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-22

Reductions in Organic Chemistry: Metal Hydride (NaBH 4 and LiAlH 4) Mediated Reductions

Hello to all of you, I hope you had the chance to go through the last lecture contents. Now we would briefly look at the lecture that we did in last time, in a brief way. We basically looked that the beta cleavage.

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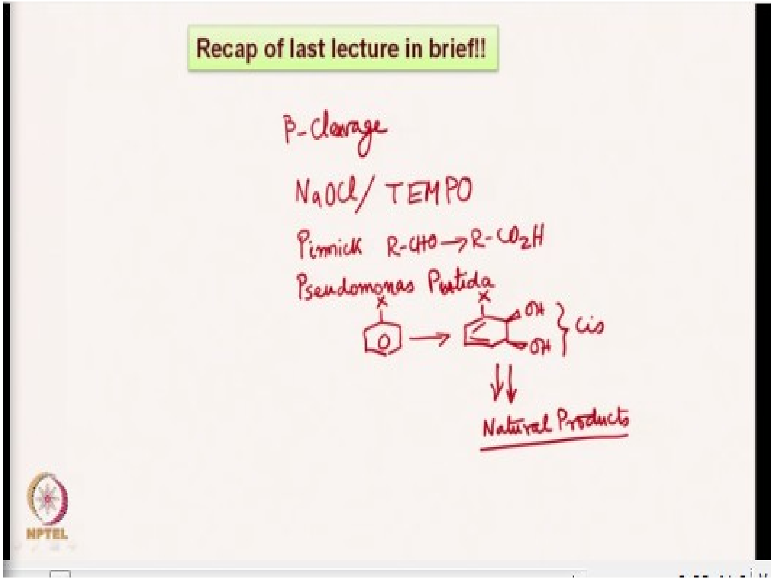

Recap of last lecture in brief!!

β-cleavage

NaOCl/ TEMPO

Pinnick R-CHO → R-CO$_2$H

Pseudomonas Putida

In this Barton type of reactions where hypo halides were utilized, actually it should be cleavage. And then we also looked at the oxidation using sodium hypochlorite based oxidation and TEMPO. And then we had a Pinnick oxidation in which we converted the aldehydes to the corresponding acid. And then finally we also looked at the pseudomonas putida based reactions.

So, we have basically pseudomonas it should be pseudomonas putida. And this allowed the oxidation of different types of benzene molecules to the corresponding 1, 2 diol where the 1, 2 diol were cis oriented. And then this can be converted to different types of natural products. Now we would stop the oxidations at this stage we have covered a large topics of oxidation of different types. And some of them old type and some of them new type, and now we would proceed to the corresponding reductions in organic chemistry.

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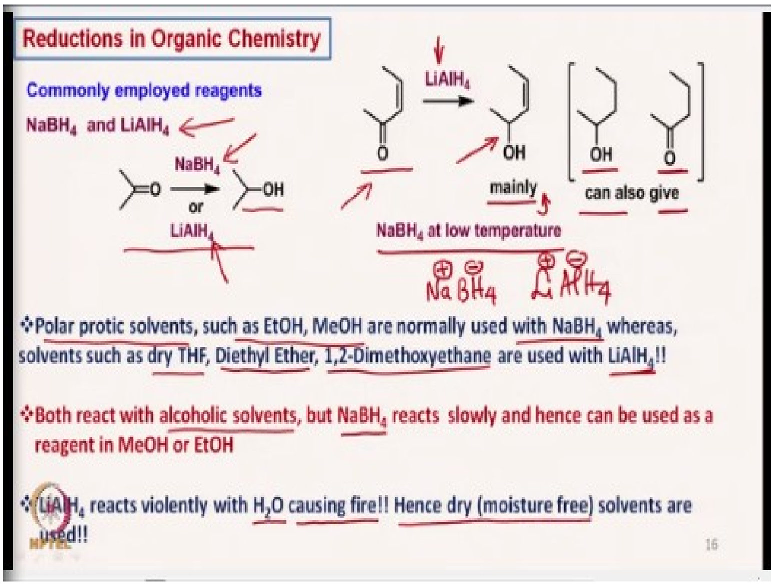

Reductions in Organic Chemistry

Commonly employed reagents

NaBH$_4$ and LiAlH$_4$

- Polar protic solvents, such as EtOH, MeOH are normally used with NaBH$_4$ whereas, solvents such as dry THF, Diethyl Ether, 1,2-Dimethoxyethane are used with LiAlH$_4$!!
- Both react with alcoholic solvents, but NaBH$_4$ reacts slowly and hence can be used as a reagent in MeOH or EtOH
- LiAlH$_4$ reacts violently with H_2O causing fire!! Hence dry (moisture free) solvents are used!!

