Essentials of Oxidation, Reduction and C – C Bond Formation
Application in Organic Systems
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Module No # 03
Lecture No # 11
Iodoxybenzoic Acid (IBX) Based Oxidations

Hello everyone I welcome to you to today's class and I hope that you had an opportunity to go through the last class where we discussed Dess-Martin periodinane oxidizing agent for the oxidations of alcohols to the corresponding carbonyl compounds.

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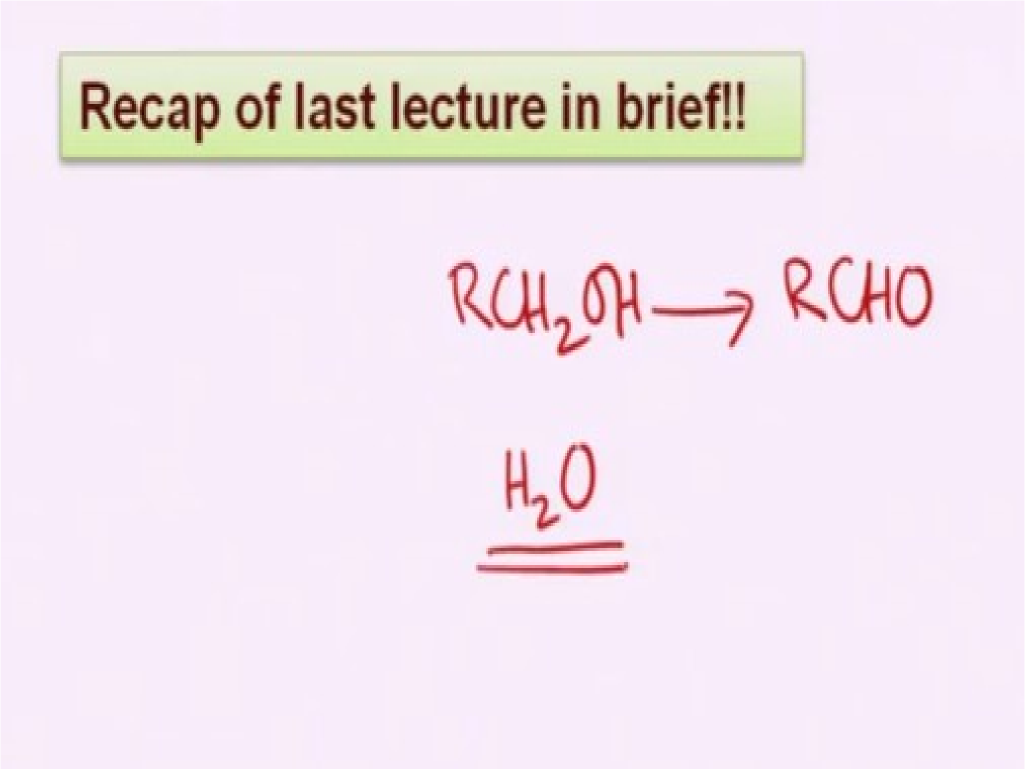

Recap of last lecture in brief!!

$RCH_2OH \rightarrow RCHO$

$\underline{\underline{H_2O}}$

As I mentioned that reagent is useful for a converting primary alcohols to the corresponding aldehyde without over oxidation. And also that, substrates which are acid sensitive are easily oxidized to the corresponding carbonyl compounds without any problem. We discuss the mechanisms involved in the oxidation using DMP or Dess-Martin periodinane reagent. And also we saw how water affects the rate of the reaction where the water plays, a very crucial to role in the mechanism allowing the oxidation to occur fast.

Now in today's lecture we will be talking about another interesting reagent which is also based on this hyper valent iodine which is called iodoxy benzoic acid.

