Heterocyclic Chemistry
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Lecture - 37
Pyridine Synthesis

Good afternoon. So, today we take up pyridine synthesis, most of you have the first hand experience on the pyridine synthesis. Just like any other heterocyclic, there are 2 broad approaches; one is directly you convert 1 pyridine derivative to the corresponding pyridine derivative, other is the ring constructions. If you follow the last few lectures you will see, I have been only just considering the constructions of the ring systems, not the conversion of a heterocyclic to another heterocyclic or the vice versa ok. So, today again we look at pyridine synthesis. And all most all of you know the pyridine nucleus is everywhere. It is found in many, many important medicines, pharmaceuticals, agro chemicals, biochemicals; like some of you probably know Isoniazid. Isoniazid is a plane pyridine derivative and which is used as a medicine for tuberculosis.

So, similarly, there are many medicines, where you will have rather many biochemical compounds, we will have this pyridine nucleus. For example, all of you know LDPH will have actually pyridine derivative, sometimes actually it is a dihydropyridine derivative. And, there another pretty useful in many cases they are useful as a reducing agent or hydrogen transfer agents. And, so likewise there are other, for example, there is a medicine called Amlodipine. Amlodipine is a medicine for reducing blood pressure. So, that is also containing a pyridine nucleus; of course, that is a dihydropyridine nucleus. So, likewise there is plenty of pyridine containing important organic molecules.

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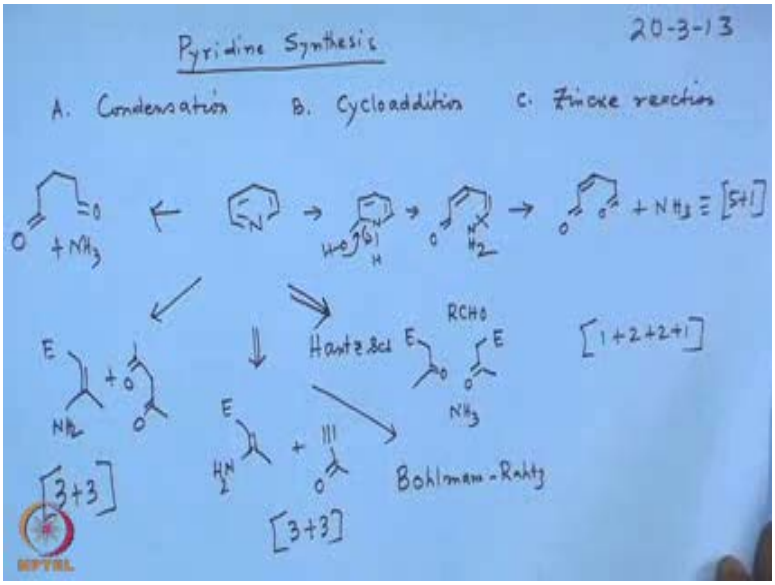

So, today we discuss about this one. And, the way we proceed again as I said before you just look at this retro synthesis and there are 2 kinds. The first kind could be the condensation approach. This is well known to many of you, condensation approach means where you will just lose 1 small molecule most likely inorganic molecules. Then, there is also another approach is known as cycloaddition approach; which includes dial - alder reactions then 2 plus 2 plus 2 cycloaddition reactions. And, in case of and these there is a small case, probably I think this is not of much use but there is a reaction call zincke reaction. Zincke reactions, actually it produces the pyridine compounds.

Now, look at the pyridine retro synthesis; like before, what you do? You break up in this molecule by hydrolytic cleavage. When I say so of course, you have to target the heteroatom in this case nitrogen. Now, when I say break open means actually you add water to it. So, and maintaining this electro negativity. Now, if you have something like this and then and what you do. You have to again break open this one. So, what we will find? You will find something like this and then you will have N H 2 .So, like if you go on next thing, what have to do? You have to break open this one. And, if you do so, what you will find? You will find a molecule of this and plus ammonia.

So, what does it mean? It means that you can get pyridine from the corresponding dike to compounds 1, 2, 3, 4, 5. 1 5 dike to compounds and ammonia you can get to this pyridine. So, this one ways to look at and it has a name krohnke reaction. But people no

longer use this. But the most important 1 I think many of you know in this series is hantzsch pyridine synthesis right, hantzsch pyridine synthesis. So, this is equivalent to the first one is equivalent to 5 plus 1 mole that means you have 5 atom systems. And, 1 atom systems hantzsch synthesis is many of you probably know.

It contains well see that let us say, we will see that actually hantzsch synthesis requires 3 components. One is the Aldehydes, the other is and with ester in my notes you will find E stands for esters. Then you have one more say beta keto esters and then n ammonia source which is ammonia.

So, it is a basically 4 component reactions is hantzsch synthesis. So, you can classify this as 1 plus 2 plus 2 plus 1 you can say. So, this is very popular. Then, 1 more which is not probably studied that well, this is becoming a very important method of making pyrrole. So, in these case takes enamine and in normally again this is E ester and acetylenic ketones, alkynic ketones this is equivalent to you can say 1, 2, 3, 4, 5, and 6. So, it should be 3 plus 3 mole and this has a name. This is known as is a natural product Bohlmann-rahtz synthesis. So, better you remember Bohlmann synthesis. This is a very useful 1. And, similar to this that is also a method which is equivalent to 3 plus 3.

