Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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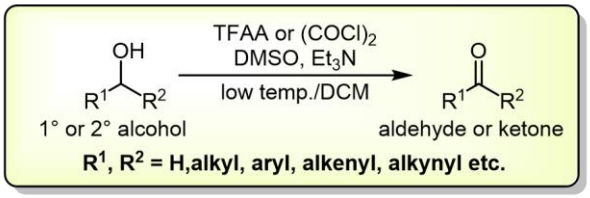
Lecture 53 : Organosulfur (Continued)

Welcome back to this a NPTEL online certification course in molecular rearrangement and in reactive intermediates. In the last two three classes I was talking about organosulfur chemistry. I talk about the discovery of the sulfurs and then the different type of organosulfur compounds and then I talk about the ylide chemistry. In the today's class my plan is to talk about some of the other important reaction I think all also if you remember in the last class I also talk about sulfur based different reagent for oxidation of alcohol to aldehyde or ketone You have seen different type of name reaction which was developed by activated DMSO based reagent and also we talk about some other variations. But I missed the one of the important reaction is the Swern oxidation so in the today's class i am going to start with the swern oxidation and then talk about the Pummerer rearrangement. very important reaction using sulphur, Mislow Evans some other [2,3] sigmatropic rearrangement reaction ok and then I will end up with using the Chugaev elimination.

I think if you remember in the last class I talk about there are several different variations of this particular reaction where what you are doing you are converting alcohol to corresponding aldehyde or ketone. So, the idea is we are using DMSO dimethyl sulfoxide I think you have seen in the several slide I talk about this always If you try to do a you do a resonance structure because of the electronegetivity difference of the sulfur and oxygen you can see there is a huge difference in electronegativity. So, you will always you can think about this the electron density is actually on the oxygen. So, you can think about S plus and O minus.

- In 1976 D. Swern and co-workers reported the the oxidation of **primary** and **secondary** alcohol using DMSO and trifluoroacetic anhydride (TFAA).
- Later on (in 1978) they modified the reaction using oxalyl chloride instead of TFAA.
- This reaction is known as Swern Oxidation.
- The reaction was carried out at low temperatures; -50 °C for the TFAA condition and -78 °C for the oxalyl chloride condition.
- Higher temperature leads to Pummerer rearrangement product.

Prof. D. Swern

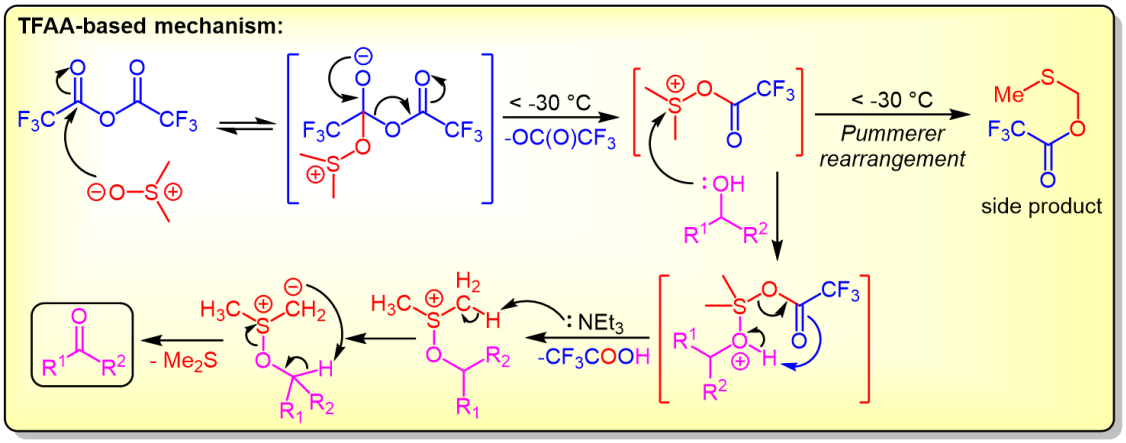


So, now you can see by using different type of other region we have seen using acetic anhydride using several other things we have talked about a SO_3 pyridine you have seen oxidation happening from alcohol to aldehyde or ketone. In Swern actually developed first initially in 1976 professor D. Swern and co-worker reported the oxidation of primary secondary alcohol using DMSO and trifluoroacetic anhydride. You can see it is a very similar to the Goldman oxidation which I have discussed in the previous class, where you have seen that was a DMSO and acetic anhydride correct So, what Swern group developed they replaced acetic anhydride with trifluoroacetic anhydride that was original discovery. Later in 1978 they modified their condition using oxalyl cloride instead of trifluoroacetic anhydride.

So, what they are doing they are trying to change this because if you remember at the beginning in this particular reaction which I talked in the last class that this O minus is attacking here to this acetic anhydride to get to the O acetyl if you remember that then it this will come back and this will break. That means you are somehow try to make this activated sulfur correct. Once you make that now you have the alcohol which going to attack here and then there will be a formation of some sort of a ylide type things and then there will be proton abstraction formation of the double bond correct. but then what happen after that discovery what they find out that this one the using oxalyl chloride becoming really better this reaction is very clean and this reaction is if you have a sensitive group it is only stopping at aldehyde it is not going to the corresponding acid so they found that if you use oxalyl chloride and DMSO and then you have to use a base here it is very important because once you understand you are you are using oxalyl chloride One of the important thing using oxalyl chloride that you will be getting some sort of a Cl minus correct. So, that is going to take H from the alcohol to make HCl.

