INTER- AND INTRAMOLECULAR REACTIONS OF DIALKOXYCARBENES

By

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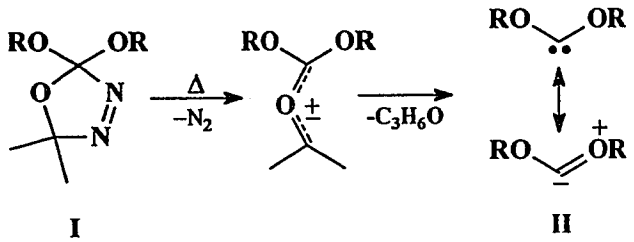
Abstract

This dissertation involved a study of the mechanistic and synthetic potential of nucleophilic carbenes in solution. More specifically, it deals with the inter- and intramolecular reactions of dialkoxycarbenes generated thermally from oxadiazoline precursors.

Dialkoxy oxadiazolines (**I**) decompose thermally via loss of N_2 and acetone to afford dialkoxycarbenes (**II**) (Scheme I). Dialkoxycarbenes are singlet carbenes which possess nucleophilic character because of heteroatom electron donation into the vacant *p*-orbital of carbon. This is best illustrated by writing the dipolar resonance contributor (**II**) with formal negative charge at the carbene carbon and formal positive charge on oxygen. This special property of dialkoxycarbenes allows them to take part in a wide variety of chemical reactions including fragmentations, and inter- and intramolecular additions.

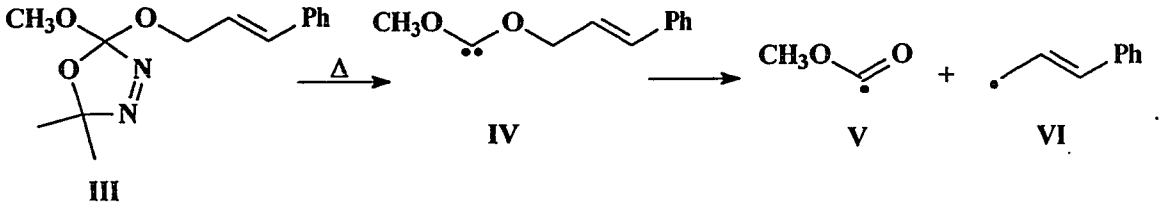


I **II**

Scheme I

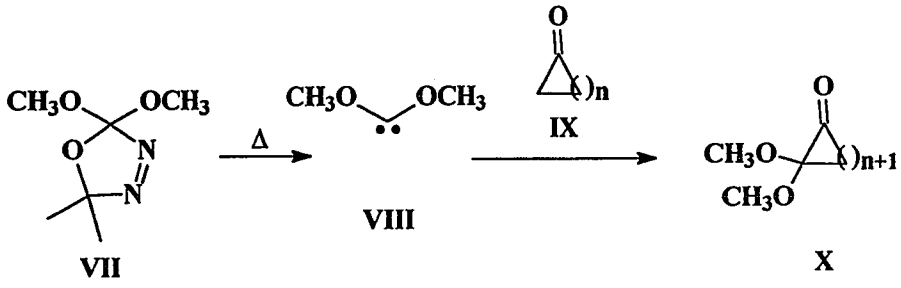
The first section of the dissertation describes the first example of a dialkoxycarbene fragmentation to radical pairs in solution in which both the carbene and the radicals could be trapped. Thermolysis of cinnamyloxymethoxy oxadiazoline (**III**)

afforded the corresponding dialkoxycarbene (**IV**) which fragmented to methoxycarbonyl radical (**V**) and phenylallyl radical (**VI**) (Scheme II).



Scheme II

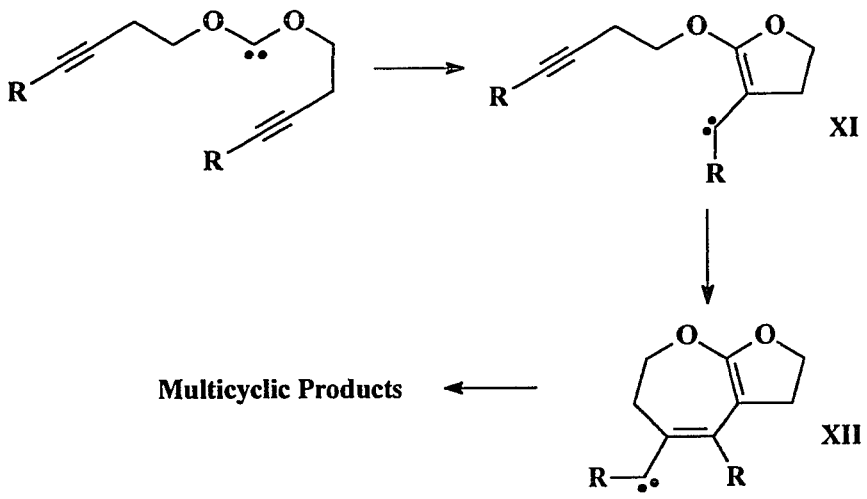
The second section describes the use of dimethoxycarbene as a convenient synthetic tool for the ring expansion of strained cyclic carbonyl compounds. Thermolysis of dimethoxy oxadiazoline (**VII**) afforded dimethoxycarbene (**VIII**), which in the presence of carbonyl compounds (**IX**) yielded products (**X**) of formal carbene insertion in-between the carbonyl group and the *alpha* carbon atom (Scheme III). In unsymmetrical carbonyl-containing compounds, carbene insertion was selective, favouring insertion in-between the carbonyl group and the most electron-rich *alpha* carbon.



Scheme III

The final section highlights advances in the area of intramolecular dialkoxycarbene additions to alkynes. In particular, a preliminary investigation into the area of tandem carbene cyclizations is discussed. This work involved the synthesis and thermolysis of dialkoxy oxadiazolines containing two tethered alkyne units. It was

envisioned that intramolecular carbene addition to one alkyne unit would afford a vinyl carbene (**XI**) which could add to a second alkyne tether to yield a second vinyl carbene (**XII**) (Scheme IV). This methodology has the potential for synthesis of multicyclic systems in a one-pot reaction.



Scheme IV

Acknowledgments

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Table of Contents

List of Figures

Chapter 1 - Introduction

Chemical reactions proceeding from A to B can either be concerted, occurring in a single step, or non-concerted, occurring in more than one step. In most examples, the transformation proceeds in a non-concerted way, via a reactive intermediate (X), according to the following schematic equation.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X \xrightarrow{k_2} B$$

This general conversion of A to B, involving a single intermediate X, can be summarized in a free energy vs reaction coordinate diagram. The reaction coordinate diagram shown in Figure 1 (I) illustrates the example when $k_2 > k_{-1}$. Two transition states, defined by local maxima, and an intermediate (X), defined by a local minimum, represented by a shallow dip on the reaction coordinate surface are depicted. If an intermediate is not present, as in the case of a concerted reaction (Figure 1 (II)), the enthalpy and free energy continuously increase until a maximum is reached, the transition state, and then decrease until a stable structural conformation is achieved.

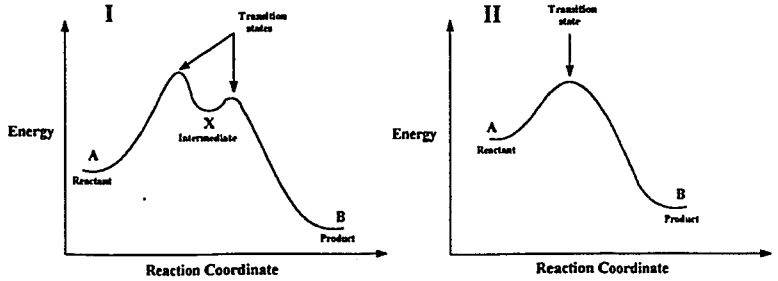


Figure 1

Many reactions in organic chemistry involve reactive intermediates.[1-4] Usually these involve species such as carbanions, carbocations, and radicals, but there also exists a class that is divalent and electron deficient. These reactive intermediates are known as carbenes.[5-8]

1.1 - Electronic Configuration of Carbenes

Carbenes are generally thought as being approximately sp^2 hybridized with four bonding electrons and two non-bonding electrons at the central carbon atom. Depending on the arrangement of these two non-bonding electrons, the carbene can exist as a singlet or a triplet. In the singlet electronic configuration there are two paired electrons occupying an in plane sp^2-orbital (σ-orbital) with a vacant higher energy p-orbital. In the triplet state there is one electron in the σ-orbital and the other in the p-orbital, with parallel spins (Figure 2).

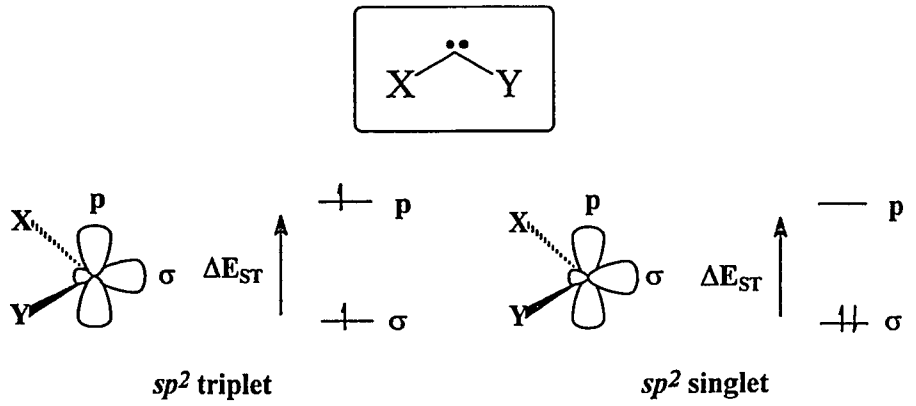


Figure 2

Singlet-triplet ground state multiplicity depends directly on the energy difference between the carbene σ-orbital and the carbene p-orbital, denoted ΔE_{ST}. In the singlet carbene, the energy separation between these two states has to be larger than the electron

correlation energy, defined as the energy required to bring two electrons together in a single orbital. Therefore, if ΔE_{ST} is smaller than the electron correlation energy, the carbene will have a triplet ground state. In terms of reactivity, singlets and triplets behave quite distinctly. Singlets behave more like charged species, whereas triplet carbenes behave like diradicals and can be detected by esr spectroscopy. In general, the substituent bond angle is also very characteristic. Singlet carbenes tend to have bond angles between 100 and 110°, whereas triplet carbene angles are between 130 and 180°.

Carbene spin state multiplicities are dramatically affected by altering the substituents next to the carbenic carbon. For example, as substituents change from H, in the simplest of carbenes, to O and N, in dioxy- and diaminocarbenes, ΔE_{ST} changes considerably (Figure 3).[9,10] Not only do substituents affect the carbene spin state multiplicity, but also the thermodynamic stability and relative reactivity in chemical reactions. A wide variety of carbenes has been studied and observed and a range of reactivities has been reported. Literature examples depict carbenes that are highly reactive, as is the case of methylene, as well as isolable diaminocarbenes,[11-17] some of which are shelf stable.

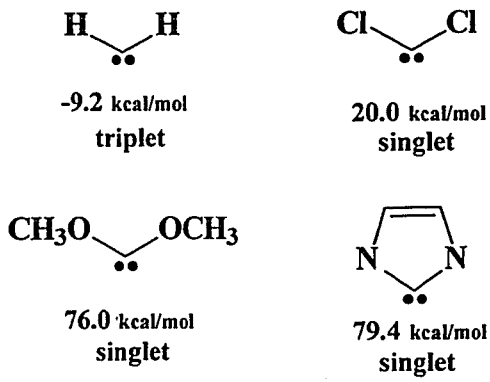


Figure 3

A knowledge of the ground state multiplicity, the singlet-triplet splitting (ΔE_{ST}), and the effect of substituents, is of utmost importance in understanding the chemistry of carbenes. Many groups have invested much time and effort into determining the singlet triplet splitting in a wide variety of carbenes with various substituents both experimentally[18,19] and computationally.[20-25] Recently, increased accuracy from *ab-initio* calculations has led to much more accurate values for ΔE_{ST} than those available in years past.[26-34]

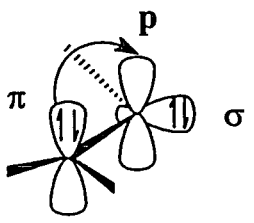
1.1.1 - Current Explanations for Observed Trends in Singlet-Triplet Gaps

The first explanation for observed trends in singlet-triplet gaps of carbenes states that ΔE_{ST} is largely affected by substituents with electron-withdrawing power.[35,23] In this case, the argument is that electron withdrawing substituents increase the s-character of the non-bonding σ-orbital by inductive effects. This hybridization change leads to an increase in the singlet triplet splitting (ΔE_{ST}). From a similar perspective, other groups have stated that electronegative groups remove charge from the carbenic carbon, leading to an increased positive charge. This increased positive charge stabilizes the *s* orbital with respect to the *p* orbital and therefore the singlet is more stabilized than the triplet.

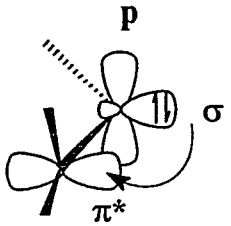
Another literature report stated that a carbene carbon atom is easier to ionize from a 2*p* orbital than it is from a 2*s* orbital.[36] Singlet carbenes, because of their smaller bond angles with respect to triplet carbenes, have more carbon *p*-character which affords stronger ionic bonds and therefore stabilization of the singlet.[36] This type of stabilization is favoured with more electronegative substituents, resulting in a larger singlet-triplet splitting the more electronegative X and Y. The reverse is true with electropositive substituents where the triplet is heavily favoured over the singlet.

A more popular explanation for the observed trends in singlet-triplet splitting is the idea of π donor substituents.[10,22,23,37] In this theory, a relatively high-lying π-orbital of a substituent mixes with the carbene *p*-orbital (Figure 4). This electron donation from the substituent to the carbene site will stabilize the singlet much more than the triplet state, since two π-donor electrons are stabilized in the process. The triplet will be stabilized to a lesser extent because of the counteractive presence of one π-electron in the carbene *p*-orbital.

Depending on the geometry of the carbene, π-acceptors can also influence the energy difference between the singlet and triplet state.[37] If the π-accepting orbital is in-line with the *p*-orbital of the carbene, it can only stabilize the triplet state. However, if rotation occurs to allow overlap with the σ-orbital, greater stabilization of the singlet state arises (Figure 4). This can be rationalized in terms of a two-electron interaction of the σ-orbital and the in-plane π^* acceptor orbital for stabilization of the singlet, whereas the one-electron interaction, in the case of the triplet, is less stabilizing.



Interaction of a π-donor with a carbene p-orbital



Interaction of an in-plane π-acceptor with a carbene σ-orbital

Figure 4

Recently, Goddard and co-workers have reported that both charge at the carbenic carbon and π-donation are contributing factors to the determination of ground state spin

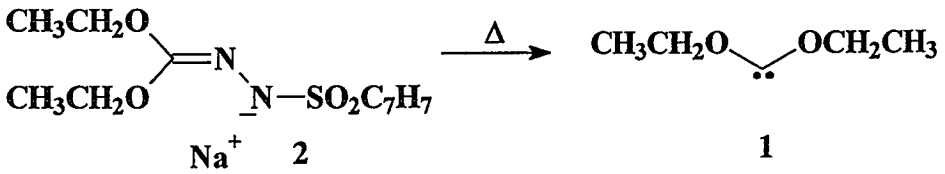
multiplicity.[20] This result was rationalized in terms of electron density withdrawal from the carbene carbon, by electronegative substituents, making it more positively charged. At the same time, this increase in positive charge at the carbene carbon makes it a better π-acceptor, resulting in enhanced π-donation from the substituent.

A similar result was reported by Moss in his study of substituent effects in carbene cyclopropanation reactions. He found that singlet selectivity was augmented by increasing both inductive electron withdrawal and $p\pi$-electron donation of substituents next to the carbene center.[38]

1.2 - Methods of Generating Dialkoxycarbenes

1.2.1 - Thermal Dissociation of Sulfonylhydrazones

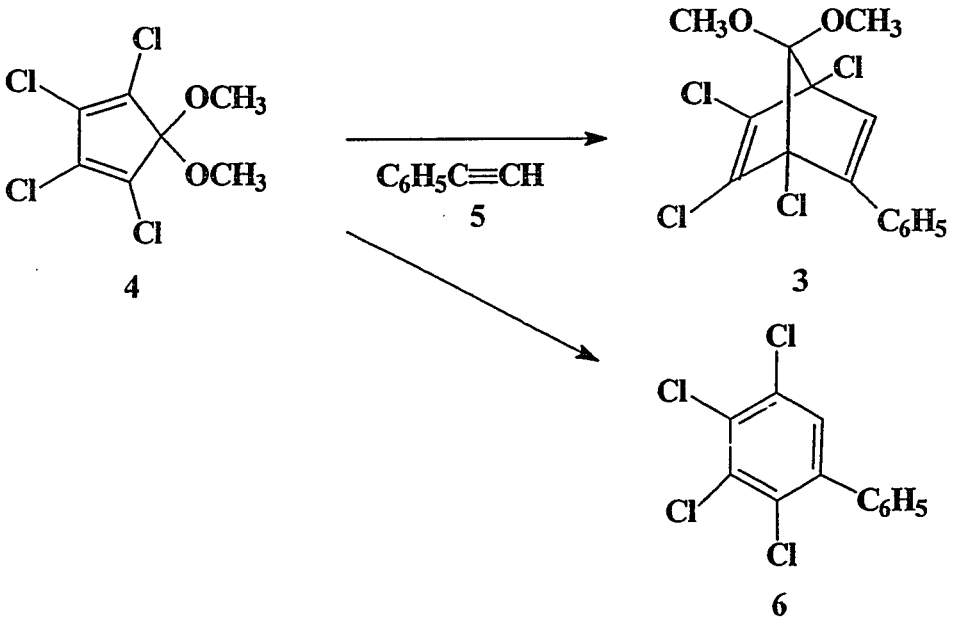
The first experimental finding that provided conclusive evidence for the presence of dialkoxycarbenes was introduced in a paper by Crawford and Raap.[39] Diethoxycarbene (**1**) was generated by thermal dissociation of a sulfonylhydrazone salt (**2**) (Scheme 1). Earlier investigations of these elusive species had been reported, however the intermediates were only presumed.[40-42]



Scheme 1

1.2.2 - Thermolysis of Norbornadienone Ketals

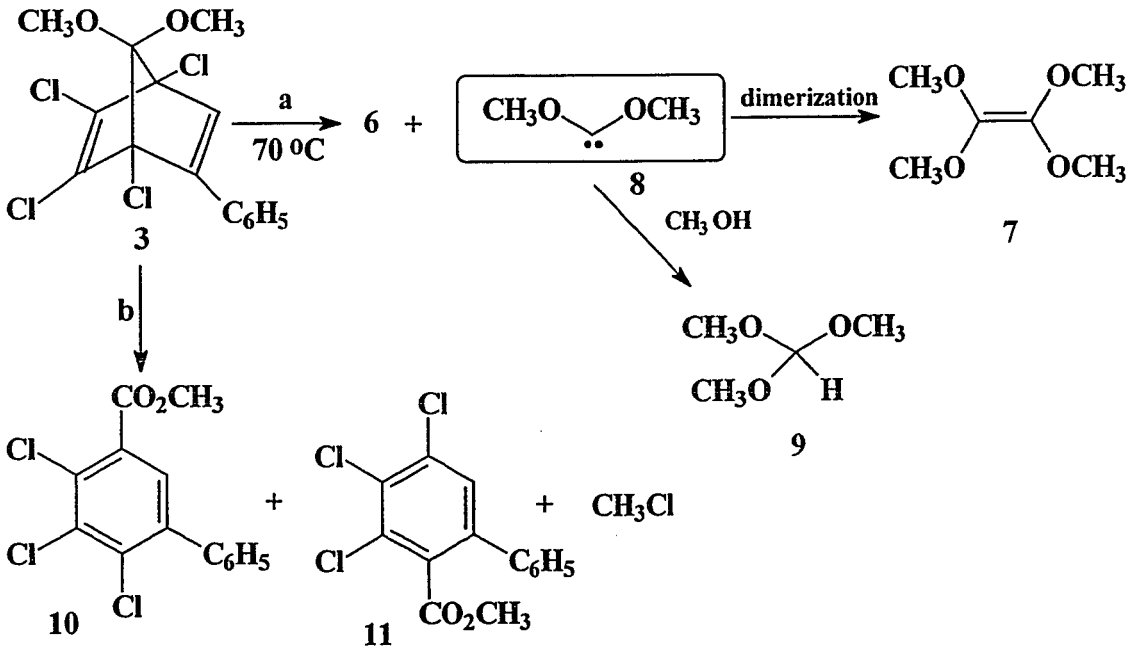
It wasn't until the work of Hoffmann and Lemal that a more convenient dialkoxycarbene source was established. In 1964, both Hoffmann[43] and Lemal[44] published papers on the synthesis and thermal chemistry of substituted norbornadienone ketals (**3**). Both groups were reinvestigating the Diels-Alder reaction of cyclopentadiene (**4**) and phenylacetylene (**5**). McBee was the first to study this reaction in an attempt to isolate norbornadienone ketal **3**, but this initial endeavor did not lead to **3** but to **6** (Scheme 2).[45,46]



Scheme 2

Hoffmann and Lemal realized that the reaction conditions that McBee was using were too harsh to sustain **3** as an isolable compound. Reflux temperatures around 70 °C were necessary for the isolation of species **3**, whereas temperatures between 100 and 150 °C led to production of **6** along with tetramethoxyethylene (**7**) as a coproduct. The production of tetramethoxyethylene (**7**) (path a) was attributed to the dimerization of

dimethoxycarbene (**8**) and was convincing evidence for a cycloreversion reaction leading to a dialkoxycarbene (**8**), depicted in Scheme 3. McBee's paper points out the isolation of **6**, but has no mention of the production of **7**. Both Hoffmann and Lemal studied the thermolysis of **3** in the presence of methanol and found a product of carbene insertion (**9**), a further indicator of a dimethoxycarbene intermediate.[43,47]

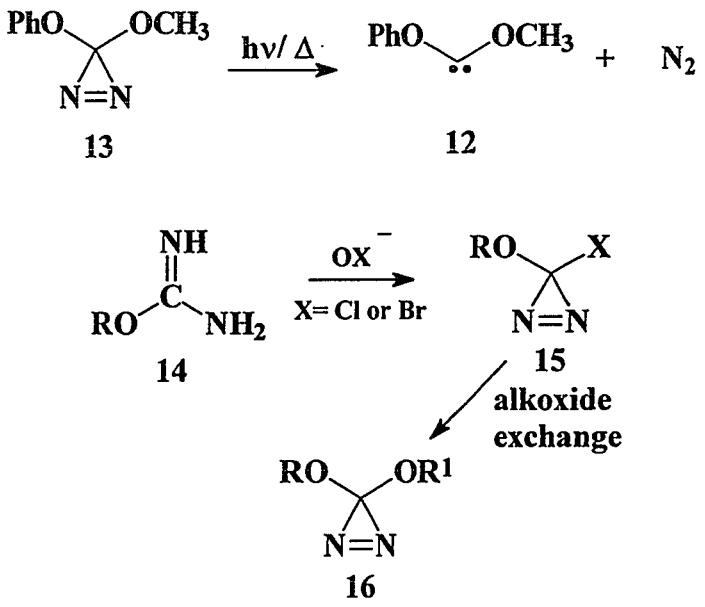


Scheme 3

It should be noted that the decomposition of norbornadienone ketal (**3**) to give dimethoxycarbene (**8**) and **6** competes with a side reaction (path b) to produce two non-cycloreversion aromatic products (**10** and **11**). This side reaction can be controlled, to some extent, by the use of non-polar solvents (Scheme 3). Although this method was the main source of dialkoxycarbenes for years to come, the approach was hindered by the production of many side products, mainly the high boiling compounds **6**, **10**, and **11**, complicating the analysis and isolation of carbene derived products.

1.2.3 - Decomposition of Diazirines

A new breakthrough in the preparation of dialkoxycarbenes was published in 1987 by Moss and coworkers.[48] The paper reports generation of methoxyphenoxycarbene (**12**) from a diazirine precursor (**13**) (Scheme 4). The carbene was generated by a photochemical or thermal elimination of N_2 to afford the desired dialkoxycarbene. Diazirines are prepared by the Graham[49] hypohalite oxidation of amidines (**14**) to 3-halodiazirines (**15**), followed by alkoxide exchange[50] to yield the desired dialkoxydiazirine (**16**) (Scheme 4). To date, this method has produced methoxyphenoxy-,[48] dimethoxy-,[51] bis-2,2,2-trifluoroethoxy-,[52] and methoxy-(2,2,2-trifluoroethoxy)carbene.[52]



Scheme 4

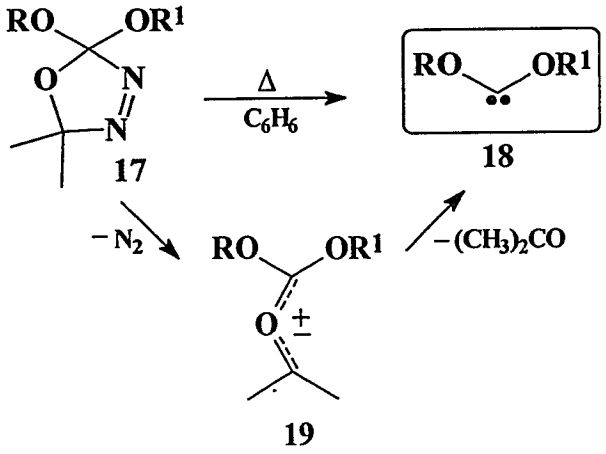
In 1988, Moss and coworkers[51] reported kinetic studies of reactions of dimethoxycarbene with methanol and alkenes, which pointed to the carbene's nucleophilicity. In the same paper they reported the UV absorption spectrum of

dimethoxycarbene (255 nm), which was obtained at 77 K (matrix isolation) and at 298 K (pentane). The half-life at 298 K in pentane was determined to be 2 ms.

Although dialkoxydiazirines have an advantage, because they are the only photochemical dialkoxycarbene source, making them suitable for matrix isolation and low temperature studies, they are poor sources of dialkoxycarbenes for other work. Neat solutions of dialkoxydiazirines are reported to be unstable because of rapid N_2 expulsion. Dialkoxydiazirines have to be isolated in dilute hydrocarbon solutions, and even then, at ambient temperature, decomposition occurs in minutes.[53,54]

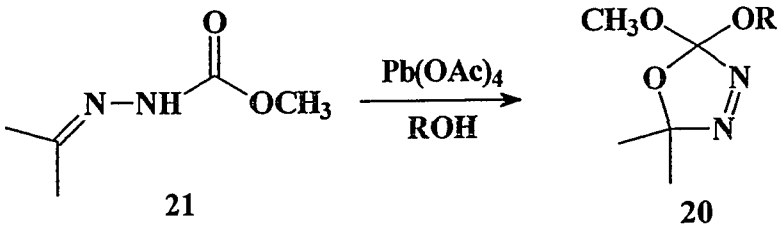
1.2.4 - Decomposition of Oxadiazolines

The newest, and probably the most exciting, dialkoxycarbene precursor was developed by Warkentin and co-workers in 1992.[55] They reported that 2-alkoxy-2-methoxy-Δ^3-1,3,4-oxadiazolines (**17**) were convenient sources of dialkoxycarbenes (**18**) when thermolysed at 100 °C in benzene (Scheme 5). The proposed mechanism[56-59] involves a thermal cycloreversion of N_2 to afford a carbonyl ylide intermediate (**19**), followed by loss of acetone to yield the corresponding carbene (**18**).



Scheme 5

Oxadiazolines of type **20** were prepared by oxidative cyclization of the methoxycarbonylhydrazone of acetone (**21**) with lead tetraacetate in a solution of CH_2Cl_2 and ROH (Scheme 6).[55,60] The yields varied from 40 to 90 %.

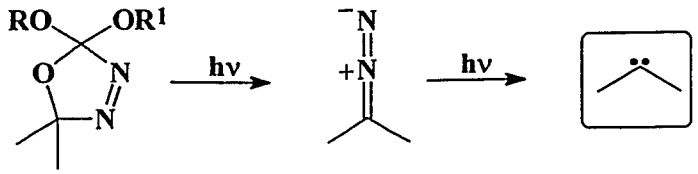


21 **20**

Scheme 6

Warkentin refers to them as "convenient" thermal sources of dialkoxycarbenes for a very good reason. Dialkoxy oxadiazolines are shelf stable at ambient temperatures for more than a year, carbenes are generated at reasonable temperatures, and the byproducts from decomposition of the oxadiazoline are acetone and N_2, both easily removed for analysis of carbene derived products. Warkentin's group has synthesized a large number of dialkoxy oxadiazolines by this method.[55,60-62] More recently, Warkentin's group has prepared a number of other nucleophilic carbenes, including dithio-,[63] oxythio-,[64] and aminooxycarbenes,[65-67] by this method.

Another interesting trait of dialkoxy substituted oxadiazolines (**17**) is their photochemical decomposition. Under photochemical conditions, dialkoxyoxadiazolines (**17**) fragment to give dialkylcarbenes (**22**) (Scheme 7).[68-71] These intermediates can be observed by nanosecond laser flash photolysis using the pyridine ylide method developed by Platz and coworkers.[72,73]



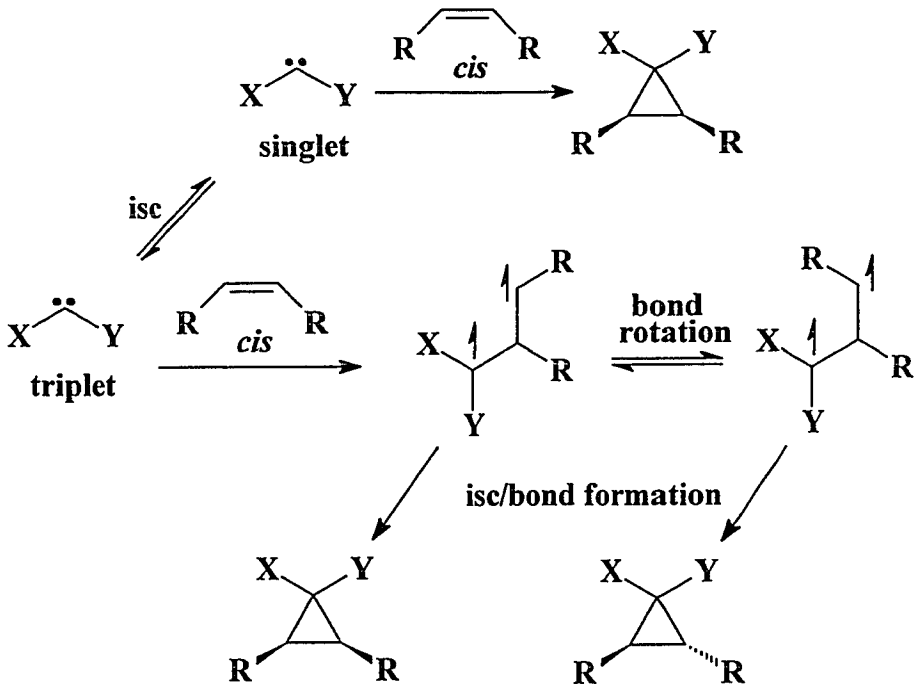
17 23 22

Scheme 7

1.3 - Carbene Additions to Alkenes

1.3.1 - First Reported Carbene Additions to Alkenes

Doering and Hoffmann were the first to report carbene additions to olefins.[74] They discovered that dibromo- and dichlorocarbenes could add to simple alkenes to form cyclopropanes with the stereochemistry of the alkene preserved. In 1956, Skell and Woodworth[75] rationalized that the addition of a singlet carbene to an alkene was concerted. On the contrary, it is not possible for a triplet carbene to add in a concerted fashion (Scheme 8). The triplet, diradical in character, has parallel electron spins, and an intermediate must be involved prior to intersystem crossing, leading to loss of stereochemistry. Skell hypothesized that, "Singlet carbenes add to olefins stereospecifically; triplet carbenes, nonstereospecifically" (Scheme 8). This hypothesis is true if bond rotation is faster than spin inversion. If spin inversion is very fast, faster that bond rotation, the triplet carbene will add stereospecifically, as illustrated in Scheme 8.



Scheme 8

1.3.2 - Theory of Carbene Additions to Alkenes

Let us consider in more detail the reaction of a singlet carbene and an alkene. Generally, the addition is regarded as concerted and therefore one should be able to use Frontier Molecular Orbital Theory[76,77] to gain insight into this fascinating simple cycloaddition reaction. Orbital symmetry rules immediately tell us that a direct linear singlet carbene approach will be forbidden because of antibonding interactions. [38,78,79] However, a sideways approach achieves an overall bonding interaction. Figure 5 clearly illustrates the difference between a linear approach and a sideways approach for both an electrophilic and a nucleophilic carbene.

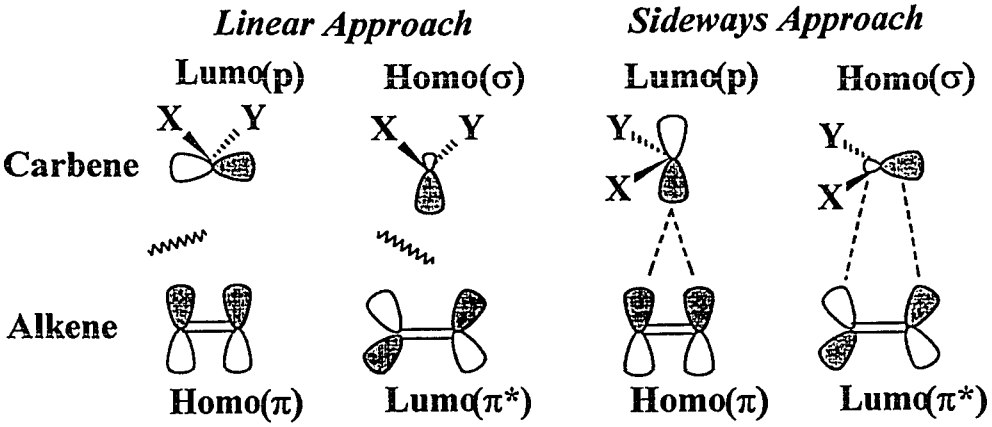


Figure 5

1.3.3 - "Philicity" of Carbenes

All carbenes are inherently electron deficient because they are two electrons short of a normal octet. However, the "philicity" of carbenes can be altered, such that they can react as nucleophiles, electrophiles, and ambiphiles. In some examples, the carbenes are so stable that they can be isolated.[12,13,80,81] As was the case in singlet-triplet multiplicity determination, substituent effects determine the "philicity" of the carbene.

Electrophilic carbenes are usually very reactive species and therefore not very selective in their reactions. Some examples of electrophilic carbenes are $:CCl_2$ and $:CF_2$. Halogen substituents are electronegative, withdrawing electron density inductively from the carbene carbon to make it more electropositive, and giving it electrophilic properties. On the contrary, heteroatom substituents such as O and N, give the carbene strong nucleophilic properties.[38] The lone pairs on O and N strongly interact with the carbene *p*-orbital, placing a formal positive charge on the heteroatom and a formal negative charge on the carbene carbon. Nucleophilic carbenes are usually less reactive and more selective in their reactions. Some examples of nucleophilic carbenes are $:C(OCH_3)_2$, $:C(OCH_3)N(CH_3)_2$, and $:C(OH)_2$. Some ambiphilic carbenes that are known include

:C(OCH$_3$)Cl and :C(OCH$_3$)F. Ambiphilic carbenes have characteristics of both electrophilic and nucleophilic carbenes. These species tend to have one electron-withdrawing substituent and one strong π-p donor substituent.

The "philicity" of a carbene toward different olefins is directly related to the HOMO-LUMO energy separation (ΔE_{H-L}) for the carbene and the olefin, defined by substituents on both the carbene and the alkene.[38]

In electrophilic carbene additions to olefins, it is the HOMO of the alkene that interacts with the LUMO of the carbene. In other words, the carbene is accepting electrons from the alkene donor. The reverse is true for nucleophilic carbene additions, in which electrons are donated from the carbene HOMO to the LUMO of the alkene. Electron-withdrawing groups next to the carbene center lower the energy of the LUMO such that the dominant orbital overlap occurs with the alkene HOMO, producing an electrophilic carbene interaction. If the substituents next to the carbene have lone electron pairs, as in the case with heteroatoms like O, N, and S, the HOMO of the carbene is raised and the dominant interaction is between the carbene HOMO and the alkene LUMO, resulting in a nucleophilic carbene interaction. When the HOMO and LUMO energies of both the carbene and the olefin are similar, the interaction is termed ambiphilic. These orbital interactions are summarized in Figure 6.

Carbene reactivity can also be enhanced by substituents on the alkene. For example, additions of nucleophilic carbenes to electron-deficient olefins occur with enhanced rates, whereas electrophilic carbene additions are enhanced with electron-rich alkenes.

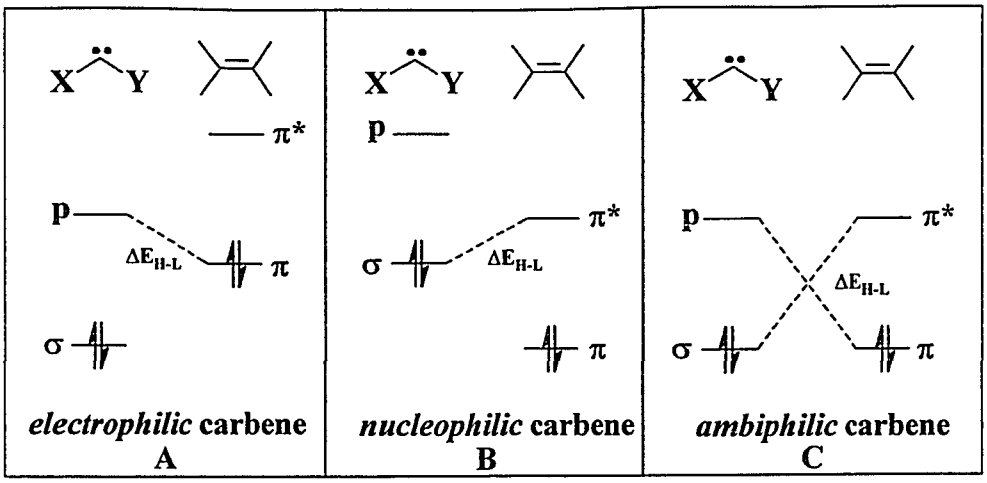
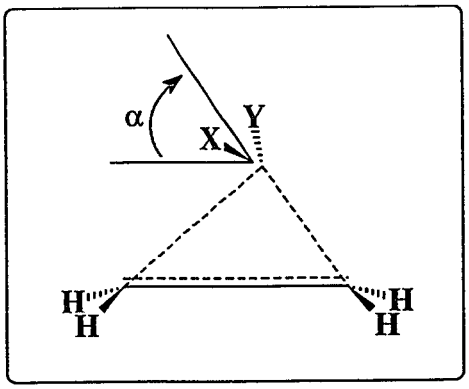
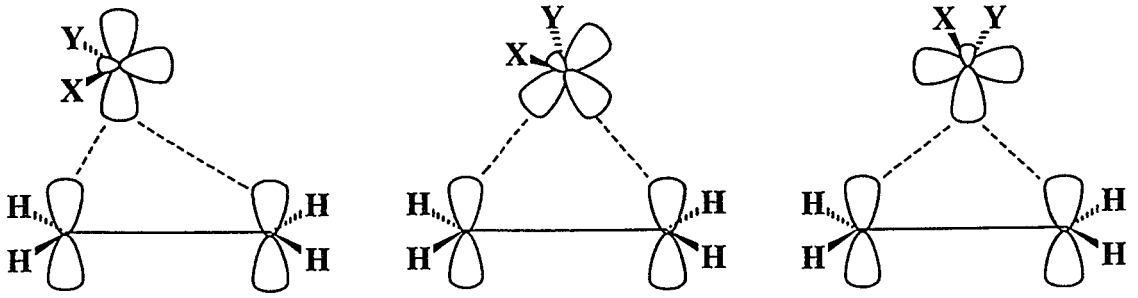


Figure 6

These simple [1+2] cycloaddition reactions have been studied intensely. Moss *et al.* have combined Frontier Molecular Orbital Theory and simple kinetics to gain insight into the reactivity and selectivity of these reactions.[38] Moss developed a method of predicting the "philicity" of singlet carbenes. He compared the reactivity of $:CCl_2$ with those of a number of other singlet carbenes (:CXY) in their reactions with a series of methyl substituted ethenes. From this work he developed what is known as the "carbene selectivity index" (m_{cxy}). Moss determined the product ratio (P_1/P_2) for singlet carbene (:CXY) additions to each of six methyl substituted ethenes and 1,1-dimethylethene (standard alkene). The same experiments were then performed with $:CCl_2$ and a plot of $\log_{10}(P_1/P_2)_{:CXY}$ vs $\log_{10}(P_1/P_2)_{:CCl_2}$ provided a linear free energy relationship in which the slope defined m_{cxy}. Based on the results of this work, carbenes could now be assigned as electrophilic, nucleophilic, and even ambiphilic. Moss compared experimental values of carbene selectivity indexes with calculated values, determined by *ab initio* methods, and found that experiment and theory were in agreement.

Rondan, Houk, and Moss performed a theoretical analysis of carbene additions to ethylene.[82] Using *ab initio* SCF theory, they found a relationship between the carbene "philicity" and the angle of carbene approach with respect to the original ethene plane at the transition state. The defined angle (α) of approach to the olefin is depicted in Figure 7. For a "pure" electrophilic approach, angle α would be equal to 0°, whereas for a "pure" nucleophilic approach, α would equal 90°. A "pure" ambiphilic carbene would approach with an angle of 45°. In general, if α < 45°, the carbene is electrophilic, if α > 50°, the carbene is nucleophilic and somewhere inbetween, the carbene is ambiphilic.





"pure" electrophilic **" pure" ambiphilic** **"pure" nucleophilic**

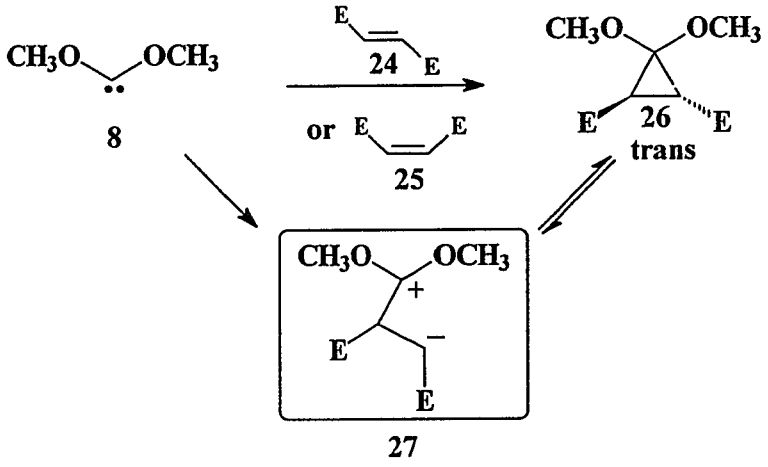
Figure 7

From the calculated data, as the $HOMO_{carbene}$ - $LUMO_{alkene}$ overlap increases, the angle (α) of addition increases, the activation energy for addition increases, and the reaction exothermicity decreases, a direct result of increase in carbene thermodynamic

stability. From a transition state point of view, a "pure" electrophilic addition would generally be exothermic and have an early transition state as compared with a "pure" nucleophilic carbene addition, where the reaction is endothermic and the transition state is late along the reaction coordinate.[82]

1.3.4 - Specific Examples of Carbene Additions to Alkenes

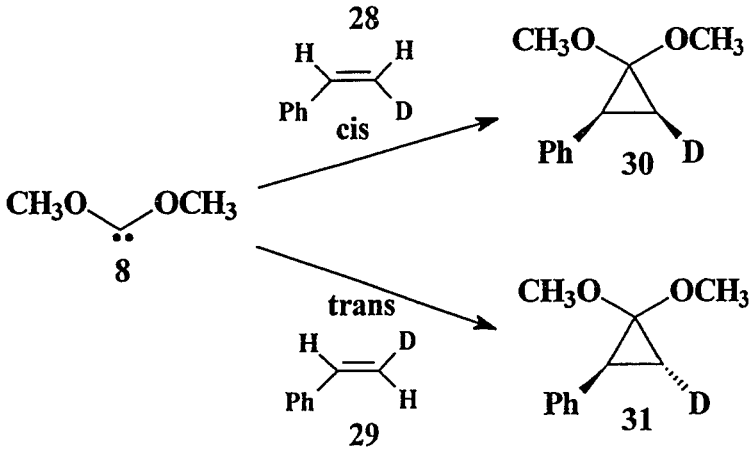
Hoffmann found that diethyl fumarate (**24**) and diethyl maleate (**25**) both reacted with dimethoxycarbene (**8**) to afford *trans*-1,2-diethoxycarbonyl-3,3-dimethoxycyclopropane (**26**) (Scheme 9).[83] Two possible mechanisms could be envisioned. There is either a concerted [1+2] cycloaddition to yield cyclopropane **26** which undergoes reversible ring opening to **27**, followed by re-closure to the more stable *trans* product (**26**), or a stepwise addition to afford **27**, followed by ion pair collapse to **26**.



