Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach

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Lecture 30
Radical Mediated C-C Bond Formation

Welcome back to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. We have been discussing the chemistry of radicals. We have seen, how radicals in the last lecture, how radicals can be generated? And what is the, what is the strategy to make the radical reaction useful reaction? We have seen that a right combination of nucleophilic radical electron deficient alkene or electrophilic radical and electron rich alkene that type of combination is required in order to have a meaningful or useful radical reaction.

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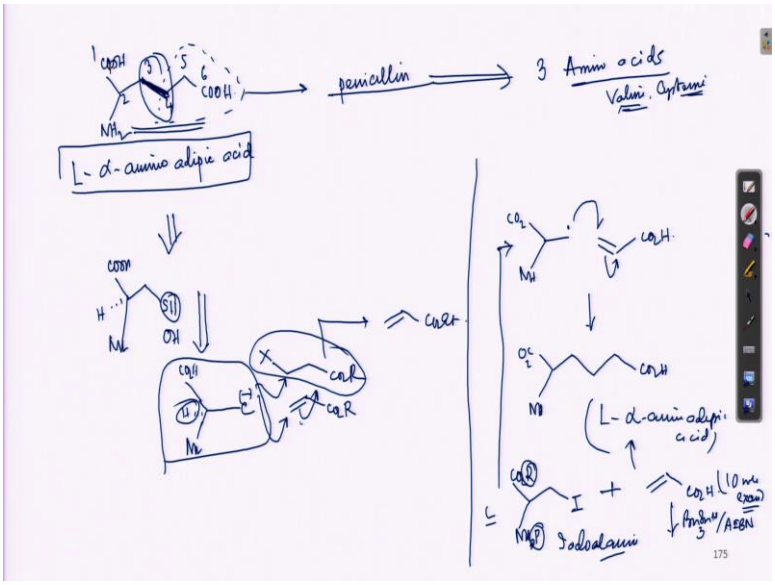

Now, let us give some examples where this radical reaction has been utilised. One is that there is an amino acid which is not a protein amino acid, which is not a protein amino acid like this, this is you see this is 1, 2, 3, 4, 5, 6 this is alpha amino or 2 amino you can say adipic acid. The lower homologue is a is a protein amino acid that is the very well-known glutamic acid. But this is not a protein amino acid.

However, this is a very important starting material for the production of penicillin. Because penicillin comes from 3 amino acids. And one of the amino acids is this alpha amino adipic acid, the other cell well known valine and cysteine. So, they are commercially available, no problems. So, if you want to make penicillin you can have valine from, add valine from

outside, cysteine from outside. But this alpha amino adipic acid with a particular configuration also L configuration, it was much more difficult to commercially obtain this because there is a difficulty in preparing this compound.

And why do you prepare? We need to prepare because this is not a protein amino acid. So, it is difficult to isolate from natural sources. So, there was this, there was this attempt to develop methods of alpha amino adipic acid. And I will tell you about a radical way, a radical method of making these type of amino acids.

If you try to dissect it, like your disconnection approach, you know that that amino acids that are naturally available, and they are also available in with a chiral integrity L amino acid. So, if you want to make a L alpha amino adipic acid, the best way is to that you have a carboxylic acid NH2 and then you come to up to this carbon. And there are plenty of amino acids with this type of system like SH cysteine, or it could be OH that is serine. So, those type of amino acids are known, and after this, that means you have already have three carbons built in the natural amino acid. And after that, you have three more carbons.

And if you look at the structure, three more carbons, you can maybe just a little imagination if you have, then what you can think of is that you have these type of amino acid three carbon amino acid, which is okay. Three carbon amino acid sorry, and then. So, this is carbon and then what you need is to add this carbon to, you have several possibilities like co2 R or you can have, you can say that I will have XCRco2R. So, basically, I want to make anion here and then I will do a Michael addition or I can do a direct SN2 elimination.

So, these are some of the possibilities that one can think of. You can also think of other strategies that I will start with glycine. And I will have this other 1, 2, 3, 4, 4 membered chain. But that does not help glycine itself is a chiral. So, where from the chiral it will come, and also a 4 carbon chain direct displacement is sometimes difficult like here.

See, if you want to take this molecule and try to do an elimination, it is extremely difficult because in presence of base, base is required to make the carbon ion. In presence of bass this will immediately undergo elimination itself to go to the alpha beta unsaturated system. So, displacement that the beta carbon of an alpha beta unsaturated system you can forget. So, only way remaining is that you can have a Michael type addition, like a carbon ion at the centre.