So, now, you need a base to quench the acid which is formed in the reaction. So, now, so this is kind of a beginning to the Swern oxidation reaction. again I think the one at the beginning the earlier discovered using trifluoroacetic anhydride here the mechanism is again the O minus reattacking as I mentioned here cleaving of this bond. So, the anhydrides these bonds are weaker you form these activated species now alcohol attacks there, one alcohol attacks there you can form this product it is very similar to the all the previous oxidation and then you can see here this this proton will be taken by this oxygen going to form this species. Now this can allow you to in place of base Et_3N allow to form generation of this type of ylide species and once that is happening this CH_2 minus can take this proton from this α-proton to this corresponding alcohol to form this carbon oxygen double bond to convert to the corresponding aldehyde or ketone.

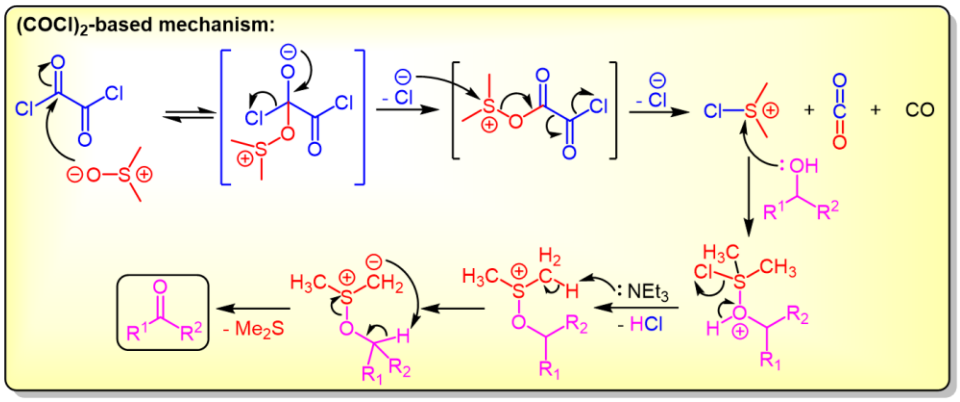
❖ **Mechanism:**



In case of oxalyl chloride you can see mechanistically now this will be a more reactive one compared to the trifluoroacetic candidate. So, this will react even at minus 78 degree Celsius this reaction can happen to get to this. So, now you are actually forming another intermediate it is not ah if you remember it is kind of mimicking the other oxidation you have hard which is they used NCS correct using N-chlorosuccinamide if you remember. So, Corey group actually develop the oxidation where they are also forming this species there. Again you can see this is sulfonium with a chloride there this is a very reactive.

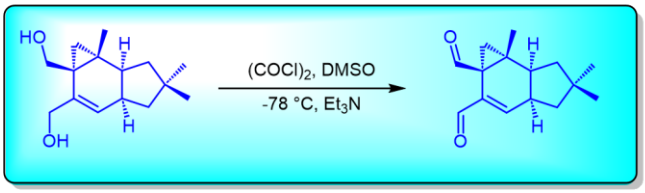
So, the alcohol going to attack the sulfur ok and then you can now this proton will be this again you can see here there will be a HCl going to form because the Cl minus going to take this H plus here. that will be quenched by triethylamine and now then again now the mechanism will be very similar you have seen in the previous case also it will be forming this ylide CH_2 minus this can take this proton from the double bond get to the corresponding product and dimethyl sulfide is your byproduct. Again you can see the one

❖ **Mechanism:**



of the important step which I did not mention might be is this so this is a very important step why i am saying that what is your byproduct look into it here you are not generating anything this is all are volatile stuff which is getting out from your reaction. So, your reaction byproduct is CO_2 and CO and dimethyl sulfide all are volatile. So, that is the important of this reaction the reactions are very clean you are not generating a byproduct which you have to kind of separate out from the reaction it is getting out from the reaction because these are gaseous compounds.

❑ **Synthetic Application:**

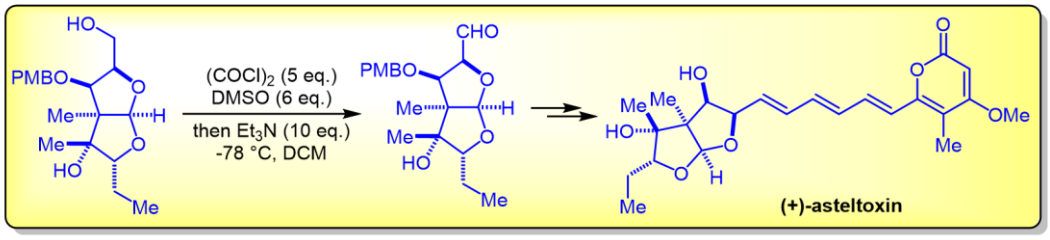


❖ Excellent yield was achieved with Swern oxidation, but decomposition of the starting material was observed with Jones oxidation.

So, this reaction has several applications if you see if you are organic synthesis lab someone must be using Swern oxidation for their synthesis. So, excellent yield was achieved in Swern oxidation for this particular transformations here you can see again minus 78 degree Celsius trimethylamine as a base and you have this alcohol here. So, what we are seeing here you have allylic alcohol one side and you have a primary alcohol both of them getting oxidized ok. But if you do this reaction using a Jones oxidation or the PCC oxidation they are first of all in case of PCC in case of Jones oxidation there will be over oxidation happening and in case of the PCC oxidation the yield was poor. Some

more example here you can see there are some sensitive functional groups in this molecule there is a tertiary alcohol here there is a primary alcohol here and again by Swern oxidation you can selectively oxidize this again this is a tertiary.