So, in this case instead of that what you do? We take this enamine system and which could be again ester and instead of taking this acetylic ketone. So, what you have to take? You have to take 1 3 dike tones. So, what you see here, this is just an in a basically there are if you look at some of the older literature, you will find there are plenty of ways to may break it. But main objective is to just come up with the right synthesis, and almost all the cases you will see that the synthesis that would be well accepted is involving readily available starting materials that is very important.

And, then you can go on changing this original version by improving the available of the starting material or, by breaking into a similar version. For example, 1 can simply think about this way without going through this hydrolytic cleavage. 1 can just think about you just begin with a 1 4 dicarbonyl compound and like ammonia. So, it is equivalent in the right hand side. But there is a little difference; you have to maintain this oxidation level.

So, you know the calculation how to do this oxidation level .For example, in these 1 if you condense this 1 4 dicarbonyl compound with ammonia you will not end up with the pyridine derivative. So, you will get oxidant dihydropyridine derivative. So, you have to

oxidize the corresponding dihydropyridine derivative to pyridine derivative. So what else, like I have written so many things here but you have to find out the commonality of all the approaches? What is the common? All of them are giving pyridine. Right, what pyridine nucleus? What else, all of them probably would be having nitrogen that is also true. But as per in the approach is concerned, you see there are how many I said I think among all these hantzsch is very popular, probably you did not know these 1 this is Bohlmann this is also becoming very popular.

And then this is the 1 of the left with 1 3 dicarbonyl compounds. It has a name but I will not tell you this is some something. Nothing, but chemically you have to find out that to develop a synthesis you have to rely on a particular type of chemical compounds. Normally, if you go to the pyrrole and furan all other places I mean we will have the similar also, starting materials. So, what could be t he starting material?

Student: Enamine ester.

Enamine ester. While, if you do not need ester then? So you have to have enamine, but 1 thing, when I write here condensation that means this belongs to categorical condensation. It must have a carbonyl group that is important. So, all of these things are having a carbonyl group.

So, and the approach is this way, that pyridine should be clipped into the corresponding hydrolytic cleavage product that is basically amine and the corresponding carbonyl compounds. We will come back to and give you the examples. So keep it in mind that we will have a focus on hantzsch synthesis and the Bohlmann synthesis. Of course, the other synthesis also would be exemplified.

Then, other possibilities of course, cycloaddition I think 2 hours the beginning of the course, we talked about cycloaddition right, dials-alder reactions and then 2 plus 2 plus 2 cycloaddition reactions are useful in carbocyclic chemistry. But heterocyclic is not very popular. But becoming very I mean more and more popular. Because it is easier to handle, and you just add them you do not lose any byproduct. And, then there are like say, what is the catalyst? Cobalt catalyst other the latest addition is the rhodium catalyst shift it to rhodium chloride catalyst.

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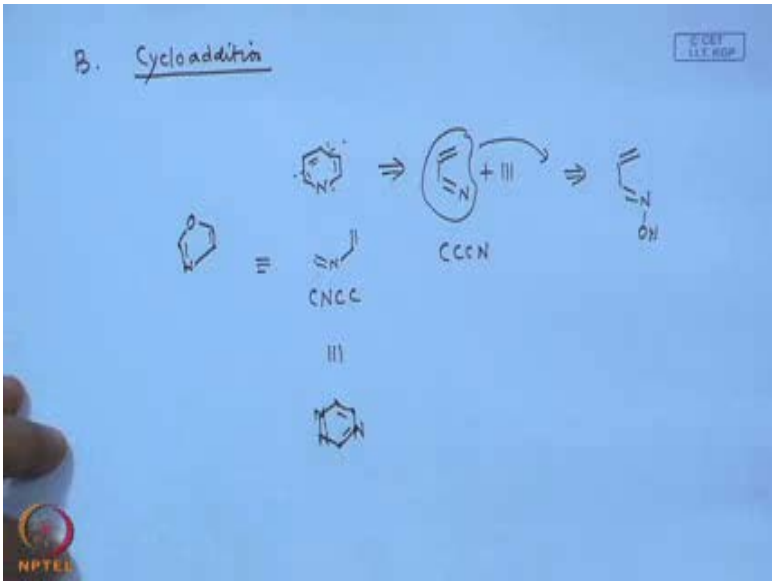

So, like this there are now a day's some ionic rhodium catalyst also are being used to promote, and very recently will give you one example may be very recently in; I mean somebody has developed Diels-alder reactions. Similar to these 4 plus 2 cycloaddition reactions, apparently it very easy to carry out. Once again, if you talk about these cycloaddition reactions. What are the different modes? I will not repeat much of them but if you look at again the nucleus, so there are ways to break. So, one of these ways would be simply, you take at these and then something like this. That means, 4 atom system is C C C N system.

Now, the other possibilities is also there, this is one of these ways; 1 can do this other possibility could be I mean this was the breakage here. So, you can cleave here also right, that means that could give you C N C C that means you have the nitrogen in a bur dine position in a frame nitrogen at the 2 positions. And, this has 2 equivalence many of you know why do you get this carbon this is quite ok right, so basically goes to; if you have a conjugated things like this and oxen hydra gene all these things can be equivalent to an Azadyne systems so that means all the Diels-alder reaction should involve either 1 Azadyne or 2 Azadyne ok.

