Heterocyclic Chemistry
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Lecture - 23
[4+2] Cycloaddition in heterocyclic chemistry

Good morning so, today's I think topic is 4 plus 2 Cycloaddition.

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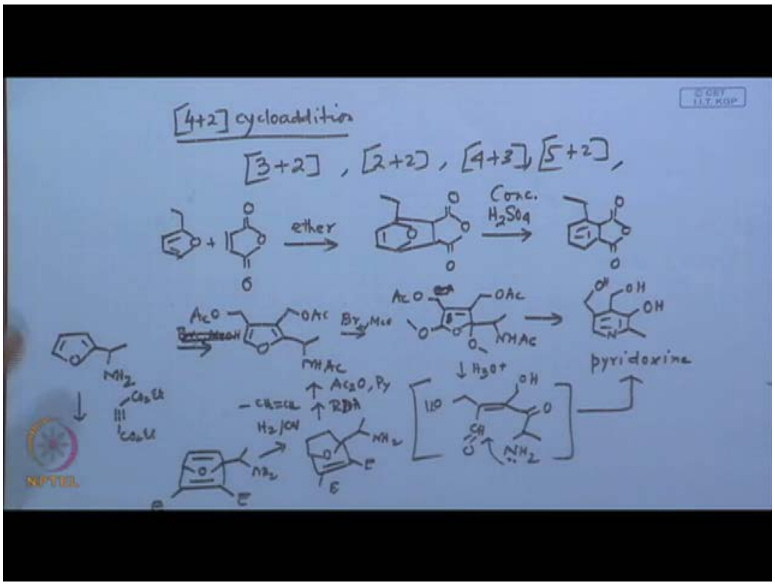

All of you have studied, this is a very powerful technique in organic chemistry especially, when you are planning to construct a six member ring system. Six member ring system, this is one of the most powerful reactions simply because, it is versatile and you can have all kinds of these dynes and dynofiles. The reaction is so useful, you can have ((Refer Time: 00:58)) fixed, you can also make acyclic compound means, you make a cyclic compound first then, you click the cyclic compound, you can get an acyclic compound with stereo define double bonds.

So, then of course, you can extend these by, what are their possible extensions, possible extension could be that, you can also do the reverse Diels Alder reactions. If a reactions you do some synthetic manipulation, you can a reverse Diels Alder reactions that means, additional reaction that is known as order louder.

No, if you have a combination of Diels Alder reactions and the reverse Diels Alder reactions that is known as Alder and recart reaction, we will come to that. So that means, these are all the different ways of looking at the same reactions and when you say Diels Alder reaction means, 4 plus 2 cycloaddition reaction, all of you know 4 signifies what, number of pi electrons or number atoms or what, both.

But, primarily actually, the number of atoms, if you go to the Young Fleming's books, he says both but normally, when you say in as you go on, we will see the actually it refers to now, only number of atoms participating in a reactions. For example, there is a class of reactions are, we will also talk about in the next class that is called 3 plus 2 cycloadditon reaction.

So, we have 4 plus 2 is one of them then, there is a class called 3 plus 2, also there is a class called 2 plus 2 and then, there is you know all kinds of 4 plus 3 then, 5 plus 2. So, if you see the number then, there are other higher order cycloaddition reactions known as higher order cycloaddition reactions. Now, what you see here then, when you say 3 plus 2 then, how many electrons are participating?

Student: Four.

Not really I mean, 4 and 2 so, it is essentially actually 4 plus 2 so that means, actually here, 3 actually refers to the number of the atoms. So, we will all talk about it but, when it comes Diels Alder reactions or 4 plus 2 cycloaddition reactions, what is the problem and what is the usefulness. First of all, as I said that, in the Diels Alder reaction I think probably, the most versatile reaction in organic chemistry I mean, we would not see any other reactions actually is so versatile and useful, I should say versatile and useful.

You can have all kinds of the variations in the dyne part, all kinds of variation in the dynofile part. You know, the dyne could be built it to a cyclic system, it could be a I mean, all acyclic then, polycyclic all kinds of things also, the Diels Alder reaction can be inversed electronically. Many of you know that, inverse electron demand Diels Alder reactions, the traditional concept that dyne should be electron ((Refer Time: 04:24)) and the dynofile should be electron deficient is no longer.

Really I mean, rather acceptable, it could be the otherwise, the dyne could be electro deficient and the dynofile could be this. So, you have all kinds that means, a flexibility but, you have to know where to start from and what are the difficulties that means, those who will be doing the calculation and DFT all these things, they will find the LUMO and HOMO. And all these things what eventually, it comes down to the working out the whole thing in the lab so, nobody knows actually what is happen.

So, how do you know, how do you extrapolate that means, you have to have a starting point, this reaction takes place so, we can go on to the next. So, again by using the organic chemistry knowledge, electron donors and ((Refer Time: 05:12)) all these things. And then also, you have to look at these reactions in terms of the reaction conditions, there will be verities of reaction conditions actually, called the Diels Alder reactions. What is the reaction conditions, the way you do the reaction, how do you do, just mixing up is not enough many times, you have to do all kinds of the variation, that way the reaction is pretty versatile. What are the reaction other than mixing, the two reagents?

