Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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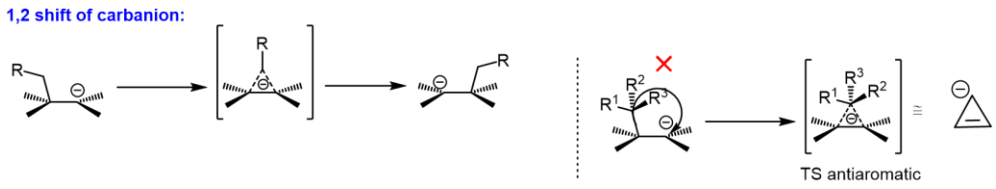
Lecture 07: Carbanion

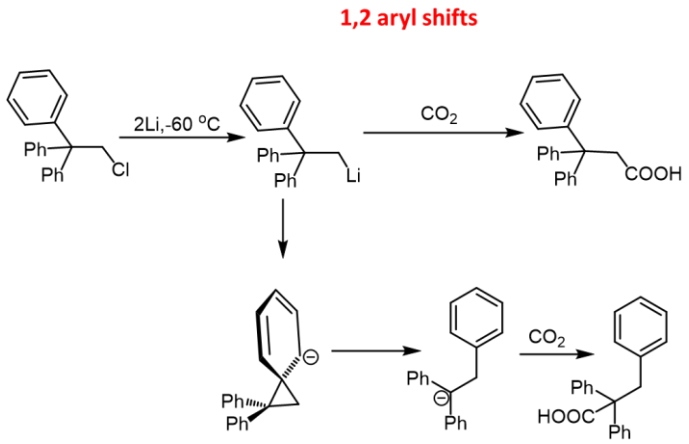
Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last class, I started talking about carbanion and I talked about the generation of carbanion and then different reactivity. In today's class, I am going to focus on different types of rearrangement reactions using carbanion. So, I am going to talk about the 1,2 shift of carbanion. Then I am going to talk about various different rearrangement reactions starting from benzilic acid rearrangement, then very important the Favorskii rearrangement, the Quasi Favorskii rearrangement, then the Ramberg–Bäcklund rearrangement. I am going to talk about the Baker–Venkataraman rearrangement and then payne rearrangement and I am going to talk about some of the example as well. So, there will be examples and mechanisms.

So, the first thing I am going to talk about that why the 1,2 shift of carbanions is less favorable. So, if you remember I think during carbocation when I was talking about 1,2 shift after the Wagner–Meerwein rearrangement, I started talking about why in the case of carbocation we know that 1,2 shift is very much favorable, but, in the case of carbanion, it is not favorable. Because what is happening here, once you go for a 1,2 shift then if you go through this transition state. We closely try to look at this transition state.

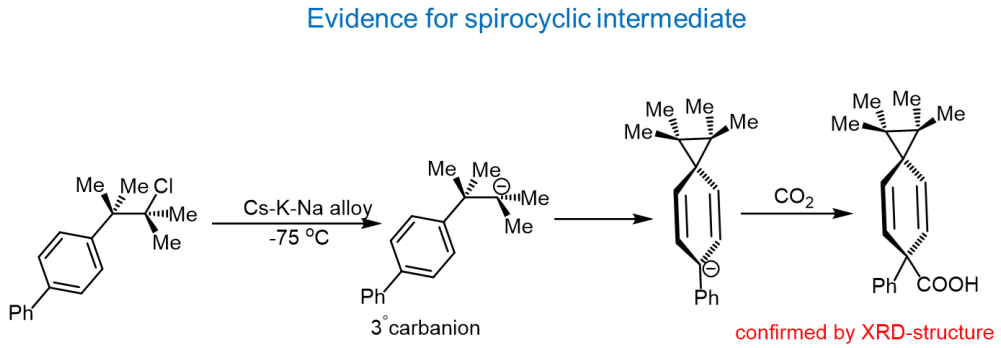


In the transition state if you see there is some sort of a cyclopropene ring and there is a carbanion. So, what is happening here, is actually generating an anti-aromatic transition state. As it is going through anti aromatic transition states that is that is why this is less favorable. So, that is why we generally do not see much of this type of alkyl 1, 2 shift,

but instead of this group if you have a phenyl group here. Suppose you have a phenyl group here, then if you have a phenyl group, things will be a little different.



In the case of phenyl group, there will be a 1 2 aryl shift. So, what is happening why in the case of phenyl it is so different? Once you have a phenyl group what is happening, this lithium is forming here through the metal halogen exchange of this carbon-chlorine bond. Now, this anion can attack here, this anion which is going to form here going to attack to form this corresponding carbanion here. Now, you can see this carbanion is getting stabilized through the resonance, you can able to draw the different resonance structures here. And then you can draw the next one going to go here and then what is going to happen, at the end of the day it is going to break this bond and going to form this carbanion which is again a di benzylic carbanion. So, that is why this carbanion- is getting very much stabilized here that is why this 1 2 aryl shift is happening.

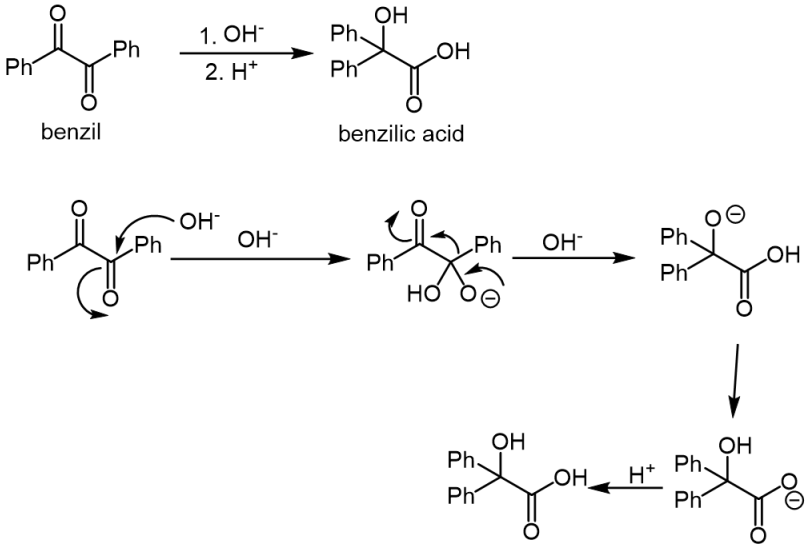


So, this aryl group now migrating from this position to this position at the end and then it is finally, trapping with CO_2 to form this product. So, we can give you some evidence of this that is happening or it is not. So, now, what is the first thing that happens from this

compound, the metal halogen exchange can generate this corresponding carbanion. I think there will be a phenyl group which was missing here. So, there will be a phenyl group here and now once this carbanion formation is happening this can attack here as I said before that is going to attack here which will generate this carbanion here.

