Heterocyclic Chemistry
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Lecture - 16
Lithiation for 5-Membered Heterocycles (Contd.)

Today, we begin with again the Lithiation for the 5-Membered Heterocycles, but before that we will just take up the problem I gave you in the last class, it was the problem on a lithiation on the saturated hetrocycle. And that two furan nucleus, if you call the problem was on thebaine, thebaine is a morphine derivative, so morphine derivative is described as a phenolphthalein kind of molecule, and furor phenolphthalein type of molecule.

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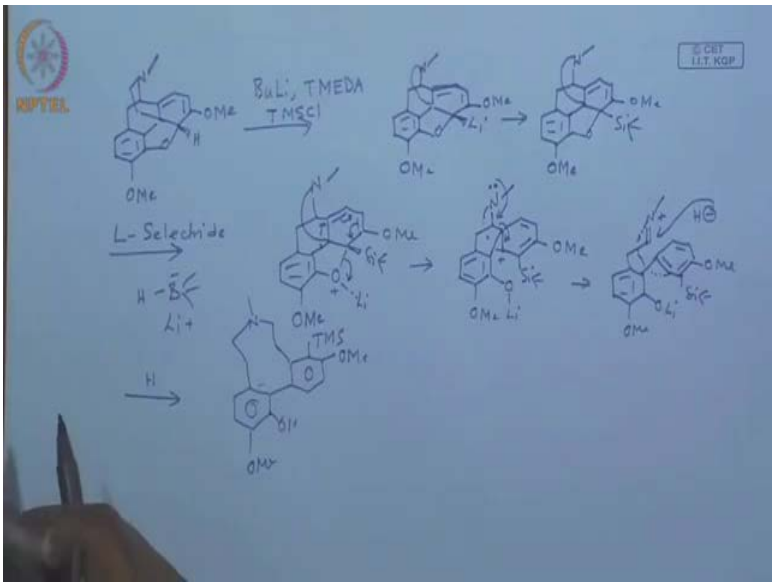

So, I write the financial structure and then, you have a furan nucleus occasionally morphine also is classified as isoquinoline derivative, actually the bio-synthetically it is derived from benzylisoquinoline, this thebaine has a structure where you have a methoxy group one of the benzene ring is aromatic. And then, subsequently all we had a structure of this kind where methoxy, the first reagent was butyllithium and then, TMEDA; TMEDA is an additive is of an use to make the base, more basic and then it was treated with TMS chloride.

Then obviously, there is a selection in the side of this lithiation, instead of ortho lithiation what happened, the reaction took place at the sort of you can say alpha to the oxygen,

that mean lithiation took place here. And then, rest of the things as it is, then you have this N methyl group of here, so N and this and then, if you use TMS chloride what you will find, you will find again the nucleus remains as it is, then you have this nitrogen all these things.

Then this is bridge here and then, you have O M e and you get these silicon incorporated in the position alpha to the oxygen, that is perfectly all right that means, only thing that you had to note that the ortho lithiation is not the dominant to one it is a C H activation, you can say C H lithiation. Especially C H lithiation is primarily, and then rest of the things as it is, what next then it was L seledrite, I think I will not write the structure, what is it is a basically boron hydrite, and you have several groups, then the counter energy lithium.

And the it is named show, because of they are reactivity pattern, when you say I mean the named implies it is somewhat selective, then you have to know what is the selectivity about, actually the name originates from the selectivity of this reagent towards redox is of the cyclic ketone. If you reduce a cyclic ketone if it is a non-symmetrical one, there you will likely to get axial alcohol or equatorial alcohol, if you use lithium aluminum hydride these are all given in calculus book, master book.

So, what is the product let us say, if you have a tertiary butyl acetate cyclohexanone, means confirmation is locked and you will reduce with lithium aluminum hydride you are likely to get axial alcohol or equatorial alcohol. And you with lithium aluminum hydride want to you get...

Student: Equatorial alcohol

Equatorial alcohol that means, hydride attacks from the axial side, so that was actually attributed to the stereo electronic effect, but when you increase the bulk of the reagent it gives the other voyage, equatorial axial alcohol. So, that is the reason why these reagent was named as L-selectride, but eventually this was found to be selective in many many cases. For example, if you reduce alpha beta unsaturated ketone with L-selectride, you will get only single reduction, reduction of the carbon carbon double bound takes place.

That means, just like lithium and liquid ammonia that means, there are some selectivity obtain from this reagent, so in organic synthesis it is quite useful, but in these case what

you see here it is little different thought. It has a remarkable effect on these oxygen coordination that means, lithium undergoes coordination is oxygen, and silicon also triggers the fragmentation reactions. So, what happens on the statement of this reagent, these oxygen of furan undergoes co-ordination.

So, you have these basic skeleton whatever it is, then you have ((Refer Time: 06:11)) this nitrogen and this is a bridge 1 methyl group and this is left hand portion remains as it is oxygen. And then, so lithium gets coordinated here, and you have the trimethylsilyl group, so what do you except, so fragmentation, fragmentation means actually today also will give you more quite of few example, where the furan gets clipped. So, in these case it is clipped that means, if this is clipped, so you will get a carbocation here, that carbocation is compensated by double bound here.