Student: ((Refer Time: 05:39))

Leukocyte.

Student: ((Refer Time: 05:42))

((Refer Time: 05:43)) no, heat that is sort somewhat like mixing high heat high temperature means, seal tube, anything else?

Student: ((Refer Time: 05:53))

Photochemical, how can you say so because, you have been learning all cyclic reactions, and the Woodward Hoffmann rules, all these things. And finally, it should be photochemical reaction, no that is not acceptable. So, likewise another then, there is a also reaction called high pressure Diels Alder reaction, see high pressure, we will have an example one or two examples actually. I think all of you understand the name of the building where, I stay that is a high pressure building, actually the ((Refer Time: 06:22)) the person who works there actually, he work for a person call W. Noble or somebody, he did high pressure Diels Alder reaction.

And theoretically, you all understand the two molecules are combining to a simple, there is activation wall, volume is decreasing when you go from this starting metal to the product. So obviously, then, if you have a high pressure then, that would assist the reaction. So, all these things are that means, is a very versatile very flexible I mean, you can do all kinds of manipulations. Then, the last extension of Diels Alder reaction, extrapolation or extension whatever you say, is putting the hetero atoms in the backbone of the dyne or dynofile.

You just put one hetero atom, who is hetero atom nitrogen, sulphur, oxygen, all these things can be done but then, there is a problem. What is the problem, that you have to know for example, butadiene is constant available, is a gas, it is used in industry and what else and isoprene is a liquid so, that is a predict stable. But, when you have an as a isoprene is unstable, is very difficult to make, absolutely difficult to make. So, you have to go to the heterocyclic chemistry and all of you know that, furan is a dyne so, furan is a dyne.

So, let us say, let us begin with the examples what we recently did in our lab and this is the reaction, we just simply mix them and just allow to sit in room temperature and ether solvent. So, all of you know what is the product, the way I have drawn, it would the furan, oxygen and dyne and the maleic anhydride. So, and the product, that one can quickly write, I will write the linear form and all of us know that, it is in endo exclusively and so, what we will get, we will get the cyclic compound.

This is all known then, what to learn from here, that is a dyne which is comfortable with maleic anhydride. That means, it carbon carbon double bond that you have to note and maleic anhydride is one of the finest and most reactive dynes, dynofiles rather. If you just substitute with ester that is, less reactive and then of course, we wanted to have this corresponding anhydride ethyl substituted phthalic anhydride, this was done very recently in our lab so, how to do it.

So, here to here, if you just again do a calculation, there is actually there is no change in the oxidation number. If you look at this, this portion right hand portion is same, this portion the benzene ring constitute oxidation level 4 and here also, you have this 2 cycle 2, 1 double bond, 1 hetero atom and 2 cycles, 1 double bond, 1 hetero atom, what else 1. So, should it be all right any case, you can just we can do that but, what we did, we just basically you do not require any oxidizing agent or reducing agent, just simply acid.

But, you have to mind it, what acid in these case you have to use, concentrated acid and that would give you the corresponding dehydration product, etcetera so, the isoprene reaction. Now, let us say, use this similar kind of chemistry but, in the preparation of let us say, vitamin B 6. Vitamin B 6 what is it, I think many of you know, I think we all included in this 4 th year class, you say pyridine derivative. What is other thing you have to note about this vitamin B 6, you say you have lot of OH groups here, there are 2 OH groups, this is pyridoxine.

This is called pyridoxine and what else, this striking feature, that you have to remember, what is the striking feature of vitamin B 6, it is a pyridine derivative. Now, actually 3 hydroxyl pyridine, how do you make 3 hydroxyl pyridine, tough so then, it is substituted and as we can see here I mean, all the substitutions are contiguously pressed 1 2 3 4, all these things. So, such a system is difficult to make obviously, the choice is what are the I mean, other than something like typical electrophilic and nucleophilic substitution reactions.

If you have a right starting metal, you can go to the product or else, you have to divide a new synthesis. How do you do pyridine synthesis for example, how do you do a pyridine synthesis, we will talk but, I think this semester, I not be able to talk about the ring constructions of the heterocycles. If you continue means, I am talking about so, we will talk about the actually these ring constructions, pyrrole, pyridine and few systems. How do you let us say, in general, how do you synthesize a pyridine nucleus other than starting from a pyridine.

So, how much do you recall from you B.Sc class pyridine.

Student: ((Refer Time: 12:50))

Hund’s, no by knowing the name is not enough so, you have to talk in terms the bonds and the mode of reactions.

Student: ((Refer Time: 13:00))

Hund's, yes hund’s pyridine synthesis perfectly all right, we will come to that though very briefly, I will just tell you. Basic, an essential reaction in pyridine synthesis is reactions of an amine with a carbonyl compound, it could be an carboxylic acid, it could be an ester, it could be a xyno then, amine. As if amine is nucleophile and one of these carbonyl groups from the different functional groups, could be the accept other electrophile.