Scheme 9

The question as to whether dimethoxycarbene (**8**) adds stereospecifically to alkenes was addressed by Moss and Huselton.[84] They observed the products of dimethoxycarbene (**8**) addition to *cis*- and *trans*-β-deuteriostyrenes (**28** and **29**). They found that, in both cases,

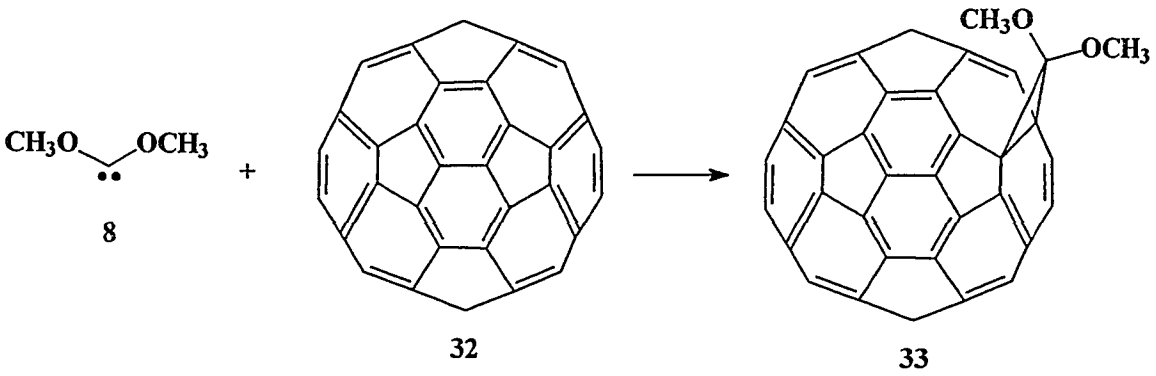
dimethoxycarbene added stereospecifically to both stereoisomers to afford the corresponding cyclopropanes **30** and **31** (Scheme 10). The stereospecific addition observed in β-deuteriostyrenes and the non-stereospecific addition seen in diethyl maleate (**25**) and diethyl fumarate (**24**) was explained in terms of the rate difference between ring closure and bond rotation of intermediate **27** and the corresponding intermediate from Scheme 10. In intermediate **27**, bond rotation must be faster than ring closure, whereas the opposite must be true in the reaction of **8** with **28** or **29** if those additions are stepwise. This postulate would explain the observed stereoselectivity in both reactions. Other electron- deficient alkenes that have been studied include ethyl cinnamate and 1,1-diphenylethene.[83] Both gave cyclopropane products derived from a formal [1+2] cycloaddition reaction. Electron rich alkenes like cyclohexene,[85] ketene acetals,[85] and alkyl substituted alkenes[51] do not react with dimethoxycarbene.



Scheme 10

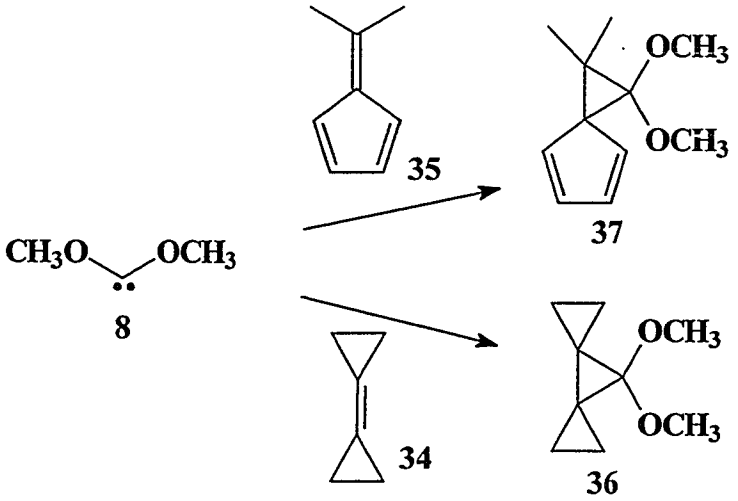
There have been two reports of dimethoxycarbene (**8**) addition to buckminsterfullerene (C_{60}) (**32**).[86,87] Both indicate a [1+2] addition to a double bond at a

[6,6] ring juncture (Scheme 11). In comparison to the [5,6] ring juncture, the [6,6] has more double bond character and therefore **8** adds regiospecifically to this site.[88]



Scheme 11

[1+2] Dimethoxycarbene additions have also been reported with dicyclopropylidene (**34**)[89] and 6,6-dimethylfulvene (**35**)[90] to give dimethoxy substituted spirocyclic compounds **36** and **37** (Scheme 12).

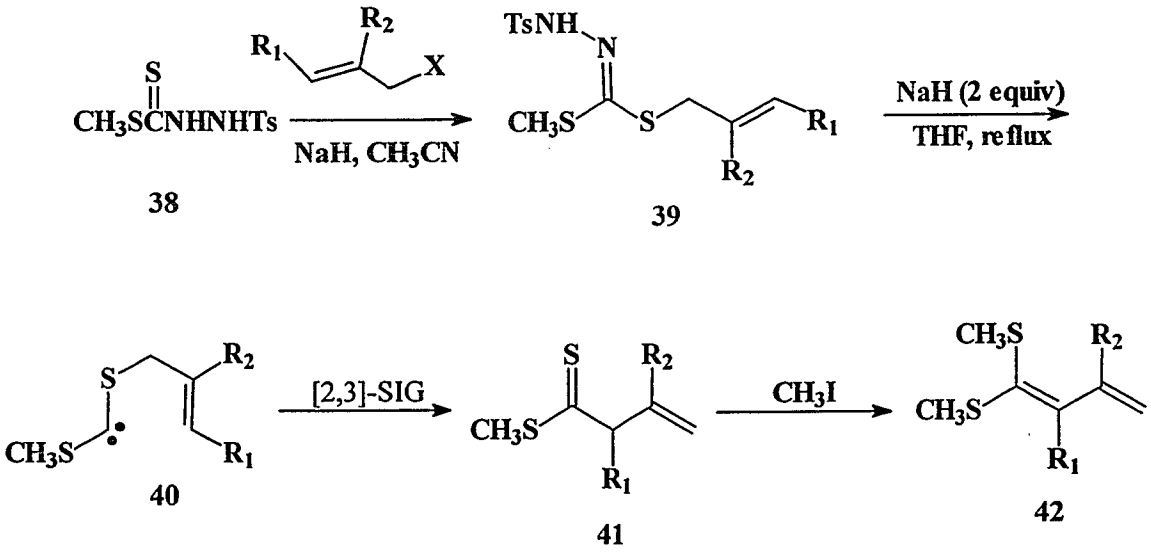


Scheme 12

1.3.5 - [2,3]-Sigmatropic Rearrangements of Nucleophilic Carbenes

There are only a few reported cases of [2,3] sigmatropic rearrangements of nucleophilic carbenes.[91-94] They were first discovered by Baldwin and Walker in 1972 with rearrangement of an allyl substituted dithiocarbene.[91]

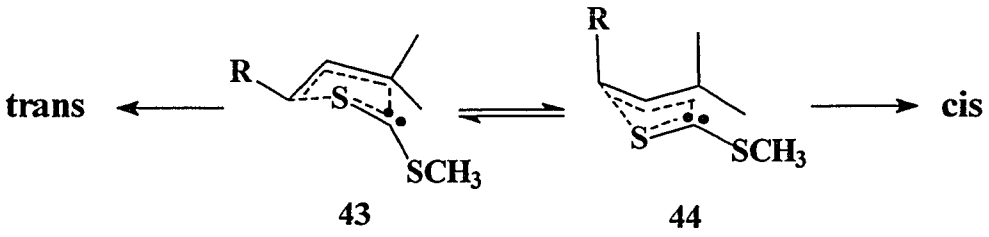
Nakai and Mikami[92] also showed that thermolysis of sodium salts of S-allyl-S'-methyldithiocarbonate tosylhydrazones (**38**) followed by methylation provided good yields of the corresponding 1,1-bis(methylthio)-1,3-butadienes (**42**). Generation of **42** was believed to proceed via a [2,3]-sigmatropic rearrangement of dithiocarbene **40** (Scheme 13).



Scheme 13

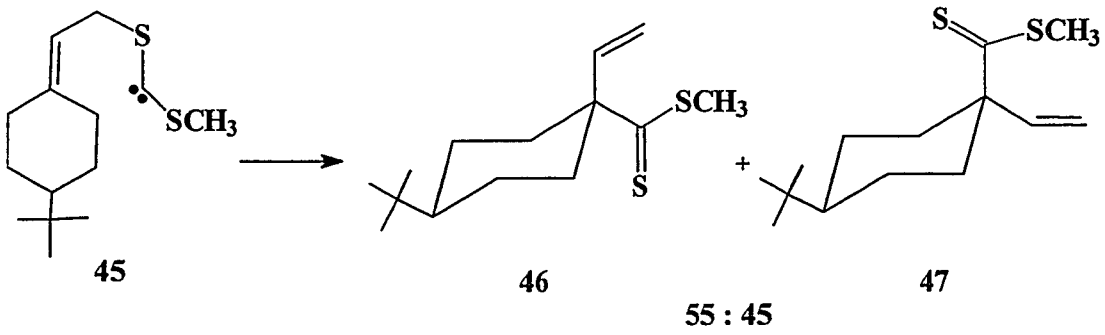
The most recent publication on carbenic [2,3]-sigmatropic rearrangements dates back to 1979.[93] Nakai and Mikami published results on the stereoselectivity of [2,3]-sigmatropic rearrangements of substituted thiomethylthioallylcarbenes. They found that the trans geometry of the newly formed double bond was favoured over the *cis* geometry. The high *trans* selectivity was explained with essentially the same argument that was

used to rationalize the comparable stereoselectivity in similar [2,3]-sigmatropic processes of sulfonium ylides[95] and sulfoxides.[96] The former was explained in terms of the formation of the more favourable folded envelope conformer **43**, where the substituent R is in a pseudoequatorial position, instead of **44**, where R is in a pseudoaxial position (Scheme 14).



Scheme 14

Nakai and coworkers also studied the selectivity of carbene addition to the double bond, that is, whether the carbene attacked the top or bottom face. This was carried out using the 4-*tert*-butylcyclohexylidine ring system (**45**) illustrated in Scheme 15.

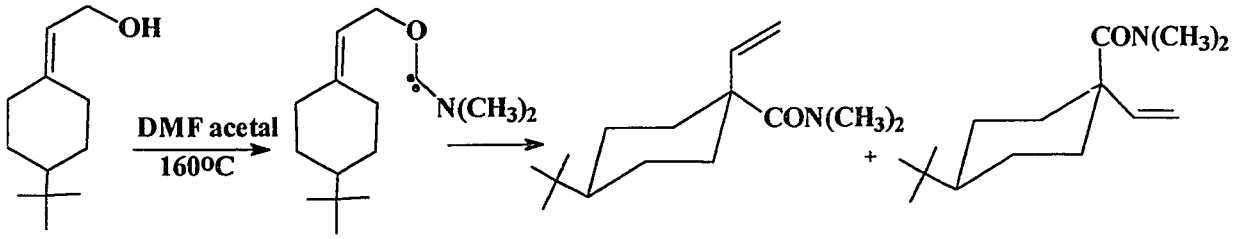


Scheme 15

Low stereoselectivity across the convex face of the cyclohexylidene ring was reported, as shown by the ratio of the two products **46** and **47** in Scheme 15. This result is in contrast to great preferences (> 90 %) for equatorial entry in similar systems for related [2,3]-

sigmatropic rearrangement of sulfoxides,[97,98] sulfonium ylides,[97,98] and ammonium ylides.[99]

The selectivity of this rearrangement was also studied on a similar system. When allylic alcohol **48** and DMF acetal were heated together in xylene at 160°C for 20 h, a 55 : 45 mixture of **50** and **51** was obtained in 21 - 28 % yields (Scheme 16).[94] A similar ratio of products was obtained with dithiocarbene **45** (Scheme 15). We are unaware of any other work in this area.



48 **49** **50** **51**

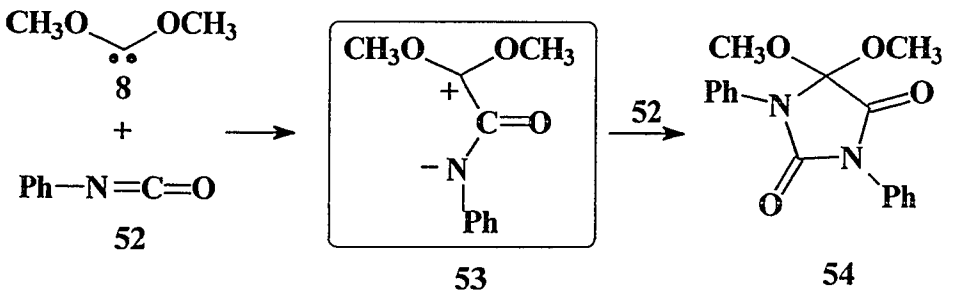
Scheme 16

1.4 - Dimethoxycarbene Additions to Isocyanates

Dimethoxycarbene has been shown to add to aryl isocyanates and aryl isothiocyanates to form 5,5-dimethoxyhydantoins and 5,5-dimethoxythiohydantoins.[100] Dimethoxycarbene (**8**) adds to the electrophilic carbon of aryl isocyanate (**52**) to give the corresponding dipolar intermediate **53**. A [3+2] cycloaddition reaction of **53** with another molecule of **2** affords 5,5-dimethoxyhydantoin (**54**) (Scheme 17).

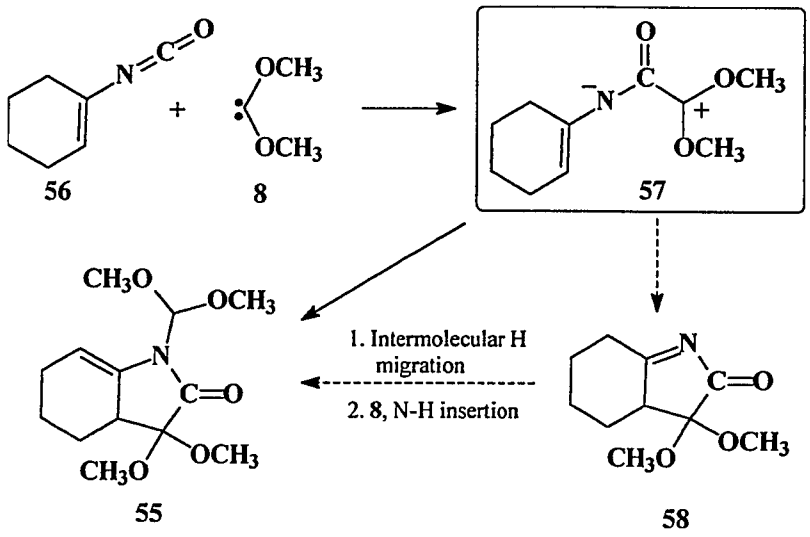
Hoffmann performed competition experiments with substituted aryl isocyanates to develop a linear free energy plot and found a ρ-value of +2.0.[101] This is in agreement

with a mechanism involving the development of negative charge in the isocyanate moiety at the transition state, from action of dimethoxycarbene as a nucleophile.



Scheme 17

Rigby[102-104] has recently demonstrated the assembly of functionally elaborate hydroindolones via [1+4] cycloaddition reactions of nucleophilic carbenes with vinyl isocyanates (Scheme 18). The overall conversion to the hydroindolone (**55**) requires one unit of vinyl isocyanate (**56**) and two units of dimethoxycarbene (**8**), whereas in the reaction of **8** with aryl isocyanate (**52**), the opposite is required (Scheme 17).

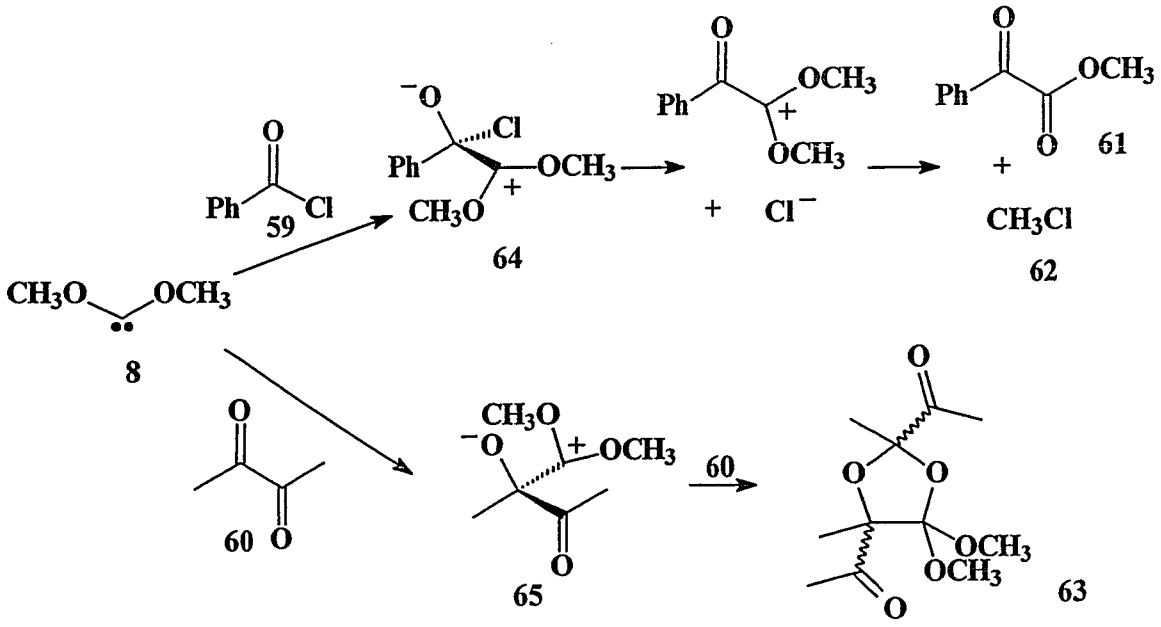


Scheme 18

Rigby has used this protocol for a major ring construction step in the synthesis of (±)-tazettine.[105]

1.5 - Dimethoxycarbene Additions to Carbonyl Compounds

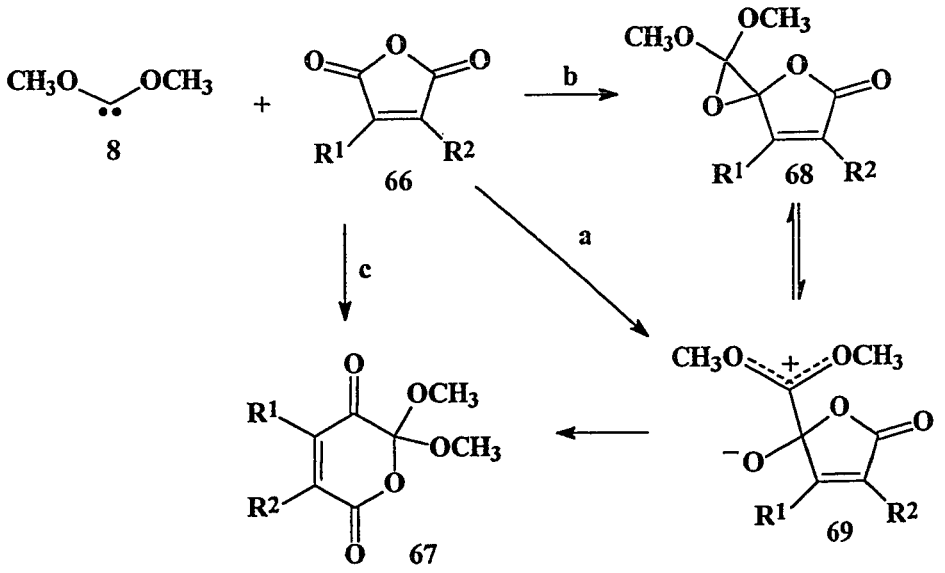
Hoffmann studied the reaction of dimethoxycarbene with two carbonyl compounds, benzoyl chloride (**59**) and biacetyl (**60**), and found products derived from carbene addition (Scheme 19).[83] The reaction of dimethoxycarbene (**8**) and benzoyl chloride (**59**) yielded methyl benzoylformate (**61**) and chloromethane (**62**). The reaction of biacetyl with dimethoxycarbene (**8**) afforded **63** (mixture of diastereomers) derived from one carbene equivalent and two biacetyl equivalents. Both proposed mechanisms involve the initial generation of a zwitterionic tetrahedral intermediate (**64, 65**), generated by nucleophilic carbene addition to the electropositive carbon of the carbonyl compound, similar to other non-carbene type nucleophilic additions to carbonyl compounds.



Scheme 19

Reactions of dimethoxycarbene (**8**) with substituted cyclic anhydrides (**66**) have been studied by Pole and Warkentin.[106] All reactions led to carbene insertion products in which the original cyclic anhydride was expanded by one carbon (**67**), and all carbene

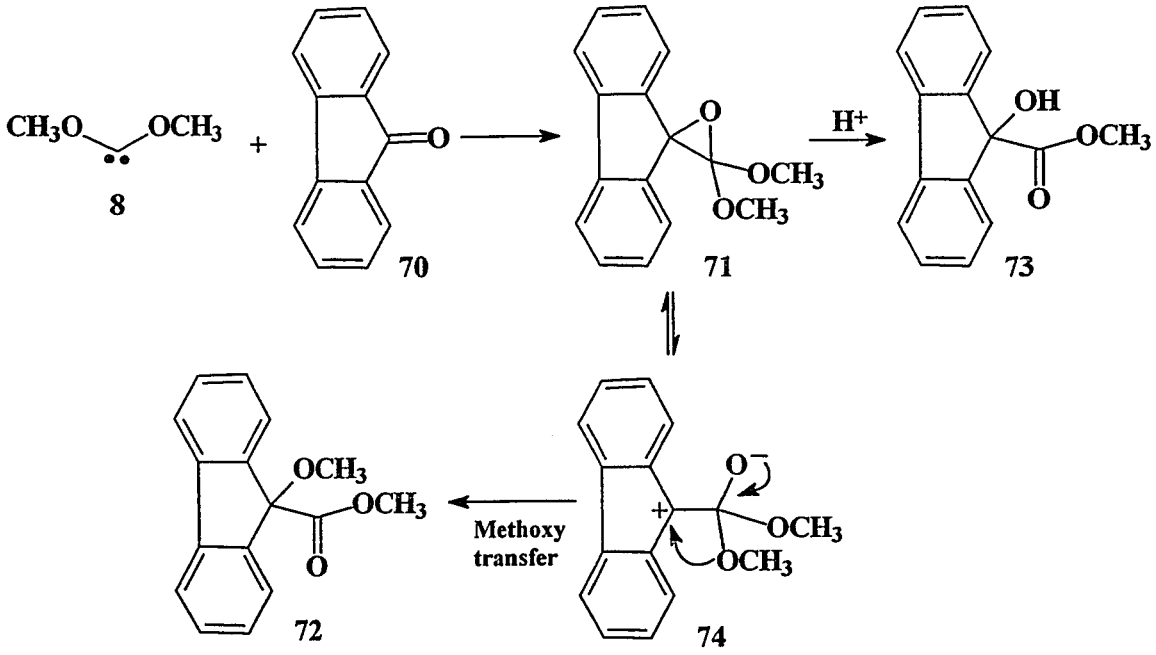
insertions occurred between the carbonyl group and the ring oxygen (Scheme 20). Warkentin and Pole postulated that the initial step is nucleophilic addition to form a tetrahedral intermediate (**69**) (path a). This stepwise addition is precedented in many reactions that Hoffmann and others have studied. Rearrangement of **69** by a 1,2 carboxylate group migration could afford **67**. Pathway c represents a direct, concerted insertion. Although the oxirane (**68**), which could arise from either concerted addition (pathway b) or reversible ring closure of **69**, was not observed, it is a possibility. Compound **68** could arise from a reversible closure of **69** in competition with ring expansion to form **67**.



Scheme 20

Thermolysis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline at 110 °C in the presence of 9-fluorenone (**70**) affords 9-(dimethoxymethylene)fluorene oxide (**71**) which undergoes a thermal rearrangement to yield methyl-9-methoxyfluorene-9-carboxylate (**72**) (Scheme 21).[107] The proposed mechanism involves a [1+2] cycloaddition reaction of dimethoxycarbene (**8**) and the carbonyl group of fluorenone (**70**)

to afford oxirane **71**. Ring opening and methoxy migration generates adduct **72** in 24 % yield (determined by NMR spectroscopy). An intermolecular rearrangement of **74** to **72** was ruled out by means of deuterium labeling experiments. Compound **73** was also isolated, indicating possible hydrolysis of oxirane **71**. This paper reports the first oxirane with two geminal alkoxy groups.



Scheme 21

Recently, Dunn and co-workers studied the reaction of dimethoxycarbene (**8**) with three perchloroketones (**75**, **76**, and **77**) (Figure 8).[108]

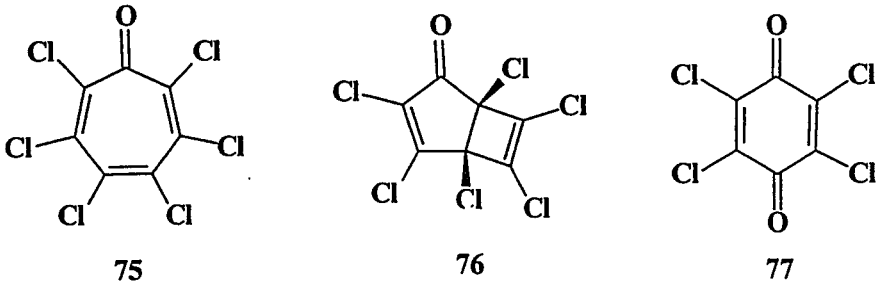
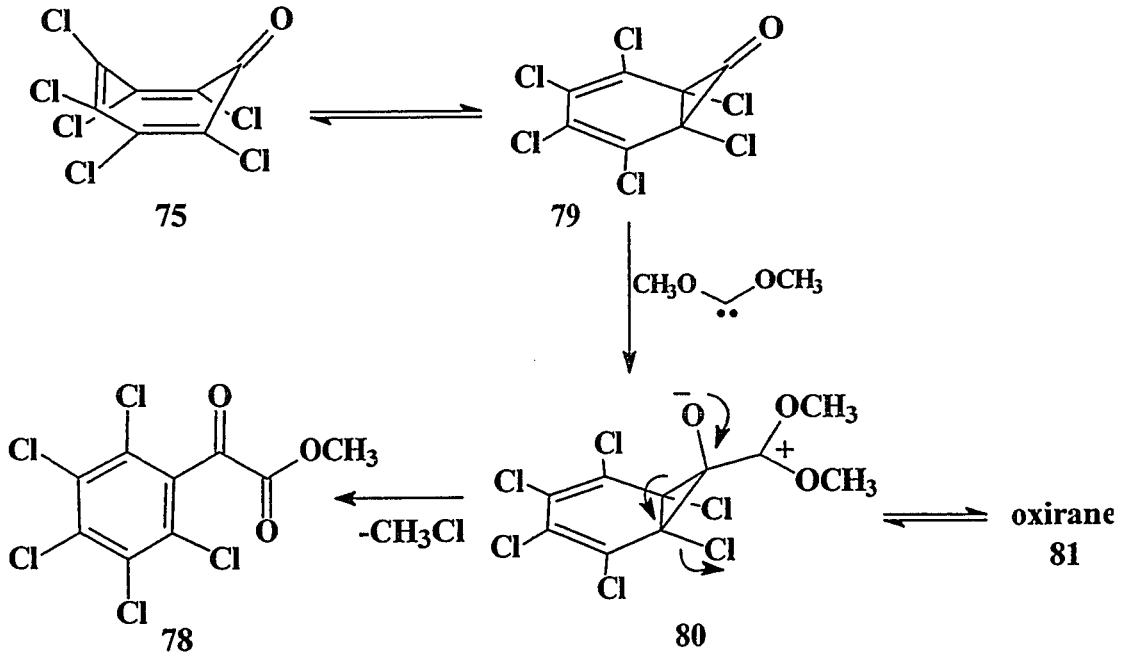


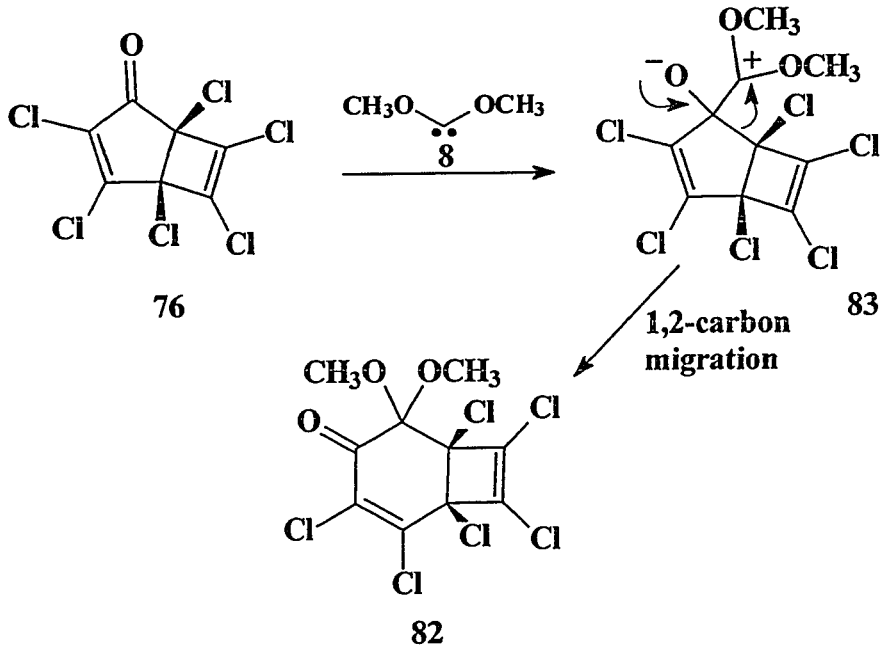
Figure 8

Different mechanistic pathways were postulated for the three isolated products. The first example with hexachlorotropone (**75**) led to the ring contraction product **78** (44 %) (Scheme 22). Compound **79** could result from nucleophilic carbene addition to the carbonyl group of **79** to produce a dipolar intermediate (**80**), which is most likely in equilibrium with the corresponding oxirane (**81**), followed by carbonyl group reformation with ring opening, and then demethylation .



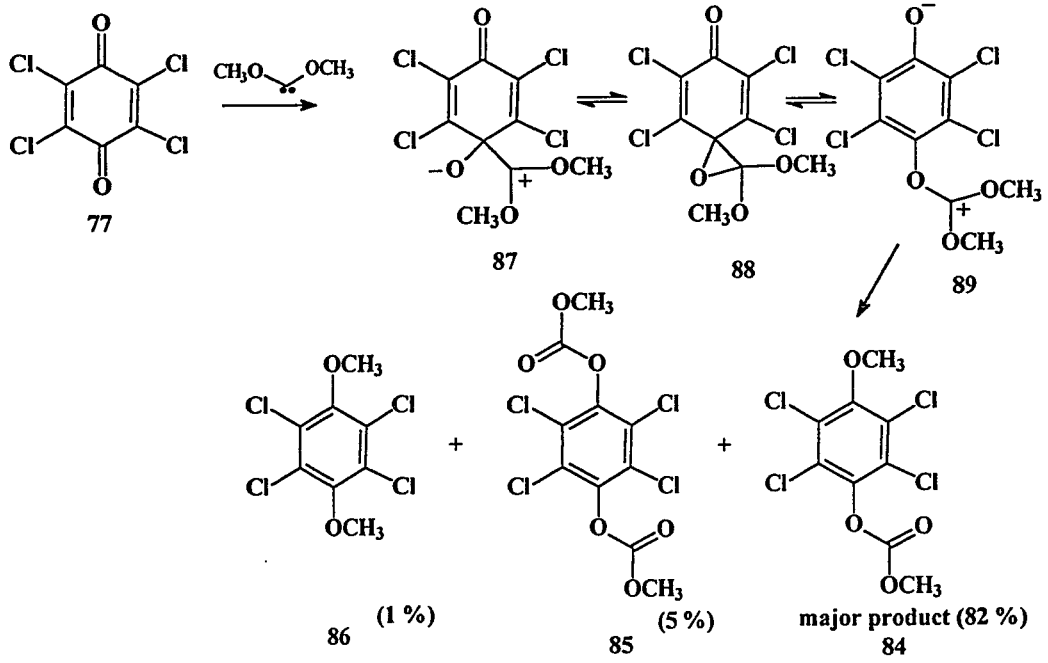
Scheme 22

In contrast to **75**, hexachlorobicyclo[3.2.0]-3,6-dien-2-one (**76**) reacted with dimethoxycarbene to yield the first formal alkoxy- or dialkoxycarbene carbon-carbon bond insertion product (**82**) (quantitative yield) (Scheme 23). It was postulated that addition of the carbene to the carbonyl group gives a dipolar intermediate (**83**) that undergoes a 1,2-carbon migration, with retention of stereochemistry, to afford the ring expanded product **82**. Evidence for a Michael addition was not observed.



Scheme 23

The reaction of tetrachloro-1,4-benzoquinone (**77**) with **8** renders product (**84**) and two minor products (**85** and **86**) (Scheme 24).

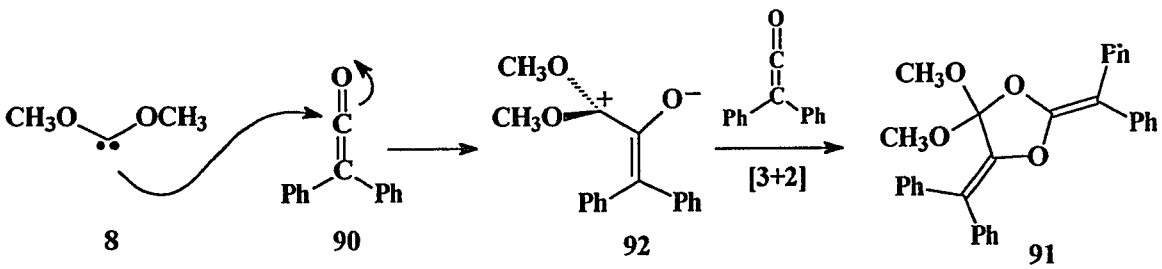


Scheme 24

Presumably initial carbene addition to the carbonyl group of **77** yields a zwitterionic intermediate **87** which is most likely equilibrated with the oxirane **88** and dipolar structure **89**. Deuterium labeling experiments[108] confirm that **84** arises from two subsequent intermolecular methyl transfers from two other molecules of **89**. Minor products **85** and **86** may have come from decomposition of methyl transfer intermediates.

1.5.1-Carbene Additions to Ketenes

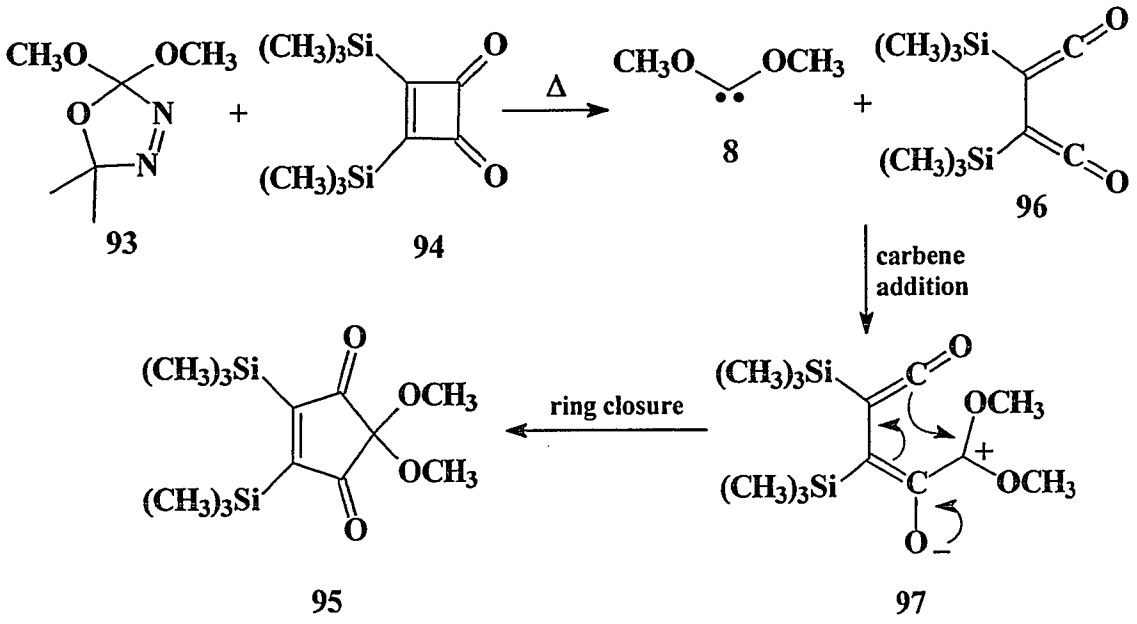
Dimethoxycarbene (**8**) additions to ketenes have also been observed. Hoffmann found that when he reacted dimethoxycarbene (**8**), generated from heating the norbornadienone ketal precursor **3**, with diphenylketene (**90**), a 1:2 carbene-ketene adduct (**91**) was produced.[83] The most likely mechanism involves addition of the nucleophilic singlet dimethoxycarbene to the electropositive carbon of the ketene to yield a 1,3-dipolar structure **92**, which undergoes a [3+2] cycloaddition reaction with another diphenylketene, to give the cyclic structure **91**, depicted in Scheme 25.



Scheme 25

Tidwell and coworkers[109] have recently provided evidence for dimethoxycarbene addition to a bisketene. Thermolysis of dimethoxyoxadiazoline (**93**) in the presence of bis-3,4-trimethylsilylcyclobutene-1,2-dione (**94**) afforded a ring expansion product (**95**) in 60 % yield (Scheme 26). Tidwell *et al.* have shown that silyl substituted cyclobutenediones undergo thermal ring opening to yield isolable bisketenes

(96).[110,111,112] Therefore it can be envisioned that under carbene generating conditions, bis-ketene **96** is formed. At the same time, oxadiazoline (**93**) decomposition is occurring to give dimethoxycarbene (**8**). Addition of the newly formed carbene to an electropositive carbon of the bis-ketene (**96**) gives a dipolar intermediate **97**. Electrocyclic ring closure affords ring expanded product **95**.

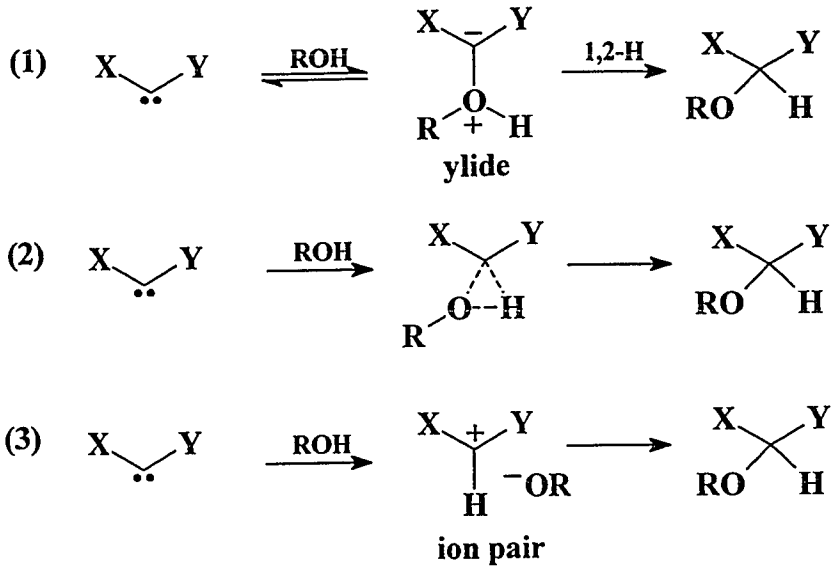


Scheme 26

1.6 - Dialkoxycarbene Insertion Reactions

1.6.1 - O-H Insertions

The insertion of singlet carbenes into O-H bonds can proceed *via* three possible mechanisms:[113] (1) Formation of an ylide by electrophilic carbene attack on an oxygen unshared electron pair, followed by a 1,2-H migration; (2) concerted insertion; or (3) protonation of the carbene, followed by collapse of the newly generated ion pair (Scheme 27).



Scheme 27

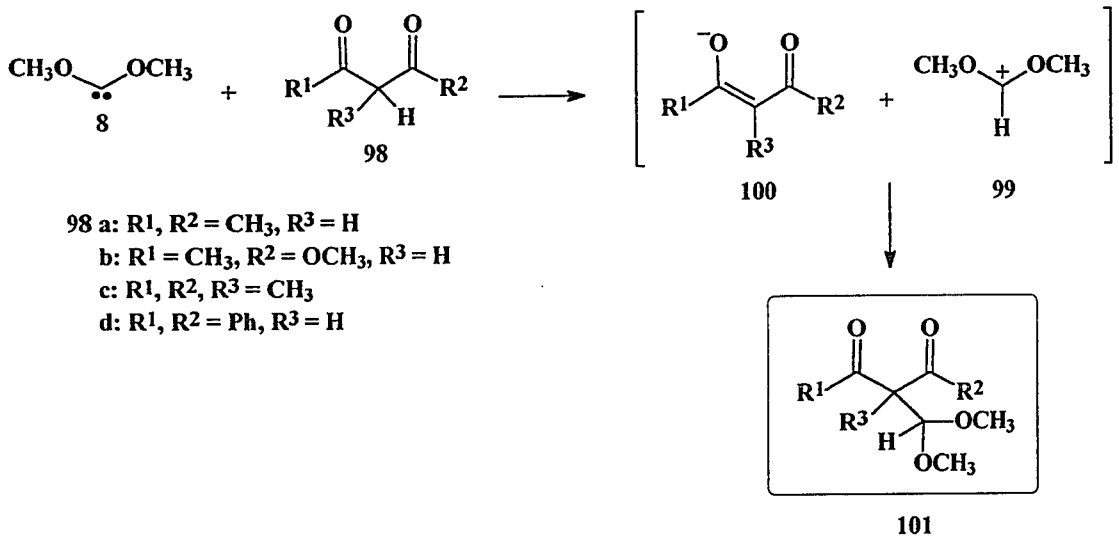
A nucleophilic carbene, in which reactivity is dependent on electron donation from lone electron pairs into its vacant *p*-orbital, should favour mechanism 2 or 3 and disfavour 1. Moss has studied the kinetic isotope effect for O-H insertion of dimethoxycarbene into oligomeric methanol using laser flash photolysis and found a primary kinetic isotope effect, $k_H/k_D = 3.3 \pm 0.5$.[114] This is a strong indicator that the mechanism involves substantial cleavage of the O-H bond in the rate determining step of the insertion. This is in agreement with mechanism 3 and possibly 2.

1.6.2 - N-H Insertions

Many examples of nucleophilic carbene insertions into O-H bonds have been reported,[54] whereas insertions into N-H bonds are not commonplace. To the best of my knowledge, there has been one reported nucleophilic carbene insertion into an NH bond.[102] In studying the reactions of dimethoxycarbene with vinyl isocyanates, Rigby postulated that the final step to form substituted hydroindolones involved an intermolecular dimethoxycarbene NH insertion.

1.6.3 - C-H Insertions

Warkentin and co-workers recently found that reactions of dimethoxycarbene (**8**) with β-dicarbonyl compounds (**98**) yield insertion products derived from apparent carbene C-H insertions.[115] Dimethoxycarbene abstracts a proton from an enol tautomer to afford a protonated carbene (**99**) and an enolate anion (**100**), which collapses to give the product (**101**) of formal carbene insertion into the C-H bond of the keto tautomer (Scheme 28).



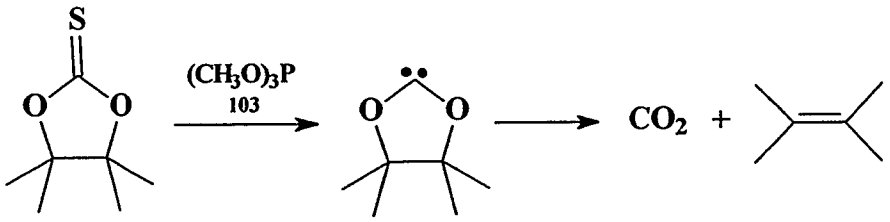
Scheme 28

1.7 - Fragmentations of Dialkoxycarbenes

There have been only a few reported examples of oxy or dioxycarbene fragmentations. Corey and Winter[42] reported that a cyclic thionocarbonate (**102**) when treated with trimethylphosphite (**103**) produces carbon dioxide and the corresponding alkene (**104**) (Scheme 29). The mechanism is believed to involve a cyclic dioxycarbene intermediate **105**, generated by desulfurization of the thionocarbonate by

trimethylphosphite, which spontaneously fragments into carbon dioxide and tetramethylethylene (Scheme 29). This procedure has become known as the Corey-Winter alkene synthesis.[42]

Crank and Eastwood[116] also proposed a mechanism involving decomposition of a cyclic dioxycarbene in the thermal decomposition of 2-ethoxy-4,4,5,5-tetramethyl-1,3-dioxolan.



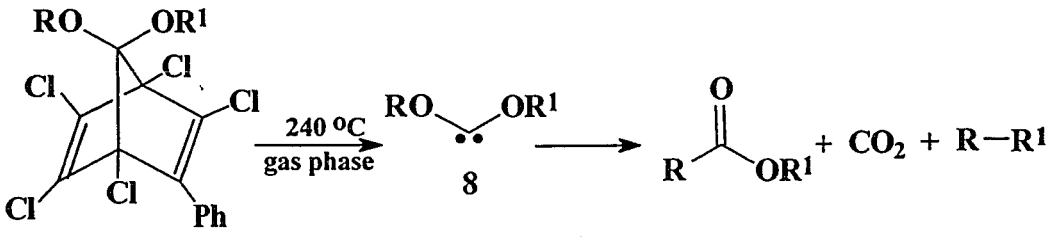
102 **105** **104**

Scheme 29

A theoretical study by Sauers[117] indicated that the loss of carbon dioxide from a saturated cyclic dioxacarbene proceeded in a concerted fashion with an activation energy of 7.1 kcal/mol (MP2/6-31G**).

Fragmentations of dialkoxycarbenes to radicals at elevated temperatures in the gas phase have been postulated.[118,119] Hoffmann reported that dimethoxycarbene (**8**), generated by gas phase pyrolysis of the corresponding norbornadienone ketal (**3**), afforded methyl acetate, carbon dioxide, and ethane (Scheme 30). These products were attributed to radical fragmentation of **8**. In the case of **106**, CO_2 and biallyl were the only observed products, attributable to formation of more stable radicals.

Oele and Louw[120] also reported radical derived products from their study of dimethoxy-and diethoxycarbene generated from the gas phase pyrolysis of methylacetate derivatives. Pyrolysis temperatures varied from 325 - 400 °C.



