Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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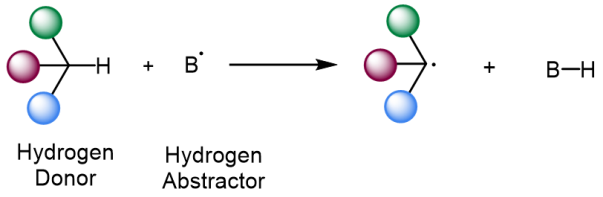
Lecture 25: Radical continued

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last class, we learned about the single electron reduction using sodium, and lithium, we have learned about the Birch reduction. In today's class, we are going to learn about another important concept in radical chemistry, which is called hydrogen atom transfer. I have used this terminology several times. When I was teaching you the Barton Decarboxylation. I also talked about hydrogen atom transfer. I was trying to talk about the tributyltin hydride, there also I talked about the hydrogen atom transfer.

But now, I am going to talk about what is the definition of hydrogen atom transfer and how that reaction is useful in radical chemistry. So, let us start with the content for today's topic. So, in today's topic, we are going to talk about the definition, some of the details, and some of the basis for the hydrogen atom transfer, and then I am going to talk about two important name reactions. One is the Barton nitrite ester reaction and the other one is the Hofmann–Löffler–Freytag reaction.

And then, I am going to talk about some of the modifications and some more examples. So, the first thing is let us talk about what is the definition of hydrogen atom transfer. So, the most important thing in this reaction is that you will find there will be a hydrogen atom donor or hydrogen donor, there will be a hydrogen abstractor and then, at the end again, what is going to happen you can see this will lose the hydrogen, it will form a radical and it will take the hydrogen from the B-H. So, it is a case where a neutral hydrogen atom is removed from a substrate to another molecule that is the important thing here. Now if you look into this reaction about the thermodynamics, then one of the important things is to get this reaction towards the product you have to understand that we already learned that in the radical reaction.

- In chemistry, hydrogen atom abstraction, or hydrogen atom transfer (HAT), refers to a class of chemical reactions where a neutral hydrogen atom is removed from a substrate, another molecule.

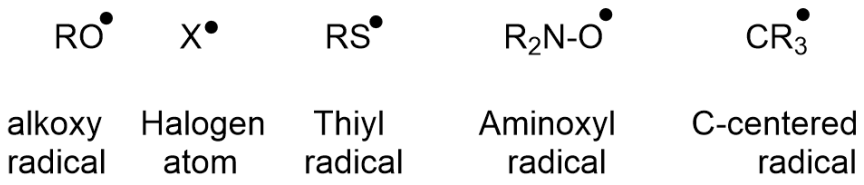


Thermodynamics-wise, the newly formed B−H bond has to be stronger than the C−H bond to cleave to provide the driving force for the overall process, despite BDE not being the only parameter to be considered.

If you remember when I was talking about this some sp^3 C-H bromination using the chlorine radical or bromine radical during the bromination or chlorination, then we already talked about that when the bond is forming, which bond is breaking and which bond is forming. What is their bond dissociation energy? That means, thermodynamics always prefers the newly formed B-H bond to be stronger than the C-H bond to cleave or to provide the driving force. As you know from the thermodynamics if this bond is the stronger bond compared to the starting one that will give you the driving force for the formation of the hydrogen atom transfer. But again that is not the only factor that is the bond dissociation energy, there are several different factors which I am going to explain. But before I go to them, I just want to give you a summary of what are the different hydrogen atom abstractors used for the hydrogen atom abstraction.

You have seen that the alkoxy radical can be formed from the pyrolysis and then you have seen about the halogen atom and the halogen radicals. When you talk about the corresponding bromination chlorination reaction. Then there is another important is a thiol radical. I am going to talk about thiol radicals and then there will be aminoxyl radicals and then the carbon center radical. So, there are more.

Hydrogen atom abstractor



I am just trying to give you some of the common ones then there are some hydrogen atom donors. I am sure you guys have seen the tributyl tin hydride, before when I was going to talk about; when I already talk about the Barton Decarboxylation reaction. Then

triethylsilane, these silanes are very useful. I think I am going to explain them again when I am going to talk about silicon chemistry and why this type of compound is a very useful compound for use as a hydrogen atom donor. Then there are some variations here. This is the $(TMS)_3SiH$. You can draw like that. There are 3 silicon groups with the 3 methyl, so that means, with a hydrogen here. And then, we are going to talk about the RSH.

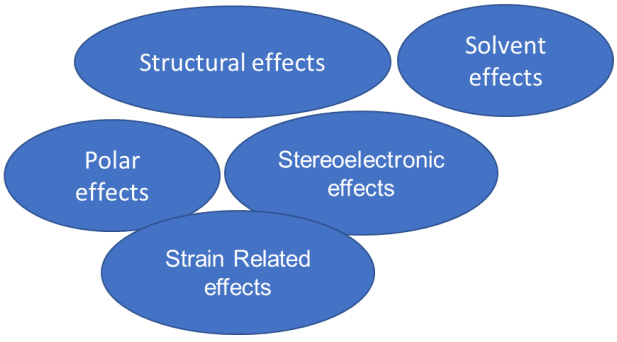
Hydrogen atom donor

nBu_3SnH Et_3SiH $(TMS)_3SiH$ RSH RH ROH

Again thiols, I am going to talk about that they are also very good hydrogen donor, then there will be some examples with alkane and alcohol. So, the important thing is when I talk about the hydrogen atom abstract and hydrogen atom donor, there is one of the things I have already mentioned in the previous classes that the radicals can be classified as an electrophilic radical or nucleophilic radical if you remember. And then, the question comes that if there is an electrophilic radical, then it will prefer to abstract hydrogen from a nucleophilic hydrogen atom donor. And, if you have an electrophilic radical then, it will prefer to abstract hydrogen from a nucleophilic hydrogen donor. So, let us try to understand what I was trying to talk about.

But in this part, I am going to cover this type of hydrogen atom transfer between this donor and acceptor as I was telling you. So, there are several different effects which is the most important factor why this hydrogen atom transfer is happening. So, there are structural effects, there are solvent effects, stereotronic effects, polar effects, and strain related effects. So, I try to give you some examples to understand how these effects are useful in the hydrogen atom transfer reaction. So, the first thing is as I was telling you there is an electrophilic hydrogen donor source and there is a radical that is nucleophilic or if you have an electrophilic radical then it will prefer a nucleophilic hydrogen source.

