GENERATION AND REACTIONS OF ARYLOXY AND DIARYLOXYCARBENES

BY

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Abstract

The research work presented is mainly in the area of the physical organic chemistry of nucleophilic aryloxy and diaryloxycarbenes and their potential in synthetic applications. Some other intermediates, including dipolar intermediates or radicals, were also involved.

2,2-Diaryloxy-Δ^3-1,3,4-oxadiazolines and 2-aryloxy-2-methoxy-Δ^3-1,3,4-oxadiazolines were synthesized by oxidation of the corresponding aryloxy or alkoxy carbonyl hydrazones of acetone followed by acid-catalysed exchange with different phenols. Subsequent thermolysis processes resulted in the generation of differently substituted diaryloxycarbenes and aryloxycarbenes. Cycloreversion to 2-diazopropane and corresponding carbonates was shown to be a competitive route.

The intermolecular reaction of the diaryloxy or aryloxycarbenes with an electron-deficient alkyne, DMAD, resulted in interesting dioxyvinylcarbenes, which did a novel intramolecular aromatic substitution. A mechanistic study showed that the substitution was nucleophilic. A further study of the *ortho* substituent effect on the *ipso* aromatic substitution revealed a novel electronic effect, a through-space stabilization of a vinylogous dioxycarbene by an electron rich group. This interesting result has not been reported before. Its synthetic application needs further study.

Thermolysis of a 2-acetoxy-2-aryloxy oxadiazoline resulted in some products that could only have come from radical reactions. Without any good radical stabilizing group, the fragmentation of a dioxycarbene to radical pairs is surprising.

Acknowledgements

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CI	chemical ionization
DAC	diaryloxycarbene
DMAD	dimethyl acetylene dicarboxylate
DMC	dimethoxycarbene
EI	electron impact ionization
ESR	electron spin resonance
GC	gas chromatography
HR	high resolution
IR	infrared (spectroscopy)
LFP	laser flash photolysis
LTA	lead tetraacetate
MS	mass spectrometry
N.A.	not available
NAS	nucleophilic aromatic substitution
NMR	nuclear magnetic resonance
VNS	vicarious nucleophilic substitution (of hydrogen)
VLVP	very low vapor pressure

Chapter 1: INTRODUCTION

1.1 Introduction

Over the last century, organic chemistry has evolved from reactions of simple compounds to a broad reaching science, which includes all carbon-related reactions. Extrapolation of known reactions to other systems, and the mechanisms of organic reactions have become the major concern and study focus of present organic chemists.

After more than one century's exploitation by organic chemists, simple achievable organic chemistry has been studied rather thoroughly. The actual mechanisms of organic reactions have become a major topic, and it is mechanistic understanding that guides further development in the area.

It is well known that many organic reactions involve one or more of the following reactive intermediates: (1) carbenium ions, (2) free radicals, (3) carbanions, (4) radical cations, (5) radical anions, and (6) carbenes (Figure 1). Carbenes, like other intermediates, are generally short-lived, highly reactive species that can occur in the course of chemical reactions, although some of them can be stable enough to have relatively long lifetimes and some are even isolable under special conditions. The characteristics of those reactive intermediates, such as their structures, their philicities and their lifetimes will ultimately determine the reaction routes in complex organic reactions. The detailed study of them will therefore result in the development of modern organic reactions, which further guide their usage in biochemistry, which has a close relationship to life. [1,2,3]

1.2 Characteristics of Carbenes

1.2.1 Configurations of Carbenes

Carbenes, a type of reactive intermediate, play increasingly important roles in organic chemistry due to their special characteristics. Generally, carbenes can exist in two spin multiplicities: singlet and triplet. In a singlet configuration (Fig. 1**a**) the two nonbonding electrons are paired in an approximately sp^2 orbital, whereas in a triplet configuration, the two nonbonding electrons are unpaired, occupying two different orbitals with substantial *p*-character (Fig. 1**b**).

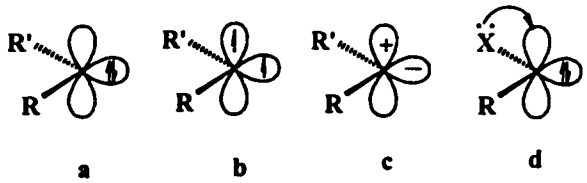


Fig. 1a. typical singlet carbene, b. typical triplet carbene, c. 1,1'-dipole, d. stabilization of a singlet carbene by π donation from a heteroatom

The singlet or triplet ground state multiplicity of a carbene is determined by ΔE_{ST}, the energy difference between the carbene σ-orbital and the carbene *p*-orbital, and the electron correlation energy, defined as the energy required to bring two electrons together in a single orbital. If ΔE_{ST} is smaller than the electron correlation energy, the carbene will have a triplet ground state. On the other hand, if it is larger than the electron correlation energy, the carbene will have a singlet ground state. The two kinds of carbenes behave very differently in chemical reactions. Singlets function more like charged species, very much like a 1,1´-dipoles (Fig. 1**c**), whereas triplet carbenes behave like diradicals and can be detected by esr (electron spin resonance) spectroscopy. The substituent bond angle of a carbene is also very characteristic of its ground state. Singlet carbenes tend to have bond

angles between 100 and 110°, whereas triplet carbene angles are between 130 and 180°.[4, 5]

Much work has been done on the study of the energy gap between the triplet and the singlet states of a carbene. [6-10] Of particular interest has been the carbene substituent effects on the singlet-triplet energy gap. It is clear now that neighboring heteroatoms can stabilize carbenes by electron delocalization to the empty *p*-orbital of the carbene carbon, and thereby decrease the ground state energy of the singlet state relative to the triplet state.[11]

Many useful singlet carbenes are heteroatom-substituted carbenes. The heteroatoms, such as sulfur,[12-16] oxygen, phosphorus,[17,18] silicon,[19-24] and nitrogen,[25-27] which are directly connected to the carbene carbon, can stabilize the singlet carbene through conjugative donation of non-bonding electrons to the formally-empty *p*-orbital of the carbene carbon. In addition, inductive withdrawal by electronegative elements, such as oxygen, also lowers the energy of the singlet state by increasing the s character of the non-bonding, in-plane σ-orbital of the carbene. Many dioxy- and diaminocarbenes are calculated to be singlets with a large singlet triplet gap.

In general, if a carbene can be stabilized by a neighboring group that donates electrons to the empty carbon pπ orbital (Fig. 1**d**), the ground state of the carbene is likely to be the singlet. This stabilization, which greatly decreases the energy of the carbene, makes the carbene lifetime long enough for it to undergo a variety of interesting reactions. Singlet carbenes react either as electrophiles, nucleophiles, or ambiphiles and both concerted and stepwise processes are possible, while triplet carbenes behave like radicals and react in a stepwise fashion with trapping reagents.

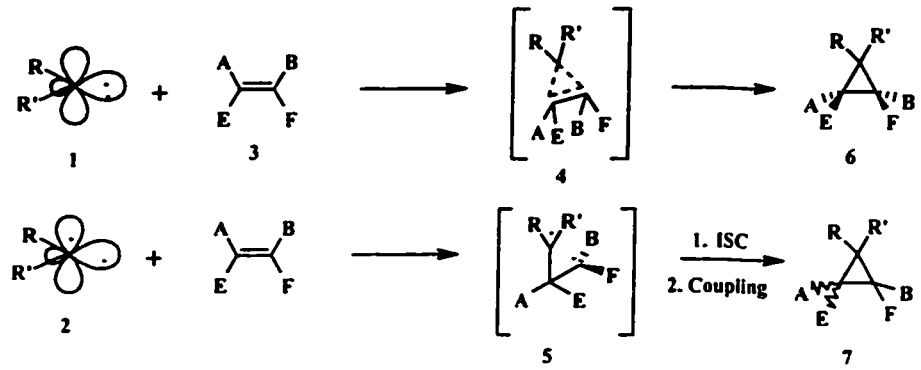
The stabilization of a carbene by the delocalization of electrons from heteroatoms increases the nucleophilicity of the carbene, but decreases its reactivity toward carbene trapping reagents. For example, the nucleophilic dioxycarbene reacts with the carbonyl group rather than the C-C double bond of maleic anhydride and analogs. In the extreme, diaminocarbenes are very slow to react or even stable enough to persist at room temperature. [31]

1.2.2 Identification of Carbenes

Although carbenes normally have very short lifetimes, direct detection of these reactive intermediates can sometimes be achieved with ultrafast spectroscopic methods. For example, coupled with UV detection, laser flash photolysis (LFP) of appropriate carbene precursors can sometimes make the study of energetics, dynamics, and reactivities of carbenes possible. [3,28,29] In several cases, the lifetimes of carbenes generated in inert rigid matrices at low temperature were sufficiently long for the carbenes to be detected by conventional detection techniques, such as UV-Vis and IR spectroscopy.[3] Electron spin resonance (ESR) spectroscopy is one powerful option for the detection of triplet carbenes because of their paramagnetic nature. This technique can provide information on ground-state multiplicities and structures of carbenes generated in frozen matrices.[1,3,30] Recently, X-ray diffraction analysis has proved to be one more useful technique, which provides unquestionable evidence of several room-temperature-stable carbenes.[31,32] However, the existence of carbene intermediates in chemical reactions is most often demonstrated with chemical trapping methods, from which knowledge of carbene structures and reactivities can be deduced.

1.2.3 Singlet *vs* Triplet Carbene Reactivity

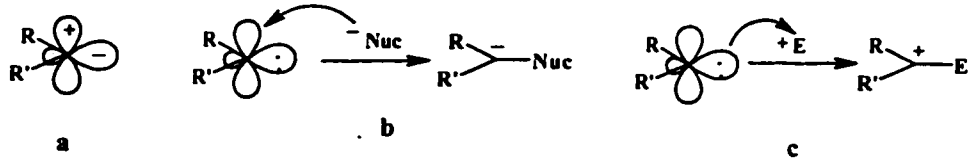
The chemistry of carbenes is strongly influenced by their multiplicity.[2] Most of the evidence comes from their reactions with carbon-carbon double bonds. The reactions of singlet carbenes with carbon-carbon double bonds proceed through a concerted mechanism for normal carbenes. Electrophilic and nucleophilic carbenes may form a dipolar intermediate, which then collapses to afford a cyclopropane. In contrast, triplet carbenes generally behave as free radicals, participating in stepwise reaction involving biradicals (Scheme 1). Concerted additions are not possible for triplet carbenes due to spin conservation requirements. *Cis-trans* isomerization can occur through bond rotation in the intermediate biradical **5**, depending on the rate of spin inversion. Skell's rule, which is based on the above ideas, has been used for several decades as a chemical diagnosis of carbene state multiplicity (Scheme 1).[33-35]



Scheme 1

1.2.4 Special Characteristics of Singlet Carbenes

A singlet carbene can be regarded as a 1,1-dipole equivalent (Scheme 2**a**). With different substituents, different characteristics will be emphasized. With electron-withdrawing substituents, the carbene is relatively electrophilic. In its trapping reactions, the empty *p*-orbital is an important factor in the process for the trapping reagent to make a new bond with the carbene carbon (Scheme 2.**b**). On the contrary, with the electron donating substituents, the carbene will show nucleophilicity through its lone pair (Scheme 2.**c**).



a **b** **c**

Scheme 2

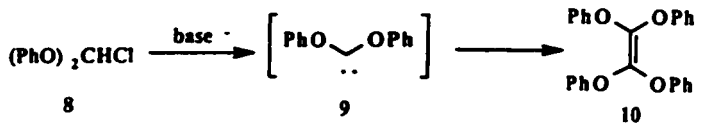
1.3 Synthesis of Nucleophilic Carbenes

H.-W. Wanzlick's work in the 1960s marked the beginnings of the chemistry of nucleophilic carbenes.[36] The importance of this kind of reactive intermediate was first exemplified by Breslow in the mechanism of action of thiamine.[37] It was then exploited by Boger and Rigby in the building up of several key skeletons of natural products that had potential uses as drugs. Among all kinds of nucleophilic carbenes, dioxycarbenes attracted most of the attention in the study of their generation, their properties and their applications, due to their convenient availability. The mechanisms by which they react appear to be generally applicable to other nucleophilic carbenes. The discoveries and studies of other nucleophilic carbenes that followed, such as diaminocarbenes and

dithiocarbenes, continued to broaden and enrich the chemistry of carbenes, especially nucleophilic carbenes.

1.3.1 Haloalkane with Strong Base

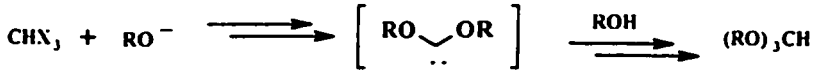
The reactions of haloforms with strong bases are classic routes to the generation of electrophilic carbenes. These were first utilized by Scheibler and co-workers to make diphenoxycarbene, or a carbenoid equivalent, in 1936 by a reaction of diphenoxychloromethane with the strong base *n*-BuOK.[38,39] The isolation of tetraphenoxyethylene (**10**) provided indirect evidence of the intermediacy of diphenoxy carbenes **9**, which presumably dimerized to the product (Scheme 3). Base treatment of dialkoxychloromethanes also gives the corresponding dioxycarbenes, or carbenoid equivalents.[40]



8 9 10

Scheme 3

More evidence for dioxycarbene intermediates came from Hine's report in 1960.[41] The reaction of haloforms with alkoxides gave orthoesters **13**. The proposed mechanism of the reaction involves dioxycarbenes **12**, Scheme 4.

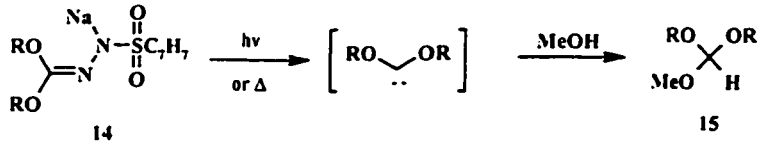


11 12 13

Scheme 4

1.3.2 Sulfonylhydrazone salts

Crawford and Rapp demonstrated in 1964 that the thermal or photochemical decomposition of sulfonylhydrazone salt **14** gave a dioxycarbene, or a carbenoid equivalent.[42] The indirect evidence came from the isolation of orthoformate **15**, which resulted from insertion of the carbene into the active OH bond of methanol (Scheme 5).



14 15

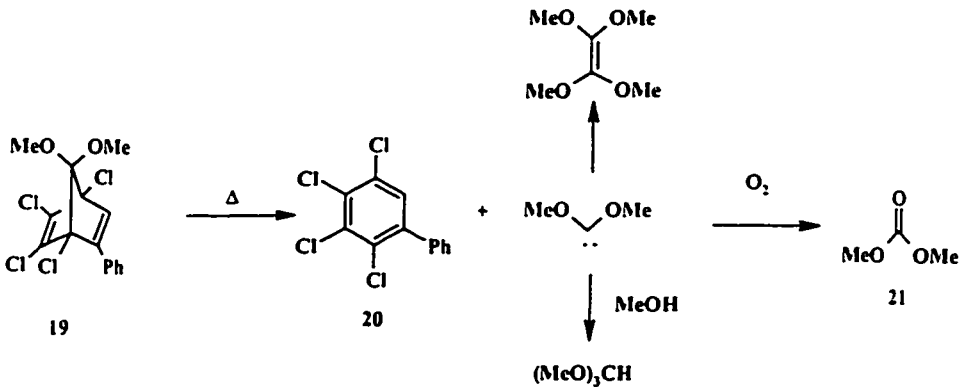
Scheme 5

1.3.3 Norbornadienone Ketals

In 1955, McBee reported an interesting result from a Diels-Alder reaction (at 150 °C) of tetrachlorocyclopentadienone ketal **16** with phenylacetylene. 2,3,4,5-Tetrachlorobiphenyl (**20**), instead of the desired 7,7-norbornadienone ketal, was isolated as the only identified product (Scheme 6). The proposed mechanism suggested that a new type of intermediate, dimethoxycarbene (DMC), was generated by decomposition of the desired ketal, which underwent a cycloelimination under the reaction conditions.[43,44]

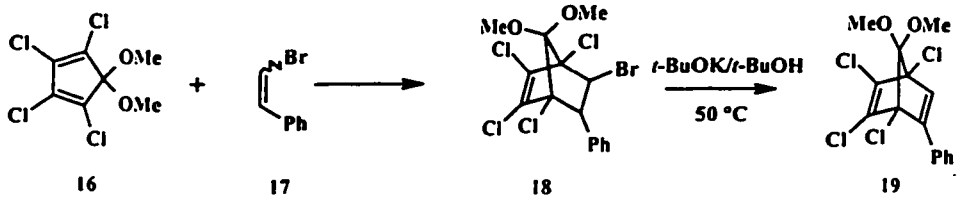
A re-investigation of McBee's results by Hoffmann[45] and Lemal[46] established the 7,7-norbornadienone ketal as a dioxycarbene precursor. In contrast to McBee's high temperature reaction conditions, Lemal found that the reaction could occur at a lower temperature (70 °C) and that the desired ketal **19** could be isolated in good yield. Similarly, the reaction of tetrachlorocyclopentadienone with β-bromostyrene (130 °C) gave a thermally stable norbornenone ketal **18** in good yield. A following elimination

reaction using a strong base (*t*-BuOK, 50 °C) gave the easily decomposable ketal, **19**, Scheme 7.



Scheme 6

The direct experimental evidence of the formation of dimethoxycarbene as the key intermediate was the isolation of tetramethoxyethylene, which is believed to derive from carbene dimerization. Additional experimental evidence came from the insertion product, trimethylorthoformate, from thermolysis of **19** in the presence of methanol. Also, thermolysis of ketal **19** in the presence of oxygen led to dimethyl carbonate as a carbene autoxidation product (Scheme 6).[45,47]

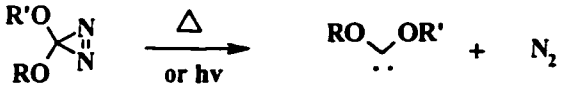


Scheme 7

The method to generate a carbene, such as DMC, by heating a ketal, such as **19**, is seriously hampered by the formation of non-volatile by-products. It is also very hard to prepare unsymmetric cyclopentadienone ketals. This method is largely limited to dimethoxycarbene.

1.3.4 Diazirines

In 1989, Moss's novel carbene source, diazirine, broke the limitations of the ketal method, and made the generation of different substituted dioxycarbenes possible.[48-56] It is believed that 3,3-dioxydiazirines (**22**) undergo thermal or photochemical cycloelimination of nitrogen to give the corresponding dioxycarbenes smoothly. Both symmetric (R = R') and unsymmetric (R ≠ R') dioxycarbenes can be generated, Scheme 8. [57]

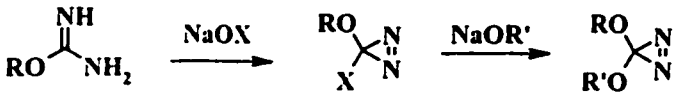


22

Scheme 8

Either the thermal or the photochemical method can be exploited to generate a desired carbene from a dioxydiazirine. The thermolysis method is generally the best for synthetic work. The photochemical method, with LFP (laser flash photolysis), is generally utilized for kinetic studies of the reactions of nucleophilic dioxycarbenes.

Dioxydiazirines (**25**) are usually synthesized by the oxidation of an amidine (**23**) with hypohalite followed by exchange of the halide of the halodiazirine (**24**) with an alcohol or phenol. This makes the preparation of different substituted dioxycarbenes possible (Scheme 9). Among them, one aryloxyalkoxycarbene, methoxyphenoxycarbene, has been generated successfully by photolysis of methoxyphenoxydiazirine.[57]



23 24 25

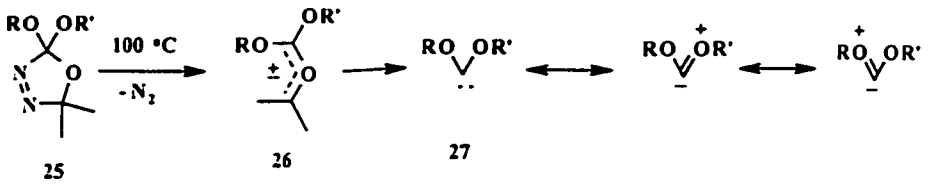
Scheme 9

Unfortunately, dioxydiazirines are unstable at room temperature and have been reported to explode under certain conditions. The instability makes dioxydiazirines un-isolable with general chromatographic separation. They can only be obtained at high dilution in hydrocarbon solvent and must be used immediately upon preparation ($\tau_{1/2}$ = 20 - 60 min, in pentane at 25 °C).[58] The inconvenience of these diazirines greatly limits the synthetic applications of dioxycarbenes. A new kind of carbene precursor, which would be stable from room to relatively high temperature, was required.

1.3.5 Oxadiazolines

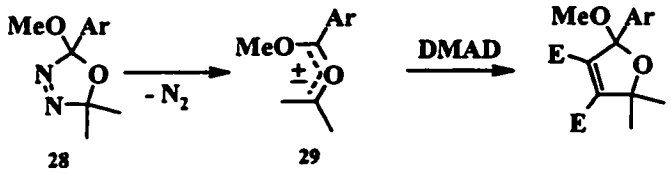
In 1992, J. Warkentin *et al.* introduced the promising 2,2-dioxy-Δ^3-1,3,4-oxadiazolines (**25**), which are versatile thermal precursors for the formation of dioxycarbenes (Scheme 10).[59] The oxadiazolines are stable compounds at a room temperature. The dialkoxy substituents give strong stabilization to the carbenes and eliminate problems with intramolecular 1,2-hydrogen transfer ($k_H = 10^8\ s^{-1}$) because dialkoxycarbenes do not possess α-hydrogens. [60] Separation of an oxadiazoline from the product mixture of which it is a component can be feasibly carried out by column chromatography. These advantages over other dioxycarbene approaches, such as Moss's low temperature diazirine route, greatly expand the applications of dioxycarbenes in organic synthetic research.

It was established that the formation of a dioxycarbene **27** from the oxadiazoline involves two steps: extrusion of nitrogen gas to form a carbonyl ylide **26**, which then loses acetone (or another ketone) to form the desired carbene (Scheme 10).



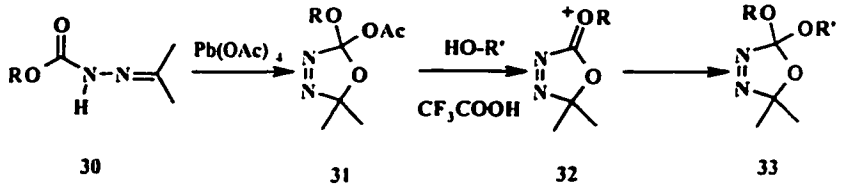
Scheme 10

No direct experimental evidence, such as the isolation of ylide trapping product, has been reported for the carbonyl ylide intermediate. A dipolarophile (dimethyl acetylene dicarboxylate (DMAD)) was once successfully used to trap the carbonyl ylide (**29**) from an aryl methoxy oxadiazoline (Scheme 11).[61] Compared with the dimethoxy carbonyl ylide, ylide **29** has an aryl substituent, which has lower electron-donating ability than an alkoxy substituent. This feature presumably decreased the energy of the carbonyl ylide and therefore increased its stability and lifetime enough to permit the trapping.[62]



Scheme 11

Oxadiazolines were usually prepared by the oxidative cyclization of the (alkoxycarbonyl)hydrazone (**30**) of acetone with $Pb(OAc)_4$ in alcohol. This method is not suitable for the formation of alkoxy aryloxy oxadiazolines because the phenol is easily oxidised during the oxidation. An alternative and more widely applicable process involves the exchange of the acetoxy group of **31** with alcohols or phenols, with acid catalysis (Scheme 12).



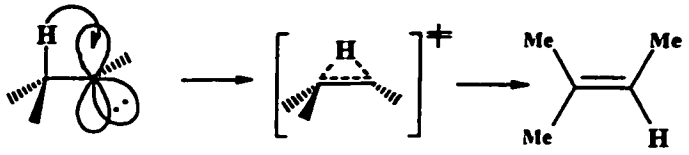
30 31 32 33

Scheme 12

1.4 Intramolecular Reactions of Nucleophilic Carbenes

1.4.1 1,2-Migrations

1,2-Migrations were initially regarded as the major reaction for alkyl carbenes. Evanseck and Houk did theoretical calculations and found a barrier of only 0.6 kcal/mol for the rearrangement of methylcarbene to ethylene, which effectively prevents bimolecular reactions of alkyl carbenes (Scheme 13).[63] The usual order of migratory ability has been assigned as: H > aryl > alkyl.[64]



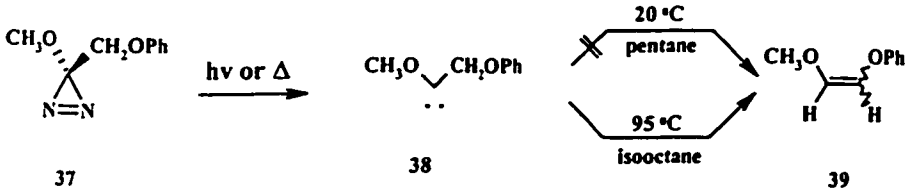
34 35 36

Scheme 13

1,2-Shifts are generally thought to involve movement of the migrating group with its pair of electrons to the formally vacant carbenic *p*-orbital. It requires co-planarity of the orbitals implicated on the way to the transition state (Scheme 13). The partially occupied *p*-orbital, through π-donation of the heteroatoms in the heteroatom-substituted carbene, increases the activation energy for 1,2-hydrogen shifts. Both theoretical calculations and experimental studies have provided evidence for this tendency. For example, Evanseck calculated the activation energies for a 1,2-hydrogen shift from the

methyl group to the carbene carbon with different electron-donating groups (X) as the other substituent of the carbenes (CH_3-C-X): H(0.6) < Cl(11.5) < F(19) < *trans*-OMe(27). [63] Thus, the presence of a heteroatom at the carbene center can considerably retard the rate of 1,2-shifts and in extreme cases the rearrangement can be effectively prevented.

Moss and co-workers found that methoxy(phenoxymethyl)carbene (**38**), generated at 20 °C by photolysis or thermolysis of the diazirine precursor, does not produce detectable amounts of alkene **39**. Only when the temperature was increased to 95 °C was the 1,2-H shift product produced (Scheme 14). [65]

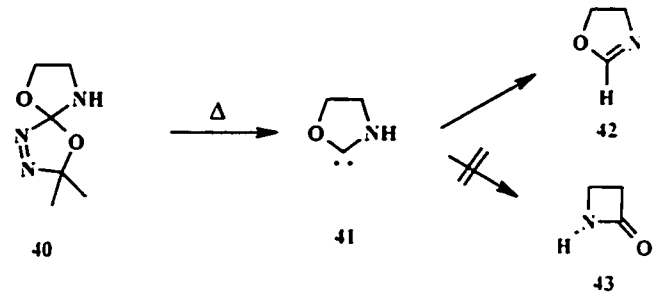


37 38 39

Scheme 14

Because of this high activation energy, 1,2-shifts are seldom reported in nucleophilic carbenes. Heinemann and Thiel have shown that all aminocarbenes, diaminocarbenes, and imidazol-2-ylidene have ΔE_{act} values for H-migration of more than 45 kcal/mol from *ab initio* calculations (TZ2P basis set). [66]

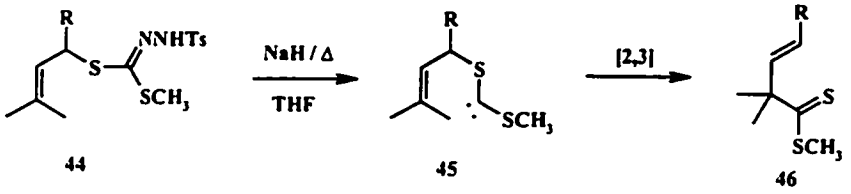
A rare hydrogen migration from N to C in a nucleophilic carbene has been observed from the VLVP (very low vapour pressure) pyrolysis MS experiment of oxadiazoline **40** at temperatures between 280-530 °C; the alternative 1,2-alkyl migration to 2-azetidinone was not observed (Scheme 15). However, when the carbene was formed at a lower temperature in NRMS (Neutralization-Reionization Mass Spectrometry) experiments, the activation energy for the hydrogen shift was found to be very high. [67]



Scheme 15

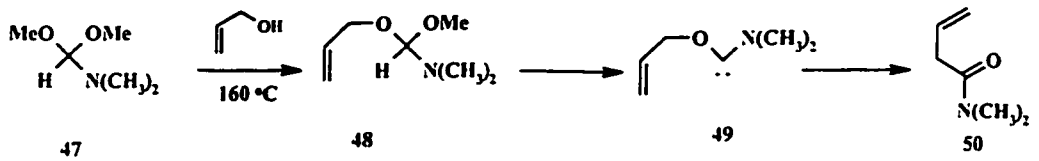
1.4.2 [2,3]-Sigmatropic Rearrangements

Generation of a heteroatom-substituted carbene with a β,γ–carbon-carbon double bond can result in a novel kind of [2,3]-intramolecular rearrangement reaction. In 1972, Baldwin and Walker first reported this kind of reaction for dithiocarbenes possessing an allylic substituent. [68] A few years later, Nakai and Mikami reported that the stereoselectivity in those rearrangements was highly controlled, favoring the *trans* geometry of the newly formed double bond (in **46**), Scheme 16. [69]



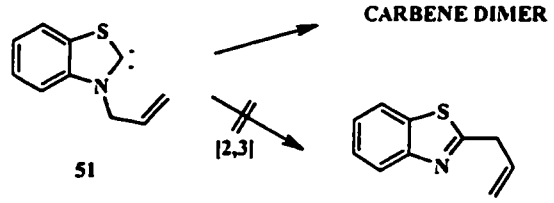
Scheme 16

The [2,3]-sigmatropic rearrangement of aminooxycarbenes has also been reported (Scheme 17).[68,70,71] The allyloxy group was used to replace the methoxy group in the acetal of *N,N*-dimethylformamide (**47**). A strong base, sodium methoxide, was then used to generate the allyloxyaminocarbene **49**, which afforded *N,N*-dimethyl-1-butenamide **50** through a [2,3]-sigmatropic rearrangement.



Scheme 17

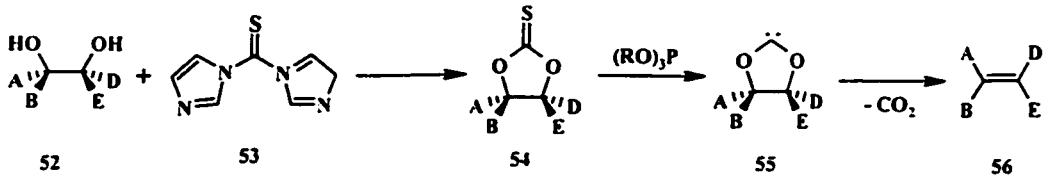
An effort to carry out a similar reaction in the allylic aminothiocarbene **51** was not fruitful. The carbene mainly dimerized in spite of the steric hindrance from the present allyl group (Scheme 18).[72]



Scheme 18

1.4.3 Fragmentation of Cyclic Carbenes

Several cyclic nucleophilic carbenes have been formed by different methods, most by the oxadiazoline method. A 5-membered thio-carbonate was initially synthesized as the precursor of a cyclic dioxycarbene by the reaction of thio-carbonyl diimidazole with a vicinal diol. A subsequent reaction with trialkyl phosphine resulted in the cyclic dioxycarbene **55**, which then fragmented to CO_2 and alkene (Scheme 19). The reaction could be used specifically to control the stereochemistry of the conversion of diols to alkenes.[73,74]

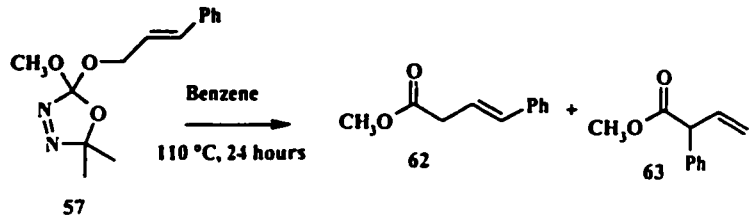


Scheme 19

Other cyclic heteroatom-substituted carbenes, such as 5-membered rings with S and N, were also synthesized and showed similar fragmentation to alkenes.[87]

1.4.4 Fragmentation to Radical Pairs

It has been established that the characteristics of carbenes are mainly dependent on the substituents. Although dialkoxycarbenes were proven to be nucleophilic, and to have singlet ground states, the introduction of radical stabilising groups on oxygen can initiate radical formation from the active carbene intermediates. Venneri and Warkentin discovered that interesting reaction when they prepared and thermolyzed **57** (Scheme 20).[75]

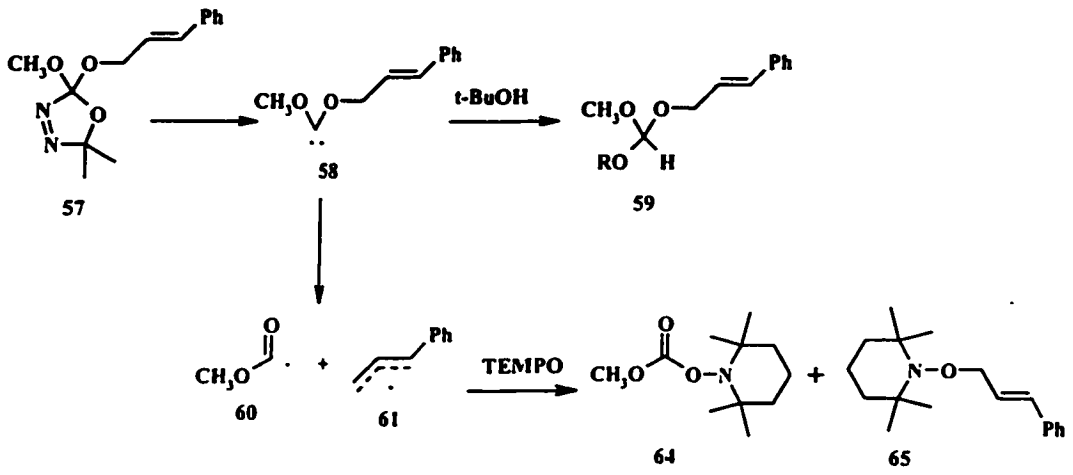


Scheme 20

Thermolysis of oxadiazoline **57** without trapping reagents led to two products, **62** and **63**, which was first thought to come from 2,3- and 1,2-sigmatropic rearrangements, respectively. Further trapping experiments of radical intermediates ruled out the rearrangement mechanisms.

Thermolysis of oxadiazoline **57** in the presence of the stable free radical, TEMPO, produced the TEMPO trapping products **64** and **65** (Scheme 21).[75] A radical mechanism was proposed for the fragmentation of **58**.

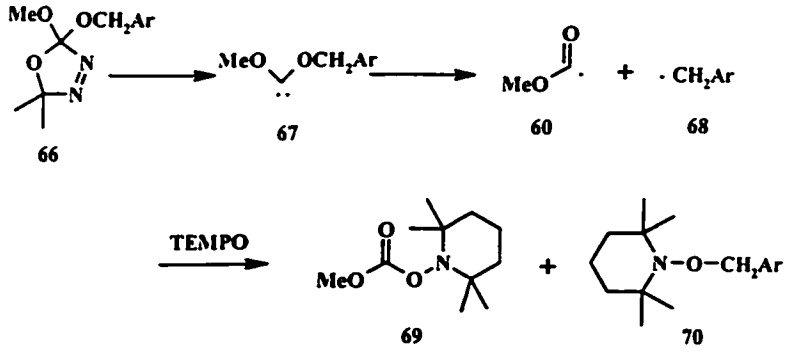
Like other nucleophilic dioxycarbenes, carbene **58**, generated by thermolysis of **57**, produced the orthoformate **59** as the major product (70%) in the presence of *tert*-butyl alcohol. Two radical coupling products, **62** and **63**, were also identified as by-products. This result implies that the decomposition of the oxadiazoline resulted in a relatively stable carbene intermediate, which could be trapped with *t*-butyl alcohol to form orthofomate **59**. With the increase of alcohol concentration in the thermolysis solution, the yields of radical coupling products were found to decrease and the yield of orthoformate increased. This interesting result revealed that the methoxycarbonyl radical and the phenylallyl radical must have originated from the carbene **58**, and not from some other source.



Scheme 21

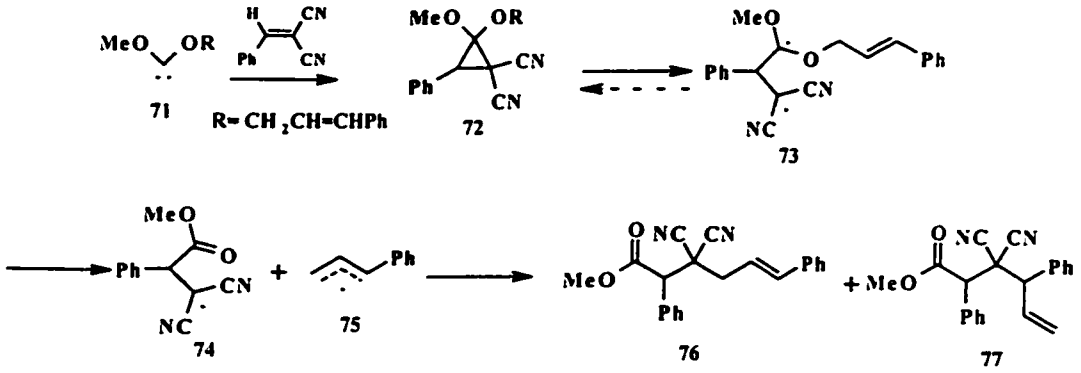
The formation of radical intermediates from dioxycarbenes was further studied by Merkley and Warkentin.[76] A thermolysis reaction of benzyloxy methoxy oxadiazoline in

the presence of TEMPO also produced products, **69** and **70**, that came from the radicals, **60** and **68** (Scheme 22). Benzyloxymethoxycarbene, generated from the thermolysis of benzyloxy methoxy oxadiazoline, was again shown to be the radical source by several trapping reactions with different concentrations of alcohol. [77]



Scheme 22

Benzylidenemalononitrile was then used as a carbene trap in the thermolysis of oxadiazoline **57**. Compounds **76** and **77** were isolated from the final product solution. It could be concluded that the carbene **71** was trapped by the benzylidenemalononitrile to produce cyclopropane derivative **72** first, which then ring opened to diradical **73**. A β-scission, generating stable phenyl allylic radical **75**, and subsequent couplings of radical **74** at the two reactive sites of radical **75** resulted in the final isomers, **76** and **77** (Scheme 23).[78]



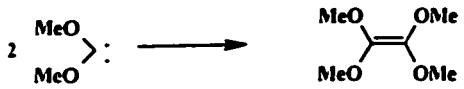
Scheme 23

The comparison of TEMPO trapping and benzylidenemalononitrile trapping reactions shows the importance of the substituents of the dioxycarbenes. If one of the oxy substituents of the carbene is a radical stabilizing group, such as a benzyl or phenyl allyl group, a free radical reaction might be initiated during the reaction course. With a strong carbene trap, such as benzylidenemalononitrile, the radical initiation can be delayed to a later step, such as a ring opening of a cyclopropane. Without a strong carbene trap, the radical formation occurs from the singlet carbene itself.

1.5 Intermolecular Reactions of Nucleophilic Carbenes

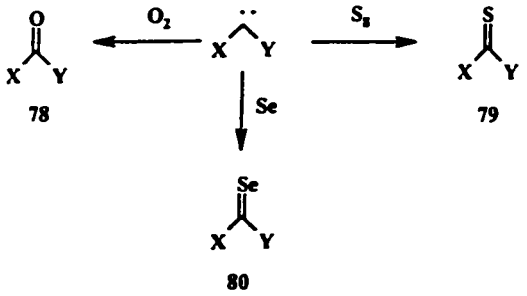
1.5.1 Miscellaneous Reactions

Dimerization is a common intermolecular reaction of most nucleophilic carbenes in the absence of reactive trapping reagents. The isolation of tetramethoxyethylene was used by Lemal in 1964 as strong experimental evidence of the existence of the short-lived dimethoxycarbene from the thermolysis of a norbornadienone ketal (Scheme 24).[39]



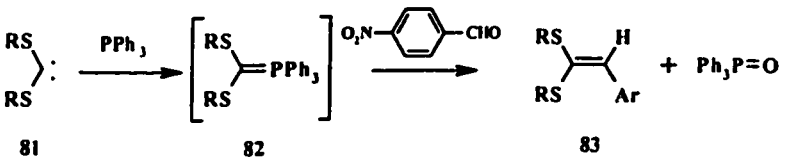
Scheme 24

The generation of nucleophilic carbenes, such as dithio-,[79] aminothio-,[80] and aminooxycarbenes[81] in the presence of oxygen, sulfur or elemental Se[79] have been observed to yield the corresponding carbonate or analogue through the formation of carbonyl, thiocarbonyl or selenocarbonyl functional groups, respectively (Scheme 25).



Scheme 25

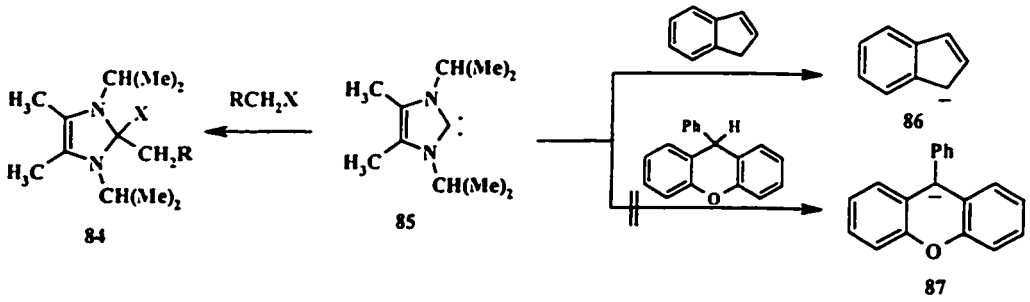
A similar reaction was carried out by the generation of dithiocarbenes in the presence of triphenylphosphine and 4-nitrobenzaldehyde (Scheme 26).[82] The proposed ylide **82** was not isolated, but a Wittig-reaction type product, dithioalkene **83**, was produced in over 64% yield for bis(methylthio)carbene and 74% yield for bis(ethylthio)carbene.



Scheme 26

Imidazol-2-ylidene **85** was once used to react with haloalkanes to test its basicity and nucleophilicity. The predominance of substitution over elimination indicated its

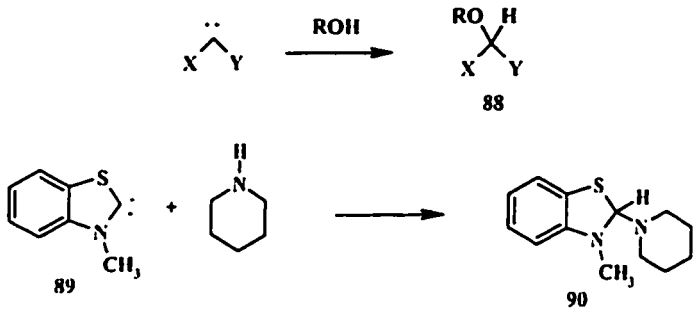
relatively high nucleophilicity. Recently, Alder reported that carbene **85** completely deprotonated indene (pK_a 20.1) in $(CD_3)_2SO$, (Scheme 27) but was not able to convert 9-phenylxanthene (pK_a 27.7) to its anion to a measurable extent. [83]



Scheme 27

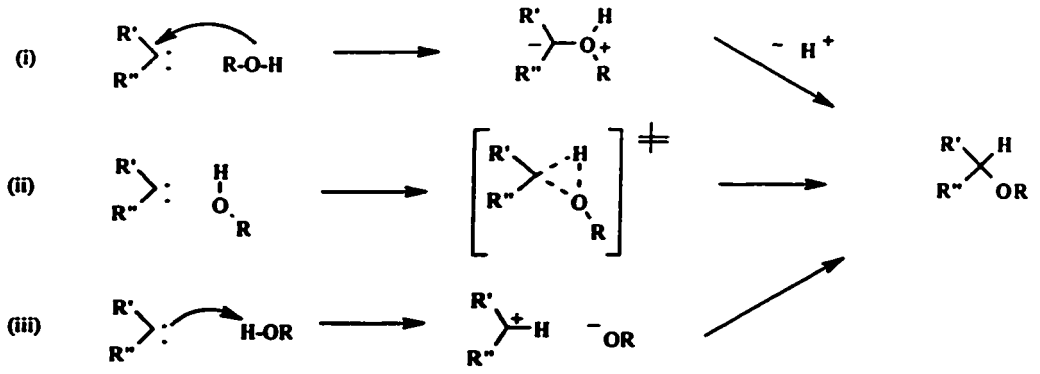
1.5.2 Insertions into Active X-H Bonds

Nucleophilic carbenes generally insert into active X-H bonds, such O-H, S-H, N-H and some active C-H bonds. Thus, alcohols and phenols are often used as chemical traps to provide evidence for the intermediacy of nucleophilic carbenes in a given reaction. Dioxy-,[48,84,85,86] diamino-,[88] dithio-[82,89] and aminothiocarbenes[80, 91, 92] have all been reported to undergo this kind of insertion reaction with bimolecular rate constants of $10^6 \sim 10^{10}$ s^{-1} (Scheme 28).



Scheme 28

Three types of mechanism are usually considered for the formal insertions of singlet carbenes into O-H bonds: [93] (i) attack of the divalent carbon at oxygen, involving interaction of the carbene LUMO with the alcohol HOMO (the non-bonding electrons on oxygen), resulting in the formation of an intermediate ylide, followed by proton transfer; (ii) concerted insertion *via* a three-membered transition state; and (iii) proton abstraction by the carbene followed by collapse of the resulting ion pair (Scheme 29). The actual mechanism is mainly determined by the nature of the carbene: electrophilic carbenes reacting by mechanisms (i) or (ii), and nucleophilic carbenes *via* (ii) or (iii).

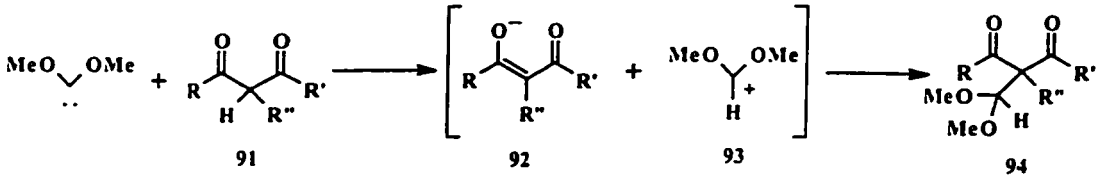


Scheme 29

A primary kinetic isotope effect (KIE) of 3.3 ± 0.5 was observed for the reaction of dimethoxycarbene with MeOH(D) is solution.[93] The result, which suggests a significant degree of O-H bond stretching in the transition state, is consistent with either mechanism (ii) or (iii) in Scheme 29. This relatively large KIE contrasts with the values measured for the less nucleophilic methoxymethylcarbene and the electrophilic phenylchlorocarbene, neither of which gave KIE values significantly different from unity.

1.5.3 Insertion into Active C-H Bonds

Pole and Warkentin reported the formal insertion of dimethoxycarbene into an active C-H bond of β-dicarbonyl compounds.[94] The proposed mechanism is similar to the nucleophilic carbene insertion into the O-H bond of an alcohol. The generated dimethoxycarbene first abstracts a proton from an enol tautomer to afford a protonated carbene **93** and an enolate anion **92**, which collapse to give the product (Scheme 30).



91 92 93 94

Scheme 30

1.5.4 Reactions with Double Bonds

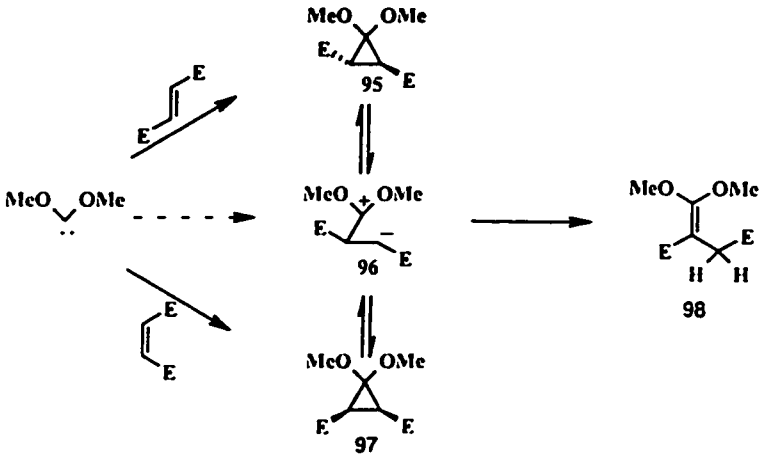
Consistent with Frontier Orbital Theory, electrophilic or ambiphilic carbenes undergo [1+2] cycloadditions with electron-rich alkenes. Nucleophilic carbenes are more likely to react with electron-deficient alkenes to afford cyclopropane rings. Selected absolute rate constants for additions of dimethoxycarbene and related carbenes to various alkenes are listed in Table 1. The trends showed the reactivities of carbenes toward each alkene: nucleophilic dimethoxycarbene will not react with dimethylethylene at all. Down the column, the more electron-deficient the alkene, the faster the cyclopropanation reaction.

Table 1. Absolute rate constants ($M^{-1}s^{-1}$ at 25°C) for cycloadditions of carbenes to alkenes, determined by LFP methods [84, 95]

Alkene	$(MeO)_2C$	MeOCCl	MeOCPh	MeOCMe
$Me_2C=CH_2$	N.A.[a]	1.8×10^3	4.0×10^4	4.8×10^3
$CH_2=CHCN$	$\sim 10^3$	1.8×10^4	1.7×10^6	1.5×10^6
$CH_2=CClCN$	5.0×10^5	5.6×10^5	3.4×10^7	4.9×10^7

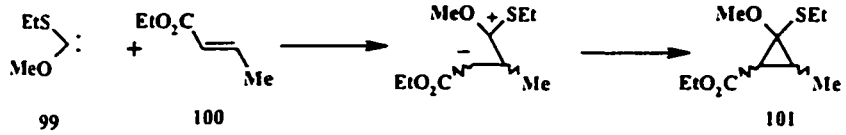
a. Quenching not observed with tetramethylethylene ($k_{abs} < 10^3\ M^{-1}s^{-1}$).

The still open question related to the addition of nucleophilic carbenes onto electron-deficient carbon-carbon double bonds is whether the mechanism is concerted or stepwise. In 1974, Hoffmann found that a ketene acetal product **98** is the exclusive product from the reaction of dimethoxycarbene with either diethyl maleate or with diethyl fumarate. The final product suggests the stepwise mechanism for the reaction, but the concerted addition of dimethoxycarbene to form a cyclopropane, which undergoes ring opening to dipolar intermediate **96** and then reaches the final product by a 1,2 hydrogen migration, cannot be ruled out (Scheme 31).



