Heterocyclic Chemistry

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Lecture - 15
Lithiation for 5-membered heterocycles

Let us review first, actually what is we talk today, and when why it should be talked. Let us first to begin with why it should be talked, because many of you know that is aromatic chemistry begins with electrophilic substitution reactions. And where you occasionally this nucleophilic substitution reactions are taught, resins are quite obvious those are the classical reactions will established the profile of the aromatics under the electrophilic conditions are well standardize. So, one can quickly predict and what should be the product or should not be the products, but there are some inherent problems

Inherent problem means, this problems of isomerism, so that means the formation of different kinds of isomers produce all of us know, and traditionally when it is start it is given the idea that the electrical substitution reactions produce ortho para motar form mono substituted benzene rings. So, in case of heterocyclic the situation even more acute, simply because if you think about nitrogen let us say pyridine, how many pyridine the mono substitute, let us a pyridine itself is having what 1 2 3 different kinds of then if you have a mono substituted period will have 4 different chemicals lead non-equivalent hydrogen’s.

So, you have the miss the problems are severe, then if you go to naphthalene for example, mono substituted naphthalene think out mono, how many chemically non-equivalent C H monos are there. In naphthalene, mono substituted naphthalene I said, how many, C H, nuclear C H bonds? No, see that is the reason, you have to as look into the problem very carefully.

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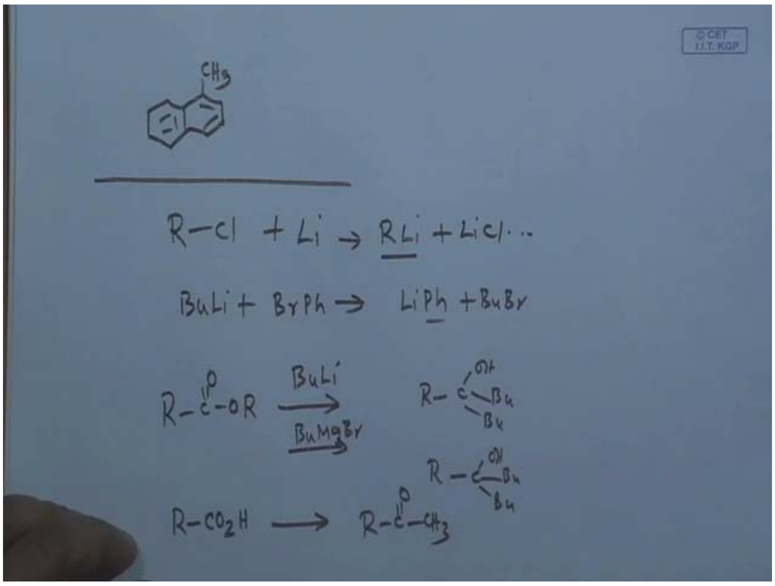

Let us say let me write, when I talk about mono substituted naphthalene, how many nuclear C H bonds are there which are chemically non-equivalent.

Student: ((Refer Time: 02:50))

So, this will, so you see let me this things are little tuff are the miss the problem are more accurate, but and as you recall last you talked about the selectivity, selectivity each one of the I mean first and for most goals in the organic synthesis. And if you recall again just go back to the last class minisci reactions, a minisci reactions ((Refer Time: 03:17)) specifically functionalizing two positions, you have so many functional group around the molecules, and so many double bounds around, but specifically one position is functionalize.

So, that is call really selective reactions, so like we are lie many of you probably know that the click reaction for example, click reaction is so selective towards the triple bond. I mean, so what about the molecular, I have in their structures the, but eventually the reaction who takes place only in the triple bond and with an arsenite. So, selective is a very important goal and; that means, then that is one of the major resins why will be talking about that lithiation today.

Why lithiation? I mean we have studied organ of magnesium right, from our very early stages of studies of organic chemistry, but lithium organolithium has a special characteristics. One of the special characteristic is that selectivity, you can achieve selectivity with organolithium compounds and that concept has been extend to heterocycles. So, today what to you do will just very briefly may, because some of you have studied my organic synthetic chemistry course, so we have talked about why do we talk organolithium chemistry their and but some of you have problem do not have not studied.

So, what we will do today just very roughly we will review you know what is organolithium, what are what are this resins why organolithium compounds are superior to organomagnesium some of the typical reactions. And then switch over to the applications in heterocycle compounds, and today again the all the discussion should be limited to the fibertec systems. Fibertec system means ((Refer Time: 05:14)) this is the order will be talking about, because organolithiums are more useful in furan chemistry and forward by a mean ((Refer Time: 05:24)) chemistry and may be little bit of these lithiation in indoor chemistry.

So, we will talk about those reactivity patterns and then towards the end of the class in the time permits, we will talk about the applications, application of these. And then so when we talk about these organolithiums, I think by now all of us know, so what do you do, how to make it first and what is the mustard reagent. If you recall butyllithium, butyllithium is the mustard reagent how do you make it.