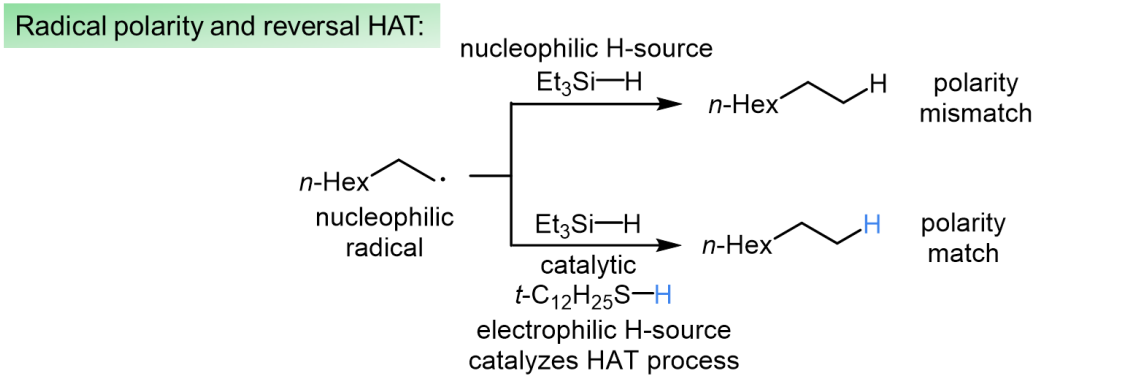
The efficiency of hydrogen atom abstraction is influenced by many different factors making its rationalization difficult.



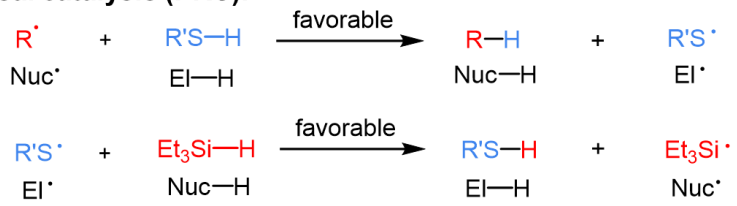
But, the problem is if there is a scenario, there is a nucleophilic radical here as I was telling you, you guys remember that if you have alkyl radical with 3 methyl or 2 methyl

or primary. So, these primary, secondary, tertiary radicals are nucleophilic. I have already explained them. So, now if you want to abstract hydrogen from a nucleophilic hydrogen source like triethylsilyl hydride or you can see from tributyltin hydride also then what is going to happen, there is a polarity mismatch. As I was telling you that, it will be preferable it will go from the nucleophilic can abstract from an electrophilic hydrogen source.

So, how to solve this problem? How to get this reaction going? The only way to get this done is if you can put some of the thiol here. So, what is the role of thiol? Now, thiol can able to go further reversal of polarity is the important thing. So, adding thiol can improve the yield of this reaction. So, now, we try to understand what is happening by this polarity reversal catalysis which is a very important terminology in hydrogen atom transfer chemistry. So, what is happening here? I am showing you there is a nucleophilic radical and the electrophilic hydrogen.



- Introducing a catalyst that replaces the polarity-mismatched step with two polarity-matched steps should result in a net favorable reaction. This phenomenon is known as **polarity reversal catalysis (PRC)**.



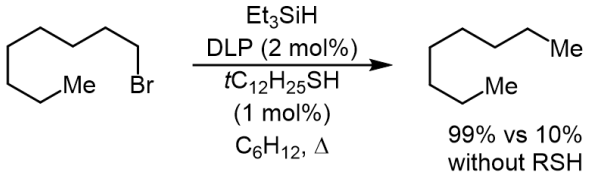
Now, once you use a thiol these are electrophilic hydrogen in a donor source. So, what is going to happen these types of reactions will be favorable because you are forming a stronger bond here, you are forming a R-H bond which is a stronger bond and you are generating an electrophilic radical. So, now, what is happening is that this reaction become favorable. So, there is a polarity match here in this one. Now, what is going to happen as you are generating an electrophilic radical that can able to take the hydrogen from this nucleophilic hydrogen donor? Then we will generate this corresponding S-H and this triethyl silicon. Again you can see there is a bond energy difference here the S-H bond will be stronger than the Si-H bond. So, that is another driving force here. So, the

polarity match is important. If there is a not polarity match, then this polarity reversal catalysis can be useful. So, here I think I am going to give you the example again for another reaction here.

So, what is happening here. This C-Br bond is getting cleaved to replace with a C-H bond. So, what is happening? triethyl silane is the hydrogen donor and DLP is the corresponding peroxide which is an initiator that cleaves this C-Br bond. So, this peroxide oxo-radical going to cleave this to generate a radical here. Now, this radical species going to get a hydrogen source. Not directly from the silane because you are using 1 mol% thiol as a polarity reversal catalysis.
So, previously if you do not use thiol means: I can say without RSH your yield is 10% and once you add this 1 mol% of corresponding thiol your yield is 99%. So, you can see the what is the difference. Again I think there are some reports also that people have replaced this corresponding tin hydride as I was mentioning that tin hydrides are toxic. So, that can be replaced by corresponding silicon hydride as well. This type of silicon hydride species is called silane.

Radical polarity and reversal HAT:

- Thus, incorporating a catalytic amount of thiol into Et_3SiH reductions of alkyl halides significantly enhances the yield.



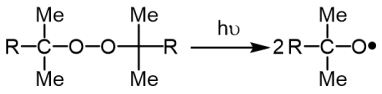
- The utilization of R_3SiH in Barton-McCombie reactions demonstrates remarkable efficiency.

So, they are very good hydrogen donor sources. So, now, I am going to talk about some of the effects. I mentioned there are some polar effects under the structural effect. You have seen there are some polar effects stereoelectronic effects. So, the first thing is this type of radical which is called the you can see here. Under hν this O-O bond is the weaker one getting cleaved. So, under the laser photolysis, it is generating this corresponding radical here and as this type of oxo radicals can be, if you change this in R by methyl then it will be this tertbutyl oxo radical here, tertbutoxide radical, or if you have a phenyl here this called the cumyloxyl radical.

Now, the important thing about this cumyloxyl radical here is that radical can be characteristic by an absorption band in the visible region of the spectrum which makes it perfectly convenient to study some kinetics. So, that is why, this radical, I am going to

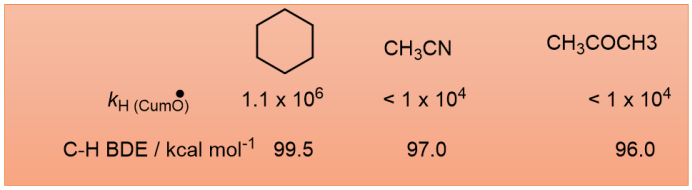
show you in a couple of slides where this cumyloxyl radical was used for the measurement of the reaction rate for different types of hydrogen atom transfer reactions. So, now you can see that I am going to show you some examples here you can see we have a cyclohexane here, we have a CH_3CN and then CH_3COCH_3 or acetone. So, acetonitrile then acetone, and then you have cyclohexane.

