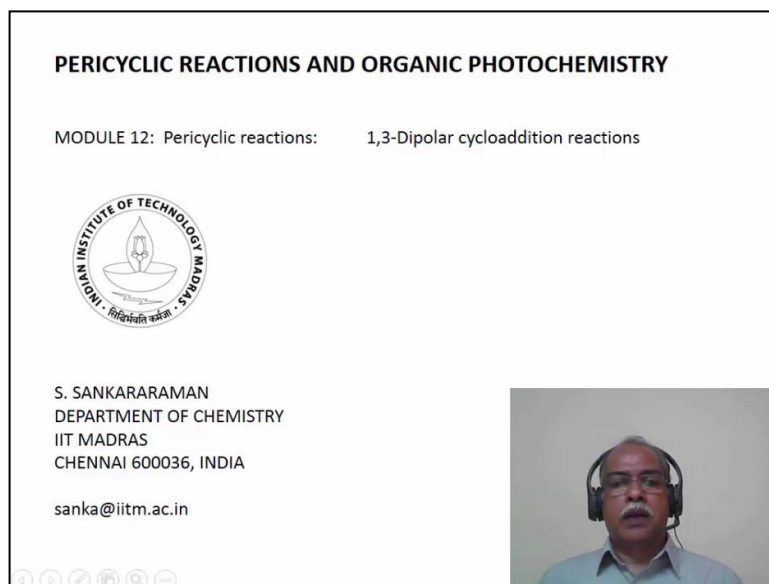


Pericyclic Reactions and Organic Photochemistry
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Module No. #03
Lecture No. #12
Pericyclic Reactions – 1,3-Dipolar Cycloaddition reactions

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PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 12: Pericyclic reactions: 1,3-Dipolar cycloaddition reactions



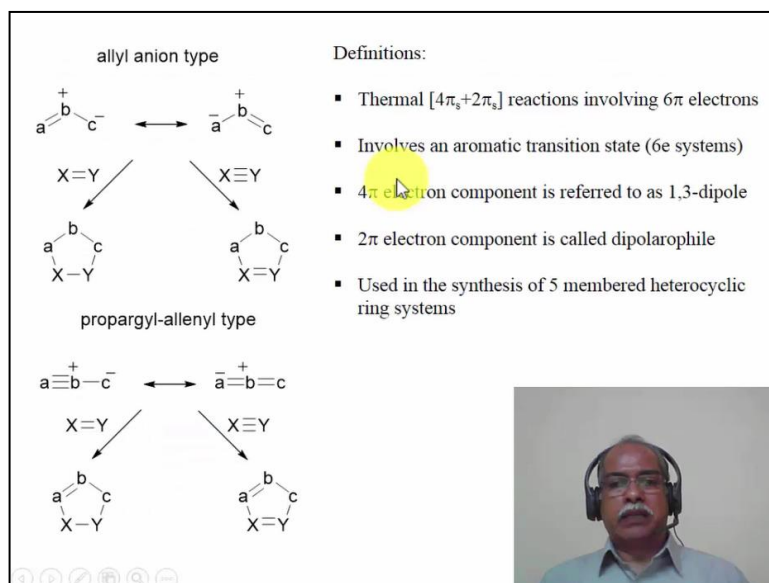
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Hello, welcome to the course on Pericyclic Reactions and Organic Photochemistry. We are now in Module Number Twelve. In this Module, we will consider a very important reaction known as, 1,3-Dipolar Cycloaddition reaction. 1,3-Dipolar Cycloaddition reactions are extremely important, because they are used in the formation or synthesis of Hetero cyclic derivatives.

As the name suggest, the 1,3-Dipolar systems are essentially polar systems, with the charged zwitter ionic system, in the Carbon number 1, or in the Atom number 1 and 3, for example. And, they do undergo Cycloaddition reaction, to produce 5-Membered rings.

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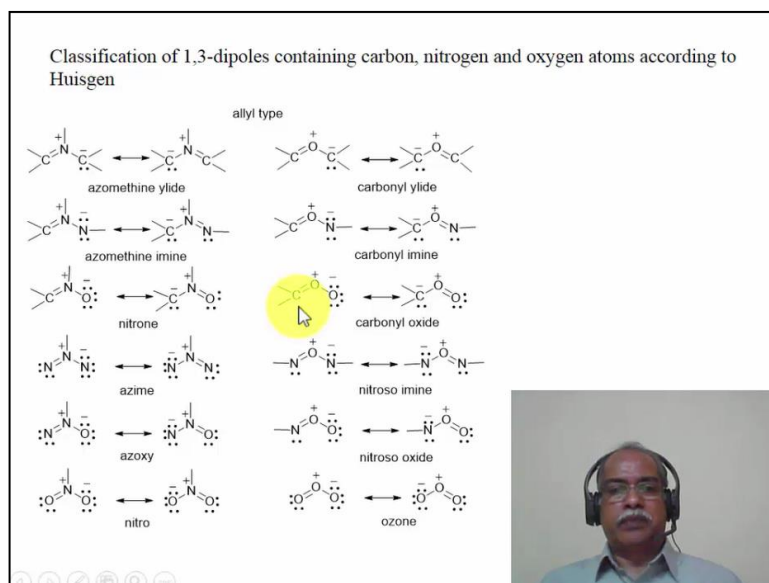
Now, the generic examples of 1,3-Dipole come in 2 forms. It could be, either in the form of Allyl Anion type, as you can see here, with the Benz structure, or Propargyl Allenyl type with the linear structure, like this. Now, this is what is known as the 1,3-Dipole. This is 1,3-Dipole, because one can always write a canonical structure, with the charges on the Atom 1 and 3. In this particular case, the charges was written in the Atom number 1 and 2, for example.