3 8

8: R = R¹ = CH_3
106: R = allyl, R¹ = CH3
107: R = R¹ = allyl

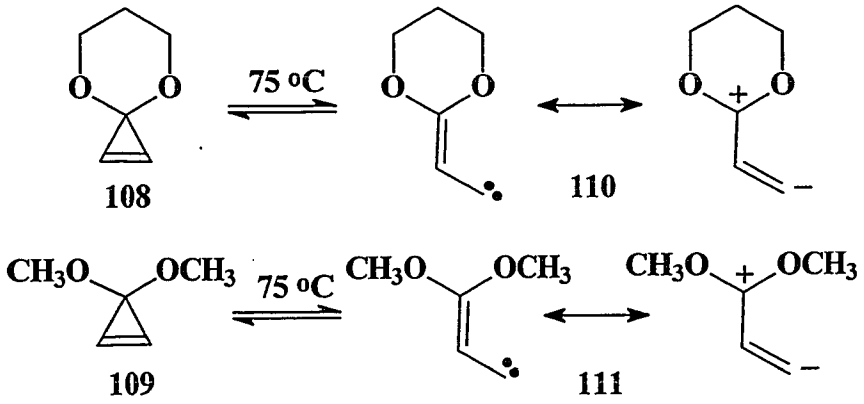
Scheme 30

1.8 - Cyclopropenone Ketals / Carbene Additions to Triple Bonds

1.8.1 - Chemistry of Cyclopropenone Ketals

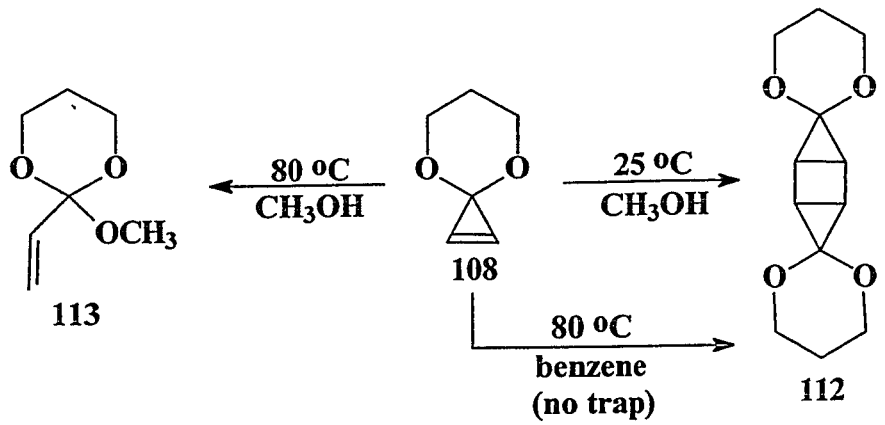
It is difficult to explain the chemistry of dialkoxycarbenes with alkynes without first discussing the chemistry of cyclopropenone ketals. It appears that every paper reporting a reaction involving a dialkoxycarbene and an alkyne has proposed a cyclopropenone ketal as a key mechanistic intermediate.

Boger and coworkers have extensively studied the chemistry of cyclopropenone ketals.[121] The two most studied (**108** and **109**) are depicted in Scheme 31.[121,122] Under thermolysis conditions, a partial or full equilibrium is established between the cyclopropenone ketal (**108** and **109**), and the ring opened form (**110** and **111**), expressed as a dipolar structure or as a singlet vinyl carbene, illustrated in Scheme 31.



Scheme 31

Initial evidence for vinylcarbenes from cyclopropenenone ketals came from temperature dependent reactions of cyclopropenone ketal **108** with methanol. At 25 °C, cyclopropenone ketal **108** in the presence of methanol afforded the dimer (**112**), however, the same reaction carried out at 80 °C led to the prime generation of orthoacrylate **113** (Scheme 32).[123] Generation of **113** can be explained by proton transfer from methanol to the negative site of **110** to afford an ion pair which collapses to give **113**. In the absence of methanol, at temperatures between 25 °C and 80 °C, **108** dimerizes to give **112**. At 25 °C, it seems that the temperature is too low for ring opening of **108**, however, at 80 °C, **108** reversibly ring opens to vinylcarbene **110** and, in the absence of traps dimerizes to **112**.



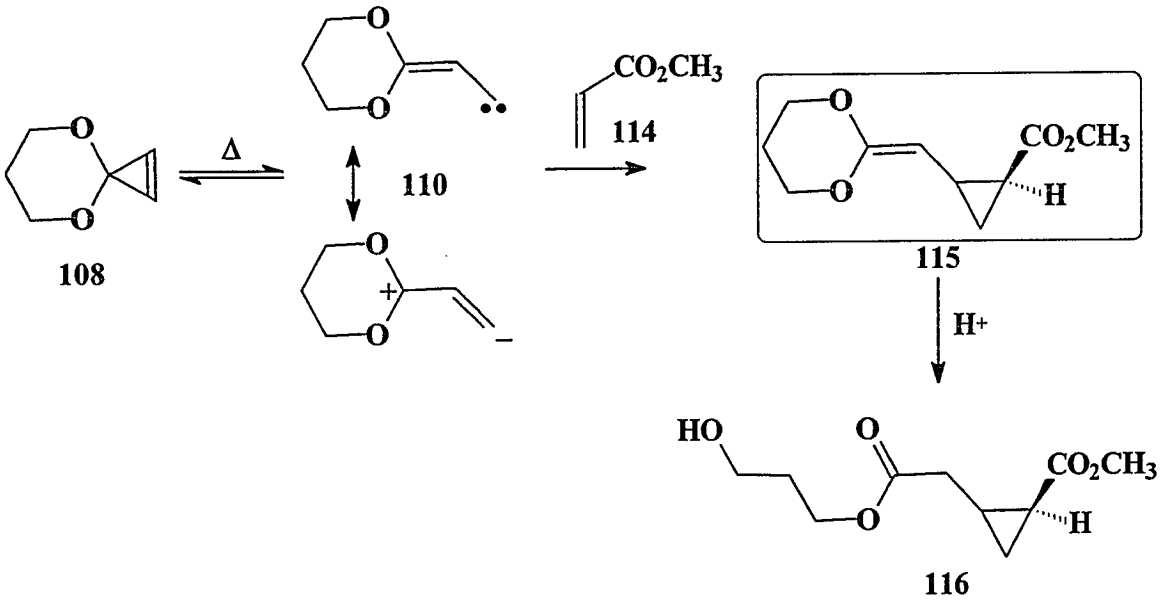
Scheme 32

The vinylcarbenes generated from cyclopropenone ketals display nucleophilic character in their reactions. The nucleophilicity observed can be attributed to electron donation into the formally vacant *p*-orbital of the carbene carbon from the *alpha* ketal functionality. This can be compared to dialkoxycarbenes where heteroatom lone pairs stabilize the singlet state. The singlet-triplet energy gap in 3,3-dialkoxyvinylcarbenes has been calculated to be approximately 9 kcal/mol.[121]

Both the dipolar and carbenic properties of intermediates **110** and **111** make them ideal candidates for intermolecular cycloaddition chemistry. Boger and co-workers have demonstrated that the vinylcarbenes generated from reversible ring opening of cyclopropenone ketals undergo [1+2],[121,124,125] [3+2],[121,124-126] and [3+4][121] cycloadditions with electron-deficient substrates. As in the case with dimethoxycarbene, a nucleophilic singlet carbene, 3,3-dioxyvinylcarbenes do not react with ketene acetals or cyclohexene which are characterized as electron-rich olefins.[121]

[1+2] Cycloaddition reactions of **108** and **109** with electron-deficient olefins bearing one electron-withdrawing substituent proved successful.[121,124,125] Reaction of **108** with methyl acrylate (**114**) afforded cycloaddition product **115**. Subsequent hydrolysis of

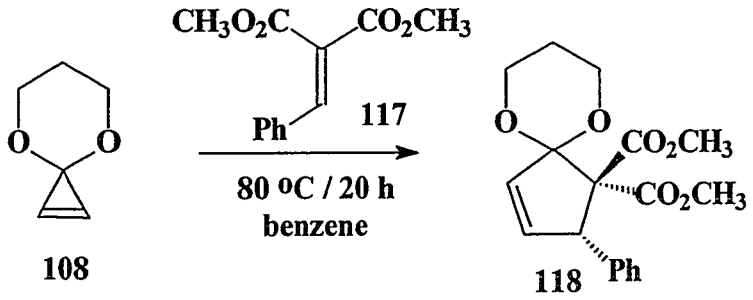
115 led to the isolation of hydrolysis product **116** (Scheme 33). The [1+2] cycloaddition reaction of **108** with a number of other olefins, including methylmethacrylate, acrylonitrile, methacrylonitrile, phenyl ethylacrylate and dimethyl fumarate, were also studied by Boger.[121,124,125] The reactions were conducted at 70-80 °C (12-20 h) and subsequent hydrolysis of the initially formed cyclopropenone ketal addition product, analogous to **115**, afforded the corresponding hydrolysis product, similar to **116**, depicted in Scheme 33.



Scheme 33

The actual cycloaddition mechanism may be stepwise, to yield a zwitterionic intermediate, or it can be concerted. To address this question, Boger studied the [1+2] cycloaddition reactions with respect to solvent polarity.[121] He observed no appreciable change in reaction rate constant as the solvent was varied from non-polar to polar. This fact opposes a mechanism involving charge build up at the transition state and, the process is probably concerted.

The most interesting and facile cycloaddition reactions of cyclopropenone ketals **108** and **109** have been their [3+2] cycloadditions with electron-deficient olefins bearing two geminal electron-withdrawing groups providing, exclusively, cyclopentenone ketals.[121,124,125,126] The reaction of **108** with an electron-deficient olefin (**117**) giving cyclopentenone ketal **118** is depicted in Scheme 34. A wide variety of geminally disubstituted electron-deficient olefins have reacted with **108** successfully.

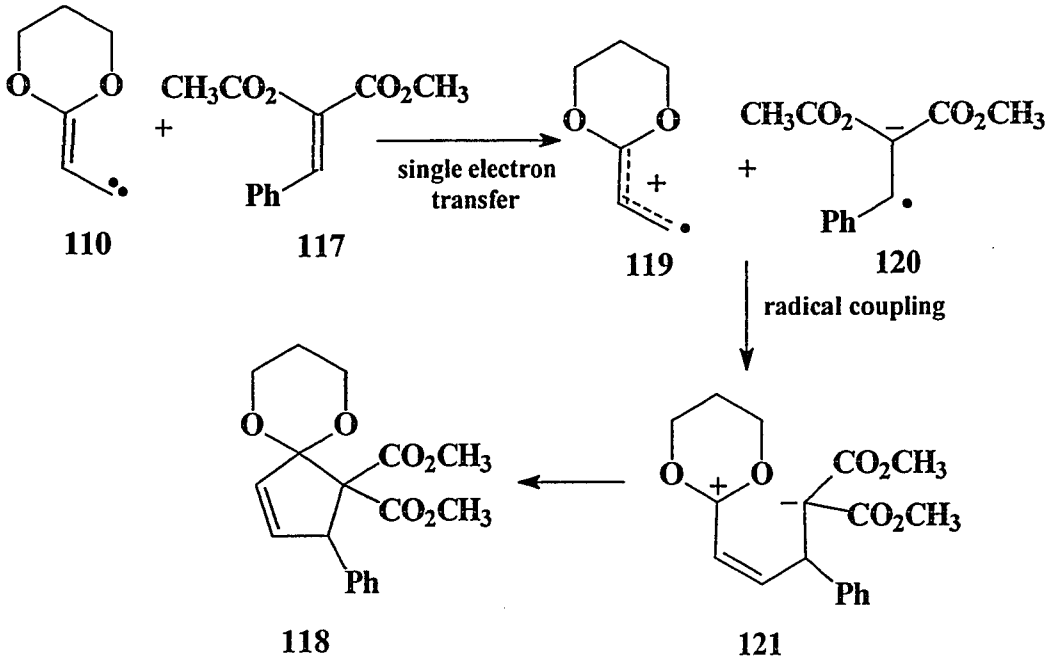


Scheme 34

A number of mechanistic possibilities can be envisioned for the above transformation. These might include: 1) concerted [3+2] cycloaddition; 2) stepwise addition to generate a zwitterionic intermediate and ion-pair collapse; 3) collapse of a biradical intermediate produced by a triplet carbene; 4) formation of a vinylcyclopropane by way of a [1+2] cycloaddition, followed a vinylcyclopropane rearrangement; and 5) electron transfer to yield a radical cation and radical anion followed by radical coupling and ion-pair collapse.

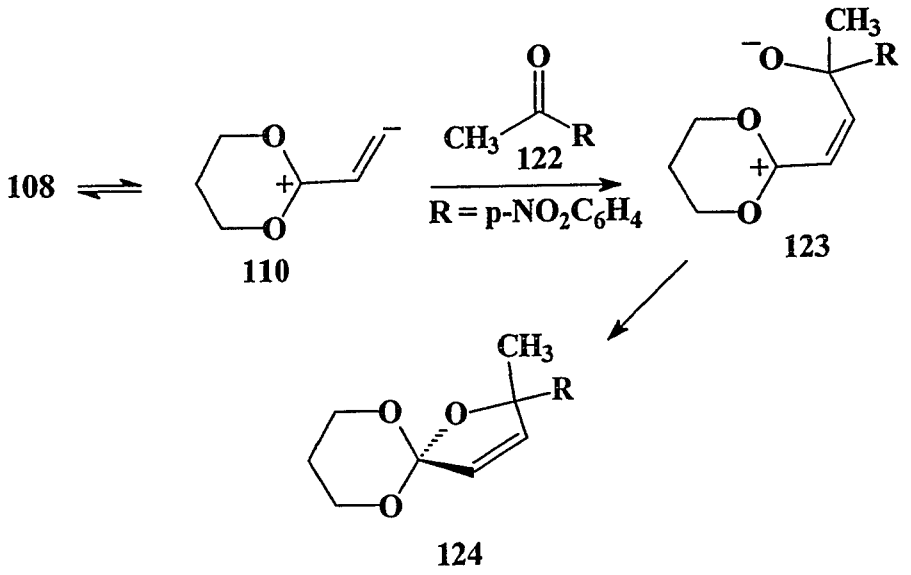
Boger performed various experiments to help understand the mechanism for the reaction depicted in Scheme 34, but most results were inconclusive. However, Boger did point out, based on his experimental observations, that the most likely mechanism might involve electron transfer chemistry.[121] Electron donation from the singlet carbene **110** to

the electron-deficient olefin **117** yields a radical cation (**119**) and a radical anion (**120**). Radical coupling, to give **121**, and ion-pair collapse, affords the desired product **118** (Scheme 35).



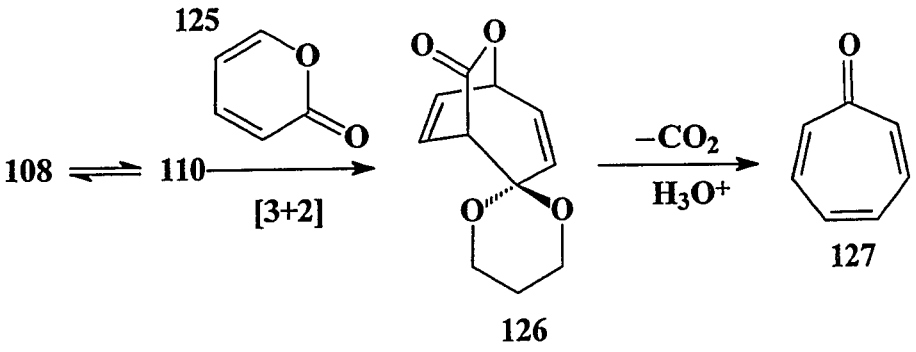
Scheme 35

Compound **110** has also been shown to undergo [3+2] cycloaddition reactions with carbonyl compounds to afford spirocyclic orthoesters. The mechanism most likely involves a nucleophilic singlet carbene (**110**) attack at the electropositive carbon of carbonyl compound **122** to generate zwitterionic intermediate **123**, depicted in Scheme 36, which collapses to yield **124**. The reaction has been successfully accomplished with *p*-NO_2-benzaldehyde and *p*-NO_2-acetylbenzene (**122**).[121]



Scheme 36

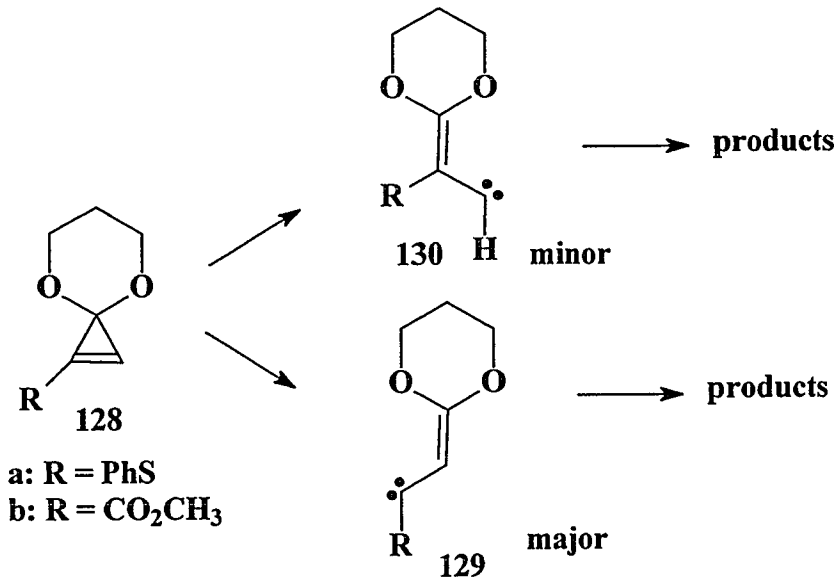
The reaction of 3,3-dioxyvinylcarbene (**110**) and α-pyrone (**125**) led to [3+4] cycloaddition adduct **126**.[121] Subsequent acid hydrolysis afforded the corresponding tropone (**127**) (Scheme 37). Reactions of **110** with other substituted α-pyrones have also been observed, with similar success.[121,124,127]



Scheme 37

Nakamura and coworkers have studied the effects of substituents on the regioselectivity of ring opening of cyclopropenone ketals.[128] They found that anion stabilizing substituents such as phenylthio and ester groups clearly afford products

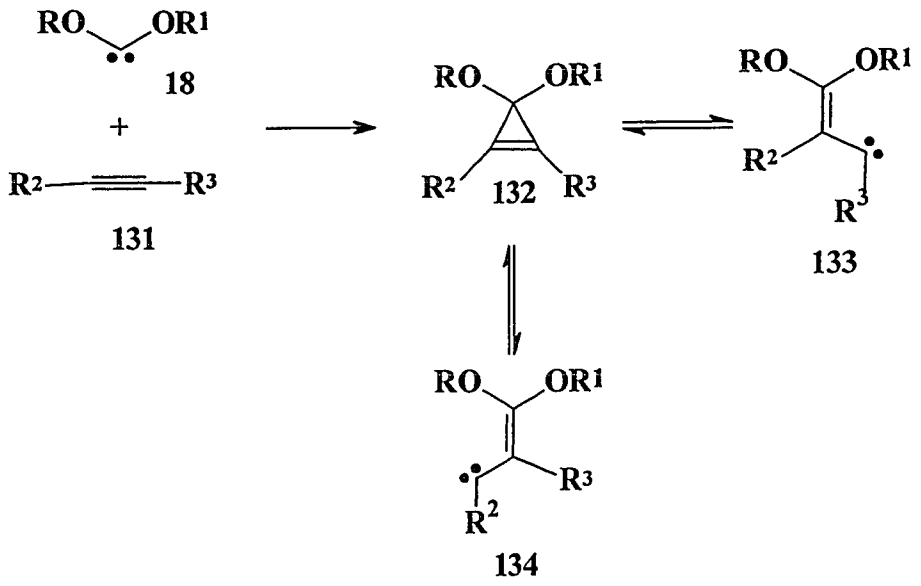
derived from regioselective ring opening (Scheme 38). In the cases of **128a** and **128b**, products derived from ring opening to **129** were highly favoured.



Scheme 38

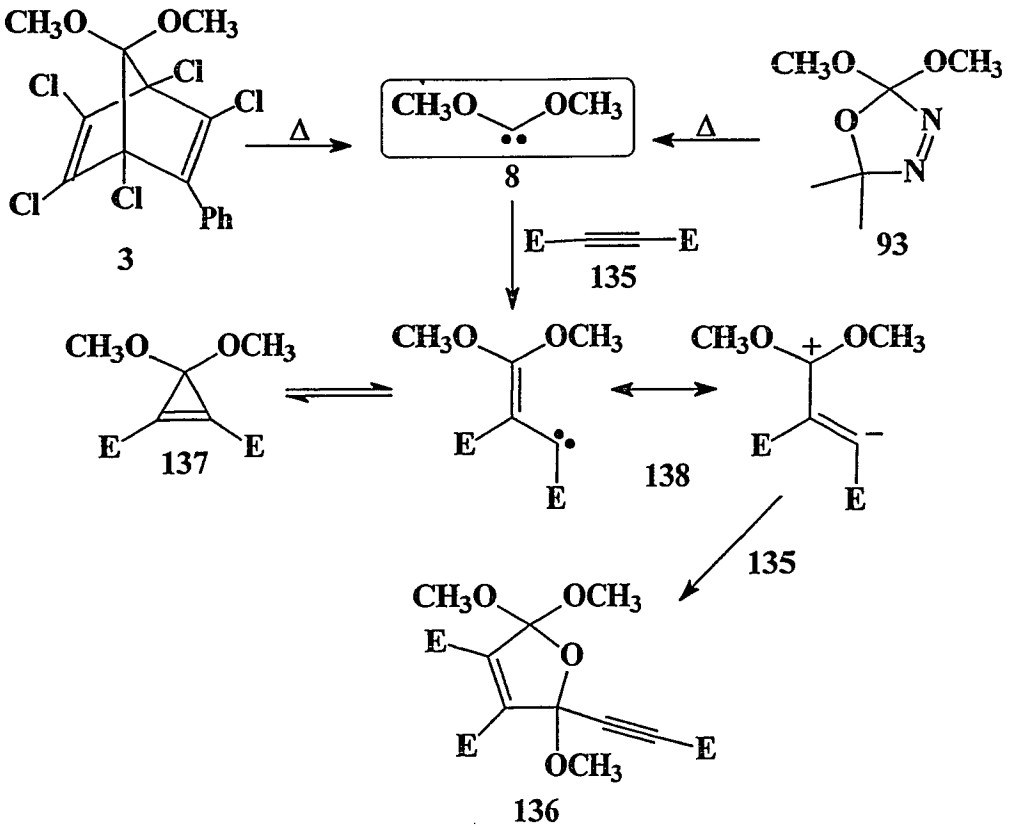
1.8.2 - Intermolecular Reactions of Dialkoxycarbenes with Alkynes

Dialkoxycarbenes (**18**) have been shown to react with alkynes (**131**) to give products that could have arisen from unstable cyclopropenone ketals (**132**) which ring open reversibly, under thermal conditions, to afford vinyl carbenes **133** and **134** (Scheme 39).[83]



Scheme 39

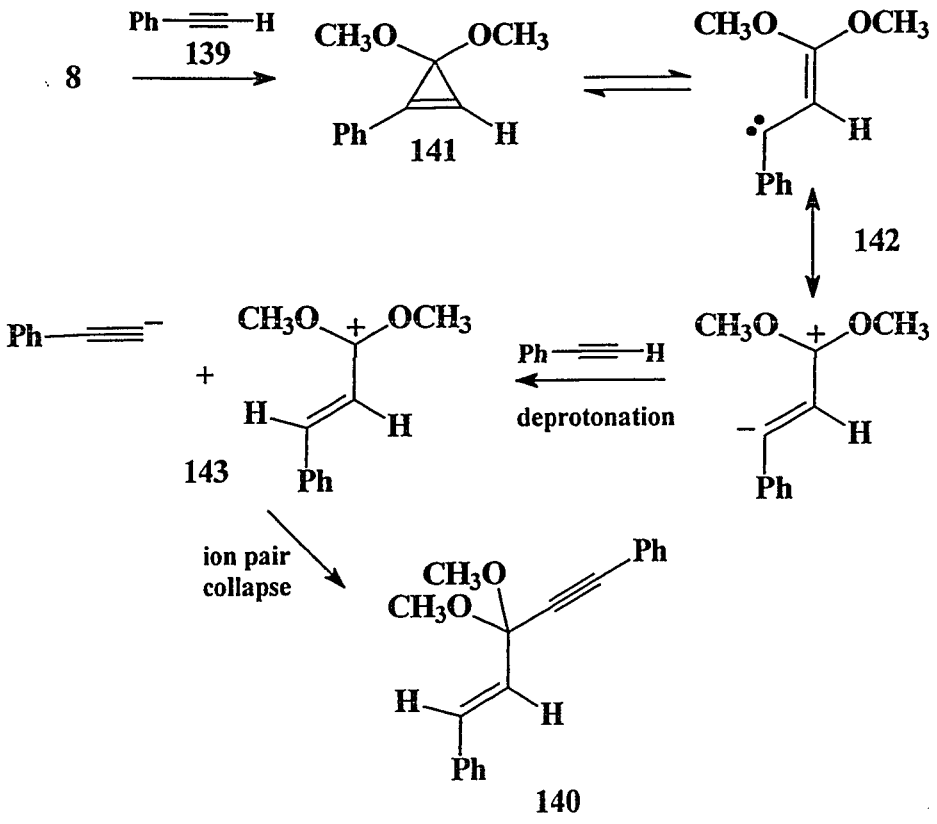
The reaction of dimethoxycarbene (**8**) and dimethylacetylenedicarboxylate (DMAD) (**135**) has been studied by Hoffmann[83] and more recently by Warkentin.[60] Although their sources for dimethoxycarbene were quite different, generation of dimethoxycarbene (**8**) in the presence of DMAD afforded product **136** derived from one unit of carbene (**8**) and two units of DMAD (Scheme 40).



Scheme 40

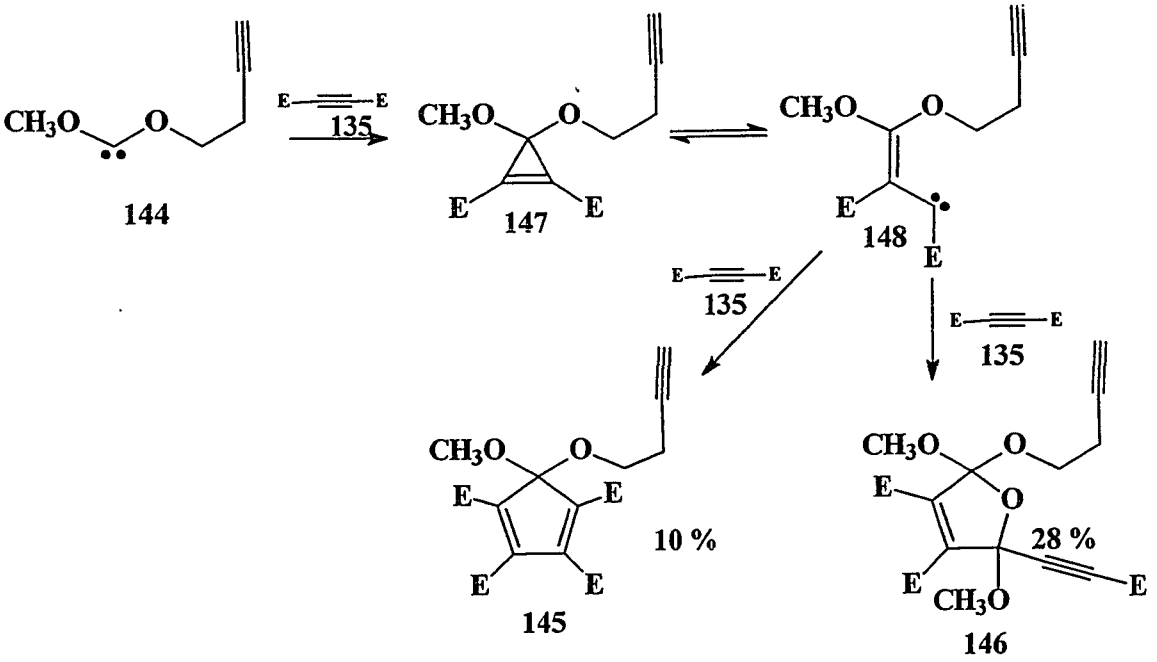
The mechanism most likely involves formation of a cyclopropenone ketal (**137**) which is unstable at thermolysis temperatures and is likely equilibrated with vinylcarbene **138**, as previously described in Boger's work.[121] A formal [3+2] cycloaddition of **138** with the carbonyl group of another unit of **135** would afford **136**.

Hoffmann discovered that dimethoxycarbene (**8**) adds to phenylacetylene (**139**) via a different pathway, affording **140** (Scheme 41).[83] A similar cyclopropenone ketal intermediate (**141**) was proposed, except that ring opening leads to **142**, which deprotonates another molecule of **139** to give an ion pair (**143**) which collapses to **140**.



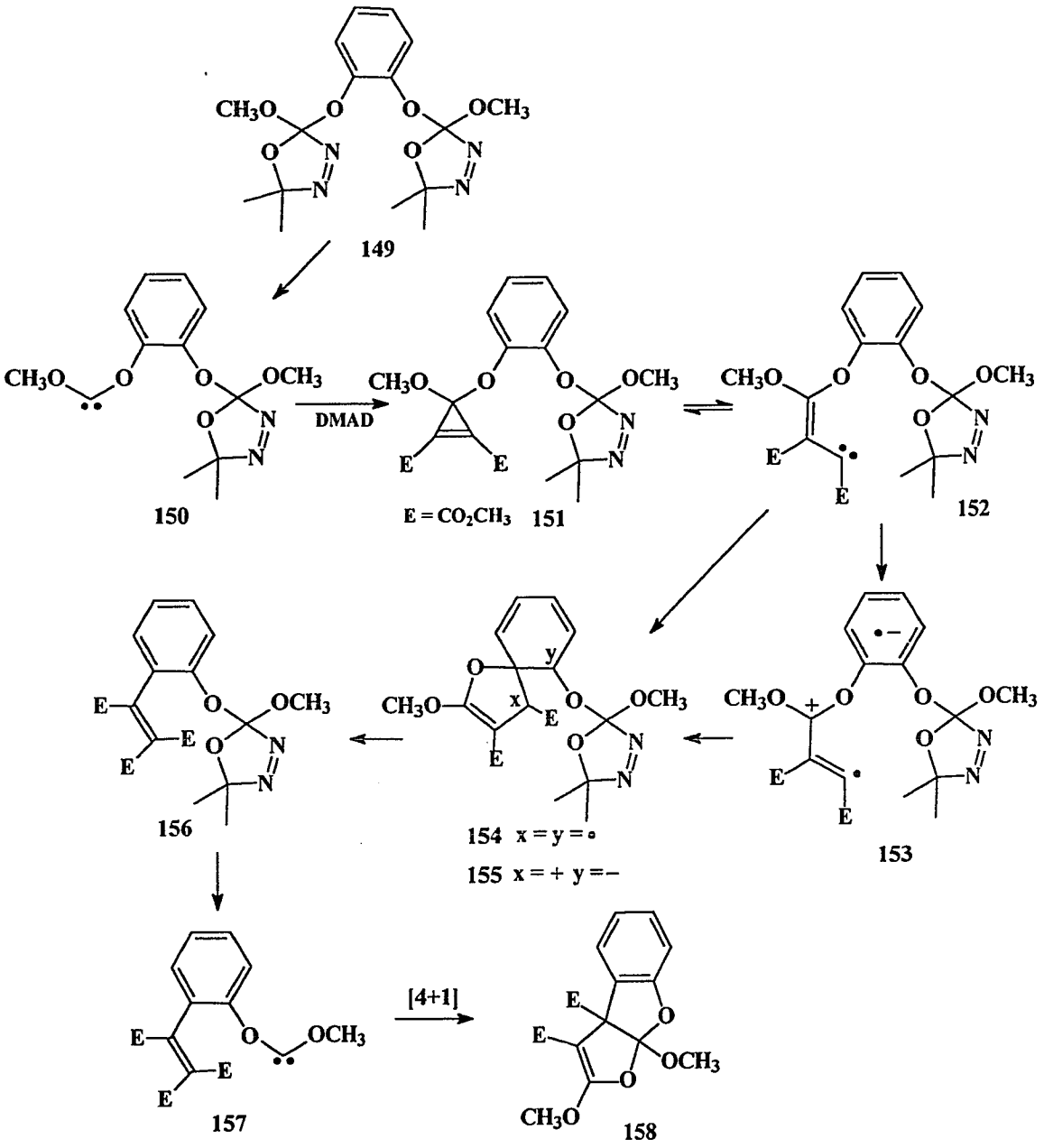
Scheme 41

Kassam and Warkentin have also shown that butynoxymethoxycarbene (**144**), generated by thermolysis of the corresponding oxadiazoline, reacts with DMAD (0.1 M) to yield products **145** and **146** (Scheme 42).[129] The formation of **146** can be described by the mechanism for formation of **136**, depicted in Scheme 40. Product **145** arises from a [3+2] cycloaddition reaction of the alkyne portion of **135**, rather than the carbonyl group, with **148**.



Scheme 42

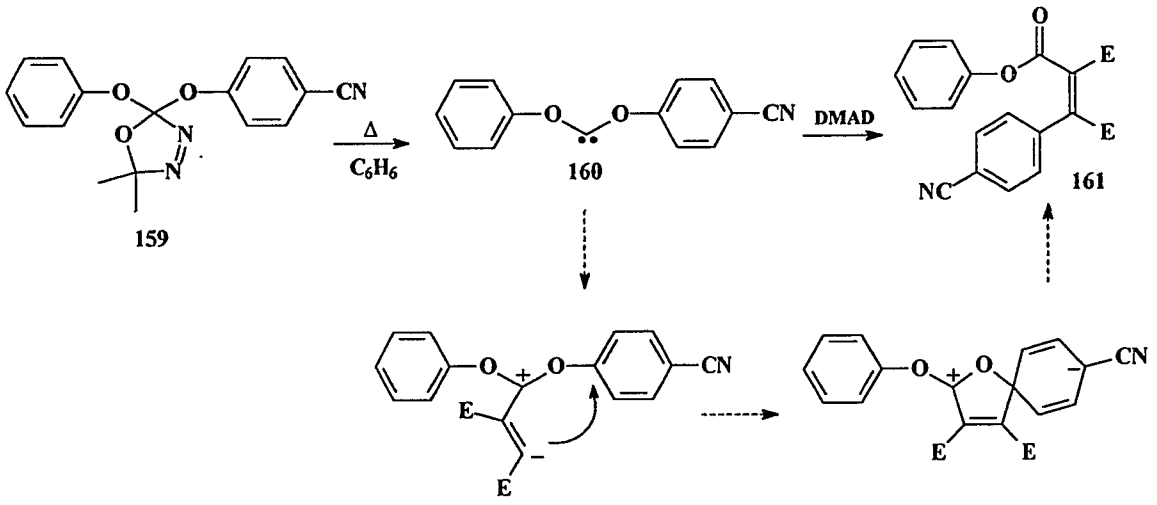
Warkentin and Lu[130] have recently reported that thermal generation of dialkoxycarbenes, from bis(oxadiazolines), in the presence of DMAD led to products derived from aromatic substitution (Scheme 43). They postulated that thermolysis of bis-oxadiazoline **149** generated dialkoxycarbene **150**. Nucleophilic attack of **150** onto DMAD afforded cyclopropene **151**, which opened reversibly to the vinylcarbene **152**, a process very well established by Boger and coworkers.[121] The next step either involves an electron transfer reaction to generate radical ion pairs (**153**) followed by coupling to give **154** or **155**, or nucleophilic vinyl carbene attack at the ipso position of the aromatic ring to afford **155** directly. In either case, **154** or **155** would ring open to generate **156**. Thermal generation of carbene **157** and a formal intramolecular [1+4] cycloaddition reaction with the tethered ester would afford **158**.



Scheme 43

Experimental evidence for nucleophilic vinyl carbene addition to the aromatic ring was strongly supported by the thermolysis of **159** in a benzene solution containing DMAD. Warkentin and Lu observed regiospecific *ipso* addition to the cyano substituted aromatic carbene substituent. This result is in favour of a mechanism involving buildup

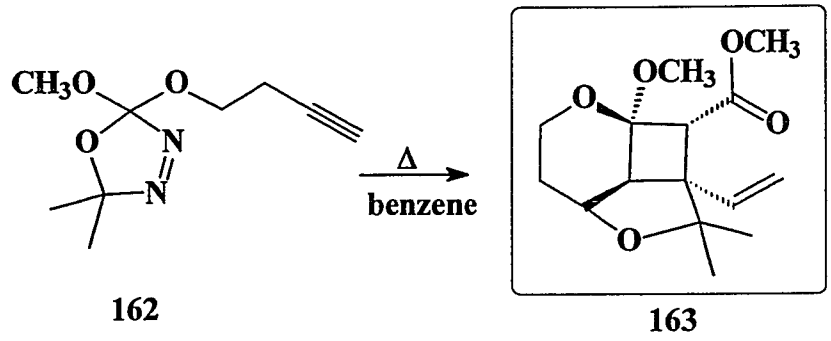
of negative charge in the aromatic ring with the p-CN substituent, an excellent anion stabilizer (Scheme 44).



Scheme 44

1.8.3 - Intramolecular Dialkoxycarbene Reactions with Alkynes

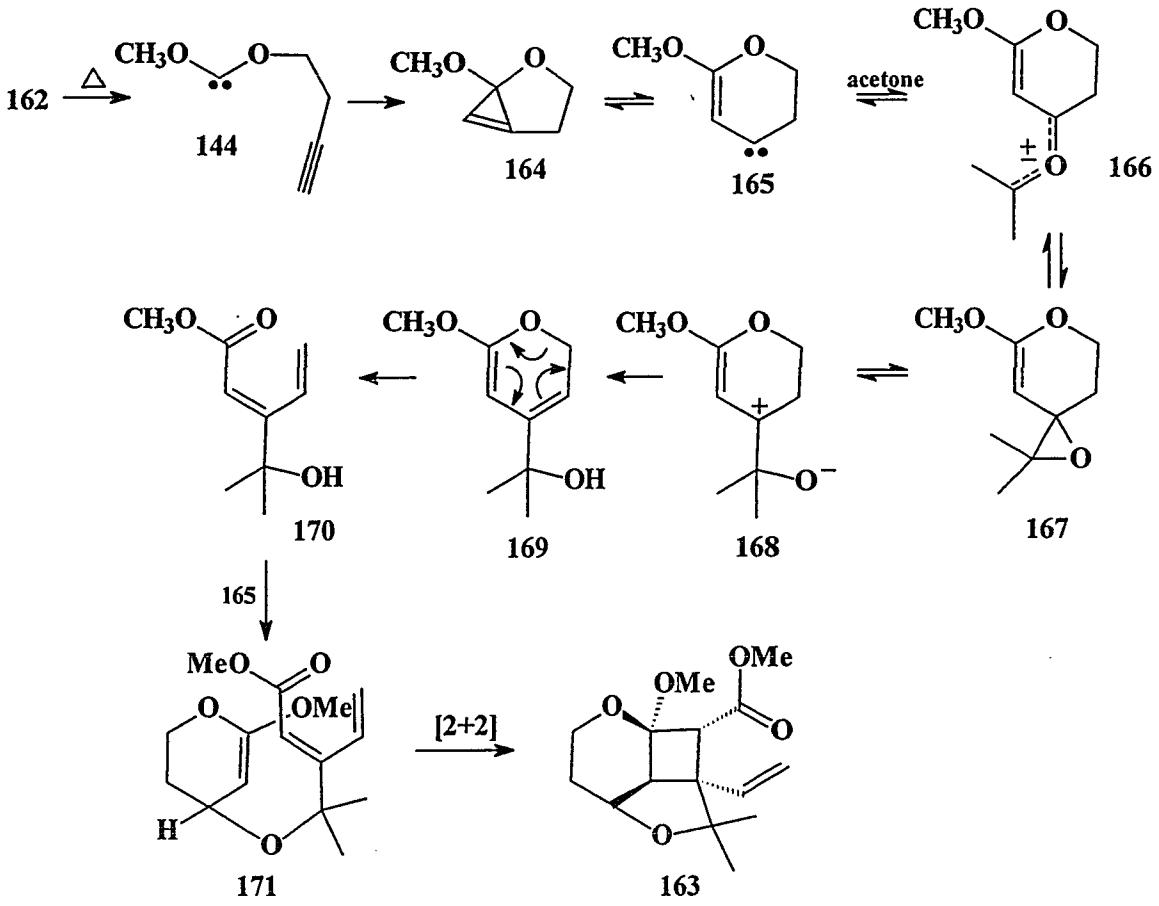
In the process of studying the reactions of dialkoxycarbenes with tethered triple bonds, Kassam and Warkentin stumbled across a remarkable reaction.[131] Thermolysis of 2-butynoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**162**), in the absence of traps, afforded a novel tricyclic product (**163**) in 74 % yield (Scheme 45).



Scheme 45

To account for this observation, Kassam and Warkentin postulated a cascade of reactions (Scheme 46) initiated by loss of N_2 and acetone from **162**, a well established process for

dialkoxy oxadiazolines, to afford butynoxymethoxycarbene (**144**). Cyclization of the free carbene (**144**) onto the tethered triple bond afforded a cyclopropene intermediate (**164**) which ring-opened reversibly, well documented by Boger and coworkers,[121] to form an endocyclic vinylcarbene intermediate (**165**). Vinylcarbene (**165**) attack on acetone, followed by proton abstraction and electrocyclic ring opening, similar to a Claisen rearrangement,[132,133] gave **170** (isolated in 5 % yield). Carbene (**165**), by insertion into the OH bond of **170**, afforded **171**. An intramolecular stepwise formal [2+2] cycloaddition of **171** yielded tricyclic compound **163** as a single diastereomer. Strong support for the hypothesized mechanism came from a series of deuterium labeling experiments. For example, intermolecular attack of **165** on acetone was confirmed by heating **162** in benzene with a four fold excess of acetone-d_6, resulting in isolation of the deuterated form of product **163**.

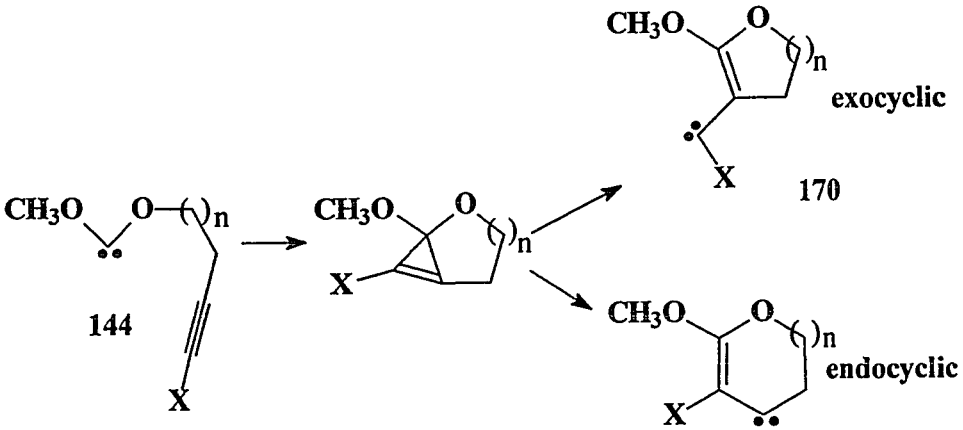


Scheme 46

Smith[134] has recently examined the cascade mechanism, proposed by Kassam and Warkentin, depicted in Scheme 46, using semi-empirical PM3 methods supported by low-level *ab initio* calculations. Smith reported that the mechanism postulated by Kassam and Warkentin was in general agreement with his calculations, however, he did mention that structure **164** could not be found as an intermediate or a transition state and that structure **168** was a transition state, not an intermediate, as reported by Kassam and Warkentin.

It should be noted that proposed intermediate **164** is a cyclopropenone ketal which has the potential to ring-open regioselectively as illustrated by Nakamura and

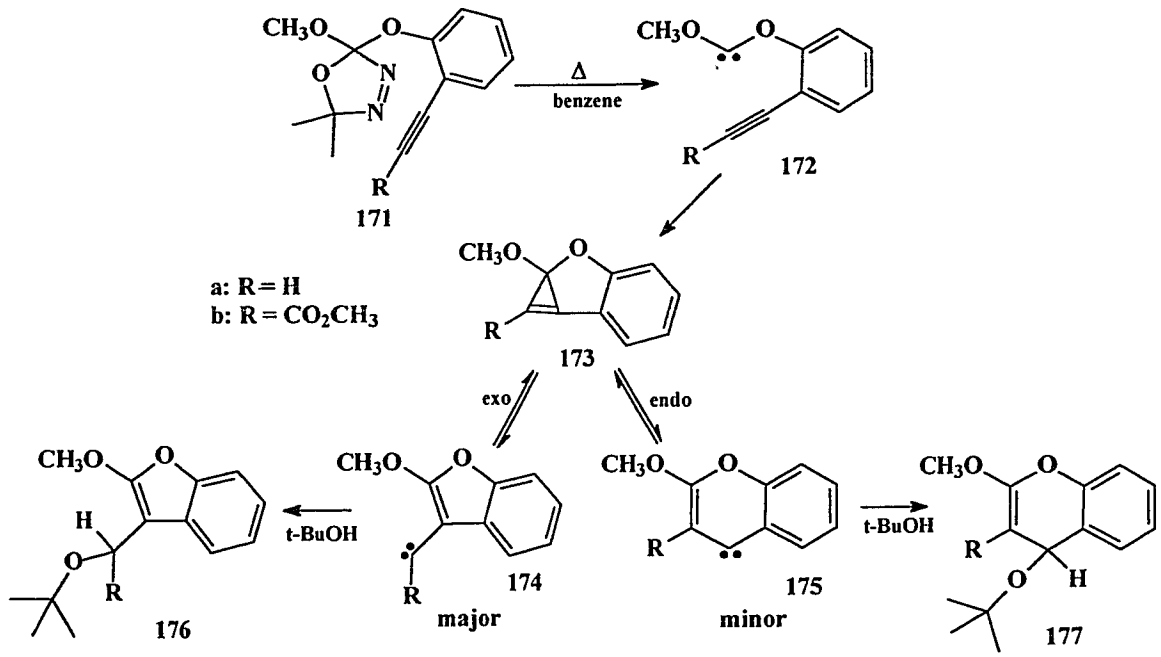
coworkers.[128] Kassam and Warkentin[131] observed, by means of trapping experiments with alcohols, regioselective ring-opening when the terminal alkyne substituent of **144** is H, CH_3 and CO_2CH_3. In the case of H and CH_3, endocyclic ring-opening leading to **165** is observed exclusively, whereas when an ester substituent is present, the exocyclic carbene (**170**) dominates (Scheme 47). When the chain length of the tethered alkyne is increased by one carbon unit, exclusive formation of the five membered exocyclic vinylcarbene occurs, independent of substituent.