So, but the question is can you make a carbon ion from the from this type of amino acid? Is it possible? If you take a 3-carbon amino acid alanine, where there is no functionality at the side chain on the methyl, if you try to make the anion at the methyl, it is almost impossible. Because you have a very acidic hydrogen which is alpha hydrogen.

So, anion generation at the, at the side chain is almost it is very difficult. I will not say it is not impossible, but it is difficult, because of the presence of the acidic hydrogen. And even if you make anion there say dianion, so you are losing the chiral integrity at the centre. So, you are the utility of the synthesis that you are going to develop will be lost.

On the other hand, now, you think of the radical chemistry because this is all anion cation chemistry. If you think of a radical chemistry, that I will have something like this and I will take this, then there is a bit with the radicals can be generated under mild neutral condition and it can add to the double bond. And the double bond if it adds then then what I will get is the desired product because that is what I need it.

So, this is exactly was done one of the earlier example of utility of radicals in the synthesis of, in the synthesis of important as well as unnatural amino acids. So, the exactly what was done? What was the precursor for this radical? The precursor is really what happens as I said, RX plus tin hydride gives R dot. So, what you need is to make co2 in each.

Of course, you have to use protected ones, because otherwise, these are difficult to work, amino acids are soluble in water. So, you make take, you make this type of compound, which can be easily made from displacement of serine. So, you have a serine OH here, you make the tosylate displace the tosylate with the iodine and then you get the iodo alanine derivative. So, it is iodo alanine derivative.

These iodo alanine will have, will be available in both L and D form depending on whether you have started with D serine, or whether you are starting with L serine. Here you are requiring L, so, you start with L serine. And the reaction is very simple. Take acrylic acid and add tributyltin hydride, this is used in 10 excess 10 mole excess. I told you why you need excess, tributyltin hydride and AIBN tiny amount and what you end up is L alpha amino adipic acid, L alpha amino adipic acid.

So, that is one of the earlier synthesis. See the important, the interesting part is that nobody could think of making this carbon carbon bond, this is kind of a very armed reactive carbon carbon bond. But these radicals have the power to, to make apparently unreactive carbon

carbon bonds, from nowhere you can you can conceive substrates by radical chemistry you can make difficultly formed our carbon carbon bonds which are apparently which apparently look very difficult to do. So, that is number one example.

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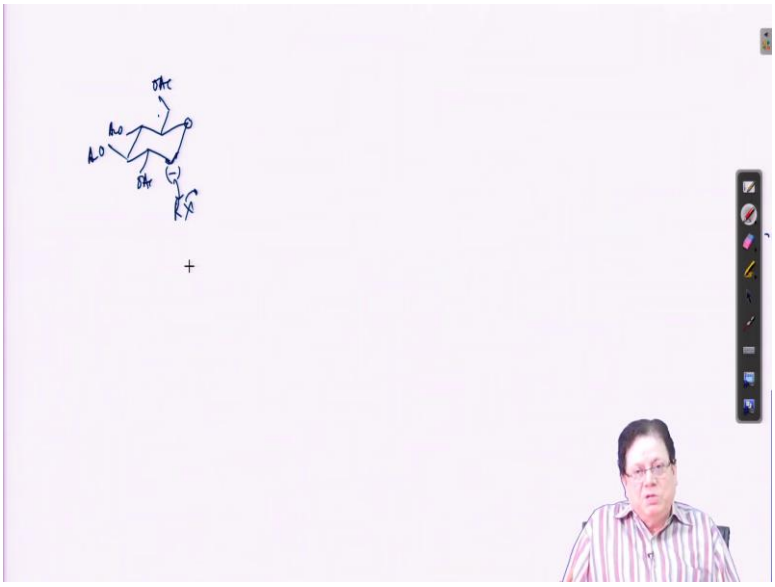

Now, the second example, the second example is in a sugar molecule, in a sugar molecule say these are all acetate, you know that the our nucleic acid chemistry are basically, nucleic acid chemistry is dominated by by sugar presence of sugar base and phosphate. And the sugar there is ribose. But people have tried to make unnatural nucleic acids by using different types of other sugars, because they may have different biological activities.

