Heterocyclic Chemistry
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Lecture - 17
Lithiation of 6-membered heterocycle and non-aromatic heterocycles

Good morning, today we will talk for actually three different topics the first one is it is ring opening of heterocycles initiated by lithiation or you can say lithiation initiated ring opening normally, this is restricted to the five membered ring systems.

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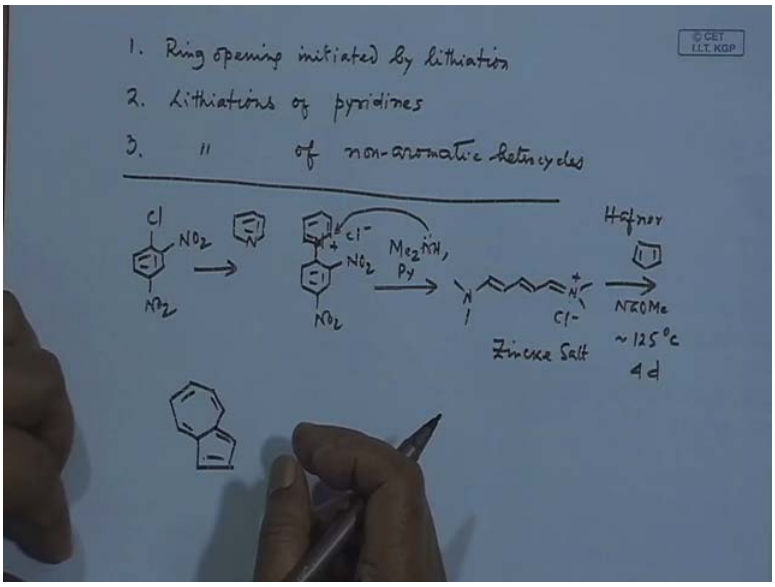

And then we will also talk about this lithiations of I would say pyridine nucleus, which is a re pyridines nucleus for 6 member heterocycles, and third item that would also of course, the lithiation of non aromatic heterocycles. So, these are different topics I will cover then may be towards the end we will have example of photosynthesis how this lithiation can be exercise to sort a photosynthesis, and add to that very quickly we talk about little bit of the azoline.

If you re call last time I will said that azoline made very easily from zinc salt, zinc salt is nothing, but salt of pyridine nucleus normally many, many of us know how to make 2 4 DNP how it made in lab. You make you use D N P, but if you are asked to make d n p how do make it chloro, so corresponding chloro compound just like sanders reagents, so what do you do. You treat this with pyridine and, but this is such a nice and special

reaction pyridine displaces also this chlorine, so eventually what you will get is a salt of pyridine; that means, pyridine plus and this chlorine minus.

And this compound is also very react with, if you react with dymothyl amine and then pyridine again, so what is amine, normally you would not expect any kind of reactions at best you will expect reaction the nitrogen, alone attacking the two positions of pyridine, because that is the most electro deficient position of the molecule. And eventually what you will get actual then if you just sit down and do the little bit of the reaction mechanism what you will find, you will find a molecule which is ring opened molecule that is the idea ring opened molecule.

And so, you will have one side you will have a donor, that means, three ammine other side ammonium accepter donor accepter kind of molecule, and this type of molecule very useful in the preparation of dyze. There is the lot of references and this salt also known compound known as zincke salt and Heffner a germen scientist what this salt of molecule.

and he react with cyclopedadine in the presence of sodium ((Refer Time: 04:12)) oxide at high temperature around 125 degree centigrade, and then also unusually the reaction was carried out for 4 days may be here is one leave, so 4 days. And product you could not expect it is very nice clean synthesis, and the product was, so what is this, ajuline, so sincerely you can say these two go on one step this is just one step two step synthesis.

If you go back original synthesis started from anybody remembers, good may be look sounds, but what of the one I require starts from cycloheptatrine, then 2 plus 2 cylco addition and forming a 4 member ring system. Then ring expansion and all these things it is take lot of time lot of steps also, so this is just an example that the heterocycles are susceptible to under go ring opening, towards the again end of the course we will have just a special topic of ring arrangement ring opening etcetera, this was in connections with the lithiation of 5 member ring system.

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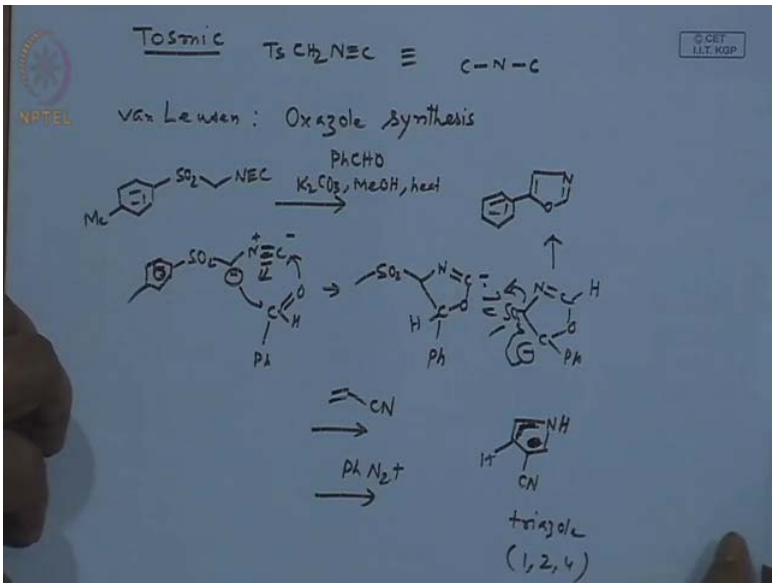