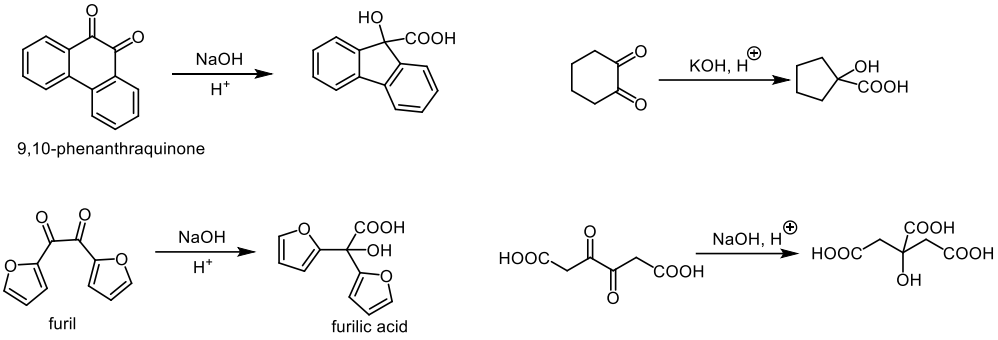
Again I said this is a a benzylic carbanion, getting stability. So, it can able to react with the CO_2 to form this corresponding product, and this compound, the last one can be isolated, and it was confirmed through the XRD structure. So, now this is kind of giving a clear evidence of this 1, 2 aryl shift.

Now, I am going to talk about a benzilic acid rearrangement. So, it is converting benzil to benzilic acid in the presence of a base. So, what is happening here? In this reaction the base is actually not able to find any proton to abstract, there are two phenyl groups. That is why, it is attacking the carbonyl group here to form this corresponding intermediate and now this O^- is coming back and allowing this 1, 2 migration of this phenyl group. That is forming this compound in which this O^- is abstracting this hydrogen which is acidic hydrogen to generate this type of anion species which can finally, take a proton to get to the corresponding OH. So, now we are going to learn about the different aspects of this benzil-benzilic acid rearrangement. One of the things is that if you have some sort of a molecule having intramolecular 1, 2-dicarbonyl compounds.

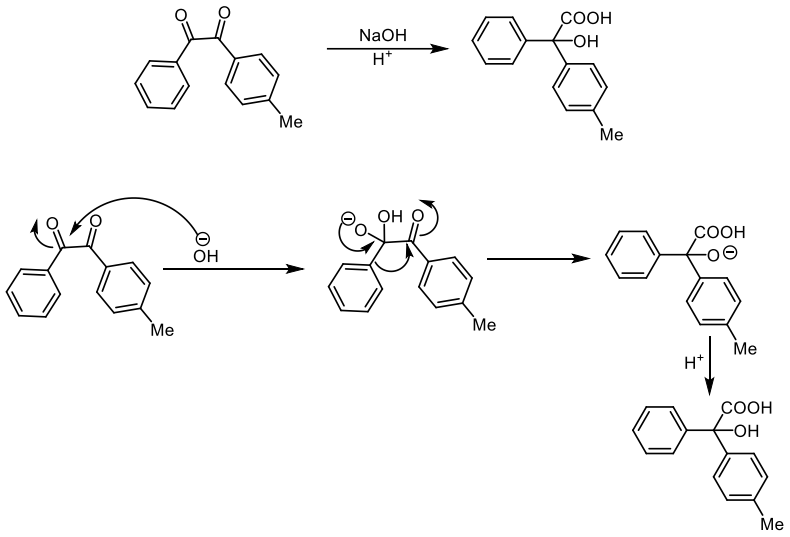


Now, what is going to happen in the presence of NaOH? Again the NaOH is going to attack here and now this phenyl group internally going to get migrated. So, once it is going to attack here, O will be O- and then what is going to happen, this will come back and this phenyl will migrate that will give this product. It can not only happen for phenyl, it can happen if you have two furans also, from furil, it can convert to furilic acid. So, at the end what is happening you are forming a carboxylic acid and a OH. It can happen

also in the case of aliphatic 1,2-diketones, but the yield will be less for sure because there will be some other reaction as I mentioned.

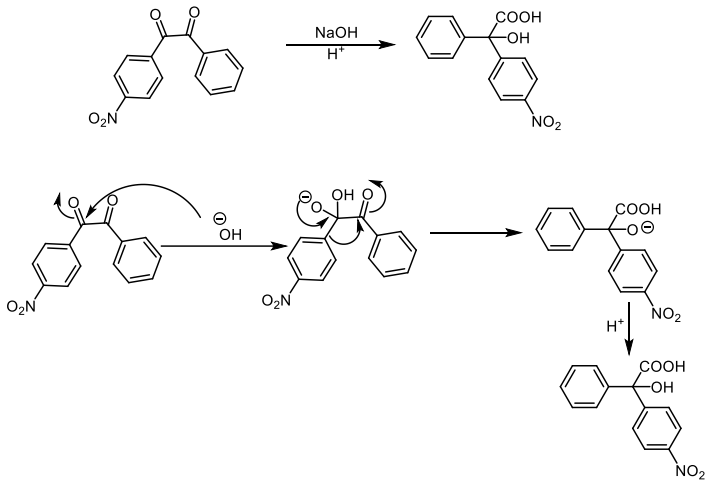


Then if you have some α-proton of this carbonyl compound, this α proton can be abstracted it can go for condensation and some other transformations. But of course, it is also going to form this particular product. So, what is happening in this reaction, is a ring contraction happening. So, if you want to do a ring contraction one of the options is you make a dicarbonyl and treat it with NaOH, it will be able to make the corresponding carboxylic acid and this can happen also in this example. Now, the question comes if you have an unsymmetrical aryl group like you have a phenyl on one side and 4-methyl phenyl on another side.