Now, we have, but are a very broad statement. Now, we have to go to the real life examples. For example, when I say C N C C I think you have seen it before. Where do you see, where do you get this 4 carbon unit or the 4 carbon symptom. 4 sorry 4 atom

symptom you will get it in and the last class we talked about the oxazole would serve 1, 2, 3 and 4. So, if you have the right that means this is a basically dyne systems which separate 4 atoms with C N C C. So, that means that can be used also for the synthesis of the pyridine nucleus.

So, likewise in one of the cycloaddition classes also, we talked about something that the same thing can be obtain from a 6 member ring systems. Any idea, where do you get it from 6 member system that means, you can get a 6 member system and then all of us know that boger's approach nitrogen which eliminated. So, that means, this portion would be eliminated that means 1, 2, 3 this is 4 atom systems. And, if you place the nitrogen this become C N C C that means you can also make use of triazenes for the Diels-alder reactions.

We have given example before and you can also look at today some of the examples. So, these are the 2 different modes; so that was the first condensation mode, and the second mode. Now, I say matter of just practicing things like this, let us look at the condensations approach we have said it before if you begin with a 1 5 dicarbonyl compound. Now, you want to convert into pyridine right, so what you have to do you have to just simply ammonia nothing else ammonia and what you get in these case if you just do the 6 base formation on one side and then other side you do then isomerizes. I think I do not have to explain to you and you are all so you will get actually 1 4 dihydropyridine.

Now, you have to know how to write dehydrogenate, then only you will get the pyridine. So, how do you get a pyridine? Dehydrogenate and so there are limitations here. In pyridine chemistry you cannot just randomly use oxidizing agents, so that is the difficulty in heterocyclic chemistry is more difficulty in although heterocyclic compounds are not having chiral centers especially aromatic ones. But they have other limitations, you cannot use all the reagents use in carbocyclic chemistry in heterocyclic chemistry.

Because, of the propensity of this nitrogen to undergo oxidation. So, the way one can do how do you oxidize the commonest one is nitric acid for some reason? But there is logic here, see between pyridine and benzene of course; all of us know pyridine is electron

deficient. So, it does not undergo easy nitration, but it can dehydrogenate so, or you can use nitrosyl also occasionally is used and other 1 is C A N some of you probably know.

Student: Ceric ammonium nitrate.

This sort of actually synthesis is useful or let us say compound I think I should write the structure. Because some of you eventually would be taking this medicine at some point, this is a very popular medicine though, especially people like us who are having the hyper tension they often take it. And almost every day I take one tablet of this molecule this is called amlodipine. And here you write, I will write here E 1 and E 2 all of you know E 1 forming ester. So, when I write E 1 actually it is a methyl ester, and E 2 actually ethyl ester fine. And, this 1 has another side chain where you will have this O and N H 2 this is known as amlodipine.

So, likewise there are quite marketed molecules which will have 1 4 dihydropyridine nucleus. Now, how do you modify this? I mean actually see this all these this is basically a modification or you can say preambles for this hantzsch synthesis. There are so many modification for example, you can take 2 components, where first you do this nova gel kind or herbal kind of reactions and to get alpha beta unsaturated compounds. And let us say like this so that means if you have benzyldehyde and the corresponding ketones condensation product, then you take once again the previous example. Like on the pyridine sorry pyrrole cases which are halo ketones then add ammonium acetate. By the way in these cases ammonium acetate is nothing but it is a source of ammonia.

So, first it converts to ammonia then the carbonyl is converted to this amine. So, then I mean you can then amine can undergo cycloaddition reactions eventually you will get you will be getting this pyridine nucleus. So, in this case you will have all kinds of the substitution here and there. And, depending on the situations, you may have this retention of the x or not it depending on the reactions conditions. So what it means, that you do not have to have 3 different components, 4 different components. You can derivatives each of them or you can just begin with an advance intermediate and converts this into the pyridine.

The other possibilities are the other you can say sort of a variation of these one is this 3 plus 3 plus 3 mode. So, in all of these 3 plus 3 modes, what we will find? These one of the components is a 1 3 dicarbonyl compound, and now if you begin with a ((Refer

Time: 21:29)) molecule of these kind and then take enamine, so you can easily predict the product of the reaction right, so what could be the product? I had what could be the product basic you have to decide which bond would be first found? That is most important, say between 2 carbonyls.

Now, you have 2 carbonyls and which 1 is more reactive we think? And that would react to the amino group. The one next esters just like you know if you remember this pyruvic acid carbonyl is more reactive than the normal carbonyl groups because of this electronic in nature. Like you have seen before that chloroacetone, bromoacetones are more reactive than the corresponding halides.

The C H 2 halides because of this that overlap of this electron in the transition state neighboring atoms. So, that means this is what will be actually the reaction then, so what have to do just invert this so you will be that means react these this 1 and this is E 2 and so E 2 would be reactive this now N H 2 and this is C N this is that means this would be condensing first here right. And then where enamine is reactivity eventually, you will be getting this E 2 here and this so you will be getting this ok. Now, I will just give another example. So, I mean this is a very interesting way of making pyridine.

