Heterocyclic Chemistry
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Lecture - 29
[2+2+2] Cycloaddition

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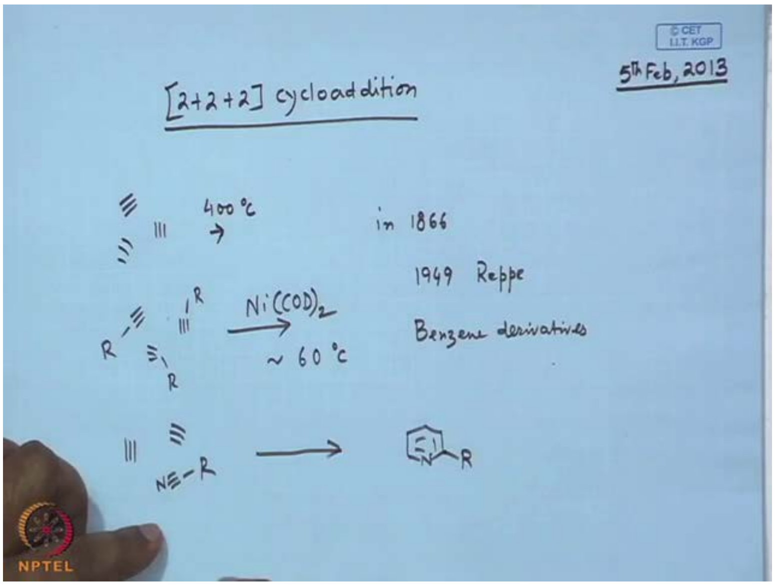

Good morning, today is the last class on cycloaddition. And in this class we will be talking about 2 plus 2 plus 2 cycloaddition reaction, in standard organic chemistry this is not given much important, but as far as the heterocyclic is concerned, this is a very important class of reaction. Why it is, so important primary because the functional group compatibility of the reactions are very useful, very versatile, I will let us say one of the acetic conditions are basic conditions. The functional groups that are not reacting may be affected, but in these in cycloaddition reactions are, so chemoselective reaction would takes place in the part of the 5 bonds are it I should says triple bond. And this reaction is so useful in fact almost every year we are having review on this particular subject.

And there is the latest one we will find in chemical reviews is in the portion call ASAP, A S A P As Soon As Possible the page number is not given, and by saying 2 plus 2 plus 2 cycloaddition I think all of you have understood, what I am going to say it is not related to the olefins, but mostly related to the alkynes. The earliest one all of us know the earliest one is the trimerization of acetylene and this was reported in 1866 by the scientist call Barthello, and the reaction was reported to take place at a very high temperature, what was the temperature has 6 not 600 degree, it is around 400 degree.

Well may be I do not know you may have seen somewhere, but wherever I have seen, it says it is a 400 degree centigrade, and that was for the preparation of many of you know to the benzene from acetylene. That is a standard reaction, but people level used it, it was of importance with respect to the science only, they are acetylene can be convert it to an aromatic compound just by heating. Then the actually the first land mark was done in 1949 that was by a scientist known as Reppe.

And what he could do the same kind of reactions means alkyne, this is a extended this alkynes and to substituted alkynes, and what else and this is he could use a transition metal transition metal. And that was actually nickel cod and at the temperature around 60 degree centigrade, this is reaction product of course, I should write here benzene derivatives.

All of us understand why benzene derivatives, because is a it could be mixture of products, it should be products normally if you have a mono substituted alkynes, you are likely to get 1 2 4 substitute benzene derivatives. Occasionally, you will get 1 3 6 that is schematical one ultra substitute compound, but mostly 1 2 and 4 substituted benzene derivatives, but what is the remarkable about repeat experiment, you can see here by the use of transition metal, you can low down the temperature to 60 degree centigrade.

There are problems with these, but at least they reaction is manageable under laboratory condition that was the advantage of this, but then there are other problems of course, there are other modifications, other developments in this area. But, in our context it should be extendable to heterocycles so; that means, what we need alkyl and possibly a nitride, so if you can do this 2 plus 2 cycloadditon reactions, you are likely to get this substituted pyridine.

So, this is one of the; that means, O H 1 can do this, and in this class what will talk about this sycloadditon, that where we will have a 1 nitrogen somewhere, or oxygen somewhere, so that you can make the heterocylces. And then what else we will see the reactions conditions under which these kind of the catalyst, what we can use that is a then what else there is a kind of substrates that was that should be available. And then what are the product that can be obtainable for this sort of reactions, but to begin with I mean there are tricks, you can get all kinds of a compounds like a carbazole, you can get phthalides, you can get I mean bis phthalates all kinds of things.

But, without doing the heterocyclic 2 plus 2 plus 2 depending on the positions of the heteroatom, you can make all kinds of heterocycles all kinds of natural products, but mostly 2 plus 2 plus 2 cycloaddition reaction in heterocyclic chemistry is limited to pyridine synthesis. Substituted pyridine synthesis, and there is class of molecule call the 2-pyridones; that means, 2-oxo-pyridine you can say.

