Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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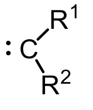
Lecture 15: Nitrene

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediate. In the previous 2-3 classes I was talking about carbene. In the today's class my focus to talk about nitrene which is a nitrogen analog of carbene. So, I am going to talk about several things about nitrene. I am going to talk about the singlet and triplet nitrene and then their structure and hybridization. I am going to talk about what are the different methods for the generation of nitrene. Then several different reactions of nitrene and at the end, I am going to talk about some examples.

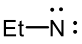


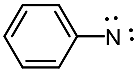
Carbene

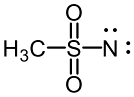
Nitrene

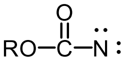
So, the first thing is that nitrene is a nitrogen analog of carbene that means, all the characteristic what you have learned in the carbene will be remain in the nitrogen. That means, the only difference here the carbon was replaced by nitrogen. So, the carbon in the case of carbene was divalent, but here it is the monovalent or univalent means, only one R group is attached to this nitrogen. Whereas in case of carbene there are R^1 and R^2. So, it was divalent. Again if you compare they have 6 valence electrons in the valence cell which means, if you talk about the bonding-wise in the case of carbene there are 2 electrons here. So, that could be pair or unpair based on the singlet and triplet, and then in the each bonding there are 2 electrons. So, total 6 here also there will be total 6. So, there will be 2 electrons on this bonding of R and N. Then there will be 2 electrons as a lone pair and then there will be 2 electrons as I said again there will be either the pair or unpair. So, the other important thing is that these are uncharged species. As I mentioned at the beginning, the carbenes are uncharged, very similarly the nitrenes are uncharged species and the nitrenes are electrophilic in nature. That means, as you see in the case of carbene or in the case of nitrene you can see there will be empty p orbital.

Once you have a empty p orbital there will be chance that if you have a lone pair or a nucleophile going to attack here. So, that means, these species will be electrophilic in nature. And then the other thing is the nitrene is unstable intermediate having very short lifetime. I think I already mentioned this carbene, nitrene species will have a very short lifetime, it is going to react very fast and form a stable compound. So, now I am going to talk about some of the nomenclature. I think I talked about the nomenclature in the case of carbene if you remember. There are if you have a like the CH_2 vs if you have an alkyl carbene. I was talking about the butyl carbene or the pentyl carbene or the phenyl carbene, but once you have a double bond I was talking about the vinylidene or if you have a cyclohexyl group I was talking about cyclohexylidene. But here in the case of nitrene, the nomenclature will be very simple I think if you have an ethyl group is ethylnitrene. If you have a phenyl, is phenyl nitrene. Very similarly if you have a carbo alkoxy group is carbo alkoxy nitrene and then if you have a methane sulfonyl it is called methane sulfonyl nitrene. Of course, there are more example here. I think I am just going to talk about some of these things in this course.

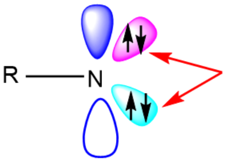

Ethylnitrene


Phenylnitrene


Methanesulphonylnitrene


Carboalkoxynitrene

So, again I can start with the singlet nitrine and the singlet nitrine structure if you look into here. The central nitrogen will be sp2 hybridized, it will have a linear structure. And then there will be an empty p orbital so that it can receive electrons from a nucleophile or from a something like atom which have a lone pair. And now this is one sp2 hybrid orbital and this is another sp2 hybrid orbital. In both sp2 hybrid orbital, in one case you have the lone pair and in the other case you have this non-bonding electron. So, there is a non-bonding electron here and there is a lone pair here in the sp2 hybrid orbital. These non-bonding electrons are paired as I talk about. So, this is a singlet as these electrons are paired you can see. Once you try to calculate the spin multiplicity, the spin will be 0 ans spin multiplicity is 1. that is why it is a singlet nitrene. So, now the singlet nitrene can participate in various reactions very similar to carbene. It can participate in Addition, CH insertion, and several other reactions. But the important thing is these reactions are going to be stereospecific. You know very similar to carbene what we have learned is that the singlet carbene with olefin reactions are stereospecific, we are going to learn a very similar thing in the case of nitrene as well.