So, now once you are trying to understand their bond dissociation energy these bonds are stronger. So, this will be stronger than this one and this will be stronger than this one. But what is happening in the hydrogen transfer rate? You can see the hydrogen transfer rate is



R = Me, tBuO•
R = Ph, CumO• cumyloxyl

CumO• is characterized by an absorption band in the visible region of the spectrum that makes particularly convenient the direct measurement of HAT rate constants by nanosecond laser flash photolysis



Despite the weaker C−H bonds, the C−H bonds of cyclohexane are at least 30 times more reactive

higher here compared to this one and compared to this one. So, these two look very similar, but this one is higher than this. So, what is happening here? You see we are cleaving a stronger bond compared to weaker bonds.

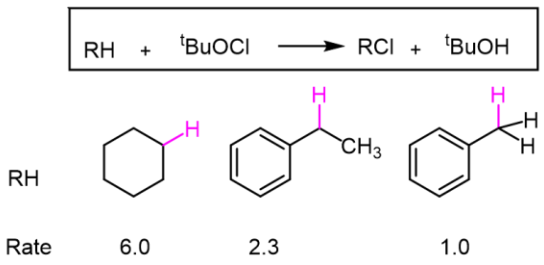
So, although it looks like that, now if you try to think about that your radical, what is your radical here? So, as I mentioned this is a radical which is an electrophilic radical. So, if you have an electrophilic radical then it will be preferred for hydrogen abstraction from a nucleophilic hydrogen source. Now, if you compare between this cyclohexane to this CH_3CN and acetone you have an electron-withdrawing group attached to this CH_3. Because this abstraction going to happen from this CH_3 only you have a CH_3 with an electron-withdrawing group. Now, this hydrogen atom abstraction going to happen from the CH_3 as you have an electron withdrawing group now this hydrogen will be not that nucleophilic hydrogen donor compared to the C-H bond in this cyclohexane. So, that is why this is going to get cleaved first compared to the CH_3CN versus the acetone.

Again there is the same example here if you use this tertbutoxide radical and if you have a primary versus secondary and tertiary alkane. What is happening you can see the alkane the rate is. So, if you have a primary, then secondary, then tertiary and you are abstracting this C-H then the rate is 1, 12.2 around 12, and then around 44 respectively. So, what is

happening here? Again you can see from primary to secondary to tertiary what is happening here. Again you can see that the C-H will be more hydrogen. So, that will be kind of you have a more electron-rich that means, that will be a better nucleophilic hydrogen donor. So, that is why the tertiary C-H is going to get cleaved or going to participate in the hydrogen atom transfer faster. Because the tertbutoxide is already an electrophilic radical and again very similar type of example here what is happening.

You can see here again you have this cyclohexyl here, then you have a benzylic and you have a toluene C-H. Again you can see the rate is higher in here compared to these two. Again if you have a more stabilized radical. So, you have to also understand the bond dissociation energy and at the same time what type of radical is forming at the end. So, here again, what is going to happen as I mentioned the K_H with increasing the bond strength was observed for substrate with C-H bond dissociation energies greater than 92.

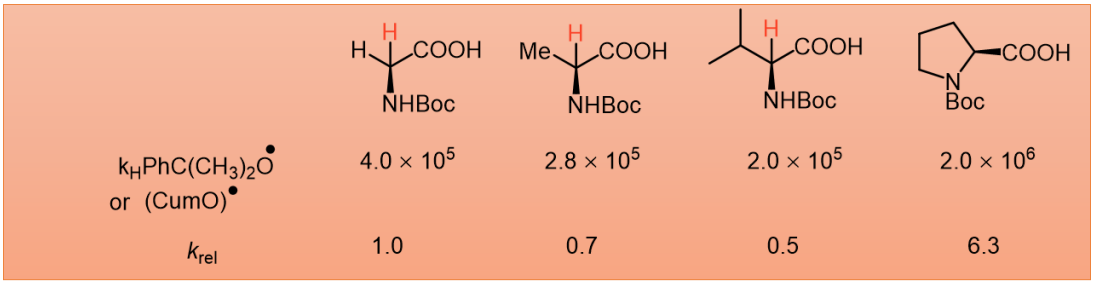
HAT from the aliphatic C–H bonds of hydrocarbons to ^{t}BuO•: 1.0, 12.2, and 44, respectively, for primary, secondary, and tertiary sites

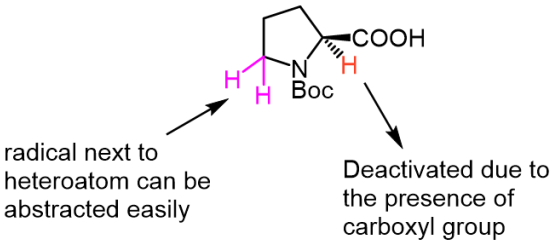


A decrease in k_H with increasing bond strength was observed for substrates characterized by C–H bond dissociation energies (BDEs) >92 kcal/mol

That means once you see here again the factor that I mentioned that the hydrogen is going to get cleaved if that is more nucleophilic then that will be cleaved faster. Then, there is another effect polar effect controlling hydrogen atom transfer. So, here you can see what we are talking about abstracting this. So, abstracting of this hydrogen here. So, in these three cases if you see these three amino acids going from glycine to valine what is happening this hydrogen atom transfer rate looks almost similar. But, once you come to proline you see the rate is higher you can see almost that if you compare them then this rate is much higher compared to this one or compared to others. So, what is happening in the case of proline? So, the thing is you might be looking into this if you try to think about that in the case of proline you have to understand that there are some other hydrogen atoms here that can also take part that means, they are saying that these hydrogen here are actually getting abstracted compared to this hydrogen here, which is actually deactivated due to the presence of carbonyl group. Now what is going

to happen because these hydrogens are attached to the nitrogen and here what is going to happen. So, these are the C-H bond which is actually next to a heteroatom. So, that means, if you have a scenario here that you have a X and you have this hydrogen if this hydrogen getting abstracted then you have to understand there is a lone pair of this X that can give an electron to the corresponding σ* of the C-H.





So, make it more activated for the hydrogen atom transfer. another example of tributyltin hydride. So, we have learned that tributyltin hydride is also used very much for the hydrogen atom donor. Now, you can see the difference for the reaction where you are actually converting from this corresponding R• + Bu_3SnH. So, this is the reaction we are talking about and you are forming this RH and Bu_3Sn•.

Tributyltin hydride also acts as a hydrogen-atom donor in free radical reactions:

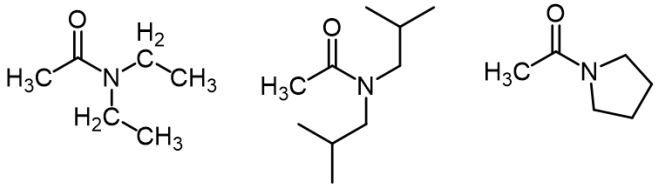
	Rate constant for reduction of $R^\bullet$ with nBu_3SnH			
$R^\bullet$	$Ph^\bullet$	$(CH_3)_2C{=}C^\bullet$	$(CH_3)_2CH_2^\bullet$	
k	5.9×10^8	3.5×10^8	2.1×10^6	8.5×10^7

The rate constant for these reactions depends on the nature of the carbon-centered radical; reactive aryl and vinyl radicals abstract hydrogen around 10^4 times more rapidly than the stabilized benzyl radical.

