Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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Recommended texts:

1. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

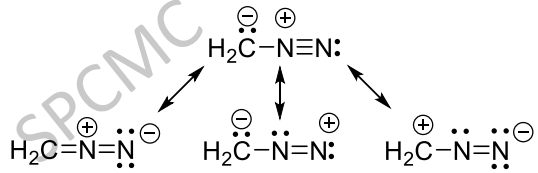
Organonitrogen Chemistry

Chemistry of diazomethane and diazoacetic ester:

Diazo compounds are defined as those that carry the azo group (N-N linkage) *at one terminal*.

In this section we would discuss about two aliphatic diazo compounds, diazomethane and ethyl diazoacetate.

Diazomethane, CH_2N_2, is a rather curious compound that has to be drawn as a dipole. There are several different ways of expressing its structure. Strictly speaking, diazomethane can be considered to be the resonance hybrid of several different canonical forms:

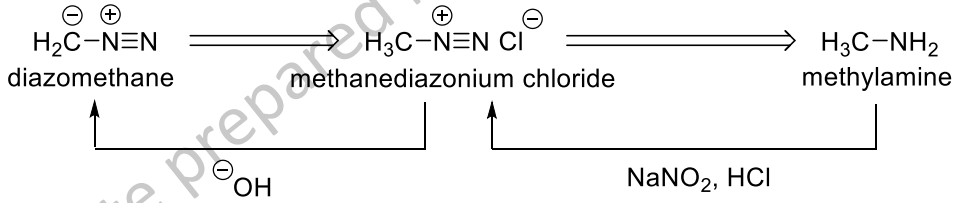


Although a dipole, contributions from all the canonical forms of diazomethane means that the dipole moment of the compound will be low (how do we infer that?).

Due to its low dipole moment (1.5 D) diazomethane is a yellow, poisonous gas with a boiling point of - 24 °C and is highly soluble in the non-polar ether solvent.

Since the ethereal solution of diazomethane is fairly safe to handle, it is prepared in ether and the reactions of diazomethane are usually carried out in ethereal solution.

Let us take a close look at the ways to prepare diazomethane. Conceptually we can propose the following retrosynthetic analysis:



Way out?

If we could carry out the diazotization of methylamine in alkaline condition, that would be ideal because as soon as the methanediazonium is produced there, hydroxide could pick off a proton from it.

Is that even possible?

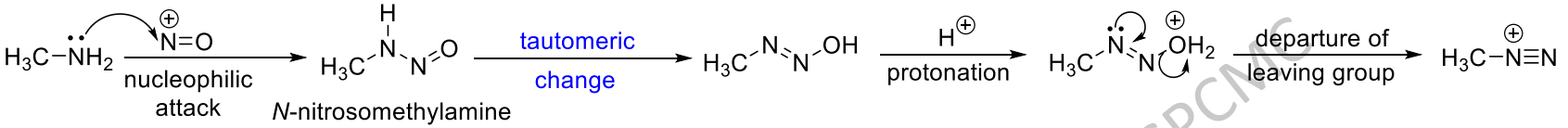
Recall that *diazotization requires acidic condition* and we know of no method which affects such a transformation in alkaline medium!

So we are in a bit of a fix.

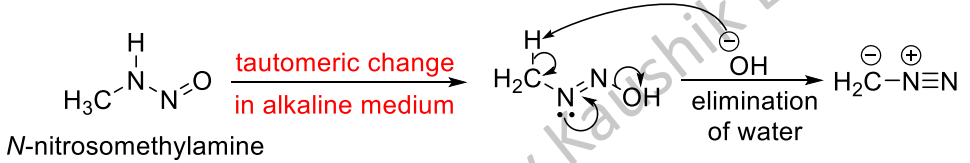
Organonitrogen Chemistry

Chemistry of diazomethane and diazoacetic ester: Synthesis of diazomethane

To solve this problem, let us proceed systematically and take a close look at the mechanistic steps of diazotization of methylamine:

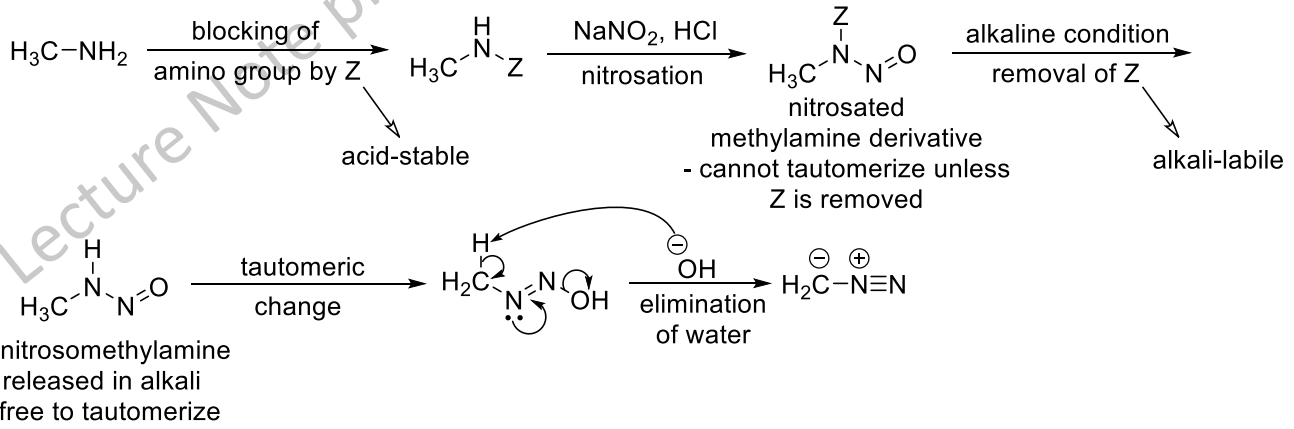


Looking at this mechanism, you should understand that if, after nitrosating methylamine in acid medium, we can somehow *arrest the tautomeric change*, then we will be able to obtain diazomethane by treating the resulting *N*-nitrosomethylamine with alkali. In alkaline medium the reaction is the expected to take the following course to yield diazomethane:



Therefore, to suppress the tautomeric change from occuring "prematurely", we have to block the "N-H" group of methylamine, i.e. we have to take a methylamine derivative where the offending H has been replaced by some group which is acid-stable so that we may be able to isolate the nitrosated methyalamine derivative.