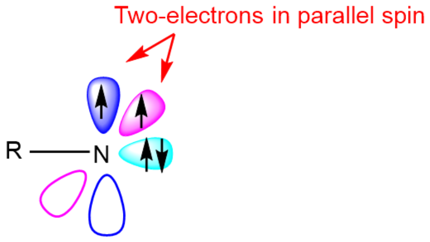


all the non-bonding electrons are paired.

sp^2-hybridized
Singlet nitrene

$$\begin{aligned}\text{Spin multiplicity} &= 2s+1\\ &= (2\times0)+1\\ &= 1\end{aligned}$$

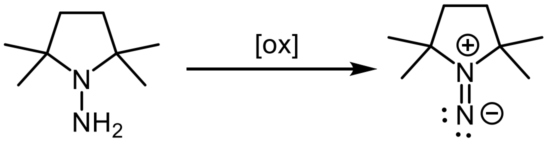
Now, I am going to talk about the triplet nitrene. So, the triplet nitrene here you can see, the nitrene is sp hybridized. Again it is a linear shape. So, now there are two unpaired electrons in the two degenerate non-bonding p orbital. Those two p orbital will have a one one electron, but they are not spin pair up. So, now, this can be you know ESR active because they have a parallel spin. So, once there is parallel spin they will be ESR active and if you can see about the spin multiplicity. Now your S value will be 1, so (2s+1) will be 3. So, this is a triplet. So, now, the one important difference you can see. So, the stability of nitrene I think if you talk about singlet vs triplet. In the case of carbene I already explained that the triplet carbene will be ~9 kcal more stable than a singlet. But here you can see a very similar thing the triplet nitrene is more stable than the singlet nitrene by almost over 30 kcal. Again, in the case of singlet nitrene both the non-bonding electrons are present in the same orbital. So, once there are the non-bonding electrons will be present in the same orbital, then there will be an electrostatic repulsion. Very similarly because of these two electrons in the same orbital. So, because of that the corresponding singlet will be higher in energy. Which I think explain a very similar thing in the case of carbene as well.



sp-hybridized
Triplet nitrene

$$\text{Spin multiplicity} = 2S+1$$
$$= (2\times1)+1$$
$$= 3$$

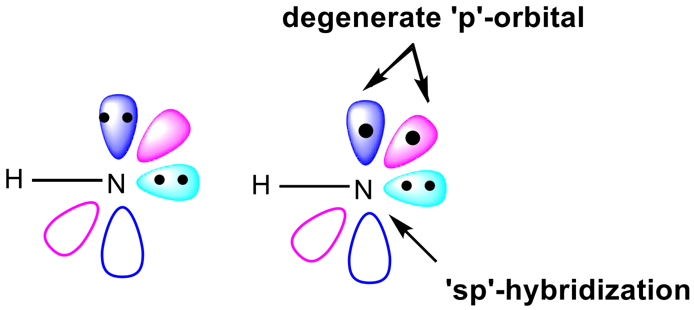
So, now the question comes if you have the nitrene attached with the electron donating group. So, once you have a nitrene that is attached with the electron donating group that is going to stabilize the corresponding nitrene. So, once you have electron donating group like here in this particular one. You are generating the corresponding nitrene from here after oxidation. So, this nitrene is getting stabilized because you have this nitrogen which is giving electron density you know to the corresponding nitrene to make it you know more stable.



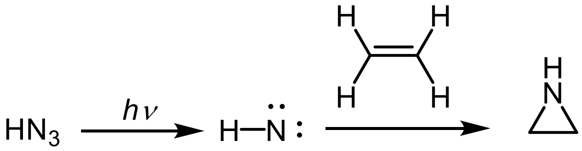
1-amino, 2,2,5,5-
tetramethyl pyrolidine

singlet state

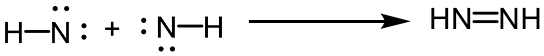
So, now I am going to talk about the very simplest nitrene called imidogen, it is the NH. So, you can see this if once you go to these nitrene structures you have this degenerate p orbital. So, there will be 2, one one electron in the degenerate p orbital having the sp hybridization. So, this will be a triplet nitrene. So, this is the simplest nitrene structure.



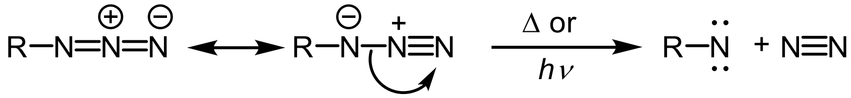
And now you can see this nitrene can be generated from hydrazoic acid once it is irradiated with UV light. So, once it is irradiated with the UV light from hydrazoic acid it generates this imidazine which participates in the addition reaction with the ethylene to form this aziridine. So, once you do not have ethylene here, it can participate in a dimerization which means, as I told you they are very reactive. So, they can form a dimer. So, now, I am going to talk about several different methods.