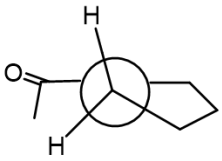
So, in this reaction we trying to compare the rate here now you can see here if you have a phenyl or if you have vinyl radical then the rate is 5.9 $x10^8$, but once you come to some sort of alkyl radical here it is much lower. So, what is happening here is that once you

have an aryl or vinyl radical, they are very reactive. So, once you are generating a highly reactive radical. Then these radicals can react much faster because they are reactive radicals if you talk about tributyltin hydride this is a nucleophilic hydrogen donor source.

So, now, these radicals are very reactive this is going to abstract hydrogen from the tributyltin hydride which is why this rate is much higher compared to this. There is an important stereo electronic effect as I was mentioning that in this particular scenario, you can see here what is happening. Here you have this amide in this amide nitrogen you have this ethyl group here, here you have a isobutyl group and here you have a pyrrolidine. So, what is happening here? Once you are talking about the hydrogen abstraction rate using this radical, this oxo radical then here the rate is much faster. So, this hydrogen abstraction is much faster compared to others.



$k_H PhC(CH_3)_2O^\bullet$ 6.6×10^5 3.1×10^5 9.0×10^6



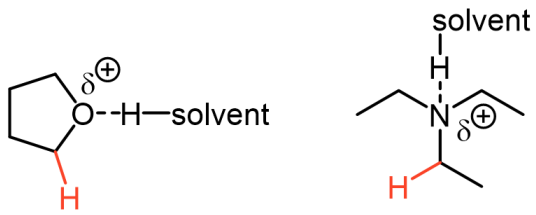
In N-acetyl pyrrolidine, the α-C−H bonds are held in a conformation where they are optimally aligned with the amide π-system providing a kinetic advantage for HAT compared with N, N-diisobutylacetamide,

So, what actually they are trying to explain this result they are saying that for the hydrogen atom abstraction once you talk about this compound and once you try to draw the confirmation here. We are talking about the abstraction of this corresponding hydrogen here and are saying that in this α C-H bond are held in a confirmation where they are optimally aligned to the π-system. So, they are saying this bond is optimally aligned to this π-system here. So, that means, there is some sort of a secondary interaction that there is this π electron is going transfer into the sorry there is this σ electron getting transferred to the some sort of a π* electron. So, this CH is getting weaker which is why this hydrogen abstraction is faster.

Again there are solvent effect. So, the idea is if you are using a polar solvent versus a polar protic solvent versus a polar aprotic solvent what is happening here? because once

that if I am going to compare that THF versus this one let us try to compare them. So, if I try to draw it tetrahydrofuran here. So, now, we are talking about the hydrogen abstraction of this same thing here this hydrogen we are trying to abstract. Now, if you have a scenario where you do not have a hydrogen bonding and here you have a hydrogen bonding.

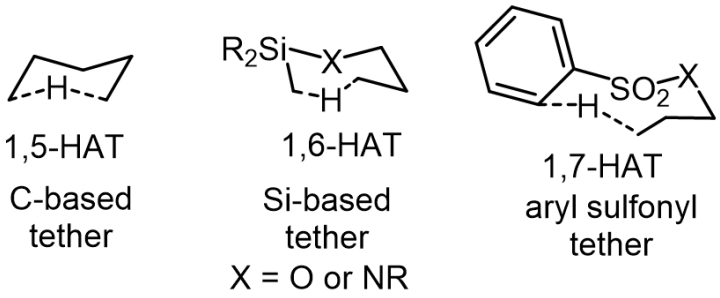
Solvent hydrogen bonding will also decrease the degree of hyperconjugative overlap between the α-C−H σ* orbital and the heteroatom lone-pair, leading to an increase in the strength of this bond, to a destabilization of the carbon radical formed following HAT, and to a corresponding decrease in k_H.



what difference is going to make, once you have hydrogen bonding here this is going to form hydrogen bonding is this hydrogen atom acceptor oxygen. So, once you form this hydrogen bonding here in this case or if you have a triethylamine in a very similar situation. once you have a hydrogen bonding then there is a generation of some sort of a δ+ charge. Now, this thing what I have mentioned here is that there is an electron donation from this n→σ* correct this nonbonding to the σ* orbital. So, that will be a hamper here once you have a corresponding hydrogen bonding. That means, once you have a hydrogen bonding going to be hampered. So, here because of this n→σ* electron donation this bond will be somewhat activated for hydrogen atom transfer, but here it is the possibility will be decreased which is why it will be less activated compared to this. So, the hydrogen atom transfer rate will be faster in THF compared to THF with a polar protic solvent or with the same thing for the triethylamine. So, I talk about some of the important fundamentals of hydrogen atom transfer. One of the important facts is there will be a lot of time I am going to talk about some intramolecular hydrogen atom transfer and this is mostly controlled by 1,5-hydrogen atom transfer.

You will see that this 1,5-hydrogen atom transfer going to control the measured intramolecular hydrogen atom transfer and you will see only a few cases where there is a 1,6 where they use this silicon or there will be this 1,7 where they use this aryl sulfonyl tether. You know the question comes that once you have this 1,5-hydrogen atom transfer the question always arises why not 1,-4 why not 1,-6? Of course, the answer to this question was given mostly by the theoretical calculation where they found out this 1,5-hydrogen transfer is favored because of the formation of this 6-member chair-like transient state. But once you come to this 1,4-hydrogen transfer there is a major thing the enthalpy barrier. So, the enthalpy barrier is 6.6 kcal/mol which actually prevents this 1,4-

hydrogen transfer. And once you come to 1,6-hydrogen transfer you can see now in the case of 1,6 the entropy plays a role, the entropy of the reaction can depend on a lot of other factors. So, this entropy factor is actually stopping this 1,6-hydrogen transfer from happening.



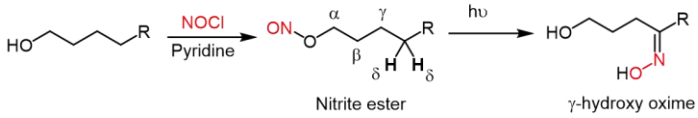
So, now I am going to talk about the important reaction called the Barton nitrite ester reaction. So, what is happening here? You know in this reaction if you see starting from this corresponding alcohol in the presence of the NOCl and pyridine it is forming this nitrite ester and then it is forming the corresponding hydroxy oxime here in this particular position. So, what is happening, in this reaction there is a hydrogen abstraction happening from this particular position. So, you can see where this is α, β, γ and δ. So, this hydrogen is getting abstracted to form this corresponding hydroxy oxime. And again I think Barton received the Nobel Prize in 1969, he has several contributions in the radical chemistry.