So, these are so; that means, these reactions are useful only for those special category, and then there are you can by pass it to make heterocyles without involving nitro atom during in the skeleton, means where component is having an nitro atom. Components mean reacting components, means tri alkynes components, mechanistically let us say what you can one can expect if you have metals if you have 2 alkynes.

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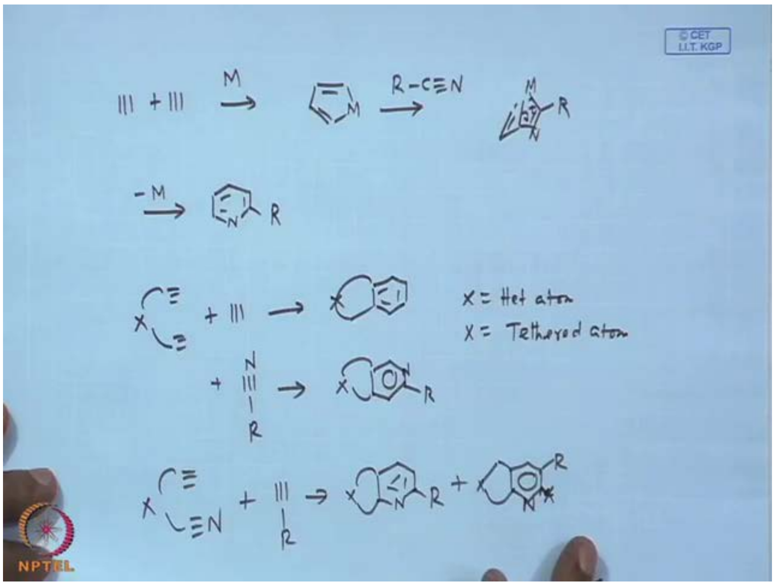

One can just simply think about right something like this, if you have metal here normally the metals not metal 0, usually low valent metals, then we will talk about what kind of metals are used. So, I think you can basically insertion of the metal oxidic insertion in to this alkyne system, and then if you have n something like this; that means, this nitride I mean there are ways to look at, but one of this way one can see that the as if there is a kind of a diels-alder kind of reactions with this like this.

So, the then what else you can think about now, and then this is one of the one of the very simple mechanism or simplified mechanism, and the next basically what you can see here, you can just a if you have lone the reaction call cheletropic reactions. So, cheletropic reactions that the basically retro dial sort by reactions sort of; that means, once again the metro comes out, so this catalytic process. So, metal should come out and what you will be ending up is nothing, but paradigm derivative paradigm derivative.

And so this is the mechanism you can just mentally working out and this, but as you find this alignment of the acrylonitrile to give particular regioisomer that will talk about, but in most cases these reactions are not very regious selective. I think one can see different possibilities for example, if you have just inter molecular version meant all the T alkyne components are separate molecules, then you have all kinds of the possibilities, if it is substituted you will have all isomers.

For example, if you have three different alkynes, one is trisubstituted, another is a disubstituted, another is a mono substituted, then how many aromatic isomers are possible arising out of these 2 plus 2 plus 2 cycloadditon reaction. Guess you understand what my question? If the alkyne compounds are different, they are all substituted one of the say mono substituted, then how many isomers of benzene derivative can you expect, I will once upon a time I counted it is more than 30 more than 30.

So, that is the serious problem that is a reason, why this kind of reaction was not very popular either in the aromatic chemistry or in heterocyclic chemistry. So, one can do, so you can just have a semi intramolecular version, semi intramolecular version means like say you have a two components attach together in one particular molecule. Then you can have one alkyne, so this is a kind of same methane two are bound to a place then other is free then chances of; that means, a what you will get, you will get the benzene derivative here.

So, this could be substituent, this could be hetero atom all kinds if it is hetero atom of course, you know what it is, so officially we can say that in to we have made an heterocyclic molecule, although what we have done really we have done basically you have constructed the benzene moiety. So, it is not truly a heterocyclic construction, but end product is heterocyclic molecule, when x could be tethered atom I think tethered atom or tethering atom may be, I think many you are meaning.

Say basically temporary atom, which has been used to joined or combined two units together and there at the end of the reaction, that is removed is not really protecting group, but it is basically purpose of these atoms are to bring two reactants together in covalent manner. And now the same kind of reactions, if you let us say instead of the alkyne if you take the corresponding nitride, so what you will be getting, you will be getting this pyridine derivative, so now, this is actually truly heterocyclic constructions.