The 1,3-Dipoles are 4-Electron system. We will see it, in a minute. They undergo a 4+2 Cycloaddition reaction, in terms of the number of electron count. They are thermal reaction. The 4 PI Components is the 1,3-Dipole components. And, the 1,3-Dipolarophile can be either an Alkene or an Acetylene, as the case may be. So, overall these are reactions involving 6 PI Electron system. So, they are governed by the Woodward-Hoffmann rule, as 4 PI Suprafacial and 2 PI Suprafacial Cycloaddition reaction.

They involve an aromatic transition state of 6-Electron aromatic transition state, something like a Cyclopentadienyl anion kind of an aromatic transition state, you can imagine. The 4 PI Component is referred to as the 1,3-Dipole, which are these structures, that are seen here. This is zwitterionic structures, resonant structures, are shown in this particular case.

The 2-Electron components are known as the Dipolarophile. Similar to a dienophile, you have a Dipolarophile, which is the Acetylenic component or the Alkenic component. They are used in the synthesis of 5-Membered Heterocyclic ring. As you can see here, the 5-Membered ring is what is formed. It could be a Heterocyclic ring, if the Atoms A, B, C are Hetero Atoms in nature, for example.

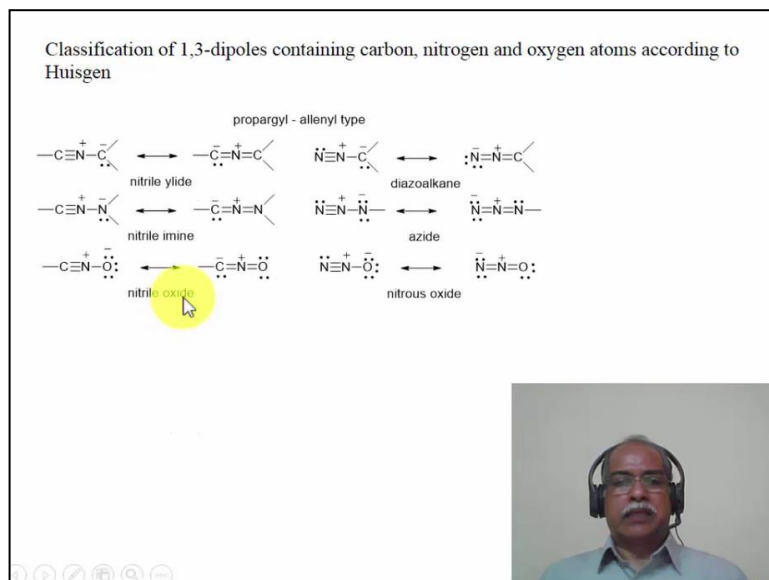
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There are several examples of 1,3-Dipoles known in the Allyl anion, Allyl type system. The classification is shown here. These are essentially, Allyl anion type, or the Allyl type of a system, is what is shown here. Typical examples are Azomethine ylide, Azomethine imine, Nitrone, Azime, Azoxy, Nitro, Ozone, Nitroso oxide, Nitroso imine, Carbonyl oxide, Carbonyl imine, and Carbonyl ylide. These are the examples, which would correspond to the Allyl anion, Allyl type of a 1,3-Dipole.

You can see here, in all these cases, atleast one Hetero Atom is being present in the 1,3-Dipole. And, that is what is responsible for the formation of the Heterocyclic ring, during the course of the Cycloaddition reaction. For the sake of this particular module, we will consider Azomethine ylide and Nitrone as examples of 1,3-Dipoles, undergoing the Cycloaddition reaction, in the subsequent transparencies.

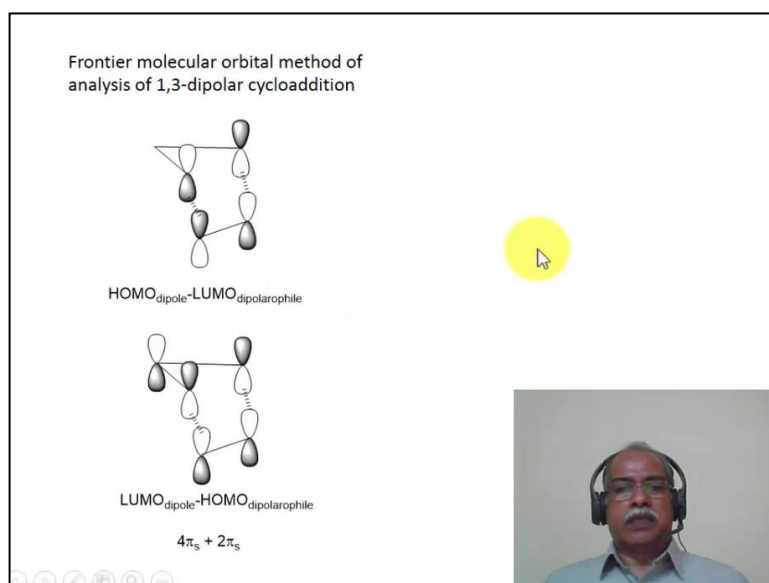
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Now, classification of 1,3-Dipole containing Carbon, Oxygen, and Nitrogen, according to the Huisgen rule, in the propargyl allenyl type, are as follows. You can have Nitrile ylides, Nitrile imines, Nitrile oxides, Diazoalkane, which are commonly known as Diazomethanes, for example. The Azide, which are very popular dipoles for 1,3-Dipoles for example, leading to the formation of Triazoles, we will see in a minute. Nitrous oxide, another example of a 1,3-Dipole.

In the module, we will see, Diazo Alkane and Azide as examples of 1,3-Dipoles, that are undergoing the 4 PI-2 PI Cycloaddition reaction, to form the 5-Membered Heterocyclic ring system, in this case.