Derek Barton

Nobel Prize in Chemistry in **1969**

For the utility of Barton reaction

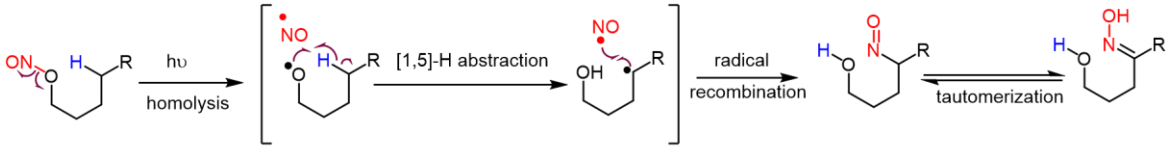
Photochemical reaction that involves the photolysis of an nitrite esters to form a γ-hydroxyl oxime.



- Nobel laureate Sir Derek Barton discovered the reaction in 1960
- Landmark in the development of remote functionalization
- Nitrites having at least 2 δ-H's are involved in this reaction
- Migration of NO group from O-center to C-center occurs

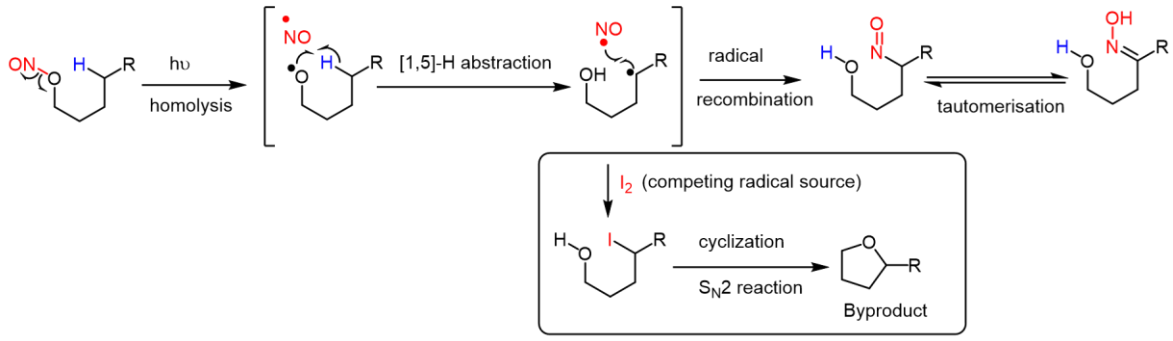
So, let us try to understand what is happening here. Once you form this compound here this nitrite what is happening here under the hν means once you put the UV light here that is going to cleave this nitrogen oxygen bond here to generate this oxygen radical here which is going for this 1,5-hydrogen abstraction. As I mentioned in the previous slide that there is a 1,5-hydrogen abstraction is an important factor for the intermolecular reaction. So, that is going to generate this radical species here. which can go for a radical recombination. Then after the tautomerization, it can form this corresponding oxime. So, it is the first photochemically induced cleavage of the nitrite O-N bond typically using a high-pressure mercury lamp. The formation of the alkoxy radical as I mentioned here in this step and then the recombination of this nitrosyl radical. So, that is very important that which is getting broken here gets again recombined. and then finally, the radical recombination and then the tautomerization given to the product.

Mechanism



- Photochemically induced cleavage of the nitrite O-N bond, typically using a high pressure mercury lamp.
- Formation of an alkoxyl radical which immediately abstracts a hydrogen atom from the δ-carbon.
- Recombination of nitrosyl radical with alkyl radical.
- Tautomerization of nitroso compounds to the oxime product

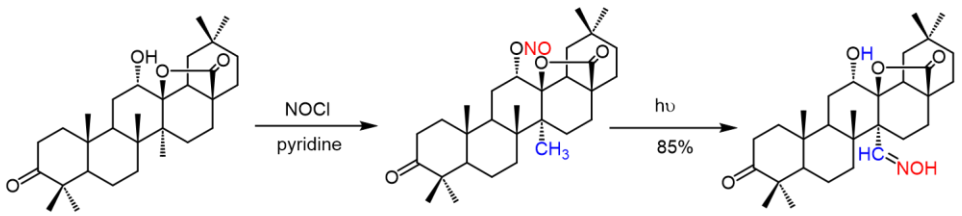
You can show here starting from this in this condition first generating the radical 1,5-hydrogen abstraction and then now if you use a I_2 as a competing radical source then in this step what is going to happen it can form this corresponding iodo compound here which can participate in the S_N2 reaction. So, this oxygen now can attack here S_N2 reaction get rid of iodine to get to this corresponding byproduct. If you want that you can use the iodine to get to that compound.



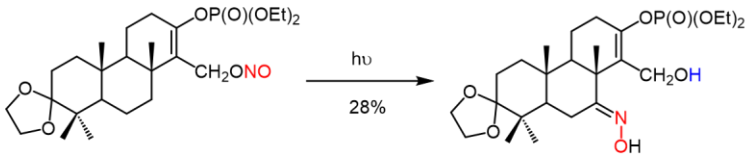
The carbon centered radical can be intercepted by other radical sources such as iodine , which results in the δ-hydrogen being replaced with iodine, then subsequent cyclization to a tetrahydrofuran by an S_N2 reaction.

So, now, we try to understand here you have a OH group here. So, the first thing is a NOCl pyridine formation of this compound. Now, you can see, this is going to abstract this. So, you can see this OH going to abstract from the corresponding methyl which will be on the same side. If we try to draw the particular conformation in this compound you will see that this is the OH and the methyl will be on the same side. So, this can abstract this hydrogen from this type of cisoid conformation and then it can get to the corresponding product here. Here again, you can see in this example also we are seeing very similar things here. First formation of this nitroso which can able to you know take the proton from this particular position. So, sorry, not a proton there is a hydrogen abstraction happening from this position. So, this is a again this is a 1,5 position here 1 2 3 4 5. Sorry 1 2 3 4 5 to formation of this product here.

Example 1.

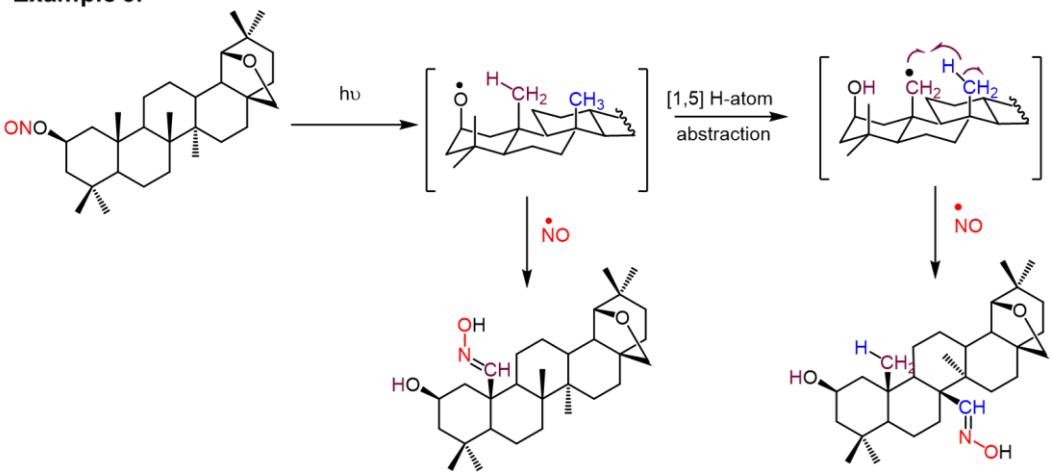


Example 2.



