Essentials of Oxidation, Reduction and C-C Bond Formation
Application in Organic Synthesis
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Lecture No. 28
Reductions with LS/KS Selectrides and NaCNBH 3

Hello, everyone, I would like to welcome you to today's class. What we discussed last time, we would recap in a brief way today.

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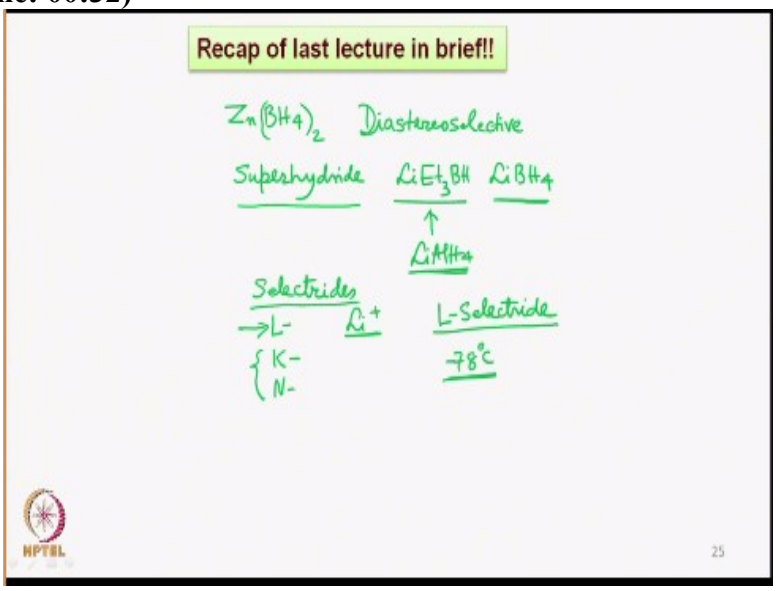

We started with zinc borohydride based reductions last time and we saw how the chelation with zinc allows highly diastereoselective reductions of ketones and we tried to look at some examples in which the chelation is seen both as a 6 member and a 5 member transient state. Then we looked at the super hydrides.

And we saw how the like lithium triethylborohydride is introduced in and compared with lithium borohydride, which is more sort of ionic than lithium triethylborohydride. Since the electron releasing nature of ethyl group makes this as a stronger reducing agent, this is called as a super hydride because it is much stronger than lithium borohydride.

And then, we also saw how it can be compared with lithium aluminium hydride where we saw the reactivity was quite different from the lithium triethylborohydride. And then, we also looked at towards the end the selectrides. And in the case of selectrides, we saw 3 different types of L-selectride, K-selectride and N-selectride. Of course, these two are not really so much popular as the L Selectride is because of the lithium+ being the stronger chelating ion than potassium and sodium.

And therefore, L-selectride is a reducing agent of a choice in which we have the secondary butyl group as a as a bulky substituent on the lithium borohydride paste reducing agent. And therefore, L-selectride was obviously, a choice for the reductions in which high diastereoselectivity is expected. And we saw some examples. We also discussed and looked

at that, these are used only in cases where high diastereoselectivity is required at low temperature.

And we then looked at the temperatures, where the some cases minus 78 degrees can also be used, because of the high reactivity of such molecules. They are called selectrides because there is a selective reduction and therefore, they are called selectrides. So, these names like superhydrides, selectrides etcetera, have been given based on the reacting nature of such molecules.

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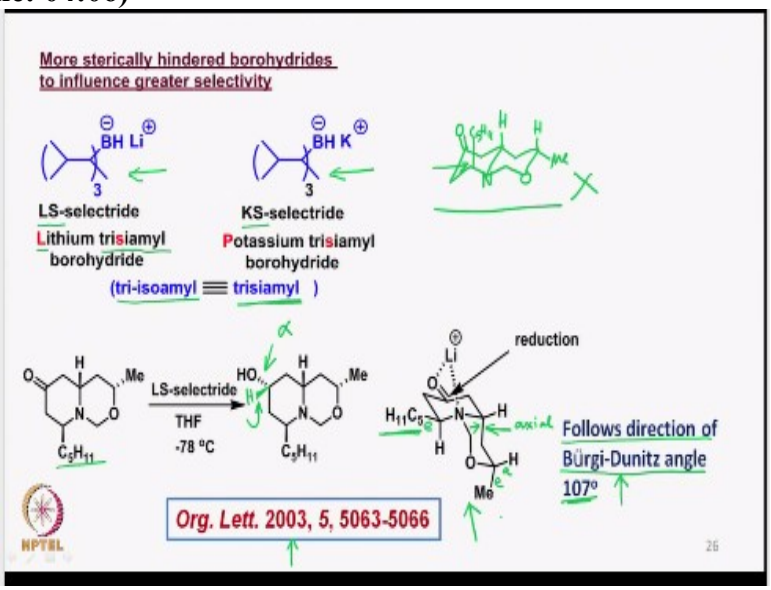

