REVIEW

Δ^3-1,3,4-Oxadiazolines.† Versatile sources of reactive intermediates

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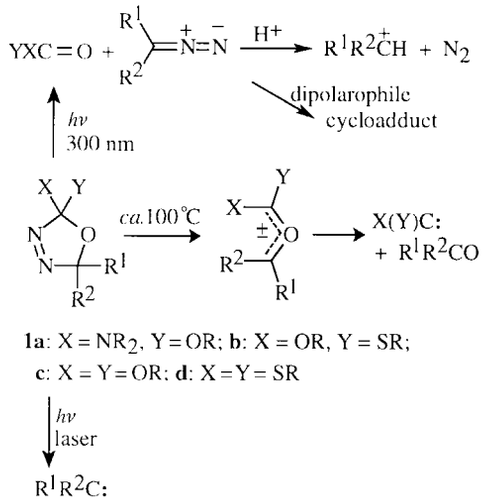
1 Introduction

5,5-Dialkyl-Δ^3-1,3,4-oxadiazolines substituted with amino, oxy, or thio substituents at C-2 have been shown to be remarkably versatile sources of reactive intermediates. By thermolysis, they afford heteroatom-substituted carbenes (N(O)C:, S(O)C:, O(O)C:, S(S)C:), most likely *via* carbonyl ylide intermediates. The carbonyl ylides themselves are not readily trapped, but the heteroatom-substituted carbenes can be intercepted as nucleophilic carbonyl-group equivalents in a variety of reactions. Alkoxy(allyloxy)carbenes and alkoxy(benzyloxy)carbenes from thermolysis of oxadiazolines fragment thermally in solution to radical pairs.

Steady state photolysis of 2-alkoxy- and 2,2-dialkoxyoxadiazolines leads to diazo compounds that have been trapped with dipolarophiles. Laser flash photolysis (LFP) affords dialkylcarbenes as well as diazo compounds. Both techniques are suitable for the study of the kinetics of fast reactions, such as carbene rearrangements and protonation of diazo compounds to afford cations (Scheme 1).

Thus, suitably substituted oxadiazolines can serve as sources of *carbonyl ylides*, *nucleophilic carbenes* (X(Y)C:), and (some) *radical pairs* by thermolysis, as well as *electrophilic carbenes* (R^1R^2C:) and *diazo compounds* by photolysis, although the photochemical portion of Scheme 1 has been established for 2-acetoxy-, 2-alkoxy-, and 2,2-dialkoxyoxadiazolines only. Protonation of the diazo compounds leads to *secondary carbocations*. Although these six types are not all primary reactive intermediates, it is clear that the oxadiazolines are versatile substrates for applications in both physical-organic and synthetic chemistry.



Scheme 1

The rich chemistry of oxadiazolines **1**, which can undoubtedly be developed further, is summarized in this review. It should be emphasized that the review is largely restricted to chemistry emanating from oxadiazolines of the above type. Some of the intermediates have been (or could be) generated by alternative methods, such as thermolysis of norbornadienone ketals[1,2] or diazirines.[3] The fact that these are omitted does not imply that they are in any way less important; reviews of the chemistry of nucleophilic carbenes include many of the methods by which they have been generated.[4] Some rather arbitrary selections of references were made and the list is not exhaustive.

2 Synthesis of oxadiazolines

2.1 Oxidative cyclization of ketone hydrazones

Oxadiazolines of type **1** can be prepared as shelf-stable solids or oils by means of oxidative cyclization of ketone hydrazones carrying appropriate substituents for cyclization to a 5-membered ring (Scheme 2).[4a,5–7] The oxidant that has been used most frequently is lead tetraacetate (LTA) but phenyliodonium acetate has been used also[8] and electrochemical oxidation has been reported.[9] Analogous oxidative cyclizations occur with X = NR or S,[10] but the corresponding triazolines and thiadiazolines are not included in this review. The substituent Y can be R, Ar, OR, OAr, or SR, although not all combinations have been reported. The groups R^1 and R^2 have generally been alkyl groups. One or both can be aryl, but the stability of the resulting oxadiazolines is reduced and their purification and handling can become difficult.[11] Analogous *aldehyde* hydrazones cannot be used because

† IUPAC name for Δ^3-1,3,4-oxadiazoline is 2,5-dihydro-1,3,4-oxadiazole.

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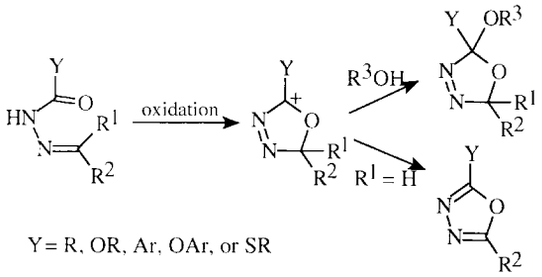
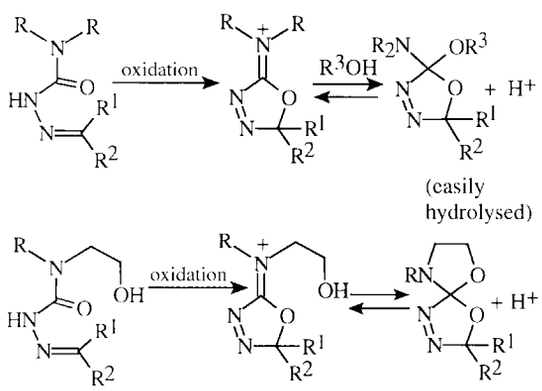


Scheme 2

H is lost at some stage, probably from a cationic intermediate, to afford an oxadiazole instead of an oxadiazoline, (Scheme 2).