Now if we look at the different types of reagents that are utilized in organic chemistry for the reduction of say aldehydes or ketones or the carbonyl compounds to the corresponding hydroxy compounds or say alpha beta unsaturated ketones to the corresponding reduced products of allylic alcohol type or saturated type or simply double bond is reduced, and that leads to the corresponding ketone.

So, the reagents that are commonly employed are sodium borohydride and lithium aluminum hydride. Now if one carries out the reduction of ketones we do not have much problem and if the molecule is not very sensitive molecule does not have other functional groups. Then the carbonyl group can be readily reduced to the corresponding alcohol using any one of them, either sodium borohydride or say lithium aluminum hydride.

And if one takes the alpha beta unsaturated ketone such as this and if one wants to convert this into the corresponding allylic alcohol, then the reagent that is commonly employed is lithium aluminum hydride. And but it also can lead to the corresponding saturated alcohol or under certain conditions can also lead to the corresponding ketone in which the double bond has been only reduced particularly at when we carry out the reaction with sodium borohydride at low temperature.

We can mainly get this but lithium aluminum hydride always gives the allylic alcohol. We can also find certain conditions under which we can get these 2 molecules with both sodium borohydride as well as lithium aluminum hydride. So, now there are several possibilities of converting different types of aldehydic or ketonic molecules to the corresponding alcohols.

One major difference between sodium borohydride reactions and lithium aluminum hydride based reactions is that sodium borohydride is normally used in polar protic solvents such as ethanol methanol or say isopropanol etc. That is because sodium borohydride is ionic or rather more ionic than the lithium aluminum hydride and therefore more protic polar solvents are used.

On the other hand lithium aluminum hydride which is very reactive towards moisture. And that is why solvents which are non protic solvents, such as dry THF tetrahydrofuran, diethyl ether or any other ether or 1, 2 dimethoxyethane which is also ether are used. Because lithium aluminum hydride reacts violently with water and therefore these solvents which are used are non protic solvent.

Because in with ethanol and methanol lithium aluminum hydride itself will react and therefore the solvents which are used are such which do not have any it within the source of proton and also it should be specifically made moisture free. At the same time both lithium aluminum hydride and sodium borohydride react with alcoholic solvents. It is not that the sodium borohydride does not react with alcoholic solvent especially methanol and ethanol, but it reacts very slowly.

And hence the alcoholic solvent such as methanol or ethanol can be utilized during the reductions using sodium borohydride. As I mentioned lithium aluminum hydride reacts violently with the water causing fire. In fact it should not even the bottle of the lithium aluminum hydride should not even be opened when there is moisture in the atmosphere. Hence the solvents which are used have to be made moisture free.

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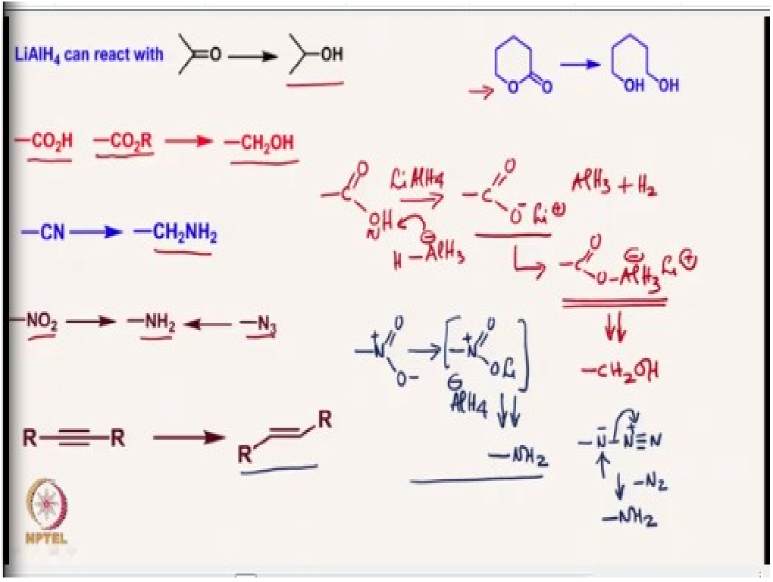

