Heterocyclic Chemistry
Prof. D. R. Mal
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture - 22
Tert-amino effect in heterocycle synthesis

Good morning. So, you know the topic right, Tert-amino. This was cover last year, may be for some of you should be partly repetition, not all of it. But those who are not expose to these will have a something new in this sense that nitrogen has a special effect, especially where it is a tracery I mean.

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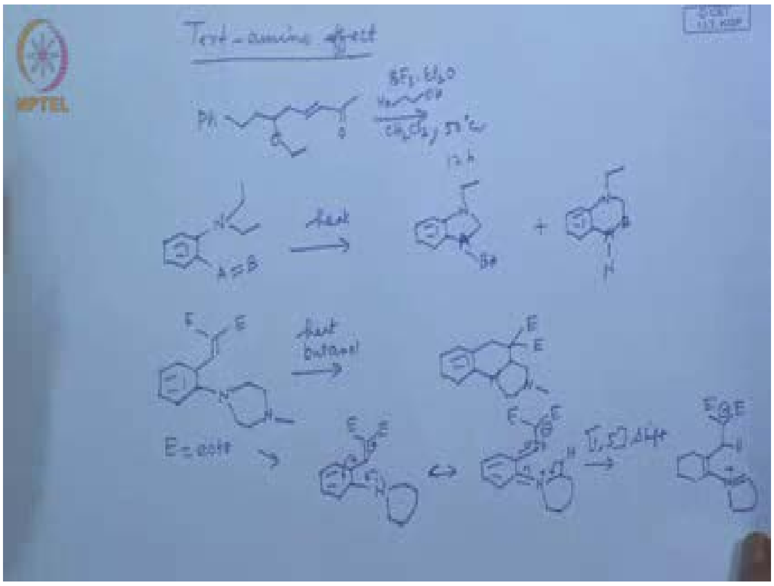

So, today topic would be Tert- amino effect and some people say Tert-amino reaction ((Refer Time: 00:59)) that means, this effect has been converted to reactions. The reactions have been very useful in synthesizing fused heterocycles, fuse heterocycles. And along with that we also talk about little bit of these oxygen heterocycles and some miscellaneous or the variant of the original Tert-amino effects. For example, towards the end of the class will have something like this, say if you have a cyclic compound. And react this with B F 3 is and with ethylene glycol and the solvent is Methylene chloride and this temperature is around 25 to 50 degree centigrade and certain 12 hours.

So, you should be able to Acidic reaction of product course the end of the class will see whether we can ((Refer Time: 02:15)) the reactions of the rather reaction products. What is the meaning of it? The meaning of it is that, it must have a Dagan ring then you must also have a ((Refer Time: 02:29)) and this should be or though substituted with a double bound. If you simply heated, that mean; reaction condition some very mild one side there is no complication in the terms of the use of the reagents of no substitute the agent what will find? will find is Hinckley product and which will be looking like this is A and B H this is one of the products the other product could be also say sorry 6 member ring, 6 mamboing system, and with hydrogen that us to nitrogen and then sorry nitrogen and this other things.

So, what you see here a single reaction can produce ((Refer Time: 03:40)) as well as the phosgene derivatives and taken example, precise example, then what will see conclude example could be and let us say. Now, take this one and switch over this ((Refer Time: 04:07)) or the top may be top and then E in our case lot of says transfer ester. And then now, the structure I mean is part of a paragon ring system.

And, the reaction condition is needed solvent. This solvent is normally little high value solvent high value polar, non polar. Non polar solvent high ((Refer Time: 04:41)) is so around that temperature and polar solvent like alcohol also refluxes what is this solvent methanol. So, just simply methanol what will find this case let me there are possibilities on the top 5 member and 6 members in this case what will find, Will find a reaction which will give a 6 member compound and on the structures could be return easily.

If you follow this common reactions given on the top and here is E. So, what is the mechanism? The mechanism you could be you can what I can just write in terms of the should be if I this is; this E this electron group the double bound and nitrogen here. And what I said tracery that this 2 should be calculated and this amino should be such that, there should be an alpha hydrogen that is the important thing.

