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

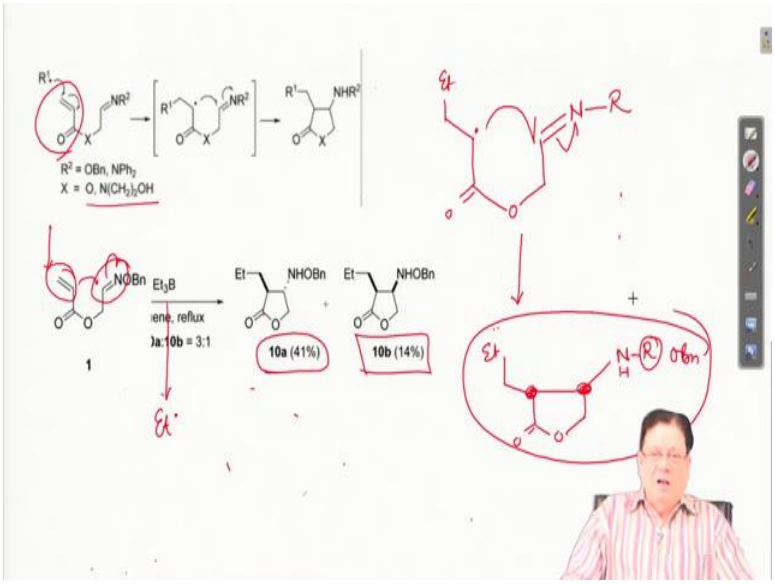
Professor Amit Basak
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture 32

Radical Mediated Decarboxylation and Deoxygenation

Hello, welcome back to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. We have seen that the different methods of generation of radicals, the tin method, the mercury method, the boron method, thiohydroxamic acid method. We have discussed so far, the tin method and the mercury method. We will quickly finish up the other two.

(Refer Slide Time: 00:57)



The boron method interestingly that here you are generating a radical which is adding bonds other than the carbon carbon double bond. Here we have seen, we have depicted this this enone sorry this enone and this X, X is a hetero atom and then it is attached to an allylic imine bond, allylic imine bond.

And interestingly if it is done in an intramolecular fashion, then the radical that will be generated with the help of a boron reagent that can add to this imine. So, now, we are seeing for the first time the addition of a radical to an imine double bond that is possible. And also, now, even bonds double bonds are weaker than they the carbonyl bonds.

So, there is a possibility that the radical can add to the imine. The other is the radical can add to also oxime double bonds, oxime like double bond NO-benzyl that means benzyllate oxime, that is also possible. Here the additional factor is that after addition of a radical at the centre you get a nitrogen radical and then which is adjacent to a donor atom which is oxygen radicals.

So, there can be resonance stabilisation by the oxygen, oxygen lone pair and then stabilising the nitrogen radical, because you know that one of the resonating structure will be nitrogen lone, nitrogen will have the both the electrons and the oxygen will sacrifice one electrons. So, oxygen becomes dot plus and nitrogen becomes negative. Otherwise, the nitrogen will be occupying only single electron and the oxygen has the two electrons.

So, these types of resonance can happen between in an oxime. So, that is why the radicals the bottom line is that radicals can add especially in an intramolecular fashion to the to double bond imine double bond or two oxime double bond. So, there are two nice examples that if you have this enone systems like this coupled with an imine double bond and oxime double bond, then what you can do utilising the triethyl borane in presence of oxygen, what happens the triethyl borane generates, I told you it generates ethyl radical.

So, now what will happen? The ethyl radical here there is no RI because the example that I told you in the last lecture was then ethyl radical will react with RI to generate another fresh radical which is R dot. Of course, there is a catch here, it will happen only if the R dot is more stable than the ethyl radical.

But here there is no R dot. So, the ethyl radical will add to this double bond, the see between these two double bonds the radical will prefer to add first to the carbon carbon double bond, because that is the weaker bond, remember that. So, the ethyl radical will add to the, to this double bond enone double bond and with the formation of a new radical. So, you have ethyl here, you have a radical there and you have this is the system that we are talking about N and then suppose this is R.

