, you have oxygen and then you have the DMSO reacting like this and of course, OTS will go as a leaving group. So, in all these cases, as you can see the leaving group once it leaves the carbon, the DMSO oxygen O - attacks and this is the carbon and of course, this is the carbon where DMSO attacked. Now, this intermediate which I have shown it here is very similar to the crucial intermediate that we are talked in Moffett Pfitzner oxidation.

And the another one is of course, this one. So, this is related to this particular intermediate. So, this intermediate here is very closely related to this intermediate as you can see that there is a carbon that holds the hydrogen, the carbon that holds the hydrogen here, here and of course, you have oxygen, then you have a sulfur positively charged and of course, you have the 2 methyls.

So, the base can pick up the proton as I have shown it here and the oxidation completes by the loss of dimethyl sulfide as we have discussed in other cases. So, this particular intermediate as shown here is similar to the intermediate that shown here even in Barton's oxidation. So, both in Barton's oxidation as well as in Moffett-Pfitzner oxidation, the last intermediate is very similar to the intermediate that is formed in Kornblum oxidation.

Except that in the case of Kornblum oxidation, the first intermediate directly comes with having an oxygen here because the DMSO is the only as a nucleophile that is acting. Whereas in the other cases, like Moffett-Pfitzner oxidation or Barton's oxidation, we activate the DMSO to form electrophilic sulfur to which alcohol attacks and gives the similar intermediate as we see in the Kornblum oxidation.

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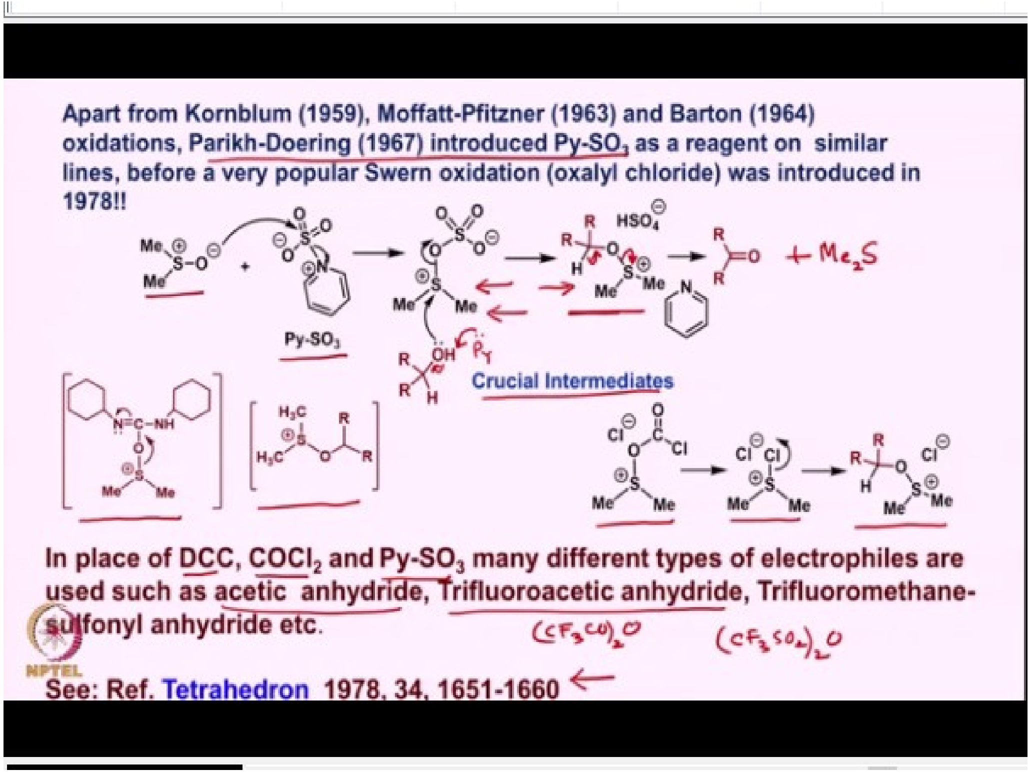

Apart from Kornblum (1959), Moffatt-Pfitzner (1963) and Barton (1964) oxidations, Parikh-Doering (1967) introduced Py-SO_3 as a reagent on similar lines, before a very popular Swern oxidation (oxalyl chloride) was introduced in 1978!!

