Essentials of Oxidation, Reduction and C- C Bond Formation
Application in Organic Synthesis
Prof. Yashwant D. Vankar
Department of Chemistry
Indian Institute of Technology, Kanpur

Module No # 04
Lecture No # 20
Barton and Related Reactions (Oxidation at Unfunctionalized Carbons) and Synthetic Applications

Hello welcome to today's lecture. What we discussed last time was basically the end part of the oxaziridines based reactions.
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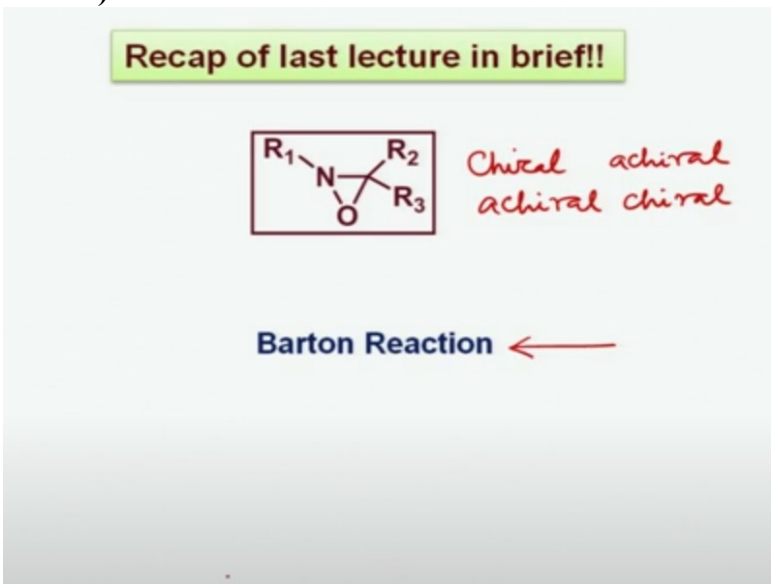

Where we checked the reactivity of chiral as whereas achiral oxaziridines with say achiral enolates and chiral oxaziridines with chiral enolates that means enolates coming from chiral substrates and the reaction with achiral oxaziridines. And we saw how the stereochemistry of the hydroxy group comes based on the steric factors and of course polar factors depending upon what substrate we take it.

We also saw how camphor based reactions can be carried out to go to the chiral substrate with high enantiomeric purity based on high diastereo selectivity when we use the auxiliaries. Then towards the end we discussed the Barton reaction which is the oxidation at the unfunctionalized carbon. So we will now proceed with the Barton reaction and related reactions where the oxidation at un-functionalized carbon can be carried out.
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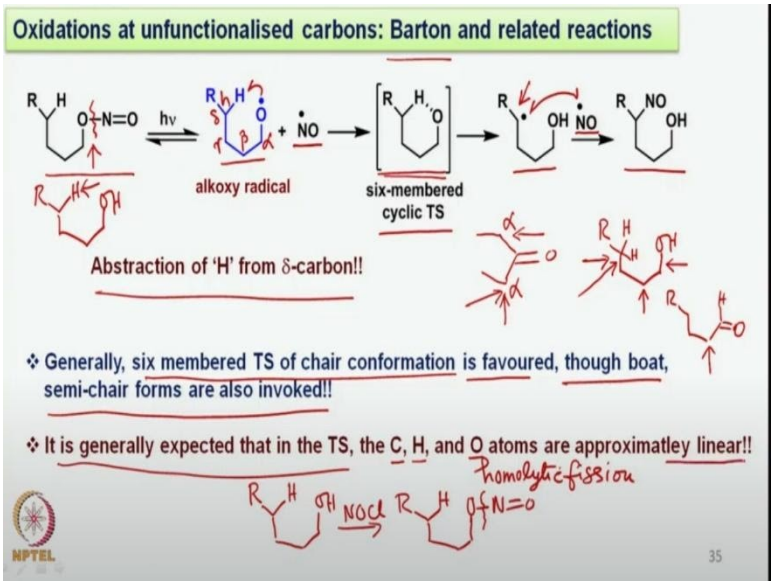

As I discussed last time that it is more, easy to do the reaction at the functionalized molecules which say for example if you have a carbonyl group here and alpha position is very easy to deprotonate and introduce an electrophile. But when we have a substrate of the kind that is shown here then of course if one wants to introduce some oxidize or introduce some electrophile at this position it is somewhat difficult.