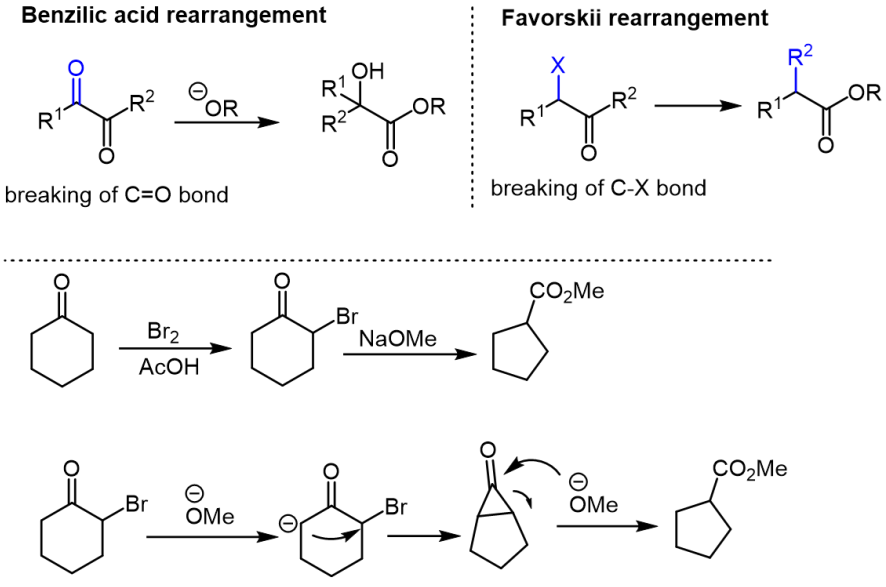


Now, what is going to happen? Now, the problem is the first step, when the base is attacking, it is going to find the carbon of the carbonyl which is more electron deficient, because you have the +I effect of this methyl, the OH- chooses to attack this carbonyl group, which allow this phenyl to migrate to get to this corresponding product. There are examples if you have a phenyl vs an electron-withdrawing group like a nitro group. So

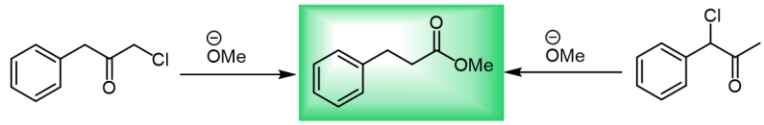
what will happen? Now, again as the nitro group has an electron pooling effect, it is taking the electron density from this carbonyl group and making this carbonyl more electron-deficient, and now the OH- can attack here on this particular carbonyl. Then this nitro phenyl can participate in 1, 2-migration here and then it is going to the corresponding product.



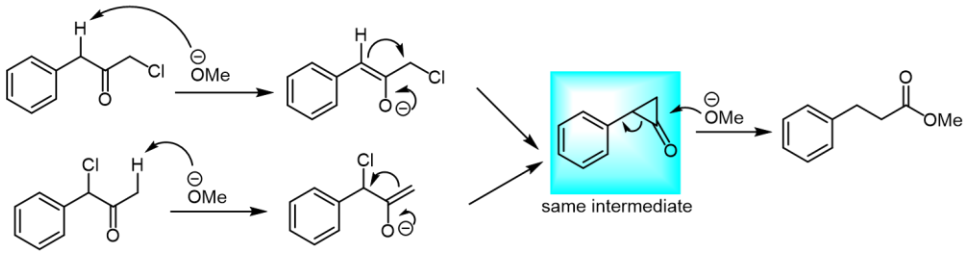
Now, we are going to move to the Favorskii rearrangement. So, what we have learned in benzil-benzilic acid rearrangement is that there will be 1,2 dicarbonyl compounds converted to corresponding products. So, what is happening, we are breaking this carbon-oxygen bond by attacking the OH-, but here we are going to break the carbon halogen bond which will end up corresponding esters. This X will be replaced by R^2. So, here is an example. So, this is an example from cyclohexanone you can able to make the corresponding α-bromo-cyclohexanone using bromine and acetic acid.



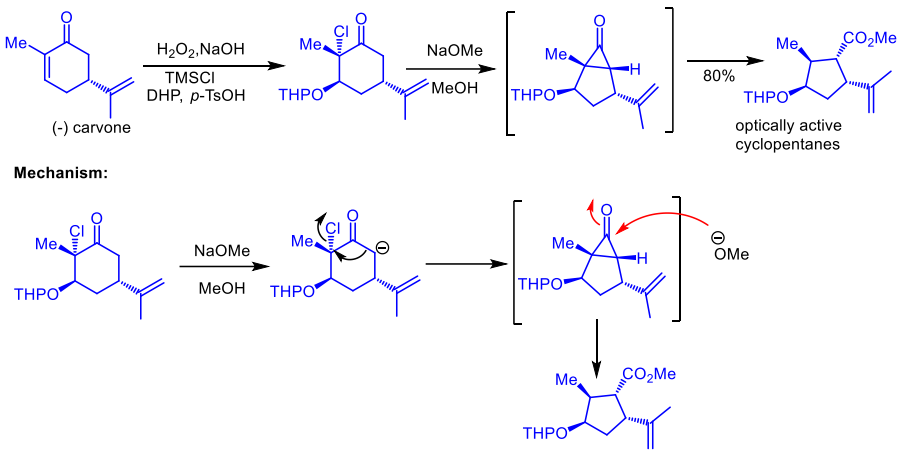
Now, once this compound is treated with sodium methoxide, what will happen? If this is my α-position and this is my α' position, it is going to abstract this proton from here and goes for S_N2 type of displacement to remove this Br. It will form some sort of a cyclopropanone intermediate which you can see here. Now, the OMe^- can attack here in the carbonyl group, and then it can open and cleave off this carbon-carbon bond here to form this product. Now of course, you said that if you want something like some other thing instead of the OMe. Based on whatever base you choose you end up with that type of product. You end up that type of esters actually.



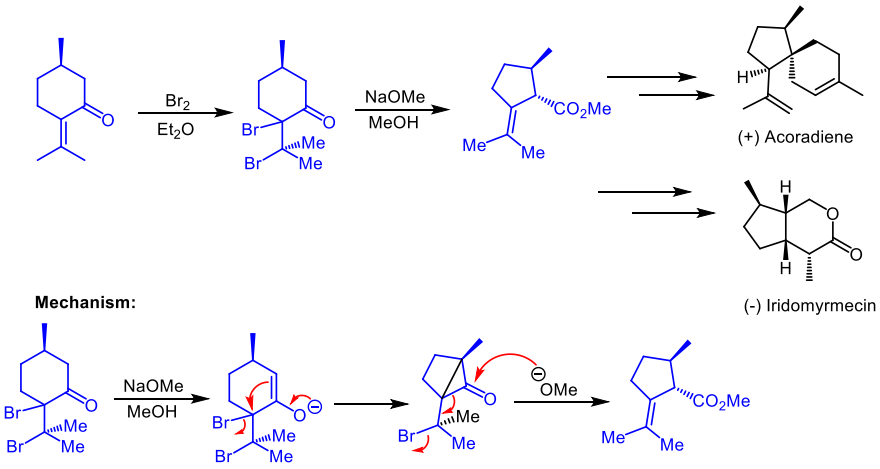
Mechanism:



Now, the question comes if you start with two different starting materials, where you have this type of α-chloro compounds or you have this chlorine next to the phenyl ring. So, starting from this compound 1 or compound 2, you still end up getting the same product after Favorskii rearrangement. So the question comes what is happening? Now, if you try to think about the mechanism of it, there is also an α and α' position. So, it is going to abstract this proton and then the anion going to get attacked here and form this type of intermediate. If it is starting from this compound also, it is going to happen a very similar thing. It can abstract this proton from here and form the negative charge that will attack here and form the same intermediate. Because it is forming the same intermediate, so the OMe^- is attacking and it gives the same product. There is an example in the natural product synthesis. Starting from this particular compound if you look at this compound they already have an α- chloro carbonyl group.