So, this is the essential mode of forming a pyridine that means, like if we can make for example, if we can make sort of furan kind of molecule here and is acetate and is again acetate here and OMe, this is OMe and this is NH and acetate. So, what is it tell you, if you hydrolyze it in presence of acid what you expect, you expect a molecule of this kind, this is OHC, this is OHC and this is now, aldehyde and the this middle one would be ketone and then, you have methyl group and this is NH.

So, this is how amine, this is hypothetical one that means, basically what you do is an hydrolysis then, if you count the number 1 2 3 4 5 6 so, what is the essential key step, essential key steps amine is reacting with an electron deficient carbon of carbonyl groups. In fact, this reaction takes place to give this pyridoxine in one step but then, if you look at this one and we know the basic thing.

So, if you take acetate here and I think all of you understand, what is the basic requirement here NH AC and the methyl. So, you have to functionalize the two and the five position so, to giving this small molecule and how to do it, I think all of us know.

Student: ((Refer Time: 15:54))

What is that, bromine and methanol, typical bromine and methanol reactions show oxidative adds to this one so, all this here, bromine and methanol. Now, how to make this, this is what that means, this is a way of making actually functionalized furan. How to make a very functionalized furan, typical we are not going for the by the typical way of doing it. I think, some of you have studied in 4 th year, I gave an example I do not whether you recall or not, this is also thought in B.Sc furan 3 for dicarboxylic acids.

How do you make furan 3 for dicarboxylic acids, starting from furan and what else?

Student: Diethyl…

Diethyl…

Student: Dicarboxylic…

Diethyl Dicarboxylic acid, no acetylene dicarboxylic so, acetylene that is what you have to do that means, so very similar to that what you have to do, you take the furan and then, here this amine is well known. And if you react this with, we call sometime dead diethyl acetylene dicarboxylic acid, what does it tell you, it tells you that this… So, if you do so, what do you expect, you expect I will write linearly so, you will expect a reaction so, I will write E as the ester and so, that is this amine and this, the double bond.

Then, what but, see you have to actually see many things here, what you learnt from here, that acetylene is an important one acetylene is an important reactive partner. Furan cycloaddition reaction is restricted to either highly electrophilic dynofile or acetylene, you will see there are some limitations, is not that very versatile we will case out. So, either furan has to be very reactive or the dynofile has to be very reactive, that is it.

So, acetylene is comfortable, one could have let us say, diethyl maleate or diethyl fumarate, etcetera but, it is not taken here. And next thing that you have know that, amine could have reacted with the ester to form corresponding amide, that is not being formed simply because, just these are all things you have to have experience. Because, HOMO, LUMO things would not tell you, which one would react faster which one reacts slower.

But, from experience, you can make out that, the reaction between the amine and the ester is much slower, require very high temperature, somewhat lot temperature this Diels Alder could be done and then of course, you have other things like acid, etcetera. The next step, I think all of you know repetitions, if you have this hydrogen and catalyst, only one of the double bond would be… And the one that is, in hydrogenation case, the one that is actually more expose to the catalyst so that means, this one would be reduced.

So, and the rest remain, as it is NH 2 and then of course, you do a retro Diels Alder reaction that loses this ethylene. And then, you do this acetylation then, what is the standard protocol, acetic anhydride and pyridine but now, we use something else. So that means, this example tells you what, that furan can be reactive provided the acetylation is triple bonded one.

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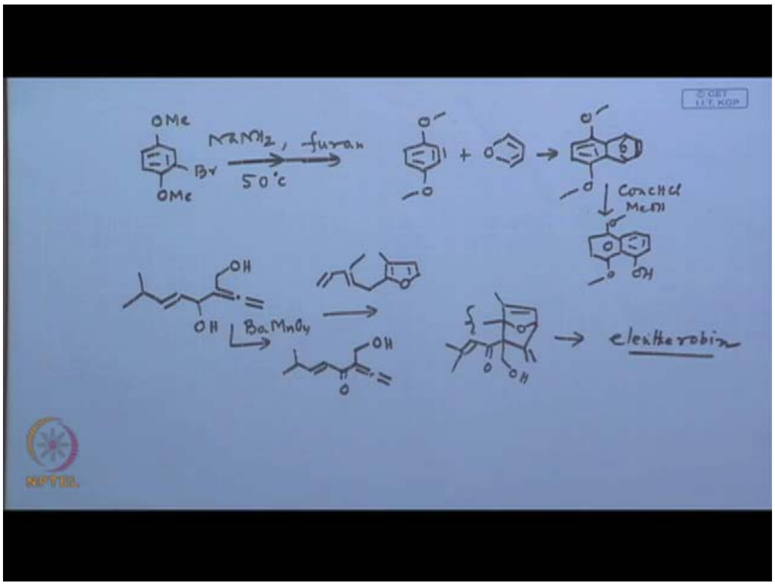

And then, but there are cases for example, very quickly let us say, like this is a case, here also you will see that, it can also typical benzene all of us know, benzene also is a reactive even more reactive than a ordinary triple bond. So, if we can produce a benzyne normal is, there are many ways but, the conventional one is sodamite and little bit of temperature at high temperature. Then, actually the reaction is done together actually in one step I should say, sodamite actually is one step reaction, all of you know.