Now, we look at even more strong reducing agent where even more steric hindrance has been introduced. For example, this is called as LS-selectride and this is called as KS-selectride, L stands for lithium and S stands from the trisamyl part that is tri iso amyl part in which the S letter has been taken up and this is how it is called as LS Selectride as you can see here.

So, this is KS selectride and this is LS selectride in which the groups which are attached are bulkier than secondary butyl, basically it is tris iso amyl or tri isoamyl group which is present now We take a case something of this kind, which is reported in literature in 2003. Now, if we take this bicyclic molecule, which is now reduced and as you can see the reduction leads to this particular hydroxy group being alpha.

If we see the conformation of these molecules, this molecule we see that if we make it as a as a trans type of molecule in which now we have a nitrogen here and a hydrogen here, then we can put the oxygen at this stage. Methyl group is alpha therefore, we can put it in this way. And now, if we put the carbonyl group which is here and then the substituent C5H11 which is beta oriented is put it here C5H11.

Now, very clear that this particular conformation is not a preferred conformation, because the bulky C5H11 is is axial. Therefore, we would imagine that this particular conformation is preferable as you can see that the C5H11 now is in equatorial orientation and the methyl here, this is axial hydrogen. This is methyl. This is also equatorial. This is equatorial hydrogen and we can remove this part here and look at methyl being equatorial.

So, both the groups equatorial and now, in this case, what is happening is that this particular CH2 two group is axial. And therefore, the reduction does not come the reducing agent does

not approach the carbonyl group from the lower side because lower side is basically offering a steric hindrance. And therefore, the reduction takes place from the top side that is a beta side.

And therefore, the reduction leads to the hydroxyl group being alpha oriented and the hydrogen is coming from the beta site, this is very easily seen by this particular conformation. And so, there are two reasons why this conformation is preferred. One is of course, you have a substituent which is expected to be in such a way that the bulky substituent prefers equatorial orientation.

And then between the 2 of them that we consider the trans as well as the cis type of the lone type of molecules. We prefer the cis one and obviously, in all these cases, wherever we have discussed the carbonyl group reduction with any reducing agent, we have to keep in mind that the reduction takes place at 107 degrees angle, which is the rule according to or the descriptions made according to the Burgi-Dunitz's kind of hypothesis or the observations.

So, in any case, the reduction has occurred in a very highly diastereoselective fashion mainly because of the very large bulky groups which are present on the LS-selectride. As we discussed earlier, it is whenever there is a preference of L-selectride versus K-selectride we prefer L-selectride. In a similar fashion when we have LS-selectride versus KS selectride, we will prefer LS-selectride where there is a solubility problem.

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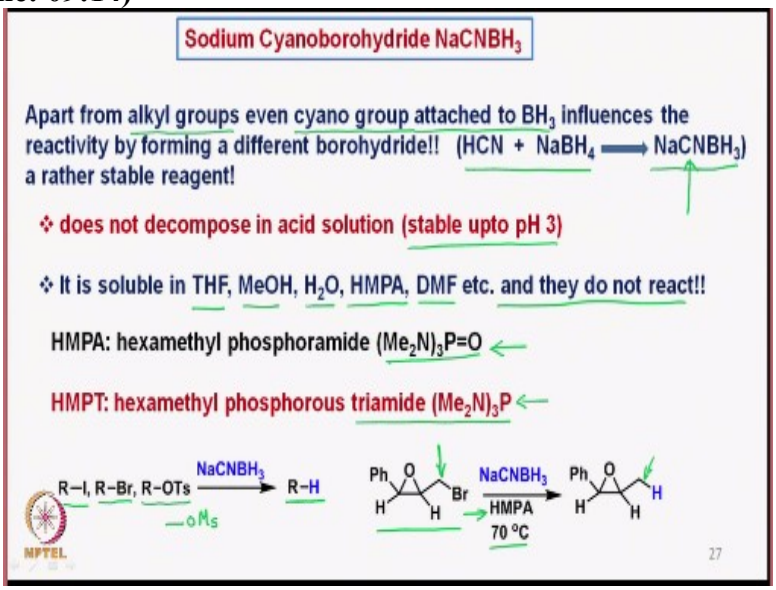