When structure I mean structure alpha to the nitrogen there must be hydrogen here and what is expected and then sort of a original structure of this kind. So, a double bound here and then E and now, kind of a sort of jute. And then is a cycle do not write something about that so what next this is what you have to find out that all of first know that is possibility of sigma tropically arrangement ((Refer Time: 06:56)) that is a possibility; I mean there is no common concentration about the mechanism. I mean all times of mechanism have been proposed; one of the mechanism is that the 1, 5 sigma tropic shift is possible at this stage there are other wise up to looking at this by internal high transfer. But that one let us say; so what you do, here you just do A. Then , inter molecular hydrogen transfer and giving this is E and negative charge here and the hydrogen is double bound nitrogen. Now, what you see that double bound has been shifted sorry.

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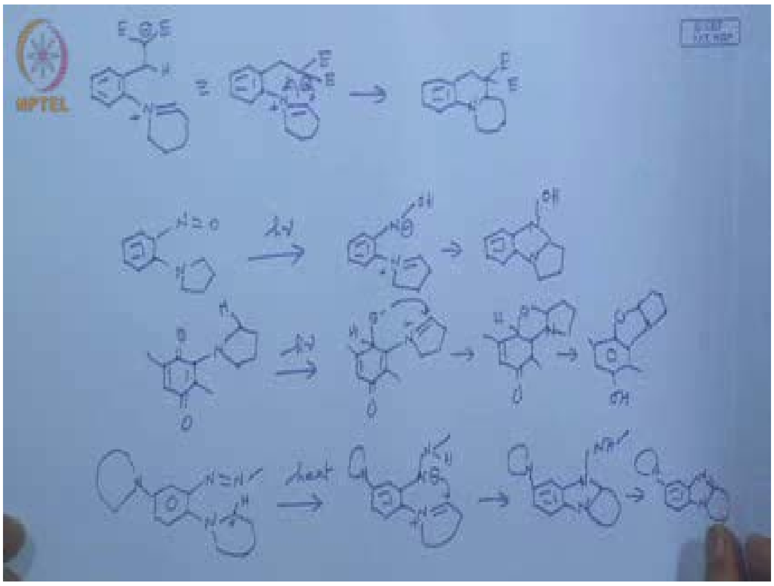

Rewrite this; so what we will find? So, hydrogen has been shifted, this ester digester contender negative charge opposition the nitrogen. And now; you have a iminium ion here which is equivalent to, if you rewrite equivalent to see all you can see just a carbon ion setting next to the iminium ion. And obviously the possible reactions that one can say see neutral of be positive charge of the nitrogen.

So, eventually what you could find? You could find a, what is that? Basically, the cyclisation process or you can say ambulation process surface at to cycle and the wire the back bone is coolant derivative and you have this 2 ester groups. So, this is one of the that means; in learning this sort of reactions, what you have to learn? Pre requisite; what is the structural pre requisite? It is a Benzene ring and it should have a double bound to and couple bound it could be tracery ion group with an alpha hydrogen, that is; what you have.

Then, let us say I have one more examples that means; the examples where is here what you see? The again benzene derivative and it does not have to be a carbon carbon double bond now. You see it could be simple multiple bound. Now, the reaction condition either heat or light depending on restriction here, if these case in this case what will see just light. So, what do you expect hydrogen transfer; basically, hydrogen transfer it could be through the 1, 5 sigma tropic seat or it could be proves direct internal hydrate transfer.

And, in this case there are possibilities but the hydrogen ((Refer Time: 10:14)) hydrogen is transfer to oxygen right. And then this is iminium ion is formed and this nitrogen is negative charge now. So, result is of course, result is somewhat different; what is it? It is in hydroxyl ((Refer Time: 10:49)). So, likewise you can also similar kind of reactions what we do in find out if you take a Carbone and fertilize it. So, what you see here, this is not exact with automatic system but it has a system it is alpha hydrogen.

So, if you fertilize it first know this the Carbone exited and this radical is generated. And you will have 1, 2, 3, 4, 5, 6 so we will have a 6 member transition you can just straight way you can this is hydrogen transfer can takes place right and or but in this case what will see hydrogen transfer to nitro carbon here, oxygen minus and this ammonium ion. So, sincere driving course for this sort of the reactions in the formation of ammonium ion and then final stability of the final product. And I mean one can also the hydro transfer to the oxygen that could be radical reaction for could have been a possibility. And so once we have these then what is expected? So, 1, 2, 3, 4, 5; so we have a 5 member now 5 member system and another 5 member with a system we said a nitrogen.