So, what is the product I think all of us can write, the product is a cycloaddition reaction, cycloaddition reactions is first forms the triple bonded OMe and then, this furan reacts. Now, you see the furan can be comfortable with this alkyne, that is it nothing else, is a triple bonded one. And now, you get a bicyclic compound say, bicyclic compound and this sort of molecule has been in literature for I mean, for long time but, people have began to use this. Because, normally this oxygenated naphthalenes are difficult to make by routine procedures and then, you do all sorts of reactions let us say, in this case, this concentrated HCL and methanol gives you the aromatized one, aromatized product.

And basically, one naphthole is produced mind it, these are all things you have to just know, when you write a reaction you have take note of the others selectivity. For example, concentrated hydrochloric acid, methanol condition the OMe groups is not lost, you know does not undergo demethylation, which often seen elsewhere. Now, what else after alkyl so, see first was the simplest alkene that is, maleic anhydride, second was alkyne, third is a special kind of alkyne then, what next you can think of, furan is common because, it belongs to the heterocyclic chemistry so, you will have a furan.

Now, what we will try to see the selectivity for example, you have a regular dyne then, there is no conjugation that means, CH 2 and then, you have a furan now, this is substituted furan so, this. So, this is that means, you have two dyne component, furan is a dyne component and the isoprene is a dyne component, between these two which one is more reactive, that is what you have to see. This example I am writing here, will also tell you is a special kind of dynofile, after alkyne one can think of, I think those who know that alkynes will have very similar chemical property with alenes.

And if you react this with very uncommon reagent actually, this is known as barium manganate. What is the use, barium manganate is a selective oxidizing agent normally, it oxidizes the benzyl allylic alcohols. But, in these case, you have two allylic alcohols and one is the secondary, one is the primary, which could be oxidized, that is it nothing else. So, you say that means, other than barium manganate or else, do you know for active MnO 2 so that means, there are not many selective oxidizing agent for allylic oxidation. But, barium manganate is very useful one, I have used and this is easy to prepare also, we can prepare in grams and grams.

So now, the next answer, what is the next answer that, which one would be reactive so that means, this example tells you that, allylic ketones also is comfortable. And in these case, the reaction takes place with the furan part and then, I will not write the rest of the things as it is. So, what we will see, this is double bond and then, you have this OH and this is a ketone part and then, this is the other dyne part, that the dyne part this is the regular.

This sort of reactions has been utilised in the synthesis of a natural products called eleutherobin something like that so that means, the reactions are useful provided you know the actually, how to use it and you have to take the risk, what else. How do you extent this sort of reactions, we have seen the reaction where, the furan is less active than compare to the other dynes. But, if you have activated dynofile, that can be done then, again you have a inbuilt dyne where, you have acyclic dyne and cyclic dyne but, you see that furan is more reactive. Now, what else can you do with this sort of cycloaddition reaction.

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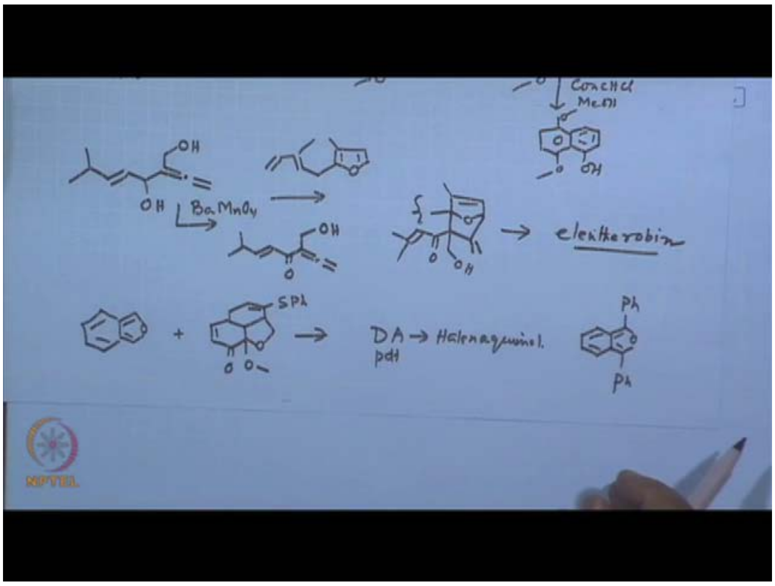

Let us say, you have a very unreactive dynofile probably, many of you do not know that this cyclohexene is not a very good dynofile, as far as the Diels Alder is concerned. And so, I write here a little complex molecule and this was met in connection with a photosynthesis, you just write all these things but essentially, what you see is a cyclohexenone, as I said before is not very good one. For example, if you try to react with cyclohexenone and isoprene, the reaction does not go very well.