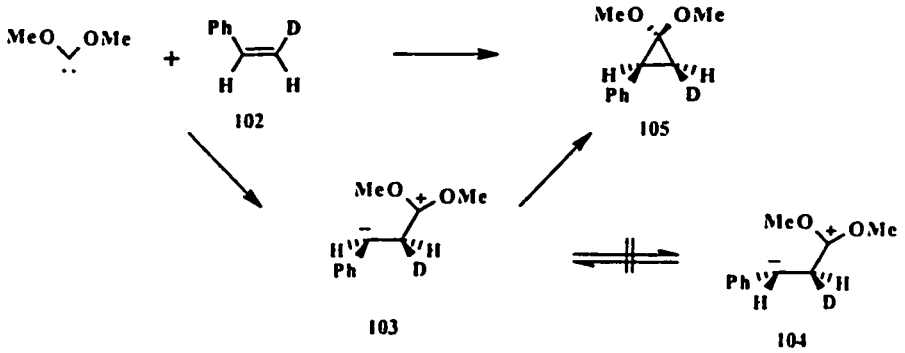
Scheme 31

A similar addition was also reported recently by Warkentin et al.[96] (Ethylthio)methoxycarbene was used to react with ethyl crotonate to yield all four possible geometric isomers of **101** (Scheme 32). Dipolar intermediates must be favored in the reaction in order to lead to the loss of stereochemistry.



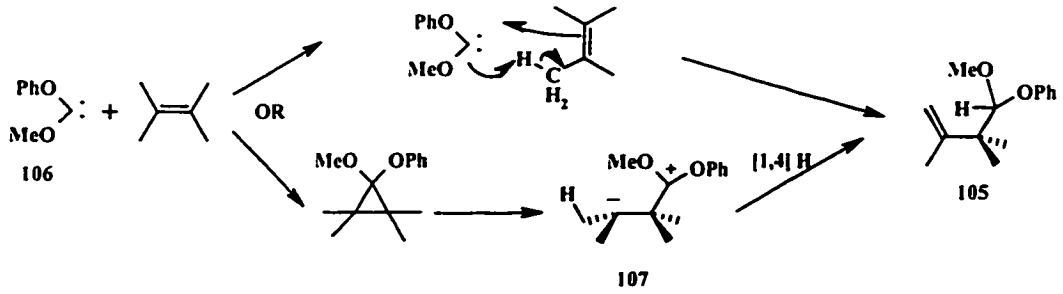
Scheme 32

Moss and Huselton reinvestigated the mechanism of the reaction of dimethoxycarbene with deuteriostyrene (*cis* **102**, Scheme 33). Dimethoxycarbene was generated by heating a norbornadienone ketal at 125 °C. It was found that the carbene added to both *E*- and *Z*-β-deuteriostyrene stereospecifically, as shown in Scheme 33.[97] This result strongly supports the concerted cycloaddition between the carbene and the weakly electrophilic alkene. But the stepwise mechanism, through dipolar intermediate **103**, which then cyclizes before bond rotation occurs to maintain the stereochemical integrity of the substrate, still cannot be ruled out.



Scheme 33

Although normal dioxycarbenes seldom react with electron-rich alkenes, methoxyphenoxycarbene **106** was found to be an exception. The reaction of **106** with tetramethylethene gave acyclic product **105**, Scheme 34.[98] The mechanism proposed was either an "ene-type" reaction or cyclopropanation followed by ring opening and 1,4-hydride migration. No further evidence has since been reported.



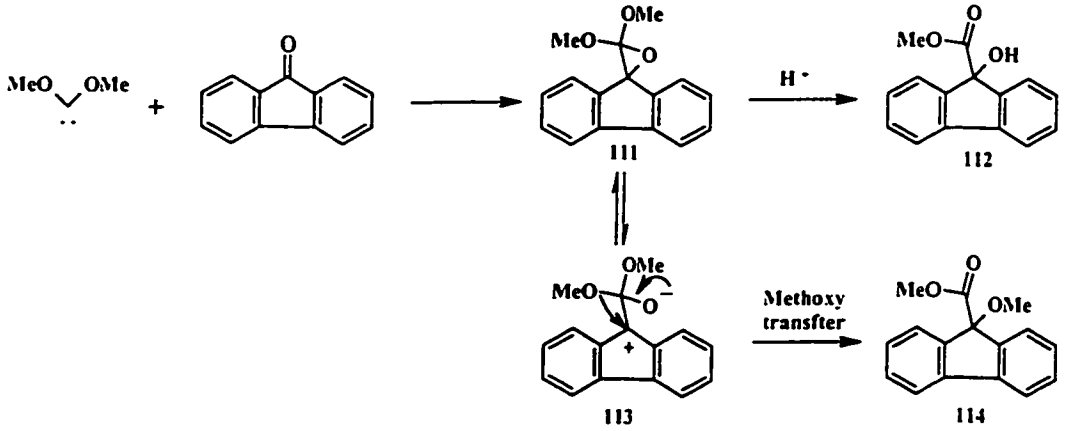
Scheme 34

1.5.5 Reactions with C=X Bonds

1.5.5.1 Unstrained C=O Bonds

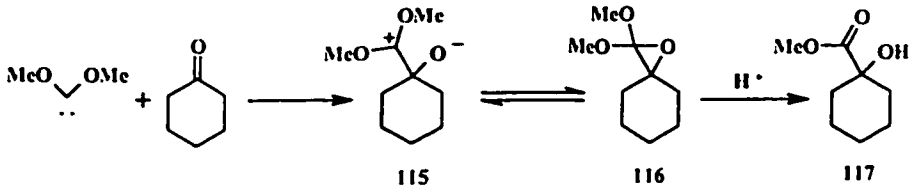
Reactions of dimethoxycarbene, identified as a nucleophilic carbene, with ketones have been studied in some detail by Warkentin and co-workers. Addition of a dioxycarbene to a carbonyl group was first reported by Warkentin and Pole.[100] Thermolysis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-oxadiazoline at 110 °C in the presence of 9-fluorenone afforded 9-(dimethoxymethylene)fluorene oxide (**111**). That oxirane was not isolated; it underwent a thermal rearrangement to yield methyl-9-methoxyfluorene-9-carboxylate (**114**) in 24 % yield (Scheme 36).[72] The proposed mechanism involves a [1+2] cycloaddition reaction of dimethoxycarbene and the carbonyl group of fluorenone to oxirane **111**. Ring opening and methoxy migration generates adduct **114**. An intermolecular rearrangement for the last step was ruled out by deuterium labeling

experiments. The product of hydrolysis and elimination, α-hydroxy methyl ester **112**, was also isolated, indicating the high moisture sensitivity of oxirane **111**.



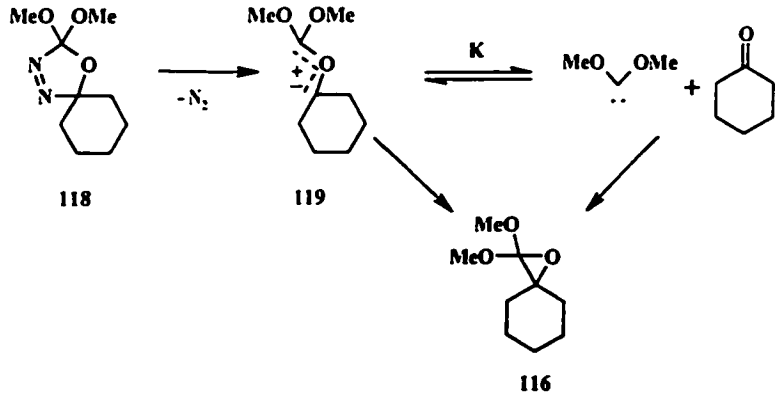
Scheme 36

At a later time, Dawid, Venneri and Warkentin reported the formation of oxirane **116** from the reaction of dimethoxycarbene with cyclohexanone. The stable oxirane with germinal methoxy groups was successfully isolated from the product mixture by semi-preparative gas chromatography in 15% yield. During the reaction course, the DMC was proposed to add to the electrophilic carbonyl group to form tetrahedral intermediate **115**, which then collapsed to the oxirane product **116** (Scheme 37). The oxirane is very sensitive to acid and can react with traces of water in the solution to form α-hydroxy methyl ester **117**.[101]



Scheme 37

To increase the yields of oxirane products and further study the mechanism of the reaction, the cyclohexane ring was directly attached to the oxadiazoline at the C-5 position. However, thermolysis of oxadiazoline **118** did not increase the yield of **116** (Scheme 38). This implies that the carbonyl ylide from thermolysis of the oxadiazoline dissociates to dimethoxycarbene and cyclohexanone faster than it cyclizes. All, or nearly all, of the **116** likely arises from addition of the carbene to the ketone.[101]



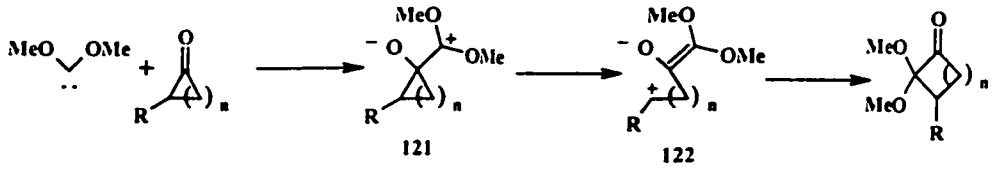
Scheme 38

1.5.5.2 Strained Cyclic Carbonyl Compounds

Because additions of nucleophilic carbenes to acyclic ketones do not occur, and cyclizations of nucleophilic carbenes with cyclohexanone only lead to 10-20 % of oxirane derivative, no synthetic potential of these reactions can be seen. The situation began to change when small ring cyclic ketones were used as carbene traps. The release of strain energy through the fast ring opening after the addition of carbene to the cyclic ketone drives the reaction to the product.

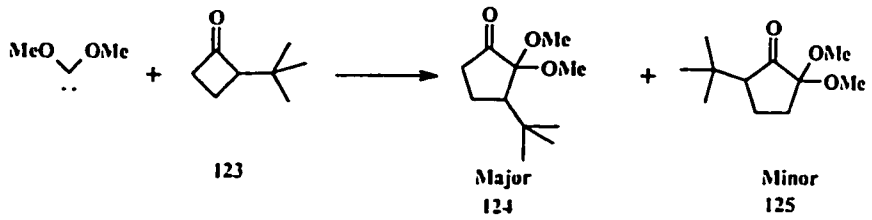
Venneri and Warkentin recently reported results for the reactions of dimethoxycarbene with strained carbonyl systems (Scheme 39).[102] Each reaction was

assumed to start with the nucleophilic addition of dimethoxycarbene to the carbonyl carbon to form tetrahedral intermediate **121** (n = 1-3). A subsequent ring opening was proposed to dominate the reaction over the dissociation of the dipole back to the carbene and ketone. The overall carbene insertion into a carbon-carbon bond resulted in ring enlargement by one carbon, in over 50% yield.



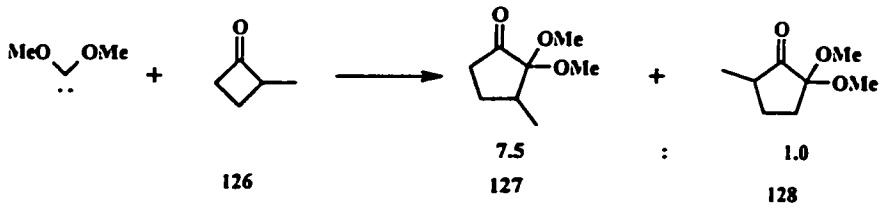
Scheme 39

It was also found that the regiochemistry of ring expansion could be controlled by substituents on the ring. It is easier for DMC to insert into the alkyl substituted side to form **124** as the major product. The reaction of 2-*tert*-butylcyclobutanone with dimethoxycarbene affords 3-*tert*-butyl-2,2-dimethoxycyclopentanone (**124**) and 5-*tert*-butyl-2,2-dimethoxycyclopentanone (**125**) in the ratio of 1.5:1.0 (Scheme 40).[102] The isomeric structures were established by means of nOe experiments. Irradiation of the *tert*-butyl signal of **124** enhanced both methoxy signals in the ^{1}H NMR spectrum, while irradiation of the *t*-butyl signal in **125** enhanced only one methoxy signal.



Scheme 40

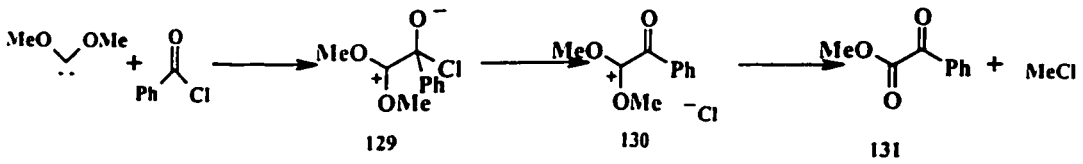
Replacement of the *tert*-butyl group with the methyl group makes the ratio of final products, **127** and **128,** change a lot, to 7.5:1.0 (Scheme 41). With these results, it was concluded that both electronic effects and steric effects influence the alkyl migration. In the transition state, modeled with **122,** the substituted alkyl group makes the carbocation more stable, compared with the formation of cation by dissociation of the other carbon-carbon bond. The dimethoxycarbene is therefore more likely to insert into the side substituted with an alkyl group. Even with the very bulky *tert*-butyl group, the electron-donating effect still overweighs the steric effect and makes **124** more favorable than **125** (Scheme 40).



Scheme 41

1.5.6 Reactions with Carboxylic Acid Derivatives

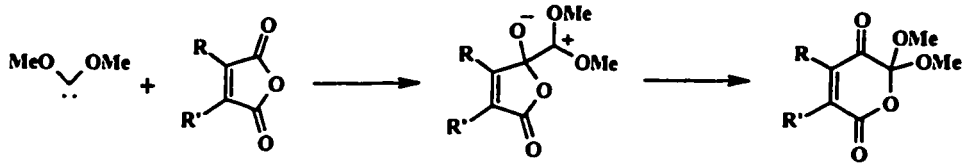
Besides a strained ring system, a good leaving group also helps the reaction of a nucleophilic carbene with a carbonyl group to go to the ring expansion step, rather than to dissociate back to the carbene and ketone. In 1974, Hoffmann reported a reaction of dimethoxycarbene with benzoyl chloride to afford the glyoxylate derivative **131** (Scheme 42).[103] It was believed that a dipolar intermediate **129** was formed as a result of addition of the nucleophilic carbene. An attack on the methyl group by chloride furnished the final α-ketoester.



129 130 131

Scheme 42

Interestingly, the reaction of DMC with unsaturated cyclic anhydrides is completely different from its reaction with an unsaturated acyclic ester, such as maleate and fumarate.[103] With unsaturated cyclic anhydrides, dimethoxycarbene exclusively attacks at the carbonyl group, with no observable products derived from addition at the olefinic bond (Scheme 43).[104] For non-symmetric anhydrides, dimethoxycarbene preferentially attacks at the most electron-deficient carbonyl group, overriding the steric effect. In competition experiments, the result showed a reactivity order: 3,4-dimethylmaleic anhydride < maleic anhydride < 3,4-dichloromaleic anhydride, in accordance with the electrophilicity of the carbene traps.[104]



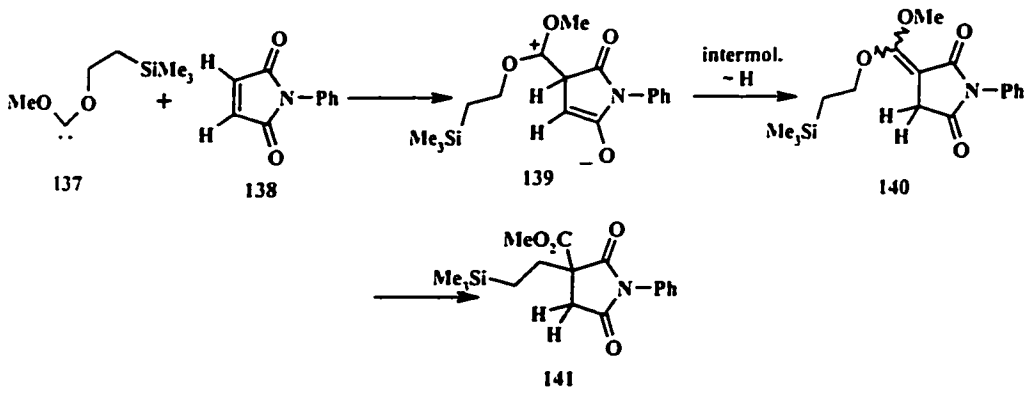
132 135 136

R, R' = methyl, H, or Cl

Scheme 43

It is not surprising that the reaction of some (alkylthio)methoxycarbenes with dichloromaleic anhydride took the same course to afford similar products with yields of 75-89%.[94] But it is surprising that δ-silyl-dioxycarbene **137** behaves differently in its reaction with the maleic anhydride analogue, *N*-phenylmaleimide (**138**). [86] The carbene attacked the C=C bond first and then a series of complicated inter- and intramolecular

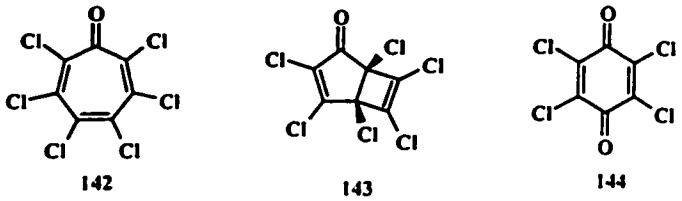
reactions led to **141** (Scheme 44). No further study of that complex but interesting reaction has been reported since then.



Scheme 44

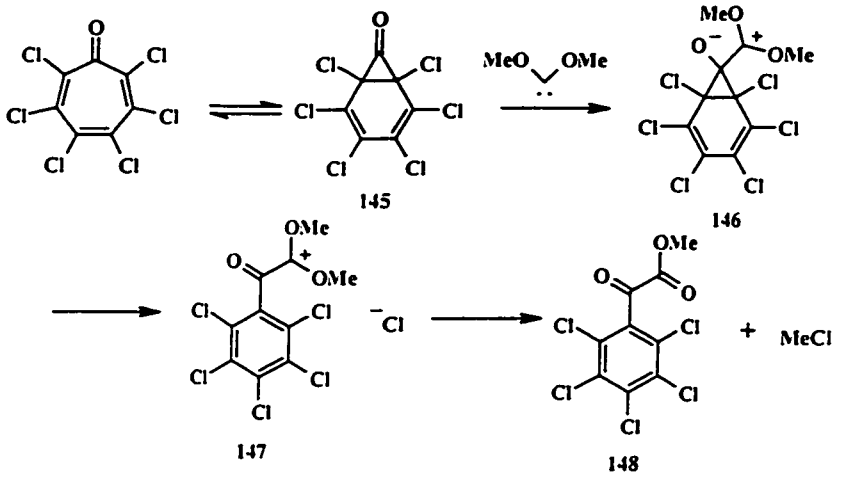
1.5.7 Reactions with Polychloro Ketones

Dunn and co-workers reported interesting results from the reactions of dimethoxycarbene with three perchloroketones, **142, 143** and **144** (Scheme 45).[105]



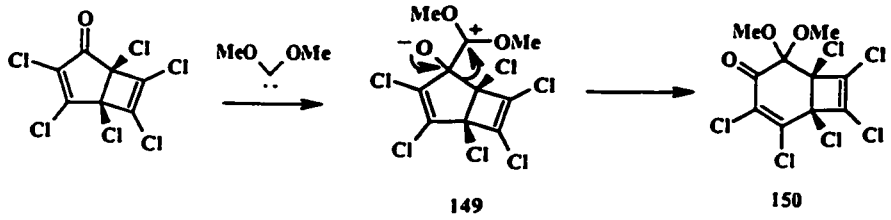
Scheme 45

For the hexachlorotropone (**142**) reaction, the final product **148** resulted from nucleophilic carbene addition to the carbonyl group to produce a dipolar intermediate **146**, followed by carbonyl group reformation with opening of the 3-membered ring and loss of chloride anion, followed by demethylation (Scheme 46).



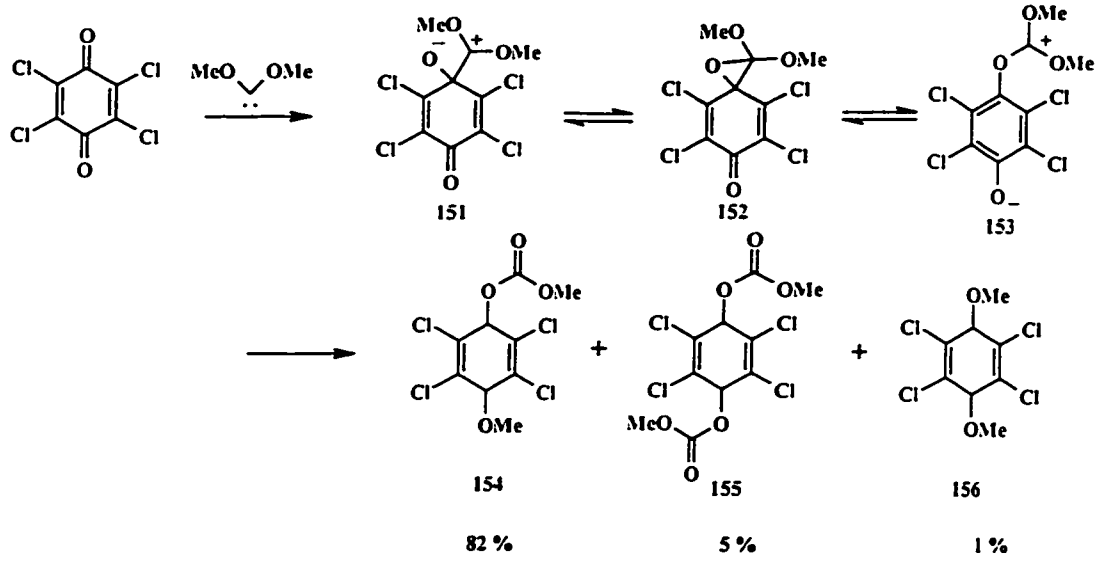
Scheme 46

In contrast to the above mechanism, in the reaction of dimethoxycarbene with hexachlorobicyclo[3.2.0]-3,6-heptadien-2-one (**143**), the presumed dipolar intermediate (**149**) underwent a fast alkyl migration with retention of stereochemistry to afford ring expanded product **150** (Scheme 47).



Scheme 47

In the reaction of dimethoxycarbene with tetrachloro-1,4-benzoquinone (**144**), after the formation of dipolar structure (**151**), the ring closure to oxirane **152** and then ring opening to form a carbonyl ylide intermediate **153** were assumed to be the key steps. The intermolecular demethylation of dimethoxy cation **153** was necessary for the formation of final products **154**, **155** and **156** (Scheme 48).

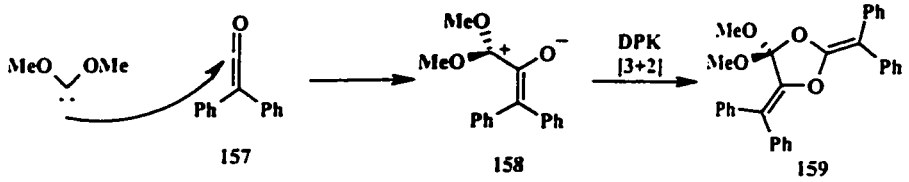


Scheme 48

Although three mechanisms were postulated for the three reactions (Scheme 47, 48 and 49), the first step in each was the same addition of the carbene to the carbonyl group. The release of the strain energy of the small ring systems, such as cyclopropane and oxirane, probably overrides other factors. No product from the carbene addition to the electron-deficient carbon-carbon double bond was detected.

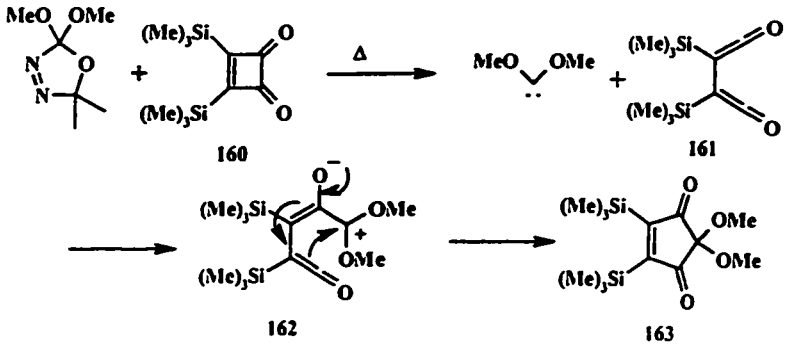
1.5.8 Reactions with Ketenes

The additions of dimethoxycarbene to ketenes also have been studied. In 1974, Hoffmann found that the relatively stable ketene, diphenylketene (DPK), could form a 1:2 carbene-ketene adduct with dimethoxycarbene. The most likely mechanism involves the addition of the carbene to the electropositive carbon of the ketene to yield a 1,3-dipole **158**, which undergoes a [3+2] cycloaddition with the second diphenylketene, to form the 5-membered-ring product **159** (Scheme 49).[103]



Scheme 49

The reaction of dimethoxycarbene with a silicon-containing bis-ketene **161**, generated from the thermal ring opening of bis-3,4-trimethylsilycyclobutene-1,2-dione (**160**),[106-108] showed a special rearrangement after the initial addition of dimethoxycarbene to the electropositive carbon of one of the ketene functional groups (Scheme 50). The formation of ring-expanded product **163** was proposed to occur through the intramolecular [3+2] cycloaddition of dipole intermediate **162** with the carbon-carbon double bond of the second ketene functional group.[109]

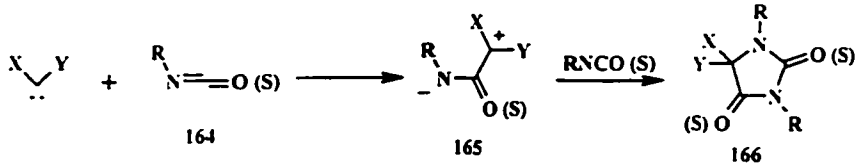


Scheme 50

1.5.9 Reactions with Phenylisocyanates

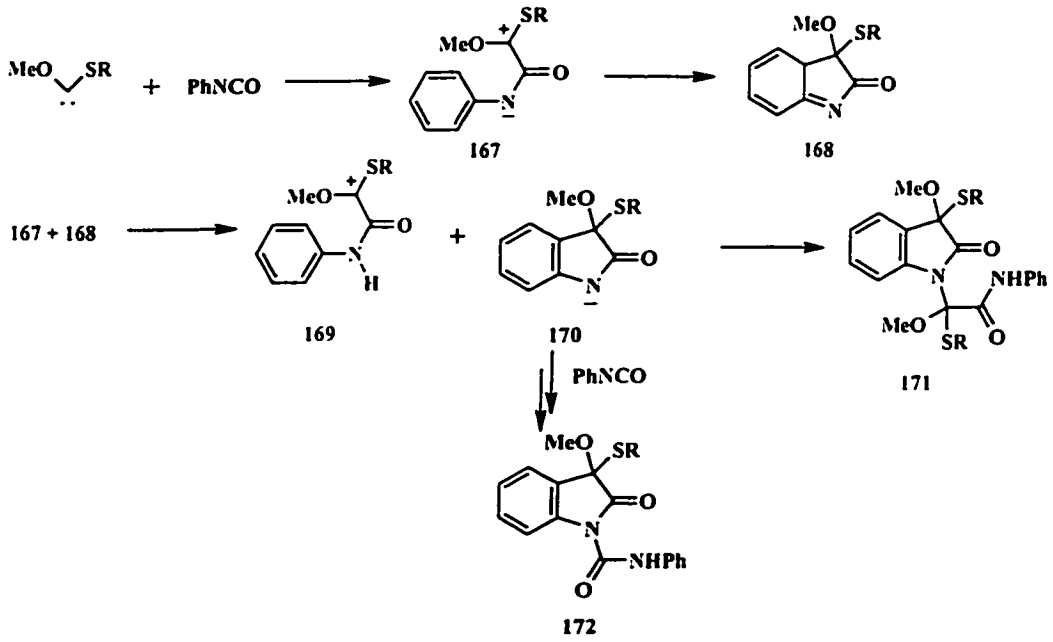
The ketene analogues, isocyanates, were also used as carbene traps. Most nucleophilic carbenes, dimethoxycarbene,[85,110,111] diaminocarbenes,[112,113] aminooxycarbenes,[81] and aminothiocarbenes,[114] form hydantoin derivatives with alkyl isocyanates and isothiocyanates. The reactions also went through the addition of carbenes

to the electropositive carbon of the isocyanate groups (Scheme 51). Then, a second isocyanate cyclizes with the 1,3-dipole **165** across the C=N bond to afford a five-membered ring **166**. Hoffmann and Reiffen reported a ρ value of 2.0 for the reaction of dimethoxycarbene with aryl isocyanates.[111] The positive sign of ρ supports a transition state where negative charge accumulates at N from nucleophilic attack of the carbene.



Scheme 51

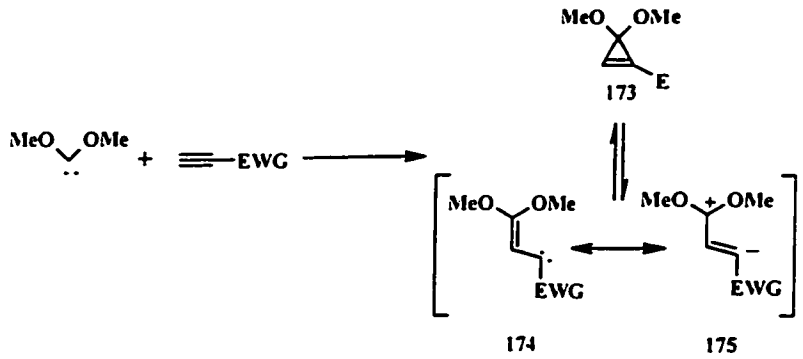
The only exception came from the reaction of oxythiocarbenes with phenyl isocyanate.[111] A pair of diastereomeric 2:2 adducts **171**, along with lactam **172**, were identified as the final products (Scheme 52). This result indicates that the fast intramolecular cyclization of carbocation **169** as well as the strong nucleophilicity of the lactam anion **170** are the controlling factors of the reactions.



Scheme 52

1.6 Reactions with Triple Bonds

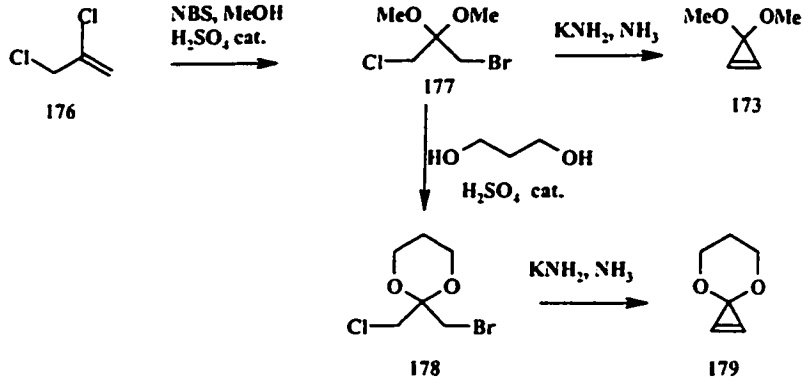
The reaction of a dioxycarbene with an electron-deficient triple bond results in an interesting cyclopropenone ketal. The presence of an electron-withdrawing group on the cyclopropenone ketal decreases the stability of the cyclopropene ring system and makes the ring open readily to the vinyl carbene under thermal conditions. Both anion- and cation-stabilizing groups, as well as the high strain energy of the cyclopropene system, are major factors contributing to the easy ring opening of the cyclopropene to form vinylcarbenes (Scheme 53). [90] The resonance contributor, **175**, is also an important one although theoretical calculations[90] showed that the vinylcarbene contributor is the major one.



Scheme 53

1.6.1 Generation of Cyclopropene Ketals

The first dioxyvinylcarbene, 3,3-dimethoxyvinylcarbene, was generated from 3,3-dimethoxy cyclopropenone ketal (**173**) under thermal condition by Butler and co-workers in 1972.[115-117] Since 1984, the chemistry of cyclopropenone ketals and the corresponding vinylcarbenes has been studied in detail by Boger.[118] The preparation of cyclopropenone ketals involves treatment of 2,3-dichloropropene (**176**) in methanol with NBS (*N*-bromosuccinimide) to provide 1-bromo-3,3-dichloro-2,2-dimethoxypropane (**177**). Subsequent cyclization was initiated by potassium amide in liquid ammonia. The spirobicyclic analogs are generated by treating **177** with 1,2-propanediol in the presence of a catalytic amount of H_2SO_4 to form **178**. Cyclization of **178** under the influence of NH_2^- leads to **179** (Scheme 54). The higher stability of **179** resulted in the wide use of spirobicyclic cyclopropenones in the study of the chemistry of dioxyvinylcarbenes.

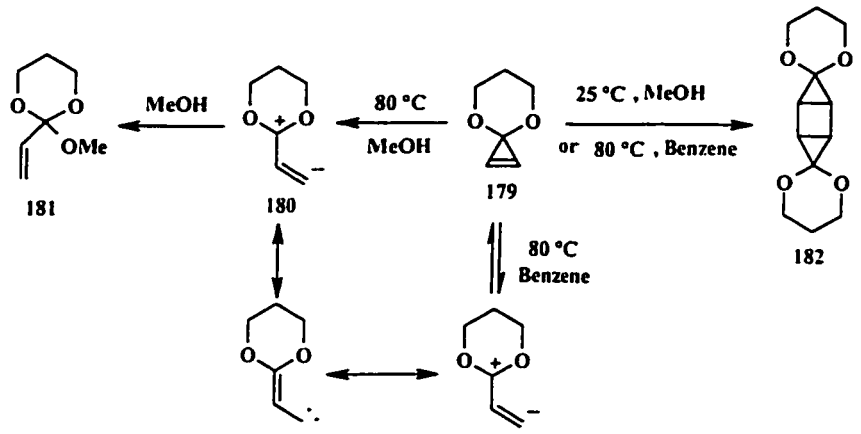


176 177 173 178 179

Scheme 54

1.6.2 Generation of 3,3-Dioxyvinylcarbene from Cyclopropenone Ketal

Initial evidence of dioxyvinylcarbene from cyclopropenone ketals came from the temperature dependent reactions of cyclopropenone ketals in methanol. At 25 °C, the cyclopropene ring opens slowly, and the dimer **182** was the only identified product. At 80 °C, the ring opened quickly to form intermediate **180**. With methanol as solvent, **180** was attacked by methanol to afford the *ortho*-ester **181**.[117] With benzene as solvent, the dimerization dominated the reaction. This indicates that an equilibrium exists between the dioxyvinylcarbene **180** and cyclopropenone ketal **179** (Scheme 55).



Scheme 55

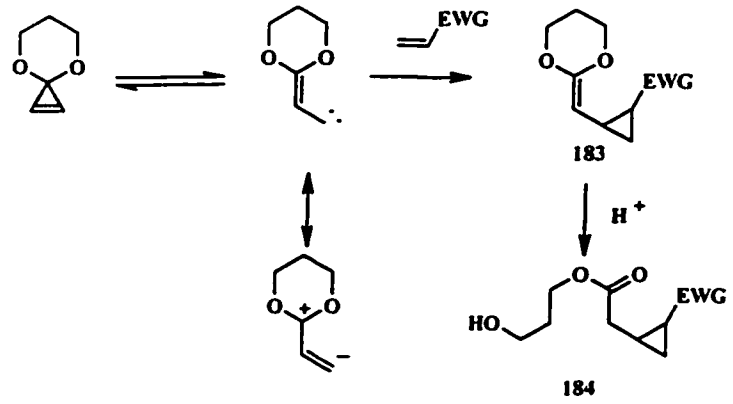
1.6.3 Characteristics of 3,3-Dioxyvinylcarbenes

The vinylcarbenes generated display strong nucleophilicity in reactions. This can be attributed to the electron donation of ketal functionalities to the formally vacant *p*-orbital of the carbene carbons, which is similar to the delocalization of electrons from oxygen in dimethoxycarbene. The singlet-triplet energy gap in 3,3-dialkoxyvinylcarbene has been calculated to be approximately 9 kcal/mol.[119]

Both the dipolar and carbenic properties of intermediates **180** give it the potential for intermolecular cycloaddition to unsaturated systems. Boger and co-workers have published several papers about their [1+2],[119-121] [3+2],[119-122] and [3+4][119] cycloadditions to electron-deficient substrates. No result has been reported about their cycloaddition with electron-rich olefins. [119]

1.6.4 [1+2] Cycloadditions of 3,3-Dioxyvinylcarbenes with Alkenes

The strongest evidence for 3,3-dioxyvinylcarbenes from cyclopropenone ketals came from the results of [1+2]-cycloaddition reactions. Methyl methacrylate, acrylonitrile, methacrylonitrile, phenyl ethylacrylate and dimethyl fumarate were used to trap the intermediates formed by heating cyclopropenone ketals at 70-80 °C. Subsequent hydrolysis of the initially formed ketene acetal to ester makes separation of the final products much easier. Normal characterization methods identified the final products as substituted cyclopropanes (Scheme 56).[119]

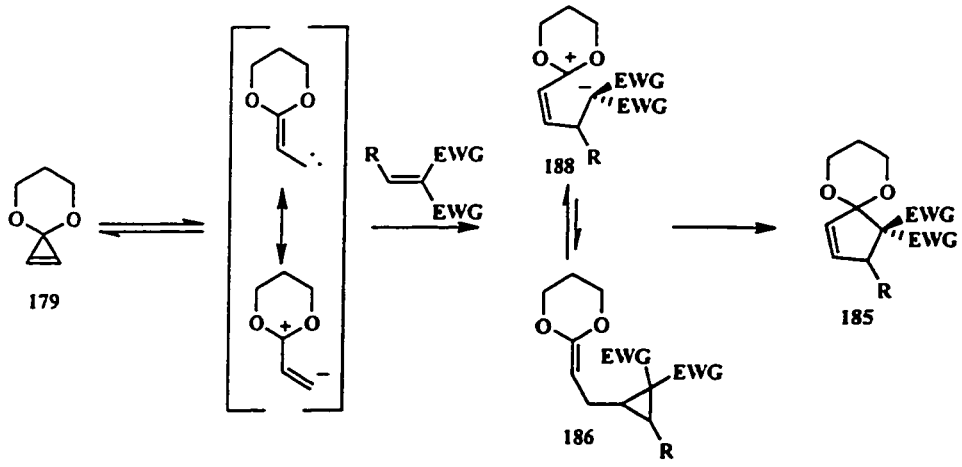


Scheme 56

The actual cycloaddition mechanism can be concerted or stepwise, through a zwitterionic intermediate. Boger studied the reaction with respect to solvent polarity. No results related to a mechanism involving charge build up at the transition state have been observed. Use of a polar solvent did not change the structure and yield of the final product, compared with the use of a non-polar solvent. The one step concerted mechanism was therefore favored.

1.6.5 [3+2]-Cycloadditions of 3,3-Dioxyvinylcarbenes with Alkenes

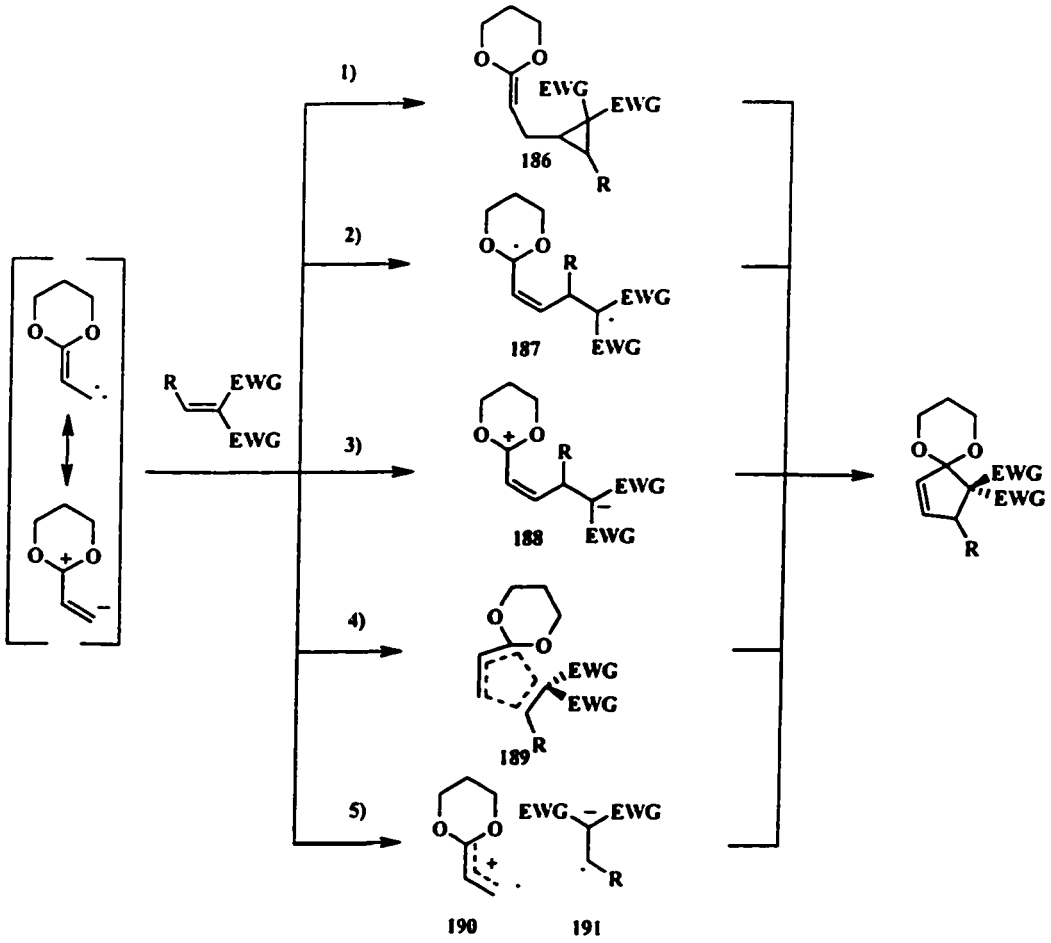
An increase of the number of electron-withdrawing groups in carbene traps leads the formation of 5-membered ring products, rather than cyclopropane derivatives. This observation was rationalized by the suggestion that the geminal electron-deficient groups, such as diesters, stabilize the dipolar intermediate **188** more strongly than one electron-withdrawing group. This made the dipolar intermediate **188** dominant over its isomer, cyclopropane **186**. [119-122]



Scheme 57

Several possible mechanistic pathways can be envisioned for this [3+2]-cycloaddition (Scheme 58). These might include: 1) initial formation of a cyclopropane ketene acetal by a [1+2]-cycloaddition, followed by biradical or zwitterionic vinylcyclopropane rearrangement; 2) a stepwise addition-cyclization of a partially delocalized triplet carbene via a biradical intermediate; 3) a stepwise addition-cyclization of a partially delocalized singlet carbene via a zwitterionic intermediate; 4) a concerted [π2s+π2a], [3+2]-cycloaddition of the π-delocalized vinyl carbene with the alkene; or, 5) a pathway involving a single electron transfer from the nucleophilic, electron-rich

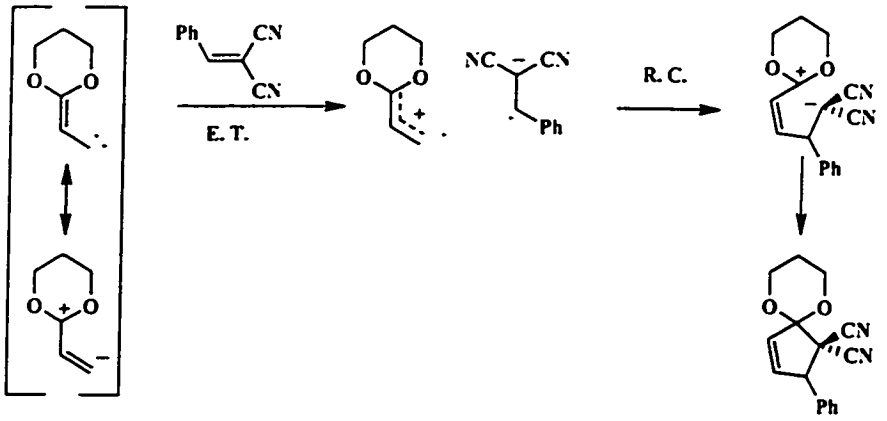
vinylcarbene to an electron-deficient alkene to generate a π-delocalized radical cation and a radical anion, followed by subsequent combination of the radical anion and radical cation (Scheme 58).



Scheme 58

A series of experiments were carried out to help figure out the most reasonable mechanism for the [3+2]-cycloaddition. Based on the experimental observations, the most likely mechanism was proposed to be the last one, which involves an electron transfer process. An electron transfer from the singlet carbene **180** to the electron-deficient olefin

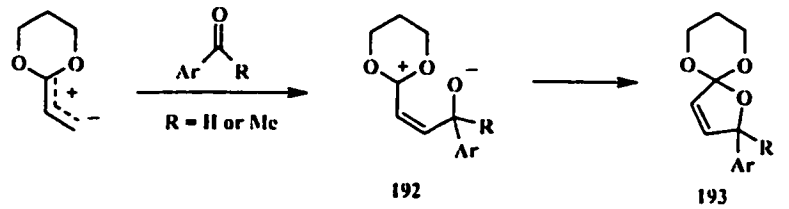
forms a radical cation and a radical anion. Radical coupling (R.C.) affords a dipolar intermediate, the collapse of which furnishes the final product (Scheme 59). [123]



Scheme 59

1.6.6 [3+2]-Cycloadditions of 3,3-Dioxyvinylcarbenes with Carbonyl Groups

The [3+2]-cycloaddition was also found in the reactions of vinylcarbenes with *p*-nitrobenzaldehyde or *p*-nitroacetophenone.[124] The reaction was assumed to begin with the addition of the carbene to the carbon of the carbonyl group, followed by the closure of the dipolar intermediate to afford the spirocyclic orthoester **193**. It is surprising that no alkyl aldehyde or ketone has been reported to undergo similar reactions (Scheme 60). The *para*-nitro group might be the critical factor in enabling the reaction by stabilizing the anion part of the dipole **192**.

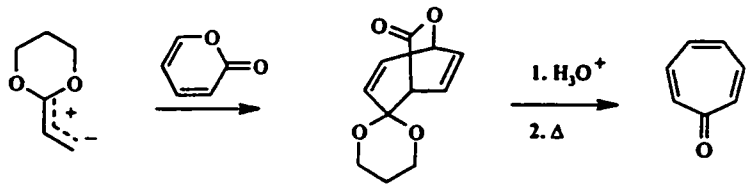


192 193

Scheme 60

1.6.7 [3+4] Cycloadditions of 3,3-Dioxyvinylcarbenes with Substituted Dienes

Unsubstituted and substituted α-pyrones were also used to react with 3,3-dioxyvinylcarbenes. A [3+4]-cycloaddition happened via a [4+2] concerted mechanism to afford a poly-ring system **194**. Subsequent hydrolysis of the ketal moiety with aqueous acid and thermal decarboxylation were deliberately carried out by Boger and Brotherton to produce a variety of unique substituted tropones, **195** (Scheme 61).[118-120,125]



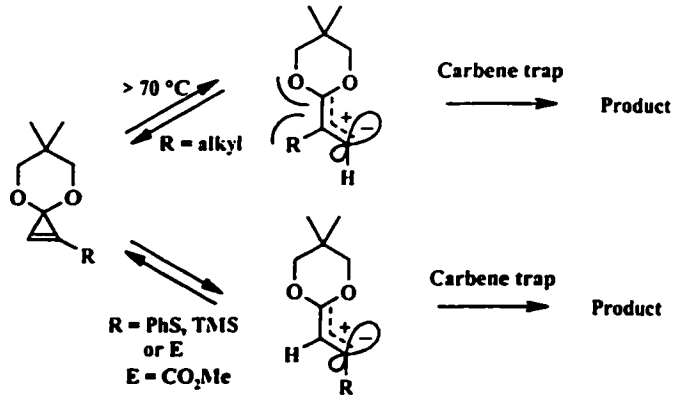
194 195

Scheme 61

1.6.8 Dioxyvinylcarbenes from Substituted Cyclopropenone Ketals

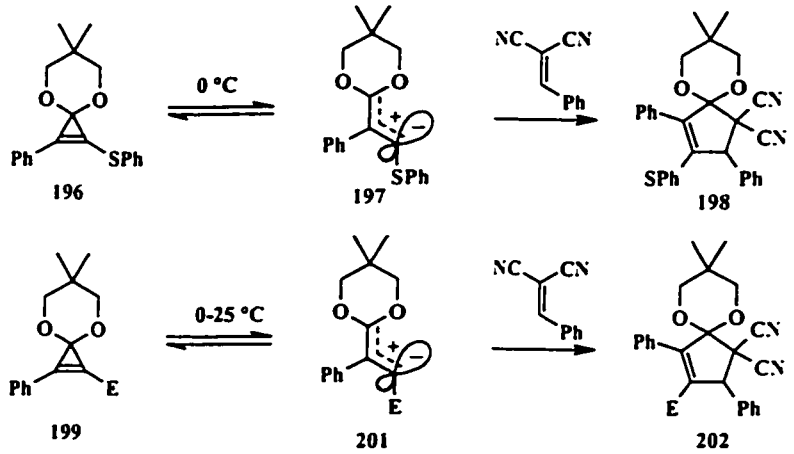
Followed the intriguing results from the ring opening reactions of cyclopropenone ketals, Nakamura and co-workers thoroughly studied the substituent effects on the ring opening direction.[126,127] It was found that attaching an alkyl group at the carbon-carbon double bond of the cyclopropene greatly retarded the rate of ring opening of the cyclopropenone ketals and led to a complex final product mixture. Attaching a trimethylsilyl, phenylthio or ester group resulted in significant regioselective ring opening and also lowered the temperature of the ring opening reaction.[126] From all these results, it was concluded that both electronic and steric factors had effects on the formation of the dipole from the cyclopropene rings. With an electron-withdrawing group or anion stabilizing group, the energy of the dipole is decreased so that the activation energy decreases and ring opening can happen at a lower temperature. Compared with hydrogen,

an alkyl group has more electron-donating ability, causing the ring opening to occur on the unsubstituted side. This places the alkyl group nearer to the ketal group and results in a higher ring-opening barrier, due to steric effect, so that the ring opening needs a higher temperature compared with cyclopropenes with two hydrogens (Scheme 62).