Then as usual lower bound, so that means eventually you general take positive cells here, so you have a positive charge, so what you likely to see...

Student: ((Refer Time: 07:05))

Want to see, so that is it and this aryl group, this aryl group will be safety to this one, accept aryl group, so hope fully I am right, let us see actually I lost the answer, rather I left the answer at home. So, will see that, so how do you see is basically you keep as it is and then that means, this bound moves here you have a positive charge, now oxygen and this is now lithium here, silicon remains as it is and that double bound moves and the double bound moves here ((Refer Time: 08:01)) the methoxy.

And you have a nitrogen and then, this the bridge carbons, then as here at least electron book keeping wise looks, then you have a methyl group here. What next is, so then you have to compensate this positive charge, that mean neutralize positive charge; and that is done by the loan pear of this loan pear effect. And then, this bound undergoes cleavage, so that means this one become, so the way it is written we can just write without disturbing anything, let us say we will have this is now double bond methoxy here, and this is a silicon.

Then you have the double bond and this O lithium O M e all these things, and what else then this breeze here and you have now nitrogen and methyl, so this is bridge, then you have the this now eminem ion. And the next thing that would be that hydride that means,

hydride would be attacking hydride from this L-selectride would be attaching, so eventually what you will get is a, you get a tri-cyclic compound, so tri-cyclic compound and if you rewrite, so it would look like this is this ((Refer Time: 10:09)).

Then you have a three carbon, one two, then one more, one more on this site, then N M e, so you will have a macro cyclic compound and this is TMS and this is O M e, just these other bond it will rotate now. So, what is the lesson we get, there are two lessons here, one is that lithiation can take place and saturated furan site, provided all other driving force existing. Secondly, the lithium also plays a important role in the ring fusion, or ring cleavage or fragmentation, we will have more example today.

But, before that just will look at some of the pyrrole derivatives, some ((Refer Time: 10:56)) derivatives and some of the derivatives continuing both of these furan, thiophen etcetera etcetera. Then some imidazole may be, some oxazoles we will have plenty of the actually, this lithium chemistry in heterocyclic is very useful; and some of you guess no you have studied before, there is a famous division call TOSMIC, how many of you know, raise a hand TOSMIC.

If you do not know ask ((Refer Time: 11:26)), she has write the review on TOSMIC, TOSMIC you must know, without TOSMIC heterocyclic chemistry, it is due to a scientist form Netherland Van Leusen, some time it is known as Van Leusen chemistry, Van Leusen regent. But, this is a very useful and versatile NCM bond, NCM symphonize would say CNC, CNC means carbon nitrogen carbon, whenever you require a nitrogen carbon nitrogen. So, you first think of Van Leusen reagent or TOSMIC will come to that, I mean there are so many things actually we will talk about today.

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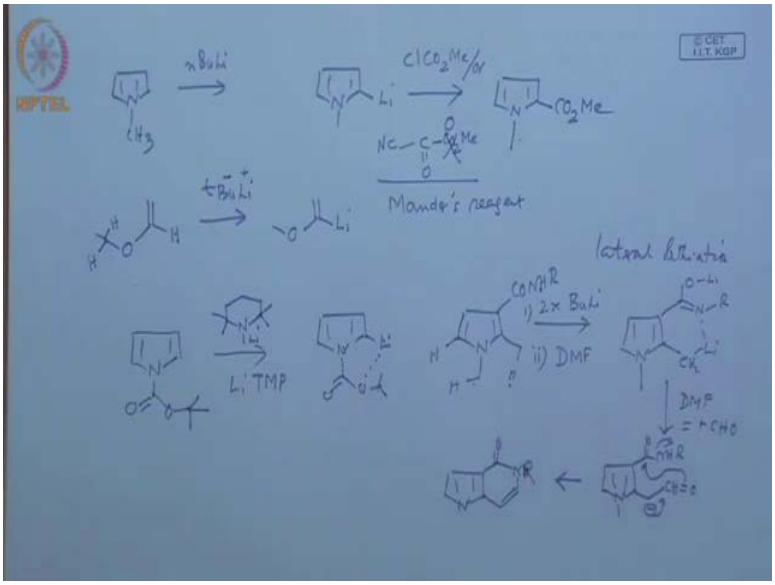

For example, you have acetone, I will just quick before, we will come back to this problem, how to do this in one step I said, then you have to study all this thing, again valuation. So, any case we will come back to that, but just quickly review in the pyrrole cases this is also pretty useful pyrrole cases, this is also pretty useful, pyrrole cases if you begin with, let us say N butyllithium, so what is expected by now all of us know.

What is our expectation?

Student: Lithiation

Lithiation is actually is driven by two important factors, you have to keep it in mind, two or three if you recall I mean, actually three different factors, the first this you should think about the hydrogen exchange. If you have hydrogen compound, I mean there is a likelihood that halogen exchange if pretty first, unless the corresponding C H hydrogen acidic. Next the important guideline is this C H acidity and third is chelation and of course, computation of all our these things are also there.