In place of DCC, $COCl_2$ and Py-SO_3 many different types of electrophiles are used such as acetic anhydride, Trifluoroacetic anhydride, Trifluoromethane-sulfonyl anhydride etc.

See: Ref. Tetrahedron 1978, 34, 1651-1660

Apart from Kornblum and Moffatt-Pfitzner oxidation and Barton's oxidation, Parikh and Doering also reported in 1967 reagent using pyridine sulfur trioxide and in a similar fashion that oxidation takes place. So, DMSO interacts with pyridine sulfur trioxide complex, where now you have electrophilic sulfur another electrophilic and a leaving group is the pyridinium iron.

So, the O - attacks onto this sulfur pyridinium and goes and this is the intermediate that is formed to which the alcohol attacks where the pyridine takes up the proton from here. So, pyridine can take up a proton from here and of course, you generate the anion of the alcohol which goes and attacks onto this and then you have this intermediate that is formed of course, pyridine is still present there.

And then pyridine can pick up a proton from here and then oxidation can take place with the loss of dimethyl sulfide. So, as you can see, it is very similar to the pyridine oxidation that we had discussed earlier. And this is another crucial intermediate here and this is another crucial intermediate. So, as we have been naming all the crucial intermediates that are similar to this is the Moffatt-Pfitzner oxidation first crucial intermediate, this is the second crucial intermediate, in Barton oxidation, this is how the one intermediate forms and then rearranges to this crucial intermediate.

And this is the second crucial intermediate after the alcohol attacks. So, in place of DCC, phosgene, pyridinium sulfur trioxide many different electrophiles are used such as acetic anhydride, trifluoroacetic anhydride and of course, trifloramethane sulfonic anhydride. So, you have CO_2O or you have CF $_3$ SO_2 twice O. So, basically these are the various kinds of intermediates, which are used. And this is a reference that you can see, which is gives the details of this oxidations.

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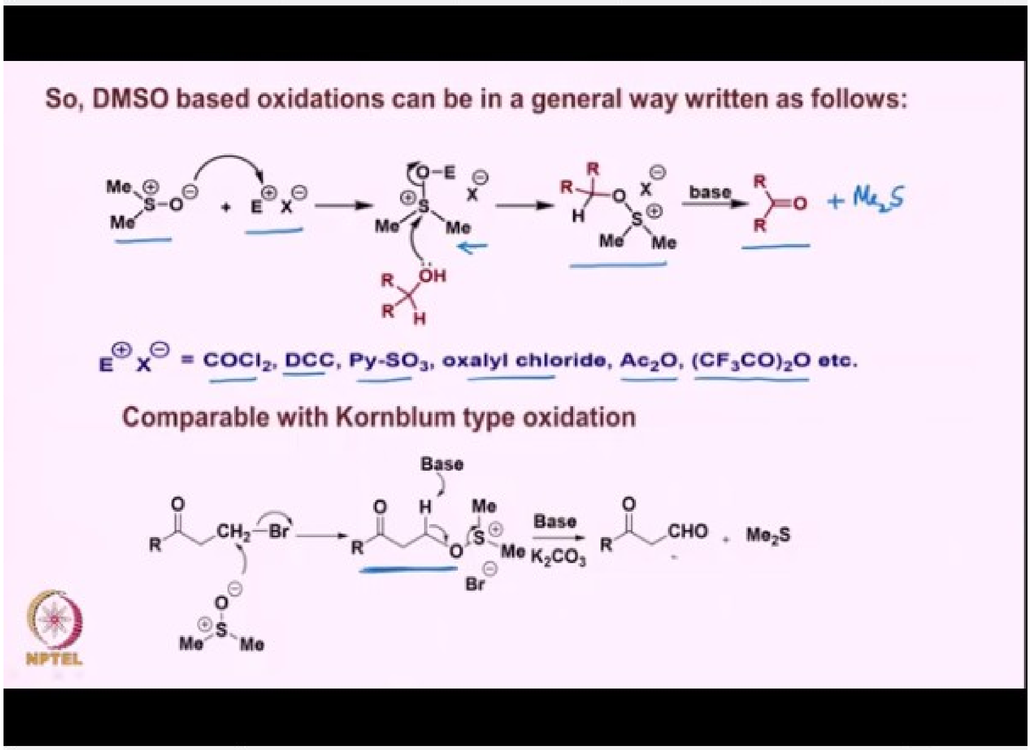

So, DMSO based oxidations can be in a general way written as follows:

$E^{\oplus}X^{\ominus}$ = $COCl_2$, DCC, Py-SO_3, oxalyl chloride, Ac_2O, $(CF_3CO)_2O$ etc.