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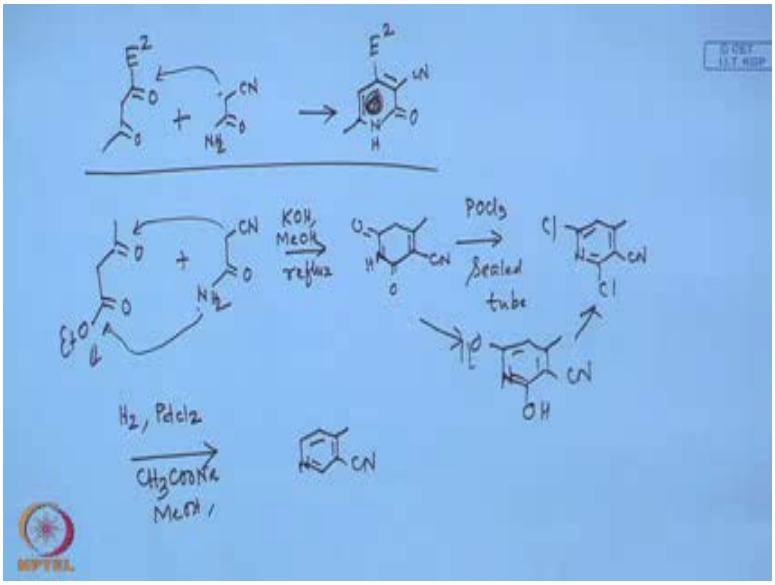

That means in addition to the hantzsch synthesis the one that 3 plus 3 mode also is very useful. I will tell you one more example, probably 2 more examples. Let us say with the same substrate that means 1 3 carbonyl here, and then you have this ester. Now, I change

the lamin portion to a 3 component, which will be looking like this. So, what it is? That you have to remember, what is this compound? Actually this is a very popular class of starting materials in heterocyclic chemistry. Cyanoacetamide easy to make corresponding and then ((Refer Time: 24:26)).

Now, if you recall that the previous example had this other part same. Now, you have to again predict the product of these reactions, to do so you have to first find out which bond would be form first that is important in this. In the previous case it was a free amine reacted with the most carbonyl reactive carbonyl compounds carbonyl groups. But in these case which one is likely under the influence of course, normally I mean a base is required a base is required so see here it is amide carbonyl amide sorry amide N H 2 amide is not a very good nucleophile say poorer nucleophile. The other hand this one may have a carbonyl group this may have reactivity towards carbonyl so that means this 1 would form first and then once this is form automatically.

You know this is a pyridine synthesis. So, you will be getting product here this is sorry this is cyano and you have a carbonyl and this is N H then this is E 2 and so you will have this double bond right, double bond up here and double bond up here. So, it is what we will be getting? Actually we will be getting the 2 pyridones, no that actually if you remember whether the first classes last semester I thought. So, there are 3different classes; pyridones, thiopyridones and let us say amino pyridones. And, what are the more popular tautomers for pyridones and thiopyridones this basically the ketone tautomers at the more predominant. But for N H 2 it is the corresponding N H 2 tautomers is the more predominant.

And, let us look at one more variation of this one example, let us say. Now, what I do? I just do a small change here and we move backward and let us see. So, how to let us say make this compound how to make this compound? I think this is this should be double bond right, how do you make this compound. So, what should be the starting material the mode is same is 3 plus 3can you identify? Ok. To help you the 1 that could be require again to emphasize the Cyanoacetamide with the starting material 1 of then tell me what is the other starting material? And the reaction condition that is used it is K O H by the way then O H methanol and reflux. So, what could be the other starting material?

Student: 1 3.

1 3 dike to compound that is all right ok.

Acid chloride is not be good reaction. Because once you give the K O H and methanol it will hydrolyze to corresponding not ester. Acid itself, If you take oneth dike tone fine. And then this should be?

Student: Ethyl ester.

So, it should be ethyl ester. So, here you just get this condensation done is carbon bond and then this carbonyl actually removes this. Right, so that gives you this 1. Now, this actually this very nice product, if you treat this with p o c l 3 excess and normally it is done in a sealed tube. So, what you are likely to gain? You are likely to gain excess amount of p o c l 3 is a standard protocol in heterocyclic chemistry. If you have pyridones with hydrogen's you get corresponding these dichlorides. So, you get cyanide here chlorine and chlorine. As, if it is this is a just like a phenol acid chloride O H is replaced by chlorine in my p o c l 3 reactions or p c l 5 reactions. So, here also if you tautomerize, it would look like it is a dihydroxy compound O H ((Refer Time: 30: 26)).

Now, there is a series of reactions I think what knows here, let us say we want to remove this chlorine and then converted to the corresponding cyano compound without chlorine. So, how do you remove this? Basically you say process call dechlorination that means you have to look for right reducing agents. There are not many, but in heterocyclic chemistry hydrogen is good enough, this sometime all these things are fairly ok.

But in these case if you use hydrogen and unlike simple paradigm is this paradigm chloride has been used and then the sodium acetate is used to, I think you can understand why sodium acetate is used. Because in the hydrogenate hydro genesis of this carbon-halogen bond you generate H C L. So, H C L should be neutralize by the base sodium acetate. And the paradigm chloride of course, all of you know under the influence of paradigm and under the atmosphere of hydrogen paradigm chloride is reduced to paradigm 0, and that hydro generalize the corresponding carbon-halogen bonds ok.

So, I think that gives you some of these ideas about the hantzsch synthesis. And, that the modifications you can say 3 plus 3 versions and next of course, is very popular to me.