And, the now, all of us what is the next FET? Next FET is the basically, the aroundization and this one etc. And this over which so basically if you can recognize a tracery I mean structural component and little bit of phi system chair and there then under mile condition. So, this is like just example that is does have a carbon double bound ((Refer Time: 13:33)) it could be carbonate oxygen nitro bond nitro site. And then other example in the next one what will find again a tracery I mean; so throughout you will see the ternary ion towards the end will towards the something little different. And then there is this group here and let us say this is something, this is something. So, and the normally, what is the function of the tracery I mean group and nitrogen double bounded nitrogen name of the functional group.

Student: assoc group.

Assoc group only undergo which the lot of ((Refer Time: 14:36)) but in this case the thermal reaction. And but since you have a ternary ion group will have a alpha hydrogen. So, we can do all kinds of mechanism either we can 6 member that means; they are in all most all of these reactions what will be talking about the reactions takes place alpha to the nitrogen that is one of the commonality throughout of the lecture today. So, we that mean 1 of these bonds these form at this carbon and it could either form this nitrogen or this nitrogen that it ok. And normally 5 members, 6 member formation is govern by the thermo dimensional dimity. And if you have 2 nitrogen ((Refer Time: 15:54)) more like lead.

So, you have hydrogen here mentally I think it is better to just think about high transfer internally that is better do this original that is mechanism where we can do little bit of the jute and formations and then one ((Refer Time: 15:46)) and then nitrogen. And alternatively you can think about is highlight transfer. So, the highlight transfer so for simplicity said may be highlight is transfer to this nitrogen here and then you will have this ammonium and here and this side the nitrogen right.

So, if the positive charge and 1 of this carbon must be and hydrogen must be negative so this is negative. And of course, then the end result is now and ((Refer Time: 16:31)) and in this case you have nitrogen that ring and N H and this method group here ok. So, what will see expect under the thermal condition in hydro cyclic chemistry one of the very common reactions like, if you have a thermal reactions will find this nitrogen as it is.

Then you have the other cyclilic portion what will be expect from the Siemens actually, I means also the good living under the conditions. And so it this methylamine is lost so eventually you get the formation of ((Refer Time: 17:27)) ok. So, what did you see so for we have given see different examples in all these ((Refer Time: 17:38)) that means; we have a 2 hydraulic that is likely hood that it would form a 5 member system.

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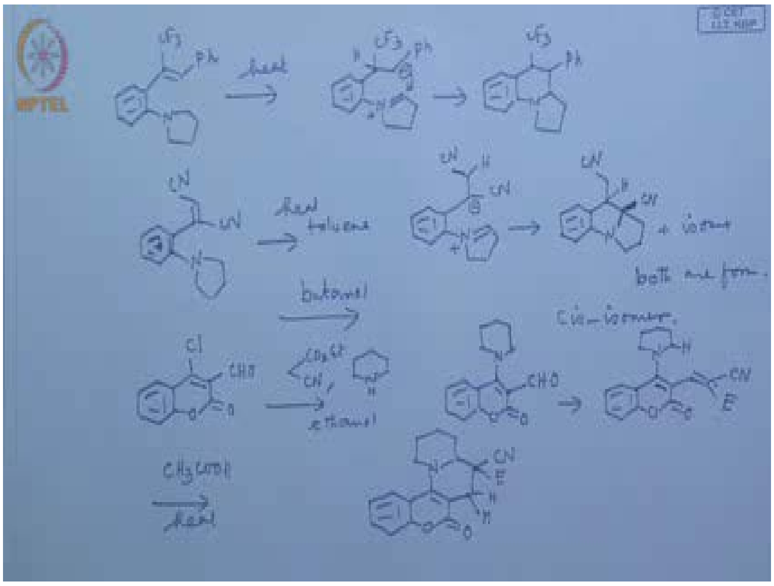

Now, let us take one more example when you have carbon bound once again so parallel group. And in this case is a carbon carbon bound reactions conditions are same as like heat and solvent. And so what we do expect? One thing what we can expect that first forms this ammonium ion right. And then you have to decide actually, whether this hydro carbide to this carbon or the other carbon. And mechanistically if the hydro transfer is required that means; it should go to the electron efficient, that means; is a electron efficient right. But in this case this carbon phenol groups should be electron efficient because T F 3electron with drawing right. But I am such is different one and so in this case this hydro is added to the end of electrons ((Refer Time: 19:29)) and then phenol gets a negative charge.