❑ **Synthetic Application:**



❖ Swern oxidation was used during the total synthesis of (+)-asteltoxin.

So, the primary alcohol is only getting oxidized, but not only that now you can see here this is the linkage here correct. So, you can see this is having some sort of a keter linkage here. So, these are not getting decomposed the product getting isolated in a good yield which is finally, converted after few step to important natural product. So, you will see that swan oxidation was used for several natural potosynthetics ah where you will see there are some sensory functions.

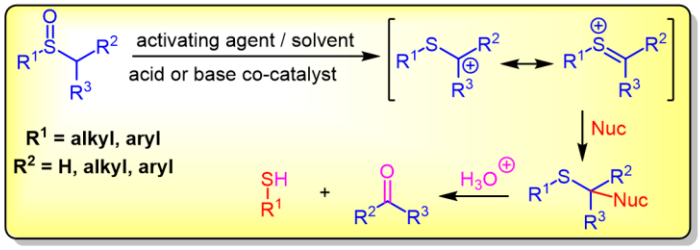
The other important the reaction using or the rearrangement using the sulfur chemistry is the Pummerer rearrangement. So, we learn about sulfoxide now we are going to learn that by starting from sulfoxide. if you can use a proper activating agent and of course, the solvent and then acid or base what you going to form you going to form a α-substituted compounds α-substituted sulfides. So, from sulfoxide you are you are synthesizing α-substituted sulfides through a rearrangement called Pummerer rearrangement it was discovered in 1909.

❖ The rearrangement of a sulfoxide (having at least one α-hydrogen) to α-substituted sulfides is known as Pummerer rearrangement. (**R. Pummerer,1909**)

❖ Acetic anhydride is the most widely used activating reagent, other activating agents are: HCl, H_2SO_4, TsOH, I_2/MeOH, TFAA, ^{t}BuBr, Me_3SiX, PCl_3, PCl_5, $Sn(OTf)_2$.

❖ Sometimes co-catalysts are used to minimize the side reactions, common co-catalysts: AcOH, TsOH, NaOAc.

❖ Upon acidic hydrolysis, the rearranged product α-acetoxy sulfide affords a thiol and a carbonyl compound.

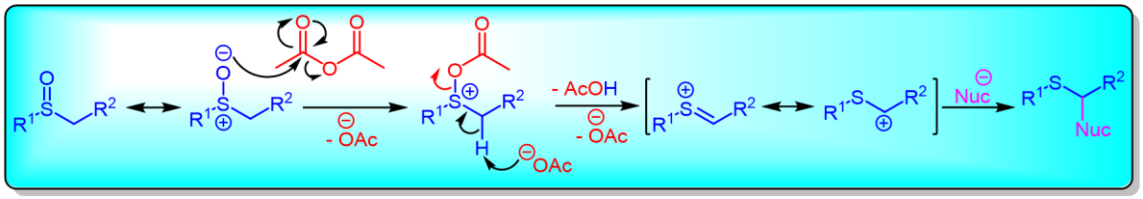


So, acetic anhydride is the most widely used activating agents for this reaction. So, most time you will see acetic anhydride is the one used for this reaction, but these are the other activating agent can be also used like the acid different type of acid, different type of Lewis acid or different other combination all can be used for this this reagent.

Sometime co-catalysts are used to minimize the side reaction. So, if there is a you go to see there are some sort of side reaction to stop them sometime you can use the co-catalyst at least. And once you form this again if you are using acetic anhydride then you end up forming this nucleophile will be a O acetyl. So, if you go for if acidic hydrolysis then you end up forming a carbonyl compound and a thiol. because you can see you can clearly see if you have a something like a OAC then this can get out from the sulphur can put the nucleophile then the if you have a H_3O plus then the water can attack then this carbon sulphur bond will be cleaved that will form the thiol and the corresponding carbon compound.

You can see the mechanism of the Pummerer rearrangement. So, as I said the again this the DMSO. So, again the sulphur is plus oxygen minus is attacking to the acetic anhydride you guys have seen that in in case of previous cases where you use this as a oxidizing agent for the alcohol. So, here what is happening first once you are taking the OAc minus. So, this part is coming out to into form this particular compound.

❖ **Mechanism:**



❖ The activated thial electrophile can be trapped by various intramolecular and intermolecular nucleophiles.

