Essentials of Biomolecules:
Nucleic Acids, Peptides and Carbohydrates
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Lecture 06
Chemical Synthesis Pyrimidine Nucleobases

Hello everybody and welcome back to the lectures so we have completed the module 1 and today I am going to start the second module, module 2. And here we are going to discuss about some organic synthesis the synthesis of the nuclei basis nuclei, nuclei sites and then of the nucleotides. So, when you look at the nucleobases adenine guanine cytosine thymine as I have mentioned that there are up to 2 types as you know already pyrimidine and the purines.

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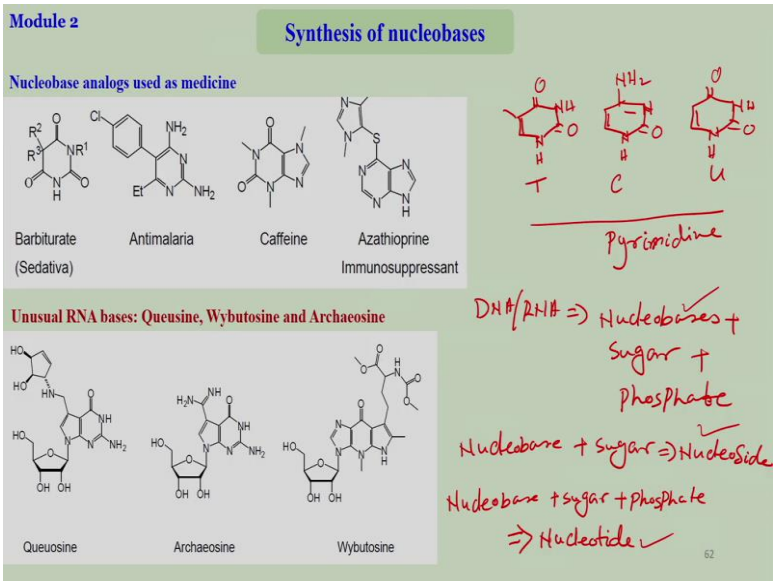

So thymine this is thymine T I am just writing the nucleobases only without the sugars cytosine and we have uracil in RNA. These 3 are they are of the pyrimedine class and adenine and guanine are of purine class. So, we will take one at a time we will discuss about the synthesis of the pyrimidine nucleuses first and then we will come to the purine rings. One thing I should mention that when you look at the DNA or RNA that they are composed of nucleobases plus sugar plus the phosphate.

Now the nucleobases are the heterocyclic compounds which are of this kind spear emitting and purine. Now when the nuclei base is attached with the sugar so nuclei base plus sugar this is known as named nucleoside and nucleobase plus sugar plus the phosphate are known as nucleoside. So, we will see how can manufacture or how can we synthesize these kinds of

entities these kinds of molecules the nucleobases the nucleoside and then the nucleotides in your laboratory.

So, why is it important to synthesize these kinds of compounds in biological cells they are biosynthesized. There are processes involved that manufactures all these nucleobases the nucleoside as well as the nucleotides within the cells with the help of enzymes the proteins. But for a scale-up operation in order to work in the laboratories you need a massive quantities of them so therefore you need to work out a plan you need to find out certain methodologies how to synthesize or how to develop these kinds of molecules in the laboratory number 1.

Number 2 there are many drugs there are many medicines in the market which have the similar structures of the pyrimidine or the purine or the nucleotides kind of structures and they act as a very good medicines for different kinds of diseases. So, therefore evolution of such molecules or the making derivatives making variations of the natural nucleobases or the natural sugars are important to develop new molecules which may have utilities.

So as you already have seen I have in my in the first lecture probably I have shown some of the molecules that are of the pyrimidine type.

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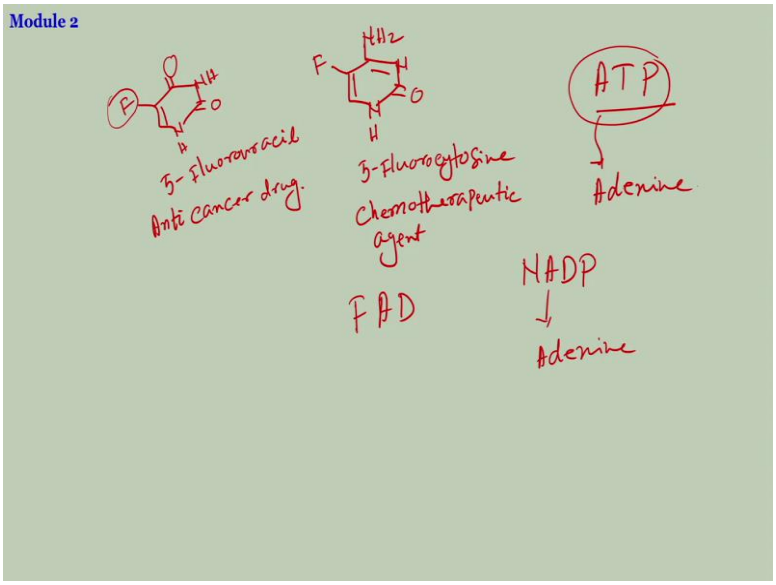

For example 5-fluorouracil I have talked about this molecule is called 5 fluorouracil and this is a very famous anti tumour agent anti-cancer drug or a chemotherapeutic drug. Here you can see that this is a pyrimidine nucleobase basically with a fluoride atom attached. Here where the CH3 was for thymine or where there was a hydrogen atom for uracil here you have a fluoride

atom and of course this is not a natural product this is not available naturally you have to synthesize it.

Similarly another molecule which looks very similar fluoride here the amine this is usually a cytosine with a fluoride here. so, this is called 5 fluoro cytosine this is 5 fluoro cytosine which is also an chemotherapeutic agent very well used to give a therapeutic agent actually. This is available in the market this is also available in the market both are commercial anti-cancer drugs that are they will early used in chemotherapy.