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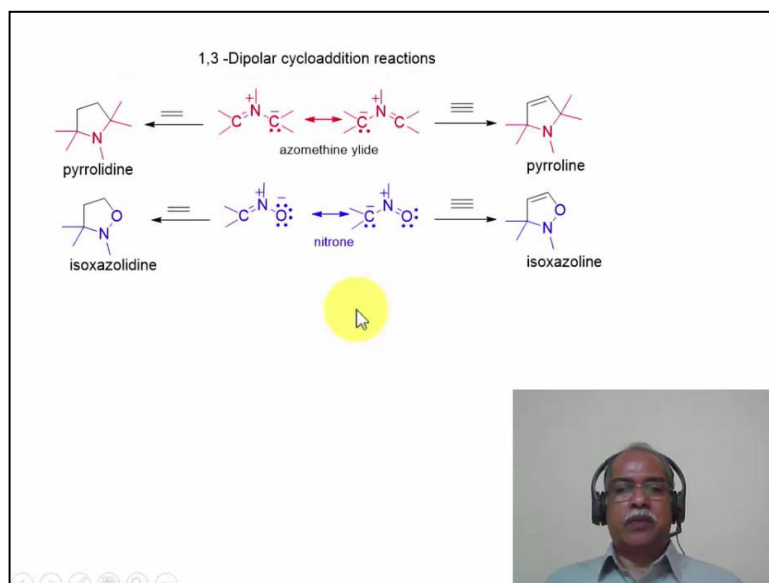
From the Frontier Molecular Orbital Methodology, one can analyze the Cycloaddition reaction, involving a Suprafacial-Suprafacial kind of an approach. In other words, a parallel approach of the 1,3-Dipolarophile, and the 1,3-Dipole. In this particular case, the top portion is a 1,3-Dipole, and the bottom portion is a 1,3-Dipolarophile. You can either consider, the Homo of the Dipole and Lumo of the Dipolarophile, or alternatively, one can consider the Lumo of the Dipole and Homo of the Dipolarophile, as the case may be.

In the case of Homo of the Dipole, Homo of the Dipole will have a one nodal point, which is the central Atom of this Dipole, for example. Whereas, the Lumo of the Dipolarophile is very similar to the Lumo of Ethylene, for example. So, if you are considering Ethylene or Acetylene, there will be one nodal point, present here. So, you can see here, this overlap is a bonding type overlap. This overlap is also a bonding type overlap.

So, under the thermal conditions, this reaction is an allowed, under the Suprafacial-Suprafacial overlap kind of a mode of approach. Alternatively, if we consider the Lumo of the Dipole, which is this particular fragment, Lumo of the Dipole, for example. The Lumo of the Dipole will have two nodal points. One nodal point on this particular bond. The other nodal point in the other bond, for example. The Homo of the Dipolarophile, which is this particular one. Homo of the Dipolarophile has no nodes at all.

So, this does not have any nodes. So, the overlap is essentially in this particular case, a bonding type of an overlap here, and a bonding type of an overlap here, which is thermally allowed process. And, this is a Suprafacial-Suprafacial overlap of the Dipolarophile and the Dipole, as the case may be. I keep telling Diene and Dienophile, because i just finish the Diels-Alder reaction. The same terminology cannot be used here, unfortunately.

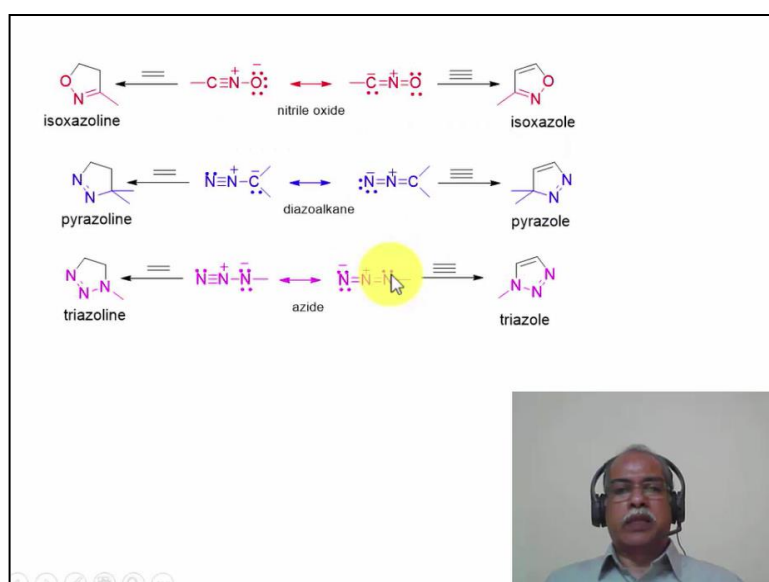
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Now, the 1,3-Dipolar Cycloaddition reaction examples are shown here. Azomethine ylide is this structure, that is shown here. This is a 1,3-Dipole. It undergoes the Cycloaddition reaction with an Alkene, to form the Pyrrolidine derivative. Or, it can form a Pyrroline derivative, if it is undergoing a Cycloaddition reaction with an Alkyne. Similarly, Nitron can also undergo a Cycloaddition reaction with an Alkene, to produce Isoxazolidine, or with an Alkyne to produce Isoxazoline.

So, these are the Heterocyclic systems that can be generated, by the Cycloaddition reaction of the Azomethine ylide and Nitron.

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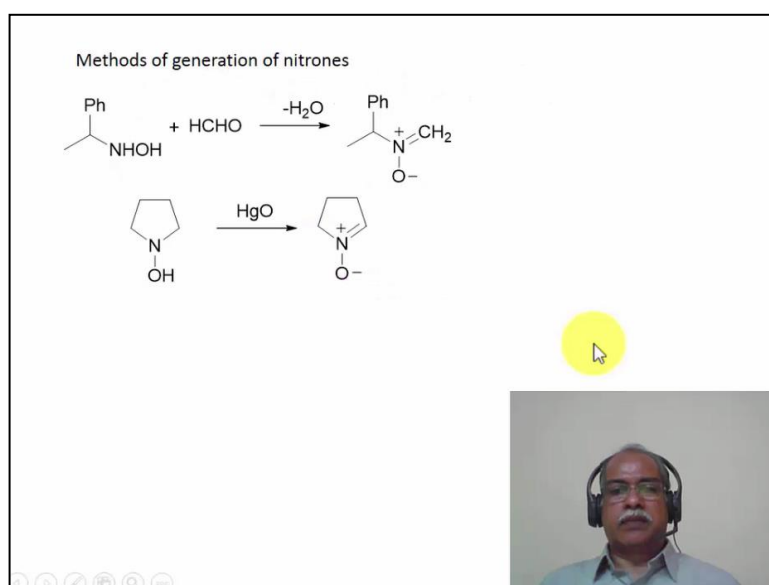


Let us see, how Azomethine ylides are generated. Before we go into that, in the case of the propargyl allenyl type of a system, you have a Nitrile oxide, Diazomethane, and Azide, as the examples. The reaction of the Nitrile oxide with an Alkene, produces an Isoxazoline.