Then what I said that will also little talk about tosmic, tosmic is very useful syntheses in chemistry and it is nothing, but tosyl group then C H 2 and N C, so isocyanides tosyl methyl isocyanides, which is equalent to carbon and nitrogen and carbon. So, if you are coming across a unit of carbon nitrogen carbon in a 5 member heterocycles, then one of the possibility could be the use of tosyl isocyanides, this tosmic. And the first person that who popularized this Van Leusen is dos chemist and people often also called van Luesen oxozole syntesis is very important molecule again in medicinal chemistry and these things.

What can be done if you elaborate the structure, it would look like sulphene C H 2 and isocyanides, these tosyl means you have methyl group of here and the reaction conditions are very easy, potassium carbonate that is not a expensive base methanol. And prod heat the other reactant is benzaldehyte; that means, the starting metal to be cheap what do you get, you get a single product. And obviously, this oxozole you get other thing tosmic acid etc accounts for the reaction, what is the mycology, mycology I think anybody can do it.

So, mycology wise only thin you have to remember reactions initiated by the carbon enformations, not the lithiation the potassiation, that means a first carbon is found, so sulphone tosyl this then or you can say this minus. And it forms the ((Refer Time: 08:32)) here this added means you have double bond right this is phenyl, so it is go there

and goes to the carbon and have this, so what you will find you will find the salphone part here nitrogen is free now carbonize oxygen and this, that is it what next.

So, basically now if you look at this is nothing, but it is an heterocycle; that means, it is an heterocycle and carbonize, so or you can say potassium salt of the carbonime potassium salt of the heterocycle. And it can undergo exchange with this hydrogen of here. So, if you have an exchange there are two I mean all other possibility, you have a sulphone of here and carbonine is found P H oxygen and this.

So, obviously, then you have a sulphone emite which comesology in living room; that means, sulphone has dual purposes and it can activate the alpha position as well as like a living room, so you get this. That is not the problem at all, so it is very standard protocol, now if you just change the other reactant for example, if you I mean just I will quickly right this if you have something like this acrylonitrile.

So, what do you expect acrylonitrile means I mean acrylonitrile, so what you will see just blindly you can write this equilateral means this portion is cyanide this is benzyal dehyde double bonded oxygen, so it is acrylonitrile. So, you have hydrogen and what else nothing sorry, so you will have is payroll you will get a photosynthesis of payroll. So, actually you can also it can be used for photosynthesis of pyrrole. Then if you let us take with the phenyl decennium salt you will get the triazole, because tosmic is one nitrogen and dyzo compound is two nitrogen you get triazole.

And that should be one since it is dyzo compound you has to one and two and then fourth triazole, I will not write this structure, so you can just work it out so; that means, is a versatile one the hysteric there first one is addition of the carbon and two electro deficient carbon. And then cycliations and forms the 5 membered ring all the 3 acceptors benzyl dehyte, acrealnitrials all the even you can use ifoilacrelites for the photosynthesis of corresponding compounds. So, it is a very useful one there are other methods today, how to make it quickly I mean how to make it, this is standard substance commercially available for a cheap.

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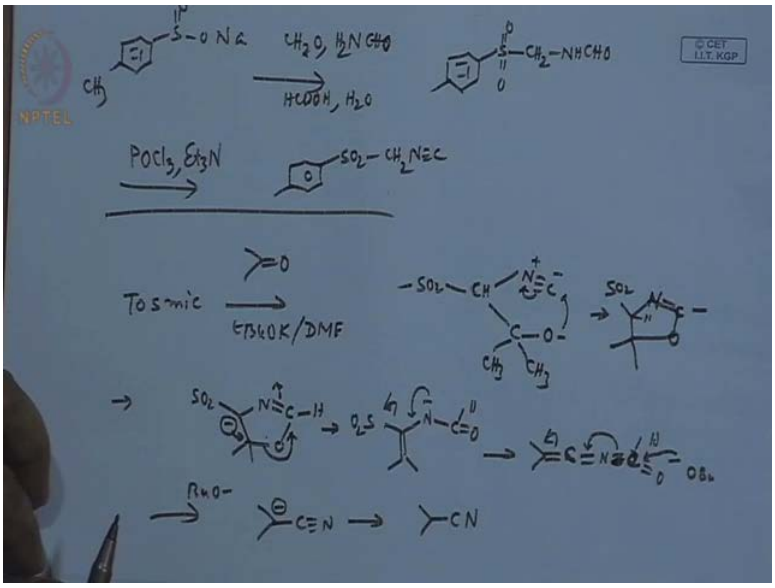

Sodium tolmon sulphenate, this is this is available in my lab you can ay if you mix with formal dehyte and phermomite and then reagent phermomite, then phermic acid is actually used solvent and water the standard protocol. So, what you will get, you will get sulfono mind it this one is starting as sulfenic acid, and now it becomes a sulphone this is to come from this formal dehyte and rest part is basically comes from the N H C H O comes from actually the promomite

So, what next then you have to know, how to make isocyanides how many methods do you know of till today, how to make isocyanides, ammine plus chloroform and sodium hydroxide, chameleon and any other methods do you know. Yes, bromide displacing that, but if just that is what it is a pharmamite, but one of the dehydrating agent required that is why, P O cl 3 and triethylamine, there many other agents, balgasting agents and all other agents, then carbon tetrachloride diphenyl phosphate all are plenty of methods, but this is most commonly used one.