144: n = 1, X = H (endocyclic)
a: n = 1, X = CH_3 (endocyclic)
b: n = 1, X = CO_2CH_3 (exocyclic)
c: n = 2, X = H (exocyclic)
d: n = 2, X = CH_3 (exocyclic)
e: n = 2, X = CO_2CH_3 (exocyclic)

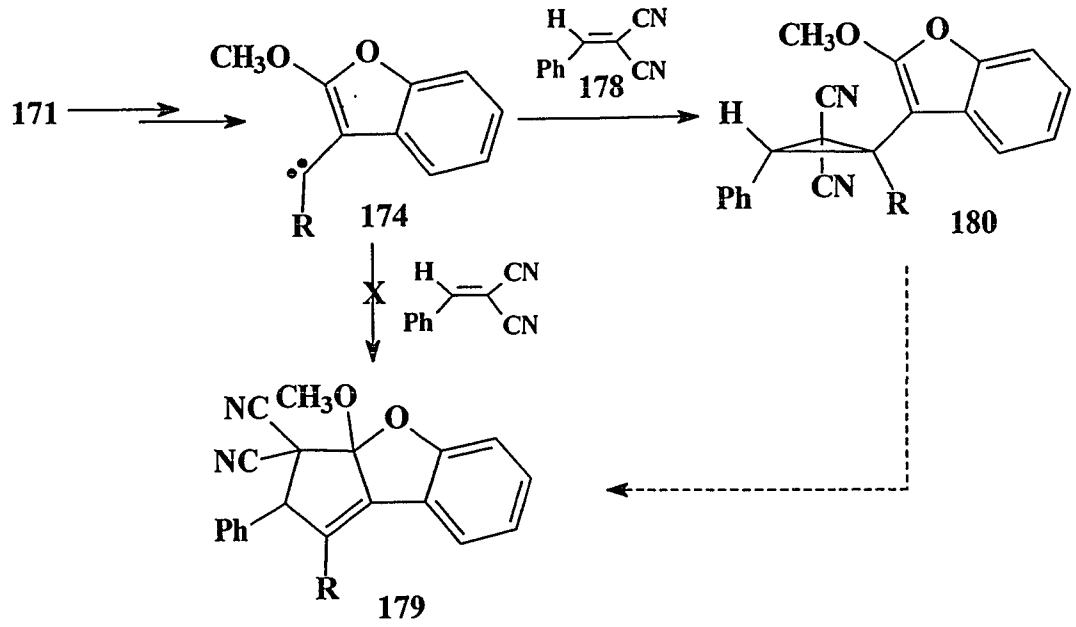
Scheme 47

With heightened interest in intramolecular carbene additions to alkynes, Warkentin, Kassam, and Venneri[135] studied the thermal chemistry of aryloxymethoxy-substituted oxadiazolines (**171**). Through a series of carbene trapping and hydrolysis experiments, products derived from regioselective ring-opening of the cyclopropene intermediate to afford primarily an exocyclic vinylcarbene were isolated (Scheme 48).



Scheme 48

The preferential generation of an exocyclic vinylcarbene (**174**) upon thermolysis of oxadiazoline **171** addressed the possibility of trapping **174** in a formal [3+2] cycloaddition with a highly electron-deficient olefin such as benzylidenemalononitrile. This would have led to a novel functionalized tricyclic benzofuran ring system **179** (Scheme 49).



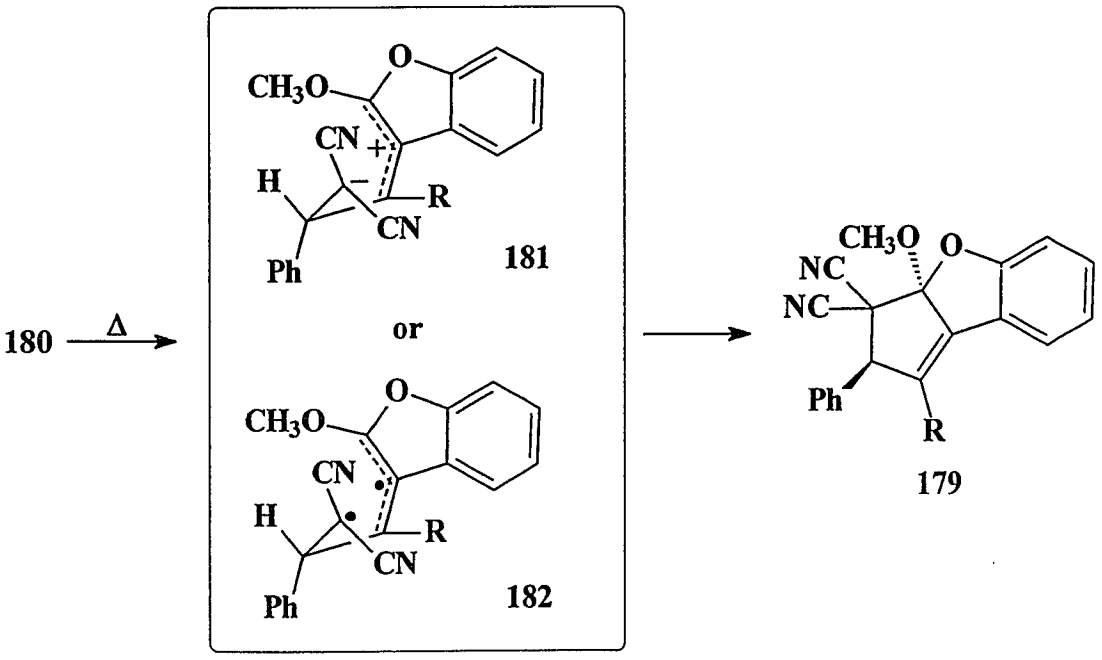
Scheme 49

Thermolysis of oxadiazoline **171** in the presence of benzylidenemalononitrile, in low concentration, led to the formation of one major product (R =H, 67 %; R = E, 37 % yield) (**180**) (Scheme 49). The formation of **180** was not expected, given that reactions of 3,3-dioxyvinylcarbene with benzylidenemalononitrile, or other similar electron deficient olefins, have been shown to form cyclopentene products in all previous examples studied. In both cases, the cyclopropane ring was formed with *trans* stereoselectivity. The formation of **180** can be attributed to a [1+2] cycloaddition of **174** with benzylidenemalononitrile. The stereochemistry observed can be explained simply on the basis of steric effects. The transition state involved in the [1+2] cycloaddition would preferentially have the benzofuran moiety anti to the phenyl group.

The surprising [1+2] cycloaddition of vinylcarbenes **174a** and **174b**, in the face of precedents for exclusive [3+2] cycloadditions by other similar systems, can be explained. Presumably both **174a** and **174b** have less 1,3-dipolar character than previously

demonstrated examples, and are therefore more likely to act as typical localized carbenes. The reduction in 1,3-dipolar character most likely arises from the aromatic nature of the benzofuran system.

It should be noted that both **180a** and **180b** undergo a slow vinylcyclopropane rearrangement to **179a** and **179b** at elevated temperatures.[135] Conversion into **179** was approximately 50 % complete after 4 days at 150 °C. Boger and Brotherton-Pleiss have shown that cyclopropyl ketene acetals such as **115** (Scheme 33), which are closely related to **180**, do not undergo vinylcylopropane rearrangement even at temperatures as high as 200 °C.[121] The observed vinylcyclopropane rearrangement, in the case of **179**, can be rationalized in terms of the presence of two cyano groups, which would help stabilize a zwitterionic (**181**) or biradical (**182**) intermediate involved in the conversion to the cyclopentenone (**179**) (Scheme 50).

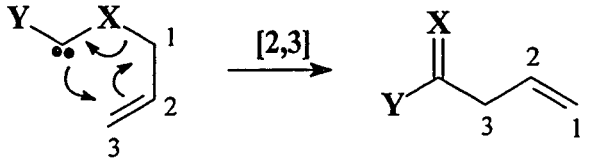


Scheme 50

Chapter 2 - Results and Discussion

2.1 - The Chemistry of Substituted Allyloxymethoxy Oxadiazolines

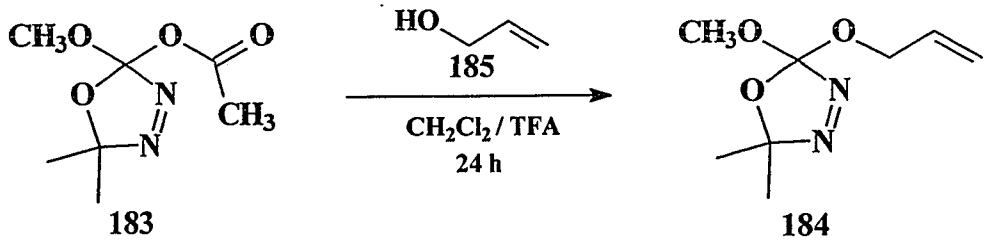
This section is an account of a detailed investigation into the thermal chemistry of substituted allyloxymethoxy oxadiazolines. Our initial efforts were focussed on observing intramolecular [2,3]-sigmatropic rearrangements of dialkoxycarbenes from an oxadiazoline precursor. It is well understood that dithio- and aminoöxycarbenes undergo this type of pericyclic process, however the rearrangement has not been observed for dialkoxycarbenes. Sigmatropic pericyclic rerrangements are concerted processes in which a bond migrates over a conjugated system. The [2,3]-sigmatropic rerrangement involves bond migration of three connected atoms over two connected atoms, a process involving reorganization of six electrons. Scheme 51 depicts a carbene [2,3]-sigmatropic rearrangement.



Scheme 51

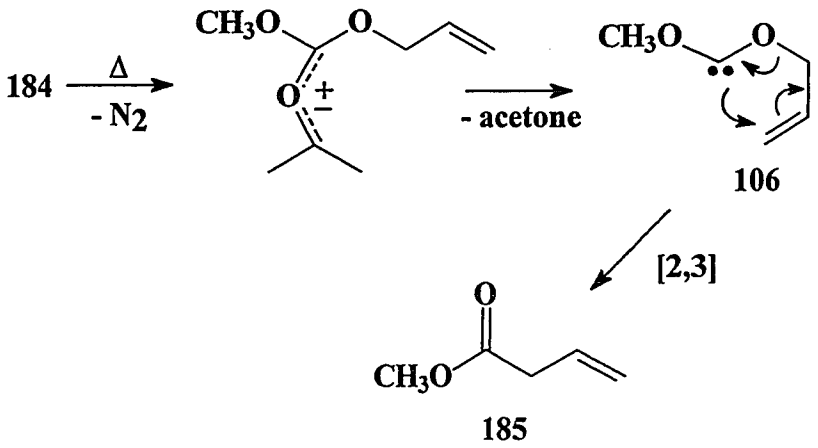
In an attempt to observe the first dialkoxycarbene [2,3]-sigmatropic rearrangement, the dialkoxycarbene precursor (**183**) was synthesized (Scheme 52). 2-Allyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**184**) was prepared by the Acetoxy Exchange Method pioneered by Warkentin and coworkers.[60] This process

involved the reaction of acetoxymethoxy oxadiazoline (**183**) and allyl alcohol (**185**). The procedure generally employs acetic acid as the catalytic acid, however, a stronger acid was needed for this exchange to proceed. Use of trifluoroacetic acid as the acid catalyst ensures virtually quantitative exchange in 24 h at ambient temperature.



Scheme 52

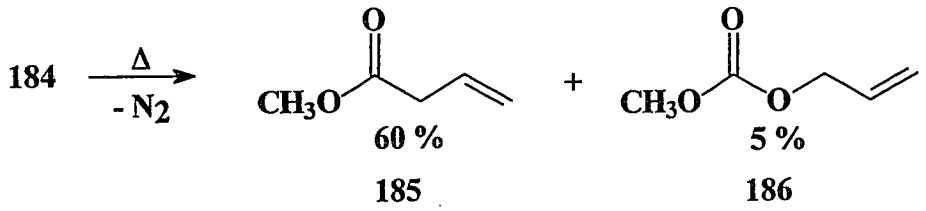
It is well established that thermolysis of dialkoxy oxadiazolines (**20**) affords dialkoxycarbenes (**18**), nitrogen, and acetone very efficiently (Scheme 53). Therefore, based on these precedents, thermolysis of **184** should afford allyloxymethoxycarbene (**106**). [2,3]-Sigmatropic rerrangement of **106** would yield the desired methyl-3-butenoate (**185**).



Scheme 53

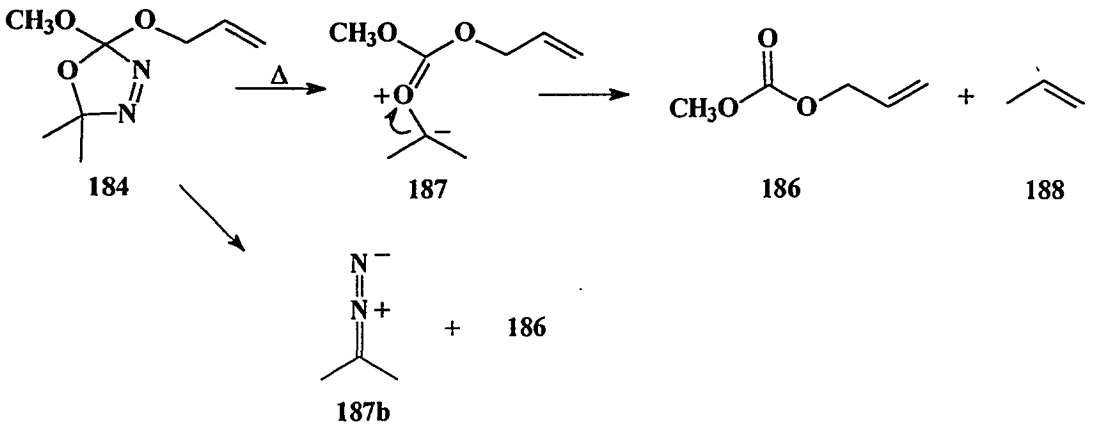
2.1.1 - Thermolysis of 2-Allyloxy-2-methoxy-Δ^3-1,3,4-oxadiazoline (**184**) in Benzene

2-Allyloxy-2-methoxy-Δ^3-1,3,4-oxadiazoline (**184**) was thermolyzed in benzene at 110 °C in a sealed tube for a period of 24 h. Analysis of the crude reaction mixture by GC and GC/MS indictated the production of one major product with a molecular ion corresponding to the mass of methyl-3-butenoate (**185**). Isolation of the major product by semi-preparative gas chromatography and its characterization by NMR spectroscopy confirmed that **185** (60 %, isolated) was indeed the major product from the thermolysis of **184**. One minor product (**186**) was isolated in 5 % yield (Scheme 54).



Scheme 54

Generation of minor product **186** was attributed to reverse decompostion of the carbonyl ylide (**187**), a proposed intermediate along the reaction coordinate pathway to carbenes (Scheme 55). Instead of affording allyloxymethoxycarbene (**106**), the ylide (**187**) could fragment in the opposite sense to yield carbonate **186** and dimethylcarbene. Dialkylcarbenes readily undergo fast 1,2-H migration, and therefore dimethylcarbene would afford propene (**188**). Although propene was not observed in this work, it has been observed in thermolyses of other oxadiazolines by Darren L. Reid (unpublished results). Another competing mechanism might involve a 1,3-dipolar cycloreversion from the oxadiazoline (**184**) to generate diazopropane (**187b**) and the carbonate (**186**) directly.



Scheme 55

At the time, the generation of **185** from the thermolysis of **184** was attributed to an unprecedented [2,3]-sigmatropic dialkoxycarbene rerrangement, depicted in Scheme 53. Synthetically, the reaction was very appealing because it constituted a convenient method for the production of β,γ-unsaturated esters.

To test the generality of the method, phenyl substituted allyloxymethoxy oxadiazolines (**189**, **190**, and **191**) were prepared (Figure 9).

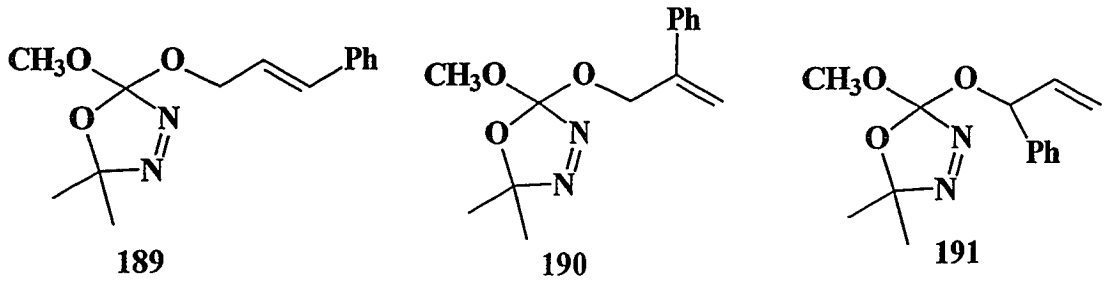
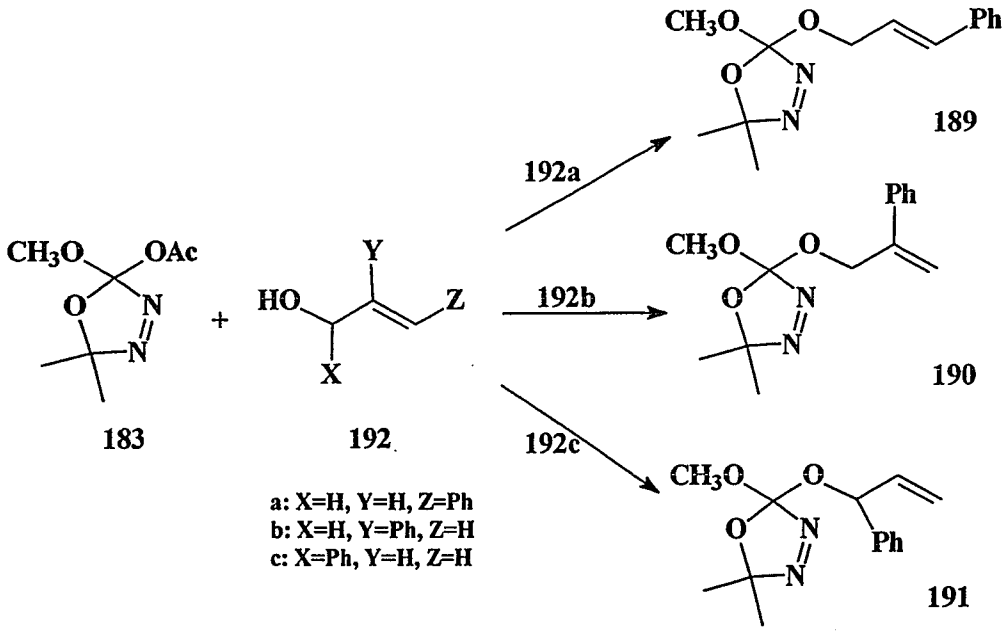


Figure 9

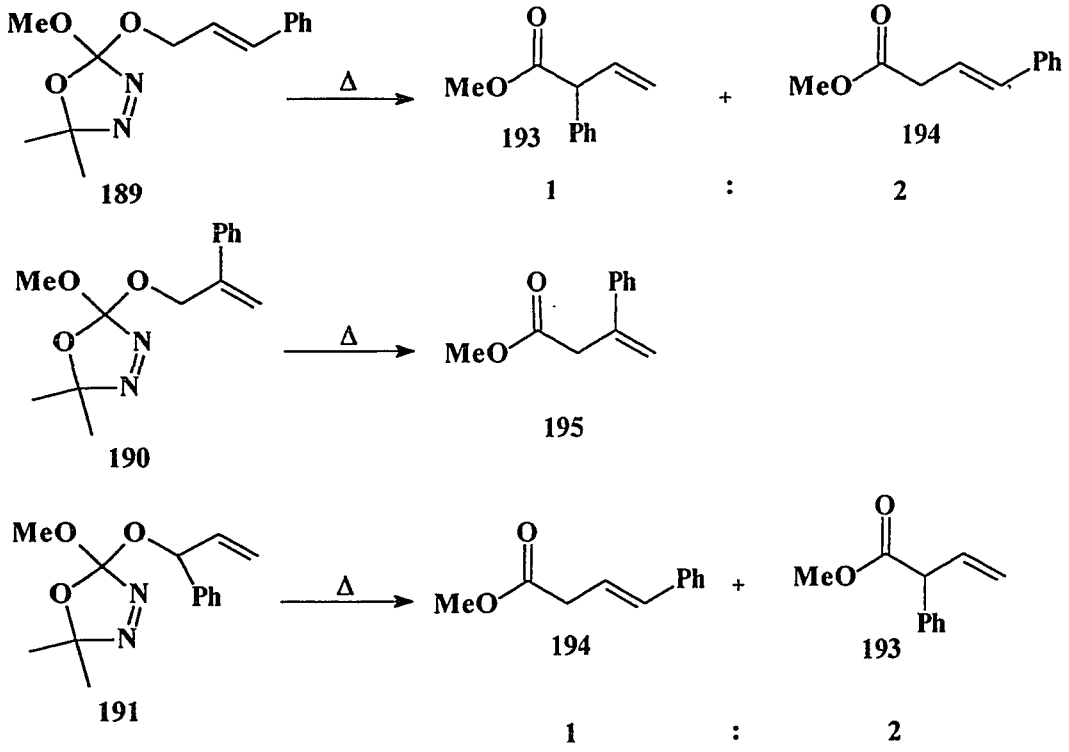
2.1.2 - Thermolysis of Phenyl Substituted Allyloxymethoxy Oxadiazolines (189-191)

2-Methoxy-2-allyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines (**189-191**) were prepared by the acid-catalyzed exchange reaction of the 2-acetoxy-2-methoxy oxadiazoline (**183**) with cinnamyl alcohol (**192a**), 2-phenyl-2-propen-1-ol (**192b**), and 1-phenyl-2-propen-1-ol (**192c**), repectively, Scheme 56. These exchange reactions were complete in 24 h when TFA was used as the catalysis acid.



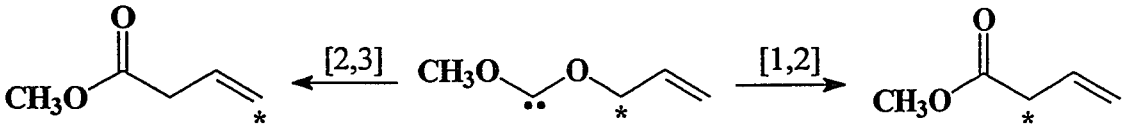
Scheme 56

Results of individual thermolysis experiments for oxadiazolines **189**, **190**, and **191** are depicted in Scheme 57. The experiments were carried out in a benzene solution (sealed tube) at 110 °C for 24 h. Both **189** and **191** afforded **193** and **194**, in a 1:2 and 2:1 ratio, respectively (total yields 60 %). Thermolysis of **190** afforded **195** as a single major product.



Scheme 57

These results might be accounted for with competitive [1,2]-migrations and [2,3]-sigmatropic rearrangements of carbene intermediates or through another mechanism possibly bypassing the carbene entirely. The pericyclic processes are illustrated in Scheme 58.

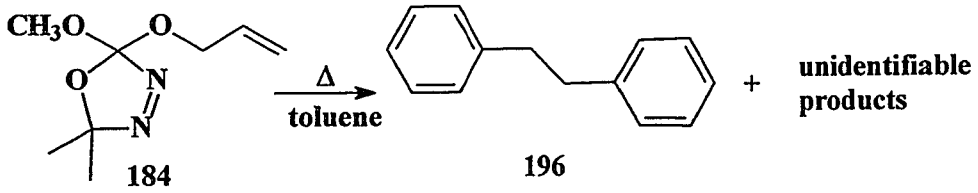


Scheme 58

2.1.3 - Thermolysis of 2-Allyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**184**) in Toluene

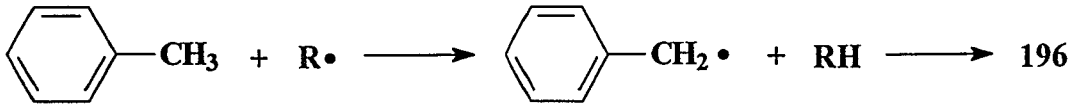
At the time, benzene was the most common solvent for studying the decompostion of oxadiazolines to carbenes. However, because of its lower toxicity and

higher boiling point, toluene often replaced benzene as the solvent of choice. When toluene was used as the thermolysis solvent for any of the allyloxymethoxy substituted oxadiazolines studied, an unusual result was observed. For example, thermolysis of allyloxymethoxy oxadiazoline (**184**) in toluene (sealed tube) at 110 °C for 24 h. afforded bibenzyl (**196**) as the only identifiable product (Scheme 59). Bibenzyl was confirmed by comparison of its GC/MS mass spectrum with a known literature mass spectrum.[136] The remainder of the GC and GC/MS traces was cluttered with many peaks, none of which could be identified except for the major peak, bibenzyl (**196**).



Scheme 59

This result prompted a serious investigation into the mechanistic aspect of the reaction sequence. The most likely explanation for the production of bibenzyl (**196**) was coupling of benzyl radicals (**197**) generated by hydrogen atom abstraction from toluene (**198**), a favourable process because of resonance stabilization of the benzyl radical (Scheme 60). The generation of radical intermediates by an alternative decomposition pathway of the oxadiazoline could initiate a host of radical reactions complicating the analysis of carbene derived products.



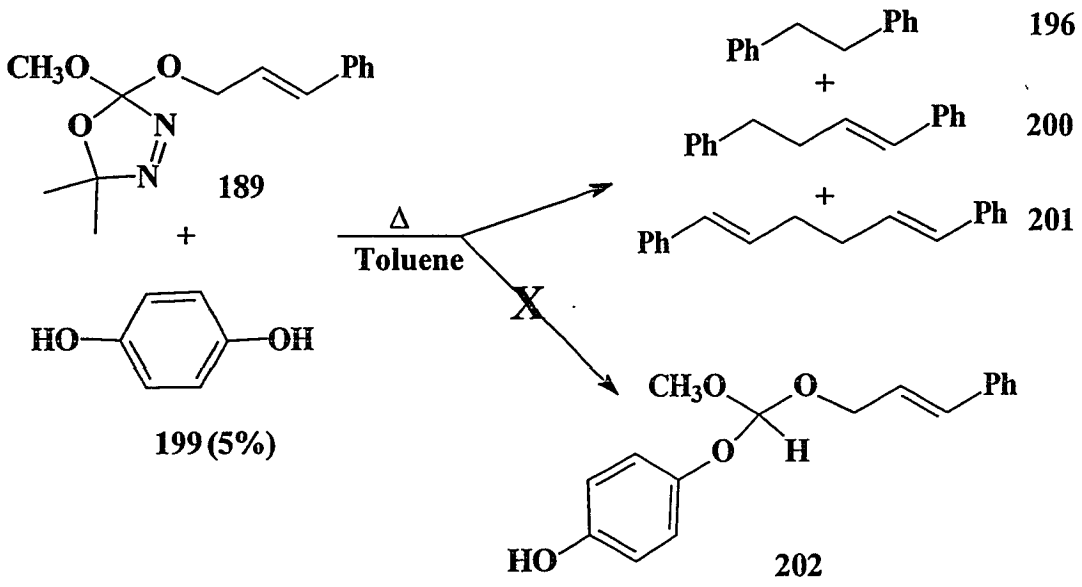
Scheme 60

In order to try to suppress the production of radical intermediates so that carbene derived products could be observed in toluene, an experiment was performed in the presence of a radical quencher.

2.1.4 - Thermolysis of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**189**) in the presence of Hydroquinone (**199**)

In order to try to suppress radical intermediates generated from the thermolysis of **189**, 5 % (w/w) hydroquinone (**199**) was added to a pre thermolysis solution in toluene. Heating the solution in a sealed tube for 24 h and analysis of the crude reaction mixture by GC and GC/MS showed a complex mixture of products, three of which could be identified by comparison with their known literature mass spectra (**196**, **200**, and **201**). The results are summarized in Scheme 61. The most likely explanation for production of **196** is coupling of benzyl radicals, as demonstrated in the previous experiment of **189** in toluene, in the absence of **199**. Compound **200** is a cross coupling product derived from a benzyl unit and a phenylallyl fragment, while **201** is accounted for by coupling of two phenylallyl fragments. Obviously, the formation of bibenzyl (**196**) derives from the solvent, toluene. If the thermolysis afforded radical intermediates, hydrogen abstraction from toluene to form benzyl radicals would undoubtedly occur giving rise to **196** by coupling of two benzyl radicals. The phenylallyl portion of compound **200** and **201** must have arisen from decomposition of the oxadiazoline moiety, however, the mechanistic detail was not understood at the time.

Carbene insertion into the OH bond of **199** to generate **202** was not observed. This was not too surprising since the thermolyis solution contained 5 % (w/w) hydroquinone with respect to oxadiazoline (**189**).

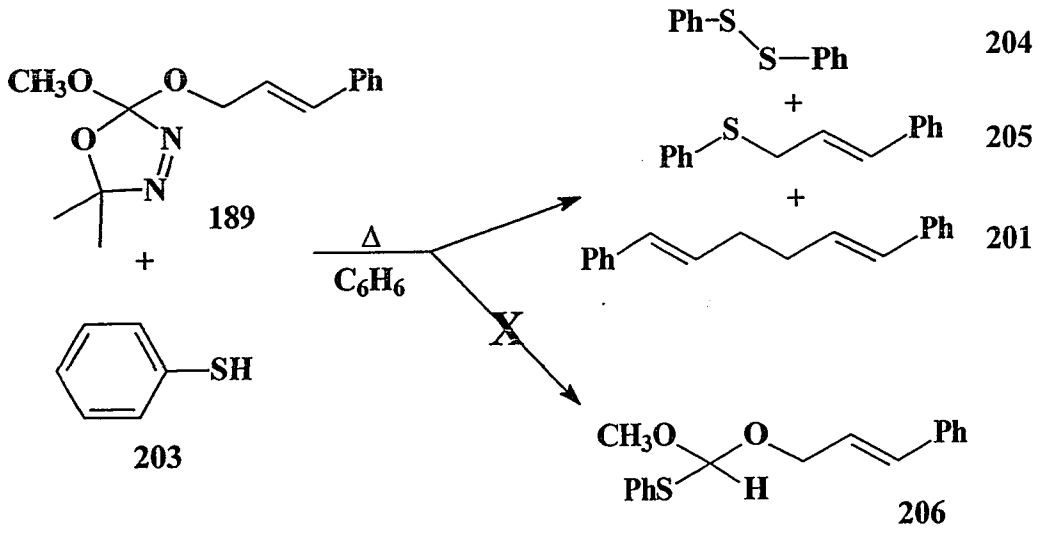


Scheme 61

If the mechanism for oxadiazoline decomposition in toluene involved the production of radical intermediates, the same radical intermediates should have been involved when the thermolysis was performed in benzene. To test this hypothesis, thermolysis of **189** in benzene containing an equimolar ratio of thiophenol (**203**) was studied. Radicals generated in the thermolysis would abstract a hydrogen atom from thiophenol to afford a phenylthiyl radical which could couple with other radicals present in the solution to form stable products. This result would provide strong evidence to support a radical mechanism.

2.1.5 - Thermolysis of **189** in the presence of Thiophenol (**203**) in Benzene

To a benzene solution of 2-cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**189**) was added an equimolar amount of thiophenol (**203**). The sample was sealed and placed into a pre-heated oil bath (80 °C) for a 20 h period. GC and GC/MS analysis of the crude reaction indicated the presence of compounds containing a phenylthiyl portion. The results are summarized in Scheme 62.



Scheme 62

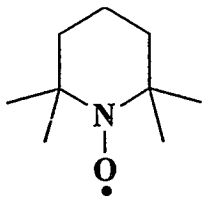
Compounds **204**, **205**, and **201** were the only identified products. The reaction mixture was very complex and evidence for the formation of **206**, the result of carbene insertion into the SH bond of **203**, and formal rearrangement products **193** and **194** could not be found, Scheme 57.

It now became questionable as to whether the mechanism for production of **193** and **194** involved a concerted pericyclic process at all or whether there was only radical pair chemistry involved. From the experiments described above, it was fair to say that radicals were involved in some way, however the extent of their involvement was not yet clear.

Through a series of trapping experiments discussed below, the initially postulated [2,3] and [1,2] pericyclic rearrangement mechanisms were shown to be incorrect.

2.1.6 - Thermolysis of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**189**) in the presence of 2,2,6,6-Tetramethylpiperidine-N-oxyl (TEMPO) (**207**)

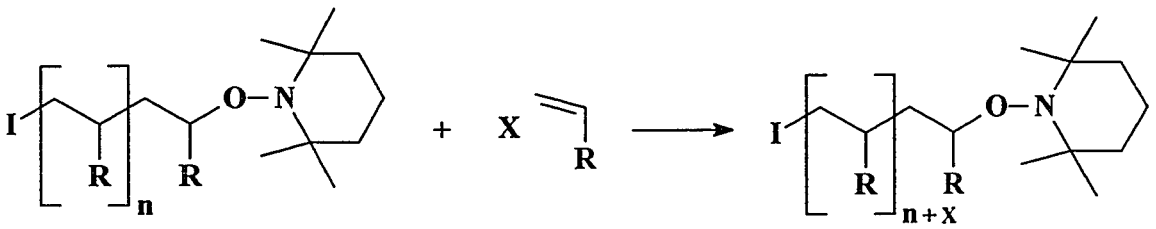
In order to gain insight into the unusual thermal chemistry of substituted allyloxymethoxy oxadiazolines we decided to try and trap some of the intermediates involved. In particular, we were very interested in trapping any radical intermediates involved in conversion of **189** to esters **193** and **194**. To accomplish this goal we decided to use 2,2,6,6-tetramethylpiperidine-*N*-oxyl (**207**) (TEMPO) (Figure 10).



207

Figure 10

TEMPO has been used extensively in the radical polymerization reactions.[137,138] In the polymer industry,TEMPO is a convenient new tool for obtaining living free radical chains that are capable of yielding polymers of uniform length. TEMPO acts by forming a weak bond with the carbon centered radical of the growing polymer. Living free radical chains are possible because of the reversible homolytic reaction to regenerate the polymer radical and the stable TEMPO radical. At this time, any excess monomer present can add to lengthen the polymer chain. TEMPO then reforms the covalent bond with the newly extended polymer chain, creating a so called "living free radical" (Scheme 63).



I = initiator, X = monomer units

Scheme 63

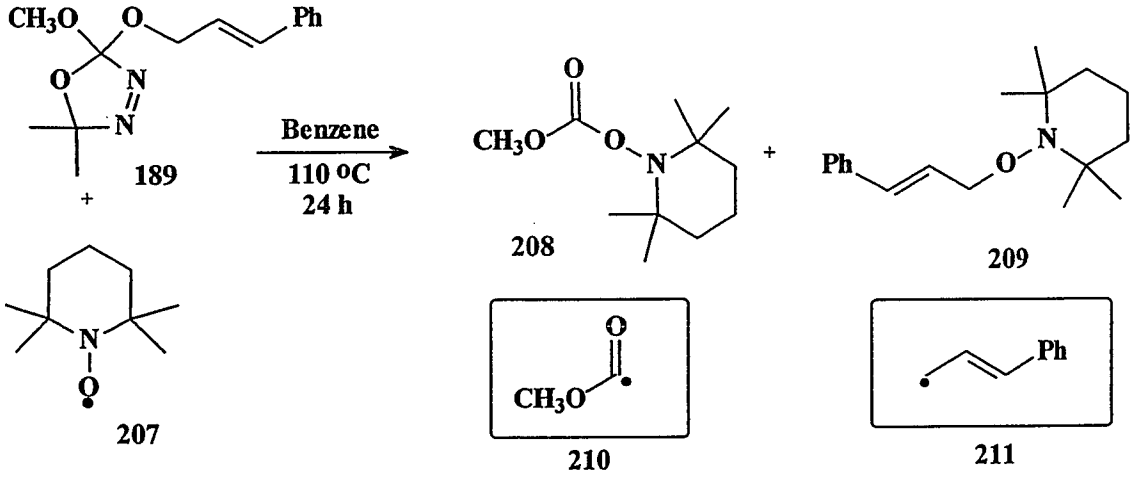
Fukuda and coworkers estimated the equilibrium constant for the reversible polystyrenyl radical coupling with TEMPO to be 2.1 x 10^{-11} mol L^{-1} at 125 °C.[139] Assuming a similar equilibrium constant and using the fact that radical coupling reactions with TEMPO have a rate constant on the order 1.0 x 10^{9} $M^{-1}s^{-1}$ (25 °C), according to Newcomb,[140] the rate constant, for the reverse reaction (TEMPO-R → TEMPO + R·) can be estimated to be at most 2.0 x 10^{-2} $M^{-1}s^{-1}$ at 110 °C.

With regard to radical trapping with TEMPO, the equilibrium at 110°C should lie very much to the side of TEMPO-Radical adducts and therefore TEMPO should be a good trap for radical intermediates from oxadiazolines and/or carbenes, whatever be their source. Initially we were unclear if **207** was a good choice, but as it turned out, it was ideal.

2.1.7 - Thermolysis of **189** in the presence of **207** in Benzene at 110 °C

Thermolysis of **189** in the presence of **207** led to the isolation of two major products (**208** and **209**) along with recovered TEMPO (Scheme 64). The products were isolated by chromatography and fully characterized by spectroscopic methods. Compound **208** is the result of radical coupling of TEMPO with methoxycarbonyl radical (**210**) while **209** arises from phenylallyl radical (**211**) coupling with **207**. GC/MS of the

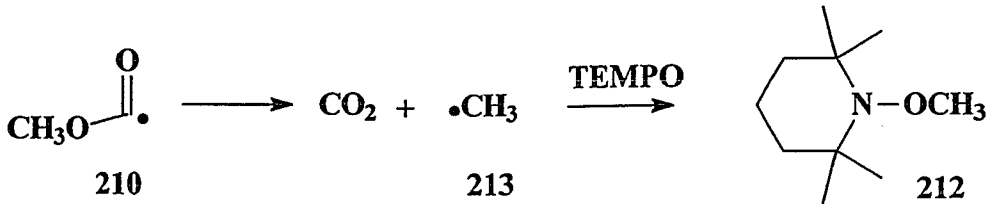
crude reaction mixture revealed the presence of esters **193** and **194**, however in much smaller quantities than observed in the absence of radical trap. Yields of **193** and **194** dropped with increasing [TEMPO], but traces of the esters (**193** and **194**) could always be detected by GC. When the [TEMPO] was as high 2M, approximately 2-5 % of combined esters **193** and **194** were observed by GC/MS. That was not surprising because TEMPO should not trap caged radical pairs and because TEMPO adducts of radicals can regenerate those radicals upon heating.



Scheme 64

2.1.8 - Thermolysis of **189** in the presence of **207** in Benzene at 80 °C

Decomposition of **189** in the presence of **207** under a different set of conditions, 80 °C for 5 days, led to an identical product composition to that of 2.1.7, except for the addition of one new product (**212**). The lower temperature experiment led to the isolation and characterization of methyl-TEMPO adduct **212** (Scheme 65).



210 213 212

Scheme 65

Trapping of the methyl radical (**213**) with TEMPO to afford **212** most likely arose from decomposition of the methoxycarbonyl radical (**210**) to yield CO_2 and **213**. Evidence for this process was demonstrated by Terlouw and co-workers in their study of **210** in the gas phase.[141] Hassinen and coworkers calculated a rate constant of $k = 1\ s^{-1}$ at 25 °C for this process by GC product studies in which **210** was generated photochemically.[142]

Trapping of **213** with TEMPO (**207**) in the low temperature experiment (80 °C / 5 d) can be readily explained. In the higher temperature thermolysis experiment (110 °C / 1 d), the rate constant for decomposition of **210** to CO_2 and **213** would be much larger than the lower temperature experiment. At the elevated temperatures described for both experiments, Levy and Szwarc have provided evidence to suggest that methyl radicals generated in the thermolysis attack benzene.[143] In the higher temperature experiment the rate constant for methyl radical addition to benzene must be larger that the rate constant in the lower temperature experiment for the same process.

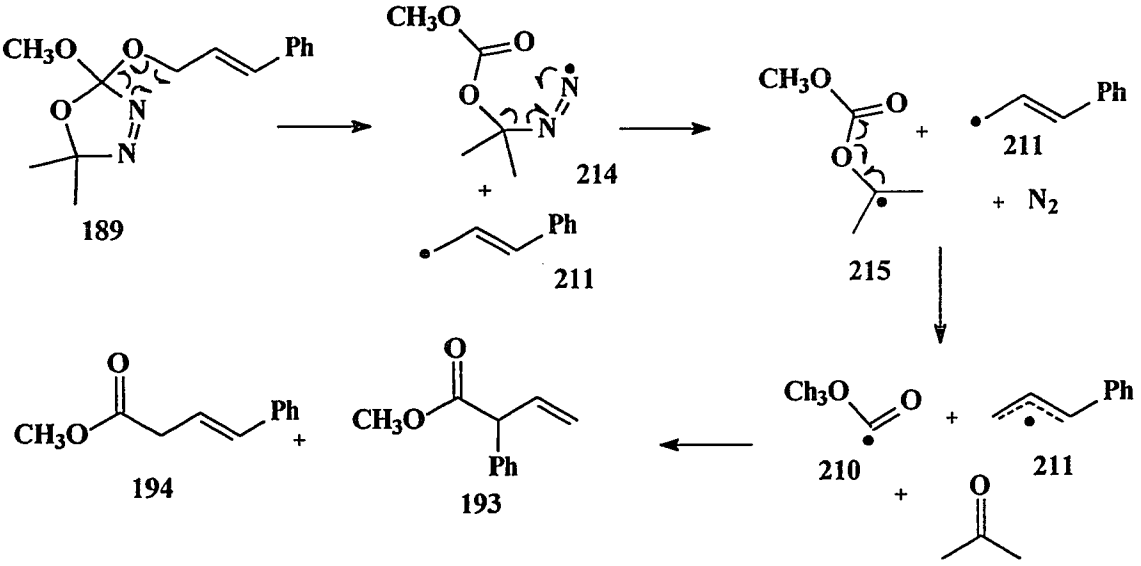
The TEMPO experiments previously described have definitely proven that methoxycarbonyl (**210**) and phenylallyl (**211**) radicals derive from thermolysis of substituted allyloxymethoxy oxadiazolines. In order to define the mechanism for conversion of substituted allyloxymethoxy oxadiazolines into the observed ester products we needed evidence for the presence or absence of a carbene intermediate.

Initial thoughts of mechanisms involving radicals were a little peculiar at the time. Our mechanistic biases favoured carbene chemistry but, putting those aside, we could envision two radical mechanisms which would yield the observed products **193** and **194**.

2.1.9 - Two Proposed Radical Mechanisms for Production of **193** and **194**

Mechanism #1:

The first idea was based upon an unprecedented oxadiazoline decomposition affording radicals directly without a carbene intermediate (Scheme 66).

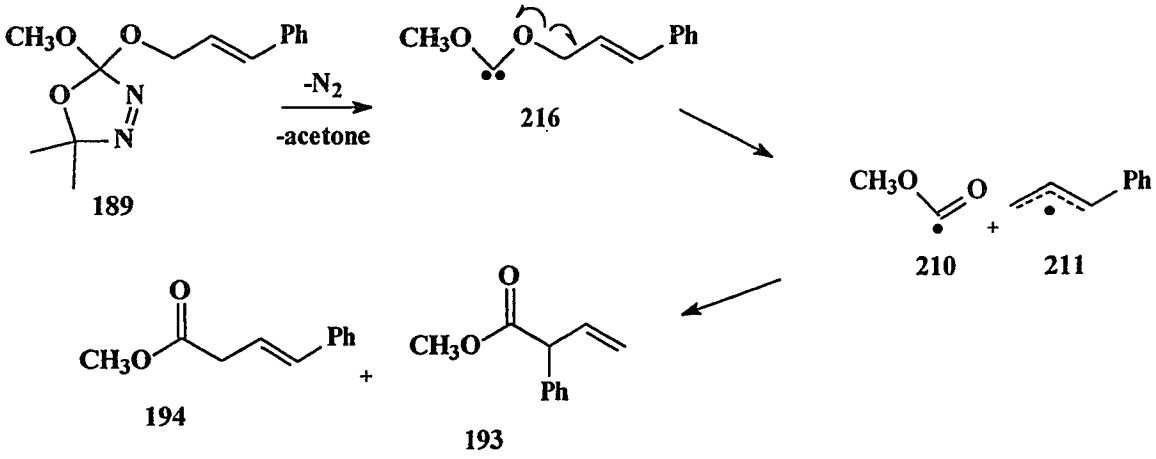


Scheme 66

The first step would involve a homolytic two-bond cleavage to afford diazenylcarbonate radical **214** and phenylallyl radical **211**. Loss of a nitrogen molecule from **214** could potentially afford radical **215**. Alternatively, the initial fragmentation could lead directly to **215**. β-Scission of **215** might afford acetone and methoxycarbonyl radical **210**. Coupling of **211** and **210** would give the experimentally observed products **193** and **194**.

Mechanism #2

In a precedented fashion, thermolysis of cinnamyloxymethoxy oxadiazoline (**189**) would lead to loss of nitogen and acetone to afford cinnamyloxymethoxycarbene (**216**) (Scheme 67). A homolytic β-scission of **216** would generate methoxycarbonyl radical (**211**) and phenylallyl radical (**210**). Coupling of **210** and **211** would give the desired esters **193** and **194**. From a Frontier Molecular Orbital perspective, β-scission of singlet carbene **216** was not completely understood at the time. The problem with β-scission of the triplet carbene was simply the inaccessibility of that carbene, with $\Delta E_{S-T} > 70$ kcal/mol.



Scheme 67

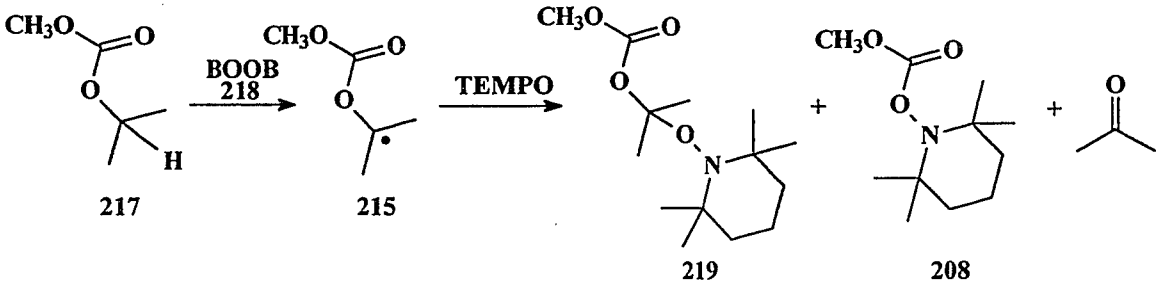
One of the best ways to determine mechanistic pathways is to trap intermediates along the way. The major differences between mechanism #1 and mechanism #2 are the intermediates. Mechanism #1 contains a proposed isopropyl methyl carbonate radical (**215**) and mechanism #2 contains a carbene intermediate (**216**). Trapping either of these intermediates would support one of the mechanistic pathways. The following

experiments describe the outcome of attempts to trap the above-mentioned intermediates (**215** and **216**).