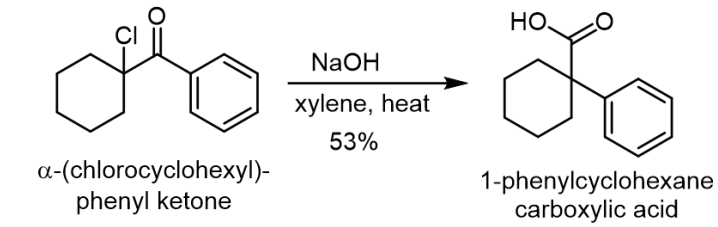


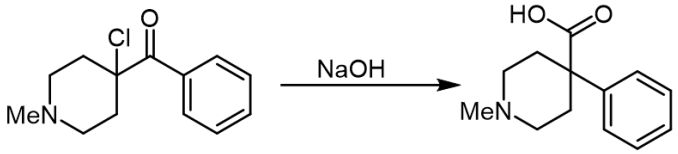
Now there is α' position, where the proton is getting abstracted and it going to attack here to get rid of the chlorine. Then in this cyclopropanone intermediate, the OMe- is going to attack here and then finally, it is going to open up this bond to form this corresponding product. Again what is going to happen if you have a dibromo species? So, you have an α here and you have a β position both have bromine. And you have a carbonyl group. So, the first thing going to happen, there is you have an α' position which will be getting abstracted. Now, it is going to attack here to get rid of this bromine to form this type of intermediate species, here the OMe^- going to get attacked. Now, this is going to cleave this bond. Instead of forming an anion, it is going to get rid of this corresponding bromine to form this corresponding product.



Then I am going to talk about another example of Quasi-Favorskii rearrangement. So, what is happening, in the case of Favorskii we have learned that there has to be an α'-H atom which is getting abstracted. Now the question comes that if you have a scenario here where you have a corresponding carbonyl group and you have this α-Cl, but you do not have this α'-H. which is the first step to abstraction by the base and then it is going to get rid of the chlorine. So, what is going to happen? Now, this will have a very similar thing. It will have a mixture of this benzil-benzilic acid rearrangement that means, we

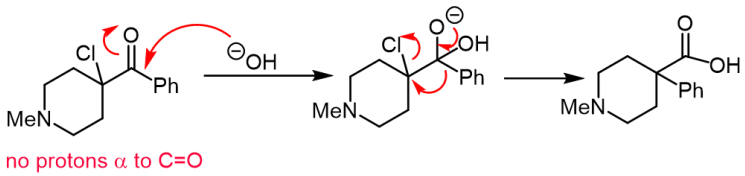
have learnt that the base can now attack to the carbonyl group. So, the base can come and attack to the carbonyl group here to form the O^-, which will come back and then this phenyl group going to get migrate and get rid of this chlorine to generate this type of carboxylic acid compound.



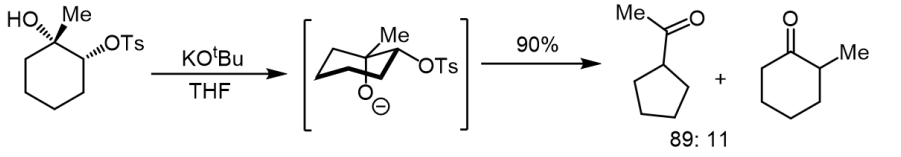


pethidine
painkiller

If you have this N-methyl instead of these cyclohexyl compounds then this compound is used as a painkiller which was synthesized using this Quasi-Favorskii rearrangement reaction. So, what is happening? Again I told you in the previous slide that this base is going to attack very similar to the benzil benzilic acid rearrangement. The first step is attacking the carbonyl group formation of the O^-. Now, as you have an α-Cl group here, it will participate in this 1, 2 migration to form this corresponding product. Now, the question comes that sometimes we also see semipinacol rearrangement, where if you have an OH and OTS. Because here we can make them from the corresponding alcohol



no protons α to C=O



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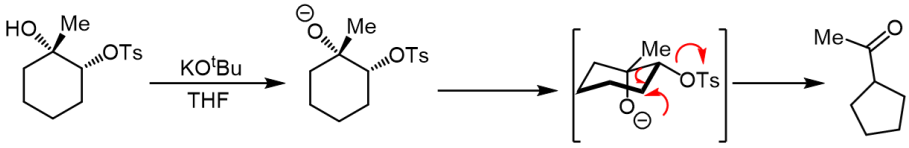
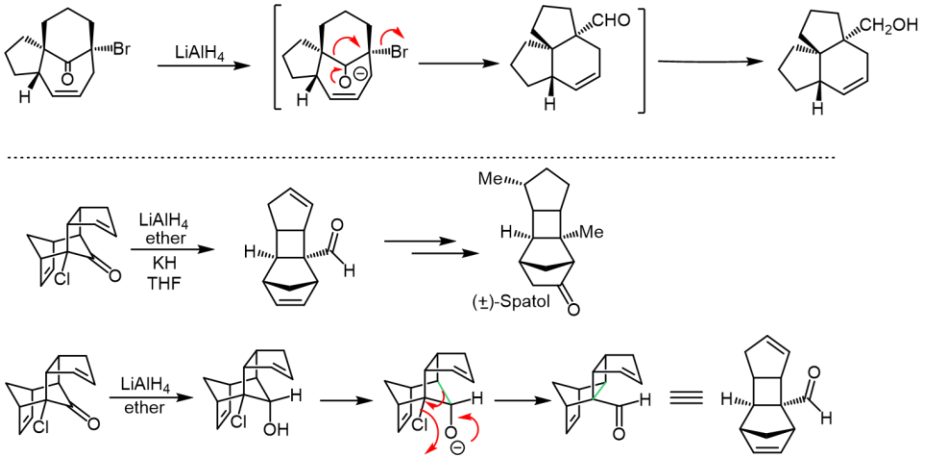
Mechanism:



