Pericyclic Reactions and Organic Photochemistry

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Module No. #02
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Pericyclic Reactions -Cycloaddition Reactions – Ketene Cycloadditions

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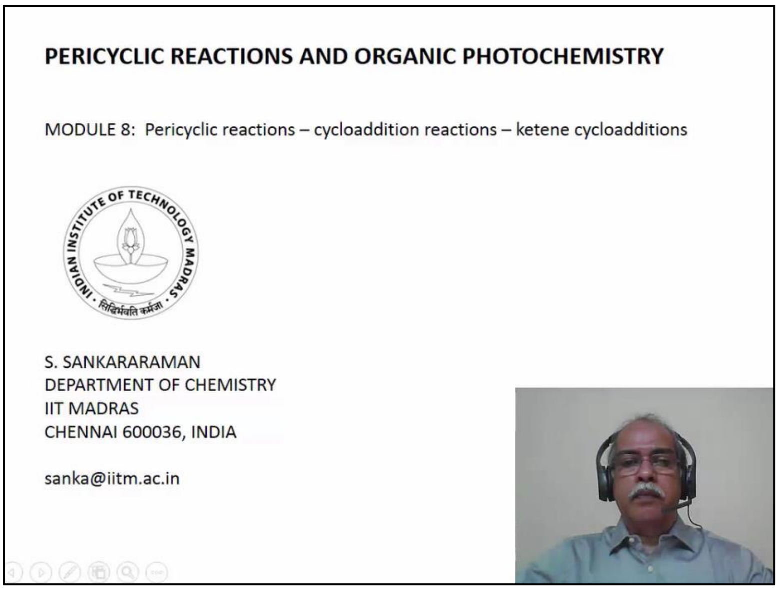

PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 8: Pericyclic reactions – cycloaddition reactions – ketene cycloadditions

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Hello, welcome to the course on Pericyclic Reactions and Organic Photochemistry. We are in module eight, now. In this module, we will consider a very important thermal cycloaddition reaction namely, the addition of Ketone to Olefins and Alkenes.

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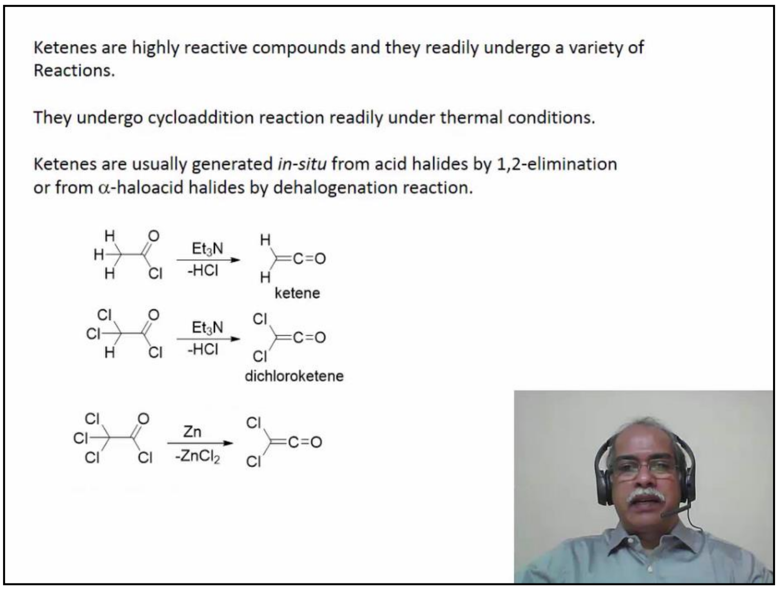

Ketenes are highly reactive compounds and they readily undergo a variety of Reactions.

They undergo cycloaddition reaction readily under thermal conditions.

Ketenes are usually generated *in-situ* from acid halides by 1,2-elimination or from α-haloacid halides by dehalogenation reaction.

Ketene is a very reactive intermediate in organic chemistry. And, it is highly electrophilic in nature, reacts with water rapidly, to give the corresponding acid. However, under anhydrous condition, Ketene can be generated in-situ. And, it can be made to undergo cycloaddition reactions, with Olefins and Alkenes. They undergo cycloaddition reaction, normally under thermal conditions. Ketenes are usually generated in-situ, by elimination reaction.

The some examples of Ketene generation, is given in this particular scheme. We can see here, if you take an acid chloride, we can do a beta elimination reaction, in the presence of Triethylamine, or some base, that produces the ketene, as the reactive intermediate, with the loss of HCL molecule, from the acid chloride. We can also take Alpha-Chloro, Alpha-Alpha-Di chloro, Acetyl-Chloride.

Here, Hydrogen Chloride elimination, produces a Dichloroketene. Dichloroketene is a relatively more stable than Ketene. It is easier to generate also. On the other hand, Ketene can also be generated by a dehalogenation reaction, using Alpha-Chloro-Acid Chloride, in the presence of metals like Zinc, and Magnesium, and so on. The dehalogenation reaction in these particular cases, essentially gives the Dichloroketene, as the product.