In this case it was o-benzyl an oxime. So, you generate this centre in presence of triethyl borane. And then this radical now is well positioned to do a 5 exo-trigonal cyclization and you will get ethyl double bond. And so, you will get a gamma lactone and N R. Obviously, there is now stereochemistry involved here and there, you are generating two stereogenic

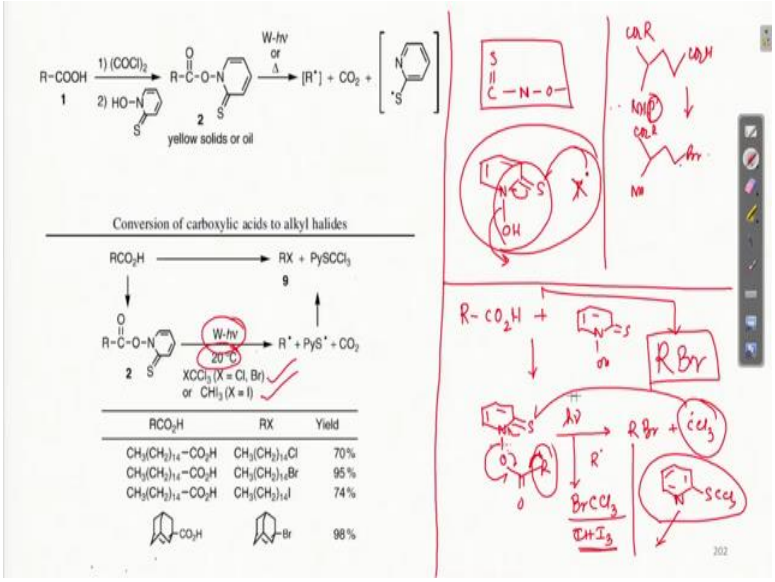
centres and the reaction is driven by the stability of the system, the trans isomer is obtained in 41 percent whereas, the cis isomer is obtained in 14 percent.

So, ultimately you will get, this will be, this will be NH this will be NHR or so, if it is benzyl then that will be o-benzyl. So, this is one example of the boron reagent that can be used to induce an intramolecular cyclization and involving an imine or involving the oxime double bond. And the important point to note here as I told you that the reaction starts by addition of the ethyl radical on to the more vulnerable or more radicophilic.

See we have not introduced this term. This is the basically the radicophile means something which is looking for radicals. So, a double bond is a good radicophile. So, I can use this term that the R dot will add to the more radicophilic double bond and that is the carbon carbon double bond and not the carbon nitrogen double bonds. So, the reaction first starts by addition to the carbon, more radicophilic moiety that is the carbon carbon double bond.

So, that is the one of the examples where triethyl borane has been used. As I said literature is flooded with examples of radical mediated chemistry and but we are just touching the ocean giving you just some basic concept about these radical reactions involving carbon carbon bond formation and their utility.

(Refer Slide Time: 07:44)



The next reaction that is, that is quite interesting that was developed by that that is what is the thiohydroximate method. The sorry thiohydroximate, let me see here. The thiohydroxamic

acid method I told you that is there another way of generating the radicals. And there are a lot of applications of this thiohydroximate.

But the thiohydroximate as I told you the basic skeleton is this. This is the basic skeleton of a thiohydroximate. Now, in case of the exact thiohydroximate acid that sir Barton used was a pyridine based one. So, a two thio, the sulphur is at the the carbon sulphur double bond is at the two position of the of the pyridine ring. And so, this is the the thiohydroxamic acid of the pyridine from the pyridine moiety.

So, this is this is thiohydroxamic acid because you have the requisite skeleton here, C double bond Sn OH. And so, what happens here, that this molecule is as a structure says it is actually it is not aromatic because of the formation of the exocyclic carbon sulphur double bond. So, its tendency will be to, so, how do you do that?

So, basically it will have a tendency to add a radical, any radical say with a X dot. So, if a radical adds to the sulphur, then this can come inside. This electron can come inside and make it aromatic, but that needs that you have to break this nitrogen oxygen bond that is required. But the chemistry of this thiohydroxamic acid basically lies in this, lies here. That is the driving force is the formation of the aromatic ring from the this two thio pyridine moiety.