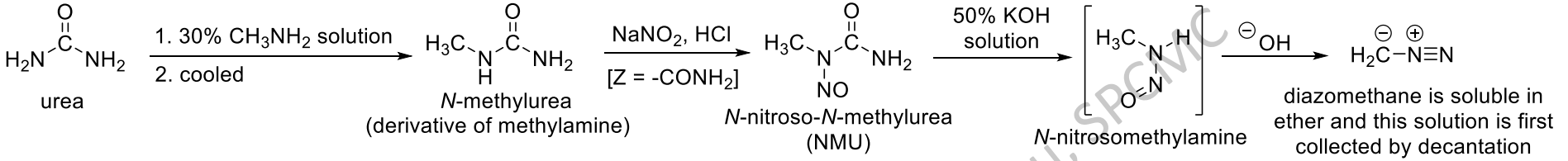
That same group, of course, has to be alkali-labile so that it gets removed easily when the nitrosated methylamine derivative is treated with alkali, releasing the *N*-nitrosomethylamine. This will now dutifully tautomerize in alkaline reaction medium and leads finally to our target diazomethane. Thus;



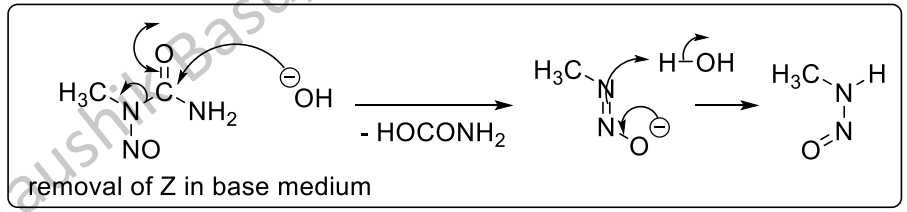
Organonitrogen Chemistry

Chemistry of diazomethane and diazoacetic ester: Synthesis of diazomethane

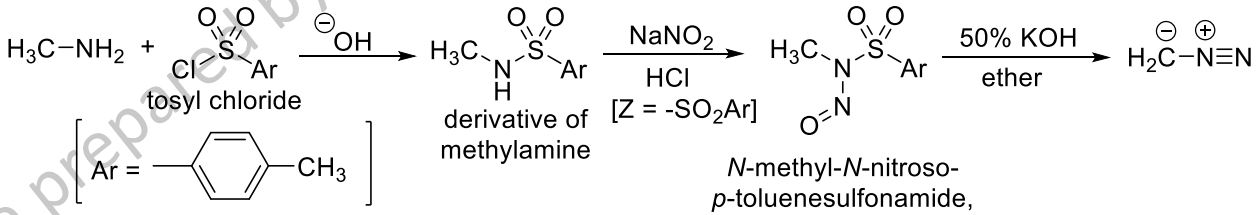
The success of diazomethane synthesis then depends upon the preparation of a suitable nitrosated methylamine derivative MeN(NO)Z, the diazomethane precursor where Z is a base-labile, acid-stable group. Following this principle, we have the classic method of diazomethane synthesis:

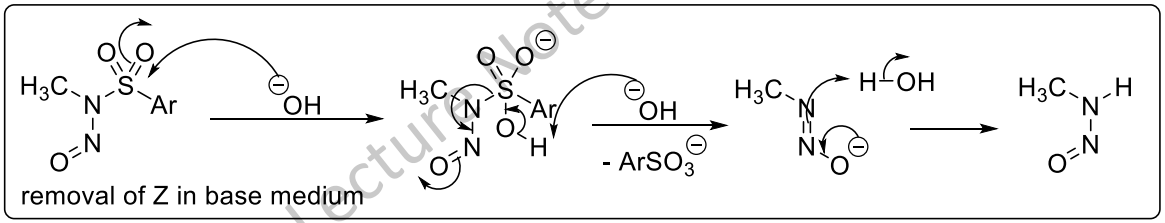


The yellow coloured solution of diazomethane is dried over anhydrous KOH and if necessary it can be distilled for further purification.

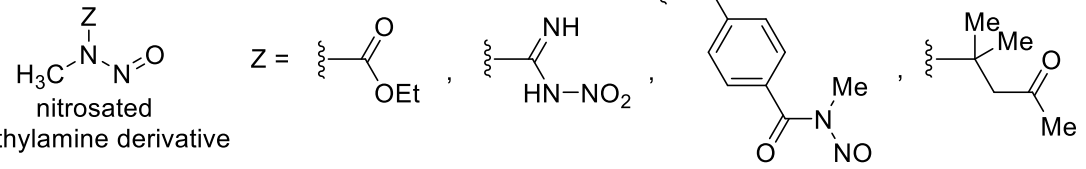


There is another method in which the amino group of methylamine is blocked via tosylation:





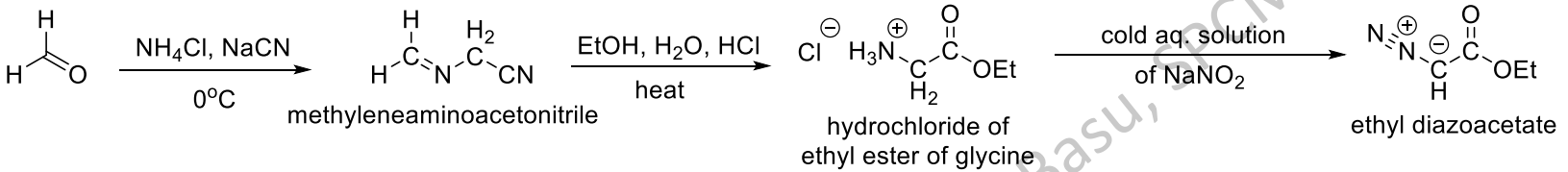
There exists a number of methods for diazomethane preparation that are based on this principle of isolating an *N*-nitrsomethylamine derivative and then subjecting it to further alkali treatment.



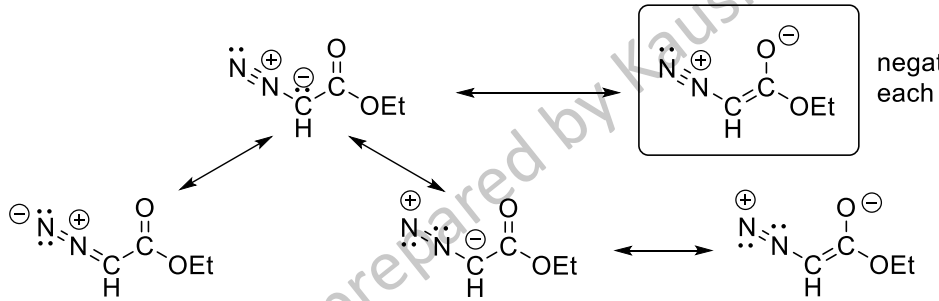
Chemistry of diazomethane and diazoacetic ester: Diazoacetic ester and its synthesis

The other important aliphatic diazo compound is ethyl diazoacetate which is often referred to the diazoacetic ester.