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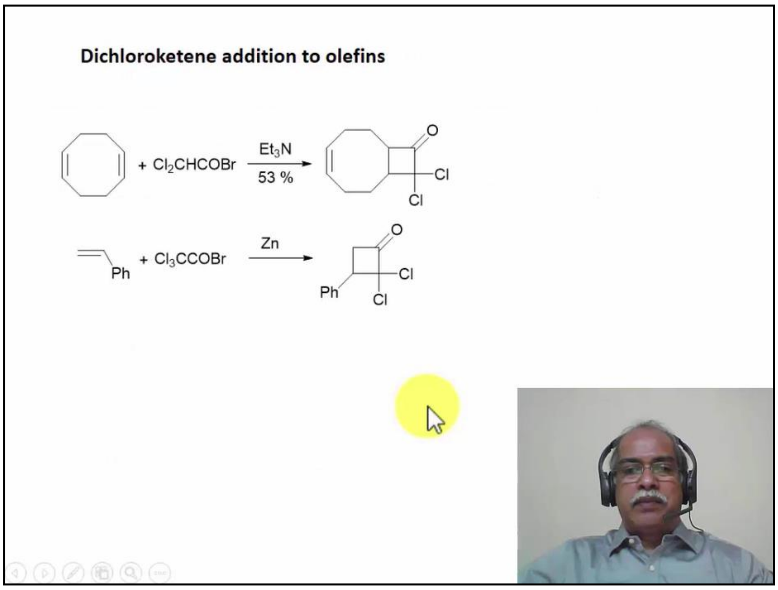

Dichloroketene addition to olefins

Now, let us have look at the examples of cycloaddition reactions of Ketene, in this scheme. Here, Octa-1,5-diene is taken. And, it is treated with Alpha-Dichloro-Acetyl-Bromide in the presence of a Triethylamine. So, it generates Dichloroketene as the intermediate, in this particular stage. The Ketene, that is produced in C2, undergoes cycloaddition reaction with the double bond here, to essentially give the Cyclobutanone as the product. Ketene cycloaddition because, it is a 2+2 cycloaddition reaction. It gives a Cyclobutane derivative.

Because, there is a carbonyl functional group, present in the Ketene, what you get essentially is the Cyclobutanone as the ring with the Olefin, or Cyclobutenone with the Alkene. Styrene reacts with Dichloroketene, to give the corresponding Dichloro derivative. In this particular case is a regio specific reaction. We can see here, the Phenyl and the Dichloro end up in the same position, with respect to each other.

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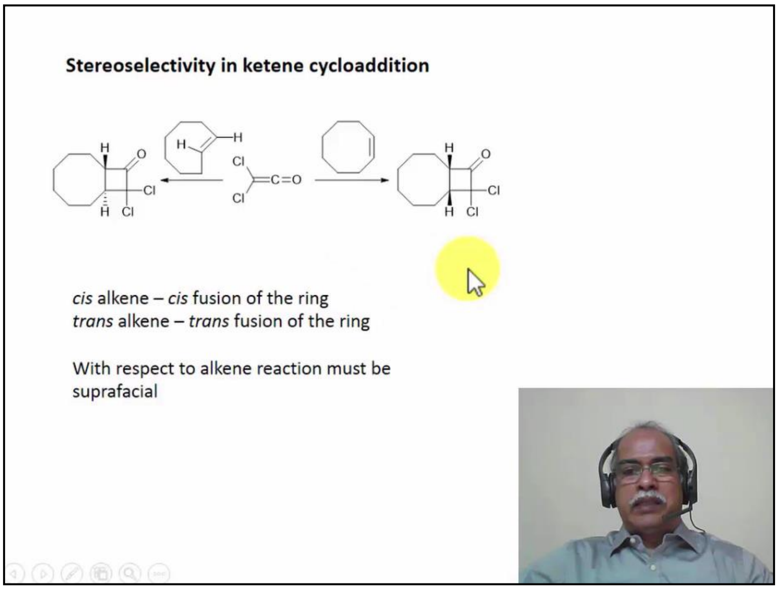

Stereoselectivity in ketene cycloaddition

cis alkene – *cis* fusion of the ring
trans alkene – *trans* fusion of the ring

With respect to alkene reaction must be suprafacial

Now, the stereochemistry of Ketene cycloaddition has been studied very well. And, the stereochemistry essentially corresponds to the Cis rule, that we will be seeing in the Diels-Alder reaction. Now, with respect to the Diene and the dienophile, we need to specify, whether the Ketene cycloaddition is Suprafacial or Antarafacial, with respect to the Olefin and the Ketene.

Here is an example, where the Dichloroketene generated from Alpha-Chloro-Acetyl-Chloride, for example, results in the formation of a Cyclobutanone derivative. And, it is so, the Cis-Olefin namely, the Cyclooctene essentially gives a cyclo-adduct, where the two hydrogens in the fusion, ring fusion are Cis with respect to each other. On the other hand, if one takes Cyclooctene, which is a Trans-Isomer, remember in the case of eight membered, nine membered rings, the Trans-Isomer is easy to prepare. And, it is fairly stable compared to the six and seven membered, the Trans-Olefins.

So, Cyclooctene, which is Trans-Isomer, essentially gives a Cyclobutanone, fused Cyclobutanone, where the fusion is Trans with respect to each other. This essentially shows us that, with respect to the Alkene, the Ketene must be undergoing a Suprafacial addition, with respect to Alkene. Because, unless the cycloaddition is Suprafacial with respect to the

Alkene, the stereochemistry cannot be retained. If it is undergoing an Antarafacial addition, it would have given a Trans-Isomer here, and a Cis-Isomer in the other case.

So, the fact that, the Cis-Olefin gives the Cis fused Cyclobutanone, and the trans-Olefin gives the Trans fused Cyclobutanone, indicates to us, that the Ketene cycloaddition to Alkenes is Suprafacial, with respect to the Alkene component.