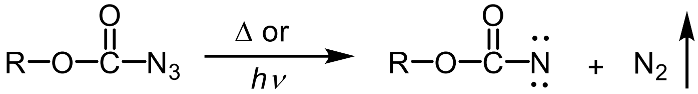


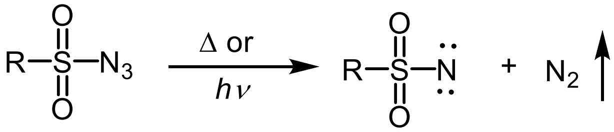
In the absence of a reagent, dimerisation takes place.



How you can generate this type of nitrene species? Mostly this type of species can be generated by photolysis or irradiating with UV light or thermolysis. So, thermolysis of azide. So, the azide could be a starting material to generate the corresponding nitrene via the photolysis or thermolysis. So, now, starting from this alkyl azide once it is goes for a thermolysis or photolysis, it is going to generate the corresponding nitrene here after the release of the N_2. From this compound also, once it is going for photolysis or hν, it is going to generate some sort of a nitrene which has the α-carbonyl group here.



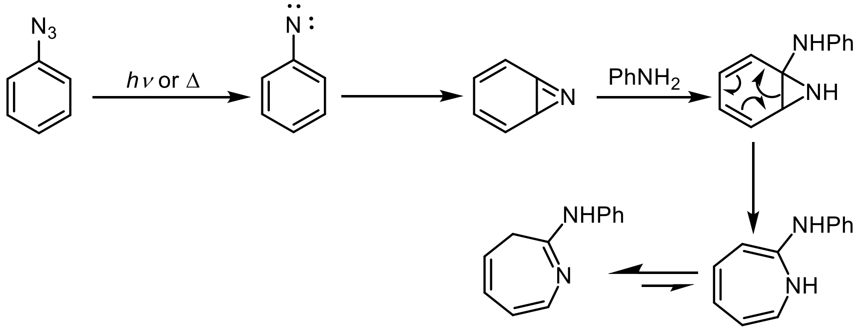




Then there are the tosyl azide which can also form the corresponding nitrene. Once it will be heated or under the photolysis it is going to form the corresponding nitrene. So, again I have shown you the example of some of the different nitrenes here. But the nitrene from the alkynyl group the alkynyl nitrene was still not prepared, but the corresponding cyano-nitrene is well understood. So, starting from this NCN_3, after the release of N_2, it can form this corresponding nitrene which can take part in several different reactions.

$$NC{-}N_3 \longrightarrow NC{-}\ddot{N}: + N_2$$

Then I am going to talk about photolysis of thermolysis of aryl azide. So, previously I talked about the alkyl you have seen, then I talked about tosyl, and then I talked about the generation of α-keto-nitrene. Here I am going to talk about the generation of the phenyl nitrene species. Again once you treat with the corresponding phenyl azide either under the hν or heat what is going to happen? It is going to form this nitrene, but it is not going to stop here. So, this nitrogen will participate in an addition in reaction to form this intermediate.

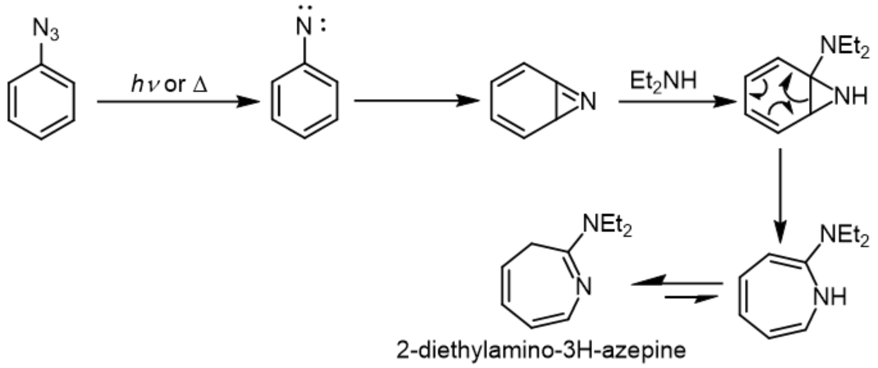


2-Phenylamine-3H-azepine

From there once you have aniline in the reaction or once you add aniline it will participate in the nucleophilic reaction first here in this position to form this compound. Now, it will participate in an electrocyclic ring-opening, to generate this compound, which can able to form this 2 phenyl-amine-3H-azepine. So, it is going to end up making a azepine. So, this is a very interesting transformations and nowadays also there are several different variation of this particular reaction was published in the literature. There is another example here starting from the sulphinyl amine.