Now, that is the possibility that is the final is ((Refer Time: 19:37)) final eventually that. So, end product is like again a coolant derivative you see the phenol substitute coolant derivative then you have all can something here. And that there are questions are about this chemistry normal we get very official we get a pure product in this. And so that means; if you can say once if you have that 2 different kinds of lateral items there is a likely hood there is a 5 members would be formed there are cases just write without the presence of hydrogen in the double bound size.

You can also expect 5 members information I mean, it will somewhat tuff to explain in why next say in the next example will see allow we have a couple double bound there is a formation of the a 5 members system in all of these examples you see ((Refer Time: 20:57)) that is to form again heat this is domain.

So, I mean now, the begin with the straightway, the right way the formation of these ammonium ion the highlight will be shifted there should have to decide in these case. And the highlight with I mean I thought the one will be highlight either highlight this position is let exposed. So, there is a possibility is the because it forms the ammonium ion here after this added to this also, I mean, since I know I able to say that the product to the 5 member ring. But from my experience what can say from that sometime hydrogen takes place so the left hand side. So, the hydride is shifted here, that means; shifted to Sino without a substituent at we get the carbon formation here next to the benzene ring.

So, the product is right this is C N. And now this is C N and of course, this other one is 5 members system. But mind it you have 2 different groups hydrogen and synod. So, there are isomers and you can see some terms in this reaction both the isomers are formed, both are formed what. Then again, there is no expression why? That is if you just see the solvent to botanic only C size isomer is formed. Again, it is not expandable it ok.

So, this is just a case you have a carbon couple double bound and just convert into the 5 member systems. And this in the next example what I will say is it could be extended to 2 kind of molecules where the lactones is very sensitive to most of the reaction condition is the thermal reaction. So, we can just simple carry out and the thermal conditions we to give very complex molecule this example a starting from a coumarin all of a small in what is coumarin? Coumarin is a bycylic molecule electron ring with oxygen.

Let us to this phenol ring electron and then there are 2 functional deserved have here is a formal group. Now, if you react with this ethyl synod format, ethyl Sino hesitate that it should no ((Refer Time: 24:38)) ethyl what is the name of the compound ethyl Sino hesitate fine Sino hesitate then 5 period in all of us best. And so what is the reaction? The reaction what should the reaction? I mean Lawton can form Lawton can open up what else, it can undergo various reactions. So, all kind of possibilities are there but at these stages you thinking should be in matured means in the sense all these reactions are reversible reactions. So, you should have a product which will not be reversely going back to the starting material. So, the product is not in ethyl reaction, the product is a displacement of chlorine with this nitrogen.

And, now you have a formal group here ok. What next now, there is no all of us know the chlorine is not a very strong ring so we can expect a ((Refer Time: 26:12)) and that is this 1. So, double bounded now, and at one side you have Sino other side you have ester which is E and this is piper dine. So, this compound is then actually, in this case the solvent is acidic acid is hesitate. So far, we have seeing that either toll win ((Refer Time: 26:52)) but in this case you have acidic acid and just simply heat. So, what you expect so we know now, the requirements are full filled that we have a double bound here ((Refer Time: 27:11)) you have to recognize this Tartary amino part with an alpha hydrogen.

So, that means; if you strait way can without thinking much we can write this back bounds remains as it is right. And then the Tartary amino remain part and as it is we can blindly draw a bound here, alpha to the nitrogen it is. Then mater of forming 5 members or 6 members that is it because you have form double couple, double bound.