Now lithium aluminum hydride as sodium borohydride reacts readily with carbonyl compounds, aldehyde or ketones to form the corresponding alcohol. At the same time the carboxylic acids or the corresponding esters can be converted to the corresponding primary alcohol using lithium aluminum hydride. But that is not the case with sodium borohydride, sodium borohydride does not readily react with acids or esters or say for example lactones or the nitriles or the nitro compound or even the acetylene.

So, in these reactions lithium aluminum hydride is supposed to be a better reducing agent. We will discuss the mechanistic aspects of conversion of the ester to the alcohol or say cyanide to the corresponding amine a bit later. But for the first we see what happens to the corresponding acid here. Obviously when we have the acid and react with say lithium aluminum hydride it forms the O- Li+ and of course you get AlH3 with the release of hydrogen.

That means the AlH4 part which is negatively charged takes up the proton first from here and we generate this species, which is what then eventually forms the corresponding oxygen containing or something of this type with a negative charge here and lithium+. So, this then undergoes reduction, this part undergoes reduction further with lithium aluminum hydride and finally via aldehyde it forms the corresponding alcohol.

So, this is how the reaction occurs. So basically what is happening is that acid molecule allows this deprotonation to form this type of intermediate, and then that undergoes the reduction. Now we also have nitrile to the corresponding amine and nitro can be converted to the amine and of course azide can be converted to the amine too. So, we have this nitro group which can react with the reducing agent.

And what we have is essentially what we have is you have something like this here. And just the way as we discuss above it can first react with lithium+ to form this and of course you have an $AlH4^-$. Now this allows the reduction to begin and then finally it leads to the corresponding amine here. In a similar fashion we have azide where we can say that we have something like this as a resurrent part of the azide.

In which basically what we have is this path here as a point where the reduction occurs with the loss of nitrogen and then eventually forming the corresponding amine and of course you lose nitrogen. So, this one can write down the mechanism and I think I suggest that you people try to write a mechanism for both the nitro to the amine, where you have stepwise transfer of a hydride from lithium aluminum hydride.

And eventually you try to work out what leaving groups are, and of course in the similar fashion you can write down the mechanism for the reduction of the azide. And then you have the acetylene and that forms the corresponding trans olefin here which is very simple, and we will discuss this a little bit later. So, these are the variety of things which can be used, which can be looked at from the reduction point of view using lithium aluminum hydride. At the same time lithium aluminum hydride which allows reduction of epoxides.

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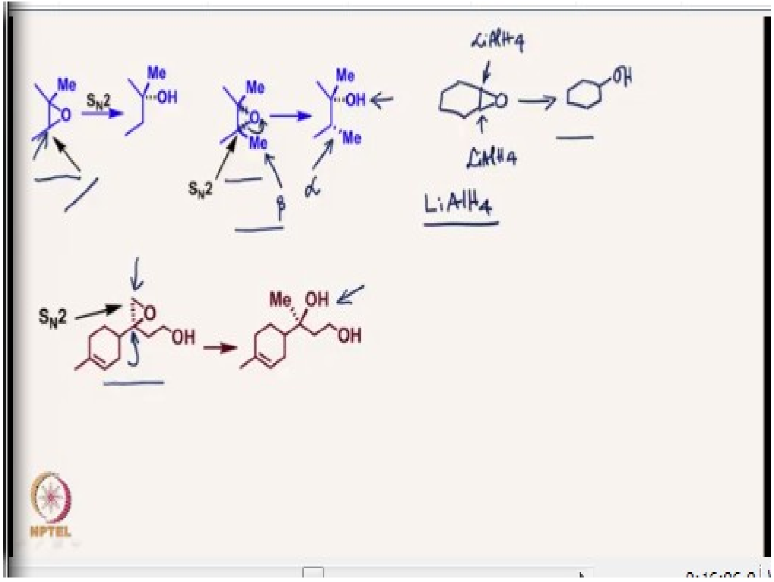