So this is also a pyrimidine class of compound and of course needs manufacturer. Apart from that if you see apart from the DNA or the RNA there are other molecules in biological cells who also contain the similar structure as the nucleobases. For example ATP as you know adenosine triphosphate this has of course adenine in it and a triphosphate. So, already the purine moiety is attached in this biomolecule apart from DNA or RNA this is not a DNA this is not an RNA but a very useful biological molecule extremely important biological molecule.

Similarly there are coenzymes that are present in our body which participates in many biological processes many enzymatic catalytic reactions like one of them is NADP nicotinamide adenine dinucleotide phosphate. Here also same adenine is there adenine or adenotion is present. Similarly FAD is another very important cofactor or a coenzyme which is present in many enzymes actually.

This is flavin adenine dinucleotide same adenine is here. So, apart from the DNA or RNA in the effort from the genetic information other kinds of biomolecules also contain nucleobases and if we can develop them in the laboratory or if we can make mimics of them that would be useful. So, here I will show some of the other drugs which have the pyrimidine or the purine kind of geometry this is a barbiturate it is a sedative drug which has a pyrimidine moiety and here there are certain groups which can vary.

This compound is an anti malaria compound this is also pyrimidine 1-3 amine this is a 2 amino pyrimidine actually 2 amino pyrimidine and then there is a aromatic ring attached here it is a highly substituted molecule. Caffeine that you isolate from coffee has a purine structure with the methylated versions here. And as a Azathioprin which is an immunosuppressant drug this is

also well commercialized in the market it is available this also has the pure ending with a sulfur and another 5 membered heterocyclic ring.

So, these are some of the commercially available molecules that belong to the class of the pyrimidine or purine. Now apart from those sometimes the unusual RNA bases there are few RNA bases that we will see that are present in RNA that we will see later on is Queusine, Wybutosine and Archaeosine these are the structures this is again a purine ring purine ring and a heterocyclic ring is purine in fused structure.

So, many of them are of the similar class so the need is of course to develop methodologies or you have to synthesize these compounds in the laboratory so that is the background of it.

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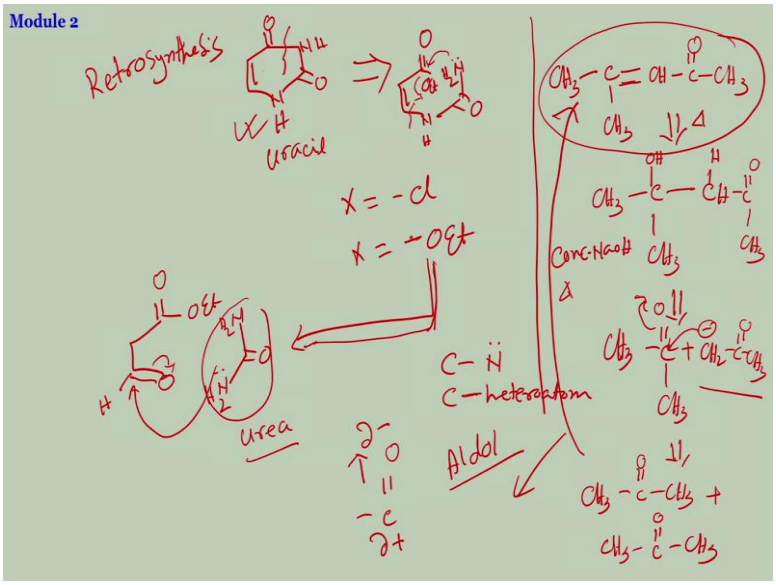

Now how do you synthesize them I will start with a simple molecule uracil. So, if you want to synthesize the DNA structure which means that comes with sugar here and then a phosphate here and then the other sugar. So, first we will see how the nucleobase is the free nucleobases can be synthesized that is one second is how the nucleobases could be attached with the sugars that is number 2 and number 3 how the full oligonucleotide or full DNA or RNA can be synthesized.

So, starting with the nick free nucleobases in this case I have taken the example of uracil. Now how can we synthesize this molecule. So, you have to look at the molecule and try to find out ways through which you can manufacture this. For organic chemists the way of doing such kind of thing is known as the retrosynthesis. We call it retro synthesis retrosynthesis means thinking

back you look at the final molecule which is your target and then try to think backward which could have been the previous step.

And then again which could have been the further previous step and then you go back likewise until you reach to a set of components which are easily available in the laboratory and from them you can manufacture it. So, while looking at the molecule you have to think the what the previous step could have been. So, here if you look at this molecule can you find out a way how to break this molecule. I will give you a further simplified example if you know this molecule if you look at this molecule.

And if I ask you how to synthesize this molecule then you can easily find out about where to start from. So, whenever you look at the molecule if you want to make a bond then you have to think of how to break the bond. And always our target should be which bond is most susceptible to break. So, then only that will be more easy to make. More susceptible to break means which is the weaker bond. Now if you look carbon-carbon single bonds are very strong carbon hydrogen single bonds are very, very strong.

Carbon-carbon double bond has one single bond and one PI bond and PI bonds are of course weaker bond carbonyl bonds are quite stable it can still break it but they are quite stable. So, if you can think that how you can make the PI bond carbon-carbon PI bond from the single bond here from the single bond if you can think how to make the double bond then you are through here. so, obviously if you are chemists then you can easily figure out that if you have a hydroxyl group here and another H then they can slight hit they can dehydrate they will lose one molecule of water and make a double bond.

So, the precursor of this is OH here and of course you have to fill the valance and this has to be an H here so minus water would give this. Now again how would you get this. The moment you see a hydroxyl group here okay it could have been the other way around OH here and H here but if you put OH here that way H would be next to a carbonyl group this is much better. Once you see that there is a H you can immediately figure out what the precursor should be that if you have a negative charge here then that would have attacked a carbonyl group and the carbonyl group has gone to the OH CH3 plus.