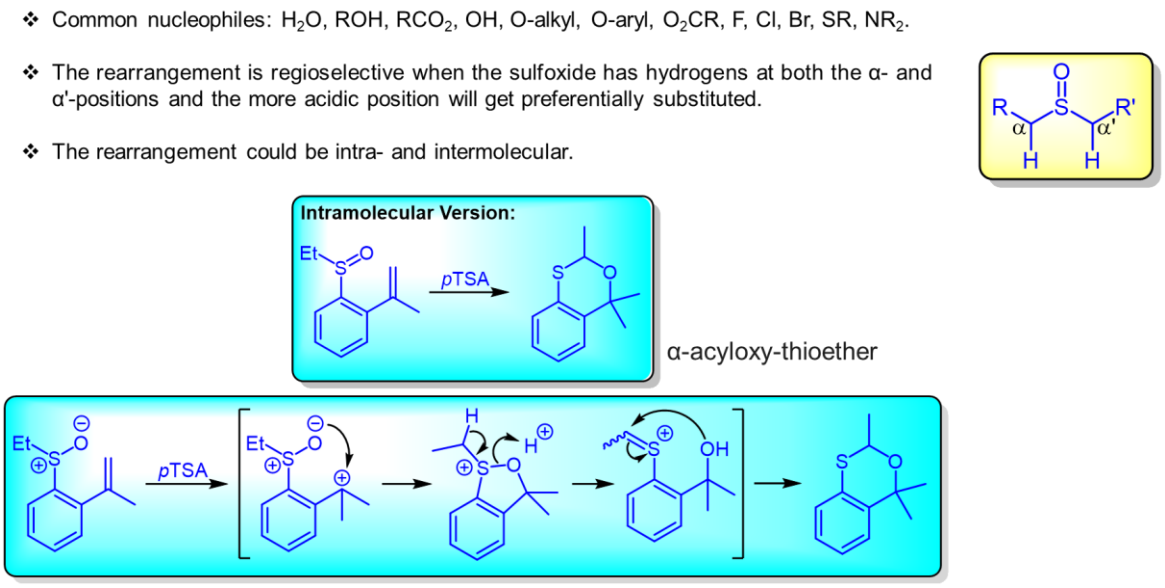
❖ The intermediate is so electrophilic that even neutral nucleophiles can be used, including aromatic rings with electron donating groups such as 1,3-benzodioxole.

Now, the OAc minus can take this proton from this carbon sulfur double bond. So, you can talk about. So, this type of compound as some sort of a thiol compound. So, if you have that you can try to draw a resonance structure now you can understand the any type of nucleophile will be attacking in this particular carbon. So, that can end up forming this particular product.

So, you can see nucleophile can be trapped in this type of activated thiol species which is forming in this reaction. So, by using an activating agent what you are doing you are kind of generating this type of species here in the reaction. where the nucleophile can be attacked and formed from this product. Again the intermediate is so electrophilic that

even the neutral nucleophile can be also used means you can think about some sort of a Friedel-Craft type of reactivity here. That means what they are saying that this particular thiol species which is forming here also you see this oxygen will get out at the end.

So, what you end up forming a double bond here. So, this type of species is a really you can see this is also attaching with an electron withdrawing group these are very reactive. So, that is why you can see if you use some sort of an electron like an electron you have an electron reach system here then they can participate in a Friedel-Craft reaction to get to this type of product. So, I talk about in the previous slide where you have seen that in the you have a nucleophile coming into the picture and you have the sulfoxide here I am talking about an intramolecular version. Again there are different type of nucleophile can be here there is a list of nucleophile I have given here could be alcohol, acid and the of course, the O aryl means again O is oxygen electron rich.

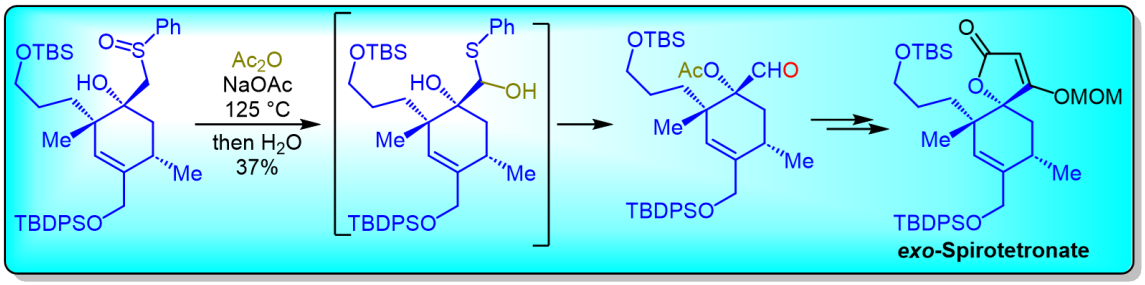


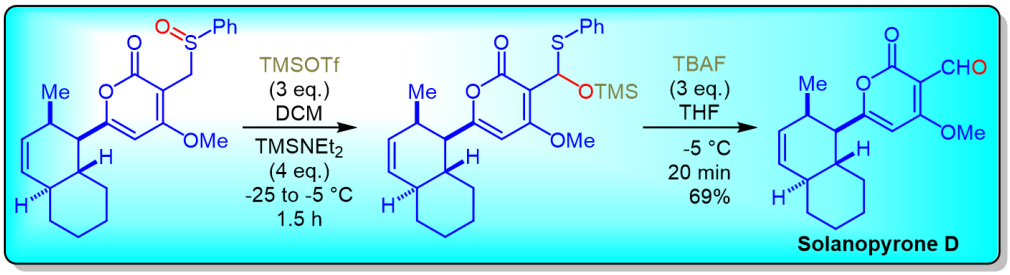
So, you are seeing the again the sulfur nitrogen they can be also. So, here I am talking about intramolecular version. So, now, you have had this sulfoxide here and you have olefin there like some sort of a styrene this is not a normal olefin this is styrene. So, once you use a PTSA what is going to happen they can protonate this styrene to generate a tertiary carbocation here which is also a benzylic. Now that can allow this you can think about that the sulfoxide as a sulfur plus O minus this can attack to the corresponding carbon.

And then it can from here you can see after formation of that the this proton can be

abstracted to form this type of thiol species here where the in the oxygen of this. So, now once this bond is getting cleaved you are generating a OH. Now the oxygen lone pair can attack the thiol in this position here. to neutralize the charge to generate the α-acyloxythioethers. So, starting from this simple sulfoxide you are generating a α-acyloxythioethers.