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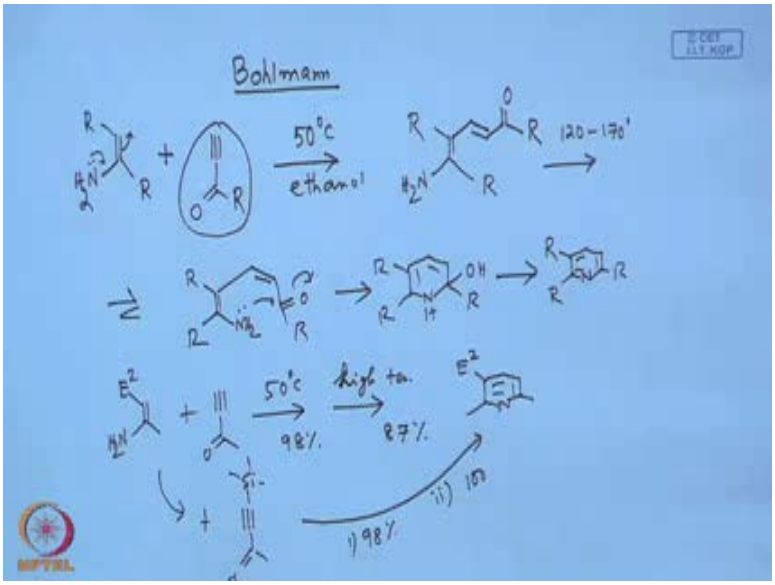

This is the one what I said, it is Bohlmann synthesis and this is sometime carried out in 1 step requirement is same as before. But in these cases, you say 3 atom is system is enamine or the enamine and so you will have R group here R group here. The other part is a 3 atom part that you have to remember. So what could be the variation, normally the variations are; in case of heterocyclic chemistry what I said before, that you will have to have a carbonyl compound right. And if you want to change a compound or substrate you make this carbonyl compounds is corresponding acetylenic derivative. Because acetylene is equivalent to a carbonyl group all of us know that it opens up hydrolyze is corresponding in ketones into the presence of mercuric sulfate catalyzed hydration ok.

So this is enamine, so it should be ketone derivative again and then this was discovered long back in 1957 by Bohlmann. And so you begin with acetylenic carbonyl compound, so you have to remember this much this is very important. As I proceed I will give you more and more examples you will see very unique reaction though, very easy to carry out. Once you have the right substrate, so and in a case like this just heat at 50 degree centigrade in ethanol, and I think all of you can guess, what would be the product? The product here in these cases what else. So, what is it? What is the product? This product is a basically a Michel addition product.

So, that means just very mild condition 60 degree. Say Michel addition product, but this Michel addition is not the hetero atom Michel it is a carbon Michel type of reactions. As

if the enamine nitrogen is preceding the electrons to the carbon and then adds to that then goes on. So, and then this was the original condition then this intermediate is heated at 120 to 170 degree centigrade .You can guess what happens under the reaction conditions, it gets isomerizes to the right directions, amine now is transposed not transposed comes to the other side and then this trans double bond. Now, go to the cis double bond and so you have this system, then all of you can guess, once you have an amino ketone is very easy to cyclize and come up with the right product. And what will be getting? You will be getting this now N H here O H here. And then the rest of the things are in order and like this.

And so as usual the aromatization is driving force and so you get nicely well define substituted pyridine derivative, so this is a format. And specific example like say, once again enamine means we have the beta keto ester corresponding enamine, let us say E 2 means ethyl ester, and then just take the corresponding ketone here. I should not say ketone acetylenic ketone and then just like that there is the 50 degree first, then in ethanol then this high temperature heating and you get this pyridine derivative the yields are fantastic. In the first case it was 98 percent, in second case it is 87 percent.

So this is here, say I mean after doing all these things here, but Bohlmann reactions are very useful. And then the same reaction when carried out with siren protection is a T M S group and other part remaining same, you get the same product. But the yield is again very high in the step. It is 98 percent and the second step it is 100 percent. So, you get the same product so with siren protection.

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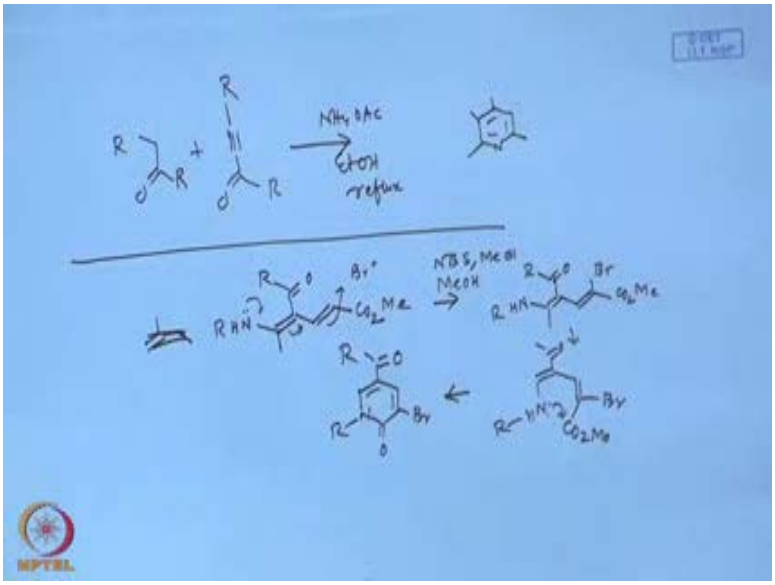

We will have more example more example I think let us say I think one more example probably, next example basically tell you that if you have, you do not have to make this enamine, you have to just take this right, ketone and the right acetylic compound the ketone up here. We can put R everywhere here and there does not matter, and then what take ammonium acetate, ethanol and reflux. What it means? You have just simplified these reaction conditions. Simplify that means you do not have to have the enamine a free prepared enamine take the ketones, the acetylic ketones and the ammonia source in straightway in one you will get this pyridine derivative ok.