Now, when you have clean polarize double bound we know what is going to happen right either should be let us to be if this is alpha carbon, beta carbon or the of the double bound is towards the Sino groups, that means; one can is hydrate is write here and the carbon is forms there. So, it should be a 6 member and this Sino and this ester so we have 1 more hydrate. So, this is how actually this compound has been actually verified by extra structure determine so there all I mean this is I take not bore you with other similar example, that means; it is a typical reaction of the chloride. If you have a chloride that nitrogen displaces the hydrogen part ((Refer Time: 28:54)) then under thermal conditions it goes so called this tracery amino effect reaction.

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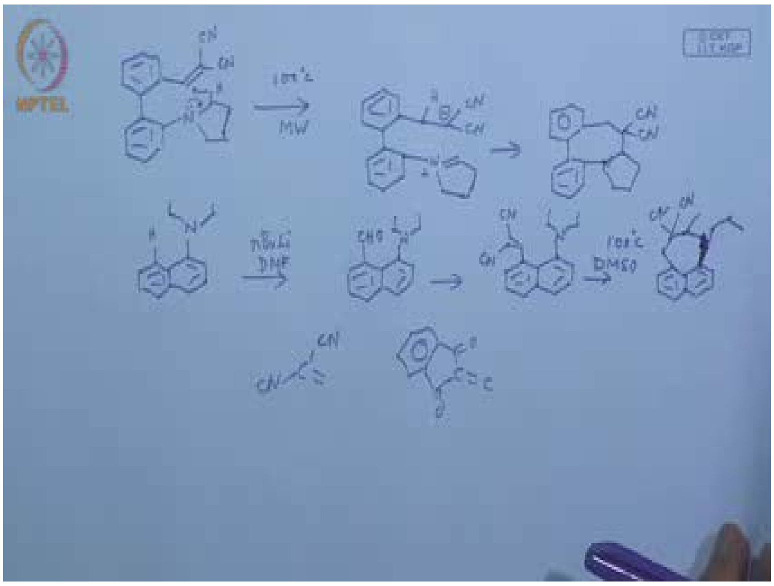


And, now, what everything is known. So, what I can do there are 2 propositional mechanism one is not sigma tropics hydrogen, other is what I say internal hydrate say. So, which one dual like to accept all this examples said till now, either explain of these mechanisms. One can quickly see that if it can be extended to macro cyclic compounds where the 15 is not possible something else which is just likely then we can propositional get shift could be better mechanism and that what happen. The next example I will say that you can produce macro cyclic. Macro cyclic means something which is bigger than 6, 7 may be, that is 8 is consider to be a macro cyclic like in this case it is a bye phenol case, that means; the back bone is the bye finial in the previous case it was derivative right.

And, this is common that ((Refer Time: 30:21)) is will see more example this then dies Jamie ion ethylene component, the iconic component so temperature is 100 degree centigrade with micro ion negative. So, what is the product? You can do all kind of thing nitrogen load pear and going through this benign ring when this thing that thing eventually you get a jotter ion positively charge this thing. But I think for us the review this reaction of this the internal hydrate transfer. So, first we have to recognize that there is in alpha hydrogen and this was and nitrogen loan pear was hydrate is shifted. So, if the hydrate is shifted to this so the back bounds the back bounds remains as it is then hydrate is shifted to this place. Then , you will get sort of a carbon an here right this nitrogen and then ammonium ion and so defiantly this reaction is very general.

And, this condition will have 1, 2, 3, 4, 5, 6, 7, and 8 so we get 8 member system. And we have nitrogen here and this 5 member and this 2 substituent is a Sino. So, that means; very general use this for this construction of an 8 member system what else we can do and how to we extend basically, at this stage you have to think about how to extend changes like many of you are resource fellows so you have to know how to change the reaction to change or other include different kinds of examples. So far, we have seen this ((Refer Time: 33:06)) all this compounds in one case we have seen the coumarin. And then now, we have a macro cycle and what will see bye finial system. Now, the next example actually is for I think 7 members system. And so in this case so it is a napalming case now, from napalming if you want to like make a 7 member ring.