So, similarly we will have all kinds of the probabilities, I mean you have all different verities, in this case we have placed a nitrogen in the a single alkyne portion, now one can think about the same thing in a different manner. Let me say one is alkyne then other is let us say cyanide here, and then this one is plane alkyne, so once again we will get pyridine derivative here X and R. And then of course, they other isomers are possible in this case, so we will have N sorry N here R could be sorry this is not R could be here X and X. So, these are all different possibilities, what are the other possibilities of course,. So, this is now a days semi kind of intra molecular version, the other possibilities could be just basically a simple other possibilities could be triple bond.

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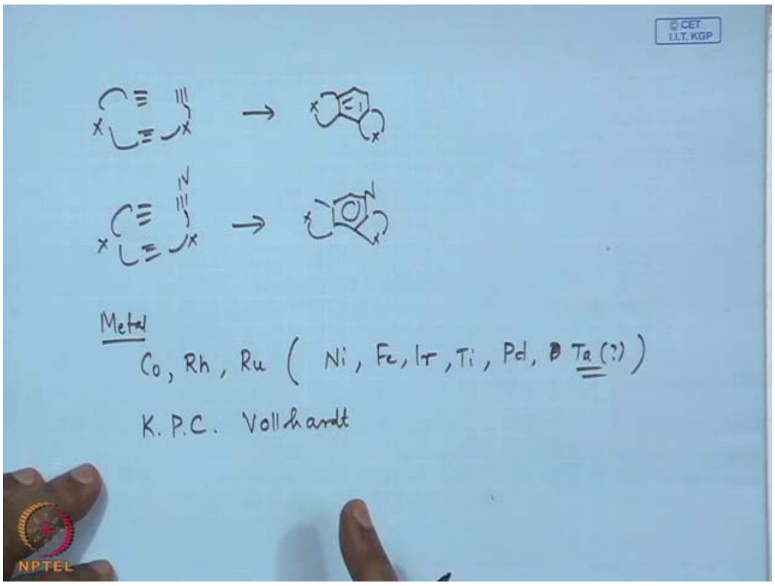

Then you put one more tether or you can just then and the alkyne, so obviously the reaction would give you benzene derivative here a tether atom on this side and tether atom on this side. And this is what very successful in organic chemistry, simply because intramolecule version, all these atoms are the reacting components are in right place, so yields are good and success rate is high. Now, if you, so just modify this version and you can converted in to basically heterocyclic model; that means, same thing x then triple bond then one more x and then and this let us say the end this acrylonitrile.

So, then eventually you will get the same thing as before, here now in the place carbon you have a hetero atom, that is it. So, but what next, next is to see how there are useful and what are the molecules, you can make number two, that is very important about the starting about the catalyst, what sort of catalysts should be used. This reactions these reactions are limited to certain kind of catalyst that the one commensally used, this is metal here metal complexes this of the cobalt complexes rest firs thing this most popular one then next one is rhodium ,and occasionally you will find ruthenium.

So, I will I would say the first two is more important than third one, and then of course, they are other minor one like a many times you will see the nickel like ((Refer Time: 16:35)) catalyst, nickel this days iron catalyst, iron, iodide and zinc combination. And people are also using radium, reason being radium has been high ((Refer Time: 16:47)) to induce asthmatic induction, so radium and occasionally titanium has been use, and there are cases like paradigm and one more may be at the movement I am not sure, that is the metal tantalum it may be a wrong mistake, but there is a possibility I have seen somewhere.

So, but at the movement I think we should concentrate on cobalt and rhodium, and then certain cases some of these specialized atoms here and what are the rhodium, so cobalt was actually first introduce I should not say first, but it was largely used by large use very well known scientist known as k p c Voll Harlt. And he is very famous throughout his carrier he had been working only the on this area 2 plus 2 plus 2 cycloaddition reactions, and occasionally he had to, but most of the times he has produce the carbocycles and he has very elegant synthesis of steroids and alkaloids.

I will give you one or two examples from the alkaloids, and mechanistically just what are the differences first of all the when you go from cobalt to rhodium, rhodium to ruthenium. You will see the mechanism is very similar for cobalt and rhodium, but as you go to ruthenium this is a different kind of if you go back to the mechanism you will see that we have made a metal cyclopentadiene.

And then you have under gone intra as sort of an addition, but some people say hat acrylonitrile undergoes insertion between metal and the carbon through, this to form a 7 member ring systems. And then some people say no that is no something like this that a diels alder product diels alder intermediate of this metalo cyclopentadiene or something they state way make this eccentric. So, all different mechanistic proposals there, but what is expected about this cobalt is at this it involves, but cyclo paradigms.

And now let us look at I mean without doing heterocyclic formations we can also make heterocycles, means without constructing the heterocyclic ring we can make heterocycle. If you have hetero atoms somewhere else, that is the example let us say I will give you for example, there is big structure I will just show you see benzene derivative here.