So what Barton did was basically starting from a substrate of this type here basically what it did was to take the corresponding hydroxy group here and react it with a source of NO^+ such as NOCl. And that allows the formation of this molecule in which the oxygen nitrogen bond can be easily cleaved in a homolytic fashion if we photolyze it. So homolytic fission that is exactly what was done here. So we start with this particular substrate which is derived from the corresponding hydroxy group and idea was to introduce a functional group at this position.

So we can prepare this and then photolyze it. During the photolysis the oxygen radical is formed and of course you have a nitrosyl radical. This alkoxy radical then takes up the hydrogen from here via this 6 member cyclic transition state and generate a radical at a very remote position which is the delta position. So if one starts numbering then you have an alpha then you have a beta, then you have gamma and then you have this delta position.

So abstraction of hydrogen from delta carbon occurs because of this 6 member transition state here. Once this radical is formed then you are released with a nitrosyl radical and this nitrosyl radical then combine here with the carbon radical to form this particular substrate where the NO group has come to an unfunctionalized delta carbon of this substrate. So generally 6 member transition state of chair conformation is favored though both or semi chair forms are also invoked.

It is generally expected that in the transition state the carbon, hydrogen and oxygen atoms are approximately linear.

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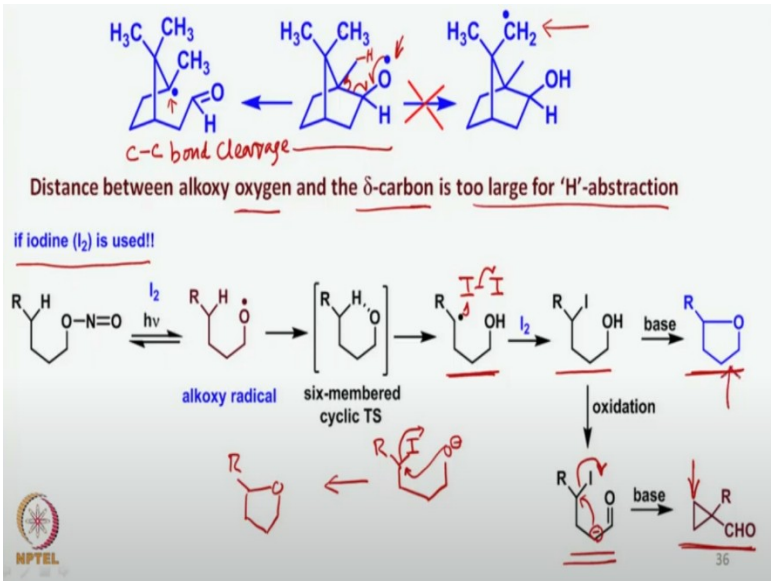

So if that happens then obviously what one expects is that the transfer of the radical occurs from oxygen to a remote delta carbon. Now so the coplanarity is an important part. For example if one starts to form the corresponding oxygen radical from the corresponding OH via the ONO type of molecule then you generate a radical here like this. Now this radical obviously cannot form this six member transition state with this because you have 1, 2, 3, 4, 5 this is a 5 member transition state and not a 6 member transition state.

The other possibility is that you have 1, 2, 3, 4, 5 and 6 so you have a possibility of 6 member transition state so that you can generate the radical at this position. But the distance and the approach of the oxygen through the hydrogen if one looks at the model of this molecule it is not easy to form this radical because the distance between the oxygen and the delta carbon is too large for hydrogen abstraction.

And therefore what happens is this particular cleavage occurs in this fashion and you break it and generate a radical on this particular carbon atom. So if one does not have a possibility of hydrogen abstraction then there is a possibility of this kind of C-C bond cleavage. So you have a C-C bond cleavage. Now because you have provided energy to the molecule and you have generated a radical. So there is a cleavage if there is no abstraction of the hydrogen.

If we use iodine in the reaction medium as we discussed in the last part that we nitroso radical attaches to the carbon and then O CNO bond is formed. And if we use iodine for example this particular radical than interacts with the iodine and what is formed is basically this iodo compound. And this iodo compound can allow the ether formation to take place or we can also oxidize these 2 corresponding aldehyde.