So, what we can do? you can start with it I substituted ((Refer time: 33:51)) and then and treat this with and D M F all of know what is going to happen right what is going to happen c h o, it is going to c h o, you going to c h o but at which position, this is; 1, 2, 3, 4, 5, 6, 7, 8, 2 position that is actually ((Refer Time: 34:39)) normally, the reaction takes place 2 position. But you have a option here representation position actually if you have Lithine you get a actually 5 member sort of a ((Refer Time: 34:52)) compound. And all though units are not good but one can quickly make in 1 step without much problem this and then we can understand what we are going to do next right.

So, ((Refer Time: 35:16)) with 2 Sino which is very easy and then you see this alkali goods so you have all kinds of alkali goods and then what the reaction condition in this case is solvent is this the temperature is the around 100 degree in 4 hour. So, we get this reactor and this have been verified by D to the M leveling and then if you take this D to the M at a time then you get this organize that D to the M transfer and eventually what will find? If you contain 1, 2, 3 sorry 1, 2, 3, 4, 5, 6, 7 I thing 7 member 4, 5, 6, 7 so 7 member ring and so the nitrogen, so will have and this one should be Sino and this one will have be this group ((Refer Time: 36:46)) so that means; these 2 example, that means; possible to make a macro cycles and does not have to follow the 15 sigma tropic see.

So, intra molecular hydrate shift could be possible to generate this reaction such been found to the ((Refer Time: 37:09)) there are qualify example instead of Sino you can take the ester even I think the component could be here you have Sino. So, it could be even like say carbon here so like you can take component will have this ((Refer Time: 37:43)) and you can take the molecule of the if you recall ((Refer Time: 37:48)) and the digesters all can something is here. So, that means; you have been that means you have rather general reaction.

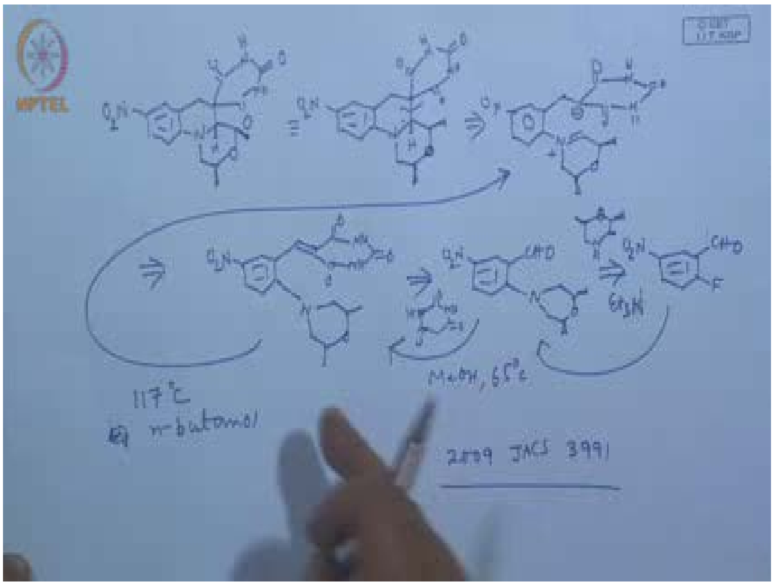
Now, what we do with this well recently in 2009 this reaction such been utilize to fabricate a new anti bacterial many of you know right. Development of anti bacterial very important field in medical chemistry why? Is a continuous process Penicillin was discovered in 1914 this was 1948. So, then what is the next kind of antibacterial agents and dividing. We have we know Penicillin we know tetra cyclic then immediate after actually something chemical ((Refer Time: 38:57)) what is it? 6 members good.

So, we all know this so latest antibiotic the role of.

Student: ((Refer time: 39:11))

2 right processive base thing would be ((Refer Time: 39:18)) own derivatives processive nothing but their own derivative. The people are still struggling to come of kind new antibiotic one what is the reason resistance what is the resistance? So, one of the drack candidate structures will nicely fixed ((Refer time: 39:48))

(Refer Slide Time: 39:53)



This structure is like this is a coolant derivative. And the other portion has a morph line kind of component and on the top will have a structure will have a nitrogen in 13 position. And then if you sort of in area right and I think my drawing is just you have to this is the methyl group here and this hydrogen also see here. And I think would give right may be I rewrite that ii give you better look may be portion and then again 6 members ring right. So, this is oxygen here, I am just rewriting basically I think this one should be let us take that little bit so what you see here in carbonize compound then N H and then N H here and then we have a ok. This was ((Refer Time: 41:32)) found to be very active antibiotic and this hydrogen here and this methyl group. So, all these hydrogen, methyl group substitute which each other.