Student: butyl chloride and lithium

Butyl chloride and lithium, so an exchange, so that is it, so that we sort of a reductive kind of the liquid; that means, and then lithium chloride etcetera, so this is the mustard reagent, methyllithium, alkyllithiums. And reason is quite obvious and that is the most basic organolithium compounds and there are other methods, then actually there are only I mean if you try to classify the preparations of lithium compound, there are only very few. If you begin with mustard reagent like alkyllithium first are the type of the preparation could be deprotonation, just abstract the proton that is one of this ((Refer Time: 06:48)).

Then second mode of a preparation I would say or else you can say first mode of preparation having an exchange, if you have an halogen and alkyllithium you get an exchange of these lithium and halogen. So, that is how, but the driving force is always the almost all is thermo dynamics; that means, the lithium organolithium that will be produce should be lesser acidic is lesser basic that the parent. Like I mean, what I talk about these; that means, I want to say you have a butyllithium for example, then and take bromobenzene, so what would like to see.

You like to see that lithium is phenyllithium is produced and butylbromide is produced, why the driving force because these phenyllithium is less basic, so that is the basically the idea. So, I mean, so we can have this, and what else what I say then the other important point about the organolithium, they are always more reactive than corresponding organomagnesium compounds, that is you have to remember. That means, let say you have an for example, this is something what to know let us say you have a reactions will be butyllithium and butylmagnesium when bromide.

So, what difference do you except out of this reaction, so that when I talk about the organolithiums, actually we always talk about their chemistry with refers to the organomagneisum compounds, reason being all of us know that they are well studied we will no lot of about organomagneisum compuounds. So, the mechanism reactivity profiles etcetera, etcetera, and if you study organolithiums with respect to organomgneisum that would be easier, in these case for example, if you what difference we except with respect to the product formations, I think very similar product, if you have excess what you will get, you will get the corresponding trash theory alcohol.

So, similarly if you have excess here you will get the same product, but what will see there is a remarkable difference in the reactivity, may be at the minus 78 degree did not would not react, but you corresponding organolithium would react very nicely. That means, by controlling the temperature, you can actually achieve the selectivity; that means, at low temperature may be you can the you can stop the reaction, you know of this burolithium at the kiton stage, there are examples also.

And also there is another so; that means, the in that organolithiums are much more reactive than the corresponding number 1, number 2 point organolithium compounds will have a tendency to undergo relations and coordination’s, that gives the some of the intermediate’s very high stability. I think, I told all these things in the fourth year, if you recall, how to straight way get to the this is a typical j equation or get questions or whatever I think all of you know, no, very good.

So, what is the secrete, secrete is that after the addition of one equivalent method lithium intermediate becomes stable because of the internal coordination's or ((Refer Time: 10:44)), you can say. So, these are the properties that actually that make difference in the reactivity, and many of you probably know I do not know that is a whether I should talk about. Let us talk about these consider again a question of the effect of the heteroatoms for example, this one amide normally do not react with organomagnesium compounds because there organomagnesiums are less reactive.

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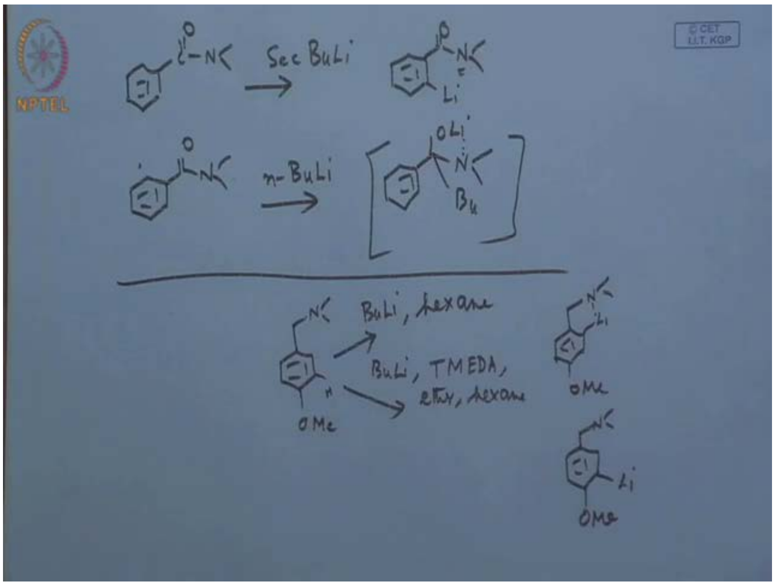

But, if you put let us say sec-butyllithium; that means, you get a different kind of the reactivity, if you compare this one absolutely there is no reaction, so this is what something I mean remarkable. In the sense in the benzene chemistry you will be getting only single product; that means, lithiation takes place here at the ortho position, and there is no positron of these isomeric formation of the isomers that is the beauty of the organolithium compounds.

And that two you see that functional relation can be done ortho 2 n electron with withdrawing substitute aprendly electronic substitute, but what is the requirement, requirement represents of an heteroatom. So, hetro is very important in the aromatic chemistry and lithiation and that will see that in the, then the effect of the heteroatom in heterocyclic chemistry also would be observed, now look at this one butyllithium. So, n-butyllithium, so what do you except, so the reaction that express here is yes, somewhat correct actually, what you will get, you will get this, simply we calls is ((Refer Time: 13:07)) very compare to the undergo that.

