Formation and Rearrangement of a 2,2-Dimethoxyoxirane from Dimethoxycarbene and Fluorenone

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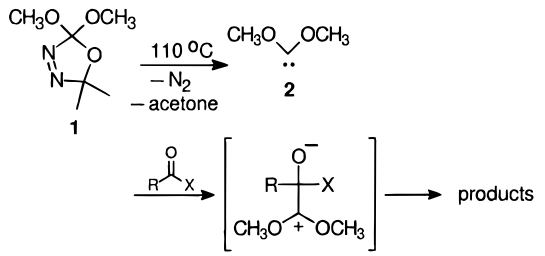
Thermolysis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**) at 110 °C in the presence of 9-fluorenone (**3**) yielded 9-(dimethoxymethylene)fluorene oxide (**4**) and methyl 9-methoxyfluorene-9-carboxylate (**5**), which are the result of the addition of dimethoxycarbene (**2**) to the carbonyl group of 9-fluorenone. While the epoxide **4** is most likely generated from direct [2 + 1] cycloaddition, the ester **5** is the result of subsequent rearrangement of the oxirane. Thermolysis of the trideuteriomethoxy oxadiazoline **1**-d_3 in the presence of fluorenone showed that **5** is not formed by an intermolecular process because evidence for crossover of the label in the product **5** was not found. The rearrangement of **4** to **5** does not proceed by ring opening and intramolecular methyl transfer either but, instead, by ring opening and intramolecular methoxy transfer. Thus, as predicted by the Baldwin rules, the strained intramolecular *5-endo-tet* methyl transfer is avoided in favor of another process.

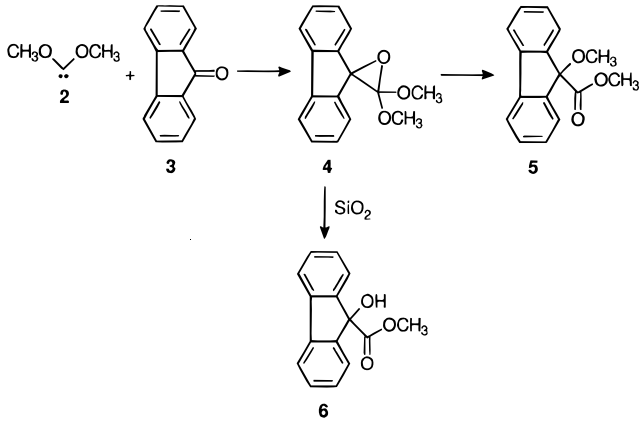
A variety of oxadiazolines with geminal alkoxy substituents (such as **1**) have been shown to generate dioxycarbenes (such as **2**) upon thermolysis (Scheme 1).[1] Reactions of **2** with the carbonyl groups of a variety of cyclic anhydrides,[1c] benzoyl chloride,[2] and biacetyl[2] have been reported previously. In these instances, products arise from rearrangement of a dipolar intermediate (Scheme 1), which is formally the result of nucleophilic addition of the carbene to the carbonyl carbon atom. While the intermediacy of oxiranes, from closure of the 1,3-dipole, is likely, they have never been observed as intermediates for reactions of dialkoxycarbenes. Furthermore, oxiranes with two geminal alkoxy groups are unknown in the literature.

We now report that dimethoxycarbene generated from **1**[1a−d,i] reacts with the carbonyl group of 9-fluorenone (**3**) to yield a 2,2-dialkoxyoxirane that is stable enough to be characterized by NMR spectroscopy. A solution of dimethoxyoxadiazoline **1** (0.21 mol/L) and 9-fluorenone (**3**) (0.42 mol/L) in benzene was heated for 20 h at 110 °C. Under these conditions, the oxadiazoline **1** decomposes completely within the reaction time.[1a] Removal of the volatiles and ^{1}H-NMR spectroscopy ($CDCl_3$) of the residue revealed several signals in the methoxy region, but GC/MS characterization revealed only a single product of high molecular weight, corresponding to an adduct of dimethoxycarbene and fluorenone. Radial chromatography of the mixture yielded two products (Scheme 2). Methyl 9-methoxyfluorene-9-carboxylate (**5**) had mass

Scheme 1



Scheme 2



and ^{1}H-NMR spectra that matched those of the major species found in the crude mixture and were in good agreement with the spectral data reported for that compound.[3] The yield of **5** was 24% on the basis of the NMR spectrum of the crude mixture using an internal standard. Methyl 9-hydroxyfluorene-9-carboxylate (**6**) was also isolated and the mass spectrum (GC/MS) found to match a literature mass spectrum.[4] Since the GC trace of the crude mixture did not contain a peak for **6**, it must be a hydrolysis product of an unidentified adduct of dimethoxycarbene and fluorenone.