But, primarily in most cases heterocyclic chemistry, it is especially for the 5-member ring it is the acidity that derives the easy lithiation and that to again, if it is next to the hetero atom. For example, I think I told you before, this is a nice way of looking at, this is only very useful and reaction, you begin with phenyl ether, now you have a C H 3 up here though, then use tertiary butyllithium.

So many thing can happened, all these hydrogen's are functionalisable, this hydrogen also next to oxygen hetero atom, this hydrogen also next to hetero atom and then, all of us know this will butyllithium is minus and this plus. So, it can also undergo Michal addition, all kinds of possibilities are there, but of all possible reactions, the reaction that you are likely to get actually is this at low temperature, so nice reactions.

And so that means, once again this is due to the acidity, first of all it was a two and then, second of all there are secondly, it is next to the oxygen, so likewise that means in this case, pyrrole case what we will see, nice lithiation done. What next I mean then you can do all kinds of carbonate chemistry our of the lithiation and the one of the important reactions in pyrrole chemistry is incorporation of an ester group, you may ask why suddenly ester group, there are regents also.

There is the regent being this ester most of the pyrrole natural products would contain an electron withdrawing group, either a two position or a high position or in both, most of the natural products. Because, the pyrrole itself pretty reactive all of us know, it can undergoes for polymerization, oxidation all kind of things take place; and so what is the reagent, regent is missing. So that means, especially there is a scholar, so reissues lab you must of the air of the readily available reagents.

What is that, cyanogen bromide then no, I have said directly one step M e 2, C O 3 does not work is pretty in act...

Student: ((Refer Time: 16:46))

No, that is what he said, it does not work it pretty in sensitive and then, there is a likelihood also it can actually produce, actually diaryle carbonyl compounds like imidazole carbonyl. Now, people first you try this one methyl chloroformate is a pretty useful reagent, but there is actually I am coming to another reagent, this is very useful which is this one, instead of the chlorine you have the cyano or methyl cyanoformate, this is very useful reagent.

Student: ((Refer Time: 17:46))

Very good and this is known as Mendors reagent, I mean there are quite a bit of advantage for example, if you use methyl chloroformate the reaction yield is low, if you

have a nucleophile, which is ambivalent means, what is that ambident nucleophile not ambivalent nucleophile, then it can attach at carbon and oxygen. So, methyl chloroformate would being hard, so many a times it undergoes a it leads to O ((Refer Time: 18:37)) reaction, O carbonyl oxidations and in that context this mander's reagent is very useful, it gives very good.

But then, there is a problem, now what is the problem here, this removal of this methyl group, if you want to have N H and this position, you have to remove the methyl group here. Then deprotection of methyl group from pyrrole it is a tuff job, whatever I try to do so obviously all of us know, what is the next option if I have to do a lithiation in two position it may a protecting group has to substitute. So, what can do as usual not mom, mom will be in our lab, what is this?

Student: BOC

BOC, we have BOC will give lot of advantage, because it can undergo chelation the lithium, for the chelation minimum requirement that it should format 5 member, and may 6 member I mean 4 member, then we suggested I do not know how good it is. But, normally if you have a 5 or 6, then chelation is very likely but, at the same time, then you have to chase a reagent, because ambivalent lithium is nucleophilic. So, you have to change the reagent, so that means you have to have a strong base, but non nucleophilic.

Student: ((Refer Time: 20:16))

Which one LDA, LDA is a nucleophilic, then you have to little more one more

Student: ((Refer Time: 20:23))

One more

Student: ((Refer Time: 20:29))

((Refer Time: 20:32)) nucleophilic, most neuclophi most basic of all, you can say tertiary butyllithium not basic, but not that nucleophilic, the other one of the safest one is tetramethyl, tetramethylpiperidinyl sometimes we call a L i TMP, sometimes simplify L TMT. So obviously, then I have the t BOC and you get the lithiation done, then what you can see here one, two, three, four, five, so oxygen can nicely coordinate of the lithium, so

lithium is favored. Now, the group can be easily protected by all of us know, by H f or H B all these things ((Refer Time: 21:30)).

Now, let us look at one more example from the pyrrole chemistry, let us say you have a situation where, now you have poly substituted pyrrole and I use it two equivalence problem let us say butyllithium. One has say butyllithium is N normal butyllithium number 1, and number 2 use DMF, so again if you just think about this structure, and the possibility reactions you will see, there are so many possibilities.

The lithiation can takes place here at the five position, what else no other position and normally you do not see, I mean very really see lithiation taking position all other position other than the... And I mean direct lithiation by de-protonism, so this is one of the possible site what else, you have a possible site here and you have a possible site here. But, one the lithiation takes place here, we call that this lithiation lateral lithiation of an do at in our lab, lateral lithiation means, lateral means site chain lithiation takes place.