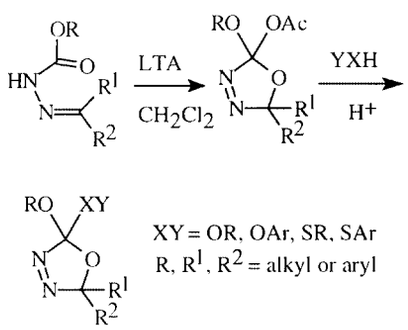
Oxidation of ketone semicarbazones in the presence of an alcohol (R^3OH) does not afford the expected alkoxy-(amino)oxadiazolines (Scheme 3) in useful yields. Most likely, such products are too easily hydrolysed to be isolated readily. However, spirocyclic analogues are available from modified ketone semicarbazones (Scheme 3).[12–15] The difference in stability of the cyclic and acyclic amino(oxy)oxadiazolines is probably entropic, at least in part. Ring opening of the spirocyclic species is more likely to be reversible, the reclosure being an intramolecular reaction.



Scheme 3

2.2 Nucleophilic substitution

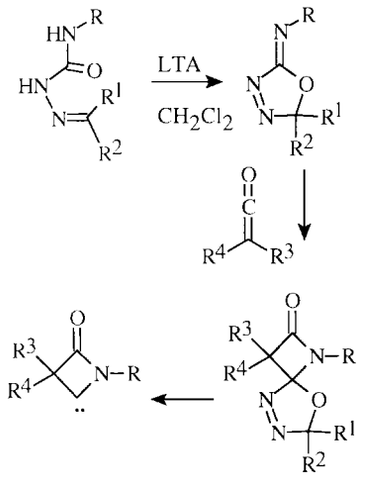
Probably the best method for the preparation of oxadiazolines with two heteroatom substituents at C-2 involves the acid catalysed displacement of acetoxy[16–19] with alkoxy, aryloxy, alkylthio, or arylthio groups (Scheme 4). Introduction of the second C-2 substituent after oxidative cyclization permits the inclusion of oxidation-sensitive compounds such as phenols and thiols. Moreover a single acetoxy substrate can serve as the source of different oxadiazolines.



Scheme 4

2.3 [2 + 2] Cycloadditions

Oxidation of ketone semicarbazones with LTA in CH_2Cl_2 leads to iminooxadiazolines.[20–23] A ketene, generated in the presence of such an oxadiazoline, undergoes [2 + 2] cycloaddition to afford a spiro-fused β-lactam oxadiazoline (Scheme 5).[21] Spiro-fused β-lactam oxadiazolines are precursors of β-lactam-4-ylidenes.[22–25]



Scheme 5

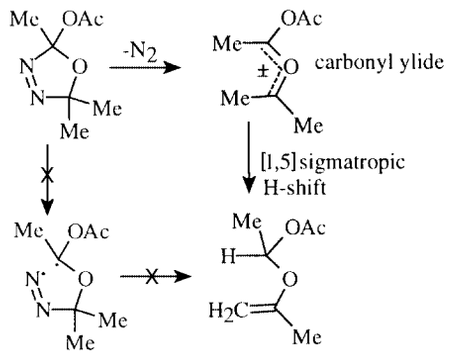
3 Mechanistic aspects

In systems that undergo both ground state (thermal) and excited state (photochemical) reactions, the mechanisms generally depend on the method by which activation is achieved. The reason is simply that there are orbital symmetry constraints[26] that dictate the requirements for concert in a given reaction involving two or more bond changes. Oxadiazolines can lose N_2 thermally by a concerted ($2\pi s + 4\pi s$) cycloreversion in which the C-2–O and C-5–O bonds are rotated such that *cis* C-2 and C-5 substituents become either both *exo* or both *endo* in the carbonyl ylide. The analogous concerted reaction from the excited state would require one of them to become *exo* and the other *endo*; a motion that prevents maintenance of conjugation as the ylide develops. The excited state reaction is therefore stepwise. Mechanistic aspects of oxadiazoline chemistry are in this section, for the most part, but some discussion of mechanism seemed to be appropriate for Section 4.

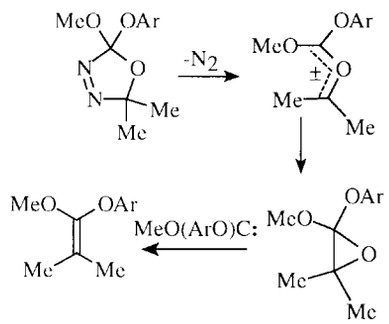
3.1 Thermolysis of oxadiazolines

Although oxadiazolines of type **1**, save for 2,2-dithio species[27,28] and some aryl derivatives,[29] are quite stable at room temperature in the dark, they fragment in solution at about 100 °C with convenient unimolecular rate constants near 10^{-5} s^{-1}.[6] Low boiling solvents can be used in strong sealed tubes, care being taken to avoid unduly high pressures by leaving enough space for the N_2 that is formed.