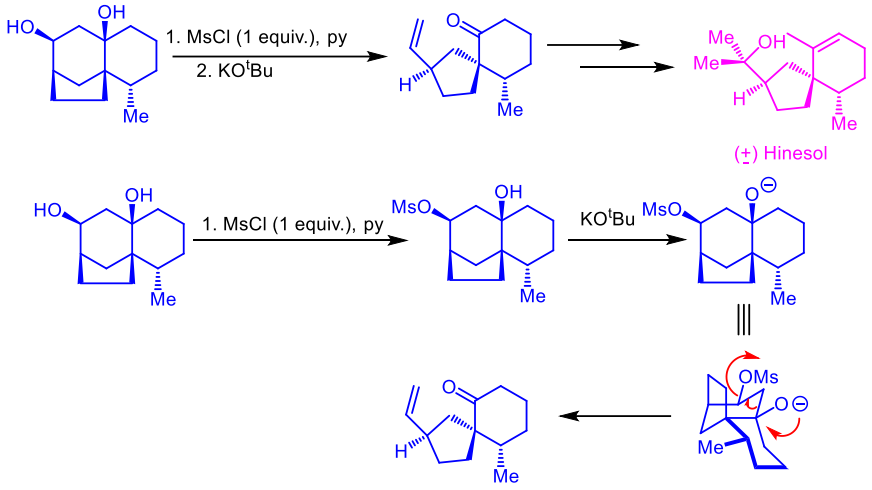
using tosyl chloride and pyridine I already talked about this type of reaction. Now, if you treat it with base, it is going to form O^- here, Now, you can see, that once it is forming in O^-, this σ bond actually aligns the antiperiplanar. So, this σ* is going to get electron density from this sigma. So, and this is actually antiperiplanar to this bond. So, that will allow this bond to migrate from here from this carbon to this carbon.

And this is going to form this product as a major product which you can see here in the in the mechanism. Now, there is another example, you can see there is a carbonyl group here and there is a carbon bromine bond. As soon as this carbonyl group was reduced using lithium aluminum hydride to make a corresponding O-, this is allowing this bond to be cleaved. Because now what is happening, as I said to you that there will be a σ* of this carbon bromine bond, where this σ bond is giving electron density. So, now, there is a ring contraction happening here. What you have seen here, this group will finally form a aldehyde and instead of 6 member, it will form a 5 membered ring. Then, there is another example here which you can see in this case also has a 5-membered ring at the beginning. I am trying to show you that 5-membered ring here. Now, what is going to happen? First, there is a reduction to form the O^-, then very similar to this, there will be a 1,2 shift going to happen which will convert this 5 member to the 4 membered ring. Now, it will become a 4 membered ring with a corresponding aldehyde.

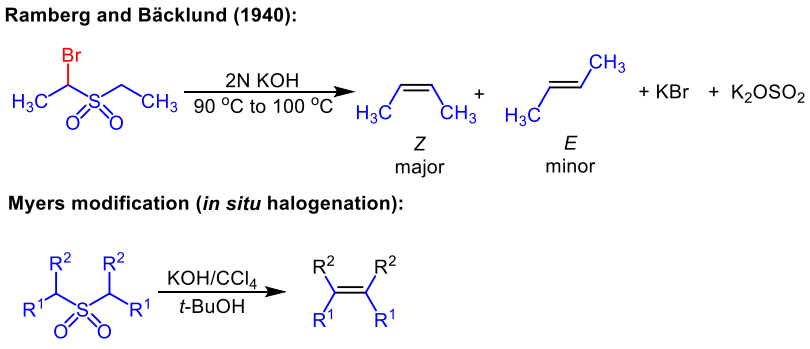


Which you have seen very clearly given in this mechanism that this particular bond is going to again participate in the shift to giving electron density in the σ* to form this product. Another example here is that you have two different alcohols. Here you can see there is one is tertiary, another is secondary. So, if you use a mesyl chloride pyridine, we have learned before also it is going to form mesyl to the less hindered alcohol. Now, once this is getting mesylated and this hydrogen is getting abstracted to make an O^-.

Now, this is allowing to shift. What is happening here? This bond is actually now ready to give electron density to the σ* orbital here. So, this σ to σ* donation is happening. It will allow to leave this bond and get rid of this OMs group. After the cleavage of this bond, you will see there will be a formation of olefin and then this will become O^-. So, there will be (+) charge going to form here which is going to O minus can give electron density to form this corresponding carbonyl.

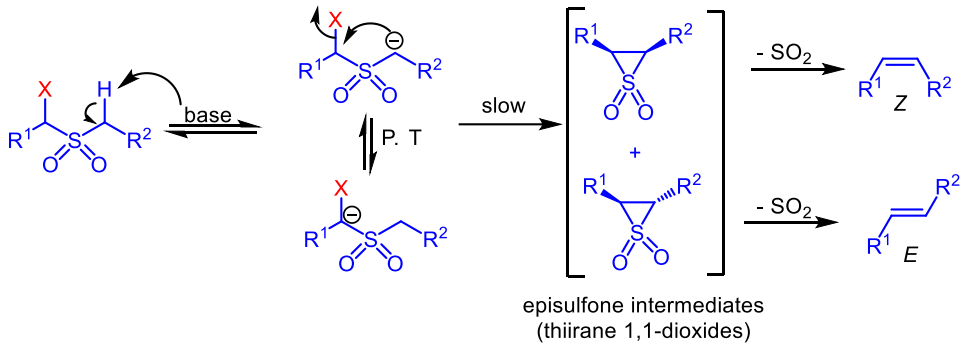


So, now we are going to move to another important rearrangement reaction called Ramberg–Bäcklund rearrangement reaction. So, this is a base-catalyzed rearrangement of α-halo sulfone to produce alkenes via episulfone intermediate. So, previously in the Favorskii rearrangement, if you remember I was talking about α-bromo carbonyl compound, but here I am talking about α-bromo sulfone. So, now, once you treat with base what is happening? In the case of Favorskii rearrangement, we have seen that there will be a ring contraction going to happen and then also the formation of ester. Here, what is happening? Formation of *E* and *Z* olefin.

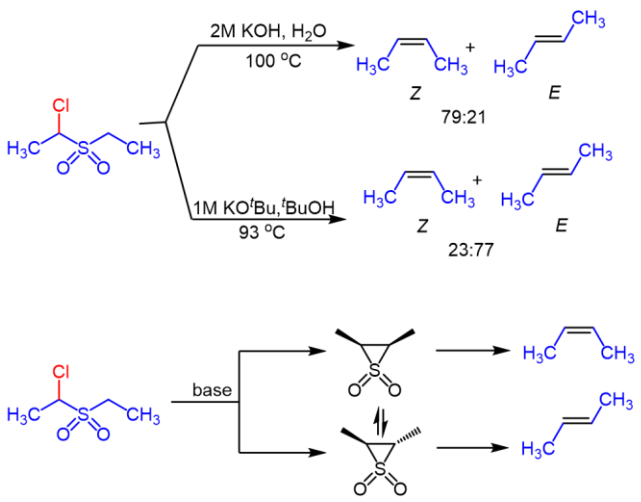


So, starting from an α-bromo sulfone is the formation of *E* and *Z* olefin. Now we are going to find out which will be major and which will be minor. But after the original was discovered the Myers group had a modified condition. Where they found out that you can start with this sulfone, you do not have to take this brominated at the beginning, treat it with KOH and CCl_4. So, that will allow to generate the corresponding starting material which is going to participate in the Ramberg-Bäcklund rearrangement.

