Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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Lecture 05: Carbocation

Welcome back guys to this NPTEL online certification course in molecular rearrangement and reactive intermediates. So, I am continuing with the carbocation. So, last two classes I have talked about various different carbocationic rearrangements. And if you remember I actually ended my last class by talking about the Beckman rearrangement. And I have shown you some examples. In today's class, I am going to show you the Beckman rearrangement, but instead of happening rearrangement something else going to happen.

So, let us start today's class. So, in today's class, we are going to cover this important topic. So, we are going to talk about the Beckmann fragmentation. So, now we are going to talk about how instead of happening the rearrangement there will be fragmentation going to happen.

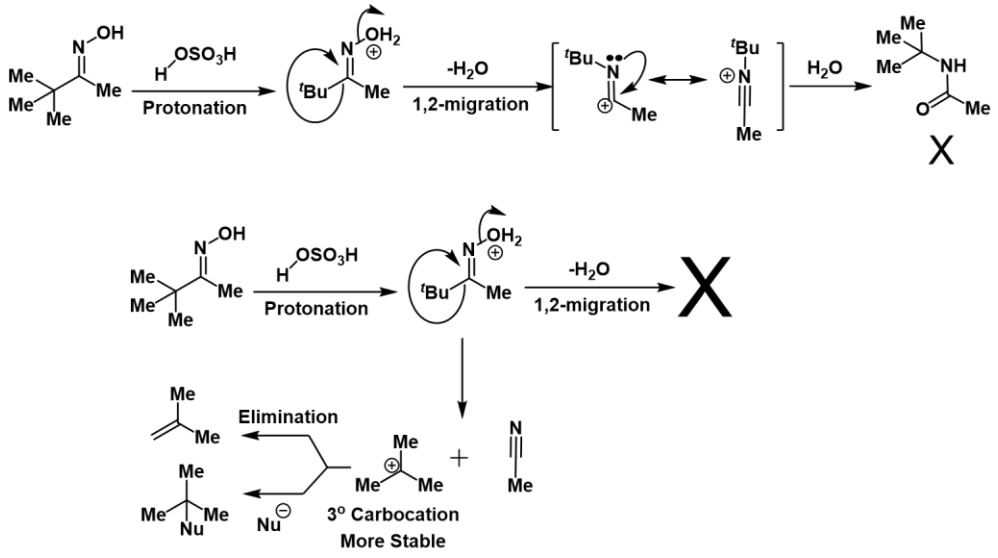
Then I am going to talk about some of these classical Friedel-crafts reactions where it is going through the formation of a carbonation intermediate forming a sigma complex. Then I am going to talk about the Fries rearrangement. and then the dienone-phenol rearrangement and some of the you know some of the exam questions I am going to discuss at the end of the lecture.

So, at the beginning, I am going to start with the place where I left in the last class. So, in the last class, if you guys remember I was talking about Beckmann rearrangement where the first step is starting from a carbonyl and a hydroxylamine, we are forming an oxime.

And if you remember once you protonate the oxime, then the group which is trans to the hydroxy group participated in 1,2 migration and elimination of water. But now if you see once we start with something like this, so we start with an oxime where one side you have a tertbutyl group, one side you have a methyl group. And you can clearly see that your tertbutyl group is trans to this OH group. So, now the first step is the protonation because these reactions were done in place of acid. So, its first step is the protonation of OH.

So, the next step is supposed to be the migration. Migration of this group which is trans to it going to get migrate and then the water is supposed to eliminate to form this type of nitrilium ion. But the problem is this reaction does not happen. So, once this reaction was studied it actually ended up forming something else. So, what is happening here is that instead of this you know migration happens as the tertiary butyls are very stable because instead of going for the migration there is this fragmentation happening here.

So, this carbon and this tertbutyl group this bond get fragmented which we generate the more stable tertiary carbocation. and then the rest of the part which is this part now you can clearly see there will be a fragmentation happening here and then as there will be a positive charge here that means, now this bond can push from this triple bond here and release the water. So, there will be a heterolytic cleavage to generate this type of carbocation and then you end up getting a corresponding nitrile. So, instead of the formation of the corresponding amide which we have learned in the last class in the Beckmann rearrangement, here we are seeing a Beckmann type of fragmentation happening, where we are getting to a stable carbocation and then corresponding nitrile. Now, this carbocation can go for elimination and can go for an E1 elimination to form this olefin or it can take a nucleophile.

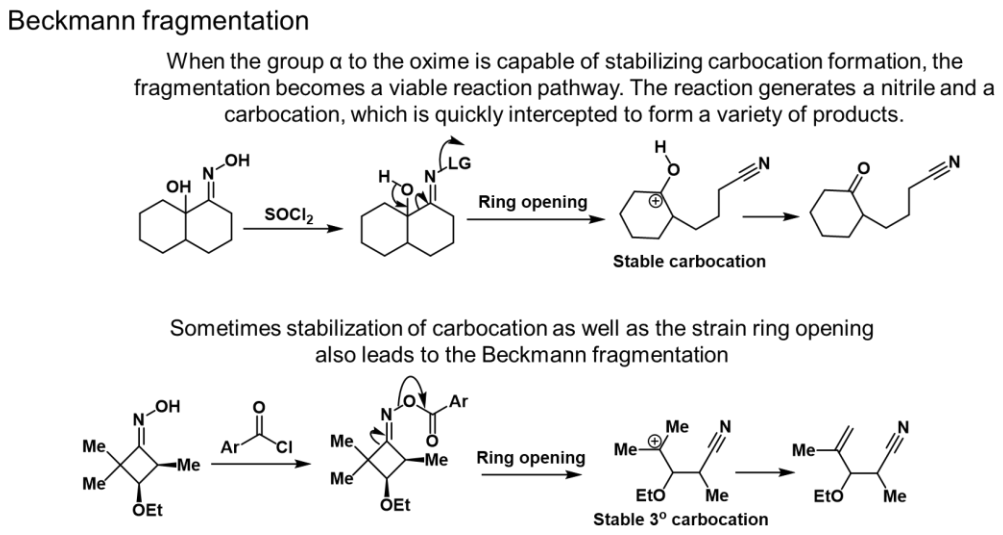


So, now, we are going to try to learn some of these examples of this reaction. So, here let us start with this example. So, here in this reaction, once we start with this particular substrate here first thing is that you are using the $SOCl_2$ that can convert that to a leaving group. Now, what is going to happen if you have a hydroxy group here, on that next carbon. So, that is allowing some sort of a migration happening because the OH is coming back and this double bond is moving to this double bond of the oxime which ends

up making this nitrile and then this lone pair is going to come back to form this carbon compound.

So, what is happening? Instead of the shift that you have learned in the Beckmann, now we are seeing that there is a ring-opening happening and we are isolating the corresponding nitrile. Because one of the reasons is you are forming a stable carbocation. So that means, if you find that in the Beckmann reaction, there is a chance that there is a formation of stable carbocation then the reaction will try to go for fragmentation instead of the desired product. There is you know one more example happening here. So, sometimes the stabilization of carbocation as well as the strained ring opening also leads to Beckmann fragmentation.