Thermolysis of oxadiazolines **1** *could* take a number of paths. Experience with unsymmetric azo compounds[30,31] would suggest that stepwise extrusion of N_2 should be considered and, some years ago, this mechanism was proposed[32] to account for a major product of thermolysis of an acetoxyoxadiazoline (Scheme 6). However, the product can be accounted for better[31] in terms of concerted, 1,3-dipolar cycloreversion to a carbonyl ylide and a subsequent [1,5]sigmatropic H-shift (Scheme 6). There is now some evidence for the intermediacy of carbonyl ylides from thermolysis of oxadiazolines. That evidence includes trapping reactions[33] and the formation of compounds that must have come from cyclization of an ylide (Scheme 7, for example).[16c] The fact that the carbonyl ylides, with some exceptions,[33] are not readily trapped under the reaction conditions probably means that they fragment easily, especially in cases that lead to a carbene that is relatively stable as a singlet.



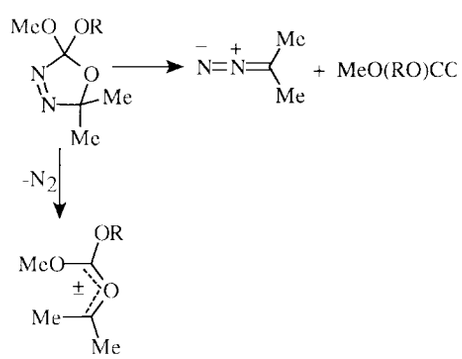
Scheme 6



Scheme 7

Dialkoxycarbenes have this property, the lowest singlet state of dimethoxycarbene lying about 76 kcal mol^{-1} below the corresponding triplet.[34]

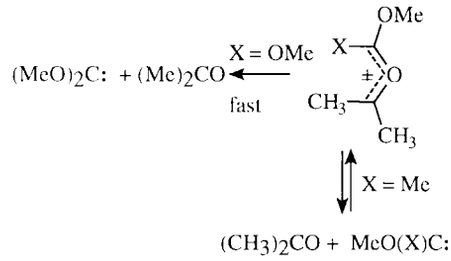
Recently, a second thermal dipolar cycloreversion of oxadiazolines has been observed (Scheme 8).[35,36] It appears to be a side reaction of some 2,2-dialkoxy-, 2-alkoxy-2-aryloxy-, and 2,2-diaryloxyoxadiazolines. The factors that determine how the two competing dipolar cycloreversions depend on substituents and reaction conditions have not yet been determined.



Scheme 8

Dialkoxycarbenes probably evolve rapidly, and possibly irreversibly, from corresponding carbonyl ylides, although methoxy(methyl)carbene reacts reversibly with acetone (Scheme 9).[37]

Diaminocarbenes, and analogous nucleophilic carbenes, may react by two-step mechanisms with carbonyl and thiocarbonyl



Scheme 9

compounds, as well as with Michael acceptors and acids. For carbonyl compounds and Michael acceptors the mechanism is not established, although some reactions appear to involve a dipolar adduct that can react again (Scheme 10).[38–41] In one case at least, a nucleophilic carbene (an imidazolidinylidene) attacks CS_2 to form a stable inner salt; that is, the reaction stops after the first step (Scheme 11).[42]

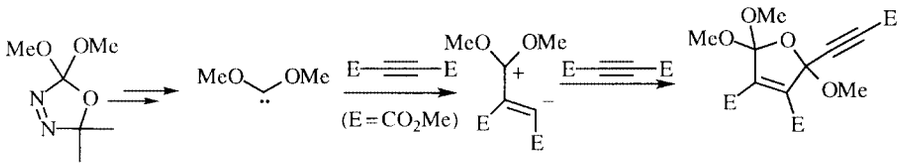
Insertion into OH bonds is probably stepwise also, at least for nucleophilic carbenes, with proton transfer from the hydroxy compound to the carbene as the first step, followed by ion-pair collapse.[43–45] The mechanism is a consequence of delocalization of electron density from the heteroatoms to the dicoordinate carbon of the carbene and to the oxy- or dioxymethyl cation developed at the transition states of such reactions (Scheme 12) for example. Oxycarbenes are nucleophilic[34,38–41,46–54] and the transition state (modelled with the product in Scheme 12) is stabilized by charge dispersal, relative to one from a more electrophilic carbene.

