A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 41
Fg based Strategies

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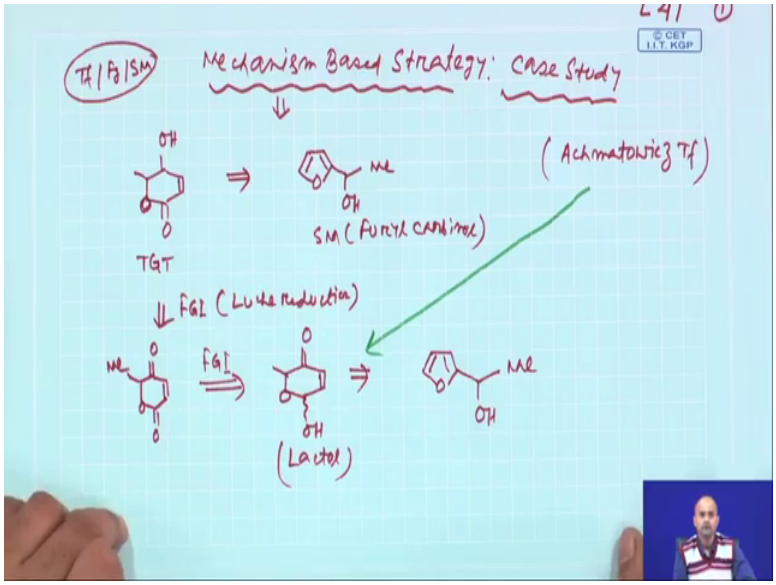

So, welcome back students we are basically discussing mainly three different strategic viewpoints transformation based, functional group based and starting material based. And I said many times that these 3 strategical approach should be combined together because this is approaches are very similar to each other.

Now, today what you will be going to discuss; we will talking about a different kind of approaches which we have already talked about mechanism based strategies will deal with some individual case study or some tip a particular problems where a specific mechanism of a name reaction or a unique transformation will help you to design the pathway. And I said repeatedly that mechanism based strategy means that, you need to be familiar with the mechanism and just by looking on that what kind of transformation is desired from you.

Now, initially I will give you a target molecule the target molecule structure; I am first drawing and then fine this was the target molecule which is required. Now the starting material, I am giving it to you the starting material is basically a furyl carbonyl system

this is the starting material. Now if you do the structural analysis of the target and the starting material; you will find that basically what you need? You just need a oxidative rearrangement of this furyl carbonyl system furyl carbonyl system.

Now, if you remember in our transformation based approach; we talked about a reaction whose name is Achmatowicz transformation it is basically a name reaction. And now I say if you have this pair information that Achmatowicz transformation basically uses a furyl carbonyl as a starting material and give you a kind of oxidative rearrangement to a 6 member ring product.

Now this ring product also having a oxygen here this structure was initially not written. So, if you find the number of carbon and things everything is same, but you need a little bit more oxygen here there are 3 oxygen's here there are only 2 oxygen's here. So, now what I am trying to do? I will do a simple straightforward retro to disconnect this molecule and then we try to figure it out how this target can be correlated with the starting material.

Now if I say this is simple FGI; this FGI what I did you basically having a a alpha beta unsaturated ketone as well as a lactone. And this ketone probably you can reduce it with a mild reducing agent which you already discussed maybe a Luche reduction.

So, Luche reduction only touch the alpha beta unsaturated ketone. So, this things we already next retro which I am now going to formulate; will be something like this I said that this particular lactol; this is basically a lactol lactol all can be oxidized to lactone by a simple FGI oxidative transformation.

Now if you now know that this torch Achmatowicz transformation is basically now you can correlate that Achmatowicz transformation here that this kind of furyl; carbinol system undergoing oxidatively rearrangement through this name reaction which is Achmatowicz reaction. Now, eventually visualization is bit difficult until and unless you know the mechanism very clearly.