And so, what you get is corresponding this one sulpone C H and N C, no problem there is no problem this is very standard technique now. And, but what happens, if you the tosmic, and then you take acetone what is the difference, acetone and the reagents are normally potassium tracery betaoxide and solvent is DMF is a polar solvent, because potassium tracery betaoxide being used. So, what do you expect so; that means, actually the elimination would not be take place, so what you will see that sulphone use there,

then C S 2 would react. You have the cyanide and then acetone, so that would lead to the C H 3, then oxygen minus then, so what you will get.

You will get again a 5 member ring, 5 member ring with a sulphone of here nitrogen double bonded carbon minus and in this case oxygen and this, but previous case with the benzal dehyte, you had an hydrogen of here, which was exchangeable. There is no hydrogen at the movement, so what is expected now, so this ((Refer Time: 15:43)) can exchange with this hydrogen, so sulphone nitrogen and this hydrogen of here methyl oxygen and this.

So, again this is a 5 member heterocycle and it has a propensity to undergo, so sulphone and this nitrogen and then double bond N H and what you will have now. What next actually, then one can see that ((Refer Time: 16:36)) here, elimination would take place. So, see now and then double bond and soluble isocyanide let us say, so I will let us complete this first and then.

So, for, so good I guess, I think we made a mistake somewhere may be no, yes, you see this one would be C H and this, then other possibility also be you can actually correspond the loss of the sulphonyte part towards the end, any other mistake OICC civil bond. So, then if you treat this with base there may be bit oxide, would de pharmulate and eventually somewhat like you know that volfican reaction.

It will form and a alpha carbon and which eventually in the presence of protic base what you will get, you will get the cyanide there are other method also to work out other possible mechanism, but what is, but essentially see that it is a direct homologuesen process direct and there is no parallel.

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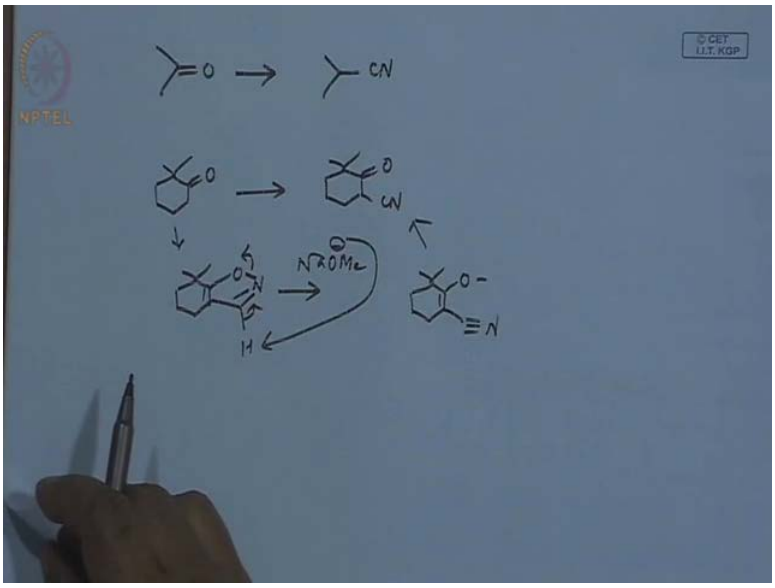

And it is very unique homologuesen process and you can just see the number of carbon and the number of oxygen all these things together can be done to get to this compound. And this is a very general reaction, in fact if you have genetic molecule, you can specifically homologic the corresponding aikido groups. Then there are very similar compounds for example, I will give you one more example heterocycles have been used to functionalize molecules for example, you have a molecule of this kind aceketone, now how do you introduce a carbon here in alpha position especially syno group.

I mean; obviously, I would to say you do the chlorination and displace the chlorine with cyanide displace the chlorine are to by cyanide, yes looks, but most of the times reactions do not really take place and the where you want. The alternatively this can be compounded into iso oxozole inolet and then yes, mechanistically, electronically they look good, but they are not, but when you have go to the lab that is the disadvantage, you can say advantage you can say, you know.

That is little problematic, I mean, when I say problematic means discovering a new organic reaction is important, that is perfectly all right at the same time you have to develop it to make it useable. That means, may be at some points some where the reaction was discovered, but then eventually it did not turn out to be the best possible method, you know so; that means, people start forgetting things the one the other you

should. So, this is another way of doing it and this iso oxozle and or interested, to see what could be the possible reactions isooxozle is a 5 member heterocycle.