So, that means, as I told you before that when you talk about carbocation a lot of the time you have seen that only the stability of the carbocation is not the factor sometimes the ring strain is also another factor. So, if you can release the strain somehow then that type of reaction is also getting favorable. So, here is what is happening first step you can see you can able to make it activated using this -OH can be converted to the corresponding leaving group here. After reacting with corresponding benzoyl chloride then what is happening now it's become a leaving group. So, now what is going to happen it can have a chance for fragmentation. So, because once is getting fragmented it is forming a corresponding 3-degree carbocation at the same time it is actually releasing the.



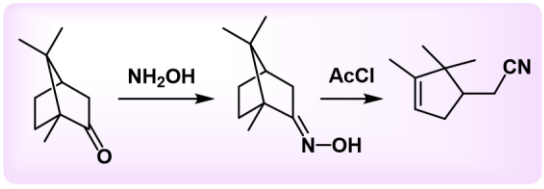
So, there is a 4-member ring. So, that ring strain is also getting released once you convert to here at the same time it is forming this nitrile and after that, there will be E1 elimination going to happen to give this corresponding product. So, that means, you can

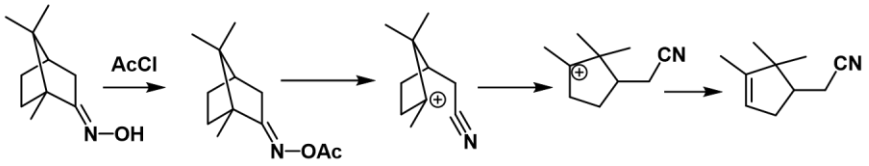
see here again there you know here there is you know two important factors, one is the formation of the most stable carbocation and the second factor is there is a you know opening of this ring. So, the ring strain is getting released.

So, let us go for the next example here. Again, the first thing will be the formation of this oxime, once you have a carbonyl compound first thing is the formation of the oxime. So, here instead of getting the protonation what is happening it is converting to the corresponding leaving group. So, it is getting converted to the corresponding living group. Once it is getting converted to the corresponding living group as you know then now there is a chance of breaking because now what is going to happen it can break either from this side or from this side.

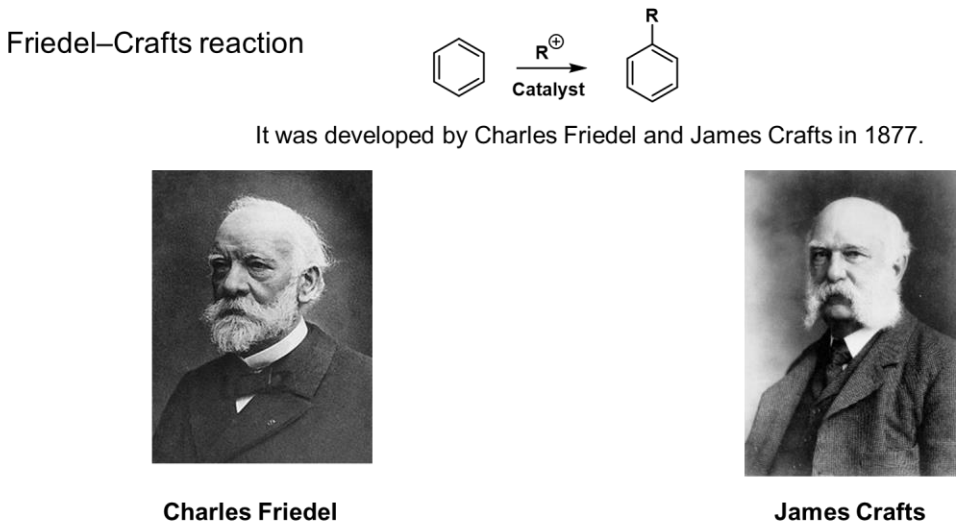
But if you see if it breaks from this side it is going to form the more stable tertiary carbocation. So, that's why the breaking from this side will be more favorable and then after that, you can see that if it is forming a carbocation, it can abstract a proton from here to form this corresponding olefin with this nitrile group there ok. I hope you guys understand this.

Beckmann fragmentation

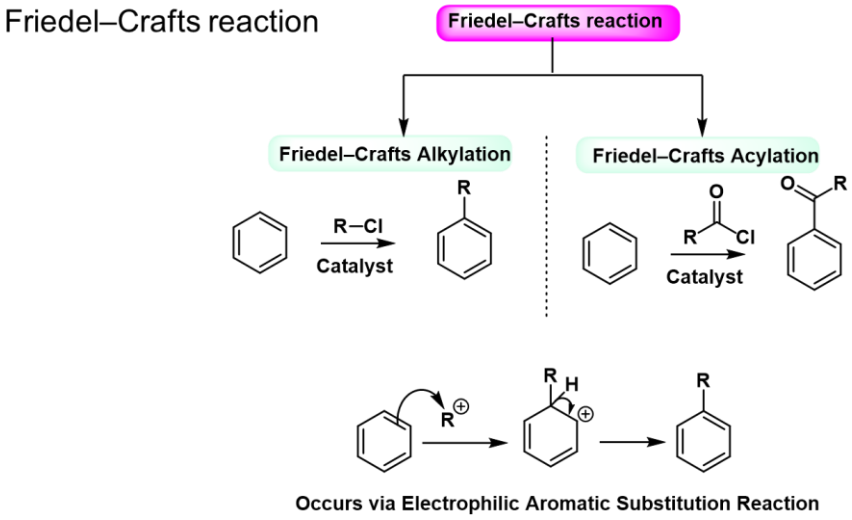




So, now actually there are more examples of this fragmentation again some of this you can find in your practice questions. So, now I am going to move to another very important reaction which is the Friedel-Kraft reaction. So, the field curve reaction is nothing, but if you take an aromatic compound and then you take a corresponding alkyl halide or corresponding acyl chloride in place of a Lewis acid it will. So, that R group which has a positive charge going to get inserted into the benzene reading. It was discovered by Charles Friedel and James crafts. So, it was discovered in 1877 and it is one of the very important reactions in organic synthesis.



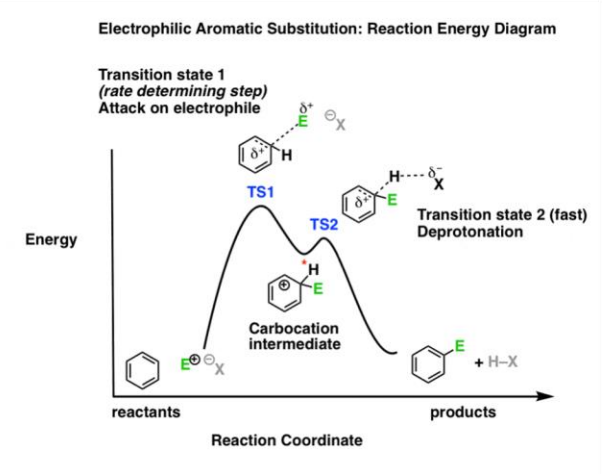
So, these reactions actually go by electrophilic aromatic substitution ok. So, generally, we are going to talk about these two different types of reaction where you have alkyl chloride and you have a catalyst which could be a mostly a Lewis acid which gives you alkylated benzenes. or it could be acyl chloride with corresponding using some Lewis acid which can give it to the corresponding acyl benzene. So, now, as I said this reaction occurs via electrophilic aromatic substitution. We are going to talk about some of the elementary steps of this reaction and then the formation of this important sigma complex.