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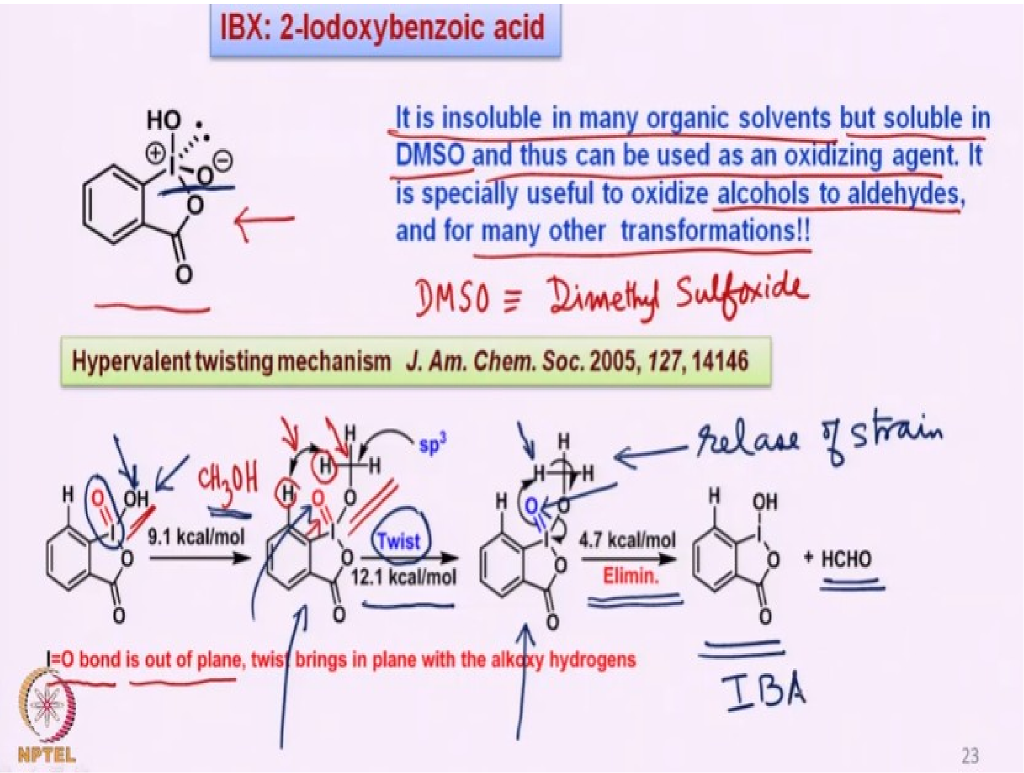

IBX: 2-Iodoxybenzoic acid

It is insoluble in many organic solvents but soluble in DMSO and thus can be used as an oxidizing agent. It is specially useful to oxidize alcohols to aldehydes, and for many other transformations!!

DMSO ≡ Dimethyl Sulfoxide

Hypervalent twisting mechanism *J. Am. Chem. Soc.* **2005**, *127*, 14146

I=O bond is out of plane, twist brings in plane with the alkoxy hydrogens

If you recall we had seen this intermediate as one of the products that forms, when ortho iodo benzoic acid is oxidized with oxone or with potassium bromate. Then one of the intermediates that is formed is this iodoxy benzoic acid which is then reacted with acetic anhydride to form the Dess-Martin periodinane reagent. Now this intermediate also has enormous potential as an oxidizing agent it is however insoluble in many organic solvents and that is of course one of the problems that it has.

However it is fortunately it is soluble in a solvent like DMSO which is DMSO is nothing but Dimethyl Sulfoxide it is a polar aprotic solvent Dimethyl sulfoxide. And it dissolves this particular reagent readily and it can thus be used as an oxidizing agent. It is especially useful of course to convert alcohols to aldehydes but then there are many other very important transformations that have been discovered and there is also a very interesting mechanistic investigation's that have been carried out.

For example if one starts with this reagent which is shown here like this so you have this iodine oxygen double bond which of course we can always write like this as I have mentioned above. However when this hydroxy group at this position is replaced by say the alcohol which is present in this particular case say methanol is used as a substrate. And the methanol when it replaces the hydroxyl group from here this is intermediate that is formed.

Now this intermediate has been very carefully looked at also by theoretical means is that the iodine oxygen bond is out of plane and one can see that there is an sp3 carbon here. And of course this iodine oxygen this carbon and this, hydrogen's around here. They basically are not in the same plane as this iodine oxygen double bond but there is a steric hindrance which is observed which has been found to take place between the hydrogen here and the hydrogen here of the alcoholic substrate.

Now the oxidation would not occur unless and until the oxygen here at this reagent this oxygen here is in plane with the hydrogen that needs to be removed during oxidation. So basically what happens is there is some sort of twist that has to occur where the iodine oxygen double bond is twisted. So that it allows the hydrogen and this oxygen basically in such a way that they are in the same plane and then the oxidation can take place.

So the first step where the alcohol is methanol but any alcohol replaces the hydroxy group here by the oxygen of the alcohol to form this intermediate here it requires approximately 9.1 kilo calories per mole to replace the hydroxy group by this alkoxy. But then the twist mechanism the twist of the iodine oxygen double bond requires more energy like 12.1 kilo calories per mole followed by now very little amount of energy such as 4.7 kilo calories per mole for the elimination to take place.

Already this intermediate is at high energy therefore it takes very little energy to then undergo oxidation by the there is a release of the strain because this intermediate which is in the middle is highly strained intermediate and that undergoes or allows elimination or the oxidation to takes place to form the formaldehyde and of course you get back the Iodosobenzoic acid this is IBA Iodosobenzoic acid.