So, let us see how it was done because our original target is to make an alkyl radical, with the help of thiohydroxamic acid. So, what was done? First Barton developed a method where he took a carboxylic acid. Now, instead of in case of tin it is RX, in case of the mercury compound it is R double bond containing an alkene moiety. In case of boron, you have again you have to have a double bond where the ethyl radical adds.

In case of Barton's method utilising thiohydroxamic as it to generate radicals, he starting material initially what he developed was a carboxylic acid, the thiohydroxamic acid as I said that it is not aromatic, that what Barton used. And so, the driving one of the driving forces is the is the getting back the aromaticity and that can happen by a radical process as is shown here.

Now, the question is it is very difficult to to cleave an NO bond unless there is a driving force other driving force that is required. So, let us see how Barton solved that problem. And also remember the fact that our main motto was to generate a radical, an alkyl radical and then subsequently do a reaction on that alkyl radical.

So, Barton took RCO2H and reacted with this thiohydroxamic acid. This is just simple DCC based coupling or you can take R COCl also and then take this this thiohydroxamic acid and what will happen, that this will form the ester O CO R hydroxamate ester. So, hydroxamic acid and the ester of hydroxamic acid. So, this is thiohydroximate. So, this that will be formed from the carboxylic acid.

Now, what will happen? This is not a very stable system, first of all there it is its intention to retain the aromaticity, that is or regain the aromaticity, that is number one. And number two is, now this bond is very vulnerable, because you can generate carbon dioxide if you do an electron flow like this. So, in presence of light, what happens? That in presence of light, you get slight, slight decomposition of this, a tiny amount is decomposed in presence of light. So that means you will generate an R dot.

Now, in the medium, suppose I have a reagent like a reagent which can donate halogen atom like CBr, CCl3 bromo trichloromethane or you can take iodoform CHI3 which can deliver or which can donate iodine atom. Or you can take CBr4 that is also possible which will donate one bromine atom. So, anyway any halogen atom donor, if you give that, so what will happen?

Now, R dot will form this RBr if it is bromo trichloromethane RBr plus CCl3 dot. Now, this CCl3 dot like whatever I have shown here, we will come back and add to this sulphur, this becomes aromatic, this cleaves in turn, because earlier the problem was the cleavage of the NO bond. This breaks in this fashion release of carbon dioxide and formation of R dot.

So basically, now, you are having continuous generation of this R dot and R dot is reacting with the bromo trichloroethane methane and then generating the trichloromethyl radical and that adds to the sulphur. So, there is a chain propagation. This is continuously being generated and as it is generated, you continuously generated the R dot and the R dot will automatically react with bromo trichloromethane generating fresh trichloromethyl radical. So, the chain propagation happens.

So, what is the product of this reaction finally? The RCO2H is ultimately converted into an important productivities RBr. Remember there is a method where carboxylic acids can be converted to can be decarboxylated to RBr and that is called hunsdiecker reaction. But that requires silver, formation of the silver salt and bromine. But this is a method which is which

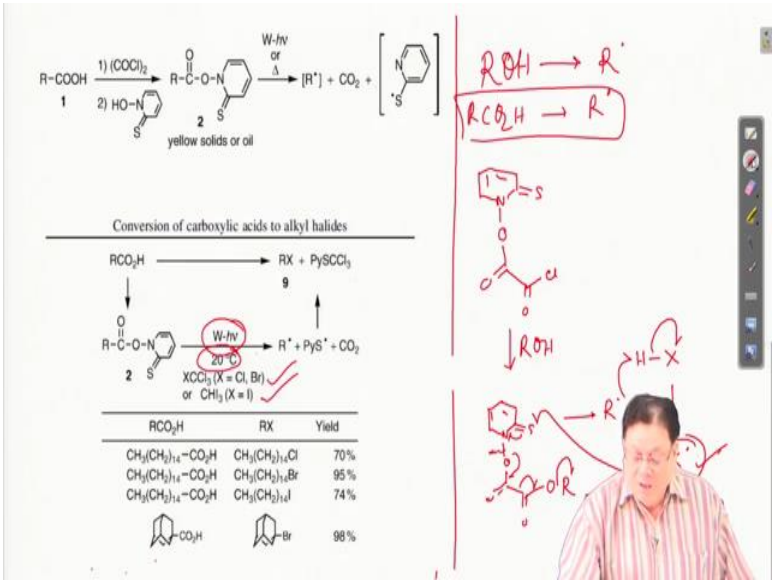
is better you actually do not handle bromine at all, instead you are you are utilising brominating reagent, bromo reagents not bromine itself.