Scheme 62

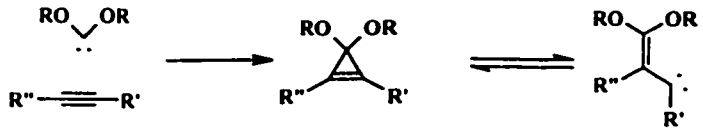
In 1,2-substituted cyclopropenes, the directed ring opening is mainly determined by electronic factors. The significant feature that needs to be noted is the low temperature of the ring opening. With the 1-phenyl-2-phenylthio (**196**) or 1-phenyl-2-ester substituted cyclopropenone ketal (**199**), the ring opening happens between 0-25 °C. The trapping alkene must be added to the cyclopropenone ketal immediately upon separation, without work-up (Scheme 63).



Scheme 63

1.6.9 Dioxyvinylcarbenes from Intermolecular Addition by Carbenes to Triple Bonds

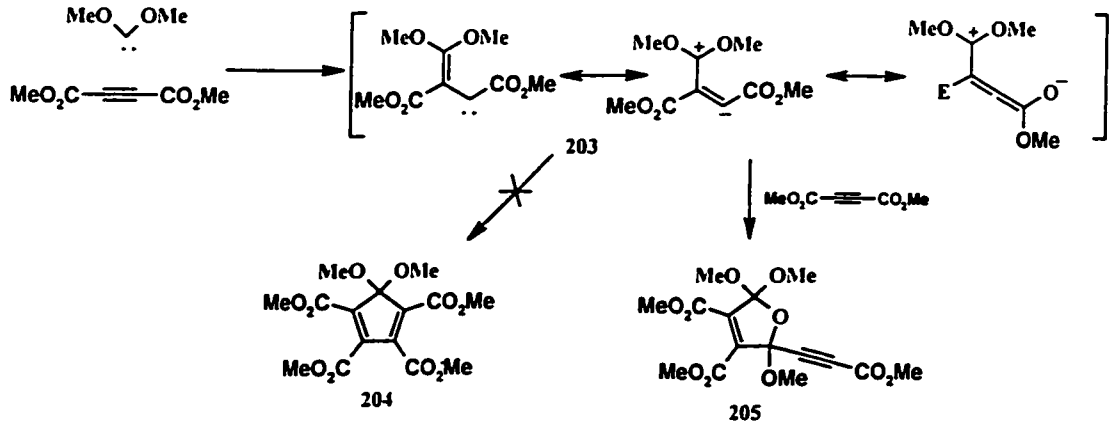
Cyclopropenone ketals can also be made through nucleophilic carbene additions on alkynes substituted with electron-withdrawing groups, such as DMAD. The cyclopropenes formed then ring open to dioxyvinylcarbenes. The ring opening direction is also determined by the comparative electron-withdrawing abilities of the substituents (R' or R", Scheme 64).



Scheme 64

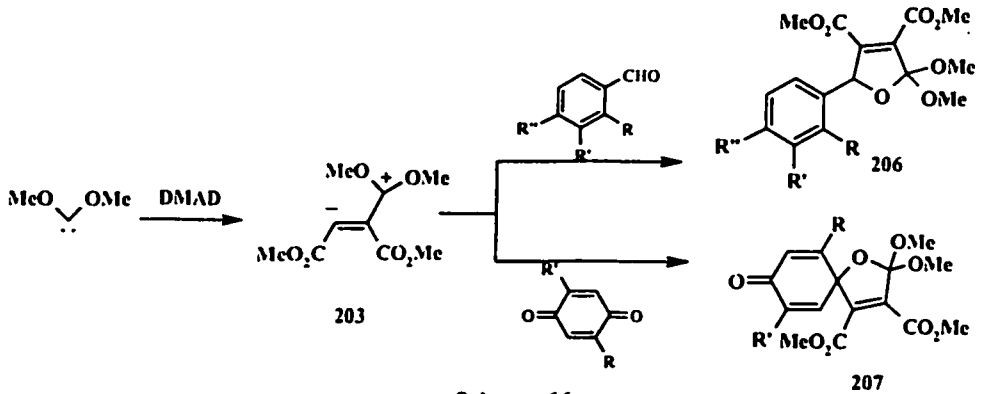
Hoffmann first studied the reaction and found that one unit of dimethoxycarbene reacted with two units of the trapping reagent to afford the final product. The addition of dimethoxycarbene to dimethyl acetylenedicarboxylate (DMAD) yielded the vinyl

carbene, which underwent a cycloaddition across the C=O bond of a second molecule of the alkyne to afford the five-membered-ring product, **205**. There was no evidence for cycloaddition of the vinylcarbene **203** across the carbon- carbon triple bond to yield a cyclopentadiene product **204** (Scheme 65).



Scheme 65

Recently, Vijay Nair reported using three reagents, including dimethoxycarbene, DMAD and benzaldehyde, in a one-pot reaction to give dihydrofuran derivatives.[99] In the proposed mechanism the carbene reacted with DMAD to make dioxyvinylcarbene (**203**) first. Subsequent cycloaddition to the carbonyl group in benzaldehydes (or quinones) formed dihydrofuran derivatives **206** and **207**, respectively (Scheme 66).

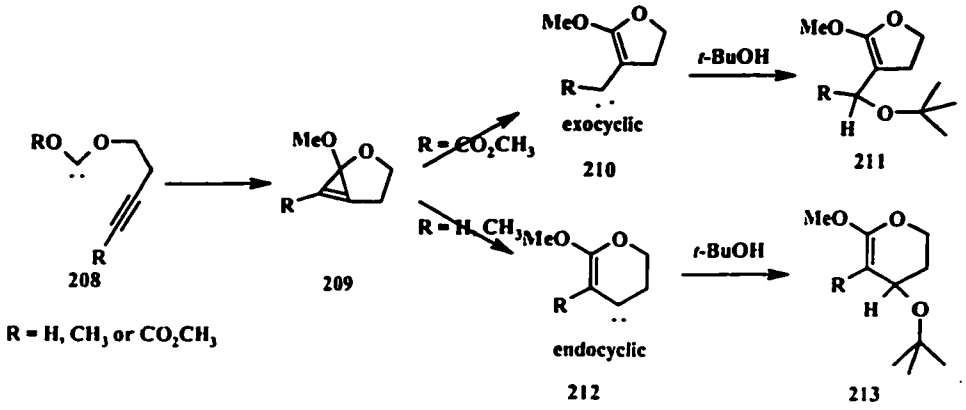


Scheme 66

1.6.10 Dioxyvinylcarbenes from Intramolecular Addition of Carbenes to Triple Bonds

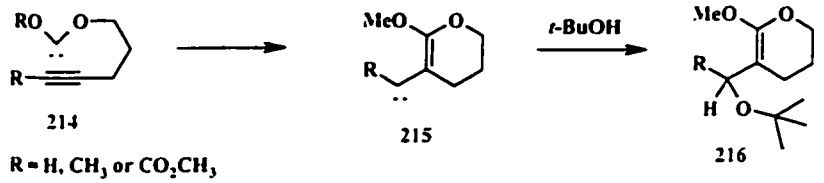
Kassam first exploited the intramolecular formation of a dioxyvinylcarbene through a carbene addition to a carbon-carbon triple bond. Carbene **208** was generated by thermolysis of an oxadiazoline precursor. Intramolecular reaction of **208** with the triple bond led to **209**, Scheme 67.[128-130] Kassam and Warkentin studied the mechanism by carbene trapping experiments with alcohols. Different types of terminal alkyne substituents, H, CH_3 and CO_2CH_3, led to different products.

With H or CH_3 on the end of alkyne, endocyclic ring opening led to the 6-membered carbene **212** exclusively, whereas when an ester substituent was present, the exocyclic carbene **210** dominated (Scheme 67).[128]



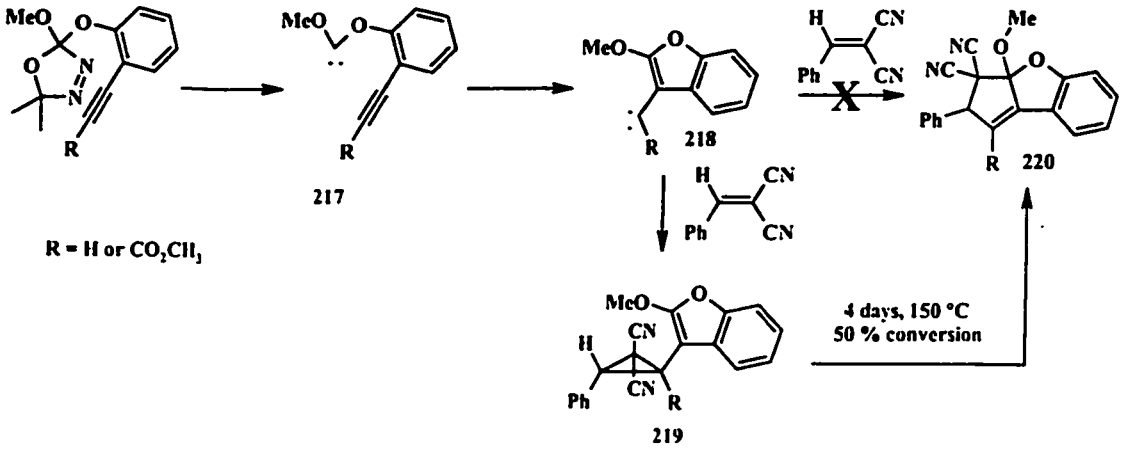
Scheme 67

If the alkynoxy group is pentynoxy, the exocyclic vinylcarbene (**215**) occurs exclusively, independent of substituent (Scheme 68).[130]



Scheme 68

Benzylidenemalononitrile was used to trap the vinylcarbene in an attempt to make the tricyclic benzofuran ring system. Unlike the reaction of benzylidenemalononitrile with 3,3-dioxyvinylcarbene, which came from the unsubstituted cyclopropenone ketal, no cyclopentene product was formed under the reaction conditions. Only cyclopropane derivative **219** was isolated. The vinylcyclopropane **219** can rearrange slowly to the 5-membered ring product **220** at an elevated temperature.[130] The conversion was approximately 50% complete after 4 days at 150 °C (Scheme 69). The observed vinylcyclopropane rearrangement can be rationalized in the terms of the presence of two cyano groups, which would help stabilize a zwitterionic or biradical intermediate involved in the conversion to the cyclopentenone ketal.



Scheme 69

1.7 Nucleophilic Aromatic Substitutions

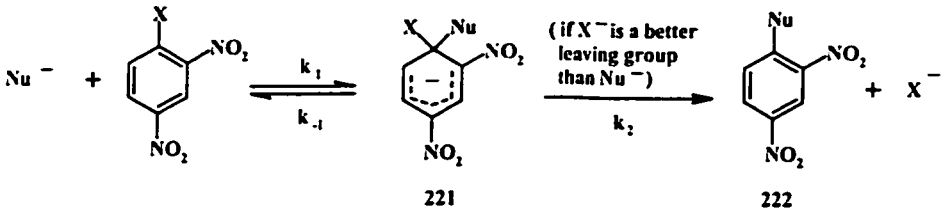
Dioxycarbenes are described as nucleophiles because they show stronger reactivity toward electron-deficient alkenes than electron-rich alkenes. Like other nucleophiles, their reactions with electrophiles has attracted much attention.

The study of nucleophilic substitution at saturated carbon has been quite thorough and many important carbon-carbon bond formations came from this type of reaction. Analogous substitutions at sp^2 carbon, especially sp^2 carbon of aromatic rings is also well known. There are three major mechanisms for nucleophilic aromatic substitution: S_NAr,[131-134] $S_{RN}1$[135,136] and VNS (the Vicarious Nucleophilic Substitution of Hydrogen).[137-140] Almost all nucleophilic aromatic substitution reactions can be explained in terms of one of these mechanisms.

1.7.1 S_NAr Nucleophilic Aromatic Substitutions

S_NAr displacement reactions form the backbone of numerous important syntheses of pharmaceuticals and potential drugs.[141-144] The key intermediate of this bimolecular nucleophilic aromatic substitution is the negatively-charged σ-bonded adduct, generated from nucleophile addition to an aromatic carbon bearing a leaving group (*ipso* position), commonly termed a Meisenheimer complex **221**, Scheme 70.[145-148] The stability of this non-aromatic intermediate and the character of the leaving group determine the degree of success of the overall S_NAr displacement. Generally, a strongly electron-withdrawing substituent, such as nitro or cyano, favors the addition-acceptor complexes. A good leaving group, such as halogen, is the ideal displacement target. The nucleophilicity of the nucleophile is also a critical factor influencing the reaction process. Graham, Hughes and

Ingold have demonstrated that the substitutions occurred more rapidly with stronger nucleophilic reagents. [149]

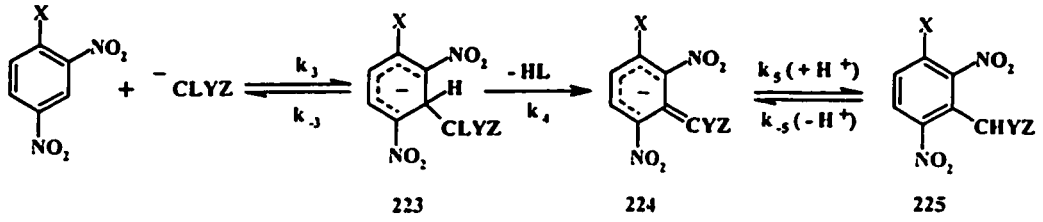


221 222

Scheme 70

1.7.2 Vicarious Nucleophilic Aromatic Substitutions

Formally regarded as a competitor of the S_NAr Nucleophilic Aromatic Substitution, the VNS proceeds through addition of the nucleophile to an aromatic carbon bearing a hydrogen to form a C-3 Meisenheimer adduct (**223**). The prerequisite of a successful VNS is that the nucleophile, a carbanion, itself contains a good leaving group (L) at the carbanion center (i.e. Scheme 72, $Nu^- = {}^-CLYZ$, where Y and/or Z are electron-withdrawing).[150,151] β-Elimination of HL, followed by protonation of the initial benzylic carbanion during workup, gives rise to an α-substituted 3-X-2,6-dinitrotoluene derivative (**225**).



223 224 225

Scheme 72

1.7.3 $S_{RN}1$ Nucleophilic Aromatic Substitutions

Kim and Bunnett first proposed the idea of $S_{RN}1$ to acknowledge a kind of aromatic substitution similar to S_N1 displacement but also pointing to the intermediacy of

radicals. [152] The normal S_NAr mechanism was ruled out because it was found that a radical scavenger (tetraphenylhydrazine) largely suppressed the aromatic substitution reactions. A radical chain mechanism was therefore proposed (Scheme 73). Though the mechanism involves radical and radical anion intermediates and an electron-transfer step, its overall effect is nucleophilic substitution.

$$[RX]^{\cdot-} \longrightarrow R\cdot + X^- \qquad (1)$$

$$R\cdot + Y^- \longrightarrow [R\text{-}Y]^{\cdot-} \qquad (2)$$

$$[R\text{-}Y]^{\cdot-} + RX \longrightarrow RY + [RX]^{\cdot-} \qquad (3)$$

Scheme 73

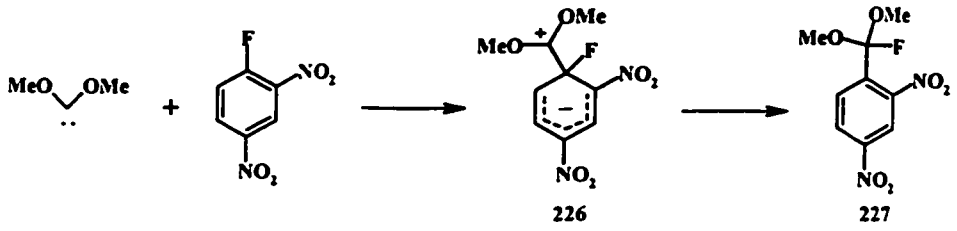
Interestingly, the $S_{RN}1$ reaction has no requirement for activation by other substituents (in contrast to S_NAr reaction).[153,154] It can occur satisfactorily with simple phenyl halides. Besides, it is remarkably insensitive to the steric effects of ortho substituents. Mesityl bromide or iodide may be employed to mesitylate nucleophiles in good yield.[155] At the present time, the scope of aromatic substituents of the $S_{RN}1$ reaction is limited to the seven nucleofugic groups: I, Br, Cl, F, SPh, NMe^+, or $OPO(OEt)_2$.[156]

1.7.4 Dioxycarbenes in Nucleophilic Aromatic Substitutions

A dioxycarbene is not a pure nucleophile. Besides its nucleophilicity, which mainly comes from the lone pair electrons of the carbene, it also has some electrophilic characteristics, which come from its *p*-orbital that is partially occupied by delocalized electrons from its neighbor oxygens. Applications of its nucleophilicity in organic synthesis include its reactions with different electrophiles, such as an electron-deficient

carbon-carbon double bond, ketone group or active X-H bond. The application of nucleophilic carbenes in aromatic substitution has only recently been explored.

To the present time, Warkentin[157a] and Kuhn et al[157b] have reported one type of reaction of a nucleophilic carbene with an aromatic ring system. Dimethoxycarbene, generated from thermolysis of an oxadiazoline, was used as a nucleophile to react with 2,4-dinitro-fluorobenzene. [157a] A product from the overall carbene insertion into the fluorine-carbon bond was identified. The reaction course was proposed to go through the carbene addition to the fluorine bearing carbon to form a C-1 Meisenheimer type of adduct **226**, which was strongly stabilized by the *ortho* and *para* nitro functional groups. With fluorine migration, an aromatic substitution product **227** resulted (Scheme 74). The overall mechanism is very similar to the S_NAr mechanism for the common nucleophilic aromatic substitution.



226 227

Scheme 74

Chapter 2: RESULTS AND DISCUSSION

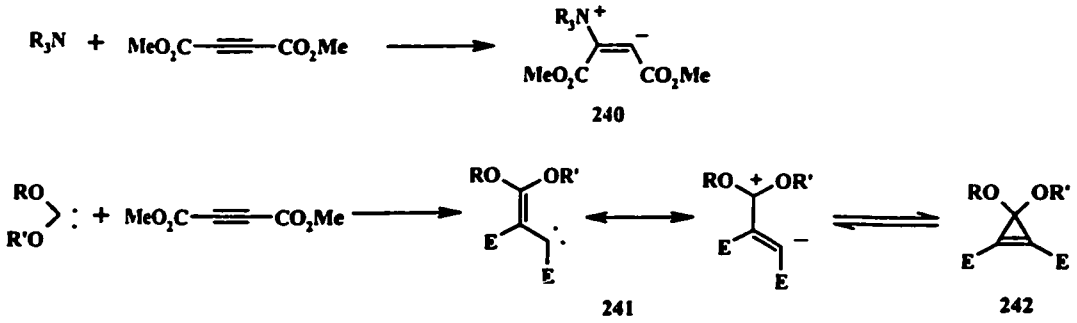
The object of my research was to explore the application of nucleophilic dioxycarbenes in organic synthesis. Separation and purification of starting materials and final products became important steps in the whole research process. Thin layer chromatography and flash column chromatography were the two main methods to achieve separation. Full characterization by all available instrumental analyses, including ^{1}H NMR, ^{13}C NMR, FTIR, EI-MS, CI-MS and high resolution MS, were vital in the identification of the desired or undesired compounds. General instrumental analyses require the compounds to be pure enough for unambiguous identification. To get pure compounds and to save separation time and solvent, the monitoring of the separation process was an important part of the experimental design. It is well known that some compounds, especially compounds bearing aromatic substituents, can be seen under a UV lamp. This knowledge led me to select aryloxycarbenes as the first choice for my research.

Interestingly, although the reactions of dialkoxycarbenes have been studied very thoroughly, as described in the introduction chapter, aryloxycarbenes or diaryloxycarbenes have not been studied systematically. This makes the study of aryloxy and diaryloxycarbenes a promising direction for research.

2.1 Reactions of a Dioxycarbene with a Michael Acceptor

Reactions of neutral nucleophiles with Michael acceptors generally involve dipolar intermediates **240**, as illustrated with Scheme 80 for the attack of an amine on dimethyl acetylene dicarboxylate (DMAD). When a dialkoxycarbene carbene is used as

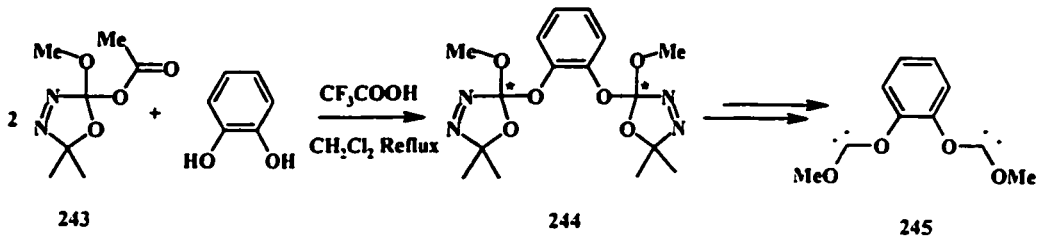
the nucleophile, the attack can produce either a dipole (**241**) or a cyclopropene (**242**), depending on whether the reaction is stepwise or concerted. It is not easy to distinguish between stepwise addition with subsequent ring closure, and concerted cyclopropene formation with subsequent ring opening. However, it is fairly clear that, with a few exceptions,[158] reactions subsequent to the initial attack often involve the acyclic dipole. Many cyclopropenes are not stable enough at higher temperatures to accumulate to detectable concentrations.[159,160]



Scheme 80

2.2 Thermolysis of a Bis-oxadiazoline with DMAD

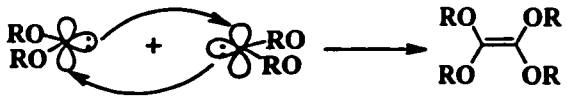
The first aryloxycarbene to be exploited was prepared from catechol and 2-acetoxy-2-methoxy oxadiazoline (**243**). The acid catalysed exchange reaction proceeded successfully with exchange occurring on both hydroxy groups of the catechol with two units of the 2-acetoxy-2-methoxy oxadiazoline. Three isomers (**244**) were produced because there are two chiral carbons in the final product, but the chirality is irrelevant because it is lost during the fragmentation of the oxadiazoline to carbene **245** (Scheme 81).



243 244 245

Scheme 81

In general, a dioxycarbene produced from thermolysis of the corresponding oxadiazoline dimerizes rapidly to form a tetraoxyethylene (Scheme 82).



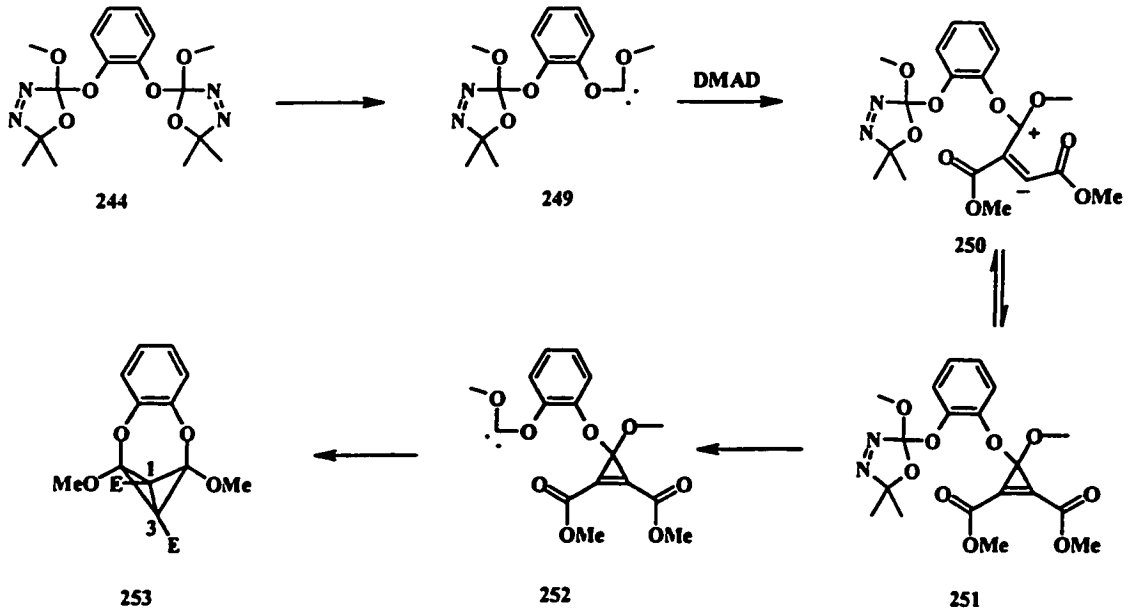
248

Scheme 82

If the dioxycarbenes could be formed very rapidly from the oxadiazoline, the chance of the dimerization would be high, especially for the intramolecular case. But in reality, the formation of dioxycarbene by the extrusion of nitrogen and acetone from an oxadiazoline proceeds slowly with a rate constant of about 10^{-5} s^{-1} at 110 °C. This makes the formation of both carbenes from one unit of **244** at same time, or in very short period of time, very unlikely. The normal case is that the second carbene forms long after the first one has disappeared by chemical trappings. A Michael acceptor, dimethyl acetylene dicarboxylate (DMAD), was utilized as a trap, as it possesses a triple bond and two ester groups. Theoretically, DMAD might serve to intercept both carbenes in sequential trapping reactions.

The result of the reaction was first predicted to be a strained bicyclobutane product **253**. Boger[120,161] has pointed out that a 1,1-dioxyvinylcarbene equilibrates with the corresponding cyclopropenone ketal at high temperature, although the equilibration

favors the ring-opened vinylcarbene intermediate. The desired bicyclobutane would be a very interesting product **253** due to the interesting bridge bond between two diagonal carbons 1 and 3. Previous theoretical studies have shown that the HOMO is localized in the C_1-C_3 region and is composed predominantly of 2p orbitals.[162] Not many similar compounds have been made to the present time.[163] There is a continued effort to find a convenient synthetic route to such compounds so that further research can be carried out to match the theoretical calculations that have been done.



Scheme 83

Through a chromatographic separation of the final products of the thermolysis reaction, a major product was isolated. General instrumental analyses were not sufficient to identify the compound completely. The ^{1}H NMR, ^{13}C NMR and MS spectra only show that the compound has one unit of bis-carbene and one unit of DMAD. A single crystal was then grown from 1:1 benzene-hexane solvent. X-ray diffraction provided an

interesting structure (**254**), in which one of the O-Ar bonds has been replaced by a new C-Ar bond.

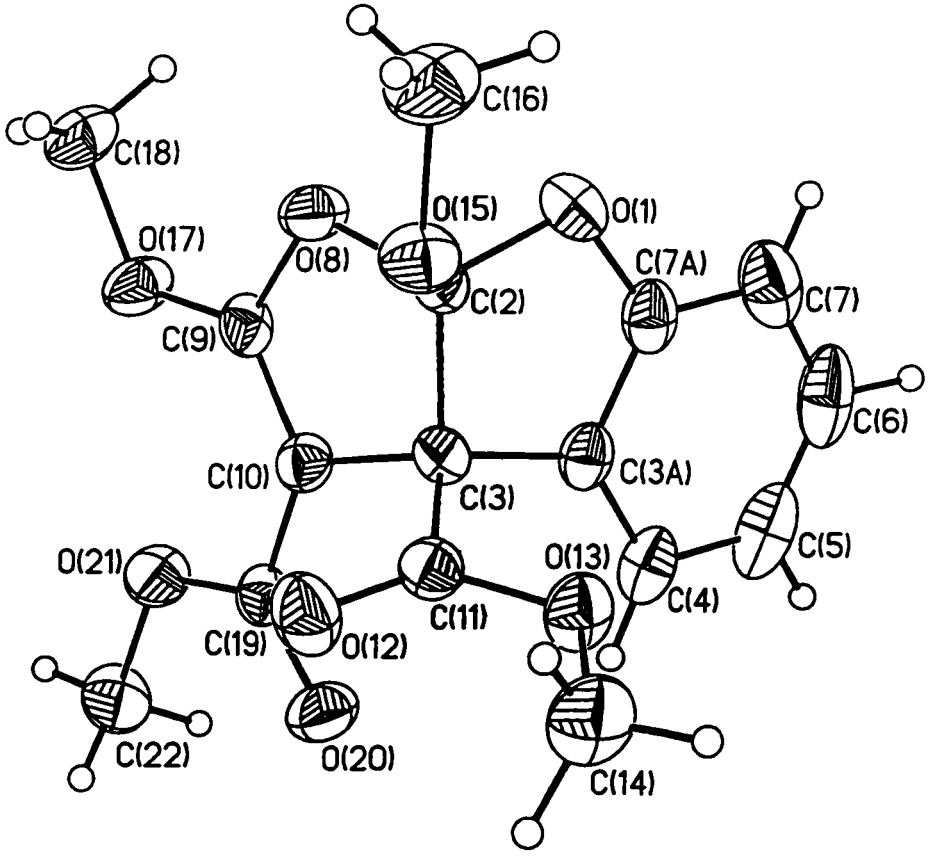
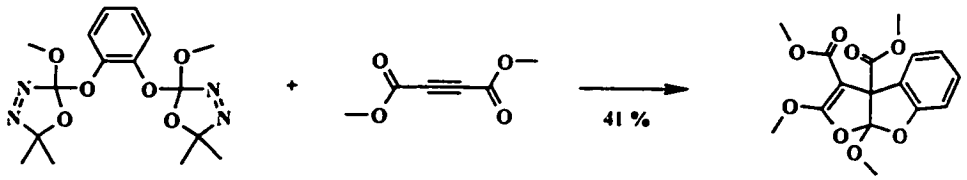


Fig.2. The structure of **254**, drawn with **50%** probability thermal ellipsoids, showing the labelling used in the tables (see Appendix 1).

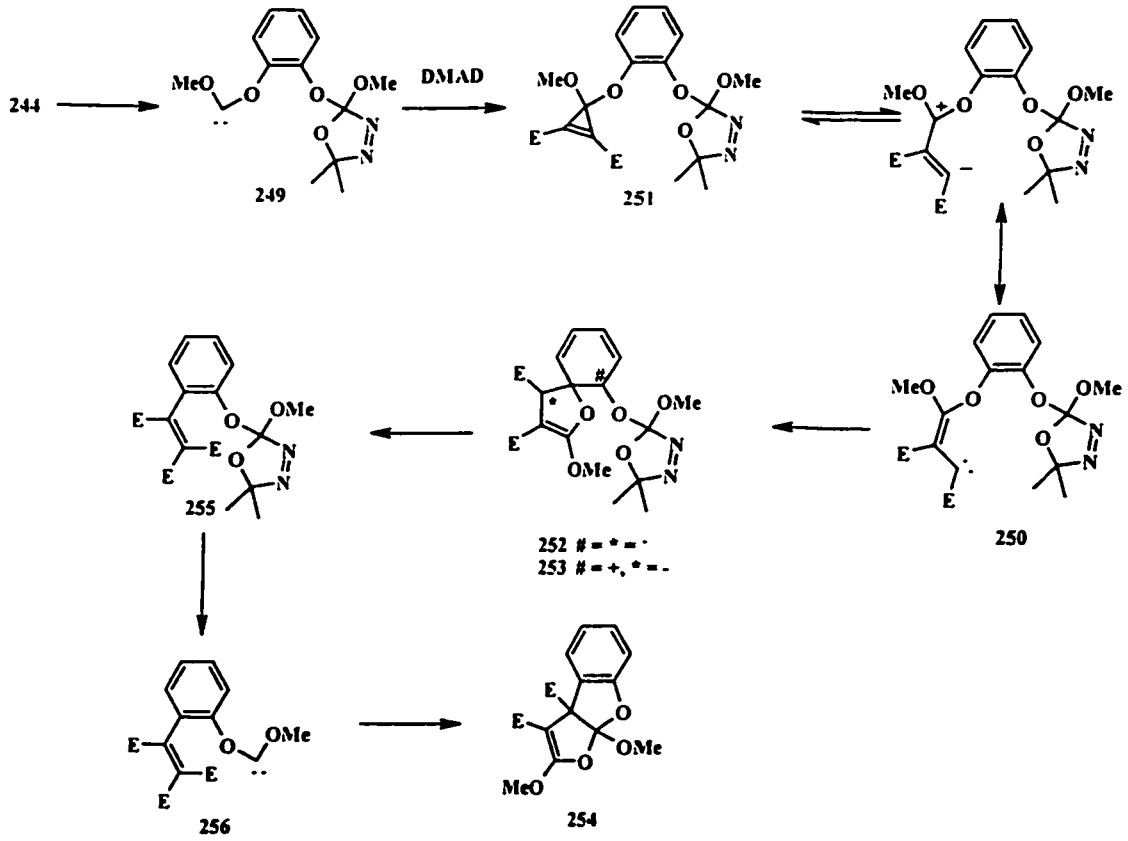
On the basis of the structure, an aromatic substitution happened during multiple step reactions.[164] The study of the mechanism of the novel reaction is therefore an interesting task, and the result will guide its future application in organic synthesis.



254

Scheme 84

A mechanism was proposed to explain the one pot reaction. Due to the small rate constant of fragmentation of dioxy oxadiazolines to carbenes (about 10^{-5} s^{-1}), it is unlikely that both sides will fragment to carbene at same time. It is reasonable to propose that the first formed carbene attacked the triple bond of DMAD to form a cyclopropene (**251**), which then equilibrated with vinylcarbene intermediate **250**. This intermediate then attacked the aromatic ring to form *spiro*-ring intermediate **252** or **253**. **255** was formed through ring opening with the driving force of rearomatization (Scheme 85). The second oxadiazoline ring then fragmented to form another carbene **256**, which reacted with the α,β–unsaturated ester by a novel [1+4]-intramolecular cyclization route to afford the final product **254**.



Scheme 85

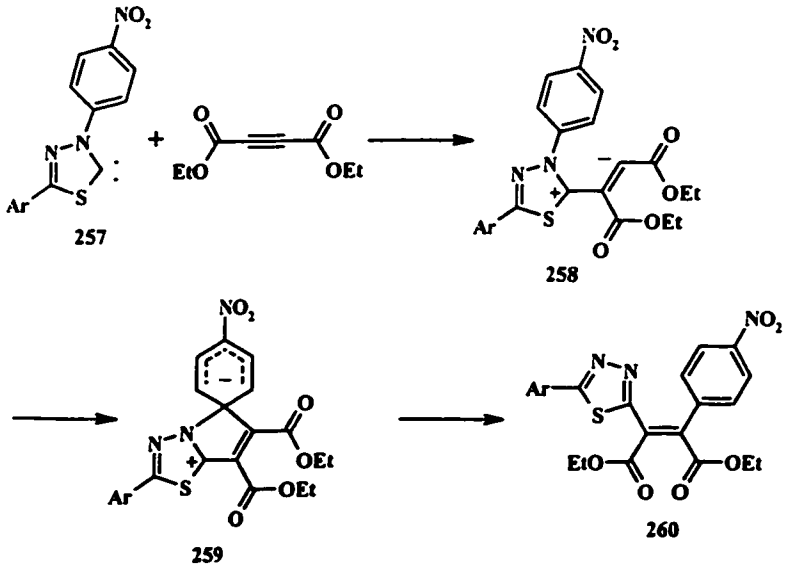
The proposed mechanism guided subsequent research on the novel aromatic substitution reactions by dioxyvinylcarbenes, generated from the intermolecular reactions of the aryloxycarbenes with DMAD.

2.3 Nucleophilic Aromatic Substitution

2.3.1 Generation of the Precursors of Aryloxymethoxycarbenes

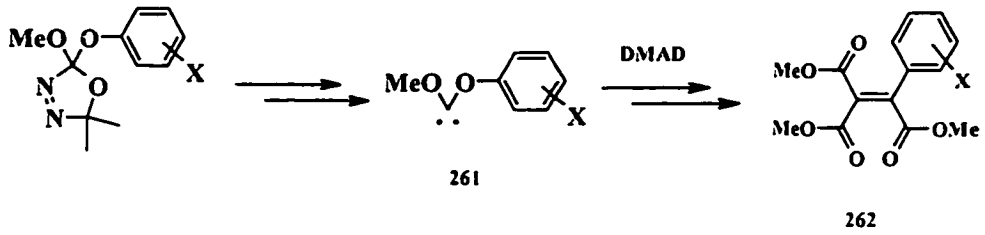
Analysis of the complex reaction leading to **254** showed two kinds of interesting processes sequentially taking place to result in the final product. Among them, the aromatic substitution reaction is vital. In the literature, only one analogous aromatic group

migration, during reaction of an aminothiocarbene **257** with dimethyl acetylene-dicarboxylate, had been reported.[165] The reaction was proposed to go through a Michael type addition of the carbene to the triple bond to form a dipolar intermediate **258**. The following *ipso* aromatic addition furnished the aryl migration product **260** (Scheme 86). No further details or related mechanisms have been reported since then.



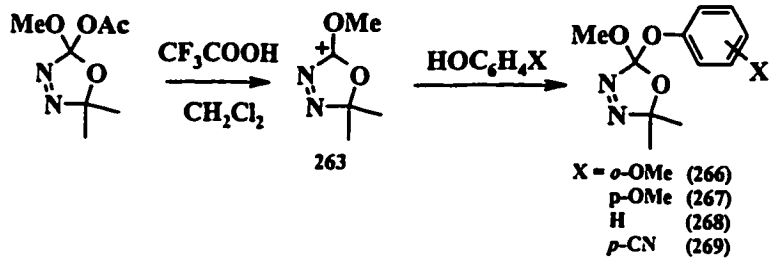
Scheme 86

To do a mechanistic study of the novel aromatic substitution, a series of aryloxy methoxy oxadiazolines with different functional groups on the aromatic rings was needed. The expected carbenes **261** from thermolysis of those oxadiazolines would react with dimethyl acetylene dicarboxylate. Based on the assumption that the properties of all of these carbenes, such as the nucleophilicities and the addition rate constants toward DMAD, are similar, the comparison of final yields of those aromatic substitution products (**262**) might aid in the understanding of the mechanism of the substitution, i.e., nucleophilic or electrophilic (Scheme 87).



Scheme 87

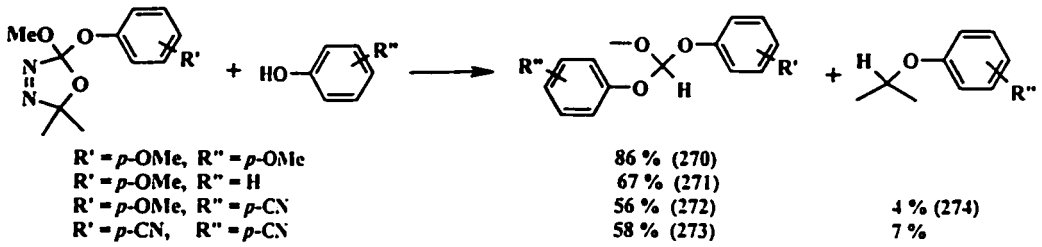
In practice, the preparation of 2-aryloxy-2-methoxyoxadiazolines can be easily accomplished by reacting 2-acetoxy-2-methoxyoxadiazoline with a substituted phenol in the presence of catalytic acid. Protonation of the acetoxy group by the acid generates a hetero-atom stabilized carbocation **263** by the departure of acetic acid. Then the substituted phenol attacks the cation to form the desired aryloxy methoxy oxadiazoline (**266-269**, Scheme 88).



Scheme 88

2.3.2 Evidence for Aryloxycarbenes

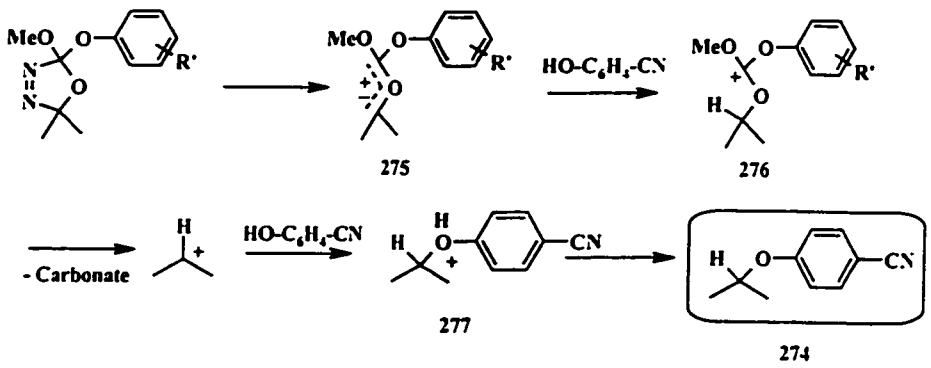
A nucleophilic carbene reacts with active bonds, such as O-H and N-H, by overall insertion. The insertion into an alcohol to form an orthoester has been used as a standard method to prove the existence of a carbene intermediate during a reaction process. In general, dialkoxycarbenes can be trapped in up to 80% yields by alcohols. The same idea was then exploited to trap alkoxyaryloxycarbenes with different phenols (Scheme 89).



Scheme 89

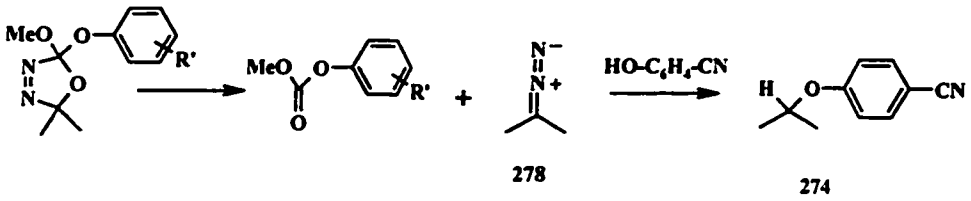
The major products of these trapping reactions were identified as the desired orthoformates (**270-273**) formed in acceptable to relatively high yields (Scheme 89). This kind of trapping experiment can also be used as a convenient method for the synthesis of orthoformates with a chiral center, from a carbene with different substituents. Chiral column chromatography might then be used to separate pure enantiomers.

From the above four reactions, an isopropyl aryl ether **274** was isolated when 4-cyanophenol was used as the carbene trap. 4-Cyanophenol has a lower pKa than 4-methoxyphenol, and should attack a nucleophilic carbene more efficiently to give a higher yield of orthoformate, assuming the efficiency of the trapping influences the final yields. The observed opposite trend from the first three thermolysis reactions of the same oxadiazoline with different phenols implies that the more acidic trap attacks the previous intermediate, the carbonyl ylide **275**, to decrease the efficiency of carbene formation. The isolation of the isopropyl aryl ether in both of the 4-cyanophenol trapping reactions provides evidence for the proposal (Scheme 90).



Scheme 90

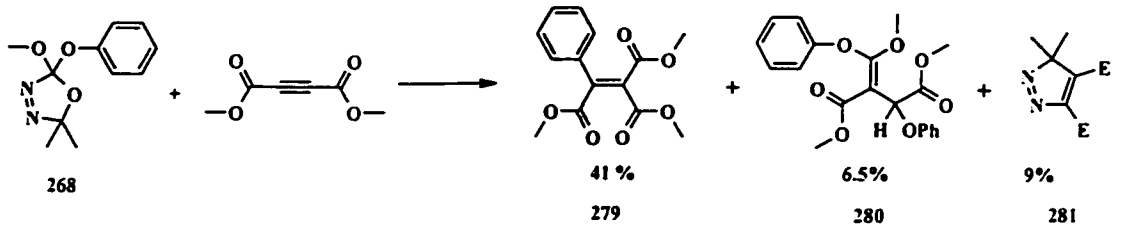
The reaction of phenol with diazopropane **278**, which can be produced by a competing cycloreversion of the oxadiazoline, also forms the isopropyl aryl ether. The fact that neither 4-methoxyphenol nor phenol gave isopropyl aryl ethers implies that the pK_a value of the phenol has an important role in the reaction of the diazopropane with a phenol.



Scheme 91

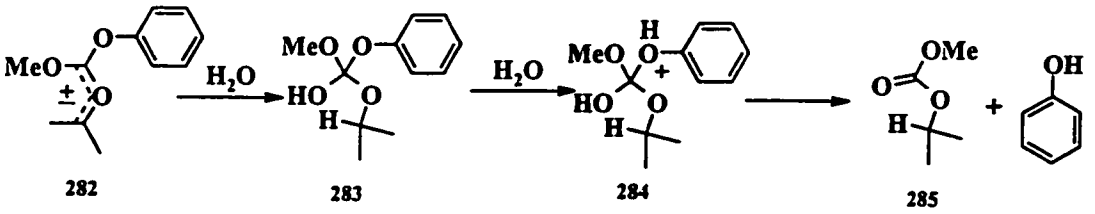
2.3.3 *ipso*-Aromatic Substitution

A thermolysis reaction of methoxy phenoxy oxadiazoline in the presence of DMAD with a trace of water furnished a very interesting product **280** along with **279**, the aromatic substitution product (Scheme 92). The structures of the final products were fully supported by the available spectroscopic data: ^{1}H and ^{13}C NMR spectra, IR and mass spectra.



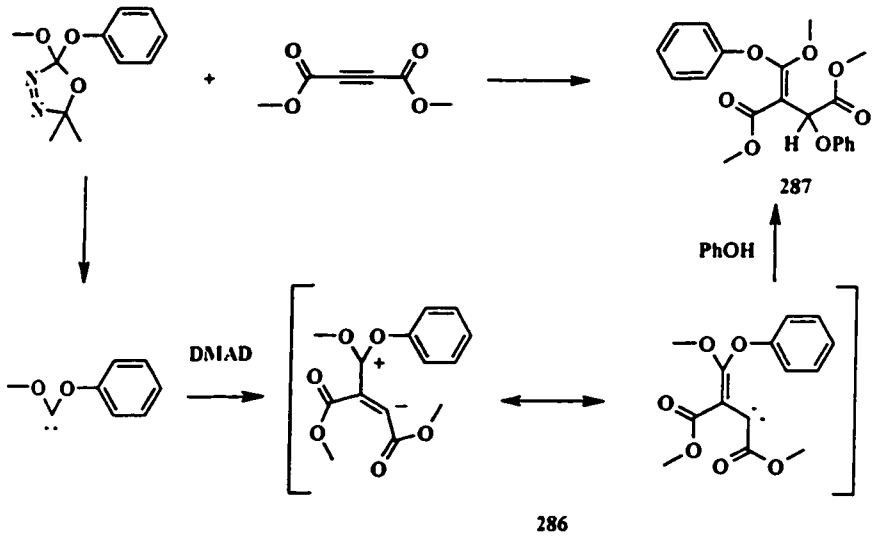
Scheme 92

This second product, which has one unit of carbene, one unit of DMAD and one unit of phenol, was shown to be **280**. The trapping phenol is proposed to result from traces of water, which reacted with the carbonyl ylide **282** to form the phenol (Scheme 93).



Scheme 93

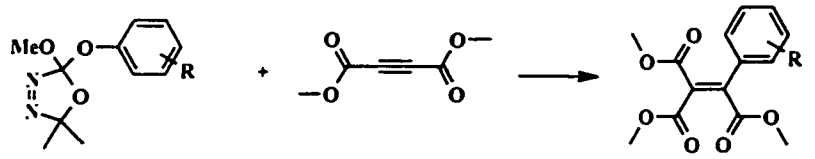
The phenol then trapped intermediate **286**, a dioxyvinylcarbene, in a stepwise or concerted way to form **287** (Scheme 94).



Scheme 94

Although the yield of **287** is only 6.5%, the isolation of this product strongly supports the proposal that dioxyvinylcarbene (**286**) was the key intermediate between the starting material and final aromatic substitution product **279**. *ipso*-Aromatic substitution to form **279** has to go through **286**.

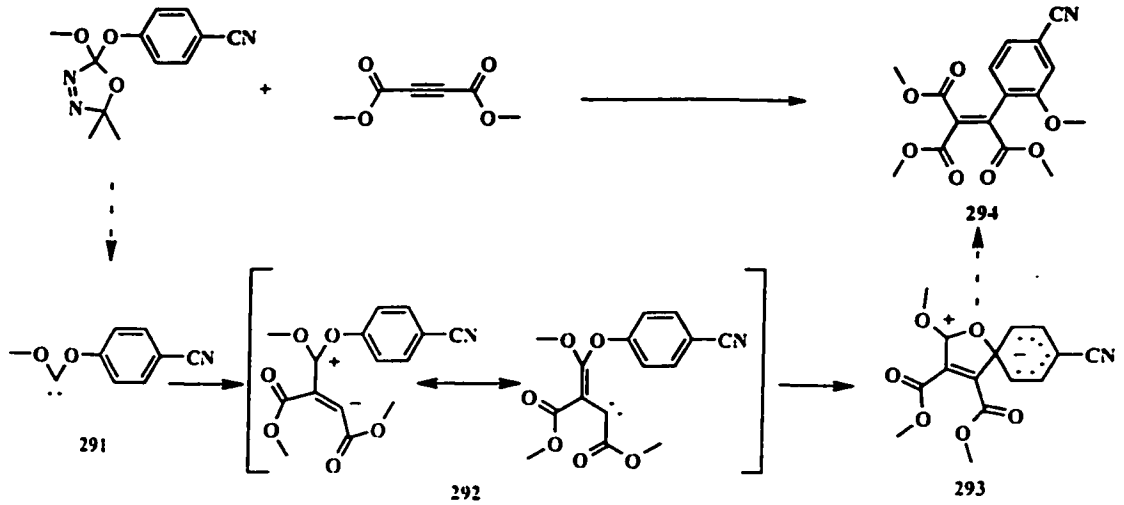
A series of thermolysis reactions under completely anhydrous conditions was carried out. 2-Aryloxy-2-methoxyoxadiazolines with phenoxy groups bearing different substituents, from the electron donating methoxy group through the electron-withdrawing cyano group, were used to do thermolysis reactions with DMAD. The yields did not show a clear dependence on electron activating abilities of the aromatic substituents. Both the *ortho*-methoxy and the *para*-cyano groups resulted in a good yield (Scheme 95). Surprisingly, no aromatic substitution products could be detected for the *para*-methoxy case.



R = *o*-OMe	Yield = 61 %	288
p-OMe	0 %	289
H	41 %	279
p-CN	72 %	290

Scheme 95

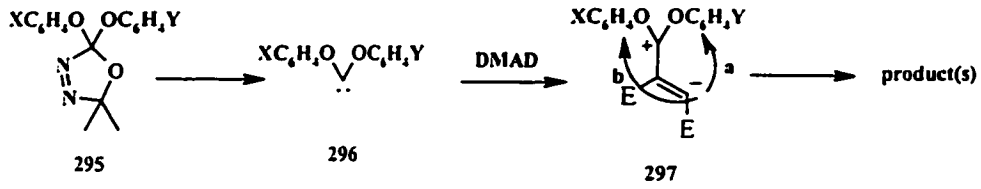
With the analysis focused on the experiments with different *para*-substituted aryloxy groups, the yields of aromatic substitution products for *p*-OMe, H and *p*-CN did give an interesting trend. From the electron donating *p*-methoxy group, passing through H, to the *para*-cyano group, the yields of aromatic substitution products increased. With this trend, the aromatic substitution is proposed more likely to be nucleophilic, rather than electrophilic, *ipso*-aromatic substitution (Scheme 96). The electron-withdrawing group accelerates the aromatic substitution by stabilizing the transition state and decreasing the activation energy.