Whereas, with an Alkyne, it produces an Isoxazole, directly the aromatic Heterocycle itself is formed, in this particular reaction.

With Diazoalkane, this is a very common reaction. Diazoalkane produce Pyrazoline or Pyrazole, depending upon. This is a 3H-Pyrazole, is what is produced, in this particular case. And, depending upon, whether it is Alkene or Alkyne, one can produce, these two types of a Heterocyclic derivatives. With Azide, Azides undergo Cycloaddition reaction with Alkene, to produce Triazoline, or with Alkynes to produce Triazole, which is an aromatic Heterocyclic compound, in this particular case.

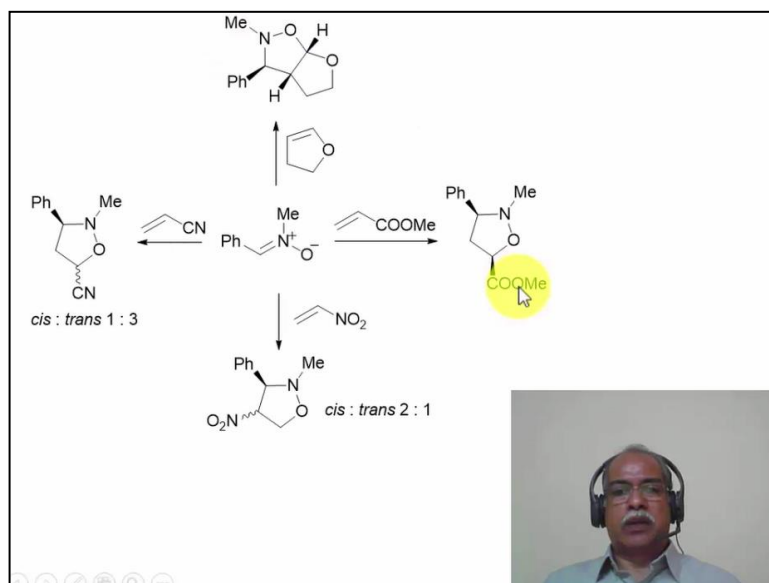
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Now, let us look at the method of generation of Nitronium, first. Nitroniums are generated by condensation of an Aldehyde, in this particular case a Formaldehyde, with a secondary Hydroxylamine. So, this is an Alkyl substituted Hydroxylamine. So, the condensation essentially with the loss of water produces, Nitronium as the derivative.

Alternatively, from a Tert-Hydroxylamine, by oxidation using Mercuric oxide, one can also produce a Nitronium. So Nitroniums, there are two Methods of producing the Nitronium, which are illustrated in this particular example.

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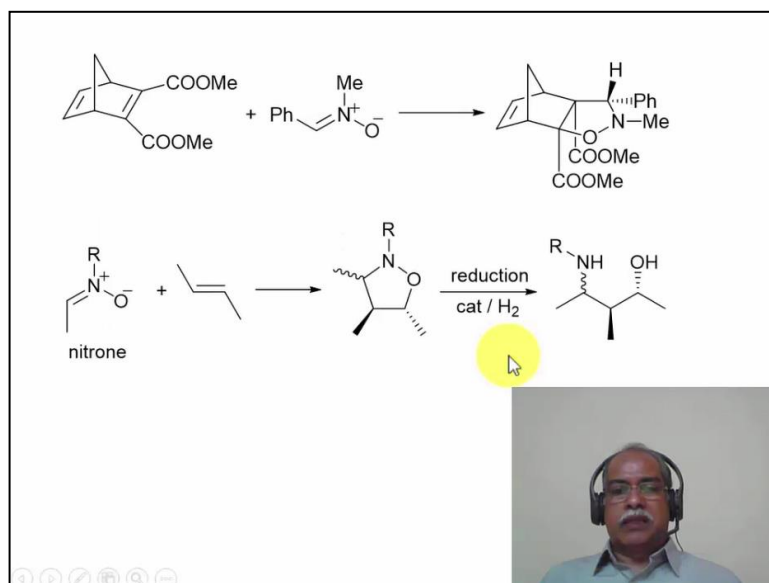


Once a Nitronium is produced, it can undergo a Cycloaddition reaction, with a variety of both the electron rich, as well as the electron deficient, Dipolarophile. This is an electron rich Dipolarophile, because of the Oxygen, that can donate a lone pair of electron, on to the double bond. This is essentially, an Enol-Ether kind of a system. Whereas, all the other ones are electron deficient Dipolarophile. You can see here, in the case of the electron rich and electron deficient Dipolarophile, the reactions are highly regio selective in nature.

In the sense that, Regio Isomer, that is formed is the, this particular Isomer that is formed, by the reaction of the Nitronium with the Dipolarophile. Whereas, in the case of the Nitroalkene, the regio selectivity is different. This is an opposite isomer, that is formed, in the case of the regio selectivity of this particular reaction. Quite often, Diastereomeric mixture can be formed, or Regio Isomeric mixture can be formed, in the case of the 1,3-Dipolar Cycloaddition reaction.