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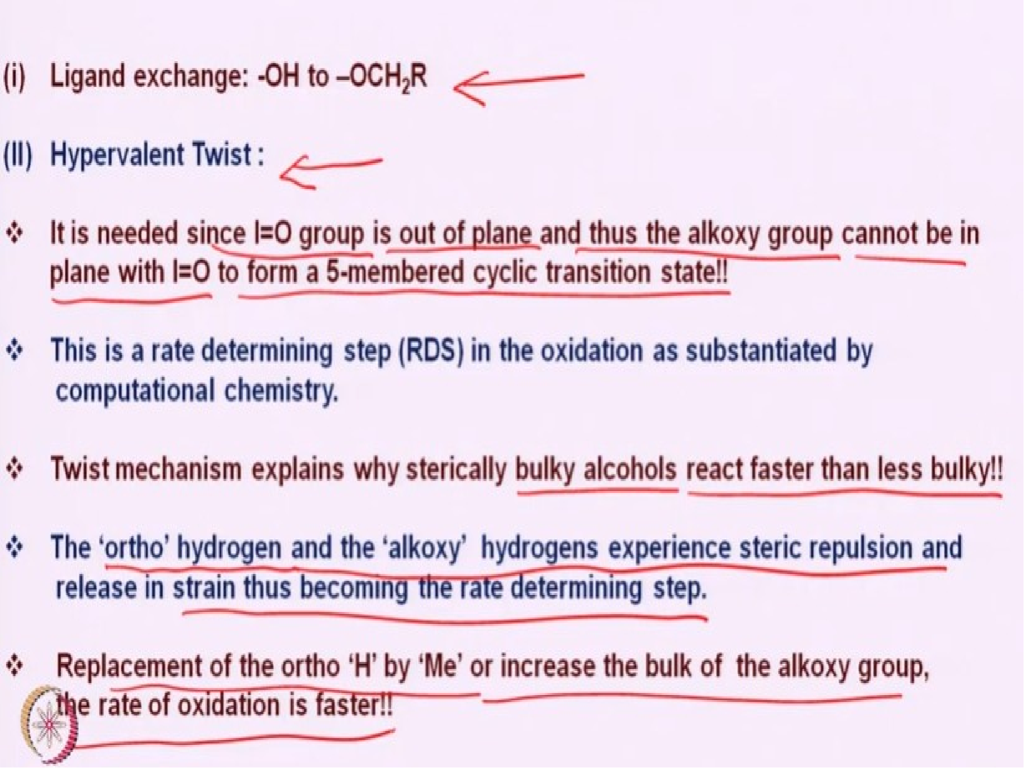

(i) Ligand exchange: -OH to $-OCH_2R$

(II) Hypervalent Twist :

- It is needed since I=O group is out of plane and thus the alkoxy group cannot be in plane with I=O to form a 5-membered cyclic transition state!!
- This is a rate determining step (RDS) in the oxidation as substantiated by computational chemistry.
- Twist mechanism explains why sterically bulky alcohols react faster than less bulky!!
- The 'ortho' hydrogen and the 'alkoxy' hydrogens experience steric repulsion and release in strain thus becoming the rate determining step.
- Replacement of the ortho 'H' by 'Me' or increase the bulk of the alkoxy group, the rate of oxidation is faster!!

So the mechanism is an interesting aspect and this has been of course theoretically done checked and confirmed. So the first step as I mentioned takes place alcohol replaces the hydroxy group then there is hyper valent Twist that takes place because the I double bond O gets twisted it is needed since IO group is out of plane and thus the alkoxy group cannot be in plane with the I double bond O to form a 5 membered cyclic transition state which I showed earlier here.

There is a 5 membered transition state that is 1, 2, 3, 4 and 5, 5 membered transition state this is a rate determining step in the oxidation as substantiated by computational chemistry. The twist mechanism explains why sterically bulky alcohols react faster than less bulky. So if you have sterically bulky alcohol then of course when the twist takes place already you are the very high energy level.

And therefore to release energy the oxidation takes place very fast and then the corresponding carbonyl compound is obtained. This can also be done by replacing the ortho hydrogen and the alkoxy hydrogen's experience steric repulsion. So if I can see here the hydrogen which is present here at the ortho position here or here whatever is having a steric interaction between these hydrogen from the alkoxy part of the alcohol.