And in these case the lithiation takes place here at the site chain, instead of the nucleolus, so look at this lithiation done here and lithiation reason being, so that means you had a x 2 equivalence of butyllithium, the one equivalent will depropanate this nitrogen N H, other which is this CH, NH. So, you get it dilithium salt, dilithium salt now you can see nicely, it can form a chelation, so again is a combination of the chelation, acidity all these things would link to this site chain lithiation.

And side chain lithiation and then, DMF, DMF mean is equivalent to is a sort of a you can say formal cation that means, formulation takes place. So, we will have formulation the CH and then, this is a double bond and here you have this thing, what next actually then if you have sufficient ways, it can just under goes cyclisation. So, what you will get, you will get nice kind of a isoquinoline, so pyridine analog of isoquinoline, pyridine analog of isoquinoline can be obtained. So, I mean you can things little is more complicated, let us look at one more example from a 5 member ring, but that this is from indole chemistry.

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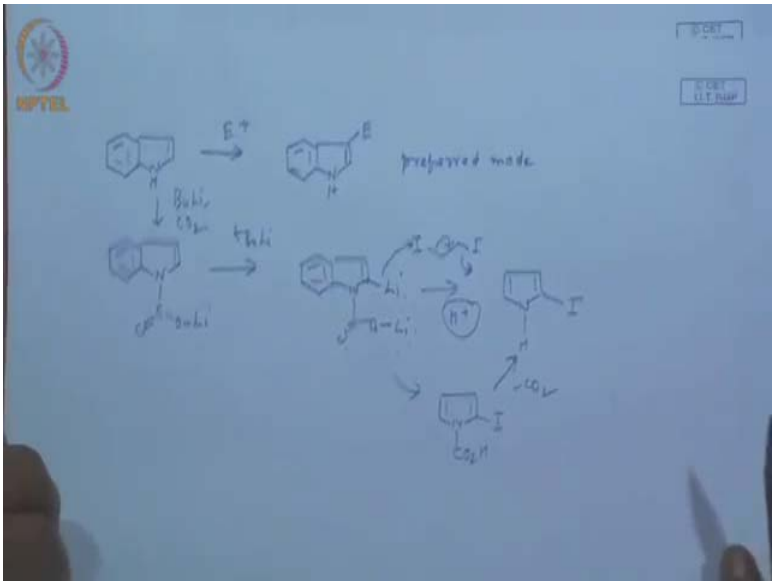

This is another way of all of us know, that indole if treated with the elector file, what is the reaction done, three position it is old one, because this the intermediate structure is stable at this three position. So, this is preferred one, preferred mode then how to prepare two substituted indole derivatives.

Student: ((Refer Time: 25:57))

There is no direct way of look at well, if they three position is blocked obviously, then next position is available that is two position and so what we have to do, you have to do a potation, in potation NH and do lithiation how is that. So, the one of these ways available is to do a potation, now again potation, de-potation means it should be dislike by organic chemistry. Because, it un necessarily reduces the yield and also the number of increases, number of steps, so you have to little careful about choosing the right protecting role.

In these case I mean what you suggest BOC, MOM all these things, but ((Refer Time: 26:48)) many of you know, octogenarian and he is I am wait how is that, so he just treated the lithium salt and then, treated with carbon dioxide. So, lithium salt and carbon dioxide what you get the this nitrogen get protected and then, that means indole, so it take butyllithium, carbon-dioxide and what you get, it is quite obviously, I do not have to write. Because, nitrogen get depotinated carbon and that undergoes nucleophilic addition, so the carboxylic carbonate carbon dioxide you get this one.

Then you get a little more powerful lithiation agent, so what we will see and without any doubt the lithiation takes place alpha 2 nitrogen and obviously, this driving force all of us know, driving force is the coordination of this oxygen with be lithium, the chelation the chelation of the oxygen and the lithium. That means, 1, 2, 3, 4, 5, so 5 member chelation this one, now you can do all kinds of things, now you have a two nucleophile, ambient nucleophile, is a carbon nucleophile, here oxygen nucleophile.

And all of us know within the carbonyl oxygen or carbonyl more nucleophilic, so whatever the electrophonic reagents are use. And this would give rise to the two substituted derivatives. Suppose, you want to put iodine up here and then, what do you do, you want to put iodine here, iodine itself it is not a very reactive one, especially polar reactions, possible in iodine succinimide is a possibility, what else...

Student: ((Refer time: 29:02))

Phenyl iodine, oxygen that would not give

Student: ((Refer Time: 29:08))

ICL is it possibility could be somewhat better, but the yield wise I think in the last year class, I have told you that bromination etcetera is done by dynamo, so di iodo ethane, actually what happened I think all of us know. So, basically it is a source and once you work it up in acidic medium, an you see here the beauty of this protective group, if you after the work up what you get, after the work up right... And what is this, it has a strong reason you can known acid, carbonic acid all of us know carbonic acid is very unstable, it will just carbon dioxide.

So, I means the carboxyl acid production is quite useful and let we see I have another example I think, I will skip that again from the indole chemistry, but very quickly just look at little few examples from the thiophilic chemistry.