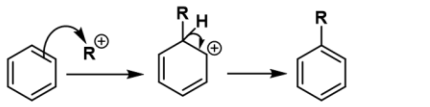


So, if you think about the transition state of this reaction, the first thing what is happening, once this in a phenyl ring is reacting with this sort of charge species, i t is getting to the species called sigma complex which is actually is a de-aromatized species.

So, there is a dearomatization happening in the benzene ring which actually generating a carbocation here. so what is happening, so this is a very high energy transition state because the benzene is losing its aromaticity. So now it is going to form some sort of a carbocationic intermediate here. So, this type of carbocation intermediate is called as sigma complex. So, now after that what is going to happen this proton is getting abstracted and once this proton is getting abstracted it is forming to the corresponding product. So, that means it is going from the transition to where this proton abstraction is happening and which is going to the corresponding product. So, this is the basic mechanism of electrophilic aromatic substitution.

Friedel–Crafts reaction

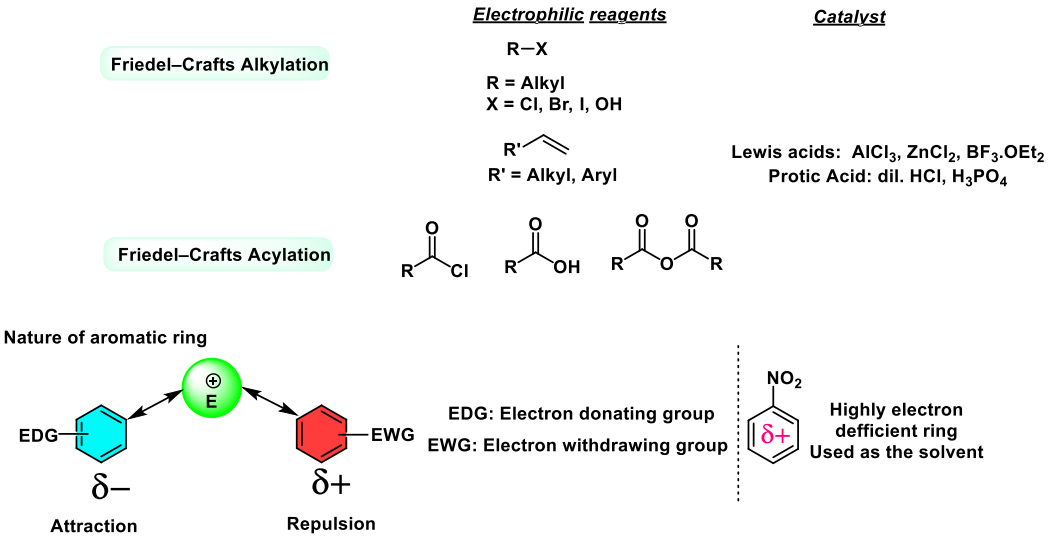




So, moving further now we are going to try to learn about the different conditions we used. For alkyl chloride we can use you know different alkyl chlorides here or we can use different you know allyl or allyl systems we can use you know different acyl chlorides as well of this. So, what is happening as you see is that generally if you have electron donating groups then this reaction will be more preferable compared to if you have an electron-withdrawing group because you are reacting with an electron-deficient species that means, the benzene ring is electronically rich then the reaction will be more favorable. And then people try to use nitrobenzene as a solvent because as you can see nitrobenzenes are very electron deficient. So, it will not be going to take part in the field cup reaction. Now, the question arises that, if you have an electron-donating group or electron withdrawing group. Now, whatever products you are going to obtain by doing the Friedel-craft alkylation or using the Friedel-craft acylation.

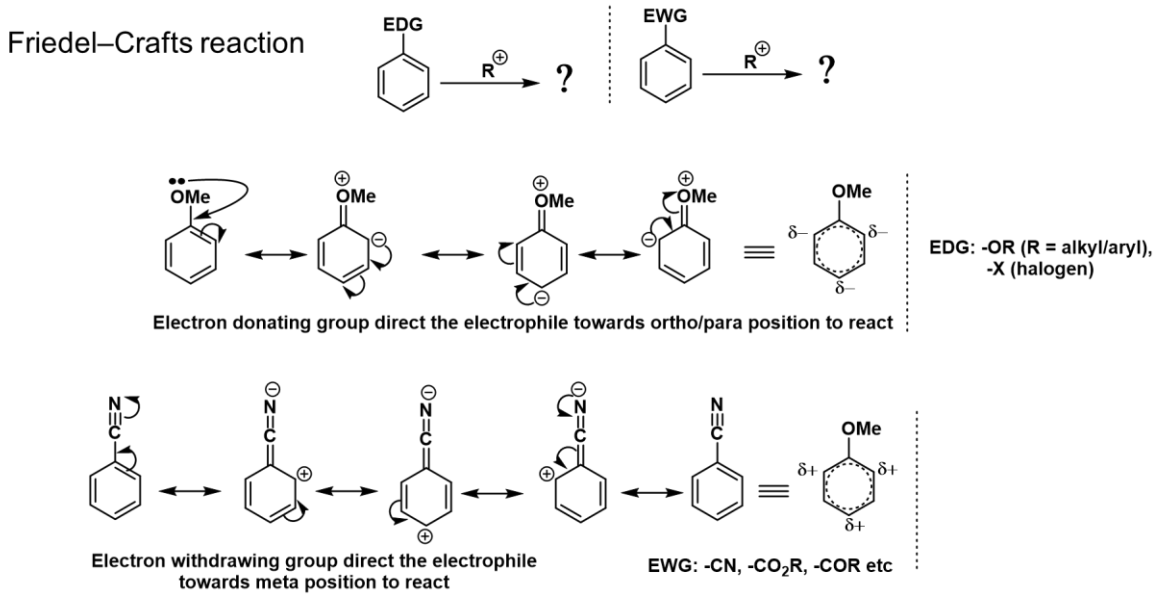
So, that can be explained simply by the resonance structures. So, the methoxy group has a +R effect. So, if you try to draw the different resonance structures you can see it can give electron density more in the ortho and para position ok. So, you can see it can give electron density more in the ortho and in para position which means if you want to trap with the electrophile then it will be more preferable to connect the electrophile in these

positions that means, the ortho and in the para positions. But once you go to the electron-withdrawing group here.



Now if you try to draw the resonance structure you can clearly see you are generating carbocationic character at ortho and para position. That means those are the positions that need to be avoided because there is already a carbocation character formation happening. So, you cannot bring another carbocation there. That means the meta position which is the one here which is going to be the place where the carbonation can connect it. So, that is why you can see for the electron-withdrawing group if you try to do a Friedel-Craft reaction it almost happens in the meta position, but if you have an electron donating group it happens in the ortho and para position.