So if one increase's instead of hydrogen if one makes it here some bulky group or you increase the bulk on this the steric hindrance will become larger the substrate will be at higher energy and therefore the oxidation takes place faster. That means the ortho hydrogen and alkoxy hydrogen's experience steric repulsion and release in strain thus becoming the rate determining step. So once the ligand exchange takes place you immediately allow a steric hindrance to takes place between the ortho hydrogen or the ortho substituent and the substituent's or the on the alcoholic part of it.

And the twist mechanism requires the IO bond to be twisted which then is required for the oxidation to takes place. But since the substrate is at a higher energy level the little energy is given and then the oxidation occurs to release enormous amount of energy and therefore the reaction occurs fast. Replacement of the ortho hydrogen by methyl or increase the bulk of the alkoxy group increases the rate of the oxidation.

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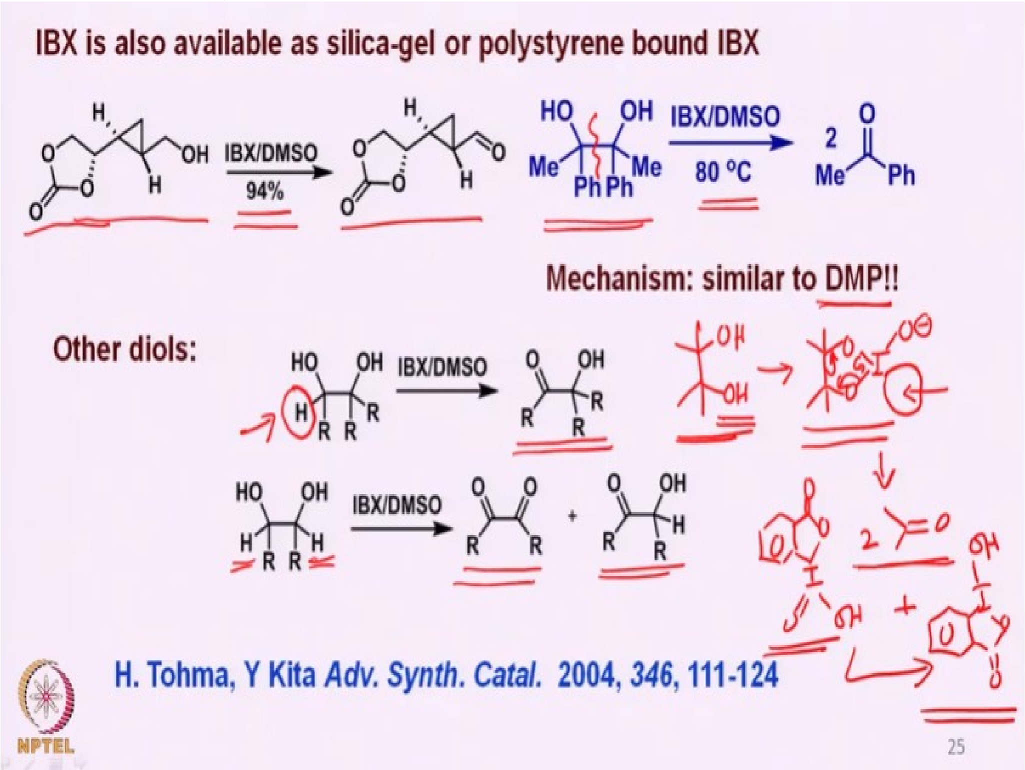

IBX is also available as silica-gel or polystyrene bound IBX

Mechanism: similar to DMP!!

Other diols:

H. Tohma, Y Kita *Adv. Synth. Catal.* 2004, *346*, 111-124

Now IBX is also available as a silica gel or polystyrene bound IBX it is a IBX can be adsorbed on silica gel or a polystyrene based IBX are also available in the market. Now as I mentioned that the substrates such as cyclopropyl alcohols with these types of functional groups being around allow the reaction to takes place and we get almost like 94% yield of the corresponding product.

Now the diols also at a 80 degrees allows the cleavage of the bond here it is similar to the DMP based oxidation which we discussed here. For example we do not have any hydrogen so obviously when you have an oxygen here , an oxygen here and IBX reacts with it. So we form an intermediate of this kind here. So you have one of the OH group going and you generate O^- here so IBX if it is taken so you have here an IBX and.

So one of the OH group can be replaced by the other one and this alcohol and the, I double bond O will give this. So you have an intermediate of this kind which can then undergo cleavage of this type to form of course you will have here the rest of the part of the here. For example this is the part that is present from the reagent. So basically what is happening is that this gives 2 of these at last what will be left is from the reagent which I can write it in that way that what you have to is an OH here.