Now, we go to another reducing agent which is sodium cyanoborohydride not only alkyl groups, which we saw in the case of lithium triethylborohydride or Selectride or LS-selectride we saw different alkyl groups which are being put in order to increase the electron releasing nature of the borohydride and as making them stronger and stronger reducing agents.

But not only alkyl groups that can be put as substituents, but even electrons drawing group such as a cyano group has been introduced and attached to the boron part of the sodium borohydride which is easily made by reacting sodium borohydride with hydrogen cyanide and that leads to the sodium cyanoborohydride. So, what is the purpose of such a reagent? That is something that we need to understand it.

Sodium borohydride is obviously, the simplest reducing agent. And that reacts with carbonyl compounds readily because, it is ionic and in ethanol or we call ethanolic solutions it reacts. But we when we put a cyano group, so a cyano group is an electron withdrawing group. This particular cyano group is an electron withdrawing group and obviously, it reduces the the nucleophilic nature of the borohydride part.

That is now in this particular case BH3 is much less than the sodium borohydride case. It is obviously not easy to reduce a particular carbonyl group with a compound that is having an electron withdrawing group as a nature, cyano group as an electron withdrawing group. And therefore, in order to increase since, we have decreased the nucleophilicity of sodium borohydride by putting cyano group. So, we need to increase the electrophilicity of the substrates that is the carbon group.

And what is interesting is that, because the nucleophilicity, nucleophilic nature of the sodium borohydride has been reduced by putting the cyano group. So, the sodium cyanoborohydride now, is not nucleophilic enough. So, it is found that it does not decompose in a solution even up to say pH 3. That means, it is stable under acidic conditions. And that is the advantage. And it is also soluble in THF, methanol, water, HMPA, that is hexamethyl phosphoramide, DMF, that is dimethyl formamide.

And these they do not react with these particular solvents. Now, just for comparison, this is a phosphoramide and this is a phosphorus triamide. But this is more used as a solvent and this is used as if kind of phosphene in comparison to triphenylphosphene or trialkylphosphene. What do the sodium cyanoborohydride allow the reductions of that is if we take a halide such as R-I, or R-BR or R-tosylate where there is a fairly good leaving group.

You have an iodide as a leaving group, bromide as a leaving group or tosylate as a leaving group or even mesylate as a leaving group. So, we have para toluene sulphonyl or this methane sulphonyl. So, sodium cyanoborohydride, reduces these molecules and the leaving groups go and then hydrogen is introduced at the R position. So, you can see here at in HMPA at 70 degrees as this kind of molecule which is somewhat sensitive molecule, we can reduce this particular carbon bromine bond and introduce here carbon hydrogen bond.

In these cases one thing which is important to remember that the reducing agent sodium cyanoborohydride is stable under acidic conditions up to pH 3. So, what are the reactions that are done? Now, as I mentioned, if we have decreased the reducing ability of sodium borohydride by, introducing a cyano group and thus the sodium cyanoborohydride is less nucleophilic.

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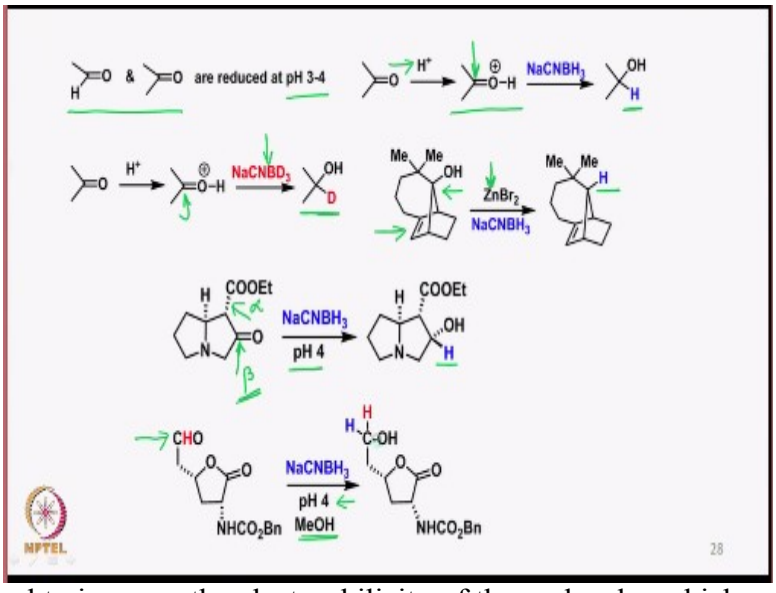