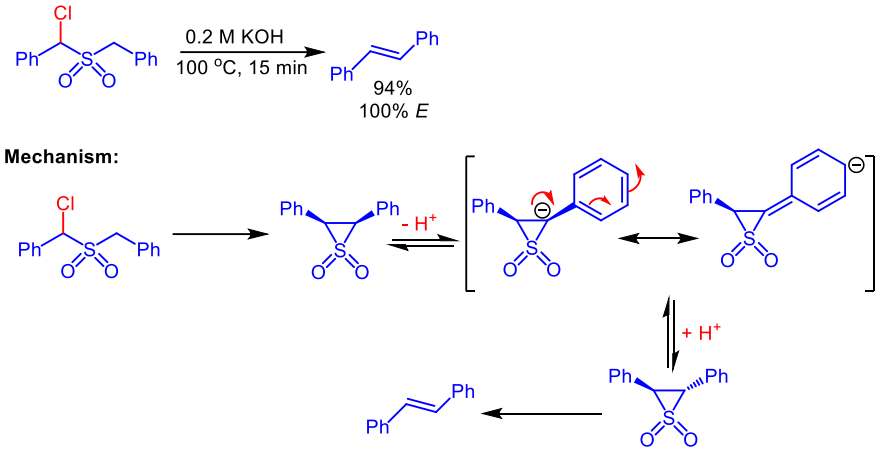
So, we are going to talk about some of this *E* vs. *Z* selectivity. So, what is happening, the first step is again the abstraction of this proton by the base to generate a carbanion. Now, this anion can attack here very similar to the Favorskii rearrangement to formation of this episulfone intermediate. Now, what is happening? once you are generating a carbanion here.



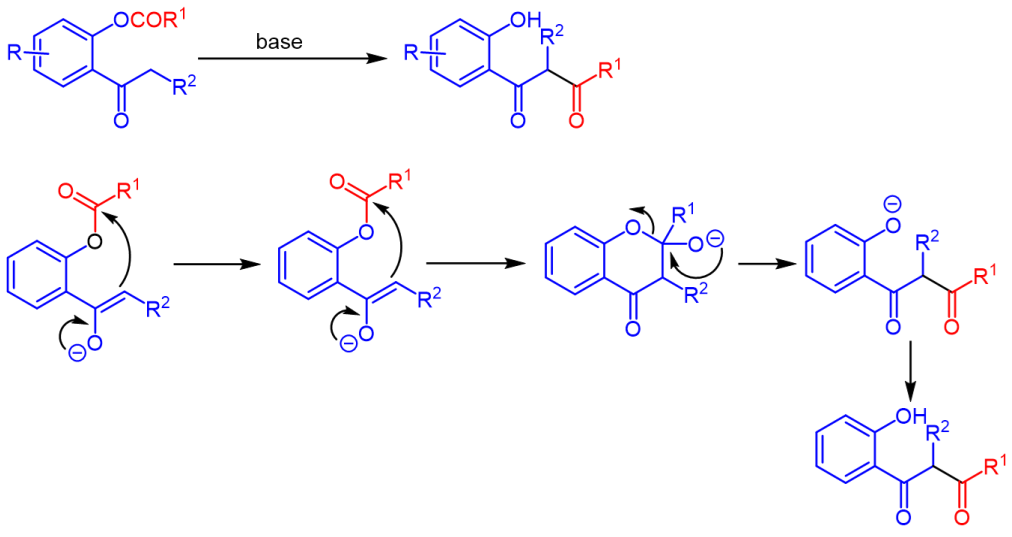
Now, if you have a stabilizing group, if R^2 becomes a stabilizing group, then what is happening? then there is a chance of epimerization. So, now, you can instead of making the *syn*-episulfone you will make a *anti*-episulfone as well. So, that means, these two group will be *anti* not *syn*. So, now, what is happening? From this two scenario, after the exclusion of sulfur dioxide it can form this olefin. So, in general, the *Z* olefin is always a major product, but what happens if there is a strong base used for this reaction? Suppose you use a Potassium tert-butoxide with tert-butanol then the *E* is given as a major product.



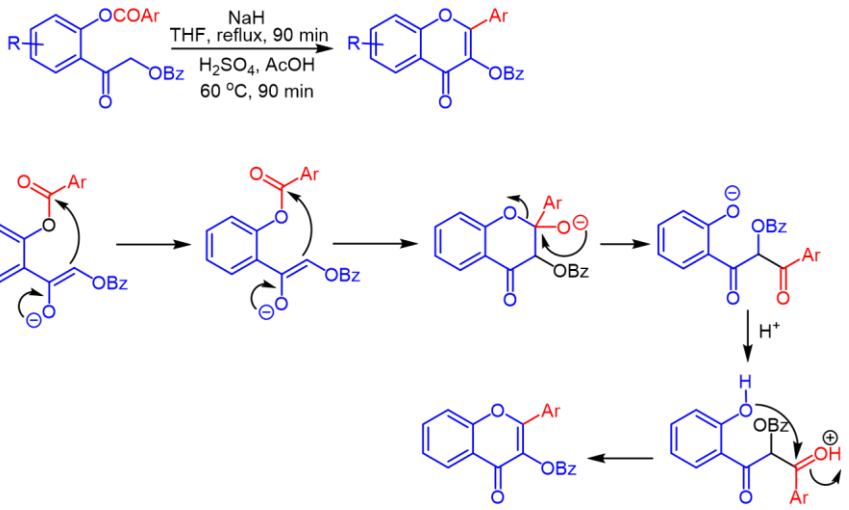
In general, with KOH condition this is the major product which is the *Z* olefin. Because in the corresponding episulfone if you see, both the methyl on the same side then after the SO_2 elimination they will form the *Z*. but if it is there in the *anti* then only they will form the *E*. So, means what is happening? once the base is becoming very strong then the *anti*-product will be a major product. We want to see that in the case of phenyl when there will be two phenyl groups here. So, this will be a phenyl instead of methyl. So, once you have a phenyl here and a phenyl here instead of methyl. What is going to happen? Then in the KOH, you can end up making it to the *trans*-Stilbene. So, what is happening? Why it is forming 100% *E*? Because what is in the corresponding transition state when is forming the episulfone? Now, if you talk about this particular stage, here because of this phenyl ring getting stabilized this carbanion as I said before. that carbanion in the phenyl ring getting stabilized. Now, this center is getting epimerized and it is going to an episulfone which is more stabilized. Because the trans will be a more stabilized episulfone intermediate which will finally, after the exclusion of SO_2, form the *trans*-Stilbene.