So your iodoxy benzoic acid has got reduced this iodoxy benzoic acid has got reduced to the corresponding iodoso benzoic acid. And the diol has undergone cleavage to the corresponding 2 ketones C-C bond cleavage. So the intermediate is very similar to the Dess-Martin periodinane reagent based. So if you have a hydrogen here if it is present here one of the hydrogen's which is present and IBX /DMSO will allow oxidation to take place to form the alpha hydroxyl ketone.

So here we had no hydrogen present as an alpha to the hydroxyl group here there is a hydrogen present into one of the hydroxyl groups here and then you get a alpha hydroxyl ketone. If of course there are 2 of the hydrogen's which are present then one can get alpha di ketone or alpha hydroxy ketone. One of the oxygen's gets oxidized and other one does not get oxidized or one can get a mixture of the (()) (14:24).

So this kind of oxidations occur when we have this substrates of diol type where we can have several possibilities along with the C-C bond cleavage one can get alpha hydroxyl ketone which is what is present here or alpha di ketone.

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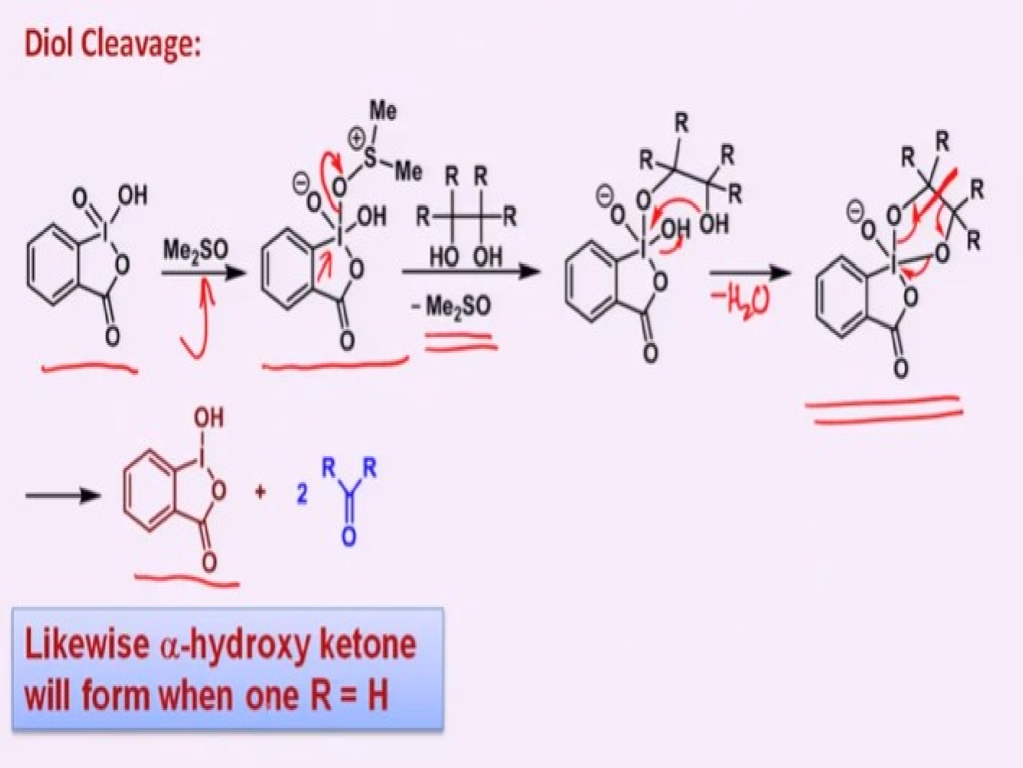

Diol Cleavage:

Likewise α-hydroxy ketone will form when one R = H

Now di ketone I just explained earlier that how the diol cleavage takes place but then there is important point that I need to mention here is that in the case of DMP the generally the temperature is not required higher because solubility is not a problem. Whereas in this case you have to use approximately 80 degrees temperature so this is the difference now here for example the same mechanistic aspects that I mention is the DMSO also sometimes also considered to act as a nucleophile to activate the iodine oxygen double bond here.

And an intermediate of this kind has been proposed which now has 4 iodine oxygen bonds with also possibility of that this as a very good leaving group. So when the diol reacts, the DMSO can also first come out so basically DMSO acts as a nucleophile to activate the IBX here generating species like this where now DMSO itself can act as a leaving group. And one of the hydroxy groups of the diol reacts with it and replaces the DMSO and form, this and then the other hydroxy groups reacts.

And then you form an intermediate of this kind because one of the hydroxyl group will be gone as a water here. And then of course oxidation by C-C bond cleavage occurs to form this IBX. So this is what the mechanistic aspects of the cleavage or the alpha hydroxyl ketones where if one of the R groups is hydrogen.