If you have a CH2 - CH3 then from here to here is very easy it attacks here is a nucleophile attacks here carbonyl opens up and gives through the OH and give you the single bond here. And this means basically that your precursor molecule is CH3 CO CH3 which is an acetone plus this is also the acetone CH3 CO CH3. So, if you mix 2 molecule of acetone and do certain chemistry then you can get back you can manufacture the first target molecule.

And this reaction of course you all are aware of this is called the aldol condensation. So, by looking at the target molecule you can think backward how to come down to the readily available materials and then find out a way to synthesize the final compound. So, from here from the 2 molecules of acetone to this final compound all you have to do is you how to add concentrated sodium hydroxide that is all.

Then you will get this compound and slight heat this is called aldol condensation. So, that is the way to think back that what could be the previous step. Now coming back to the nucleobase if you look at the uracil then you have to think what could have been the previous step. Now if I see here as I mentioned which bonds are weaker to make there is a PI bond which of course can be weaker at the same time if you see the heteroatom carbon nitrogen bonds or carbon anything any hetero atoms if it is present there.

Those bonds would be easier to make because there is a huge difference of electronegativity. The hetero atoms contents lone pair of electrons or they can be made electron rich very quickly very easily and your carbon can be made electron deficient as you are seeing the carbonyl compounds carbonyl compounds can be made very electron deficient and they are already electron deficient. Because if you have a carbonyl compound this is Delta minus so it drags the electron towards itself that creates positive charge on the central carbon.

So this carbon centre is electron deficient and if you use a hetero atom which is electron rich that can readily attack here. So, making a carbon heteroatom bond is easier. So, in this case you can think that you can break this bond quite easily. So, if you break this bond then what will have you can break this also what this is easier to make I mean even if you do not break it, it will come back very easily that you will see.

So at first I am breaking this CO you have these NH CO if you break this bond then you have amine NH2 now there has to be something here what is it if the nucleophile if the lone pair of

electrons on nitrogen attacks here something has to release something has to go away and if that is a good leaving group then the thing is becomes very easier. So, if this becomes a good leaving group x and I am directly writing here.

For example okay x this x can be for example if it is a halogen atom chloride then the nitrogen can attack chloride can go out because CL would like to go away as CL minus it is highly electronegative. So, you need a good leaving group present in this position or it can be a OET for example OC OC CH3 ethyl group which can be made and in that case this is an ester which can be made a very good leaving group.

So this thing you can convert it into and a star for example it can be CL it can be a star then this becomes an ester and if the nitrogen lone pair attacks here then this will release very easily it is a nucleophilic substitution reaction and you will get this bond. So, it is easier to cleave such a bond. Now once you have done that what is the next step or rather the previous step is the breaking this bond. I can break this one very easily the same way actually CO I am keeping this as OET.

And then this becomes NH2 and NH2 I mean I am coming here and we come this part just in a minute now this molecule if you break here is urea which is readily available material and very easy very cheap. Now how can it attack here so if you have the urea the urea has to attack this carbon which means this carbon has to be electron deficient how to make that carbon electron deficient? I can do that if this is a carbonyl group which means this is an aldehyde basically then this can attack very easily.

And now think a little bit at once if it attacks here this will become OH and if it OH there is H here it will dehydrate it will eliminate water molecule and give you this double bond. So, you have to do a little bit permutations and combinations and think a little bit of organic chemistry then you can easily figured out and this is easy actually it is not very difficult to do. So, a combination of urea and this molecule can give rise to your target molecule.

That is according to your scheme now such kind of molecule is known as if this is a ketone or an aldehyde this is beta if this is a ketone then this is called beta keto ester which are also kind of available materials. Now the question is whether you can make this compound out of these 2

reagents or out of these 2 starting materials. In other words now we have to do the forward process so this is called the backward process.

Now we have to do the forward process whether the scheme we have developed is feasible or not. You may develop different kinds of schemes and then they have to meaningful then you have to find out whether from the starting point you can actually go down to the target molecule. So, we will start with the starting points and then see whether we can synthesize the uracil or not.

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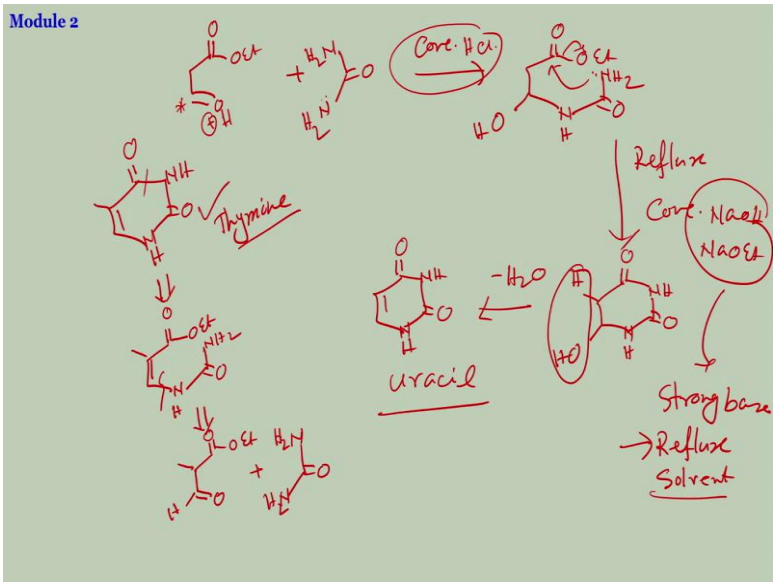

So here OET this can be any other living groups also just like halogens and chloride so this will become acid chloride which is not bad which is also okay. And this is a aldehyde plus now we have urea. If you take these 2 compounds what do you get if you use concentrated base or acid actually if you use concentrated acid for example then the acid will protonate where it can protonate this it can protonate there.