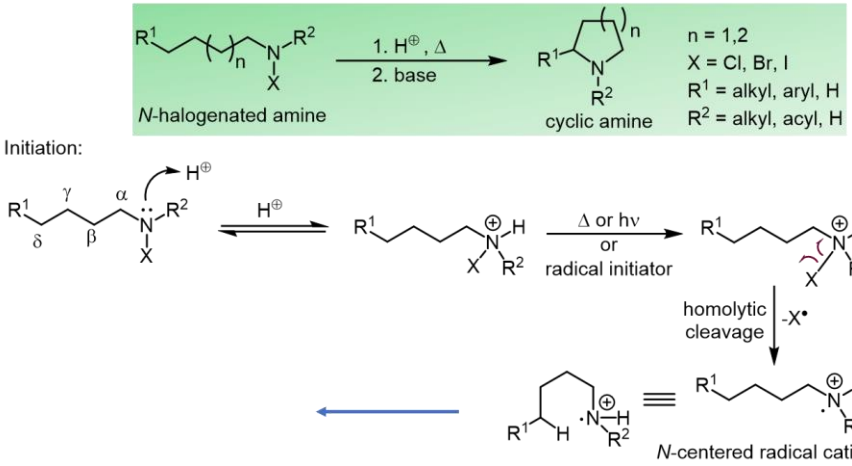
There is another example very similar example in the previous slide you have seen first there is a cleavage formation of this oxo radical which is on the same side of this CH_3 going for a hydrogen atom abstraction going to make this CH_2• it is going for another sequential hydrogen atom abstraction to form this product or it can go for this first in hydrogen atom abstraction and go to this product.

Example 3.

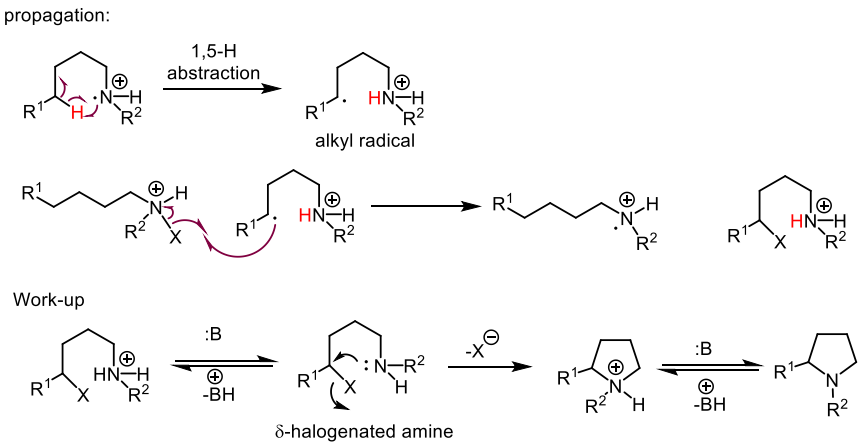


Then I am going to talk about another important reaction which is the Hofmann-Loffler-Freytag reaction. This is another important reaction. You start from this N-halogenated amines and you are going to convert to the cyclic amine here. So, in this reaction what you need in this reaction need a halogenated amine in a strong acid that is the, and then you need to irradiate using a ultraviolet light.

- The Hofmann–Löffler–Freytag (HLF) reaction serves as a late-stage functionalization technique for generating pyrrolidine heterocyclic ring systems.
- The reaction is effected by warming a solution of the halogenated amines in strong acid(e.g. H_2SO_4 or CF_3CO_2H), or by irradiation of the acid solution with ultra-violet light.



So, what is happening in this reaction first thing is the protonation as you have a strong acid it is going to protonate this corresponding N halogenated compound. Then under this UV light, the nitrogen and the halogen bond going to get cleaved to generate the X• and then generate this corresponding N•. So, it is as I said this is a a charged species as well as a radical species on the nitrogen which we can see in the in the next slide. From there it is going to go for a 1,5-hydrogen abstraction and then it is going to form this alkyl radical and then this alkyl radical can take this X from here to form this species. And, which can finally, going to there will be proton abstraction from this nitrogen using a base to generate this nitrogen which has a lone pair that can attack here *via* S_N2. So, now, what is going to happen, you can end up forming a pyrrolidine. So, starting from a linear compound you end up making a cyclic product.

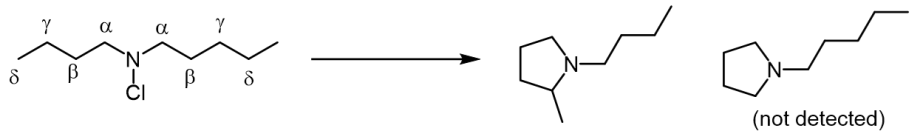


There is a radical attack that exhibits a strong preference for the secondary over the primary. That means, what is happening if there are two different positions where the

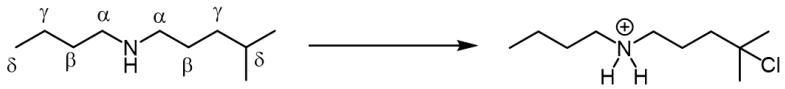
radical can be formed then it will prefer going for the secondary over the primary as the stability of the radical is an important factor.

Selectivity of hydrogen transfer:

- The radical attack exhibits strong preference for the 2° over 1° hydrogen.



- This result suggests a high selectivity for the 3° hydrogen, while the intermediate tertiary chloro compound undergoes rapid solvolysis.

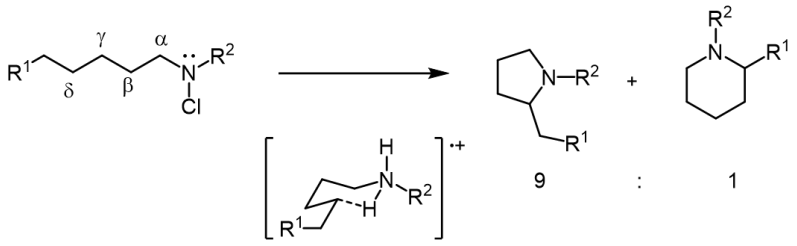


- Similarly, no cyclic amine was observed with the reaction of *n*-amylisohexylamine, which demonstrates the selectivity for the 3° vs. 2° hydrogen migration.