So, you have to use all kinds of acids and research all these things but, things are not very good, one of the reasons that, the cyclohexenone polymerizes. But, if you try to do say do the Diels Alder reaction is furan so, what is a prediction. So, let us say, if you have a sort of a furan molecule so, should they or should it react with this dynofile. Then, you have to active furan ring, how do you do activate, how do you activate furan ring. Make it like, how do you activate alkyne, make it strand means, I put it in benzyne form then, it becomes more active.

Similarly, how do you make furan part very active?

Student: ((Refer Time: 28:26))

That is one of the reason, yes it is possible electron reading that is traditional one, the other way is to look at this, just make a systems which is little strand uncommon, this benzo iso furan. And obviously, from the electron density see after the reaction, the double bond would be insided into the benzene ring and you will get, this is actually less aromatic than the corresponding benzo iso furan. And by the way, so obviously because, I will not write, you get the Diels Alder product and this has been taken to one natural products called halena or halena quinol.

And probably, in this connection, let me tell you something I think, this is commercially some probably, I recall the molecule now, with this 1 3 di phenyl benzo iso furan is probably is commercially available in all these catalog. And it has some utility in biochemical system, what is the possible use, possible use is actually is singlet oxygen scavenger. Whether if you are carrying out the reaction and you have to let us say, possibility in that, the reaction is proceeding through singlet oxygen, you just trap it.

That means, singlet oxygen under goes Diels Alder reaction in this so, it can naturally trapped as end peroxides. So, that is it that means, either you can activate furan or you can activate this but, mind it, furans are not very good intermolecularly for alkalinic double bonds or alkalinic dynofile. One of the say very nice synthesis though, actually when we are graduate students we studied this, I will tell you something, this is a very simple molecule apparently, very simple molecule and name is cantharidin.

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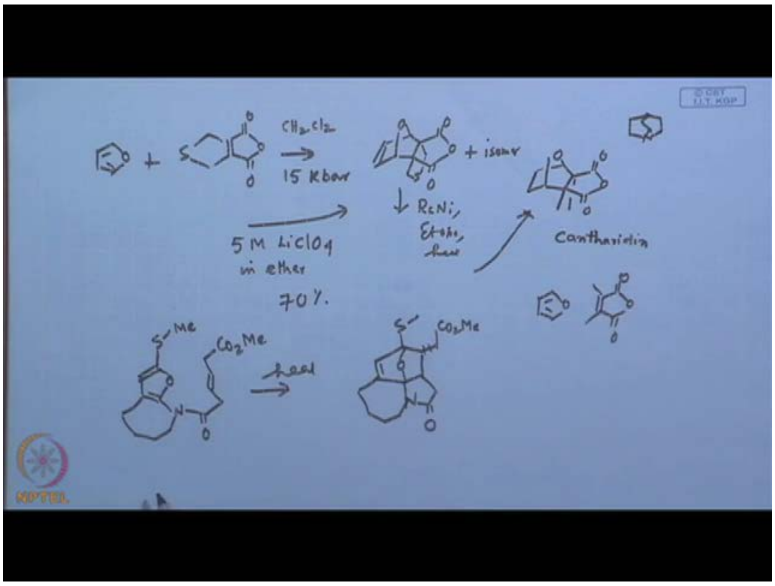

The structure is looks very simple, that is it then, this is a natural product obtain from beetles, I think all of you know what it is?

Student: ((Refer Time: 31:21))

In any insect [FL] have you seen it.

Student: Picture.

A picture but, I have seen it actually ((Refer Time: 31:35)) plenty of them so, there is natural occurring but, interestingly, is useful too, it is known as blistering agent. You know what could be the use of this blistering agent suppose, you have an solid tumor benign tumor, how to I mean, one of the way is to operation, you just to remove it, just do the surgery and remove it. Other way is to inject with the blistering agent so, it will form a blister and then, automatically slowly disappear, this is one of this potential candidate for the as blistering agent.

Someone says, it is being used but, yesterday I look at the Google I did not see but, it says that, it has a property to create blistering, a blisters. Any case, for us is synthesis, how do I do, very simple apprehended looks that, this could be done from this furan. And in this case, this dimethyl maleic anhydride, believe me the reaction does not work and this reaction was tried by my grandfather, you understand my PG advisers professors, W.G. Doven at Washington university.

The reaction does not but, in 1980, he reported the reaction to be successful so, what can he do, what could be the major I mean, region why the reaction felt. Actually, dynofile is weaker somewhat, because of the electron density is reduced, because of the methyl groups that is, number 1. Number 2, I think in the transitional steric effect, steric effect probably so, what he did , he just made a small twist in the requirement. So, like you have studied before, if you just join the two tails and put it in a cycle that becomes less sterical hinder.

Remember this debko and this triethyl amine, which one is more basic and which was less basic, should I write or not.