Now, the the nucleosides can be of many types depending on what type of bond or what type of atom is attached to the anomeric carbon. In the nucleic acid that is nitrogen attached to the anomeric carbon. So, that is called N nucleosides. Then you have C nucleosides. Suppose, you attach S carbon here. So, that will be a C nucleoside. If you attach a nitrogen here N nucleoside. If you attach a sulphur, then thio nucleosides, or if you attach oxygen O nucleosides. So, all sorts of nucleosides are possible.

Now, out of these suppose I tried to make C nucleosides, I want to make C nucleosides, that means I want to make carbon carbon bond here. I want to make a carbon carbon bond irrespective of whether alpha anomer or beta anomer, we are not talking about that. Obviously, the alpha aomer may predominate because if you go by radical chemistry you know that alpha radical is the, is the most stable one. We have seen we have seen that in the anomeric effect.

So, if you want to make carbon carbon bond here, what is your option? Your option is that you can, you can make an anion here which is very difficult. Anion making at the alpha to an oxygen functionality is very difficult. If you can make an anion here and then took an RX, you want to do the displacement. But that is that is a difficult proposition. Rather than, see this is where radical chemistry becomes useful, where anions cannot be generated, think of radical.

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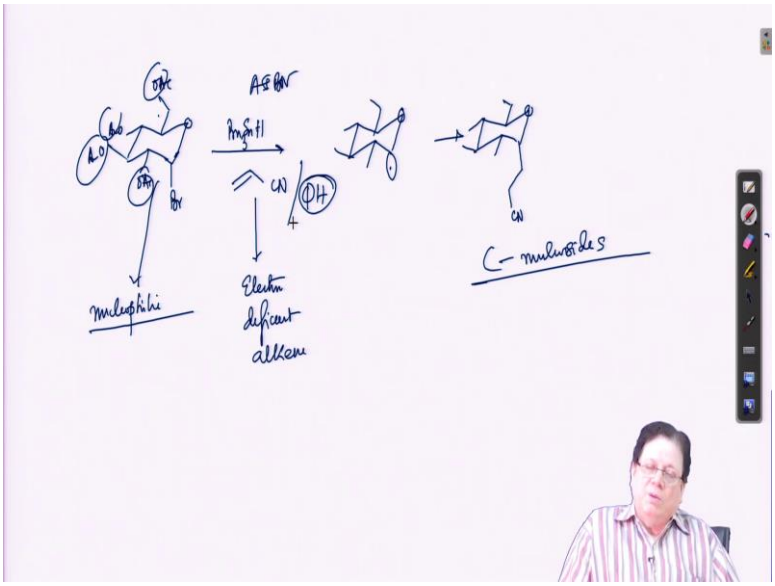

And how can you think of radical? That if you, it is easy to make these type of halo systems because there is a bromide, there was a OH here you can always displace the OH to the HBr and it will be the bromo sugar you can get. So, if you get the bromo sugar that is what you need it, add tributyltin hydride and your whatever suppose cyanide, acrolein a double bond with cyanide. You need electron deficient alkene because it is a nucleophilic radical.

Remember always try to check whether the what is the nature of the radical, nucleophilic radical, electron deficient alkene. And then what will happen? Tributyltin hydride AIBN that is there tiny amount. So, you get to the radical here and then that will add to the acrylonitrile. So, your ultimate product will be this and this is a very nice way.

Later on, lot of C nucleosides which have got very good biological activity C nucleosides have been prepared by this route. Here the anion route is almost ruled out because you have an oxygen there anion route is almost ruled out and because of so many other functionalities you see acetate they are also vulnerable. But as you are doing it the reaction in a solvent like benzene, see solvent choice is also very important.

If you use a solvent which cannot donate any hydrogen. So, you cannot see basically, ethereal solvents are not encouraged or halogenated solvents are not encouraged because they are halogen atom donors, benzene which can only develop sigma radical, which is very difficult to develop because CH bond strength is very high or vinylic CH bond strength is very high. So, you can use benzene, benzene will will be okay because it is not a hydrogen donor.

But if you say I will xylene, toluene then you have to be careful because they are potential hydrogen donors. They have benzylic hydrogens. So, it all depends on the reactivity of the radicals that you are generating versus the radical the hydrogen donating ability of toluene or benzene usually toluene or xylene, usually those solvents are not used.

