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

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Lecture-23
Reductions Using Disobutylaluminum Hydride (DIBAL-H)

Hello, welcome you all to today's lecture. I expect that you had gone through the reduction part which I initiated last time. We will briefly look at what we did and then proceed with the remaining part of the lecture.

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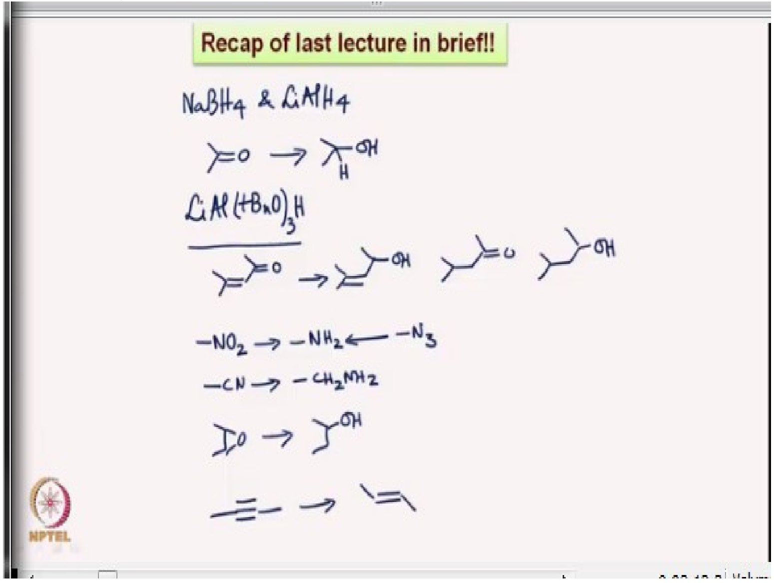

Recap of last lecture in brief!!

Now what we did was to introduce reducing agents which are sodium borohydride and lithium aluminum hydride. And we discussed that normal simple carbonyl groups such as aldehyde or ketones can be reduced to the corresponding hydroxy group with either of the reagents. We also saw that the reactivity of sodium borohydride or lithium aluminum hydride could be altered for making them sterically hindered by reacting them with alcohol, such as methanol or ethanol or even tertiary butanol.

And in this respect I explained that lithium aluminum tri tertiary butoxy hydride is a basically a very strong and sterically hindered reducing agent. And then we also saw the reductions of alpha beta unsaturated ketones or aldehydes. And accordingly as we discussed it is not a simple case with lithium aluminum hydride and it can lead to the corresponding allylic alcohol or the corresponding ketone or the corresponding saturated alcohol depending on various conditions.

We also discussed that reduction of other functional groups especially with lithium aluminum hydride such as nitro and the azide to the corresponding amine can occur with lithium aluminum hydride. The cyano can be converted to the corresponding primary amine. And of course epoxides can be converted to the corresponding alcohols, and we discussed various steric aspects of epoxides.

And of course we can also convert the corresponding to the trans alkenes we will discuss more aspects of these reactions in a while. So, these are the various things that we discussed last time.

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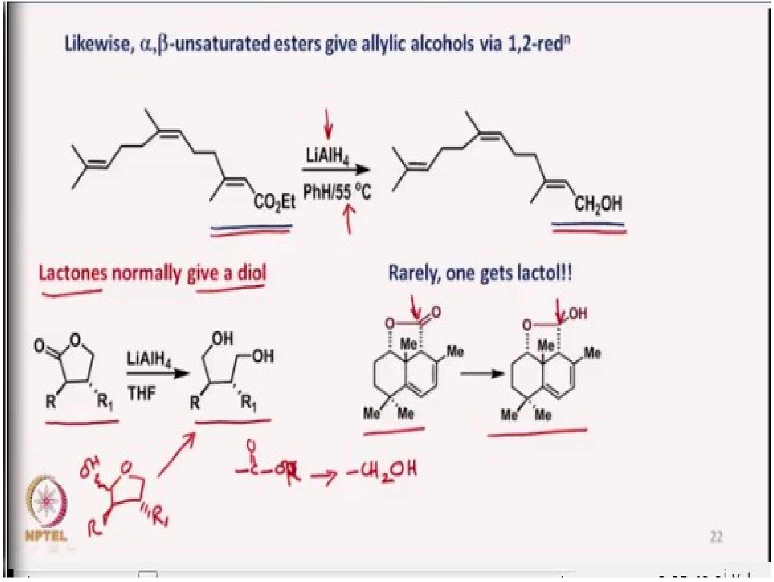

Likewise, α,β-unsaturated esters give allylic alcohols via 1,2-red^n

Lactones normally give a diol

Rarely, one gets lactol!!