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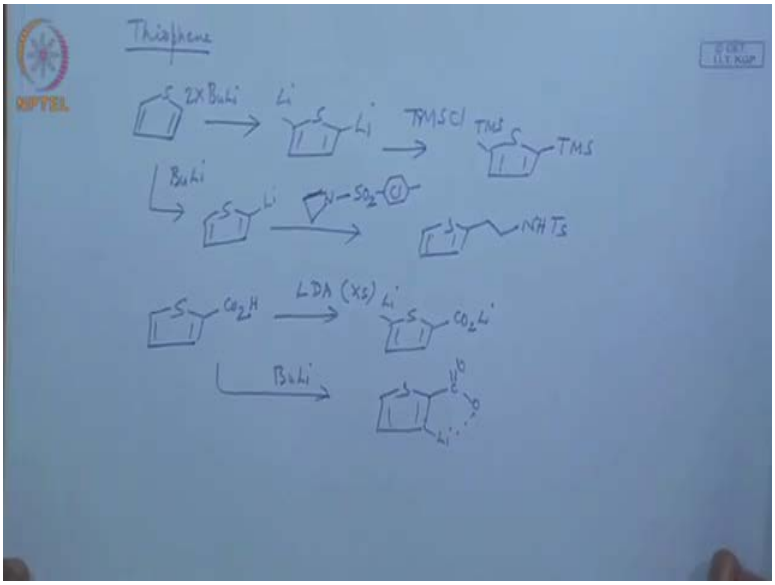

So, once again it is a very similar one, the reactions of thiophine are quite similar to the furan and the pyrrole. And so, if you use again, but if you see for example, butyl lithium depending on the equivalence, so and what do we expect, this lithiation would takes place. Then, if you compare, I think I gave you the example in the last class, if you have furan and thiophine, which one undergoes preferential lithiation, it depends on the reaction condition and thermo dynamic conditions.

But, under coordinating conditions it is furan, under acidic condition means, strongly basic conditions it is the thiophine. So that means, thiophine CH is more acidic towards the orgonal lithium compounds, because of second d orbital. So, this is an example, actually some for example, you do not have to do any step wise reaction, if you use two equivalent butyl lithium, so you will get two of them and then, TMS chloride. Obviously, I think all of us by now know, so you will get incorporation of two TMS units ring.

So, I mean, similarly let us say if you want to make a two substituted compounds, for example, the compounds could be two carbon side chain, let us say with NH 2 or NH something like this. So, what is the missing reagent that means, one equivalent butyl lithium, you get the mono lithiation done and then, you have to look for a right electrophile. So, what could be the electrophile?

Student: ((Refer Time: 32:51))

Actually acetylene, but acetylene alone, just plane acetylene would not do anything, even alkylated acetylene would do not anything, the acetylene chemistry requires n activating protective group. In this case, this tossile, so tossile group and then, it will undergoes ring opening. So, if for example, we have ester here, the acetylene would undergo ring opening reactions. And one more example I will give you, this is something quite interesting though that means, by changing the reaction condition, you can also change the reaction products.

For example, if you have a thiophine carboxylic acid and use excess of LDA, so what do you expect, the first equivalent would go to depropanate the carboxylic acid, all of us know. Next one, 1 2 3 4 5 positions, reason being that, LDA is non coordinating, that is what you remember, it is very basic. Butyl lithium also is basic, but it is coordinating means, it can undergo coordination with hetero atoms. But, LDA would not undergo any coordination, because nitrogen is there, it is pretty basic and in this case, we will have lithiation done in this here.

But, if you use butyl lithium what do you expect, it is a coordinative that means, it is a 3 position I mean, exponential could be I do not know how it is. So, may be have the lithiation and then, you see that means, LDA would break this coordinations, because nitrogen is there, nitrogen can preferentially undergo coordinations with this thing and that thing. So that means, I should say, I could not coordinations with the chelation, chelation is prevented under the LDA conditions.

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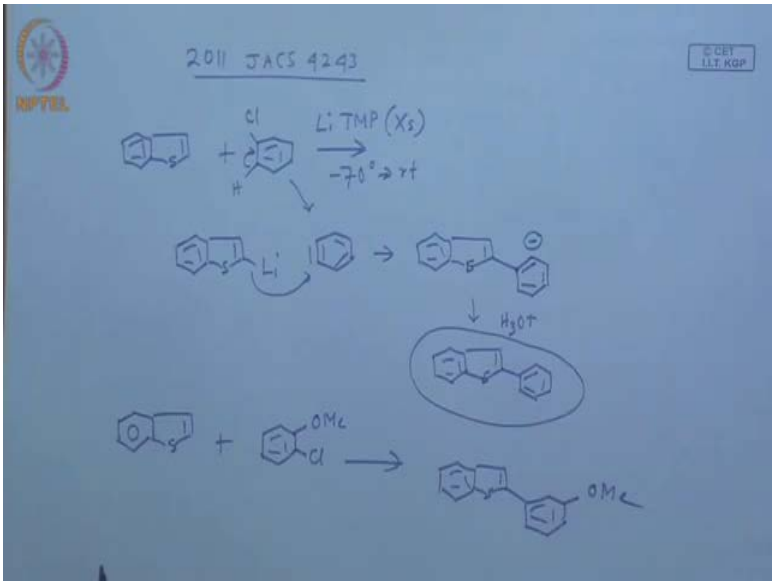

And last example probably from five member ring, will have one more example from the thiophine and this is a recent paper in the last year published by the scientist from George Teck, it is 2011, it is a JACS paper, you will see the paper I mean, almost apparently the discover is mainly apparent means, apparently apparent means very simple. Like say, if you have reaction done on benzo thiophine and let us say, the chloro benzene then, lithium TMP and as usual temperature, etcetera, minus 72, room temperature.