So if we take this particular iodo compound and react with the base then you generate a negative charge here that can attack to this carbon and form the corresponding tetrahydrofuran based product. On the other hand if we oxidize this alcohol to the corresponding aldehyde then we use a base then you can generate an anion alpha to the aldehyde and that undergoes the intramolecular reaction to form the corresponding cyclopropane.

So if we use iodine then we have a possibility of a cyclopropane formation or an ether tetrahydrofuran type of ether formation is also possible.

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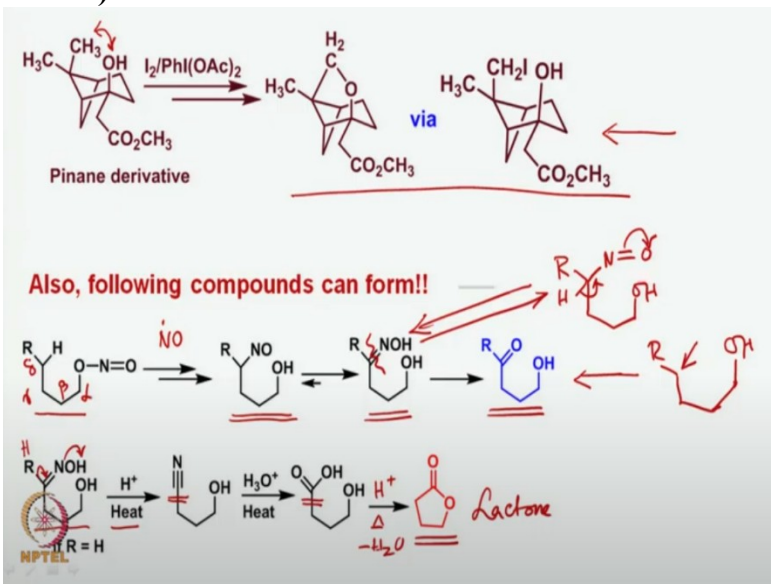

Now what can also happen is we can use some other reagent system such as iodine and phenyl iodo diacetate and also have somewhat similar type of reactions as we discussed as you can see from here as you have the proximity. This there is proximity of the 2 particular centers here. You have 1, 2, 3, 4, 5, 6 so you have a 6 member transition that can form the iodine PhIOAc twice that is phenyl iodo diacetate gives I+ and this I+ allows the O H to form O I and that undergoes cleavage.

We will discuss this particular part little bit later. Now what can also do is that if one gets the corresponding molecule of this type NO dot has reacted at this particular center here so we get this. This is basically nothing but the plus corresponding oxime because this molecule here is nothing but nitroso and then that is in equilibrium with corresponding oxime. So this oxime and this is basically an in equilibrium with each other.

And one can cleave it with different condition of oxidizing or reducing way by which you can cleave the oxime to the corresponding ketone. So what we have done it is we have started with this kind of substrate coming from say here OH here and after the going through the nitrate ester what we have formed is the functionalization at the remote delta position. Now one can also do that if oxime of this type if R is equal to nitrogen then we can also do the dehydration.

That means if this R is hydrogen here instead of any alkyl group or phenyl group we can do the dehydration here under acidic condition and heat it and one can get the corresponding nitrile which can be hydrolyzed to the corresponding acid and then if we use acid here and heat it and remove water then one can get the corresponding lactone. So even lactone formation can take place so you have several such possibilities depending on what is the structure of the starting molecule?

So you can get delta functionalization as I mention alpha, beta, gamma and delta a functionalization at delta position. So we can the proximity is an important part and how are we

going to generate this oxygen radical which can form a 6 member transition state that is also an important part of it.