2.1.10 - Isopropyl Methyl Carbonate (**217**) + BOOB (**218**) + TEMPO (**207**)

One way to test mechanism #1 (Scheme 66) was to generate intermediate **215** independently in the presence of TEMPO. Product analysis revealing both **219** and **208** adducts would provide evidence for mechanism #1 (Scheme 68).

The simplest method for generating **215** appeared to be hydrogen atom abstraction from isopropyl methyl carbonate (**217**) (Scheme 68).



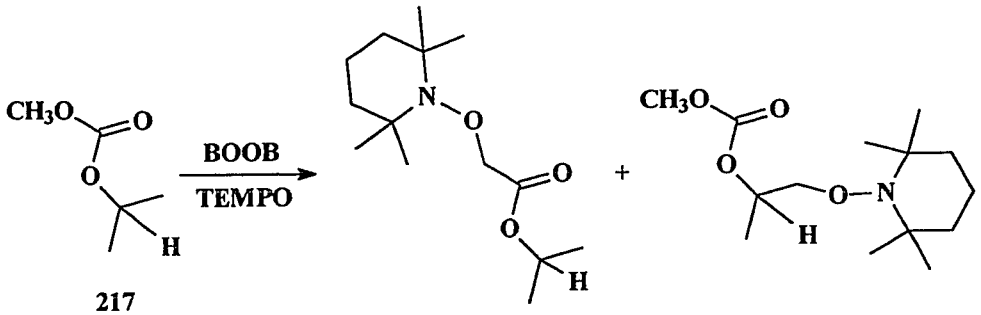
217 215 219 208

Scheme 68

Isopropyl methyl carbonate (**217**) was prepared by a base catalyzed reaction of isopropanol and methylchloroformate. It was thought that radical **215** could be generated by reaction with *tert*-butoxyl radicals. Di-*tert*-butylperoxide (BOOB) decomposes either thermally or photochemically to generate *tert*-butoxyl radicals which could potentially abstract the methine hydrogen of **217** to produce radical **215**.

Given that the decomposition rate constant[144] of BOOB is 1.4 $x10^{-6}s^{-1}$ at 110 °C, isopropyl methyl carbonate (**217**), TEMPO (**207**) and BOOB (**218**) were combined and heated in a sealed thermolysis tube at 110 °C for 24 h. Two products (**220** and **221**) were isolated from the reaction mixture and characterized by NMR spectroscopy and mass spectrometry (Scheme 69). These products are a direct result of H abstraction from two

of the three possible positions on **217,** followed by radical coupling with TEMPO. Although **220** and **221** were the only identifiable products, generation of **215** could not be ruled out. It is possible that **219** reverts to **215** and TEMPO with a rate constant much larger than that of **220** and **221.** This makes sense because one is comparing a primary radical to a tertiary one. Compound **215** could then have disproportionated to give a volatile product that was removed in vacuo.



217 **220** **221**

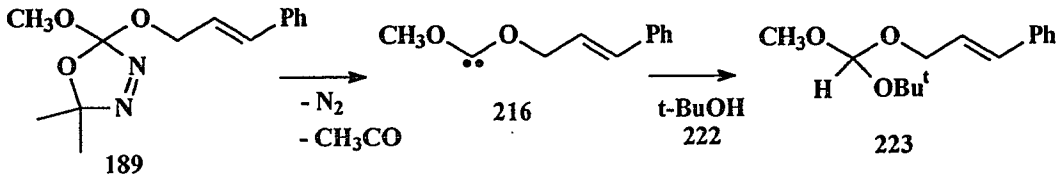
Scheme 69

No conclusions could be made from the isopropyl methyl carbonate experiment. Further attempts to prove mechanism #1 were abandoned as a result of the following experiment.

2.1.11 - Thermolysis of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (189) in the presence of *tert*-Butyl Alcohol (222)

Conclusive evidence for formation of cinnamyloxymethoxycarbene was obtained from the thermolysis of cinnamyloxymethoxy oxadiazoline (**189**) in the presence of *tert*-BuOH (**222**). Dialkoxycarbenes are known to react with alcohols to form orthoformate products via carbene insertion into the OH bond of the alcohol. Therefore, observation of an orthoformate product, in the case of dialkoxycarbenes, identifies the presence of carbene intermediates.

Thermolysis of cinnamyloxymethoxy oxadiazoline (**189**) in the presence of *tert*-butyl alcohol afforded the desired orthoformate as a major isolated product in 70 % yield (Scheme 70). Isolation and identification of **223** provided conclusive evidence for carbene intermediate **216**. The yields of esters **193** and **194** as a function of [*tert*-BuOH] were shown to be interdependent, as the [*tert*-BuOH] was increased, more orthoformate was generated and less ester products were produced (Figure 11). This information was very important because it revealed, for the first time, that the methoxycarbonyl radical (**210**) and the phenylallyl radical (**211**) must have originated from **216** and not from another source.



Scheme 70

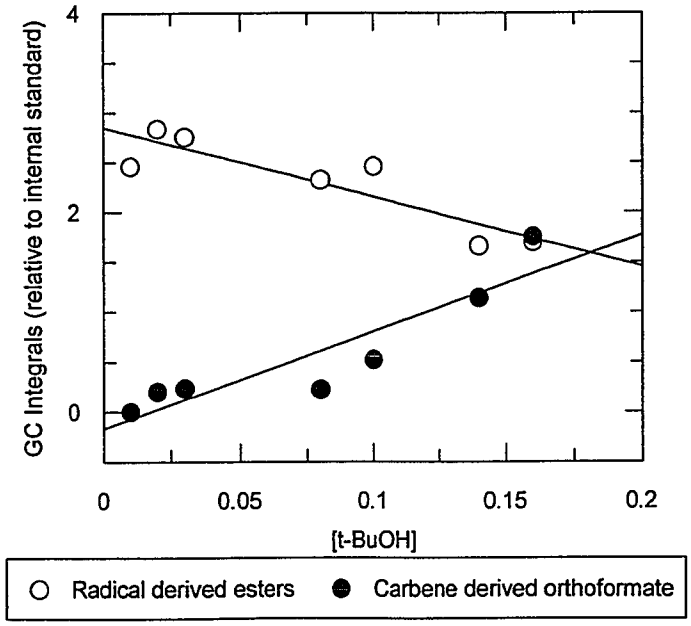


Figure 11

2.1.12 - Unimolecular Decomposition Rate Constant For Thermal Dissociation of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**189**)

The rate constant for the unimolecular thermal dissociation of cinnamyloxymethoxy oxadiazoline (**189**) was determined by NMR spectroscopy. The oxadiazoline concentration at 110 °C with respect to time was monitored by ^{1}H NMR spectroscopy. A plot of the ln [oxad] vs time afforded a rate constant of 7.5 x 10^{-5} s^{-1} (Figure 12). This value was similar to other thermal dialkoxy oxadiazoline decomposition rate constants determined by the same method, indicating a similar mechanism of dissociation.

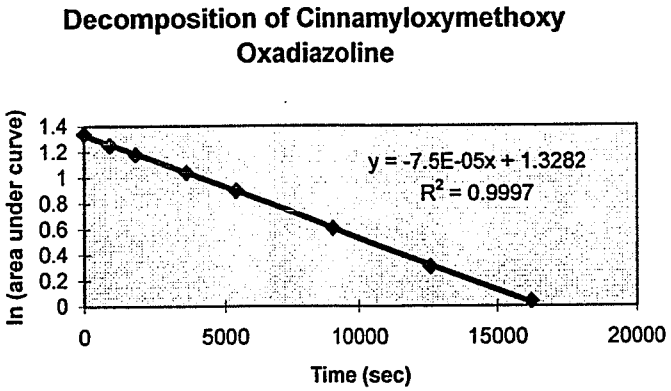
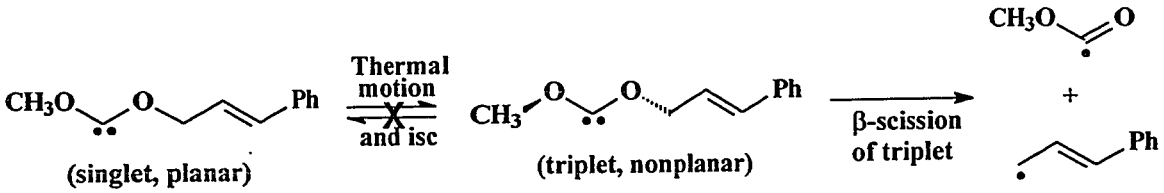


Figure 12

2.1.13 - Recent Theoretical Investigations into Homolysis of Singlet Dioxy- and Dialkoxycarbenes

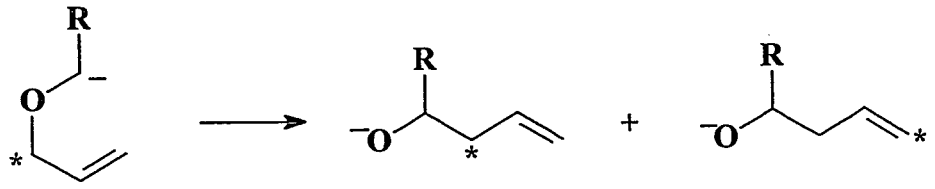
Given that sigmatropic rearrangement of analogous (bisheteroatom) carbenes is well known,[91-93, 118] the fragmentation of allyloxycarbenes to radicals was surprising. One mechanism to explain the fragmentation of carbene **216** to radicals (Scheme 11)

would involve intersystem-crossing to the triplet carbene and formation of the double bond of the methoxycarbonyl radical by β-scission (Scheme 71).



Scheme 71

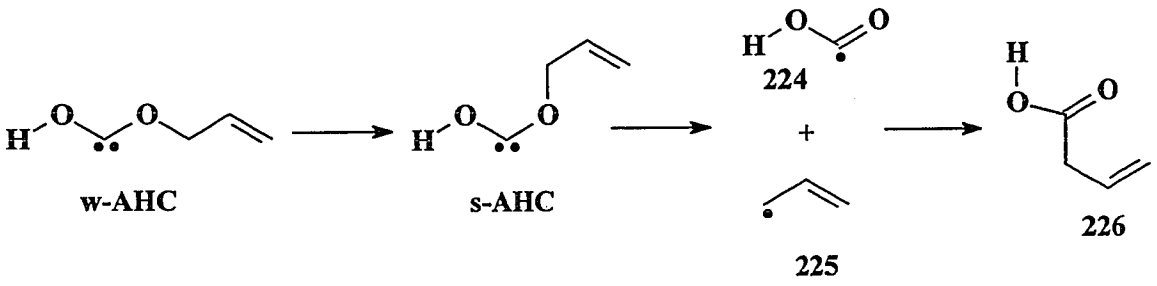
Although the singlet and triplet states of nonplanar dihydroxycarbene are almost degenerate at lower levels of theory[145] and separated by ca. 20-37 kcal mol^{-1} at higher levels of calculation,[146,147] there is a barrier between the planar singlet ground state and the nonplanar triplet state of ca. 76 kcal mol^{-1} (in dimethoxycarbene (**8**)).[51] Thus the triplet mechanism is most unlikely. Moreover, it is difficult to accommodate the observed preference for the ester that is most closely related to the geometry of the starting carbene with a triplet mechanism. That preference, although it is not completely understood at this time, implies very fast coupling, competitive with separation by diffusion. The [2,3]-Wittig rearrangement (Scheme 72), which occurs with partial retention of configuration,[148,149] is reminiscent of the "memory effect" observed here.



Scheme 72

There have been only a few theoretical investigations of the mechanism by which dialkoxycarbenes dissociate into radical pairs.[150,151] Recently, Reid and Warkentin have performed density functional and Moller-Plesset calculations on the model system,

CH_2=$CHCH_2O(OH)C$:.[152] They compared the calculated energy values for the [1,2]-migration, [2,3]-sigmatropic rearrangement, β-scission of the triplet, and homolysis from the singlet state. They determined that the lowest energy path to the ester analogues of **193** and **194** was through homolysis of the singlet carbene to radicals, followed by coupling. The proposed pathway involves an initial carbene conformation change from the w-confomer to the s-confomer of the singlet carbene, followed by homolysis to afford the hydroxycarbonyl radical (**224**) and allyl radical (**225**), which couple to the observed ester **226** (Scheme 73).



Scheme 73

Reid and co-workers also performed a theoretical study of hydroxycarbene as a model for the homolysis of oxy and dioxycarbenes at the CAS and MRCI levels of theory using the cc-pVDZ basis set.[153] The atomic and molecular properties were examined using the Theory of Atoms in Molecules.[154] That study also indicated that homolysis of the singlet carbene is a viable mechanism.

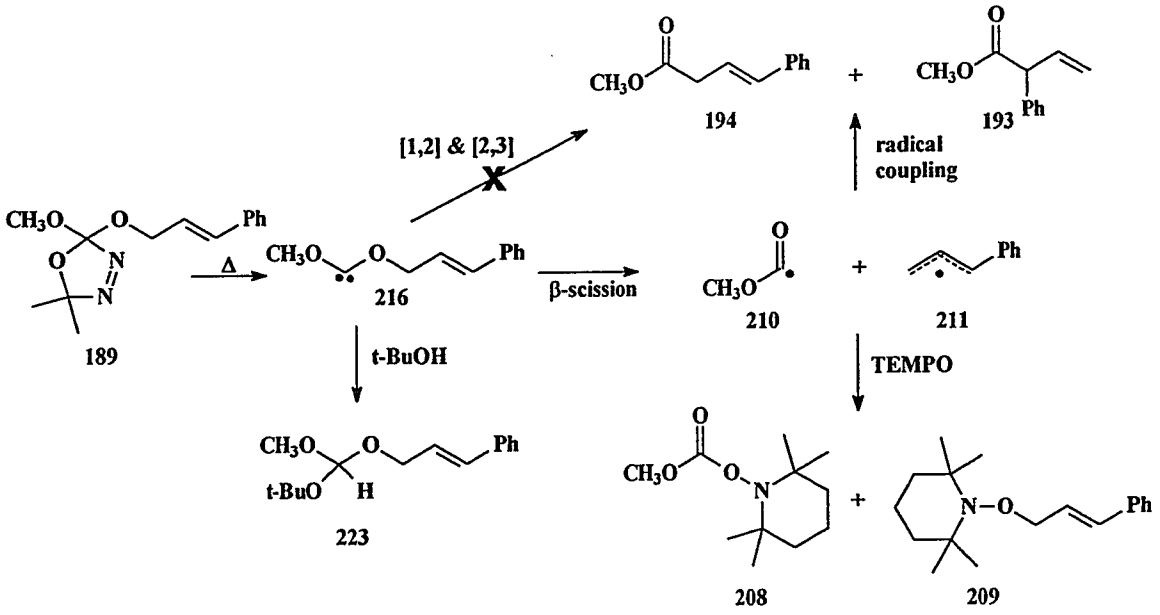
2.1.14 - Summary: Thermolysis of Substituted Allyoxymethoxy Oxadiazolines

Cinnamyloxymethoxy oxadiazoline (**189**) decomposes thermally with a rate constant of 7.5 x $10^{-5}s^{-1}$ to afford cinnamyloxymethoxycarbene (**216**) cleanly. Carbene formation was heavily supported by carbene trapping with *tert*-butyl alcohol. In the

presence of TEMPO, methoxycarbonyl (**210**) and phenylallyl (**211**) radicals were trapped to give product **208** and **209**, while in the absence of traps and hydrogen donors, products **194** and **193** were observed (Scheme 74).

This work provided the first conclusive evidence for dialkoxycarbene fragmentation to radicals in which both the carbene and the radicals could be trapped.[155] Calculations using model systems favour a mechanism involving homolysis of the singlet carbene, which is in agreement with the presence of a large energy barrier between the singlet and triplet state.

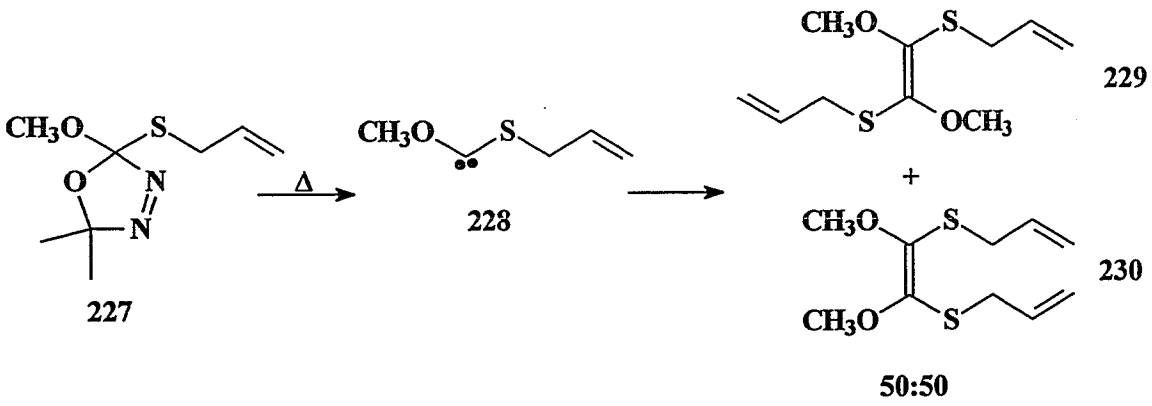
Recently, Merkley and coworkers have discovered that benzyloxymethoxy- as well as dibenzyloxycarbenes also dissociate to radical pairs in solution.[156,157]



Scheme 74

2.2 - Thermolysis of 2-Allylthio-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (227)

In studying thermolyses of substituted allyloxymethoxy oxadiazolines we also became interested in the possible sigmatropic rearrangements of allylthioalkoxy oxadiazolines. Allylthiomethoxy oxadiazoline (**227**) was prepared by the acetoxy exchange with commercially available allyl mercaptan. Thermolysis of allylthiomethoxy oxadiazoline in dichloromethane did not afford the sigmatropic product but did afford carbene dimers **229** and **230** (Scheme 75). Products derived from fragmentation of the carbene to radicals were not observed.

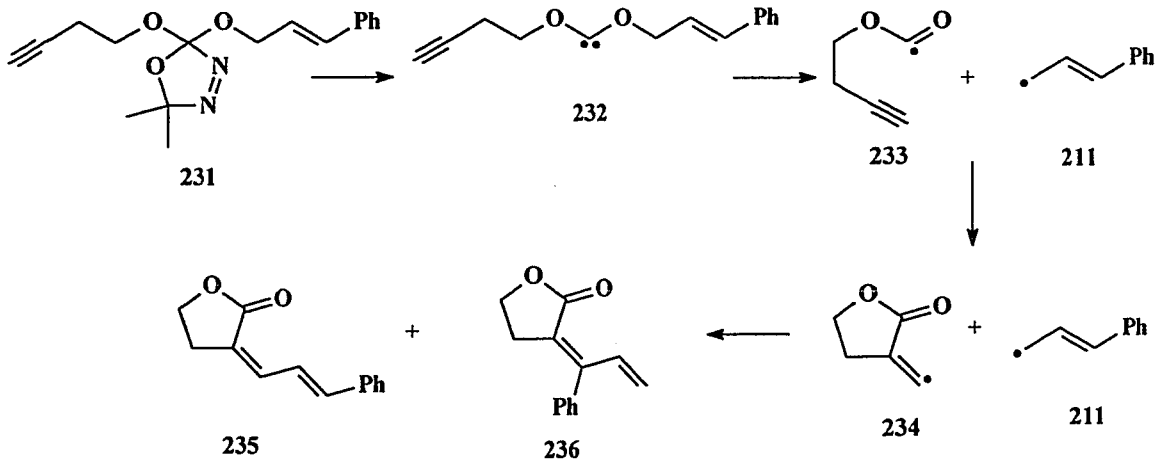


Scheme 75

The replacement of oxygen with sulfur has a dramatic effect on the product outcome. The sulfur atom appears to lower the reactivity of the carbene relative to the oxygen analogue and the carbene prefers to dimerize rather than rearrange or fragment.

2.3 - Thermolysis of 2-Butynoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (231)

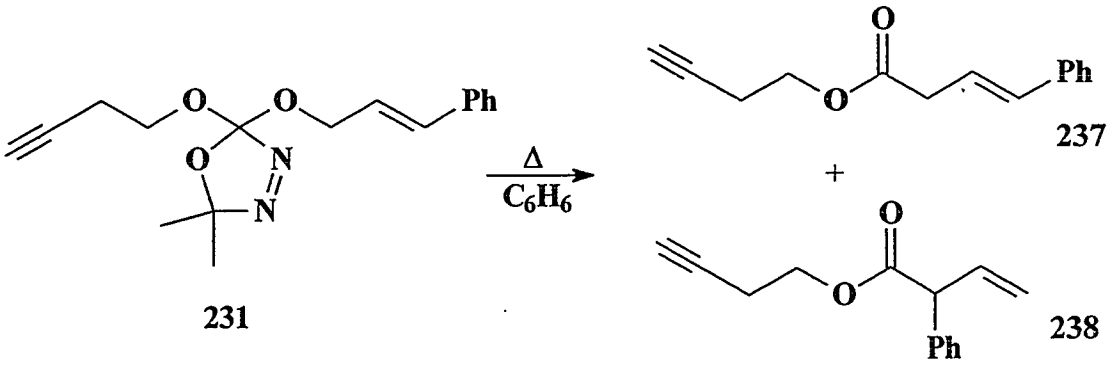
In an attempt to study intramolecular radical cyclizations initiated from carbene homolyses, oxadiazoline **231** was prepared. It was initially postulated that thermolysis of **231** would afford carbene **232**, which might fragment to radicals **233** and **211**. Cyclization of the newly generated butynoxycarbonyl radical (**233**) onto the alkyne would potentially afford radical intermediate **234**. Coupling with phenylallyl radical (**211**) would terminate the process to afford compounds **235** and **236** (Scheme 76).



Scheme 76

2.3.1 - Thermolysis of 2-Butynoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (231) in Benzene

Heating a solution of **231** in benzene for 24 h at 110 °C led to the isolation and characterization of compounds **237** and **238** in a ratio of 2:1.



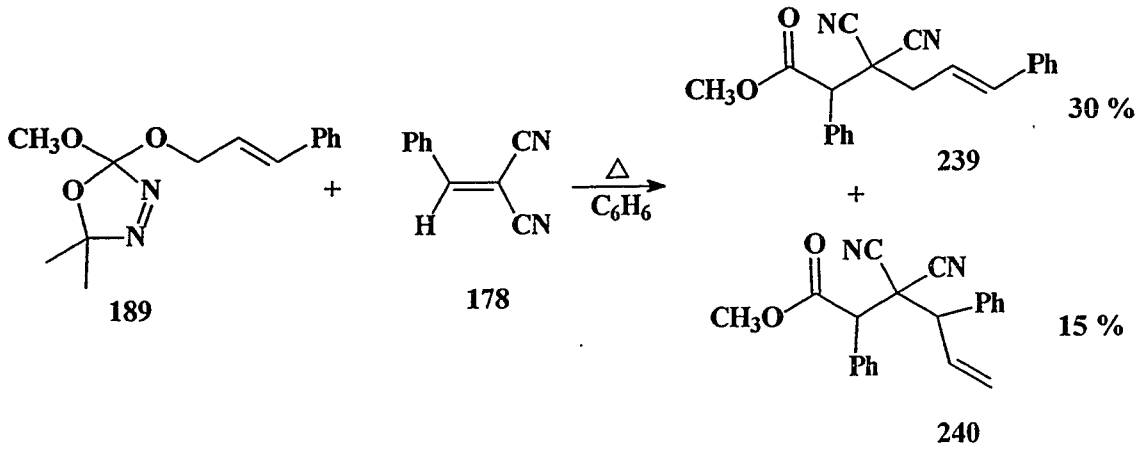
Scheme 77

The observed products can be accounted for by thermal decomposition of **231** to afford **232**, followed by homolysis of **232** to radicals **233** and **211** which couple to yield compounds **237** and **238**. Products derived from both intramolecular radical and intramolecular carbene additions to the tethered alkyne were not observed. It appears that fragmentation to radicals occurs with a rate constant that is larger than that of intramolecular carbene addition to the alkyne.

2.4 - Carbene Homolysis Followed by Regioselective and Order-selective Radical Addition to an Olefin

This section will provide details of an unusual reaction involving a regioselective and order-selective radical addition to an electron-deficient olefin.

Thermolysis of cinnamyloxymethoxy oxadiazoline (**189**) in the presence of benzylidenemalononitrile (**178**) in benzene at 110 °C for 24 h afforded products **239** and **240** in 2:1 ratio (Scheme 78) in a combined, isolated yield of 45 %

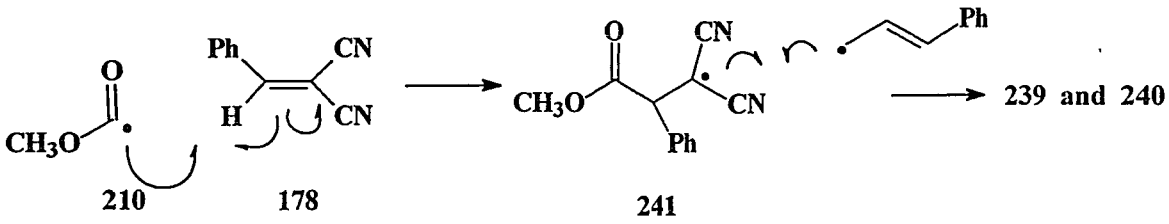


Scheme 78

A radical mechanism is most likely because the recently-described[155] thermolysis chemistry of cinnamyloxymethoxy oxadiazoline (**189**) showed that, under the reaction conditions for the experiment described here, cinnamyloxymethoxy carbene (**216**) is generated first. A β-scission of that carbene yields the methoxycarbonyl (**210**) and the phenallyl (**211**) radicals, which couple to afford esters **194** and **193** (Scheme 74).

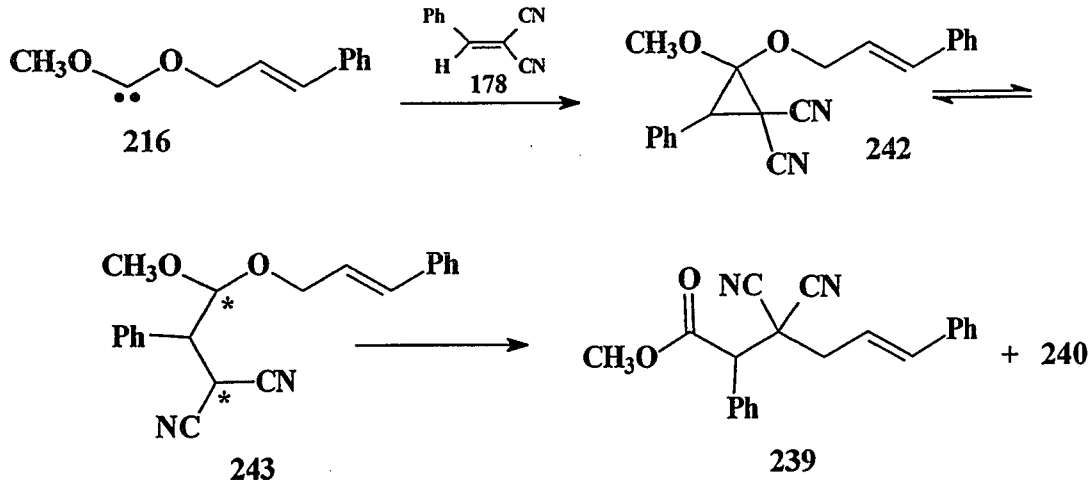
Analysis of the products of the benzylidenemalononitrile experiment (Scheme 78) by GC/MS indicated the presence of trace amounts of **194** and **193** as well as two products derived from combination of phenallyl radicals (**211**). This result is a further indicator of a mechanism involving radicals.

Addition of the methoxycarbonyl radical (**210**) to benzylidenemalononitrile (**178**) at the benzylic position would produce a 1,1-dicyanoalkyl radical (**241**) which, upon coupling with the phenallyl radical **211** would yield the corresponding products **239** and **240** (Scheme 79).



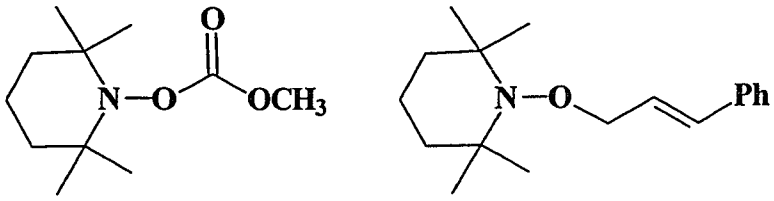
Scheme 79

An alternative mechanism might involve addition of carbene **216** to **178** in a [1+ 2] cycloaddition reaction to generate a cyclopropane intermediate **242**, followed by subsequent rearrangement via a dipole or a diradical (**243**) (Scheme 80).



Scheme 80

To probe further for a reaction mechanism, a stable free radical (TEMPO) was included with cinnamyloxymethoxy oxadiazoline (**189**) and benzylidenemalononitrile (**178**) in an attempt to intercept any radical intermediates. The major products isolated from this reaction were **208** and **209**, generated from radical coupling of the methoxycarbonyl (**210**) and phenylallyl (**211**) radicals with TEMPO (Figure 13). The alternative product of trapping the phenallyl radical was not observed. Trace amounts of



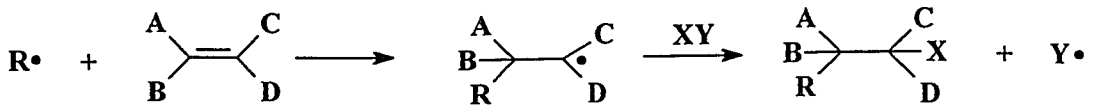
208 209

Figure 13

esters **193** and **194**, as well as the products of coupling of phenylallyl radicals were detected by GC/MS. Compounds **239** and **240**, which would also be expected if Scheme 80 were applicable, were not detected. These results, together with the background information about **216**, provide strong evidence that a radical pair mechanism is at work.

None of the other three products possible from addition of the two different radicals to benzylidene malononitrile were found. Thus, the radical additions appear to be not only regioselective but also order-selective, the methoxycarbonyl radical (**210**) adding first, in the sense of Scheme 79. The adduct radical so formed (**241**) then couples with phenylallyl only (primarily). The apparent selectivity of **241**, favouring phenallyl over methoxycarbonyl radicals is not likely to be real, because coupling reactions should not have large activation energies. Most likely it is the result of a buildup of the concentration of phenylallyl radicals (**211**) relative to that of the more reactive methoxycarbonyl radicals (**210**). Such a concentration gradient would have to follow if methoxycarbonyls were to add much faster than phenallyl radicals.

The ability to add radicals as diverse as **210** and **211** to a double bond is clearly of interest. In general, effective radical additions to alkenes are chain transfer processes involving a radical-alkene addition followed by a radical-molecule reaction, Scheme 81.

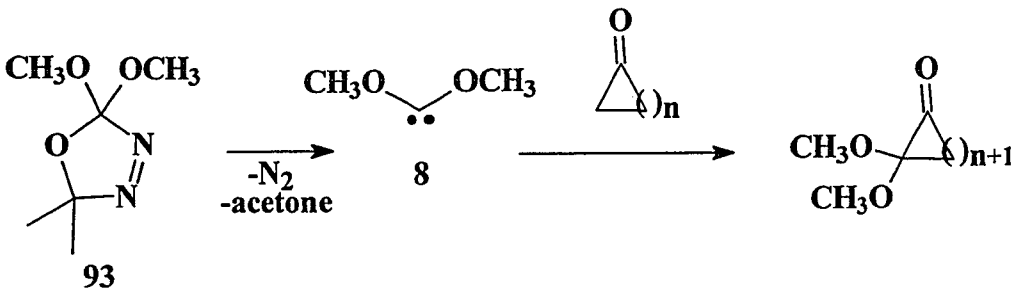


Scheme 81

Reactions in which both entities, R and X, act as radicals in efficient overall additions, are relatively rare. Other systems are currently being investigated to determine whether such reaction patterns have some generality.

2.5 - Reaction of Dimethoxycarbene (8) with Strained Cyclic Carbonyl Compounds

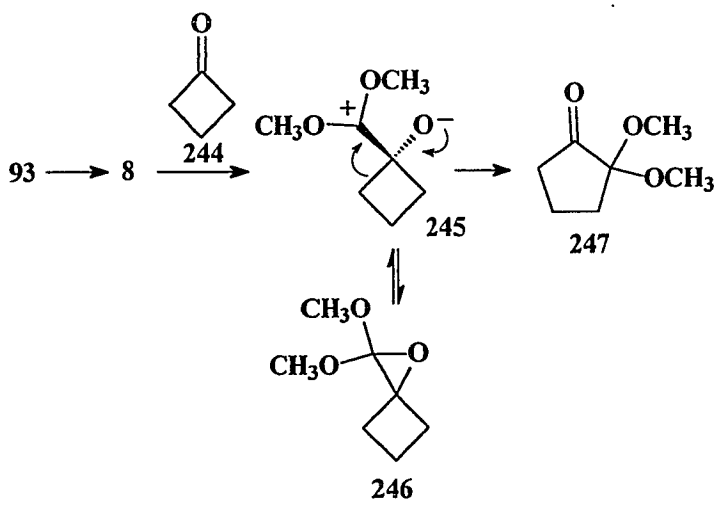
To gain a better understanding of nucleophilic carbene additions to carbonyl-containing compounds, we decided to investigate the reactions of dimethoxycarbene (**8**) with strained cyclic carbonyl compounds. Our initial ideas were based on developing convenient synthetic methods for the ring expansion of cyclic ketones (Scheme 82). Dimethoxy oxadiazoline (**93**) is a convenient source for dimethoxycarbene (**8**), and for this reason, was used in this study. The reactions of dimethoxycarbene (**8**) and a series of carbonyl containing systems were investigated.



Scheme 82

2.5.1 Reaction of **8** with Cyclobutanone (**244**)

Heating of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**93**) with cyclobutanone (**244**) in benzene at 110 °C afforded 2,2-dimethoxycyclopentanone (**247**) (Scheme 83) in 75 % yield (isolated). The ring expansion is presumably the result of



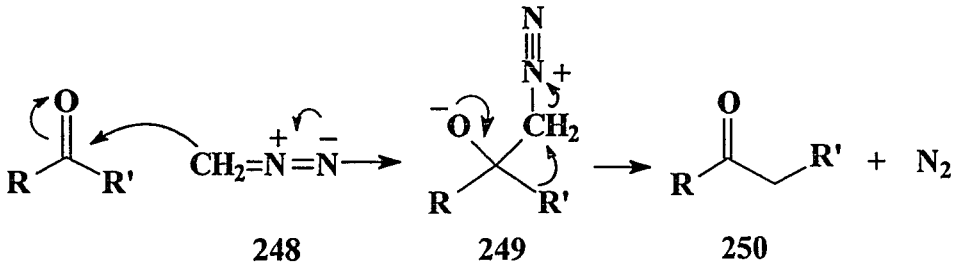
Scheme 83

either concerted insertion of dimethoxycarbene (**8**) between the carbonyl group and the *alpha*-carbon atom or the result of stepwise reaction in which dimethoxycarbene (**8**) attacks the electropositive carbon atom of the carbonyl moiety as a nucleophile, to generate a zwitterionic intermediate (**245**), which is most likely equilibrated with oxirane **246**. By *alpha*-carbon migration, cyclopentanone (**247**) is born (Scheme 83). These mechanisms differ in that **245** is a transition state in the one case and an intermediate in the other.

The reaction can be compared to homologations of alkanones with diazomethane (**248**).[158] The first step is thought to be addition to the carbonyl group to generate intermediate **249** (Scheme 84) that, by alkyl migration with loss of nitrogen, gives the homologous ketone (**250**).

The insertion preference was not clearly predictable on the basis of precedents from ring expansions with diazomethane, in which migration of the more electron-rich *alpha*-carbon[158] is generally favoured but in which steric effects can dominate. For example, 2-methyl-3-benzyloxycyclobutanone affords 3-methyl-4-benzyloxycyclopentanone with a 3:1 preference over 2-methyl-3-benzyloxycyclopentanone.[159] On the other hand, 2-phenylcyclohexanone reacts to afford 2-phenylcycloheptanone (37 %, by migration of CH_2) and 3-phenylcycloheptanone (12 %, by migration of CHPh). [158,160] Phenyl is electron-withdrawing, inductively, and sterically hindering relative to H. Steric hindrance must be important because 2-cyclohexylcyclohexanone gave only ca 5 % of ring expansion products[161] and 3,5,5-trimethylcyclohexanone affords more 3,3,5-trimethylcycloheptanone (21 %) by migration of the less hindered primary carbon than 3,5,5-trimethylcycloheptanone (12 %) by migration of the more hindered primary carbon.[162,163] Thus phenyl, which is similar to cyclohexyl in steric demand, must be partially compensating for its steric and inductive effects with weak conjugative stabilization and an early transition state with some cation character in the migrating group is indicated.

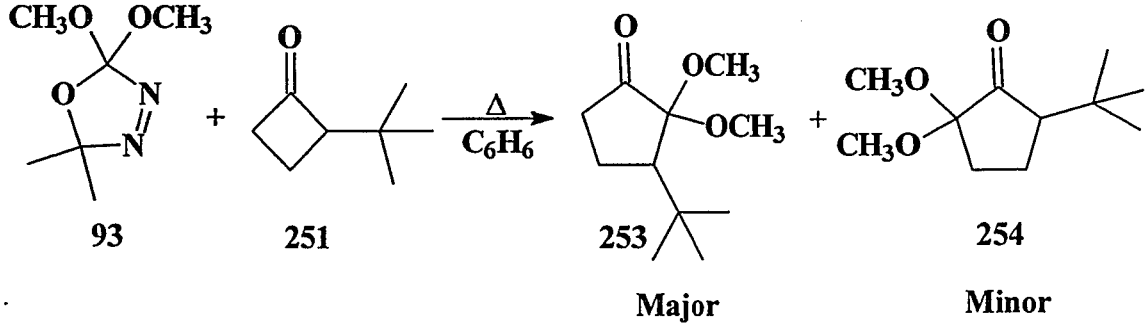
In order to assess the electronic and steric effects on the insertions of dimethoxycarbene into the cyclobutanone ring, we tested 2-*tert*-butylcyclobutanone (**251**) and 2-methylcyclobutanone (**252**).



Scheme 84

2.5.2 - Reaction of **8** with 2-*tert*-Butylcyclobutanone (**251**)

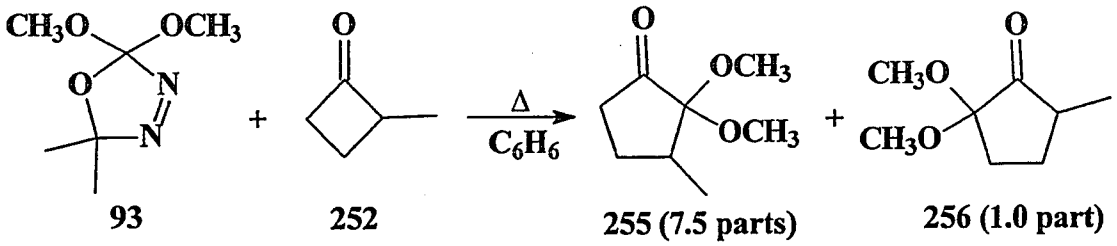
Thermolysis of dimethoxy oxadiazoline (**93**) in the presence of 2-*tert*-butylcyclobutanone (**251**) afforded *tert*-butyl-2,2-dimethoxycyclopentanones (**253** and **254**) in a ratio of 1.5:1.0, as determined by NMR spectroscopy (Scheme 85). The major product is that from formal carbene insertion between the carbonyl group and the more substituted *alpha*-carbon while insertion into the other *alpha*-site led to the minor product. The isomeric structures were established in two ways. First, irradiation of the *tert*-butyl signal of the major isomer (**253**) (NOE experiment) enhanced both methoxy group signals in the ^{1}H NMR spectrum, while irradiation of the *tert*-butyl signal in the minor component (**254**) enhanced only one methoxy signal.[164]



Scheme 85

Second, the fragmentation patterns in the mass spectra of the major and minor isomers were quite different. That of the major isomer had the base peak at m/z = 129 (144 - $CH_3^{\cdot}$), signifying the connectivity $(CH_3O)_2CCHC(CH_3)_3$ of **253**. On the other hand, the base peak in the mass spectrum of the minor isomer was at *m/z* = 88, indicating the connectivity $(CH_3O)_2CCH_2$ of **254**. These results establish the position of the *tert*-butyl group in each isomer.

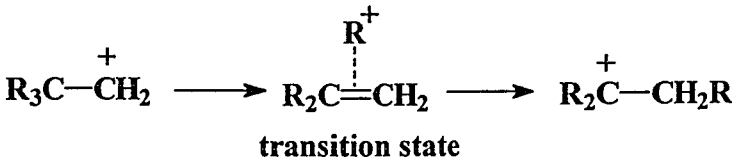
Preferential migration of the $CH(CH_3)_3$ group during reaction of **8** with 2-*tert*-butylcyclobutanone (**251**) indicates that electronic effects must outweigh steric effects. The importance of the latter could be assessed qualitatively with cyclobutanone **252**, which afforded **255** and **256** in 7.5:1.0 ratio, Scheme 86.



93 **252** **255 (7.5 parts)** **256 (1.0 part)**

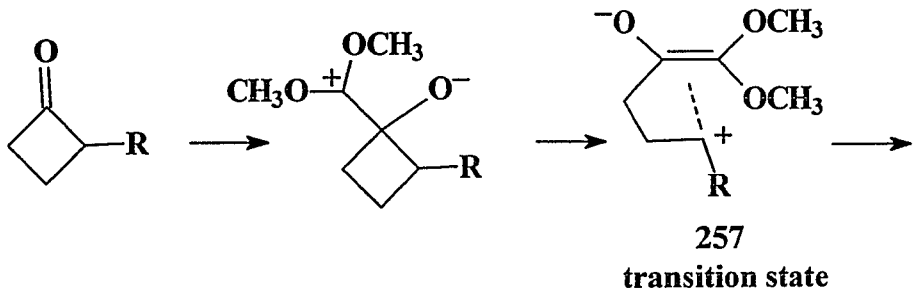
Scheme 86

The electronic substituent effect of a alkyl group is presumably worth about one order of magnitude in rate enhancement because the result with **252** must reflect both electronic enhancement and steric deceleration, by the methyl group. Thus, the migration preference is that observed in carbocation rearrangements, which are often described as resembling a π-complex of an alkene and a cation (Scheme 87).[165,166,167] To retain this model for the rearrangement of a dipolar intermediate from **251** and **252**, one



Scheme 87

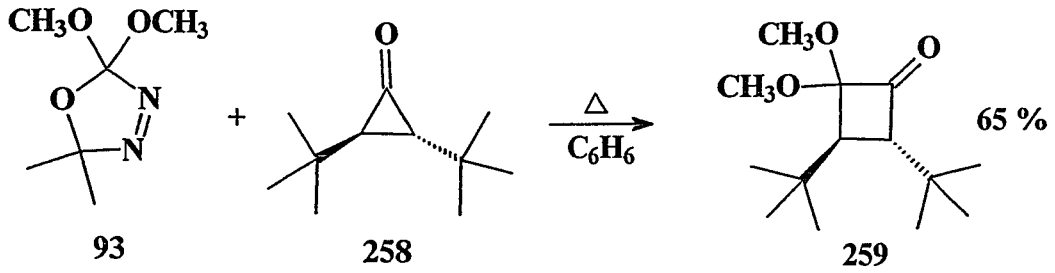
would draw the transition state (**257**) with enolate character; in other words, the carbonyl group of the product would be only weakly expressed at the transition state (Scheme 88) and the migrating group would move with cation character, rather than anion character.



Scheme 88

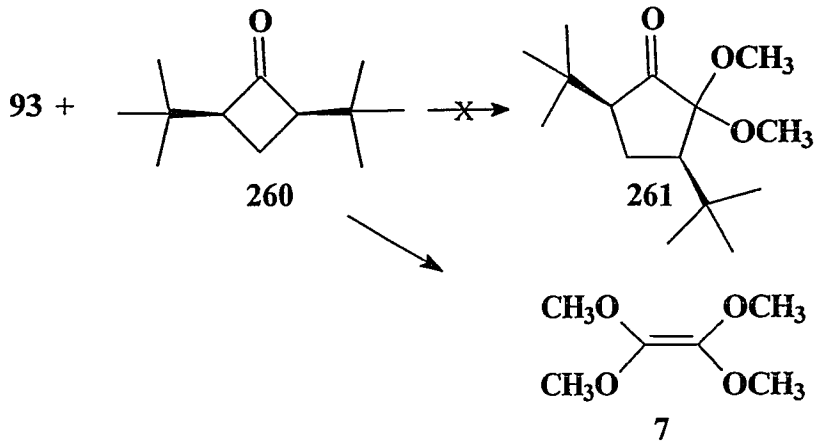
2.5.3 - Thermolysis of **93** in the presence of *trans*-Di-*tert*-butylcyclopropanone (**258**), *trans*-Di-*tert*-butylcyclobutanone (**260**), 2,2,4,4-Tetramethylcyclobutanone (**262**), 1,2-Diphenylcyclopropenone (**263**), and 3,4-Dimethoxycyclobutene-1,2-dione (**264**)

Generation of dimethoxycarbene (**8**) in the presence of *trans*-di-*tert*-butylcyclopropanone (**258**) gave cyclobutanone **259** in good yield (Scheme 89). The large relief of strain from quaternization of the CO group of a cyclopropanone is



Scheme 89

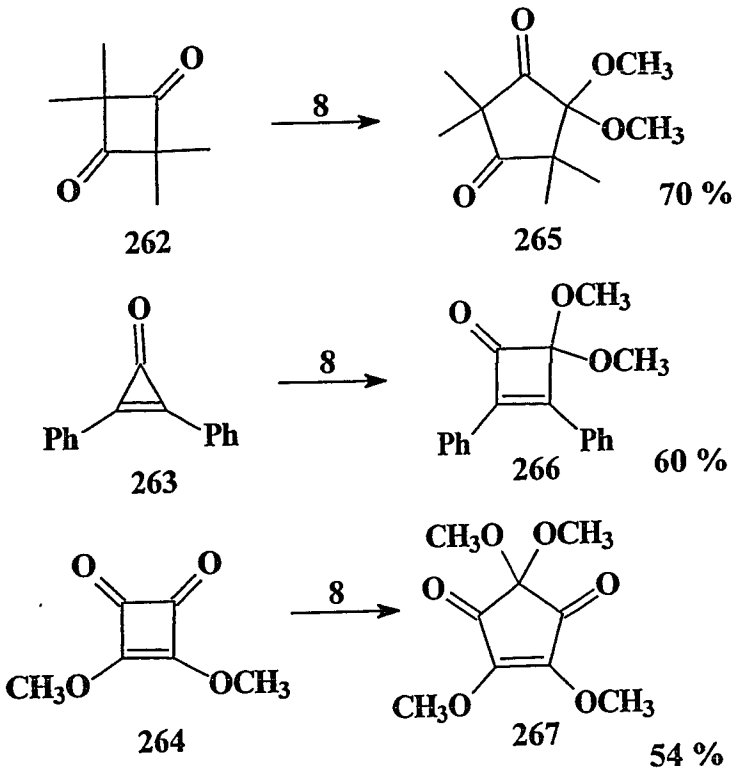
presumably responsible. On the other hand, the corresponding reaction of **93** with *cis*-di-*tert*-butylcyclobutanone (**260**) to produce **261** (Scheme 90) could not be detected. Only **260** and **7** were isolated from the thermolysis mixture. It appears that the *tert*-butyl groups in the *alpha* position hinder the attack at the carbonyl group and the carbene prefers to dimerize. This was surprising since the cis conformation of the *tert*-butyl groups should allow for carbene addition at the less hindered face. It is possible that initial attack at the carbonyl carbon does occur from the unhindered position, but as the carbonyl oxygen is pushed toward the bulky *tert*-butyl groups, as is the case in a tetrahedral intermediate, steric interactions dominate and carbene addition reverses. This unreactivity can also be explained by Newman's Rule of Six.[168-170] This is an empirical rule stating that addition reactions to carbonyl groups or other unsaturated groups will be hindered by atoms in the sixth postion, numbered from either the attacking atom or the carbonyl oxygen in carbonyl groups.