Diazoacetic ester, boiling point 141°C/720mm, may be readily prepared by treating a cold solution of the hydrochloride of ethyl ester of glycine with cold aqueous solution of sodium nitrite:



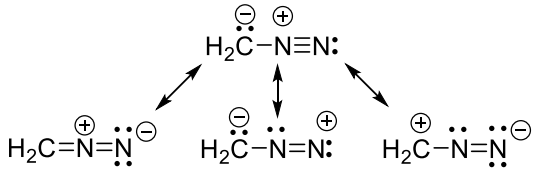
The stability of diazoacetic ester may be attributed to the extended conjugation with the participation of the ester functionality:



negative charge on electronegative O, each element has octet

$\chi_O > \chi_N > \chi_C$

Thus there will be a greater resonance energy than for diazomethane, and so the latter is less stable than diazoacetic ester.



Organonitrogen Chemistry

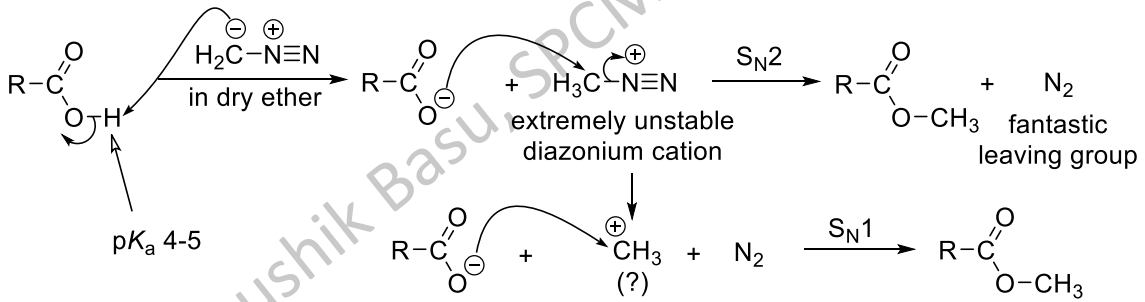
Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

A] Formation of methyl esters from carboxylic acids and methyl ethers from phenols and alcohols:

Diazomethane carries a carbon bearing a negative charge, so it is not difficult to imagine that it can act as a base, given a reaction partner that contains an acidic hydrogen.

Thus it reacts cleanly picks off the proton from a carboxylic acid. The reaction, however, does not stop there.

Protonated diazomethane is extremely reactive because it carries within it the super leaving group molecular nitrogen attached with an electrophilic carbon that offers least steric resistance to any nucleophilic attack.

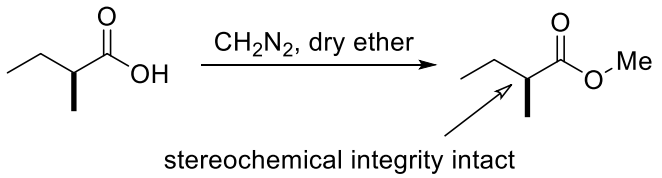


Even a weak nucleophile like carboxylate cannot let this opportunity to go by and substitutes the nitrogen cleanly, the result being the formation of a methyl ester.

The nucleofugality of nitrogen is so enormous in magnitude that some SN1 reaction pathway cannot be ruled out, even though the methyl carbocation formation is otherwise very unlikely.

This is one of the most convenient method for preparing methyl esters in laboratory scale. Industrial application of this technique is limited because diazomethane is rather difficult to prepare or handle in large quantities.

The method is particularly convenient for carboxylic acids that have a stereogenic chiral centre at the α-carbon because the other, common methods of esterification, such as conversion of the acid to an acid chloride and then treating that with an alcohol, may compromise the stereochemical integrity of the starting material.

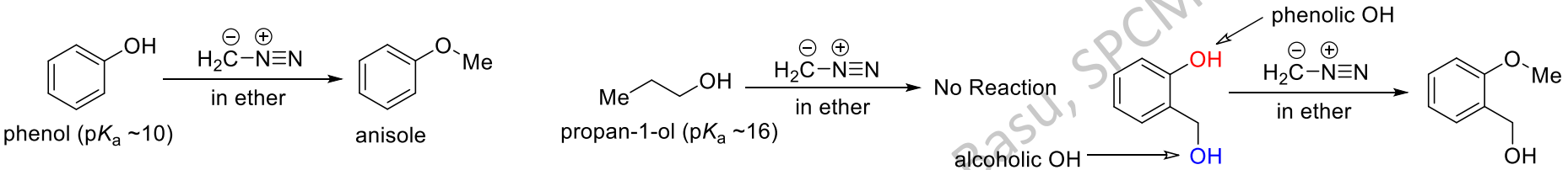


This methylation reaction also forms the basis of the method used to analyse the purity and to measure the quantity of a diazomethane sample. Diazomethane is titrated by adding a known quantity of benzoic acid to an aliquot of the solution such that the solution is colourless and excess benzoic acid remains. Water is then added, and the amount of benzoic acid remaining is back-titrated with a sodium hydroxide solution of known strength. The difference between the amount of acid added and the amount remaining reveals the amount of active diazomethane present in the aliquot.

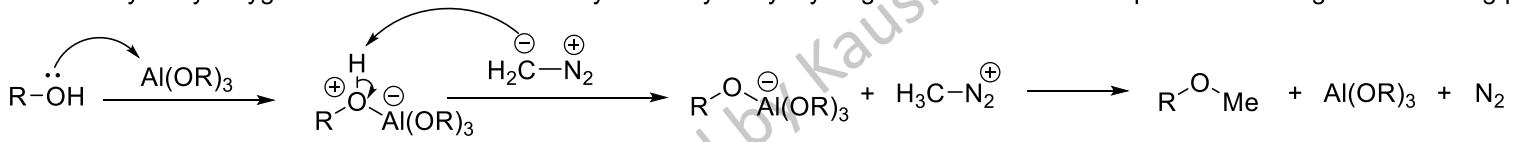
Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

A] Formation of methyl esters from carboxylic acids and methyl ethers from phenols and alcohols:

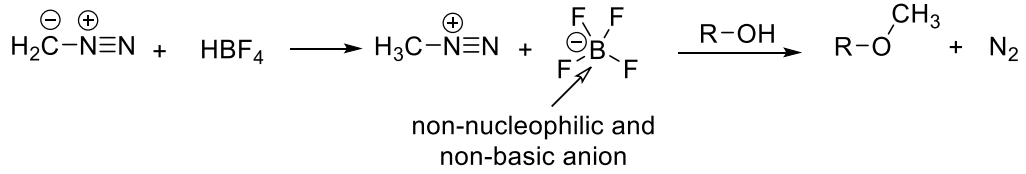
With a pK_a hovering in the range of 5, carboxylic acids are acidic enough to protonate diazomethane leading to a successful methylation. So are phenolic compounds with pK_a ca. 10, meaning they can also be methylated. But alcohols are not so acidic (pK_a ca. 16) and the methylation reaction with diazomethane is thus a failure there.



