2-Alkoxy-2-amino-Δ^3-1,3,4-oxadiazolines as Novel Sources of Alkoxyaminocarbenes

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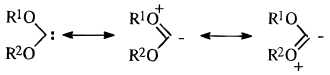
The chemistry of carbenes that bear one or two π-donor heteroatoms directly linked to the carbene center can be dramatically different from that of other carbenes. Heteroatoms such as N and O stabilize the carbene singlet state substantially by conjugative donation to the formally vacant p-orbital at the carbene carbon, raising the singlet/triplet energy gap to about 76 kcal mol^{-1} for dimethoxycarbene.[1] Such carbenes have dipolar character (structure **1**) and can act as nucleophiles or ambiphiles.[2] With two alkoxy substituents, a carbene is distinctly nucleophilic[2] and reacts at the carbonyl group rather than at the C−C double bond of maleic anhydride and analogs.[3] The reduced carbene reactivity seen with dialkoxycarbenes is exaggerated in cases of some diaminocarbenes. Arduengo and co-workers[4] have prepared diaminocarbenes that are very slow to react or even persistent at room temperature. To date, there is little published information concerning alkoxyaminocarbenes.[5]



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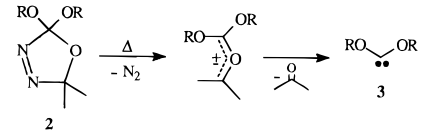
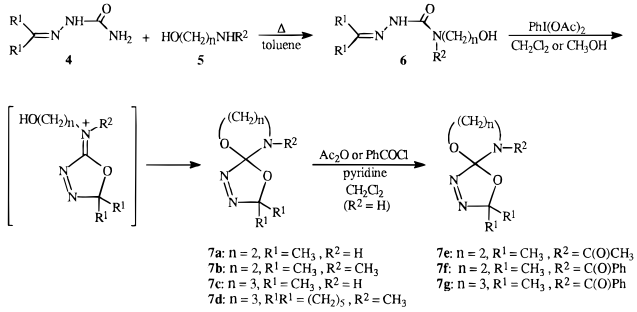
2,2-Dialkoxy-Δ^3-1,3,4-oxadiazolines of type **2** have been used as convenient thermal sources of dialkoxycarbenes, **3** (Scheme 1).[6] By analogy, thermolysis of 2-alkoxy-2-aminooxadiazolines should yield alkoxyaminocarbenes. Spiro-fused oxadiazolines **7a**−**g** were synthesized as outlined in Scheme 2.[7,8] The semicarbazone of acetone (**4**, $R^1 = CH_3$) or of cyclohexanone (**4**, $R^1R^1 = (CH_2)_5$), prepared by standard methods,[9] was refluxed with the appropriate amino alcohol (**5**) in toluene[10] for 7−15 h, to give the substituted semicarbazones **6** in 60%−81% yield. These compounds were oxidized with $PhI(OAc)_2$ in dichloromethane or in methanol to afford oxadiazolines **7b** (57%) and **7d** (35%), as well as **7a** and **7c** which were acetylated or benzoylated by standard methods, usually without prior purification, to afford **7e**−**g**, in 10%−33% yields (from the semicarbazones **6**).