Or you can take also iodine compounds which can deliver iodine atoms and it happens in a much milder condition, even amino acids, if you want to take if you want to convert glutamic acid and do this decarboxylation you protect the glutamic acid with suitable protecting growth and then you do the reaction. So, the Barton decarboxylation method and you get get the Br.

Remember one thing we should remember that if you do not use any brominating agent but if you use the hydrogen donor instead then what you will end up is basically RH. So, that is nothing but a decarboxylation of a carboxylic acid. And you know decarboxylation of carboxylic acids require harsh conditions soda lime and then heat, but in this process if you take a hydrogen donor instead of this bromine donor then your ultimate product will be RH. But this is happening only at room temperature. And so, that is the beauty of the reaction.

The other point is that the by-product of this reaction is CCl3 is a basic compound. So, you can always wash this out, wash this out using an aqueous acid. So, pyridine compounds will be washed out. So, workup is easy and the yields are high. And the reaction takes place very mild condition, you see the temperature 20-degree centigrade tungsten light and then you can use various halogen halogen atom transfer reagents. So, that is the, that is what is Barton decarboxylation method.

(Refer Slide Time: 18:11)



Then Barton did one more, one more extension of this method. And that is suppose if you do not have all the time you do not have the carboxylic acid to generate the R dot. So, some people thought that it could be a limitation. So, whether whether this method is useful information of R dot from ROH, whether that can be possible. Because earlier the method was RCO2H giving you R dot.

So, in order to do that, it is a clever trick employed by sir Barton that is so, he first made the half ester of oxalyl chloride. So, if you take oxalyl chloride that means COCl COCl and add half equivalent of this thiohydroxamic acid. So, what you will get in presence of a base? You will get the half ester and then once you have the half ester, now you add your alcohol sorry, you add the alcohol part from where you want to generate the R dot. So that will form OCO then CO and then OR.

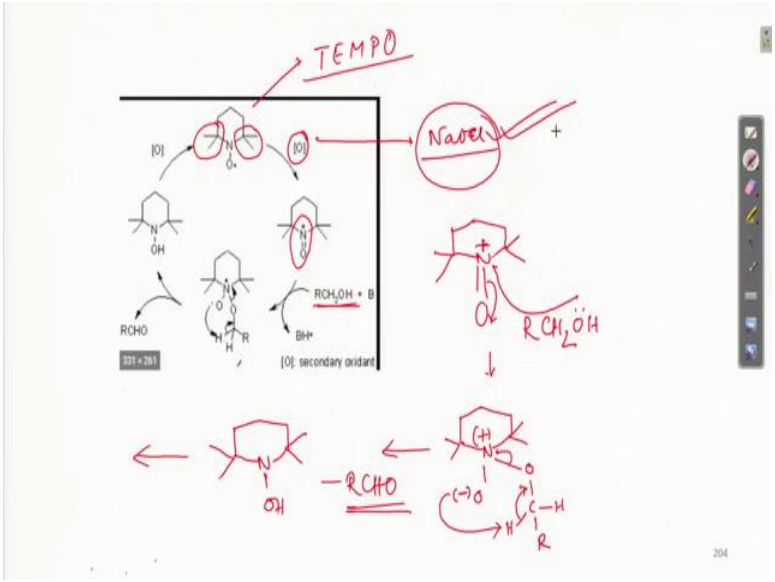
Now, again you see in presence of light this is the vulnerable bond because you can generate carbon dioxide. In fact, you can generate two molecules of carbon dioxide that will come out and then you have basically with this decomposition process you have generated your desired R dot. But that what you need in a tiny amount, because then if you have your whatever hydrogen atom donor reagent you have HX, so that will be, that could be a thiol.