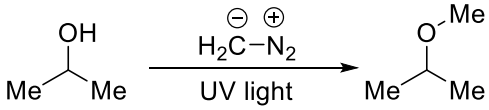
However, in presence of a suitable Lewis acid catalyst, e.g. an aluminum alkoxide, alcohols too, can be methylated with diazomethane. Here aluminum alkoxide coordinates with the hydroxyl oxygen and increases the acidity of the hydroxyl hydrogen. Thus the reaction proceeds through the following pathway:



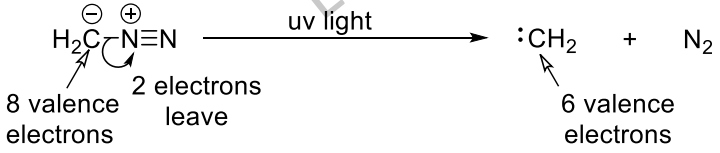
Fluoroboric acid is also a popular catalyst for the methylation of alcohols. Here the reaction proceeds through the protonation of diazomethane by fluoroboric acid in the following way:



Alcohols can also be methylated by diazomethane if the mixture is irradiated with UV light.



The mechanism is now totally different. Light energy promotes loss of nitrogen from diazomethane without protonation, thus generating a singlet methylene (carbene) species. With only six electrons on the carbon atom, this carbene can act as an electrophile.

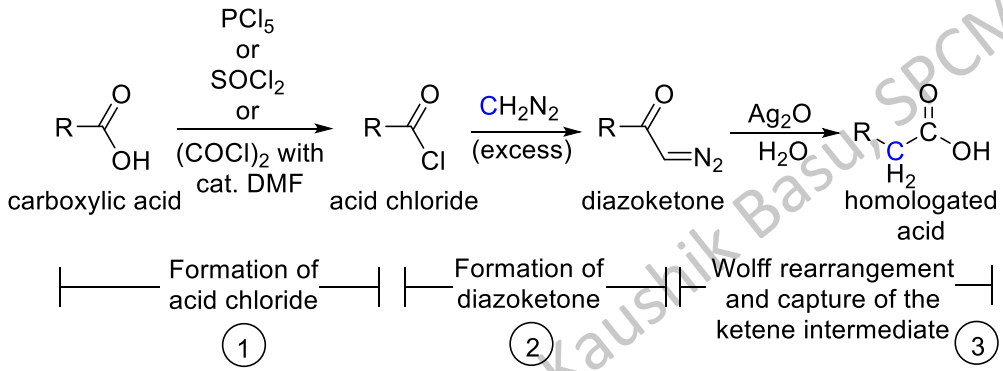


As we have just seen, this carbene is trapped by alcohols to form methyl ether, but more importantly, carbenes can also react with alkenes to form cyclopropane derivatives and also inserts into C-H bonds.

Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

B] Arndt-Eistert Homologation of carboxylic acid:

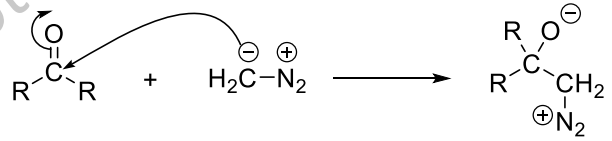
This one was exhaustively discussed earlier, so we get to see only the outline here. The reaction has three stages as shown below:



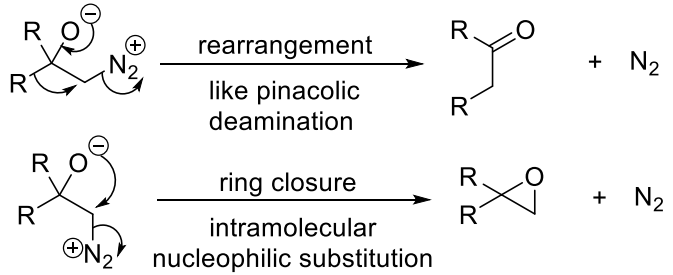
Make sure you thoroughly understand the mechanism of at least the last two steps. Also convince yourself why one would need to employ excess diazomethane in the second stage, and what could go wrong with the reaction if only one equivalent of diazomethane is used there.

C] Homologation of ketones using diazomethane:

Arndt-Eistert reaction uses diazomethane to homologate a carboxylic acid. Diazomethane is also useful for homologation of a ketone. When a ketone is treated with diazomethane, it undergoes a nucleophilic addition to form an intermediate analogous to that encountered in pinacolic deamination of β-amino alcohol:



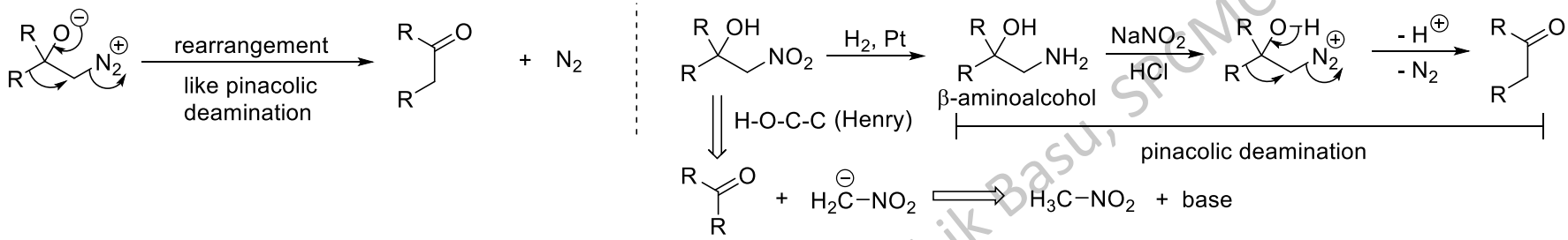
This intermediate may undergo either rearrangement to yield a higher homologue of the given ketone or it may participate in a ring-closure reaction that leads to an epoxide. These two pathways are competing in nature and often epoxidation may become the principal reaction.