So if it proton its here this becomes a positive charge and this carbon becomes electron deficient therefore this can readily attack. So, I can go down here this will become OH and I can get NH NH2 if it attacks here this will lose one proton and this is the weight it will get this and in presence of high heat we usually need to do reflux in presence of solvent then this reaction can happen you have OH here.

Now since you are heating it up already then OH and H they will eliminate water very easily dehydration in high temperature is very feasible reaction. You have your uracil so this is one of

the ways you can synthesize the uracil molecule from the very easily starting materials one is this another is the urea now there are other methods available lot of different permutations and combinations can be done I will mention few simple ones one or two simple ones and I will show you how we can do in their very essence how we can do chemical modifications to such structures.

Now the problem of these kinds of methods is that you have to use highly amount of concentrated acid then in this case you sometimes need to hydrolyze the ester that by using concentrated sodium hydroxide concentrated base or sometimes even stronger base sodium ethoxide it is a very strong base. And you have to use high temperature reflux so you have to make all the compounds soluble in a solvent so you need a lot of solvent organic solvent.

And you need or the reflux temperature for the solvent. So, high amount of acid and high amount of base concentrated base is required for such reactions you need huge amount of solvent and huge temperature to carry out such kinds of reactions. So, you can see the thymine if it is time in there will be a methyl group here. So, in similar way you can try to find out the precursors or the backward steps for synthesizing the thymine.

Now can you do it if we use the same protocol cutting here and then cutting there these NHh this should be I am writing OH here you can use any other leaving group also still fine this next cut is here OET this should be ketone there would be methyl this would be H and that is basically it urea and urea NH 2 + NH 2 so that makes urea. So, if you start with this compound mix it with urea in presence of strong acid followed by strong base and then reflux it then you can expect to get the thymine. You know this is thymine so this is one of the protocols to synthesize the nucleobases.

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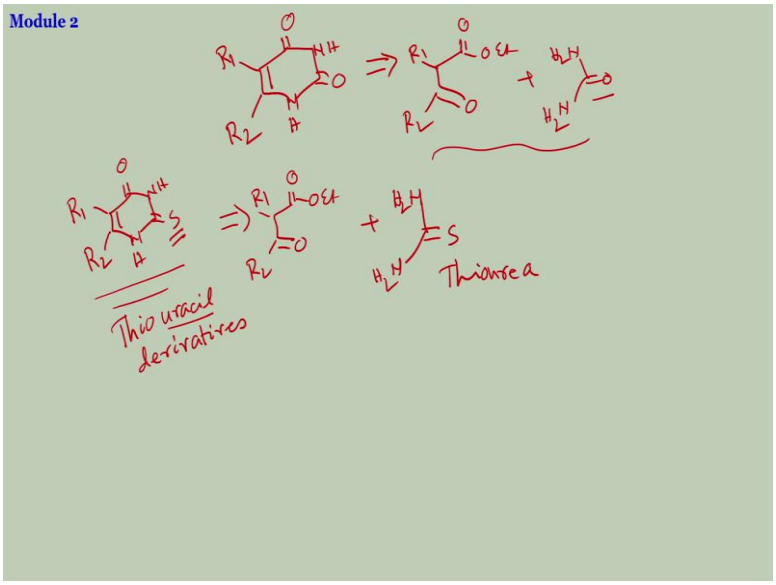

Now the pyrimidine I am just sticking still to uracil and thymine kind of thing which has the common geometry of this common structure not geometry which is the common structure as I will give you give it a name R1 and R2. Now making it a general structure R1 and R2, now R1 and R2 can be any substitutions depending upon the choice depending upon your need. So, as you have seen the examples there are many molecules which has this core structure and then varying the substitutions here and there.

So in general if you want to synthesize such kind of molecule your precursor would be this here R1 CO here R2 plus the urea and this is one of the very old technique and very old method where it is synthesized in this fashion using the strong acid and base. Now I will show you that we have been working in this area for some time and we have synthesized many different kinds of variations of the pyrimidine nucleobases and like this and other ones I will just show you.

And we have developed named methodology how to synthesize these kinds of molecules from the same kind of precursor but changing the reaction conditions and that gives you much better yield very less time and without the presence of solvent. So, solvent factor is one essential factor and if you can reduce that then you save lot of money as well as you save the environment. So, it is to some extent environment friendly procedures that you do not if you do not use organic solvents.

Because there will be lot of waste of organic solvents if you carry out your organic reactions and that is not good for the environment.

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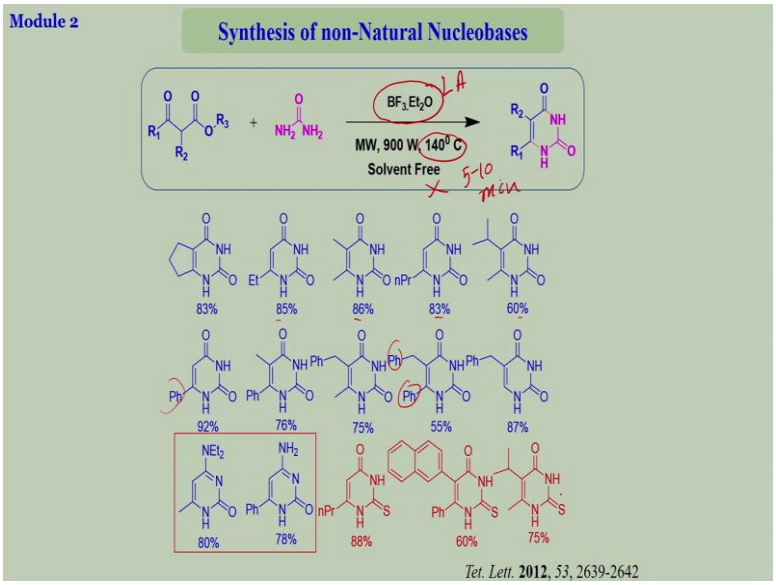

So I will show you a method I will just come back here just in a brief period this is what we have developed and published. If you have this is the same beta keto ester as you have seen earlier and this urea and instead of using a huge amount of strong acid and strong base if you just use we can acid in this case we are using the Lewis acid which is BF3 that always presents in a ether mostly is solubilized in ether.