But, what will find is stops there, in case of ester you had the over addition, and a state way went to the tertiary alcohol, but in these case this reactions stops here, because of the gain coordination’s. That is these are the properties basically, that is what you have to is very reactive it can be controlled because the coordination’s etcetera, etcetera, and so and also the third point that I has to be noted that organolithiums have tendency to be solvable in organic solvents.

So, at end of course, I think many of you know who is the father of organolithium compounds, you have to know little bit of history also, history Hendry Gilman, but what you people do not know gorge Wittig also was the inventor of organolithium compounds. And there is actually rearrangement call Wittig rearrangement, I do not know either you know or not, rearrangement it is a ((Refer Time: 14:21))arrangements, so that mean gorge Wittig I mean is not only known for his Wittig reactions while, so I known for this is.

And so I think we have sufficiently talked about the background let us look at little difference, actually let us see and there is a trick there are several trick is differences, maybe we can talk about I think, I just give you one example that will. So, from the aromatic chemistry, what will find if you have a sub state differentially functionally subs state, within one case you have a nitrogen, in other case you have a methoxy here, you see there is also diversity in the reactivity pattern.

So, this is basically example of that under very similar condition, but with little difference you can have a different kinds of the reactivity, let us say if you react these with butyllithium. Just when I write butyllithium is basically it meant to be n-butyllithium, and this solvent is very critical that is what this example is about solvent x n. In one other case if you have a let us say butyllithium and TMEDA, many of you know tetramethyl ethylene diamine, ethylene diamine and ether and hexon also little bit and so there is a remarkable difference.

So, what do you except, in the earlier example you have seen that if you have a functional group containing a heteroatom, it can induce ortho lithiation and if the agent is a not bulky one, that it can straight way react with the communal group. So, it has to be tertiary butyl lithium or secondary butyl in most cases ortho lithiations are done with secondary and tertiary.

Now, here is a case that what you see that the conditional difference, I mean the reaction conditions effective reaction conditions that would also let you something about the factors, which actually dictate the positions of the lithiations or the reactivity of the lithiation. Let us say that to, so when I say butyllithium and hexon, what does it mean you have to have a little meaning of it; that means, butyllithium itself structurally like a cube in kind of structure many of you know.

Student: Tetraamine

Tetraamine, that means they have they are suppose to be an aggregates of the 4 units, but when you add TMEDA, actually it breaks up it breaks ((Refer Time: 17:10)) free, so it becomes more basic; that means, it is makes it non-coordinating, this is a system which non-coordinating. That means, it cannot forms relation etcetera all these things; that means, it will be guided by the acidity and basicity, now I think all of us guess which one in these case which one is acidic and which one is basic.

Let us say let us begin with the first one let us say first one what I said is a non-coordinating; that means, if the lithiation takes place alpha to these this one or this one then there is a preference to undergo coordination's Now, if you look this if your lithium here and lithium here which one would be having a better coordination, no, nitrogen or oxygen?

Student: Nitrogen

Nitrogen, obvious so; that means, under the non-coordinating conditions, so the lithiation that to take place is this one, because nitrogen is more basic and these solvent is not undergo in any coordinates so inter molecularly show this is a chance. And the other case; obviously, the other case the coordination there is a diversity, basically what I am trying to say if you just keep on changing trying different solvent system, and what will find in these case and apperendly it is very difficult to say apperendly this is actually due to these acid.

Student: Acid

Acidic, that because oxygen is more negative to it and there is a possibility, and the of course, condensen is there, but these this may not be undergo in coordination's it is primary due to the higher acidity of this hydrogen adjacent to this oxygen could be the driving force. I mean here sometimes these arguments are not really acceptable, but I mean it is an useful working guide line, then acidity, so the means lithiations are dictated by two important thing what is that this acidity and the coordination's. So, these are the two acidity and the coordination's, and there are other examples may be sometimes also you have to talk about the repulsion between the aloins and the lonpears.

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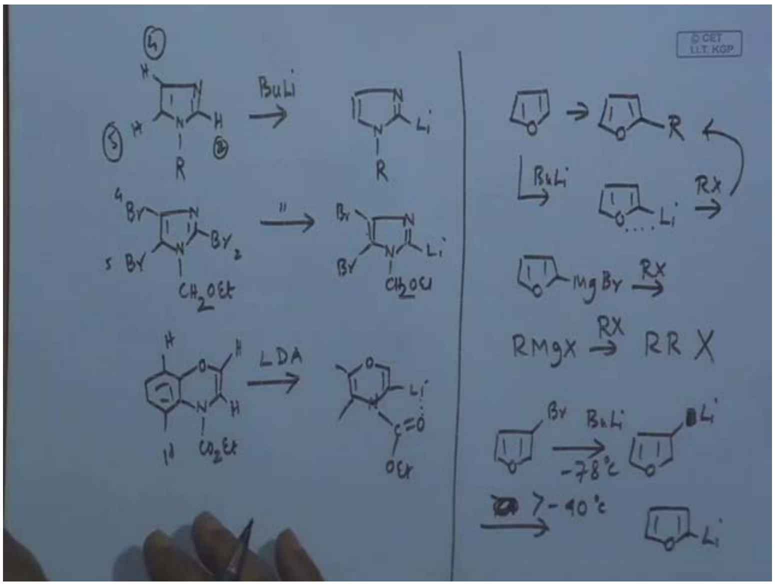

Let us now straight way come to these high member heterocycle, I think I will begin with imidazole is a n protected imidazole and you have lets r, now what you can see you have three different chemical e non-equivalent hydrogen's are there. Now, if you are use butyllithium, what is expected? So, many thing is expected actually, when you any for any reaction your starting point should be the reagent, so you have to first have idea about the reagent, one of the different reactivity profiles of the reagent, that you have to write at. So, as soon as you see butyllithium we can recognize it has two properties acidic properties and nucleophilic properties.