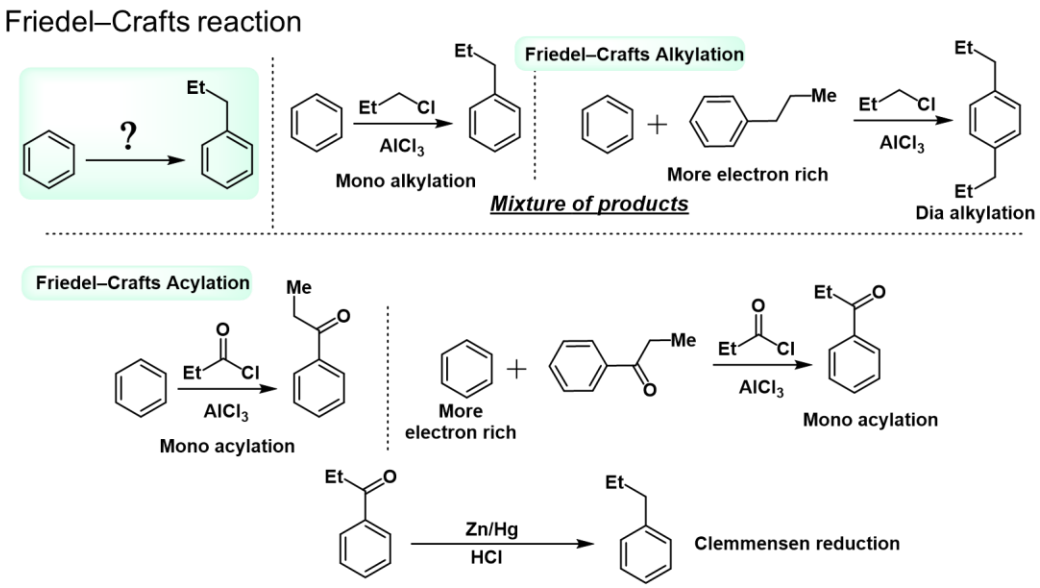
So, now we try to see some of the things here that So, one of the other important things about this is we try to understand what mechanism these reactions happening. Suppose if you are reacting with $AlCl_3$ and this type of chloride. So, what it does actually? Actually, if you have a compound like $EtCH_2Cl$, $AlCL_3$ first activate the chlorine and at the end what is going to form? It forms some sort of a carbocationic character. So, it actually generates a carbocationic character here. So, that means, you can clearly see that if you make a carbocation which is a tertiary versus a primary versus a secondary then the reaction rate will depend on the on that particular thing that which carbocation will be more stable. Because if it is going through a tertiary then the reaction will be faster compared to a secondary compared to a primary.



And, now the problem is supposed if you do a Friedel-craft reaction, Friedel-craft alkylation and you want to stop this reaction in the monoalkylation step. That means, you want to do the first reaction and you want to stop it, but that does not happen. The reaction continuously happens because once you do the first monoalkylation, now this benzene ring is even more electron-rich. So, it can go for the next sort of a Friedel-craft reaction to give you the mixture. So, you end up getting the dialkylation and monoalkylation.

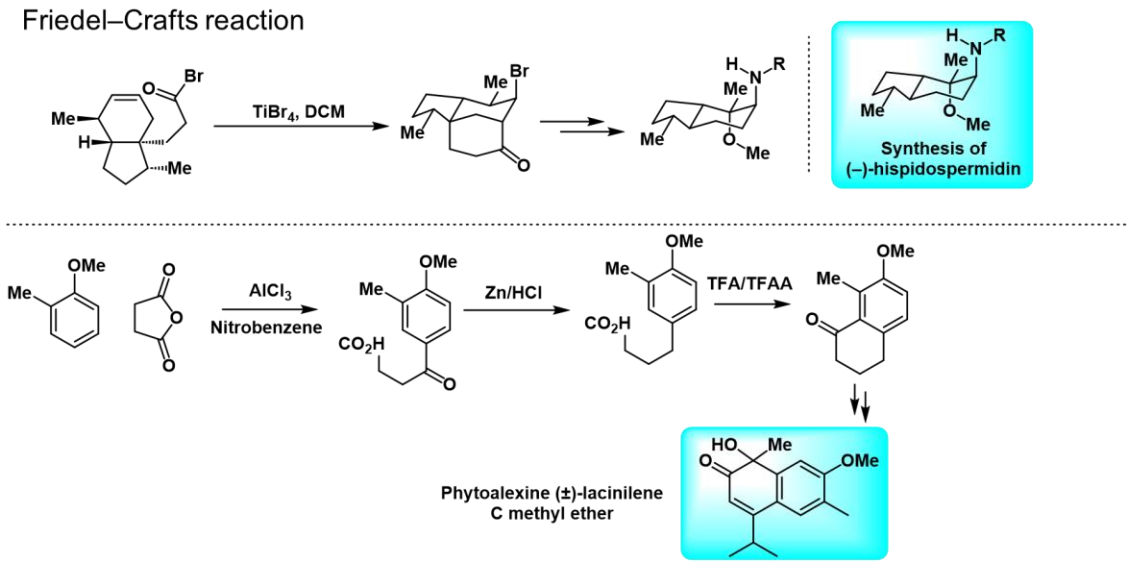
So, now the question comes if I want only the monoalkylation product what are the you know best approach? The other approach is if you can do acylation, again this acylation can be done with $AlCl_3$ and other Lewis acid. So, what is happening here if you try to understand the mechanism here, again you have this chlorine here, and now the $AlCl_3$ is activating this. Now, this oxygen lone pair now can push the electron to get rid of this chlorine to form. So, this is called an acylium ion.

So, it is forming this acylium ion. So, now, this benzene ring can come and attack here ok. Now, you can see there once you form this first acylation product, what is going to happen next? Now, what you have done you put an electron-withdrawing group into the benzene ring. if you put an electron-withdrawing group then your tendency to react again is getting decreased it is not going to. So, if you compare them if you compare this one and this one then this is more electron-rich which means, there is no way this can go for a diacylation. So, that way you can stop in the acylation, and after that you can just able to remove this carbonyl group through Clemmensen Reduction and other reactions to get to the corresponding product.

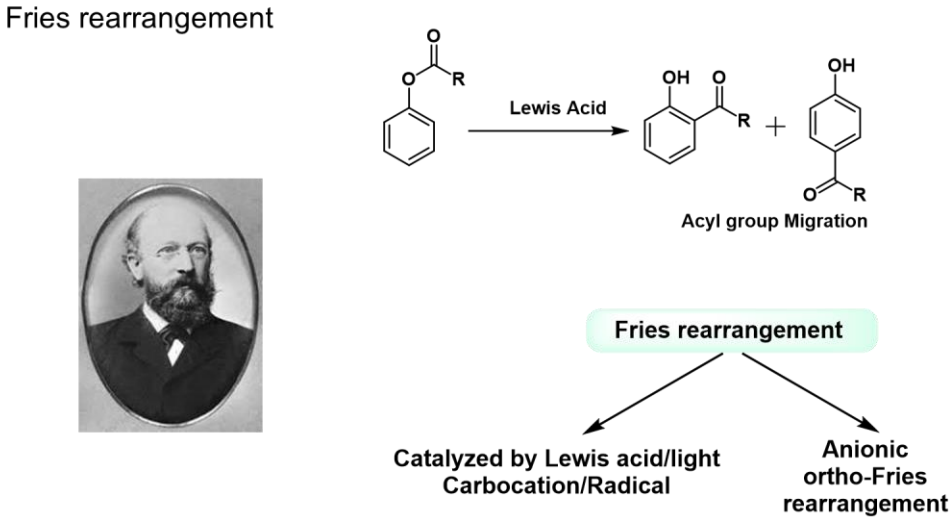


So, instead of going for alkylation, you can do acylation and then the reduction of the carbonyl group. So, there are some examples here added to this example. So, this is used for the synthesis of very important compounds here. The first thing is going for the Friedel–Crafts reaction as you can see there is this ortho and para position that can go for the Friedel–Crafts as you see there if you bring in ortho there should be a steric effect. So, that's why it prefers to go for this para position and then after this transformation, several transformations go to the corresponding product.