Acyclic dialkoxycarbenes (or acyloxycarbenes) from oxadiazolines or from other sources can rearrange by formal alkyl (or acyl) group transfer from O to C.[29,55–58] In the gas phase environment of a mass spectrometer, electron-withdrawing substituents favour the rearrangement. Thus, ethoxy(trifluoroethoxy)carbene rearranges by migration of the trifluoroethyl group exclusively, suggesting that negative charge accumulates in the migrating group at the transition state.[19] The rearrangement may be mechanistically analogous to 1,2-H-migration in carbenes.[59,60]

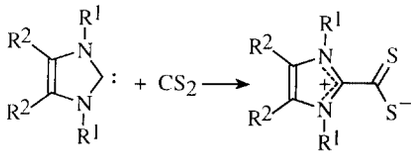
Alkoxy- and dialkoxycarbenes can fragment to radical pairs[2,61–65] but the reaction has usually been run under severe conditions. If one of the alkoxy groups is allylic or benzylic then a dioxycarbene can fragment under relatively mild conditions, in solution, to a radical pair.[66] The fragmentation pathway of lowest energy, determined by means of computation, involves the singlet state in a conformation in which the carbenic electron pair and the cleaving OC bond are *anti* (Scheme 13).[67]

3.2 Photolysis of oxadiazolines

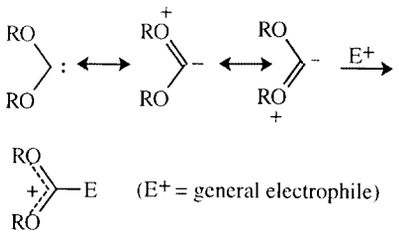
The first photolysis of a Δ^3-1,3,4-oxadiazoline appears to be that reported by Hoffmann and Luthardt[29] in 1968. Excitation of an alkoxy-, dialkoxy-, or acetoxyoxadiazoline[29] at *ca.* 300 nm, to the n→π* singlet state, followed by intersystem crossing to the triplet and β-scission of the latter by cleavage of one CN bond, presumably affords a diazenyl diradical (Scheme 14 for the case of dialkoxy). Triplet sensitization with benzophenone leads to the same products.[68] The diradical intermediate could undergo β-scission in two different ways. Path a, leading to a



Scheme 10



Scheme 11



Scheme 12

diazoalkane and a carbonate, is predominant in steady state photolysis; formation of products from a carbonyl ylide intermediate is not observed. Under LFP conditions (300 nm), an alkylidene is generated within the time period of the flash.[35,69–71] Alkylidene formation under LFP conditions is not well understood.

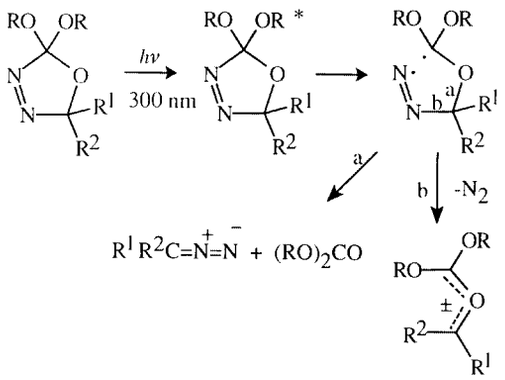
4 Reactions and applications of oxadiazolines

4.1 Diazoalkanes and carbocations

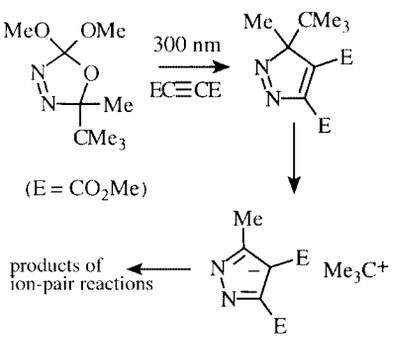
The ability to generate a diazoalkane by photolysis of an oxadiazoline has two major advantages. First, by working in an inert solvent at a low temperature, one can generate the diazo compound largely free from the azine that normally contaminates it, because the self-reaction to form azine is then slow. For studies of the azines themselves (by spectroscopy, for example), that should be an advantage. Second, the diazo compound can be removed at a higher temperature, as it is formed, by trapping it with a dipolarophile that is present at a relatively high concentration in the photolysis solution. Such a trapping reaction can keep the concentration of diazoalkane low enough to suppress the bimolecular formation of the azine, affording a relatively clean addition product. Contamination with azine can be a nuisance in synthetic applications of dialkyl diazo compounds. For example, in distilled ethereal solutions, 2-diazopropane has a half-life of only about 3 h at 0 °C.[72]

A series of relatively pure 3*H*-pyrazoles, prepared by photolysis of oxadiazolines in the presence of DMAD (Scheme 15, for example) led to the discovery of some stepwise rearrangements in systems that normally undergo concerted [1,5]sigmatropic rearrangements.[73,74]

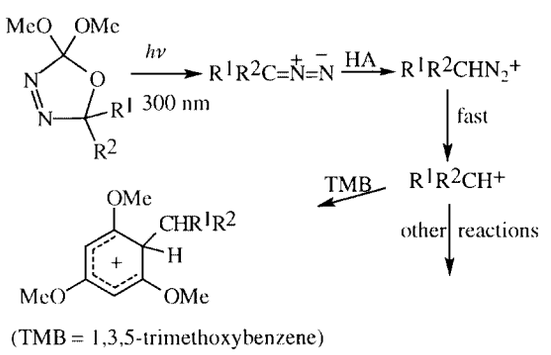
Laser flash photolysis of oxadiazolines in the presence of acids leads to the rapid formation of secondary carbocations, *via* protonation of diazoalkane intermediates. Transparent carbocations can be visualized by trapping them as cyclohexadienyl cations with 1,3,5-trimethoxybenzene (TMB) (Scheme 16).[75,76] The trapping rate constant has been calibrated by means of competition with azide ion,[76] and reactions of the secondary carbocations can now be 'clocked' by that method. Some inferences about the mechanism by which diazo compounds alkylate DNA could be drawn.[76]