Scheme 1

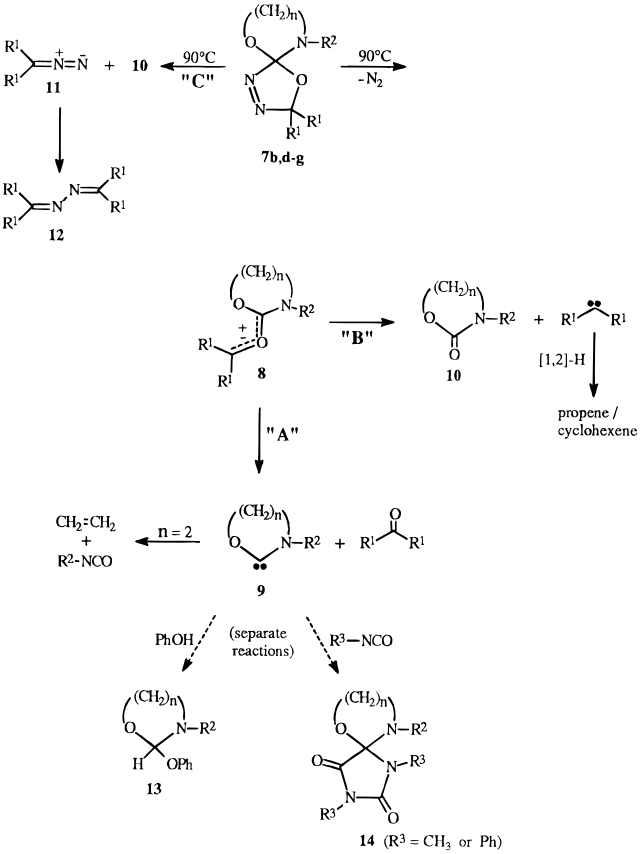


Scheme 2



7a: n = 2, $R^1 = CH_3$, R^2 = H
7b: n = 2, $R^1 = CH_3$, $R^2 = CH_3$
7c: n = 3, $R^1 = CH_3$, R^2 = H
7d: n = 3, $R^1R^1 = (CH_2)_5$, $R^2 = CH_3$
7e: n = 2, $R^1 = CH_3$, $R^2 = C(O)CH_3$
7f: n = 2, $R^1 = CH_3$, $R^2 = C(O)Ph$
7g: n = 3, $R^1 = CH_3$, $R^2 = C(O)Ph$

Scheme 3



Oxadiazolines **7b**,**d**−**g** decompose thermally in benzene at 90 °C with first-order rate constants ranging from about 4.8×10^{-5} to 4.5×10^{-4} s^{-1}, as determined by monitoring the disappearance of starting material in solutions sealed in NMR tubes. Product studies[11] demonstrated the occurrence of up to three competing decomposition pathways, as generalized in Scheme 3. Thus, for compound **7b**, the intermediate carbonyl ylide **8b** ($n = 2$, $R^1 = R^2 = CH_3$), formed by the initial extrusion of N_2, fragments predominantly *via* pathway A to form 3-methyl-2-oxazolidinylidene, **9b** ($n = 2$, $R^2 = CH_3$), and acetone. In the absence of an efficient trap, some of carbene **9b** fragments to ethene (>5% yield by NMR) and methyl isocyanate; this is analogous to the known fragmentations of

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(7) Compound **7a** was previously prepared by a similar method: Zoghbi, M. Ph.D. Thesis, McMaster University, Hamilton, Ontario, Canada, 1991.
(8) The identity of oxadiazolines **7b**,**d**−**g** was confirmed by mass spectrometric experiments involving LRP and HRP electron impact, collisional activation spectrometry, and chemical ionization using ammonia. Results are available as supporting information.
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(11) Larger scale thermolyses were typically done using *ca.* 5×10^{-4} mol of oxadiazoline in 10 mL of benzene.

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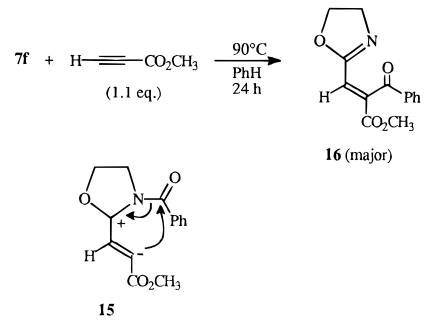
the dioxa[12] and dithia[13] equiv of **9b**. Formation of carbene **9b** was unambiguously demonstrated by trapping it by insertion into the OH bond of phenol to give **13b** ($n = 2$, $R^2 = CH_3$) in 59% yield (by NMR). In addition, when **7b** was thermolyzed in the presence of phenyl isocyanate, a 1:2 (carbene:phenyl isocyanate) adduct, **14b** ($n = 2$, $R^2 = CH_3$, $R^3 = Ph$), was isolated in 27% yield;[14] this product is analogous to those formed in the reactions of dimethoxycarbene[15] and (dimethylamino)-methoxycarbene[5e] with phenyl isocyanate. The formation of other products such as 3-methyl-2-oxazolidinone[16] (**10b**, $n = 2$, $R^2 = CH_3$), propene, and acetone azine (**12b**, $R^1 = CH_3$), in the thermolysis of **7b** leads us to postulate the occurrence of an alternative fragmentation for **8b**, pathway B, to give 2-propylidene (which undergoes a 1,2-H shift to form propene in >16% yield) and 3-methyl-2-oxazolidinone, **10b** ($n = 2$, $R^2 = CH_3$), found in approximately 31% yield (by NMR). Traces of acetone azine (**12b**, $R^1 = CH_3$), detected in thermolyzed mixtures of **7b**, also suggest the occurrence of a second primary 1,3-dipolar cycloreversion, pathway C, to 2-diazopropane (**11b**, $R^1 = CH_3$) and **10b**. This pathway may be more important than anticipated from the amount of **12b** formed since a substantial quantity of an unidentified product possibly derived from 2-diazopropane forms in the thermolysis of **7b**. The possibility that the propene produced comes from 2-diazopropane can be discounted because previous work in our laboratory showed that 2-diazopropane generated under similar conditions gives acetone azine without apparent formation of propene.[17]