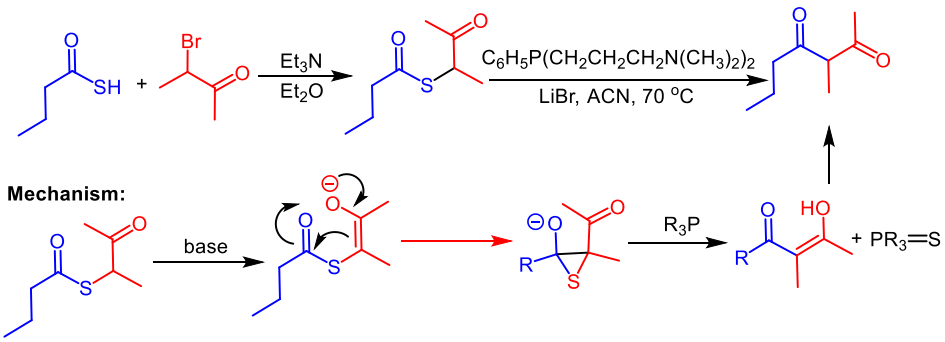
So, now I am going to talk about the Baker –Venkataraman rearrangement which is an another important rearrangement. So, this is also a base-induced rearrangement of 2-acetoxyacetophenone to 1, 3 diketones. So, what is happening, it is a rearrangement of the two acetoxy acetophenone. Now, in the presence of the base, this proton is getting abstracted. Which going to form an enolate which is going to come back and take this group here for the COR^1 group which is getting transferred. And now after this stage what is happening? This O^- is coming back and cleaving this carbon-oxygen bond forming this corresponding phenol. So, what is happening? At the end, it is taking a proton to go to the phenol and this 1,3-dicarbonyl compound. So, in this reaction after this happening if you are treated with H_2SO_4, then it ends up forming substituted chromones. So, now starting from this compound, it can end up making the substituted chromones.



Again the first step is formation of this enolate which is attacking this center again and then it is getting transferred here. And now again cleavage of this. So, this O^- comes back and cleavage of this carbon-oxygen bond. The formation of this intermediate, which is getting protonated. But once you have more acid in this medium, stronger acid, this can protonate this corresponding carbonyl group here. Now, this oxygen can attack through this lone pair and then after elimination of the H_2O, it can form chromones.



The another important rearrangement is the Eschenmoser sulfide contraction. So, what is Eschenmoser sulfide contraction? We are going to learn that this is a synthesis of 1,3-dicarbonyl compound that is your product and now what is your starting material? Again you have a α-bromocarbonyl compounds and you have a thioester. So, starting from a thioester and α--bromocarbonyl compound in presence of a base, is converting to a 1,3-dicarbonyl compound and also using a phosphine. Using lithium bromide and ACN as solvent at 70 ° C is forming 1,3-dicarbonyl compound.

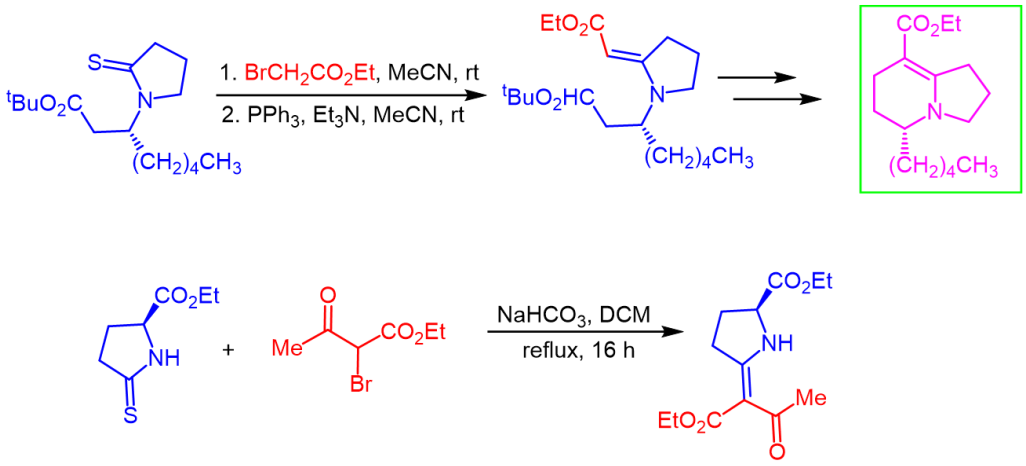


What is happening? The first thing is you can see sulfur is very good nucleophile, you are going to attack this carbon bromine bond through S_N2 to form this compound, then in the presence of a base what is going to happen? Base it will come to form a enolate and it is going to come back and then going to attack here to this carbonyl to form this type of intermediate. Now, the phosphorus going to come to the system, phosphorus going to

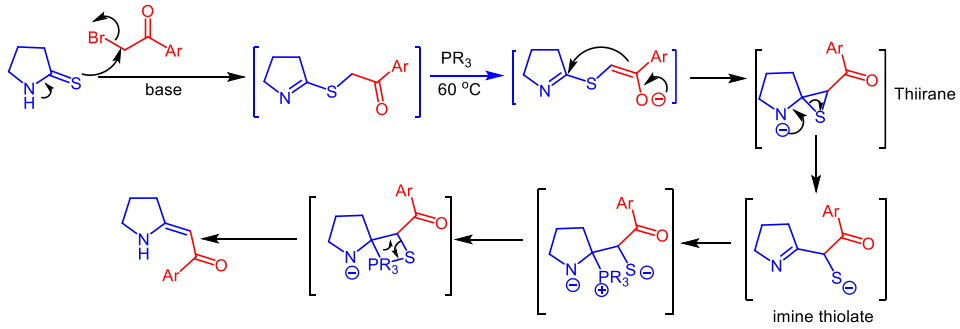
react here and after that it will going to get rid of this corresponding PR^3= S compound and it is getting protonation to this corresponding compound.

Previously we have seen the formation of the 1, 3 dicarbonyl compound, but if you start with the thioamide instead of thioester, then it end up forming an α- β unsaturated ester. Again you have to use this α-bromo ester or α-bromo carbonyl compound here. Again, there is another example also given here. So, this bromo is next to α to the carbonyl, α to the ester which can also form this α-β-unsaturated compounds.