So BF3 is the Lewis acid LA for Lewis acid you do not need strong acid you do not need strong base just a little bit amount of the Lewis acid and then if you do the reaction in micro oven not the kitchen micro oven there are micro oven reactor that are available for the chemical reactions. So, microwave for reactor at our own 140 degree Celsius you do not require any solvent then you get this kind of molecule R1 and R2 with variations.

And we have made plenty of molecules which has a complicated geometry which other ways if you will strong acid and strong base as you have seen earlier you cannot synthesize most of these molecule complicated molecules using that methodology or using that reaction conditions so here we have used many different kinds of molecules which has a branched chain which has a longer alkyl chain which has aromatic ring attached also 2 aromatic rings attached here.

And all of them are coming at very high yield and this reaction takes only 5 to 10 minutes. So, when you have seen that reflux method this method they take overnight or 2 days or 3 days sometimes even 3 days of reaction in reflux condition. So, in this case microwave oven reactions then the all reactions were mostly finished between 5 and 10 minutes of the reaction and you get quite a high yield of the molecules.

We have synthesized few other different class like I will just show you now here instead of using urea you have used the higher or thio urea. So, next class is so this comes with urea now if this is your target molecule I am sticking to the simple molecules actually I am not going to the complicated molecules S if it is S instead of the O here which is and then what will be the precursor of course the same precursor for this part plus instead of urea you can use this.

This is known as thio urea, so thio area can be fused with this molecule that will generate thio uracil kind of molecule this is called thio uracil derivatives. So, they are basically all class of uracil derivatives because without R1 and R2 it is basically urea uracil. So, if there is one S then it is thio uracil so these are thio uracil derivatives and many of such molecules have been synthesized.

And by other people and many of them are actually has shown nice properties like inhibitors many of them are actually being used as anti malaria agent and other kind of structures are there. There are a lot of molecules that have pharmaceutical activities of this kind of structures.

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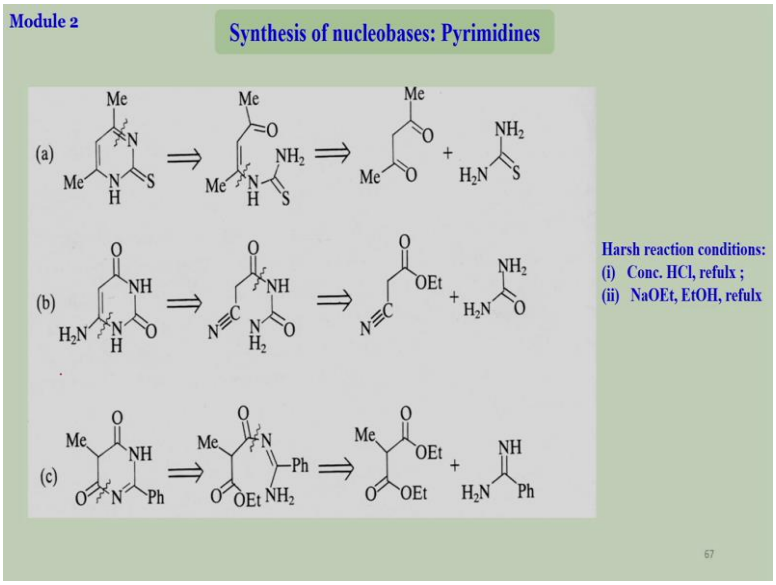

So, here I have kind of summarized how to break the molecules depending upon the structure. So, if it is thio urea and this kind of structures if this is your target then you can go back go back go back and you ultimately get down to this. This will come one by one.

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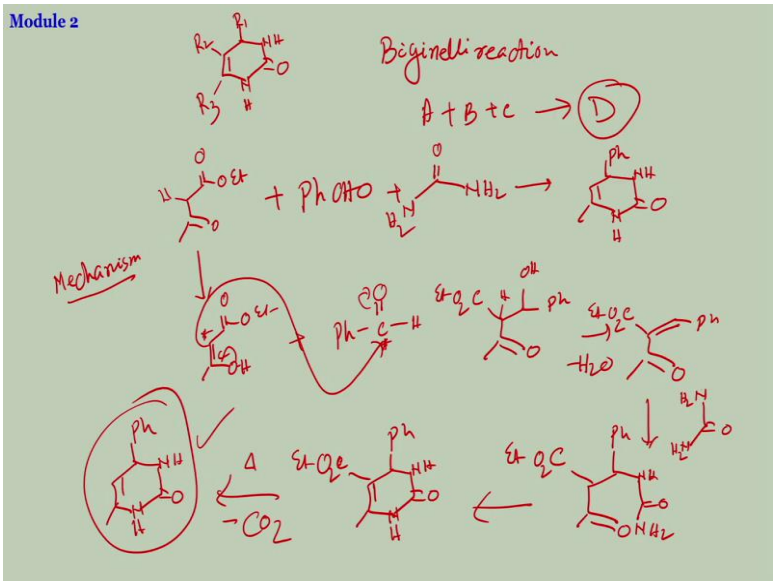

Now the same molecule so there is another way if I take the general structure as these so this is also pyrimidine if you do not have the carbonyl group here if you have for example here a R1 here R2 here R3 this is also pyrimidine molecule. Now how would you synthesize such molecules? So, you can go back in the same way as we have seen previously or there is another method which I will come directly from this starting point is known as the Beginalli reaction.