So, here this results as the high selectivity for the 3° hydrogen over the others. Here what is happening the preferential abstraction γ hydrogen atom corresponds to a 6-member transition state. So, that is also a very important factor here it is going for the hydrogen atom abstraction it is going for forming of this 6-member transition state and that is how this product is becoming the major product compared to this one. So, we are talking about that why not in the next one why not it is forming going for abstraction from this one. Because here the 6-member transition state is the favour one.

Selectivity of hydrogen transfer:

- The preferential abstraction of the δ–hydrogen atom corresponds to a six-membered transition state, which can adopt the unstrained cyclohexane chair-type conformation.

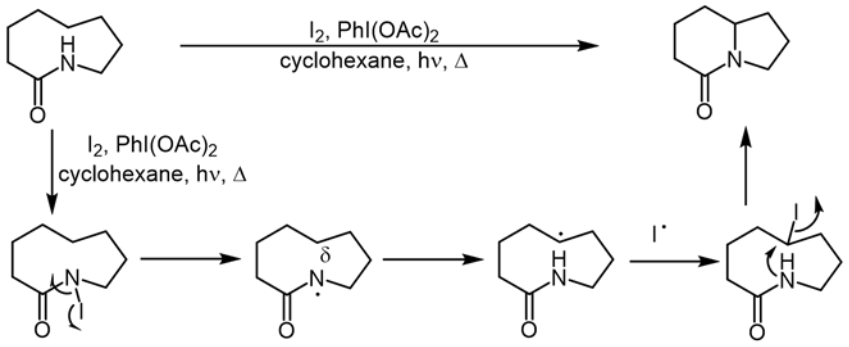


There is an example here again. It is a modification using PIDA and iodine here. The first thing is the formation of this N-I which is going to get oxidized to form this N•, from there it can go for this 1,5-hydrogen atom abstraction. So, 1,5-hydrogen abstraction to

make this dot which can combine with the I• to make iodine then internal that attack for to get rid of the iodine and get to this product.

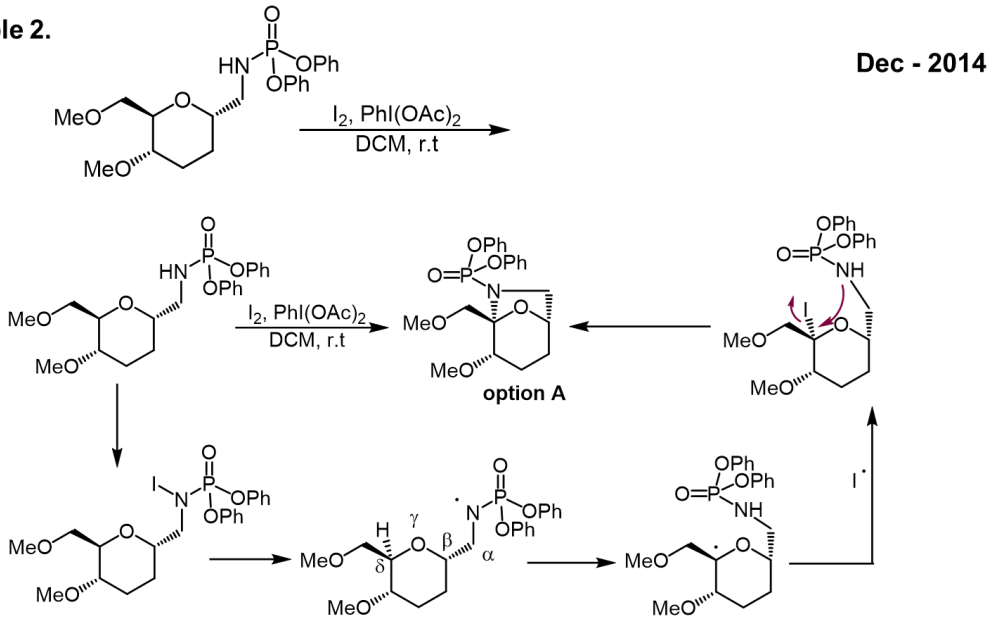
- To avoids the harshly acidic conditions it has been developed.

Example 1.



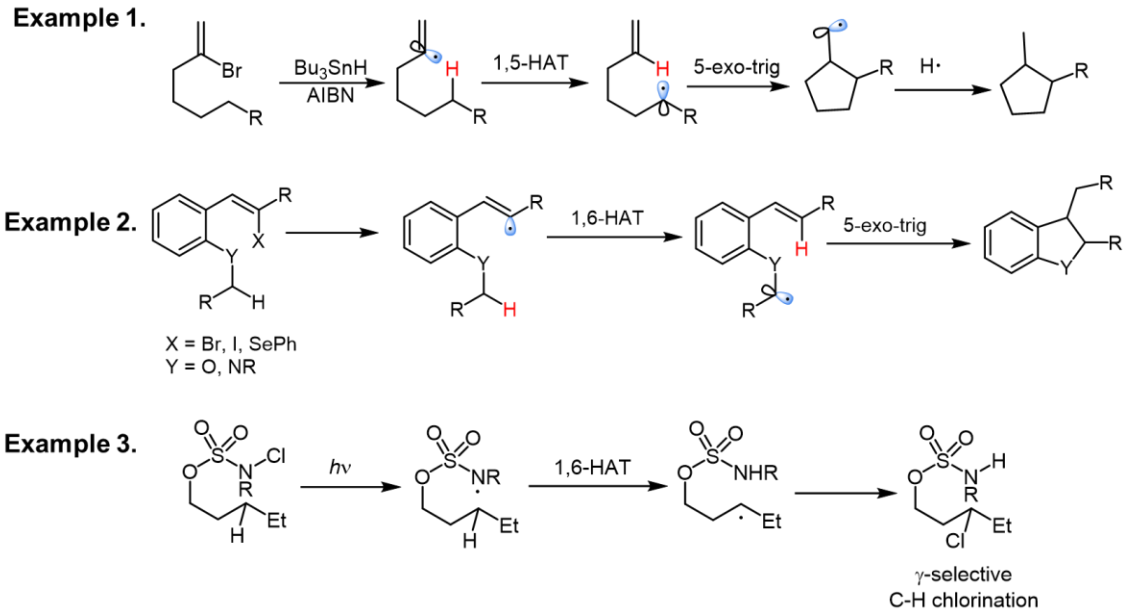
Another example here with PIDA and iodine. You can see in this molecule, you have this compound here which can be you have amine there. So, PIDA and iodine will form this N-I then go for making the dot and then it goes for the hydrogen abstraction, and finally, I• and then cyclization which can go to this product.