Therefore, we need to increase the electrophilicity of the molecules which we need to reduce. And for that purpose since sodium cyanoborohydride is stable up to pH 3 to 4, we can add acid into the molecule where carbonyl group gets now protonated to form the corresponding oxonium ion which then now is fairly good electrophilic in nature to which sodium cyanoborohydride then reacts and then your hydrogen is transferred as a hydride and corresponding alcohol is formed.

So, we can also do in this fashion that we put H+ and then we have sodium borodeuteride and obviously, we can introduce the deuterium here and form the corresponding deuterated alcohol. So, this utility of sodium cyanoborodeuteride to the corresponding deuterated alcohol is also utilized it. Now, in all these cases what we have seen is that, we have introduced the acid to the reaction medium in order to increase the electrophilicity of the carbonyl group.

We can also utilize the nature of this sodium cyanoborohydride which is stable under acidic conditions in such a way that for example, if we take an alcohol of this kind and see that the alcohol which is a tertiary alcohol can easily be reacted with a Lewis acid and could be ready to form a sort of carbocation which is a tertiary carbocation. In this particular case is a just a rigid molecule.

And therefore, the alcohol when it coordinates with the zinc bromide, it releases the OH part and then sodium cyanoborohydride attacks from the same side and the hydrogen is introduced where the OH group was present. Basically only because the reagent sodium cyanoborohydride is stable under acidic conditions. So, it is this basically what we are talking is that you have a sort of carbocation that is formed.

So, carbocation allows the reduction to take place. Even here in this case, as we can see that this carbonyl group is reduced to the corresponding alcohol and the at pH 4, the reduction allows the approach of the hydrogen coming from the beta side here because of the ester group which is the alpha oriented. So, you have a beta hydrogen to come at the carbonyl carbon.

So, not only it is releasing it at lower pH, but is also of course following the same principle of stereo selectivity. Now, in this case in the last example, here, the aldehyde is also reduced

again at pH 4 in the methanol as a solvent. So, one can go all the way. So, you have a possibility of going via a carbocation. We have a possibility of protonating the carbonyl groups and therefore, under these conditions the sodium cyanoborohydride being stable can allow the reaction to take place.

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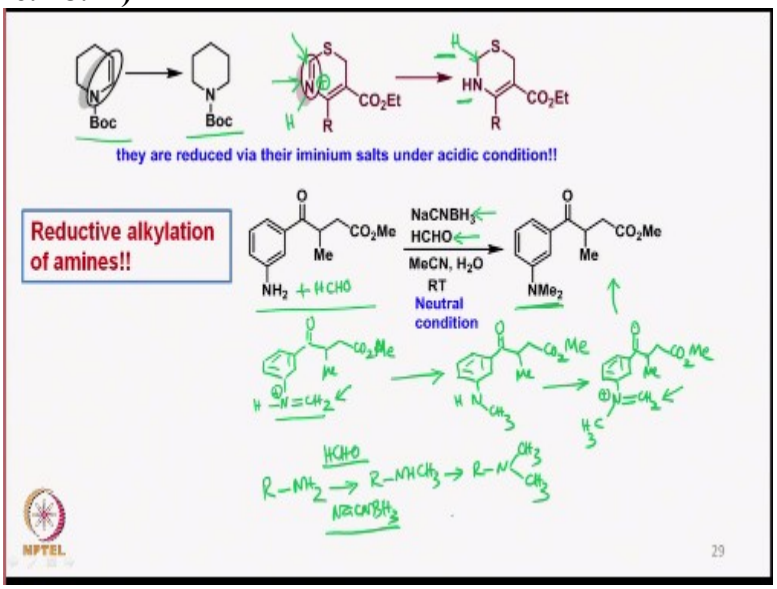

Now, because carbocations can be formed, as you can imagine that we have an enamine and this enamine can be reduced to the corresponding saturated molecule. Basically, because you have the enamine which is kind of nucleophilic in terms of the fact that we can move the electron density to the proton. So, if we have under acidic conditions, the reaction to take place in the presence of sodium cyanoborohydride then, we can expect an intermediate to form something of this sort.