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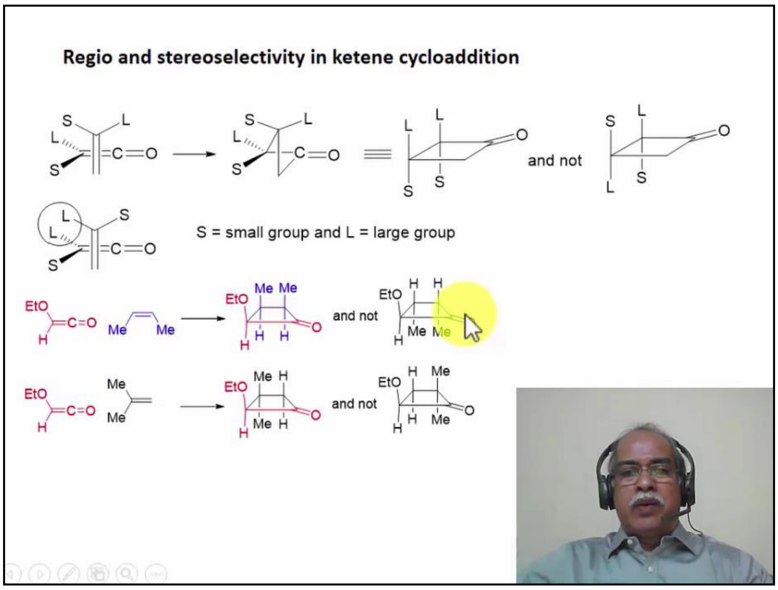

Regio and stereoselectivity in ketene cycloaddition

S = small group and L = large group

Now, let us see, what happens to the regio chemistry of the Ketene cycloaddition reaction. Suppose, if the Ketene is a di-substituted Ketene, where you have two functional group, one is a large size functional group, other one is a small size functional group. And, the Olefin also has a geminal disubstitution, where one has a large functional group, and a small functional group. The Ketene cycloaddition, because it is perpendicular approach of the Ketene with respect to the Olefin, this is a kind of approach, that is followed.

And, this particular approach, you can have two possible orientation, in the transition state. One orientation is, where the large groups are further away from each other. Another orientation, where the large groups are closer to each other, or on the same side, with respect to the PI bond of the Olefin, for example. This would be a sterically more hindered approach, because of the steric interaction between the two-large group, compared to this approach, where the two large groups are further away from each other.

Therefore, Ketene cycloaddition proceeds through the approach, in this particular manner, where the two large groups are further away from each other, in the transition state, resulting in a twisted Cyclobutanone formation, which eventually will have the two or large groups, Cis with respect to each other, in the product. Although, thermodynamically stable product is formed, the thermodynamically stable, they energy corresponding to this transition state must be lower, corresponding in comparison to the energy, corresponding to this particular transition state.

And, that is why, this product is formed in predominantly, or exclusively. And, this product is not formed, where this is another Stereo-Isomer. If you consider this to be a Trans-Isomer, and this to be a Cis-Isomer, the Cis-Isomer is usually formed, and not the Trans-Isomer. This is illustrated with couple of examples, that is shown here. Now, if you consider the addition of Ethoxy Ketene to Cis-Alkenes, in other words, Cis-2-Butene, in this particular case, there are two possible products, one can get. The passive group, and the two methyl groups, can be Cis with respect to each other, as in this particular case.

On the other hand, the other Isomer from a different approach, can have the Ethoxy groups and the two Methyl groups, Trans with respect to each other. In fact, is the sterically crowded Isomer is what is formed in the reaction, for the reason that is stated with the above mechanistic explanation. And, this sterically less hindered product is not formed, in this particular case.

Similarly, when you have the regio chemistry of the reaction considered, the Gem Dimethyl Alkene that is shown here, for example, preferentially undergoes the regio selective reaction, at this particular carbon, and the ethoxy substituted carbon, resulting in the formation of this particular Cyclobutanone, and not the other Cyclobutanone.

This Cyclobutanone would have arrives on, if the Methoxy-Ethoxy substituted carbon were to overlap with this particular carbon, here. So, these examples essentially illustrate, that the cycloaddition process is highly regio selective, as well as stereo selective, in the sense that, the most crowded Cyclobutanone, is what is formed in the reaction. Because, that proceeds through the least sterically hindered transition state, as it is shown in this two structures, here. This is applicable only if you assume, that the Ketene cycloaddition, is taking place by a perpendicular approach.

Perpendicular approach is possible in this particular case, because this is an SP carbon. It is divide of substituent. So, it does not pose any kind of a steric interaction, or steric hindrance, for the perpendicular approach, unlike two Olefins approaching perpendicular to each other. Here also, two Olefins are approaching perpendicular to each other, except this particular carbon happens to be an SP carbon. The Ketene carbon is an SP carbon. So, that is a reason, this reaction is able to proceed by a perpendicular approach, in this manner.

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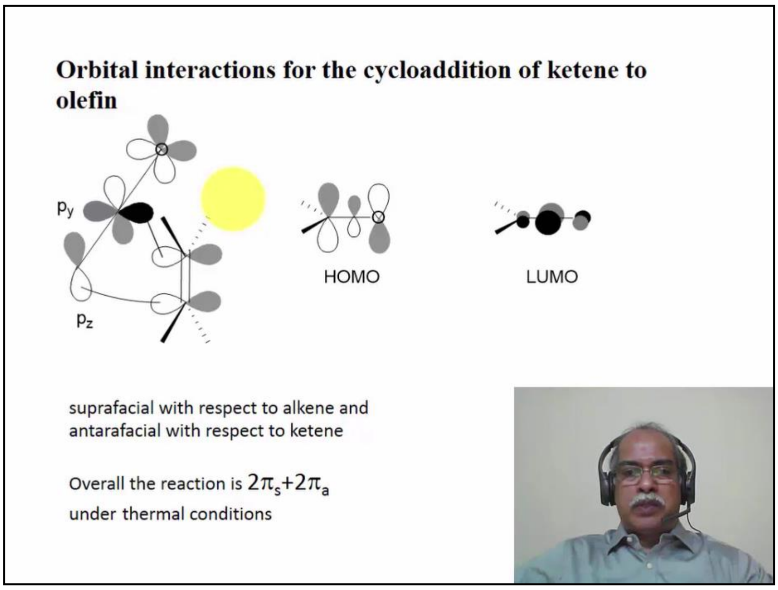