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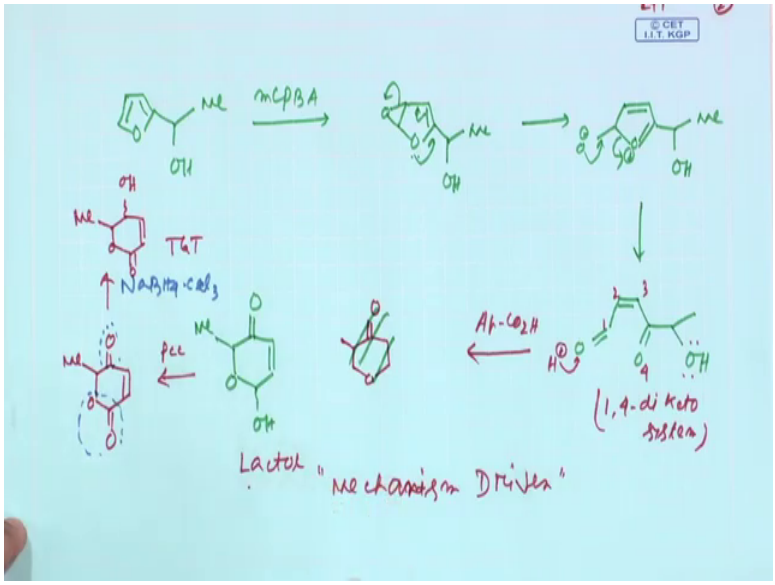

So, now we will try to explain how this mechanism is operating. We have properly explained earlier, but still we talk about this mechanism. A furyl carbinol was taken and initially this was basically subjected to mCPBA a oxidizing agent.

So, the initial stage the one of this furin double bond ring undergoing a epoxidation reaction. And this epoxidation reaction was initially takes place and then it was basically the ring opening of this furan oxygen occurs through this way to give you a species where oxygen now become oxonium ion. And then you have this remaining part its there, your epoxide basically now opens up to give you a oxygen minus alkoxide.

Now, this O minus O helps to discharge its electronic thing and opens the furan ring in this fashion. So, basically you will be having a aldehyde here and here you get the corresponding ketone. So, basically now furan ring is opening to a 1, 2, 3 4; 1, 4 die carbonyl system 1, 4 die keto system and this was basically a very characteristic reaction of furin system or furyl carbinol system.

Now, if you closely analyze this structure this particular structure in the mCPBA medium this medium is already acidic because the corresponding meta chloro of benzoic acid is there. And this benzoic acid what it does it basically helps to protonate this aldehyde to helps this by this h plus donation.

And then this alcohol at the extreme right hand side it now attacks in a nucleophilic fashion to this electrophilic carbonyl oxygen; which is basically activated through this because they you are having aldehyde as well as ketone aldehydes are much more reactive than the ketone then this aldehyde this wage alcohol attacks here you basically get the lactol which is our main product. Sorry this structure was wrong you need to draw the structure again you see the rings 1, 2, 3, 4, 5, 6.

So, there will be a 6 member a ring is will be formed; you have this OH this double bond 2, 3 is there and then you are having this ketone and this methyl. So, basically this methyl is this methyl this OH is this oxygen this reacts here. So, C h OH this a new bond this 2; 3 this 2; 3 is basically this double bond and then you have this C O. So, in this way now you are basically getting the lactol. So, this after you get the lactol then if you have this lactol which can be easily oxidized by PCC.

So, once you know oxidize this lactol to PCC, you will now get the lactone. Now this lactone if you see the structure you will basically having a a carbonyl group here a carbonyl group simple ketone and you are having a ester carbonyl. Now; obviously, Luche condition sodium borohydride and cerium chloride will give you the reduction at this particular activated ketone carbonyl and you get the target molecule whose structure was earlier given.

So, which is the entire pathway it is purely mechanism driven mechanism driven. So, if you know the particular mechanism of the Achmatowicz reaction is a mechanism driven pathway. You can basically also categorize the entire strategy in either transformation based approach or starting material based approach or functional group approach no matter.

But eventually if you are quite sure about the mechanism then the mechanistic pathway which will tell you the furyl carbonyl can efficiently be converted to corresponding 6 membered lactone or 6 membered lactol basically hemiacetal which can be oxidized back.

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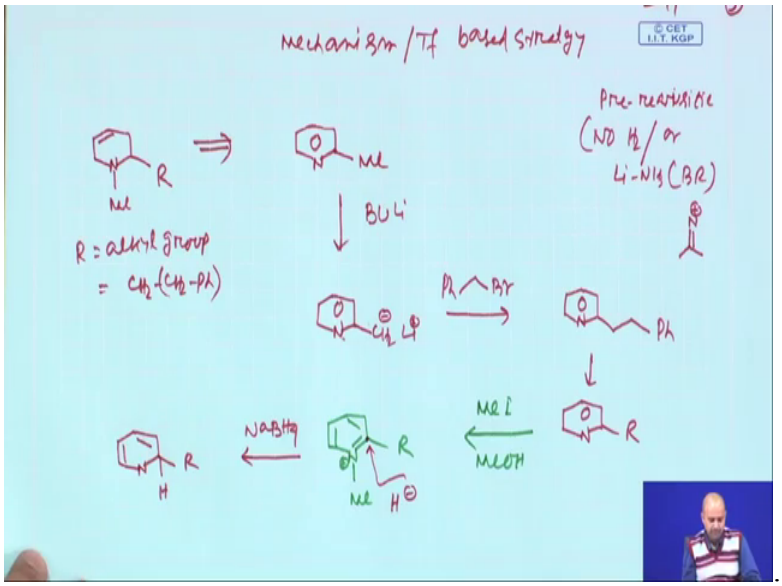