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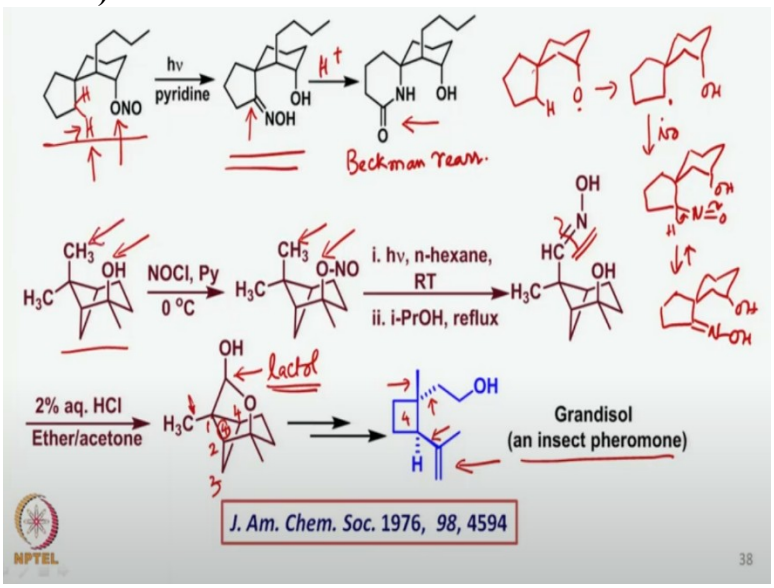

Now let us take another example for example you can have hydrogen here and there is hydrogen here. And if this substrate is photolyze it is very clear that we can get the corresponding radical here. That radical attracts the hydrogen radical form here and then eventually this oxime is formed at this stage. So what is happening is from here is very clear that you have the possibility of such a radical to form and this radical then leads to corresponding next radical which is here.

And then, this is attached by the NO radical to form the corresponding N double bond O which then is in equilibrium with the corresponding oxime. And this is what the substrate that we have got it. This is the product that we have got it. Now if we carry out under the acidic condition the Beckman rearrangement then we can have rearrangement then we can get this particular lactam. So this is a very interesting method for functionalizing the carbon atom which is remotely placed.

And then due to the proximity of the oxygen radical coming from this particular part of the molecule and the corresponding hydrogen which is approachable one can functionalize at the unfunctionalized carbon atom. In a similar fashion like one of the previous example which I took is that we take this OH group here use NO 1 nitrosyl chloride pyridine functionalize it to make this particular OH group into the O NO part of it and then photolyze it.

And eventually this particular hydrogen can be converted to the corresponding oxime. And this oxime can be hydrolyzed from here to the corresponding aldehyde. And the aldehyde is will exist at this lactol. Now this particular lactol has been converted to the corresponding such 4 member ring as you can see there is 1, 1, 2 then 1, 2, 3 and 4 member ring. This is the 4 member ring that is formed here which is what is this; 4 member ring here.

Then there is a methyl group here, this is the methyl group here. And of course then the other part of the molecule is eventually transformed into this particular side chains. And this is a molecule name as Grandisol which is an insect pheromone that has been synthesized by using

this Barton's photolytic reaction of functionalizing at the unfunctionalized carbon atoms. So basically it was dependent on the functionalization of this particular molecule at this methyl group at an unfunctionalized carbon.

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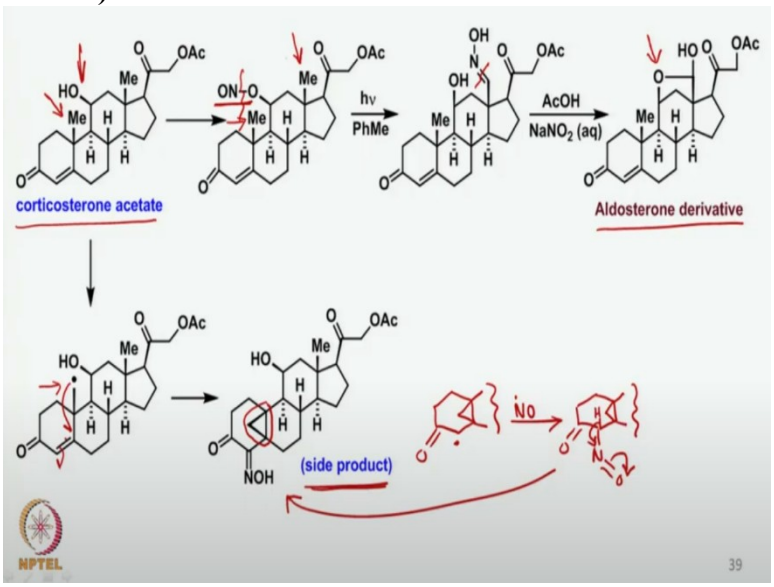

This Barton reaction has also been utilized in many steroidal molecules as you can see that corticosterone acetate here is basically, having a hydroxy group at this position and you can convert into the corresponding ONO group here photolyze it. And then either this particular methyl group can take the hydrogen or even this between the 2 of them this particular methyl group appears to be more easily approachable.