Orbital interactions for the cycloaddition of ketene to olefin

suprafacial with respect to alkene and
antarafacial with respect to ketene

Overall the reaction is $2\pi_s + 2\pi_a$
under thermal conditions

Now, let us look at the orbital interaction for the cycloaddition reaction of Ketene to an Olefin. Now, if the two components are approaching perpendicular with respect to each other, then it is possible to have an Antarafacial interaction, between the Ketene and the Alkene, in which case, the Ketene will be the Antarafacial component, and the Suprafacial component will be Olefin. Please recall, the Woodward-Hoffmann rule for 2 PI + 2 PI cycloaddition reaction, under thermal condition.

Under thermal condition, the 2 PI-2 PI cycloaddition reaction will take place, only if one of the component is an Antarafacial component. In other words, either the Olefin has to be Antarafacial, or the Ketene has to be Antarafacial. Stereo chemistry clearly tells us that, the Olefin cannot be Antarafacial, because Cis-Olefin gives Cis-Cyclobutanone product, and Trans-Olefins gives Trans-Cyclobutanone product, Trans-fused and Cis-fused Cyclobutanone product.

As we have seen, in the case of Cyclooctene derivative, Cis and Trans Cyclooctene derivative. So, it must be the Ketene, that must be undergoing the Antarafacial overlap. Let us analyze it, by looking at the highest occupied molecular orbital of the Ketene. This is the highest occupied molecular orbital picture of the Ketene. And, this is a lowest unoccupied molecular orbital of the Ketene.

So, both are actually molecular orbitals of Ketene only. What is important is, the central Ketene Carbon orbital size of this particular lobe, is much higher than the size of the other two lobes. In other words, this large size lobe is what is being responsible for the preferential overlap of the perpendicular orbital, with the orbital of the Olefin. In other words, the large orbital initiates the interaction with the Olefin. And, essentially the Olefin, with respect to the Olefin, if you look at, this is Suprafacial. Because, the orbital lobes from the same side of the

PI bond, is essentially undergoing the interaction with the Ketene. In the case of Ketene, this lobe is interacting with this one. Although, this lobe initiates the interaction, eventually, this is the lobe, that is going to undergo the bond formation, with this one. So, this is with respect to Ketene, Antarafacial, very clearly. And, that is a reason, the 2 PI component of the Ketene is an Antarafacial component, in the overall reaction for the thermal cycloaddition reaction, between the Ketene and the Olefin.

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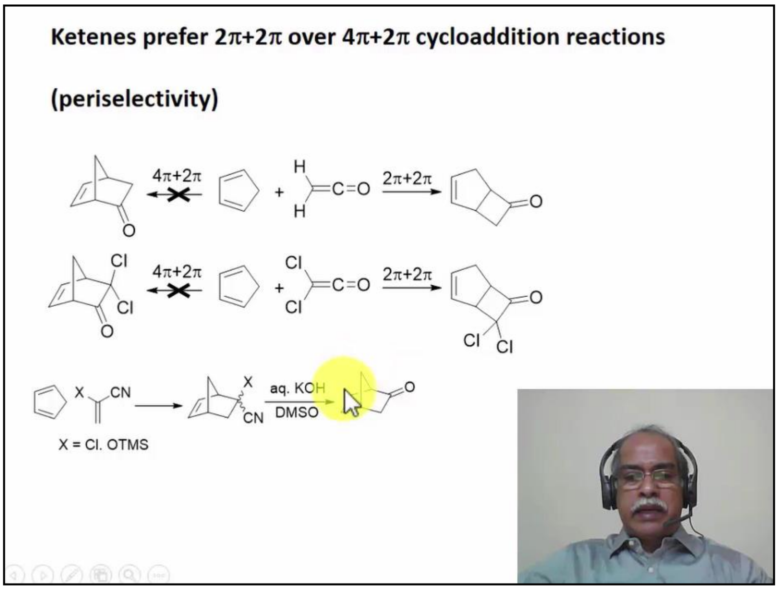

Ketenes prefer 2π+2π over 4π+2π cycloaddition reactions

(periselectivity)

Now, Ketene prefers to undergo a 2 PI-2 PI cycloaddition reaction, even if a Diene is present as a counter component. This is something one can explain, on the basis of Peri-Selectivity. There must be a two-transition state, one corresponding to a 4 PI-2 PI cycloaddition reaction. In other words, this will act as a 4 PI component. Ketene will act as a 2 PI component. It can undergo, Diels-Alder kind of a reaction, to give this Bicyclic Ketone. But, that does not happen, in the case of the Ketene cycloaddition reaction with the Cyclopentadiene, for example.

Similarly, Dichloroketene also does not undergo cycloaddition reaction, with Cyclopentadiene, in a Diels-Alder fashion. So, these Ketones cannot be prepared by a cycloaddition reaction, from Ketene and a Diene, in this particular case, the Cyclopentadiene, for example. It undergoes preferentially a 2 PI-2 PI cycloaddition reaction, to give this Regio-Isomer of the fused Cyclobutanone, as the product. So, if you want to prepare the 2,2,1-Bicyclic Ketones of this kind, it is possible only through, the involvement of, what are known as the Ketene equivalents.

These are actually Ketene Cyanohydrin directives. If it is a Chlorine here, then it will be Alpha-Chloro-Acrolein-Nitrate. If it is a OTMS here, that will be a Ketene-Cyanohydrin-

TMS-Ether is, what is being represented. These molecules, readily undergo Diels-Alder reaction, to give an intermediate, which is this particular intermediate. This intermediate can be aqueous basic condition. It can be hydrolyzed, for example, to give the corresponding Bicyclic Ketone.