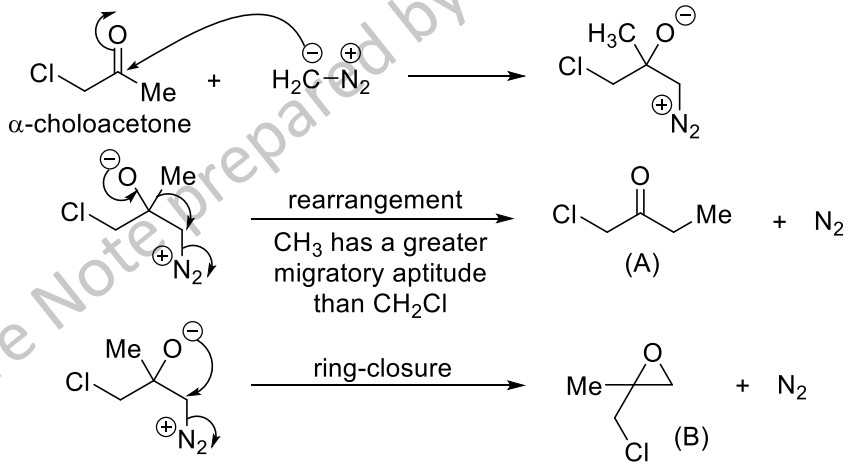
Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

C] Homologation of ketones using diazomethane (contd.):

The rearrangement is indeed like the pinacolic deamination of β-aminoalcohols as encountered in our discussions regarding pinacol-pinacolone rearrangement:



Also note that the epoxide and the homologated ketone are isomeric as they have the same molecular formula. In a similar token:

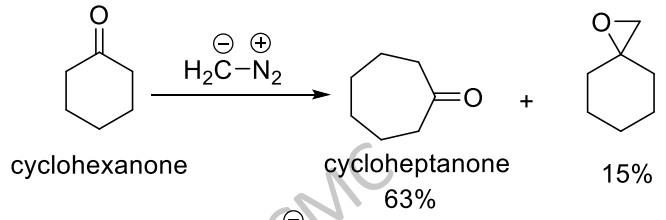


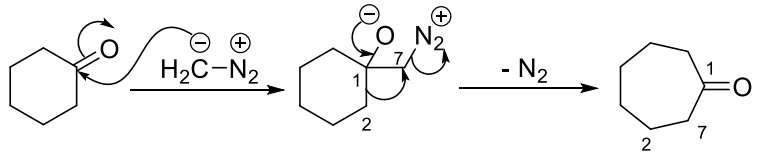
As expected, the ketone (A) and epoxide (B) are isomers with molecular formula C_4H_7OCl. The methyl group has a greater migratory aptitude than the chloromethyl unit here because it is, after all, a migration to an electron-deficient carbon centre and the better electron-releaser will be more welcome there.

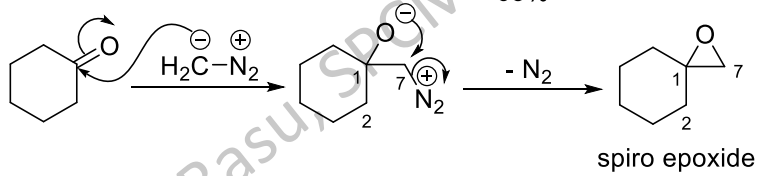
Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

C] Homologation of ketones using diazomethane (contd.):

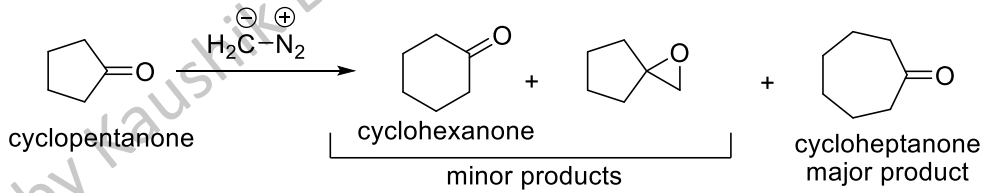
This process of homolaogation is also used for the expansion of cycloalkanone rings. Let us consider the following examples:



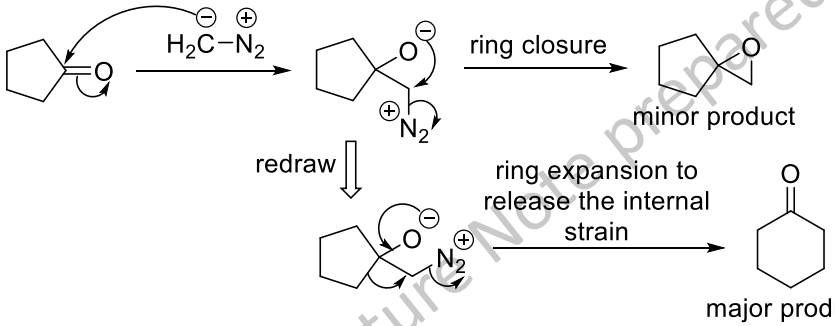




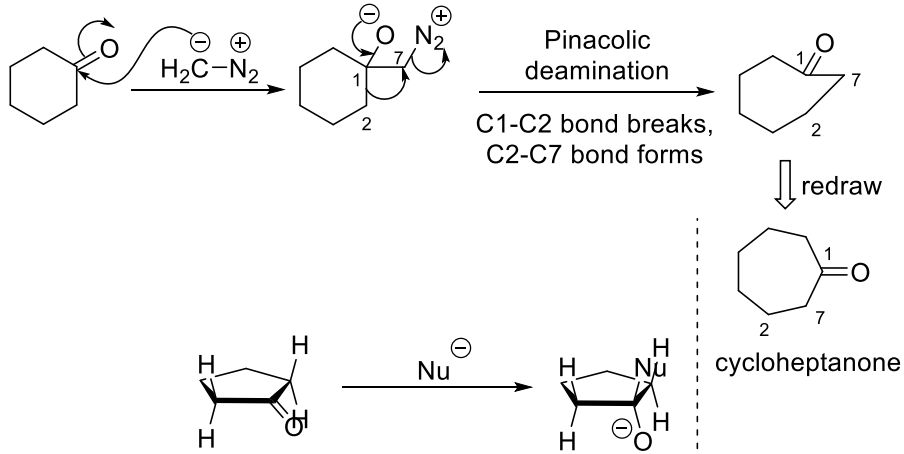
On the other hand, the same reaction on cyclopentanone offers a curious result:



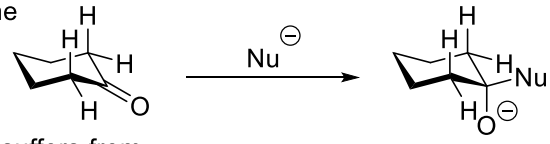
The epoxide and cyclohexanone are formed in the following way:



The major product cyclohexanone is more reactive than the reactant cyclopentanone towards nucleophilic addition. So the reaction proceeds further.