Comparable with Kornblum type oxidation

Now, if you look at it very carefully, what we have seen is that DMSO base oxidations in general can be written up like this, that DMSO reacts with an electrophile whether it DCC phosgene or pyridine sulfur dioxide or anything of that sort you get basically activation of the DMSO by the electrophile and leading to this intermediate here to which the alcohol attacks and forms this intermediate from where the aldehyde or ketone gets released along with dimethyl sulfide.

So, essentially what is happening is whether the EX phosgene DCC pyridine sulfur dioxide or oxalyl chloride or acetic anhydride or trichloroacetic anhydride any other electrophile and of course the intermediate is comparable with Kornblum type of oxidation here. Now this is the crucial intermediate which then undergoes loss of proton and along with dimethyl sulfide here to form the carbonyl group.

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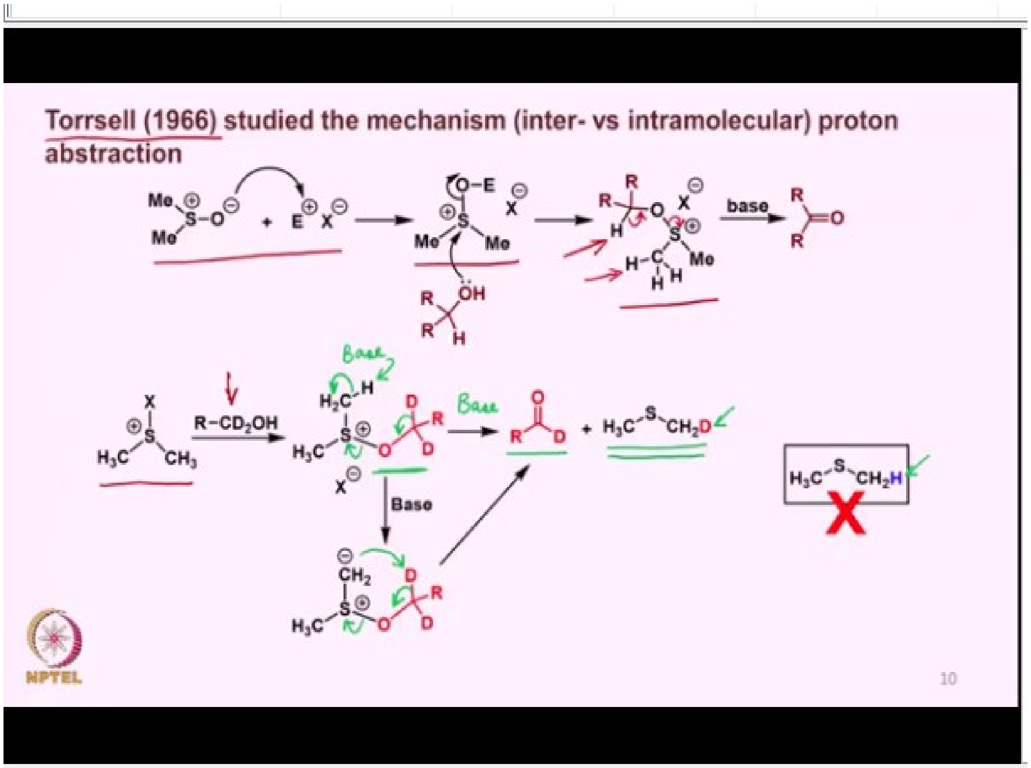

Torrsell (1966) studied the mechanism (inter- vs intramolecular) proton abstraction

Now whether the reaction is involving an abstraction of a proton in an intermolecular fashion or an intermolecular fashion was basically studied in detail by the scientist named Torrsell here in 1966. What he did of course, as we have seen in general that DMSO gets activated with an electrophile forming this intermediate to which the first crucial intermediate to which alcohol attacks and forming this second crucial intermediate form where either this proton can get abstracted essentially to lose dimethyl sulfide and give the ketone.

But then is there a possibility of removing this proton first, because this carbon is next to the sulfur which is positively charged, this is what the scientist or the chemist Torrsell did it, he took the intermediate of this type from any of these DMSO activated based intermediates and reacted with the alcohol that contain CD_2OH, that means that it is a deuterated alcohol.