Beginalli reaction is a famous reaction which uses 3 components or 3 starting molecules to synthesize one single molecule and all 3 are fused together to produce a single molecule A+B+C that gives you a target molecule D. So, how it goes it starts with the same beta keto ester in this case there are a lot of examples of Beginelli reactions I am just sticking to the simple one actually.

If you start with this simple beta keto ester plus if you take benzaldehyde plus urea then your final product would be NH here would be the pheniol NH CO this would be your final compound. Now how would you get down here the mechanism of this reaction goes like this first this forms an enolate this is basically carbonyl compound which has alpha hydrogen so that will form the enolate structure OH and the methyl.

And your benzaldehyde is electron deficient on the carbon. So, this can it is a basically in all that reaction and here it can go back that will give you OET or I will write in different fashion so this carbon and this carbon would be coupled together. So, your CO2 ET this is the CO2 ET will is untouched and here what you are getting is C OH and PH and here you are getting back the carbonyl this is formed.

Now this will dehydrate and we will give you CO2 ET and your PH there would be a double bond here minus water this OH and this H go away now if you fuse it with urea this will go here it can come, so you will have the PH here CO2 it comes back NH CO NH2 and then this fuse and of course that will form the double bond OH and then it will form the double bond. This you can figure out very easily you can have PH you still have the CO2 ET left.

Now if you heat this up you get a very quick decarboxylation minus CO2 carbon dioxide will go away will be eliminated and that will give you the plain structure pH. So, it is a 3 component reaction goes via some multiple steps but the reaction is very quick and instant it gives you the single product without much other side products. Now this is this is for the uracil kind of moiety.

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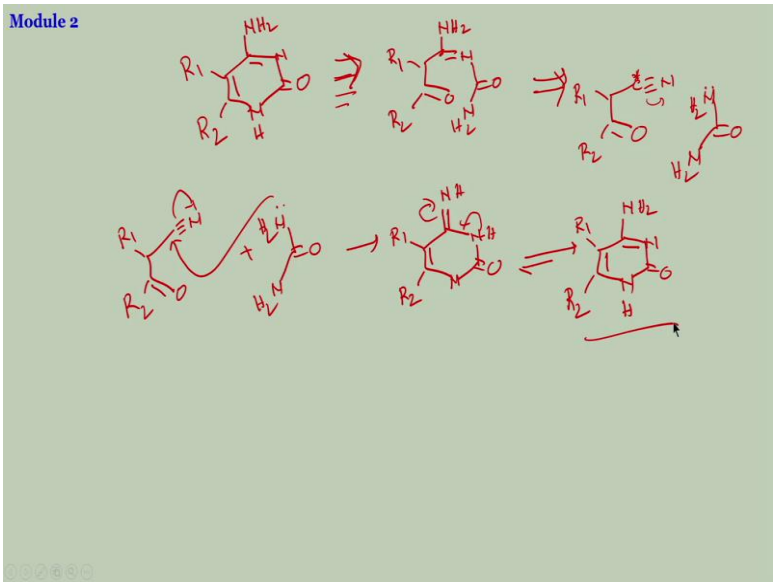

Now if you take the cytosine cytosine has amine group here in NH this if I make it general R1 R2. How to synthesize this molecule now, if you go back now double bond again so which can now we have to think a little bitch here. So, this part can be the same so I can keep this for the moment NH2 and this becomes this R2 R1. Now if you cleave this bond this nitrogen becomes NH 2 which is fine.

Now you have to think or you to find out a way to make this carbon electron deficient so that the amine can react this NH2 of the urea can react. Now here you have to think what could be the precursor of amine that has electron-deficient center and for organic chemists it is easy that

this is a cyanide. If there is a cyanide group here cyanide carbon is of course electron deficient and therefore the lone pair of electrons or the urea can activate it away.

If you make this can readily react here it will open up so sorry I should write in this fashion whenever you are writing a retrosynthesis this is usually the representation that we do instead of writing a single arrow we represent the previous step in this fashion. This means that you are going towards the backward direction this is not going to the forward direction. So, now let us go to the forward direction if you start with the cyanide and the urea whether you get the cytosine compound CN R1 R2 and double bond.

Urea if this attacks here this opens up so what you get is double bond NH and I am not showing I will fuse it straight because you already know this there will be double one here this is R2 R1. So, you get already one double bond NH and of course double NH is not stable so that will total mores itself quite towards the forward direction and you will get you the NH 2 there will be a double bond here easy your cytosin derivative is it is synthesized.

So, in this slide you can see that if you have thio then this will be the root here you have an amine so same as that I have just shown if you cut this it will come down to a cyanide and then if you chop this it will be this compound plus the urea. If it is this kind of geometry then you can have the ester here as well. And this one is start to ester you can actually do this from 2 both esters instead of the beta keto ester.

We have used this one ester and R1 ketone you can use both esters also you will get down to the same thing same kind of molecule if you want a carbonyl group in this position. So, I will show you what are the variations we have done and what are the mechanism of this. So, in this case using the BF3 ether beta keto ester and urea you can get down to the uracil kind of derivative as well as the thio uracil kind of derivative.