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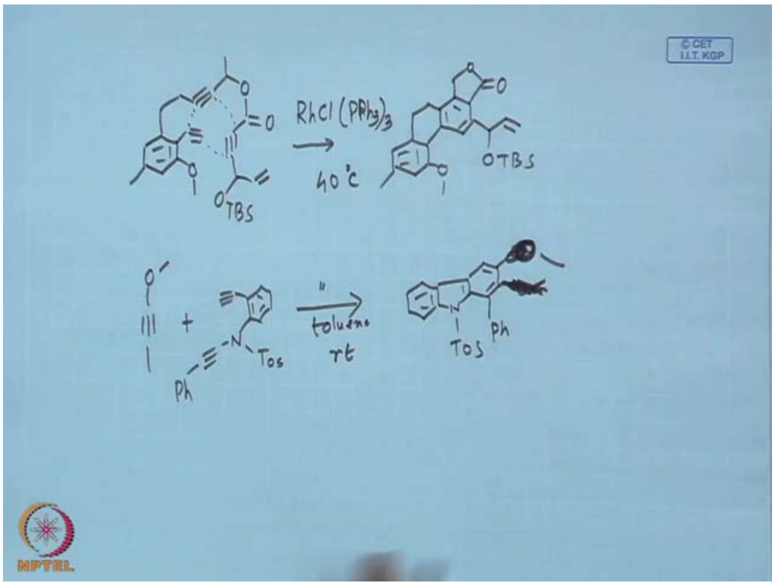

Then you have a side chain ortho side chain with alkyne, and then you have another alkyne and then you have a another alkyne on this side, then what you see backbone is now not backbone I should say it is a substituent is a having a lactone moiety here. Then I mean, so one more alkyne, then T B S tributyl sorry not tributyl, tertiary butyl dimethyl silyl and then you have double bond here a methoxy here, these are methal group.

Now, what you see I think the way I have written it is pretty easy to understand what is going to happen, so it first have basically you will get a new benzene ring, this one would form a new benzene ring and then what else this is a lactone here now and this O B and O T B S. So, the, so how did it form basically you have to identify the alkyne portions, so in this alkyne get the connected chain and as you if the means you start from anywhere let us say from normally what do you do this start from in terminal.

So, 1 2 3 4 5 6 so; that means, this should be connected with here, and this should be connected here, so you get basically three new bonds here and then of course, three triple bonds become the double bond. And then rest of the things remains as it is and this, so what you see here we have constructed basically benzene ring, but net result is you seen heterocycle molecule; that means, what we call this portion, this is basically phthalide or benzoic furan load benzoic furan load. And what has to be noted here anything that tertiary butyl group survives that silyl group survives what else do you see there is a pretty interesting thing here.

Lactone ring survives anything else that is that have to remember, see there was a possibility the double bond could also be involved in the cycloaddition reaction, so it did not; that means, the triple bond are more reactive then the not really actually here also you have to take care of the geometry important. I mean you have sit down and see whether that do geometrically permit or not, so it is very difficult to pin point whether double bond more reactive, but triple bond is, but this sort of reactions I would say more successful with the triple bonded compounds alkynes.

And let me take you to, but what I missed to them, I missed a what is the catalyst, so when I say what is the catalyst then you have to think about cobalt or rhodium, and when it is come to rhodium; obviously, all of us know what it is. Rhodium Cl and within bracket something p p h 3, whole 3 what is it Wilkinson catalyst, so that is the beauty Wilkinson catalyst; that means, Wilkinson catalyst also I mean many of us only know that Wilkinson catalyst useful for hydrogenation.

And occasionally there also useful for in standard organic chemistry useful for reverse deformulation, actually call decarbonization, and now you see here it also in the say is a very useful and there are plenty of examples where the Wilkinson catalyst has been useful for 2 plus 2 plus 2 cycloaddition reactions. One more example may be alkyl give you snd so here you see here advantage, what is the advantage rhodium and number two it should be number two it is an intramolecular, so intramolecular version base more successful.

Now, let us look at one more example where it is semi intramolecular like say if you have a benzene derivative with alkyne and then nitrogen substitution is tosyl group and then you have another. So, what you have by writing this structure, what you can see you have actually joint it down all these alkyne portions, you can identify the different alkyne components. Now, what you have to do you have to choose a catalyst so; obviously, the cobalt one is preferable because that has been more successful, but within rhodium this is Wilkinson is more reasonable available one can just buy it.

So, do that and what you will find just in 12 is the reactions is carried out in toluene, and just reflux sorry is a room temperature just room temperature. So, mind it now if you go back to the bartolozzi experiment it was 400 repige was 60 then actually the previous one watch only 40 degree centigrade that is basically dichloromethane boiling point and now you see the room temperature.

So, I mean there is significant improvement as for as the energies concern convenience is concern the scaling of a reaction is concerned, and I goes or if sit down you will be able to write the structure, so what should be the structure and what is the product say is a carbazole and a tosyl. So, this benzene this one and this methoxy here and then carbon it is now, so phenyl nitrogen and this one is this triple bond, so I think methoxy should be somewhere here or benzene and this is tosyl group sorry this is this should be phenyl.