And if you treat this with sodium methoxide this is a strong base what do you expect, normally you would expect there is a methoxide it will and oxozole means you have a carbon double bonded nitrogen. So, it is a sixth base, but sixth base analogy is only can be drawn for 6 membered ring, pyridine and the corresponding iso cululine, kululine etc all these things, but not in the 5 membered ring they are 5 excessive. So, again if you have too many nitrogen's then you can being the analyze of the sixth base in 5 membered heterocycles other wise not, so what is the other possibility, other possibility is that this hydrogen is sufficiently acidic so, but it becomes nitrogen hydrogen.

Here, and said the beginning it would ring opened and formed the corresponding cyanide corresponding cyanide and so; obviously, then what you will get, you will get the corresponding things you done. That means, one thing you have to keep it in mind whenever you thinking of these basic reactions in heterocyclic chemistry especially in 5 membered ring. There is a propensity of the ring opening that is what you have to remember, that is it that is particularly true for oxozole and iso oxozoles.

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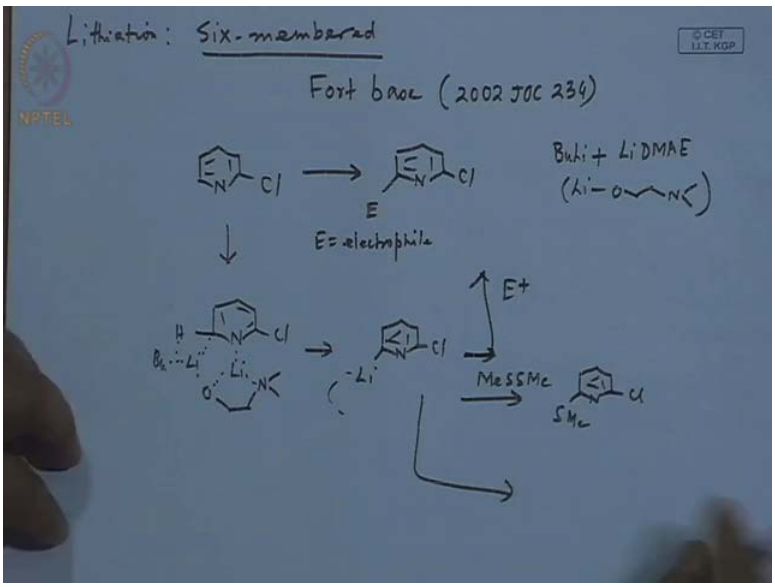

And next item is this 6 membered heterocycles, lithiations once again lithation is important an all of us know the pyridine case for example, so when we talk about 6 membered our reference is pyridine. Pyridine electro deficient and to carryout all these

kinds of electro deficient substitutions of reactions are not that very easy, so you have to think out the alternative for functionalizations, we have been talking about the reactions.

We have ignore some of this classical reactions, but in many cases you have reserve to the classical reactions like halogenation sulponation etc, beyond that the lithiation is a very useful reactions. For example, and if you have epidermal say lets say in the example have been talking about, let us say we have chlorine of here how do you introduce a substituents.

So, when I say E actually E stands for electro file, so this is the problem, now equivalent think all the routine electro file substitution reaction, and almost all wise routine electro file substitution reaction is a mess, it gives mixture of product sometimes, it destroy the study material all these problems of there. So, you have to little specific you will should be high and you will should be region selective and these case the problem was sort by a new kind of a base, which is now known as fort base, if you are interested the reference is 2002 JOC page number 2 3 4.

It is not a very new base, what it is, it is actually is a combination of butolithium means n butolithium plus I mean there is a abbreviation call LIDMAE lithium dymethyl ammeno ethoxide or; that means, lithium oxygen. Then you have two groups and this lithium dy amino ethoxide, so again what is the advantage I mean there are all working hypothesis, but this combination actually forms a nice kind of a chalet with nitrogen.

The proposed model actually the proposed model looks like this, it forms a chalet with all kinds of things here and there chlorine appear, there and lithium I mean you can sit down and do little bit of homework, then write all kinds of possible structure. It is a that there is a small chalet and the chalet, lithium chalet that is called nitrogen, which eventually activate the hydrogen at the two position, sorry six position, hydrogen at the six position.

That is it; that means, both the elegance and the lithiatic agent is betel lithium and the elegant is that dyammino tracery butoxide, ethoxide and all these things first form coordinations with here. And there delivers I this beto lithium to the six positions that is it, this is the working hypothesis works well and; obviously, then this induces the lithiations here at six positions. And so, you can write this and you can also write something some thing here, but eventually when you put this E plus p the substitution

takes place at the 6 position. And this methodology has been utilized for many, many things for example, if you use dyethyl disulphide, so you can introduce SME of here.