If one looks at the model then we can become very clear and then we can make the corresponding oxime and then again hydrolyze and make the corresponding lactol which is what, is an aldosterone derivative. So basically what has been done is this particular methyl group which is remotely place but accessible for the 6 member transition state to form and that allows the aldosterone derivative to form.

So it is a very easy way of converting a corticosterone to an aldosterone derivative. On the other hand if this particular oxygen radical which is formed from this cleavage of this particular oxygen nitrogen bond, that gives the radical by abstraction of this particular methyl group here leads to the radical formation on this particular methyl carbon. And that can undergo interestingly that can undergo attachment to this carbon and this can move to this carbon forming 3 membered cyclopropane ring and a radical on this carbon.

So basically what are happening is? You have a radical that is going to form on this particular part and then you have a 3 membered ring which is like this. Now this reacts with you know NO radical to form this oxime via the nitroso molecule to form the corresponding I can show in this fashion that this is how it is going to form. So this appears to be a side product but it is an interesting side product because such a reaction is a possible if the other radical is formed.

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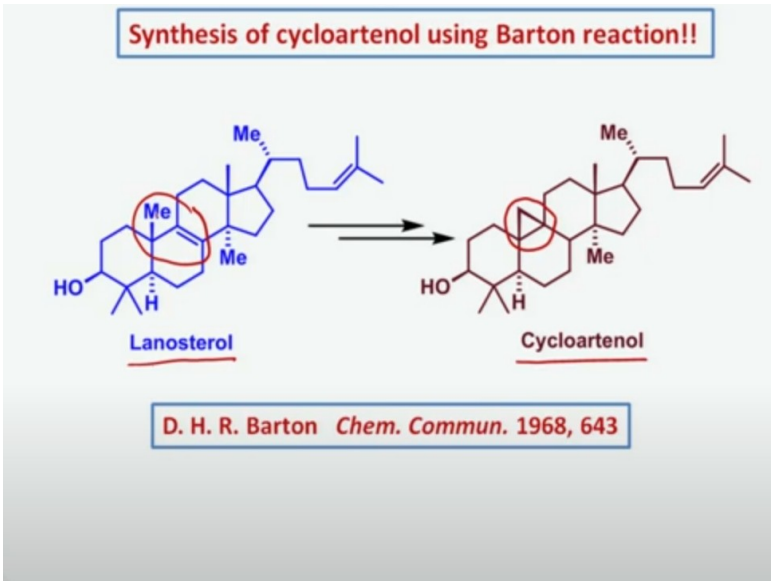

Now there is another very celebrated example of converting one of the steroid, molecule called lanosterol to the corresponding molecule which is called a cycloartenol. If you look at the 2 molecules you can see the difference the only difference that you can see is that there is a cyclopropane ring here whereas that is not the case here. So there is a double bond which is present here and there is a methyl group that is present there in the lanosterol whereas that is not the case.

Otherwise rest of the part is exactly the same. So this one was very easily converted the lanosterol was easily converted to cycloartenol in a very specific fashion by Barton.

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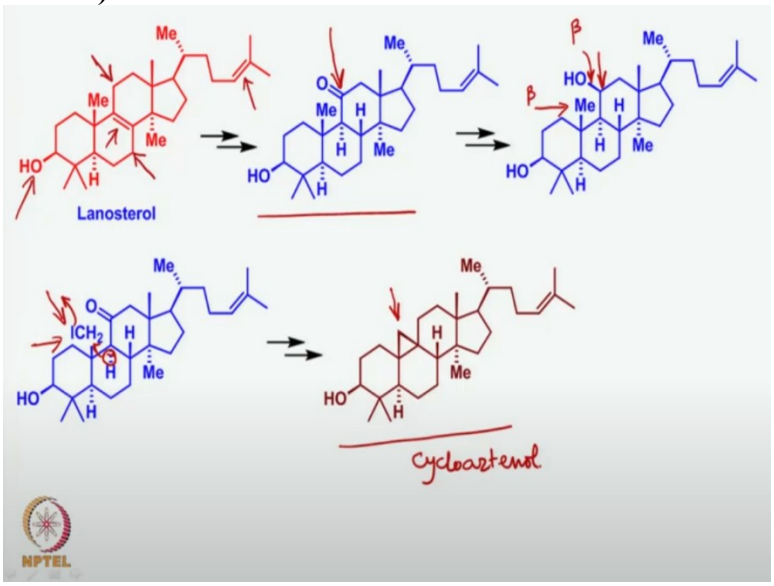