This should be nitrogen phenyl and this come from benzene this one this should be methyl, this will be methyl and this one is methoxy, so this one is methoxy this one is methoxy this is methyl. And this so; that means, you see here this is nice way of looking at reaction; that means, you can, but essentially what you did you actually constructed a is not is not a truly heterocyclic construction you have constructed only the benzene ring, but just by placing hetero order here and there you have come with the formation of heterocyclic molecule.

And so then how do make heterocyclic molecule, how do and what should be the approach in truly intermolecular reactions are very few, as I said either semi intra molecular or total intralmolecular reaction. Now, you want to think about the heterocyclic construction so; obviously, your component one of the component should be the more commonest one acrylonitrile.

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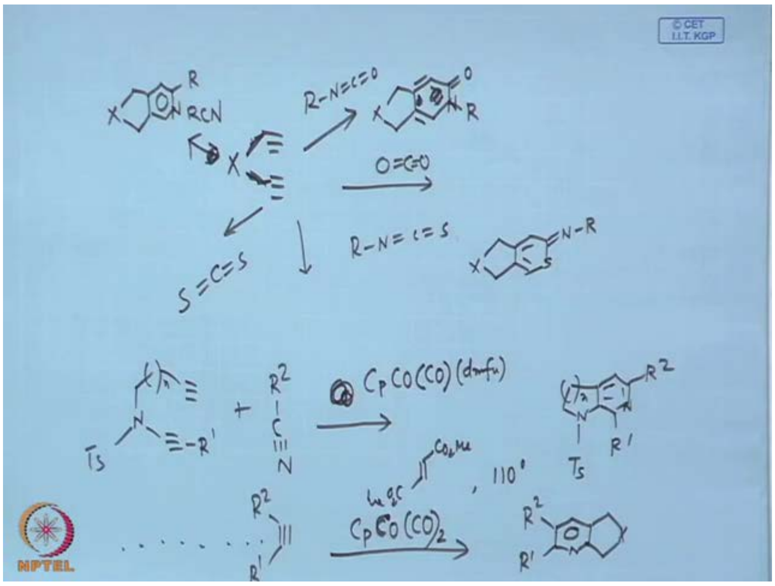

And you have already seen; that means, if you have a substrate of this kind; that means, semi intramolecular, then sorry then react with an acrylonitrile, and acrylonitrile, so what we have already seen before we can get pyridine derivative, but the same substrate. If use with a isocyanide, so what you will be getting, you will be getting a again a 6 member ring, sorry this is C H 2 this is C H 2 x, so the easy to remember x.

Now, C H 2 double bond sorry, and then now what double bond should be placed here and here and he told then R, so what will be getting, you will be getting ring redole, nitrogen somewhere here, so nitrogen. So, that means, it is the carbon double bond that is imine portion, imine portion is reacting with this participating you have to make out here, there are you have to just understand that the one that is less polarized or which is more covalent in nature under goes this sort of reactions.

But, there are cases, but there are not many low, there are cases where you can also use carbon dioxide, in the case of carbon dioxide any of the double bond should be reacting that is not at all a problem. So, then what is the other possibilities you can take isocyanide, you can take carbon disulfide; that means, now carbon; that means, one can also think about this carbon disulfide, then all people can about this R N C double bond S.

So, all these possibilities are there, but among them among all these possibilities there are two or which are more prevalent, which are those one is the pyridine formation another is the pyridone formation. And will just have few examples basically how to make pyridine derivatives and then what are the different kinds of the catalyst which could I mean there are wide verity of catalyst wide verity of catalysts, n number of catalysts. You can just modify the catalyst with a particular like end it works and without particular like end does involve.

So, there are all verities, all kinds of verity in and sometimes this allegiants are such simple one which are not normally sort about, let us say the example I have kinds of reactions again semi once. So, in the semi once what you semi intramolecular once what you do you take I will say dialkynes or alpha omega alkynes and then I think about acrylonitrile. So, in principle this should have to what at the room temperature, but when you increase the substituent the temperature has to be increased, and in this case the catalyst has to be used is a.

Student: ((Refer Time: 32:49))

In this case not more polarizable I should say more covalent, in nature more covalent which one is more covalent, I suppose yes, so in this case actually what you are expected to get of this kind where, sorry no. Actually, in this case the carbon double bond is sulfur has to be reacted, carbon double bond is sulfur and this imine portion and so this is call thiropyramines, again that to analyze specific conditions.

So, these are not very reason I did not talk about this is not there are isolated only examples, so now, we have a substrate here ready for 2 plus 2 plus 2 cycloadditon reactions now you have to choose catalyst. The of course, the first one should be the cobalt one the cobalt is more popular, so what do you use that all of you know C p and then cobalt and then what?