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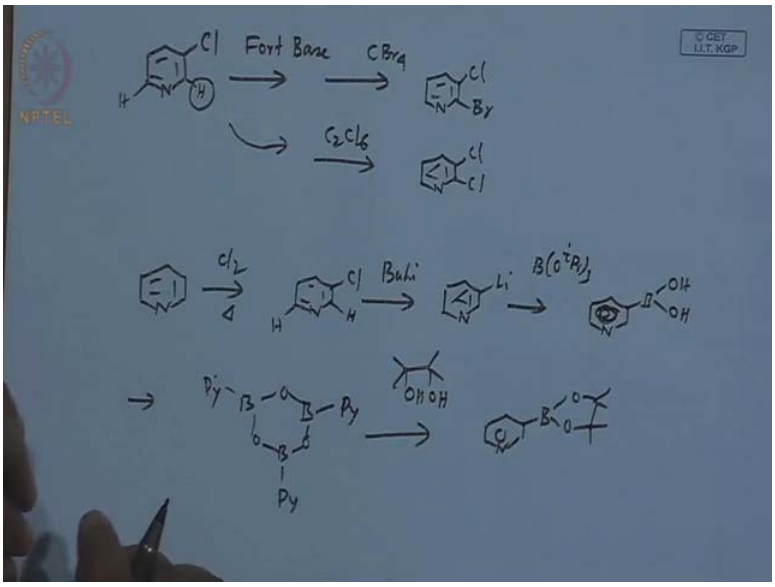

If you for example I mean in this example let us say I do not have this other examples may be I will give one more example think the exact example what we have let us begin with one more that one the 2 chloro pyridine. Now, if you use 3 chloro pyridine for example, now like the problem, now 3 chloro pyridine and fort base, first thing second thing that let us say use carbon tetra bromide.

So, what do you expect, so you know fort base undergoes co ordination at the nitrogen, it delivers the betel lithium at the adjacent position it could be at the 2, it could be at the 6, 2 and 6, but in this case two and six are un non equivalent. So, just you have to make a guess which one; that means, these are two possible sites two chlorine, because there is; that means, if you back of your mind if you remember the acidity also is an important factor in the lithiations. So, it is likely to be on this site, and that is what happens, so; that means, certain hydrogen would be deprotinated or lithiated, then what next, what is the role of carbon tetra bromide.

Yes, is, so it will be bominated, it is brominating agent lets say if you want to produce dychloro for example, see mind it, if you want to appreciate the merit of a method you have to think about the alternatives. Is the any other simpler alternative for these, then you know these method is very good, so like wise you use the fort base, then you have to

use electro folic chlorine and all of us know what is electro folic chlorine n chloro succinimide.

Even chlorine it self is ((Refer Time: 30:19)), but then, but then that is chemistry is actually synonymous with what call compatibility, I mean we can think of plus and minus, minus and plus all these things electro moving here and there. But, eventually when it comes to the fluck, there should be compatibility between the two reagents, so that is the, and so like you will be talking about n chloro succinimide, chlorine, iodine chloride iodine plus, so like this, but they do not work.

And alternatively that is what also I thought, because last time we talked about that also did not work on this case, similarly because there is an abstractival hydrogen, so if you have to have molecule very similar to like suggested, but it has to been free from having hydrogen, no extra chloro ethane. So, it is two extra chloro ethane that this to this one, and so, if you for example, if you want to put the groups three positions in case of predium what is the normal practice, normal practice this is all of us know that this is actually typical coordination reactions and high temperature that we know.

Then other methods very useful, if you use a betel lithium just pen betel lithium, what do you expect these are the thing you have to be little, practice basically the two possibilities, 2 or 3 different or 4 different possibilities. That is what happens the first you have to think about all the possibilities, and then you cut down the possibilities what are the possibilities, it can abstract the proton from this side, it can abstract the proton from this side, it can do the halogenation halogen exchange, third is ((Refer Time: 32:45)).

So, you have all possible now you have matured person, you are senior person, so you have to rank them, which one is most fessoil and which one is next least fessoil that how you have to reject some of the possibility. Then probably exemption on the prediction should be somewhat close to the right answer, so which one do I take halogen exchange analyze the acidity is very high halogen exchange is preferred path.

So, what you get here, you get this lithium done and then, but this is not very again you mind see here this is not a good one, though this is not a good reagent why this is not very stable if you recall pyridine reacts with buto lithum phenyl lithium in the ((Refer Time: 33:44)). They can under go self kind of combinations and reactions, so you have

to trap it the convenient traping agent is isopropile boret, it is predily available, methyl ((Refer Time: 34:02)) is perfectly all right, but it is low boiling.

Trimethyl solin is good very good, but there is a difference now. So, we will talk about all these things I think again in next month, because next class we talk about cross coupling and other things. If you recall again most popular one is most popular cross coupling reaction if you recall in fouth year we thought three different cross coupling three or four, there are many more three or four you have to rank them most popular is Suzuki, next popular.

I would say, I will not take I will take Negaci on my base my judgment, third one Hake fourth one could be ((Refer Time: 35:17)) and many other thing, so now, you can see which one should I borone that is what, so borone is very actually user friendly. You cans store them, you can keep them, you can do any all kind of reactions, if you open up an recent organic latent issue what do will find someone has done very simple reaction.

And he is published in orgulet, who is that, research callers this is a question to be research callers, some one from India has very recently used organo borine and did this reaction he got a paper out of it in orgunolitus. And he is very younger just only 4 5 years senoir to you he recently joined Bombay IIT, and he is also award from our place, so what did he do he took a oregano warm compound this much nitrate, he got nitrovegin. What I am trying to say, all the borines are very user friendly, nontoxic can be produced in large quantity and remove.