The explanation of higher reactivity of cyclohexanone than cyclopentanone towards nucleophiles:



TS for addition experiences relief of strain

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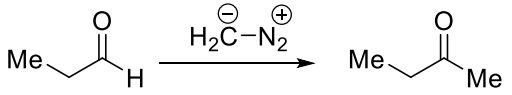
Organonitrogen Chemistry

Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

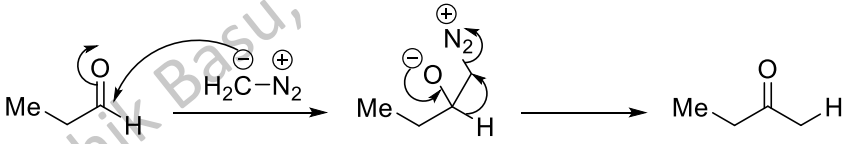
C] Homologation of ketones using diazomethane (contd.):

Diazomethane reacts with aldehydes to form methyl ketones. Thus;



propanal 2-butanone

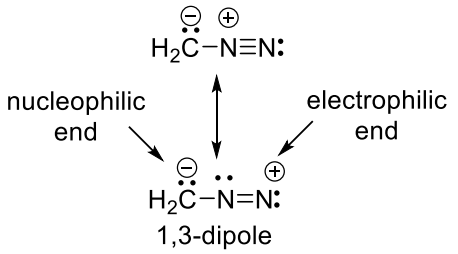
The reaction starts off with the usual a nucleophilic attack by diazomethane on the carbonyl group of the aldehyde. A [1,2]-H shift then takes place to generate the ketone. Recall from Pinacol-Pinacolone rearrangement that hydrogen generally has a greater migratory aptitude than alkyls.



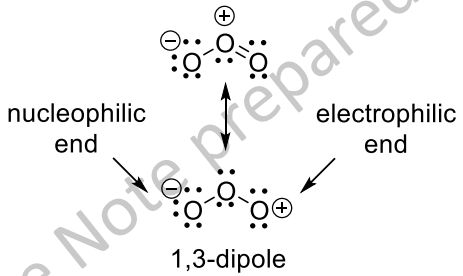
propanal butanone

D] Cycloaddition reactions of diazomethane and diazoacetic ester: Construction of Heterocyclic compounds:

Diazomethane is, like ozone, a 1,3-dipole, as evident from the following canonical structures:



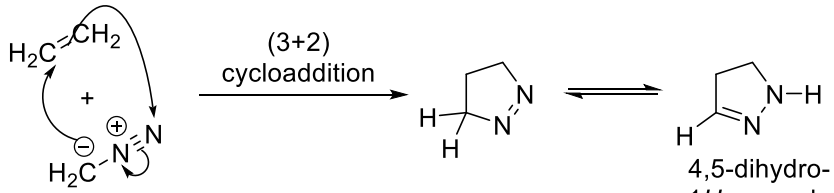
1,3-dipole



1,3-dipole

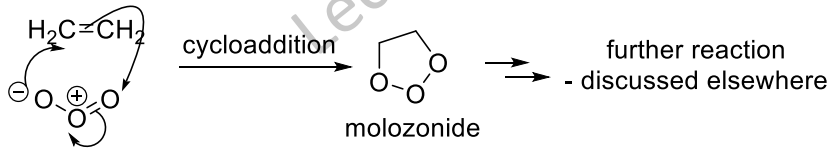
number of atoms form one component ⟵ (3+2) ⟶ number of atoms form the other component ⟹ five-membered ring

Therefore, like ozone, it adds to ethylenic compounds to form pyrazoline derivatives; with ethylene, pyrazoline is formed.



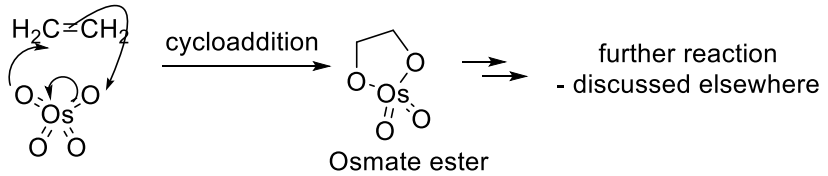
4,5-dihydro-1*H*-pyrazole

Compare this with the addition of another 1,3-dipole ozone to ethylene:



molozonide

Or with the first step of the osmimum tetroxide-mediated *syn*-dihydroxylation of alkenes (Upjohn dihydroxylation):



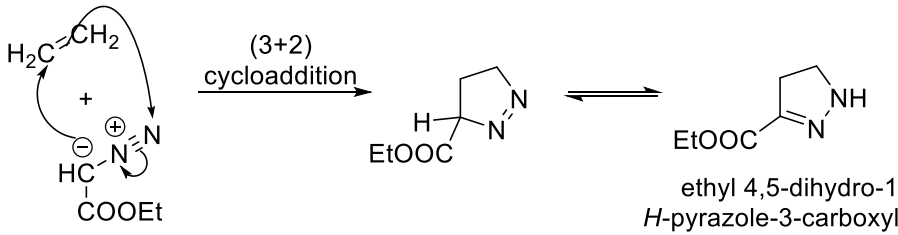
Osmate ester

Organonitrogen Chemistry

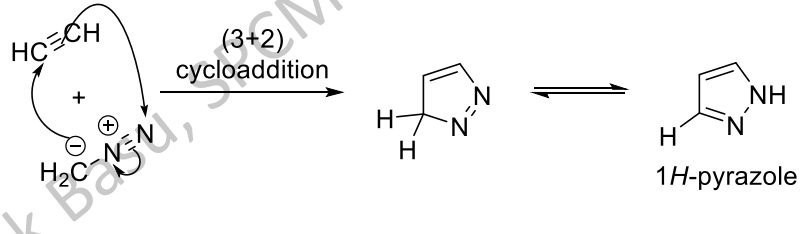
Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

D] Cycloaddition reactions of diazomethane and diazoacetic ester:
Construction of Heterocyclic compounds (contd.):