$$\mathrm{Ph{-}NH_2 \xrightarrow{SOCl_2} Ph{-}N{=}S{=}O \xrightarrow{\quad\Delta\quad} Ph{-}\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}} + SO}$$

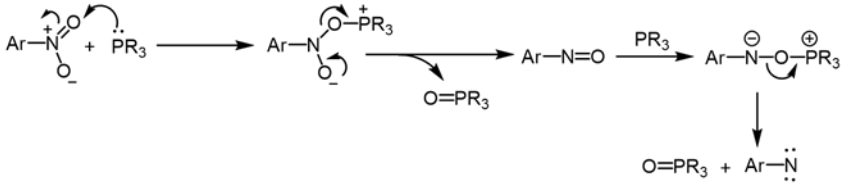
From the corresponding aniline, it forms this type of compound from there it is going to heat to generate the corresponding phenyl nitrene species. There is another example here I think in the previous slide I talked about using aniline. But here I am talking about, you can also use diethylamine instead of the aniline and the result will be the same. Instead of aniline, you will have a diethylamine which is going to attack here and then the electrocyclic ring opening going to form this corresponding product and then finally the tautomerization will end up forming this type of azepine compound.



So, now I am going to talk about some of the other method for the generation of nitrene intermediate. So, I talk about the photolysis or the thermolysis of the corresponding alkyl azide or the corresponding phenyl azide, but here I am talking about the deoxygenation of nitro. So, now my starting materials are corresponding nitro or nitroso compounds. In the presence of deoxidizing agents nitro and nitroso compounds are deoxygenated and nitrenes are going to be formed. So, trialkyl phosphines are the best deoxidizing agent. So, using trialkyl phosphines starting from the corresponding nitro compound there will be one after another reduction going to happen of the nitro which ends up generating the corresponding nitrene. Again these trialkyl phosphines are highly reactive. So, they are very strong nucleophiles. So, I have shown here the mechanism. So, starting from this nitro species, the trialkylphosphine has a lone pair which are going to attack this bond and generate this type of compound. The formation of this trialkylphosphine oxide is the driving force.

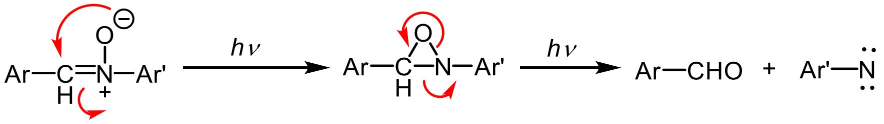
$$Ar{-}NO_2 \xrightarrow[\Delta]{(C_2H_5)_3P} Ar{-}\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}$$

$$Ar{-}NO \xrightarrow[\Delta]{(C_2H_5)_3P} Ar{-}\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}$$



So, that is why this (-) will come back and then it will form this type of trialkylphosphine oxide to get it to the nitroso. So, it will participate in one more round of reduction using this trialkyl phosphine to generate this particular compound. From there after cleaving of this nitrogen oxygen bond it will generate this corresponding aryl nitrene. You can see here starting from the nitro or nitroso, it can able to generate this corresponding aryl nitrene.

So, now, I am changing the starting material. So, now, from nitrone. What we have learned? we can generate from alkyl azide, we have learned from the corresponding nitrobenzene and now we have come to the corresponding nitrone. So, on photolysis of the nitrone 3 3-membered oxazirane will form which further produces the nitrene by the ring opening. So, there will be oxazirane which is going to form here. So, starting from here once you have this corresponding nitrone that can be easily synthesized, and then once you take it to the photolysis it is going to form the oxazirane here, and the oxazirane will now open up to generate the corresponding aldehyde and then it is going to form the corresponding nitrene.