Now, there are other ways. So, let us say and why this is so popular? I think I will give you 2 applications. May be I will give you 1 more examples, where you can divert this reaction to pyridine derivative. For example, if you take sorry initial Michel addition product, which is a conjugated dyne system with enamine. Right, conjugated dyne system R and then this R here, can you recognize what it is? This 1 is nothing but in enamine system here and then ((Refer Time: 40:04)) ester conversion product was addition product. Then if you trade this with N B S, methanol so you get sodium meth oxide you can divert this reaction into a pyridione derivative. Can you guess what could be the product? I said before pyridine derivative sorry pyridione derivative. So what is the starting point? What reaction can you think of N B S methanol is a source bromonium iodide.

So, bromonium iodide that means this lone pair would direct this bromination here right, then you have in system sodium meth oxide and eventually what you will be getting, let us say so R double bond then this again N H R. So, initially it would form first this corresponding bromo derivative. And then what? Isomerizes all these things should be isomerizes like previous example. That amine would come on this side, the carbonyl on this side, this double bond would move, the bromine move here.

Again thermal isomerizes then you have this ester here, and then nitrogen would now attack the carbonyl of the ester group. So, you will be getting R here then this pyridione derivative. So, pyridione derivative and the carbonyl up here this is R again this is R, this is R. so essentially what it is now is not a pyridine derivative you see pyridione derivative ok. Let us look at 2; I think I have 2 examples to show you about these applications of this reaction. And let us see first 1 and then we will see the second 1 later may be towards the end of the class.

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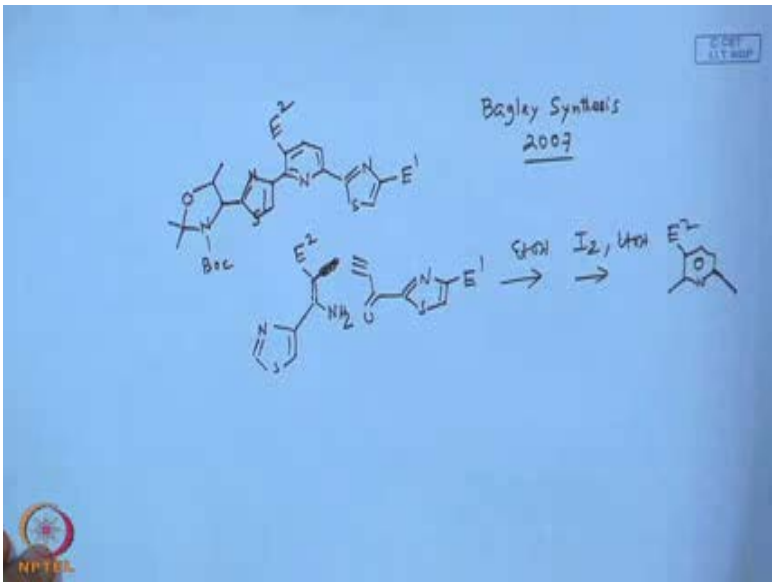

Let us say if you have a problem like this, it is a very complex molecule, this was require in the program of a total synthesis of a very ((Refer Time: 42:55)) molecule thiopeptide are nothing but cyclo peptides with sulfur. And you have a pyridine nucleus here, and the other portion is a thiazole, and on these side one more 5 member heterocyclic and this is also a thiazole. And then, maybe I will write this will have oxazole now, oxazolidine with these and then this is just a small molecule, I mean compare to the photosynthesis. I

have, I will be talking about this is actually there is a name called Bagley so this is Bagley synthesis. I would say and it has been published in 2007 but we are concerned about this structure. How to make this pyridine 2 5 dash substituted pyridine.

Obviously the obvious option should be you take this enamine this thing, that thing, we go back to the hantzsch synthesis but I would the authors have preferred this Bohlmann synthesis. So Bohlmann synthesis that means, what we need then Bohlmann synthesis corresponding enamine. Right enamine, so in these case the authors have taken enamine, so the enamine let us say from the left hand side, so this was the enamine on this side , and so if you that means it N H 2 up here, and O H sorry I think I made mistake here. There is an ester here.

So, now you can guess so this E 2, so we have to take E 2 here and, so enamine and what else? 1, 2, 3 so that means you cannot take this 1 right. What else you have to take? The these 2 carbons would come from the acetylene, and the other 1 this carbon comes from ketone and that is it. So that means, the life is easier now that means if you have in retro synthesis based on this Bohlmann is pretty easy. Only thing you have to remember, you have to that the starting point is acetylenic ketone, and enamine acetylenic ketone is first then this just you look at the structure, and just do this all these things. Although appendage looks simple, but getting the substrate itself requires so many steps, this one took some in 9 steps the other one took 11 steps then ,once you have know the process is very easy just mix them and heating it. In fact the reaction was done once again in ethanol.

Once you do this ethanol reaction, and like before you can do this what ethanol actually assets this first steps, that is the Michel addition. Then cyclication is done by either heating or by different reagents. In this case, there are many kinds of reagents; I do not have the list here, there are many other kinds of reagents, but the one that is popular is iodine. So, if you just take 20 percent of iodine, once again in methanol and the cyclication takes place and you will be getting the right pyridine derivative and this and then this.