What is used is benzene, most common reagent solvent is benzene, because that does not allow to donate any hydrogen. So, no side reactions, no self-quenching from or quenching from hydrogen coming from outside, because anyway you have to remember solvent has to be concentration of solvent is the highest in a reaction. So, that part is important. So, this is there.

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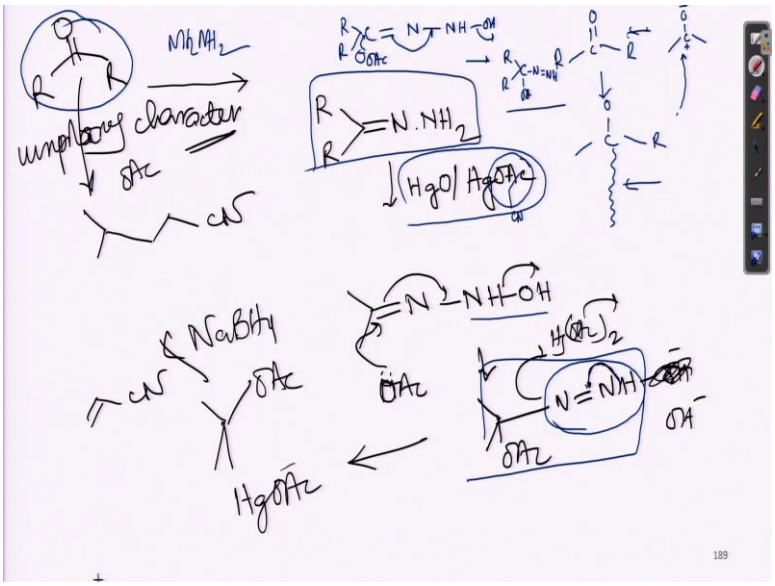

Now, let us see what is in store for us. Let us go to other examples. We will take up only very critical examples where there is a change in the chemistry that we generally believe to happen. One is this Umpolung character. Remember I told you about the umpolung character that the character gets changed after every addition to the to the double bond. Earlier you started with a nucleophilic one that became electrophilic. If you started with the electrophilic that become nucleophilic. That is a change up the character that means an umpolung is happening at every addition.

Now, let us talk about another umpolung chemistry, which is the chemistry of the carbonyl carbon. We know that the carbonyl carbon, the carbon is the electrode deficient carbon and so, it is susceptible to attack by a nucleophile. However, in the last 30, 40 years lot of advancement has been has taken place specially in the hydra zone type of chemistry, where the carbon can be made to act as a nucleophile. This is what is the umpolung character of the carbonyl carbon, that that is that is done.

Even simple benzoin condensation, if you remember benzoin condensation that is the condensation between two benzaldehyde molecules in presence of cyanide that is also an example of umpolung character, that the carbonyl carbon the aldehyde carbonyl carbon becomes anion and that attacks another aldehyde molecule. So, you change the character of that carbon. So, that is umpolung.

Similarly, in radical chemistry you can have, you can also have a very similar sort of change of character of a carbonyl carbon and that is shown here. This if you take a ketone like this. And if you add, if you make it a hydrazone. So, I added NH2 NH2. So, added hydrazone means added hydrazine and I got to the hydrazone.

Actually, many of these umpolung chemistry developed on the carbonyl or based on the hydrazone, tosyl hydrazone all these things. It is actually not different from that, but here it is a radical based umpolung reaction. So, what we are trying to do is utilise this carbonyl carbon and make new carbon carbon bonds. So, make new carbon carbon bonds utilising radical chemistry.

However, we know that the carbon, the resonance structure of this is actually O minus C plus. So, it is difficult to do this only nucleophile are supposed to attack like this. So, how to make a carbon, a carbon radical at the centre, so that it can add to double bonds. And that is the reaction that I am talking about.

So, if you take a carbonyl from the hydrazone and then you add mercuric oxide and, in this case, mercuric oxide mercuric acetate. Mercury oxide is an oxidising agent. So mercuric oxide will oxidise possibly one of these NH2 into NHOH, that is the next oxidation product of amine. The first oxidation product of amine is hydroxylamine, then nitroso, N double O then nitro like that. So, if we utilise the first oxidation product of NH2 you can say that that is NH OH.

So, as soon as that has formed NH OH then the acetate ion that is there, the acetate ion now attack the the carbonyl carbon and generate nitrogen not yet generate N double bond N and the OH leaves. So, you get a system like this. I can I can repeat this again. So, what I am saying is that you have R R C double bond in in H OH. Now, your acetate comes this goes here, that goes out. So, you get R R C N this is acetate N double bond N and has a hydrogen.