Let us for example, if you want to for example, the convert a ((Refer Time: 36:35)) you can take oregano borine oxidize, it with hydrogen chloroxide, that will give directly O H, I mean then somebody else very recently, you are just go to the literature there is a scientist called Garry Millender from ((Refer Time: 36:56)) or somewhere else from their.

He did something like this, he took tetra flora boride, phenyl tetra flora boride and reacted with something like bromine or something you got a bromo compound, so again nice obligation. So, conclusion oregano borans are very useful, very versatile that is the reason I have chosen this example, first of all; that means, you can easily functionalize once you have a borone of here, a hydrolyze it. So, what will you get, you will get the

corresponding predile bornic acid, but then there is a problem it is under stable, so what you get, you get what is it, it is again a heterocycle molecule.

What is the molecule 6 memebered means what is the name 6 membered, in bore ox borxoyzen, so you will have pyridine of here. So, unstable in detail; that means, you have then again it becomes, so stable it does not react, so you have to open down, and now you see the use of what is it pinochle. So, you studied pinochle in the context of mechanism and all these things, but we are now in oregano bore chemistry pinochle is very useful, there is a dy pinochleto dy borine, do you know are not that is very useful agent yes, many, many cases.

So, that means, what you will get, you will get nice oregano borent; that means, you can go on doing this thing, that thing and now let us ((Refer Time: 39:19)) so; that means, this is just an example of these a few example of this lithiation in ((Refer Time: 33:32)) chemistry.

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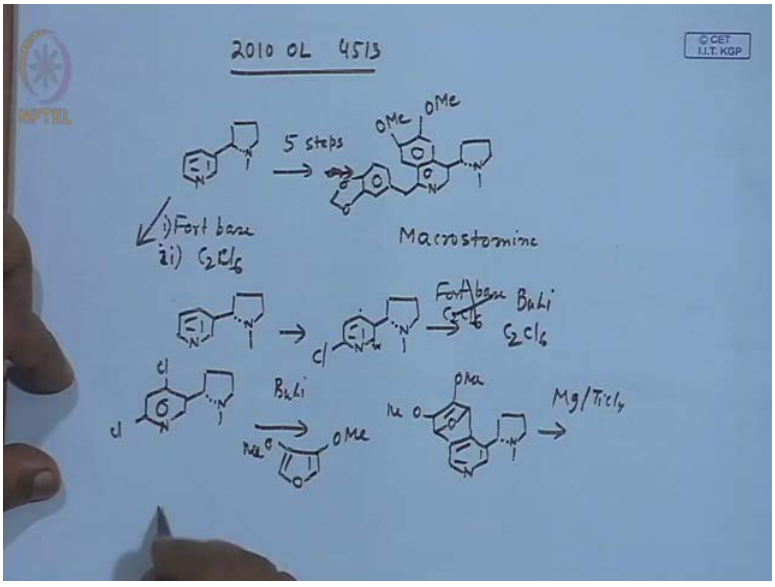

Now, I will give you very useful example from the current literature, this is again OL paper and published last couple of years ago, this is very this about the synthesis or other I should say elaboration of pyridine sorry, nicotine in very few steps to a national product. Isokululine kind of national product, where you can say benzyl isokululine, normally isokululine, isokululines are benzyl isokululine, and then you have this dioxolyne breach.

And so, this was done in 5 steps, what I will do, I will not give you the problem, I will give you the answer, just I will write the reactions you have to predict first, then I will write the answer. This compound is known as macrostomine is a national product, which an alkaloid. And it has beneficial effect is a national product, which an alkaloid and it has beneficial effect; that means, on cardiovascular, functions cardiovascular means related to the hot. It is not a drug, but there is a drug call papaverine, many of you know papaverine is useful as a cardiovascular drug is in market is a national board is a danger ((Refer Time: 41:24)).

This is an alkaloid this is nice illustration of these oregano lithium on the chemestric part, and obvious choice was nicotine simply, because you see molecule resemble very strongly with the nicotine. Now, so if you let us say begin with something like this, I think I will if you write fort base, number 1, number 2, hexa chloro ethyne. So, what is the product, so you have 1 2 3 4 5 6, now you have to have a prediction at least I can safely write by now, that it would not under go ring, because it is not a 5 membered ring, 5 membered ring ((Refer Time: 42:48)).

Then there is see here there is a lesson you have to also learn, aromatic nucleus and non aromatic nucleus and next lesson is actually lithiation of non aromatic nucleus we have not talked about it. So, you can by negation you can discard; that means, it can go to the aromatic nucleus, and now you have 2 and 6, in previous occasion it can there was a chlorine.

So, chlorine assist it, but in this case have eletrodolidine, again at the same time we think about there is a possible of the coordination of nitrogen ((Refer Time: 43)21), so if you have a lithiumiun 1 2 3 4 5. So, then which one do you think you should go, because if you recall these fort base work in fashion to ((Refer Time: 43:41)) doubly triply chilated things, so if that is, so it would prefer to have a titillation towards the less exposed satirically hindered side. So, obviously, the lithiation would take place on this side, and hence the chlorination on this side on this side.