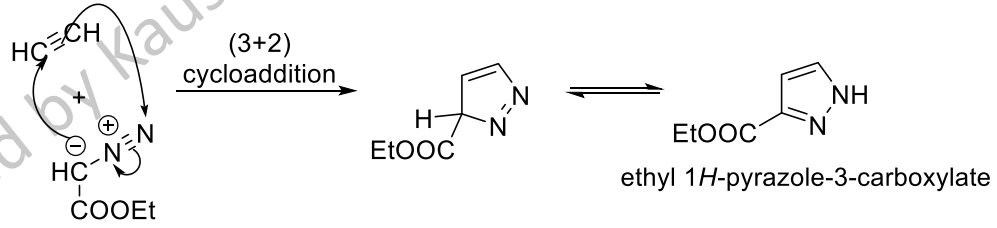
Similarly, diazoacetic ester reacts with ethylenic compounds to form pyrazoline derivatives, e.g. with ethylene it forms pyrazoline-3-carboxylic ester:



like



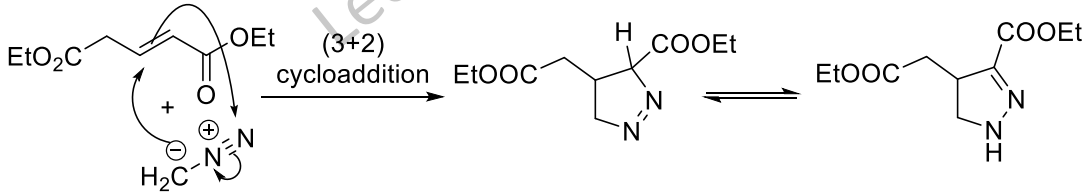
Similarly, diazoacetic ester adds to acetylenic compounds, e.g. with acetylene it gives pyrazole-3-carboxylic ester:



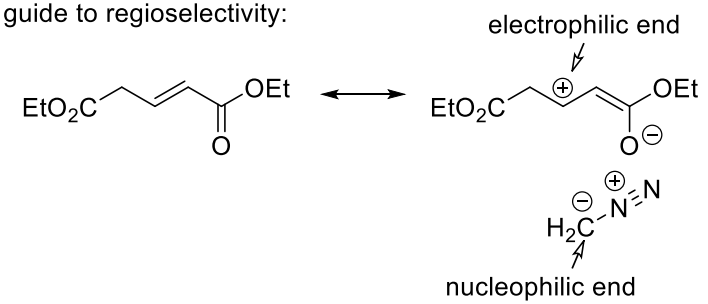
The common pattern of additions such as these involves a molecule containing three atoms in a chain with its terminal atoms carrying a positive and a negative charge (the 1,3-dipole component) and a molecule containing a multiple bond (a dipolarophile component, like the dieneophile as seen in the Diels-Alder Reaction)

Like the Diels-Alder cycloadditon reactions, these are also pericyclic in nature and are referred to as 1,3-dipolar cycloadditions (Huisgen cycloaddition or (3+2) cycloaddition, counting the number of atoms of each component that get involved in formation of the five-membered ring).

The addition of diazoalkanes is regioselectivein appropriate cases:



guide to regioselectivity:

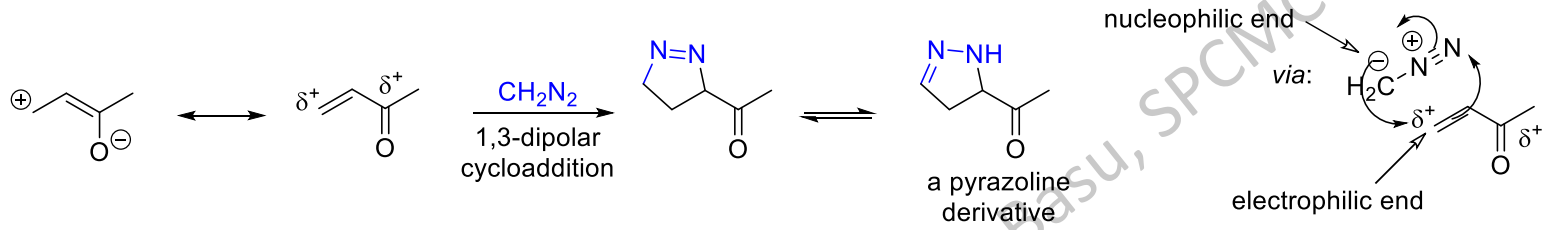


Organonitrogen Chemistry

Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

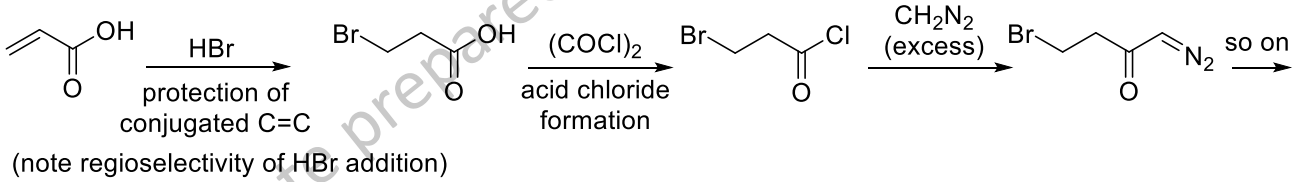
D] Cycloaddition reactions of diazomethane and diazoacetic ester: Construction of Heterocyclic compounds (contd.):

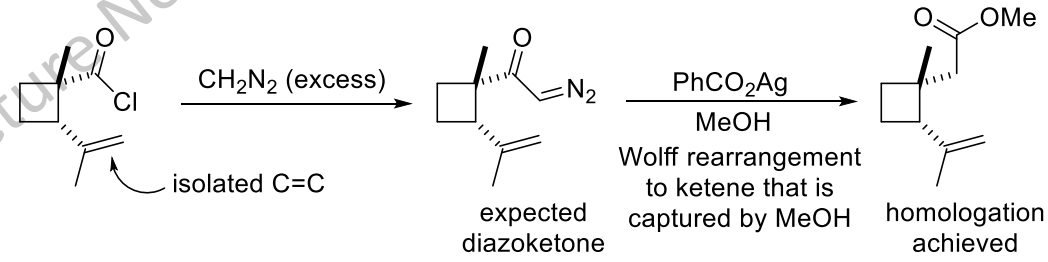
A curious example is the addition of diazomethane to an α,β-unsatutrated ketone such as methyl vinyl ketone. There are two electrophilic sites in this substrate and the diazomethane's nucleophilic end may attack either the carbonyl carbon leading to a homologation or the β-carbon leading to an 1,3-dipolar cyloaddition. In reality, the latter outcome is found:



The cycloaddition is regioselective, the negative end of the 1,3-dipole choses the remote β-carbon, and not the α-carbon. From the unsaturated ketone's point of view, this selectivity is akin to the Markovnikov addition where the negative part of the addendum goes to the electrophilic β-carbon.