Probably, I will give you let us say, excess amount of means, more than or may be three equivalence of Li TMP. So, what do you expect?

Student: Benzene

No, I will not expect not benzene, first thing I will expect deprotonation, first see whenever you are doing a lithium chemistry, I have told you in the very beginning of the class, let look for any halogen exchange, that will take place, go for a lithiation by deprotonation. That is not done then, of course nucleophilic addition, etcetera, all these things. So, the first thing that I would assume, that there is a reaction would form lithiation and the site of the lithiation is very same, but easy to predict now next to the hetero atom.

What next that you can say, because excess we have, so we will have, now you can see, once again a deprotonation, this one also driven by deprotonation and the chlorine especially, so benzene formation takes place. What next, all of us know benzene is an electron sink, it can accept electron, so and the reaction product would be this aromatic ring here. So, simple addition takes place and eventually, what you will get, you will get, one work up what you will get, you will get this.

Now, you have to justify, why this reaction or why this particular paper has been accepted in JACS, not our paper, you say what is the special feature of this reaction. If you look at the target molecule here, what is it, it is a biaryl, but unsymmetrical biaryl, for symmetrical biaryl we know the solutions, Ullman coupling, there for a corresponding modification, etcetera would do. But, for unsymmetrical biaryls you have a problem, so that is the reason and the problem was solved largely by who, those person last year novelerist, Suzuki, Negasi, all those people.

But then, I mean, those problems are solved then, why this paper should go to JACS, you have to justify. What I am try to say, JACS means, all of us know you all agree, that is the high standard journal, that is perfectly all right that means, quality of the work also should be act for with the standard. So, what is this extraordinary quality of this reaction?

Student: ((Refer Time: 39:55))

Very good answer, there is no transition metal, why transition metal is not welcome, because expensive, of course not all, I would not accept all this thing they are very cheap, but these organo boron, this thing that thing they are pretty expensive then, palladium is quite expensive. So, this is transition metal, that was the title of the paper actually, transition crystal metal field by the synthesis and the heterocycles. And I give you one more example probably, I think that is, of course there are many many salient features of these reactions, this is one of this, the transition metal field.

And I have I mean, may the paper has still there about 30, 40 different examples and each examples gives you a particular lesson. For example, the next example would give you lesson, you have to find out the lesson here, what is the lesson you learned, if these two component I reacted under the same condition and the products that is obtained is this. So, what is the lesson, in most cases I will tell you the yields are above 70 percent,

in some cases the yields are close to 90 percent means, reactions are excellent, number 1, number 2 when I say that, Li TMP is the base.

But, there are many examples which could be performed with LDA that means, very cheaper base, there is also one more base that is, actually lithium dicyclo hexyl amide. So that means, is a pretty general, in terms of the base the reaction is general, in terms of the substrate, on the left hand side right hand side is quite general, but the generality has been illustrated with various examples, one of the example is this one. Now, you have to identify the speciality of this particular example.

Student: ((Refer Time: 42:38))

It will be more, actually metal substituted.

Student: ((Refer Time: 42:46))

What substitution?

Student: Chelation substitution.

No, it is not chelation substitution.

Student: ((Refer Time: 42:57))

Yes, basically it is regio specific means, it gives you a single isomer, in B.Sc you have studied, if you have a benzyne, it could add from either side, but here actually from only one side, why?

Student: ((Refer Time: 43:21))

Not really, actually there also is possible, in case of ((Refer Time: 43:29)) benzyne let us say, what is the base we use, sodium amide that is also possible.

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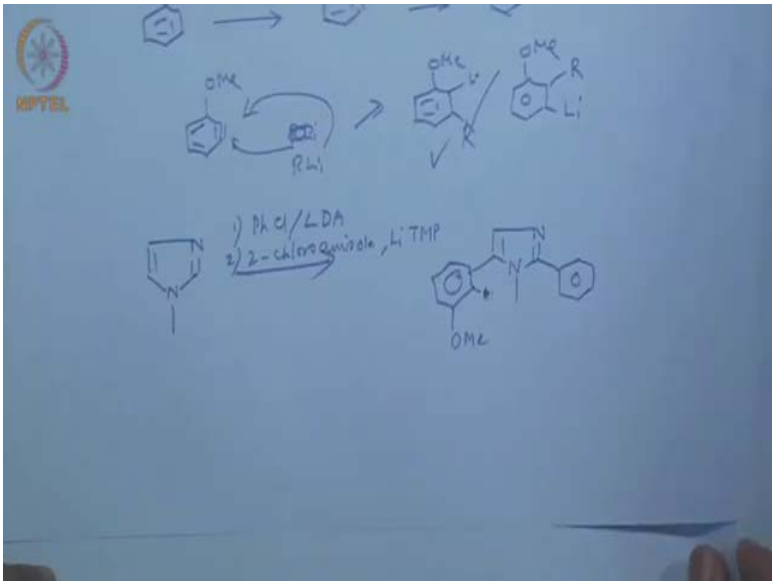