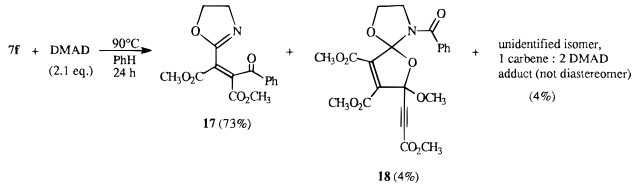
In the case of oxadiazoline **7d**, competition between pathways A and B for the decomposition of carbonyl ylide **8d** ($n = 3$, $R^1R^1 = (CH_2)_5$, $R^2 = CH_3$) was found to favor pathway B; thus, observed NMR yields were 77% for carbonyl compound **10d** ($n = 3$, $R^2 = CH_3$)[18] and *ca*. 65% for cyclohexene, compared to 13% for cyclohexanone, the coproduct in the formation of carbene **9d** ($n = 3$, $R^2 = CH_3$). However, no conclusive evidence (^{1}H-NMR, GC−MS) could be found for product **13d** ($n = 3$, $R^2 = CH_3$) from thermolysis of **7d** in a sealed NMR tube in the presence of phenol.

The *N*-carbonyl derivatives **7e**−**g** are much more efficient sources of 2-oxazolidinylidenes or tetrahydro-1,3-oxazin-2-ylidenes than are their *N*-methyl counterparts. Thermolysis of oxadiazoline **7f** yielded mainly carbene **9f** ($n = 2$, $R^2 = C(O)Ph$), which reacted with phenol added to the thermolysis solution to give **13f** ($n = 2$, $R^2 = C(O)Ph$) in 94% yield (by NMR), compared to a <5% yield[19] for carbonyl compound **10f** ($n = 2$, $R^2 = C(O)Ph$).[20] Generation of **9f** in the presence of an excess of phenyl isocyanate resulted in the formation of **14f** ($n = 2$, $R^2 = C(O)Ph$, $R^3 = Ph$) in 76% isolated yield. With this oxadiazoline, no evidence for the formation of acetone azine (**12b**, $R^1 = CH_3$) (pathway C) was found. Again, in the absence of an efficient carbene trap, **9f** decomposes to ethene and, in that case, benzoyl isocyanate; the latter then acts as a trap for **9f** to form a final product in apparent high yield. The structure of that product is currently under investigation. Similarly, carbene **9e** ($n = 2$, $R^2 = C(O)CH_3$), generated in the thermolysis of compound **7e**, reacted with phenol to give **13e** ($n = 2$, $R^2 = C(O)CH_3$) in 89% isolated yield, and its reaction with phenyl isocyanate gave **14e** ($n = 2$, $R^2 = C(O)CH_3$, $R^3 = Ph$) in 87% isolated yield. Thermolysis of oxadiazoline **7g** in the presence of phenol or methyl isocyanate resulted in the quantitative formation of **13g** ($n = 3$, $R^2 = C(O)Ph$) and **14g** ($n = 3$, $R^2 = C(O)Ph$, $R^3 = CH_3$), respectively.

Scheme 4



Scheme 5



Dialkoxycarbenes are known to participate in intermolecular[21] and intramolecular[22] reactions with activated triple bonds. In order to probe the reactivity of our azaoxacarbenes, oxadiazoline **7f** was thermolyzed in benzene with 1.1 equiv of methyl propiolate (Scheme 4). A ^{1}H NMR spectrum of the crude thermolyzed mixture showed that **16** was the major product in this thermolysis. This product apparently was formed *via* an interesting benzoyl group transfer from N to C in the 1,3-dipolar intermediate **15**. Purification of **16** by centrifugal chromatography on silica gel resulted in its partial decomposition, and the purified product was obtained in only about 4% yield. Carbene **9f** could be trapped efficiently with a more electrophilic alkyne. Thus, when **7f** was thermolyzed in the presence of 2.1 equiv of dimethyl acetylenedicarboxylate (DMAD) in benzene, the major product, **17**, which could be purified without observable decomposition, was obtained in 73% yield (Scheme 5). In addition, two 1:2 (carbene:DMAD) adducts were recovered in 4% yield each. Spectroscopic data for one of them[23] are consistent with structure **18**, the analog of a product isolated in the reaction of dimethoxycarbene with DMAD;[21] the nature of the second minor product has yet to be determined.

The fact that carbenes **9** ($n = 2$) can be trapped efficiently in a variety of intermolecular reactions stands in sharp contrast to the prediction[12b] that the dioxa analog fragments to ethene and carbon dioxide too rapidly for trapping to compete.

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Supporting Information Available: Typical procedures for syntheses of the oxadiazolines and their precursors and for thermolyses of the oxadiazolines; NMR, IR, and mass spectral data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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