So, how do you synthetically approach, that means; when you try to develop synthesis what is the first requirement actually so we call ((Refer Time: 42:01)) we talked about. Let us see a given task of synthesizing molecule so what is the starting point? The starting point is to

Student: (Refer Time: 42:12)

No, if you what to see if you begin with literal syntheses first thing you start

Student: (Refer Time: 42:21)

Functional group this is very important wherever if you let us go to any kind of topic you are starting very important. All of us know good beginning is of the

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

So, similarly, starting is a very important wherever you go so in such a think actually in the for a synthesis this starting is to recognize the structural pattern, that is; important towards organic chemistry. We have seen we dealing very few things what are the things and how many multiply bonds and then how many hydro atoms, that is, it and they are internal alternatives.

So, since it is hydro atom basically ((Refer Time: 43:24)) so what are the hydro cycle nitrogen hydrogen etc their internal essentials. What I can see that one you have benzene you substitute in it and then you go to the large number of methods by and for funnel may be 100 methods are there. And then you have a here motherliness and to little more preside we load we can see at and what is B C we see something here, what is it has common man right for which so that is what ((Refer Time: 44:17))

So, how do you do? So, how do break it that means; break it here is right and what will find? That means; will have to somehow make this and N H. And N H this is a carbon this is bad drawing but we are interested in them how you have to make this that is it so we have recognize, that means; we have ion should be there and then this.

Now, we know how to do what next we have to left this part mention as it is I mean somehow we have to make this by which wait. And this part as we can guess should be something like this so; this should be most appropriated starting material. And now, one can quick what next this double bound, carbon carbon double bound is form to the reaction. So, the next one should be this here and ((Refer Time: 45:56)) marperlate, marpholine and all of us know this can be I mean use to this edition reactions of ((Refer Time: 46:13))

You have a nitro group of here so and if you begin with a Florien substituent and hide ((Refer Time: 46:23)) actually, what was tuff to make this marpholine will not talk about it. But if you begin with substitute with the marpholine here and is the reaction condition is simple just try amino. So, you get to this compound you get to this compound from here to here what is the obviously reagent. I am absolutely know this base is required ((Refer Time: 46:56)) just heating in methanol and 65 degree centigrade would give the noble product. What next, that means; you have to go to the tracery amino effect reaction the reaction should be known as tracery amino effect reaction it sounds odd but basically, you have to now, do the reaction. What are the reaction conditions? Populization condition is again from the temperature is make out 117 degree, so it is allow. So, it is n-butonol ok.

So, you get to this product. And this was published see very simple right very simple nothing basically, this sort of compounds or know will known in the literature and boil with this marpholine try filament then heating it in methanol this corresponds to ((Refer Time: 48:12)) N H carbon l N H this is little available all of us know. Now, it is up tend from Margret and urea. So, chip methanol is chip just simply heat it, just simple reaction and it was published in JACS. That was simple and 3991there are some other things and that is in actually interesting also that is an interested feature and Probably I about tell you to the movement. But if you have the paper with me you can go to the or new paper there will find if you keep an heating different kind of solvent these either takes place in the motion methyl group there is in I have forgot in some Iso Moise possible there are aspects why accepted in.