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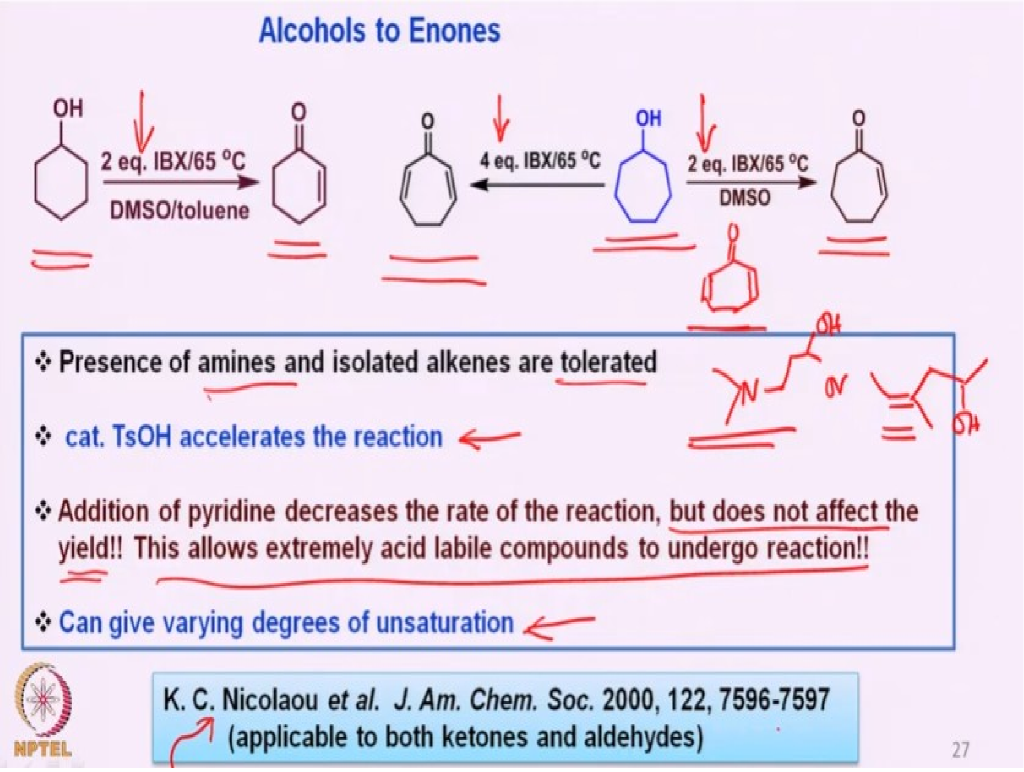

Alcohols to Enones

- ❖ Presence of amines and isolated alkenes are tolerated
- ❖ cat. TsOH accelerates the reaction
- ❖ Addition of pyridine decreases the rate of the reaction, but does not affect the yield!! This allows extremely acid labile compounds to undergo reaction!!
- ❖ Can give varying degrees of unsaturation

K. C. Nicolaou *et al.* *J. Am. Chem. Soc.* 2000, 122, 7596-7597
(applicable to both ketones and aldehydes)

Now there is another interesting aspect of this particular IBX which has been reported by a scientist named K.C. Nicolaou in the United States who has published a large number of papers on this utility of IBX in various organic transformations. For example here you if you take alcohol so if one takes, a cyclohexanol and use instead of one equivalent of IBX which will convert to the corresponding cyclohexanone.

If one takes 2 equivalents of IBX at 65 degrees in DMSO toluene you straight away can get the corresponding enone. Now this is interesting reagent aspect because such conversion of an alcohol to corresponding enone is somewhat difficult or it takes a few steps. Similarly a very interestingly if one takes cycloheptanol and if you use 2 equivalents of IBX then of course as expected you get an enone similar to the one that I mentioned here.

But if one takes 4 equivalents of IBX then you can also introduce the other double bond that means on this side of the double bond. So the first equivalent allows the oxidation to takes place to form cycloheptanone and then second one allows the introduction of the enone or the double bond there and then you need 2 more equivalents because then the rate of reaction becomes little bit slow. So you need more re-agent and then you can also introduce another double bond on the left side.

So this is how these oxidations are described in the literature now these react oxidations with IBX the presence of amines and isolated alkenes are tolerated. That means this oxidizing agent is a mild oxidizing agent so anywhere if you have nitrogen or an alkene in the reaction medium somewhere anywhere. Like for example you have an alcohol which is like this or if you have an alcohol like this. Then the nitrogen as well as the double bond gets tolerated under the reaction condition.