❖ **Synthetic Application:**





Again there are several synthetic applications here I am just trying to show you some of them here now you can see this SO_2Ph sorry this SOPh which is the corresponding the sulfoxide using acidic anhydride and and sodium acetate. You see some cases you have to use sodium acetate what it is doing it is going to convert this and then you once you put water it is going to convert them to this species can at the end get rid of this alcohol. So, you can you can think about now this can come back. So, it and then get rid of this part sorry it will be going to get rid of this part to get to the corresponding aldehyde. you have seen it is a first activation and then you have a nucleophile which is going to attack you have the water is a nucleophile which is attacking here getting rid of that species going to the corresponding carbon compound ok.

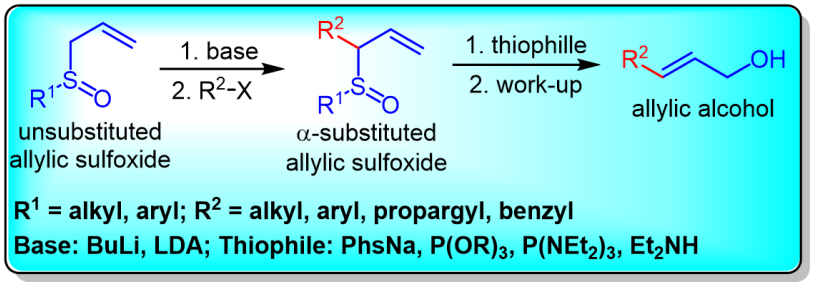
So, from sulfoxide you you are getting the sulfoxide eliminated and this carbon getting oxidized to the corresponding aldehyde which can be convert to the very important component here There is another example here you can see you have this the sulfoxide here now you are using TMS triflate. So, again the TMS triflate if you remember TMS triflate can activate the oxygen here the O minus can be from the OTMS here and once you have OTMS once you use a TBAF here. So, once you use TBAF the this is going to form a O minus it is going to come back and get rid of the SPh. So, it is going to form the corresponding thiophenol and and this going to convert to the corresponding aldehyde.

So, the you can you can clearly see that in this cases this is the oxygen which was there in the corresponding sulfoxide which actually coming to the corresponding aldehyde.

So, the aldehyde oxygen is coming from there ok, but here in the in the previous case if you seen there this is the water actually which is going to getting attacked. So, the water alcohol the water sorry in the water in a OH group actually finally, you can see that ah in the aldehyde oxygen. So, the oxygen from the water is actually transferring to the water of the the aldehyde. I am going to talk about the Mislow Evans rearrangement reaction here. So, this is a thermal arrangement of allylic sulfoxide I am talking about allylic sulfoxide to allylic alcohol.

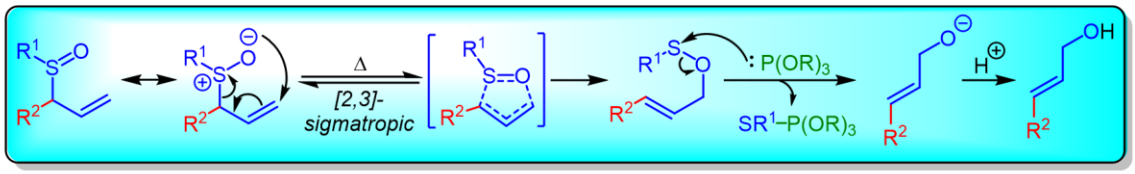
So, if you have a allylic sulfoxide and you want to convert to corresponding allylic alcohol then you can use this Mislow Evans rearrangement. It was discovered by 1966 by Kurt Mislow and then in later the Evans group have done some further development. So, this reaction is a [2,3]-sigmatropic rearrangement. So, you can see here I am going to go to the mechanism in a minute, but the before that what you are going to learn here what is happening from here to here all the way, thing we can use base and R^2-X. So, if you have a base and R^2-X you can clearly understand these are the protons which are acidic going to form a carbanion, then you are going to there will be SN2 to form this product. So, that can go for SN2 to form this carbon carbon bond. Now, once you have a thiophille and workup. So, this is the step where you are going to see this [2,3]-sigmatropic is going to happen to get to the corresponding product. again R^1 could be alkyl aryl and R^2 could be again alkyl aryl or propargyl or even benzyl and in case of base you can use butyllithium or LDA for this reaction and there are several different thiophille which can be used.

- Thermal rearrangement of allylic sulfoxide to allylic alcohol is known as Mislow-Evans rearrangement.
- In 1966 Kurt Mislow reported the prototypical reaction and David A. Evans published further developments.
- The reaction involves thermal *[2,3]*-sigmatropic rearrangements to form a sulfonate ester which reacts with a thiophine followed by acidic work leading to the allylic alcohol.

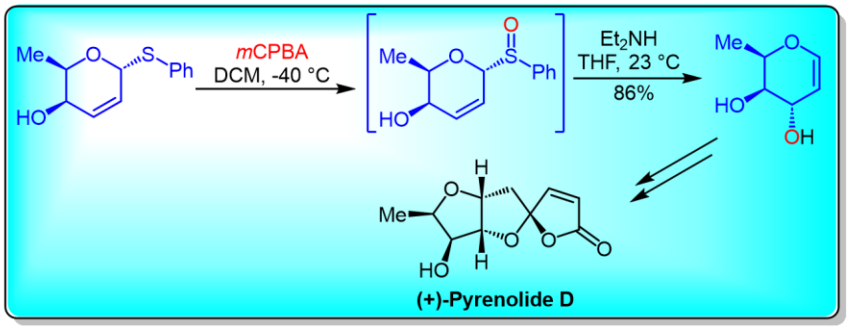


So, thiophile means this is a nucleophile which is going to take the sulfur. So, let us try to understand the mechanism of this reaction what is so this as I mentioned there is a [2,3]-sigmatropic shift happening here. So, after the formation of this bond now what is happening you have to put heat. Again you can think about this the sulfur is a sulfur plus oxygen minus. So, this O minus we can think about this as a 1 2 and this can be a 1 2 3.