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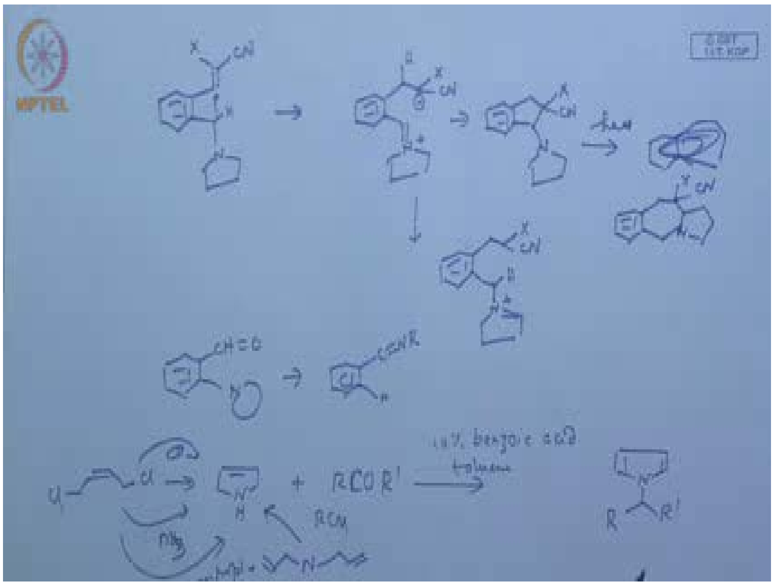

So, what next we have many example, such think actually what next what we have known tracery amino effect for normal systems, then we have see amino effect for this making the macro cycles, then we have a typical antibiotic synthesis and what we can think of? you have to change the structure, then we change the structure for example, some body has done like this X and now the amino is different here, in all the previous example nitrogen was attached to the phenol ring. Now, there is a ((Refer Time: 50:26)) what do you expect? Without going to the symmetric one would expect to this right. So, that is that is so you see and this X C and this is N hydrate is let us to know this nitrogen here and this ammonium ion right. So, what you get the sort of indent derivative with X C Sino and this nitrogen this one and this is form.

Then if you heat it what you expect I think I will not write the mechanism. But all of you can guess what are the product it is a 7 member rings are with nitrogen and this and x and see. So, how it is happening I think you we can write, you can do it. What you can do actually, during this there is also a possibility that this can undergo one see can tropic one see can hydrate I say that is it. Then , forms actually certain conditions it forms this. So, you have more example so what else we can do under say, very decant in 2009 you gave JACS paper what the deed instead of these you should of the carbon carbon double bound we just form the ammonium sort just ((Refer Time: 53:05)) they form let us say really structure modification just think of right. Let us say nitrogen here and if you take primary ion so what will find will have a ((Refer Time: 53:28)) base then one more I will tell you like say this is again a JACS paper you take R CO R prime.

And, the reaction condition is nothing just 10 percent benzene seat 10 percent benzene acid it was heated in what we expect? So, pyroline so 1, 2, 3 pyroline and what you expect is a new pyro syntheses just you can see down and do the mechanism very easily without any problem this is the product. So, again ammonium sort is formed now, internal hydrate and for the this pyroline I think from these all of you know how to make this pyroline can to make from this sis chloride with amine this is obtained for the correspond ((Refer Time: 54:52)) hydrogenated in chloride formations in this and then this ok. This is one of the easiest or else what we can do without using ammonia we can use urea are close but not in the somebody example, that is; euro tropic.

And then alternatively one can think about what it is aluminum. So, there are so many methods by which one can make this and this kitons are little chemistry literature just mix them heat them you get the all define kinds of the substituted a pyro derivatives that is why it was published in JACS.

And, lastly I think I will talk about first example. So, what is the first example so if you recall first example. What was it at the end we should be able to answer this questions. What is the product? This one first one so we know do not lot of about the ((Refer Time: 56:41)) amino affect homo rather than macro cycle formation all kinds of carbon carbon double bond, carbon carbon triple bond all things. But carbon carbon triple bond are missed so may be one day someone would do. I will have the example where, hydrogen hydrate transfer to carbon carbon triple bond with nice activity nice research problem and this is again recent example what you can think off that there is no nitrogen now there is oxygen. And the condition is that butonol to dial means like utilization actually some of them try to do so.

But eventually, the product that ((Refer Time: 57:30)) and with nice previous activity is increase. And this carbon will have here of course, the hydrogen has been shifted from here this hydrogen. So, it is say ((Refer Time: 57:52)) say secondary you can say oxygen effect you can say that also ((Refer Time: 57:58)) amino effect secondary. So, all of us know this oxonium ions or more right so that, to this transformation and there are examples. Now, this are reactions when without acidic you can do means, by using simple ((Refer Time: 58:29)) all of us know one of the important reactivity of formation of an oxygen.