We will see, more of these example, at a later stage, when we discuss the Diels-Alder reaction. For the time being, try to understand that, the Peri-Selectivity, in other words, selectivity over 2 PI-2 PI cycloaddition reaction, and 4 PI-2 PI cycloaddition reaction, the 2 PI-2 PI cycloaddition reaction is preferred reaction in the case of the, a Ketene-Diene cycloaddition reaction. Probably, because of the lower transition state energy, corresponding to the 2 PI-2 PI cycloaddition reaction.

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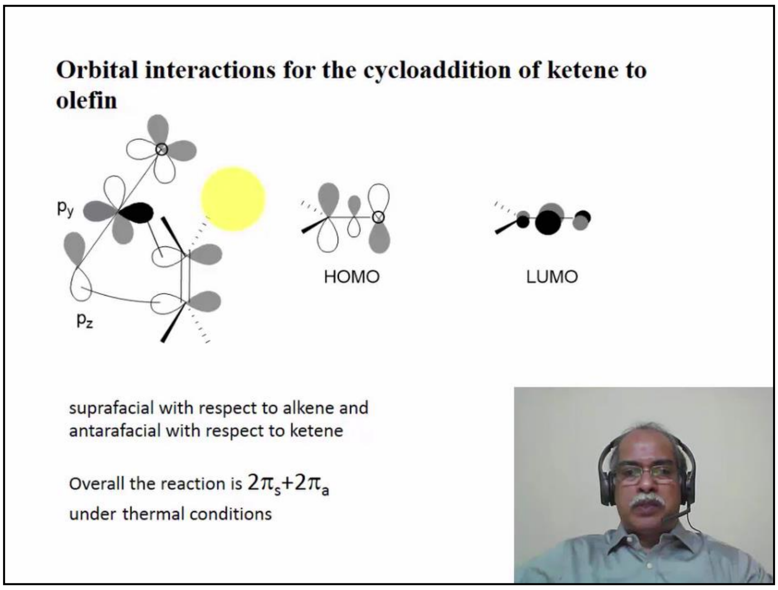

Orbital interactions for the cycloaddition of ketene to olefin

suprafacial with respect to alkene and antarafacial with respect to ketene

Overall the reaction is $2\pi_s+2\pi_a$ under thermal conditions

That is probably triggered, by the large molecular orbital, size of the molecular orbital of the central Ketene carbon, which initiates the reaction as a 2 PI-2 PI initiation, for the cycloaddition process to take place.

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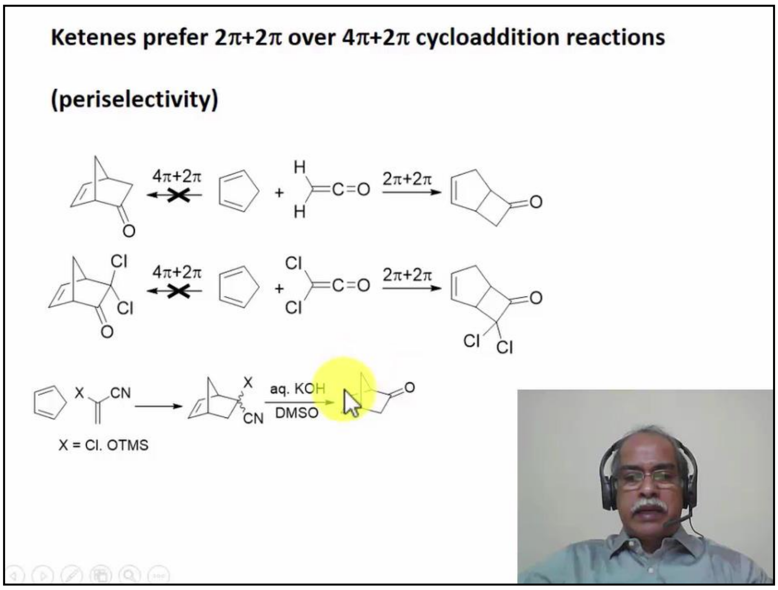

Ketenes prefer 2π+2π over 4π+2π cycloaddition reactions

(periselectivity)

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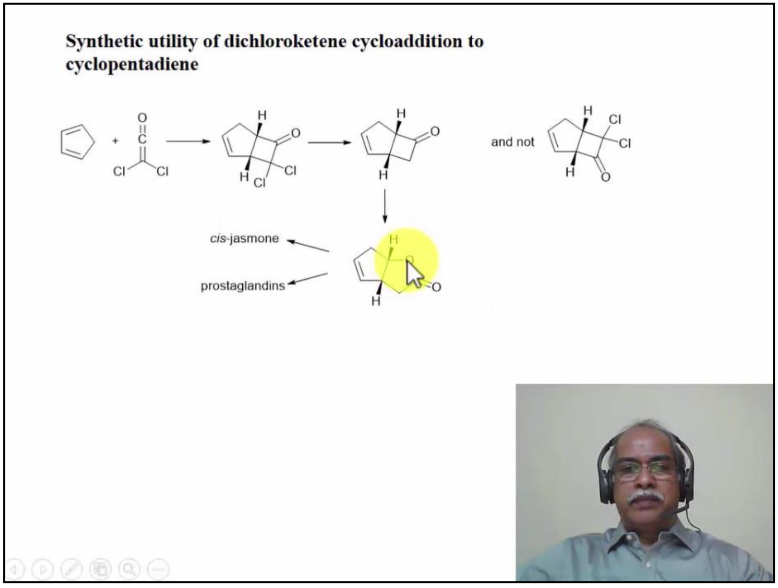

Synthetic utility of dichloroketene cycloaddition to cyclopentadiene

Now, let us look at some synthetic utility of the Ketene cycloaddition reaction. Ketenes undergo, both inter molecular, as well as intra molecular, cycloaddition reaction. If Ketene and Alkene are part of the same molecule, then one can expect a intra molecular cycloaddition reaction. Here is an example, which we have already seen. A Dichloroketene, undergoing a cycloaddition reaction with the pentadiene, in a regio selective manner, to give this particular Isomer. This Isomer is not produced. This is the other Regio-Isomer of the molecule, which is not produced, in this particular case.