Now, between the we have to choose one of them, so after we go for the acidic properties or basic properties, because that is the first reactions normally proton abstracting reactions are faster reactions. So, that is one of the reason, second; obviously, we have take care that addition to the electrophiles, so these are the things you have to take care and I when you talk about these abstraction of the proton, now we have see different kinds of the proton. So, which one is and how do you know which one is more acidic most acidic, now the three, so I 5 recognize number say this is 1, sorry this is let us say 2 and this is 3 this is 4 and this is 5.

Student: 2

2, what about what is the reason

Student: ((Refer Time: 21:40)) 2 minus

Good, so very simple then so; that means, if electron add and negative atom and it is falked by two nitrogen atom, so it is likely, and in fact, the answer is, yes so; that means, you can quickly actually predict the sight of the lithiation and the lithiation takes place here. Let us look one more example, where you have a different kind of substrate, where you have this is, now you have an well define producting loop C H 2 O E t, now once again the reaction conditions are same butyllithium. So, what we except

Student: ((Refer Time: 22:50)) 4 position

So, that means, again this is 2 and 4 and 5, and what is the reasoning said is 4 position.

Student: Do not have negative charge, because there is bromine.

No that is both adjusting to both bromins nitrogen or pair actually, if you draw nitrogen is there close to each other, once again the actually the reaction takes place one of the two position. So, that means, stability corresponding conjugate base, so I mean although the process is different; that means, the basic guide line is that you have that it is the acidity that would drag the reactions to a specific positions, so this is all these things.

Now, let me give you one more example, let us say one more example, but it is 6 member heterocycles, you have nitrogen of oxygen, Benz oxygen and ester loop here. These case not butyllithiums is LDA, LDA is you have to know little bit about the difference between the butyllithium and LDA, what is the difference.

Student: Bulk LDA respond this.

LDA is bulky.

Student: Non-nucleophilic

Non-nucleophilic, then it can because of this bulkyness actually, nucleophilicity is reduced that we have to remember, and also acidity wise also it is less sorry basicity wise less basic then butyllithium. You can guess because p corresponding an ion is most stable for the LDA, now what do you except out here, so LDA; that means, not nucleophilic; that means, not reacted it will not react with the carbamet carboneled.

So, that means, it is it should undergo it should actually promote deprotnation, and that is no halogen in this case deprotnation, there are what you can see so many hydrogen and all this things this hydrogens. I mean if you recall the carbonyl chemistry, in carbonyl chemistry you do not see often a vinyl carbon never, but that is the beauty of the organolithium compound you can produce vinyl carbon.

Now, you have options now adjutant to oxygen and nitrogen and which one is and again the more electronegative atom which one, oxygen that is what yes, but unfortunately the answer is not that. In this case little complication, it is because of the ester group; that means, the lithiation takes place here is nitrogen now ester lithium here this is so at the same time not; that means, what I am trying to say you have to have a composite kind of a factors acidity, chelation all the then reaction conditions all these things are to be taken together then evaluate.

So, what you will get it get the lithiation done here, now come to the real life examples furan this is a very let us say if you want to do a furan chemistry, furan chemistry how to do this furan chemistry. All of us now furan is consider to be aromatic partly it behaves like a dying system, and although participately behaves like more preciously like a phenol reactivity, so good.

So, many of you know the phenol alkylation of phenols are not very standard good reactions, simply because of the condense of the oxygen’s with the alumninum condensation etcetera, etcetera. So, if you want to let us say produce alpha alkylated phenol is tuff let us phenol plus formaldehyde all of us know or the agent required, nothing just mix them, it will form a polymer. Phenol formaldehyde polymer etcetera, if you ask this all these phenol formaldehyde

Student: Bases

Base, acid anything; that means, you do not need any aluminum chloride anything like that, basically alkylation acylation, so then if, so reactive; that means, it is an it is difficult to control. Exactly, in case of furan also although, if you go to the books they will say suggest such things can be done by alkylations of alkylation etcetera. But, rarely people do it the you will said not that good, and the reactive, so high it is difficult to control of an you get the poly alkylated furnace. So, again organolithium is organolithium although its reactive, but you can you can just control the reactivity, you just treat this with butyllithium and you get monolithiated furan.

What is it actually, what will find the lithiation takes place here at the two position, once again this, because of the oxygen that hydrogen is highly acidic, and one can of course, the oscillation is something in one can just extra polite, the oscillation also little bit may be is oxygen lump are can as such stipulations that is a possibility. What next?