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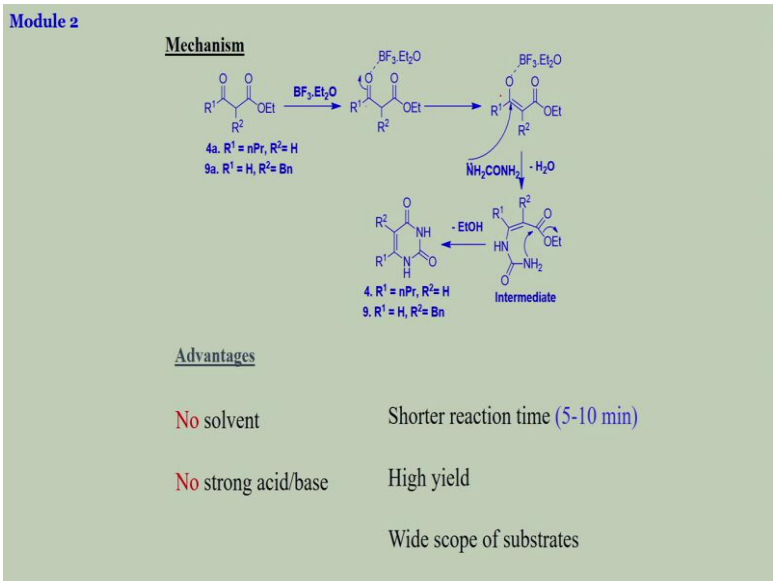

This is the mechanism of this reaction which is quite important actually. So, as I have shown earlier that when you use strong acid that activates the carbonyl compound in this case also use of BF3 as a Lewis acid that will activate this carbonyl group. Ester will remain intact the carbonyl will be better activated or more prone to be activated by the Lewis acid so this would be a kind of Lewis bond which drags the electron density BF3 has empty orbital which attracts electrons electrons.

So, BF3 is electron deficient so oxygen electron can go towards the BF3 that makes this carbon this carbon electron deficient. So, therefore the urea the lone pair of nitrogen of urea can react very easily attack very easily of course you can make the enolate formation also that gives you this then once you get the double bond this reacts eliminating the ester and you get your uracil derivative.

So, advantage of this procedure is as I mentioned that we do not need to use any solvent which is slightly it has advantage towards the environmental factor you are not using strong acid or a strong base which again is beneficial for the environment because most of those things go to the water drain after the reaction is over you have to discard the acid unused part of it so that that will contaminate water. Reaction time is very short 5 to 10n minutes.

The yield is quite high many of them compounds that we have made cannot be synthesized using that classical method and yeah of course in the wide scope of substrate means you can make several variations.

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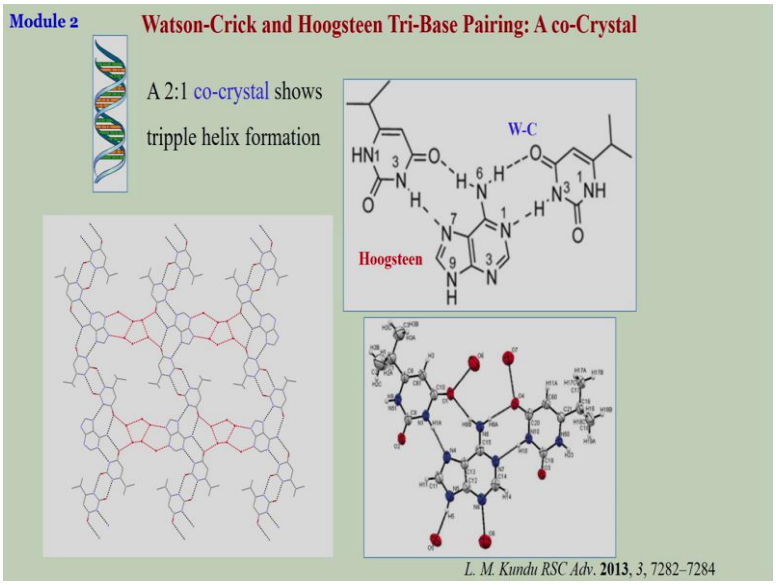

And we have seen one particular compound has shown the artificial base pairing also. So, this is just for a kind of a small kind of information that you have seen when we have done the Watson-Crick base pairing that adenine pairs with thymine. And here what we have found out we have found out the crystal structures that if you have instead of the thymine if you have this group isopropyl group so this is 1 2 3 4 5 6 thymine was methyl at the 5 position.

So, this compound is isopropyl in the 6th position 6 position isopropyl and this molecule shows actually this is also the same molecule 2 of this molecule they pair up with a single adenine. So, usually one adenine versus one thymine this case we have seen the 2 of such kind of thymine derivative pairs off with one molecule of adenine and the mode of hydrogen bonding what we have figured out is this part is Watson Crick and the other part is Hoogsteen.

So I had remember I had shown that triple helix formation so if this is kind of triple helix formation from this artificial nucleobase. And so therefore you can make artificial base pairing also you can use these molecules to form artificial base pairings as well.

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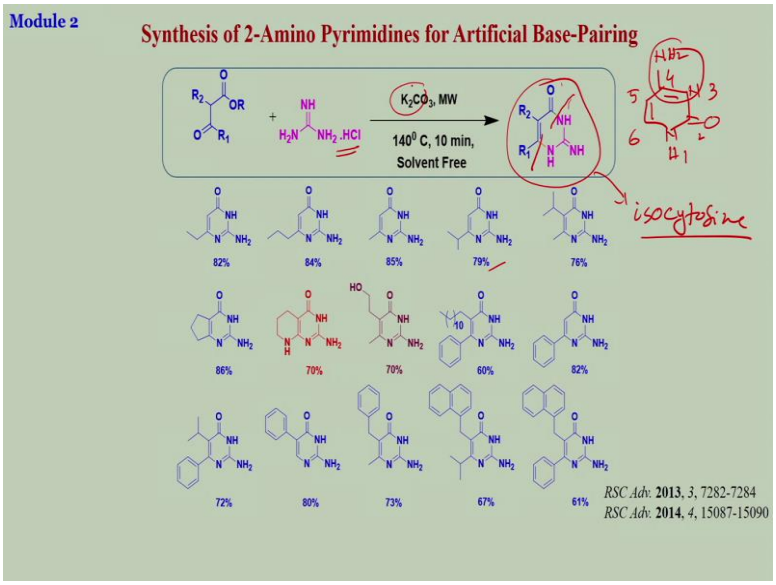

So, now a second kind of example is if you want to synthesize this kind of molecule which is just the reverse kind of cytosine. Your cytosine was here there was the amine that double bond in here thymine was there at 4 position. So, 1 2 3 4 5 6 in this case and there was this 2 position was there was a carbonyl. In this case they have kind of exchanged the amine group came to the 2 position second position and the carbonyl is in the 4th position.