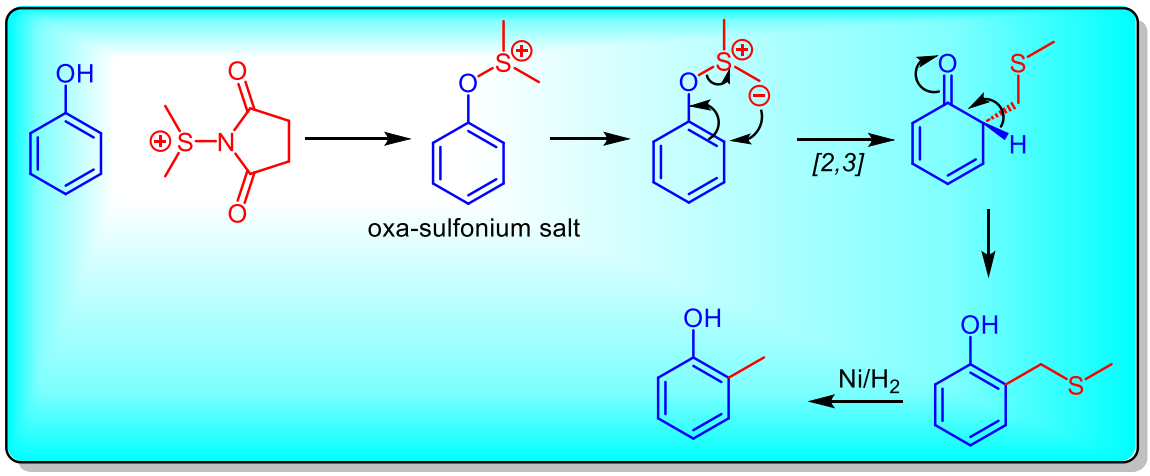
❖ **Mechanism:**



❖ **Synthetic Application:**

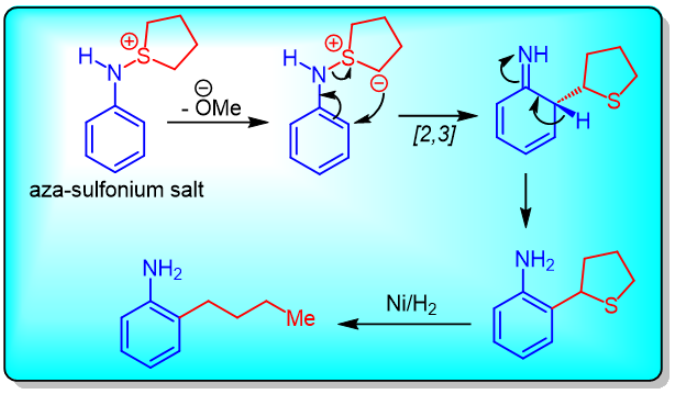


So, this can tell you this is a [2,3]-sigmatropic shift. So, the O minus is attacking here in this position and this double bond is pushing here breaking this carbon sulfur bond to get to this type of intermediate here from there it is going to form this compound. Now you have to use a thiophille it could be a phosphorus it could be a nitrogen which is going to attach to the sulfur cleave the sulfur oxygen bond to form this corresponding compound corresponding allylic alcohol after the protonation ok. Again there is a synthetic application here. So, again as I mentioned that from corresponding disulfide if you use a mCPBA it is going to convert to the corresponding sulfoxide.



Now you have this allylic sulfoxide here and once you look into allylic sulfoxide you should doubt that if you see some sort of a phosphorus or nitrogen based reagent you should always think about that there is a [2,3]-sigmatropic shift happening. Here what is happening again you can think about a sulfur as a plus this is a minus. So, this can come and go for a [2,3]-sigmatropic shift and there will be cleavage of the carbon sulfur bond and then once you have this. SO then the once you have that compound where you will have you have a methyl here OH and you will have an again you can you can understand that once this the stereochemistry here is a kind of getting shifted here. So, in this rearrangement you end up generating a OSPh ok. and then what is going to happen then you are using this diethylamine.