So, if we have a simple epoxide like this where there is no discrimination in terms of the 2 carbons here. So, it does not matter where the reduction occurs and readily you can get the corresponding hydroxy group. So, basically the lithium aluminum hydride can react on either side of it and lead to similar molecule. On the other hand when we have an unsymmetrical epoxide like this where there is one tertiary center and then quaternary center, then obviously the reduction takes place at the less hindered carbon atom.

Because the lithium aluminum hydride base reductions occur in a SN2 fashion. So, if SN2 reaction is taking place it has to be at the sterically less hindered carbon. But at the same time if there is such a molecule where both the carbons are similar. But they are also equally sterically hindered then obviously the reaction will occur. And now as you can see that if the stereochemistry here is alpha.

Then as you can see that the geometry of the methyl group here upon SN2 reaction has changed to the corresponding alpha orientation. Because it was originally a beta orientation, now it has become alpha because there is an SN2 reaction. And of course the hydroxyl group is lost from here to here which retains the geometry from the alpha side. So, the difference between this and this, and this is only the degree of substitutions on either end of the epoxide.

This was not substituted, so it does not matter, this was substituted but then we had a choice of between more substituted and less substituted, and of course the reaction occurred at the less substituted carbon. In this case the reaction occurs on any of the 2 carbons because they are symmetrical, but there is a change in the stereochemistry of the substituent because it is an SN2 reaction.

And in such cases where the reaction has to take place at the highly substituted carbons you might have to provide energy by heating the reaction medium. At the same time as you can see that one can have molecules like this. In which there is a possibility of having an asymmetric carbon atom, and the epoxide has a less substituted epoxide terminal where the reduction leads to the formation of this tertiary alcohol.

So, one can start with such kind of complicated molecules where the reduction could lead to the desired molecule via an SN2 based reductions using lithium aluminum hydride. Now where there are steric factors that can be allowed to be put on this sodium borohydride and lithium aluminum hydride.

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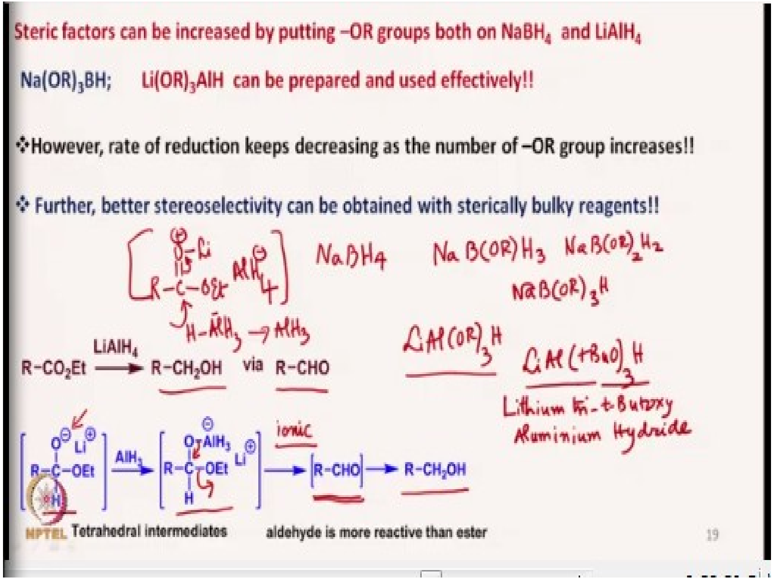

Steric factors can be increased by putting –OR groups both on $NaBH_4$ and $LiAlH_4$

$Na(OR)_3BH$; $Li(OR)_3AlH$ can be prepared and used effectively!!

❖However, rate of reduction keeps decreasing as the number of –OR group increases!!