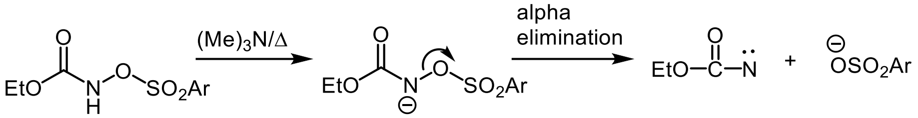


The next thing is by the oxidation reaction of cyanamide, if you take a cyanamide then if you take a PIDA which is an oxidizing agent, it is going to generate a nitrene as well. There is another example here. You can use the Pb(OAc)₄ to generate a nitrene.

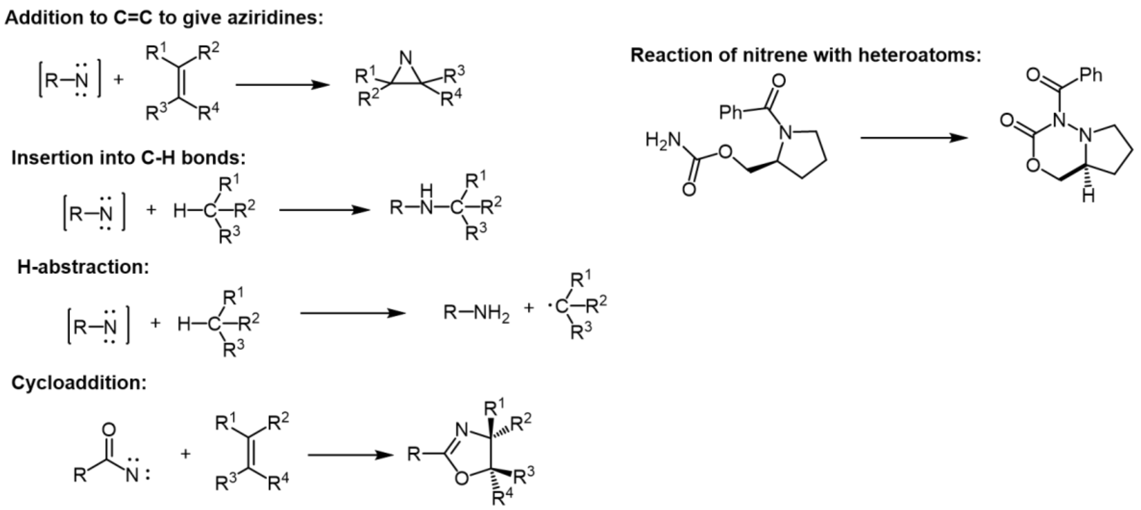
$$\underset{\text{Cyanamide}}{NC{-}NH_2} \xrightarrow{PhI(OAc)_2} NC{-}\ddot{N}\!:$$

$$R_2N{-}NH_2 \xrightarrow[Pb(OAc)_4]{[O]} R_2N{-}\ddot{N}\!: + Pb(OAc)_2 + 2AcOH$$

Now, I am going to talk about the α-elimination reaction. So, we have learned a lot about α-elimination in the carbene chapter. Where I talk about starting from chloroform or bromoform using a strong base you can able to go for α-elimination to generate the corresponding dibromo or dichloro carbene. Here I am going to talk about α-elimination reaction, but a different substrate here? And here what is going to happen? Starting from this compound, so this is an O-arene-sulphonylhydroxylamine will undergo α-elimination in the presence of trimethyl amine, and under heat, there will be cleavage of this bond nitrogen-oxygen bond which will end up generating this corresponding nitrene.



So, now I am going to talk about the different reactions of nitrene. So, first thing is the addition reaction. So, I think it is a very important reaction because it is end up making aziridine which is a very important compound which is present in a different drugs and in a bioactive compounds. So, this is happen once the nitrogen add to the corresponding olefin. You can compare that in case of carbene it is the cyclopropane, here it is the aziridine. Then insertion to the CH bonds is a very important reaction because in the end you are introducing a carbon-nitrogen bond by replacing a carbon-hydrogen bond. So, this is called the insertion reaction. So, you can end up making amine starting from the nitrogen. Then there is hydrogen abstraction reaction which can generate a radical and then a corresponding amine. Then there will be cycloaddition reaction.