But, if you recall, this is a reactions actually this should have been thought you know BSC, but it is not output, what is the reaction, is a regio specific lithiation and this one and we call ortho lithiation. Ortho lithiation is a very famous reaction, I told you that the discover of ortho lithiation is who Gilman and

Student: V t.

V t, this is a actually this should have been thought, and then it means electrophile you will get I mean there is no other alternatives, and there will you get this carbo phenile electrophile. You take carbon di oxide, you get the carboxylic acid, you get this DMF, you get this fermaid, all these things are possible and almost always you get just a single product, there is no question of getting meta or para, so such a beautiful reactions. Not only that you can accommodate all kinds of electrophile adjacent to an electro with drawing groups also.

So this is a very versatile reaction, very useful reaction, but somehow I do not know why the people are not use to teaching this sort of things in under graduate. So, what is the gain the driving force, that to driving force 2, because the inductive oxygen, this the adjacent hydrogen is I should say field effect, this hydrogen becomes more acidic number one not the resonance effect, then of course this chelation, so because if the chelation; that means, the lithiation I think both chilazon and acidity, the lithium and the ortho position is very stable.

That means, whenever you have a benzene, for example and you have R something some R Li should add, so it can add on this side or on this side, so there are two possible orientations. One lithium on this side and of course, and the meta position and this is R and this is R, and now you know the ortho lithiation; that means, the lithiation at the adjacent when oxygen is stabilize, so this one would be stabilize and then the explains the regio chemistry.

And then I will give you one more example from this direct arylation without transition metal, let us taken case of imidazole for example, first condition is carbo benzene LDA, that is the 2 step reactions. Second is 2 chloro emizole and a lithium TMP, so what do you expect that would actually there are 2 very similar reactions, in one first case LDF, second case I mean sometime the choice of bases is done the bases of the experience error etcetera. So, what is the product you expect; that means, from the first one you get the phenol incorporation, the second one you get the anisole incorporation.

But, only thing that you have to make the judgment, which one will be placed at this place that is it; that means, the basic skeletons remains basics remains as it is and in all these examples we see that the iolatin takes place the nucleus. So, now I will tell you the first one would be this one, obvious now is a obvious, that is the clue, because it is plant by 2 hetero atoms, so what should be the n group, it should be the phenyl group, so if that is, so I mean in other side you will have the anisole that is it. So, the anisole, then why it could be methoxy group, meta position because the lithium would be here and remain methoxy, so that means, regio chemistry why, orientation why is a very good reaction, and he had done plenty of reactions, so it should imidazole it is.

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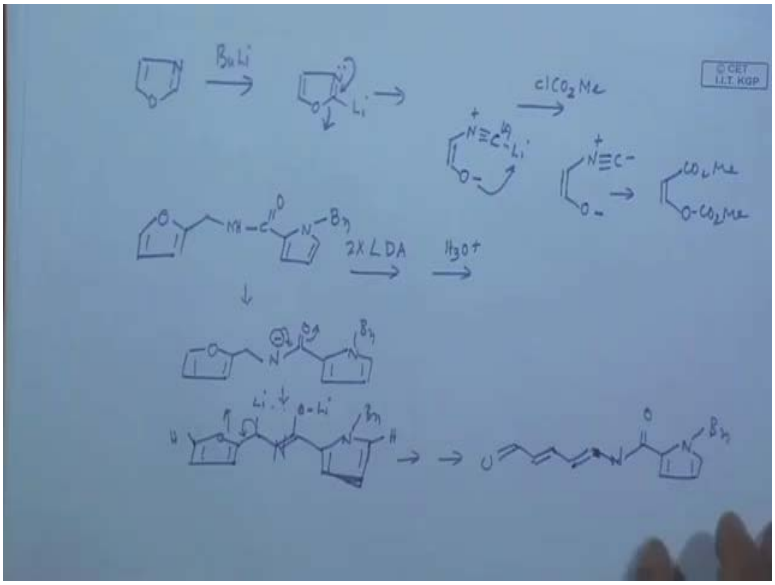

Now, let us look at oxazole case, what do you expect, lithiation square at now the nomenclature 2 position and what next, I can tell you whatever the reaction product was could not be isolated; that means, it was pretty reactive. So, it was trapped with ethyl as a methyl chloroformate, so what do you expect, so here something happened, depropotional very good no problem lithiation took place.