It is observed that catalytic amount of para -toluene sulphonic acid increases the rate addition of periodinane decreases the rate of the reaction. Now it is just exactly opposite of para -toluene sulphonic acid so an acid catalyst increases the rate but the basic catalyst like periodinane decreases the rate of reaction. But does not affect the yield it does not really affect the yield it might take a little longer.

This allows extremely acid level compounds to undergo reaction it is very similar to the Dess-Martin periodinane oxidations. But this particular reagents allows a few others transformation to occur also can give various degrees of unsaturation. That means you have possibility of getting such kind of as I mentioned above is unsaturations here. So this one can see a in this particular paper some aspects of this reaction.

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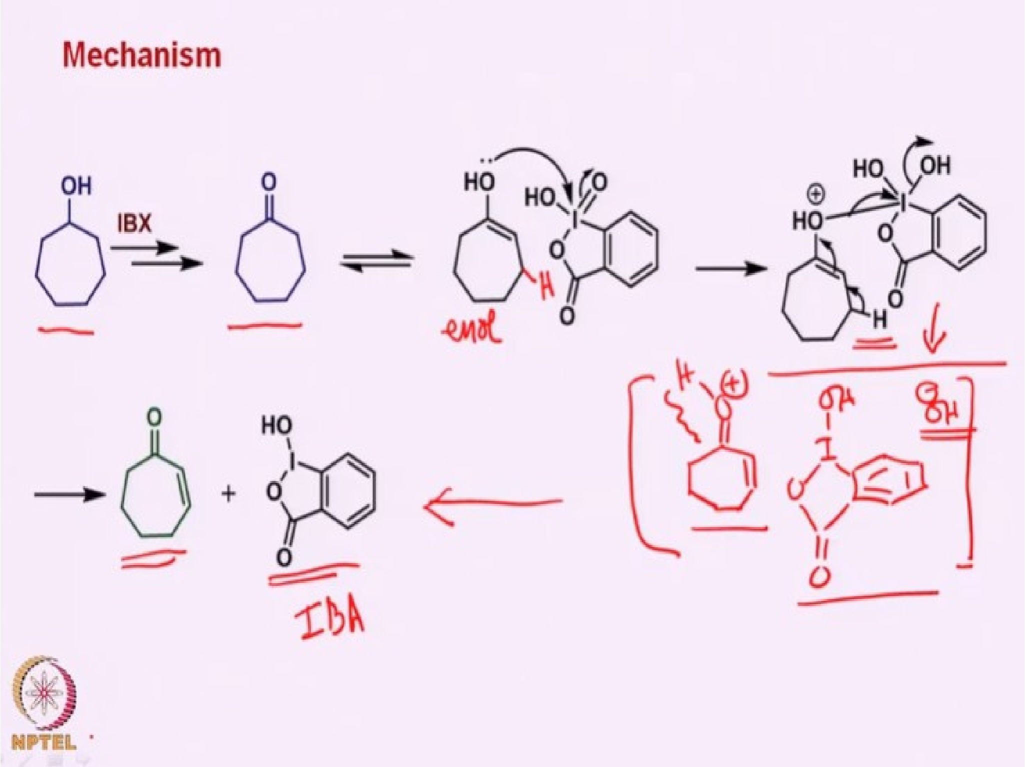

Mechanism

Now what is the mechanism of the conversion of this alcohol to enones the first is that the alcohols get's oxidized to the corresponding ketone which is the normal mechanism which I discussed. And then of course it can exist as a ketone enol this is a enol which then can react directly with the iodine here to form an intermediate of this kind. Now already there is hydrogen which is at this position this is what is the position here shown that can undergo this kind of electron transfer.

So that you generate one of the species that will come out of course would be oxygen H$^+$ here and you of course will have and OH$^-$. So if one can see what is coming out of from here to here is this plus this. So this is the reagent this is the substrate and then the two of them with OH$^-$ and this particular part of this governing group will give the corresponding carbonyl compound and this IBA. So this is how the oxidation takes places where an alcohol is first oxidized to the corresponding ketone followed by this step of reaction.