Addition to C=C to give aziridines:

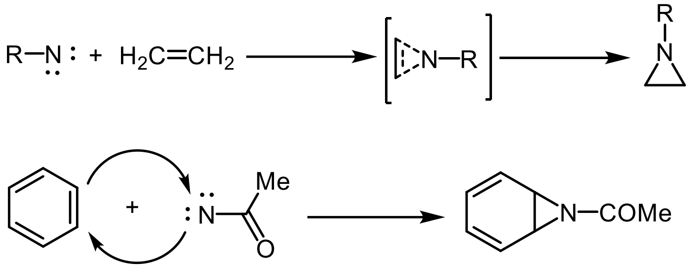
Insertion into C-H bonds:

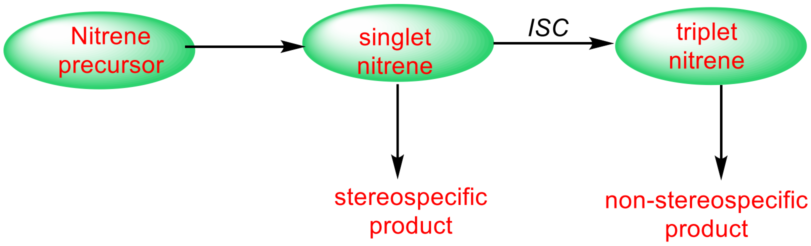
H-abstraction:

Cycloaddition:

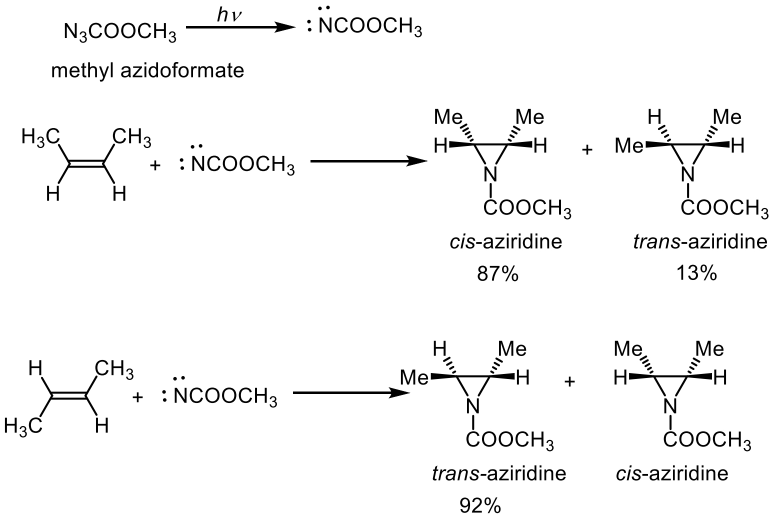
Reaction of nitrene with heteroatoms:

So, now, I am going to talk about them one after another. So, the first thing I am going to talk about is the addition reaction. Here you can see in this addition reaction what is going to happen. There is nitrene and there is ethylene, it is going to form this corresponding aziridine. It can also react with the benzene ring and then it is going to form this corresponding product as well. So, now what is going to happen? So, these are the reactions if you see the first thing is there will be a singlet and triplet nitrene. So, the nitrene precursor can form a singlet nitrene or if there is a inter-system crossing then the singlet nitrene will convert to a triplet nitrene. Now, what is going to happen from singlet nitrene, there will be a stereospecific product very similar to the carbene, but from triplet nitrene, it will be non-stereospecific product.

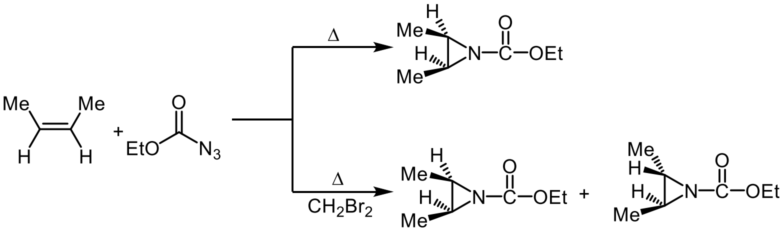




Let us see some examples here. So, here in the first one you can see there is a methyl azidoformate, it is actually generating this corresponding nitrene, which actually participates in the reaction with a *cis*-olefin and it is forming very high selectively the *cis* and starting from the *trans* it is forming very high selective corresponding *trans* product` So, what we are seeing here? So, it is generating a corresponding singlet nitrene that is why these reactions are very high stereospecific.