So, after lithiation what will be felt, normally you think about whether it is a kinetically control or thermo dynamically control, the reaction is allowed and as I am saying that the reaction is prelong that means, it should give thermo dynamic product. Thermo dynamic product could be due to the excess of the lithiation and or else among stable product, you get an very unique reaction actually, or unique reaction again it is a lithium controlled. In a very first minute what I said, the lithium can cause if you recall of all metals, lithium is a nice small metal, it is soluble in organic solvents, it aquardness, that is important say; that means, that oxygen lithium coordination is a very powerful bondage.

So, what do you expect then; that means, lithium should transfer to oxygen, and that is possible; that means, it undergoes ring cleavage, so ring cleavage and eventually, so what you will find this that means, this is what, this plus this is minus and now lithium. So, and obviously, what you get is then, what is it just in isocyanides and now; that means, situation arises when the lithiation takes place in isooxazole, and isooxazole have a tendency to undergo ring opening, that is what you have to keep it in mind.

The previous case what imidazole, imidazole dianode are pretty stable, I mean you can step wise could lithiation do these things and then the final product would be this is I think we will we will talk about the TOSMIC chemistry tomorrow may be. Well I will give one more important kind of a reaction, see this ring opening and let me give one more example, like in this case it is not a it is not imidazole, but is a furan, then amine and amide carbonyl, and this amide carbonyl is link to a pyrrole moiety benzyl.

Now, you have furan nucleus, you have pyrrole nucleus you have learned all these lithiation etcetera, previous one was the oxazole, next previous one was imidazole, now we will have a reaction quite just reactions LDA and then this, so what we expect. Since we have already 1 N H here, so active hydrogen, so you require two more equivalent of bases, two equivalent of bases what do you expect.

So, first equivalent would give rise to a formation of minus here ((Refer Time: 55:00)), then this pyrrole unit fine and or all of us know they should undergo original stabilization, and eventually it would give lithium there, then you have benzyl. Now, second equivalent, what will happened with the second equivalent see so many ((Refer Time: 55:42)) furan, this hydrogen pyrrole, so what else if you go back there was a case pyrrole case, we had N methyl, we had site chain methyl, when this thing that thing.

Student: ((Refer Time: 56:08))

So, it is the lateral lithiation that means, there is a lithiation takes place here at this position, what is the driving force chelation in previous case also that means, you have to always keep track of whether, any group is present in the molecule which is suitable for chelation. And this chelation takes place with this oxygen, here is nitrogen that is it, but then if you acidify you get study metal back, because protonate here, protonate here you get the study metal back.

Now, you it does not give new product, then once you have this nothing else is possible, then you think of again a fragmentation reaction and affinity towards oxygen. So, it will undergo cleavage, undergo cleavage and if you go on go on basically eventually what will get, you will get... So, what is the conclusion, conclusion is that furan can give a cyclic structure with 4 carbon, 1, 2, 3, 4 this was originally was there. So, 1, 2, 3, 4 and that is this is that benzyl carbon then nitrogen, so you can get this, so if that is so then, I mean actually there are this sort of reactions has some precedents.

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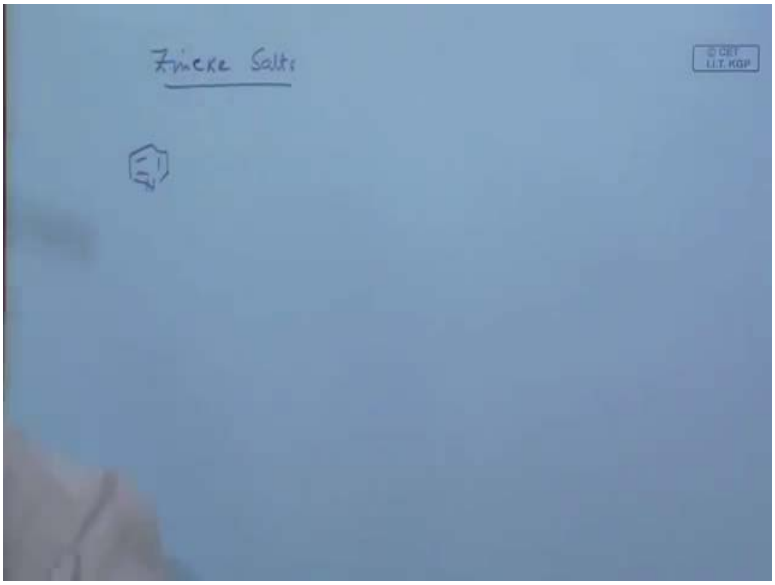

For example, I think maybe you can go to the literature, I think maybe yes, this yes there is a, what called zincke, zincke actually the name of a scientist actually, zincke salts. What is it fine, maybe we will talk about this thing maybe in next class, we start from zincke salt and this thing, actually we will continue this topic for quite some time, another 1 or 2 weeks. This lithiation and then, we will talk about the magnetizations, magnetizations means is a new word, actually all of us know organo magnesium compounds. So, if you have C H hydrogen, if you put magnesium on the place of hydrogen, it is known as like lithiation we call magnesians, so these days actually magnesians is pretty useful reaction.