Scheme 96

The lack of a clear relationship between the σ-constants of the aromatic substituents and the final yields of the aromatic substitution product can be explained as follows. The yields of the reaction might be controlled by two factors: the efficiency of aryloxymethoxycarbene formation from the corresponding oxadiazolines and the efficiency of subsequent addition of the carbene to DMAD. The fragmentation of an oxadiazoline to a desired carbene proceeds through several steps, in which different substituents influence the formation and stabilization of intermediates. The efficiencies of formation of carbenes from oxadiazolines are therefore expected to be different. The efficiencies of addition of the carbenes to DMAD are also influenced by the substituents of the carbenes.

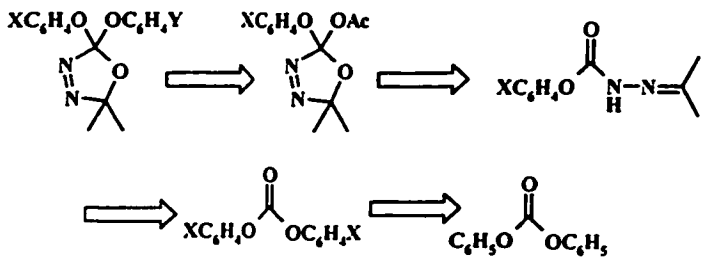
Considering that the *ortho* methoxy group might help to stabilize the positive charge of the dipolar intermediate in some other way, such as through space, rather than through a pure resonance effect, the relatively good yield of aromatic substitution product from the *o*-methoxy system could be interpreted in terms of a different mechanism. To support these proposals, nucleophilic aromatic substitution and an existing specific *ortho* substituent effect, a series of competition reactions was designed to give a clearer result. This series of experiments, which involved the addition of diaryloxycarbenes bearing different substituents to DMAD, was designed to eliminate the influence of other factors on the aromatic substitution (Scheme 97). The scheme requires the generation of a source of diaryloxycarbenes **296**, the diaryloxy oxadiazolines **295**.



Scheme 97

2.4 Diaryloxycarbene Precursor: Diaryloxy Oxadiazoline

The two aryloxy groups were introduced into the oxadiazoline in different steps. The first aryloxy group was put in before the LTA oxidation process. The second aryloxy group was introduced with acid catalysis after the oxidation of the hydrazone. With this stepwise operation, the unsymmetric diaryloxycarbene precursors could be synthesized relatively easily, as shown in Scheme 98.



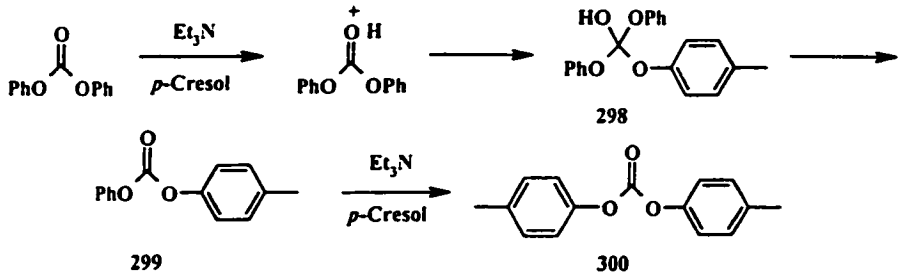
Scheme 98

2.4.1 Synthesis of Diaryloxy Oxadiazoline

The multi-step synthesis of oxadiazolines started from diphenyl carbonate, which was converted to hydrazinocarboxylate **301** by taking advantage of the good leaving ability of the aryloxy group.

p-Cresol was chosen as the first aryloxy group to be introduced. Its methyl substituent was also used as the internal standard to monitor reactions in later steps, such

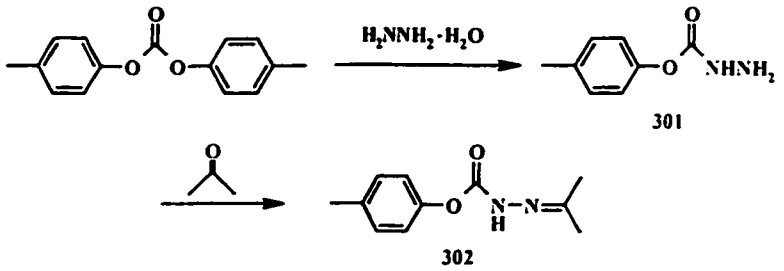
as the formation of the hydrazinocarboxylate. Di-*p*-tolyl carbonate was made by the basic exchange of phenoxy groups from diphenyl carbonate with two 4-methylphenoxy groups through tetrahedral intermediate **298** in a two-step process (Scheme 99).



Scheme 99

As an alternative approach, the acid-catalyzed exchange of phenoxy groups by 4-methylphenoxy groups also succeeded, but the acid process needs a longer reaction time and a relatively high reaction temperature, 120 °C. The success of these experiments made it unnecessary to use the much more toxic phosgene as the starting material.

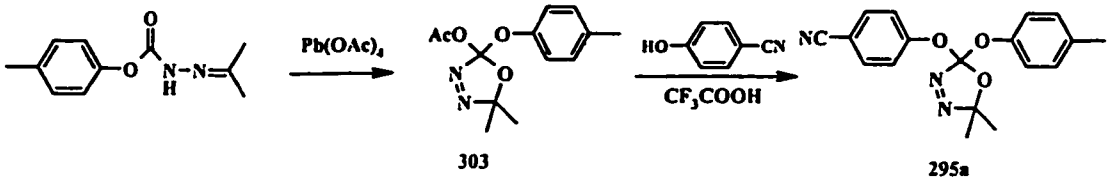
Hydrazine monohydrate was used to replace one aryloxy group of the carbonate to make the hydrazinocarboxylate **301**. The formation of **301** greatly decreases the nucleophilicity of the NH_2 end because of the strong electron-withdrawing ability of the carbonyl group. However, the NH_2 end is still sufficiently nucleophilic to attack another unit of carbonate. To minimize the chance of double exchange of both aryloxy groups of the carbonate, the ratio of carbonate to hydrazine was 1:1.2 and an ice bath was used from the beginning to increase the selectivity. Recrystallization gave the pure *p*-tolyl hydrazinocarboxylate **301** in 53% yield (Scheme 100).



Scheme 100

Acetone was used as both solvent and reagent to react with **301** to make **302**. To drive the reaction to product, anhydrous magnesium sulphate was used to absorb the water produced. Recrystallization gave the desired pure product **302** in 63% yield.

Standard oxidation of the hydrazone **302** by lead tetraacetate produced acetoxy *p*-methylphenoxy oxadiazoline **303**. Flash column chromatography was then used to isolate the acetoxy aryloxy oxadiazoline from the deep brown product mixture. Subsequent exchange of the acetoxy group by an aryloxy group in the presence of catalytic acid furnished di-aryloxy oxadiazolines (Scheme 101).



Scheme 101

Oxadiazolines **295b-e** were made by analogous approaches.

2.4.2 Rate Constant for Thermolysis of Diaryloxy Oxadiazolines

The formation of dioxycarbenes in the presence of oxygen results in an auto-oxidation product, the carbonate. Therefore, oxygen-free conditions are required for the

dioxycarbene reactions. The degassing procedure was achieved with a high vacuum pump after the reaction solution was solidified with liquid nitrogen. Then the reaction container was flame sealed.

The rates of decomposition of the oxadiazolines were monitored by ^{1}H NMR spectroscopy at 300 MHz. Samples typically containing 1.25×10^{-4} mol of an oxadiazoline and 7 mg of *p*-xylene, used as an internal standard for integration, in 0.5 mL of C_6D_6 were degassed and sealed into medium-walled NMR tubes. At appropriate time intervals during thermolysis, the tubes were removed from the thermolysis bath and quickly chilled to room temperature to record ^{1}H NMR spectra. Linear regression analyses were performed for the plots of $\ln(I/I_0)$ vs. time, where I and I_0 are the normalized integrals of a given resonance at time t and at time zero, respectively. The first-order decomposition rate constants were obtained from the slopes of the calculated best lines forced to pass through the origin.

Thermolysis of 2,2-diphenoxy oxadiazoline in benzene was found to occur with first order kinetics, with $k_{110\,°C} = 1.18 \times 10^{-4}\ s^{-1}$; about 10-fold faster than thermolysis of the 2,2-dimethoxy analogue.[59] Rate constants for four of the diaryloxy oxadiazolines are gathered in Table 2. The *p*-substituent of the aromatic ring has only a small effect on the rate constant for the fragmentation of a diaryloxy oxadiazolines, but there is a connection with the electron-withdrawing abilities of the substituents. Fragmentation of the *p*-cyano substituted oxadiazoline proceeded almost two times faster than the *p*-methoxy substituted oxadiazoline.

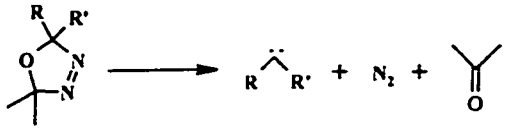
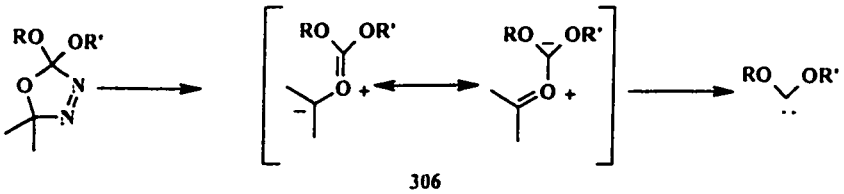


Table 2. Rate constants for thermolysis of diaryloxy oxadiazolines

R, R'	C_6H_5O, *p*-$MeOC_6H_4O$	C_6H_5O, *p*-MeC_6H_4O	C_6H_5O, C_6H_4O	C_6H_5O, *p*-CNC_6H_4O
Rate constant ($x10^5$ s)	9.3	11.7	11.8	17.9
Relative rate	0.8	1.0	1.0	1.5

The relationship between substituent and rate constant of oxadiazoline fragmentation provides more evidence to support the existence of a carbonyl ylide intermediate in the stepwise sequence of thermolysis of an oxadiazoline. Compared with an alkoxy group, the less electron-donating aryloxy group lowers the energy of the ylide intermediate so that a diaryloxy oxadiazoline fragments 10 times faster than a dialkoxy one. Similarly, the different aryloxy substituents, such as 4-cyano and 4-methoxy groups, lead to the different rate constants of fragmentation in thermolysis. The 4-cyano-bearing oxadiazoline fragments almost two times faster than the 4-methoxy-bearing oxadiazoline because the more electron-withdrawing 4-cyano group stabilizes the carbonyl ylide (**306**) better than the 4-methoxy bearing oxadiazoline (Scheme 102).

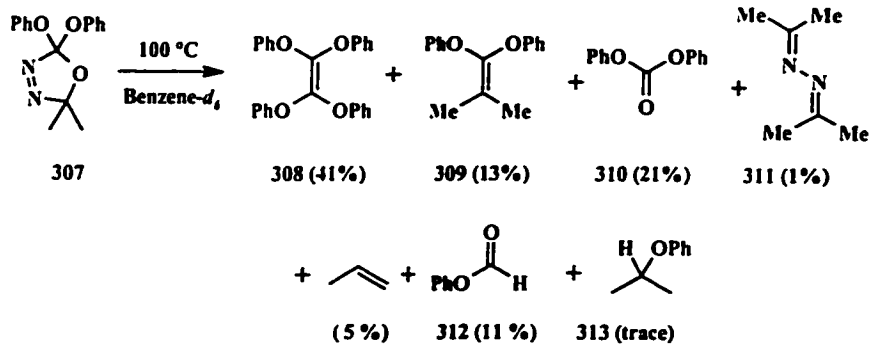


306

Scheme 102

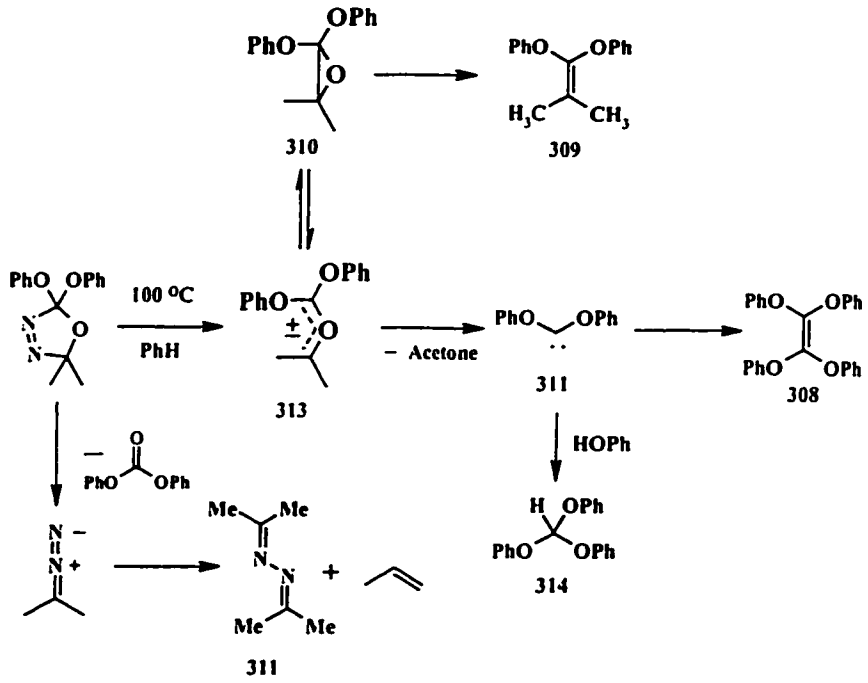
2.4.3 Thermolysis of Diaryloxyoxadiazoline in the absence of Trapping Reagent

To demonstrate that a carbene is formed upon thermolysis, **307** was heated in benzene alone or in benzene containing phenol. From the thermolysis of **307** in the absence of a trapping agent, the carbene dimer (tetraphenoxyethene, **308**) was isolated in 41% yield, together with 13% ketene acetal **309**, 21% diphenyl carbonate (**310**) and 11% phenyl formate (**312**), Scheme 103.



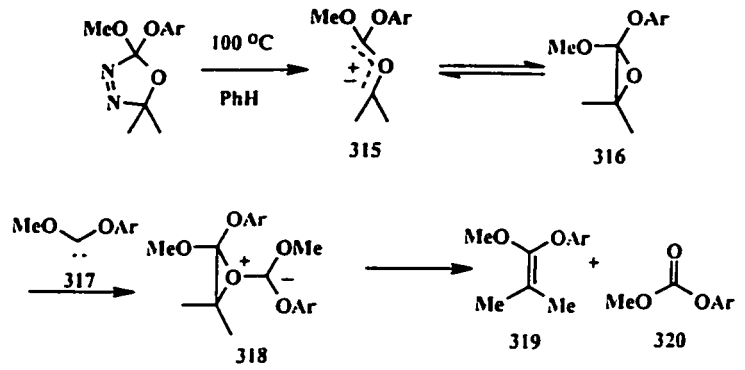
Scheme 103

All products from dioxy oxadiazoline **307**, except the ketene acetal **309** and the carbonate **310**, are similar to the products from thermolysis from dialkoxy oxadiazolines to dialkoxycarbenes (Scheme 104).



Scheme 104

Formation of ketene acetals from aryloxy methoxy oxadiazolines has also been proposed by Couture and Warkentin.[167] According to Couture's results, ketene acetal **319** is most likely derived from a carbonyl ylide intermediate (**315**). The ring closure gives the key intermediate, oxirane **316**. Then another unit of carbene attacks **316** to transfer the oxygen from the oxirane to the carbene to afford ketene acetal **319** and carbonate **320** (Scheme 105). The proposal was only partially supported by Couture's experimental results because no other ketene acetal, except methyl 4-nitrophenyl ketene acetal, could be isolated. Four other ketene acetals were implied from ^{1}H NMR chemical shifts (MeO and Me) of minor products. Those shifts were similar to those of the ketene acetal that could be isolated.

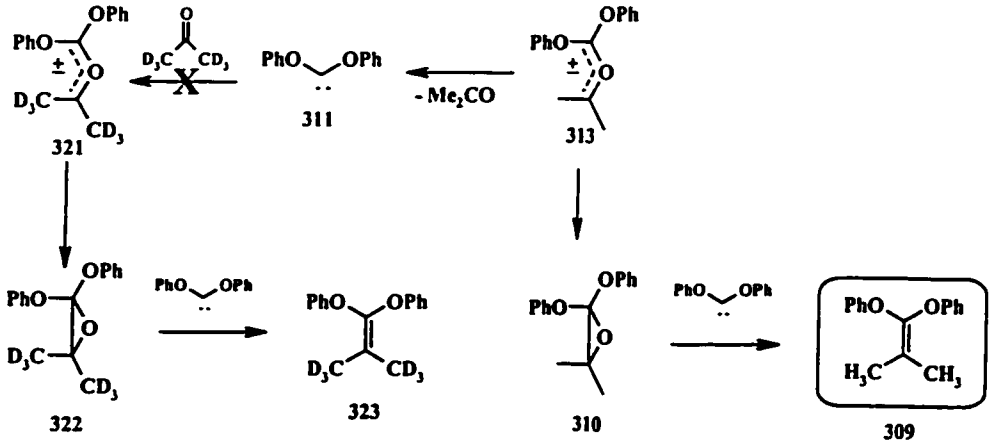


Scheme 105

Couture's proposal and the isolation of 4-nitrophenyl ketene acetal did suggest that less electron-donating groups, such as 4-nitrophenoxy, might result in more stable oxiranes and ketene acetals. This idea was supported in the present case by the production of the stable ketene acetal **309** (Scheme 104). The low yield of ketene acetal product could be the result of two factors: the small chance of the formation of ylide **318** by reaction of dioxycarbene with oxirane and the limited source of oxirane **316**.

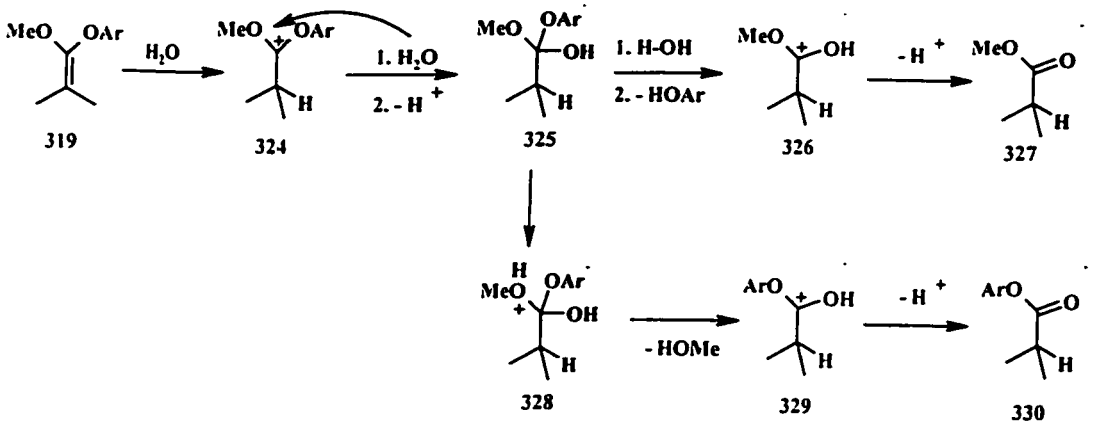
The chances of making ylides similar to **318**, from the addition of nucleophilic dioxycarbenes onto oxiranes, is really very low. Pezacki recently reported deoxygenation of oxiranes and desulfurization of thiiranes through an ylide by nucleophilic dialkoxycarbenes.[168] His experiments showed that less nucleophilic carbenes generally are more reactive toward the oxygen in oxiranes and that dialkoxycarbenes are too nucleophilic to attack the oxirane oxygen. Therefore, little or no oxygen transfer happened and conversion of dialkoxy oxadiazoline to ketene acetal during thermolysis was not observed. The decreased nucleophilicity of alkoxyaryloxycarbenes and diaryloxycarbenes increased the oxygen transfer rate in the analogous process to furnish isolable amounts of ketene acetals.

The rate constant for formation of oxirane **316** from carbonyl ylide **315** may also be low due to the high strain energy of **316**. In competition with closure to oxirane, **315** can also dissociate to dioxycarbene **317** and acetone. Deliberate addition of acetone-d_6 to the benzene solvent by Reid[169] proved that neither the ylide nor the oxirane arise from attack of the carbene on acetone, because no product with deuterium incorporation could be isolated. Thus, there is no equilibrium between the carbonyl ylide and the carbene and ketone (Scheme 106).



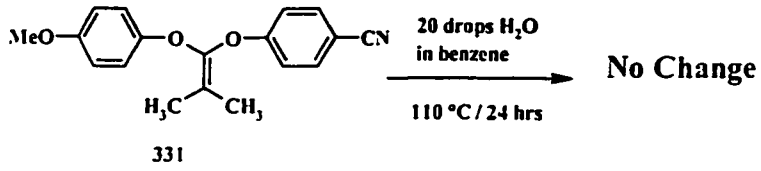
Scheme 106

The stabilities of the ketene acetals also determine the isolated yields of such compounds. In Couture's study, only methyl 4-nitrophenyl ketene acetal was successfully isolated. In the other similar acetals, the substituent on the aromatic ring has less electron-withdrawing ability than the nitro group, and the ketene acetals (**319**) formed did not survive during the chromatographic separation on silica gel. In general, the ketene acetals are easily hydrolyzed to phenol and ester (Scheme 107).



Scheme 107

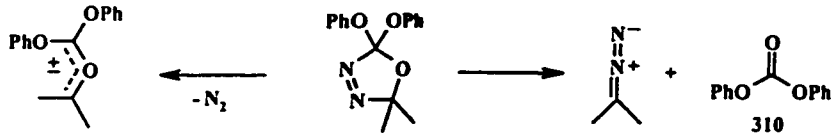
It was surprising to find that the replacement of both alkoxy groups of dioxycarbenes by aryloxy groups did change the stability of the ketene acetal formed. For each thermolysis reaction of diaryloxy oxadiazolines, more than 10 % of the appropriate ketene acetal was isolated. The stabilities of all these ketene acetals were sufficient to permit their isolation by chromatography. A specific reaction was set up to measure the stability of the diaryl ketene acetal. About 20 equivalents of water were deliberately added into the benzene solution with pure *p*-cyanophenyl-*p*-methoxyphenyl ketene acetal (**331**). Then the reaction solution was sealed into a NMR test tube and heated in an oil bath for 24 hours at 110 °C. A comparison of ^{1}H NMR spectra before and after the heating showed that there was almost no change of the intensity of the NMR signals of the ketene acetal. The replacement of alkoxy groups by aryloxy groups is the key reason for this interesting result. The lower electron-donating ability of aryloxy groups makes the diaryl ketene acetals less nucleophilic toward electrophiles, such as water, and therefore changes ketene acetals from moisture sensitive to relatively water stable compounds (Scheme 108, Appendix 3).



331

Scheme 108

The formation of the diaryl carbonate indicates that the uncommon fragmentation route of dioxy oxadiazolines has become more important. Dialkoxy oxadiazolines extruded only nitrogen to afford carbonyl ylides. Fragmentation of diaryloxy oxadiazolines, such as diphenoxy oxadiazoline in Scheme 109, has an additional cycloreversion route to diazopropane and carbonate besides the route to the carbonyl ylide.

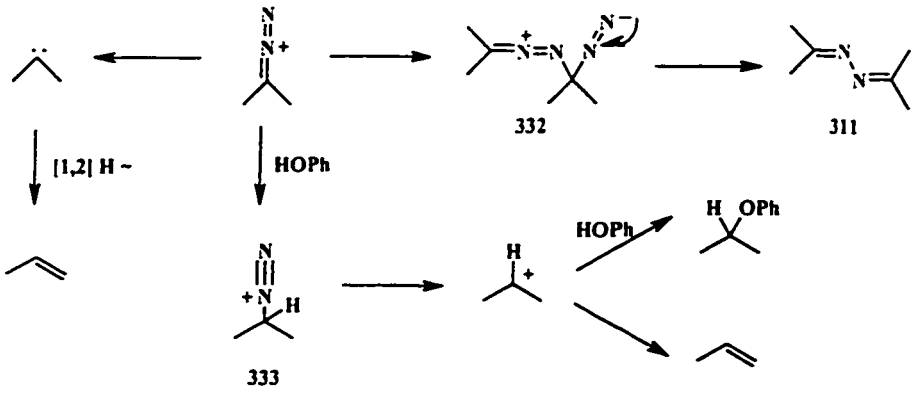


310

Scheme 109

The competitive cycloreversion to diazopropane is strongly supported by both the formation of diaryl carbonate and acetone azine (312), which can only be produced by the reaction of two units of diazopropane. The process to diazopropane must be a relatively minor one because of the low total yield of products derived from diazopropane. In the presence of traces of phenol (presumably derived from reaction of an intermediate or product with adventitious water) diazopropane is expected to be protonated to afford 2-propyl cation/phenoxide ion pairs, which could lead to both propene and isopropyl phenyl ether. The possibility that most of the propene arises from dimethylcarbene, by fragmentation of the carbonyl ylide intermediate to dimethylcarbene and diphenyl

carbonate in competition with its fragmentation to diphenoxycarbene and acetone, can be excluded. Although dimethylcarbene would certainly afford propene, the rate constant for 1,2 H-migration is very large ($\geq 6 \times 10^7\ s^{-1}$ at room temperature)[43] and detection of isopropyl phenyl ether from carbene insertion into phenol at low concentrations of adventitious phenol (from water) cannot be expected.

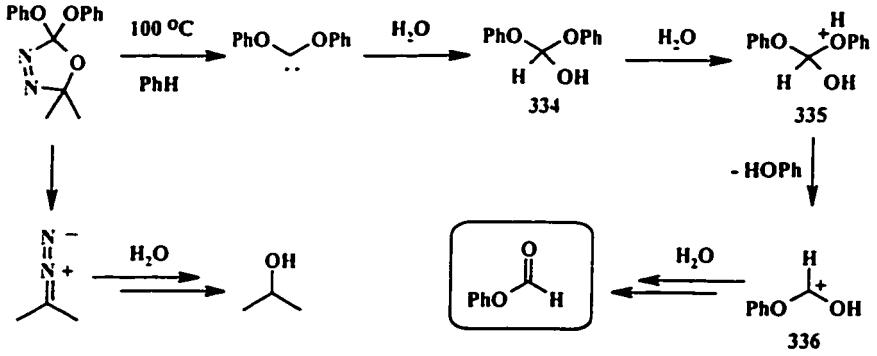


Scheme 110

The autoxidation of diaryloxycarbene to carbonate can be ruled out because the solution was degassed before heating. The two sources of carbonate from thermolysis of oxadiazoline can be attributed to cycloreversion of **307** to **310** directly and the oxygen transfer from oxirane to form carbonate indirectly. This proposal agrees with the higher yield of carbonate than ketene acetal, assuming that the separation loss would be similar for both, Scheme 103.

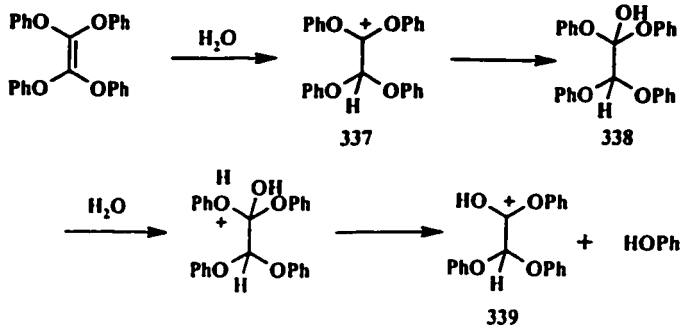
The 11 % phenyl formate mainly comes from the capture of diphenoxycarbene by traces of water. Deliberate addition of water prior to thermolysis of **307** in benzene did lead to phenyl formate in relatively higher yield. Although the water also trapped the diazopropane, the product formed, isopropyl alcohol, was lost during the

chromatographic separation because it could not be detected by the UV lamp (Scheme 111).



Scheme 111

Water could also be responsible for the loss of some diphenoxycarbene dimer, although the water content should be very low after its trapping of diphenoxycarbene to give phenyl formate. A trace amount of phenol, which could be attributed to hydrolysis of carbene dimer, Scheme 112, was found. Phenol from the hydrolysis then captured some diazopropane to generate the trace of isopropyl phenyl ether by its reaction with 2-diazopropane (Scheme 110).

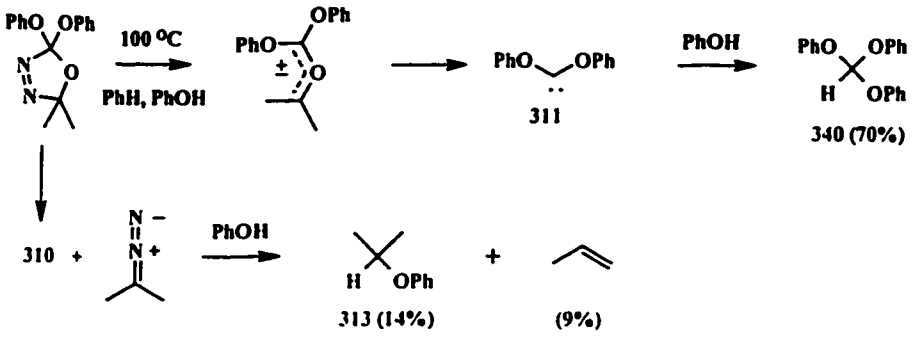


Scheme 112

2.4.4 Thermolysis of Diphenoxy Oxadiazoline in the presence of Phenol

Since phenols have been used to trap aryloxycarbenes successfully, it is reasonable to continue using them to prove the existence of diaryloxycarbenes. In practice, only one phenol trapping reaction was done. Other diaryloxycarbenes are thought to have analogous behavior when they are produced from the corresponding oxadiazolines.

Thermolysis of 2,2-diphenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in benzene with added phenol led to the desired phenyl orthoformate (**340**) in 70% yield (Scheme 113). Diphenyl carbonate was a by-product (15% yield), as well as isopropyl phenyl ether (**313**) and propene, but not acetone azine. A likely source of **313** is diazopropane, which is expected to react efficiently with excess phenol, to prevent the formation of acetone azine and to afford **313**. The GC-characterized propene presumably comes from the diazopropane via protonation followed by loss of nitrogen (Schemes 110 and 113).



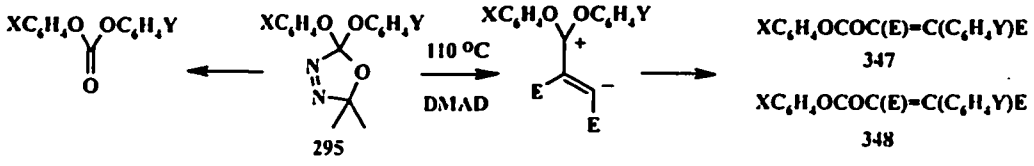
Scheme 113

2.4.5 Reactions of Diaryloxycarbenes with DMAD

With the results from thermolysis of diaryloxy oxadiazoline in the absence of carbene trap and in the presence of phenol, carbene intermediacy is strongly supported. Next a series of thermolysis reactions were carried out to explore the previously discovered aromatic substitution.

Thermolysis of oxadiazolines **295** as benzene solutions containing one equivalent of DMAD, at 110 °C in sealed tubes, gave one or both of the isomeric esters (**347, 348**) in yields (or composite yields) between 25 and 40 % and a diaryl carbonate in about 30 % yield, Scheme 114. The ester(s) were separated from other products by column chromatography and they were separated from each other, in reactions that gave both, by capillary gas chromatography. Assignment of structure followed from the NMR spectra of the product and mainly from the electron impact MS and chemical ionization (ammonia) MS.

Scheme 114 shows five diaryloxy oxadiazolines (**295**) that were thermolyzed in the presence of DMAD, as well as the two possible triester products from competitive aryl group migrations.



a: X=*p*-OMe, Y=*p*-CN; b: X=*p*-Me, Y=*p*-CN; c: X=H, Y=*p*-CN; d: X=H, Y=*p*-OMe; e: X=H, Y=*o*-OMe; E=CO_2Me

Scheme 114

In EI mass spectra, aryl esters afford major signals (base peaks) from loss of the fragment XC_6H_4O in case of $XC_6H_4OCO(E)C=C(C_6H_4Y)E$, and from loss of YC_6H_4O in case of $C_6H_4YOCO(E)C=C(XC_6H_4)E$. It was, therefore, easy to assign the structures of isomeric esters that could not be identified by NMR and IR spectra.

For example, thermolysis of 4-cyanophenoxy-4-methoxyphenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the presence of DMAD gives one aromatic substitution product in 37 % yield. Its ^1H NMR spectrum showed three methoxy singlet peaks and some multiplet peaks in the aromatic region. Its ^{13}C NMR spectrum gave the number of carbons in the compound. But with these alone, it is impossible to tell which aromatic group has migrated. The nOe NMR was predicted to be not very promising because no two substituents are in close enough proximity to give a good nuclear Overhauser effect (nOe).

Helpful information came from the following EI and CI mass spectra. The EI mass spectrum gave a small molecular ion, m/z 395, and a small peak m/z (M-31) for the fragment formed by losing the methoxy group from the compound. The base peak of the spectrum was m/z 272, which fits for $(M-(OC_6H_4OMe))$.

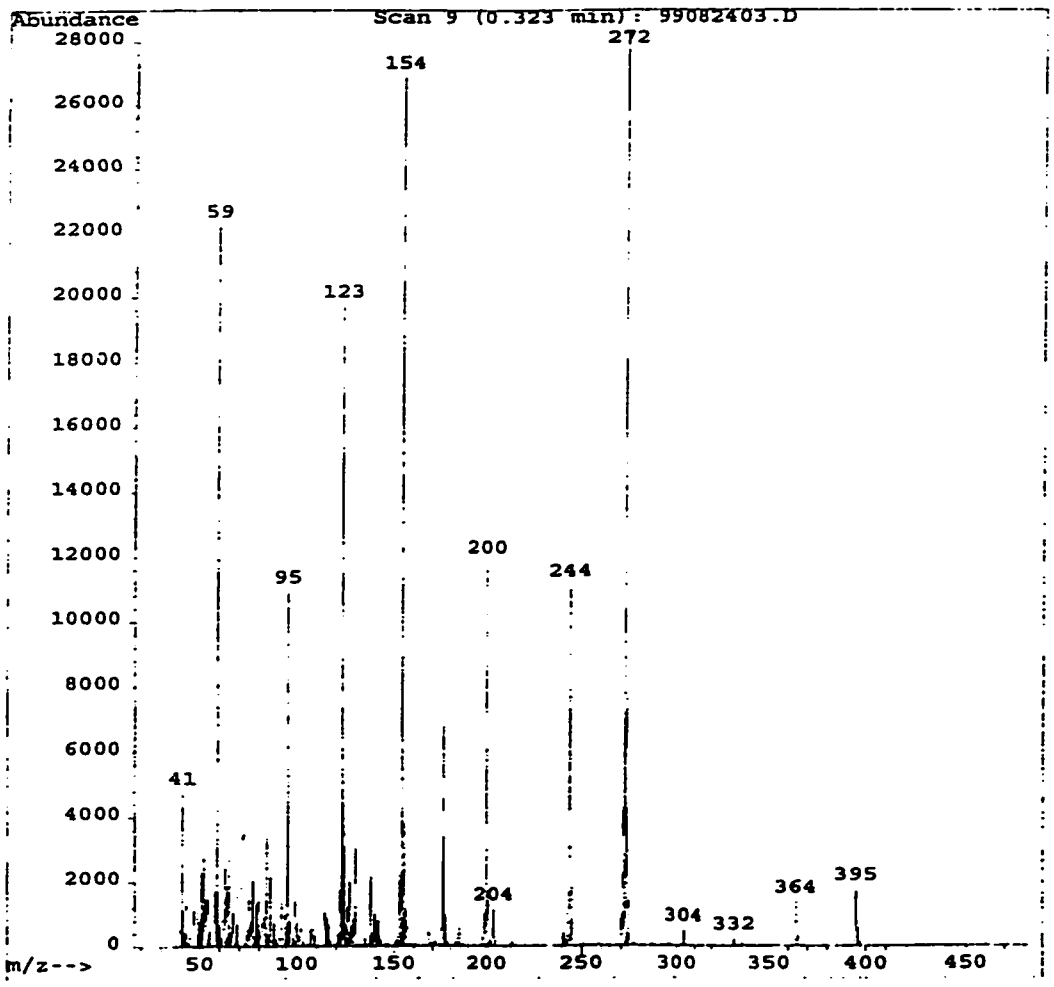
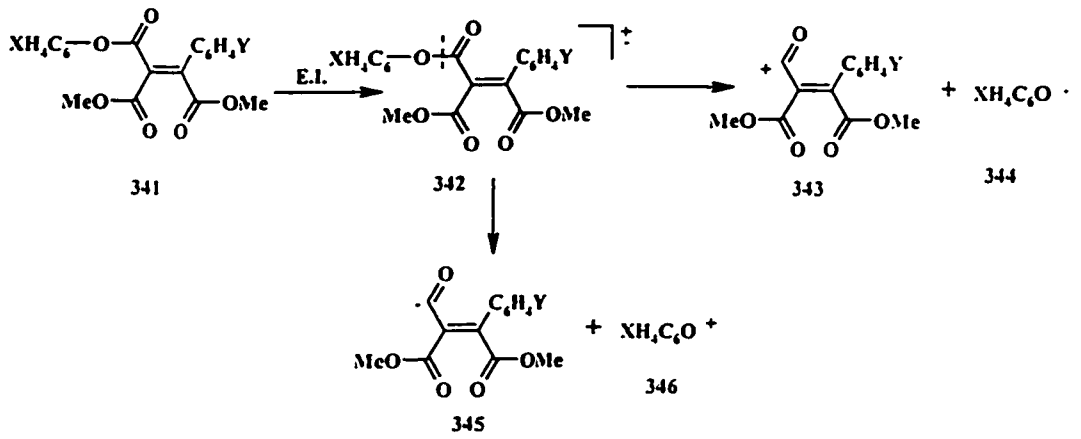


Fig. 3. EI mass spectrum of 341

It is known that aryloxy groups of esters are lost more easily than methoxy groups. Thus, although there are two methyl esters and only one aryl ester, the base peak is the one from the fragmentation of the latter (Scheme 115).



Scheme 115

For the aromatic substitution reaction, two possibilities exist: the 4-methoxyphenyl group migrates or the 4-cyanophenyl group migrates. If the 4-cyanophenyl migrates, the mass spectrum should show m/z (M-OC_6H_4OMe), which is m/z 272, and m/z (M-OC_6H_4OMe), which is m/z 123. On the other hand, if the 4-methoxyphenyl migrates, one should see m/z 277 and m/z 118 for M-OC_6H_4CN and OC_6H_4CN. The EI mass spectrum shows m/z 272 as a base peak and m/z 123 as a 70 % intense peak. No peak with either m/z 277 or m/z 118 appears at all. Thus, 4-cyanophenyl was concluded to be the only migrating group.

Confirmation of the above assignment came from the single crystal X-ray diffraction experiment. A good single crystal was grown slowly from 1:1 benzene-hexane solvent and X-ray diffraction showed that the structure of the aromatic substitution product was the ester that came from the migration of 4-cyanophenyl from oxygen to carbon (Fig. 4). The X-ray structure also establishes the *cis* relationship between the aryl and aryl ester substituents.

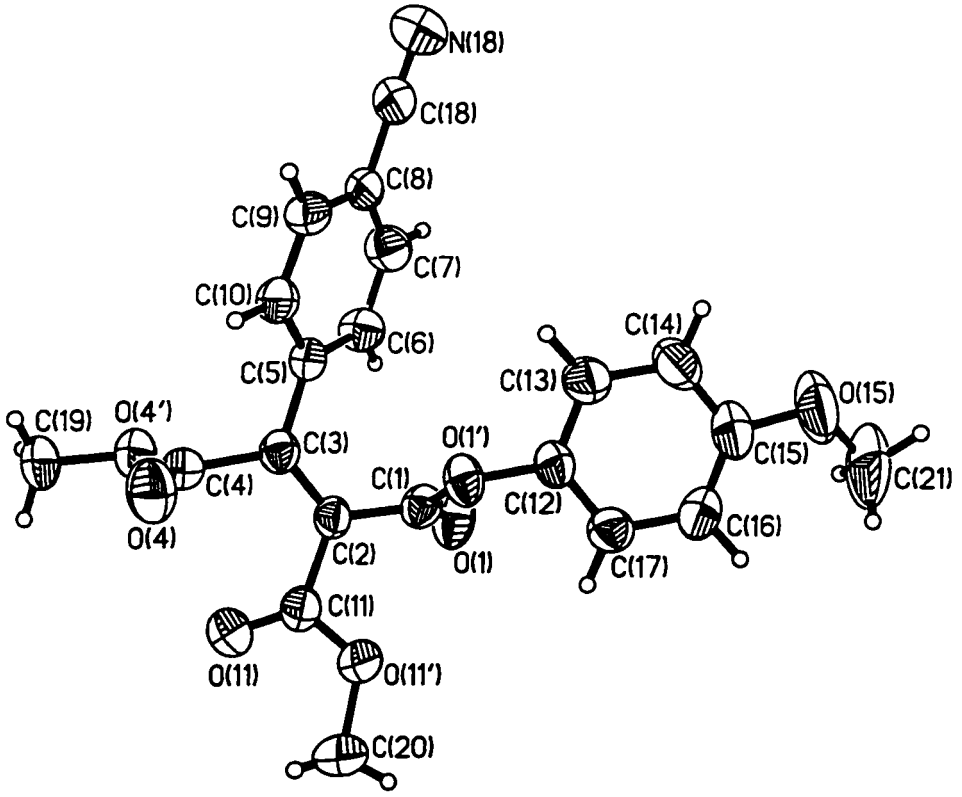


Fig. 4. 50% thermal ellipsoid probability plot for 341, showing the atomic labeling (Appendix 2).

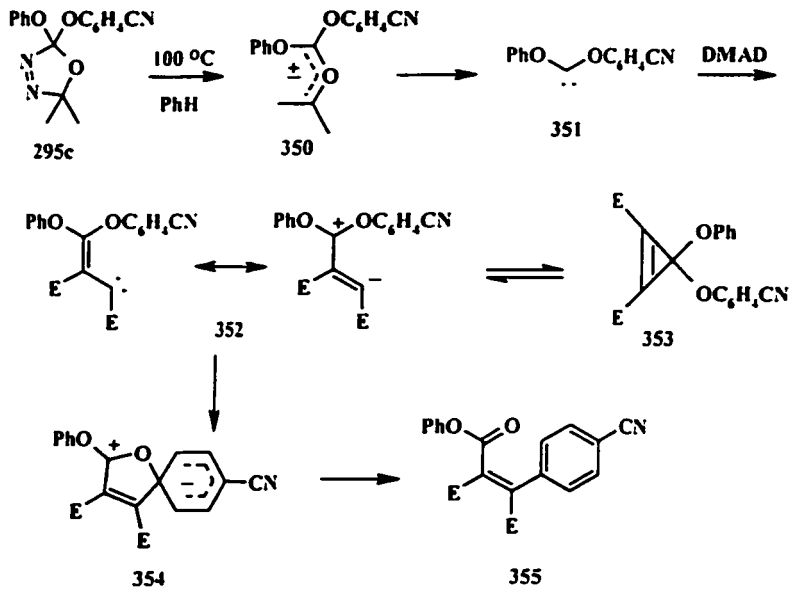
Using similar EI and CI mass spectrometric analysis, the effects of substituents on the ease of *ipso* substitution were shown to follow the order *p*-CN >> *o*-MeO > H > Me > *p*-MeO, Table 3. It is clear that an electron-withdrawing group in the *p*-position increases the migratory aptitude of an aryl group. Unfortunately, all substrates, except the *ortho*-methoxy case, gave only one of the two possible esters and it was not possible to construct a Hammett plot. This means that the sensitivity of the rearrangements to substituents cannot be small; moreover its sense is unmistakable.

Table 3. Yields of **347** and **348** from oxadiazolines **295** (for Scheme 114)

	347 (%)	**348** (%)	**348:347**	**349** (%)
a.	36.7	n.d.*	Small	28.6
b.	28.0	n.d.*	Small	26.0
c.	36.7	n.d.*	Small	30.4
d.	n.d.*	38.4	Large	32.3
e.	11.0	25.0	0.44	35.0

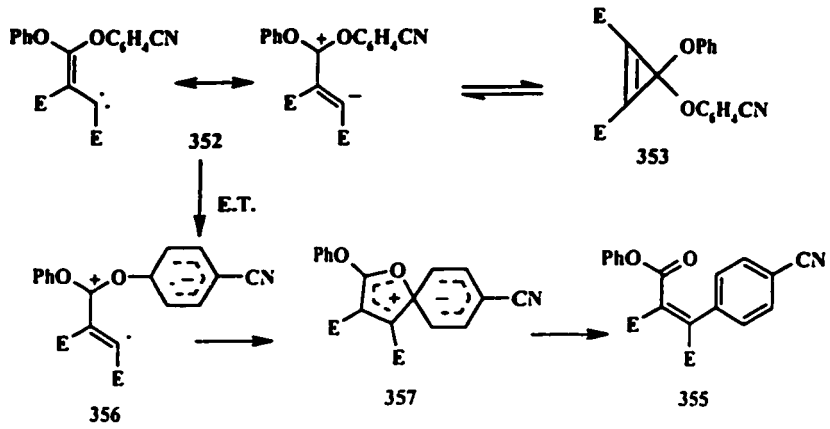
* Not detected. We did not experience any difficulties with detection of the isomeric esters by ^{1}H NMR spectroscopy, and therefore have no doubt that the yield of the detected isomer was at least 20-fold greater than that of the isomer that was not detected.

With the results from the above experiments, a nucleophilic aromatic substitution mechanism to account for the migratory aptitudes is strongly suggested. The multi-step mechanism is illustrated in Scheme 116, for the case X=H, Y=CN. The nucleophilic carbene attacks DMAD to form the dioxyvinylcarbene, which equilibrates with a cyclopropene through reversible ring-opening/ring-closure. The vinylcarbene **352** then acts like a nucleophile to do an intramolecular aromatic substitution, which is similar to a S_NAr process, to form a spiro dipolar intermediate **354**. Ring opening of the five-membered ring furnishes the final triester **355** with the driving force of rearomatization and formation of a conjugated system, Scheme 116.



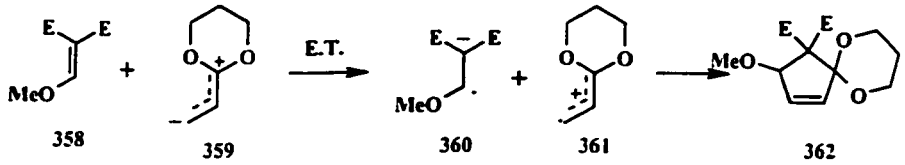
Scheme 116

Besides the above mechanism, a more complex stepwise process, involving electron transfer (E.T.) *before* ring closure but leading to the observed result, is also possible, Scheme 117.



Scheme 117

Some intermolecular chemistry of **358** is thought to involve electron transfer from a π-delocalized vinylcarbene intermediate **359** and subsequent coupling of a radical cation (**361**)/ radical anion (**360**) pair, Scheme 118.[123]



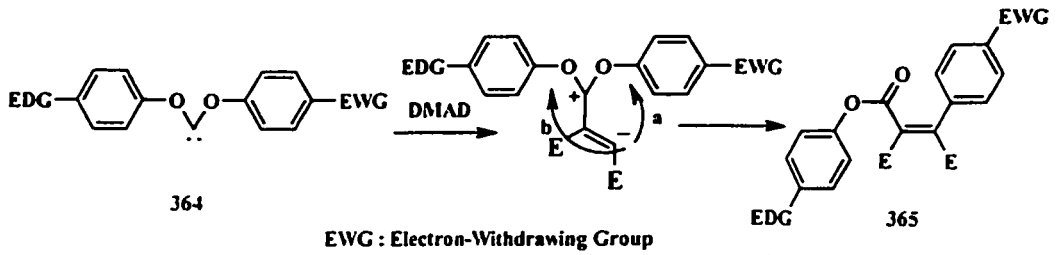
358 359 360 361 362

Scheme 118

This non-chain radical mechanism, which is not similar to the $S_{RN}1$ radical-chain route, is less likely to be the major reaction process. In a standard non-chain radical mechanism ($S_{RN}2$),[171] attack of the radical cation at the *ipso* position was found to be slower than at ring positions carrying hydrogen. The halo substituents, the one that would be replaced, were observed to exert opposing electronic and steric effects on rate constants for *ipso* attack.[172] The fact that there was no product from the substitution on a position carrying hydrogen partially ruled out the radical route.

2.5 The *ortho* Substituent Effects on the *ipso*-Nucleophilic Aromatic Substitution

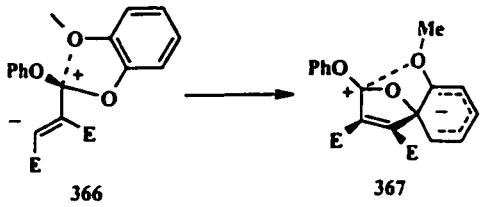
With only *para* substituents on the aromatic ring, steric effects are absent and the nucleophilic aromatic substitution mechanism was supported because an electron-withdrawing group in the *para* position favoured aryl group transfer whereas an electron donor group disfavoured transfer (Scheme 119).



Scheme 119

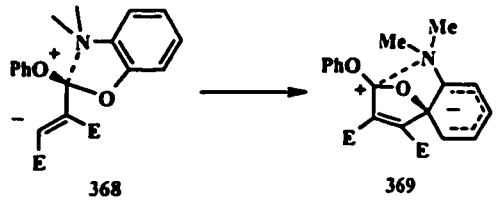
For example, *p*-cyanophenyl migrated exclusively when competing with phenyl and phenyl migrated exclusively when in competition with *p*-methoxyphenyl. A surprising observation was that *o*-methoxyphenyl had a migratory aptitude comparable to that of phenyl, suggesting that the *o*-methoxy substituent exerts opposing effects, an electronic effect presumably analogous to that of the *p*-methoxy substituent, disfavouring substitution, and a second effect favouring it.

A special interaction must be invoked for the *o*-methoxy substituent, which was next to *p*-cyano in promoting migration whereas the *p*-methoxy group was not effective. Given that the likely mechanisms involve a dipolar intermediate **366** (a zwitterion or a pair of radical ion sites) it is logical to propose that the *o*-methoxy group exerts its effect through space, rather than through bonds (Scheme 120). Such an involvement would differentiate strongly between the *o*- and *p*-methoxy groups, which presumably have comparable conjugative effects.