It is not always, the reaction is highly regio selective in nature, it is possible that one can produce a mixture of Regio Isomers also, in the case of 1,3-Dipolar Cycloaddition reaction. Here, a mixture of *Cis* and *Trans* Isomer is formed, with respect to the relative stereochemistry of this two substituents, that is present in this Isoxazoline ring system, that is formed during the course of the reaction.

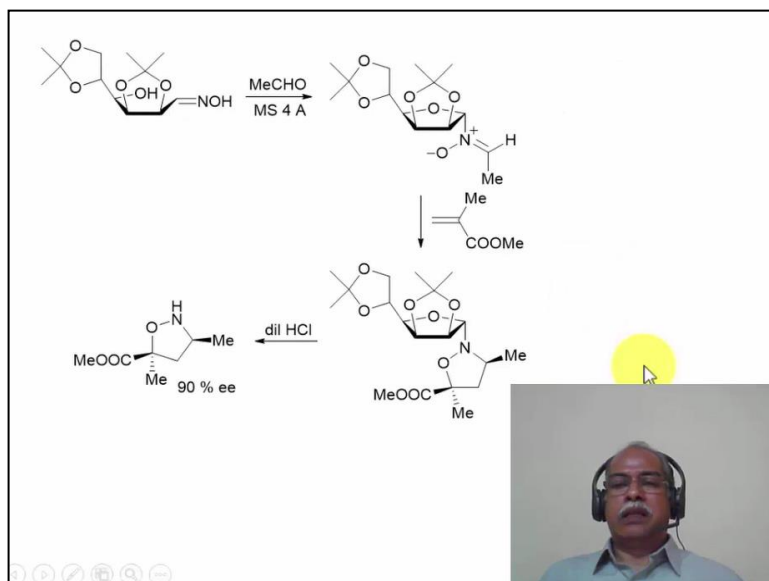
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This particular Nitronium, undergoes Cycloaddition reaction with electron deficient Dipolarophile, in preference to an electron rich Dipolarophile. There are two double bonds here. One is an electron deficient, because of the carboxylic acid Ester groups, that are substituted. This is relatively speaking, electron rich. Dipolarophile are electron deficient, and Dipoles are electron rich in nature. So, that combination, electronic character combination, perfectly suited for this type of a reaction.

You can see here, this cycloadduct is what is formed, exclusively during the course of the reaction. Now, the Nitronium Cycloaddition reaction produces an Oxazoline, Isoxazoline. And, the Isoxazoline can be made to undergo reductive cleavage of the Oxygen-Nitrogen bond, to produce Beta Amino alcohol, of this type. So, other than forming Heterocyclic ring, they can also be used to form stereo selectively, the Beta Amino alcohol derivatives of this kind, in organic synthesis.

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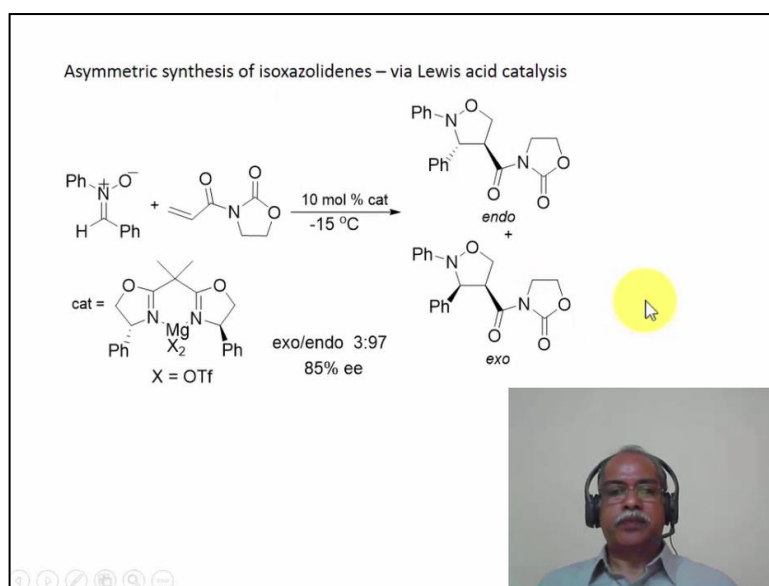


Here is an example, where a Furanose derivative is formed, by the initial addition of the Hydroxy onto the Oxime, to produce this Nitrone, which is formed by condensation of the initially formed Hydroxylamine with the Acetaldehyde for example, resulting in the formation of this particular Nitrone, that undergoes Cycloaddition reaction with Alpha Methyl Acrylate, to produce regio selectively, this particular Isomer of the cycloadduct.

This is the cycloadduct. It is actually an aminol, which is this particular Iminol, is what is undergoing the Hydrolysis, to produce the Isoxazoline, Isoxazoline ring in a 90% enantioselective manner, because the starting material is Chiral in nature. This is a Sugar derivative. So, whatever the Chiral center, that is produced, is enantioselective produced.

So, this is an example of a first-generation Asymmetric transformation, where you start with an enantio-physically pure starting material, producing the enantiomerically pure product, after the Cycloaddition reaction is over.

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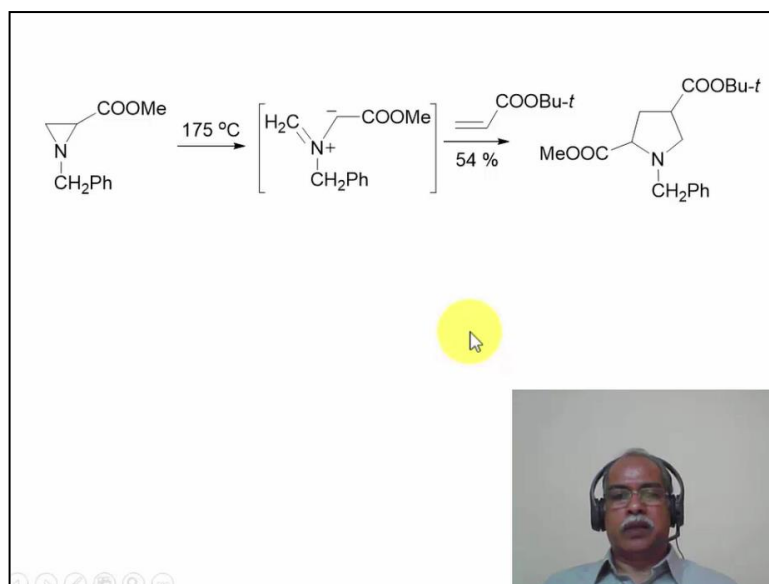


In this case, the Asymmetric synthesis of Isoxazolidenes via Lewis acid catalysis, was illustrated. The Nitronium derivative undergoes Cycloaddition reaction, with this particular Olefin. And, 10 mole percent of this Magnesium complex is used as a Chiral Lewis acid, for example.