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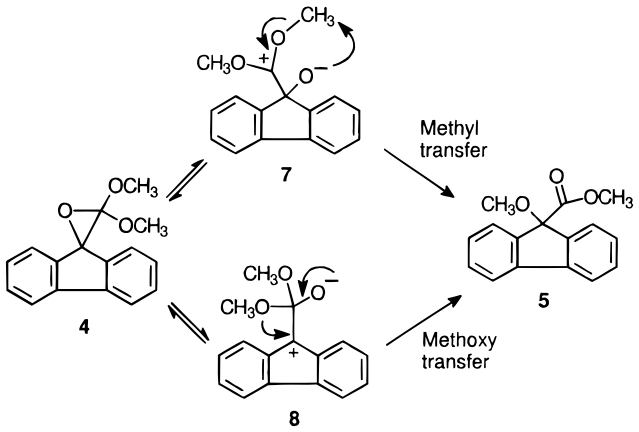
S0022-3263(97)00198-9 CCC: $14.00

Scheme 3

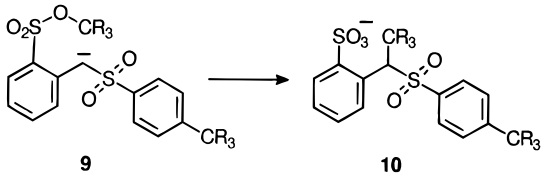


We propose that this second adduct is the oxirane **4** that should hydrolyze readily on silica to yield **6** and is likely to be unstable to gas chromatography. Furthermore, we propose that **4** is the primary product of reaction of dimethoxycarbene with fluorenone and that **4** rearranges thermally to **5**. To test the hypothesis that **5** is derived from **4**, a shorter thermolysis time was used to attempt to generate a solution enriched in **4**. The 500 MHz ^{1}H-NMR spectrum of the crude reaction mixture from thermolysis of **1** in the presence of **3**, for 6 h at 110 °C, provided support for the hypothesis. In addition to a methoxy signal for remaining **1** (δ = 3.45), one other methoxy signal (δ = 3.55) of approximately equal integration was found. This methoxy singlet was assigned to **4**. The yield of **5** from 6 h of thermolysis, estimated by ^{1}H-NMR spectroscopy, was only 10% while the yield of **4** was 39%, each based on the oxadiazoline consumed (70%). Compound **4** could still be identified from one of the signals in the ^{1}H-NMR spectrum of the crude mixture after 20 h of heating (~15% yield of **4** by NMR).

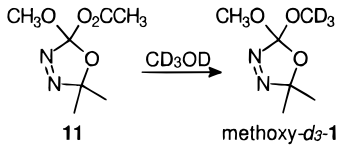
Since the ^{1}H-NMR spectrum at this thermolysis time was quite clean and showed significant signals for **1**, **3**, **4**, and **5** only, the ^{13}C-NMR signals for **4** could be identified in the spectrum of the crude mixture from the 6 h thermolysis. Signals for the methoxy group (δ = 52.9), the oxirane carbon atoms (δ = 74.9 and 105.1 ppm), and all six aromatic signals corresponding to **4** were found. The oxirane **4** did not survive gas chromatography or silica gel chromatography, making further characterization of **4**, mixed with other components, very difficult. The observed high hydrolytic reactivity of **4** is in keeping with the assigned structure. Oxiranes with a 2-alkoxy group and 3,3-diaryl groups are known to be stable compounds,[5] but we are not aware of reports of oxiranes with two geminal oxy substituents, alternatively described as carbonyl-protected α-lactones.

Mechanism of Formation of 5. We became intrigued with the mechanism of formation of the methoxy ester **5**. There are two intermediates that could undergo group transfer to form **5** (Scheme 3). Intramolecular methyl transfer in zwitterion **7** could yield the observed product directly. Zwitterion **7** is probably equilibrated with **8** through the oxirane **4**, and **8** too could yield **5**, but by a 1,2-methoxy transfer. Rearrangements of alkoxyoxiranes to yield products similar to those observed in this work are reported in the literature,[6] but mechanistic studies to determine how they arise have not been performed. There are two important considerations. First, the *5-endo-tet* methyl transfer from **7** is disfavored according to the Baldwin rules,[7,8] which caution that there must be a linear geometry between nucleophile, reaction center, and leaving group—a geometry that is impossible to achieve with small rings. Second, the energy of **8** is expected to be higher than that of **7**, since the cation portion of **8** is nonaromatic, whereas that of **7** is stabilized by two alkoxy groups (Scheme 3).