Now how it is done is that you take the lanosterol as is here and this is the final molecule. Now, what is done is this molecule is somehow converted to this particular carbonyl group. How can we do it? Obviously if we take this double bond here and this is the allylic position. So if we use a strong oxidizing agent we can introduce 2 carbonyl groups on both the side's one here and one

here. This particular position is sterically hindered position because of the methyl group and it is also known to be sterically hindered of this steroid molecule.

But then we have to take care of this double bond we also have to take care of the hydroxy groups. So it was done in a very specific manner by protecting this hydroxy group and the protection of this double bond. And finally reducing the corresponding double bond which; is here as well as carbonyl group that is going to come here. Basically it is a very specific way of introducing the carbonyl group at this particular position by a few steps, but that was possible.

Once that was done then without worry about the protection and deprotection of the other groups once the carbonyl group was introduced here it was reduced. And they got the corresponding hydroxy group like this which was through the ONO that is nitrosyl chloride the pyridine based and then photolysis in the presence of iodine led to the formation of corresponding CH_2I. So this particular methyl group which was having similar orientation as the hydroxy group which is beta this is also beta oriented.

And therefore the abstraction 1, 2, 3, 4, 5 and 6 the hydrogen here and then when can I prepare the corresponding radical and which in the presence of the iodine leads to the corresponding CH_2I. And now once this is happen then they used a strong base to deprotonate this particular hydrogen here. And then this negative charge attack down to this particular carbon and then iodine goes as a leaving group and eventually the cyclopropane ring is formed here.

So this is a very interesting celebrated example of conversion of lanosterol to another molecule which is cycloartenol. Of course it is involved many steps and protection and deprotection but it was a very brilliant example of the power of the Barton reaction.

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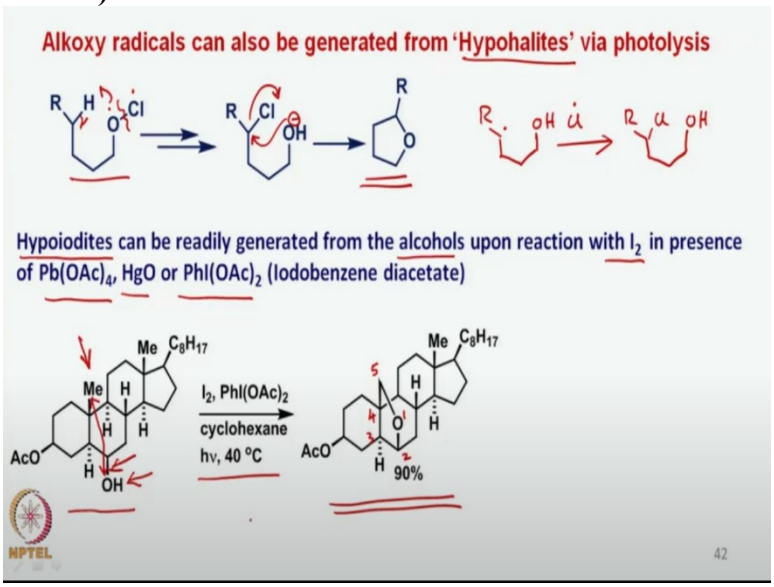

(rerfer time: 23:46) Now the alkoxy radicals can also be generate from hypohalites. So if you can take the hypohalite here and we do the photolysis here then we can generate the corresponding radical. So if that radical is formed here this radical can pick up the hydrogen from here to, form the corresponding radical at this centre. And of course you can get the attachment of the chlorine from the substrate or via chlorine radical and of course you can get this.