And now we look at that not only alpha beta unsaturated ketones or aldehydes but also alpha beta unsaturated esters such as this can be reduced to the corresponding allylic alcohols by reacting with the lithium aluminum hydride. But as you can see the reaction is done generally at high temperature 55 degrees obviously because the esters are less electrophilic in the nature relative to the carbonyl compounds such as aldehyde or a ketone.

So, the esters we discussed that the esters can be reduced to the corresponding primary alcohols, you have here R group, any R group and that can be converted to the corresponding primary alcohol. But then as this particular ester is in conjugation with the double bond and therefore the reduction of the ester gives the corresponding allylic alcohol. Now we had taken cyclic esters which are nothing but lactones and they give the corresponding diol.

So, we have electron like this which gives the corresponding diol via obviously the corresponding lactol. So, in this particular simpler case when the reduction occurs we have the intermediate as the lactol which is then further reduced to the corresponding diol. Because a lactol is nothing but a hydroxy aldehyde because this once this opens it is going to form the omega hydroxy aldehyde.

Now in some cases especially in this example as it is reported in the literature, that the reduction of this lactone gives the corresponding lactol and the reaction stops at this particular stage for steric reasons. And therefore such rare conversions of the lactone to the corresponding lactol are not normally seen in the literature, they are generally found to lead to the corresponding diol.

But then there are different reagents which are useful for stopping the reaction from ester to the aldehyde or lactone to the lactol. If one tries to look at the reactivity of those reagents and compare with lithium aluminum hydride.

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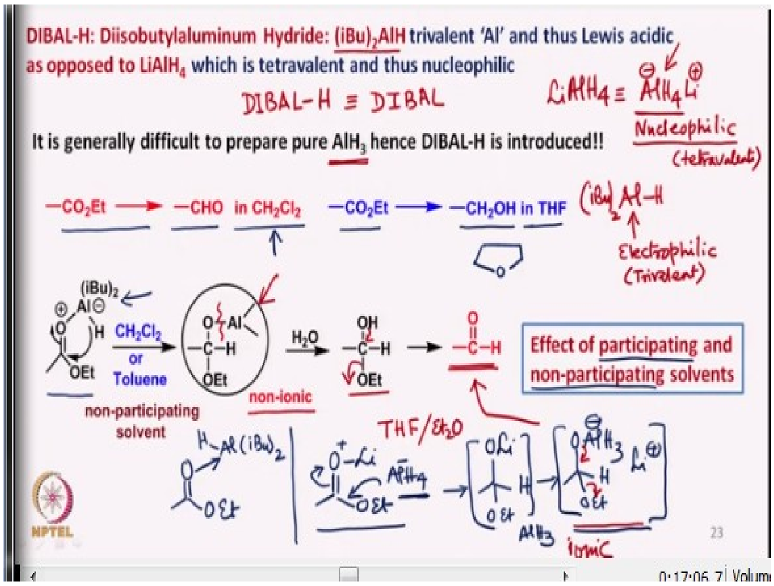
DIBAL-H: Diisobutylaluminum Hydride: $(iBu)_2AlH$ trivalent 'Al' and thus Lewis acidic as opposed to $LiAlH_4$ which is tetravalent and thus nucleophilic

It is generally difficult to prepare pure AlH_3 hence DIBAL-H is introduced!!

$-CO_2Et \rightarrow -CHO$ in CH_2Cl_2 $-CO_2Et \rightarrow -CH_2OH$ in THF

Effect of participating and non-participating solvents

Now before we proceed to that, I just wanted to show that the lithium aluminum hydride which we have used is an ionic reagent. And in which we have basically the aluminum part as negatively charged species. And where the AlH_4 species is basically a nucleophilic species. Now if we try to look at modifications that have been done in the literature and introduced different types of reagents.

One has introduced a very interesting reagent known as DIBAL or diisobutylaluminum hydride. And in many places they write is as DIBAL-H that is diisobutylaluminum hydride or simply DIBAL or many type places you will see simply DIBAL. So, this DIBAL, as the name says and it is diisobutylaluminum hydride, so it is something like this. So, you have here isobutyl 2 of them and of course there is 1 hydrogen.

Now if you look at the aluminum part here and compared with the aluminum part of lithium aluminum hydride, you can see that this is electrophilic in the nature, that is because it is trivalent whereas lithium aluminum hydride case it was a tetravalent. So, there is a difference in the 2 of these reagents and therefore it is not surprising that there is a difference in terms of the reactivity.