Then R x, so you get this product, but think of a reaction for example, I would you except reaction, less reactive then organolithium and most cases in this case I do not know exactly. Most cases if you let us say R M g x, and let us say R x then this sort of reactions are very, very poor reactions, we have told you in the fourth year class, that is the one of the I mean serious drawbacks of with organomagnesium compounds.

And that is the reason why one Japanese scientist has become famous, I mean for all these reactions coupling reactions etcetera, which is Japanese guide kumara coupling. What is kumara coupling? Kumara coupling is something like this, only thing that you have to add just not really iron ((Refer Time: 30:16)), and there are now a days there are plenty of if you just go by another scientist who has also done extensively on this kumara coupling is known as Eiichi Nakamura, E Nakamura.

So, I mean then his students also has been working on that also if you go to the very recent papers in orgalate, they have done something I do not at the moment I cannot recall, but it something this sort of coupling, s p 3 s p 3 coupling. In the presence of iron I do not know recall this, so any case; that means, what I am trying to say organolithiums are useful and in this case you see just mono lithiation only taking place, lithiation takes place only gives a mono lithiated compound, and that can be use for various purpose will give you more examples later on.

Similarly, if you have you just to have to keep also you have to little causes about it for example, if you have now you see separate situation now bromo compound and butyl lithium. No, that two possibilities deprotonation and halogen exchange, now you have to know which one is faster.

Student: Halogen exchanger

Normally, when you talk about these sort of carbon chemistry after we said the such a tiny atom the deprotonation is on the fastest reactions, especially in organic chemistry acid based titration. The fastest possible relation zero activation energy, but when it comes to this deprotonation here, I mean you have a, so many you have actually, so many factors to take care, but deprotonation and helogen exchange equally compete with each other.

Let me what is meant by; that means, I mean the two possibilities could be 50, 50 the deprotonation and these, but from my experience I will tell, if it is bromo one. Then sometime halogenation is much faster, halogenation is if sterically free and if it is a bromine then actually halogen exchanger is faster than the deprotonation especially in heterocyclic chemistry.

So, this will tell you something then sorry this is lithium what next if you this is normally done all of us know this is normally done at minus 78 degree centigrade, if you increase a temperature have up minus 40 degree centigrade, you get another reaction done. What is it, economically more stable product means two lithiated product, so that is what you have to keep it mind; that means, there are possibilities of the rearrangements also after the initial.

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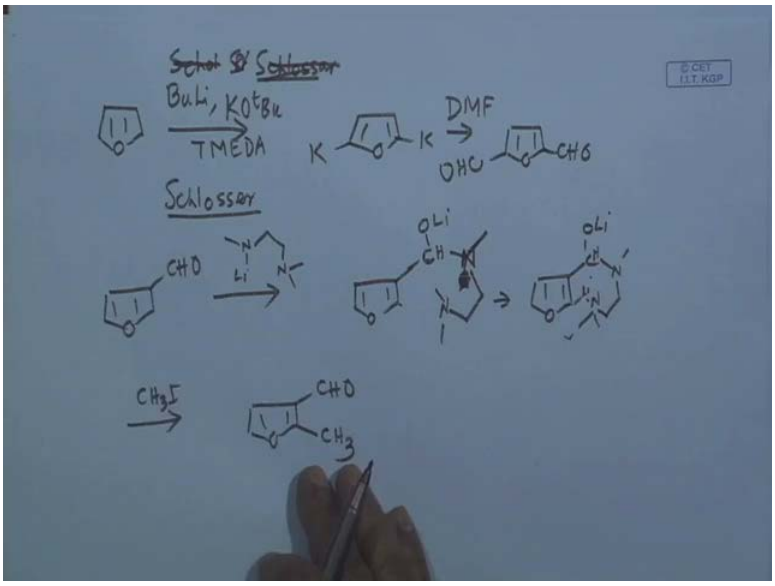

Now, have one more example in these you use process base, I do not know whether you recall or not let us see how much you recall anybody know or remember slow sorry, so schlosser. Something like that I forgot process base I will come to that later, but we are more titration chemistry schlosser base, just check the ((Refer Time: 34:15))and see what is, what else we talked about it in, pyrethrums butoxide that means, it is a sort of aggregate free butyllithium bring is some more to free.

And then also often is in combination with TMEDA, and if you use excess, what will find, you will find a reaction; that means, this is the production sort. So, basically you are getting a dilanyan kind of a thing and; obviously, the corresponding reactions are corresponding reactions. Let us see if you have a excess amount of the DMF, what is the product DMF is nothing but say formulating agent, so what you will get actually 2 C H O 4, why so important.

That is there are very few electrophilic substitution reactions, where you can you know simultaneously introduce two other than nitrogen etcetera, etcetera and harsh condition you can introduce two electron with drawing roofs, so this is how one can look. Then there are reactions also very what do you see here this specifically 2 and 5 positions 3 or 4 are reacted, and similarly let us say if you have say functionalize furen now.

And you tried you can make use of this, functional group may two direct the lithiations either on this left hand side one is 4 position sorry 1 2 3 4 position or 2 position. How, that means, you have to make it in directing groups and temporary you can do it, this is like you can say again a lithium reagent very similar to the EDTA ethylene tetra, any problem, you cannot see, what happened, now good.