And now we have a base which deprotonates and of course then that attacks on to this carbon and then one can get the tetrahydrofuran. One can also start to use hypoiodites that can be generated from the alcohols upon reaction with iodine in presence of Lead tetra acetate or mercuric oxide or iodobenzene diacetate. This is an example of that and these conditions at 40 degrees. For example you can have the generation of oxygen radical from this OH and this is also beta oriented.

And then one can, through the iodine mediated reaction can also have a connection between this particular oxygen and this carbon to form these 5 membered rings. This is 1, 2, 3, 4 and this 5. So this is very interesting such molecule having a tetrahydrofuran unit embedded in the steroid molecule by this reaction. So this example is an extension or related reaction to the Barton reaction by using hypohalite hypoiodite.

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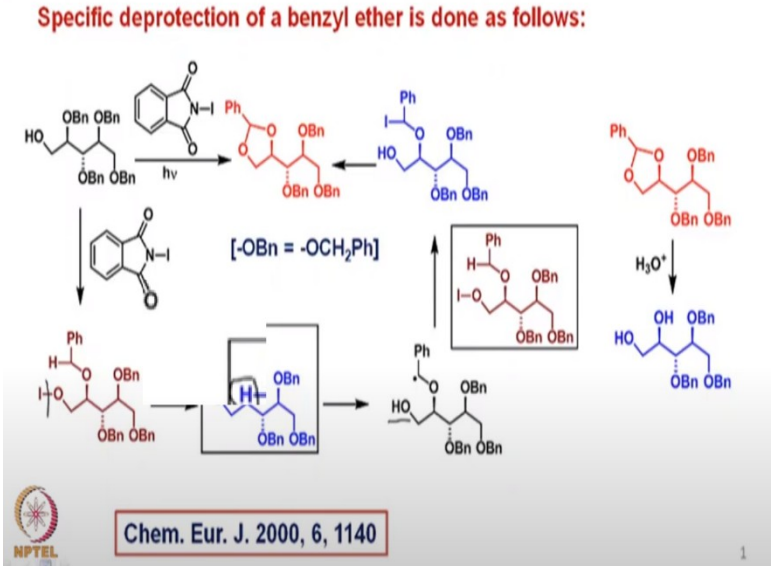

Now how to we make use of the hypohalite based chemistry in specific deprotection of benzyl ether. Now if we take a compound of this kind which has 4 different types of benzyl ethers. The benzyl ether is nothing but an OCH2 phenyl group. Now if, we have these 4 types of benzyl ether present in this particular molecule and we want specifically this particular O benzyl group to be deprotected to form this diol.

Then this particular chemistry of hypohalite based chemistry under photolytic condition allows the formation of this ketal which can be hydrolyzed under acetic condition to give this particular diol which is what is a result of a specific deprotection of this particular benzyl group. Now what happens is that when this particular molecule is allowed to react with N iodo thalamite then OH group here interacts with the iodonium ion here to form the hypo iodide of this type.

Now when we do the photolysis then this particular iodine oxygen bond undergoes cleavage to form the oxygen radical here and of course iodine radical will go away. And this oxygen radical intramolecularly picks up the hydrogen from here as a hydrogen radical and becomes an OH group here at this position here like this and generate a radical here at the benzylic position because his radical is then stabilized by the phenyl ring also it is stabilized by the oxygen.

Now this particular radical then reacts with the same hypoiodite which is shown here and picks up the iodine radical from here and generate oxygen radical which is the same as this particular species. And once this hypoiodite reacts with this radical leading this to iodo-compound then there is an intra-molecular closure of this particular part of the molecule leading to the ketal of this type. Now this ketal of a having 3 benzyloxy groups can then be hydrolyzed under acidic condition because these benzyl ether groups are stable under acidic condition.

But this ketal is not stable and undergoes hydrolysis to form the corresponding diol. So it means that we have started with a monohydroxy compound having 4 types of benzyloxy ethers and eventually we get a diol and with 3 benzyloxy group intact. So this is how a specific deprotection of benzyl ether is done under these conditions using hypoiodite based chemistry under photolytic condition.

This particular work has been reported in this journal Chemistry Europe in general in 2000. So we will stop it at this stage today and take some aspects of the Barton reaction specifically the beta cleavage the C-C bond cleavage in some synthetic transformation and then proceed further. We will stop and at this stage and I expect that you will go through these things which I have thought today and I will see you the next time thank you.