Example 2. **Dec - 2014**



So, this came in the exam. So, as I mentioned I have also tried to give you some examples from the exam. Another example here, we can see from this compound if you use tributyltin hydride and AIBN. If you remember, AIBN going to make this radical going for hydrogen atom abstraction making the corresponding tin radical which is going to cleave this C-Br bond. So, there will be debromination to generate this radical 1,5-

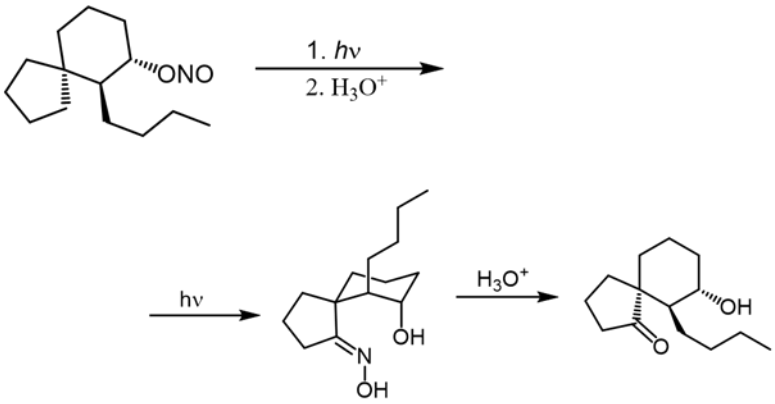
hydrogen abstraction generate this radical then there is an exo-trig cyclization which I am going to explain in the next class about the intramolecular radical cyclization to form this product after the hydrogen abstraction. Here is another example you are forming a vinyl radical under the radical initiator source then what is happening there is. So, if you are why is oxygen then there is no way there is a 1,5-hydrogen. So, that is why it will go for a 1,6-hydrogen shift and then there will be intramolecular radical cyclization which I am going to explain going to form this compound. Again there is another example here you have a N-R which can generate a radical then it will be. So, there will be 1,6-hydrogen atom abstraction as there is the 1,6 is more favorable here to form this corresponding product.



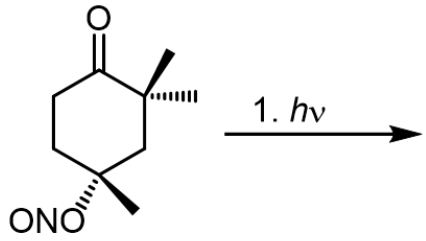
So, again this came in the exam that if you start with this compound what will be your product. again if you try to draw this one that is there is a 6-member here and a 5-member. Now, you can clearly see that this will be the position where the hydrogen atom abstraction going to happen to form this compound which are in the H_3O+ going to form the corresponding ketone.

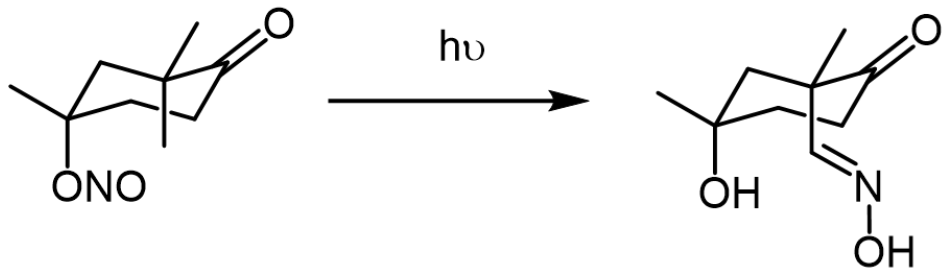
The major product for the following reactions is

Dec - 2016

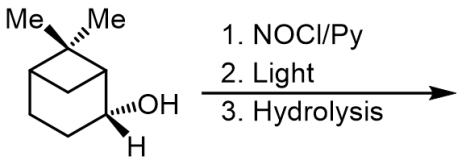


Another example here also you can see that if you have if you try to draw them in this particular conformation you can clearly see that this is going to abstract form this methyl hydrogen going to be hydrogen abstraction going to happen to get to this product under if you put H_3O+ it will go into the corresponding aldehyde.

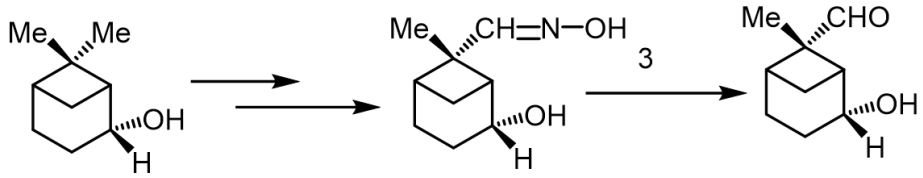




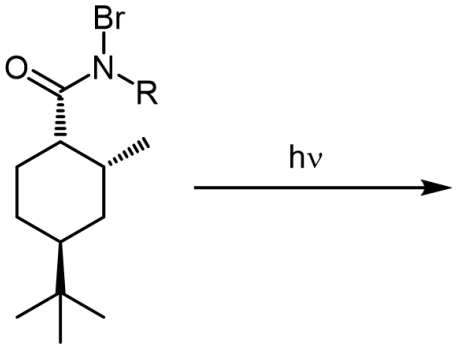
Another example came in the gate here what you are going to see here you have this you know OH group and then you have this methyl. So, OH is going to form the corresponding NO going for hydrogen abstraction from the methyl 1,5-hydrogen abstraction, and then if you put the hydrolysis condition it will go to the corresponding aldehyde.

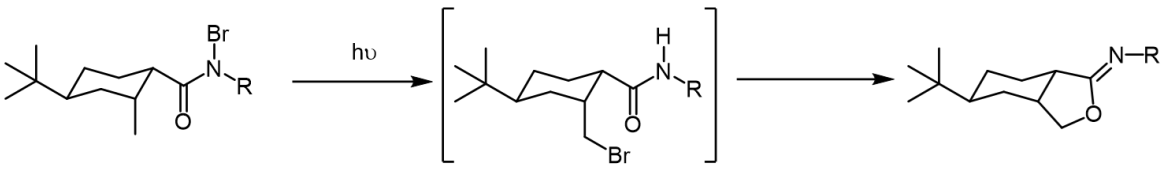


GATE -2010



Another example here, in this compound again you have this N-bromo which is going to go for hydrogen atom abstraction. So, there will be again 1, 2, 3, 4, 5. 1 for hydrogen abstraction get this corresponding bromide, and then what is going to happen it can go for intramolecular cyclization to form this product.





So, I hope in this class I talk about some of the basics of hydrogen atom transfer, I talk about 1,5-hydrogen atom transfer, and under that category, I talk about the Barton nitrite ester in reaction and the Hofmann-Loffler-Freytag reaction and some of the modification.

- The rate of 1,5-HAT is at least 10 times faster vs the 1,4 or 1,6 variants.
- Barton nitrite ester reaction.
- Hofmann–Löffler–Freytag (HLF) reaction
- Modification of the HLF Reaction

Here are some of the textbooks you can follow. Thank you for coming to the class and I am going to see you guys in the next class.