The Magnesium triflate, which is coordinated to this Bis-Isoxazoline ring system, which is a Chiral ligand, for example, produces a Chiral Lewis acid. The Chiral Lewis acid in turn, coordinates or chelates with this two Oxygen, producing a Chiral derivative of the Dipolarophile. And, that undergoes the Cycloaddition reaction to Endo selectively, to give this particular product, for example, in an enantioselective manner.

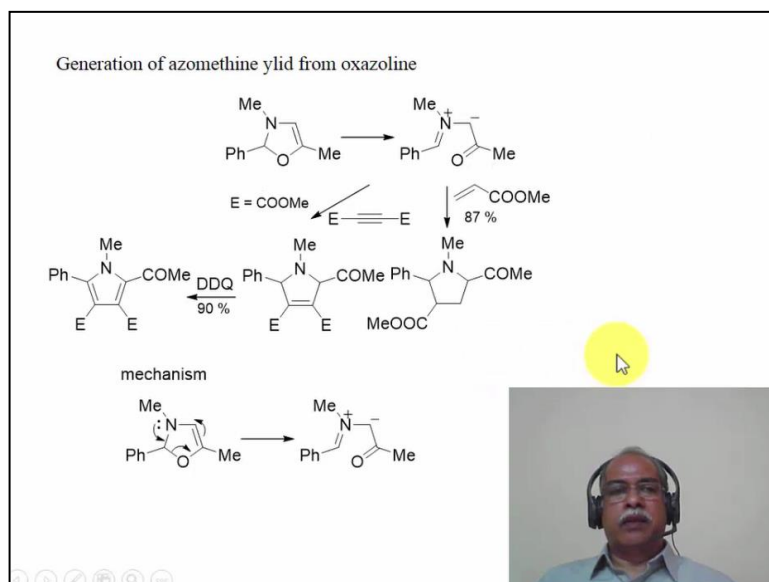
The Exo-Endo ratio is Endo selective. It is 97% Endo. And, that 97% Endo is formed, in about 85% of enantiomeric excess. So, overall this is a Chiral Lewis acid catalyzed 1,3-Dipolar Cycloaddition reaction of an Nitronium, to form Asymmetric synthesis of Isoxazolidenes as the final product, in this particular case.

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Here, the Azomethine ylide is generated by the decomposition of an Aziridine. This is an Azomethine ylide, that is generated by the composition of the Aziridine. When the Aziridine is heated to about 175 degree, that produces this 1,3-Dipoles as an intermediate, which is trapped by a Dipolarophile, which is in this particular case, Tertiary Butyl Acrylate for example, resulting in the formation of a, regio selective formation of this particular cycloadduct, in this case.

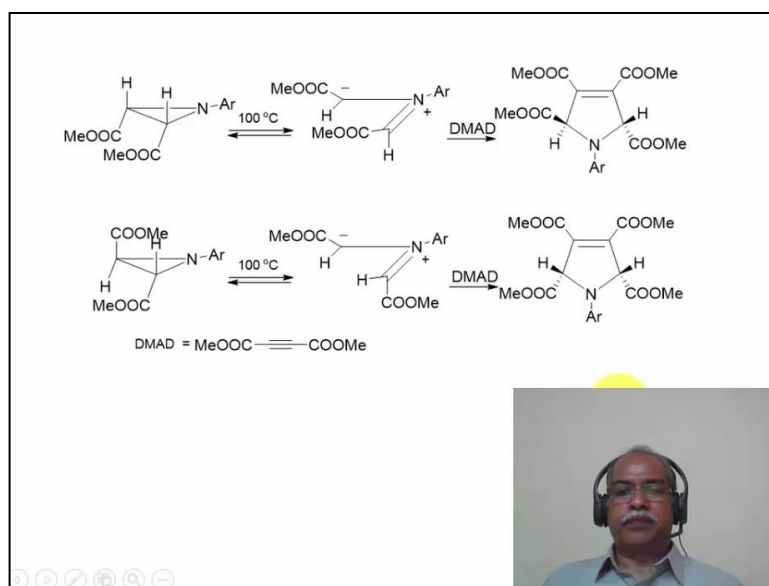
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Generally, Azomethine ylides can be generated from the decomposition of Aziridine. Alternatively, they can also be generated by the decomposition of Oxazoline. Oxazolines undergo decomposition to produce ring opening reaction, to produce Azomethine ylide derivative. That can be trapped either with an Alkyne or an Alkene, as the case may be, to produce the corresponding Heterocyclic system, in this case.

This Dihydro Hetero cyclic system can be aromatized, by oxidation with the DDQ, to form the Pyrrole derivative, which is this particular derivative, that is shown here. The mechanism of formation of the Azomethine ylide from Oxazoline, is given here. It is a simple thermal decomposition, involving the lone pair of Electron on the Nitrogen, resulting in the formation of the cleavage of the Carbon-Oxygen bond, resulting in the formation of the 1,3-Dipole, which is shown in this mechanism.