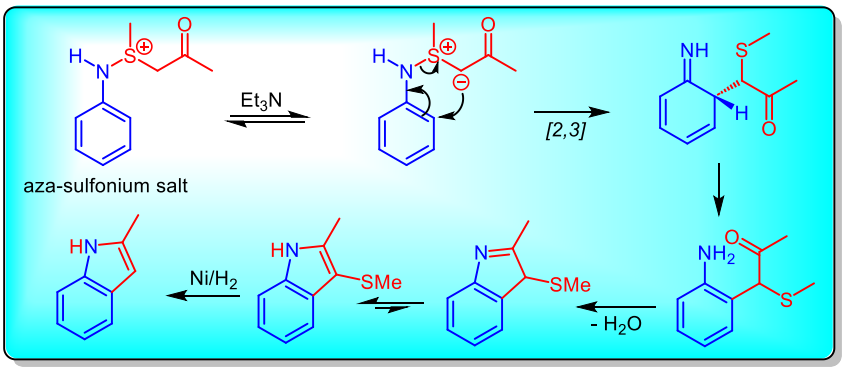
So, Et_2NH. So, that amine in lone pair can attack on the sulfur cleave this bond and then that O minus will be taking proton to get to the corresponding product ok. So, there are several other variations of this ah again you can see this is a as I mentioned in this particular variation what you are seeing you have a some sort of a azosulfonium in a salt some sort of azosulfonium species here. This azosulfonium species once you have the the phenol; the phenol can react here in the sulfur to keep this sulfur nitrogen bond to form the oxasulfonium salt. Once you have a oxasulfonium salt in place of base these are the proton going to be abstracted to form the corresponding carbon ion here. Now this carbanion can able to attack here you can see very similar to some sort of a like Smiles type rearrangement here. This can attack here through a [2,3]-sigmatropic rearrangement then going to form the double bond oxygen from this intermediate this proton will be abstracted to form the ah get back to the corresponding phenol and now you have this CH_2SCH_3. So, you have the disulfide in the ortho position of the phenol So, after the nickel if you do a rani nickel reduction then this carbon sulfur bond will be cleaved it will generate the corresponding ortho methyl phenol ok. You know several other variations of this type of reaction now as I mentioned in the previous slide that you are starting from this azasulfonium salt and then you are making the oxasulfonium, but you can start from this azasulfonium salt in case of aniline. if you have aniline then it can react with that



if you have some sort of a species like Cl ah then that can be you have a like a leaving group here plus then that can be attacked by corresponding aniline to form this. it will form the azasulfonium now again if you have this base in the medium this protons will be the acidic proton going to be abstracted from this type of ylide and now it can participate in this [2,3]-sigmatropic rearrangement from this intermediate now this proton will be getting abstracted to form a aniline and then you have this the tetra hydro thiophene which if you use a nickel hydrogen then these bonds will be cleaved which will end up giving you the butyl group in the ortho position.

So, you will get a ortho butyl aniline ok. So, this is a very interesting way to introduce substitution ah in the ortho position of phenol and the aniline. Another example here ah. So, this is a very interesting example because here you end up making starting from this azasulfonium salt you end up making a very important compound called indole and not only that you are introducing. So, if you see indole has this 2 and 3 poison you are forming a 2 methyl indole ok. So, sometime if you can see the Fischer indole synthesis this method will be comparatively better.

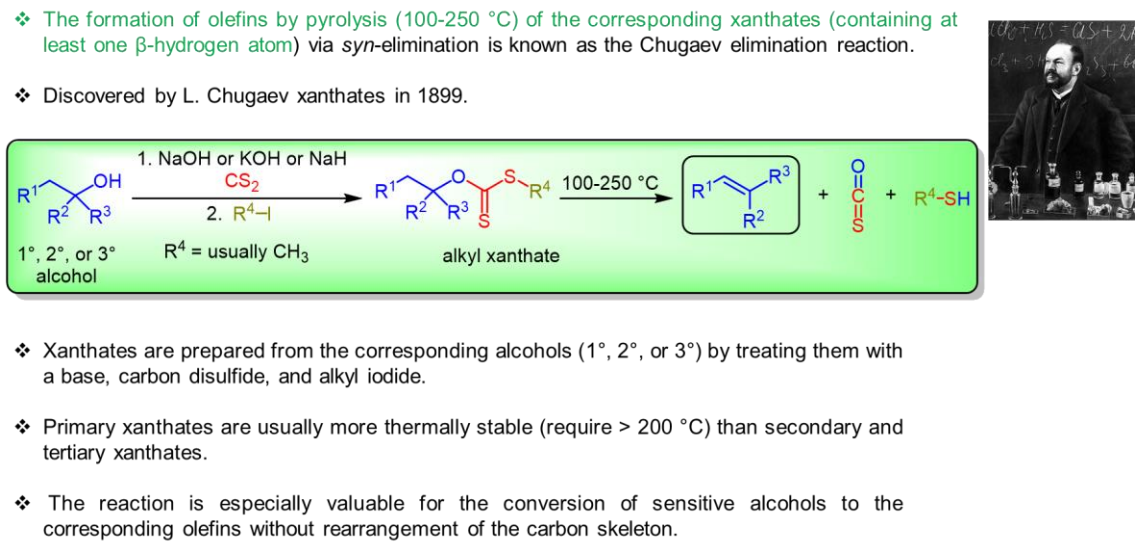
you can able to form this as a sulfonium salt from the corresponding aniline. And now if you have a triethylamine in the medium then it can able to form this corresponding ylide by abstracting this proton. And once you have a ylide and you can see this can take part in the [2,3]-sigmatropic rearrangement to attacking here formation of the carbon nitrogen double bond cleavage of the nitrogen sulfur bond. to form this intermediate again if that this proton will be abstracted to form a double bond here and a NH finally, it will take a proton to form NH_2. and now you can see you have a amine and you have a carbonyl group.