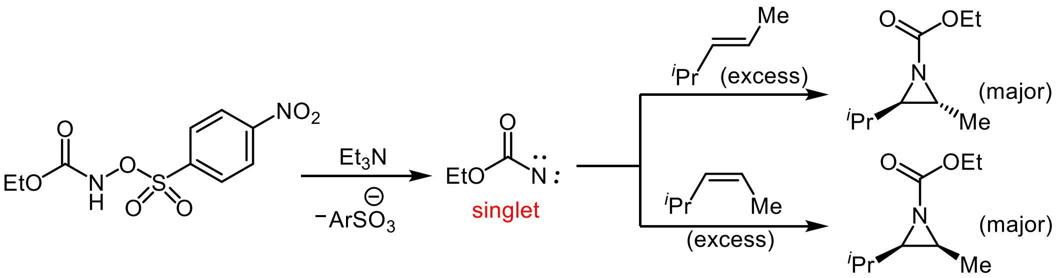


Then there is another example here. If you see this reaction what is happening? There is a generation of this corresponding nitrene as I said there will be α-ketone nitrene going to form. Now, if you take heat it is going to form a single product. See once in the reaction if you use some sort of an inert solvent like dibromomethane, then there is a mixture of products. So, what is going to happen? Why there is a mixture of *cis* and *trans*? That means there is some sort of a singlet to triplet conversion is happening in presence of a inert solvent. So, what is happening? If there is an inert solvent, then your singlet nitrene is interacting with the inert solvent, so there will be a collision with the inert solvent. And through the collision, the singlet will convert to triplet.That is why you are seeing a mixture of products.

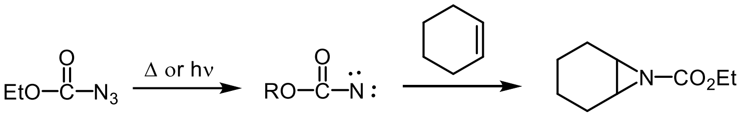


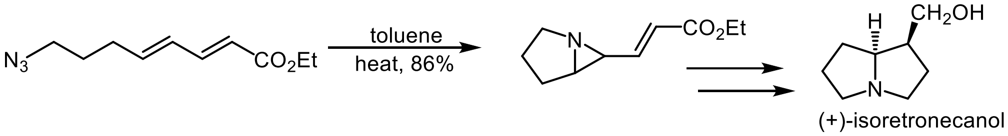
Then there is another example of generation of a singlet nitrene. So, there are two different scenarios again if you use this type of olefin *trans,* you get a *trans* product or if you use a *cis* you end up getting a *cis* product. So, in the presence of excess alkene, the *cis* olefin gives *cis*, and *trans* olefin gives *trans*, but now the question is the low concentration of alkene. Now, singlet nitrene undergoes an inter-system-crossing to a triplet which leads to a mixture of products. So, in this reaction what is going to happen if the olefin concentration is less? Because once the olefin concentration is less then what is going to happen, the reaction will not be that fast.

So, as the reaction will be slow, so there will be a timeline where the singlet will slowly going to interact with your solvent or it will be a collision or slowly there will be inter-system crossing and it will convert to a triplet. So, that is why, when you have a less amount of olefin there will be a chance of a mixture once it is excess you will get a single product. From *trans* you will get a *trans* from *cis* you will get a *cis* aziridine.



So, now we are going to learn about some more examples of addition reactions. The first one you can see here we are also generating a nitrene again. It is reacting with this cyclohexene to form this corresponding product. And then there is a very interesting example here because now you can see in this particular example you are generating nitrene from this corresponding alkyl azide under heat, but here are two different olefin. We try to compare about this olefin you can see this one will be electron deficient. So, now the question will be that which is going to react? It is going to react with electron-rich one, not the electron-deficient one. So, that is why this nitrene is going to interact and then form this. So, let us try to understand how this is happening. So, what is going to happen is that this nitrene is going to make an aziridine by interacting with this olefin.





So, it is going to form this. It is going to form this this product and then after that it will going to transform into this corresponding natural product. So, that is going to convert this isoretronecanol to this natural product.

So, in this particular topic, we have learned about nitrene, we have learned about the generation of nitrene and we have learned about the different approaches for reaction starting from the corresponding alkyl azide. Then we have learned how you can generate the nitrene from corresponding phenyl azide. You have seen that in the case of phenyl azide, the nitrene is phenyl nitrene is not stable. It is getting for successive transformations. And then we have learn some of the reactions like the addition reaction and there are some other reaction which I am going to discuss in the next class. Thank you so much and I am going to see you guys in the next class. Thank you.