No, not whole 2 that is actually more popular one the more popular one, C p cobalt and then carbon monoxide whole 2, but if the one that has been used, in this case I am is something like D M F U it is nothing, but is a very simple compound dimethyl fumarate. All dimehtyl fuamrate all of you know I guess right this is dimethyl fumarate, that is why I am telling that ligand could be may have different kinds.

The commonest one is C P C O C P cobalt and then carbonyl twice, that is the carbonyl twice, that is the commonest one that is actually exclusively used by the K P C board, but in this particular example and this has been more successful. And the reaction is carried out at 110 degree centigrade, so what you get now of course, you get now diago compounds or the pyridine derivatives, nitrogen R 2 here, R 1, then tosylate and then C H 2 is end. So, you have in a all kinds of this, and I have more examples, I will skip some of them.

And the next category of the examples are what I have here is very similar to this one; that means, you say bicyclic pyridine derivative, then the nest example what I have this nitrogen is within the first component, and the third one sorry second one is just to plane alkyne. In that case the example that is the this C P C O that is sorry I think cobalt and then this broods reagent that has been used.

So, I mean I will not write the very similar, substrate in this case nitrogen on the left hand side and the this one is the plane alkyne and so one would be able to get this kind of molecule here R 1 and R 2. R 1 R 2 comes from; that means, one can write very quickly R 1 R 2 are comes from this alkyne and the pyridine nitrogen comes from the tethered di ion portion, so and this in this case temperature is not mentioned in temperature means.

So, likewise will have more examples may be 2 hours the end of the class, let me tell you one more example which is been developed by k p or the c order and with a target to synthesis a natural products, many of you probably you would know this name, but you do not know the structure l s d, how many of you know L S D.

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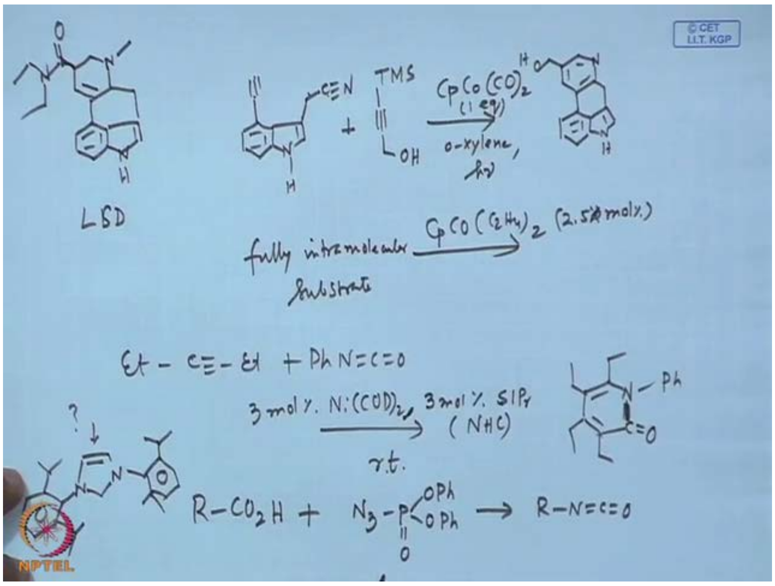

What is the full form of L S D, I thought all IIT’ians know L S D Lie Searching Acid, diethylamide, it is a molecular of this kind is an indole you can look at as in indole derivative. And then, so best I will just if you just write down the this name L S D in the Wikipedia or Google, so you will find the name is pretty well known among say basically, used by the drug addicts and the structure is like this.

So, you will have it basically amide moiety diethyl amide moiety, so this has been synthesis by many roots, for one of the possible roots could be you can see here, one could roots possible you have a say pyridine moiety here on you left. And two examples whether this 2 plus 2 cycloadditon could be a possibility, so k p c ((Refer Time: 39:13)) here done here taken a idole derivative here. And syanide of course, what in else you need if you just alkyl, and what else one more alkyl; that means, the see somewhat like a semi tethered again or two components are joint together.

And the third one you say alkyne is an T M S and this O H, so if you write ((Refer Time: 39:59)) take this here, 1 2 3 4 5 6, so you have 6 atoms would be reacting, and in this case the example is C p again then cobalt. And then carbonyl, carbonyl 2 of them, but mind it here this one equivalent was needed, and eventually he could get this structure very structure, very similar to what is there for L S D, this one and it is not exactly the L S D what you will get is ((Refer Time: 40:48)) without the silicon here by the by silicon is knocked out during this reaction.

So, what you get is the entire skeleton has been assembled by the just one single step, and mind it there is no protection for the O H group, there is no protection for the nitrogen. So, you can get to this see we have been working on the heterocyclic chemistry alkaloids for long time in, but most cases you know most cases what do you do, we protect the nitrogen and do all kinds of reaction. Otherwise, and then we end of the difficulties having to by in having this protecting group to be remove so all kinds of problem.