Student: ((Refer Time: 34:24))

Debko are corresponding as a like bicyclic compound I think this one is, this is not really debko though.

Student: ((Refer Time: 34:34))

So, simply because, if you are that means, this is now tighten on the one end so, it is more basic so, exactly that is what we did, put these two methyl groups. And but, you all known though that, this sulphur can be very easily removed just using renae nickel. So then obviously, the reaction was done and we will see solvent is methylene chloride and pressure is 15 kilo bar what does it mean, 15000 bar.

How danger acetenes, we had high pressure technology, when I joined in 1987 I asked the teacher who is to work and what is the pressure here, any guess what could have been the pressure, how do you increase the air pressure, you have to booster compressor. So, the compressor is to work but, you have to again you have to repressure gauge and pressure gauge is to record not ((Refer Time: 35:59)) was, I have to do the little calculations definitely, less than 1 kilo bar.

So, it is 15 kilo bar probably, you have not seen in the lab, I happen to see the lab in US in my university and that would be lab was basically, like any other lab but, the roof was made of a glass. So, reactor was there so, if anything happens actually, it go to the top so, that was the lab but, nobody has done. I mean, in my time tell you, nobody has done this experiment but, here also the case is but, he had the vented to do that, 15 kilowatt pressure and the reaction was successful.

And as you can expect but, there is a little problem, it was not endoselective, it was actually exo selective and this was the measure product. Then of course, this other one was the isomer so, other isomer endoisomer and now what, renae nickel and other solvent is ethyl acetate and of course, little heat and you get to this product. So, essentially, what you do, just two reaction and one jacks paper say, by just doing two reactions I am getting a jacks paper is tough.

And so, now, you can see the imagination part, experience, everything facility, all these things, this was published in 1980. 10 years after, there is one scientist called Paul Greco, student of Gilbert Stork, he made a quick, he made a trick without going through a pressure, he could do the same reaction and exactly same ratio, the yield was also fairly good say, 70 percent. And what is it, any idea no normal pressure, room temperature.

Student: ((Refer Time: 38:27))

Again a jacks paper, yes we search it, what we search it?

Student: ((Refer Time: 38:31))

No, that is what in PET, the acid is 5 molar lithium per chlorate in ether, that is it and the lithium per chlorate is available quarshy available, is obtain from ((Refer Time: 38:53)). So, you do this, I just substitute this, the reaction goes to same product same ratio I mean, same products and same ratio, the yield is fantastic. Let us continue with little more like, one more reaction probably, this would tell you something additional, this is the reactions I am writing now, it is an inter molecular version.

Once again say, seven member ring, carbonyl up here then, double bond, methyl group and is sulphur and methyl up here, heat it, what you get say, seven member ring. And then, you get a six member ring, double bond, this furan, SMe and then, acetate unit that and this then, you have this nitrogen up here so, you have this. Then, you can go on, all of you can understand basically, what we are looking for, we looking for a dyne and dynofile.

And in these case, what you see that dyne is little active, because of the substitute of the sulphr so, dyne active. Now, mind it, this is not a dynofile though, is not a regular dynofile, neither it is conjugate in the two driving group or anything nor a triple bond, this is just a single double bond. So, what is the driving force for this reaction, inter molecular effect. So, likewise there are plenty, I think I have one more example, I think this is a nice example I will give you. This inter means, if your dyne is not very active, if your dynofile is not very active, if it is inter moleculation, there is a possibility reaction can takes place, that is what you have to remember, that is it.

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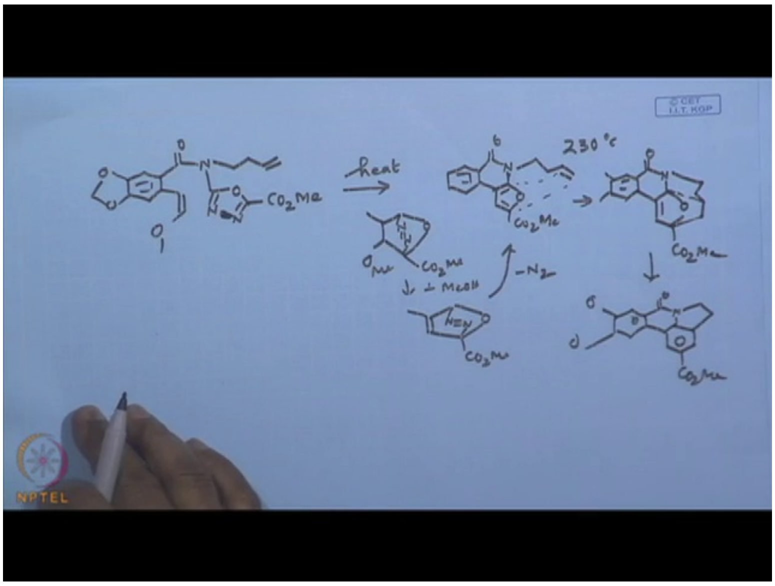

And this is something very interesting, this example tell you many things actually, this is again here, you have an olefin and though these are of the typical natural products skeleton that, dioxylene then, you have amide group here, this amide is functionalized with 4 carbon. Then, this is now connected to oxadiazole, oxadiazole means, in these case, 1 3 4 oxadiazole and simply heat, that is the beauty of Diels Alder reactions. If you are properly designed substrate, you can do a Diels Alder reactions, what you do, what do you expect, what is the difference between the earlier examples.