There are other reactions here which is not from the aromatic ring. So, there is the olefin which is actually reacting with your corresponding acyl bromide. So, you have the acyl bromide and the olefin in the same molecule. Once you activate this with a titanium bromide which is a Lewis acid is going to allow this double bond to react here with this. And, the bromine will come back and then be attached here as soon as it forms a carbocation the bromine will come back and attached here to form this compound which can be further converted to the formation of these you know natural products.



Another rearrangement so, we have learned about the Friedel–Crafts now there is another important rearrangement from which you actually convert the phenolic esters into the hydroxyaryl ketone. So, you start with these phenolic esters and use a Lewis acid which actually we are going to bring again the $AlCl_3$ here and it ends up giving you the acyl going to get migrated from the ortho or in the para position. So, you end up getting to this ortho and para product. So, this was discovered by the German chemist Karl Theophil Fries who discovered this reaction. So, I am going to talk about the Lewis acid catalyst in the Fries rearrangement and I am going to talk about some of the anionic Fries rearrangement.

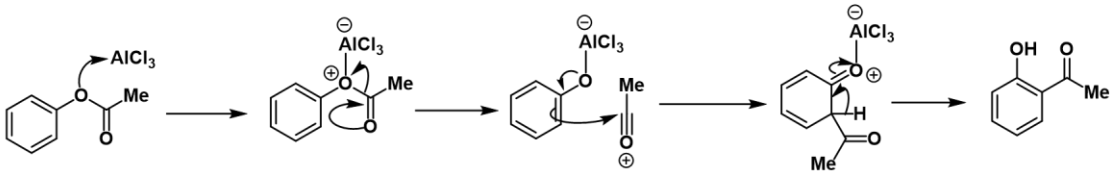


So, we are also going to talk about the Photo-Fries during the radical chemistry. So, here first thing what is happening once you have this compound this oxygen is going to bind

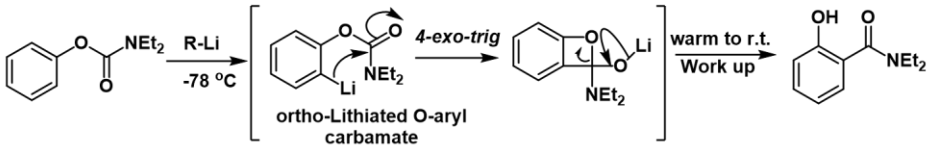
with this $AlCl_3$ making a positive charge. What is doing after that? This oxygen lone pair now pushing the electron density to form this particular compound here and this acylium ion. So, once it is forming the acylium ion which is very reactive. Now, you can see this Friedel–Crafts type reaction happening which is attacking here, and then after that, there is a proton abstraction happening here to form these desired compounds.

So, this is about the Fries reagent, and in the case of the anionic Fries reagent what is happening? We have this type of carbamate group which acts as a directing group if you use an organo-lithium reagent. So, it will form a corresponding lithium here which you are seeing and once it is forming the lithium, now the lithium is very much reactive. So, it can go for an intramolecular attack to this amide and then it will open up the ring it forms this type of four-member ring here after that opening up this bond of carbon and oxygen it will end up making this corresponding product. So, what is happening now this -$CONEt_2$ actually moved from this oxygen to the neighboring carbon. So, this is an example of an anionic Fries rearrangement.

Via Lewis acid catalyzed:

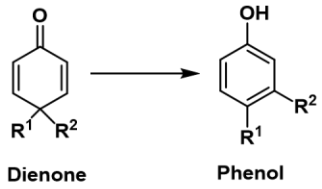


Anionic ortho-Fries rearrangement



And now we are moving further to another important reaction which is called dienone phenol rearrangement ok. This is also done in presence of acid. So, this is an acid-catalyzed rearrangement where you start with a dienone and then it will convert to the corresponding phenol. And if you look into this the important changes happen if you started from dienone you can see the only thing that happened the R_2 moved from this position to this position. So, that is the only change that happens and your dienone actually converted to the corresponding phenol. But if you look into this your molecular weight did not change at all ok. So, this reaction was discovered by Karl von Auwers, and then Karl Ziegler. So, this was a catalyst by the protic acid.

Dienone-phenol Rearrangement



Catalyzed by Protic acid

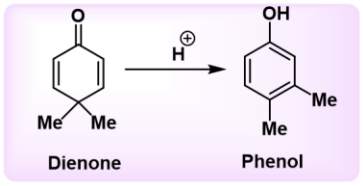
Karl von Auwers Karl Ziegler

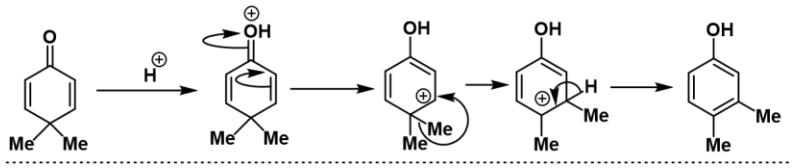
It was first discovered by Karl von Auwers and Karl Ziegler in 1921

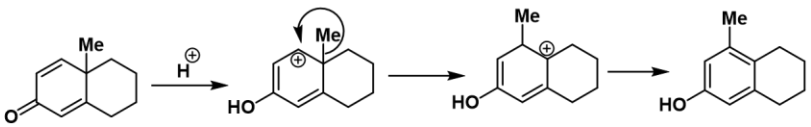
So, now we try to understand the mechanism of this reaction. So, the first thing is that once you put a H^+ it is going to protonate this oxygen. Once it is going to protonate now it is going to double bond getting delocalized to generate a positive charge here. And once you have seen there is a generation of a positive charge. So, now there is a 1,2-shift happening of this methyl group from this position to this position to generate the more stable tertiary and allylic.

So, previously it was a secondary allylic now it is a tertiary and allylic. So, after that there will be a proton abstraction is going to convert you to the corresponding phenol. So, there is another example here very similar this is getting protonated first. Once it is protonating you are forming a carbocation here, this is allowing this methyl group to migrate to form this carbocation here. After that, you can see there is proton abstraction to form this corresponding phenol.