So, the aluminum in diisobutylaluminum hydride is trivalent and therefore electrophilic in the nature. Whereas in the case of lithium aluminum hydride it is tetravalent and therefore nucleophilic in the nature, because there is a negative charge on the aluminum. Now this is something which is very interesting but before the DIBAL was introduced people had also tried to look at the reactivity of aluminum hydride.

But there was a problem because the aluminum hydride is not easy to handle, therefore they try to look at the diisobutylaluminum hydride which is relatively more easy to handle. But then there is a comparison between the aluminum hydride and diisobutyl aluminum iodide that both of them are trivalent in the nature, and therefore are electrophilic towards their reduction with an ester or carbonyl group.

In the reactions which have been studied in detail, it is found that the ester is easily converted to the corresponding aldehyde in dichloromethane reaction medium. That means esters reduction to the aldehyde could be stopped using dichloromethane. It does not mean that ester cannot be converted to the corresponding alcohol in dichloromethane, it can be converted but at an under certain conditions which I will discuss.

And on the other hand if one takes the ester and if one reacts with DIBAL in THF for example, then the alcohol is formed, and it is difficult to stop the reaction at the aldehyde stage. So, there are 2 different conditions one is esters reaction in dichloromethane and the other is the reaction of ester in the THF medium. Now THF as you know is tetrahydrofuran, so there is something called as effect of participating and non participating reagents or solvents.

For example when the reaction of an ester is carried out with diisobutylaluminum hydride in dichloromethane or toluene, these solvents are basically non participating solvents. That is they do not have any interaction with any of the electrophilic species which are present during the reaction. So, if you take an ester and react it with the diisobutyl aluminum hydride, so you start with something like this where you have the aluminum species here, with the hydrogen being here and isobutyl group being here.

And then there is an interaction between the lone pair of electron on the ester oxygen to the aluminum of diisobutylaluminum hydride that leads to this ionic species. That is not the case with lithium aluminum hydride, in the case of lithium aluminum hydride the reducing species is AlH $_4^-$ which is nucleophilic, and lithium + is electrophilic, lithium + interacts with the oxygen of the ester, and initiates the reaction where the nucleophilic species AlH_4^- then interacts at this center to form this.

That the difference between these 2 is that, the interaction of the ester oxygen to the DIBAL since it leads to such an ionic intermediate. Where now the aluminum which was originally trivalent in the diisobutylaluminum hydride, now has become tetravalent with a negative charge and therefore it is now capable of transferring a hydride. On the other hand in the case of lithium aluminum hydride the reducing species was already present to transfer as a hydride.

But then the initiation of the reaction occurs with the lithium+ coordinating to the oxygen and thereby the hydride transfer the reagent, so this is the difference. Another difference is as you can see that in the case of lithium aluminum hydride. As we discussed earlier we have this intermediate where we have this, and that leads to eventually the formation of this particular ionic intermediate where there is a lithium as well as the aluminum species which are present as this, and this is an ionic species.

This is the intermediate formed starting with this where you have an AlH3 here. So, this particular intermediate is ionic intermediate. On the other hand when in the case of DIBAL when the DIBAL which is a trivalent to start with eventually becomes a tetravalent and transfers the hydride the way I have shown it here. That leads to the formation of an intermediate which is non-ionic.

So, there is a difference between this intermediate and the intermediate which is formed via the reaction of lithium aluminum hydride, this is a non-ionic intermediate and this is an ionic intermediate. And since I mentioned that ionic intermediate is more unstable and therefore decomposes faster whereas the non ionic intermediate does not decompose readily, it is stable under the reaction conditions.

And then water is added which leads to the hemiacetal and of course that breaks to form the corresponding aldehyde. Whereas here the ionic intermediate is not stable and during the reaction itself it leads to the corresponding aldehyde by the loss of this particular ethoxy group, and it gives directly to the corresponding aldehyde. That means during the lithium aluminum hydride reductions before you quench the reaction by adding water.

There is formation of aldehyde and since there is excess of lithium aluminum hydride, the aldehyde gets reduced. But in the case of DIBAL-H the reaction is quenched while the tetrahedral intermediate of this type which is non ionic intermediate, remains as it is and when the water is added the cleavage of this takes place. And then that leads to hemiacetal, and then when it cleaves it forms aldehyde.

But then by the time the diisobutylaluminum hydride is also not present in the reaction. So, this is the major difference between the 2 of them say in a reaction in dichloromethane or toluene when they are non participating solvents for diisobutylaluminum hydride. Of course in the case of lithium aluminum hydride, you use THF or diethyl ether as the solvent for reaction because lithium aluminum hydride reacts violently with the water.