So, regio selectively, this particular Isomer is being formed, in this particular reaction. Dehalogenation can result in the formation of the, fused Bicyclic Butanone derivative. This fused Bicyclic Butanone derivative, can be converted into the Lactone, by a Baeyer-Villiger type of an oxidation. And, this Lactone is extremely useful in organic synthesis, for the synthesis of molecules like Cis-Jasmone, which is a terpenoid molecule. And, Prostaglandin kind of molecules can be synthesized, from this intermediate stage. So synthetically, the Ketene cycloaddition can be extremely useful, for the synthesis of several natural products, and so on.

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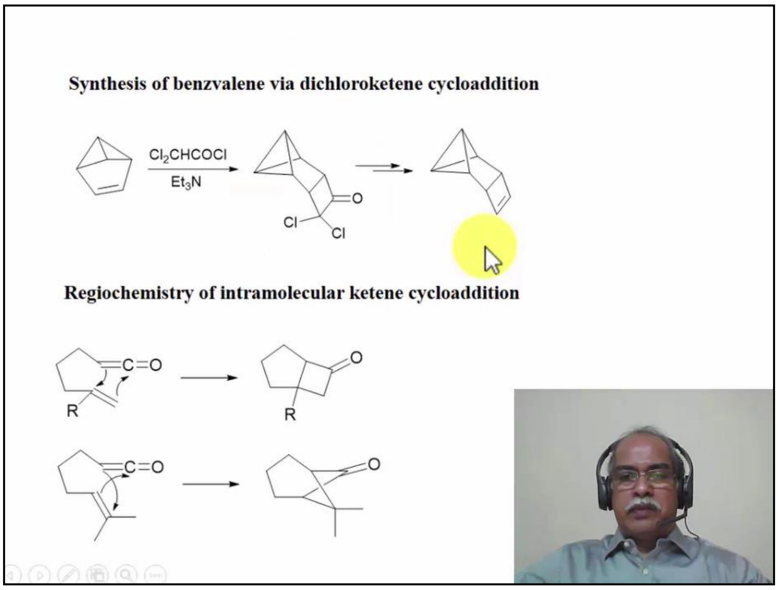

Synthesis of benzvalene via dichloroketene cycloaddition

Regiochemistry of intramolecular ketene cycloaddition

Here is another example of Benzvalene. This compound is known as Benzvalene. This undergoes Dichloroketene cycloaddition reaction, for example. The Alpha-Dichloro-Acetyl-Chloride under the basic condition, undergoes hydrogen chloride elimination, to give the Dichloroketene as an intermediate, which undergoes the Ketene cycloaddition reaction, to give the Cyclobutanone, is a dichloro Cyclobutanone, is what is derived. And, the Cyclobutanone is now reduced, and it is made to undergo carbonyl reduction, as well as the carbon halogen bond reduction, to give the corresponding alcohol.

That alcohol can be dehydrated, to give this Olefin here. Now, in the case of intra molecular cycloaddition reaction, it depends on the substitution pattern of the Olefin. If it is a Geminally disubstituted derivative like this one, for example, undergoes a simple 2+2 cycloaddition reaction. On the other hand, if it is a tri-substituted Olefin, where the terminal carbon is geminally substituted like this, then it undergoes a criss-cross cycloaddition reaction, to give the bridged bicyclic system, of this kind.

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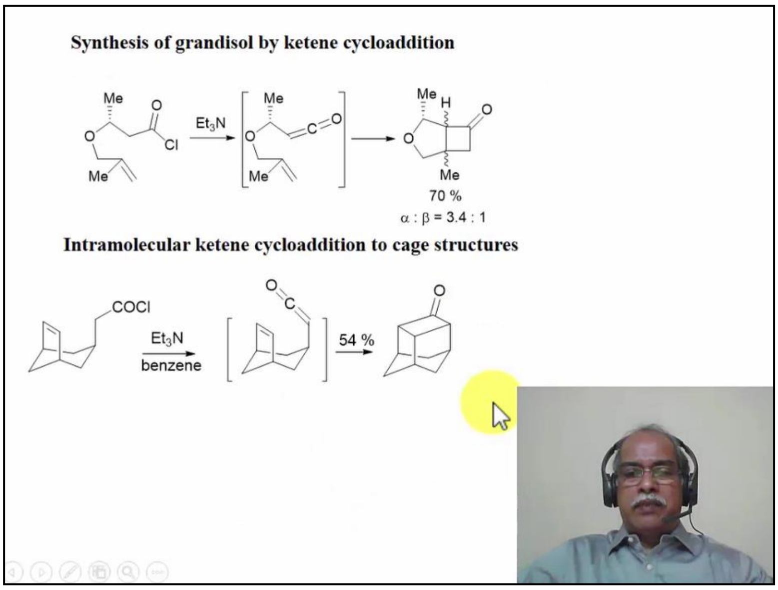

Synthesis of grandisol by ketene cycloaddition

70 %

α : β = 3.4 : 1

Intramolecular ketene cycloaddition to cage structures

We will see, some examples of this kind of cycloaddition reaction, now. Now, Grandisol is a terpenoid molecule. It is a naturally occurring molecule. That is generated by a simple 2+2 cycloaddition reaction. This Acetyl Chloride, this Acid Chloride, is treated with Triethylamine, the intermediate Ketene is generated, which undergoes readily a 2+2 cycloaddition reaction, to give the fused bicyclic derivative. The stereochemistry, the relative stereochemistry between these two centers is either, can be Alpha or Beta, with respect to this Methyl, here.