So, they will condense to form a imine and that can able to finally, this proton will be going to form a NH here you can see now you can clearly see you have a SMe group at the C-3 position and C-2 position having a methyl group. Now, once you treat with the Raney nickel and hydrogen this is going to cleave the carbon sulfur bond to form the 2

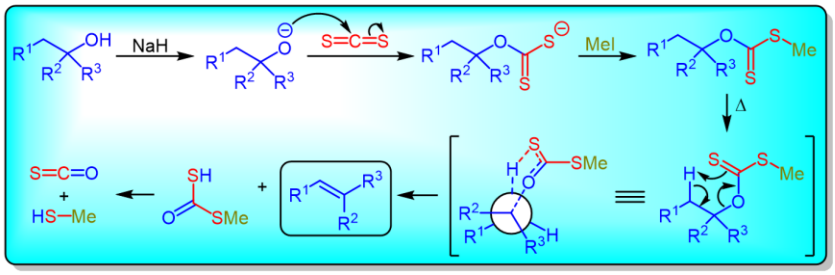
methyl indole. So, in this part I think I am going to finish in this part introducing a very important elimination reaction which is called the Chugaev elimination. So, this is a formation of a olefin by pyrolysis. So, I talk about this in the before also that if you have a xanthate which you are formation which you are forming then if you are hitting the corresponding xanthate then it can participate in a syn elimination.

So, this is called a Chugaev elimination which was which was discovered in 1899. Again you start with an alcohol 1 degree 2 degree or third degree alcohol you use a base to deprotonate the alcohol treat with carbon disulphide to form and then you use the corresponding alkyl halide to get the corresponding alkyl xanthate and once you have an alkyl xanthate once you heat up the alkyl xanthate it is going to form this corresponding olefin. So, again this is a syn elimination happening and we going to come back to the mechanism in a minute. So, the xanthates are prepared from the corresponding alcohol by treating them with a base with carbon disulfide and alkyl iodide. Primary xanthate is usually more thermally stable compared to the secondary and tertiary as you can see that in case of in case of secondary tertiary the reaction is happening faster compared to the primary.



Again it is a very important reaction for conversion of sensitive alcohol to the corresponding olefin without rearrangement of the carbon skeletal. So, let us try to learn the mechanism first as I mentioned your kind of forming this alkyl xanthate this mechanism is very easy you are deprotonating the alcohol attacking to this carbon disulfide then again there will be S_N2 reaction to form this corresponding alkyl xanthate. Now once you heat up the xanthate what is going to happen again the sulfur or nucleophile this can able to take this

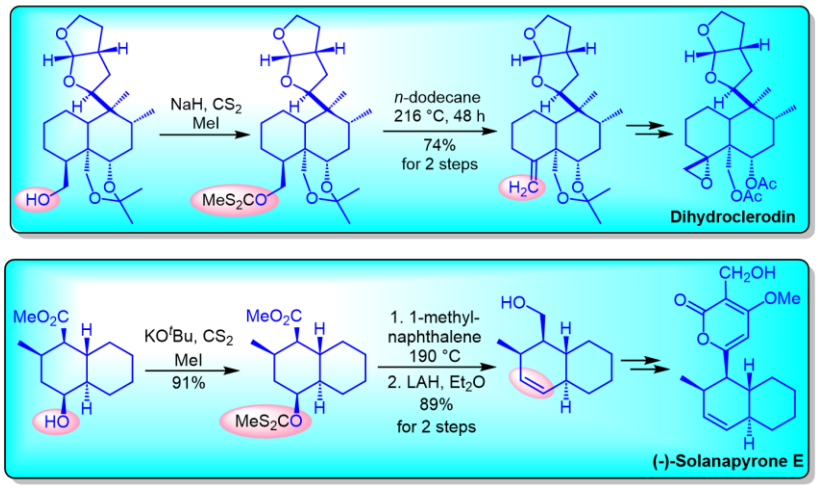
❖ **Mechanism:**



proton form the double bond and it will form the carbon oxygen double bond. So, that is a driving force here you are cleaving a carbon oxygen single bond to form a carbon oxygen double bond at the end. and you can see it can you we have shown here it is going through some sort of a transition state here where the H and the corresponding xanthate will be on the same side they will go for a syn elimination that is why if you see the there will be a steric interaction here to avoid that you have to you have to heat the reaction at the high temperature.

So, that this will be feasible to get to the corresponding product through the syn elimination. Again this has used for again for several natural product syntheses one of the example here. So, in this in a synthesis they want to get rid of this corresponding alcohol primary alcohol to form this olefin and that was converted to the corresponding natural product. So, now, I think that again the sodium hydride and carbon disulphide again sodium hydride will be selectively forming the O minus that will treat with carbon disulphide. then if you treat with methyl iodide that will go for SN2 to form the corresponding xanthate and now you have to just heat up the reaction with over 200 degree Celsius.

❖ **Synthetic Application:**



Once you do that this reaction will be clean and formation of the corresponding olefin here and then again there is another example here in this particular reaction you have see this is a here this is a secondary alcohol potassium tertbutoxide is used and to abstract this proton then react with carbon disulfide methyl iodide. to get to this xanthate now you have to you are treating with 190 degree Celsius. If you treat with 190 degree Celsius you can see there is a this is the proton which is again xanthates are sterically bulk. So, it will try to find a proton which are kind of having a less steric and also as you see this is a syn elimination.

So, that is why this proton is actually not in the same side. this is in the opposite side. So, that is why it is going to take this proton which are in the same side. So, you can think about there will be two protons one is like this one is like this. So, it is going to take this proton which are in the same side and form the corresponding olefin here. And now if you use the lithium aluminum hydride if you remember lithium aluminum hydride can convert the corresponding ester to the corresponding alcohol and after that you can able to get to the corresponding natural product.

So, in this particular part I talk about the Swern oxidation and then the very important the Pummerer rearrangement and you have seen Mislow-Evans this [2,3]-sigmatropic shift and again I end up in talking about the Chugaev elimination. Again these are the text book again the Clayden books is very good if you try to follow this chemistry. Again thank you so much for coming to the class and I am going to see you guys in the next class. Thank you.