Repeat again fort base and hexa chloro ethyne, what do you expect sorry, I should not say it is just now, it is not the fort base, this is now, it is benzylic hydrogen could be one of this reasons, but because the nitrogen the sixth base. So, it should actually lithiate

either the two positions in this two, sorry now it is 6 either this one or this one I thought, I would sewing that this one, but the our prediction itself.

Actually, I do not know, how he predicted, professor Kimonos, from north Canada state university, he actually I have to look at the literature, but eventually it was found that this fourth position relatively to the nitrogen has been position; that means, lithium actually deprotinates that one. I mean then again betel lithium, what do you expect lithiation, likely then what.

Student: benzyne.

Benzyne, yes actually that is what the benzyne, benzyne has been trapped with this dy methoxi furene, so what you will got on the benzyne would forming that is the possibility either these and that, but again unless you will know very closely. This benzyne is formed on this site ad then so obviously, 6 member transaction, 6 member like their furen part at this methoxi of here, and then the payroll in part remains as it is.

So, you have to aromatize it, so how do you aromatize, if you look at the final structure the essentially a, so what of benzyne ring, sorry this is a methoxi of here 2, sorry you correct the structure here. So, you have to de oxygen it is not an actually aromatization, aromatization is normally I will you can say de oxygenative aromatization, and this has been done with magnesium titanium tricloride, tretanium triculie activate this carbon oxygen bond and magnesium is a reducing agent. So, you can only other hand you can say magnesium reduces this titanium triculie two corresponding, tretanium 0.

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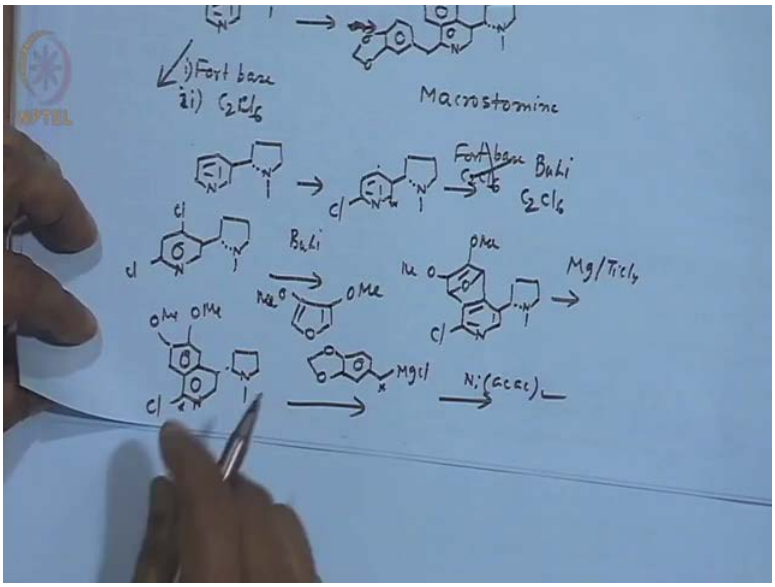

And what you will get, you will get an isocululine, now 2 substituted iso cululine, then you have methoxygen of here, methoxygen of here and this site, you have this the pyridine nucleus. And if you look at now, what you have to do, you have to connect one benzyl group; that means, is oxoline bleach; that means, basically you have to connect two units. One is this one; that means, this start position and in this case start position should be connected this is, where you have to know larder about this cross coupling reactions.

When you say cross coupling reactions you have to know the metals and corresponding counter part, and as well as you have look at the hybridization of the carbon and reactivity of all these things. So, these other two things you have to take care and now let us, but already on this part you have fixed chlorine atom, position has fixed now you have to choose something here. So, chemistry wise all the cross coupling has eased many synthesis, but at the same time it complicated the chemistry part, but because you have know too many things, but choice is very difficult.

You have to make a right choice, when too many things choice is also, so what can we do, so what group would take here, that is it nothing else you have an halogen here. So, any cross coupling reactions, we have to have a metal or metallites, so first one you would think from the left borone, then what do you think, metal. Tin, that is go to lake coupling in between zinc, so you have to lot down little bit zinc or aluminum, these

things and one more which is becoming very popular, and next we talking about magnesium.

Magnesium is now becoming very popular, there are a quite few persons are engaged in develop the magnesium, because all of us know it is very cheap it can optimal very easily magnesium and in these case you have this magnesium, magnesium chloride that is it. So, once the choices are done means in this case it is chlorine and you have magnesium then the problem is solved then you have to have a right catalyst, and how do you choosing catalyst if you do not know anything about the catalyst just say pyradium.

So, pyradium has become, so popular, these days I think any thing payradium, so just like our potato, you know if you do not have any vegetable just put potato. So, but well there is a call will brother of payradium also what is nickel, you think ((Refer Time: 51:52)), so it is basically a very compluensive example of this lithiation benzyl and all these aromatic chemistry, which are really compatible to heterocycle chemistry.