Scheme 14



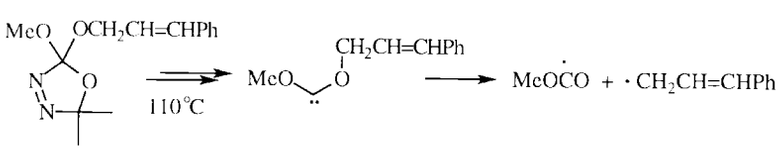
Scheme 15



Scheme 16

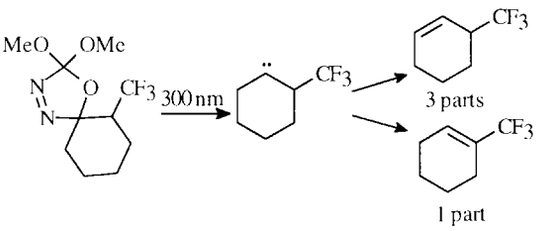
4.2 Dialkylcarbenes

This section is also restricted to studies of oxadiazolines as sources of cycloalkylidenes and alkylidenes. Photolysis of 2-alkoxy- or 2,2-dialkoxyoxadiazolines with 300 nm light leads to fragmentation to form an ester and a diazoalkane (Section 3.3). With an intense beam (laser), the carbene corresponding to the diazo compound is also generated. The fact that oxadiazoline precursors can be prepared readily from ketones means that a number of carbenes are available by a new route. Several approaches to a given carbene are desirable, because a particular precursor may generate products that appear to be carbene-derived but are actually born directly from the excited state (for example) of the precursor.[59,60b,71,77–89] Erroneous conclusions about a carbene's properties could result.



Scheme 13

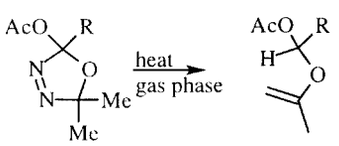
Laser flash photolysis (LFP) of appropriate carbene precursors in the presence of pyridine[90–102] gave strong signals for the corresponding pyridine ylides. Oxadiazoline precursors permitted estimates of rate constants for 1,2-H-migration in cyclohexylidene, substituted cyclohexylidenes, and acyclic carbenes.[69] The rate constant for the 1,2-H-migration was shown to be only moderately larger than those for the corresponding migrations in acyclic carbenes. Moreover, adamantylidene was shown[70,102] to be much more reactive than earlier studies, based on the diazirine precursor, had indicated. Finally, the sense of charge separation at the transition state (migration origin having lost electron density) was confirmed by showing that equatorial 2-trifluoromethylcyclohexylidene transfers H primarily from the methylene group rather than the axial H from the $CH(CF_3)$ group (Scheme 17).[69]



Scheme 17

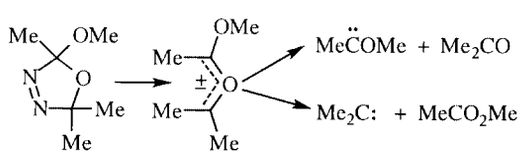
4.3 Oxycarbenes

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline and the 2-acetoxy-2-alkyl (or 2-aryl) analogues are readily prepared by oxidative cyclization of substituted hydrazones of ketones with lead tetraacetate in dichloromethane.[7,57,103,104] Thermolysis of the 2-acetoxy-2-methoxy system in the gas phase leads to an enol ether (Scheme 18).[104] The 2-acetoxy-2-methyl system behaves analogously.[32] In solution the 2-methoxy-2-methyl compound leads to products expected from a carbonyl ylide intermediate that fragments further in two ways to afford both methoxymethylcarbene and dimethylcarbene (Scheme 19).[37,103] This duality means that similar oxadiazolines are less useful in thermal processes than the dioxy analogues discussed below.



(R = OMe, alkyl or aryl)

Scheme 18

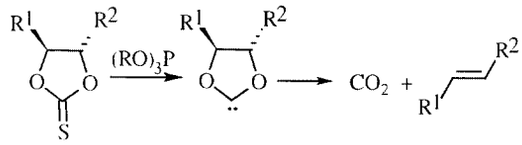


Scheme 19

4.4 Dioxycarbenes

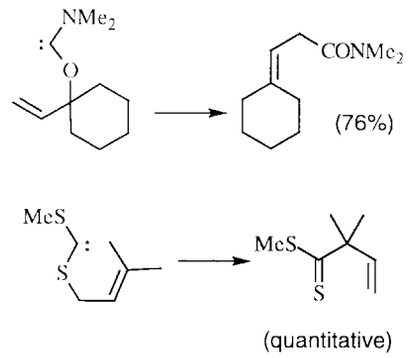
4.4.1 Intramolecular reactions

The best-known application of an intramolecular reaction of dialkoxycarbenes is the unimolecular fragmentation of cyclic, 5-membered carbenes to CO_2 and alkenes; the Corey–Winter reaction for converting 1,2-diols to alkenes (Scheme 20).[105,106] Oxadiazolines have not been applied in that sense, and probably never will be, as the Corey–Winter procedure is much easier. Oxadiazolines also have not been used to effect sigmatropic rearrangements, as might be expected of alkoxy(allyloxy)-