Scheme 90

To test for the importance of ring strain, **8** was generated in the presence of cyclopentanone. A small amount of substituted cyclohexanone (12 % yield) was obtained but the major product was the carbene dimer (**7**), which is also the major product from the thermolysis of dimethoxycarbene in the absence of a carbene trap.[55] Thus, as expected, the yield of carbene insertion product is dependent on the ring strain of the cyclic ketone.

Other cycloalkanones that react with **8** to afford products of ring expansion in acceptable yields are **262**, **263**, and **264**. The results are shown in Scheme 91.

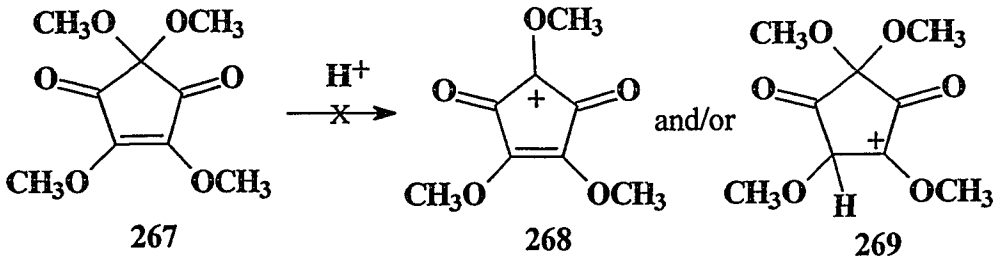


Scheme 91

It is interesting to note that an sp^2 hybridized carbon atom can migrate, as in diphenylcyclopropenone (**263**) and dimethoxycyclobutendione (**264**). Products of attack in the Michael sense were not found in either case and, in the case of **264,** the product of insertion between the CC double bond and the carbonyl moiety was not found.

Compound **267**, although it is an acetal as well as an enol ether, was easily isolated by chromatography. Its resistance to hydrolysis was demonstrated when it was found to be unaffected when stirred with 10 % sulphuric acid for 2 h. Some reaction to form a complex mixture did occur during stirring for 24 h with a 50/50 solution of 10 % sulphuric acid in methanol, although much of the starting material was left unchanged. The resistance of **267** to acid is readily accounted for. The cations that need to develop

during acetal hydrolysis (**268**) or enol ether hydrolysis (**269**) are destabilized by neighbouring carbonyl functionality (Scheme 92).

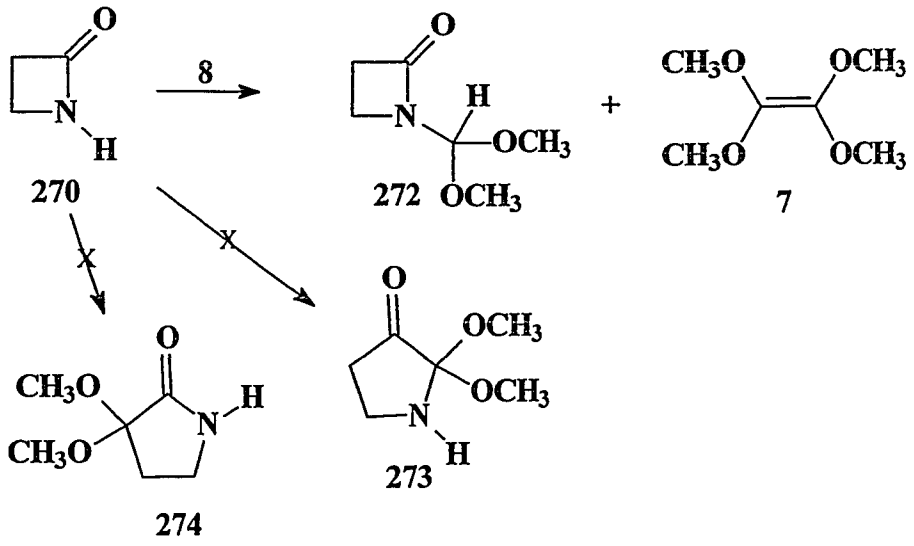


267 268 269

Scheme 92

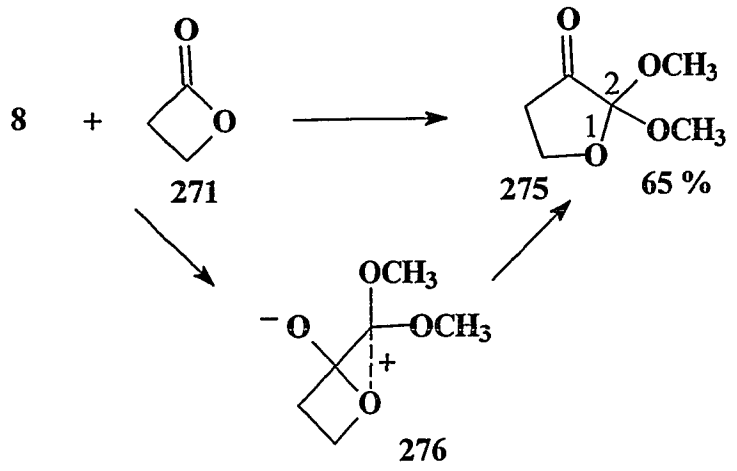
2.5.4 - Reaction of **8** with 2-Azetidinone (**270**) and β-Propiolactone (**271**)

The successful reactions of **8** with small-ring cycloalkanones led us to examine two other 4-membered rings, namely 2-azetidinone (**270**) and β-propiolactone (**271**), Scheme 93 and 94. With **93** and two equivalents of 2-azetidinone (**270**), insertion of **8** into the N-H bond[171] was the dominant pathway, leading to **272** (76 % by GC). Insertion leading to a ring expansion product (**273** or **274**) did not take place. Use of two equivalents of **93** led to insertion into the N-H bond but not to subsequent ring expansion of the β-lactam (**272**) *via* a second carbene insertion. Instead, the excess carbene dimerised to **7**. It is not well understood why ring expansion of the β-lactam (**270**) to produce **273** and/or **274** did not occur. Presumably, amide resonance is important enough to reduce the electrophilicity of the carbonyl carbon atom. Whether insertion into the NH bond is concerted or stepwise is not known.



Scheme 93

Reaction of **8** with **271** afforded one major ring expansion product (**275**) in 65 % yield (Scheme 94). Insertion between the carbonyl carbon atom and the *alpha*-oxygen cannot be accommodated within the mechanism invoked to explain the results from 2-*tert*-butylcyclobutanone (**251**) and 2-methylcyclobutanone (**252**). An enolate-like transition state would necessarily deplete the migrating ring atom of electron density and lead to migration of the CH_2 group instead. We postulate that the ring oxygen interacts with the developing positive site as the carbene begins to bond to the carbonyl carbon. Instead of a zwitterionic intermediate analogous to **245** (Scheme 83), a bicyclic intermediate (or transition state) **276**, with the new bond between O_1 and C_2 partly developed, is reached. This picture differs subtly from the previous one in that the migrating atom initially bonds to the migration terminus with an unshared pair rather than with σ-electrons.

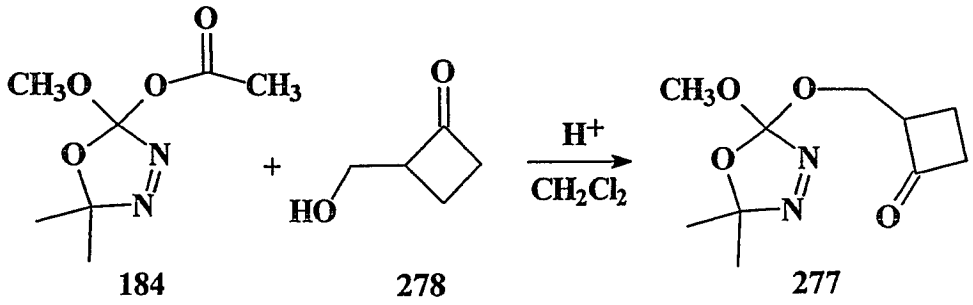


Scheme 94

2.5.5 - Thermolysis of 2-(2-Cyclobutanonemethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (277)

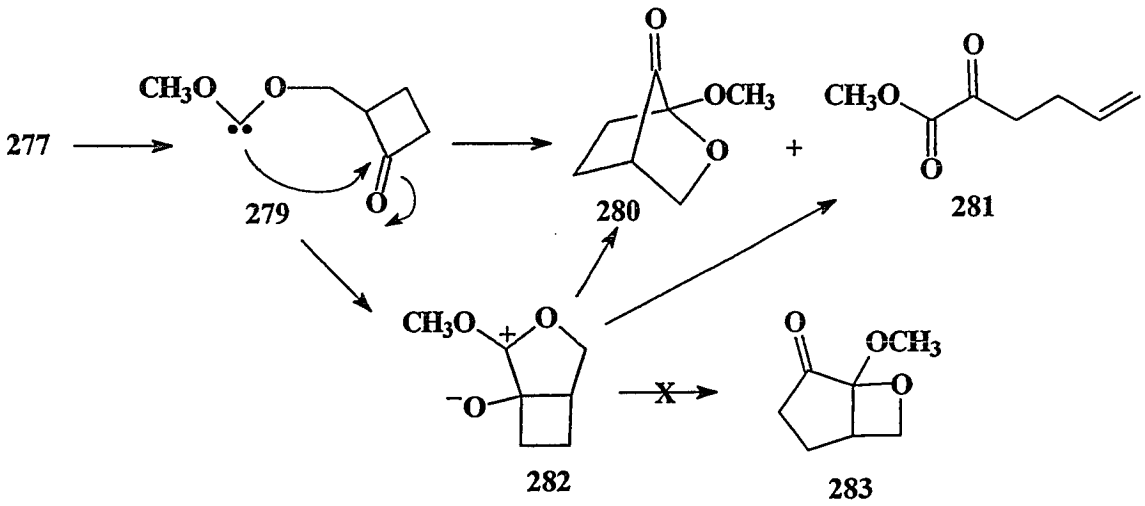
To investigate the potential of ring expansion reactions for the preparation of bicyclic ketones, an intramolecular variant was examined (**277**). The cyclobutanone system illustrated in Scheme 95 was chosen because of the high yield of the product of ring expansion in the intermolecular chemistry of dimethoxycarbene (**8**) and cyclobutanone (**244**). A one-carbon link between the oxygen of the oxadiazoline and cyclobutanone would lead to a five-membered transition state from attack of the carbene at the carbonyl group of the cyclobutanone ring.

2-(2-Cyclobutanonemethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**277**) was prepared by the acetoxy exchange method (Scheme 95).[55] Acetoxymethoxy oxadiazoline (**184**) and 2-hydroxymethylcyclobutanone (**278**), made by a literature procedure,[172,173] reacted in dichloromethane containing a catalytic amount of trifluoroacetic acid to yield the desired oxadiazoline (**277**), which was identified spectroscopically by means of ^{1}H and ^{13}C NMR spectroscopy, and MS.



Scheme 95

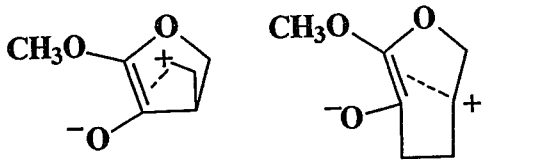
Thermolysis of **277** led to the new bicyclic ketone **280** and to compound **281**, (Scheme 96), which are accounted for as follows. Loss of nitrogen and acetone from **277**



Scheme 96

gives carbene **279**, and intramolecular carbene addition to the tethered carbonyl group affords intermediate **282**. Substituent migration in **282** could proceed in two ways. Ring enlargement by migration of the least substituted *alpha*-carbon atom would give rise to **280** and expansion through migration of the most substituted *alpha*-carbon would afford **283**. However, **283** was not obtained but, instead, the product of double ring cleavage (**281**) was obtained. The ratio **280:281** was 1.2: 1.0 and the combined yield was 60 % (isolated). These results can be fitted into the proposed enolate-like transition state

(Scheme 88). Geometric constraints in the cyclic transition state (B, Figure 14) leading to **280**, with 5-membered rings only, should be less severe than those for formation of **283**, which has a new four-membered ring. Moreover, the bond that needs to break in order to form **283** is orthogonal to the vacant orbital at the migration terminus. Bond cleavages, to relieve strain and to generate a new carbonyl group become competitive instead.



transition state A **transition state B**

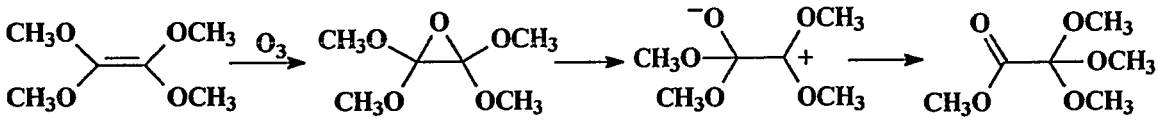
Figure 14

All the mono acetals of monocyclic β-dicarbonyl compounds (**247, 253, 254, 255, 259, 265, 266, 267** and **275**) are new compounds. Similarly, the bicyclic system **280** was unknown. The first are readily accessible by reaction of dimethoxycarbene with small-ring carbonyl compounds and the last was obtained by an intramolecular variant of the others. The fact that dialkoxycarbenes are now available in quite a variety, and that other nucleophilic carbenes (e.g. $RO(R_2N)C$:) may undergo similar reactions, suggests that the type of reactions introduced above could become quite useful.

2.6 - Epoxide of a Ketene Acetal. The First Isolable 2,2-Dialkoxyoxirane

This section describes a single reaction which led to the first isolation of a 2,2-dialkoxyoxirane.

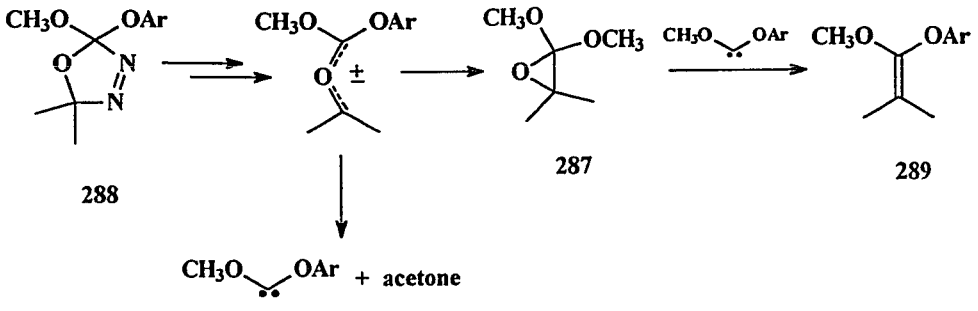
Although oxiranes are very well known[174] and easily prepared with a variety of substitutents, 2,2-dialkoxy-, 2,2-alkoxyaryloxy-, and 2,2-diaryloxyoxiranes have never been isolated, nor are analogous trioxy or tetraoxy compounds known. Kopecky and coworkers studied the ozonolysis of tetramethoxyethylene (**7**),[175] which afforded methyl trimethyoxyacetate (**284**). The latter compound appeared to be derived from opening of oxirane **285** to a dipolar intermediate (**286**) that rearranged (Scheme 97). As depicted in Scheme 21 of the introduction of this thesis, Pole and Warkentin generated dimethoxycarbene (**8**) at 110 °C in the presence of fluorenone, and obtained **72** which



7 **285** **286** **284**

Scheme 97

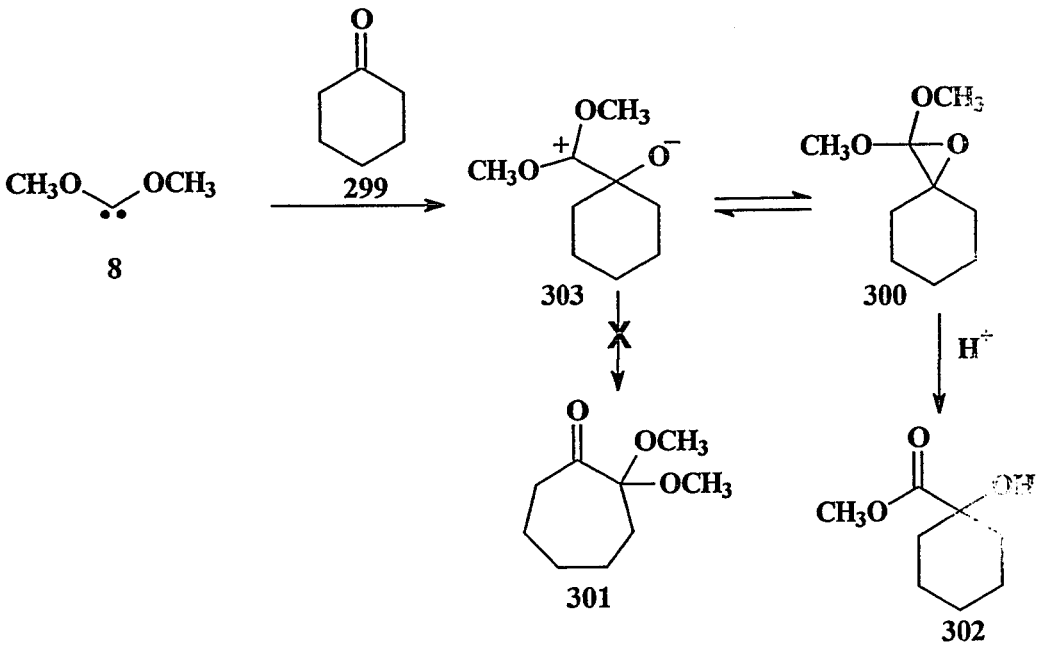
must have come from oxirane intermediate **71**. Although **71** could not be obtained in pure form, they were able to glean its ^{13}C NMR spectrum from the spectrum of a mixture.[107] Couture *et al.* inferred the intermediacy of 2-methoxy-2-aryloxyoxiranes (**287**) on a path from oxadiazolines **288** to ketene acetals **289**, Scheme 98, but such intermediates were not seen.[59]



Scheme 98

Apart from these cases, the literature does not appear to contain any reports of 2,2-dialkoxyoxiranes, which can also be viewed as strained orthoformates or carbonyl-group-protected α-lactones. We now report the isolation of the first member of the family by using gas chromatography.

Thermolysis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**93**) in the presence of cyclohexanone (**299**) gave a mixture from which **300** could be isolated by means of semi-preparative gas chromatography (15 % isolated yield). The crude reaction mixture did not appear to contain the product of ring expansion, **301**. A reasonable mechanism for the formation of **300** is depicted in Scheme 99.



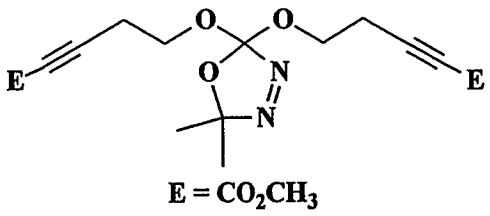
Scheme 99

Oxirane **300** was characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and by MS. Hydrolysis of the oxirane afforded alcohol **302**, a strong indicator of an oxirane precursor. Based on this unprecedented isolation of oxirane **300**, it is likely that analogues of **300** are formed in general from reactions of dialkoxycarbenes and ketones, although not necessarily with efficiency. Some of them may be thermally labile at 110 °C; the usual temperature for dissociation of dialkoxy oxadiazolines. Subtle differences in the ground state stabilities of analogues of **300**, and in the rate constants for the forward reaction of analogues of **303** to ring expanded products, could determine whether or not an analogue of **300** can be isolated.

2.7 - Tandem Carbene Cyclizations

The final section of the thesis describes advances in the area of intramolecular dialkoxycarbene additions to alkynes. In particular we were interested in the possibility of tandem intramolecular carbene cyclizations. This idea originated from the work of Kassam and Warkentin regarding intramolecular carbene additions to mono-tethered alkyne units.[131] As discussed in the introduction of this thesis, Scheme 46, Kassam and Warkentin reported a cascade reaction from thermolysis of 2-butynoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**162**) affording tricyclic product **163**. This final section presents a preliminary investigation into the mysterious realm of tandem carbene chemistry.

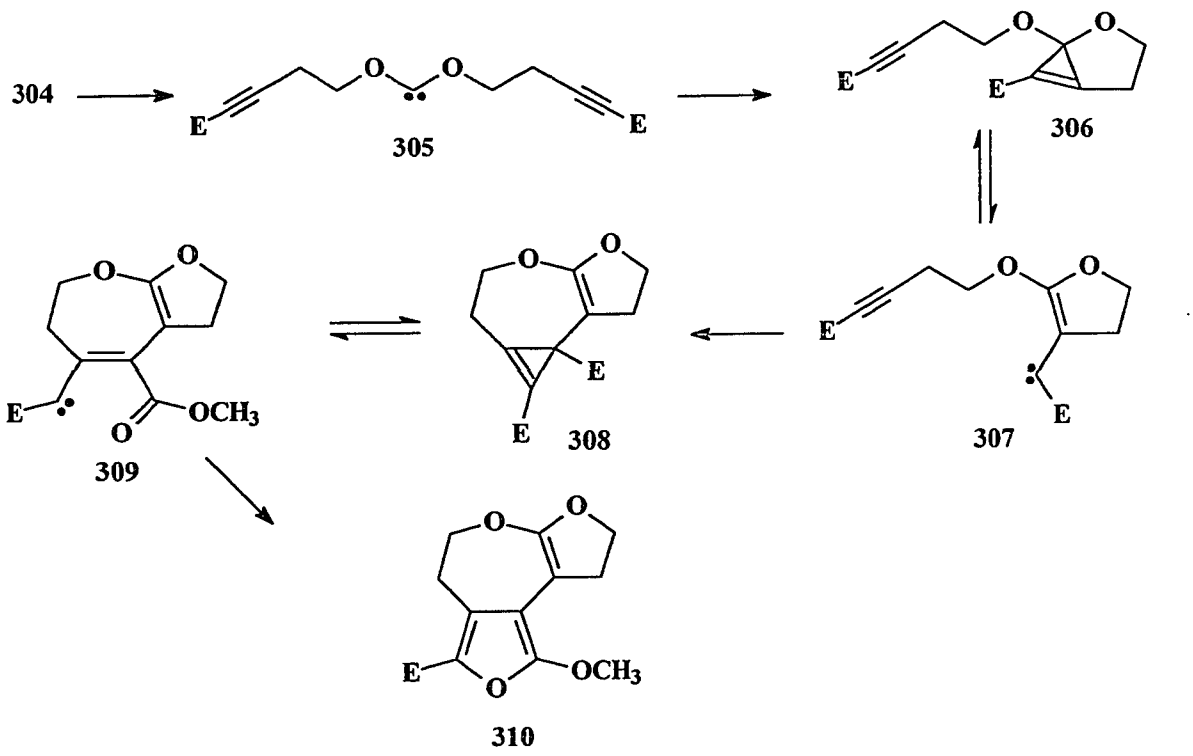
First investigations were focused on a two tethered alkyne oxadiazoline system (**304**) depicted in Figure 15.



304

Figure 15

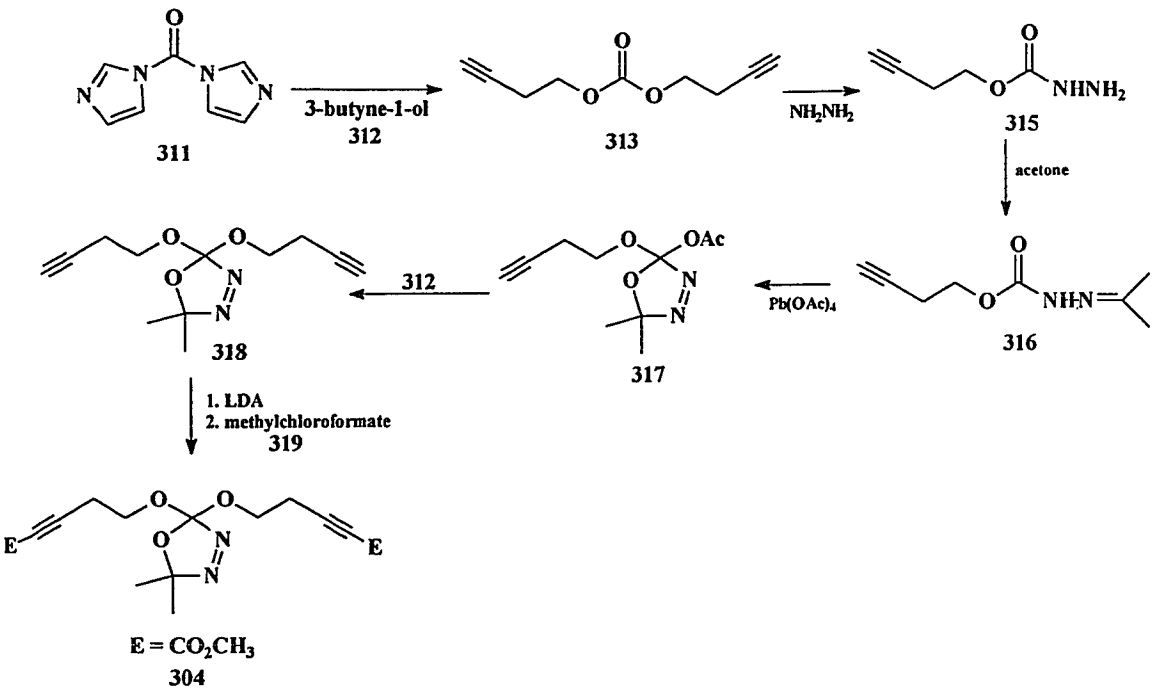
Based on former precedents, the following reaction mechanism was hypothesized for the thermolysis of **304** (Scheme 100).



Scheme 100

Loss of nitrogen and acetone from **304** would afford carbene **305**. Cyclization in the normal fashion, established by Kassam, affords exocyclic vinylcarbene **307** which is most likely equilibrated with the corresponding cyclopropene intermediate **306**. Addition of **307** to the second tethered alkyne could potentially yield vinylcarbene **309** also equilibrated with **308**. Electron reorganization and cyclization could potentially afford the aromatic furan **310**.

Since the hypothesized mechanism seemed realistic, synthesis of **304** was initiated. Scheme 101 clearly illustrates the steps involved in designing the two tethered alkyne moiety **304**.



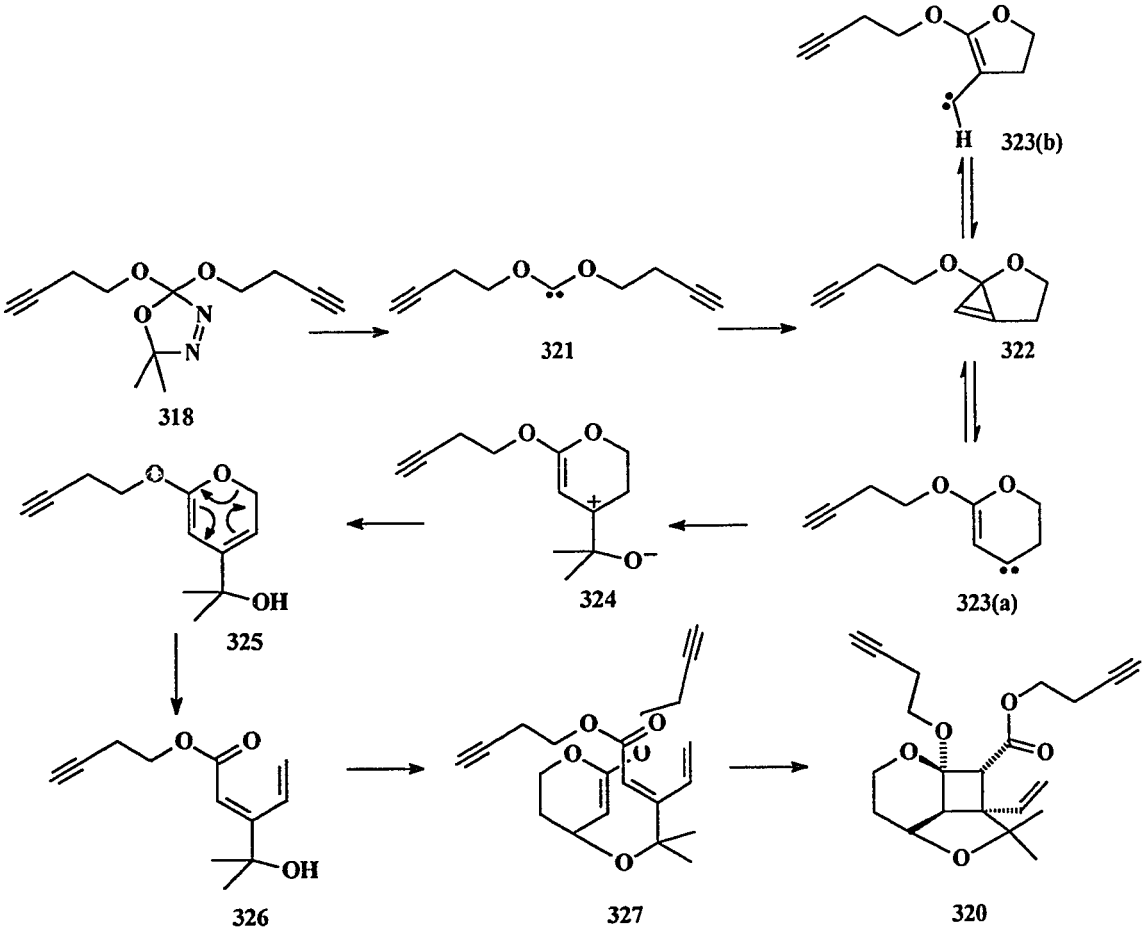
Scheme 101

1,1'-Carbonyldiimidazole (**311**) and 3-butyne-1-ol (**312**) were dissolved in dichloromethane and stirred overnight to afford carbonate (**313**) which was subsequently reacted with hydrazine monohydrate (**314**) to give hydrazide **315**. Reaction with acetone yielded the corresponding hydrazone **316**. Oxidative cyclization with lead tetraacetate in dichloromethane afforded oxadiazoline (**317**). Acid catalyzed exchange with 3-butyne-1-ol (**312**) yielded oxadiazoline (**318**). Esterification at the terminal ends of the alkynes with LDA and methylchloroformate (**319**) yielded **304**.

This successful synthesis allowed for the investigation into the thermal chemistry of two new oxadiazolines (**318** and **304**). Before the thermolysis of oxadiazoline **304** was performed the thermolysis of **318** was studied.

2.7.1 - Thermolysis of 2,2-Dibutynoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (318)

2,2-Dibutynoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**318**) was dissolved in benzene and heated for 24 h at 110 °C. Chromatography of the crude thermolysis mixture led to the isolation of tricyclic compound **320** in 25 % yield. Compound **320** is the analogue to Kassam's identified tricyclic product (**163**).[131] The mechanism is believed to be the same as that reported by Kassam (Scheme 102).[131]



Scheme 102

Decomposition of **318** would most likely afford dibutynoxycarbene (**321**) via loss of nitrogen and acetone. Cyclization of the carbene (**321**) onto one of the tethered alkynes would yield endocyclic vinylcarbene (**323a**) with potential reversible closure to

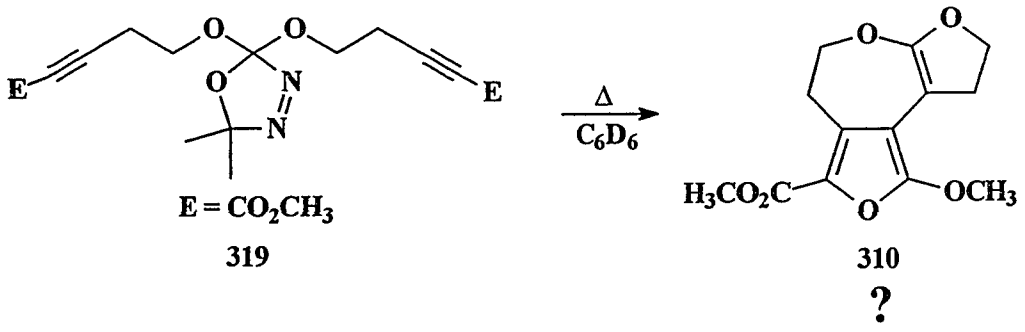
the cyclopropene intermediate (**322**). In this example, a second carbene cyclization is disfavoured because of the large geometric constraints required for addition of an endocyclic vinylcarbene to the second tethered alkyne. Instead, addition of the vinyl carbene (**323a**) to acetone generated from initial decomposition of the oxadiazoline occurs, as in Kassam's example, to afford alcohol **325**. Bimolecular vinylcarbene insertion into the OH bond of **326** and a stepwise formal [2+2] cyclization affords tricyclic product **320**.

If carbenes **323a** and **323b** are formed by reversible opening/closure of **322**, then the possiblity for exocyclic vinylcarbene (**323b**) addition to the alkyne was present. Even if **323a** was the favoured carbene, as established by Kassam and Warkentin, a subsequent reaction could drain off the less-favoured carbene (**323b**).

2.7.2 - Thermolysis of 2,2-di-(4-Methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**304**)

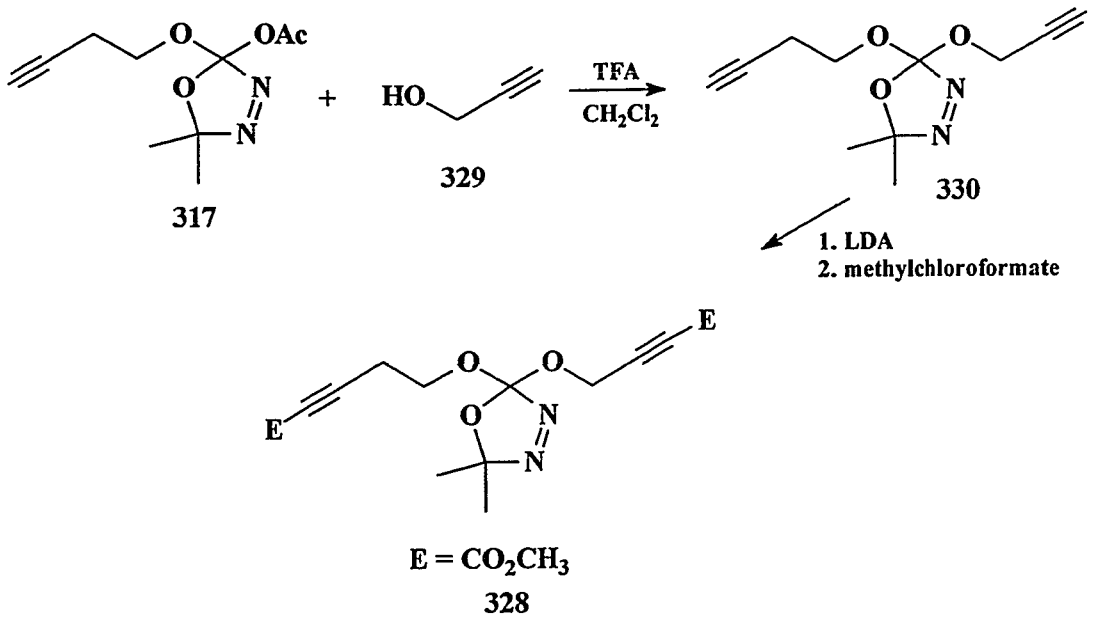
2,2-di-(4-Methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**304**) was dissolved in benzene and dispensed into a thermolysis tube. The solution was thermolyzed at 110 °C for 24 h. Analysis of the crude by GC and GC/MS indicated the presence of many peaks, however, the spectra were dominated by a single component. The component was isolated by column chromatography and analyzed by NMR. The ^{1}H NMR spectrum of the isolated compound had characteristic absorptions similar to what would be expected for the ^{1}H NMR spectrum of **310** (Scheme 103). Further analysis of the sample was hampered by hydrolysis of all the isolated material in the $CDCl_3$ solution in which the sample was stored. Hydrolysis was not surprising, since the predicted component was a ketene acetal, which under acidic conditions would hydrolyze. It is

well known that $CDCl_3$ contains a small amount of HCl, enough to initiate sample hydrolysis. Other attempts at isolation of **310** were unsuccessful.



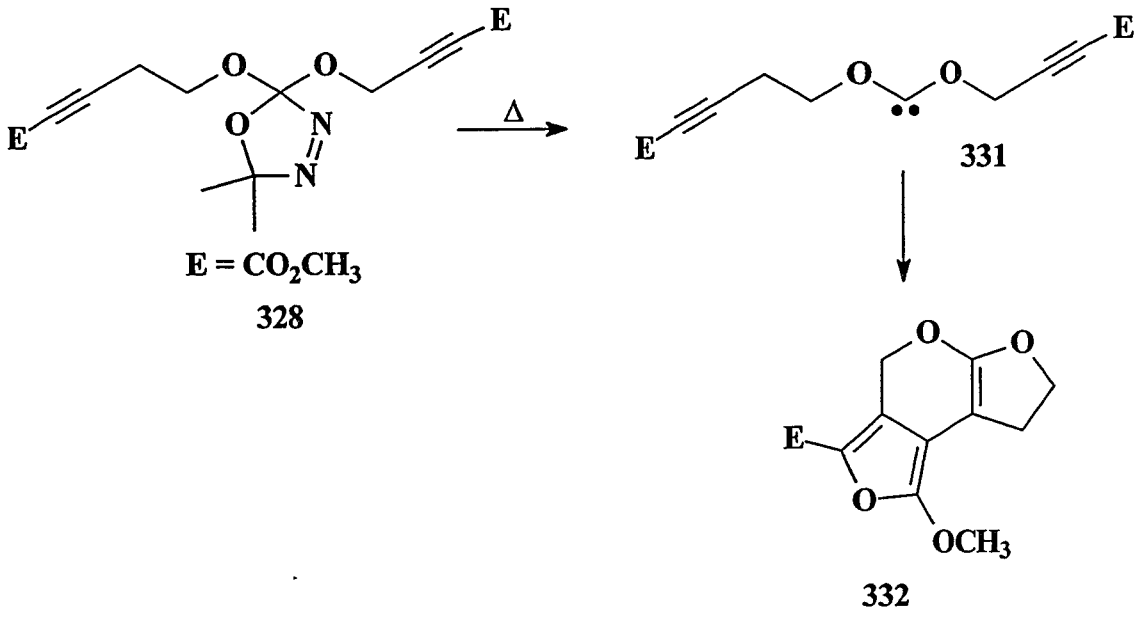
Scheme 103

One of the problems facing the second carbene addition to the alkyne is the fact that a seven membered ring must be formed in the second carbene addition step. It was thought that a system having the ability to form a six membered ring might be favoured. This led to the synthesis of 2-(4-methoxycarbonyl-3-butyn-1-oxy)-2-(3-methoxycarbonyl-2-propyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**328**). Compound **328** was synthesized by the acid catalyzed exchange of acetoxybutynoxy oxadiazoline (**317**) and propargyl alcohol (**329**). Esterification by reaction with LDA and methylchloroformate afforded the desired oxadiazoline **328** (Scheme 104).



Scheme 104

It was believed that thermolysis of **328** could potentially afford tricyclic product **332**, analogous to that proposed in the case of **304**, except with a six-membered ring instead of a seven-membered ring (Scheme 105).



Scheme 105

Compound **328** was successfully synthesized according to the above Scheme 104. However, thermolysis of **328** led to a mixture of products, none of which could be identified completely.

2.7.3 - Summary

The results obtained from studying intramolecular carbene cyclizations are very much preliminary. Time constraints have not allowed for further exploration into this fascinating area of chemistry. It is possible that a completely different system needs to be designed for advancement in this area.

Chapter 3 - Experimental

Chemical shifts for ^1H NMR spectra were measured with TMS or $CHCl_3$ (δ = 7.24) in $CDCl_3$, or C_6HD_5 (δ = 7.15) in C_6D_6 as internal reference and ^{13}C NMR spectra were referenced to the C_6D_6 triplet (δ = 128.0) or the $CDCl_3$ triplet (δ = 77.0). Mass spectra were recorded with a VGH ZAB-E double focusing mass spectrometer or with a Hewlett Packard MSD GC/MS. IR spectra are from a Bio-Rad FTS-40 instrument. Semi-preparative gas chromatography was performed with a Varian Star 3400 CX gas chromatograph with a thermal conductivity detector and a steel column (6' x 0.25") packed with 10 % OV-217 or a glass column (6' x 0.25") packed with 10 % OV-17. Analytical GC work was performed on a Varian Vista 600 gas chromatograph equipped with a flame ionization detector and a megabore capillary column DB-1 (0.53 mm x 30 m). Unless otherwise stated, benzene was dried with activated molecular sieves and all chromatography solvents were distilled before use. Toluene and THF were distilled from benzophenone ketyl. Silica gel from Silicycle (230-400 mesh), in a 30 cm x 2.5 cm glass column with a Teflon stopcock, was used for flash chromatography.

General Procedure A - *Preparation of Thermolysis Vessel*

A Pyrex glass tube (25 mL volume) fitted with a Teflon valve was washed, first with acetone (50 mL), then aqueous sodium bicarbonate (10 %, 50 mL), and finally with distilled water (100 mL). The tube (without the Teflon valve) was heated in an oven at

100 °C for 2 h. Subsequently, the glass tube (with the valve in place) was flame dried with the exit port attached to a vacuum line (0.01 - 0.1 mmHg) to remove most of the residual moisture.

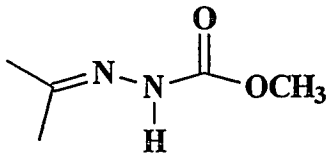
General Procedure B - *Acetoxy Alcohol Exchange Method*

Into a dry round bottom flask (100 mL) was added dichloromethane (30 mL) followed by acetoxymethoxy oxadiazoline (**183**) (0.64 g, 3.4 mmol), exchange alcohol (6.8 mmol), and trifluoroacetic acid (4 drops). The mixture was stirred at room temperature under a continuous stream of nitrogen for 24 h - 48 h. The reaction was monitored by TLC in order to ensure that the exchange reaction was complete. Most exchanges were complete in 24 h at ambient temperature. A freshly prepared 10 % sodium hydroxide solution (20 mL) was added and the resulting heterogeneous mixture was stirred vigorously for 2 h. The heterogeneous solution was transferred to a separatory funnel and the top aqueous layer was removed. The organic layer was extracted with 10 % sodium hydroxide (2 x 20 mL) and dried with anhydrous magnesium sulfate (10 g) to remove traces of water. Magnesium sulfate was removed by vacuum filtration through a sintered glass funnel. An extra 20 mL of dichloromethane was used for rinsing. The filtered light yellow solution was concentrated in vacuo to afford a light yellow oil. Purification by chromatography (25 g of silica gel, 5 - 10 % ethyl acetate in hexanes) afforded the desired oxadiazoline in yields varying from approximately 60 - 95 % depending on the alcohol used for exchange.

Synthesis of The Carbomethoxyhydrazone of Acetone (21)

Carbomethoxyhydrazone of acetone (**21**) was prepared according to the procedure reported by Kassam.[176] Methyl hydrazinocarboxylate (Aldrich) (10.0 g, 0.111 mol), reagent grade acetone (200 mL), and anydrous sodium sulfate (10 g) were added to a round bottom flask. The solution was stirred for 15 h at ambient temperature before it was filtered by vacuum filtration through a sintered glass funnel. Evaporation of the excess acetone afforded carbomethoxyhydrazone of acetone (**21**) in 85 % yield.