So, once the deuterated alcohol reacts with it, you have 2 deuterium here onto the carbon atom and when the base was added to it base, so, the base allow the oxidation to take place where of course, one would expect that this oxidation would take place and you get the corresponding ketone with the deuterium, but the release dimethyl sulfide lead to the formation of the compound of this type in which there was a deuterium here.

And not this that means, if only such an oxidation is taking place as I have shown here, then we would expect the hydrogen to be retained at the 2 ends of the sulfur as CH_3 and CH_3, but what was observed was at one end it was CH 3 and the other end it was CH 2 D. So, the mechanism that was proposed that the base picks up the proton from here generating negative charge of this type. And this undergoes an intramolecular abstraction of the deuterium and then it forms the corresponding ketone and of course, the dimethyl sulfide containing 1 deuterium.

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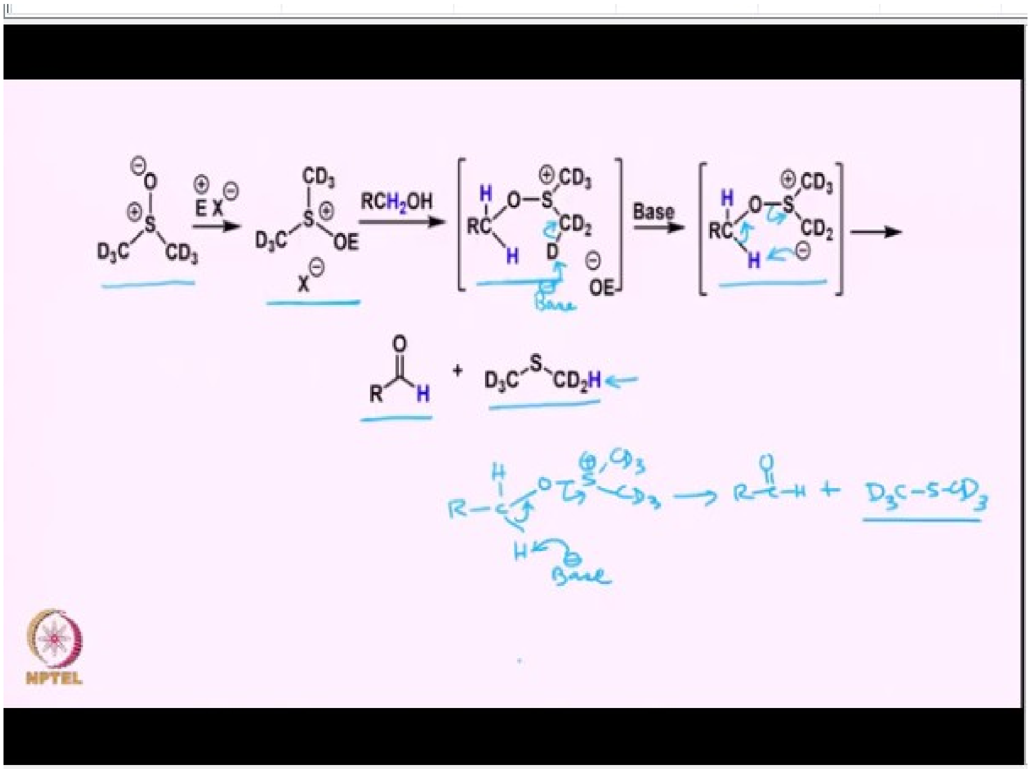

Yet another experiment what he did was, he took the DMSO which was having 2 CD_3 groups attached to it and of course, you activate with any electrophile that we have discussed so far and this is the crucial first intermediate that is formed to which now normal alcohol is added not a deteriorated alcohol because the deuterium is now incorporated in that the DMSO. So, this is the intermediate that one would expect it for.

Now, if this reaction occurs in a similar fashion as we have discussed that the deuterium the proton or the deuterium that is present on to the carbon atom attached to sulfur takes gets deprotonated then of course, the base will pick up the proton from here and of course, you will get an intermediate of this kind. Had it been a directly then of course, you would get back the DMSO as dimethyl sulfide as it is.

But if in an intramolecular fashion the proton abstraction is taking place. Then of course, one can generate an intermediate of this kind and which then loses a proton from here in an intramolecular fashion and then leads to the formation of the aldehyde as normally expected, but then the dimethyl sulfide which has come out contains the hydrogen rather than the deuterium.