Scheme 4



Scheme 5



Eschenmoser and co-workers have shown that intramolecular methyl transfers tend to avoid the *5-endo-tet* transition state in favor of bimolecular transfer.[9] They used deuterium-labeled and -unlabeled **9** (50% R = D, 50% R = H, Scheme 4) to show that methyl transfer to give **10** involved crossover of the label and, therefore, occurred in a bimolecular sense. McGarrity and King similarly concluded that methyl transfer was normally avoided even through a cyclic 8-membered ring transition state.[10] Schaumann and co-workers found that transfers of methyl groups in dipolar species simlar to **7** and **8** also proceed via intermolecular mechanisms.[11] Bimolecular reactions of **7** or **8** should therefore be possible, but they are unlikely because of the expected low concentrations of the zwitterions in equilibrium with the oxirane in benzene.

Isotopic labeling studies served to distinguish between intramolecular and intermolecular group transfers and between methoxy and methyl transfer. The trideuteriated dimethoxyoxadiazoline **1**-d_3 was prepared from exchange of the acetoxymethoxyoxadiazoline **11** with methanol-d_4 (Scheme 5).[12] With **1**-d_3 to generate labeled carbene (**2**-d_3), it was possible to distinguish between the two pathways. Purely intramolecular rearrangement of zwitterions **7** or **8** would produce products with only one trideuteriated methoxy group. Purely bimolecular rearrangement would result in crossover of the CD_3 groups to afford 25% d_0, 50% d_3, and 25% d_6 isotopomers, assuming a statistical distribution and ignoring kinetic isotope effects.

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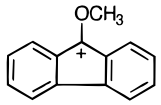
Ester **5** shows a molecular ion in both the EI and CI mass spectra that was used to monitor the isotopic composition. Thermolysis of oxadiazoline **1**-d_3 in the presence of fluorenone yielded **5**, which was found to have *retained* the isotopic distribution of the oxadiazoline precursor. The observation that isotopic crossover did not occur is consistent with the formation of **5** solely through an intramolecular rearrangement.

Intramolecular methyl transfer could be distinguished from methoxy transfer by means of ^{18}O labeling of fluorenone. The mass spectrum of unlabeled **5** has a base peak at *m*/*z* 195 that corresponds to the 9-methoxyfluorenyl cation (**12**) from loss of $[CO_2CH_3]^{\bullet}$. The methyl transfer mechanism should result in retention of the ^{18}O label in that ion while the methoxy transfer mechanism should result in its loss (Scheme 3).



12

9-Fluorenone (**3**, 42% ^{18}O), prepared by a literature method[13] from 50% $H_2{}^{18}O$, reacted with dimethoxycarbene to afford labeled [^{18}O]-**5**. The $^{16}O/^{18}O$ ratio of the molecular ion was 2.1:1, while the corresponding ratio of the fragment ion **12** was 66:1, indicating complete incorporation of the label into the carbonyl group of **5**. These labeling results demonstrate that the mechanism of group transfer to form **5** is exclusively intramolecular methoxy transfer. Bimolecular reactions, unlikely because of the low concentrations of reactive intermediates that are formed slowly as the oxadiazoline decomposes, are eschewed in favor of intramolecular methoxy transfer. A necessary consequence of these results is that the oxirane **4** must be an intermediate in the formation of **5**, and as discussed earlier, oxirane **4** could be identified in the crude reaction mixture. Although the existance of **4** does not shed any light onto the mechanism by which dialkoxycarbenes add to carbonyl groups (stepwise versus concerted), it is clear that oxiranes of this sort are viable species that, in a situation disfavoring bimolecular processes, may be identified.

The data do not provide any information on the relative stabilities of the two dipoles **7** and **8**, but their relative stabilities can be gauged by examining the cationic portions. The highly stabilized dimethoxymethyl cation is anticipated to be favored over the nonaromatic fluorenyl cation,[14] and **7** should predominate over **8** in an equilibrium between **7**, **4**, and **8** (Scheme 3). Thus, the observed chemistry results from rearrangement of the minor equilibrium component and may explain, in part, the long lifetime of the oxirane in solution.

The formation of oxiranes in the reactions of other carbenes is well established, but addition of dimethoxycarbene (**2**) to the carbonyl group of 9-fluorenone (**3**), to yield oxirane **4** as the initial product, is the first evidence for an oxirane intermediate in the addition of a dialkoxycarbene to a carbonyl group.