So, R dot will take the take the hydrogen and generate the X dot which will carry the chain forward. So, X dot again will now add to the sulphur, this becomes aromatic and this type of breakage would continuously take place. And so, it is a chain, it is a chain propagation, the propagator is basically the X dot which is continuously being generated.

So, you see, you can generate R dot from RCO2H, then you have to form the directly from the ester with this hydroxamic acid. If you want to generate R dot from alcohol, then you have to use the half ester, you use oxalyl chloride. So, half of the hydroxamate is tied to one part of the oxalic acid and the other oxalic acid part is tied up to the alcohol at then by shining light you can generate the R dot in presence of a hydrogen donor which is usually a thiol. So, that is that is the Barton reaction.

So, we have covered all these four methods that are usually employed to generate generate radicals and there are useful radical reactions that we have discussed. Now, just one more thing, I want to tell you that there are I earlier I have be in the beginning I told you that radicals are very short-lived species which is true and they are only generated in C2 during the course of reaction.

(Refer Slide Time: 21:37)



However, there are some molecules which are stable radicals and which can be stored in a bottle and they can be purchased they can be utilised. So, they are quite stable and one of the compounds is what is called TEMPO tetramethyl pyridine, pyridine, tetramethyl pyridine N oxide radical. Tetramethyl pyridine N oxide radical.

Now, this is very stable radical, because of the presence of these four methyl groups which are acting as a steric shield to protect this radical, this radical cannot be quenched because other molecules it is difficult for the other molecules which are hydrogen atom donors or those types of species difficult to approach, approach and quench this radical. So, that is the that is one of the reasons that why this TEMPO or the N oxide radicals are very stable.

Many of the N oxide radicals are quite stable. And one very common reagent is this TEMPO. I forgot to mention another point when I was talking about detection of radicals in a reaction sometimes what happens that you do the reaction in presence of TEMPO. And if a radical is generated in C2 then what will happen, that can be quenched by TEMPO and you will see a gradual reduction of the EPR lines in presence of the TEMPO.

So, this TEMPO based experiments in EPR is also done or sometimes the reaction is inhibited in the presence of TEMPO because as like oxygen which inhibits radical reactions. Similarly, other radical species like TEMPO can inhibit the rate of the, the rate of a radical reaction. There is one example where TEMPO has been utilised as an oxidising agent that is quite interesting. TEMPO based oxidation.

And I want to finish up the radical chemistry by showing this slide that is the what is called TEMPO based radical, TEMPO based oxidation of alcohols to aldehydes. What happens here this is you are the TEMPO molecule. Big reagents cannot approach, difficult to approach this oxygen radical.

However, what you can do, you can do electron transfer processes that can happening because electrons after all will not, does not require any space. So, what you do, if you can further oxidize this molecule, if you add an oxidising agent like sodium hypochlorite bleach, common household bleach. If you add sodium hypochlorite then what will happen?

This there will be loss of one electron from the nitrogen and so, nitrogen will become one dot and oxygen one dot and that will become form, that will form this in double bond O, but the nitrogen will be positively charged, because it has lost one electron. So, that is oxidation. So, you can remove one electron from the nitrogen and the result is that formation of this nitrosamine. And so, you have to use an oxidising agent and that oxidising agent is very often is sodium hypochlorite.

And now, this is a new oxidising agent that you have generated. So, in presence of a say primary alcohol RCH2 OH. The alcohol now, let me write here N double bond O plus and these are the tetramethyl groups. And now you have RCH2 OH. So, now the now what will happen? This will be you cannot actually write this type of; this is okay. So, it attacks the nitrogen with the, with the result that it is the NO bond is broken and that will form an intermediate.