And, it is formed in the ratio of 3.4:1, alpha to the beta ratio, for example, in this case. Intramolecular cycloaddition reaction can also result in the structure of, cage type of structures in the cycloaddition process. If you look at this molecule, this Acid Chloride can generate the Ketene. And, the Ketene and the Olefin are essentially close together, in terms of the proximity effect. This is actually 1,3-Diaxial interaction, is what we are talking about.

These two bonds are, 1,3-Diaxial in nature. And, these two bonds are also, 1,3-Diaxial in nature. So essentially, if you follow the cursor, these three bonds, which are vertical bonds, are Diaxial, 1,3-Diaxial kind of a bond. So, the Ketene so generated in this particular position, can undergo or access this double bond, to undergo the cycloaddition reaction, to give the Cyclobutanone derivative. Now, this is a cage kind of a structure, is what is formed in this particular reaction.

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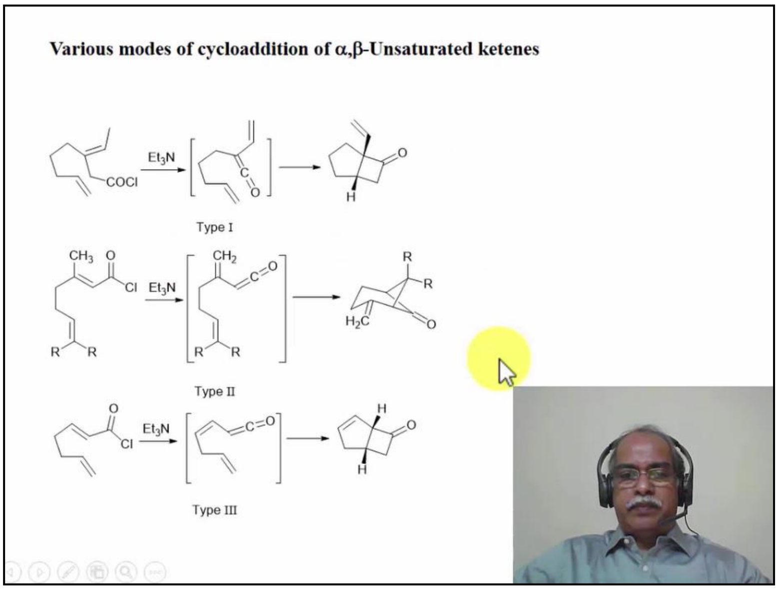


Various modes of cycloaddition of α,β-Unsaturated ketenes

Type I

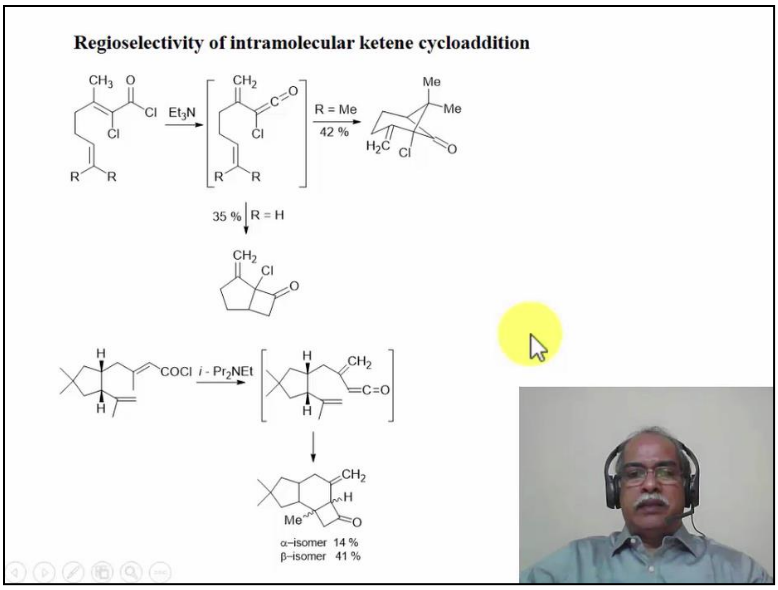
Type II

Type III

Ketene intra molecular, Ketene cycloaddition reaction, can be for the case of the Alpha Beta Unsaturated Ketenes, in this particular case. Alpha Beta Unsaturated Ketenes can be generated conveniently from the Acid Chloride, by treatment with the base, for example. In this case, the Ketene is generated, by deprotonation from the homo allylic position, which is this particular position, with respect to the Ketene here, for example. The deprotonation, essentially results in the formation of the acid derivative, the Ketene derivative in this case.

And, a simple 2+2 cycloaddition reaction, gives the Cyclobutanone derivative with the Cis fusion, with respect to the ring fusion of the derivative. Now, the second type of Ketene cycloaddition reaction, again the Alpha Beta Unsaturated Ketene is generated, by deprotonation of the Methyl Proton, followed by the loss of the Chloride Ion here, to generate this Alpha Beta Unsaturated Ketene. And because, the Olefin is geminally disubstituted in the terminal position.