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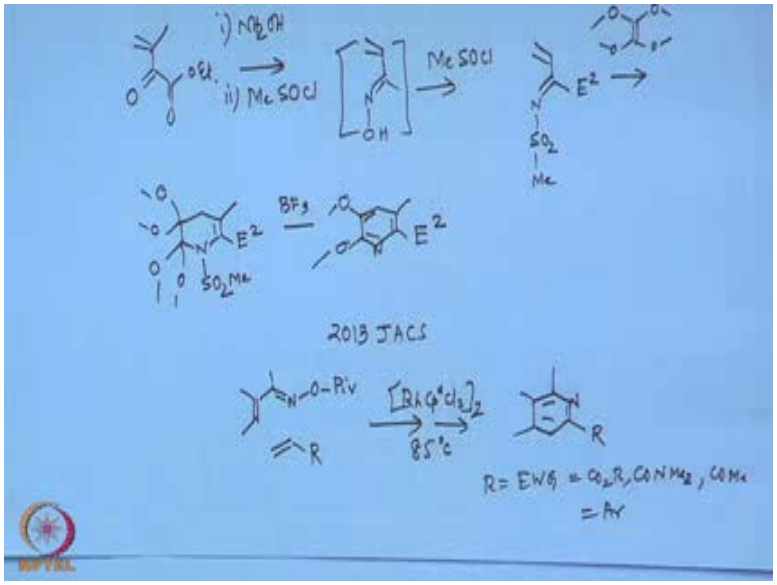

So, we will go to the next topic, what is the next sub topic? Diels-alder reactions has been thought before, but the plane Diels-alder that means 1 Azadyne system was not very popular or, not readily available I will just give you 1 instants; where a alpha beta unsaturated ketone has been converted to dyne system. Like if you begin with the sort of a pyrobit ester then hydroxylamine and next thing is the sulfenyl chloride that is not a sulphoneyl chloride by the way is a sulfenyl chloride. There are 3, 4 different kinds of the acids; where you have in the, so you will be getting here corresponding oxen and then this actually first it forms right, I will not write the whole structure you can guess ideas now so this on reaction with sulfenyl chloride very interestingly it undergoes sort of disproportionation. And, it gives you this sulfonamides is produced.

And, this is in this case this is now E 2 here. So, that means 1 as a butadiene's are very easy to make. So that is reason why, the Diels-alders are not very popular. So, people are going towards the organometallics approach so I will give you 1 more examples later. And, then this require a particular, what you said dipolarophile? I should say dipolarophile is this 1 that means is say tetraoxiginated. And, 1 can guess the Diels-alder means 6 member rings, and then you will have the all kinds of the substituent's here and there. Obviously the purpose was a total synthesis, then here you had this sulfone or sulfonamide part then if you treat this with B F 3. So, you get oxygenated pyridine now, deoxygenated pyridine so which is nothing, but these ester here E 2.

So, what is the lesson? The lesson is that the Diels-alder reactions are not very common, but on the certain cases you can do it. ((Refer Time: 50:38)) is only published this year very recently in last few months ago. There was a paper by Robes, it is published in 2013 and JACS, and what is it? It is again a kind of an oxen. Now, this oxen, oxygen has been link to piv. Piv means pivaloyl group, now if you take an again an alkenes systems that means the other 2 pi system. And the base is used here rhodium C p star and chloride, so is a dimmer of that, dimmer of this. And heat it at only around 85 degree centigrade; very interestingly in one pot you will be getting the pyridine derivative. This in unique as that this is published in JACS because of the simplicity .Only thing that you have to of course, choosing the right catalyst also require a sort of experience insides about the reaction mechanism etcetera.

If you go through the reaction mechanism, what will find the last carbon nitrogen bond is being formed is basically the carbon nitrogen bond. So, that dictates the substituent's to be here R adjacent to nitrogen. Then rest of the groups are whatever it was required it is there are there and the R in this case of course, electron withdrawing group, and which is ester carboester, it could be amide ,it could be carbonyl or, sometimes it could be even aryl so, it is a very versatile reaction ok.

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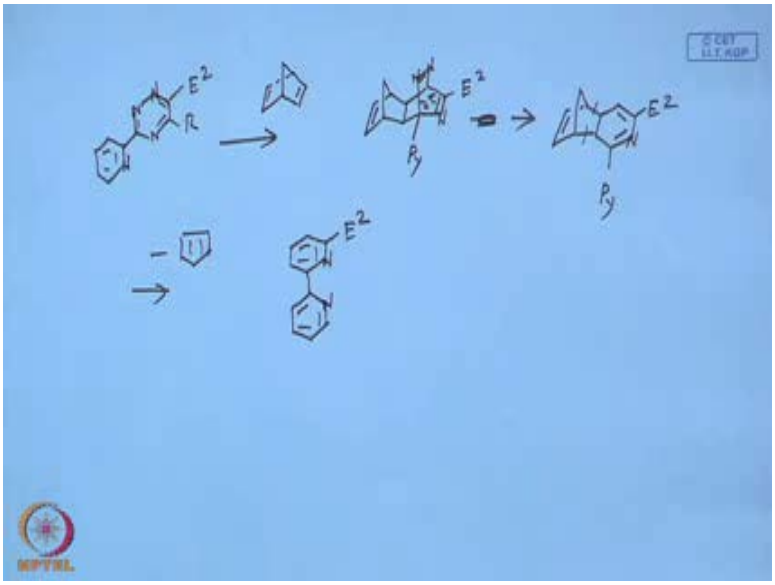

Let me give you just last example, is a very facility example though somewhat like bloggers approach. If you begin with triage system you will have, let us say triage system

like this E R let us say E 2 and in these case it is a pyridine. Now, you just heat with norbornadiene system and, what you expect? you expect a reaction of course, what is the reaction? The reaction is if you mix them together, so basically you have a binuclear system like 2 different heterocyclic systems.