So, this is the intermediate that will form which then gets reduced under the conditions to basically have the reduction taking place at the centre. And then such molecule is coming. So, this particular model, hydrogen is coming from the acid and this particular hydrogen is coming from the sodium cyanoborohydride and that is how we get this saturation of the double bond.

In a similar fashion, this is an imine which is very easy to understand that it gets protonated under the conditions to form the corresponding positive charge on the centre and therefore, the nucleophile sodium cyanoborohydride would attach it here and then your hydrogen will come there. So, this hydrogen comes from sodium cyanoborohydride and this hydrogen comes from the corresponding acid.

Therefore, such reductions are quite useful in order to which cannot be easily done by means of sodium borohydride because, such possibility of formation of an imonium ion or a carbocation is not there. If we now look at the this aspect of it here of examples in which we have done the alkylation, this is very interesting. Now, I would like to discuss it in detail about it that how does this particular alkylation of amines takes place.

So, we let me remove this particular part of it, which we discussed just now. And look at it here, if we take this particular molecule and react with formaldehyde and of course, sodium cyanoborohydride. And under these conditions, what happens is first the formation of and

something of this sort occurs after the nitrogen of the molecule methyl interacts with the formaldehyde.

That means, there is a condensation with the formaldehyde and an imine is formed. And this imonium ion then gets reduced at this stage here with sodium cyanoborohydride to form here NHCH3. And of course, the corresponding carbonyl group is present and the corresponding ester is also present. Now, here there are 2 aspects. One of course, we have deliberately added formaldehyde.

Therefore, the reaction occurs by condensation of amine with the formaldehyde and we form this secondary amine. Now, if we continue the reaction, the secondary amine also will undergo condensation and form this type of CH3. And here you have a double bond CH2 positive charge. So, the second condensation occurs of the secondary amine here and again the reduction takes place at this centre with sodium cyanoborohydride here leading to the formation of dimethylamino group.

So, what we have done is we have introduced say you have an R and then you have NH2 we have gone stepwise. So, to form R-NHCH3 and then you have R-NCH3 and CH3. So, that is because of the formaldehyde and sodium cyanoborohydride and that is a very straightforward and an easy way of introducing a dimethyl group on a primary amine, using the properties of sodium cyanoborohydride reducing a cationic species.

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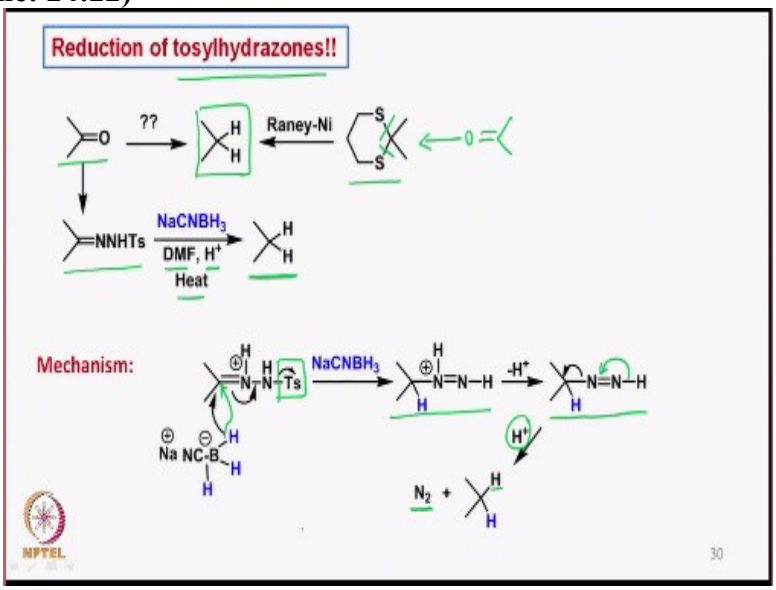

So, interesting way of converting a carbonyl group to the saturated sort of molecule like this hydrocarbon here. What are the ways by which such a reduction can be done? That means if we have a carbonyl group, of course, we can carry out Wolff-Kishner reduction and then we have another possibility that we protect the carbonyl group here as dithioketal. And once we have the dithioketal with reduction can be done by Raney nickel, a special nickel catalyst which on the surface of which hydrogen is adsorbed.