Carbomethoxyhydrazone of Acetone (21)



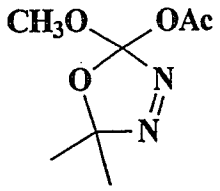
White solid: mp 79.0 - 82.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.85 (s, 3H), 2.06 (s, 3H), 3.84 (s, 3H), 7.62 (broad singlet, 1H)

Synthesis of 2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (183)

To an ice-cooled heterogeneous mixture of lead tetraacetate (38.5 g, 86.9 mmol), acetic acid (0.5 mL), and CH_2Cl_2 (38 mL) was added a solution of the carbomethoxy hydrazone of acetone (**21**) (10.0 g, 77.3 mmol) in CH_2Cl_2 (24 mL). The addition was performed slowly by means of an addition funnel. The yellow mixture was stirred with a mechanical stirrer with a continuous purge of nitrogen. Following the addition of the hydrazone, the ice bath was removed and the mixture was allowed to warm to room temperature with continued stirring (2 h). The mixture was then filtered using a sintered glass funnel with a layer of Celite and the filtrate was washed with dilute sodium

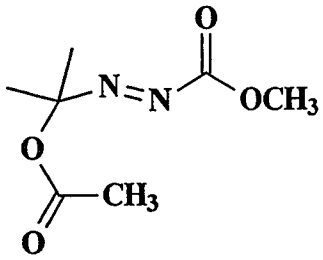
bicarbonate (4 %). The solution immediately turned dark brown and the two layers were difficult to distinguish. An additional 20 mL of CH_2Cl_2 was then added to make the two layers more distinct. The organic layer was collected and the aqueous layer was further extracted with CH_2Cl_2 (2 x 20 mL). (If the organic layer is still dark brown, it can be filtered with a sintered glass funnel containing a layer of Celite) The combined organic extracts were then dried over anhydrous sodium sulfate and filtered with Celite. Removal of the solvent in vacuo gave a yellow oil in 90 % yield which consisted of a 75 : 25 ratio of oxadiazoline (**183**) to impurity (**333**). Spectroscopy was in agreement with the reported literature.[60]

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (183)



Yellow Liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.51 (s, 3H), 1.62 (s, 3H), 2.10 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.7, 21.7, 24.2, 52.6, 122.3, 134.0, 166.4; MS (CI/NH_3) *m/z*: 189 ($M^{+\cdot}$ + 1), 206 ($M^{+\cdot}$ + 18)

Methyl-2,3-diaza-4,4-dimethyl-4-acetoxybut-2-enoate (333)



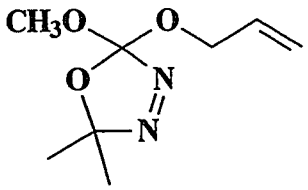
Yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.61 (s, 6H), 2.08 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.7, 24.1, 54.9, 101.7, 161.7, 169.2; MS (EI) *m/z* (rel.

intensity): 129 ($M^{+\cdot}$-$C_2H_3O_2^{\cdot}$, 5), 117 (7), 101 (50), 84 (15), 73 (8), 59 (95), 43 (100); MS (CI/NH_3) *m/z*: 206 ($M^{+\cdot}$+18)

Synthesis of 2-Allyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (184)

2-Allyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**184**) was prepared according to general procedure B. Allyl alcohol (**185**), purchased from Aldrich, was used for the exchange reaction with acetoxymethoxy oxadiazoline (**183**).

2-Allyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (184)



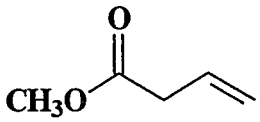
Clear Liquid: 90 % isolated yield; ^{1}H NMR (500 MHz, C_6D_6) δ: 1.24 (s, 6H), 3.25 (s, 3H), 4.20 (ddt, ^3J = 12.9 Hz, ^3J = 5.5 Hz, ^2J = 1.5 Hz, 1H), 4.27 (ddt, ^3J = 12.9 Hz, ^3J = 5.5 Hz, ^2J = 1.5 Hz, 1 H), 4.96 (dt, ^3J = 10.5 Hz, ^2J = 1.6 Hz, 1H), 5.17 (dt, ^3J = 17.2 Hz, ^2J = 1.6 Hz, 1H), 5.80 (m, ^3J = 17.2 Hz, ^3J = 10.5 Hz, ^2J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ: 23.9, 24.0, 51.6, 65.7, 116.6, 119.0, 133.9, 137.8: MS (CI/NH_3) *m/z*: 187 ($M^{+\cdot}$ +1)

Thermolysis of 2-Allyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (184) in Benzene

Into a clean dry NMR tube (medium wall) was added allyloxymethoxy oxadiazoline (**184**) (34 mg, 0.18 mmol) along with benzene-*d*6 (0.5 mL). The solution was frozen, pumped, and thawed through 3 cycles. This procedure was performed with a

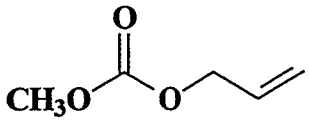
vacuum pump (0.03 mmHg) and to freeze the sample a slurry of Dry Ice / isopropanol was employed. The sample tube was placed into a preheated oil bath (110 °C) for 24 h. The crude thermolysis was analyzed by NMR, GC, and GC/MS. Methyl-3-butenoate (**185**) was isolated by semi-preparative gas chromatography in approximately 60 % yield. Allyl methyl carbonate (**186**) was identified in approximately 5 % yield.

Methyl-3-butenoate (185)



Clear liquid, 60 % isolated yield; ^{1}H NMR (200 MHz, C_6D_6) δ: 2.77 (dt, 2H), 3.26 (s, 3H), 4.85-4.97 (m, 2H), 5.78-5.92 (m, 1H); ^{13}C NMR (50 MHz, C_6D_6) δ: 38.8, 51.1, 118.0, 130.9, 204.0; GC/MS (EI) *m/z* (rel. intensity): 100 ($M^{+\cdot}$, 1), 84 (100), 66 (21), 56 (26), 54 (34), 52 (51), 42 (23), 28 (17)

Allyl Methyl Carbonate (186)

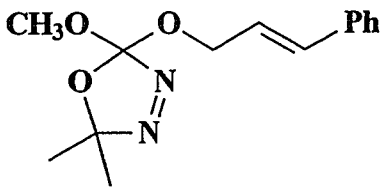


^{1}H NMR (200 MHz, C_6D_6) δ: 3.30 (s, 3H), 4.39 (dt, 2H), 5.00-5.15 (m, 2H), 5.80-5.92 (m, 1H); GC/MS (EI) *m/z* (rel. intensity): 101 ($M^{+\cdot}$ - 15, 53), 75 (100), 57 (24), 47 (38), 41 (58), 39 (56)

2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (189)

2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**189**) was prepared by acetoxy exchange with cinnamyl alcohol (**192a**) purchased from Aldrich according to general procedure B.

2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (189)



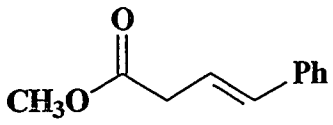
Clear liquid: 92 % isolated yield; ^{1}H NMR (300 MHz, C_6D_6) δ: 1.27 (s, 3H), 1.29 (s, 3H), 3.29 (s, 3H), 4.34-4.48 (m, 2H), 6.17 (ddd, ^3J = 15.9, ^3J = 6.1, ^3J = 6.0 Hz, 1 H), 6.48 (d, ^3J = 15.9 Hz, 1H), 7.01-7.18 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.2, 24.2, 52.0, 65.5, 119.3, 124.6, 126.5, 127.8, 128.5, 132.7, 136.5, 137.0; MS (CI/NH_3) *m/z*: 263 ($M^{+\cdot}$ +1)

Thermolysis of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (189)

A 10 mL thermolysis tube was prepared according to general procedure A. Cinnamyloxymethoxy oxadiazoline (**189**) (0.20 g, 0.76 mmol) along with dry benzene (3 mL) were added to the thermolysis tube, before 1 mL of benzene was removed by an azeotropic distillation directly from the thermolysis tube. Following the distillation, the thermolysis tube was sealed and to remove oxygen from the sample, the solution was frozen, pumped, and thawed through 3 cycles. This procedure was performed with a vacuum pump (0.03 mmHg) and a slurry of Dry Ice and isopropanol to freeze the sample. After allowing the solution to reach ambient temperature, it was immersed in an oil bath (110 °C) for a period of 24 h. The crude sample was analyzed by GC and GC/MS. Methyl-4-phenyl-3-butenoate (**194**) and methyl-2-phenyl-3-butenoate (**193**) were isolated by semi-preparative gas chromatography in a combined 60 % yield. GC and GC/MS analysis indicated a 2:1 product ratio. Cinnamyl methyl carbonate (**334**) was also found

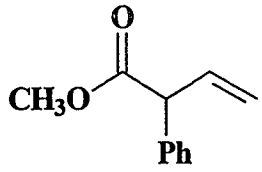
in approximately 5 % yield. Spectroscopic data were consistent with those in the literature.[177,178]

Methyl-(E)-4-phenyl-3-butenoate (194)



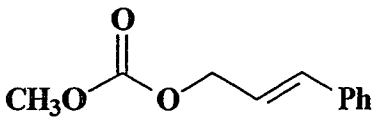
Clear liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.24 (dd, ^3J = 6.8 Hz, ^4J = 1.0 Hz, 2H), 3.70 (s, 3H), 6.27 (dt, ^3J = 15.9, 6.8 Hz, 1H), 6.48 (d, ^3J = 15.9 Hz, 1H), 7.20-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 38.2, 51.9, 109.7, 121.6, 126.3, 127.6, 128.5, 133.5, 167.3; MS (EI) *m/z* (rel. intensity): 176 ($M^{+\cdot}$, 37), 134 (12), 117 ($M^{+\cdot}$-59, 100), 115 (63), 91 (23)

Methyl-2-phenyl-3-butenoate (193)



Clear liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.69 (s, 3H), 4.30 (dt, ^3J = 7.9 Hz, ^4J = 1.0 Hz, 1H), 5.12 (ddd, ^4J = 1.0 Hz, ^3J = 16.0 Hz, ^2J = 1.9 Hz, 1H), 5.20 (ddd, ^4J = 1.0 Hz, ^3J = 10.2 Hz, ^2J = 1.9 Hz, 1H), 6.20 (ddd, ^3J = 10.2 Hz, ^3J = 16.0 Hz, ^3J = 7.9 Hz, 1H), 7.25-7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.2, 55.6, 117.5, 127.4, 127.9, 128.7, 135.7, 138.0, 150.0; MS (EI) *m/z* (rel. intensity): 176 ($M^{+\cdot}$, 20), 117 ($M^{+\cdot}$-59, 100), 115 (70), 91 (25)

Cinnamyl Methyl Carbonate (334)

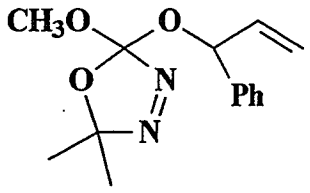


Clear liquid: 5 % isolated yield; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 4.77 (dd, ^3J = 6.4 Hz, ^4J = 1.2 Hz, 2H), 6.27 (dt, ^3J = 15.9 Hz, ^3J = 6.4 Hz, 1H), 6.68 (d, ^3J = 15.9 Hz, 1H), 7.25-7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 54.8, 68.4, 122.4, 126.7, 128.2, 128.6, 134.8, 136.0, 155.6; MS (EI) *m/z* (rel. intensity): 192 ($M^{+\cdot}$, 45), 163 (5), 148 (15), 133 (22), 115 (95), 105 (100), 91 (60), 77 (61), 59 (25), 51 (30); MS (HR): calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0796

2-α-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (191); a Mixture of Two Diastereomers in 1 : 1 Ratio

2-α-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**191**) was synthesized by acetoxy exchange with (±)1-phenyl-2-propenol (**192c**), according to general procedure B, to afford a mixture of diastereomers. (±)1-Phenyl-2-propenol (**192c**) was prepared by the Grignard reaction of vinyl magnesium bromide with benzaldehyde according to the procedure by Goering and Dilgren.[179]

2-α-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (191)



Clear liquid: 90 % isolated yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 3.36 (s, 3H), 3.38 (s, 3H), 5.14-5.25 (m, 4H), 5.48-5.60

(m, 2H), 5.97-6.05 (m, 2H), 7.25-7.33 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.7, 23.9, 24.0, 52.0, 77.7, 77.8, 115.7, 115.9, 119.3, 119.4, 126.6, 127.0, 127.6, 127.7, 128.2, 128.3, 137.3, 138.4, 140.5

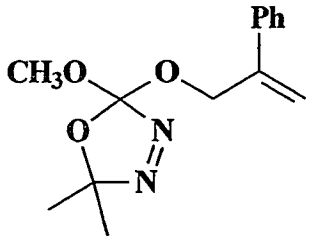
Thermolysis of 2-α-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (191)

A thermolysis tube (10 mL) was cleaned and dried by general procedure A. 2-α-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**191**) (0.20 g, 0.76 mmol) and dry benzene (3 mL) were dispensed into the thermolysis tube, before 1 mL of benzene was removed by azeotropic distillation. The Teflon stopper was closed and the solution was frozen, pumped and thawed, using a vacuum pump (0.03 mmHg) and Dry Ice/isopropanol bath, through 3 cycles. The thermolysis was carried out for 24 h in a preheated oil bath (110 °C). The volatiles were removed in vacuo and the remaining crude yellow oil was analyzed by NMR, GC, and GC/MS. Methyl-4-phenyl-3-butenoate (**194**) and methyl-2-phenyl-3-butenoate (**193**) were isolated by semi-preparative gas chromatography in a combined 60 % yield. GC and GC/MS indicated a 1:2 product ratio.

2-β-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (190)

2-β-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**190**) was prepared by reaction of acetoxy oxadiazoline (**183**) and 2-phenyl-2-propenol (**192b**) in accordance with general procedure B. 2-Phenyl-2-propenol (**192b**) was made by the literature procedure of Hawthorne.[180,181]

2-β-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (190)

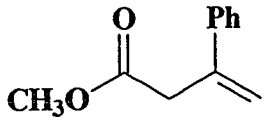


Clear liquid: 93 % isolated yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.47 (s, 3H), 1.55 (s, 3H), 3.45 (s, 3H), 4.57 (d, ^2J = 12.5 Hz, 1H), 4.69 (d, ^2J = 12.5 Hz, 1H), 5.38 (s, 1H), 5.50 (s, 1H), 7.28-7.41 (m, 5H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 24.0, 24.0, 52.0, 66.2, 114.5, 119.3, 126.0, 127.8, 128.3, 136.9, 138.3, 143.1

Thermolysis of 2-β-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (190)

A 10 mL thermolysis tube was prepared according to general procedure A. 2-β-Phenylallyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**190**) (0.20 g, 0.76 mmol) along with dry benzene (3 mL) were added to the thermolysis tube. Following, 1 mL of benzene was azeotropically removed directly from the tube. Following the azeotropic distillation, the thermolysis tube was sealed and to remove oxygen from the sample, the solution was frozen, pumped, and thawed through 3 cycles. The procedure was performed with a vacuum pump (0.03 mmHg) and a slurry of Dry Ice / isopropanol to freeze the sample. After the solution reached ambient temperature, it was immersed into a preheated oil bath (110 °C) for a period of 24 h. The crude sample was analyzed by GC and GC/MS. The volatiles were then removed in vacuo. Methyl-3-phenyl-3-butenoate (**195**) was isolated in 60 % yield by semi-preparative gas chromatography.

Methyl-3-phenyl-3-butenoate (195)

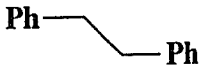


Clear liquid: 60 % isolated yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.51 (d, ^{2}J = 0.9 Hz, 2H), 3.64 (s, 3H), 5.22 (d, ^{2}J = 0.9 Hz, 1H), 5.53 (d, ^{2}J = 0.9 Hz, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 41.0, 52.0, 116.3, 125.7, 127.8, 128.4, 139.7, 140.8, 171.8; MS (EI) *m/z* (rel. intensity): 176 ($M^{+\cdot}$, 57), 147 (13), 118 (100), 115 (80), 103 (17), 91 (47), 77 (13), 59 (14)

Thermolysis of Allyloxymethoxy Oxadiazoline (184) in Toluene

A 100 mL round bottom flask and condenser were base washed with 50 mL of a 10 % potassium hydroxide solution and then rinsed with both distilled water and acetone. The flask and condenser were then placed into an oven (100 °C) for 1 h and then flame dried under a stream of dry nitrogen. Following this procedure, 50 mL of dry toluene was then dispensed into the round bottom flask along with allyloxymethoxy oxadiazoline (**184**) (111 mg, 0.597 mmol). The water condenser was then attached and the solution was heated to boiling and refluxed for 24 h. After the elapsed time period, the solution was cooled to ambient temperature and analyzed by GC and GC/MS. Both methods of analysis revealed a major component along with numerous other smaller peaks. By comparison with known mass spectra in the literature,[136] the dominant component was determined to be bibenzyl (**196**).

Bibenzyl (196)

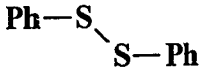


GC/MS (EI) *m/z* (rel. abundance): 182 ($M^{+\cdot}$, 27), 165 (6), 91 ($M^{+\cdot}$-$PhCH_2^{\cdot}$, 100), 77 (8), 65 (28), 51 (10), 39 (11)

Thermolysis of Allyloxymethoxy Oxadiazoline (184) and Thiophenol (203) in Benzene

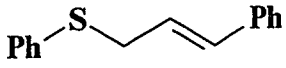
A reflux apparatus consisting of a 200 mL round bottom flask and condenser was cleaned and flame dried under a stream of dry nitrogen. Cinnamyloxymethoxy oxadiazoline (**184**) (50.0 mg, 0.191 mmol), thiophenol (**203**) (21 mg, 0.191 mmol), and dry benzene (80 mL) were added to the round bottom flask. The water condenser was attached and the solution was refluxed for 20 h, before it was analyzed by GC and GC/MS. The reaction yielded many products, three of which were identified by comparing with mass spectra from the literature.[136]

Diphenyldisulphide (204)



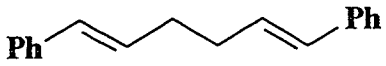
GC/MS (EI) *m/z* (rel. abundance): 218 ($M^{+\cdot}$, 95), 185 (19), 154 (29), 140 (10), 109 ($M^{+\cdot}$-$PhS^{\cdot}$, 100), 82 (10), 69 (20), 65 (29)

1-Phenyl-3-phenylthio-1-propene (205)



GC/MS (EI) *m/z* (rel. abundance): 226 ($M^{+\cdot}$, 6), 165 (3), 117 ($M^{+\cdot}$-$PhS^{\cdot}$, 100), 115 (48), 91 (24), 65 (13)

1,6-Diphenyl-1,5-hexadiene (201)

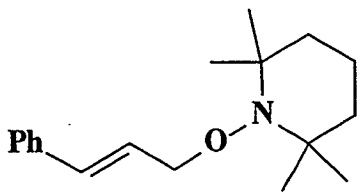


GC/MS (EI) *m/z* (rel. abundance): 234 ($M^{+\cdot}$, 5), 118 (11), 117 ($M^{+\cdot}$-$PhCHCHCH_2^{\cdot}$, 100), 115 (33), 91 (20), 65 (3)

Thermolysis of 2-Cinnamyloxy-2-methoxy-Δ^3-1,3,4-oxadiazoline (189) in the Presence of 2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO) (207) - 110 °C / Benzene

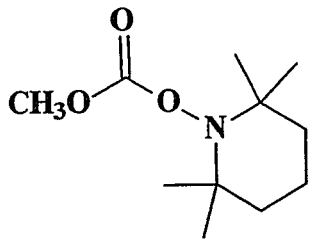
Into a 20 mL thermolysis tube, prepared according to general procedure A, was added TEMPO (**207**) (0.120 g, 0.770 mmol), cinnamyloxymethoxy oxadiazoline (**189**) (0.100 g, 0.382 mmol), and dry benzene (25 mL). Following the above mentioned procedure, 5 mL of benzene was removed by azeotropic distillation. The solution was then frozen, pumped, and thawed through three cycles using a vacuum pump (0.03 mmHg) and a slurry of Dry Ice / isopropanol. The thermolysis tube was sealed and immersed into a preheated oil bath (110 °C) for 24 h. The contents were transferred into a vial and the sample was analysed by GC and GC/MS. The solvent was then removed in vacuo and products were isolated by chromatography (Chromatotron, 1 mm silica plate, 5-20% ethyl acetate in hexanes). Two products were isolated and fully characterized (**211** and **210**).

1-Cinnamyloxy-2,2,6,6-tetramethyl-1-piperidine (211)



Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.31 (s, 6H), 1.38 (s, 6H), 1.27-1.59 (m, 6H), 4.60 (d, ^3J = 5.8 Hz, 1H), 4.61 (d, ^3J= 5.8 Hz, 1H), 6.36 (dt, ^3J = 16.0, 5.8 Hz, 1H), 6.69 (d, ^3J = 16.0 Hz, 1H), 7.11-7.34 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ: 17.5, 20.3, 33.3, 40.0, 59.9, 78.5, 126.0, 126.8, 127.6, 128.9, 131.8. 137.6; MS (EI) *m/z* (rel. intensity): 274 ($M^{+\cdot}$ + 1, 11), 156 ($M^{+\cdot}$ - 117, 100), 117 ($M^{+\cdot}$ - 156, 52), 69 (22), 41 (19); MS (HR) *m/z*: calcd for $C_{18}H_{27}NO$ 273.2093, found 273.2081

Methyl-1-(2,2,6,6-tetramethyl piperidinyl carbonate (210)

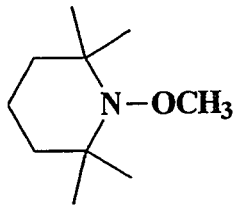


Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.09 (s, 6H), 1.25 (s, 6H), 1.08-1.56 (m, 6H), 3.39 (s, 3H); ^{13}C NMR (25 MHz, C_6D_6) δ: 17.2, 20.4, 31.7, 40.0, 54.3, 60.4, 147.0; MS (EI) *m/z* (rel. intensity): 215 ($M^{+\cdot}$, 2), 200 ($M^{+\cdot}$ - 15, 100), 156 (5), 83 (77), 69 (24), 55 (96), 41 (52); MS (HR) *m/z*: calcd for $C_{11}H_{21}NO_3$ 215.1521, found 215.1510

Thermolysis of 2-Cinnamyloxy-2-methoxy-Δ^3-1,3,4-oxadiazoline (189) in the Presence of 2,2,6,6-Tetramethylpiperidine-N-oxyl (TEMPO) (207) - 80°C / Benzene

A sample of cinnamyloxymethoxy oxadiazoline (**189**) and TEMPO (**207**) was prepared as described previously except that the thermolysis was carried out at 80 °C for 5 days. In addition to **211** and **210**, **212** was identified by GC/MS and further confirmed by its synthesis from an independent method.

1-Methoxy-2,2,6,6-tetramethyl-1-piperidine[182] *(212)*

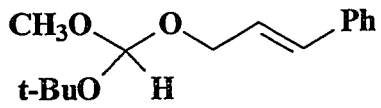


Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.15 (s, 6H), 1.22 (s, 6H), 1.05-1.53 (m, 6H), 3.56 (s, 3H); ^{13}C NMR (25 MHz, C_6D_6) δ: 17.4, 20.1, 33.3, 39.9, 59.7, 65.3; MS (EI) *m/z* (rel. intensity): 171 ($M^{+\cdot}$, 7), 156 ($M^{+\cdot}$-$H_3C^{\cdot}$, 100), 125 (5), 109 (10), 100 (9), 88 (19), 69 (16), 55 (17), 41 (21); MS (CI/NH_3) *m/z*: 172 ($M^{+\cdot}$ + H)

Thermolysis of 2-Cinnamyloxy-2-methoxy-Δ^3-1,3,4-oxadiazoline (189) in the Presence of *tert*-Butyl Alcohol (222)

A 5 mL thermolysis tube was cleaned and dried according to general procedure A. Cinnamyloxymethoxy oxadiazoline (**189**) (0.100 g, 0.380 mmol), *tert*-butyl alcohol (**222**) (0.100 g, 1.35 mmol), and benzene (1 mL) were dispensed into the 5 mL thermolysis tube. The contents were frozen, pumped, and thawed through three cycles and following, the tube was placed in an oil bath (110 °C) for 24 h. The crude sample was analyzed by GC and GC/MS. The volatiles were removed with a rotary evaporator and vacuum pump (0.03 mmHg). NMR indicated that the crude oil did not need to be purified further (70 % isolated material) (**223**). The sample can also be further purified by semi-preparative gas chromatography if desired.

Orthoformate (223)



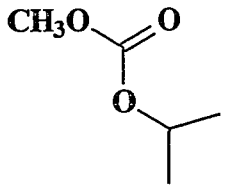
Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.17 (s, 9H), 3.24 (s, 3H), 4.24 (d, ^{3}J= 5.6 Hz, 1H), 4.25 (d, ^{3}J= 5.6 Hz, 1H), 5.40 (s, 1H), 6.25 (dt, ^{3}J = 15.9, 5.6 Hz, 1H), 6.61 (d, ^{3}J = 15.9 Hz, 1H), 7.01-7.24 (m, 5H); ^{13}C NMR (50 MHz, C_6D_6) δ: 28.8, 49.8, 63.7, 73.9, 109.6, 126.8, 127.7, 128.3, 128.8, 131.6, 137.5; DEPT expt: showed one negative peak at 63.7 ppm (CH_2 group); MS: molecular ion not seen. In methyl orthoformate the orthoformyl ^{1}H signal is at δ = 4.80,[183] and the corresponding ^{13}C signal is at δ = 115 (CCl_4). In ethyl orthoformate the orthoformyl ^{13}C signal is at δ = 112.5.[184]

Synthesis of Isopropyl Methyl Carbonate (217)

A round bottom flask (250 mL) with a fitted water condenser was cleaned and flame dried under a stream of nitrogen. 2-Propanol (20.0 g, 0.330 mol), pyridine (39.6 g, 0.500 mol), and dichloromethane (50 mL) were added to the flask. The mixture was stirred at ambient temperature (10 min). The reaction flask was then cooled with an ice / water bath (10 min). A solution of methylchloroformate (29.1 g, 0.310 mol) and dichloromethane (50 mL) was added dropwise over a period of 0.5 h through an addition funnel attached to the top of the condenser. An additional 30 mL of dichloromethane was added to aid in stirring the mixture. The mixture was stirred for 4 h before workup. The solution was extracted with 10 % HCl (50 mL x 3), saturated NaCl (50 mL x 3), and 5 % sodium bicarbonate (50 mL x 3). The resulting organic layer was dried with anhydrous magnesium sulfate and filtered using a sintered glass funnel and aspirator vacuum.

Distillation gave isopropyl methyl carbonate (**217**) (bp 120 °C / 760 mmHg) (50 % isolated yield).

Isopropyl Methyl Carbonate (217)

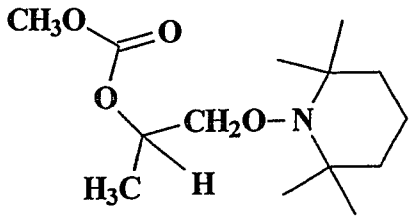


Clear Liquid: bp 120 °C / 760 mmHg; ^{1}H NMR (200 MHz, C_6D_6) δ: 1.27 (d, ^{3}J = 6.3 Hz, 6H), 3.74 (s, 3H), 4.85 (m, ^{3}J = 6.3 Hz, 1H); ^{13}C NMR (50 MHz, C_6D_6) δ: 21.8, 54.4, 72.0, 155.3; MS (CI/NH_3) *m/z*: 119 ($M^{+\cdot}$ + 1) and 136 ($M^{+\cdot}$ + 18)

Thermolysis of Di-*tert*-butylperoxide (218) in the Presence of Isopropylmethyl Carbonate (217) and TEMPO (207)

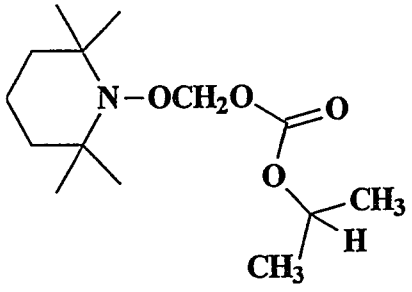
In accordance with general procedure A, isopropylmethyl carbonate (**217**) (3.0 g, 0.250 mol), TEMPO (**207**) (147 mg, 0.942 mmol), and di-*tert*-butylperoxide (**218**) (370 mg, 2.53 mmol) were added to a 10 mL thermolysis tube. Three freeze, pump, and thaw sequences were performed before placing the tube in an oil bath (110 °C) for 24 h. The crude sample was analyzed by GC and GC/MS and following, the sample was concentrated in vacuo and analyzed by NMR spectroscopy. Three compounds were isolated by semi-preparative gas chromatography (**212**, **221**, and **220**).

Methyl-1-(1-methyl-2-(2,2,6,6-tetramethylpiperidinyl)ethyl) Carbonate 221



Clear liquid: ^{1}H NMR (500 MHz, C_6D_6) δ: 1.02 (d, ^3J = 6.3 Hz, 3H), 1.08-1.41 (m, 6H), 1.10 (s, 6H), 1.11 (s, 6H), 3.36 (s, 3H), 3.80 (dd, ^2J = 10.0 Hz, ^3J = 3.9 Hz, 1H), 3.90 (dd, ^2J = 10.0 Hz, ^3J = 6.7 Hz, 1H), 5.05 (m, ^3J = 6.3 Hz, ^3J = 6.7 Hz, ^3J = 3.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ: 16.8, 17.4, 20.1, 21.6, 33.1, 40.0, 54.0, 73.2, 79.2, 155.9; MS (GC/MS/EI) *m/z* (rel. intensity): 273 ($M^{+\cdot}$, 3), 258 (8), 156 (20), 142 (100), 140 (26), 123 (5), 109 (3), 83 (13), 69 (12), 55 (18), 43 (26)

1-Isopropyl-1-((2,2,6,6-tetramethylpiperidinyl)methyl) Carbonate 220

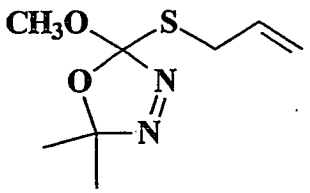


Clear liquid: ^{1}H NMR (500 MHz, C_6D_6) δ: 1.02 (d, ^3J = 6.3 Hz, 6H), 1.07-1.36 (m, 6H), 1.08 (s, 3H), 1.20 (s, 3H), 4.83 (m, ^3J = 6.3 Hz, 1H), 5.51 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 17.4, 20.2, 21.6, 33.4, 40.0, 60.0, 71.5, 96.4, 154.6; MS (GC/MS/EI) *m/z* (rel. intensity): 273 ($M^{+\cdot}$, 1), 258 (6), 156 (10), 140 (5), 117 (100), 83 (17), 69 (11), 55 (22), 41 (13)

Synthesis of 2-Allylthio-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (227)

2-Allylthio-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**227**) was synthesized by the acetoxy exchange reaction with allyl mercaptan (General procedure B). Allyl mercaptan was received from Aldrich as an 80:20 ratio of allyl mercaptan to sulphides. It was used as received for the exchange reaction. The components were stirred in the absence of light for a 48 h period. The crude exchange yield was 76 %. The crude sample was purified by column chromatography (silica gel / 10 % ethyl acetate:in hexanes - 1 g of crude sample : 20 g of silica gel - Rf = 0.6)

2-Allylthio-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (227)



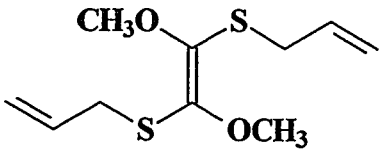
Yellow liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.20 (s, 3H), 1.25 (s, 3H), 3.20 (s, 3H), 3.42 (ddd, ^2J = 13.7 Hz, ^3J = 7.4 Hz, ^4J = 1.0 Hz, 1H), 3.58 (ddd, ^2J = 13.7 Hz, ^3J = 6.7 Hz, ^4J = 1.1 Hz, 1H), 4.89 (m, ^3J = 10.0 Hz, ^2J = 2.7 Hz, ^4J = 1.0 Hz, 1H), 5.02 (m, ^3J = 16.9 Hz, ^2J = 2.7 Hz, ^4J = 1.1 Hz, 1H), 5.89 (m, ^3J = 6.7 Hz, ^3J = 7.4 Hz, ^3J = 16.9 Hz, ^3J = 10.0 Hz, 1H); ^{13}C NMR (50 MHz, C_6D_6) δ: 23.1, 24.7, 33.7, 51.3, 117.3, 122.6, 134.6, 137.6; IR (CCl_4) cm $^{-1}$: 1636 (C=C), 3088 (=CH_2)

Thermolysis of 2-Allylthio-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (227)

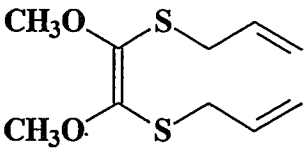
According to general procedure A, 2-allylthio-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**227**) (0.100 g, 0.495 mmol) and dry benzene (2.0 g) were added to a 5 mL thermolysis vessel. Following three freeze, pump, and thaw sequences the vacuum sealed

tube was immersed into an oil bath (70 °C) for 17 h. The crude sample was analyzed by GC and GC/MS. The volatiles were then removed in vacuo and the remaining crude yellow oil was analyzed by NMR spectroscopy. The crude NMR spectrum indicated an approximate 70 % yield of allylthiomethoxycarbene dimer (50:50 mixture of both isomers).

Allylthiomethoxycarbene dimers (50:50) (229 and 230)



trans



cis

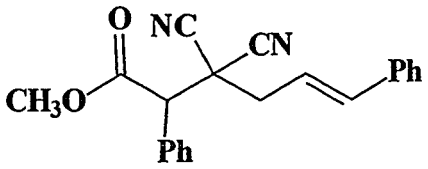
^{1}H NMR (200 MHz, C_6D_6) δ: 2.75-3.16 (m, 4H), 3.20 (s, 3H), 3.61 (s, 3H), 4.85-5.10 (m, 4H), 5.66-5.95 (m, 2H); ^{13}C NMR (50 MHz, C_6D_6) δ: 32.0, 42.5, 51.0, 58.6, 96.4, 117.1, 118.2, 132.4, 133.8, 134.5; MS (EI) *m/z* (rel. intensity): 232 ($M^{+\cdot}$, 4), 191(17), 159 (67), 127 (66), 99 (29), 75 (100), 41 (68); MS (HR) *m/z*: calcd for $C_{10}H_{16}O_2S_2$ 232.0595, found 232.0591

Thermolysis of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (189) in the Presence of Benzylidenemalononitrile (178)

A 25 mL thermolysis tube was prepared according to general procedure A. Cinnamyloxymethoxy oxadiazoline (**189**) (300 mg, 1.15 mmol), benzylidene-malononitrile (**178**) (300 mg, 1.95 mmol), and 10 mL of dry benzene were added to the thermolysis vessel. Next, 2.5 mL of benzene was azeotropically removed and following, three freeze, pump, thaw sequences were performed to remove oxygen from the sample.

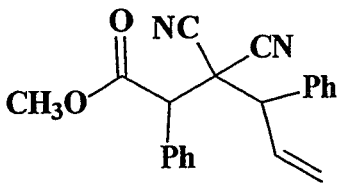
The vacuum sealed tube was then placed into an oil bath (110 °C) for 21 h. The crude sample was analyzed by GC and GC/MS and then concentrated in vacuo. Two major products were isolated by flash column chromatography (**239** and **240**) with 25 g of basic alumina (Fisher Brockmann I) which was activated at 120 °C for 24 h. The column dimensions were 2 cm x 15 cm and the elution solvent consisted of 30 % ethyl acetate in hexanes.

Methyl-3,3-dicyano-2,6-diphenyl-5-hexenoate (239)



Clear liquid: 30% isolated yield; ^{1}H NMR (500 MHz, C_6D_6) δ: 2.30 (dd, ^2J = 13.9 Hz, ^3J = 7.4 Hz, 1H), 2.40 (dd, ^2J = 13.9 Hz, ^3J= 7.4 Hz, 1H), 3.15 (s, 3H), 3.73 (s, 1H), 6.08 (dt, ^3J = 15.7 Hz, ^3J = 7.4 Hz, 1H), 6.27 (d, ^3J = 15.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ: 39.3, 40.8, 52.2, 55.5, 114.2, 114.6, 118.9, 126.8, 128.3, 128.3, 129.2, 129.5, 129.6, 131.1, 135.9, 138.0, 168.7; MS (EI) *m/z* (rel. intensity): 330 ($M^{+\cdot}$, 1), 299 (1), 271 (1), 154 (6), 150 (59), 117 (100), 115 (49), 91 (41), 77 (24), 59 (14), 51 (8); MS (CI/NH_3) *m/z*: 348 ($M^{+\cdot}$+18); IR (CCl_4) cm^{-1}: 1750 (C=O)

Methyl-3,3-dicyano-2,4-diphenyl-5-hexenoate (240)



Clear liquid: 15 % isolated yield; ^{1}H NMR (500 MHz, C_6D_6) δ: 3.10 (s, 3H), 3.70 (s, 1H), 4.08 (d, ^3J= 9.0 Hz, 1H), 5.05 (dt, ^3J = 10.2 Hz, ^2J = 1.0 Hz, 1H), 5.12 (dt, ^3J= 16.8

Hz, ^{2}J = 1.0 Hz, 1H), 6.25 (ddd, ^{3}J = 16.8 Hz, ^{3}J = 10.2 Hz, ^{3}J = 9.0 Hz, 1H), 6.94-7.38 (m, 10 H); ^{13}C NMR (125 MHz, C_6D_6) δ: 47.3, 52.3, 54.1, 54.4, 113.9, 114.4, 121.8, 129.0, 129.1, 129.3, 129.4, 129.8, 130.4, 131.8, 133.8, 136.2, 169.0; MS (CI/NH_3) *m/z*: 348 ($M^{+\cdot}$ + 18)

Thermolysis of 2-Cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (189) in the Presence of Benzylidenemalononitrile (178) and TEMPO (207)

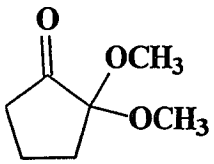
A 25 mL thermolysis tube was prepared according to general procedure A. Cinnamyloxymethoxy oxadiazoline (**189**) (300 mg, 1.15 mmol), benzylidenemalononitrile (**178**) (300 mg, 1.95 mmol), TEMPO (**207**) (300 mg, 1.92 mmol), and 10 mL of dry benzene were added to the thermolysis tube. The solution was frozen, pumped, and thawed through a total of three cycles and sealed under vacuum. The tube was then placed into a preheated oil bath (110 °C) for 21 h. Two major products were isolated by column chromatography and fully characterized by spectroscopic methods; the phenylallyl-TEMPO (**209**) and methoxycarbonyl-TEMPO (**208**) adducts were found as major products. GC/MS analysis revealed trace amounts of esters **193** and **194**, however, no radical addition products (**239** and **241**) were observed.

Thermolysis of Dimethoxy Oxadiazoline (93) in the Presence of Cyclobutanone (244)

A Pyrex glass tube (25 mL) was charged with dimethoxy oxadiazoline (**93**) (0.200 g, 1.25 mmol), cyclobutanone (**244**) (Aldrich) (0.175 g, 2.50 mmol) and benzene (5 g). After three freeze-pump-thaw sequences with liquid nitrogen as coolant, the glass tube was sealed and immersed for 24 h in an oil bath at 110 °C. After the contents had cooled

to ambient temperature, the reaction mixture was transferred to a 25 mL round-bottomed flask. The solvent and volatiles were removed with a rotary evaporator and a vacuum pump, yielding 2,2-dimethoxycyclopentanone (**247**) (75 % yield). Spectroscopic data was in agreement with values in the literature.[185,186]

2,2-Dimethoxycyclopentanone (247)



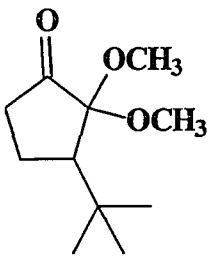
Clear liquid: 75% isolated yield; ^{1}H NMR (500 MHz, C_6D_6) δ: 1.36 (tt, ^3J = 7.0 Hz, ^3J = 7.6 Hz, 2H), 1.61 (t, ^3J = 7.0 Hz, 2H), 1.82 (t, ^3J = 7.6 Hz, 2H), 3.14 (s, 6H); ^{13}C NMR (50 MHz, C_6D_6) δ: 16.9, 33.3, 35.2, 49.9, 100.7, 207.8 (C=O); MS (CI/NH_3) *m/z*: 162 ($M^{+\cdot}$ + 18)

Thermolysis of Dimethoxy Oxadiazoline (93) in the Presence of 2-*tert*-Butylcyclobutanone (251)

A 5 mL reaction vessel for thermolysis was charged with dimethoxy oxadiazoline (**93**) (0.078 g, 0.49 mmol), 2-*tert*-butylcyclobutanone (**251**)[187] (0.060 g, 0.48 mmol), and benzene (2.0 g). After three freeze-pump-thaw cycles the tube was sealed and heated at 110 °C for 24 h in an oil bath. The contents of the vessel were transferred to a 5 mL round-bottomed flask and the volatiles were removed with a rotary evaporator and then a vacuum pump (0.1 - 0.5 mmHg) leaving a yellow oil. Semi-preparatory gas chromatography of the mixture gave two major components (60% combined yield). 2,2-Dimethoxy-3-*tert*-butylcyclopentanone (**253**) and 2,2-dimethoxy-5-*tert*-

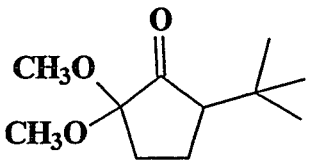
butylcyclopentanone (**254**) were in a 1.5:1.0 ratio as determined by uncorrected GC analysis and NMR.

2,2-Dimethoxy-3-tert-butylcyclopentanone (253)



Clear liquid: ^{1}H NMR (500 MHz, C_6D_6) δ: 1.07 (s, 9H), 1.38-1.42 (m, 1H), 1.51-1.65 (m, 3H), 1.95-2.01 (m, 1H), 3.01 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, C_6D_6) δ: 18.9, 29.2, 32.4, 34.7, 48.4, 50.3, 51.5, 103.8, 210.0 (C=O); GC/IR cm^{-1}: 1762 (C=O); MS (EI) *m/z* (rel. intensity): 172 ($M^{+\cdot}$ -28, 5), 153 (3), 144 (13), 129 (100), 113 (10); NOE experiment: irradiation of the *tert*-butyl signal caused enhancement of both methoxy group signals. In the mass spectrum, the base peak was at *m/z* = 129, consistent with loss of a methyl radical from 1,1-dimethoxy-3,3-dimethyl-1-butenyl radical cation (*m/z* = 144).

2,2-Dimethoxy-5-tert-butylcyclopentanone (254)



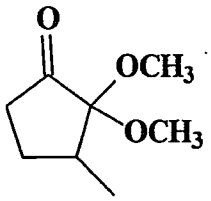
Clear Liquid: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.95 (s, 9H), 1.30-1.51 (m, 3H), 1.63 (dd, ^{3}J = 11 Hz, ^{3}J = 8.8 Hz, 1H), 1.88 (ddd, J = 12.7 Hz, J = 6.3 Hz, J = 1.5 Hz, 1H), 3.13 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 20.6, 27.7, 31.5, 33.0, 49.6, 49.9, 56.0, 101.0, 213.3 (C=O); IR (CCl_4) cm^{-1}: 1749 (C=O); MS (EI) *m/z* (rel. intensity): 172 ($M^{+\cdot}$ -

28, 6), 169 (7), 157 (4), 113 (110), 88 (100); NOE experiment: irradiation of the t-butyl signal caused enhancement of only one methoxy signal ($\delta = 3.16$). In the mass spectrum the base peak was at $m/z =$ 88, consistent with 1,1-dimethoxyethene radical cation.

Thermolysis of Dimethoxy Oxadiazoline (93) in the Presence of 2-Methylcyclobutanone (252)

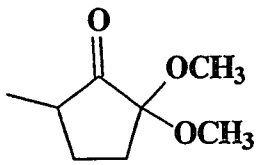
Dimethoxy oxadiazoline (**93**) (0.19 g, 1.2 mmol), 2-methylcyclobutanone (**252**) (0.10 g, 1.2 mmol), prepared according to the procedure by van Leusen,[188,189] and benzene (5.0 g) were dispensed into a 25 mL Pyrex glass tube fitted with a Teflon valve. To remove oxygen from the pre-thermolysis sample, the mixture was frozen, pumped, and thawed through three cycles and sealed under vacuum. The thermolysis tube containing the above three components was immersed into a pre-heated oil bath (110 °C) for a 24 h period. Removal of the volatiles by a rotary evaporator and vacuum pump left a light yellow oil residue (59 %). NMR analysis of the oil indicated a two component mixture of 2,2-dimethoxy-3-methylcyclopentanone (**255**) and 2,2-dimethoxy-5-methylcyclopentanone (**256**) in a ratio of 7.5:1.0. The major and minor isomers were distinguished by their characteristic mass spectral fragmentation patterns, similar to those observed for **253** and **254**.