It undergoes a criss-cross cycloaddition reaction, to give the bridged bicyclic system of this kind. Simple cycloaddition reaction is what is taking place, in this particular case. By deprotonation from this particular carbon, to produce this Alpha Beta Unsaturated Ketene, a simple 2+2 cycloaddition reaction, gives the Cyclobutanone, fused Bicyclic Cyclobutanone derivative. And, this is called a type three kind of a cycloaddition reaction of the Ketene. (Refer Slide Time: 18:55)



Regioselectivity of intramolecular ketene cycloaddition

Now, these are examples of the type one, type two, and type three, of cycloaddition reaction, that we discussed in the previous slide, for example. The Alpha Beta unsaturated derivative of the Ketene, is formed by deprotonation, from this Methyl group. And, when these two R-groups are Hydrogen, in other words, this is a terminal Olefin. A simple 2+2 cycloaddition reaction takes place, to give the fused bicyclic system of this kind.

On the other hand, when the two R-groups are Methyl, in other words, the geminally disubstituted derivative of the Alkene is reacting with the Ketene, then it undergoes a criss-cross cycloaddition reaction, to give the bridged bicyclic Ketone of this kind, for example. Now, this is a geminally disubstituted terminal Olefin, in this particular case. The Ketene is generated, by deprotonation from this position, this Methyl group is deprotonated, for example, with Diisopropylethylamine.

It is a hindered Ketone, that is why, the terminal Hydrogen is being deprotonated, rather than the internal Hydrogen, from this Methylene group, for example. That produces, the Alpha Beta Unsaturated Ketone of this kind, which undergoes the 2+2 cycloaddition reaction. Here, the relative stereochemistry can be either Cis or Trans, with respect to the Methyl and the Hydrogen. This is formed, in this particular ratio, that is being shown in this slide.

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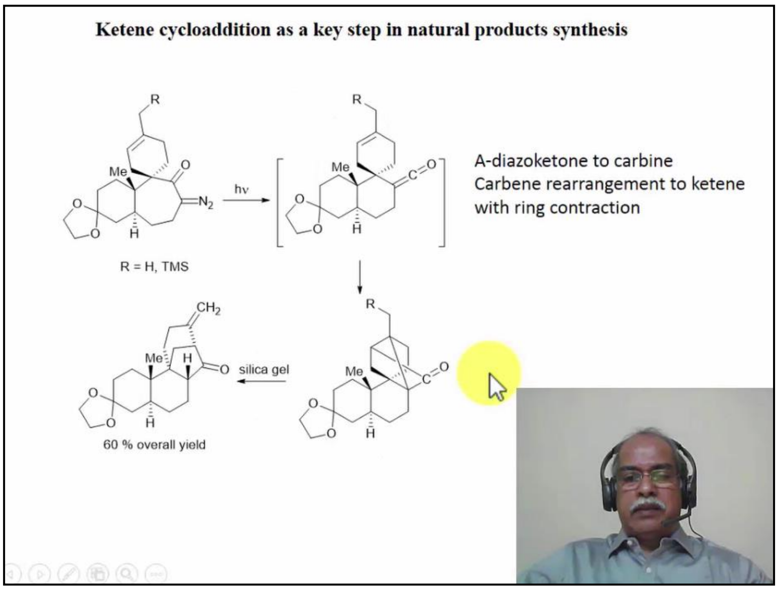

Ketene cycloaddition as a key step in natural products synthesis

A-diazoketone to carbine
Carbene rearrangement to ketene
with ring contraction

Finally, the Ketene cycloaddition as a key step for the natural products synthesis, is what is shown here. Ketene can also be generated, by another methodology. If you take an Alpha Diazo Ketone, Alpha Diazo Ketone can be generated, from the corresponding Diazo transfer reaction, from the Ketone, from Tosyl-Azide, for example. This is a reaction, that is fairly common in organic synthesis. You take a Ketone.

Generate the Enolate. And, treat it with Tosyl-Azide. The Diazo transfer reaction takes place, to give the Alpha Diazo Ketone. So, Alpha Diazo Ketones of this kind, are not difficult to generate. They are fair and easy to generate. What is important is that, when you fertilize this compound, it undergoes the loss of Nitrogen, and generates the corresponding Carbene, in this particular Carbon.

So, the Alpha Diazo Ketone generated, generates Carbene, not Carbine, for example. This is a spelling mistake here. This should be Carbene, and not Carbine. The Carbene, so generated, will undergo rearrangement, to give the Ketene by a ring contraction process. In other words, if you have a Carbene center in this particular Carbon, this Carbon-Carbon bond is broken, and it is migrated over here.

So, there is a ring contraction process, that takes place. With the concomitant generate, after the Ketene as the intermediate. And, such generated Ketene, so generated, undergoes intramolecular cycloaddition reaction, with this particular Olefin in a criss-cross manner, as it is shown here. And, this intermediate is not very stable, under silico gel condition. When it undergoes chromatography, a deprotonation, or the d-xylonation takes place, depending upon, whether it is a Xylyl derivative or the Methyl derivative.

The Xylyl derivative can easily lose, Trimethyl Xylyl cation, whereas the Methyl derivative can lose Proton, and result in the formation of rearrangement, to give this bicyclic, bridged bicyclic Ketone, from this bridged bicyclic Ketone, that is shown here. By the loss of Proton, from this elimination, from this particular molecule, with the concomitant rearrangement to give the, a bridged bicyclic derivative of this kind. So, what we have seen in this module, is the generation of Ketene, and the modes of cycloaddition of Ketene to Olefins and Alkenes.

And, in undergoing a 2+2 cycloaddition reaction of Ketene with the Olefin, it produces a Cyclobutanone. Whereas, with an alkane, it produces a Cyclobutene. When intramolecularly the reaction takes place, there are several modes by which, the Ketene cycloaddition reaction can take place. Stereo chemical information tells us, the Suprafacial component is the Alkene component, whereas the Antarafacial component is the Ketene component. And, with this, we will conclude this particular session. Thank you very much, for your kind attention.