But, without using protecting group if you make synthesis that would be definitely this better than the one that one can think of, but then this has been the problem and it was done in ortho xylene; that means, at higher temperature, temperature higher than 130 degree centigrade at the same time it was expose to write. And if you know little bit of the this reaction mechanism of the organ metallics, from you become know why the light is used here, anybody light very good activate the cobalt complex.

It actually it just carbon monoxide then this alkynes and alkenes can undergo co ordinations on this cobalt surface, so that is some time required sometimes not required depending on the situation, but in this even sometimes simple heating also activate the cobalt. And you will see more in fact, more kinds of the catalysts carbon is reached not there a very similar catalyst, but; that means, carbonyl complex there is a problem you have to activate it by the owing the carbonate.

So, if you have pre catalyst, you know which will have other than carbonyl which is easy to leave the cobalt metal, that was also could be useful and the one of the means basically diethylene complex. In the place of carbonyl if you have diethylene complex that also would serve the catalyst for this sort of reactions, and impact I will not give you the example it will take time.

So, next example on this lysergic acid synthesis has used this cobalt ethylene complex, cobalt ethylene complex and to the extend of 2.5 percent, means in this one, one equivalent of cobalt ((Refer Time: 43:40)) pretty expensive. And the other example is very similar to that other example, it was nothing is new catalyst is a cobalt here and this ethylene complex and the percentage use is 2.5 more percent as been used.

The substrate is little different go, in this case here all the triple bonds are is same in one single substrate; that means, this is a basically a fully intramolecular substrate I should, I will not write the structure, basically what you do the join all of these 3 alkynes together. So, in that case actually the percentage of the cobalt complex is much less and if you are interested I can give you sometime later, but, so what next. There are other examples where you will have this nickel catalyst, titanium catalyst may be will just keep them, but what I will just show you one of this important examples are 2 pyridine synthesis and the one that is pretty well known here is you take diethyl acetylene and then phenylisocyanate and then a catalyst.

In this case the catalyst was nickel cord and the percentage is nickel cord three more percent, so I should write here the 3 mole percent nickel would and then 3 mole percent of S i P r, I will tell you what it is. Is say N H C, I think some of you know many of you know, I guess N H C, Nitrogen Heterocyclic Carbons. So, N H C and the reaction can be carried out at room temperature and the reaction product of course, all of you can guess and sorry, single bond this is phenyl, so you get the basically two pyridone derivatives.

So, carbon double bond nitrogen is more covalent in nature that participate to the reaction, eventually you get this compound what rest to be known phenylisocyanate. Phenylisocyanate where do you get is a commercially available, but if you cannot get it in and you have to make it, how do you make it phenylisonyanate, you have to also know this phenylisocyanate, how do you make phenylisocyanate.

I will make it go we know, how to write and from Hoffman degradation, but we do not isolate from they are is an intermediate, but if you want isolated isocyanate, you have to use I mean there are all kinds of things. You can do reductive carbon nitrogenation nitrobenzene again transition metal under catalyst, you can reduce the nitrobenzene to nitrene and the carbonyl undergoes incretion to from this nitrene.

Then if you have corresponding easier derivative you can do the dehydration and but in the chemical laboratory, there is a very useful reaction important reaction, you take the carboxylic acid. And then you walk out the mechanism may be you will see in next time, next tomorrow process ((Refer Time: 48:09))not take class, so I will take the class depending on the situation either here or in the department.

And if you ready then I will take you class here, otherwise I will take the class in the department, so you workout this problem, and then this is a reagent. I am I think I will be able to write rho, long time before I ((Refer Time 48:37)) this, diphenyl asilo diphenyl phosphonate hope fully, 1 2 3 4 5, yes see in one shot we will get this isocyanate is a very useful reaction. Hopefully, I think I am almost correct.

And so what else, there is a compound I should write, that N H C, what is N H C, N H C again in this case I should a S i P r I transfer actually imidazole, it little have this imidazole. And then isopropyl and then I n isopropyl and sorry not isopropyl it is actually benzene isopropyl, sorry diisopropyl benzene and benzene. We will have diisopropyl groups here and there and the note from, where I have taken this example it does not give the double bond here, but I presume they are should be double bond they are could be a double bond.

So, I have to go to the original literature there are N H C, where will have the double bond and without double bond all kinds, so this is actually the symmetrical one. So, that is a reason why symmetric S i P r and some times also this, sorry this actually S transfer the S configuration of the this aryl system. So, but this example just show you that it can that N H C can be also useful ligand, and what else I think we have talked about many important things here, may be you have missed 1 or 2 points.