Experimental Section

Thermolysis of Dimethoxyoxadiazoline 1 in the Presence of Fluorenone (3). Dimethoxyoxadiazoline **1** (0.20 g, 1.3 mmol) and 2 equiv of 9-fluorenone (**3**, 0.45 g, 2.5 mmol) in 6 mL of benzene were sealed into a thermolysis tube and heated for 20 h at 110 °C. The reaction mixture was concentrated and separated by centrifugal chromatography (silica; 98% hexanes:2% ethyl acetate). Product **5** was eluted as a band following fluorenone, and **6** was eluted as a second band following those of both **3** and **5**. The crude reaction mixture, analyzed by NMR spectroscopy with an internal standard added after the thermolysis, showed that final product **6** was not present in the crude, although **4** was present. Yields of 24% and 10% for **5** and **4**, respectively, based on oxadiazoline, were obtained. Analysis of the reaction mixture by NMR spectroscopy after a thermolysis time of 6 h revealed yields of 39% and 10%, respectively, for **4** and **5**. Those yields corresponded to 70% decomposition of the oxadiazoline during the truncated reaction time.

9-(Dimethoxymethylene)fluorene oxide (4): ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.55 (two OCH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 52.9 (OCH_3), 74.9, 105.1 [*C*(OCH_3)$_2$], 119.9, 125.2, 127.5, 129.6, 138.1, 141.4.

Methyl 9-methoxyfluorene-9-carboxylate (5): ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.89 (s, 3H, OCH_3), 3.60 (s, 3H, CO_2CH_3), 7.29 (m, 2H, aromatic), 7.40 (m, 2H, aromatic), 7.50 (m, 2H, aromatic), 7.65 (m, 2H, aromatic); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 51.7, 52.7, 88.4, 120.2, 124.6, 128.0, 129.9, 141.5, 171.2 (one aromatic signal not observed); MS (EI) *m*/*z* 254 (5), 223 (2), 195 (100), 180 (35); MS (CI, NH_3) *m*/*z* 272 $[M + NH_4]^+$ (40), 242 (45), 240 (100); mp = 118−120 °C lit.[15] mp = 125 °C.

Methyl 9-hydroxyfluorene-9-carboxylate (6):[4] MS (EI) *m*/*z* 240 $[M]^+$ (8), 195 (13), 181 $[M - C_2H_3O_2]^+$ (100), 152 (28); MS (CI, NH_3) *m*/*z* 258 $[M + NH_4]^+$ (100); exact mass ($C_{15}H_{12}O_3$) found 240.0792, calcd. 240.0786.

Reaction of Methoxy(trideuteriomethoxy)oxadiazoline [(Methoxy-d_3)-1] with Fluorenone (3). Trideuterated oxadiazoline (methoxy-d_3)-**1** was prepared from the reaction of methanol-d_4 with acetoxyoxadiazoline **11** by means of the procedure described in the literature.[12] A solution containing 0.20 g (1.2 mmol) of (methoxy-d_3)-**1** and 0.45 g (2.5 mmol) of fluorenone (**3**) in 6 mL of benzene was heated at 110 °C in a constant temperature oil bath for 24 h. The reaction mixture was separated by radial chromatography, and the fraction corresponding to labeled **5** was analyzed by mass spectrometry.

(Methoxy-d_3)-1: MS (CI, NH_3) *m*/*z* 184 $[M\text{-}d_6 + NH_4]^+$ (<1), 181 $[M\text{-}d_3 + NH_4]^+$ (100), 178 $[M\text{-}d_0 + NH_4]^+$ (5).

5-d_3: MS (EI) *m*/*z* 260 $[M\text{-}d_6]^+$ (0), 257 $[M\text{-}d_3]^+$ (100), 254 $[M\text{-}d_0]^+$ (9).

Reaction of Dimethoxyoxadiazoline 1 with [^{18}O]Fluorenone ([^{18}O]-3). Labeled fluorenone (0.093 g, 0.5 mmol) was prepared according to the procedure of Proctor et al.[13] by dissolving fluorenone (0.093 g) in 4 mL of benzene, 4 mL of methanol, 1 μL of HCl, and 50 μL of $H_2{}^{18}O$ (50 atom % ^{18}O). The solution was sealed into a glass tube and heated at 80 °C for 18.5 h. Most of the solvents were removed by distillation, and the solid remaining was subjected to reduced pressure to remove residual solvent. A solution of 0.041 g (0.26 mmol) of **1** and 0.046 g (0.26 mmol) of [^{18}O]-**3** in 1 mL of benzene was then heated in a sealed tube at 110 °C for 24 h. GC/MS analysis of the reaction mixture revealed that **5** contained the oxygen label.

Methyl 9-methoxyfluorene-9-carboxylate-[^{18}O] (^{18}O-5): MS (EI) *m*/*z* 256, M^+ (1.5), 254, M^+ (2), 197 [[^{18}O]-**12**] (1.5), 195 [[^{16}O]-**12**] (100), 180 (70), 163 (15), 152 (36).

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