So, now you see again a lithiated ligent, so what do you except the expectation is well you have a lithiating agent and so it is sufficiently basic or nucleophilic whichever, but what do you from the resel it has been suggested this nitrogen sorry this is nitrogen. And then you have two carbon, then I again nitrogen here this methyl group and this is a methyl group. So, the it undergoes nucleophilic addition, this is like if you take morpholine aniline nitrogen aniline that also undergoes addition to the carbonate group, so it forms these sort of a terminal oxygen nitrogen compound or intermediate, what next.

So, with this presence of this nitrogen ligent here, the lithiation either can takes place on this side or on this side and all of us know the this hydrogen the two position hydrogen are two position is more acidic and the lithiation would take place and nicely undergoes coordination’s. So, the reagent; that means, the lithiation that would be the result is again C H nitrogen and then two nitrogen these and so you have now a sort of a intramolecularly coordinated or you can say acylated sort of lithium and acylated lithium.

And a then if you trap this with methyl iodide the reaction that will be getting is the methylated product and the early head, so that is it; that means, in C 2 you are producing a directing group and during the workup the reaction this directing group is being knocked off from the system. Let me you do not really in actually you are doing use of other making use of the protecting groups instead is a temporary sort of a producting group in the whole operation from this aldehyde to this one is a single step reaction. That likewise the other examples may be the time permits will come, let us say similar reactions are known in the literature will I with comeback little examples.

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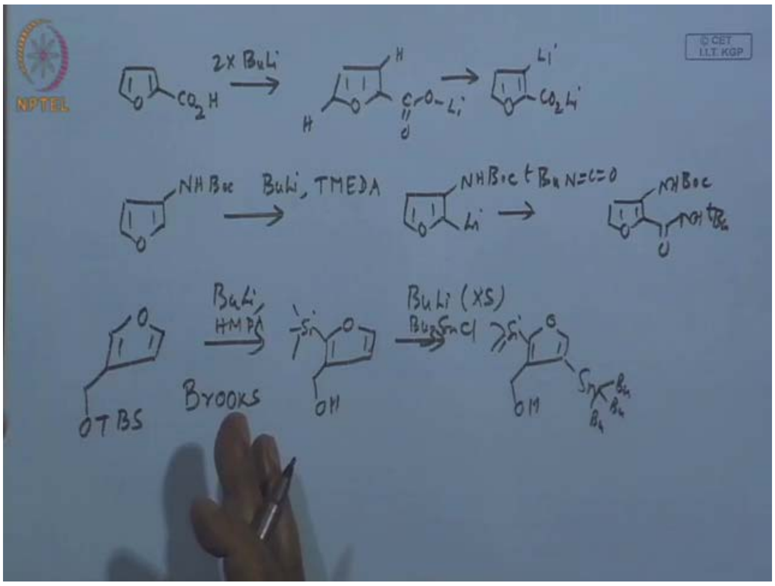

Then another directing groups in case of the furan for example, is a carboxylic acid and this is also true for other systems carboxylic acid let us say, this is a case now is a butyl lithium it will be a butyllithium, add butyllithium of course, minimum two equivalence. Now, you have all kinds of possibilities butyllithium can nucleophilically attacked the carboxyl group it can deprotonate this hydrogen and so many things can happen, but with few examples you know you can just make a guess.

For example, if you recall conversion of carboxylic acid to the methyl ketone is done by methyl lithium, when it comes to butyllithium nobody talks about it why; that means, the butyllithium is sufficiently sterically hindered to or hindered to undergone nucleophilic addition to the corresponding carboxylic salt. So, if you knows that then you can predict what is going to happen, so then the first thing that to happened is that the carboxylic, that mean this one would be sufficiently stable it would not react with butyllithium; that means, butyllithium will not undergo any addition to this carboxylic group.

Now, there is a question which hydrogen would be deprotonated, there is a hydrogen alpha to this oxygen and there is this one, and then 1 2 3, so 3, why? Chelation effect that means, these are the thing actually, so how do I know, the chelation effect, we know early acidity effect how do I know? Your answer is correct.

You just the clue the key word is that carboxylic acid in heterocyclic chemistry is a directing group, if you remember this then you should be able to safely predict the location of the lithiation. Carboxylic acid group many, many cases are the nice directly goes, even in aromatic chemistry also so; obviously, the next step would be this lithiation here and the carboxylic acid. And the, so we have given you let me let us similarly if you just taken example, very similar example kind of thing, so you have N H and Boc now the conditions again butyllithium, TMEDA, so what do you expect; that means, when I say what is the expectation may you have to find out the position 2 or 3 which one?

So, the means once again N H is more powerful actually, N H amide amides are more powerful directly in groups, actually there is a ((Refer Time: 42:54)), if you are interested there is a nice order of they have presented all these directing groups in nice orders. Then from there you can find out which one is more strongly directing, which are moderate directly, weakly directing, all these things, so see in some time we called anionic aromatic chemistry some time orthometallation some time and if there are different names.

So, you can actually form there are you can predict, which one is strongest possible directing ((Refer Time: 43:28)), and then amide apparently electron withdrawing, but yet more adhered stronger directing group then the corresponding methoxy groups. And the, so in this case amide group and the product; obviously, it is a product is now is direct lithiation; that means, the N H directing lithiation not the acidity of this.