Dienone-phenol Rearrangement





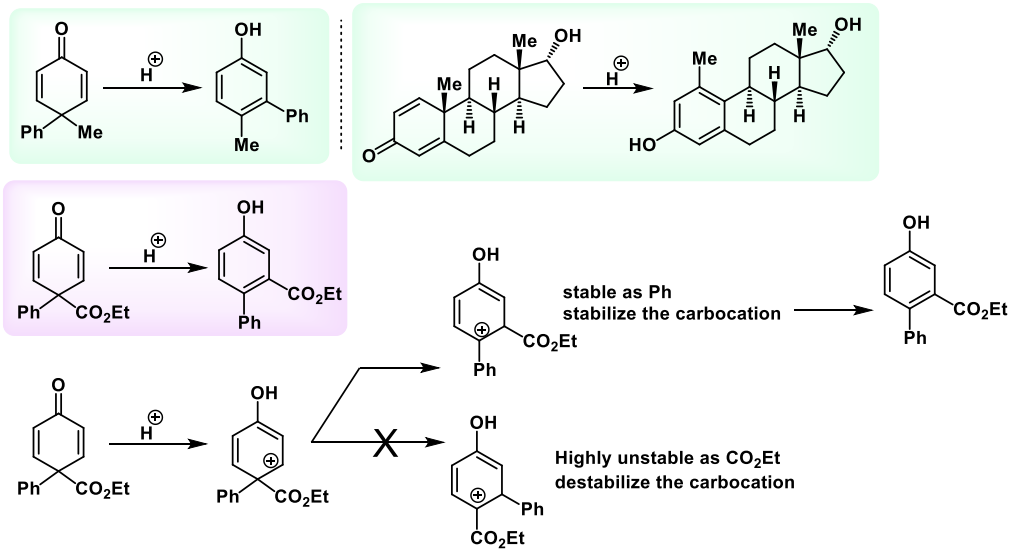


So, now we are going to see some of the examples. So, the problem is that we have learned in the dienone phenol rearrangement that there will be always two groups here. So, in the case of dienone you have two different groups in this position. So, one is going to get migrated. So, again I think you can see clearly that when the migration is happening the migrating group is carrying some sort of a partially positive charge which I am telling you from this previous from the Wagner-Marwin to the pinnacol in all the different rearrangements you have seen that there is a formation of some sort of 3c-2e species and I am sure very similar things are happening here. So, now the thing is as you see that your migrating group is carrying some sort of a partial positive charge that means, once it is getting you know migrated.

So, that means, if you have a phenyl versus methyl the phenyl is going to get migrated. So, that is why you have seen here in this reaction phenyl is getting migrated instead of the methyl. And if you have a phenyl and ester again you can see ester is an electron-withdrawing group, but phenyl is an electron-stabilizing group, but what we have observed here we have seen the product where the ester is migrated not the phenyl. So, there must be something different.

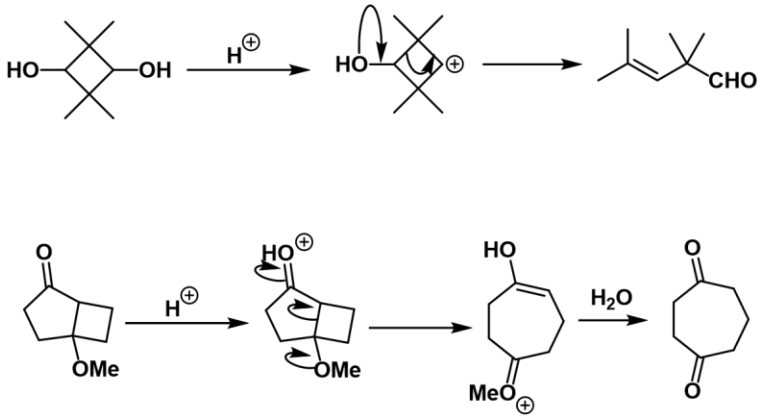
So, let us try to understand what is happening. Once you protonate first here then there will be formation of a carbocation. now as soon as you have the formation of a carbocation the next question is what migration suppose you have a phenyl migration Once your phenol migrate you have to think about what carbocation is forming that is also important. Because the carbocation that is forming, is very unfavorable it is next to the electron-withdrawing group then there is very less chance of the formation of this carbocation. It will prefer to form this particular carbocation where it will be getting stabilized. So, that means, that is also another important thing that in the dienone-phenone arrangement after the migration the carbocation also has to be get stabilized.

So, that is why because the phenyl is stabilizing this carbocation, now the ester is getting migrated to form this product. We can see another example here where you can see there is a methyl group clearly trying to get migrated once you protonate here because once you protonate this will make a positive charge that will allow this methyl to migrate to neutralize the charge to get to this product. So, here are some examples of fragmentation.



So, you can see we have two different hydroxy groups here. So, it is a very symmetrical molecule once it is getting protonated to form a positive charge. Now, to avoid the ring strain there is a tendency to open up ok. So, that will form this double bond and corresponding aldehyde compounds. Although these these alcohols are not in the vicinal position, but still because of the ring strain it is trying to open up. and it will form this corresponding product there is another example here. So, once you protonate this you get this OH+ now to neutralize this charge there is a chance of fragmentation again there is a 4-member cyclobutane ring that tries to expand to avoid the strain. So, this you know lone pair can attack here open the ring and you can able to make starting from this fused compound you can make this corresponding 1,4 diketone compounds.

Ring fragmentation using carbocations

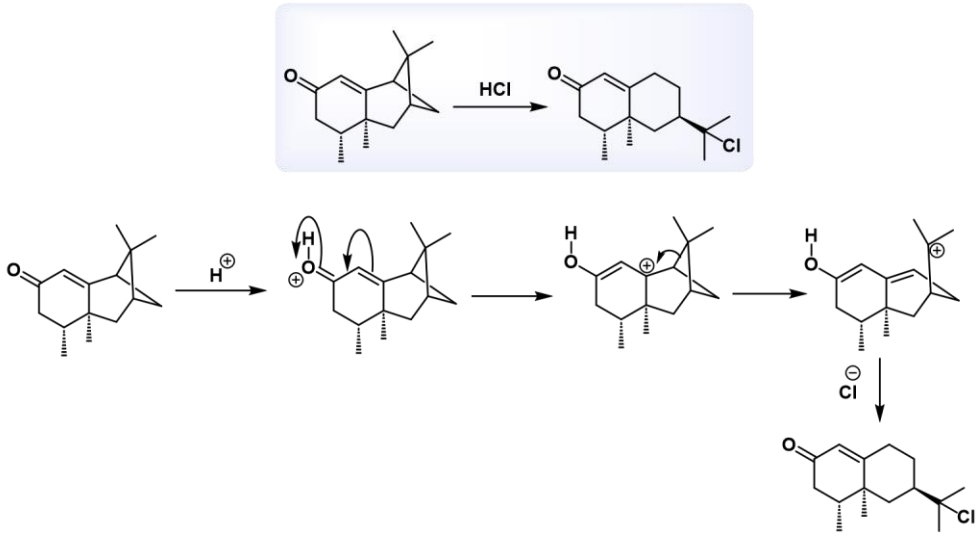


So, now, you know moving further we have another example about fragmentation. Now, once this one gets protonated what is going to happen? One is very similar, so we have learned in this that the dienone phenol rearrangement that you see once is getting

protonated is forming some sort of a carbocation character So if you forming a carbocationic character here, now to neutralize the charge, what is going to happen? I think we have already talked about this type of 1,2-shift. So that type of 1,2-shift going to happen to form this carbocation here. So again, I think this will be a more stable carbocation here, which can take this Cl^- to form this corresponding product. As you can see this carbocation formation happening in this position where there is a ring fusion.

So, it will be very difficult to get a planarity. So, that is why it will automatically go for this 1,2-shift to form this product.