Diazomethane has high affinity to undergo 1,3-dipolar cycloaddition with olefenic double bonds conjugated to an electron-withdrawing group. Thus when the Arndt-Eistert synthesis is attempted on α,β-unsaturated acid chlorides, cycloaddition to the alkene is observed in the product. In order to prevent this, the alkene must first be protected by addition of HBr and then the reaction carried out in the normal way. Cycloaddition to isolated alkenes, however, is not competitive with addition to acid chlorides. The following examples are illustrative.





Did you notice the retention of configuration of the migrating group in the second example? Considering the intramolecular nature of the rearrangement step, this is what is expected.

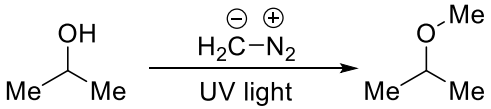
Organonitrogen Chemistry

Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

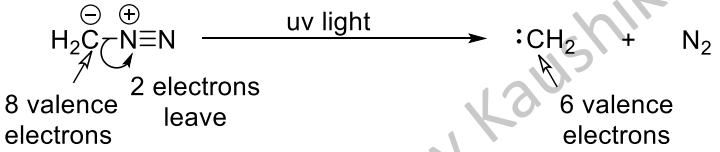
E] Photochemical reactions of diazomethane and diazoacetic ester:

Recall that, unlike carboxylic acids and phenols, alcohols are not acidic enough (pK_a 16) to get methylated by diazomethane.

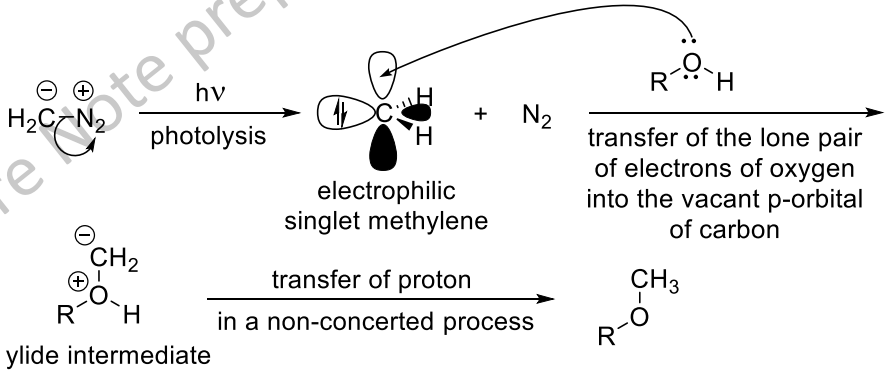
However, methylation does happen if the mixture of alcohol and diazomethane is irradiated with UV light.



The mechanism is different from what we have seen so far. Photochemical activation promotes loss of nitrogen from diazomethane which forms initially a singlet carbene:



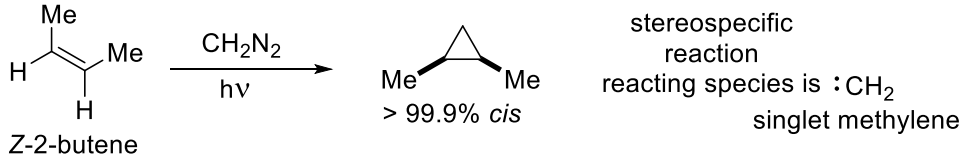
This carbene possesses an empty *p*-orbital on carbon and is electrophilic in nature. It accepts the oxygen lone pair promptly in that vacant orbital and an ylide intermediate is generated. Subsequent proton transfer, which probably occurs in some non-concerted pathway, completes the methylation sequence:



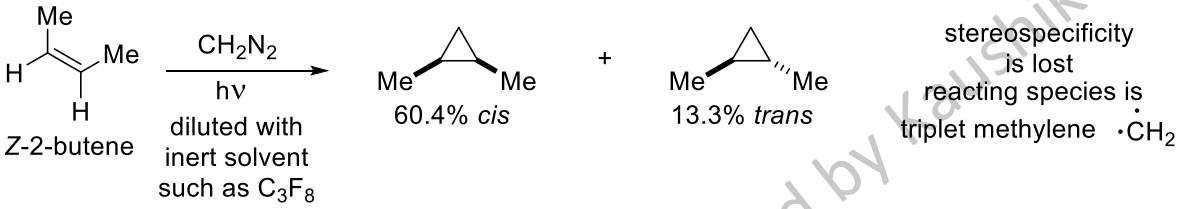
Chemistry of diazomethane and diazoacetic ester: Reactions of diazomethane

E] Photochemical reactions of diazomethane and diazoacetic ester (contd.):

Similar to this trapping of carbenes by alcohols, alkenes also react with carbenes to afford cyclopropane derivatives. Carbene also insert into C-H bonds. We have dealt with all these reactions when we talked about the chemistry of carbenes. Here is a summary of the stereospecific nature of the addition reaction to alkenes and the subsequent loss of stereospecificity when the singlet carbene gets an opportunity to turn over to the triplet and then react:



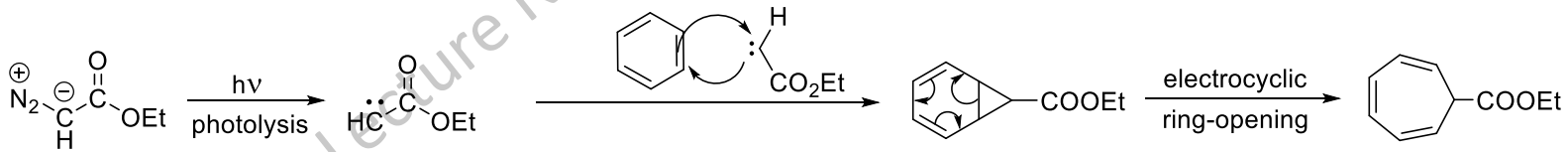
Make sure you can explain this outcome and familiarise yourself with the related mechanisms.



Buchner ring expansion: accessing 7-membered rings:

E. Buchner
(1860-1917)

Just like the photolysis of diazomethane, in some of its reactions, the diazoacetic ester also undergo photolytic decomposition to yield :CHCOOEt, carbethoxy methylene. Presence of an electron-withdrawing group adjacent to the carbene carbon endows it with very high electrophilic nature, for which it can react with even benzene, destroying the latter's aromaticity:



ethyl cyclohepta-2,4,6-triene-1-carboxylate

The product is not stable, and immediately undergoes an electrocyclic ring opening to release the ring strain as shown above. Recall that carbenes having substituents bearing lone pairs adjacent to the carbene carbon atom are stabilized through resonance and thereby much less electrophilic in nature. Conversely, carbenes substituted with electron-withdrawing groups such carbonyls are expected to be more powerful electrophiles than carbenes like $:CCl_2$ or $:C(OMe)_2$. This is actually the case.