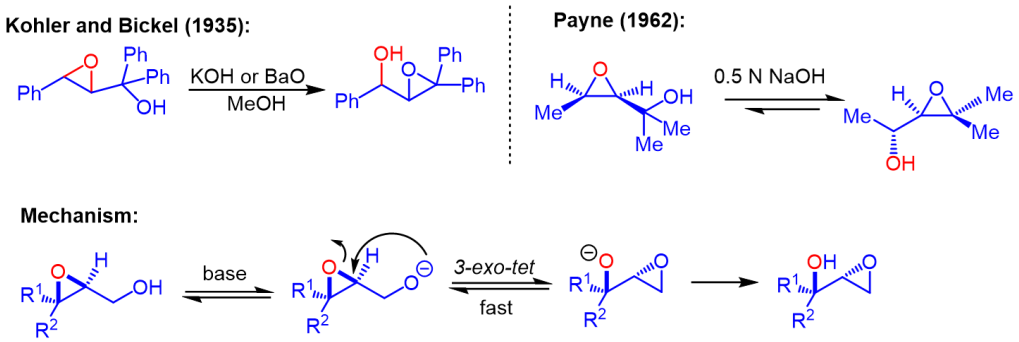
Synthesis of αβ-unsaturated ester starting from thioamide



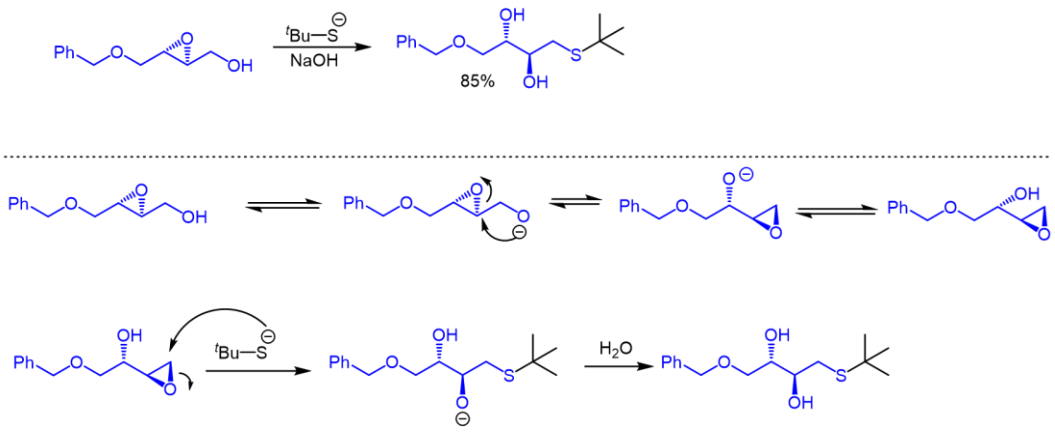
So, now, we try to understand the mechanism of this reaction and what is happening. Again the sulfur attacks first through an S_N2 to form this corresponding intermediate species. Now, what is happening? Again this proton is getting abstracted in the presence of a base to form an enolate that enolate is coming back and attacking here. Then it forms this type of thiirane intermediate. This thiirane intermediate is getting open to form this type of imine thiolate. Now what is happening? The PR_3 is getting whatever the phosphines are there, attacking here, forming this type of transition state. And then this type of intermediate species, which can now able to form this phosphorous-sulfur bond, and after that they able to get rid of this part of P=S very similar to the Wittig-olefination to form this corresponding product.



The other rearrangement I am going to talk about is the Payne rearrangement here. So, in the Payne rearrangement, what is happening? So, it is a base-induced intramolecular rearrangement where 2-3 epoxy alcohol is converted. So, it is actually a displacement of 2, 3-epoxy alcohol is known as a Payne rearrangement. So, what you are going to see is that the 2, 3-epoxy alcohol is converted into the 1, 2-epoxy alcohol mostly you are going to see there. These are 2, 3-epoxy alcohol is converted to the 1, 2-epoxy alcohol in the presence of base. So, what is happening? In the presence of the base, this OH proton is getting abstracted. which is now attacking through a S_N2 reaction. So, there will be a stereo inversion happening and then opening up this another epoxide in the molecule. I am showing here in the presence of base after abstraction of this proton then attacking here and so, this is going to open through 3-exo-tet according to Baldwin's rule. This will be a favorable one and then it is going to form the product. Now, if you have a scenario here that if you start with this particular compound and if you treat with this particular base what is going to happen? So, if you have a ^{t}Bu-S-, now you have a NaOH. So, now what is going to happen? So, here first thing is again as you see, there is a base going to abstract this oxygen proton making an O^-. And now once the abstracting the proton, first thing is a stereo inversion. So, you should be careful looking into this, once it is done, here we are making this epoxide. So, the first thing is a S_N2 happening. Next, there is this oxygen which is forming a O^-, which is getting proton, forming this particular compound.



But as you see that you have this ^{t}Bu-SH which is getting deprotonated in the presence of the base. So, now, this particular thiol is also attacking here to the unhindered position of the epoxide. Once it is opening up it is forming this particular compound. So, now, you have a kind of a diol here with this ^{t}Bu-S group attached to it. And if you take a proton, it is getting protonated to form this product.



So, in today's class, what we have learned? We have started with the carbanion, we have learned about the 1, 2 shift, and we have learned why the 1, 2 shifts are not favorable at the beginning if you have alkyl. Then we talk about if you have a phenyl there, then the 1, 2 shift is happening. For the phenyl group is getting 1, 2 shift, because the corresponding anion that is generating the dibenzylic carbanion, is getting stabilized through the resonance. And then we talked about the various different rearrangement reactions, we started with the benzilic acid rearrangement where you have seen starting from benzil, we are getting benzilic acid. So, the base is attacking the carbonyl then there will be a 1, 2, shift to get to the corresponding product. We have learned about the Favorskii rearrangement. that if you have an α-bromocarbonyl compound and if there is an α '-H, it can be abstracted with a base to get rid of the bromine and then that ketone can be attacked with the corresponding base and opening up of this cyclopropanone intermediate to the corresponding esters. We have learned about the Quasi-Favorskii rearrangement where you do not have α '-H. So, it is attacking of the oxygen followed by the1,2 shift happening to get rid of the chlorine. Then we talked about the Ramberg–Bäcklund rearrangement, and we talked about the Baker–Venkataraman rearrangement.

So, we talk about the formation of the phenol and the 1, 3-dicarbonyl compounds. We talk about the Eschenmoser sulfide contraction. There also we talk about how this reaction is very important to the formation of this product. We talk about the Payne rearrangement. And again the reference will be the very similar things you can go through the Clayden and the Carey, Sundberg, and the Smith of organic chemistry and the modern physical chemistry by Dougherty.

If you have any doubts or any questions please feel free to reach me. Thank you all for the coming to the class and I am going to look forward to see you guys in the next class.