Scheme 120

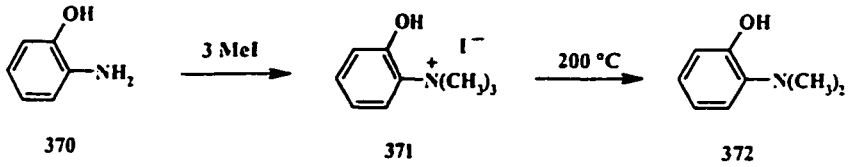
Besides the *ortho*-methoxyphenoxy group, the *ortho*-dimethylaminophenoxy group, with an electron lone pair on the nitrogen, was also planned as one substituent of a diaryloxycarbene (**368**). Comparing with the unsubstituted phenoxy group, the dimethyaminophenoxy has a strongly electron donating amino group, which would destabilize the intermediate in nucleophilic aromatic substitution. However, it too could act through space to help the aromatic functional group to migrate competitively from oxygen to carbon (Scheme 121).



Scheme 121

o-Dimethylaminophenol (**372**) is not a commercially available compound. Due to the strong electron donating ability of the *o*-dimethylamino group, the compound is very easily oxidized by oxygen to a quinone derivative at room temperature. The preparation of it was done by the reaction of *o*-hydroxyaniline with three equivalents of methyl iodide. The replacement of hydrogen by the methyl group makes the amino group more nucleophilic so that the reaction proceeds quickly to give an ammonium iodide salt (**371**). A subsequent high temperature (200 °C) distillation, under N_2 flow, broke one nitrogen

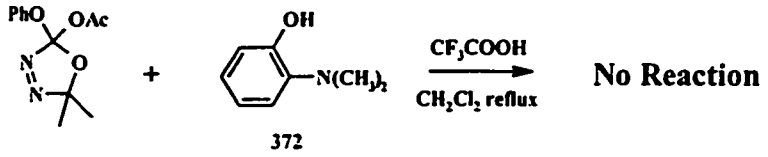
carbon bond to form methyl iodide and the desired *o*-dimethylaminophenol, which was distilled into a collecting vial.



370 371 372

Scheme 122

The so generated *o*-dimethylaminophenol, identified as a pure compound, was then used to attempt an exchange reaction with acetoxyphenoxy oxadiazoline in the presence of trifluoroacetic acid. The amount of trifluoroacetic acid was gradually increased to two equivalents with respect to the phenol. One equivalent of acid was consumed to protonate the dimethylamino group, while the rest of the acid was assumed to protonate the acetoxy group and thus to promote the exchange reaction. Unfortunately, after two weeks of refluxing, the reaction solution had not changed. By that time, some of the oxadiazoline had opened to an acyclic by-product. The strong steric effect of the *ortho*-dimethylamino group presumably hindered the exchange reaction (Scheme 123).



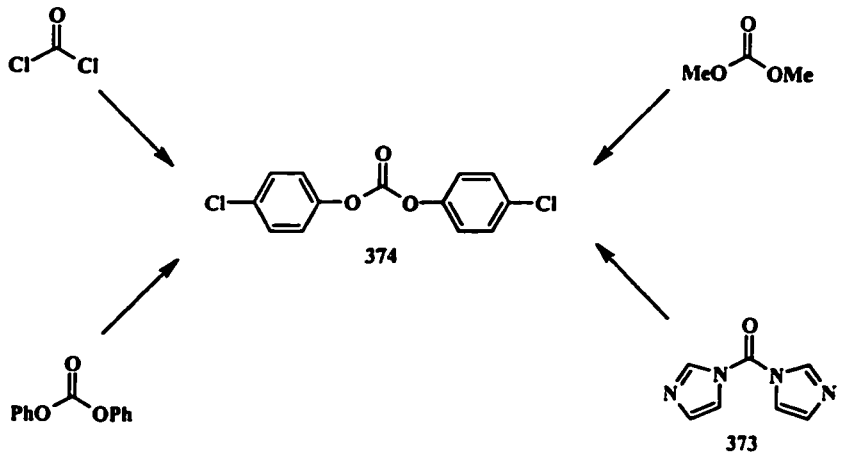
372

Scheme 123

Failure to make 2-*o*-dimethylaminophenoxy-2-phenoxy oxadiazoline made it impossible to compare the migration ability of the *ortho*-dimethylaminophenyl group with that of the unsubstituted phenyl group. The further study of this *ortho* substituent effect on the aromatic substitution therefore changed to the comparative study of the migration abilities of the 4-chlorophenyl and 2-bromophenyl or 2-iodophenyl groups.

2.5.1 2-Acetoxy-2-(*p*-chlorophenoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline

2-*p*-Chlorophenoxy-2-*o*-bromophenoxyoxadiazoline and 2-*p*-chlorophenoxy-2-*o*-iodophenoxyoxadiazoline were prepared starting with bis-4-chlorophenyl carbonate. With the commercially available starting materials, four methods could be used to prepare the necessary bis-4-chlorophenyl carbonate (**374**). They are: 1. reaction of phosgene with two equivalents of 4-chlorophenol; 2. transesterification of dimethyl carbonate with 4-chlorophenol; 3. transesterification of diphenyl carbonate with 4-chlorophenol; and 4. double esterification of 1,1'-carbonyl diimidazole by 4-chlorophenol.

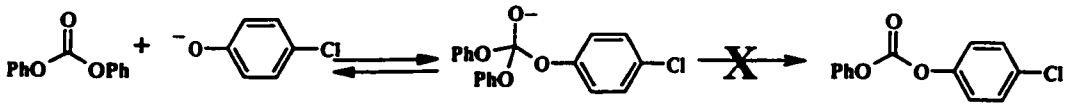


Scheme 124

Due to the well-known toxicity of phosgene, the phosgene route was ruled out, although it would be more feasible with the use of a (commercial) solution of 0.2 M phosgene in toluene instead of gaseous phosgene. The transesterification of dimethyl carbonate to bis-4-chlorophenoxy carbonate, with tri-*n*-butyltin oxide as a catalyst, was carried out once. But the conversion from dimethyl carbonate to the desired carbonate and the yield of the desired carbonate product were very low. The by-product, methanol, made

an azeotrope with the dimethyl carbonate.

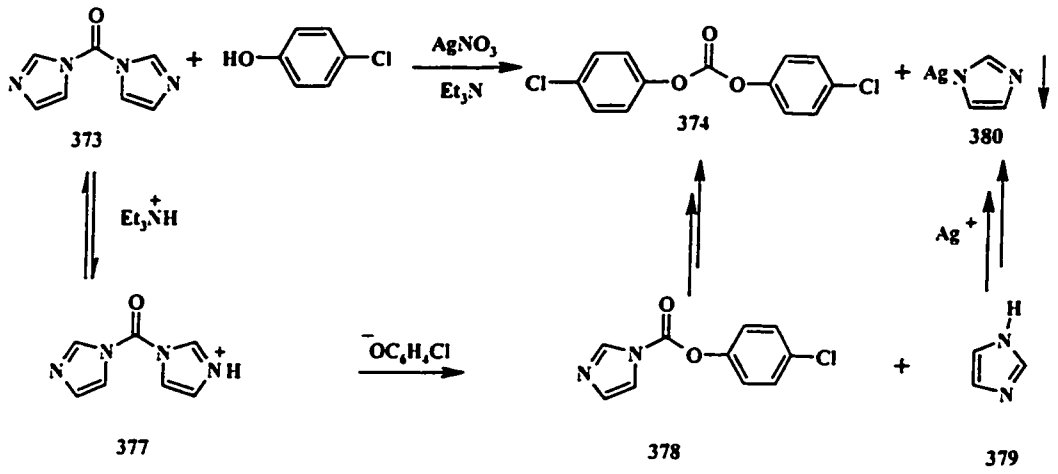
Preparation of bis-4-chlorophenyl carbonate from diphenyl carbonate was also ruled out because the phenoxy anion is a worse leaving group compared with a 4-chlorophenoxy anion. After formation of tetrahedral intermediate **375** by the addition of a 4-chlorophenoxy anion to the carbonyl group of diphenyl carbonate, the phenoxy group would not compete with a 4-chlorophenoxy anion as a leaving group. For that reason, the replacement of both phenoxy groups in diphenyl carbonate with 4-chlorophenoxy groups will not work very well, even if the concentration of 4-chlorophenol is set to ten times than that of the carbonate (Scheme 125).



375 376

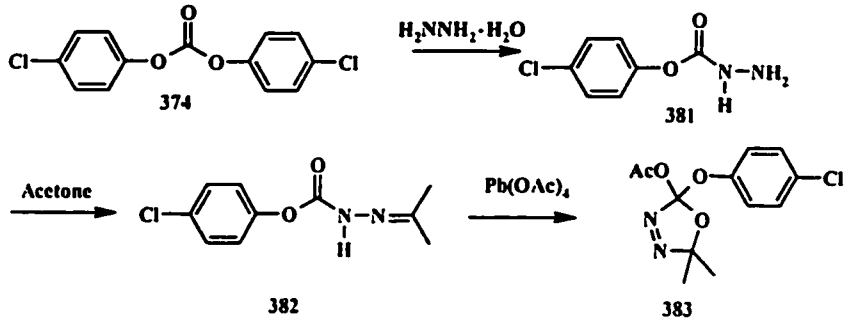
Scheme 125

The successful method was found to be the reaction of 1,1'-carbonyl diimidazole with 4-chlorophenoxy anion, which came from the deprotonation of 4-chlorophenol by triethylamine and protonation of **373** by the ammonium ion, in the presence of two equivalents of silver nitrate. The silver ion reacted with the imidazole **379** to form a light yellow solid (**380**), which had very low solubility in the reaction solvent. The formation of this solid drives the reaction to the product **374**. This successful formation of the pure bis-4-chlorophenyl carbonate (**374**) in 56% yield eliminates the use of the highly toxic phosgene reagent (Scheme 126).



Scheme 126

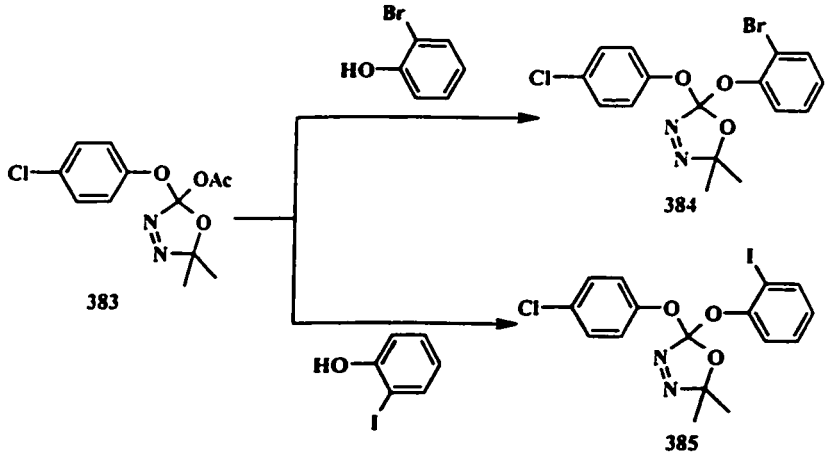
Carbonate **374** was then converted into acetoxy aryloxy oxadiazoline **383** by means of hydrazinocarboxylate (**381**), the hydrazone of acetone (**382**), and standard oxidation to 2-acetoxy-2-aryloxy oxadiazoline (Scheme 127). The formation of **381** was accompanied by formation of one equivalent of 4-chlorophenol. The latter product had to be removed before the oxidation step because it reacts with LTA. The best way to get rid of it was found to be the use of a 1:1 benzene-hexane mixture to wash the crude hydrazinocarboxylate thoroughly, because the phenol is quite soluble in that medium and the hydrazinocarboxylate does not dissolve at all.



Scheme 127

The subsequent exchange reactions to form the desired diaryloxy oxadiazolines

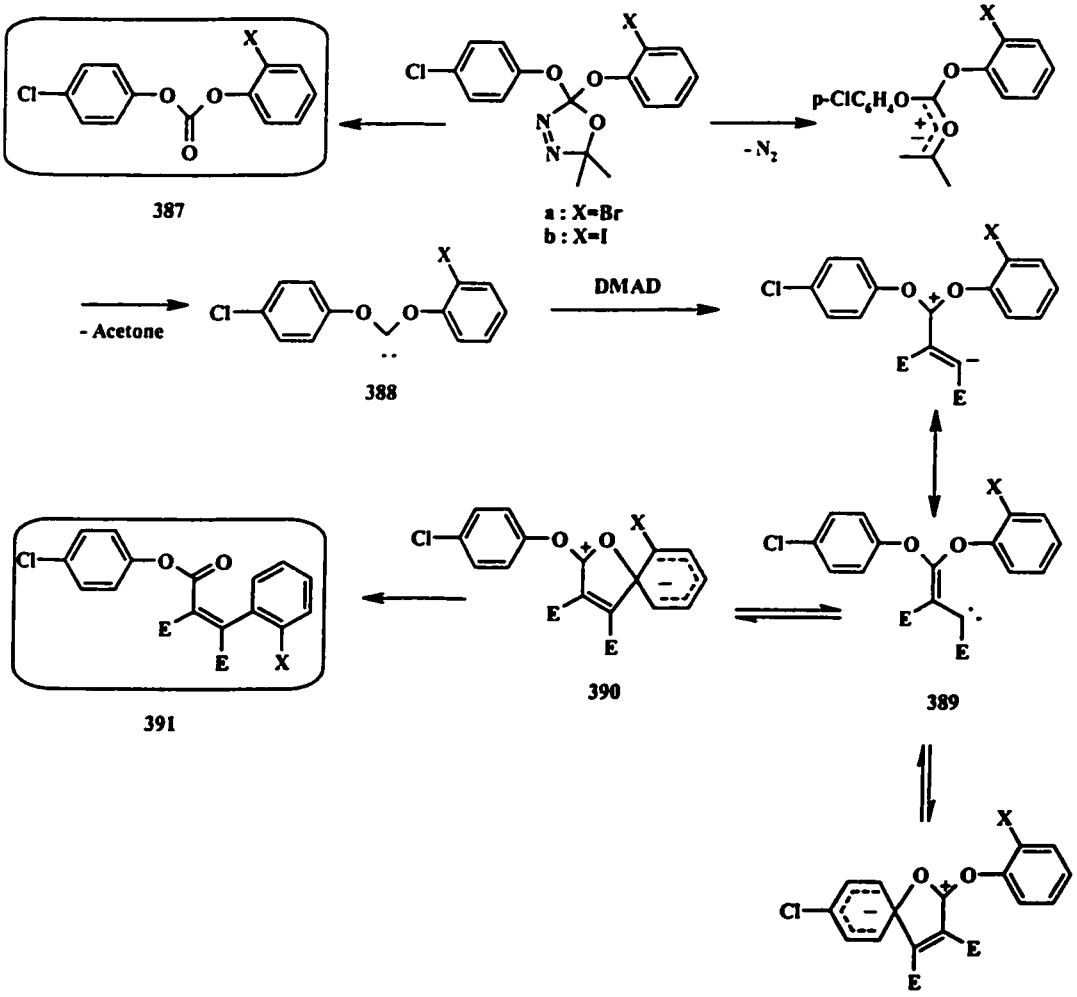
(**384** and **385**) are similar to the preparations of previous diaryloxy oxadiazolines, except that the reactions take a much longer time because of the steric hindrance of the *ortho*-substituents (Scheme 128).



Scheme 128

2.5.2 Thermolysis of 2-(*p*-Chlorophenoxy)-2-(*o*-halophenoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the presence of DMAD

Thermolysis of **384** and **385** in benzene generated carbonates **387a,b** and diaryloxycarbenes **388a,b** by competing 1,3-dipolar cycloreversions (Scheme 129). The diaryloxycarbenes, which arise from fragmentation of carbonyl ylides, reacted with dimethyl acetylenedicarboxylate (DMAD) to form (potentially) isomeric triesters through migration of an aryl group from oxygen to carbon. In both cases, **391** was the only triester formed.

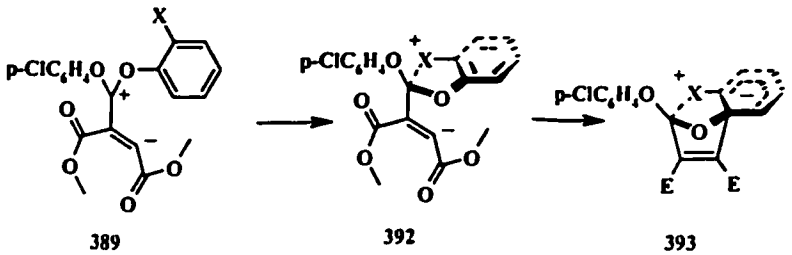


Scheme 129

Attack by the carbenes **388** leads to dipolar intermediates **389**, either by attack at one *sp*-carbon of DMAD or by concerted cycloaddition to afford the appropriate cyclopropenes (not shown) that open to **389**. Assuming that the Curtin-Hammett principle applies, the group that is transferred by *ipso* aromatic substitution is selected on the basis of the relative stabilities of the transition states, not the ground states. Given that assumption, it is clear that *o*-iodophenyl is transferred more rapidly than *p*-chlorophenyl and that the migratory aptitude of *o*-bromophenyl is also greater than that of *p*-

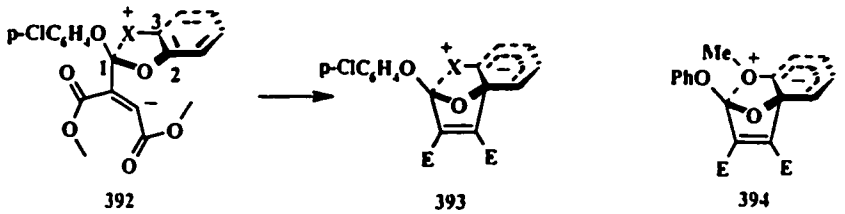
chlorophenyl. From previous work, we know that the cyano group in the *para* position is a strong facilitator of migration whereas a *para* methoxy group stops migration, both relative to H. Although it was not possible to construct a Hammett plot and to determine the value of ρ, a minimum value can be estimated as follows. If as much as 2 % of an undetected isomer could have been missed due to the separation, then the migration rate ratios were *p*-CNC_6H_4/ C_6H_5 > 37/2 and *p*-$MeOC_6H_4$/ C_6H_5< 2/38. The ratio $k_{p\text{-}CN}/k_H$=18.5 and log ($k_{p\text{-}CN}/k_H$)= 1.27 while $k_{p\text{-}OMe}/k_H$= 1/19 and log ($k_{p\text{-}OMe}/k_H$)= -1.28. With $\sigma_{p\text{-}CN}$= 0.63 and $\sigma_{p\text{-}OMe}$= -0.27, the predicted value of ρ is at least +3 and, with $\sigma_{p\text{-}Cl}$= 0.23, the *para* chlorophenyl group should migrate at least five times as fast as phenyl. Since *o*-iodophenyl and *o*-bromophenyl migrated exclusively over *p*-chlorophenyl, it is clear that both the *ortho* iodo and *ortho* bromo substituents enhance migration relative to H. The fact that *o*-iodo is strongly rate enhancing relative to *p*-chloro cannot be a consequence of their relative electron-withdrawing abilities, which are very similar: $\sigma_{p\text{-}I}$= 0.28; $\sigma_{p\text{-}Cl}$= 0.23.

The most likely explanation for the observed *ortho* effects (*o*-MeO>> *p*-MeO; *o*-I; *o*-Br >> *p*-Cl) is that such an *ortho* group donates electron density toward the developing positive site stabilizing the transition state for the formation of the intermediate (393) for nucleophilic aromatic *ipso* substitution, illustrated in Scheme 130.



Scheme 130

Stabilization of the positive part of the dipolar intermediate (**392**) by the donation of electron density to the empty *p* orbital of the dipole from the electron-rich *ortho* group through space tilts the *ortho* substituted aromatic ring toward orthogonality relative to the plane of the dipolar intermediate. This orthogonal configuration makes the anion addition to the *ipso* carbon much easier compared to addition at the rotating 4-chlorophenoxy group on the other side. To accomplish this kind of stabilization, part of the electron density between X and C_3 delocalizes to the region between X and C_1 (Scheme 131a). This "delocalization" greatly decreases the electron donating effect of X to the aromatic ring, especially for the *ortho*-methoxy cases (Scheme 131b). Although no experimental data have shown the change of the resonance effect of a methoxy group upon protonation, the analogous formation of an ammonium ion from an amine changes the σ_p value from –0.63 to 0.82, converting the pure electron donating amine into a strongly electron-withdrawing group. Analogously, the characteristics of the methoxy group would have a similar change if this kind of coordination really exists.



Scheme 131

Besides the coordination mentioned above, the *ortho*-methoxy group also provides one more possible effect on the reaction, a steric effect. The steric effect, which comes from the bulk of the *ortho*-methoxy group, will make the substituted aromatic ring

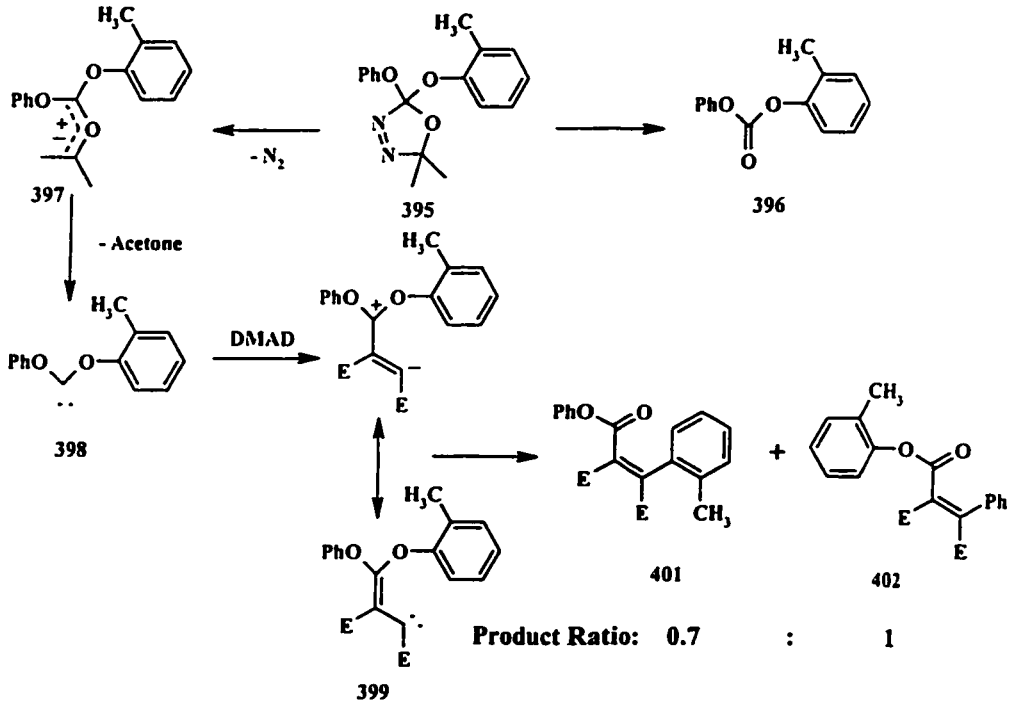
sit at an angle relative to the dipolar plane. This also gives the anion a better chance to attack the *ipso* carbon.

Considering that no *ipso* aromatic substitution product has been isolated from the reaction of methoxy(*p*-methoxyphenoxy)carbene with DMAD, the resonance donating effect of methoxy is strong enough to block the nucleophilic attack of the anion on the aromatic ring. Without the decrease of electron donating ability by coordination, it is hard to explain the fact that aromatic substitution occurred on the aromatic groups bearing a donor substituent.

2.5.3 Thermolysis of 2-(*o*-Methylphenoxy)-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the presence of DMAD

To check for the existence of the [1,5]-stabilization in the *ortho* substituted cases, an *ortho*-methyl substituted phenoxy group was introduced into an oxadiazoline to compare its migration ability with that of the phenoxy group. The methyl group does not have non-bonding electrons to make a coordinate bond with the positive carbon, but it still has a steric effect. Thermolysis of 2-*o*-methylphenoxy-2-phenoxy oxadiazoline with DMAD should show the pure steric effect on the aromatic substitution.

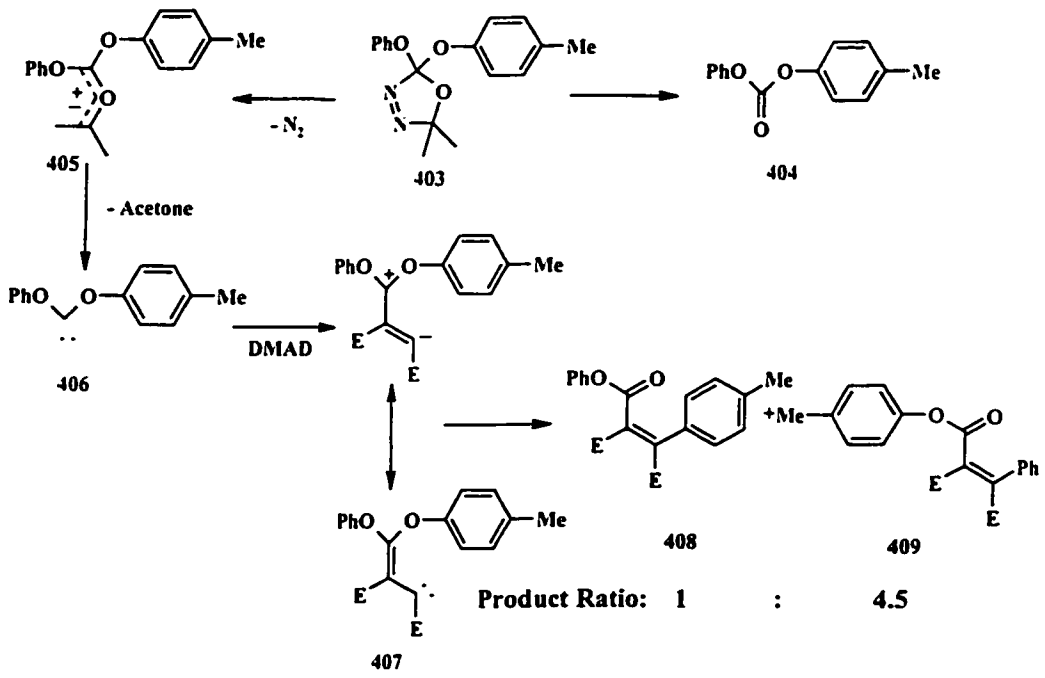
Interestingly, the reaction of carbene **398** with DMAD gave two isomers, **401** and **402**, in the ratio of 0.7 : 1. Without the proposed cation stabilization by an electron-rich group through space, the presence of the *ortho* methyl group also promoted the aryl group migration. This strongly supports that the steric effect can guide the migration by itself.



Scheme 132

The results from thermolysis of 2-(*p*-methylphenoxy)-2-(phenoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the presence of DMAD gave more support to the above conclusion. In the *para* position, the methyl group decreases the migration ability of *para*-methylphenyl group a lot, relative to the migration of phenyl (ratio = 1: 4.5), Scheme 133. This result agrees with the prediction made on the basis of a nucleophilic aromatic substitution reaction; an electron-deficient aromatic substituent should help the aryl group to migrate. The *para*-tolyl group should migrate more slowly than the phenyl group, even though $\sigma_{p\text{-Me}}$ is only - 0.14.

Quantitatively, in the overall aryl migration, the methylphenyl group migration has increased from 20% for the *para*-methyl case to about 40% when the methyl group is in the *ortho* position. The 20% difference can be attributed to a steric effect.



Scheme 133

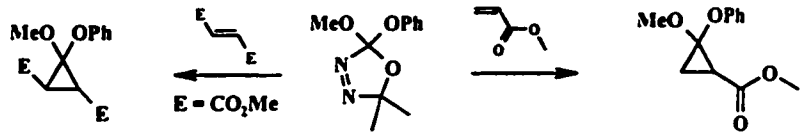
In addition, the observation of the importance of the steric effect also provides strong support for the importance of the electronic effect in the aromatic substitution. In both methyl cases, no matter where the methyl group is positioned, the aryl group bearing the methyl group migrates more slowly than the phenyl group. But the *ortho*-methoxyphenyl group migrates faster than the phenyl group whereas the *para*-methoxyphenyl group migrates more slowly than phenyl. On the base of the assumption that the *ortho*-methyl and *ortho*-methoxy groups have a similar steric effect, the more electron-donating methoxy group should not make the aryl group migrate faster than phenyl, unless the electronic effect is a very important factor driving the *ortho*-methoxyphenyl group to dominate the migration. In fact, the *ortho*-methoxyphenyl group is favored in migration over the phenyl group in a 2.5 : 1 ratio (Table 3). Although this

novel [1,5] electronic stabilization through space is not well understood, its potential for synthesis is not hard to see.

2.6 Miscellaneous Reactions of Aryloxy and Diaryloxycarbenes

2.6.1 The Novel [1+4]-Cycloaddition of Aryloxycarbene with an α,β-Unsaturated Ester

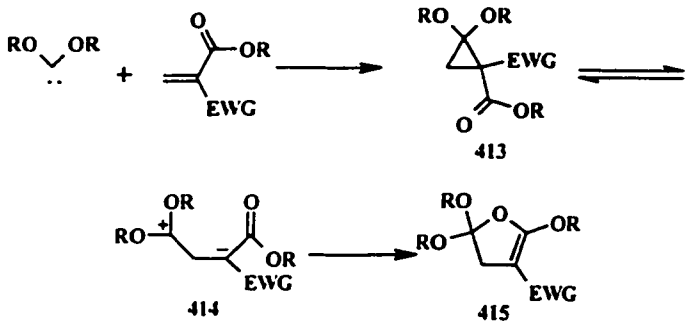
In the one-pot reaction of bis-oxadiazoline (**244**) with DMAD, a new kind of [1+4] cycloaddition was proposed as a necessary step to afford the ultimate three fused ring product (**254**). The conditions required for this kind of cycloaddition are being pursued. Methyl acrylate and fumarate were used to react with methoxyphenoxycarbene. Surprisingly, only cyclopropane derivatives (**411** or **412**) were produced from the reactions. No five-membered ring product was isolated (Scheme 134).



Scheme 134

In the literature, ring-opening reactions of vicinally donor-acceptor-substituted cyclopropanes have been described thoroughly.[166] The heterolytic ring opening reaction proceeds smoothly to give a 1,3-dipole intermediate because the ring strain is released and the separated charges can be stabilized by the neighbouring substituents. In general, a nucleophile, electrophile or dipolarophile is needed to trap the 1,3-dipolar intermediate to allow the reaction to proceed to a larger ring product, such as a furan derivative. Without it, stronger donor and acceptor substituents, such as those in **413**, are proposed as the

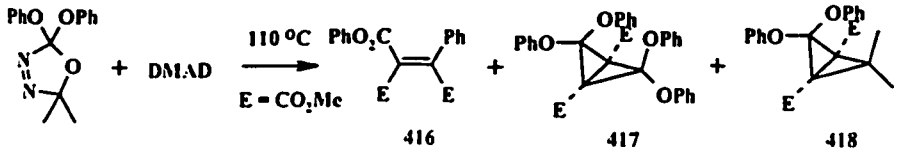
prerequisite to make the lifetime of the dipolar intermediate **414** sufficiently long to permit the intramolecular reaction to occur (Scheme 135).



Scheme 135

2.6.2 Novel Bicyclo[1.1.0]butanes

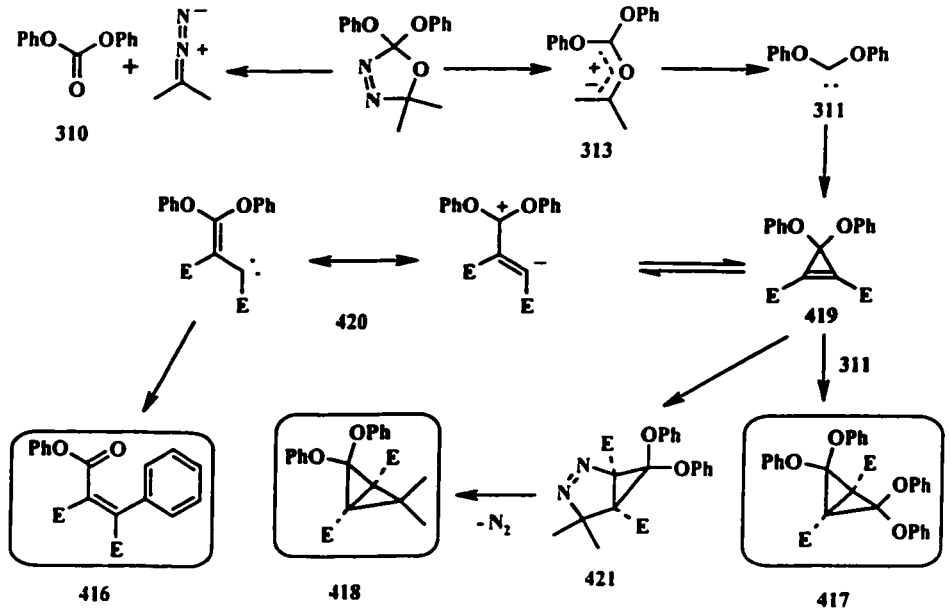
From the thermolysis reaction of diphenoxy oxadiazoline in the presence of DMAD, two interesting new products have been isolated. When the concentrations of starting materials, diphenoxy oxadiazoline and DMAD, were controlled to 0.2 M:0.2 M, dimethyl 2,2,4,4-tetraphenoxybicyclo[1.1.0]butane-1,3-dicarboxylate (**417**) and dimethyl 4,4-dimethyl-2,2-diphenoxybicyclo[1.1.0]butane-1,3-dicarboxylate (**418**) were isolated and identified (Scheme 136).



Scheme 136

The thermolysis involves two competing 1,3-dipolar cycloreversions, one leading to N_2 and a carbonyl ylide and the other to diphenyl carbonate (**310**) and diazopropane, Scheme 109. Diphenoxycarbene, which came from the fragmentation of the carbonyl

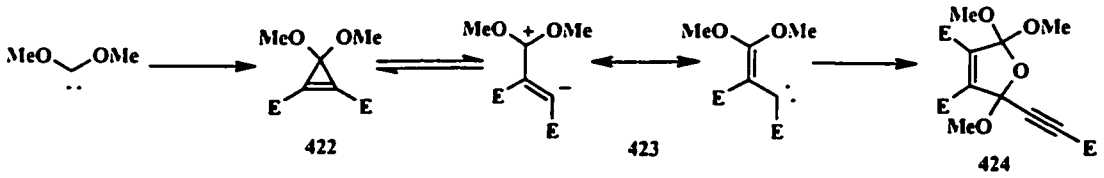
ylide **313**, adds to DMAD to make diphenoxycyclopropene **419**. Reversible opening of **419** to **420** leads to *ipso* aromatic substitution to form phenyl (*E*)-2,3-bis(methoxycarbonyl)-3-phenyl propanoate (**416**) in 40% isolated yield. Addition of diphenoxycarbene (**311**) to the reactive cyclopropene **419** would generate dimethyl 2,2,4,4-tetraphenoxybicyclo[1.1.0]butane-1,3-dicarboxylate (**417**), obtained in *ca.* 8% yield. Cycloaddition of **419** to diazopropane would initially form pyrazoline **421** (Scheme 137), and then loss of N_2 at 110 °C would lead to dimethyl 4,4-dimethyl-2,2-diphenoxybicyclo[1.1.0]butane-1,3-dicarboxylate (**418**) isolated in *ca.* 4% yield.



Scheme 137

The three products provide indirect evidence for the equilibration of **419** with **420**. The equilibration of cyclopropenes with vinylcarbenes has been proposed before[120] and it is known to be facile for 3,3-dialkoxycyclopropenes.[123,124] Compound **416** presumably arises from the intramolecular reaction of the ring-opened species. **417** and **418** are the result of cycloaddition to the ring-closed species **419**.

Products **417** and **418** suggest that the phenoxy substituents, relative to alkoxy substituents, destabilize an intermediate such as **420** or increase the stability of the cyclopropene, thereby diverting some material though the reactions of **419**. Analogous products that could be generated by addition to a cyclopropene intermediate are not obtained from reaction of dimethoxycarbene with DMAD (Scheme 138).



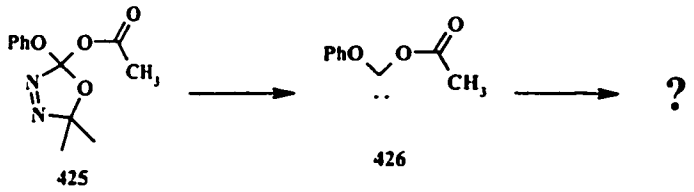
Scheme 138

Neither diacetals of bicyclo[1.1.0]butan-2,4-dione (e.g., **417**) nor acetals of bicyclo[1.1.0]butanone (e.g., **418**) have been reported previously. Other bicyclo[1.1.0]butanes have been studied intensely, in particular to try to discover which orbital of the system is the HOMO.[162] Compounds **417** and **418** are of considerable interest, not only in their own right but also as precursors of other bicyclo[1.1.0]systems, by reactions of the ester groups for example. Efforts to improve the yields, by increasing the concentration of oxadiazoline to 0.80 M, led to enhancement of the yield of **417** to 32%.

2.6.3 Thermolysis of a 2-Acetoxy-2-phenoxy Oxadiazoline

In the process of making diaryloxy oxadiazolines, lead tetraacetate was used to oxidize the phenoxyacyl hydrazone of acetone to make acetoxy phenoxy oxadiazoline. Due to the presence of some phenol in the solution, oxidation brought about a change in the color of the solution to deep brown. To make further reactions easier to monitor, flash

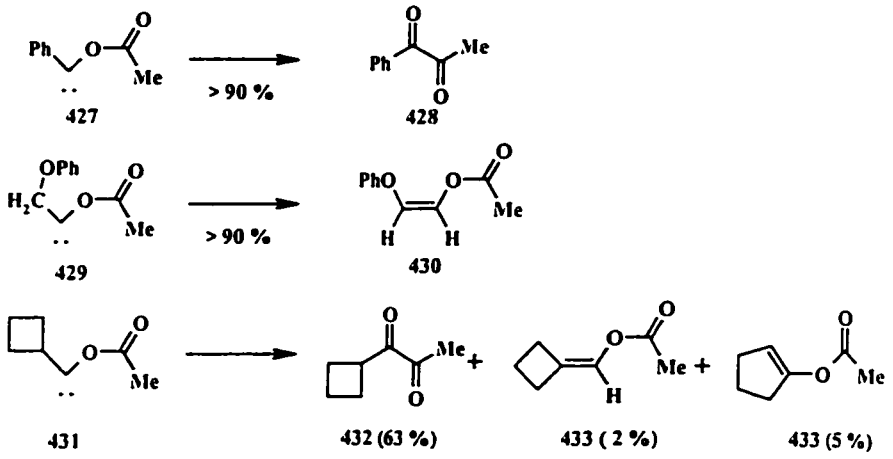
column chromatography was used to separate the desired oxadiazoline from the by-products. It was surprising to find that the acetoxy phenoxy oxadiazoline **425** is stable at room temperature. A thermolysis reaction was then carried out to study the chemistry of the interesting acetoxyphenoxycarbene **426**.



Scheme 139

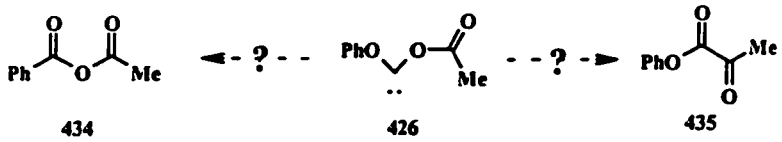
The chemistry of acetoxymethoxycarbene has not been studied because of the instability of the acetoxy methoxy oxadiazoline. An effort to isolate the pure acetoxy methoxy oxadiazoline with silica gel chromatography resulted in the complete decomposition of the compound. The ambient-stable acetoxy phenoxy oxadiazoline makes such a study possible.

In the literature, acetoxycarbenes have been reported three times by Moss.[173-175] Three types of reaction occur when the acetoxycarbene is generated under LFP conditions in the absence of a carbene trap. For the acetoxyphenylcarbene **427**, rearrangement to 3-phenyl-2,3-propanedione (**428**) dominates the reaction and the yield is over 90%. For acetoxyalkylcarbene **429** bearing an α-hydrogen, a hydride shift to *cis*-alkene, precludes the alternative but slower 1,2-acetyl shift. A similar alkyl shift, with the driving force of releasing cyclobutane strain energy, also constituted a small part of the reaction when acetoxycyclobutylcarbene (**431**) was generated (Scheme 140).



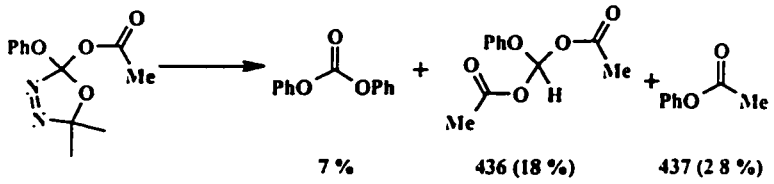
Scheme 140

The introduction of a phenoxy group to replace an alkyl group eliminates any possible alkyl or hydride migration. The possible acetyl shift to ketoester or the possible phenyl migration to acid anhydride was the initial interest in the reaction, Scheme 141.



Scheme 141

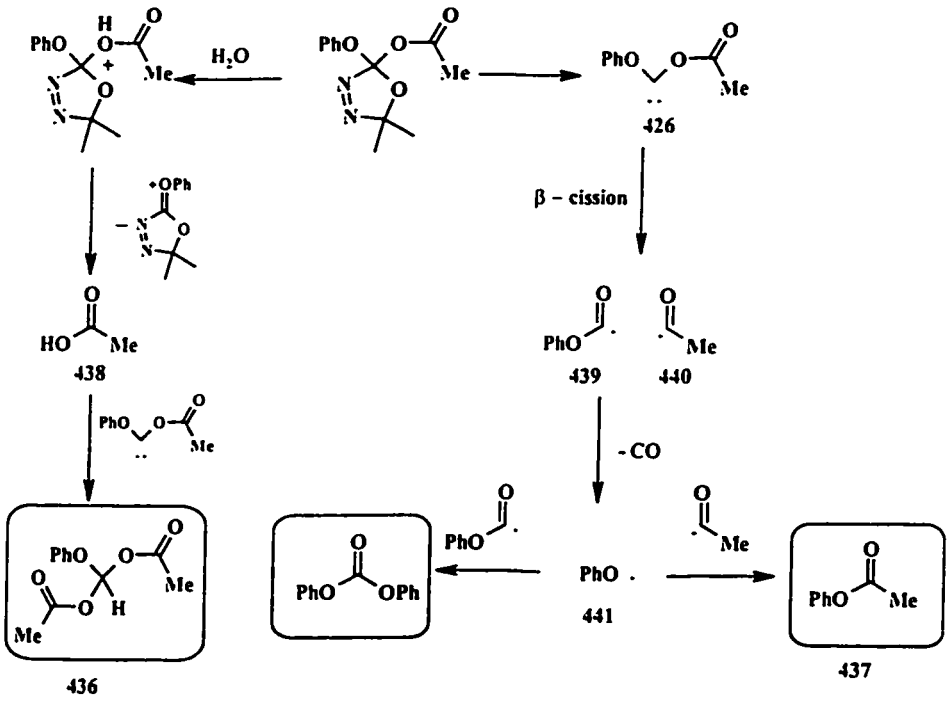
Surprisingly, thermolysis of pure acetoxyphenoxy oxadiazoline did afford 18 % ketoester (**435**) as well as some unexpected compounds: 7 % of diphenyl carbonate and 18 % of orthoformate (**436**), which might came from trapping of an acetoxyphenoxycarbene by acetic acid (Scheme 142).



Scheme 142

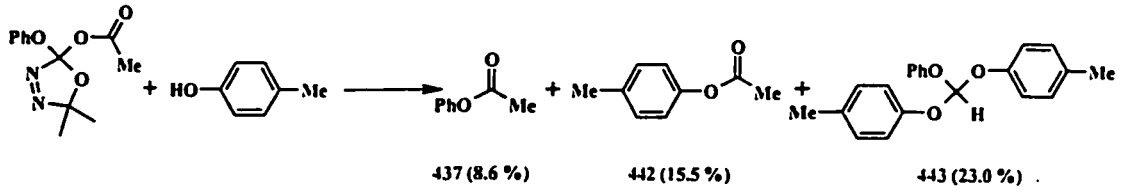
The *ortho* formate was assumed to come from the carbene, trapped by the acetic acid formed due to a trace of water in the benzene solution (Scheme 143). But the diphenyl carbonate and phenyl acetate cannot be formed through a normal dioxycarbene reaction. A radical mechanism is proposed as a key route to their formation.

By a carbene-radical mechanism, similar to those discussed in the introduction, [170] the results of the reaction can be explained as follows. The acetoxyphenoxycarbene was generated by thermolysis of acetoxyphenoxy oxadiazoline. Part of the carbene was trapped by the acetic acid (**438**) formed by the reaction of a trace of water with the oxadiazoline to give orthoformate **436**. The process to make acetic acid is very similar to the acid catalytic exchange reaction, which forms acetic acid and a cationic intermediate through the protonation and subsequent departure of acetic acid. The rest of the carbene underwent β-scission to form a radical pair **439** and **440**. The phenoxy acyl radical continued to fragment to the relatively stable phenoxy radical (**441**). Coupling of the phenoxy radical with the acetyl radical and the phenoxyacyl radical, respectively, furnished phenyl acetate and diphenyl carbonate.



Scheme 143

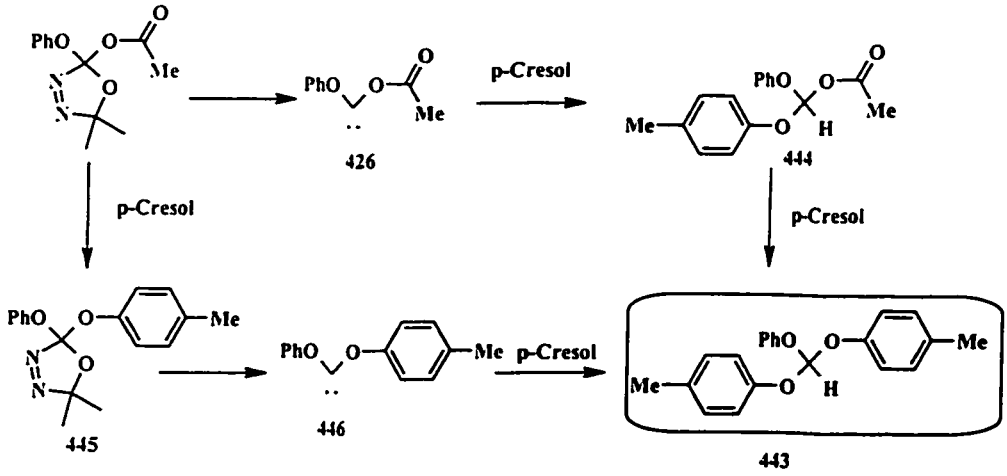
This radical process also happens in the trapping of acetoxyphenoxycarbene with *p*-cresol. No product of carbene trapping by cresol was isolated, but an *ortho* formate **443**, in 23 % yield, and 4-methylphenyl acetate (**442**) (15.5 %) were fully identified as new products (Scheme 144).



Scheme 144

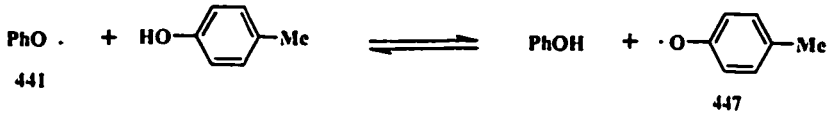
Two possible routes might account for the formation of the *ortho* formate **443**. The first possibility initiates from the replacement of the acetoxy group by the *p*-methylphenoxy group before the oxadiazoline fragments to the carbene. Then, thermolysis results in the formation of 4-methylphenoxy(phenoxy)carbene (**446**), which is

then trapped by the existing cresol. The second possibility comes from the cresol trapping of acetoxyphenoxycarbene. The *ortho*-formate **444** so formed is then protonated and the acetoxy group is replaced by a methylphenoxy group. Neither route can be ruled out easily, Scheme 145.



Scheme 145

The formation of phenyl acetate is similar to the above reaction and 4-methylphenyl acetate presumably comes from the hydrogen transfer from the 4-methylphenol to the phenoxy radical. The 4-methylphenoxy radical (**447**) so formed then couples with the acetyl radical to afford 4-methylphenyl acetate (**442**).



Scheme 146

Thermolysis of acetoxyphenoxy oxadiazoline in the presence of *t*-butyl alcohol was also carried out. Unfortunately, no product of carbene trapping by the alcohol was isolated. All final products were the same as those from the reaction in the absence of alcohol. Therefore, *t*-butyl alcohol was considered to be too weakly acidic to trap the

intermediates, **426**, which fragmented rapidly to radicals.

Overall, thermolysis of acetoxyphenoxy oxadiazoline did generate the desired acetoxyphenoxycarbene, which can do an acetyl shift rearrangement in the absence of a carbene trap or can be trapped by phenol. The free carbene also fragments to a radical pair to initiate several radical reactions.

Chapter 3. Experimental

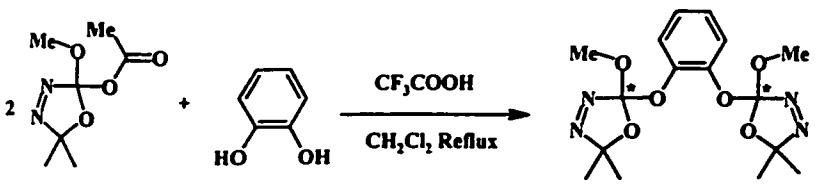
3.1 General Methods

NMR spectra were recorded on a Bruker AC-200 or AC-300 NMR spectrometer. 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). Infrared spectra were recorded with a Biorad FTS-40 spectrophotometer, with the sample in CCl_4. The IR bands are labeled qualitatively with the symbols br for broad and s or m for strong and medium intensities, respectively. Mass spectra were recorded with a VGH ZAB-E double focusing mass spectrometer or with a Hewlett Packard MSD GC/MS. Semi-preparative gas chromatography was performed with 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 megabore capillary column DB-1 (0.53 mm x 30 m). Unless otherwise stated, benzene was distilled and then dried with activated molecular sieves and all reaction solvents were distilled before use. Melting points were recorded on a Thomas Hoover capillary melting point apparatus, and are uncorrected. Silica gel from Silicycle (230-400 mesh), in a 30 cm x 2.5 cm glass column with Teflon stopcock, was used for flash chromatography.

General Method for Thermolyses

All thermolyses were carried out by immersing the sealed thermolysis tubes containing the samples (*ca.* 0.2 mol in 10-15 mL of benzene, dried by refluxing over CaH_2) in a constant-temperature oil bath at 110.0 ± 0.2 °C for 24 h. All spectroscopic data came from chromatographically isolated products. Radial chromatography was used for small-scale reactions (0.05 - 0.3 g) and column chromatography for larger scale reactions (0.3-2 g of oxadiazoline).