You have a pyridine here, and triage system ((Refer Time: 53:55)) so the triage systems are good dynofile sorry, good dyne. That means it co electron component and, norbornadiene system double bond is not that activated. But it is an inverse electron demand Diels-alder reaction. That means it is electron rich double bond, this dyne part is electron poor so it will undergo again a 4 plus 2 cycloaddition reaction. And, in these case; obviously you can write this 2 plus sorry, 4 plus 2 this ester would be here. Then nitrogen double bond now, nitrogen and this double bond then you have pyridine nucleus right.

So, it does not stop here all of you know, once we have a double bond nitrogen so there would be a retro Diels-alder reaction. So, what we will have? We will have liked this double bond here right, then you have again a dyne system here, the nitrogen and E 2 and a pyridine nucleus should be hanging at the bottom. What next? I think is quite obvious to all of you right, what is obvious next so it does not stop there though, see basically whenever you see a double bond a reaction is under thermal conditions. You have to think about retro Diels-alder reactions, even cyclo hexane would undergo retro Diels-alder reactions give you butadiene and ethylene.

So, we see a double bond up here, means the allelic bond would be clipped. In other words, what you will be getting this Cyclopentadiene and a pyridine nucleus right, now the bottom pyridine is now borne up and, it would look like this and you have E 2 ester. So, what did we achieve you achieve 2 2 prime by pyridine derivative. And is it a big deal, is it worth doing that is important. You have seen when you do chemistry, you have to justify yourself. Chemistry that you are doing is important, useful, is it useful organometallics chemist? Right, once your organometallics chemist legend, that means impact if you can produce 2 2 prime bipyridile let us say in lower price. You know will be rich. It is very difficult to make, you know what people do? If I remember correct it is done by some oxidative coupling of pyridine, under the influence of paradigm something to the percent of 5 percent, 10percent and of course, all of us know that pyridine is not

easy to get by right. So I mean you have to some other methods, this is 1 of these ways; how 1 by pyridine can be synthesized.

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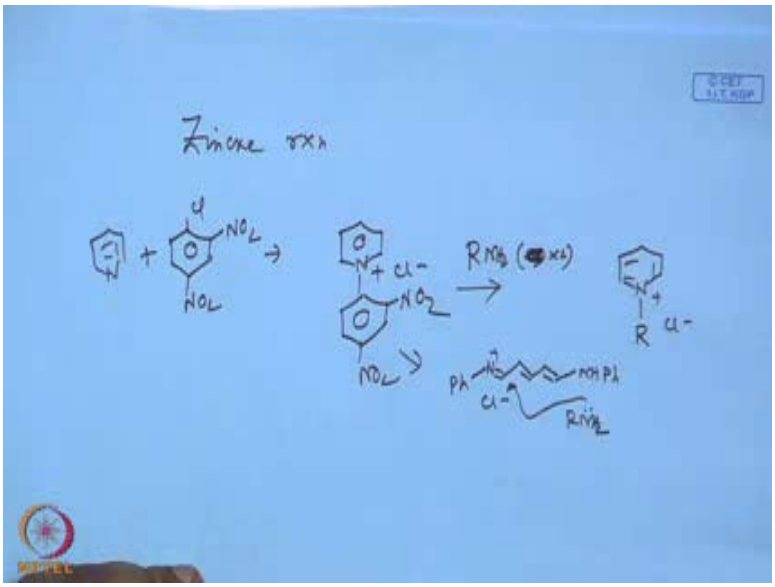

And last reaction, it is not that important as I said. But most of the text books will have this, it is known as zincke reaction. Zincke reaction is nothing, but what you do? You begin with dichlorobenzene sorry, dinitrochlorobenzene and then take pyridine you get the actually quaternization of nitrogen.

So, you will be getting N O 2 up here and, N O 2 up here then nitrogen plus chlorine minus. Now, if you treat with this excess ammonia sorry excess amine so, what you are likely to get is something like this nitrogen does not belong to this pyridine nitrogen now it is basically this nitrogen comes from the corresponding amine. And the mechanism suggested is that it opens up to go to this kind of conjugated tri amines with N H and P H, and this is chlorine minus. So, then R N H 2 again you know just like typical nucleophile substitution reactions. It will go like this and, then this cyclize to corresponding alkyl pyridinium salt this is known as this.

So summary, in the previous I think long back during the cycloaddition reactions we talked about lot of things and, in general there are 2 modes; condensation and cycloaddition mode. But there are other possible synthesis could be what the other possible synthesis is? 3 plus 3 kind of annulations. But all of them will have the ketone, but the Diels-alder reactions will not have. And there is also a method which is not talked

about, but it is not very popular that is call all of you know R C M ring closing metathesis ring.

Closing metathesis is not very useful in the case of aromatic pyridine chemistry. It is useful, but that would give you what is call non-aromatic heterocyclic compounds by pyridine derivatives etcetera .And then many times is of a carbonyl group this R C M is not really very predictive. So that is a reason I have not talked about that. So to close this lecture I think we should remember that Bohlmann synthesis is a very good synthesis.