Now, what you can do? Now, the hydrogen will be lost like this, you can generate nitrogen in the process and so, you can generate nitrogen nitrogen leaves out and this bond now attacks a mercuric acetate and forms a carbon mercury bond. So, basically what happens? After this maybe I can, I can do it.

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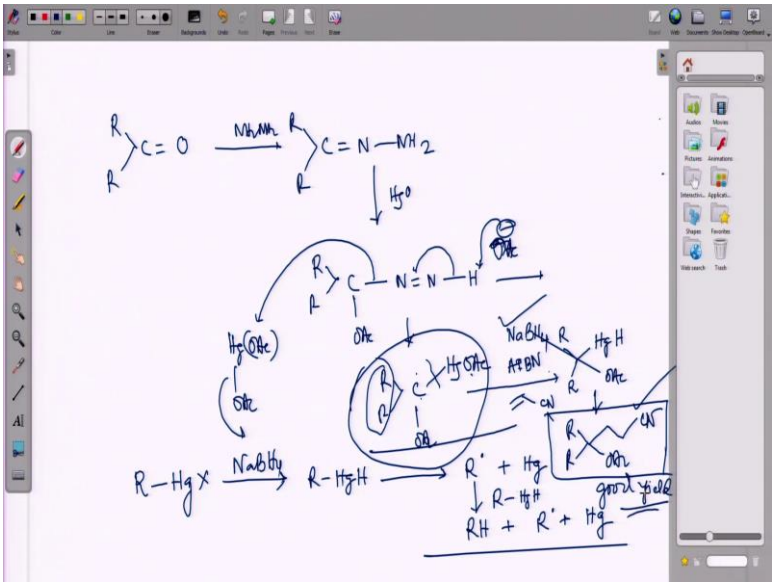

So, we have started with our R R C double bond O NH2 NH2. So, R R R R R C double bond in NH2. Then mercuric oxide I have already shown you how he generated the N double bond N day in and then H. Now, what will happen? This base like acetate suppose that comes abstracts the hydrogen removes the nitrogen and then then attacks a mercuric acetate. So, with one acetate unit gone. So, that will give you R R C OAC and then you have HgOAC. That is the species.

Now, one chemistry that I did not mention yet that was apart from tin hydride, you can have another way of making the making the radical and that is R, if you have R HgX that means if you can make a compound a mercury compound, then if you reduce that with sodium borohydride or other borohydride type reagents, then what will happen, this will become R HgH and this is not a stable molecule this will go to R dot plus Hg and then this R dot can abstract hydrogen from another RgH RH and form this R dot plus Hg.

So, basically, there is another way of generating the R dot by having an alkyl mercury bond because these are also very vulnerable. So, that decomposes even in light or in presence of AIBN, slight sort of initiator. So, you R dot and then it abstracts the hydrogen. So, a very similar reaction. So, you have making now carbon mercury bond. So, if you add say AIBN and if you add say acrylonitrile. So, what will happen? This will break form the carbon radical and the carbon radical then, I am sorry sodium borohydride is there. So, that will form C Hg H.

So, with sodium borohydride AIBN and acrylonitrile, what will happen? This will form this HgH like the earlier I have shown and then that will decompose form the radical at this carbon and you have acetate will remain. And finally, that will add to the acrylonitrile OAC. So, this will be your final product.

First there is a radical that will be generated, that will again react with this RgH and form the abstract the hydrogen from here and to become neutral. Just to repeat first the carbonyl, so, this is umpolung addition of a of a radical carbonyl carbon is usually electron deficient, but you can make it a radical and not only a radical a nucleophilic radical. So, carbonyl hydrazine, it becomes hydrazone mercuric oxide oxidation in presence of mercuric acetate generates this organomercury compounds and then you add sodium borohydride AIBN and acrylonitrile.

Sodium borohydride is there to convert it to HgH and then that decomposes into the carbon radical and because of the oxygen presence it will become a nucleophilic radical as well as these two R groups are present. So, that will add to the acrylonitrile electron deficient alkene and ultimately form the product in good yields. So, this is a nice example of how the umpolung, how the umpolung, how the carbonyl character can be changed from an electron deficient one into an electron donor one in the form of a radical. Thank you very much.