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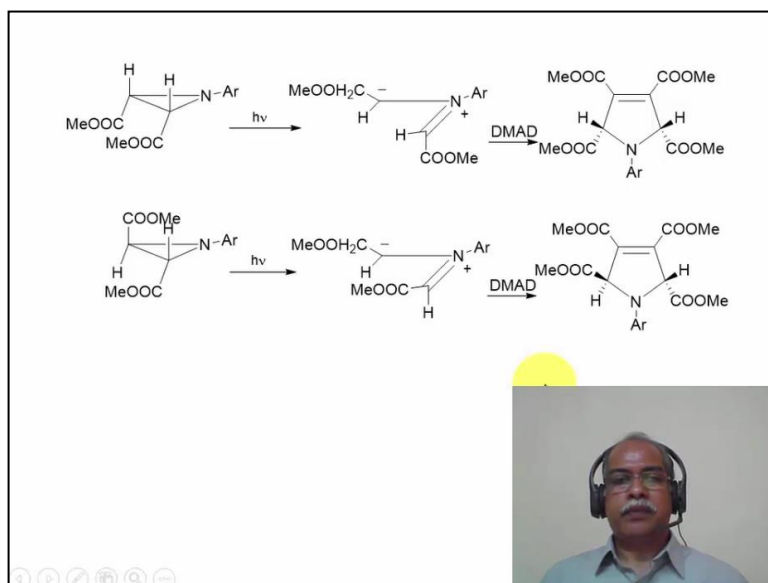


Here is an example, which is already seen, in the case of a electrocyclic ring opening reaction. This also constitutes as an example of a 1,3-Dipolar Cycloaddition reaction. That is why, this is brought in back here. This is an Aziridine, which undergoes thermal electrocyclic ring opening reaction. This is a 4-Electron system, undergoing conrotatory thermal electrocyclic ring opening reaction, to produce this particular Isomer of the Azomethine ylide.

The Azomethine ylide thus produced, is undergoing a Cycloaddition reaction with Dimethyl Acetylene Dicarboxylic acid, resulting in the formation of this particular adduct. Since, the stereochemistry of the 1,3-Dipolar derivative, is this particular stereochemistry, the two Ester functional groups are Trans, with respect to each other.

When the other Diastereo Isomer is produced, by the thermal decomposition of the Diastereo Isomer of the Aziridine, then the Diester that is produced, in this particular case is Cis Diester. Because, the two Carboxylic acid functional groups here, are outside of the PI framework. In other words, the stereochemistry in these two Carbon matters, as far as the stereochemistry of the two Carbon centers that are produced, in this particular derivative of the cycloadduct.

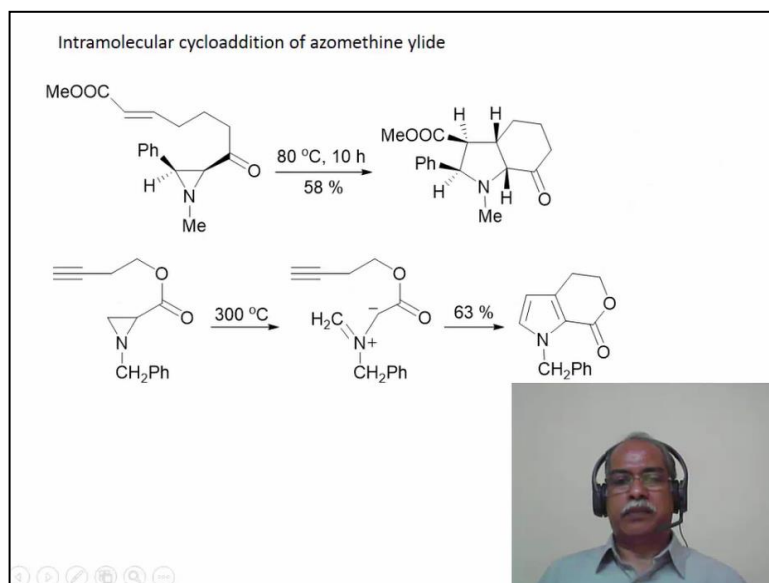
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Under photochemical condition, of course, this will undergo disrotatory ring opening. So, producing exactly the opposite stereochemistry. Initially, you saw in the case of thermal rearrangement, thermal condition, the Cis Isomer produces this particular compound. Whereas, the Cis Isomer under photochemical produces, an opposite Diastereo Isomer, that is trapped by Dimethyl Acetylene Dicarboxylic acid, to give the Cis Ester, in this particular case.

The Trans Isomer produces the opposite Diastereo Isomer of the Azomethine ylide, and that is trapped by Dimethyl Acetylene Dicarboxylic acid, to give the corresponding cycloadduct with this particular stereochemistry, that is shown here.

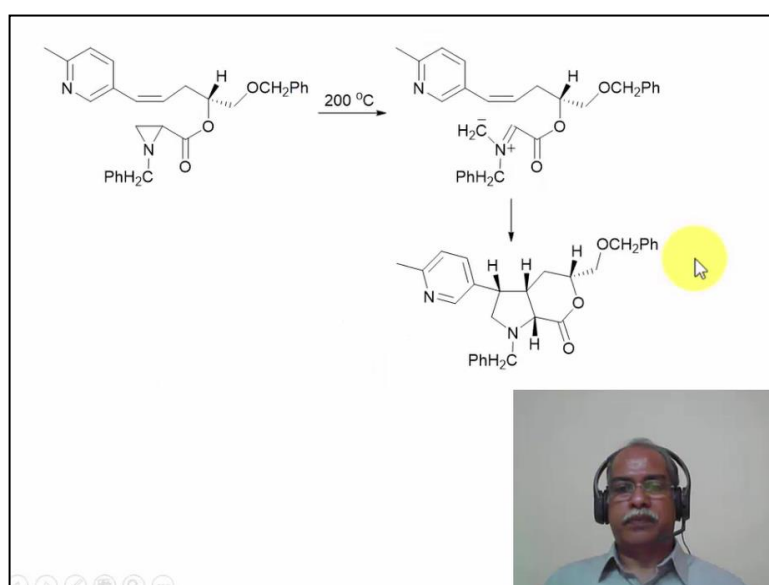
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Here is another example of an, Intramolecular cycloaddition of the Azomethine ylide. This Aziridine is decomposed. And, there is an in-built double bond, which is the Dipolarophile in this particular case. So, the Dipole that is formed, is trapped by the Dipolarophile, which is this Dipolarophile, resulting in the formation of this adduct, in this case.