The similar way will be doing will be analyzing another interesting reaction, we said I just mechanism or transformation based strategy. This particular was pretty interesting we say the target molecule is something like this where R could be any alkyl group; any alkyl group.

And now I am saying the starting material starting material let us say R is here a benzyl group C H 2 C H 2 Ph just for a case study. And then I am saying your initial starting material is two methyl pyridine two methyl pyridine.

Even it looks very interesting it basically gives you a idea that you basically need to have a selective reduction of other pyridinium pi electron so, that this double bond remains unaffected. Your prerequisite I am giving you a prerequisite your precondition prerequisite that no hydrogenation or lithium liquid ammonia like birch reduction you cannot use.

So, this is absolutely important prerequisite. So, you cannot use something like this; now this particular problem was solved very nicely event you have the starting material was given this and the R group probably a C H 2; C H 2 Ph means that somehow you need to add extra C H 2 Ph group.

Now two substituted pyridine are very good reagent if you or they can easily react it with a base like butyl lithium and eventually you can generate this C H 2 minus L i plus very

easily. And this C H 2 minus can act as a nucleophile it react with a very good electrophile benzoyl bromide to initially get the C H 2; C H 2 Ph. So, which you will now call it as a R.

So, this R pod was initially done; now next what we will be doing? You have to do the selective reduction in addition you need to put a extra methyl to this nitrogen. So, initially the approach was first it was subjected to methyl iodide in a methanol solvent. Now methyl iodide what it does it basically give a quaternary ammonium salt or quaternary pyridinium salt.

So, now nitrogen is plus this R remains similar; now when you do this species if you have a close look is basically a iminium species. This particular C and double bond n is basically iminium species. So, iminium iminium species are basically this kind of species n iminium species.

So, iminium species are electrophilic in nature, you can add any nucleophile it is basically like a aldehyde or carbonyl compound instead of oxygen you have a C double bond a nitrogen and as this nitrogen becomes positive nucleophile can adopt to this carbon now here initially what we will do ?.

We will be using a mild hydride agent like sodium borohydride to give a hydrogen source. And this hydrogen source basically will adopt to this electrophilic carbon. So, eventually then what happens? So, will initially this nitrogen will now takes this hydrogen, this is typically done.

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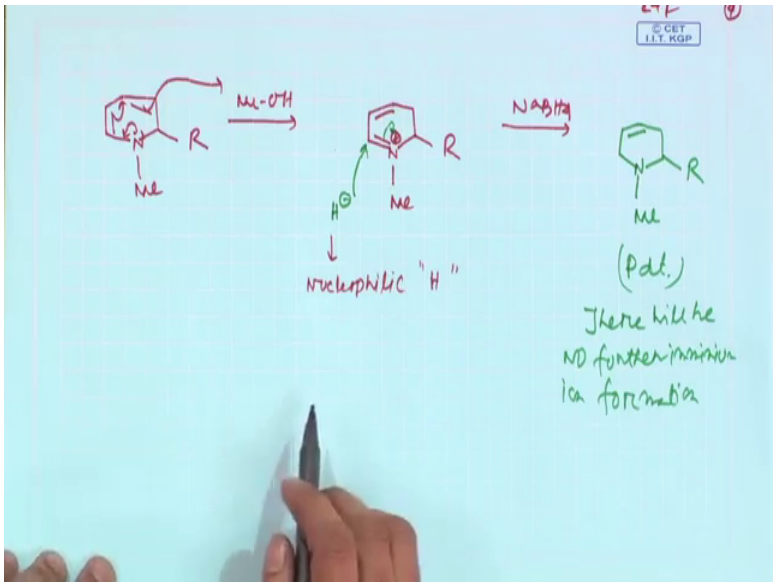

So, once initial this reduction was done through a iminium kind of thing. Now see next how you can do the earlier structure there will be a methyl thing there will be a methyl thing.