3.2 Bis-oxadiazoline



243 244

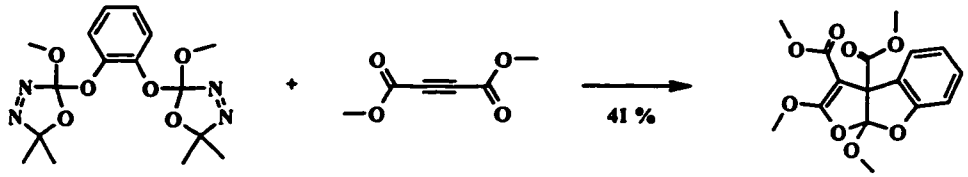
3.2.1 Generation of Bis-oxadiazoline (244) (Diastereomers)

Bis-oxadiazoline **244** was prepared by the exchange reaction of catechol with 2-acetoxy-2-methoxy oxadiazoline with trifluoroacetic acid as catalyst. In the procedure, 2.85 g (15.2 mmol) of 2-acetoxy-2-methoxy oxadiazoline and 0.54 g (4.9 mmol) of catechol were dissolved by 100 ml CH_2Cl_2. The reaction solution was heated to reflux for 24 hours. The solution was then washed with three portions of aq. $NaHCO_3$ (5%), and with water, and dried by $MgSO_4$. The organic solvent was then evaporated and the resulting oil was separated by flash column chromatography. **244** was obtained in 36.0 % yield (0.65 g); yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.25 & 1.27 (s, total 6H), 1.53 (s, 6H, Me), 3.64 (s, 6H), 7.00-7.09 (m, 2H), 7.23-7.33 (m, 2H); ^{13}C NMR (50 MHz,

$CDCl_3$) δ: 23.1, 23.2, 24.2, 52.4, 52.5, 120.7, 122.6, 124.6, 136.7, 143.9, 144.0; MS (electron spray) m/z: 373.1 $(M+ Li)^+$, 389.1 $(M+ Na)^+$, 405.1 $(M+ K)^+$.

3.2.2 Thermolysis of Bis-oxadiazoline with DMAD

Bis-oxadiazoline **244** (0.38 g, 1.04 mmol) and 0.15 g (1.06 mmol) dimethyl acetylene dicarboxylate were dissolved in 20 mL anhydrous benzene and put into a thermolysis tube. The solution was degassed by high vacuum pump after it was solidified by liquid nitrogen. The thermolysis tube was sealed by flame. After 24 hours heating at 110 °C in an oil bath, the reaction solution was transferred into a 50 mL round-bottomed flask. Evaporation of the solvent followed by radial chromatographic separation on silica gel, gave 0.14 g (41 % yield) of **254** as a major product.



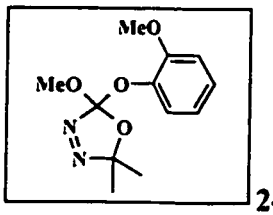
254

Three-ring fused Product (254): white solid, mp 107.5- 108.0 °C; 0.14 g (41% yield); ^1H NMR (200 MHz, $CDCl_3$) δ: 3.72 (s, 6H, OMe), 3.76 (s, 3H, OMe), 4.02 (s, 3H, OMe), 6.88 (d, ^3J = 8.0 Hz, 1H), 7.00 (dd, ^3J = 8.0 Hz, ^3J = 8.5 Hz, 1H), 7.23(dd, ^3J = 8.5 Hz, ^3J = 7.6 Hz, 1H), 7.55 (d, ^3J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 50.9, 52.5, 53.1, 57.6, 66.7, 83.7, 109.7, 122.6, 126.9, 127.7, 128.6, 129.3, 156.6, 163.8, 165.2, 168.5; IR (CCl_4) cm^{-1}: 2999m, 2955s, 2857w, 1752s, 1726m, 1692s, 1657s, 1551br, 1468s, 1387m, 1294m, 1268m; MS (EI) m/z: 336 (M^+, 48), 305 (M-OMe, 18), 277 (100); MS (CI, NH_3) m/z: 337 (M+1, 100).

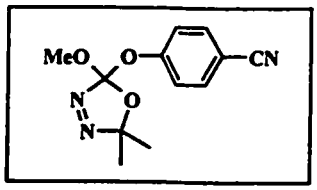
3.3 Aryloxy Oxadiazolines

3.3.1 Generation of Aryloxy Oxadiazolines

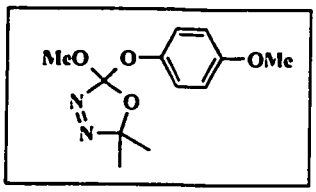
The general method to synthesize 2-aryloxy-2-methoxy-5,5-dimethyl-Δ^3-oxadiazolines uses 2-acetoxy-2-methoxy oxadiazoline and the appropriate phenol to do an exchange reaction with acid catalysis. The reaction solution was normally stirred and heated to reflux for 16 to 24 hours. After heating, an equal volume of 10% NaOH was added into the solution. About two hours of vigorous stirring was used to remove the residual phenol and to hydrolyze the acyclic by-products. Three portions of 5% Na_2CO_3 and one portion of distilled water were used to wash the reaction solution. After separation of the organic layer from the aqueous layer, anhydrous $MgSO_4$ was used to dry the organic solution. Evaporation of the organic solvent by rotary evaporator followed by flash column chromatography or radial chromatography on silica gel with a gradient increasing the polarity of the eluting solution (2.5% - 20% EtOAc in hexane) gave the desired 2-aryloxy-2-methoxy oxadiazoline. The isolated oxadiazolines were identified by means of ^{1}H NMR, ^{13}C NMR and IR. Mass spectrometric analysis was tried several times to identify the compound, but the oxadiazoline decomposed in the instrument because of the high temperature (~ 200 °C) and no useful information could be obtained. Because of this problem, the identification of the oxadiazolines was done only by NMR and IR analysis.



2-Methoxy-2-(*o*-methoxyphenoxy) Oxadiazoline (266) was obtained in 70% yield by the exchange reaction of acetoxymethoxy oxadiazoline with *o*-methoxyphenol in the presence of trifluoroacetic acid. Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (s, 3H, Me), 1.52 (s, 3H, Me), 3.65 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.80-7.24 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.1, 24.1, 52.4, 55.8, 112.4, 120.3, 123.4, 125.6, 137.1, 140.7, 152.4; IR (CCl_4) cm^{-1}: 3070w, 2994m, 2951m, 2839w, 1770w, 1598m, 1503s, 1460s, 1382w, 1368w, 1303m, 1261s, 1209s, 1179s, 1158s, 1117s, 1093s, 1050m, 986w, 921w.



2-Methoxy-2-(*p*-cyanophenoxy) Oxadiazoline (269) was obtained by the exchange reaction of acetoxymethoxy oxadiazoline with *p*-cyanophenol in the presence of catalytic trifluoroacetic acid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.46 (s, 3H, Me), 1.64 (s, 3H, Me), 3.53 (s, 3H, OMe), 7.36 (d, ^{3}J = 7.0 Hz, 2H), 7.62 (d, ^{3}J = 7.0 Hz, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.8, 23.9, 52.5, 107.3, 118.5, 120.5, 121.5, 133.5, 135.8. 155.6.

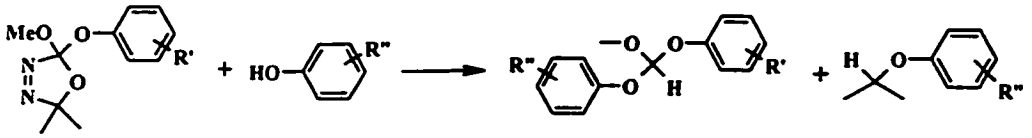


2-Methoxy-2-(*p*-methoxyphenoxy) Oxadiazoline (267): was obtained by the exchange reaction of acetoxymethoxy oxadiazoline with *p*-

methoxyphenol in the presence of catalytic trifluoroacetic acid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (s, 3H, Me), 1.53 (s, 3H, Me), 3.62 (s, 3H, OMe), 3.76 (s, 3H, OMe), 6.79 (d, ^3J = 6.8 Hz, 2H), 7.07 (d, ^3J = 6.8 Hz, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.4, 24.2, 52.5, 55.4, 114.0, 120.2, 123.3, 136.8, 145.1, 156.6.

3.3.2 Thermolysis of 2-Aryloxy-2-methoxy Oxadiazoline in the Presence of Phenol

For each of the following trapping reactions of an aryloxycarbene with phenol, about 0.2g of oxadiazoline and 3 equivalents of phenol were dissolved in 20 mL of benzene, which had been dried by refluxing in the presence of CaH for 24 hours. The solution was then degassed and immersed into a 110 °C oil bath for 24 hours. Evaporation of the solvent, followed by the flash column chromatography, afforded pure products.



R' = *p*-OMe, R" = *p*-OMe	86 % (270)	
R' = *p*-OMe, R" = H	67 % (271)	
R' = *p*-OMe, R" = *p*-CN	56 % (272)	4 % (274)
R' = *p*-CN, R" = *p*-CN	58 % (273)	6 %

Thermolysis of 2-Methoxy-2-(*p*-methoxyphenoxy) Oxadiazoline in the Presence of 3 Equivalents of *p*-Methoxyphenol

Methoxy-(*p*-methoxyphenoxy) oxadiazoline was thermolysed with *p*-methoxyphenol to afford **270** as the only product, which was isolated in 86% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.57 (s, 3H, OMe), 3.76 (s, 6H, 2OMe), 5.96 (s, 1H, H), 6.84 (d, ^3J = 6.8 Hz, 4H), 7.03 (d, ^3J = 6.8 Hz, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 50.7,

55.5, 112.9, 114.5, 119.3, 148.0, 155.5; MS (EI) m/z: 51 (12), 77 (49), 92 (9), 109 (19), 137 (100), 167 (43), 229 (8); MS (CI, NH_3) m/z: 137 (100), 167 (73), 229 (15).

Thermolysis of 2-Methoxy-2-(*p*-methoxyphenoxy) Oxadiazoline in the presence of 3 Equivalents of Phenol

Methoxy-(*p*-methoxyphenoxy) oxadiazoline was thermolysed with phenol. Orthoformate **271** was isolated as the only product in 67 % yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.57 (s, 3H, OMe), 3.76 (s, 3H, OMe), 6.07 (s, 1H, H), 6.84 (d, ^3J = 6.8 Hz, 2H), 7.01-7.09 (m, 5H, ArH), 7.24-7.34 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 50.6, 55.6, 112.9, 114.6, 117.6, 119.3, 123.0, 129.5, 148.0, 154.4, 155.6.

Thermolysis of 2-Methoxy-2-(*p*-methoxyphenoxy) Oxadiazoline in the Presence of 3 Equivalents of *p*-Cyanophenol

Methoxy-(*p*-methoxyphenoxy) oxadiazoline was thermolysed with *p*-cyanophenol. Orthoformate **272** was isolated in 56% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.57 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.12 (s, 1H, H), 6.85 (d, ^3J = 4.5 Hz, 2H), 7.01 (d, ^3J = 4.5 Hz, 2H, ArH), 7.14 (d, ^3J = 4.6 Hz, 2H), 7.60 (d, ^3J = 4.6 Hz, 2H, C_6H_4-CN); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 50.9, 55.6, 106.2, 111.6, 114.7, 117.9, 118.7, 119.3, 133.9, 147.6, 156.0, 157.6; MS (EI) m/z: 51 (6), 64 (14), 77 (18), 102 (15), 139 (11), 162 (100), 167 (83), 254 (M-31, 6); MS (CI, NH_3) m/z: 162 (56), 167 (100), 254 (M-31, 5).

Thermolysis of 2-Methoxy-2-(*p*-cyanophenoxy) Oxadiazoline in the Presence of 3 Equivalents of *p*-Cyanophenol:

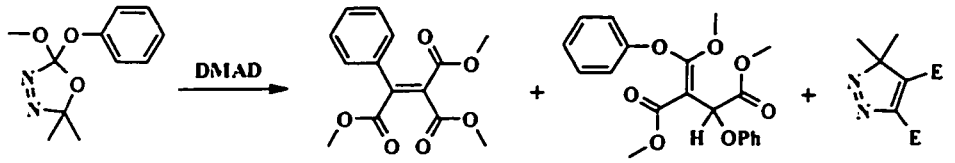
Methoxy-(*p*-cyanophenoxy) oxadiazoline was thermolysed with *p*-cyanophenol. Orthoformate **273** was isolated in 58 %. ^{1}H NMR ($CDCl_3$): 3.59 (s, 3H, OMe), 6.39 (s, 1H, H), 7.16 (d, ^3J = 7.3 Hz, 4H), 7.64 (d, ^3J = 7.3 Hz, 4H, -C_6H_4-CN); ^{13}C NMR (50 MHz): 51.0, 106.6, 109.9, 117.7, 133.9, 156.8; IR (CCl_4) cm^{-1}: 3042w, 3002w, 2952w, 2851w, 2232s, 1904w, 1607w, 1581m, 1505s, 1448w, 1361w, 1292m, 1257m, 1171s, 1116s, 1069s, 988.6s; MS (EI) m/z: 51 (10), 64 (12), 90 (11), 102 (29), 119 (19), 162 (100), 221 (5), 249 (7); (CI, NH_3) m/z: 162 (100), 204 (25), 221 (7), 249 (10), 281 (M+1, 11), 298 (M+18, 73).

3.3.3 Thermolysis of Aryloxy Oxadiazolines with DMAD

The reaction of aryloxycarbenes, generated from thermolysis of the corresponding oxadiazolines, with DMAD was done in a sealed thermolysis tube. The carbene source, oxadiazoline, and DMAD were dissolved into about 30 mL of benzene with the concentration about 0.2 M to 0.5 M. Unless otherwise specified, the reaction solution was normally heated to 100 °C by an oil bath under nitrogen flow to distill 5 to 10 mL of benzene out over about 30 minutes. This process distills almost all of the water from the solution azeotropically, and the temperature was not high enough for significant decomposition of the oxadiazoline. After this azeotropic distillation, the reaction solution was cooled and solidified by liquid nitrogen and a high vacuum pump system was used to degas the sample. Then the solution was sealed in a thermolysis tube and immersed into a

110 °C oil bath for 24 hours. Evaporation of the organic solvent, benzene, followed by chromatography afforded pure products.

Thermolysis of 2-Methoxy-2-phenoxy Oxadiazoline with DMAD in undried Benzene



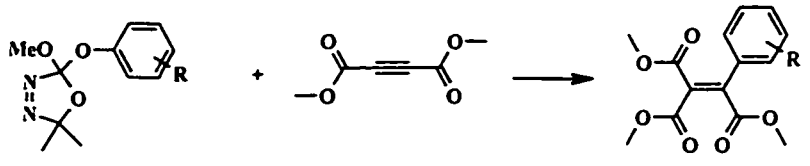
268 | 41 % 279 | 7% 280 | 9% 281

Aromatic Substitution Product 279

Thermolysis of 2-methoxy-2-phenoxy oxadiazoline (0.21 g, 0.94 mmol) in the presence of 1.3 equivalents of DMAD (0.18 g, 1.27 mmol) afforded the aromatic substitution product **279** in 41% yield (0.11 g). ^{1}H NMR (200 MHz, CDCl3) δ: 3.63 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.39 (s, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.6, 52.9, 126.8, 127.5, 128.7, 130.2, 132.9, 147.3, 163.1, 165.0, 167.2; MS (EI) m/z: 43 (33), 59 (70), 75 (33), 102 (25), 115 (25), 129 (100), 151 (20), 175 (22), 191 (8), 215 (9), 219 (58), 247 (27), 278 (M, 27); MS (CI, NH_3) m/z: 279 (M+1, 100), 296 (M+18, 52).

280: obtained in 7% yield (0.02 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.51 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.87 (s, 3H, OMe), 6.02 (s, 1H, H), 7.03-7.31 (m, 10H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 51.0, 52.2, 52.6, 113.1, 120.2, 123.7, 124.5, 129.2, 143.8, 152.3, 164.1, 165.2; MS (EI) m/z: 341 (M-31, 7), 279 (M-OPh, 100), 219 (42), 167 (39), 77 (77); MS (CI, NH_3) m/z: 341 (M-31, 6), 279 (M-OPh, 100).

281 was obtained in 9% yield (0.02 g). The spectra of **281** have been published.[183]



R = *o*-OMe	Yield = 61 %	288
p-OMe	0 %	289
H	41 %	279
p-CN	72 %	290

Thermolysis of 2-Methoxy-2-(*o*-methoxyphenoxy) Oxadiazoline in the presence of DMAD

Triester (**288**): Thermolysis of 2-methoxy-2-(*o*-methoxyphenoxy) oxadiazoline (0.27 g, 1.07 mmol) in the presence of DMAD (0.152 g, 1.07 mmol) afforded aromatic substitution product **288** in 61% yield (0.20 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.61 (s, 3H, OMe), 3.79 (s, 6H, OMe), 3.85 (s, 3H, OMe), 6.88-6.98 (m, 2H, ArH), 7.17 (d, ^3J =7.0 Hz, 1H), 7.38 (dd, ^3J = 8.0 Hz, ^3J = 7.6 Hz, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.4, 52.7, 52.8, 55.6, 111.0, 120.6, 122.9, 129.8, 130.6, 131.5, 142.8, 156.8, 164.4, 164.5, 167.0; IR (CCl_4) cm^{-1}: 3460w, 3028w, 3004m, 2953s, 2904w, 2841m, 2286w, 2056w, 1745s, 1627w, 1599m, 1577m, 1551m, 1492m, 1462m, 1436m, 1328m, 1287s, 1163w, 1120w, 1088w; MS (EI) m/z: 45 (50), 59 (100), 77 (66), 103 (28), 115 (38), 131 (66), 159 (25), 185 (24), 217 (100), 249 (31), 277 (75), 308 (M, 38); MS (HR) m/z: calcd. for $C_{15}H_{16}O_7$ 308.0896, found 308.0896.

2-Methoxy-2-(*o*-methoxyphenoxy)carbene Dimer: Thermolysis of methoxy-(*o*-methoxy-phenoxy) oxadiazoline (0.25 g, 0.99 mmol) in the presence of DMAD (0.17 g, 1.2 mmol) afforded 5% of carbene dimer (0.018 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.84 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.94-6.99 (m, 2H), 7.10-7.26 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 55.4, 55.8, 112.5, 120.6, 122.3, 127.1, 140.0, 151.1, 153.9.

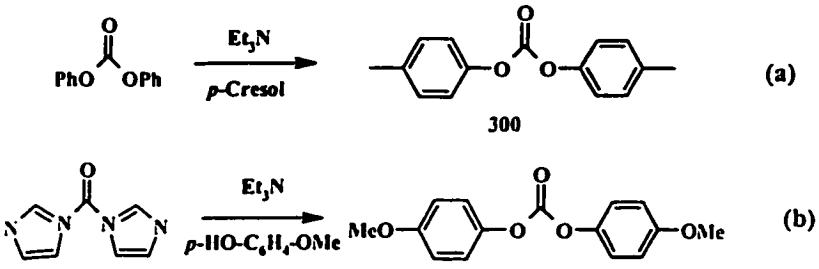
Thermolysis of 2-(*p*-Cyanophenoxy)-2-methoxy oxadiazoline with DMAD:

Aromatic substitution product (**290**): Thermolysis of 2-*p*-cyanophenoxy-2-methoxy oxadiazoline (0.25 g, 1.01 mmol) in the presence of 1.2 equivalent of DMAD (0.165 g, 1.16 mmol) afforded 72% (0.22 g) of **290**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.65 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.50 (d, ^3J = 6.7 Hz, 2H), 7.71 (d, ^3J = 6.7 Hz, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.7, 53.0, 53.1, 113.5, 117.8, 128.2, 129.3, 132.1, 137.2, 144.2, 162.7, 163.7, 165.8.

3.4 Diaryloxy Oxadiazolines

3.4.1 Synthesis of Diaryl Carbonates

Diphenyl carbonate is commercially available. Other diaryl carbonates were prepared by (a) *trans*-esterification of diphenyl carbonate or by (b) treating 1,1'-carbonyl diimidazole with a substituted phenol.

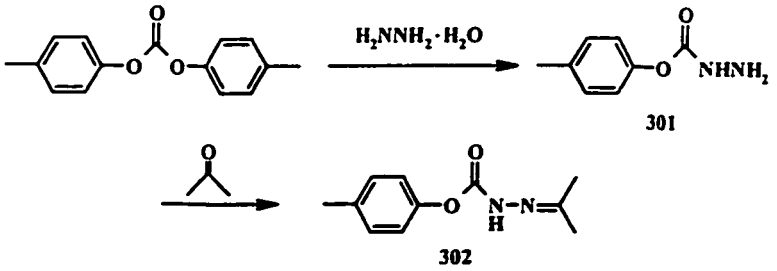


Bis-*p*-tolyl Carbonate (300): Di-*p*-tolyl carbonate, mp 113-114 °C was obtained as a white solid (41.8 g, 69%) by refluxing a solution of 53.5 g (0.25 mol) of diphenyl carbonate with *p*-cresol (162 g, 1.5 mol) in toluene (300 mL) containing 151.5 g of

triethyl amine (1.5 mol) (Method (a)). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.35 (s, 6H), 7.11-7.25 (m, 8H).

Bis-*p*-methoxyphenyl Carbonate: Di-*p*-methoxyphenyl carbonate (mp = 93 - 94 °C, lit. mp = 95.5-96 °C)[176] was prepared in 66% yield (18.2 g) by reaction of 1,1'-carbonyl diimidazole (16.2 g, 0.10 mol) with *p*-methoxyphenol (49.6 g, 0.4 mol) (Method (b)). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.80 (s, 6H), 6.88-7.20 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 114.5, 121.7, 144.7, 152.8, 157.6.

3.4.2 Synthesis of 2-Acetoxy-2-aryloxy Oxadiazolines



Aryl Hydrazinocarboxylates: In the general procedure, a solution of diaryl carbonate (25g) in diethyl ether (100mL) was cooled to - 30 °C by dry ice in acetonitrile. 1-1.2 Equivalents hydrazine hydrate (6g) was added into the solution in one portion. After 30 minutes stirring, the reaction was allowed to continue for another 20 minutes in room temperature. Most of hydrazinocarboxylate gradually precipitated. With vacuum filtration, a relatively pure product was obtained. A further wash with a 1:1 benzene-hexane solution cleaned out the by-product, phenol, and left the pure hydrazinocarboxylate as white crystals.

Phenyl Hydrazinocarboxylate was prepared according to previously published methods.[177] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.88 (s, 2H, NH_2), 6.40 (s, 1H, NH), 7.11-7.23 (m, 5H, ArH). mp = 104-105 °C (Lit.[178] mp=105-106 °C).

***p*-Cresyl Hydrazinocarboxylate (301)** was obtained in 53% yield (9.68 g) by the reaction of bis-tolyl carbonate (27.5 g, 0.11 mol) with hydrazine monohydrate (6.8 g, 0.13 mol). ^{1}H NMR ($CDCl_3$): 2.33 (s, 3H, Me), 3.86 (s, 2H, NH_2), 6.39 (s, 1H, NH), 6.99-7.26 (m, 4H, ArH); ^{13}C NMR (50 MHz): 20.8, 121.0, 129.9, 135.2, 148.5, 157.1.

***p*-Methoxyphenyl Hydrazinocarboxylate** was obtained in 51% (6.13 g) yield by the reaction of 18.1 g (0.066 mol) of di-*p*-cresyl carbonate with 4.0 g (0.08 mol) of hydrazine *mono*-hydrate in 100 mL of CH_2Cl_2. White solid, m.p = 116-117 °C (Lit. [178] 115-117 ° C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.86 (s, 2H, NH_2), 6.39 (s, 1H, NH), 6.99-7.26 (m, 4H); ^{13}C NMR (50 MHz) δ: 20.8, 121.0, 129.9, 135.2, 148.5, 157.1; IR (CCl_4) cm^{-1}: 3457m, 3355w, 3309w, 1753s, 1632w, 1549m, 1510m, 1462s, 1255m, 1220s, 1206s, 1171w, 1024m; MS (EI) m/z: 166 (M, 8), 108 (MeC_6H_4O, 100), 91 (8), 77 (16), 65 (7), 51 (9); MS (CI, NH_3) m/z: 184 (M+18, 28), 167 (M+1, 100).

Phenoxycarbonylhydrazone of Acetone

Phenyl hydrazinocarboxylate (5.74 g, 37.7 mmol) and anhydrous Na_2SO_4 (~6 g) were stirred in acetone (150 mL) for 12 h. The crude reaction mixture was filtered and concentrated to give pure (phenoxycarbonyl)hydrazone of acetone (6.87 g, 35.7 mmol), in 94% overall yield, as a white solid, mp 125-126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.84 (s, 3H), 2.06 (s, 3H), 6.79-6.85 (m, 1H), 7.15-7.40 (m, 4H), 7.98 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.2, 25.2, 115.4, 121.5, 125.6, 129.3; MS (EI) m/z: 192 (M, 2), 98

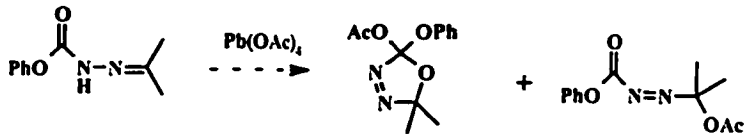
(M-HOPh, 30), 94 (HOPh, 100), 66 (22), 65 (20), 56 ($N{=}C(CH_3)_2$, 13); MS (CI, NH_3) m/z: 210 (M+18, 15), 193 (M+H, 25).

***p*-Cresoxycarbonylhydrazone of Acetone (302)**

In an analogous reaction, bis-*p*-cresyl carbonate (27.47 g, 0.113 mol) gave 11.4 g (49 %) of the *p*-cresoxycarbonyl hydrazone of acetone as a white solid, mp 122-124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.87 (s, 3H), 2.09 (s, 3H), 2.33 (s, 3H), 7.03-7.26 (m, 4H), 7.79 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.2, 20.8, 25.4, 121.2, 129.8, 135.3, 148.5, 152.3; IR (CCl_4) cm^{-1}: 3250m, 2922m, 1781m, 1735m, 1720s, 1508m, 1491m, 1390m, 1361s, 1253m, 1216s, 1202s, 1018m; MS (EI) m/z: 206 (M, 7), 108 (MeC_6H_4O, 100), 99(15), 77 (7), 6 (6), 41 (4); MS (CI, NH_3) m/z: 207 (M+1, 53).

Other aryloxycarbonyl hydrazones of acetone were synthesized according to the above procedure.

Oxidation of hydrazones to 2-Acetoxy-2-aryloxy Oxadiazolines

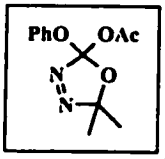


303

The general procedure to make acetoxyaryloxy oxadiazoline involved dropwise addition, over 1-2 h, of a solution of an aryloxycarbonyl hydrazone of acetone (5 g, 0.02 mol) in CH_2Cl_2 (60 mL), under dry nitrogen, to a stirred solution of 1.2 equivalents (*ca.* 10 g) of lead tetraacetate at 0 °C. After the addition, the solution was kept in the ice bath for 2 h and then at room temperature overnight. The solution was washed with 10% aqueous $NaHCO_3$ (4 × 50 mL) and the organic layer was dried with anhydrous $MgSO_4$.

Filtration and evaporation of the solvent left a yellow oil containing the desired oxadiazoline (about 70 %) and an acyclic isomer (about 30 %) estimated by means of integration of the ^{1}H NMR spectrum.

The 2-acetoxy-2-phenoxy oxadiazoline was prepared by adding lead tetraacetate ($Pb(OAc)_4$) (12.69 g, 28.62 mmol) and methylene chloride (30 mL) to a 100 mL two-neck flask under nitrogen. This mixture was stirred and cooled in an ice bath. Using a dropping funnel, (phenoxycarbonyl)hydrazone of acetone (5.0 g, 26.0 mmol) in methylene chloride (20 mL) was added slowly over 20 minutes. During this addition the solution turned from yellow to brown. The solution was stirred for an additional 2h during which time the ice bath was allowed to melt. A small amount of brown precipitate was observed. Water (~10 mL) and CH_2Cl_2 (~10 mL) were added to the reaction mixture which was then was filtered through a Celite pad. The filtrate was washed with sodium bicarbonate (5% w/v) until the bubbling stopped and extracted with CH_2Cl_2. The extract was dried over anhydrous $MgSO_4$, filtered and concentrated. This produced 4.48 g of a mixture containing 58% of (**303**) and 42% of an acyclic side product ($PhOCON{=}NC(CH_3)_2OAc$). Unlike 2-acetoxy-2-methoxy oxadiazolines, the 2-acetoxy-2-aryloxy oxadiazolines can be isolated by chromatography on SiO_2 (radial or column) with 5% ethyl acetate in hexane as the eluting solvent.

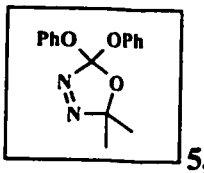


2-Acetoxy-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (303): Pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.66 (s, 3H), 2.08 (s, 3H), 7.15-7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2, 22.6, 23.9, 121.7, 123,4, 125.0,

129.1, 133.1, 151.3, 165.9. (In 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines the C5 and C2 signals in the ^{13}C NMR spectrum are near 119 and 137 ppm, respectively.) Other 2-acetoxy-2-aryloxy oxadiazolines were not separated from their acyclic isomers. The crude products from oxidation were used directly for preparation of diaryloxy oxadiazolines.

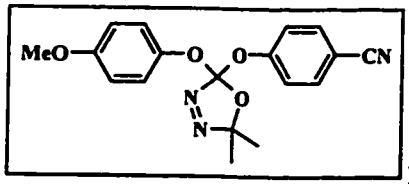
3.4.3 Synthesis of diaryloxy oxadiazolines

In general, both symmetric and unsymmetric 2,2-diaryloxy oxadiazolines were synthesized by exchanging the acetoxy group of a 2-acetoxy-2-aryloxy oxadiazoline by a second aryloxy group. A solution of a 2-acetoxy-2-aryloxy oxadiazoline (*ca.* 5 g) and 3 equivalents (*ca.* 7 g) of a substituted phenol in CH_2Cl_2, was acidified with catalytic trifluoroacetic acid (*ca.* 12 drops). After refluxing for 16 h, the solution was extracted with three 30 mL portions of 10% NaOH to remove excess phenol and to destroy the acyclic acetoxy compound. Separation of the organic layer, drying with anhydrous $MgSO_4$, and filtration resulted in a solution of the 2,2-diaryloxy oxadiazoline in CH_2Cl_2. Evaporation of the solvent and purification of the residue by chromatography afforded the oxadiazoline in pure form.

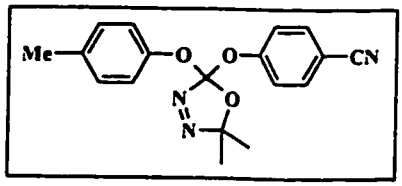


5,5-Dimethyl-2,2-diphenoxy-Δ^3-1,3,4-oxadiazoline(307): White solid. A typical procedure for the synthesis of 5,5-dimethyl-2,2-diphenoxy-Δ^3-1,3,4-oxadiazoline involved charging a 50 mL round bottom flask with an impure acetoxy phenoxy oxadiazoline (57% oxadiazoline) (1.05g, 2.39 mmol), phenol (0.412g, 4.378 mmol), a

catalytic amount of trifluoroacetic acid (0.06 mL, 0.74 mmol) and CH_2Cl_2 (8.5 mL). The solution was stirred for 24 h at room temperature. Aqueous NaOH (10 mL, 10% w/v) was then added to the solution and left to stir for 3 h. The solution was extracted with CH_2Cl_2 and water. The extract was then filtered, dried ($MgSO_4$) and concentrated to give a clear oil **307** 0.197 g (51% yield), which gradually changed to white solid, mp 59.5-60.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22 (s, 6H), 7.09-7.33 (m, 10H); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 23.5 ($C(\underline{C}H_3)_2$), 121.5 (C2), 122.1 (C2 or C3 of Ar), 124.9 (C4 of Ar), 129.1 (C3 or C2 of Ar), 136.0 (C5), 151.6 (C1 of Ar); IR (CCl_4) cm^{-1}: 3071m, 3047m, 2996m, 1785s, 1594s, 1492s, 1459m; MS (EI) m/z: M^+ not observed, 215 (11%), 191 (M- OPh, 100%), 135 (37%), 119 (78%), 105 (46%), 77 (Ph, 43%).

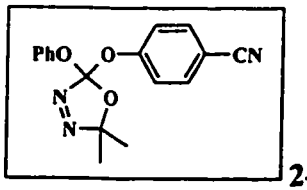


2-*p*-Cyanophenoxy-2-*p*-methoxyphenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (295a). Light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (s, 3H), 1.43 (s, 3H), 3.73 (s, 3H), 6.78 (d, ^3J = 9.1 Hz, 2H), 7.05 (d, ^3J = 9.1 Hz, 2H), 7.46 (d, ^3J = 8.9 Hz, 2H), 7.6 (d, ^3J = 8.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.0, 23.9, 55.2, 107.5, 113.9, 118.3, 121.0, 122.2, 123.5, 133.4, 135.3, 144.0, 155.4, 157.0.

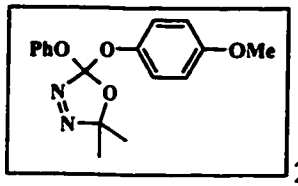


2-*p*-Cresoxy-2-*p*-cyanophenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (295b). Light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.24 (s, 3H), 1.43

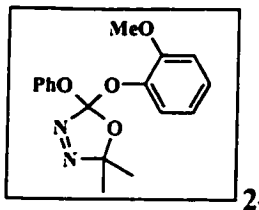
(s, 3H), 2.26 (s, 3H), 7.04 (s, 4H), 7.04 (s, 4H), 7.45 (d, ^3J = 8.9 Hz, 2H), 7.61 (d, ^3J = 8.9 Hz, 2H, Ar-CN); ^{13}C NMR (50 MHz) δ: 20.4, 23.0, 23.8, 107.5, 118.2, 120.9, 121.8, 122.2, 129.5, 133.3, 134.9, 135.1, 148.5, 155.3; IR (CCl_4) cm^{-1}: 3038.9m, 3106m, 2996m, 2939m, 2870m, 2231s, 1898m, 1780m, 1606s, 1503s, 1383m, 1370m, 1290m, 1133s, 1018m, 989m.



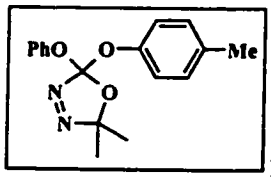
2-*p*-Cyanophenoxy-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (295c). Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.26 (s, 3H), 1.46 (s, 3H), 7.14-7.27 (m, 5H), 7.45 (d, ^3J = 6.7 Hz, 2H), 7.62 (d, ^3J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3, 24.1, 107.8, 118.5, 121.2, 122.1, 122.5, 125.5, 129.3, 133.6, 135.2, 151.0, 155.4.



2-*p*-Methoxyphenoxy-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline(295d). Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.17 (s, 3H), 1.21 (s, 3H), 3.73 (s, 3H), 6.78 (d, ^3J = 6.9 Hz, 2H), 7.12 (d, ^3J = 6.9 Hz, 2H), 7.21-7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.4, 23.6, 55.4, 113.9, 121.3, 122.0, 123.7, 124.8, 129.1, 136.2, 144.9, 151.7, 156.9; IR (CCl_4) cm^{-1}: 3069m, 2996s, 2938s, 2909s, 2838s, 1837m, 1780s, 1599s, 1511s, 1383m, 1369m, 1296m, 989m.



2-*o*-Methoxyphenoxy-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (295e). Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18 (s, 3H), 1.21 (s, 3H), 3.77 (s, 3H), 6.8-7.36 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.1, 23.5, 55.8, 112.5, 120.2, 121.6, 121.8, 123.9, 124.6, 126.0, 128.9, 136.3, 140.5, 151.7, 152.5. MS (EI) m/z: 245 (M-N=N=C$(CH_3)_2$+1, 9), 221 (M-PhO, 38), 191 (M-OC_6H_4OMe, 72), 165 (34), 149 (100), 135 (65), 119 (27), 77 (65); MS (CI, NH_3) m/z: 332 (M+18, 17); MS (Electron Spray): calc'd for $C_{17}H_{18}N_2O_4Na$: 337.1164, found: 337.1180.



2-*p*-Cresoxy-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (403): Clear oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (s, 6H), 2.27 (s, 3H), 7.07-7.29 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.6, 23.5, 121.3, 122.1, 124.8, 129.1, 129.5, 134.5, 136.1, 149.4, 151.8; IR (CCl_4) cm^{-1}: 3068w, 3039m, 2994s, 2939m, 2869w, 1780m, 1593s, 1507s, 1494s, 1458m, 1383m, 1369m, 1288m, 1087br, 1020w, 989m.

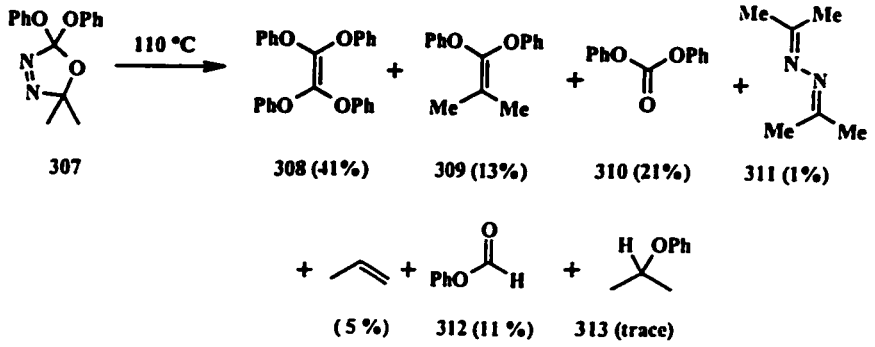
3.4.4 Thermolysis Rate Constants

The rates of decomposition of the oxadiazolines were monitored by ^{1}H NMR spectroscopy at 300 MHz. A sample, typically containing 1.25×10^{-4} mol of an oxadiazoline and 7 mg of *p*-xylene (internal standard) in 0.5 mL of C_6D_6, was degassed and sealed into a medium-walled NMR tube. At appropriate time intervals during

thermolysis, the tube was removed from the oil bath and quickly chilled to room temperature to record the ^{1}H NMR spectrum. All oxadiazoline thermolyses were run simultaneously. Linear regression analyses of the data, ($\ln(I/I_0)$ vs. time, where I and I_0 are the normalized integrals of a given resonance at time t and at time zero, respectively) gave first-order decomposition rate constants from the slopes of the calculated best fits including the origin. Rate constants for thermolysis of four members of the diaryloxy oxadiazolines are in Table 2, page 75.

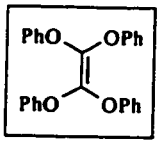
3.4.5 Thermolysis of Diaryloxy Oxadiazolines in the absence of Trapping Reagents

Thermolysis Products from 2,2-Diphenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the absence of Trapping Agents:

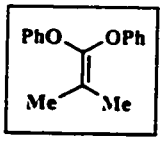


2,2-Diphenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**307**) (0.82 g, 2.88 mmol) was heated at 110 °C in 25 mL of benzene for 24 hours. The solvent was evaporated and the residue was subjected to radial chromatographic separation, which gave carbene dimer in 41% yield (0.234 g), ketene acetal in 14% yield (0.09 g), and carbonate in 21% yield (0.13 g). Yields came from a thermolysis experiment carried out in a sealed NMR tube containing *p*-dimethoxybenzene as internal standard. After the thermolysis, the ^{1}H NMR

spectrum was acquired and integrated without opening the tube, with use of a 300 s relaxation delay.



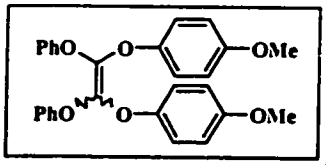
Dimer of Diphenoxycarbene (308): white solid, mp = 162-163 °C. (lit m.p. = 165-166 °C).[179] ^{1}H NMR (200 MHz, C_6D_6) δ: 6.74-7.28 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.7, 123.3, 129.5, 137.4, 155.7; IR (CCl_4) cm^{-1}: 2955w, 1595m, 1495m, 1335w, 1290w, 1225m, 1206s, 1310m, 1105m, 1075m; MS (EI) m/z: 396 (M, 4), 291 (4), 199 (25), 153 (20), 141 (30) 105 (18), 77 (100), 51 (89); MS (CI, NH_3) m/z: 397 (M+1, 2), 199 (100).



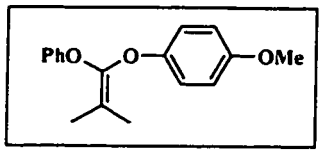
1,1-Diphenoxy-2-methylpropene (ketene acetal 309): White solid, mp = 41 – 42 °C. ^{1}H NMR (200 MHz, C_6D_6) δ: 1.75 (s, 6H, Me), 6.96-7.29 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5, 105.0, 116.1, 122.4, 129.3, 144.4, 155.8; IR (CCl_4) cm^{-1}: 3100w, 3079w, 3023w, 2948m, 2895w, 1725s, 1600s, 1498s, 1380w, 1290w, 1242s, 1200s, 1120br, 1078m, 1060w; MS (EI) m/z: 141 (M+1, 10), 140 (M, 33), 147 (10), 119 (100), 91 (50), 77 (45), 41 (37); MS (CI, NH_3) m/z: 241 (M+1, 100), 240 (M, 33), 119 (100).

Thermolysis products from 2-(*p*-Methoxyphenoxy)-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the absence of Trapping Agents:

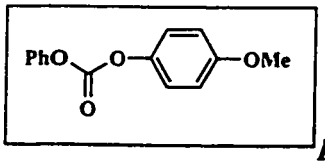
2-*p*-Methoxyphenoxy-2-phenoxy oxadiazoline (0.67 g, 2.14 mmol) was heated at 110 °C in 20 mL of benzene. The solvent was evaporated and the residue was subjected to radial chromatography which give carbene dimers as a 1: 1 mixture of isomers in 39% yield (0.19 g), ketene acetal in 11% yield (0.064 g), and carbonate in 23% yield (0.12 g). Yields came from a thermolysis experiment carried out in a sealed NMR tube containing *p*-xylene as internal standard. After the thermolysis, the ^{1}H NMR spectrum was acquired and integrated without opening the tube, with use of a 300 s relaxation delay.



Dimers of *p*-Methoxyphenoxy(phenoxy)carbene: white solid, mp = 99-101.5 °C. The *E*- and *Z*- isomers, in *ca.* 1: 1 ratio from the proton NMR spectrum, could not be separated. Composite spectra for two isomers are listed. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.74 (d, 6H), 6.60 (d, ^3J = 4.5 Hz, 4H), 6.77-7.31 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 114.6, 116.7, 118.0, 123.2, 129.4, 137.7, 149.6, 155.7; IR (CCl_4) cm^{-1}: 3072w, 3046w, 3002m, 2952m, 2909w, 2836m, 1595s, 1503s, 1466m, 1442w, 1297m, 1199br, 1102s, 1041s; MS (EI) m/z: 457 (M +1, 12), 351 (9), 321 (10), 239 (16), 184 (15), 135 (100), 92 (52), 78 (100), 51 (38); MS (CI, NH_3) m/z: 458 (M+2, 64), 457 (M+1, 10).



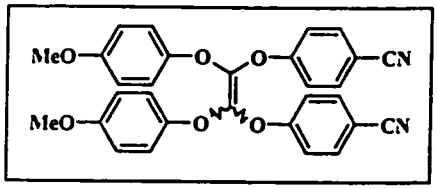
1-(*p*-Methoxyphenoxy)-1-phenoxy-2-methylpropene: clear oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.72 (s, 3H), 1.77(s, 3H), 3.73 (s, 3H), 6.28 (d, ^{3}J = 4.6 Hz, 2H), 6.78~7.29 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5, 55.6, 104.1, 114.4, 116.1, 117.2, 122.3, 129.3, 144.9, 149.6, 155.1, 155.9; IR (CCl_4) cm^{-1}: 2916m, 2835w, 1715s, 1594s, 1550m, 1504s, 1492s, 1465m, 1443w, 1245m, 1217s, 1192s, 1158br, 1103m, 1043m; MS (EI) m/z: 270 (M, 45), 149 (100), 119 (85), 91 (68), 77 (60), 41 (40); MS (CI, NH_3) m/z: 271 (M+1, 100); MS (HR) m/z: calc'd for $C_{17}H_{18}O_3$: 270.1262, found: 270.1256.



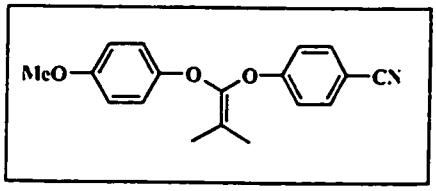
***p*-Methoxyphenyl Phenyl Carbonate:** white solid, mp= 90-92 °C. (lit. mp = 92-94°C).[180,181] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.78 (s, 3H), 6.58 (d, ^{3}J = 6.0 Hz, 2H), 6.84-7.05 (m, 5H), 7.14 (d, ^{3}J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 114.5, 120.9, 121.7, 126.2, 129.5, 144.6, 151.1, 152.4, 157.6; IR (CCl_4) cm^{-1}: 3049m, 3006m, 2955m, 2912m, 2838m, 2229w, 2055w, 1779br, 1596s, 1502br, 1462s, 1442m, 1296s, 1232br, 1178br, 1103m, 1039s, 1009s; MS (EI) m/z: 244 (M, 42), 200 (11), 185 (22), 157 (4), 123 (83), 107 (12), 95 (30), 77 (100), 65 (30), 51 (31); MS (CI, NH_3) m/z: 262 (M+18, 100), 244 (M, 82).

Thermolysis of 2-*p*-Cyanophenoxy-2-*p*-methoxyphenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline in the absence of Trapping Agents

2-*p*-Cyanophenoxy-2-*p*-methoxyphenoxy oxadiazoline (**295a**) (0.48 g, 1.40 mmol) was thermolysed in 20 mL of benzene. The solvent was evaporated and the residue was subjected to radial chromatography which give carbene dimers as a 1.25: 1 mixture of isomers in 28% yield (0.10 g), ketene acetal in 12% yield (0.05 g), and carbonate in 16% yield (0.06 g).

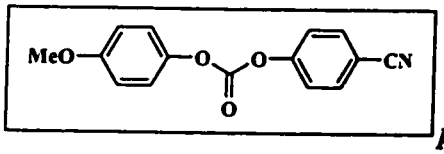


Dimers of *p*-Cyanophenoxy(*p*-methoxyphenoxy)carbene. The spectra are composites of the *E*- and *Z*-isomers (isomer ratio 1.25: 1) estimated from the ^{1}H NMR spectrum. It was not possible to determine which isomer was the major one. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.76 (s, 3H), 3.77 (s, 2.4H), 6.78-7.64 (m, 14.4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 107.3, 114.8, 117.2, 117.3, 117.8, 118.0, 118.4, 134.1, 137.2, 148.7, 148.9, 156.2, 158.5, 158.6; IR (CCl_4) cm^{-1}: 3004w, 2954m, 2911w, 2838, 2232m, 1604s, 1503s, 1495w, 1442w, 1296m, 1216s, 1183s, 1168m, 1099s, 1040m; MS (EI) m/z: 506 (M, 8), 135 (100), 123 (36), 107 (28), 102 (45), 77 (70), 43 (68); MS (CI, NH_3) m/z: 524 (M+18, 3).



1-(*p*-Cyanophenoxy)-1-*p*-methoxyphenoxy-2-methylpropene (*p*-Cyanophenyl-*p*-methoxyphenyl Acetal of Dimethyl Ketene): light

yellow solid, m.p. = 89-91 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.70 (s, 3H, Me), 1.78 (s, 3H, Me), 3.75 (s, 3H, OMe), 6.78 (d, ^3J = 9.2 Hz, 2H), 6.88 (d, ^3J = 9.2 Hz, 2H), 7.06 (d, ^3J = 8.8 Hz, 2H), 7.58 (d, ^3J = 8.8 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3, 16.4, 55.6, 105.7. 105.8, 114.6, 116.8, 117.0, 118.8, 133.9, 143.9, 149.2, 155.4, 159.2; IR (CCl_4) cm^{-1}: 3005w, 2936m, 2919w, 2837w, 2230m, 1781w, 1717m, 1605m, 1504s, 1464w, 1444w, 1296w, 1232s, 1194s, 1155br, 1136m, 1105w, 1041m; MS (EI) m/z: 295 (M, 28), 149 (100), 124 (34), 116 (22), 77 (15), 41 (61); MS (CI, NH_3) m/z: 313 (M+18, 24), 296 (M, 90); MS (HR) m/z: calc'd for $C_{18}H_{17}NO_3$ 295.1122, found 295.1153.



***p*-Cyanophenyl *p*-Methoxyphenyl Carbonate:** 28.6% yield, white solid, m.p = 103-105 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.79 (s, 3H, OMe), 6.92 (d, ^3J = 9.2 Hz, 2H), 7.18 (d, ^3J = 9.2 Hz, 2H), 7.42 (d, ^3J = 8.8 Hz, 2H), 7.73 (d, ^3J = 8.8 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5, 110.1, 114.5, 117.9, 121.5, 121.9, 133.7, 144.2, 151.4, 153.8, 157.7; IR (CCl_4) cm^{-1}: 3004m, 2932m, 2838m, 2232m, 1781s, 1717m, 1605s, 1505s, 1465m, 1296m, 1225s, 1183s, 1041m; MS (EI) m/z: 269 (M, 34), 254 (31), 225 (9), 210 (23), 154 (6), 123 (100), 107 (84), 77 (77), 65 (32); MS (CI, NH_3) m/z: 287 (M+18, 48), 269 (M, 89), 123 (100).

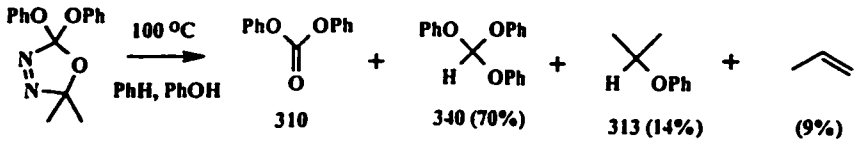
Attempted Hydrolysis of the *p*-Cyanophenyl-*p*-methoxyphenyl Acetal of Dimethyl Ketene

An attempt to hydrolyse one of the ketene acetals was carried out. *p*-Cyanophenyl-*p*-methoxyphenyl acetal of dimethyl ketene and 20 equivalents of water were added to benzene-d_6 as well as one equivalent of *p*-xylene as internal standard. The solution was

degassed by means of the usual procedure and sealed into a medium-walled NMR tube. Then the solution was immersed into a 110 °C oil bath for 24 hours. The comparison of ^{1}H NMR spectra, with use of a 300 s relaxation delay, taken before and after the heating showed no change of the compound. The spectra are in Appendix 3.