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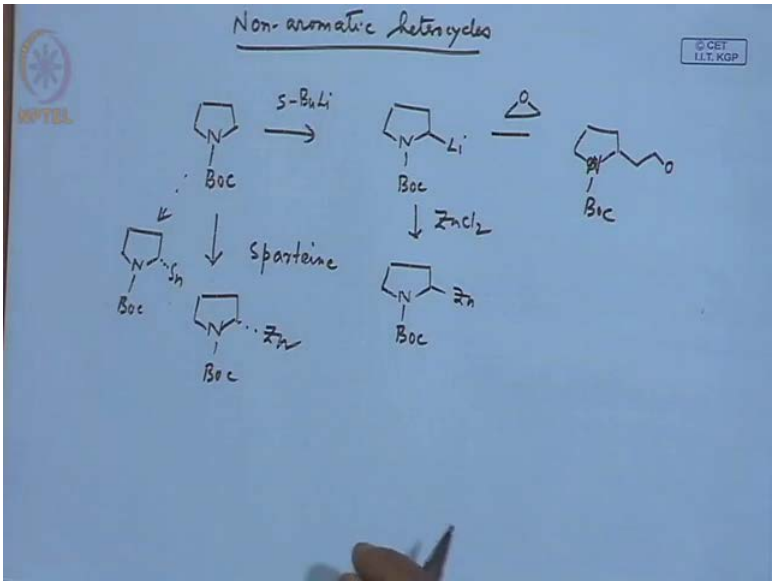

Next example, I think very quickly we look at non aromatic hetero cycles, I think there are not many examples, there are cases also sometime unique, but I think I will just take one or two examples, this a payroll d in case if you have Boc protected payroll d and then sicbetolithum. One can although see direct lithiation adjacent to this nitrogen, and you can do all kinds of things, once to you have a lithiation done, then you can do this

homologation and see oxidant, and you can do two carbon homologation, you can do all these things.

Now, you put zinc chlorite, so this one is organic electro file and you have this electro file and what is this reaction known as Boc, what do you expect, so again if you look at the Joules book, they will say zinaction, like magnesiation lithition then this is zinaction. That means, you will have a zinc there and often we talk about this sort of transformation in the name transmutation, so transmutation moderates the reactivity oregano lithium's are very violently reactive.

So, if you want to moderate the reactivity you just do a transmutation, transmutation to heavier metals, like you can do it you can do it substitute lithium by magnesium also or zinc cadmium all other things. So, zinc; obviously, you wants to have a zinc here then your options are now very clear well defined, you can do this negoital coupling, then there are methods, where one can just stereos specifically produce zinc here; that means, this is a Boc.

There are methods, so what do you do first do the lithiation first, and then you can put tin here sterious specifically with tin, and normally this sterious lithiation done by elegant all spertaine. I think many of you know right spertaine nothing, but a tricyclic alkaloid so; that means, this lithiation can be extended to these things, I think I may be will stop here or I will give you one more important example. In fact, this morning I try to look at some of the examples, what I could not get it, but may be I think many of you know I guess let us see all other how many of you know that that is important here, this is very unique reaction these reactions, so heterocycles non aromatic hetereocycles.

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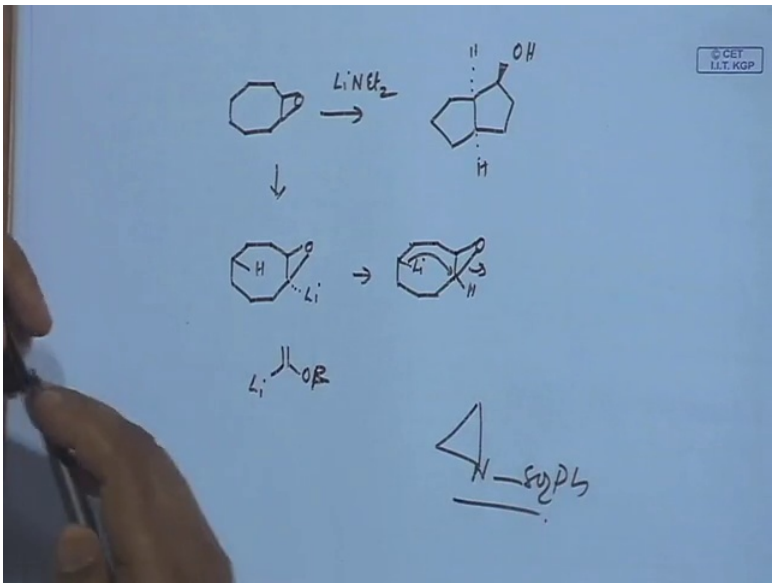

Now, if you react these with a amide this here, like LDA, so dy ethyl amide, what do you expect, anybody know it, it is very interesting reaction, that should tell you the essence of the I have been talking about. I have been talking about, what is the section is about that lithiation of non aromatics heterocycle, this is an heterocycle, so you can guess what it is, normally if you have an oregano lithium and etc epoxies opens up. If you have an acidic hydrogen that is coordinate and then epoxies opens up all kinds of possibilities here, but in these case I think I will give you the answer and then what you will get, you will get here what is this.

This is bicyclic compound, with O H and trans hydrogen and hydrogen, I hope you will be able to come up with the answer, the paper I could find actually just few minutes before coming to the class is this one. It is does not give, but just I suggest that I am probably quite correct, normally the epoxide there is no other possibility you to undergo lithiations. Here, if it is a highly substituted there no other possibilities are there then epoxination take place adjacent to the I mean you can quickly recall, phenyl easers.