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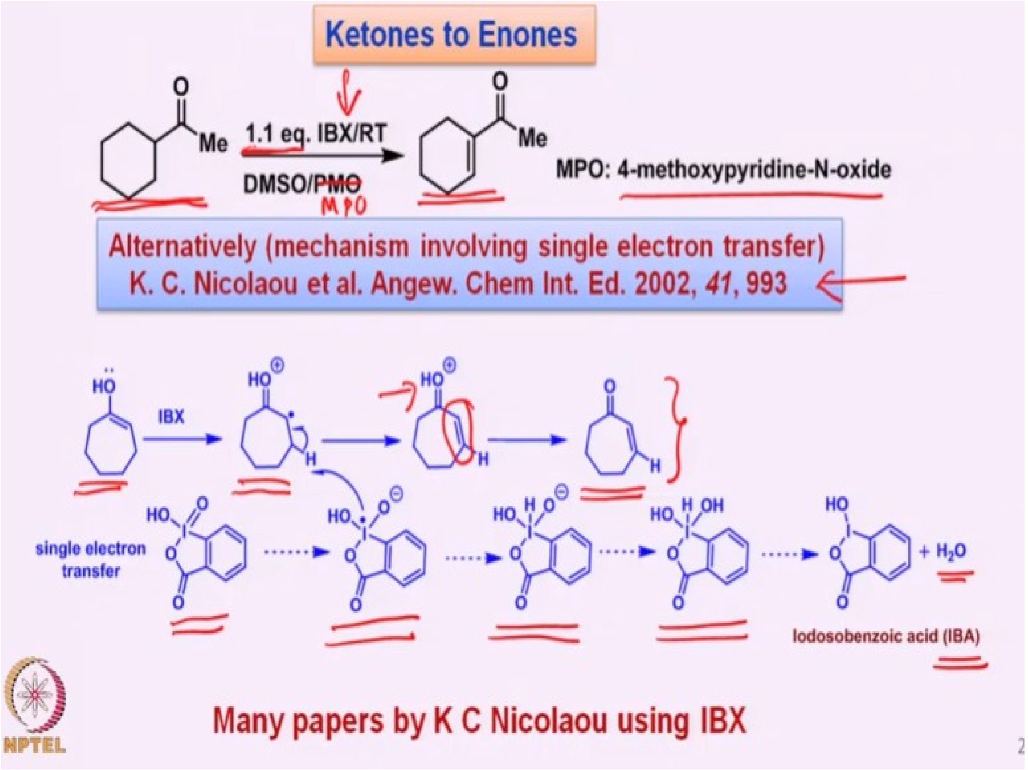

Ketones to Enones

MPO: 4-methoxypyridine-N-oxide

Alternatively (mechanism involving single electron transfer)
K. C. Nicolaou et al. Angew. Chem Int. Ed. 2002, *41*, 993

Many papers by K C Nicolaou using IBX

Now there is a possibility also of converting now why of course in this reaction we have converted an alcohol to the ketone and then to an enone or dienone. This is dienone when there are 2 double bonds this is dienone. So now one can also just start with ketone instead of diketone one can start with the ketone and you can get the corresponding enone. So in this particular case the reagent of course is IBX here and now you need only one equivalent of the, or the reagent.

Because you already have ketone we do not have an alcohol so you can start with one equivalent but then it is found that 4 methoxy pyridine n-oxide oxide which is what it called it should be MPO not PMO. And that is used as a ligand to for reaction to a take place faster or to allow this reaction to take faster. Now what is the mechanism that is proposed is that first is enol formed and then what you have is basically a single electron transfer.

So what you have is when this IBX reacts with this enol then we generate a radical cation here or radical cation by the transfer of this electron to the IBX to form this particular radical anion. So you have a radical cation here and the radical anion here and then the electron from here picks up the hydrogen from here and forms a double bond and then you in the process you form this intermediate.

And then this intermediate takes the proton from here this proton is lost from here and one forms the enone and the reagent is converted to the corresponding another intermediate of this type which looses water and forms IBA. So basically what is happening is a single electron transfer and there is a mechanism which is supported by some experiment in this case and that is available in this particular reference.

So you start with the enol which is present in the reaction medium from the ketone itself and then that allows an electron transfer to take place from here to here. So then you can have the formation of an enone via these types of intermediates. So this is a something an interesting aspect of the reaction. And we will stop it at this stage and take the other aspect of oxidizing agents in the next class.

So I suggest that you see this lecture carefully using IBX where we have done the oxidation of alcohol to the corresponding ketone diol cleavage preparation of alpha hydroxyl ketones. And then the oxidation of alcohols to the corresponding enone or the corresponding dienones depending on, how many equivalents of IBX are taken. If you take 2 equivalents of IBX and then alcohols gets transformed to the corresponding enone. If you take 4 equivalents of IBX then the alcohol gets transformed to the corresponding dienone.

Then if one starts with a ketone then you can use one equivalent of IBX and get the corresponding enone which has been found to essentially progress via an electron transfer type of mechanism which of course one can easily check using EPR that is electron paramagnetic resonance spectroscopy. And there is a good mechanism support that has been found and published in the reference that I gave. So you can go through theses oxidations and then we will see you next time so take care and thank you.