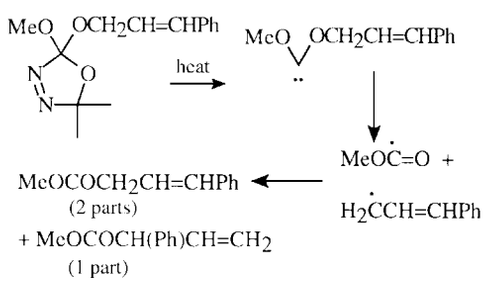


Scheme 20

carbenes (Scheme 21). Whereas allyloxyaminocarbenes[107] and allylic dithiocarbenes[108] undergo this rearrangement (Scheme 21), *trans*-cinnamyloxy(methoxy)carbene rearranges in benzene, at 110 °C, by a free radical mechanism to afford two esters (Scheme 22).[66a]



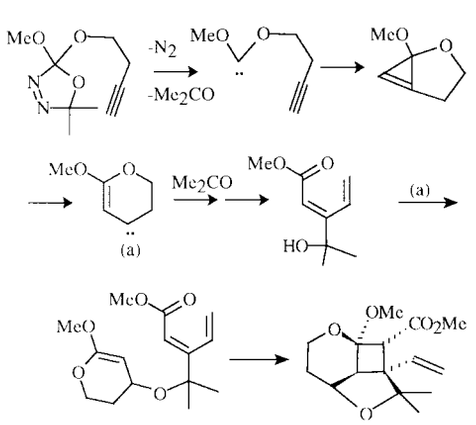
Scheme 21



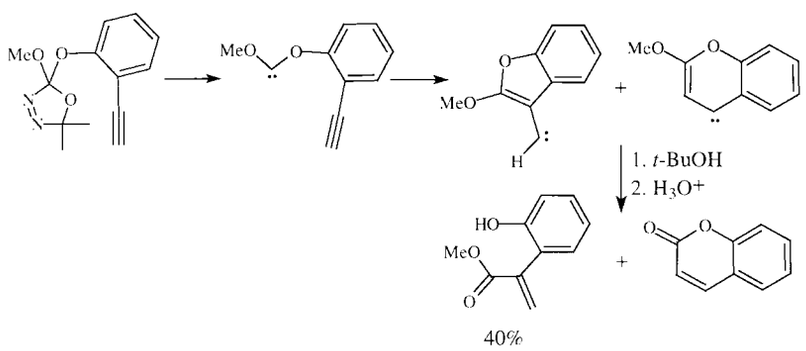
Scheme 22

Sigmatropic rearrangement plays only a minor role, if it occurs at all. Benzyloxymethoxy- and bis(benzyloxy)carbenes also fragment to radical pairs in solution.[66b]

An intriguing reaction of butynyloxy(methoxy)carbene is shown in Scheme 23. Cyclization to a dialkoxycyclopropene is part of a cascade leading from the oxadiazoline starting material to the final product in 74% yield.[5b,6] Related cyclizations of an alkynyloxy(methoxy)-[16] and an aryloxy(methoxy)-carbene with an alkynyl group in the *ortho* position also led to cyclopropenation and opening to new carbenes that were trapped with *t*-BuOH; hydrolysis of the intermediate ketene acetals gave the products in Scheme 24.[17]

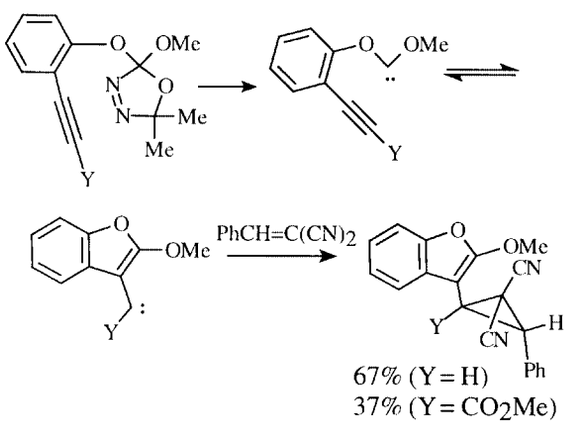


Scheme 23



Scheme 24

Scheme 25 illustrates the conversion of a similar first-formed carbene into a secondary carbene that is trapped with benzylidenemalononitrile.[17]