So this is known as 2 amino pyrimidine or they are also called the isocytosine just the opposite of cytosine or the derivative Iso mode cytosine, Isocytosine very important class of molecules some of them so pretty good activities as pharmaceutical agents. So, if you want to synthesize such kind of molecule then all you have to do is instead of the urea in this part here you chopped here there is another chop here.

So, instead of urea you use this molecule you own it this is called ownidine chloride and then almost the same way only thing is that previously we have used acid in this case since there is a little bit of acid already here you have to use base to abstract that acid other than that everything is fine. If you mix this 2 thing in a microwave reactions or even in the normal classical way reflux condition with solvent if you use microwave oven then there is no solvent no need of solvent free reaction takes only 10 minutes and it gives you this molecule. And there can be a large variety of such kinds of molecules.

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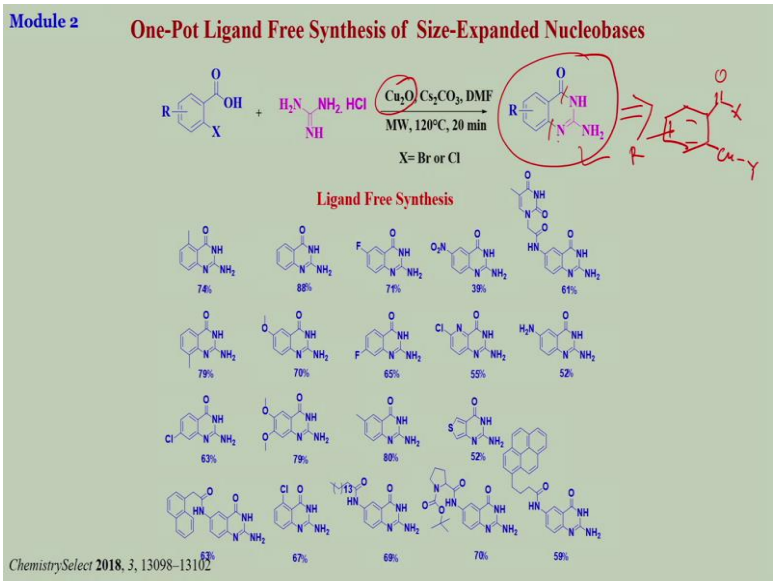

This is one kind of structures which is again expanded of the pyramidion this is the pyrimidine part with the fused aromatic ring this you can synthesize. You can try to figure out there can be many, many other ways to synthesize this. You can try to figure out the other ways how we can make this molecule. Of course if you cleave here then what you have is you have the R and then this O it can be OH or x I am writing or simply x the leaving group and here you need another leaving group.

So, you have to fuse here this is little bit tricky because if you think straight then the nitrogen lone pair has to attack aromatic ring aromatic carbon. And aromatic carbon is already high in electron so it is already electron rich ring therefore nucleophilic substitution is unfavourable very, very much unfavourable. So, you have to think other ways how to make this bond that is what is the trick and that is why this is not straightforward.

We had usually such kind of reactions are done by coupling reactions they are called the metal coupling reactions using metal ligands. There are many named reactions that are available which describes the formation of this bond aromatic and nitrogen bond many, many new reactions are there. So, in this case it is pretty simple we had used a copper oxide as the ligand and then cesium carbonate as a base microwave reactions 20 minutes of time and that gives you this.

So, what it basically does is it forms a complex here in this case. Oxidative addition followed by reductive elimination and then since you have the copper that has come in between the

aromatic carbon and this group copper is electropositive it drags the electrons therefore makes the aromatic ring little bit less electron-rich and then your reaction can happen.

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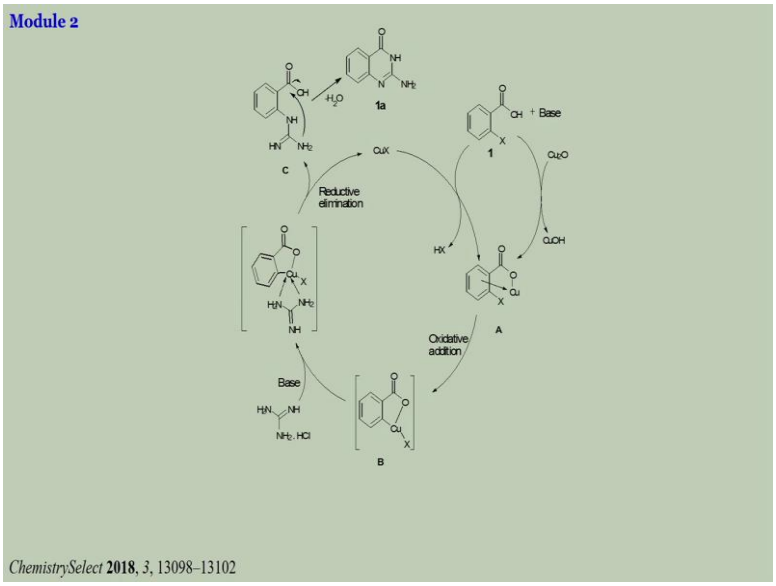

So, this is the mechanism of this process which is little bit complicated if you are not this is little bit in advanced chemistry. So, where it goes for oxidative addition followed by reductive eliminations this is what we had figured out, thank you.