3.4.6 Thermolyses of Diaryloxy Oxadiazolines in the presence of Phenols

Thermolyses of Diphenoxy Oxadiazolines in the presence of *p*-Cresol



2,2-Diphenoxy-5,5-dimethyl-Δ^3-1,3,4- oxadiazoline (**307**) (1.0 g, 3.50 mmol) was heated at 100 °C for 24 hours in 25 mL of benzene containing 3.3 g (35 mmol) of phenol. The products that could be isolated were diphenyl carbonate and triphenyl orthoformate (**340**).

340: mp 73-74 °C, a white solid in 76 % yield (0.77 g);[182] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.81 (s, 1H, $(PhO)_3C\underline{H}$), 7.06-7.33 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.9, 118.2, 123.6, 129.6, 153.9; IR (CCl_4) cm^{-1}: 3069m, 3046m, 1784m, 1597s, 1491s, 1363m, 1289m, 1228s, 1206s, 1061s, 1028m, 997m; MS (EI) m/z: 199 (100), 171(7), 153 (31), 141 (4), 94 (17), 77 (72), 65 (20), 51 (31); MS (CI, NH_3) m/z: 199 (M-93).

Thermolyses of Diaryloxy Oxadiazolines in the presence of *p*-Cresol

A solution of 2,2-diphenoxy oxadiazoline (**307**) (1.14 g, 4.02 mmol) in 25 mL of benzene containing *p*-cresol (4.32g, 40 mmol) was heated at 105 °C for 24 h. *p*-Cresyl diphenyl orthoformate was isolated as a white solid, mp 82-83 °C, in 65% yield (0.80 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.27 (s, 3H), 5.56 (s, 1H, CH), 6.98-7.31 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.5, 111.0, 118.0, 123.4, 129.6, 130.0, 133.0, 151.5, 153.8; IR (CCl_4) cm^{-1}: 3069m, 3043m, 2927m, 2869m, 1596s, 1495s, 1457w, 1363m, 1288m, 1194s, 1171s, 1032s; MS (EI) m/z: 213 (M-OPh, 98), 199 (M-OC_6H_4OMe, 100), 167 (16), 153 (21), 108 (16), 91 (46), 77 (85), 55 (40), 51 (28); MS (CI, NH_3) m/z: 213 (M-OPh, 100), 199 (M- OC_6H_4OMe, 81). By GC/MS it was possible to detect traces of p-cresyl isopropyl ether and diphenyl carbonate.

Thermolyses of 2-(*p*-Cyanophenoxy)-2-phenoxy Oxadiazolines in the presence of *p*-Cresol

Similarly, a solution of 2-(*p*-cyanophenoxy) 2-phenoxy oxadiazoline **295c** (0.2g, 0.65 mmol) and *p*-cresol (0.56g, 5.18 mmol) in 25 mL of benzene was heated at 105 °C for 24 h. *p*-Cresyl *p*-cyanophenyl phenyl orthoformate was isolated as a pale yellow oil, in 84% yield (0.18 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 6.62 (s, 1H, CH), 6.96-7.30 (m, 4H), 7.31 (d, ^{3}J=5.6 Hz, 2H), 7.61 (d, ^{3}J= 5.6 Hz,2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.6, 106.8, 110.6, 118.1, 118.6, 124.0, 130.0, 130.2, 133.7, 133.9, 151.2, 153.5, 156.9; IR (CCl_4) cm^{-1}: 3067m, 3039m, 2926m, 2231m, 1607s, 1549m, 1508s, 1257m, 1208s, 1172s, 1068s; MS (EI) m/z: 238 (M-OPh, 55), 224 (M-OC_6H_4Me, 88),

213 (M-OC_6H_4CN, 93), 196 (19), 185 (9), 167 (9), 153 (7), 123 (5), 107 (17), 91 (62), 77 (100), 65 (45), 51 (21); MS (CI, NH_3) m/z: 238 (M-OPh, 37), 224 (M- OC_6H_4Me, 47), 213 (M- OC_6H_4CN, 100).

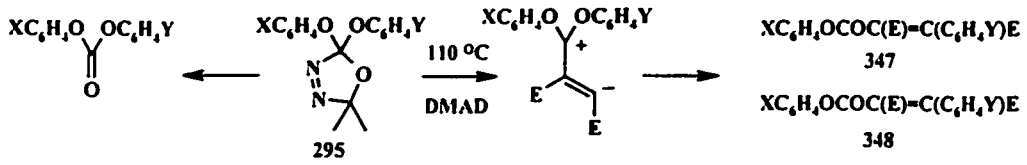
Thermolyses of 2-(*p*-Methoxyphenoxy)-2-phenoxy oxadiazolines in the presence of *p*-Cresol

2-(*p*-Methoxyphenoxy)-2-phenoxy oxadiazoline **295d** (0.47 g, 1.50 mmol) in 25 mL of benzene containing *p*-cresol (1.29 g, 11.94 mmol) was heated at 105 °C for 24 h. The major product was *p*-cresyl *p*-methoxyphenyl phenyl orthoformate, obtained as a pale yellow oil in 70% yield (0.353 g). ^1H NMR (200 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 3.74 (s, 3H), 6.47 (s, 1H, CH), 6.81 (d, $^3J = 4.6$ Hz, 2H), 6.99-7.32 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.6, 55.5, 111.7, 114.6, 118.1, 120.0, 123.4, 129.5, 130. 0, 132.9, 141.6, 147.4, 151.7, 154.0, 155.9; IR (CCl_4) cm^{-1}: 3038m, 3004m, 2953m, 2934m, 2836m, 1592m, 1549m, 1507.9s, 1463m, 1247m, 1208s, 1070s, 1042m, 1016m; MS (EI) m/z: 243 (M-OPh, 19), 229 (M-OC_6H_4Me, 31), 213 (M-OC_6H_4OMe, 100), 185 (7), 167 (13), 152 (6), 123 (12), 107 (16), 91 (32), 77 (49), 65 (24), 51 (13); MS (CI, NH_3) m/z: 243 (M-OPh, 40), 229 (M-O C_6H_4Me, 59), 213 (M-OC_6H_4OMe, 100).

3.4.7 Thermolysis of Diaryloxy Oxadiazolines with DMAD

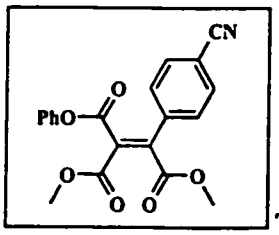
Similar thermolysis reactions were done to let diaryloxy carbenes react with DMAD. Generally, oxadiazoline (0.2-1g) and 1.2 equivalent of DMAD were added into the thermolysis tube. Azeotropic distillation was done to remove a trace of water. The thermolysis tube was heated for 24 hours in oil bath and then separation was done. The

structure of the aromatic substitution product was mainly deduced from the mass spectrum.

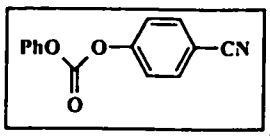


a: X=*p*-OMe, Y=*p*-CN; b: X=*p*-Me, Y=*p*-CN; c: X=H, Y=*p*-CN; d: X=H, Y=*p*-OMe; e: X=H, Y=*o*-OMe; E=CO_2Me

Thermolysis of 2-(*p*-Cyanophenoxy)-2-phenoxy Oxadiazoline (295c) with DMAD



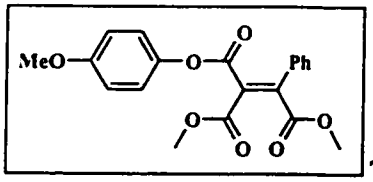
The Aromatic Substitution Product (347c): 37% yield; light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.77-7.76 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.4, 114.0, 117.8, 120.7, 126.6, 128.6, 128.7, 129.6, 132.5, 137.1, 145.4, 149.6, 162.0, 165.9; IR (CCl_4) cm^{-1}: 3038w, 3007w, 2955m, 2847w, 2233m, 1742b, 1638m, 1593m, 1550m, 1492s, 1457w, 1436s, 1407w, 1307m, 1267b, 1233b, 1189s, 1160m, 1074s, 1010s; MS (EI) m/z: 365 (M, 2), 334 (M-OMe, 7), 272 (M-OPh, 100), 244 (17), 200 (13), 176 (8), 154 (14), 77 (9), 59 (37); MS (CI, NH_3) m/z: 383 (M+18, 84), 272 (M-OPh, 100).



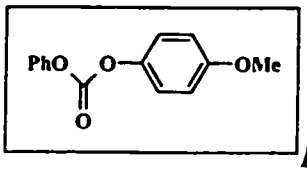
***p*-Cyanophenyl Phenyl Carbonate (349c):** 30% yield, white solid, m.p = 79-80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.26-7.46 (m, 7H, ArH), 7.73 (d, ^3J = 4.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.3, 118.0, 120.7, 122.0, 126.7, 130.0, 133.9, 150.7, 151.1, 153.9; IR (CCl_4) cm^{-1}: 3049w, 2235m, 1782s, 1603m, 1550m, 1507m,

1495m, 1457w, 1412w, 1294w, 1221b, 1186s, 1163s, 1103w, 1071w, 1008m; MS (EI) m/z: 239 (M, 33), 195 (22), 167 (28), 140 (5), 121 (13), 102 (21), 77 (100), 65 (35), 49 (30), 43 (76); MS (CI, NH_3) m/z: 257 (M+18, 21), 239 (M, 89).

Thermolysis of 2-*p*-Methoxyphenoxy-2-phenoxy Oxadiazoline (295d) with DMAD:



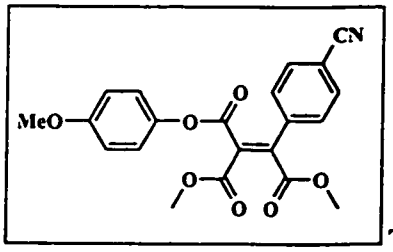
The Aromatic Substitution Product (347d): 38%yield, light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.75 (s, 3H, OMe), 3.90 (s, 6H, OMe×2), 6.67 (d, ^3J = 9.0 Hz, 2H), 6.80 (d, ^3J = 9.0 Hz, 2H), 7.25-7.49 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.0, 53.1, 55.5, 114.4, 121.7, 126.3, 127.7, 128.9, 130.4, 132.8, 143.4, 148.0, 157.6, 162.7, 163.4, 167.0; IR (CCl_4) cm^{-1}: 3064w, 3004m, 2954m, 2909w, 2839m, 1743b, 1633m, 1598w, 1505s, 1464w, 1437m, 1269s, 1232s, 1188s, 1070m, 1039m, 1012m; MS (EI) m/z: 370 (M, 2), 339 (M-OMe, 5), 311 (7), 277 (6), 247 (100), 219 (41), 151 (16), 129 (22), 95 (10), 59 (27); MS (CI, NH_3) m/z: 388 (M+18, 8), 371 (M+1, 15), 247 (100).



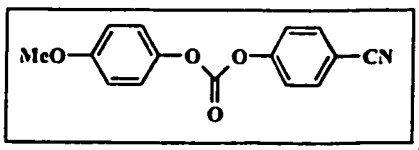
***p*-Methoxyphenyl Phenyl Carbonate (349d):** 32% yield, light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.80 (s, 3H, OMe), 6.90 (d, ^3J = 9.0 Hz, 2H), 7.16-7.44 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$)δ: 55.6, 114.5, 120.9, 121.8, 126.2, 129.5, 144.6, 151.1, 152.4, 157.6; IR (CCl_4) cm^{-1}: 3047w, 3006m, 2956m, 2912w, 2838m, 1780s, 1596m, 1507s, 1465m, 1442m, 1298m, 1229s, 1182s, 1103m, 1071m,

1041m, 1010m; MS (EI) m/z: 245 (M+1, 21), 244 (M, 100), 200 (15), 185 (32), 157 (11), 124 (60), 123 (46), 95 (25), 77 (95), 65 (30), 41 (24); MS (CI, NH_3) m/z: 262 (M+18, 100), 244 (M, 100).

Thermolysis of 2-*p*-Cyanophenoxy-2-(*p*-methoxyphenoxy) Oxadiazoline (295a) with DMAD



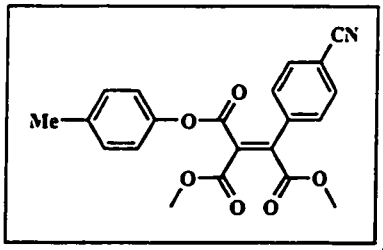
The Aromatic Substitution Product (347a), 37 % yield, light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.76 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.70 (d, ^3J = 4.6 Hz, 2H), 6.82 (d, ^3J = 4.6 Hz, 2H), 7.59 (d, ^3J = 4.6 Hz, 2H), 7.72 (d, ^3J = 4.6 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.3, 55.5, 113.9, 114.5, 117.8, 121.4, 128.5, 128.9, 132.4, 137.2, 143.1, 145.2, 157.7, 162.3, 162.4, 165.8; IR (CCl_4) cm^{-1}: 3007m, 2955m, 2910w, 2839w, 2234m, 1746br, 1637w, 1608w, 1505s, 1461m, 1437m, 1270s, 1232s, 1188s, 1103w, 1073s, 1038m, 1010m; MS (EI) m/z: 395 (M, 7), 364 (M-31, 6), 272 (100), 244 (40), 200 (42), 154 (96), 123 (71), 95 (40), 59 (80); MS (CI, NH_3) m/z: 413 (M+18, 19), 396 (M+1, 17), 272 (100).



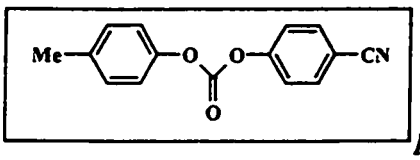
***p*-Cyanophenyl *p*-Methoxyphenyl Carbonate (349a),** 29% yield, white solid, m.p = 103-105 °C: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.79 (s, 3H, OMe), 6.90 (d, ^3J = 9.2 Hz, 2H), 7.17 (d, ^3J = 9.2 Hz, 2H), 7.40 (d, ^3J = 8.8 Hz, 2H), 7.68

(d, ^3J = 8.8 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5, 110.1, 114.5, 117.9, 121.5, 121.9, 133.7, 144.2, 151.4, 153.8, 157.7; IR (CCl_4) cm^{-1}: 3004m, 2932m, 2838m, 2232m, 1781s, 1717m, 1605s, 1505s, 1465m, 1296m, 1225s, 1183s, 1041m; MS (EI) m/z: 269 (M, 34), 254 (31), 225 (9), 210 (23), 154 (6), 123 (100), 107 (84), 77 (77), 65 (32); MS (CI, NH_3) m/z: 287 (M+18, 48), 269 (M, 89), 123 (100).

Thermolysis of 2-*p*-Cyanophenoxy-2-(*p*-methylphenoxy) Oxadiazoline (295b) with DMAD

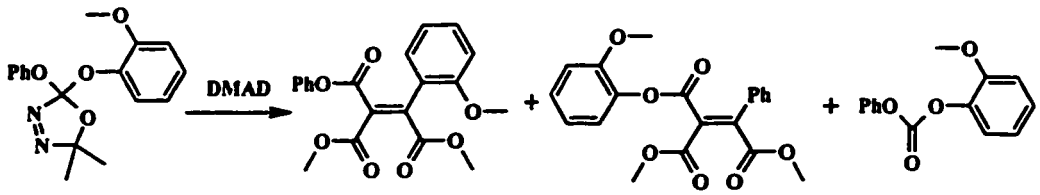


Aromatic Substitution Product (347b): yield 26%, light yellow oil; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H, Me), 3.88 (s, 3H, OMe), 3.13 (s, 3H, OMe), 6.66-7.13 (m, 4H, -C_6H_4-Me), 7.58-7.73 (m, 4H, -C_6H_4-CN); ^{13}C NMR (50 MHz) δ: 20.7, 53.3, 99.8, 113.9, 117.8, 120.3, 120.6, 128.6, 130.0, 132.4, 136.3, 137.2, 145.2, 147.5, 162.1, 162.4, 165.8; IR (CCl_4) cm^{-1}: 3465w, 3037w, 3006w, 2955m, 2926w, 2846w, 2233m, 1746s, 1638m, 1610m, 1507s, 1437s, 1407w, 1306w, 1269s, 1229s, 1189s, 1163w, 1074s, 1010s; MS (EI) m/z: 51 (9), 59 (32), 77 (23), 107 (8), 154 (46), 176 (14), 200 (23), 244 (23), 272 (M-$OC_6H_4CH_3$, 100), 348 (M-CH_3); MS (CI, NH_3) m/z: 272 (M-$OC_6H_4CH_3$, 100), 380 (M+1, 20), 397 (M+18, 33).



***p*-Cyanophenyl *p*-Methylphenyl Carbonate (349b):** yield 28%, white solid, m.p = 91-92 °C. ^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H, Me), 7.12-7.25 (m, 4H, -C_6H_4-Me), 7.13 (d, ^3J = 5.6 Hz, 2H), 7.23 (d, ^3J = 5.6 Hz, 2H), 7.42 (d, ^3J = 5.8 Hz, 2H). 7.71 (d, ^3J = 5.8 Hz, 2H, -C_6H_4-CN); ^{13}C NMR (50 MHz) δ: 20.8, 110.3, 117.9, 120.4, 122.0, 130.2, 133.8, 136.4, 148.6, 151.3, 154.0; IR (CCl_4) cm^{-1}: 3041w, 2928w, 2867w, 2234m, 1782s, 1604m, 1506s, 1452w, 1412w, 1381w, 1286m, 1229s, 1188s, 1167s, 1105w, 1018m, 1006m; MS (EI) m/z: 65 (30), 77 (33), 91 (100), 102 (19), 209 (13), 253 (M^+, 23); MS (CI, NH_3) m/z: 253 (M+1, 37), 271 (M+18, 18).

Thermolysis of 2-(*o*-Methoxyphenoxy)-2-phenoxy Oxadiazoline (295e) with DMAD:

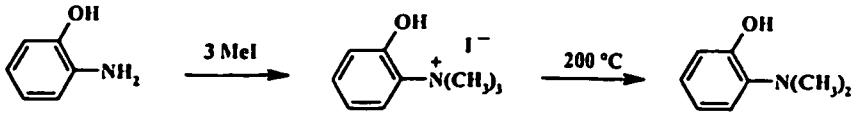


Aromatic Substitution Product (348e): yield 25%, light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.80 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.77-7.46 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.9, 53.0, 55.8, 111.3, 120.8, 121.0, 123.0, 126.1, 129.3, 130.0, 130.1, 131.8, 144.2, 150.1, 156.9, 162.7, 163.9, 166.9; IR (CCl_4) cm^{-1}: 3070w, 3005m, 2954s, 2841m, 1745b, 1592s, 1550b, 1493s, 1461m, 1436m, 1321w, 1226b, 1162m, 1117m; MS (EI) m/z: 371 (M+1, 4), 339 (10), 277 (M-93, 100), 249 (100), 219 (10), 205 (28), 181 (18), 159 (20), 131 (45), 103 (12), 65 (40); MS (CI, NH_3) m/z: 388 (M+18, 34), 371 (M+1, 40), 277 (M-93, 100).

Aromatic Substitution Product (347e): yield 11%, light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.74 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.63-7.60 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.0, 55.8, 112.6, 120.7, 122.3, 126.1, 127.3, 128.1, 128.7, 130.3, 132.6, 138.9, 148.2, 151.2, 162.5, 163.0, 167.2; IR (CCl_4) cm^{-1}: 3068w, 3005w, 2954m, 2841m, 1760m, 1742b, 1633m, 1609m, 1501s, 1460w, 1436m, 1308m, 1263b, 1232b, 1198b, 1174s, 1110s, 1069m, 1010m; MS (EI) m/z: 371 (M+1, 5), 247 (M-123, 100), 219 (53), 175 (19), 151 (16), 129 (31), 95 (22), 77 (28), 59 (33); MS (CI, NH_3) m/z: 388 (M+18, 38), 371 (M+1, 12), 247 (M-123, 100).

***o*-Methoxyphenyl Phenyl Carbonate (349e):** yield 35%, white solid, m.p = 58-59 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OMe), 6.92-7.44 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.0, 112.6, 120.7, 120.9, 122.2, 126.1, 127.3, 129.5, 140.0, 151.0, 151.2, 11.6; IR (CCl_4) cm^{-1}: 3074w, 3048m, 3012w, 2962m, 2946w, 2841m, 1784s, 1590w, 1550b, 1503b, 1465m, 1310m, 1233b, 1191s, 1173s, 1113m; MS (EI) m/z: 244 (M, 100), 200 (28), 185 (10), 151 (20), 124 (20), 95 (33), 77 (84), 65 (37); MS (CI, NH_3) m/z: 262 (M+18, 100), 244 (M, 100).

3.4.8 Generation of Diaryloxy Oxadiazolines bearing *ortho* Substituents



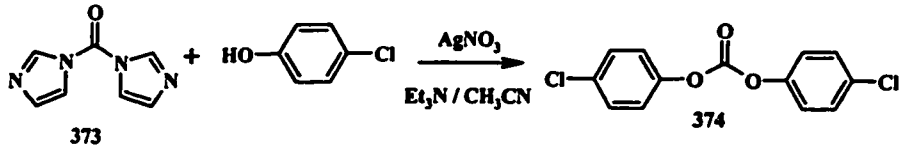
370 371 372

***o*-Hydroxy *N,N*-dimethyl aniline (*N,N*-dimethylaminophenol) (372):** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.67 (s, 6H, $N(C\underline{H}_3)_2$), 3.49 (s, 1H, O<u>H</u>), 6.96-7.26 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 45.3, 114.3, 120.1, 120.8, 126.3, 140.3, 151.5.

An attempt to do the exchange reaction of 2-acetoxy-2-phenoxy oxadiazoline (1.37 g, 5.48 mmol) with *N,N*-dimethylaminophenol (1.31 g, 10.31 mmol) in dichloromethane containing catalytic trifluoroacetic acid was carried out. Progress was monitored by TLC and GC, but the desired exchange did not occur during three weeks at reflux.

3.4.9 Generation of 2-Acetoxy-2-*p*-chlorophenoxy Oxadiazoline

Bis-4-chlorophenyl Carbonate (374) by the reaction of 1,1'-Carbonyldiimidazole with 4-Chlorophenol:

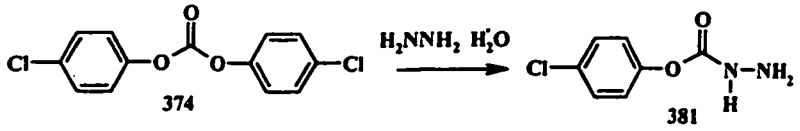


373 374

1,1'-Carbonyldiimidazole (9.72 g, 0.06 mol), 15.24 g (0.12 mol) of 4-chlorophenol, 20.4 g (0.12 mol) of silver nitrate and 12.12 g (0.12 mol) of triethylamine were combined in a round-bottomed flask with 100 mL of acetonitrile. The solution was heated and kept refluxing for 16 hours. Then it was cooled to room temperature after filtration. Hexane was added until no more precipitate was formed. Water vacuum filtration was used to separate the white needles (9.6 g, yield 56.5%) from the slightly dark solution. The white crystal was identified as the desired bis-4-chlorophenyl carbonate: white crystals, mp = 146 – 147 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.20 (d, ^3J = 9.0 Hz), 7.37 (d, ^3J = 9.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 122.3, 129.8, 132.0,

149.4, 151.7; IR (CCl_4) cm^{-1}: 1781s, 1549w, 1488s, 1278m, 1224br, 1187s, 1163m, 1104m, 1085s, 1013s; MS (EI) m/z: 284 (M, 54), 282 (M, 90), 238 (52), 168 (25), 128 (42), 111 (100), 99 (59), 75 (68), 63 (46); MS (CI, NH_3) m/z: 300 (M+18, 10), 282 (M, 27).

_p_-Chlorophenyl Hydrazinocarboxylate (381):



Bis-4-chlorophenyl carbonate (4 g, 0.014 mol) was dissolved in 30 mL CH_2Cl_2 and the solution was cooled with a Dry Ice bath for 15 minutes. Then 0.71g (0.014 mol) of hydrazine monohydrate was added in one portion. The Dry Ice was taken away and the solution was stirred for 20 minutes while it warmed gradually to room temperature. Then hexane was added to precipitate white needles. Vacuum filtration furnished pure *p*-chlorophenyl hydrazinocarboxylate: 1.06 g, yield 40%; mp = 144-145 °C; ^1H NMR ($CDCl_3$): 3.87 (s, 2H, NH_2), 6.35 (s, 1H, NH), 7.07-7.31 (m, 4H, ArH); ^{13}C NMR (50 MHz): 122.9, 129.6, 131.2, 149.3, 156.7; IR (CCl_4) cm^{-1}: 3458m, 3304m, 1757s, 1586w, 1549s, 1462m, 1215s, 1091w, 1010m, 978m.

p-Chlorophenoxycarbonyl Hydrazone of Acetone (382):

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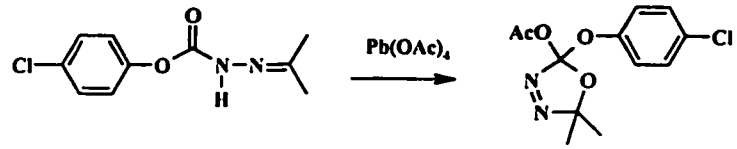
p-Chlorophenyl hydrazinocarboxylate (3.73g, 0.02 mol) and three spoonfuls of anhydrous magnesium sulfate were added to 60 mL of acetone. Stirring for 24 hours resulted in the full formation of the desired hydrazone. Filtration followed by evaporation of all acetone produced pure *p*-chlorophenoxycarbonyl hydrazone of acetone (**382**) as white crystals, yield 92% (4.16 g); mp = 98 – 102 °C; ^{1}H NMR ($CDCl_3$) δ: 1.88 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 7.13 (d, ^{3}J = 6.6 Hz, 2H), 7.34 (d, ^{3}J = 6.6 Hz, 2H, ArH), 7.97 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4, 25.5, 123.0, 129.5, 131.1, 149.3, 153.1; IR (CH_2Cl_2) cm^{-1}: 3383m, 1761s, 1482m, 1356m, 1262s, 1201m, 1122w, 1090m, 1012m; MS (EI) m/z: 229 (M+1, 5), 227 (M+1, 15), 128 (74), 99 (100), 56 (37); MS (CI, NH_3) m/z: 229 (M+1, 32), 227 (M+1, 100).

2-Acetoxy-2-(*p*-chlorophenoxy) Oxadiazoline (383):



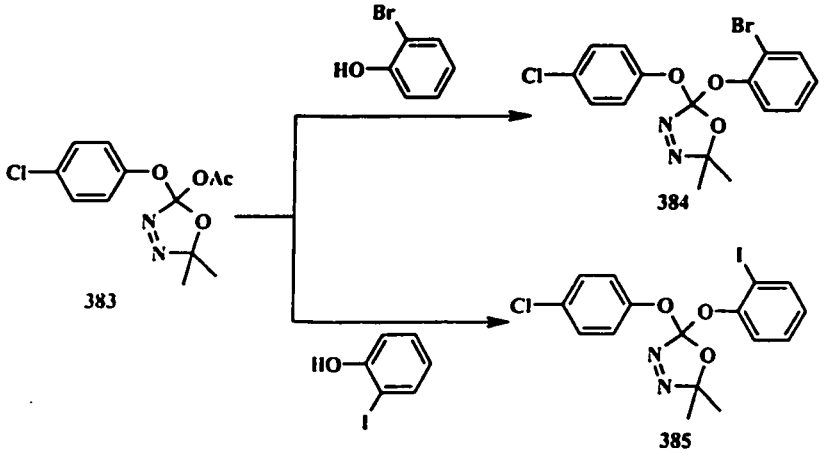
382 383

Lead tetraacetate (LTA) (11.4g, 2.57 mmol) was dissolved in 60 mL CH_2Cl_2 and cooled by Dry Ice in 2-propanol to – 30 °C. *p*-Chlorophenoxycarbonyl hydrazone of acetone 4.84 g (2.14 mmol) in 20 mL of CH_2Cl_2 was added dropwise into the LTA

solution. The solution was gradually warmed to room temperature and stirred overnight. Then the solution was washed three times with 5% $NaHCO_3$ and dried with anhydrous $MgSO_4$. After complete evaporation of the solvent, flash column chromatography was used to isolate pure acetoxy 4-chlorophenoxy oxadiazoline as a yellow oil, yield 36% (0.22 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40 (s, 3H, Me), 1.67 (s, 3H, Me), 2.08 (s, 3H, COMe), 7.16 (d, ^3J = 8.8 Hz, 2H), 7.28 (d, ^3J = 8.8 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 22.7, 24.2, 123.0, 123.8, 129.3, 130.4, 133.0, 150.1, 165.9; IR (CCl_4) cm^{-1}: 2995s, 2930s, 2873m, 1797br, 1735s, 1588m, 1490s, 1462m, 1434m, 1405w, 1371m, 1278m, 1231br, 1013m, 985m.

3.4.10 Generation of Diaryloxy Oxadiazolines bearing an *ortho* Bromo or Iodo Substituent

2-(*p*-Chlorophenoxy)-2-(*o*-iodophenoxy) Oxadiazoline:

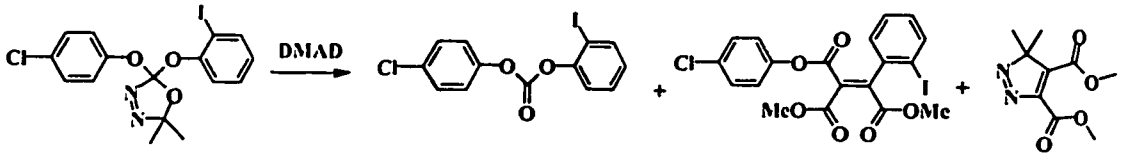


2-Acetoxy-2-(*p*-chlorophenoxy) oxadiazoline (1.81 g, 6.36 mmol) and 1.54 g (7.00 mmol) of 2-iodophenol were dissolved in 60 mL CH_2Cl_2 with catalytic

trifluoroacetic acid. The solution was refluxed for 24 hours. Flash column chromatography was then used to separate pure *p*-chlorophenoxy *o*-iodophenoxy oxadiazoline (**385**) as a yellow oil in 43 % yield (1.21 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (s, 3H, Me), 1.37 (s, 3H, Me), 6.80-7.30 (m, 4H, ArH), 7.49 (d, ^3J = 8.2 Hz, 2H), 7.76 (d, ^3J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.5, 23.7, 90.4, 121.4, 122.3, 123.2, 123.8, 126.2, 129.2, 130.5, 135.7, 139.6, 149.9, 151.5; IR (CCl_4) cm^{-1}: 2996w, 1584m, 1550m, 1486s, 1469m, 1252w, 1209s, 1155s, 1105m, 1087s, 1014m, 985w.

2-(*o*-Bromophenoxy)-2-(*p*-chlorophenoxy) Oxadiazoline (384): yellow oil, yield 30%; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.33 (s, 6H, 2Me), 6.99-7.55 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.5, 23.7, 116.4, 122.4, 122.8, 123.6, 126.0, 128.0, 129.2, 130.5, 133.5, 135.7, 148.8, 149.9; IR (CCl_4) cm^{-1}: 3072w, 2996m, 2938w, 1584m, 1550m, 1488s, 1476s, 1443m, 1384w, 1370w, 1279w, 1209br, 1155br, 1108s, 1086s, 1031m, 1014m, 978.8w.

3.4.10.1 Thermolysis of 2-(*p*-Chlorophenoxy)-2-(*o*-iodophenoxy) Oxadiazoline with DMAD

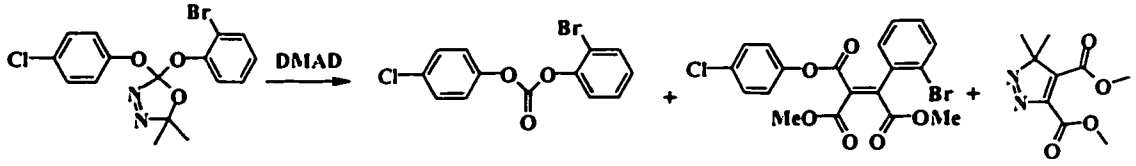


2-(*p*-Chlorophenoxy)-2-(*o*-iodophenoxy) oxadiazoline (0.28 g, 0.62 mmol) and 0.11 g (0.77 mmol) of dimethyl acetylene dicarboxylate were put into a thermolysis tube with 20 mL of dried benzene. The solution was heated at 110 °C in an oil bath for 24 hours. A small amount thermolysis solution was used to do the GC-MS analysis directly. The solvent was removed from the rest of the solution with a rotary evaporator. Ethyl acetate 5% in hexane was then used as eluting solvent for flash column chromatography to separate the mixture into three pure products: carbonate (0.069 g, 30% yield), aromatic substitution product **391b** (0.12 g, 38% yield) and pyrazole (0.03 g, 23% yield).

***p*-Chlorophenyl *o*-Iodophenyl Carbonate (387b):** 30% yield; white solid, mp = 81-82 ° C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.99-7.44 (m, 6H, ArH), 7.86 (d, ^{3}J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 89.7, 122.3, 128.3, 129.7, 131.9, 139.7, 149.4, 150.8, 151.0; IR (CCl_4) cm^{-1}: 1782s, 1549m, 1488m, 1469m, 1441w, 1279w, 1225br, 1190s, 1090m, 1044w, 1016m, 979w; MS (EI) m/z: 376 (M, 3), 374 (M, 14), 247 (13), 203 (26), 168 (100), 139 (20), 111 (52), 82 (26), 76 (74), 63 (60); MS (HR) m/z: calc'd. (for $C_{13}H_8{}^{35}ClIO_3$) 373.9207, found 373.9213.

The Aromatic Substitution Product (391b): 38% yield; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.82 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.72 (d, ^{3}J = 8.6 Hz, 2H), 7.09-7.41 (m, 5H, ArH), 7.88 (d, ^{3}J =7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.3, 96.4, 122.2, 128.1, 129.3, 129.4, 130.4, 131.7, 132.9, 139.0, 139.1, 146.6, 148.2, 160.9, 163.8, 164.8; IR (CCl_4) cm^{-1}: 2954w, 1738br, 1550w, 1487m, 1463w, 1435m, 1315w, 1278m, 1257m, 1229s, 1197s, 1163w, 1092m, 1074m, 1047w, 1013s, 980w; MS (EI) m/z: 373 (M-(O-C_6H_4-Cl), 100), 255 (38), 246 (53), 215 (57), 187 (48), 173 (39), 128 (100), 115 (53), 99 (67), 64 (67), 59 (86); MS (CI, NH_3) m/z: 518 (M+18, 100), 501 (M, 43).

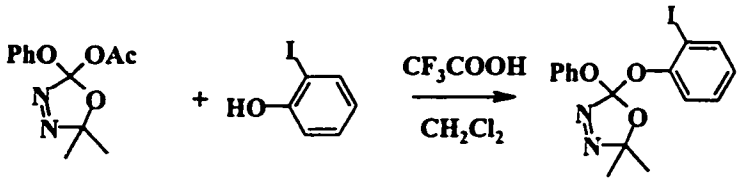
3.4.10.2 Thermolysis of 2-(*p*-Chlorophenoxy)-2-(*o*-bromophenoxy) Oxadiazoline with DMAD



***o*-Bromophenyl *p*-Chlorophenyl Carbonate (387a):** 23% yield; white solid; mp = 98.5 –99.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.18-7.65 (m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 116.0, 122.4, 123.3, 128.2, 128.9, 129.8, 132.1, 133.8, 148.3, 149.6, 150.9; IR (CCl_4) cm^{-1}: 1784s, 1488m, 1476m, 1229br, 1194s, 1091m, 1050w, 1015w; MS (EI) m/z: 330 (M, 10), 328 (M, 40), 326 (M, 28), 247 (14), 168 (100), 155 (37), 143 (20), 111 (63), 75 (66), 63 (66); MS (CI, NH_3) m/z: 346 (M+18, 100).

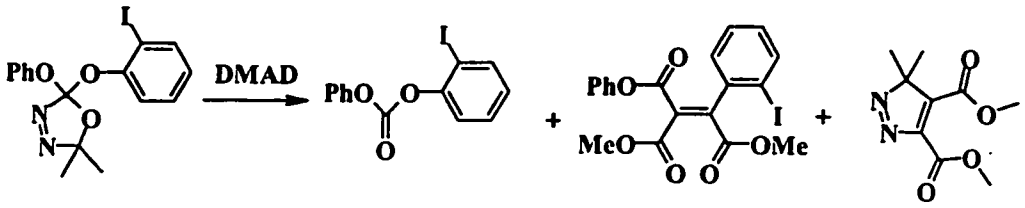
The Aromatic Substitution Product (391a): 38% yield; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.82 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.73-7.61 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.5, 1168, 122.4, 127.6, 129.6, 130.2, 130.9, 131.9, 133.0, 135.1, 148.3, 161.3, 164.0, 165.1; IR (CCl_4) cm^{-1}: 2954w, 1740br, 1487m, 1436m, 1258m, 1230s, 1197s, 1092m, 1072m, 1045w, 1013m; MS (EI) m/z: 423 (M-OMe, 4), 373 (M-Br, 12), 327 (98), 325 (M-(O-C_6H_4-Cl), 100), 297 (58), 246 (31), 209 (92), 207 (92), 128 (62), 99 (90), 59 (77); MS (CI, NH_3) m/z: 472 (M+18, 100).

3.4.10.3 2-(*o*-Iodophenoxy)-2-phenoxy Oxadiazoline



2-Acetoxy-2-phenoxy oxadiazoline (2.69 g, 0.011 mol) and 2.84 g (0.013 mol) of 2-iodophenol were dissolved in 60 mL of CH_2Cl_2 with catalytic trifluoroacetic acid. The solution was refluxed for 24 hours. Flash column chromatography was then used to separate pure *p*-chlorophenoxy *o*-iodophenoxy oxadiazoline as a yellow oil in 38% yield (1.71 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (s, 3H, Me), 1.38 (s, 3H, Me), 6.83-7.78 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 23.8, 90.6, 121.5, 122.2, 122.8, 125.1, 125.4, 126.2, 129.2, 136.1, 139.6, 151.3, 151.9; IR (CCl_4) cm^{-1}: 3070m, 2995m, 2940w, 1769m, 1593m, 1492s, 1469s, 1440m, 1383w, 1369m, 1283w, 1203br, 1156br, 1105br, 1021m, 969m.

Thermolysis of 2-(*o*-Iodophenoxy)-2-phenoxy Oxadiazoline with DMAD:



20 % 45 % 16 %

***o*-Iodophenyl Phenyl Carbonate:** 20% yield; clear oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.02-7.43 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 89.9, 121.0, 122.6, 126.6, 128.3, 129.8, 129.9, 139.8, 151.2, 151.3; IR (CCl_4) cm^{-1}: 3071m, 3048w, 1788br, 1594m, 1560w, 1494s, 1469s, 1441m, 1290w, 1238br, 1220br, 1186br, 1163m, 1071w, 1044m,

1022m, 1007m; MS (EI) m/z: 340 (M, 16), 220 (15), 213 (17), 169 (46), 141 (47), 84 (68), 77 (100), 51 (43); MS (HR) m/z: calc'd. 339.9596, found 339.9602.

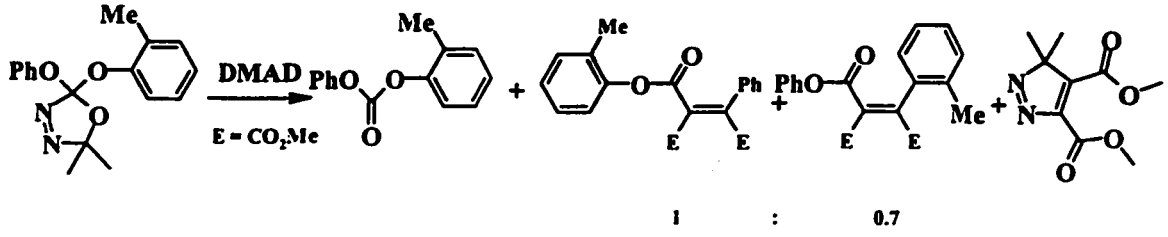
The Aromatic Substitution Product: yellow oil in 45% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.81 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.74-7.90 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.5, 96.7, 121.1, 126.5, 128.3, 129.6, 130.6, 133.7, 139.3, 146.4, 149.9, 161.3, 164.2, 164.9; IR (CCl_4) cm^{-1}: 979w, 1012m, 1047w, 1075w, 1161w, 1192s, 1231s, 1256m, 1435m, 1463m, 1492w, 1550m, 1591w, 1739br, 2660m, 2929m, 2958s; MS (EI) m/z: 435 (M-OMe, 2), 373 (M-I, 67), 339 (93), 255 (60), 246 (M-(OPh), 100), 215 (80), 173 (40), 128 (100), 65 (100), 59 (78); MS (CI, NH_3) m/z: 484 (M+18, 100), 467 (M+1, 30).

3.4.10.4 2-(*o*-Methylphenoxy)-2-phenoxy Oxadiazoline:

Acetoxy phenoxy oxadiazoline (0.88 g, 3.52 mmol) and 1.14 g (10.7 mmol) of 2-methylphenol were dissolved in 60 mL of CH_2Cl_2 with catalytic trifluoroacetic acid and the solution was refluxed for 24 hours. Pure *o*-methylphenoxy phenoxy oxadiazoline was separated by flash column chromatography as a yellow oil in 53% yield (0.58 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13 (s, 3H, Me), 1.23 (s, 3H, Me), 2.21 (s, 3H, *o*-$C_6H_4C\underline{H}_3$), 7.00-7.28 (m, 9H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 16.8, 23.4, 24.8, 121.3, 122.4, 122.9, 125.1, 125.3, 126.4, 129.2, 131.1, 131.8, 136.8, 150.1, 151.8; IR (CCl_4) cm^{-1}: 3067m, 3044w, 3033w, 2994m, 2939m, 1592m, 1492s, 1460m, 1383m, 1369m, 1291w, 1207br, 1156br, 1121br, 989m.

Thermolysis of 2-(*o*-Methylphenoxy)-2-phenoxy Oxadiazoline in the presence of DMAD:

2-(*o*-Methylphenoxy)-2-phenoxy oxadiazoline (0.18 g, 0.604 mmol) and 0.1 g DMAD (0.704 mmol) were dissolved in 20 mL of dried benzene. The solution, in a thermolysis tube, was degassed by high vacuum pump after it was cooled to solid by liquid nitrogen. Then the thermolysis tube was sealed and heated in an oil bath at 110 °C. After 24 hours of heating, the reaction solvent was removed by rotary evaporation. Successive flash column and radial chromatography were used to separate the products. Among them, the aromatic substitution products were found to stay together and could not be separated. They were identified together and the ratio of them was calculated from the integration of ^{1}H NMR peaks as well as the intensity ratio of their fragmentation peaks in the EI mass spectrum.



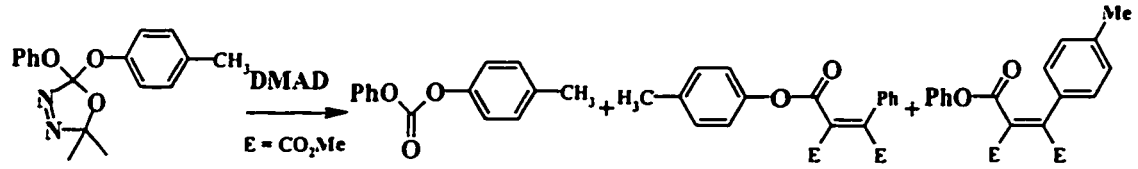
***o*-Methylphenyl Phenyl Carbonate:** yellow liquid; 31 % yield (0.042 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.32 (s, 3H, Me), 7.19-7.45 (m, 9H, ArH). ^{13}C NMR (50.3 MHz, C_6D_6) δ: 16.1, 121.0, 121.4, 126.4, 126.7, 127.2, 129.7, 130.1, 131.5, 149.7, 151.2, 152.0, 159.3; IR (CCl_4) cm^{-1}: 3068w, 1781s, 1493m, 1232br, 1172s, 1113m; MS (EI) *m/z*: 229 (10, M+1), 228 (27, M), 183 (13), 107 (35), 91 (100), 77 (95), 65 (73); MS (CI, NH_3) m/z: 246 (100, M+18).

Aromatic Substitution Products (mixture): yellow liquid; 47 % overall yield (0.10 g); the ratio of two compounds is 1 : 0.7; ^{1}H NMR (200 MHz, $CDCl_3$) (two compounds) δ: 1.97 (s, 2.6H, *o*-$C_6H_4C\underline{H}_3$), 2.39 (s, 3H, *o*-$C_6H_4C\underline{H}_3$), 3.85 (s, 3H, OMe), 3.90 (s, 5.6H, OMe), 3.92 (s, 2.6H, OMe), 6.54-7.51 (m, 16.8H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) (two compounds) δ: 15.7, 19.8, 53.2, 121.1, 126.0, 126.4, 126.5, 126.9, 128.0, 128.4, 129.1, 129.5, 129.7, 130.3, 130.6, 131.3, 132.8, 136.5, 148.2, 148.7, 149.9, 162.5, 163.0, 166.6, 167.2; IR (CCl_4) cm^{-1}: 2954w, 1742s, 1492w, 1436w, 1265m, 1231s, 1191m, 1171w, 1071w, 1011w; MS (EI) *m/z*: 356 (M+2, 6), 323 (M-OMe, 10), 261 (M-OPh, 67), 247 (M-OC_6H_4Me, 100), 233 (73), 219 (53), 189 (30), 175 (20), 143 (43), 129 (87), 115 (70), 91 (22), 65 (35); MS$^-$(CI, NH_3) m/z: 374 ((M+2)+18, 65), 356 (M+2, 100).

3.4.10.5 2-(*p*-Methylphenoxy)-2-phenoxy Oxadiazoline (403):

Thermolysis of 2-(*p*-Methylphenoxy)-2-phenoxy Oxadiazoline in the presence of DMAD:

2-(p-Methylphenoxy)-2-phenoxy oxadiazoline (0.8 g, 2.28 mmol) and 0.388 g (2.73 mmol) of DMAD were dissolved in 20 mL of dried benzene. The solution, in a thermolysis tube, was degassed by high vacuum pump after it was cooled to a solid by liquid nitrogen. Then the thermolysis tube was sealed and heated in an oil bath at 110 °C. After 24 hours of heating, the reaction solvent was removed by rotary evaporation. Flash column chromatography and radial rotary chromatography were used to separate the products.

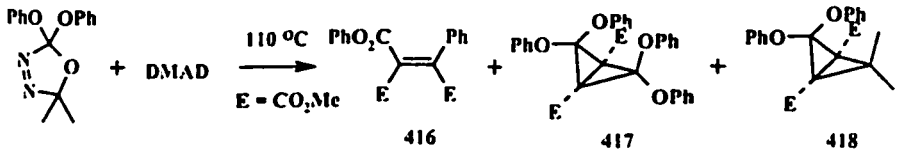


4-Methylphenyl Phenyl Carbonate: 29 % yield (0.15 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ : 2.33 (s, 3H, *p*-$C_6H_4C\underline{H}_3$), 7.11-7.43 (m, 9H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 20.9, 120.7, 121.0, 126.3, 129.6, 130.1, 136.1, 148.9, 151.1, 152.4; MS (EI) m/z: 228 (M, 90), 184 (40), 107 (17), 91 (92), 77 (100), 65 (64); MS (CI, NH_3) m/z: 246 (M+2, 100), 228 (M, 27).

Aromatic Substitution Products (mixture of isomers, ratio: 4.5:1): yellow oil; 42 % yield (0.34 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.29 & 2.38 (both singlets, overall 3H, *p*-$C_6H_4C\underline{H}_3$), 3.90 (s, 6H, OMe), 6.62-7.53 (m, 9H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 21.0, 53.2, 117.3, 120.8, 121.2, 127.9, 129.1, 129.6, 129.8, 130.1, 130.6, 132.9, 136.2, 147.9, 148.2, 162.9, 163.4, 167.2; MS (EI) m/z: 356 (M+2, 1), 323 (M-31, 2), 261 (22), 247 (100), 219 (88), 129 (36), 107 (9), 93 (2), 77 (32), 59 (28); MS (CI, NH_3) m/z: 374 ((M+2) + 18, 25), 373 (M+19, 100), 372 (M+18, 31), 355 (M+1, 28), 354 (27).

3.5 Formation of Bicyclobutanes

The formation of bicyclobutanes **417** and **418**:



In the thermolysis reaction of diphenoxy oxadiazoline and DMAD, in the ratio 1:0.9, **417** and **418** were isolated as by-products.

Diphenoxy oxadiazoline (0.49 g, 1.726 mmol) and 0.223 g (1.570 mmol) of DMAD were dissolved in 20 mL of dried benzene. The solution, in a thermolysis tube, was degassed by high vacuum pump after it was cooled to a solid by liquid nitrogen. Then the thermolysis tube was sealed and heated in an oil bath at 110 °C. After 24 hours heating, the reaction solvent was removed by rotary evaporation. Flash column chromatography and radial rotary chromatography were used to separate the products.

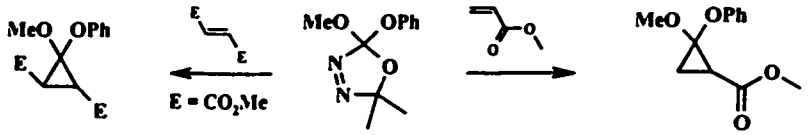
Phenyl (*E*)-2,3-Bis(methoxycarbonyl)-3-phenyl Propionate (aromatic substitution product): clear oil, 41% yield (0.24 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.90 (s, 6H, OMe), 6.74-7.55 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 53.0, 53.1, 121.0, 126.2, 127.7, 128.9, 129.4, 130.4, 132.8, 148.1, 150.0, 162.7, 163.0, 167.0; IR (CCl_4) cm^{-1}: 3066m, 3034m, 3003m, 2954s, 2844w, 1761br, 1735br, 1634m, 1593s, 1492s, 1436s, 1323s, 1306s, 1271br, 1230br, 1186br, 1161s, 1068s, 1012s; MS (EI) m/z: 341 (M+1, 8), 309 (M-31, 16), 247 (100), 219 (62), 175 (25), 151 (31), 129 (100), 105 (26), 59 (100); MS (CI, NH_3) m/z: 358 (M+18, 100), 341 (M+1, 38), 247 (100); MS (HR): calc'd: 341.1025, Found: 341.1026.