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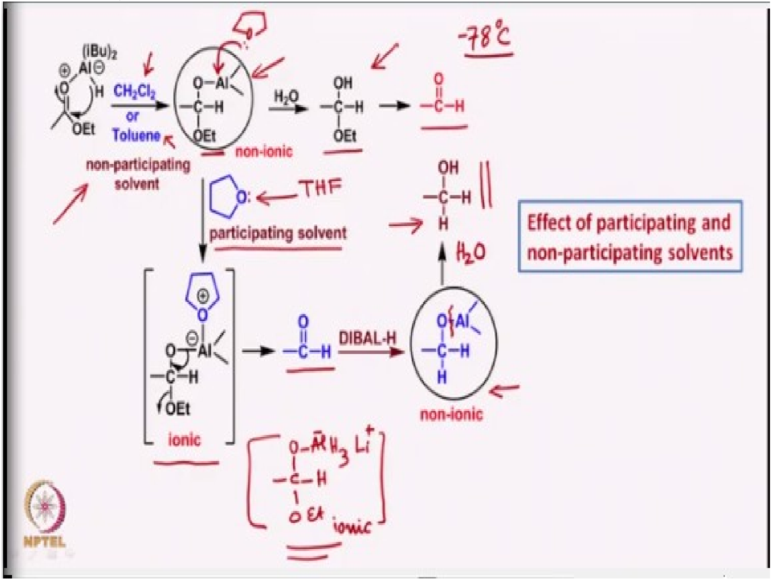

Effect of participating and non-participating solvents

Now if we see the participating solvent, we saw the non participating solvent and these are the things which are basically used in dichloromethane or toluene. Now if we take a participating solvent which is what is tetrahydrofuran, this is tetrahydrofuran. If we take this particular solvent instead of dichloromethane similar type of reaction occurs similar type of DIBAL interaction would occur with ester and similar intermediate is formed.

But then since this particular intermediate is non ionic, trivalent aluminum based non ionic intermediate. Here now the THF which has oxygen here with a lone pair of electrons on it interacts with the trivalent aluminum and forms an ionic intermediate of this type. So, now if you look at this particular intermediate which is ionic in the nature and compare it with say similar type of intermediate which is formed during the reaction with lithium aluminum hydride, then we have similar ionic intermediate.

So, this ionic intermediate is similar to this ionic intermediate, so but basically what we have done it is in the reaction of diisobutylaluminum hydride what we are trying to do is, to generate a similar type of intermediate. Such as this ionic intermediate which is formed from lithium aluminum hydride and therefore such ionic intermediate where there is a tetravalent aluminum is not stable and decompose while there is still diisobutylaluminum hydride present in the reaction.

And it forms the corresponding aldehyde and which again then reacts with diisobutylaluminum hydride in a normal fashion forming this intermediate which is now it should be a nonionic intermediate. And then when you add water the reaction is quenched and you can break this oxygen aluminum bond and then this alcohol is formed. So, this is how the reaction occurs when in participating solvent such as tetrahydrofuran is used.

And therefore it is difficult to control the reaction at the aldehyde stage. So, in case of using use of diisobutylaluminum hydride if one wants to stop the reaction at the aldehyde stage. Then one takes non participating solvent, such as dichloromethane or toluene. And use diisobutylaluminum hydride at low temperature here generally at - 78 degrees. And then you use only one equivalent of the reducing agent and slowly bring the reaction temperature up.

And in such a situation this nonionic trivalent intermediate is stable and at that point you add water to quench and then you go via this hemi acetal and the aldehyde is formed. On the other hand if one wants to use the same dichloromethane or toluene as a non participating solvent, and want the reaction to go all the way to the corresponding alcohol. Then you use excess of diisobutylaluminum hydride over at least 2 equivalence of diisobutylaluminum hydride.

At the reagent at lower temperature and or at a little bit higher temperature such as room temperature, and then warm the reaction to the corresponding say room temperature or something like that. Then what happens that you have an intermediate which is a nonionic intermediate. It then breaks at a relatively higher temperature when I mean higher temperature I mean room temperature or something like that.

It breaks and goes to the aldehyde and then of course the aldehyde then gets reduced to the corresponding alcohol. But on the other hand if you use participating solvent such as THF then of course you can easily go to the corresponding alcohol directly. So, both the possibilities exist and under both the conditions the reactions have been reported in the literature. Now what happens to the esters and ester and lactone reductions with diisobutylaluminum hydride or DIBAL-H or DIBAL.