And in this example what been done it has been reacted with an isocyanide it will isocyanide tertiary butyl isocyanide because is pretty reactive. It is an also it can give the corresponding amide and most of the this sort of amides, many of you know they are used as agrochemicals. Let me, so what you see here in most cases we have been basically functionalizes the furan, at the two position, if it is in the two position, then it is three position.

Now, this is an example of air and you can do a lithiation in three position, the next example see here is a furan, now OTBS butyl lithium and HMPA hexa methyl phosphor amide, what is expected out of it. Again you see there are basically a three different positions, which are equally probable, these 2 4 and 5, two important factor chelation factor and the acidity factor. If it is a strongly directing group; obviously, like amide amide is a strongly directing group, so we can just the middle one we can without any fail we can write the two lithiation, but in these case whether it is in acidity driven reactions or the chelation driven reactions.

It is the acidity driven relations as well as thermodynamic kind of acidity; that means, both acidity and chelation how is that, if both acidity and chelation then which one is the position, two position, but what will find here the reaction gives you this is O H and here is the silicon. That means, what is the name of the reaction on indole, you say name reaction other, I thought all of you know rehide, Brooks not Brook, Brooks, here what is it Brooks I mean basically transfer of silicon from oxygen to levering carbon.

No, carbon it has to be the end; that means, thermodynamically more stable, now what next if you again you use excess butyl lithium, and butyl tin chloride, now you can what would be the reaction, the lithiation would take place at there is no other option.

Student: 3 position

3 position that is it; that means, you can direct the lithiations in at your depending on the situation; that means, silicon can be removed very easily from this, and so eventually and let us say the next; that means, the product what will be getting is the silicon here the C H 2 here, and tin here. So, we will have all kinds of; that means, functionalizations and side by the side by the way, so 1 2 3; that means, in aromatic chemistry you know if you want to prepare a 1 2 3substituted aromatics is quite difficult.

So, these are the all the difficult problems can be solved by this lithiation chemistry and let us look at an example and little exercise on the heterocyclic chemistry this is a weak structure, here you do not have to worry about the structures just look at the features of the structural feature here.

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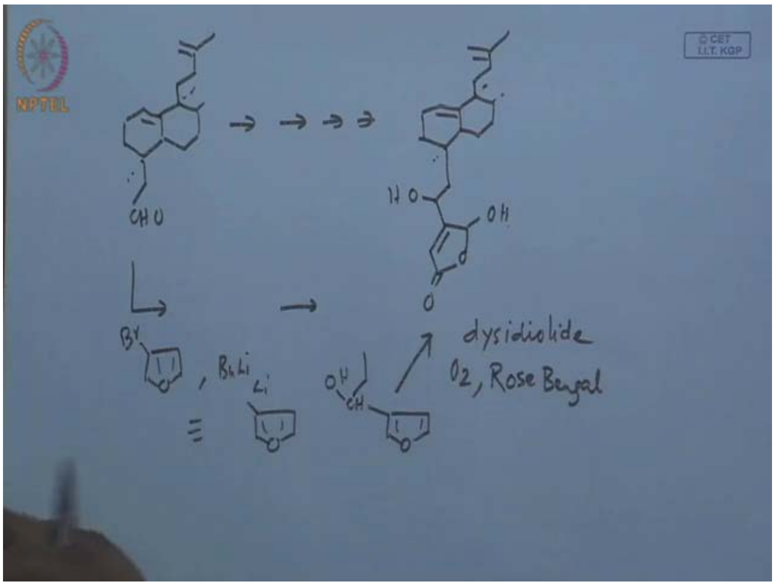

So, what are the features basically you look at, so if you are to convert these into these this is very similar molecule may or may not write this structure, but only this look at the concentrate on the features. What we will have what is the features is a bicyclic compound you have an isolated olefin, and also you have an endocyclic olefin, this hydrogen these are the all these methyl groups here and there.

So; that means, this and the important structural features here is now we will see a kind of a lactone that is it, so what you do; that means, you have to fill in the blanks, the blank is basically blank is say two steps say you do one step here, and one more step it will give state way this product. So, you have to identify the missing reagents from this; that means, you can; that means, you have to compare the starting metal and the product, if you look at; that means, you have to have a 4 carbon symptom that is it what else 4 carbon symptom means.

Student: 4 carbon symptom.

So, 4 carbon symptom means very obvious choice is,

What? Succinic acid, any other 4 carbon dimethyl maleate, any other I mean; that means, the synthesis itself is very tough unless then you have to you know little bit of this organic chemistry. For example, actual I will give you the answer, that it begin with this one furan you have been talking about this then bromofuran, butyllithium i think, now you know what is going to happen.

Actually, this is equivalent to 3 lithiofuran, I think if you are not well works with the furan chemistry, you will see most of the natural products, most of the this is also a natural product named as dysidiolide, olide means all of us know, means say macrolytes actually goes to this. So, most of the natural products containing furan molecules are three substituted, most of that there is an obvious reason of course, if you look at the isoprenoids, and if you functionalize convert this isoprenoids into corresponding furan automatically the substituent’s becomes a 3 substituent’s.