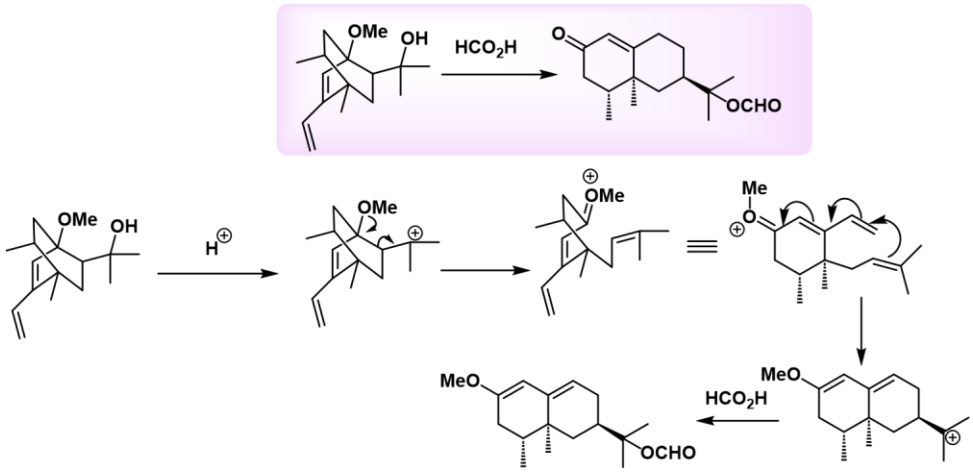
Ring fragmentation using carbocations



There is another example here first thing you can see you can have a protonation of this OH group forming a carbocation. Once you form a carbocation and once you have a methoxy group in this position. So, what is going to allow it is going to give the lone pair back and then it is going to form this double bond. and then this can get to the corresponding now once it is forming this allows for an intermolecular cyclization reaction.

So, now this double bond electron density can be transferred here to form this type of compound this is going to form a tertiary carbocation which can react with this formic acid to form this corresponding product.

Ring fragmentation using carbocations

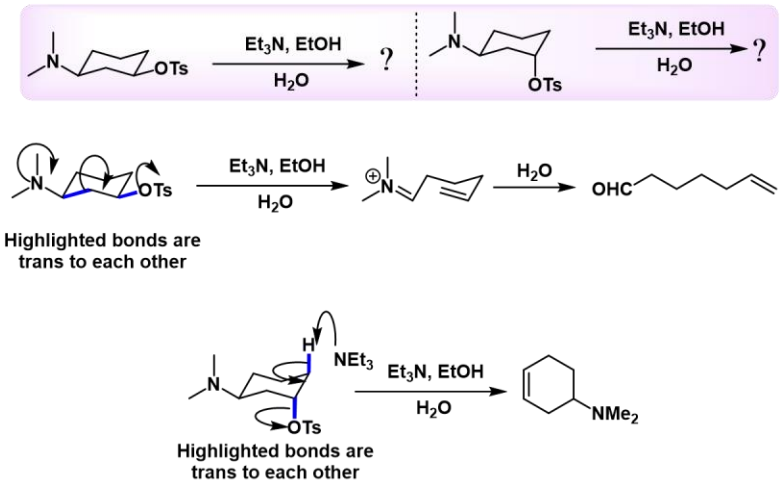


We have another example of a ring fragmentation where you have a N,N dimethyl group here and the -OTS group here. As I said previously you have seen an example where you have an -OMe group here and then after the one carbon you have an OH group. So, that was allowing you to do a lot of this chemistry. So, once you have a carbocation here after the -OH elimination this can allow you to migrate.

Now, here we have an -NMe_2 group which is very similar to what is happening once this tosyl is ready to leave. Now, this nitrogen can give the electron density to cleave this bond, and as you can see also this is a sigma-star here getting electron density from this corresponding sigma bond. So, they are anti-periplanar as I said before once they are anti-periplanar they can give electron density to form this from there it can you can see now once you get the corresponding water it can cleave here to form this corresponding aldehyde We know that. It very similar thing happening now if you change the position. Now if you have instead of having OTs in the equatorial now if in the axial position.

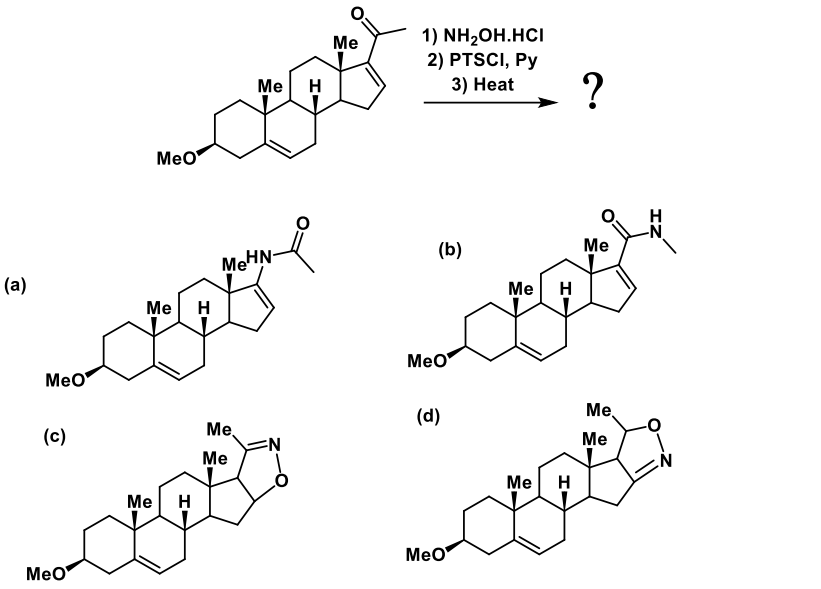
If it is an axial position then as I said there is a -CH group which is going to be antiperiplanar So, that will allow to after this hydride here to form this corresponding compound.

Ring fragmentation using carbocations

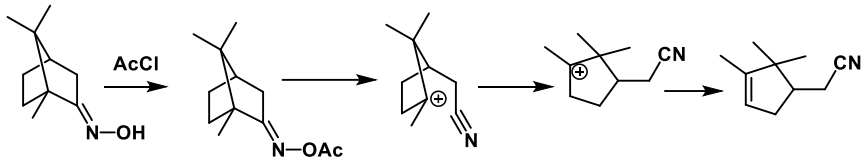


So, now I am going to talk about some of the questions here GATE-2012 we can see this question here. So, this is a question about the Beckmann rearrangement you can clearly see we are giving the oxime first. So, we are giving the hydroxylamine to form the oxime and then there is p-Toluenesulfonyl chloride here. So, what is going to happen here? You can now try to think about for a moment that what type of reaction going to happen.

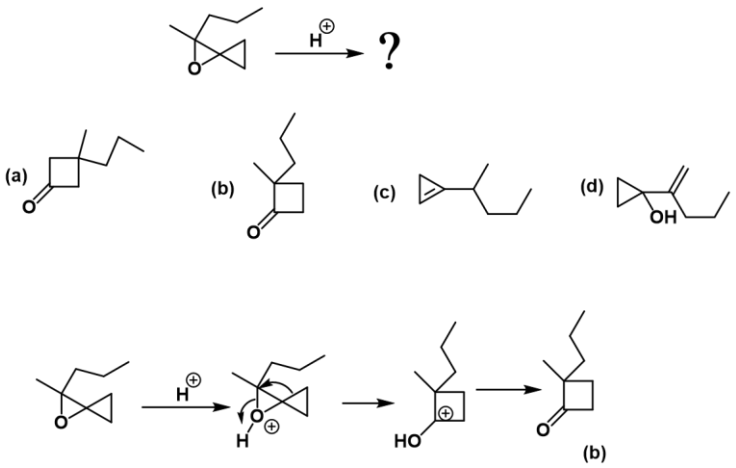
The first thing will be the formation of the oxime here and then you guys know that once the oxime is going to form here, that will go for, what is going to happen? That will go for this 1,2 shift. So, that will form oxime then it is going to get protonated then there will be a 1,2 shift going to happen which will end up forming the product. So, then after the 1,2 shift, there will be the intermediate going to form, and where there will be water going to get attacked to form this corresponding product. So, you will end up getting an amide.