So, now this quaternary methyl now become a trivalent methyl your R is here. Now you have a methanol as a solvent which is also a potent source. So, now what happened this oxygen sorry nitrogen lone pair will try to give this kind of resonances and this minus will now abstract the proton from this methanol.

So, basically nitrogen will again become a quaternary thing and this time it will become a iminium species again; iminium species again. Now by virtue of this reactivity we know that iminium species are electrophilic in nature. So, you again subject to a sodium borohydride and this sodium borohydride now attacks on this carbon and nitrogen charge will be now neutralized that is fine.

So, now this is the final product; so, you may now argue that sir again this nitrogen is it possible to form another iminium ion? The answer is no initially you have a conjugated system that is why the iminium ion formation is quite possible like for this case initial case the lone pair gives this electron donation it is having a allylic system it comes here and it abstracts the proton.

So, iminium ion formation is possible only twice; now this case there will be no further iminium ion formation, there will be no further iminium ion formation iminium ion formation. And that is how the reaction now will complete as there is no iminium ion formation; the reaction will be now completed and this will be isolated as the major product or the final product.

So, if you see the entire reaction the reaction basically goes through a simple formation of a quaternary salt; quaternary ammonium salt which is iminium and electrophilic in nature and you just simply add a sodium borohydride as your hydrogen source; it is your hydrogen source which basically gives a nucleophilic hydride this thing is there nucleophilic hydride or hydrogen.

And once you have a two round of successive iminium ion which can be attacked by the nucleophilic hydride or hydrogen; then the reaction will stop because further iminium and formation is absolutely not possible. So, your mechanism will basically dictate you that where to stop and what product will be expecting. We will be trying to give you a similar kind of very interesting reaction.

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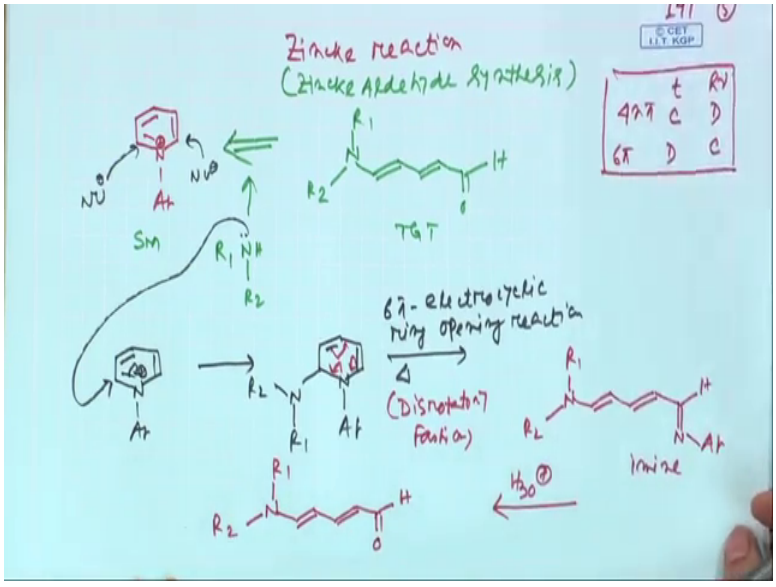

Now, this reaction will be just on this similar topic; the topic which I have just explained chemistry of iminium ion. This reaction basically is named as Zincke reaction is it is it pretty old reaction sometimes its referred as Zincke reaction or sometimes is named as Zincke aldehyde synthesis.

Now, this reaction is named in this way because it was invented first by the scientist Zincke in long ago. The synthetic potential of this reaction was not explored earlier in traditional retrosynthetic terminology, you can basically write this reaction in this way. The target molecule I am writing in the green color of this pen and final product is basically this kind of conjugated aldehyde is the main product which is the target molecule.

The starting material was basically this one and the reagent which is a normally supplied a diamine; this diamine was supplied as a reagent they eventually this reaction is very interesting this reaction if you see the mechanism is a pyridinium nucleus and pyridinium nucleus normally they react either to position or 6 position by a nucleophile nucleophile.

So, in this case once the parent pyridinium ion is there your nucleophile is R 1 N H R 2 this amine. So, this amine first attacked at this carbon of this two position. And then basically it is basically comes here this quaternary nitrogen is quenched. So, basically have this this R and then this nitrogen acting as a nucleophile this amine R 1 R 2 R 1 R 2 could be anything depending on your choice.