Dimethyl 2,2,4,4-Tetraphenoxybicyclo[1.1.0]butane-1,3-dicarboxylate (417): yellow oil, yield 8% (0.07 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.66 (s, 6H, OMe), 6.88-7.25 (m, 20H, OPh); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.7, 96.9, 117.0, 119.0, 123.7, 124.4, 129.2, 129.3, 152.8, 154.6, 158.6, 165.9; IR (CCl_4) cm^{-1}: 2951m, 1734s, 1705s, 1645m, 1591s, 1562m, 1491s, 1436m, 1337m, 1301m, 1273m, 1254m, 1193s, 1163s, 1063s; MS (EI) m/z: 538 (M, 4), 445 (11), 341 (3), 219 (5), 105 (17), 77 (100), 51 (39); MS (CI, NH_3) m/z: 539 (M+1, 52); 445 (69); MS (HR) m/z: calc'd: 538. 1628, Found: 538.1629.

Dimethyl 4,4-Dimethyl-2,2-diphenoxybicyclo[1.1.0]butane-1,3-dicarboxylate (418): yellow oil, 4% yield (0.023 g); ^{1}H NMR (200 MHz, C_6D_6) δ: 1.35 (s, 3H, Me), 1.65 (s, 3H, Me), 3.29 (s, 6H, OMe), 6.70-7.52 (m, 10H, OPh); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 21.8, 42.2, 48.6, 52.0, 117.2, 117.4, 122.4, 123.0, 128.3, 129.1, 129.8, 154.5, 154.8, 164.8; IR (CCl_4) cm^{-1}: 2954m, 1729br, 1593m, 1550m, 1494s, 1439m, 1334m, 1266s, 1206s, 1081s, 1013m; MS (EI) m/z: 382 (M, 25), 351 (M-31, 22), 323 (12), 289 (100), 261 (50), 229 (16), 197 (27), 169 (15), 77 (23), 49 (28); MS (CI, NH_3) m/z: 400 (M+18, 10), 382 (4), 351 (100); MS (HR) m/z: calc'd: 382.1416, found: 382.1426

3.6 Thermolysis of Methoxyphenoxy Oxadiazoline with Electron-Deficient Alkenes

3.6.1 Thermolysis of Methoxyphenoxy Oxadiazoline with Methyl Acrylate



411 412

Thermolysis of methoxy phenoxy oxadiazoline (0.212 g, 0.955 mmol) with 1.2 equivalents of methyl acrylate (0.09 g, 1.05 mmol) afforded 8% of acetal **412** (isomer mixture, 0.017 g). ^{1}H NMR (benzene-d_6): 1.16 (dd, ^{2}J = 2.4 Hz, ^{3}J = 6.1 Hz, 2H), 1.82 (dt, ^{3}J = 6.1 Hz, ^{3}J = 7.2 Hz, 2H), 2.14 (dd, ^{2}J = 2.4 Hz, ^{3}J = 7.2 Hz, 2H), 3.16 (s, 3H, OMe), 3.19 (s, 3H, OMe), 3.28 (s, 3H, OMe), 3.36 (s, 3H, OMe), 6.79-6.88 (m, 2H, ArH), 7.04-7.30 (m, 8H, Ph); ^{13}C NMR (50 MHz): 18.2, 19.4, 28.3, 28.8, 51.4, 51.6,

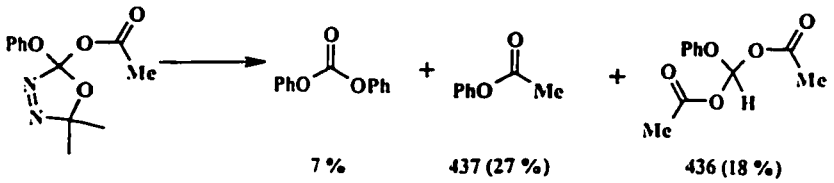
54.1, 54.8, 90.8, 91.4, 116.9, 117.4, 122.4, 122.6, 129.5, 129.7, 156.1, 156.8, 168.3, 168.4.

3.6.2 Thermolysis of 2-Methoxy-2-phenoxy Oxadiazoline with Dimethyl Fumarate

Thermolysis of methoxy phenoxy oxadiazoline (0.329 g, 1.48 mmol) with dimethyl fumarate (0.236 g, 1.639 mmol) afforded 33% of cyclopropane derivative **411** (0.137 g). ^{1}H NMR (benzene-d_6): 3.15 (d, ^3J = 6.8 Hz, 2H), 3.19 (s, 3H, OMe), 3.25 (s, 3H, OMe), 3.28 (s, 3H, OMe), 6.82 (dd, ^3J = 8.6 Hz, ^3J = 8.9 Hz, 1H), 7.08 (d, ^3J = 8.6 Hz, 2H), 7.29 (d, ^3J = 8.9 Hz, 2H); ^{13}C NMR (50 MHz): 32.6, 34.3, 51.8, 52.0, 55.0, 91.6, 117.2, 123.0, 128.3, 129.8, 155.9, 166.4; IR (CCl_4) cm^{-1}: 3004w, 2954.4m, 2841w, 1743s, 1595w, 1495m, 1452w, 1438w, 1417w, 1324m, 1286m, 1216s, 1180m, 1137m, 1074m, 1030w, 994w, 959w; MS (EI) m/z: 43 (100), 59 (35), 77 (19), 113 (21), 121 (12), 161 (24), 189 (25), 216 (14), 221 (13), 248 (16), 281 (5); MS (CI, NH_3) m/z: 281 (M+1, 100).

3.7 Thermolysis of 2-Acetoxy-2-phenoxy Oxadiazoline

3.7.1 Thermolysis of 2-Acetoxy-2-phenoxy Oxadiazoline in the absence of Trap



7 % 437 (27 %) 436 (18 %)

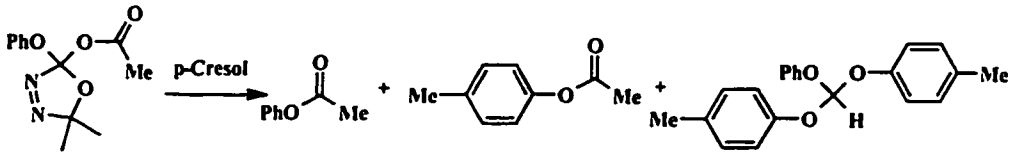
Acetoxy phenoxy oxadiazoline (0.5 g, 2.0 mmol) was dissolved in 20 mL of un-dried benzene. The solution, in a thermolysis tube, was degassed by high vacuum pump after it was cooled to a solid by liquid nitrogen. Then the thermolysis tube was sealed and heated in an oil bath at 110 °C. After 24 hours heating, the reaction solvent was removed by

rotary evaporation. Flash column chromatography and radial rotary chromatography were used to separate the products.

Phenyl Acetate 437: oil, 27% yield (0.073 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.29 (s, 3H, $COC\underline{H}_3$), 7.06-7.41 (m, 5H, Ph); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 21.1, 121.5, 125.8, 129.4, 150.7, 169.3; MS (EI) *m/z*: 136 (M, 28), 94 (100), 69 (28), 66 (29); MS (CI, NH_3) m/z: 154 (M+18, 34), 136 (M, 8).

Orthoformate 436: clear oil, 18% yield (0.081 g); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.16 (s, 6H, $COC\underline{H}_3$), 7.06-7.37 (m, 5H, Ph), 7.71 (s, 1H); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 20.8, 103.0, 118.6, 124.4, 129.7, 153.5, 168.1; MS (EI) *m/z*: 165 (M-59, 6), 136 (28), 94 (100), 65 (6), 43 (83); MS (CI, NH_3) m/z: 242 (M+18, 3).

3.7.2 Thermolysis of 2-Acetoxy-2-phenoxy Oxadiazoline in the presence of *p*-Cresol



437 (9 %) 442 (16 %) 443 (23 %)

2-Acetoxy-2-phenoxy oxadiazoline (0.43 g, 1.72 mmol) and 1.11 g (10.3 mmol) *p*-cresol were dissolved in 20 mL of un-dried benzene. The solution, in a thermolysis tube, was degassed by high vacuum pump after it was cooled to a solid by liquid nitrogen. Then the thermolysis tube was sealed and heated in an oil bath at 110 °C. After 24 hours heating, the reaction solvent was removed by rotary evaporation. Flash column chromatography and radial rotary chromatography were used to separate the products.

***p*-Cresyl Acetate (442)**: clear oil, 16% yield (0.04 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.28 (s, 3H, $COCH_3$), 2.34 (s, 3H, $C_6H_4C\underline{H}_3$), 6.93-7.25 (m, 4H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 20.9, 21.1, 121.2, 129.9, 135.4, 148.4, 169.7.

Orthoformate 443: yellow oil, 23% yield (0.126 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.29 (s, 6H, $C_6H_4C\underline{H}_3$), 6.52 (s, 1H, CH), 6.98-7.35 (m, 13H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ: 20.6, 111.2, 118.0, 118.1, 123.4, 129.6, 130.0, 132.9, 151.6, 153.9; IR (CCl_4) cm^{-1}: 3038m, 2927m, 2867w, 1592m, 1510s, 1497s, 1366m, 1206br, 1175m, 1070br, 1018m.

SUMMARY

The accomplishments reported in this thesis in the field of dioxycarbene chemistry can be summarized as follows.

First of all, the successful preparation of the sources of diaryloxycarbenes, the diaryloxy oxadiazolines, has opened a fascinating field of nucleophilic carbene chemistry. It also opens the possibility to introduce organometallic chemistry through complexation with the aryloxy group in the diaryloxy oxadiazoline.

Second, the reaction of nucleophilic diaryloxycarbenes with electron-deficient carbon-carbon triple bonds extended the study of dioxyvinylcarbenes, which started with the work of Boger and Nakomura. The intermediates formed by addition of diaryloxycarbenes or aryloxycarbenes to the carbon of the triple bond, rather than on the carbonyl group, formed dioxyvinylcarbenes. It was found that these dioxyvinylcarbenes acted as nucleophiles to do nucleophilic addition on the *ipso* position of the aromatic ring, although one of the substituents of the dioxyvinylcarbene was an electrophilic ester group. This was the first type of nucleophilic aromatic substitution that was done by a dioxyvinylcarbene. The detailed study of the mechanism of the reaction established the characteristics of the nucleophilic aromatic substitution, and makes its application in organic synthesis a promising direction.

Third, the study of the *ortho* substituent effects on the *ipso* nucleophilic aromatic substitution established the importance of the steric effect and the electronic effect. Interestingly, the electronic effect came from a novel [1,5] stabilization by an electron rich group, such as the methoxy group, and this type of stabilization has not been reported

before for vinylogous dioxycarbenes. It is not hard to see that the [1,5] stabilization might be generalized to similar reaction cases.

Fourthly, the reaction of diaryloxycarbenes with DMAD also set up a novel method to prepare some of the most interesting molecules, bicyclobutanes, which have two types of bent σ bonds. The bicyclobutane molecule has attracted much focus as a very strained system. Many theoretical calculations have been done to study its HOMO σ bond. A method for its preparation was therefore needed to make more bicyclobutanes with different substituents for experimental study.

Finally, a novel carbene-radical conversion has been found in the study of an acetoxyaryloxycarbene, generated from thermolysis of a 2-acetoxy-2-aryloxy oxadiazoline. Before this work, a similar result was reported by Venneri and Merkley. In their work, a radical stabilizing group was found to be important for the carbene-to-radicals conversion. In the present work, the carbene does not have a radical stabilizing group such as benzyl. In another similar study by Moss, acetoxyphenylcarbene did not dissociate at all to radicals. The interesting result with acetoxyphenoxycarbene might be attributed to the presence of the phenoxy group.

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Appendix 1. X-Ray Crystallography Data for **254**

Table 1. Crystal data and structure refinement for **254**.

Empirical formula	$C_{16}H_{16}O_8$	
Formula weight	336.29	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 29.051(6) Å	α= 90°.
	b = 8.485(2) Å	β= 120.40°.
	c = 14.874(3) Å	γ = 90°.
Volume	3162.5(11) $Å^3$	
Z	8	
Density (calculated)	1.413 Mg/m^3	
Absorption coefficient	0.115 mm^{-1}	
F(000)	1408	
Crystal size	0.1 x 0.2 x 0.2 mm^3	
θ range for data collection	2.53 to 27.63°.	
Index ranges	-37<=h<=36, -5<=k<=11, -16<=l<=19	
Reflections collected	11020	
Independent reflections	3634 [R(int) = 0.0607]	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3634 / 0 / 282	
Goodness-of-fit on F^2	1.034	
Final R indices [$I>2\sigma_I$]	R1 = 0.0575, wR2 = 0.1059	
R indices (all data)	R1 = 0.1310, wR2 = 0.1328	
Extinction coefficient	0.0017(3)	
Largest diff. peak and hole	0.236 and -0.230 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **254**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	922(1)	5073(2)	312(1)	41(1)
C(2)	1024(1)	5272(3)	1339(2)	31(1)
C(3)	1211(1)	6997(3)	1693(2)	27(1)
C(3A)	1204(1)	7652(3)	741(2)	29(1)
C(4)	1345(1)	9115(4)	541(2)	41(1)
C(5)	1321(1)	9342(5)	-403(3)	52(1)
C(6)	1160(1)	8150(5)	-1128(3)	56(1)
C(7)	1022(1)	6681(5)	-940(2)	51(1)
C(7A)	1048(1)	6481(3)	8(2)	35(1)
O(8)	1473(1)	4251(2)	1996(1)	34(1)
C(9)	1872(1)	5181(3)	2714(2)	29(1)
C(10)	1761(1)	6737(3)	2618(2)	28(1)
C(11)	832(1)	7797(3)	1988(2)	30(1)
O(12)	869(1)	7691(2)	2826(1)	42(1)
O(13)	448(1)	8583(2)	1179(1)	37(1)
C(14)	36(1)	9251(4)	1338(3)	48(1)
O(15)	598(1)	4849(2)	1425(1)	38(1)
C(16)	378(2)	3313(4)	1019(3)	53(1)
O(17)	2311(1)	4465(2)	3392(1)	39(1)
C(18)	2318(2)	2757(3)	3424(3)	41(1)
C(19)	2090(1)	8034(3)	3235(2)	30(1)
O(20)	1936(1)	9394(2)	3082(1)	43(1)
O(21)	2581(1)	7603(2)	3982(1)	37(1)
C(22)	2922(1)	8879(4)	4618(3)	45(1)

Table 3. Bond lengths [Å] and angles [°] for **254**.

O(1)-C(7A)	1.391(3)	C(7A)-O(1)-C(2)	107.6(2)
O(1)-C(2)	1.412(3)	O(15)-C(2)-O(1)	111.6(2)
C(2)-O(15)	1.357(3)	O(15)-C(2)-O(8)	109.3(2)
C(2)-O(8)	1.454(3)	O(1)-C(2)-O(8)	106.3(2)
C(2)-C(3)	1.557(3)	O(15)-C(2)-C(3)	113.3(2)
C(3)-C(10)	1.506(3)	O(1)-C(2)-C(3)	108.9(2)
C(3)-C(3A)	1.509(3)	O(8)-C(2)-C(3)	107.0(2)
C(3)-C(11)	1.536(4)	C(10)-C(3)-C(3A)	114.6(2)
C(3A)-C(7A)	1.372(4)	C(10)-C(3)-C(11)	112.7(2)
C(3A)-C(4)	1.387(4)	C(3A)-C(3)-C(11)	115.7(2)
C(4)-C(5)	1.384(4)	C(10)-C(3)-C(2)	101.4(2)
C(5)-C(6)	1.376(5)	C(3A)-C(3)-C(2)	101.1(2)
C(6)-C(7)	1.381(5)	C(11)-C(3)-C(2)	109.5(2)
C(7)-C(7A)	1.383(4)	C(7A)-C(3A)-C(4)	119.4(2)
O(8)-C(9)	1.362(3)	C(7A)-C(3A)-C(3)	108.8(2)
C(9)-O(17)	1.307(3)	C(4)-C(3A)-C(3)	131.7(2)
C(9)-C(10)	1.350(3)	C(5)-C(4)-C(3A)	118.3(3)
C(10)-C(19)	1.441(3)	C(6)-C(5)-C(4)	121.1(3)
C(11)-O(12)	1.198(3)	C(5)-C(6)-C(7)	121.5(3)
C(11)-O(13)	1.333(3)	C(6)-C(7)-C(7A)	116.5(3)
O(13)-C(14)	1.449(3)	C(3A)-C(7A)-C(7)	123.2(3)
O(15)-C(16)	1.442(3)	C(3A)-C(7A)-O(1)	113.5(2)
O(17)-C(18)	1.450(3)	C(7)-C(7A)-O(1)	123.3(3)
C(19)-O(20)	1.216(3)	C(9)-O(8)-C(2)	107.4(2)
C(19)-O(21)	1.342(3)	O(17)-C(9)-C(10)	128.6(2)
O(21)-C(22)	1.449(3)	O(17)-C(9)-O(8)	116.5(2)
		C(10)-C(9)-O(8)	114.8(2)
		C(9)-C(10)-C(19)	129.3(2)
		C(9)-C(10)-C(3)	109.1(2)
		C(19)-C(10)-C(3)	121.6(2)
		O(12)-C(11)-O(13)	124.8(2)
		O(12)-C(11)-C(3)	124.4(2)
		O(13)-C(11)-C(3)	110.8(2)
		C(11)-O(13)-C(14)	115.5(2)
		C(2)-O(15)-C(16)	115.6(2)
		C(9)-O(17)-C(18)	118.7(2)
		O(20)-C(19)-O(21)	123.3(2)
		O(20)-C(19)-C(10)	122.9(2)
		O(21)-C(19)-C(10)	113.8(2)
		C(19)-O(21)-C(22)	115.3(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **254**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	49(1)	42(1)	30(1)	-8(1)	17(1)	-2(1)
C(2)	28(1)	33(1)	26(1)	-4(1)	10(1)	-1(1)
C(3)	26(1)	29(1)	26(1)	-4(1)	12(1)	-2(1)
C(3A)	23(1)	36(1)	28(1)	6(1)	13(1)	6(1)
C(4)	36(2)	45(2)	41(2)	14(2)	19(2)	9(2)
C(5)	37(2)	67(2)	56(2)	31(2)	27(2)	15(2)
C(6)	47(2)	91(3)	38(2)	27(2)	26(2)	23(2)
C(7)	44(2)	73(2)	32(2)	0(2)	18(2)	15(2)
C(7A)	28(2)	45(2)	31(2)	6(1)	15(1)	9(1)
O(8)	29(1)	25(1)	38(1)	-3(1)	10(1)	0(1)
C(9)	22(1)	34(1)	26(1)	0(1)	7(1)	-1(1)
C(10)	27(1)	27(1)	27(1)	1(1)	13(1)	-2(1)
C(11)	30(2)	28(1)	31(2)	-2(1)	14(1)	-4(1)
O(12)	45(1)	55(1)	32(1)	0(1)	23(1)	6(1)
O(13)	30(1)	46(1)	36(1)	5(1)	18(1)	11(1)
C(14)	41(2)	57(2)	54(2)	6(2)	30(2)	18(2)
O(15)	30(1)	35(1)	46(1)	-6(1)	18(1)	-9(1)
C(16)	39(2)	40(2)	67(3)	-2(2)	17(2)	-13(2)
O(17)	29(1)	27(1)	44(1)	1(1)	6(1)	1(1)
C(18)	36(2)	29(2)	52(2)	6(1)	19(2)	7(1)
C(19)	30(2)	31(2)	29(1)	2(1)	14(1)	-1(1)
O(20)	45(1)	27(1)	45(1)	-2(1)	14(1)	-1(1)
O(21)	31(1)	32(1)	37(1)	-3(1)	9(1)	-8(1)
C(22)	38(2)	43(2)	41(2)	-7(2)	12(2)	-16(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **254**.

	x	y	z	U(eq)
H(4)	1434(10)	9924(30)	1011(19)	29(7)
H(5)	1423(13)	10295(40)	-543(24)	67(11)
H(6)	1134(13)	8366(37)	-1799(26)	70(10)
H(7)	905(11)	5905(34)	-1392(22)	46(9)
H(14C)	-154(12)	8381(35)	1492(23)	56(9)
H(14B)	194(11)	10067(34)	1924(22)	49(8)
H(14A)	-212(14)	9734(39)	692(26)	72(11)
H(16C)	125(15)	3073(39)	1225(25)	74(11)
H(16B)	676(13)	2536(36)	1295(23)	53(9)
H(16A)	221(14)	3336(38)	279(27)	71(11)
H(18C)	2656(13)	2480(34)	3866(23)	48(9)
H(18B)	2228(14)	2350(38)	2733(29)	71(11)
H(18A)	2055(16)	2477(41)	3624(27)	82(12)
H(22B)	2980(11)	9596(34)	4145(23)	56(9)
H(22C)	2758(12)	9431(35)	4981(22)	57(9)
H(22A)	3252(13)	8398(35)	5111(24)	54(9)

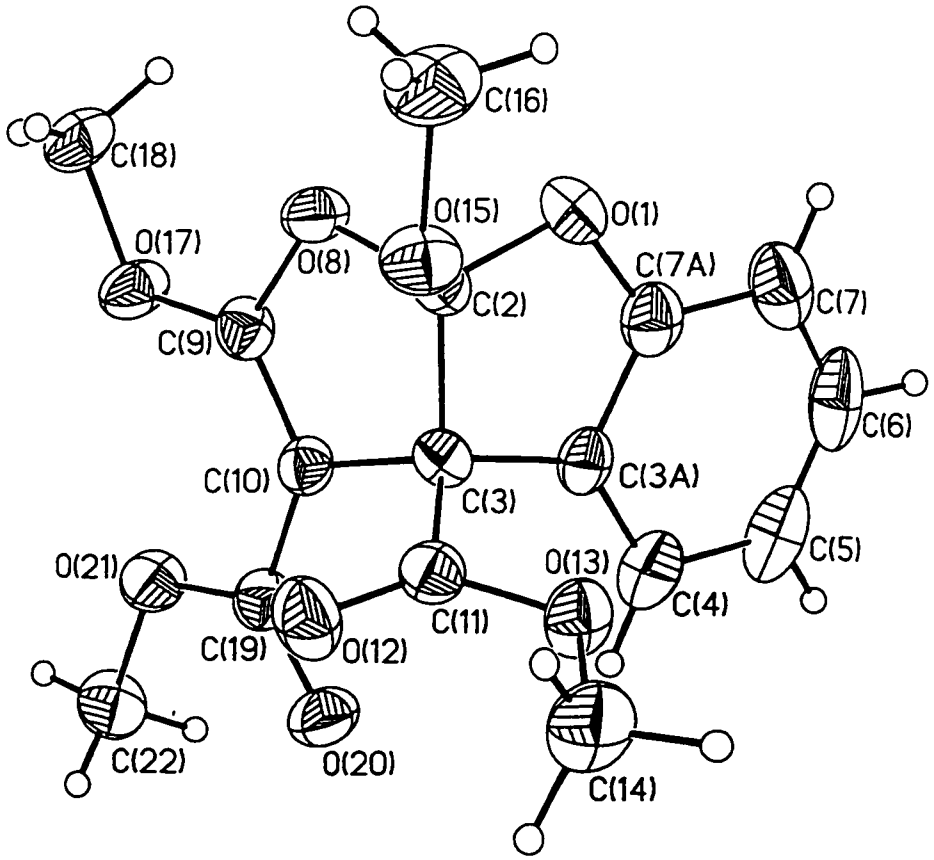


Fig.2. The structure of **254**, drawn with 50% probability thermal ellipsoids, showing the labelling used in the tables.

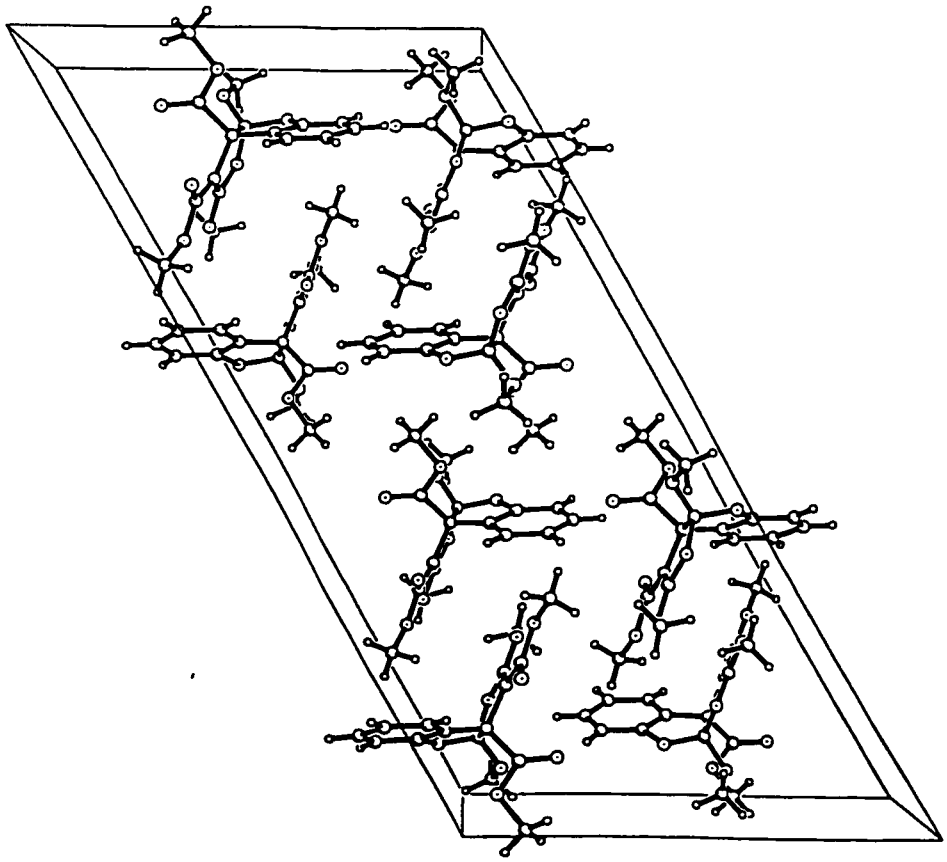


Fig. 5. The packing of **254** in the monoclinic cell. The view is down the **b**-axis, with the **c**-axis horizontal.

Appendix 2. X-Ray Crystallography Data for **341**

Table 1. Crystal data and structure refinement for **341**.

Empirical formula	$C_{21} H_{17} N O_7$	
Formula weight	395.36	
Temperature	299(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 14.050(2) Å	α= 90°.
	b = 8.4577(14) Å	β= 94.262(3)°.
	c = 16.883(3) Å	γ = 90°.
Volume	2000.6(6) $Å^3$	
Z	4	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	824	
Crystal size	.04 x .22 x .23 mm^3	
θ range for data collection	1.82 to 23.26°.	
Index ranges	-14<=h<=15, -9<=k<=9, -18<=l<=18	
Reflections collected	12891	
Independent reflections	2875 [R(int) = 0.0463]	
Completeness to θ = 23.26°	100.0 %	
Absorption correction	SADABS	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2875 / 0 / 331	
Goodness-of-fit on F^2	1.016	
Final R indices [$I>2\sigma_I$]	R1 = 0.0393, wR2 = 0.0883	
R indices (all data)	R1 = 0.0758, wR2 = 0.1047	
Extinction coefficient	0.0094(12)	
Largest diff. peak and hole	0.153 and -0.136 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **341**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1')	3304(1)	1646(2)	8873(1)	50(1)
O(4')	6253(1)	-1501(2)	7778(1)	63(1)
C(2)	4454(2)	901(2)	8011(1)	43(1)
O(1)	2786(1)	955(2)	7627(1)	65(1)
C(3)	4973(2)	-282(2)	8352(1)	42(1)
C(5)	4587(2)	-1488(2)	8881(1)	40(1)
C(12)	2360(2)	1924(3)	9092(1)	44(1)
O(11)	5565(1)	1889(2)	7126(1)	86(1)
O(11')	4433(1)	3454(2)	7544(1)	86(1)
C(8)	3843(2)	-3601(2)	9929(2)	47(1)
C(17)	1805(2)	3083(3)	8739(2)	50(1)
C(6)	3715(2)	-2230(3)	8692(2)	55(1)
C(1)	3422(2)	1151(3)	8131(2)	45(1)
O(4)	6596(1)	451(2)	8648(1)	74(1)
C(7)	3347(2)	-3277(3)	9211(2)	59(1)
C(11)	4892(2)	2100(3)	7502(2)	55(1)
C(10)	5091(2)	-1873(3)	9592(2)	46(1)
C(16)	900(2)	3356(3)	8988(2)	58(1)
C(4)	6038(2)	-372(3)	8271(2)	49(1)
C(15)	585(2)	2460(3)	9595(2)	63(1)
C(13)	2062(2)	1042(3)	9706(2)	60(1)
C(9)	4720(2)	-2912(3)	10113(2)	49(1)
O(15)	-300(1)	2623(3)	9884(1)	101(1)
C(18)	3459(2)	-4662(3)	10492(2)	62(1)
C(19)	7270(2)	-1736(5)	7697(3)	81(1)
C(14)	1166(2)	1322(4)	9952(2)	73(1)
C(20)	4772(4)	4779(6)	7086(4)	124(2)
N(18)	3158(2)	-5495(3)	10942(2)	95(1)
C(21)	-1003(3)	3507(8)	9423(4)	121(2)

Table 3. Bond lengths [Å] and angles [°] for **341**.

O(1')-C(1)	1.343(3)	C(1)-O(1')-C(12)	118.43(18)
O(1')-C(12)	1.422(3)	C(4)-O(4')-C(19)	115.5(3)
O(4')-C(4)	1.316(3)	C(3)-C(2)-C(11)	121.3(2)
O(4')-C(19)	1.460(3)	C(3)-C(2)-C(1)	123.3(2)
C(2)-C(3)	1.342(3)	C(11)-C(2)-C(1)	115.36(19)
C(2)-C(11)	1.490(3)	C(2)-C(3)-C(5)	124.0(2)
C(2)-C(1)	1.495(3)	C(2)-C(3)-C(4)	120.5(2)
O(1)-C(1)	1.198(2)	C(5)-C(3)-C(4)	115.31(18)
C(3)-C(5)	1.486(3)	C(10)-C(5)-C(6)	118.5(2)
C(3)-C(4)	1.514(3)	C(10)-C(5)-C(3)	119.7(2)
C(5)-C(10)	1.386(3)	C(6)-C(5)-C(3)	121.7(2)
C(5)-C(6)	1.392(3)	C(17)-C(12)-C(13)	121.7(2)
C(12)-C(17)	1.363(3)	C(17)-C(12)-O(1')	121.4(2)
C(12)-C(13)	1.368(3)	C(13)-C(12)-O(1')	116.8(2)
O(11)-C(11)	1.190(3)	C(11)-O(11')-C(20)	117.2(3)
O(11')-C(11)	1.319(3)	C(9)-C(8)-C(7)	119.9(2)
O(11')-C(20)	1.461(4)	C(9)-C(8)-C(18)	119.1(2)
C(8)-C(9)	1.378(3)	C(7)-C(8)-C(18)	120.9(2)
C(8)-C(7)	1.380(3)	C(12)-C(17)-C(16)	119.7(3)
C(8)-C(18)	1.441(4)	C(7)-C(6)-C(5)	120.7(3)
C(17)-C(16)	1.387(3)	O(1)-C(1)-O(1')	124.6(2)
C(6)-C(7)	1.373(3)	O(1)-C(1)-C(2)	124.3(2)
O(4)-C(4)	1.195(3)	O(1')-C(1)-C(2)	111.0(2)
C(10)-C(9)	1.373(3)	C(6)-C(7)-C(8)	120.0(2)
C(16)-C(15)	1.373(4)	O(11)-C(11)-O(11')	124.7(2)
C(15)-C(14)	1.372(4)	O(11)-C(11)-C(2)	125.7(2)
C(15)-O(15)	1.376(3)	O(11')-C(11)-C(2)	109.6(2)
C(13)-C(14)	1.375(4)	C(9)-C(10)-C(5)	120.7(2)
O(15)-C(21)	1.424(5)	C(15)-C(16)-C(17)	119.1(3)
C(18)-N(18)	1.141(3)	O(4)-C(4)-O(4')	125.9(2)
		O(4)-C(4)-C(3)	122.4(2)
		O(4')-C(4)-C(3)	111.6(2)
		C(16)-C(15)-C(14)	120.1(3)
		C(16)-C(15)-O(15)	124.0(3)
		C(14)-C(15)-O(15)	115.9(3)
		C(12)-C(13)-C(14)	118.3(3)
		C(10)-C(9)-C(8)	120.1(3)
		C(15)-O(15)-C(21)	117.9(3)
		N(18)-C(18)-C(8)	179.5(3)
		C(15)-C(14)-C(13)	121.0(3)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **341**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^{*2}U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1')	36(1)	71(1)	41(1)	-6(1)	1(1)	0(1)
O(4')	49(1)	63(1)	79(1)	2(1)	20(1)	12(1)
C(2)	37(1)	53(1)	40(1)	6(1)	4(1)	5(1)
O(1)	50(1)	91(1)	53(1)	-17(1)	-8(1)	16(1)
C(3)	37(1)	49(1)	40(1)	-1(1)	1(1)	1(1)
C(5)	37(1)	41(1)	43(1)	-2(1)	4(1)	4(1)
C(12)	32(1)	57(1)	43(1)	-2(1)	4(1)	0(1)
O(11)	73(1)	85(1)	106(2)	34(1)	47(1)	20(1)
O(11')	86(1)	67(1)	109(2)	39(1)	46(1)	28(1)
C(8)	48(2)	42(1)	54(2)	2(1)	11(1)	2(1)
C(17)	54(2)	49(1)	47(2)	0(1)	9(1)	0(1)
C(6)	55(2)	58(2)	50(2)	7(1)	-10(1)	-10(1)
C(1)	43(2)	50(1)	42(2)	2(1)	-2(1)	5(1)
O(4)	44(1)	88(1)	90(2)	-9(1)	1(1)	-6(1)
C(7)	48(2)	56(2)	70(2)	5(2)	-3(2)	-15(1)
C(11)	47(2)	61(2)	57(2)	13(1)	10(1)	12(1)
C(10)	36(1)	51(1)	50(2)	2(1)	-3(1)	-2(1)
C(16)	55(2)	60(2)	59(2)	-5(1)	4(2)	15(1)
C(4)	46(2)	50(1)	52(2)	11(1)	7(1)	3(1)
C(15)	46(2)	85(2)	61(2)	-6(2)	12(2)	6(1)
C(13)	51(2)	74(2)	55(2)	16(2)	7(1)	6(1)
C(9)	52(2)	51(1)	44(2)	5(1)	1(1)	2(1)
O(15)	54(1)	154(2)	99(2)	6(2)	30(1)	22(1)
C(18)	57(2)	58(2)	74(2)	10(2)	19(2)	6(1)
C(19)	54(2)	82(2)	113(3)	18(2)	39(2)	21(2)
C(14)	55(2)	103(2)	62(2)	24(2)	18(2)	4(2)
C(20)	118(4)	83(3)	179(6)	78(3)	67(4)	32(3)
N(18)	90(2)	92(2)	108(2)	37(2)	37(2)	5(2)
C(21)	55(3)	180(5)	130(4)	-13(4)	11(3)	41(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **341**.

	x	y	z	U(eq)
H(10)	5682(17)	-1390(20)	9713(13)	57(7)
H(13)	2456(18)	240(30)	9966(15)	74(8)
H(9)	5061(16)	-3090(20)	10612(15)	56(7)
H(17)	2048(16)	3680(20)	8352(14)	52(7)
H(7)	2762(17)	-3790(30)	9086(14)	70(8)
H(6)	3385(16)	-2100(30)	8202(15)	62(7)
H(16)	498(17)	4200(30)	8765(14)	70(8)
H(14)	952(18)	790(30)	10376(17)	80(9)
H(19C)	7270(20)	-2640(40)	7290(20)	128(13)
H(19B)	7530(20)	-870(40)	7460(19)	107(12)
H(19A)	7600(30)	-2090(40)	8200(20)	143(17)
H(21A)	-750(30)	4620(60)	9400(30)	180(30)
H(21B)	-1090(30)	2960(40)	8900(30)	145(18)
H(21C)	-1540(30)	3360(50)	9730(30)	180(20)
H(20C)	5390(30)	4940(40)	7190(30)	132(18)
H(20B)	4340(30)	5530(40)	7130(20)	130(14)
H(20A)	4740(40)	4300(60)	6490(30)	200(30)

Table 6. Torsion angles [°] for **341**.

C(11)-C(2)-C(3)-C(5)	178.4(2)
C(1)-C(2)-C(3)-C(5)	0.5(4)
C(11)-C(2)-C(3)-C(4)	4.0(3)
C(1)-C(2)-C(3)-C(4)	-173.9(2)
C(2)-C(3)-C(5)-C(10)	-133.4(2)
C(4)-C(3)-C(5)-C(10)	41.2(3)
C(2)-C(3)-C(5)-C(6)	45.2(3)
C(4)-C(3)-C(5)-C(6)	-140.2(2)
C(1)-O(1')-C(12)-C(17)	-64.4(3)
C(1)-O(1')-C(12)-C(13)	119.6(2)
C(13)-C(12)-C(17)-C(16)	-1.9(4)
O(1')-C(12)-C(17)-C(16)	-177.7(2)
C(10)-C(5)-C(6)-C(7)	2.2(3)
C(3)-C(5)-C(6)-C(7)	-176.4(2)
C(12)-O(1')-C(1)-O(1)	1.7(3)
C(12)-O(1')-C(1)-C(2)	-179.27(17)
C(3)-C(2)-C(1)-O(1)	-110.7(3)
C(11)-C(2)-C(1)-O(1)	71.3(3)
C(3)-C(2)-C(1)-O(1')	70.3(3)
C(11)-C(2)-C(1)-O(1')	-107.7(2)
C(5)-C(6)-C(7)-C(8)	0.1(4)
C(9)-C(8)-C(7)-C(6)	-2.1(4)
C(18)-C(8)-C(7)-C(6)	178.3(2)
C(20)-O(11')-C(11)-O(11)	0.8(5)
C(20)-O(11')-C(11)-C(2)	179.4(4)
C(3)-C(2)-C(11)-O(11)	27.8(4)
C(1)-C(2)-C(11)-O(11)	-154.2(3)
C(3)-C(2)-C(11)-O(11')	-150.8(2)
C(1)-C(2)-C(11)-O(11')	27.2(3)
C(6)-C(5)-C(10)-C(9)	-2.7(3)
C(3)-C(5)-C(10)-C(9)	176.0(2)
C(12)-C(17)-C(16)-C(15)	0.8(4)
C(19)-O(4')-C(4)-O(4)	-0.1(4)
C(19)-O(4')-C(4)-C(3)	-176.7(2)
C(2)-C(3)-C(4)-O(4)	76.9(3)
C(5)-C(3)-C(4)-O(4)	-97.9(3)
C(2)-C(3)-C(4)-O(4')	-106.4(2)
C(5)-C(3)-C(4)-O(4')	78.8(2)
C(17)-C(16)-C(15)-C(14)	0.6(4)
C(17)-C(16)-C(15)-O(15)	-179.5(2)
C(17)-C(12)-C(13)-C(14)	1.6(4)
O(1')-C(12)-C(13)-C(14)	177.6(2)
C(5)-C(10)-C(9)-C(8)	0.8(3)
C(7)-C(8)-C(9)-C(10)	1.6(3)
C(18)-C(8)-C(9)-C(10)	-178.7(2)
C(16)-C(15)-O(15)-C(21)	14.4(5)
C(14)-C(15)-O(15)-C(21)	-165.6(4)
C(9)-C(8)-C(18)-N(18)	35(37)
C(7)-C(8)-C(18)-N(18)	-145(37)
C(16)-C(15)-C(14)-C(13)	-0.8(4)
O(15)-C(15)-C(14)-C(13)	179.2(3)
C(12)-C(13)-C(14)-C(15)	-0.3(4)

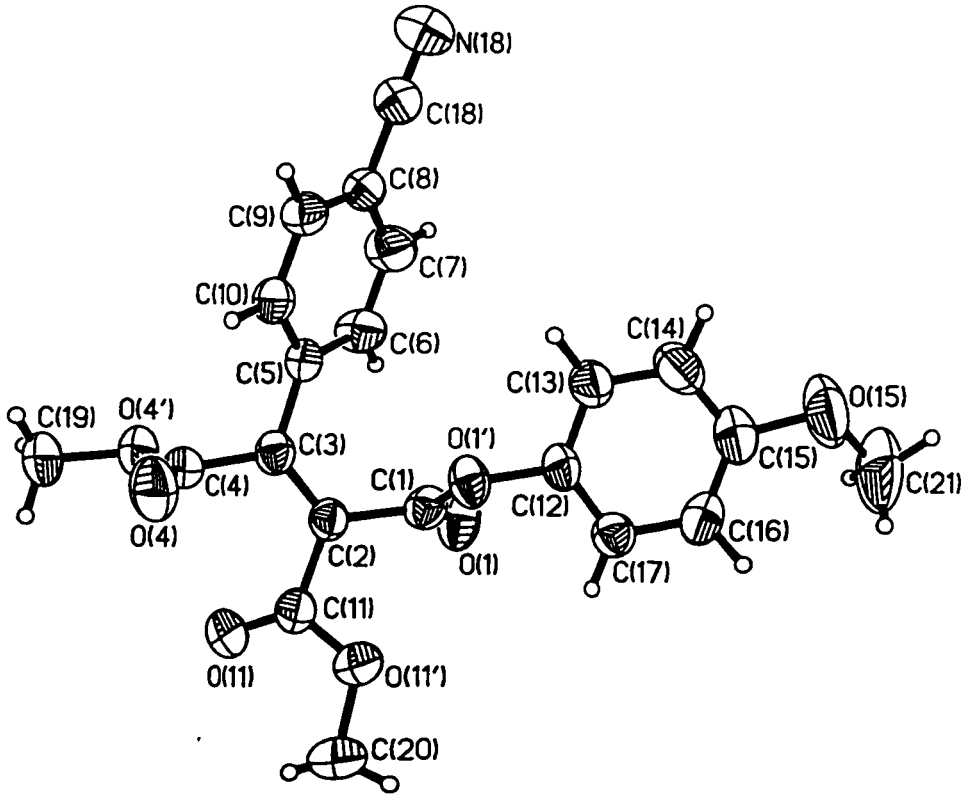


Fig. 4. 50% thermal ellipsoid probability plot for 341, showing the atomic labeling.

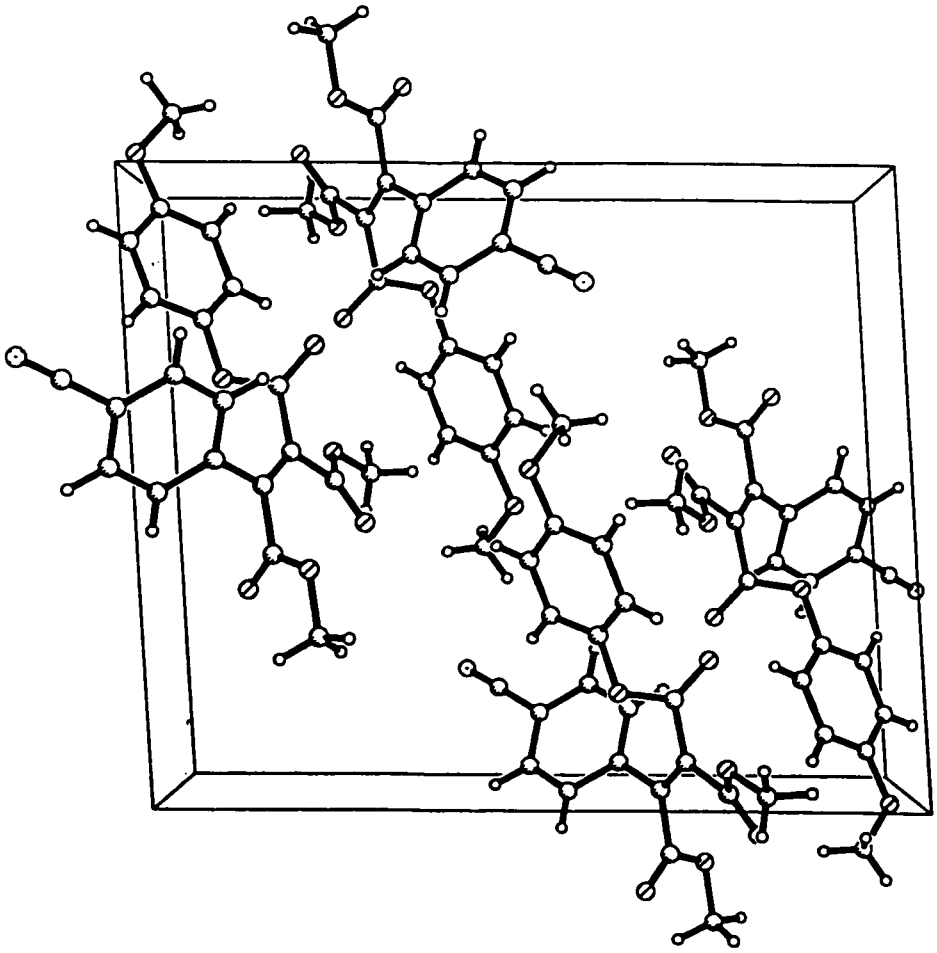
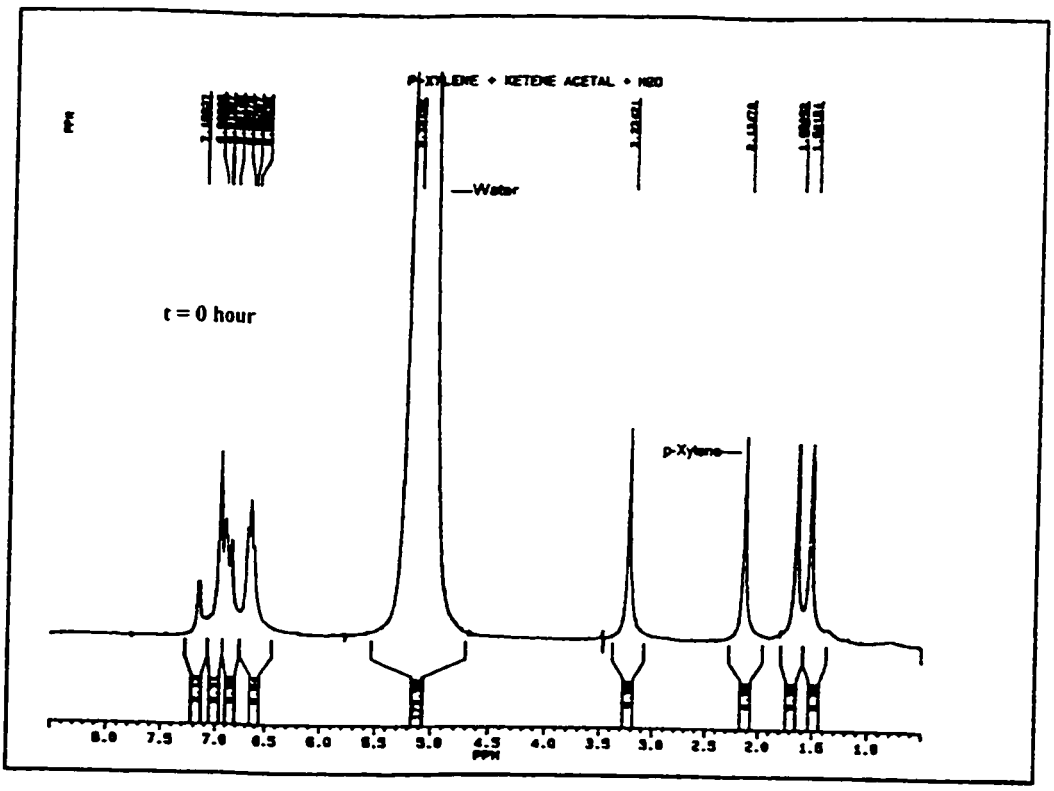
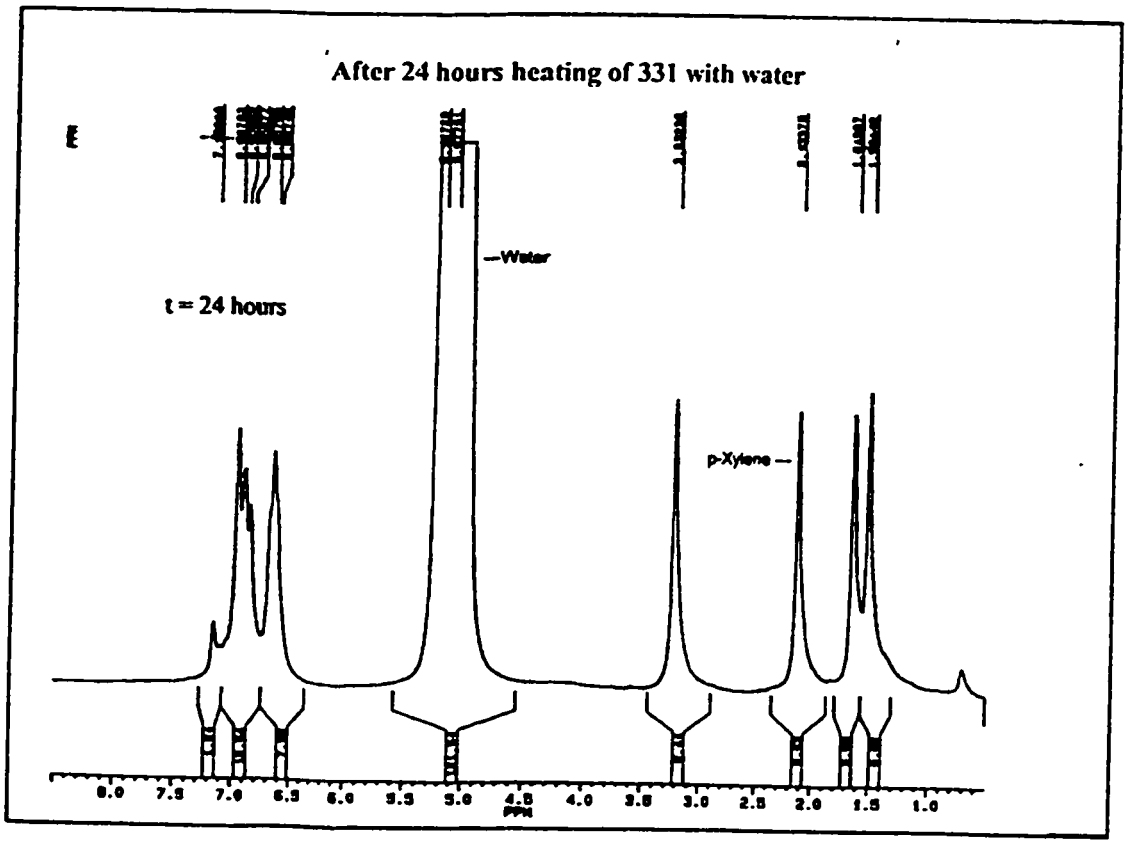


Fig.6. The packing of **341**, viewed down the b-axis, with the c-axis horizontal.





Appendix 3. Attempted hydrolysis of ketene acetal 331