There is another question here which came in NET if you treat with acetyl chloride. So, just now I covered it in the discussion that you will form a carbocation. So, there will be again a Beckmann fragmentation going to happen which going to convert to the corresponding olefin and then it will be going to convert to the corresponding nitrile.

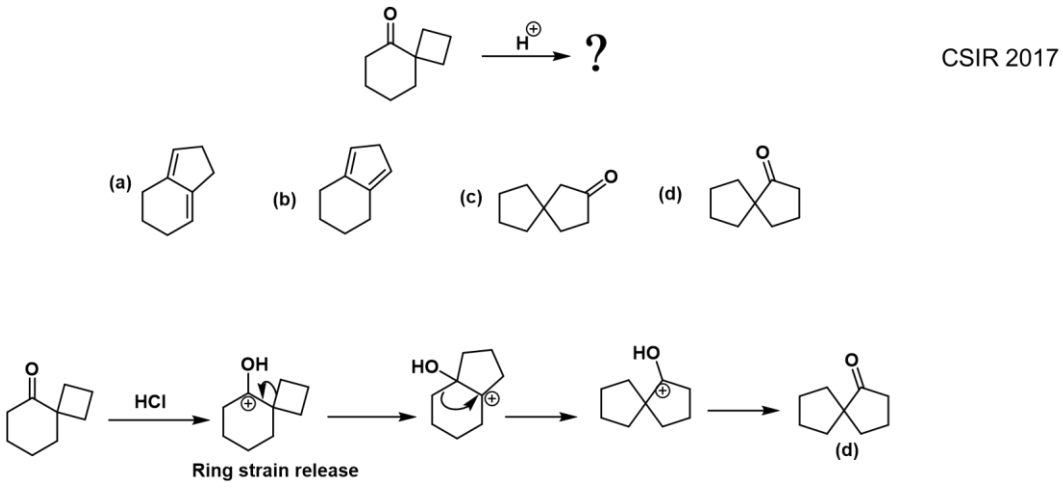


There is one more question from CSIR 2016. So, if you take this compound and give a H+ what is going to happen? As soon as you put a H+ as you can see. So, there is a possibility after getting for the protonation. So, this bond can be going to bend break, and expand here to open up the epoxide to form this type of 4-member carbocation here which can able to. So, the oxygen lone pair can stabilize it to form this corresponding product. So, you can see option-B will be the right answer here.



So, now we have another example here if you take this compound and then put H^+ what is going to happen? So, this came in the NET-2017. So, here is what is going to happen first step once you get its H^+ here again you can see the first thing that is going to happen is there is a ring expansion to neutralize it. So, you end up making some sort of a species here. So, there will be carbocation here, and as you can see that is again getting to this in the bridgehead position.

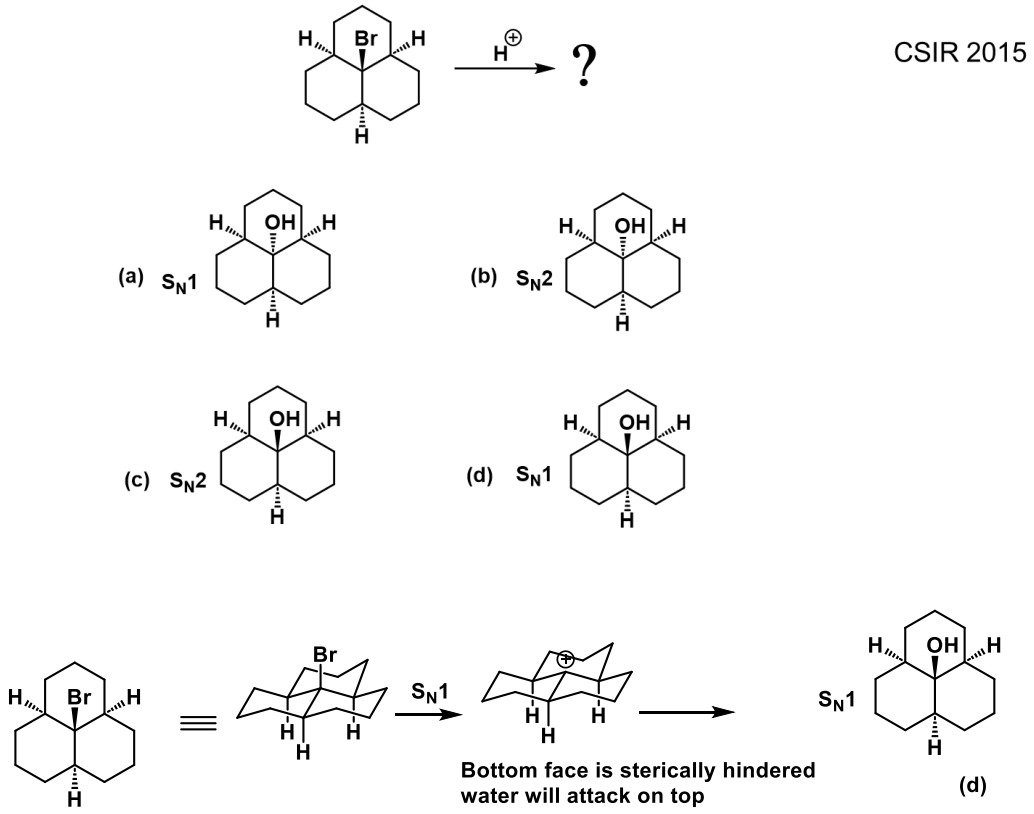
So, that is not going to be stabilized more. So, this bond going to break and move here to neutralize the charge to make a carbocation next to the oxygen which can give the lone pair to form this corresponding product. You can practice this question I think that will help you a lot in the exam.



So, in this question, first, you have to understand about this question that what exactly happening here. So, we are talking about there is a C-Br bond. So, we give a H+. So, what type of reaction this could be? So, this is a tertiary C-Br bond ok. So, definitely, we are talking about an SN_1 type of reaction. So, now think about it if you are trying to

go for an S_N1 reaction what will be your product? We all know that if it is going for S_N1 reaction then the first step will be the ionization of the C-Br bond and then the formation of the carbocation. So, if you form a carbocation the next thing is going to be where the nucleophile is going to attack because if you see all the different products you see they have very same structure, but different stereochemistry.

That means it is trying to guide you that there must be -OH come from a particular face. To understand that you have to kind of draw the structure of it. So, if you can able to draw the structure of it using this cyclohexane, then you can able to find out where the carbocation formation is happening. So, if there is ionization of this C-Br bond to form a carbocation here, now you can see that your nucleophile if you try to approach from this face is going to get hindered because of these three C-H bonds here. So, these three C-H bonds in axial position that is not going to allow you. So, instead of that the nucleophile will come back from the top face. and it will end up giving you this product. So, that means, you should also practice stereochemistry which is also going to guide you with some of the problems.



In today's class, I tried to cover the Beckmann rearrangement, the Friedel-crafts reaction, Fries rearrangement, the dienone phenol rearrangement, and then the ring opening and using the carbocation. and also we talk about some of the problems in the

NET and GATE. I am sure I am going to provide more problems during the practice questions. I am going to provide you with more problems in the practice questions and with that. I think you can go through the references and thank you all for coming to the class and I am looking forward to seeing you guys in the next class.