Now, it is very interesting I am not sure whether you would know it, but I am probably this is a very interesting reaction it is a is a pericyclic reaction 6 pi electro cyclic ring opening reaction; I am sure all of you have studied this reaction this reaction occurs in thermal fashion 6 5 electro cyclic ring opening.

So, the rule for the selection rule is 4 n pi thermal and photochemical; thermal is conrotatory and photochemical is dis rotatory 6 n pi or 6 pi thermal is dis rotatory photochemical is conrotatory the selection will pericyclic reaction or electro cyclic reaction I am sure all of you know it.

So, now if you are doing this particular 6 pi electro cyclic ring opening through a dis rotatory fashion dis rotate tory fashion; you will find that now this reaction basically occurs in this way. And now you will be basically having this pyridinium nucleus will be now clipped will be now clipped to give you a 6 pi open system which is basically nothing, but a imine, but a imine it is a imine.

Now, this imine can simply be hydrolyzed through a acidic work up; simply be hydrolyzed through a acidic workup and then basically you can get a this conjugated

aldehyde, this conjugated aldehyde which is now generated. Now this Zincke reaction has a significant usefulness in the field of organic syntheses.

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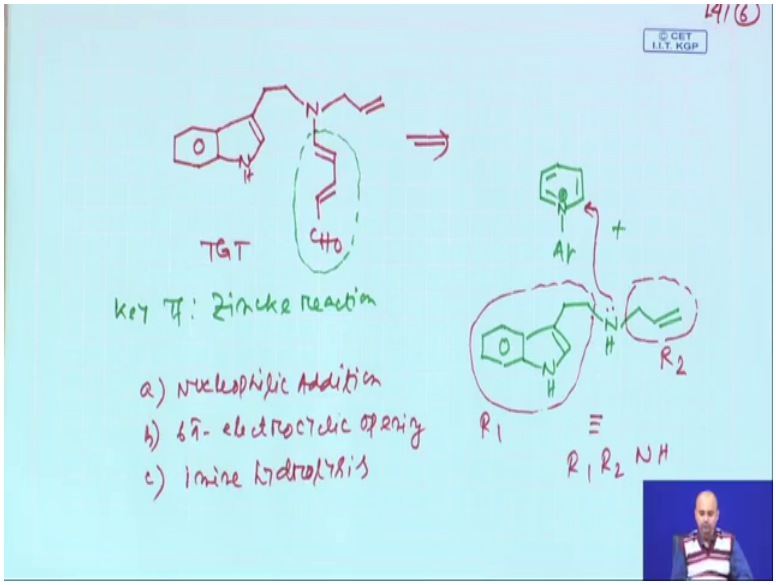

And probably if I do a target molecule something like this I say I am giving you a target molecule you have to apply a Zincke reaction the target molecule first let us draw the structure I am saying this target molecule is having this structure CHO.

Now, this is a target molecule target molecule you have to identify the starting materials and your key hint is key transformation you have to use the Zincke reaction now the Zincke reaction mechanism we have explained. Now you try to analyze we said that this particular part this alpha beta unsaturated I mean this conjugated aldehyde, you can construct by Zincke reaction.

So, basically what you need? You need two amine. So, this is one part of this amine, this is one part of this amine. So, now you formulate how you can do this reaction. So, if you have this particular pyridinium species as a starting material and the amines what are the amines basically unit you need? You basically need this diamine this indole based diamine C H 2 C H 2 N H and this allyl.

So, this imine this is basically if you go back to the general site this is the group which is R 1 and this is the group aryl group which is now R 2. So, in this way this R 1 and R 2 will be R 1 R 2 N H; so, which is now simplified as R 1 R 2 N H.

And this R 1 R 2 N H this nitrogen attacks to this 2 carbon in the pyridine in. And then you get the initial neutrophilic edition I initial steps are nucleophilic addition; nucleophilic addition and then you have this 6 pi electro cyclic ring opening 6 pi electro cyclic opening and then at the end you are having this imine hydrolysis imine hydrolysis.

So, this all steps together will give you this Zincke reaction which is very useful and Zincke reactions are absolutely useful in the field of organic synthesis; you can use this reaction very efficiently. So, we will continue our discussion on the mechanism based strategies and we will be basically trying to give you more uncommon reaction whose mechanism probably you are not sure about or you are not familiar.

We can discuss that mechanism first, then you will try to figure it out how this mechanism based strategies will address a how a specific target can be achieved from a given starting material.

So, we will come back to the next lecture till then good bye.