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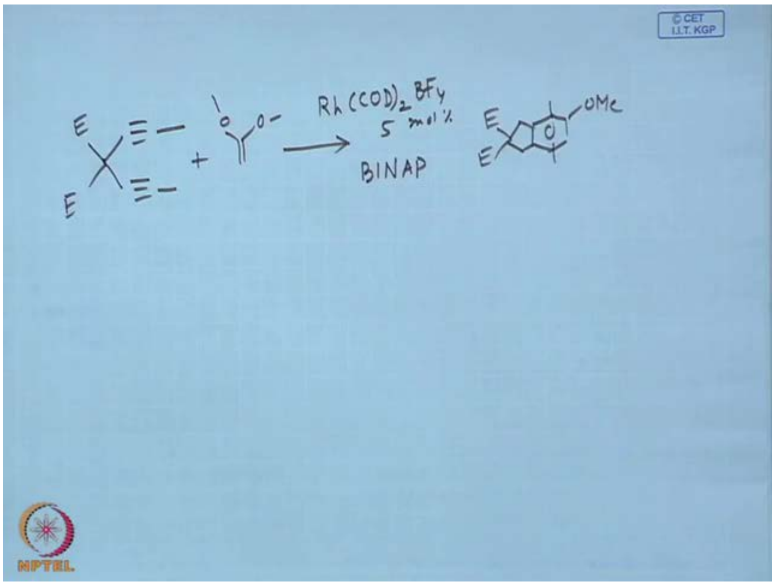

That let me see yes, this is a very important one say if the reaction takes place what do you do, let us this is not a heterocyclic example, but let us say we have a alkyne here tethered alkyne. And they let us say I write here E is an ester here, and then alkyne let us say you want to do 2 plus 2 cycloaddition reactions here, the confessional Wilkinson catalyst does not know what.

The conventional bollard catalyst; that means, the carbonyl complex does know what ethylene complex dose know what, so what can I do so; that means, basically you have to activate the alkynes. So, and in this case mind it one of the means not an alkyne, what is it alkene, so you have to have a real active catalyst, so how do you make this catalyst active; that means, you increase the ionic character.

So, this Wilkinson catalyst it is basically rhodium based catalyst, you have C O D and then 2 and 2 make Wilkinson, you had the chlorine to make it ionic in nature, so what you have to do, you have to basically change the counter ion.. So, what counter ionion

((Refer Time: 52:30)) you do use R flow rate, one of this R flow rate the other is that is it I am you recover, only 5 mole percent.

And then of course, there is a ligand here that is for other reason all of us know that BINAP, BINAP is a famous phosphorus base ligand, this is used just to explore some other thing, because there is an asymmetric version. And there are you can make you, so this sort of ligands, so there are examples, where you can make biaryls and in which one of the means heterocycle in optimally active form provided the your BINAP is optically active.

But, any case in this case, so you can smoothly make the corresponding benzene derivative so; that means, choice of catalyst is important, and then you have all different verities of catalyst, all different verities of the ligand N H C 2 dimehtyl fumarate all kinds of things. And so there are examples you can use cyanogens many of you know, cyanogens is what is that, cyanogen is two cyano groups together, just like see the halogen. So, that means, you have to cyanone; that means, acetonitrile is one of the component in 2 plus 2 plus 2, but there are also examples where you can use a cyanogens.

And so let see summary what is the summary, 2 plus 2 plus 2 cycloadditon reactions are limited to pyridine synthesis and pyridone synthesis, and occasionally they can use to make other alkaloids provided, it contains a benzene ring where you construct the benzene ring. Third important point the cobalt and the rhodiums are more useful, so cobalt has 2 verity, carbonyl 2 and then ((Refer Time: 54:51)) 2, and there are other points could be the rhodium, where you use the rhodium. Well, actually one should go for rhodium first rigidly available, but it is apparently it is less reactive then the corresponding cobalt.

But, rhodium can be made reactive by in changing the counter ion, and also you have to keep it in mind rhodium based catalyst have been use for totally itramolecular reactions, when you have all these things are in one molecule then it is easiest to carry out with rhodium catalyst. And all of us understand that regious selectivity problem, I can be solved by tethering all these trialkyne in one molecule; that means, if you make this molecule reactions intramolecular versions.

Asymmetric versions are there, but I should say it is not very popular, but people are still exploring two make all these reactions asymmetric, when you save asymmetric means actually not traditionally. You are generating the kyrole centers, it is basically kyrole axis you are generating; that means, by aryls can be made from this sort of molecules.

And what else I think we have give you the most of the important aspects, as I said before it is not very popular with carbon disulfide is one of the reacting component, and all this 5 isocynates carbon dioxide. But, there are examples we will find which can be which can involve alyne systems; that means, the just isolated alkynes are now very, very reactive, but if you have reimpart just simply it can also participate in the 2 plus 2 plus 2 cycloadditoin reactions.

That mean two are the aklynes and third one is the alyne, that is also possibility there are examples, so you can make use of and I think that is we have other then this guess, we have talked most important aspects is of the 2 plus 2 plus 2, and I think you have taken care of most of the important thing see.