And that allows the cleavage of this carbon sulphur bonds by the hydrogen and then you get the corresponding molecule in which the oxygen is replaced by two hydrogens. Now, there is another way by which we can do the same reaction by converting carbonyl group to the corresponding N-tosylhydrazone, that is what the reduction is that we are discussing and if

we use a protic source in the in DMF and heat it we can get the same reduction but then it is via tosylhydrazone.

Now, what is the mechanism and the acidic condition the nitrogen, the first nitrogen here of the tosylhydrazone gets protonated here and we regenerate immonium ion here to which now sodium cyanoborohydride donates hydride here and the double bond moves with the loss of tosyl group here. It goes off, leading to the formation of this particular intermediate which then is is losing a proton.

And goes to another molecule like this, which can now be expected to be somewhat like this that we have loss of nitrogen in this fashion and then under the protic condition, the anion which is formed here is grabbed by the proton which is present here. So, the blue hydrogen is coming from the sodium cyanoborohydride and once that allows the formation of this protic species here this can rearrange by the loss of nitrogen and the proton is coming at this stage this is how the reaction occurs.

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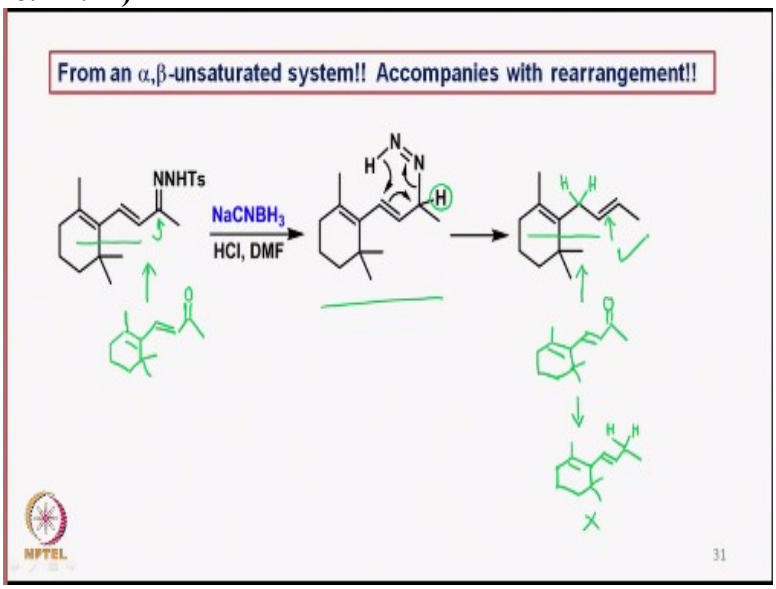

Now, if we take a alpha beta unsaturated system, we have seen that the normal tosylhydrazones are reduced to the corresponding molecule in which the carbonyl group has now through tosylhydrazone replaced to the corresponding 2 hydrogens. But if we take an alpha beta unsaturated system, which is from molecule like this if we take a molecule like this.

We can convert into the corresponding tosylhydrazone which then under the similar condition forms the corresponding hydrazine type of molecule like this which then undergoes rearrangement in this fashion to move the double bond to this position which is this was a conjugated system. Now, what we have found that under these conditions, it undergoes d-conjugation and the hydrogen is coming at this stage here the hydrogen is coming here.

So, are the original hydrogen had come at this stage here this should be blue in colour, and then we have a rearrangement. That means, now, what we have started, we started with this molecule in which we had the carbonyl group like this, eventually, what we have got is this. So, it is not only the reduction of the carbonyl group to the corresponding hydrogens which we would have expected to give something like this.

If it was normal reduction, then we would have expected the two hydrogens to come here, but that is not the case what we have got is is the two hydrogens which have come are basically at this position here. Eventually, so, instead of getting this molecule which we did not get it, we got this molecule via the tosylhydrazone. So, this is how the reactions of sodium cyanoborohydride take place. So, we will stop it.

Today at this stage we have seen the various aspects of ah these reducing agents. And now we will take up the other reducing agents next time you can go through the notes of today's class and get ready for the next class. Till then bye and thank you.