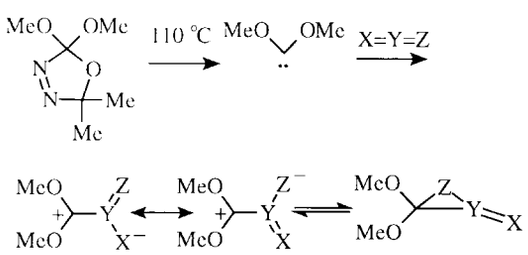


Scheme 25

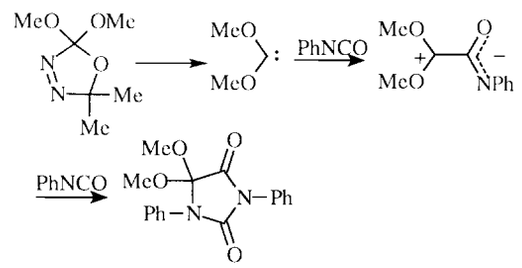
4.4.2 Intermolecular reactions

Dioxycarbenes are nucleophilic enough to attack electrophilic unsaturated centres to generate a dipolar intermediate that is probably equilibrated with the corresponding 3-membered ring(s). Scheme 26 shows one of these (X ≠ Z). If X = Y = Z is an isocyanate, attack by dimethoxycarbene leads to a hydantoin (Scheme 27) from cycloaddition of the intermediate to a second isocyanate molecule.[41] Dimethoxycarbene reacts similarly with phenyl isothiocyanate[41] and it reacts with a bisketene to afford a 1:1 adduct.[109] Vinyl isocyanates afford hydroindolones,[49,110,111] (Scheme 28). It is not necessary for the trap to be a cumulene; double bonds of strained ketones[112] and of perchloroalkenes are reactive enough[113] (Schemes 29 and 30), for example. Ring expansions analogous to those of Scheme 29 were observed also with cyclic anhydrides,[114] and with hexachlorobicyclo[3.2.0]hepta-3,6-dien-2-one.[113] Although it is convenient to represent the reaction in terms of a dipolar intermediate, the reader should keep in mind that the mechanism has not been established.

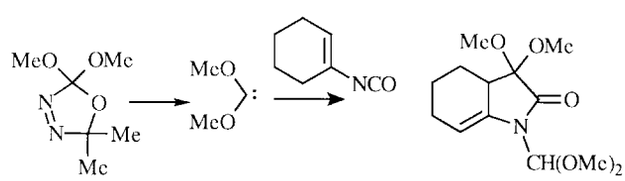
Oxadiazolines have been used to alkylate enols, which probably react by protonation of the carbene, subsequent ion-pair



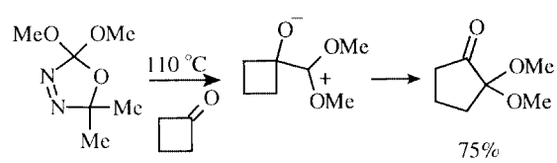
Scheme 26



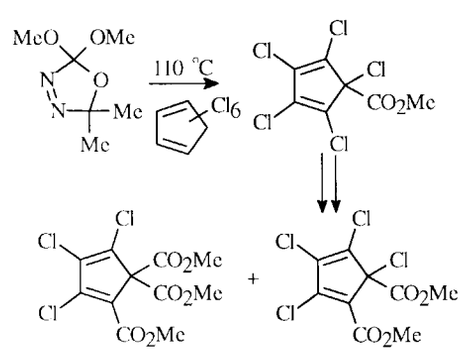
Scheme 27



Scheme 28



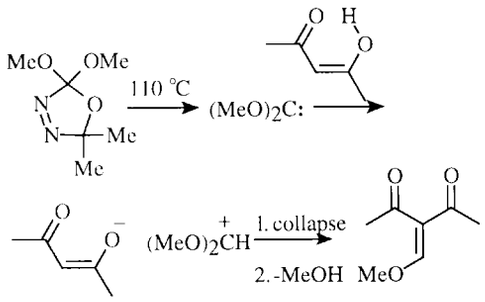
Scheme 29



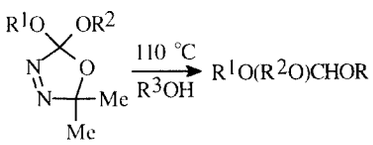
Scheme 30

collapse to carbon of the enolate, and loss of alcohol (Scheme 31).[115] Alcohols and phenols afford the appropriate orthoformates, including members in which the orthoformyl carbon is a stereocentre (Scheme 32).

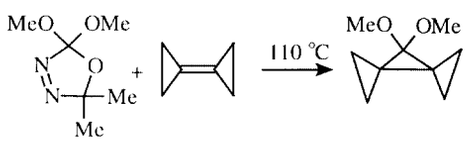
Unstrained alkenes react very slowly, if at all, with nucleophilic carbenes. Cyclohexene does not react[116] nor does *E*,*E*-1,4-diphenylbutadiene.[117] On the other hand, strained alkenes, with or without one or more electron-withdrawing groups, react with dimethoxycarbene (Scheme 33), for example.[5] It also adds to C_{60} to afford an adduct with a 6,6-closed structure.[118–120]