Same example, except the Dipolarophile, now it is an Alkyne. It undergoes the Cycloaddition reaction by the Azomethine ylide, that is produced by the decomposition of the Aziridine ring, to form the corresponding Pyrrole derivative in this particular case, and Pyrroline derivative in this case.

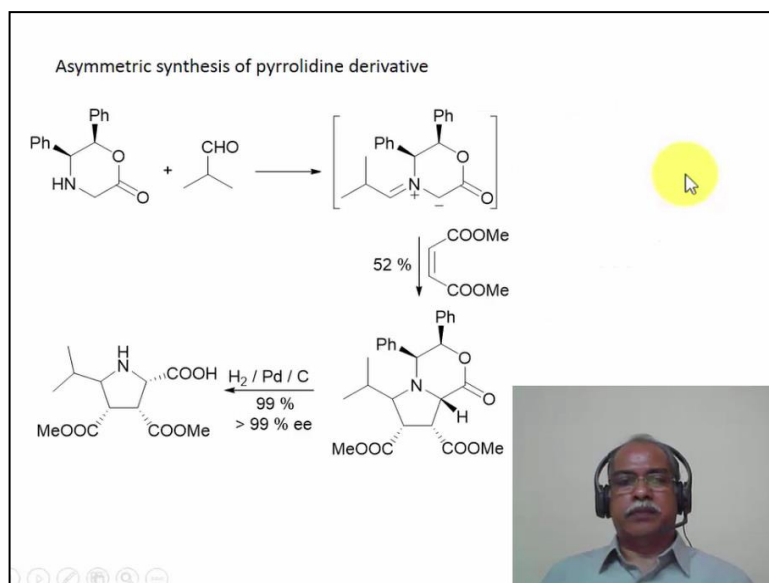
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Some more examples of, Intramolecular versions of the trapping of the Azomethine ylide, by an Alkyne. Here is a Pyridine substituted Vinyl derivative, that undergoes 3+2 Cycloaddition reaction, to produce this corresponding Heterocyclic derivative in a regio selective manner.

Because, there is only one Regio Isomer, that is possible for this tether group, that is being attached to the Azomethine ylide, in this particular case.

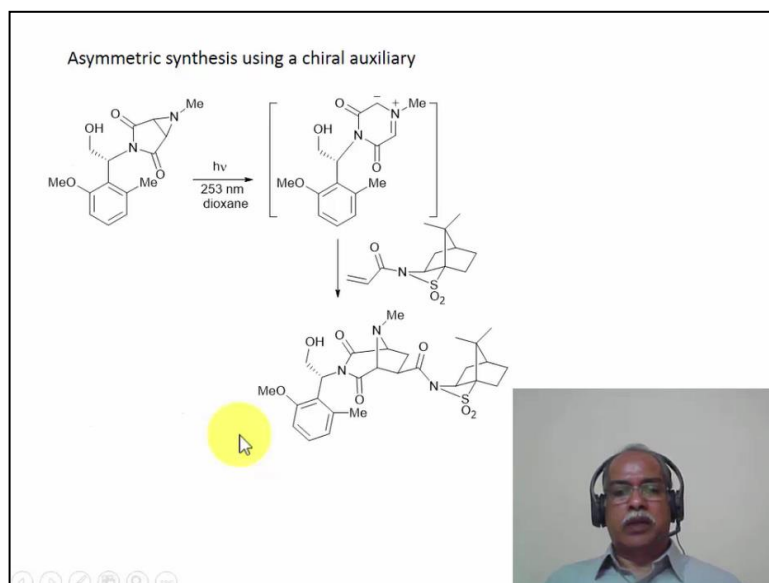
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Now, this slide tells you something about, the Asymmetric synthesis of Pyrrolidine derivatives. We are starting with an Asymmetric Optically Pure Isomer of a derivative, which is this particular derivative, which is a secondary Amine, that is condensed with the Aldehyde, to produce the Azomethine ylide. Azomethine ylide, thus produced is trapped by Dimethyl Ester of the Maleic acid, for example, resulting in the formation of this particular derivative.

This derivative, now undergoes Hydrogenolysis of this Benzyl Carbon-Nitrogen bond, and the Carbon-Oxygen bond, to produce the corresponding Pyrrolidine derivative, where three stereo centers are produced. The fourth stereo center is not very well defined, in this particular case. However, the compound that is formed is produced in 99% yield, with 99% of enantiomeric excess, of only one of the Diastereo isomers of this particular molecule, that is produced here.

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Another example of an Asymmetric synthesis using Chiral auxiliary. Here, in this particular example, this decomposition of this Aziridine derivative, produces the Azomethine ylide, which is this particular molecule. And, here is a Sultam, which is used. This is the Camphor derived Sultam. And, the Dipolarophile is attached to a Camphor derived Sultam, as a Chiral auxiliary.

Cycloaddition reaction between the Dipole, that is produced with a Dipolarophile, which is a Chiral Dipolarophile, results in the formation of an enantiomerically excess. In other words, constituting an Asymmetric synthesis, using a Chiral auxiliary of this particular Pyrrolidine derivative, that is given here. So, what we have seen, in this particular module is, examples of 1,3-Dipoles, from the point of view of the Allyl anion type, as well as the Propargyl Allenyl type.

And, the Cycloaddition reactions of the Allyl anion type of a system's namely, the Azomethine ylide and the Nitron derivatives, to form the corresponding Heterocyclic derivative. Thank you very much, for your kind attention.