So, when you use a tetravalent nitrogen, you have to you have to break the other bond at the same time, because pentavalent nitrogen is not possible. So, that is why, what I was doing is at the same time you are attacking the nitrogen and you are breaking the NO bond. So, that will form in O minus and this will be OCH because this is CH2 and that is R. So, this intermediate is formed.

Now, there will be an intramolecular hydrogen hydrogen transfer because the N oxide will abstract the hydrogen, see ultimately you want to do the oxidation of the alcohol to the aldehyde. So, it has to lose hydrogen and this is how it is doing, that first oxidation of the TEMPO. So, TEMPO you add in minute amount. And then you add an oxidising agent TEMPO is oxidised to this nitrosamine.

The alcohol adds to the nitrosamine and then very similar to what happens to a carbonyl that the nucleophile adds attacks the carbonyl, here it is nitrogen. The electrophilic centre is the nitrogen. And you form this intermediate and the oxygen now abstracts the hydrogen in an intramolecular fashion, this goes here and and that comes back. The nitrogen is still remember nitrogen is still placer because nitrogen has lost the has has not gained anything. It has lost two electrons and it has gained that two electrons from the alcohol.

So basically, it remained positively charged. And that goes there and this comes here. So, what it makes? It makes first of all this goes at as aldehyde RCHO that what you wanted the oxidation product of the alcohol and what about the species from the TEMPO? So that becomes the, this is the tetramethyl and now you have N this will be OH.

So, N hydroxy compound, this is not TEMPO, but you have used one equivalent of sodium hypochlorite. So, now sodium hypochlorite will start oxidising it, first it removes the hydrogen to form the TEMPO. So, this is N oxide radical and then that is further oxidised to the to the nitroso compounds, nitrosamine. So, that is the method basically recycles.

So, this is you need excess of sodium hypochlorite because you have to do oxidation twice, one is this N hydroxy back to TEMPO and then TEMPO to the nitrosamine. So, you have to use excess of this oxidising agent and a tiny amount of TEMPO, but this is a very mild way of doing oxidation of alcohol to the aldehydes.

There are many methods of oxidation of alcohol to aldehydes. The famous ones are the chromium-based methods, but they are quite harsh methods. Earlier it was chromic acid then it was modified to PCC, then PDC and then there are reagents called swern oxidation, they are these Dess-martin, periodination, but this is another method a TEMPO based oxidation, which is which uses a co oxidant and that is usually the sodium hypochlorite.

So, you see the the breadth of the radical chemistry. The radical chemistry it started, it started all from the from your formation, the formation generation, how you can generate radicals and then where it can be useful if you talk about the para-benzynes where diradicals were generated, radicals are very useful materials from the standpoint of biology, because they are the intermediates for showing anti-cancer activity, they are the intermediates for making carbon carbon bonds, they are the intermediates for making polymers, that how the radical chemistry generated and they are the intermediates for generating for decarboxylation for the

dehydroxylation like ROH2 RH and for formation of various skeletons, interesting skeletons which are important for biological standpoint.

And finally, what we have done the use of a radical best material a TEMPO to oxidise for a mild oxidation of an alcohol to an aldehyde. I think with this we come to the end of the radical chemistry and from so, we have actually orchestrated, we have arranged this this course in such a way that initially we had the, we had discussed the structure of a molecule because our initial lectures were mainly on stereo chemistry, then the how to describe the stereochemistry of a molecule in terms of the symmetry elements.

Then, we did the conformational analysis of several bicyclic, poly cyclic compounds. Then we went for one important aspect that controls the reactivity of molecules and that controls how a reaction can go which pathway it will take that is namely the stereoelectronic effects in organic chemistry, then the Baldwin cyclization rules that we have done and then we came on to some of the real-life molecules like the arynes, the alkynes, the allenes, the ketenes, and now the radical. So, we have done all these.

So, next day will now talk about some other functionality which can generate, which are also very useful for carbon carbon bond forming reactions. And we will discuss the stereochemistry of those reactions. Our specific target will be the addition reaction on to carbonyl compounds. So, till then, goodbye today. Thank you very much.