Scheme 31

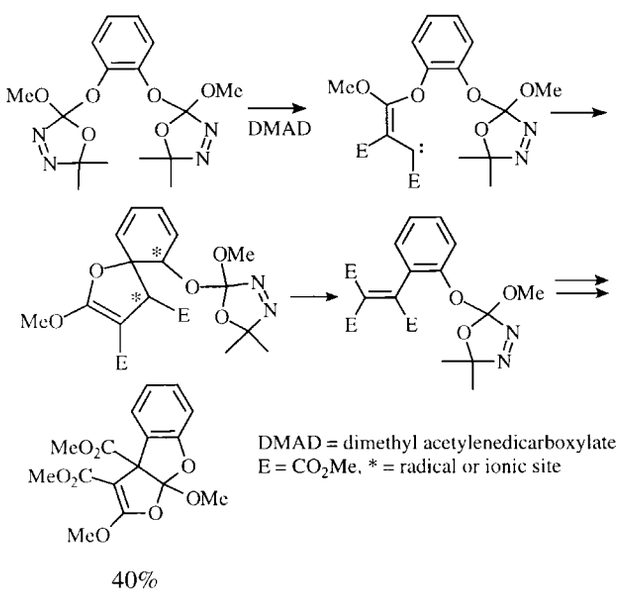


Scheme 32



Scheme 33

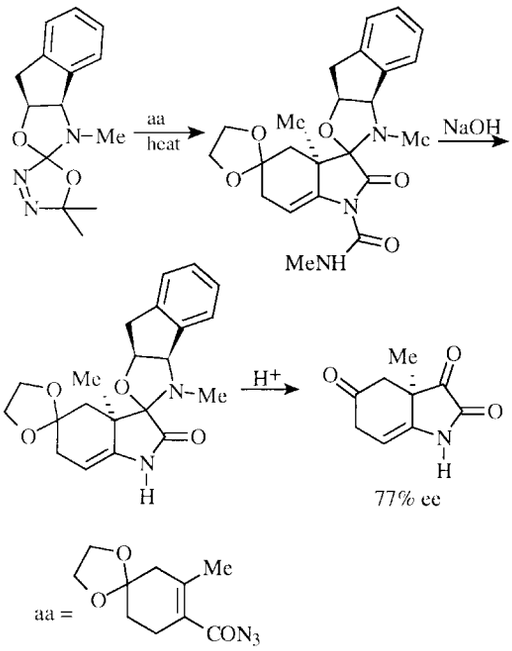
A bis-oxadiazoline could, in principle, afford a biscarbene upon thermolysis. In practice, this cannot happen, of course, because the small rate constant for oxadiazoline thermolysis (about 10^{-5} s^{-1} at 110 °C) means that a first-formed carbene would have to be extraordinarily stable to survive until the second carbene site could be generated from the same substrate molecule. However, sequentially-formed carbene sites permit assembly of a fairly complex structure in one pot (Scheme 34).[121]



Scheme 34

4.5 Amino(oxy)carbenes

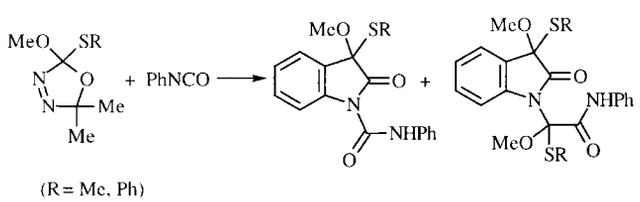
Analogous amino(oxy)carbenes,[13–15,49,115] have been generated by thermolysis of the appropriate oxadiazoline precursors. For example, heating a spirocyclic, chiral oxadiazoline with an acyl azide (precursor of a vinyl isocyanide) gave (−)-hydroisatin in three steps (Scheme 35).[12] Thermolysis of a spirocyclic aminocarbene precursor gave a β-lactam-4-ylidene that cyclized by intramolecular insertion into a phenolic OH group.[122]



Scheme 35

4.6 Oxy(thio)carbenes

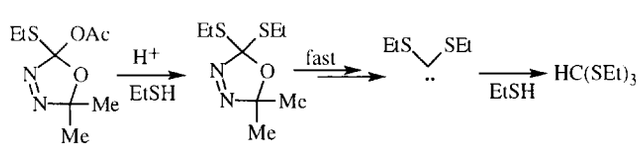
2-Alkoxy-2-alkylthiooxadiazolines and the corresponding phenylthiooxadiazolines have been prepared.[18] Thermolysis of these compounds occurs at a lower temperature (60–80 °C), presumably because the sulfur substituent stabilizes a carbonyl ylide intermediate, but carbenes are the ultimate fragments. These carbenes react normally with Michael acceptors but the products from reaction with phenyl isocyanate were not the expected hydantoins, but oxindoles (indol-2-ones) (Scheme 36).[18]



Scheme 36

4.7 Dithiocarbenes

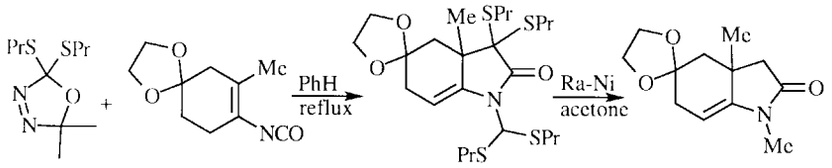
2,2-Bis(alkylthio)oxadiazolines are very much less stable than oxythio or dioxy analogues and they have not been isolated. An attempt to prepare the oxadiazoline with two EtS groups at C-2 gave $HC(SEt)_3$ as the only product.[4a] It is presumably derived from the corresponding oxadiazoline according to Scheme 37. Dithiocarbenes, generated from unstable oxadiazoline precursors, have recently been applied in the synthesis of N-heterocycles[27,28] (Scheme 38), for example.



Scheme 37

5 Summary

Δ^3-1,3,4-Oxadiazolines of the type reviewed here are clearly remarkably versatile precursors of reactive intermediates. Presumably they will continue to provide new chemistry, from



Scheme 38

reactions of these intermediates with new substrates or possibly from intermediates not yet discovered.

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