So, that is a separate issue, but any case and 3 substituted furans are in literature also is very expansive, furoic acid to they are all very if you want to make a 3 furoic acid, it is not that easy thought you have studied in B.Sc, what is that who knows, 3 furoic acids how do you make ((Refer Time: 52:25)) in organic synthesis. No, then we see you have to make 3 bromo, how do you get 3 bromo, very expensive only it is available in the ((Refer Time: 52:40)). So, expensive it is starts from furan it is furan plus dimethyl acetylene dead, acetylene dicarboxylic acid reaction, I think some of you know remember.

Then partial hydrogenation the reactions that is not all, you can 3 4 dicarboxylic ester, you have to reduce the sorry hydrolyze it, then if you heat it selectively one of them would go of see this. That means, you have so many steps such a small molecule has to be made by a multistep sequence, so it is quite expense very case, but if you do so what will find the product that would be forming here, this is C H of course, this is just like typical kind of this reactions, so what will is this one. That is it, what next, one step you will get some mixture, but this one step you will get this product I have thought this what is this?

Triplet oxygen is sensitive, plenty of oxygen nothing is happening we are all organic molecules, they are all organic molecules this thing that thing everything organic molecule nothing is happening. You have to have a photosensitizer, and what is the photosensitizer good at least you know, now Rose Bengal, because it is acetated with Bengal. So, you must know this it is a fluorescein dye, and the reaction is very I mean if it works is nice, I will I think let us I think I will skip one of the examples, rather I will give you a puzzle, for the next class and see whether you can you try at home.

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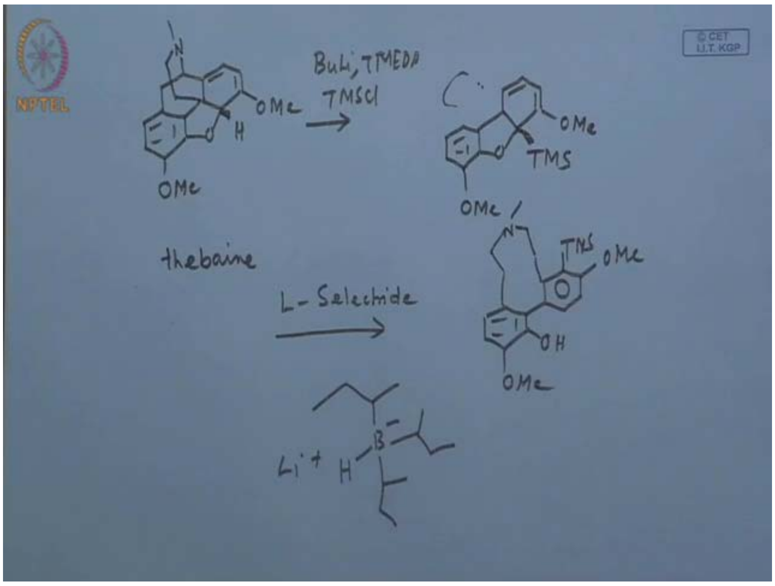

If you fell I will give you the answer later and so this is a kind of a molecule looking like morphine, you know morphine is a basically phenolphthalein system, and you have a furan ring, then aromatic ring system here, methoxy. And then and two carbon, this and you have to know this name this is very famous name, in morphine chemistry.

No, is indole, this is a morphic, morphic means as it can be viewed as a benzene, it can be viewed as a viewed as a isoquinoline, so I mean actually morphin biosynthetically is produced from.

Student: ((refer time: 56:17)).

((Refer Time: 56:19)) this is thebaine, if you now do this again our the lithiation chemistry, butyl lithium TMEDA and TMS chloride, which position would be lithiated. So, I will not write the full structure, I will write only this structure, where the lithiation would takes place and so you have a methoxy of here you see there is no aromatic nucleus and you have a methoxy of here methoxy is well known ortho directing group in the metallation lithiation reaction. So, lithiation can takes place here, lithiation can takes place here, so all these one then also you have a benzylic position here actually lithiation takes place here.

So, you have the TMS is proved rest is same rest is nothing, I mean no change just basically this hydrogen this indicated hydrogen is now substituted by this. This is a is quite difficult one, I mean I would have expected a lithiation here, ortho to the methoxy or this one by the again you see here abstraction of the proton deprotonation is taking place. It is a sort of a benzylic position or ortho to the oxygen, but what next this is l-selectride, you must know, what it is, l-selectride would give you a rearrange product, I will write the rearrange product, you try to figure out the mechanism.

In the next class you try to figure out the mechanism, this OMe just TMS, these then this re expanded product and OMe, you figure out the reaction and l-selectride, anybody knows. Say selective reducing agent the name tells you, and l stands for lithium and any all the selectrides are boron hydrides, and that mean I mean is it remember that you just take trialkil borane and lithium hydrate together that is basically the lithium.

In this case it is the secondary butyl; that means, three of them, and then as I said lithium hydride; that means, hydrogen minus lithium plus, why it is l-selectride, because it selectively reduce the carbon-carbon double bond, like system you want to reduce the carbon-carbon double bond then this is the reagent.