❖ Further, better stereoselectivity can be obtained with sterically bulky reagents!!

$$R{-}CO_2Et \xrightarrow{LiAlH_4} R{-}CH_2OH \text{ via } R{-}CHO$$

Tetrahedral intermediates

aldehyde is more reactive than ester

As I mentioned that sodium borohydride as well as lithium aluminum hydride both react with alcohols. Only difference is the sodium borohydride reacts relatively slowly and the lithium aluminum hydride reacts violently with alcoholic solvent or even water. So, if one wants to increase the steric bulk of these reducing agents, then what one can do is to react deliberately say sodium borohydride with say methanol or ethanol or any other alcoholic solvent.

And gradually increase the bulk, say for example one can have only one alcohol and then we have this 3 or we can have 2 of them and then we will be left out with 2 hydrogens. And like this; one can go to the corresponding tri-substituted, this sodium boro alkoxy hydride. In a similar fashion one can convert this lithium aluminum hydride using any one of these to this ultimately ulparticular molecule.

Now, one can also use in this case and it is available even commercially is one can put the very bulky tertio butyl group. And you have this lithium tri-tertiary butoxy aluminum hydride. So, you have lithium tri-tertiary butoxy aluminum hydride. So, basically such reducing agents can be generated, can be prepared or some of them are commercially available.

And we can make use of these for the reductions where the steric hindrance can be utilized to the maximum extent. For example if one has an epoxide where we are going to reduce and if the epoxide happens to be not that sterically hindered. So, there is a possibility of getting reductions at the both the end. Although it is an SN2 reaction but it can give reduction at both the ends and one of them being major.

But at the same time if we use say lithium tertiary butoxy aluminum hydride then the chances of getting one product in a very large ratio or very high. This lithium aluminum hydride base reductions using ester to the corresponding alcohol proceed via aldehyde, the corresponding aldehyde. Now basically the difference what happens is that we have the ester in which we have the carbonyl group here.

And it could react with the lithium+ to form this type of intermediate, and this it should be H 4. And then what can happen is it can then react with aluminum hydride where the hydride transfer occurs onto the carbonyl carbon which is now coordinating with the lithium+. And therefore this carbon is electrophilic and then you form the intermediate of this type which is a tetrahedral intermediate.

And this O^- then reacts with the released because once the aluminum hydride reacts by the transfer of hydrogen as a hydride to the ester, this is the intermediaries form. But what is released from here is AlH3 and which is a trivalent aluminum, and that is electrophilic in nature. And therefore this O^- reacts with the AlH3 to form another tetrahedral intermediate of this kind.

Now these tetrahedral intermediate as well as this tetrahedral intermediate are both ionic in nature. And therefore these are not so stable and decomposed under the reaction conditions to form the corresponding aldehyde. Now we have started with an ester and as soon as the reaction occurs we get the aldehyde. Now there is a competition for reaction with the aldehyde and the ester towards lithium aluminum hydride.

And it is obvious that the aldehyde is more reactive because the aldehyde carbonyl carbon is more electrophilic, and therefore the reduction gives directly to the alcohol. And like this the reaction takes place and so the conversion of ester to the alcohol which occurs via aldehyde is cannot be easily stopped at the aldehyde stage. Mainly because the tetrahedral intermediates which are formed in these reactions are ionic in nature and therefore are not stable under the reaction conditions and decompose faster to the corresponding aldehyde. In a similar fashion the nitrile reacts with the lithium aluminum hydride.

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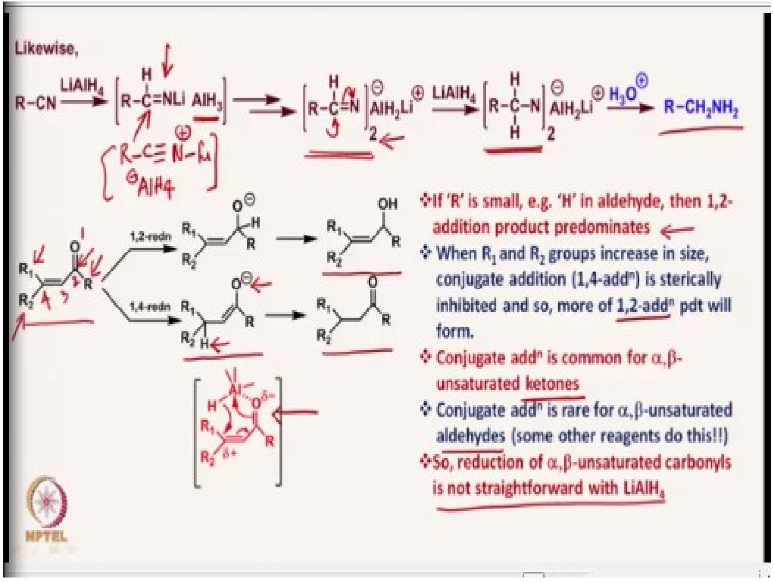
Likewise,