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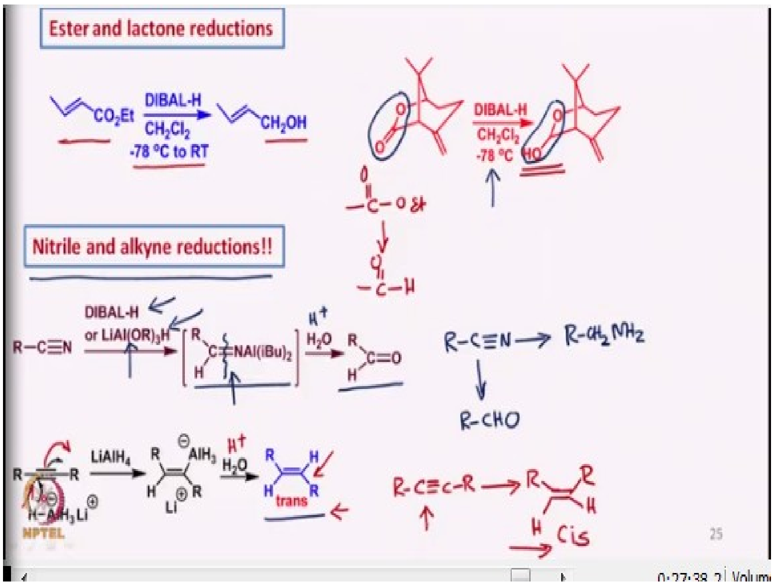

Simply is that we take the corresponding alpha, beta unsaturated ester and as I mentioned that if we simply take the excess of the reagent and start at from low temperature bring it to the room temperature. The reduction occurs via aldehyde and eventually to the corresponding alcohol and we can isolate the alcohol easily. In the case of lactone since we are in a position to stop the reaction of an ester to the corresponding aldehyde.

It also means that we can stop the reaction of a lactone to the corresponding lactol. As we can see here that if we take a lactone of this type here and we can stop the reaction at the lactol stage if the DIBAL-H is added at - 78 degrees. And we do not allow the reaction to go to a higher temperature with excess of DIBAL-H. Then of course and we quench after the reduction is done at low temperature, then we can get the corresponding lactol.

In the reduction of nitrile and alkyne also diisobutylaluminum hydride can be utilized. And for example here nitrile reacts with say diisobutylaluminum hydride or this sterically hindered lithium aluminum tri alkoxy hydride. And we can stop the reaction at by transferring 1 hydrogen and see in the case of DIBAL to this stage. And now we do not have an excess of hydrogen, we do not use DIBAL in excess, we do not use this lithium aluminum tri alkoxy hydride in excess, we just use one equivalent, and therefore we can stop the reaction at this stage.

And after that if we here say you add a small amount of acid and add water this gets hydrolyzed and one can stop the reaction at the aldehyde stage. Otherwise as we have already discussed that we can start with a nitrile and go with the reducing agent like lithium aluminum hydride to the corresponding amine. That is not the case here and therefore there is a possibility of converting this nitrile to the corresponding aldehyde.

If one tries to use a reagent like DIBAL-H or lithium aluminum tri tertiary alkoxy hydride where only one hydrogen is utilized. At the same time if one looks at the reducing nature of lithium aluminum hydride towards acetylene as we discussed earlier, we get the corresponding trans alkene. What is happening is here when the aluminum hydride AlH_4^- interacts with the triple bond the pi cloud electron cloud is moving away to the other side of the double bond.

And the hydrogen from the aluminum hydride which is negatively charged attacks from the opposite side of that particular movement of an electrons. As a result if the hydride is attacking from the lower side then the corresponding shift of electron density occurs from the top. And therefore the negatively charged part of the molecule then graphs the AlH_3 to form this AlH_3 carbon bond here with the negative charge and aluminum.

When this is quenched with water in the presence of the H + here then you break the carbon aluminum bond and have the hydrogen coming here, which leads to the trans olefin. And if we take diisobutylaluminum hydride then we can go to the corresponding alkene but then the reaction occurs in such a fashion that it gives cis olefin. So, we have a possibility of converting stereo selectively a triple bond to the cis or a trans double bond depending on which reagent we use.

Of course we can also use hydrogenation conditions where we use Rosenmund reduction with a poisoned catalyst. So, we will take up this remaining part of how to convert the acetylenes to the corresponding cis olefins with diisobutylaluminum hydride and some other reductions and transformations where reductions are used in organic chemistry in the next class. So, till then you take care of reductions and then look at it, study it and then will take up next time, thank you and good bye.