Here, you have a furan by dyne as a furan so, when you say nitrogen, all of us know it becomes electron deficient compare to furan. So now, you have an ester group up here then, you have a nitrogen which conjugated to carbonine that means, this is also somewhat like electron withdrawing group. That means, essentially this dyne is electron deficient so, unlike the furan, it is electron deficient then, what is required then, electron rich olefin.

And that is what we have here, electron rich olefin that is, this methoxy group that is it and what else, that you have this inter molecular version. So, all these driving force are in the same directions that means, it this electron deficient, this electron rich, intermolecular and the reaction takes place of course, I write the full structure so, you just see here, I think all of you can write. So, it first form that means, OMe and this is the aromatic portion then what, this nitrogen and this oxygen, oxygen and adjacent to it, you have this ester here, what else that is it.

Then actually, under thermal condition actually, we lose methanol so, you will have something like nitrogen thenm oxygen up here and then, ester here. Now, you can see what is going to happen, retro Diels Alder so, you say recart procedure, Alder recart procedure and lose of nitrogen, that also you have to note. See, I have many more example, you will talk about all these things in the next class, this lose of nitrogen is a very important driving force in cycloaddition reactions.

So, once you have this then that means, you have methyl group and you have this homo arylic kind of appendage, what next. So, actually one more the same process with this double bond and so, what we will see, you will see so, double bond here, this ester here and this. So, all these reactions and it is carried out elevated temperature at 230 degree centigrade and what else you can think of, basically one more inter molecular Diels Alder reactions between the furan unit and the olefin unit.

So, once again this is an example to show that, furan unactivated then, dynofile has to be activated. If they are not activated that way then, you have to put them in a simple molecule in inter molecular fashion to give the corresponding product. What next, cycloaddition, we have been talking about cycloaddition, so far we have talked about this furan, talked about this oxadiazole, we have seen different examples alkynes, alkenes and if it inter molecular, the reactions will be done.

And what you see here, actually this reaction does not stop here, the reaction actually goes straight way to the corresponding benzene derivative with a polycyclic structure. And so, you get this sort of compound, what else, what else can you do with the cycloaddition reactions, just give me a suggestions. So, as if we have learned everything then, what can be done, what modification basically I mean, most very few fundamental reactions are being discovered these days. All these fundamental discovers reactions are already discovered, we have been just modifying, manipulating, all these things.

So, how do you extend this sort of Diels Alder reaction to other of course, one of this wise to put more number of hetero atoms, you have put two hetero atoms here, you may have made it electron deficient. So, dynofile should be electron rich and so, there are cases for example, very recently in industry, if vitamin B 6 is produced by Diels Alder reaction, I do not know how many you know or not. Vitamin B 6, the one we sold pyridine derivative but, the dyne is oxazole.

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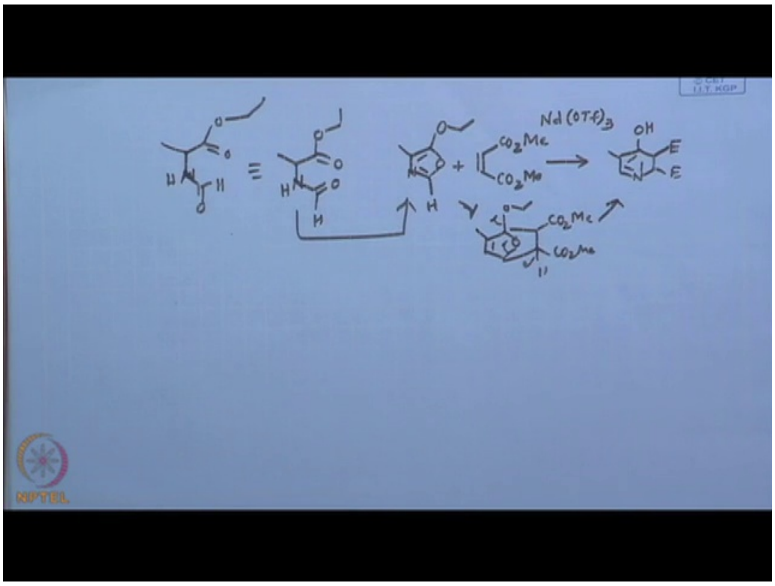

Oxazole means you say, 5 member ring with of course, oxygen and nitrogen, nitrogen at the three position so, nitrogen is the three position. If you begin with an oxazole and let us say, I will put it here is hydrogen and this is let us say, methyl group here, this O and ethoxy and this the carboxylic ester. And see, whether this reaction would go or not, that is what we have to, we have to have some idea about this, our idea comes from the background we know.