- If 'R' is small, e.g. 'H' in aldehyde, then 1,2-addition product predominates
- When R_1 and R_2 groups increase in size, conjugate addition (1,4-addn) is sterically inhibited and so, more of 1,2-addn pdt will form.
- Conjugate addn is common for α,β-unsaturated ketones
- Conjugate addn is rare for α,β-unsaturated aldehydes (some other reagents do this!!)
- So, reduction of α,β-unsaturated carbonyls is not straightforward with $LiAlH_4$

So, we have the nitrile group here which interacts with the lithium+ here like this forming nitrenium ion here and AlH4$^-$ which leads to the formation of this intermediate here. And since there is a possibility of transferring, another hydrogen onto this species here another molecule reacts with the AlH3 part. And there were 2 of these are associated with the reducing agent and then lithium aluminum hydride reacts and reduces this imine to form this.

And eventually this is then hydrolyzed to the corresponding amine. So, this is how the reaction of a nitrile takes place. So, nitrile reduction occurs in such a fashion that the lithium+ interacts first with the nitrile nitrogen, aluminum hydride transfers a hydride to form this imine. And then that undergoes reaction with another nitrile and forming 2 of these, such imine moieties associated with the aluminum and the lithium.

And then eventually the remaining lithium aluminum hydride reduces this imine to the corresponding amine. Of course it is ionic in the nature and therefore protonation under water condition finally gives the amine. Now if you look at the reduction of alpha beta unsaturated ketones or aldehydes. There is an interesting observation that has been reported in the literature.

For example if one takes an alpha beta unsaturated system like this, where there is a substitution of R at the carbonyl which can be hydrogen or other substituent such as R 1 and R 2. Now if 1, 2 reduction takes please that is this is the 1, 2, so you have 1, 2, 3 and 4. So, if one looks at the 1, 2, reduction if the hydrogen directly reacts as a hydride at the carbonyl carbon here, one directly gets this particular species.

And then that upon protonation gives the allylic alcohol that means double bond is not affected. On the other hand if there is 1, 4, reduction that means the hydride attacks are the fourth position and eventually you get an enolate of this kind where hydrogen is reacting at the fourth position and anion is coming at the first position. So, it is a 1, 4 reduction and then that after the protonation forms the corresponding ketone, because the enol will go to the corresponding ketone.

There is a possibility of this type of transfer of hydrogen at the 1,4th position where the oxygen interacts with the aluminum eventually. But first with the lithium and then aluminum and then one can transfer the hydride in this fashion. If R is a small group like hydrogen in aldehyde, then 1, 2 addition product dominates this is what is observed. When R 1 and R 2 substituents increase in size conjugate addition is sterically inhibited.

Obviously when we have the R 1 and R 2 which are big in size therefore attack of the hydrogen at the fourth carbon would be the inhibited and more of 1, 2 reductions take place. So, for 1, 2 reduction to take place it is aldehyde which is an alpha beta unsaturated aldehyde or substituents having large groups at the R 1 and R 2 lead to 1, 2 direction. On the other hand conjugate addition is more common to alpha beta unsaturated ketones, not the aldehydes.

And conjugated condition is rare for alpha beta unsaturated aldehydes. That means because mainly the reduction occurs at the carbonyl carbon of the aldehyde directly. So, reduction of alpha beta unsaturated carbonyls is not really a straightforward path using lithium aluminum hydride because it depends on various factors whether it is aldehyde or a ketone or the substituents etc.

So, we will stop it at this stage today and we will continue with the reduction of various organic compounds using different types of reducing agents in the next class and subsequently in the next classes. So, in the meanwhile you can go through and brush up all the things that I have discussed today as far as reductions are concerned and we will see you next time, goodbye and thank you.