2,2-Dimethoxy-3-methylcyclopentanone (255)



^{1}H NMR (200 MHz, C_6D_6) δ: 0.79 (d, ^3J = 7.0 Hz, 3H), 1.06-1.24 (m, 1H), 1.60-2.03 (m, 4H), 3.07 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ: 13.9, 25.0, 32.8, 37.3, 49.9 (OCH_3), 50.2 (OCH_3), 102.4 (C_2), 208.3 (C=O); GC/MS (EI) *m/z* (rel. intensity): 158 ($M^{+\cdot}$, 1), 130 ($M^{+\cdot}$-28, 7), 102 ($(CH_3O)_2CCHCH_3^{+\cdot}$, 100), 85 (30), 72 (14), 57 (61); MS (CI/NH_3), *m/z*: 159 ($M^{+\cdot}$+1), 176 ($M^{+\cdot}$+18); MS (HR) *m/z*: calcd for $(CH_3O)_2CCHCH_3$ (base peak, isomer identification) 102.0703, found 102.0681;); IR (CCl_4) cm^{-1}: 1758 (C=O)

2,2-Dimethoxy-5-methylcyclopentanone (256)



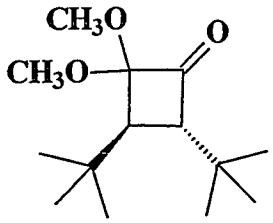
^{1}H NMR (200 MHz, C_6D_6) δ: 0.95 (d, ^3J = 7.0 Hz, 3H), 1.05-1.23 (m, 1H), 1.59-2.02 (m, 4H), 3.13 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ: 15.1, 25.9, 32.0, 41.9, 49.7, 50.2, 101.0, 207.6; MS (EI/GC/MS) *m/z* (rel. intensity): 158 ($M^{+\cdot}$,1), 130 ($M^{+\cdot}$-28, 13), 99 (9), 88 ($(CH_3O)_2CCH_2^{+\cdot}$, 100), 71 (16), 58 (19), 43 (78); IR (CCl_4) cm^{-1}: 1758 (C=O)

Thermolysis of 93 in the Presence of *trans*-2,3-Di-*tert*-butylcyclopropanone (258)

A medium-walled NMR tube containing **93** (0.023 g, 0.14 mmol), *trans*-di-*tert*-butylcyclopropanone (**258**)[190-192] (0.020 g, 0.12 mmol) and benzene (1.0 g) was sealed under vacuum after three cycles of freeze-pump-thaw degassing. The tube was then heated for 24 h at 110 °C in an oil bath before it was cut and the contents were transferred to a 3 mL glass vial. Concentration of the sample and column chromatography (10 %

ethyl acetate in hexanes) gave *trans*-3,4-di-*tert*-butyl-2,2-dimethoxycyclobutanone (259) in 65% yield.

trans-3,4-Di-tert-butyl-2,2-dimethoxycyclobutanone (259)

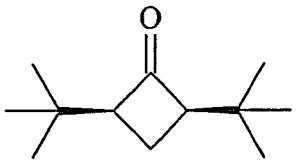


Clear liquid: ^{1}H NMR (300 MHz, C_6D_6) δ: 0.96 (s, 9H), 0.99 (s, 9H), 2.03 (d, ^3J = 7.1 Hz, 1H), 2.62 (d, ^3J = 7.1 Hz, 1H), 2.98 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ: 28.9, 29.0, 30.7, 48.6, 51.0, 51.9, 66.1, 99.6, 111.2, 207.8 (C=O); MS (EI) *m/z* (rel. intensity): 185 ($M^{+\cdot}$ -57, 5), 157 (100), 129 (15), 74 (51), 57 (55); MS (CI/NH_3) *m/z*: 260 ($M^{+\cdot}$ + 18); 243 ($M^{+\cdot}$ +1); IR (CCl_4) cm $^{-1}$: 1783 (C=O)

Thermolysis of 93 in the Presence of *cis*-2,4-Di-*tert*-butylcyclobutanone (260)

Into a 5 mL thermolysis tube, prepared in accordance with general procedure A, was added dimethoxy oxadiazoline (**93**) (46.1 mg, 0.288 mmol), *cis*-2,4-di-*tert*-butylcyclobutanone (**260**) (40.0 mg, 0.219 mmol), and benzene (2.0 g). The contents of the tube were frozen, pumped, and thawed through three cycles and sealed under vacuum, and following, the tube was placed into an oil bath (110 °C) for a 24 h period. GC/MS and ^{1}H NMR spectroscopy of the crude mixture revealed that no carbene reaction with **260** had occurred. Dimethoxycarbene dimer (**7**) along with unreacted *cis*-2,4-di-*tert*-butylcyclobutanone (**260**) were the only two products identified from the crude reaction mixture.

cis-2,4-Di-tert-butylcyclobutanone (260)[187,193]

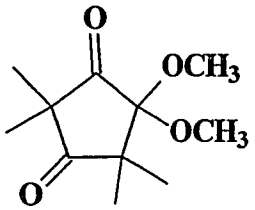


^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.92 (s, 18H), 1.67 (dd, ^3J = 9.4 Hz, ^2J = 19.0 Hz, 1H), 1.96 (dd, ^3J = 10.4 Hz, ^2J = 19.0 Hz, 1H), 2.86 (dd, ^3J = 9.4 Hz, ^3J = 10.4 Hz, 2H)

Reaction of 93 with 2,2,4,4-Tetramethylcyclobutane-1,3-dione (262)

A 5 mL thermolysis tube was charged with dimethoxy oxadiazoline (**93**) (0.200g, 1.25 mmol), 2,2,4,4-tetramethylcyclobutane-1,3-dione (**262**) (Aldrich, 0.168 g, 1.20 mmol) and benzene (5.0 g). After three freeze-pump-thaw cycles the tube was sealed and heated for 24 h in an oil bath at 110 °C. Removal of the volatiles, as described above, left a yellow oil from which the major product was isolated, either by semi-preparative gas chromatography or by flash column chromatography (70 % isolated) (silica gel-10 % ethyl acetate in hexanes - Rf = 0.75).

2,2,4,4-Tetramethyl-5,5-dimethoxycyclopentane-1,3-dione (262)

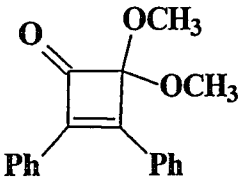


Clear Liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.06 (s, 6H), 1.09 (s, 6H), 2.91 (s, 6H); ^{13}C NMR (50 MHz, C_6D_6) δ: 18.8, 22.8, 48.6, 50.3, 54.4, 103.9, 208.3 (C=O), 215.5 (C=O); MS (EI) *m/z* (rel. intensity): 186 ($M^{+\cdot}$ -28, 12) 149 (8), 116 (32), 101 (16), 84 (28), 43 (100); MS (CI/NH_3) *m/z:* 232 ($M^{+\cdot}$ + 18); IR (CCl_4) cm^{-1}: 1735 (C=O)

Thermolysis of 93 in the Presence of 1,2-Diphenylcyclopropenone (263)

A solution of dimethoxyoxadiazoline (**93**) (0.200 g, 1.25 mmol) and 1,2-diphenylcyclopropenone (**263**) (Aldrich, 0.450, 2.20 mmol) in benzene (5.0 g), in a 25 mL thermolysis tube, was treated as described above. Flash column chromatography on silica gel (5% ethyl acetate in hexanes, Rf = 0.23) of the residue left after pumping off the volatile components, afforded 4, 4-dimethoxy-2,3-diphenyl-2-cyclobuten-1-one (**266**) in 60 % yield.

4, 4-Dimethoxy-2, 3-diphenyl-2-cyclobuten-1-one (266)



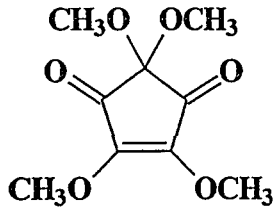
Yellow liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 3.47 (s, 6H), 6.98-7.03 (m, 6H), 7.76-7.81 (m, 2H), 7.87-7.92 (m, 2H); ^{13}C NMR (50 MHz, C_6D_6) δ: 53.6, 118.1, 128.3, 128.7, 128.9, 129.0, 129.2, 130.0, 130.9, 131.6, 149.0, 170.7, 193.2; MS (EI) *m/z* (rel. intensity): 280 ($M^{+\cdot}$, 16), 265 ($M^{+\cdot}$ -15, 6), 249 ($M^{+\cdot}$ -31, 18), 220 (38), 205 (16), 192 (55), 178 (100), 152 (29), 121 (38), 115 (77), 91 (38); MS (HR) *m/z*: calcd for $C_{18}H_{16}O_3$ 280.1090, found 280.1099; IR (CCl_4) cm^{-1}: 1758 (C=O)

Thermolysis of 93 in the Presence of 3,4-Dimethoxy-3-cyclobutene-1,2-dione (264)

A solution of dimethoxyoxadiazoline (**93**) (0.200 g, 1.25 mmol) and 3,4-dimethoxy-3-cyclobutene-1,2-dione (**264**) (Aldrich, 0.170 g, 1.20 mmol) in benzene (5.0 g) was prepared and heated as described above. Flash column chromatography of the

residue, after removal of the volatiles (10-30 % ethyl acetate in hexanes), gave from the first yellow band, 2,2,4,5-tetramethoxy-4-cyclopentene-1,3-dione in 54 % yield.

2,2,4,5-Tetramethoxy-4-cyclopentene-1,3-dione (267)



Yellow solid: mp 37.0-38.0 °C; ^{1}H NMR (200 MHz, C_6D_6) δ: 3.47 (s, 6H), 3.60 (s, 6H); ^{13}C NMR (50 MHz, C_6D_6) δ: 51.8, 59.2, 91.0, 150.8, 188.6 (C=O); MS (EI) *m/z* (rel. intensity): 216 ($M^{+\cdot}$, 100), 185 ($M^{+\cdot}$ -31, 57), 173 (85), 157 (28), 129 (29), 86 (14), 75 (51), 59 (81); MS (CI/NH_3) *m/z*: 234 ($M^{+\cdot}$+18); MS (HR) *m/z*: calcd for $C_9H_{12}O_6$ 216.0641, found 216.0634; IR (CCl_4) cm^{-1}: 1702 (C=O)

Attempted Hydrolysis of 2,2,4,5-Tetramethoxy-4-cyclopentene-1,3-dione (267)

10 % Sulphuric Acid / 2 h

A 3 mL volume of 10 % sulphuric acid was added to 2,2,4,5-tetramethoxy-4-cyclopentene-1,3-dione (**267**) (50.0 mg, 0.230 mmol) in a 5 mL round bottom flask. The mixture was stirred for 2 h. at ambient temperature. The starting material was unchanged.

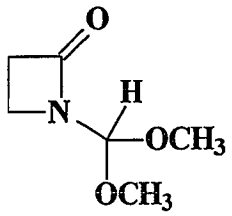
50:50 Mixture of 10 % Sulphuric Acid and Methanol / 24 h

A 3 mL volume of a 50:50 mixture of 10 % sulphuric acid and methanol was added to 2,2,4,5-tetramethoxy-4-cyclopentene-1,3-dione (**267**) (50.0 mg, 0.230 mmol) in a 5 mL round bottom flask. The mixture was stirred for 24 h. at ambient temperature. Work up involving an ether extraction and volatile removal indicated, by NMR, that most of the starting material was intact (~ 80-90 %).

Thermolysis of 93 in the Presence of 2-Azetidinone (270)

The procedure described above gave, from dimethoxy oxadiazoline (**93**) (0.200 g, 1.25 mmol) and 2-azetidinone (**270**) (Aldrich, 0.178 g, 2.5 mmol) in benzene (5.0 g), a residue that was worked up by semi-preparative gas chromatography. 1-(Dimethoxymethyl)-2-azetidinone (**272**) (76 % by GC) was isolated.

1-(Dimethoxymethyl)-2-azetidinone (272)

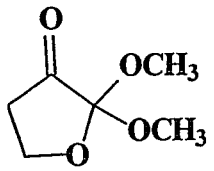


Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 2.24 (t, ^{3}J = 4.5 Hz, 2H), 2.79 (t, ^{3}J = 4.5 Hz, 2H), 2.99 (s, 6H), 5.38 (s, 1H); ^{13}C NMR (50 MHz, C_6D_6) δ: 35.5, 36.1, 53.2, 99.5, 166.5; MS (EI) *m/z* (rel. intensity): 145 ($M^{+\cdot}$, 1), 130 ($M^{+\cdot}$ -15, 1), 114 (18), 87 (33), 75 ($(MeO)_2CH$, (100), 72 (30), 42 (35); IR (CCl_4) cm^{-1}: 1770 (C=O)

Thermolysis of 93 in the Presence of β-Propiolactone (271)

Heating of a solution of **93** (0.200 g, 1.25 mmol) and β-propiolactone (**271**) (Aldrich, 0.090 g, 1.20 mmol) in benzene (5.0 g), and workup as described above, left a yellow oil. Flash column chromatography (silica gel - 30% ethyl acetate in hexanes, Rf = 0.50) afforded 2,2-dimethoxy-3-oxacyclopentanone (**275**) in 65% yield.

2,2-Dimethoxy-3-oxacyclopentanone (275)



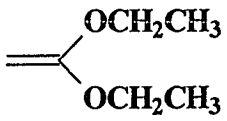
^{1}H NMR (500 MHz, C_6D_6) δ: 1.75 (t, ^3J = 7.0 Hz, 2H), 3.25 (s, 6H), 3.50 (t, ^3J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ: 33.5, 50.2, 60.4, 110.0, 202.8 (C=O); GC/MS (EI) *m/z* (rel. intensity): 118 ($M^{+\cdot}$ - 28, 29), 115 (40), 91 (90), 59 (100); IR (CCl_4) cm^{-1}: 1741 (C=O)

Synthesis of 1,1-Diethoxyethene (334)

1,1-Diethoxyethane (**334**) was prepared according to the procedure by Thweatt.[173] A fractional distillation apparatus consisting of a two-necked, round-bottomed flask (50 mL), magnetic stirring bar, addition funnel (20 mL), fractionating column (20 cm), 3-way Claisen head with thermometer, condenser (20 cm), and a receiving flask (50 mL) with a vacuum attachment was flame dried under vacuum. The addition funnel was removed and solid potassium *tert*-butoxide (11.4 g, 102 mmol) was added to the flask. The addition funnel was reattached and 2-bromo-1,1-diethoxyethane (15.3 ml, 20.0 g, 101.5 mmol) was added with a glass syringe to the addition funnel through a rubber septum. The reaction flask was cooled with an ice/water mixture (5 min) and 2-bromo-1,1-diethoxyethane was dispensed into the round bottom flask (1 min). A white dense smoke formed immediately. After the reaction appeared to be complete (5 min), the mixture was heated with an oil bath (120-130 °C), and t-butyl alcohol (82-83 °C / 760 mmHg) generated from the reaction was removed by distillation. The system was then attached to

a water aspirator and 1,1-diethoxyethene (**334**) was distilled from the crude reaction mixture (46 °C /28 mmHg) (6.70 g, 57 %). The product was used on the same day in the next step.

1,1-Diethoxyethene (334)

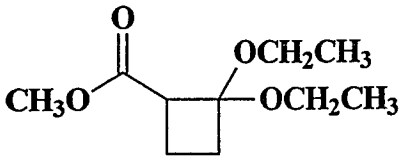


Clear liquid: bp 46 °C / 28 mmHg; ^{1}H NMR (200 MHz, C_6D_6) δ: 1.02 (t, ^{3}J = 7.0 Hz, 6H), 3.17 (s, 2H), 3.55 (q, ^{3}J = 7.0 Hz, 4H); ^{13}C NMR (25 MHz, C_6D_6) δ: 14.5, 56.6, 63.4, 165.7

Synthesis of Methyl (2,2-diethoxycyclobutane)carboxylate (335)

A solution of 1,1-diethoxyethene (**334**) (6.70 g, 58.0 mmol) and methyl acrylate (4.97 g, 58 mmol) was refluxed in dry acetonitrile (40 mL) for 8 days. Acetonitrile was distilled out through a Vigreux column, followed by methyl (2,2-diethoxycyclobutane)carboxylate (**335**) (48 °C / 0.8 mmHg) (2.0 g, 17 %), lit.[173,187] 60-63 %.

Methyl (2,2-diethoxycyclobutane)carboxylate (335)



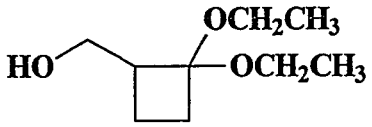
Clear liquid: bp 48 °C / 0.8 mmHg; ^{1}H NMR (200 MHz, C_6D_6) δ: 0.97-1.24 (m, 1H), 1.01 (t, ^{3}J = 7.0 Hz, 3H), 1.11 (t, ^{3}J = 7.0 Hz, 3H), 1.58-2.37 (m, 4H), 3.17-3.65 (m, 4H),

3.42 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 14.8, 15.3, 15.4, 31.0, 49.6, 51.1, 56.6, 57.1, 102.6, 170.8

Synthesis of (2,2-Diethoxycyclobutyl)methanol (336)[194]

To a suspension of $LiAlH_4$ (0.25 g, 6.70 mmol) in ether (15 mL) was added, dropwise with stirring, methyl (2,2-diethoxycyclobutane)carboxylate (**335**) (1.35 g, 6.70 mmol). After the addition the mixture was heated to boiling for 1.5 h before it was cooled with an ice/water bath and the excess $LiAlH_4$ was quenched with ethyl acetate (15 mL), followed by water (15 mL, slow addition). The fine-grained $Al(OH)_3$ that formed was filtered with a sintered glass funnel. The filtered, heterogeneous solution was extracted with diethyl ether (3 x 25 mL) and the combined organic fractions were dried with anhydrous magnesium sulphate. Filtration through a sintered glass funnel and removal of the volatiles afforded (2,2-diethoxycyclobutyl)methanol (**336**) in 95 % yield. The crude product was used without purification. Purification by distillation (61 °C / 0.8 mmHg) has been reported.[194]

(2,2-Diethoxycyclobutyl)methanol (336)

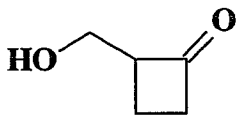


Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 0.92 (t, ^3J = 7.1 Hz, 3H), 1.08 (t, ^3J = 7.1 Hz, 3H), 1.35-2.60 (m, 6H), 3.10-3.90 (m, 6H); ^{13}C NMR (25 MHz, C_6D_6) δ: 14.2, 15.3, 15.5, 30.6, 45.9, 56.1, 56.5, 63.1, 103.9.

Hydrolysis of (2,2-Diethoxycyclobutyl)methanol (336)[172]

2,2-(Diethoxycyclobutyl)methanol (**336**) (0.51 g , 2.93 mmol) was stirred with 3 % H_2SO_4 (30 mL) for 20 min in a 50 mL round bottomed flask. The mixture was extracted with ether (3 x 15 mL) and the combined ether extracts were washed with 5 % $NaHCO_3$ (3 x 20 mL). The yellow aqueous layers were combined in a separatory funnel and CH_2Cl_2 (60 mL) and H_2SO_4 (3 %, 30 mL) were added. The yellow aqueous layer was extracted with CH_2Cl_2 until the yellow colour of the aqueous layer was completely dissipated. The organic layers were combined and dried with anhydrous magnesium sulphate. Filtration through a sintered glass funnel and removal of the solvents yielded the desired 2-hydroxymethylcyclobutanone (**278**) (75 %).

2-Hydroxymethylcyclobutanone (278)



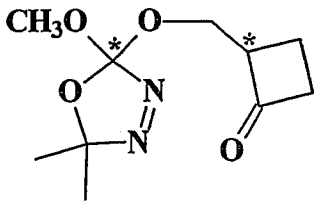
Clear liquid: ^1H NMR (200 MHz, C_6D_6) δ: 1.45-1.75 (m, 2H), 2.38-2.68 (m, 2H), 2.90-3.10 (m, 2H), 3.37-3.70 (m, 2H); ^{13}C NMR (25 MHz, C_6D_6) δ: 13.5, 45.4, 60.1, 62.8, 210.2

Reaction of 2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (184) with 2-Hydroxymethylcyclobutanone (278)

Trifluoroacetic acid (4 drops) was added to 2-acetoxy-2-methoxy-Δ^3-1,3,4-oxadiazoline (**184**)[60] (0.700 g, 3.72 mmol), 2-hydroxymethylcyclobutanone (**278**) (0.220 g, 2.20 mmol), and dichloromethane (35 mL) in a 100 mL round bottomed flask and the solution was stirred under nitrogen for 48 h at room temperature. Sodium bicarbonate

(10 %, 20 mL) was added and the contents were stirred for 10 minutes before the aqueous layer was separated and discarded. The extraction was repeated before the organic layer was dried with anhydrous magnesium sulphate. Filtration and removal of the volatiles afforded a yellow oil. 2-(2-Cyclobutanonemethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**277**) was obtained as a 50:50 mixture of diastereomers, in 54% yield, by flash column chromatography on silica gel (20 % ethyl acetate in hexanes). The diasteromers could be separated by TLC (20 % ethyl acetate in hexanes; Rf = 0.4 and 0.3), but the bulk of the material was used as a mixture of diastereomers.

2-(2-Cyclobutanonemethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (277)

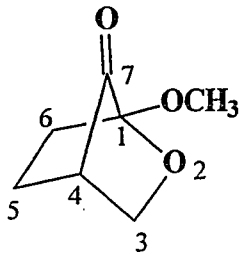


Clear liquid: 50:50 mixture of diastereomers; ^{1}H NMR (200 MHz, C_6D_6) δ: 1.21 (s, 6H), 1.23 (s, 3H), 1.28 (s, 3H), 1.32-1.71 (m, 4H), 2.34-2.52 (m, 4H), 2.87-2.99 (m, 2H), 3.17 (s, 3H), 3.21 (s, 3H), 3.60-4.00 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ: 14.1, 14.2, 23.7, 23.7, 24.0, 24.1, 45.0, 45.0, 51.6, 51.6, 60.0, 60.0, 62.1, 62.3, 119.3, 119.3, 137.5, 137.5, 206.3, 206.5; MS (EI) *m/z* (rel. intensity): (molecular ion not observed) 129 ($M^{+\cdot}$ -99, 14), 117 (7), 83 (35), 73 (31), 55 (100); MS (CI/NH_3) *m/z*: 229 ($M^{+\cdot}$ +1), 246 ($M^{+\cdot}$ +18) IR (CCl_4) cm^{-1}: 1790 (C=O)

Thermolysis of 2-(2-Cyclobutanonemethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (277)

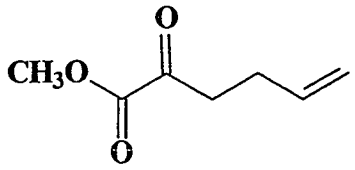
2-(2-Cyclobutanonemethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**277**) (0.140 g, 0.614 mmol) in benzene (16.5 g) was heated in a 25 mL thermolysis tube as described above. Removal of the volatiles and GC analysis indicated the presence of two major products (**280** and **281**), in 1.2:1.0 ratio. These were isolated by semi-preparative gas chromatography in a combined yield of 60 %.

1-Methoxy-2-oxabicyclo[2.2.1]heptan-7-one (280)



Clear liquid: ^{1}H NMR (500 MHz, C_6D_6) δ: 1.17 (dt, ^3J = 5.2 Hz, ^2J = 12.0 Hz, ^3J = 12.0 Hz, 1H, $H_{5\alpha}$), 1.28 (m, ^3J = 3.1 Hz, ^4J = 3.0 Hz, ^3J = 12.0 Hz, ^2J = 12.0 Hz, ^3J = 5.0 Hz, 1H, $H_{5\beta}$), 1.37 (dd, ^3J = 3.0 Hz, ^3J = 3.1 Hz, 1H, H_4), 1.63 (ddd, ^3J = 5.2 Hz, ^2J = 13.2 Hz, ^3J = 12.0 Hz, 1H, $H_{6\alpha}$), 1.84 (ddd, ^2J = 13.2 Hz, ^3J = 12.0 Hz, ^3J = 5.0 Hz, 1H, $H_{6\beta}$), 3.45 (d, ^2J = 7.2 Hz, 1H, $H_{3\alpha}$), 3.48 (s, 3H, OCH_3), 3.76 (dt, ^2J = 7.2 Hz, ^3J = 3.0 Hz, ^4J = 3.0 Hz, 1H, $H_{3\beta}$); ^{13}C NMR (125 MHz, C_6D_6) δ: 22.4 (C_5), 28.7 (C_6), (-)37.8 (C_4), (-)52.3 ($O\underline{C}H_3$), 69.6 ($\underline{C}_3$), 99.5 (C_1), 208.1 (C_7); MS (EI) *m/z* (rel. intensity): 142($M^{+\cdot}$, 20), 124 (21), 97 (25), 81 (53), 55 (100); MS (CI/NH_3) *m/z*: 143 ($M^{+\cdot}$ +1), 160 ($M^{+\cdot}$ +18); MS (HR) *m/z*: calcd for $C_7H_{10}O_3$ 142.0629, found 142.0629; IR (CCl_4) cm^{-1}: 1790

Methyl-2-oxo-5-hexenoate (281)

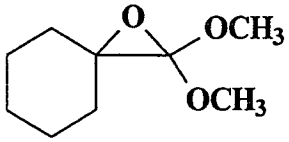


Clear liquid: ^{1}H NMR (500 MHz, C_6D_6) δ: 2.08-2.13 (m, 2H), 2.45 (t, ^{3}J = 7.2 Hz, 2H), 3.20 (s, 3H), 4.84-4.90 (m, 2H), 5.52 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ: 27.1, 38.5, (-) 51.9, 115.6, (-)136.5, 161.8, 192.7; MS (EI) *m/z* (rel. intensity): 142 ($M^{+\cdot}$, 1), 124 (10), 83 (55), 55 (100); MS (CI/NH_3) *m/z*: 160 ($M^{+\cdot}$ +18), 143 ($M^{+\cdot}$ +1); IR (CCl_4) cm^{-1}: 1750

Thermolysis of 93 and Cyclohexanone (299)

Dimethoxy oxadiazoline (**93**) (0.100 g, 0.625 mmol), cyclohexanone (**299**) (0.123 g, 1.25 mmol) and benzene (5.0 g) were added directly to a 10 mL thermolysis tube, prepared according to general procedure A. The contents of the tube were frozen, pumped, and thawed through three cycles using a vacuum pump (0.03 mm Hg) and a Dry Ice / isopropanol slurry. The tube was sealed under vacuum and then immersed into an oil bath (110 °C) for 24 h. The sample was allowed to cool to ambient temperature before the crude solution was monitered by GC and GC/MS. The sample was then concentrated in vacuo and semi-preparative gas chromatography led to the isolation of spiro[2,5]-2,2-dimethoxy-1-oxaoctane (**300**) in 15 % isolated yield.

Spiro[2,5]-2,2-dimethoxy-1-oxaoctane (300)

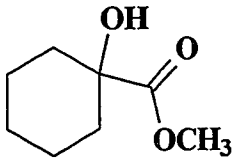


Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.52-1.89 (m, 10H), 3.25 (s, 6H); ^{13}C NMR (50 MHz, C_6D_6) δ: 21.7, 26.4, 32.1, 51.4, 77.9, 113.3; MS (EI) *m/z* (rel. intensity): 173 ($M^{+\cdot}$+1, 9), 141 (4), 105 (100), 81 (12), 59 (14); IR (CCl_4) cm^{-1}: 1450, 2850-2990 (C-H)

Hydrolysis of Spiro[2,5]-2,2-dimethoxy-1-oxaoctane (300)

To the NMR tube containing the isolated sample of spiro[2,5]-2,2-dimethoxy-1-oxaoctane (**300**) in C_6D_6 was added 1 drop of water and 1 drop of trifluoroacetic acid. The NMR tube was capped and the sample was shaken and allowed to stand at ambient temperature for 24 h. The contents of the NMR tube were then concentrated with a rotary evaporator and, following that, with a vacuum pump for 10 min. NMR analysis in C_6D_6 of the remaining material indicated that the oxirane had been completely hydrolyzed to methyl (1-hydroxycyclohexane) carboxylate (**302**).[195-197]

Methyl (1-hydroxycyclohexane) Carboxylate (302)

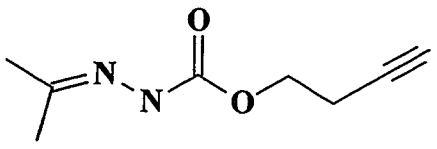


Clear liquid: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.35-1.80 (m, 10H), 3.23 (s, 3H), 3.70 (broad singlet, 1H); ^{13}C NMR (50 MHz, C_6D_6) δ: 21.5, 25.6, 35.1, 52.0, 73.7, 177.7; MS (EI) *m/z* (rel. intensity): 99 ($M^{+\cdot}$-CO_2CH_3, 21), 84 (38), 75 (4), 49 (100); IR (CCl_4) cm^{-1}: 1730 (C=O), 2850-2990 (C-H), 3542 (O-H)

Synthesis of (3-Butynoxycarbonyl)hydrazone of Acetone (316)

The (3-butynoxycarbonyl)hydrazone of acetone (**316**) was prepared according to the following procedure. 1,1'-Carbonyldiimidazole (**311**) (18.0 g, 0.111 mol), 3-butynol (**312**) (18.0 g, 0.257 mol), and dichloromethane (300 mL) in a 500 mL round bottomed flask were stirred at ambient temperature for 12 h. The reaction mixture was extracted with water (100 mL x 3) and to the organic layer was added anhydrous magnesium sulfate (10 g), hydrazine monohydrate (40 mL) and methanol (150 mL). After 15 h of stirring at ambient temperature, the heterogeneous mixture was filtered using a sintered glass funnel and vacuum aspirator. The filtrate was concentrated with a rotary evaporator and unreacted hydrazine was removed by vacuum distillation to afford a light yellow solid. It was very important not to overheat (> 45 °C) the distilling flask so that no further reactions took place with the excess hydrazine. To the light yellow solid was directly added acetone (300 mL) and magnesium sulfate (5 g). The mixture was stirred for 15 h and then filtered with a sintered glass funnel and vacuum aspirator. The volatiles were removed in vacuum to afford (3-butynoxycarbonyl)hydrazone of acetone (**316**).

(3-Butynoxycarbonyl)hydrazone of acetone (316)

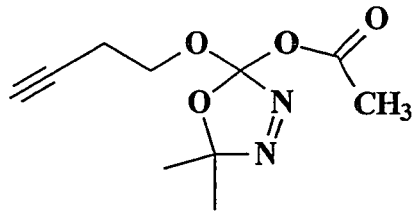


Light brown solid: mp 40.5 - 43.2 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.81 (s, 3H), 2.01 (s, 3H), 1.98 (t, ^4J = 2.6 Hz, 1H), 2.55 (dt, ^4J = 2.6 Hz, ^3J = 6.8 Hz, 2H), 4.27 (t, ^3J = 6.8 Hz, 2H), 7.60 (broad singlet, 1H)

Synthesis of 2-Acetoxy-2-butynoxy-Δ^3-1,3,4-oxadiazoline (317)

2-Acetoxy-2-butynoxy-Δ^3-1,3,4-oxadiazoline (**317**) was prepared by oxidative lead tetraacetate cyclization of **316**. Experimental details were similar to those for lead tetraacetate oxidation of **21**.

2-Acetoxy-2-butynoxy-5,5-Δ^3-1,3,4-oxadiazoline (317)

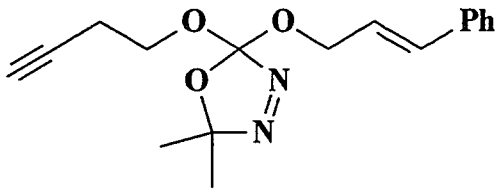


^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 3H), 1.64 (s, 3H), 1.96 (t, ^4J = 2.6 Hz, 1H), 2.10 (s, 3H), 2.51 (dt, ^4J = 2.6 Hz, ^3J = 7.1 Hz, 2H), 3.89-4.11 (m, 2H)

Synthesis of 2-Butynoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (231)

2-Butynoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**231**) was prepared according to general procedure B. Acetoxybutynoxy oxadiazoline (**317**) was reacted with cinnamyl alcohol (**192a**) (Aldrich) to afford the desired oxadiazoline.

2-Butynoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (231)



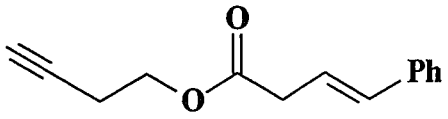
Light yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.55 (s, 3H), 1.56 (s, 3H), 1.96 (t, ^4J = 2.6 Hz, 1H), 2.53 (dt, ^4J = 2.6 Hz, ^3J = 7.0 Hz, 2H), 3.79-3.93 (m, 2H), 4.36 (ddd, ^3J = 6.1 Hz, ^2J = 12.4 Hz, ^4J = 1.0 Hz, 1H), 4.43 (ddd, ^3J = 6.1 Hz, ^2J = 12.4 Hz, ^4J = 1.1 Hz,

1H), 6.26 (dt, ^3J = 15.9 Hz, ^3J = 6.1 Hz, 1H), 6.61 (d, ^3J = 15.9 Hz, 1H), 7.23-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.9, 24.1, 24.2, 62.9, 63.7, 65.6, 69.7, 80.4, 119.5, 124.4, 126.4, 126.5, 127.9, 128.6, 132.9

Thermolysis of 2-Butynoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (231)

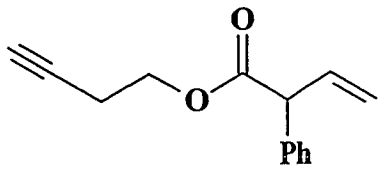
Into a clean and dry NMR tube (medium wall) was added 2-butyneoxy-2-cinnamyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**231**) (30.0 mg, 0.100 mmol) and benzene-*d6* (0.5 mL). The NMR tube containing the added components was attached to a vacuum pump and the sample was frozen, pumped, and thawed through a total of three cycles. The tube was then flame sealed under vacuum before it was immersed into a an oil bath at 110 °C for a total of 24 h. The tube was then removed from the oil bath, the exterior was washed with dichloromethane, and the NMR spectrum of the crude sample was obtained. The tube was then cooled and opened for analysis of the contents by GC and GC/MS. Column chromatography of the crude mixture afforded two identifiable components (**237** and **238**).

Compound 237



^{1}H NMR (500 MHz, C_6D_6) δ: 1.73 (t, ^4J = 2.7 Hz, 1H), 2.24 (dt, ^4J = 2.7 Hz, ^3J = 6.9 Hz, 2H), 3.56 (t, ^3J = 6.9 Hz, 2H), 4.13 (dd, ^4J = 1.4 Hz, ^3J = 5.9 Hz, 1H), 5.97-6.42 (m 3H), 7.02-7.23 (m, 5H); GC/MS (EI) *m/z* (rel. intensity): 214 ($M^{+\cdot}$, 14), 172 (10), 162 (5), 144 (5), 117 (100), 115 (47), 91 (20), 53 (12)

Component 238

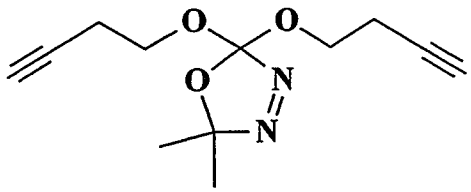


^{1}H NMR (500 MHz, C_6D_6) δ: 1.71 (t, ^4J = 2.7 Hz, 1H), 2.06 (dt, ^4J = 2.7 Hz, ^3J = 6.7 Hz, 2H), 3.88-3.99 (m, 2H), 4.53 (dt, ^3J = 6.4 Hz, ^4J = 1.1 Hz, 1H), 6.00-6.41 (m, 3H), 7.08-7.37 (m, 5H); GC/MS (EI) *m/z* (rel. intensity): 214 ($M^{+\cdot}$, 1), 169 (2), 145 (3), 117 (100), 115 (40), 102 (2), 91 (15), 53 (11)

Synthesis of 2,2-Dibutynoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (318)

Acetoxybutyneoxy oxadiazoline (**317**) was reacted with 3-butyn-1-ol (**312**) according to general procedure B.

2,2-Dibutynoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (318)

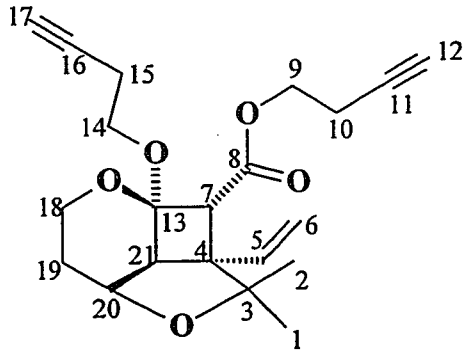


Yellow Liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 1.95 (t, ^4J = 2.6 Hz, 2H), 2.51 (dt, ^4J = 2.6 Hz, ^3J = 7.0 Hz, 4H), 3.78 (dt, ^3J = 7.0 Hz, ^2J = 9.6 Hz, 2H), 3.86 (dt, ^3J = 7.0 Hz, ^2J = 9.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.9, 24.1, 62.8, 65.5, 69.7, 80.3, 119.7; MS (EI) *m/z* (rel. intensity): molecular ion not present; 167 ($M^{+\cdot}$-OCH_2CH_2CCH,100), 149 (7), 115 (21), 91 (22), 53 (92); MS (CI) *m/z*: 254 ($M^{+\cdot}$ + 18)

Thermolysis of 2,2-Dibutynoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (318)

2,2-Dibutyneoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**318**) (200 mg, 0.848 mmol) and dry toluene (15 mL) were dispensed into a 25 mL thermolysis tube prepared according to general procedure A. Three freeze, pump, thaw cycles were performed and following, the tube was vacuum sealed and placed into an oil bath (110 °C) for 24 h. The crude sample was analyzed by GC and GC/MS before the volatiles were removed by a rotary evaporator and vacuum pump. Column chromatography afforded tricyclic product **320** (25 %, isolated) (silica gel - 10 - 20% ethyl acetate in hexanes).

Tricyclic compound 320



(Arbitrarily Assigned)

Yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.96 (s, 3H, H_1), 1.29 (s, 3H, H_2), 1.73 (ddd, ^2J = 14.8 Hz, ^3J = 2.1 Hz, ^3J = 3.0 Hz, 1H, $H_{19\alpha}$), 1.80 (ddt, ^2J = 14.8 Hz, ^3J = 4.9 Hz, ^3J = 2.7 Hz, 1H, $H_{19\beta}$), 1.92 (t, ^4J = 2.7 Hz, 1H, H_{17}), 1.94 (t, ^4J = 2.7 Hz, 1H, H_{12}), 2.41 (m, ^3J = 6.5 Hz, ^2J = 10.4 Hz, 1H, $H_{15\alpha}$), 2.42 (m, ^3J = 6.1 Hz, ^2J = 10.4 Hz, ^3J = 2.7 Hz, 1H, $H_{15\beta}$), 2.48 (dt, ^3J = 7.2 Hz, ^4J = 2.7 Hz, 1H, $H_{10\alpha}$), 2.49 (dt, ^3J = 7.2 Hz, ^4J = 2.7 Hz, 1H, $H_{10\beta}$), 2.90 (d, ^3J = 7.2 Hz, 1H, H_{21}), 3.55 (dt, ^2J = 9.0 Hz, ^3J = 6.5 Hz, 1H, $H_{14\alpha}$), 3.72 (dt, ^2J = 9.0 Hz, ^3J = 6.1 Hz, 1H, $H_{14\beta}$), 3.78 (s, 1H, H_7), 3.86 (ddd, ^2J = 12.0 Hz, ^3J = 4.9

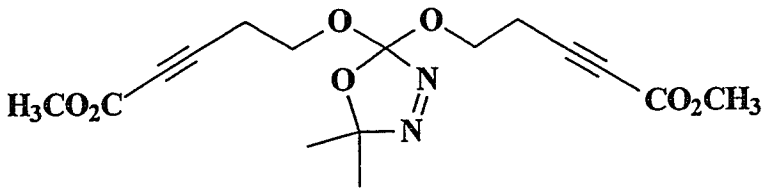
Hz, ^3J = 2.1 Hz, 1H, $H_{18\alpha}$), 4.04 (dt, ^2J = 12.0 H, ^3J = 2.7 Hz, 1H, $H_{18\beta}$), 4.12 (dt, ^3J = 7.2 Hz, ^2J = 10.5 Hz, 1H, $H_{9\alpha}$), 4.23 (dt, ^2J = 10.5 Hz, ^3J = 7.2 Hz, 1H, $H_{9\beta}$), 4.28 (dt, ^3J = 3.0 Hz, ^3J = 7.2 Hz, 1H, H_{20}), 5.13 (dd, ^3J = 17.3 Hz, ^2J = 1.4 Hz, 1H, $H_{6\alpha}$), 5.20 (dd, ^3J = 10.8 Hz, ^2J = 1.4 Hz, 1H, $H_{6\beta}$), 6.14 (dd, ^3J = 17.3 Hz, ^3J = 10.8 Hz, 1H, H_5); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0 (C_{15}), 20.1 (C_{10}), 21.4 (C_2), 22.9 (C_1), 26.6 (C_{19}), 44.1 (C_{21}), 48.6 (C_7), 55.9 (C_4), 59.0 (C_{18}), 60.5 (C_{14}), 61.7 (C_9), 69.3 (C_{17}), 69.7 (C_{12}), 70.0 (C_{20}), 80.1 (C_{16}), 81.2 (C_{11}), 83.3 (C_3), 95.7 (C_{13}), 115.5 (C_6), 133.9 (C_5), 167.9 (C_8); MS (EI) *m/z* (rel. intensity): 358 ($M^{+\cdot}$, 3), 343 (5), 289 (19), 261 (21), 203 (12), 177 (9), 151(35), 135 (75), 105 (43), 91 (54), 79 (30), 53 (100); MS (HR) *m/z*: calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1783

Synthesis of 2,2-(4-Methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (304)

A 50 mL round bottom flask was flame dried under a stream of dry nitrogen. Under a continuous nitrogen purge, freshly distilled diisopropylamine (1.49 mL, 10.6 mmol) and THF (20 mL) (sodium / benzophenone still) were added to the round bottom flask. The contents were then cooled to 0 °C and n-BuLi (6.63 mL of a 1.60 M solution in hexanes, 10.6 mmol) was added dropwise (20 min) through a rubber septum with a 10 mL syringe. The mixture was stirred for 1 h at 0 °C before cooling to –78 °C for 15 min. This freshly prepared LDA[198] was added via a cannula (15 min) to a solution of dibutyneoxy oxadiazoline (**318**) (1.25 g, 5.3 mmol) in THF (20 mL) which had been previously cooled to –78 °C. The solution was stirred at –78 °C for a 1 h period. Following, a solution of freshly distilled chloromethylformate (1.23 mL, 16.0 mmol) in

THF (20 mL) was cooled to –78 °C and added dropwise via a syringe (20 min). The mixture was stirred at –78 °C for 4 h and then quenched with methanol (30 mL) before it was concentrated in vacuo. The resulting residue was dissolved in chloroform (30 mL) and washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous magnesium sulfate (10 g) and filtered using a sintered glass funnel and vacuum aspirator. 2,2-(4-Methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**304**) was purified by column chromatography (silica gel - 5 - 20 % ethyl acetate in hexanes) (60 %, isolated).

2,2-Di-(4-methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (304)



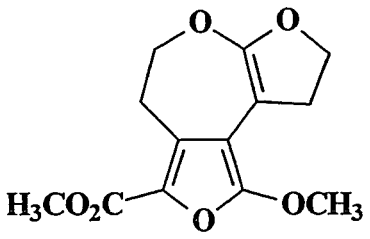
Yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.43 (s, 6H), 2.57 (t, ^3J = 6.7 Hz, 4H), 3.62 (s, 6H), 3.65-3.86 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.8, 23.8, 52.0, 61.5, 73.6, 85.1, 119.8, 135.8, 153.5; MS (CI) *m/z*: 370 ($M^{+\cdot}$ + 18)

Thermolysis of 2,2-di-(4-Methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (304)

A reflux apparatus, consisting of a 250 mL round bottom flask and condenser was base washed and flame dried under a stream of dry nitrogen. Oxadiazoline (**304**) (50.0 mg, 0.142 mmol) and dry toluene (50 mL) were added, the water condenser was attached, and the solution was refluxed for a 24 h period under a stream of dry nitrogen. When the solution had cooled to ambient temperature it was analyzed by GC and GC/MS. The

volatiles were removed in vacuo with a rotary evaporator and, following that, with a vacuum pump (0.03 mmHg). Chromatography of the crude led to the isolation of the major component. The isolated component was analyzed by GC/MS and ^{1}H NMR. Sample hydrolysis prevented further spectroscopic analysis. The isolated product has been tentatively assigned the following tricyclic structure (**310**).

*Tentative Tricyclic Structure **310***

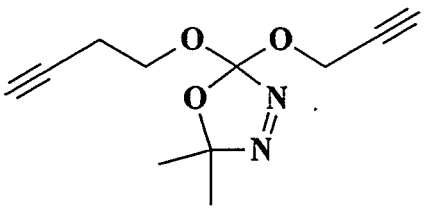


^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.77 (t, ^3J = 8.9 Hz, 2H), 3.18-3.22 (m, 2H), 3.40 (s, 3H), 3.49 (s, 3H), 3.77-3.82 (m, 2H), 4.00 (t, ^3J = 8.9 Hz, 2H)

Synthesis of 2-Butynoxy-2-propargyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (330)

2-Butynoxy-2-propargyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**330**) was prepared by the general alcohol exchange procedure B. Acetoxybutynoxy oxadiazoline (**317**) was reacted with propargyl alcohol (**329**) (Aldrich) in dichloromethane containing a catalytic amount of trifluoroacetic acid.

2-Butynoxy-2-propargyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (330)

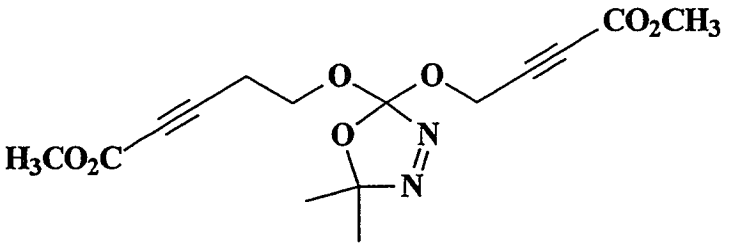


Yellow liquid: 80% isolated yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.54 (s, 3H), 1.55 (s, 3H), 1.96 (t, ^{4}J = 2.7 Hz, 1H), 2.43 (t, ^{4}J = 2.4 Hz, 1H), 2.51 (dt, ^{4}J = 2.7 Hz, ^{3}J = 7.0 Hz, 2H), 3.79 (dt, ^{3}J = 7.0 Hz, ^{2}J = 9.5 Hz, 1H), 3.89 (dt, ^{3}J = 7.0 Hz, ^{2}J = 9.5 Hz, 1H), 4.42 (d, ^{4}J = 2.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.8, 24.0, 24.1, 52.8, 63.0, 69.8, 74.7, 78.5, 80.2, 120.4, 136.0; MS (CI) *m/z*: 240 ($M^{+\cdot}$ + 18)

Synthesis of 2-(Methoxycarbonyl-3-butyn-1-oxy)-2-(3-methoxycarbonyl-2-propyn-1-oxy)-5,5-dimethyl-Δ^{3}-1,3,4-oxadiazoline (328)

Esterification of butynoxypropargyloxy oxadiazoline (**330**) followed the procedure for dibutynoxy oxadiazoline (**318**).

2-(Methoxycarbonyl-3-butyn-1-oxy)-2-(3-methoxycarbonyl-2-propyn-1-oxy)-5,5-dimethyl-Δ^{3}-1,3,4-oxadiazoline (328)



Yellow liquid: 50 % isolated yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.55 (s, 6H), 2.67 (t, ^{3}J = 6.8 Hz, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 3.82 (dt, ^{3}J = 6.8 Hz, ^{2}J = 9.6 Hz, 1H), 3.91 (dt, ^{3}J = 6.8 Hz, ^{2}J = 9.6 Hz, 1H), 4.50 (d, ^{2}J = 16.6 Hz, 1H), 4.60 (d, ^{2}J = 16.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.0, 24.0, 52.4, 52.7, 52.8, 62.0, 74.0, 82.2, 85.0, 102.4, 121.1, 135.6, 153.3, 153.8; MS (CI) *m/z*: 356 ($M^{+\cdot}$ + 18)

Thermolysis of 2-(Methoxycarbonyl-3-butyn-1-oxy)-2-(3-methoxycarbonyl-2-propyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (328)

A reflux apparatus, consisting of a 100 mL round bottom flask and condenser was base washed with 4 % sodium bicarbonate and flame dried under a stream of nitrogen. **328** (100 mg, 0.296 mmol) and 50 mL of toluene were added to the flask. The condenser was attached and the solution was refluxed for 24 h under a stream of dry nitrogen. When the solution had cooled to ambient temperture it was analyzed by GC and GC/MS. Removal of the volatiles in vacuo and TLC of the crude mixture revealed the presence of many components, none of which could be isolated.

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