Because the other possibility which we can think about it is of course, without involving intramolecular activation or removal of a proton, we can think that, if it is an intermolecular hydrogen, then of course, the base can pick up the hydrogen from here and when can get the oxidation of course, but then one would get R C O H + the DMS that is formed should be this carbon here.

So, this is how it should form, but what was observed was that the hydrogen gets incorporated onto the carbon atom that means, the mechanism is an intramolecular removal of the hydrogen from the intermediate that is the crucial intermediate that we talk about it. So, now having established this particular type of intermolecular abstraction of a proton, then of course, many more oxidations have been reported.

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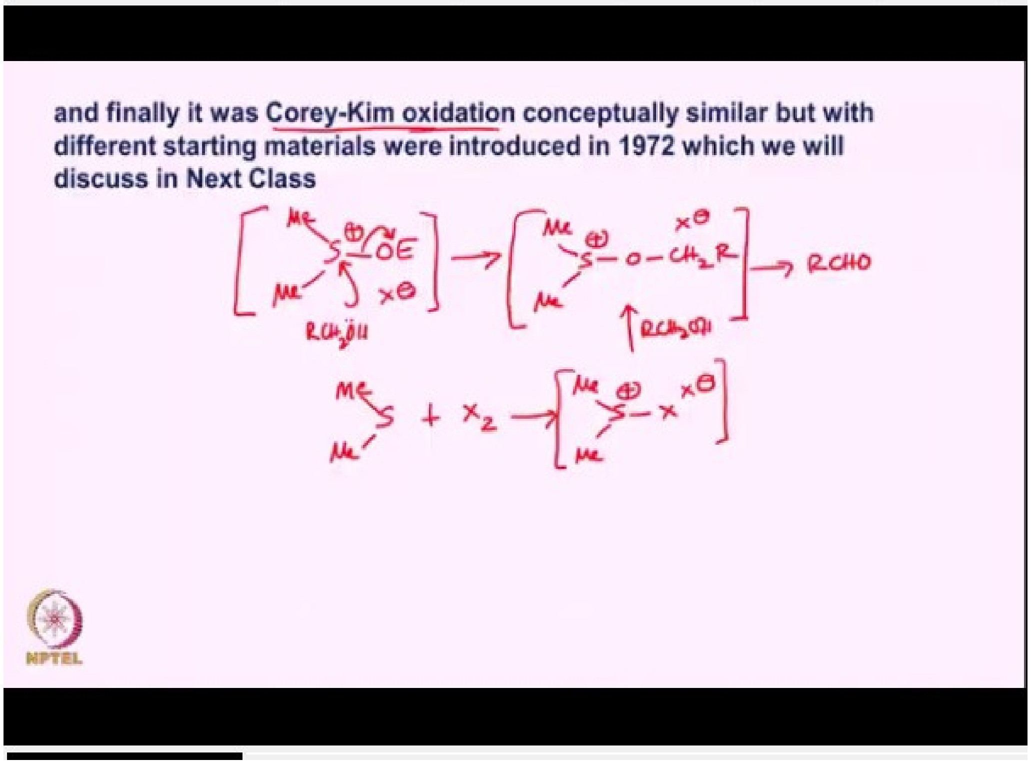

and finally it was Corey-Kim oxidation conceptually similar but with different starting materials were introduced in 1972 which we will discuss in Next Class

And it was finally Corey and Kim, who also utilized conceptually similar, but somewhat different study materials. For example, one can also get this intermediate which we call it as from the crucial intermediate, which is what is comes from the dimethyl sulfide. And here you have a leaving group here. So, this is the intermediate that is expected to form and all derived from the DMSO to which alcohol reacts.

And forms the next intermediate that allows the formation of the ketone or aldehyde depending on what alcohol one uses, but then you have this intermediate, which is what it is formed. So, in order to get this intermediate of course, you have an x minus you in order to get this intermediate one can also start not from DMSO, but even can also start from say for example, dimethyl sulfide and react with some electrophiles such as halogen.

And generate an intermediate of this type here, which can also act as a good intermediate crucial intermediate to which alcohol can react and of course, can form the intermediate of this kind, which eventually gives the aldehyde or ketone. So, this was developed by Corey and Kim, which we will discuss in our next class, more in detail. So, you please go ahead and complete look at whatever I have discussed today, and get ready for the next class. Till then, bye and see you next time. Bye. Thank you.