So far, we have known all the details about the furan chemistry and also one example we have seen, that was inter molecular version but, this is in inter molecular version. Now, you have to evaluate, whether this reaction is a feasible one or not of course, once we have written here it means, it has to be feasible. But, what is the background, it is very similar with nitrogen so, what does nitrogen make difference here, what do you expect, nitrogen makes a little electron deficient.

But, that is compensated by electron donaring group, ethoxy group, what else that is what, you have to remember. In very early classes actually, we talked about the effect of nitrogen, instead it can alter the p k values, what else it can let us say, very simple thing from benzene to pyridine. What do you expect, what change do you see, the electrophilic sites are changes, the nucleophilic sites are changed that means, and if you do HOMO LUMO what we will see, resonance energy is less.

So, if resonance energy is less that means, the propensity of this heterocycles to undergo Diels Alder reaction is more and that is what happens. This was the reaction actually goes on to this, I will just quickly write goes on to produce this, straight way to this methyl group here. I think should I workout the mechanism, mind it the reaction very uniquely I mean, previously it was done in an industry, some more heating and the little bit of acids, etcetera.

And very recently, someone has done it with an unusual catalyst and he says it is a commercially cheap catalyst, what is this ND, NeoDymium triflate 40 mole percent. It gives you straight way, this Alder recart means, Diels Alder followed by all these cyclization, etcetera. Now, retro Diels Alder, if you just workout this mechanism, you will see it is not a really Diels recart reaction, it is then finally, you have this rearrangement taking place under the presence of acid.

So, we will have ring opening then, the ethoxy loss in under the presence of the acid, the yields are very good and what you get is a nice ((Refer Time: 52:28)) paper. This was published in 2012, see is just same reaction absolutely, just only thing that what he has found, this neodymium triflate and the yield is good in one step, that is the beauty. In other cases, you have to do the Diels Alder reactions then, you have to do acid catalyzed isomerizations or cleaning, etcetera to get to this compound. This is nice precursor and that is not all, how do you make this though that means, oxazole how do you make oxazole, that you have to know, the standard protocol.

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Standard oxazole means this one let us say, this one for example, how do you make it, there are ways, there are plenty ways. Probably, many of you by now know that, two books in heterocyclic chemistry name reaction in heterocyclic chemistry a thick book that volume 1, one more volume recently has come out volume 2, that is lying in my office. So, I mean there are so many things to be learned but, normally we do not burden ourself by learning many things, we have to have some systematic way of looking at.

How do you look at, coming back to this erito synthesis class, there are three ways actually, these days this metal is little simplified, because of the scifinder. So, you go to the scifinder, if scifinder works perfectly all right but, if you want to do some research like you can do this, there are five steps, you can do it in one step. That sort of thing you can do but, if you want to get your compounder that is important, if you have a fixed target, you want to get that compound then, situations are difficult.

In fact, you try to make a 4 ethyl thalide you know, we could not do it very efficiently though, we did it like the one, the very first example I showed you, ethyl furan plus maleic anhydride gives you the corresponding anhydride. But, when you convert this into thalide means, one of this is, which one carbonyl should be reduced then, we had actually two products, both the isomers, one the carbonyl adjacent to ethyl was reduced and this olefin also was reduced.

So that means, that synthesis was not a good one so, how do you make it let me say, again a retro synthesis and retro synthesis, what are the major, there are very first step what you do in retro synthesis.

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Very good at least olefins is a catalyst next that means, we have to see the structural components first, identify the structural components, major structural components. Next step, hydrolytic cleavage, hydrolytic or oxidative these are the typical cleavages hydrolic and oxidative one. And third one, that should be your transform based, transform based means the reaction based. There are tell you many often, I rather quite often that, there are not many reactions in organic chemistry though, only handful.

Other than oxidation reductions, we have very handful of reactions I mean, if you start thinking about, we will have only this Michel addition, this Diels Alder, imine formations, inreaction that is it. Something like this, not on the present condensation. And biosystems, how many reactions do you know which are actually occurring in biological systems let us say. Once upon a time, I should see actually biological chemistry, I summarized you do not find I mean, many biological reactions that means, organic reactions in biological systems.

Only few very few, that trans emulation, all these things they have takes place through the cyst based formations. And Diels Alders are not common, one vocationally people find Diels Alder, etcetera then, present condensation Michel additions and few oxidation and reduction that is it. So that means, you do not have to have many reactions to come up with a direct complex molecule so, any case so, this is what is very important, oxazole.

How do you do so, I mean just do the oxidizing cleavage or hydro radical cleavage, if you do the hydro radical cleavage, what we will find. If you break it, this is N H and this, that is it or little bit fairly written this. So that means, N formulated amino acid so that means, all these alpha amino acids can be converted into the corresponding oxazole. And how do you do it, if it is in hydro radical cleavage how do you do it so, dehydrated cycloaddition, reverse of hydrated cleavage is dehydrated cyclocondensers.