Structure of a spiro-fused, 2,2-dioxy-Δ^3-1,3,4-oxadiazoline

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Dedicated to Professor O. S. Tee on the occasion of his 60th birthday

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Abstract

3,4-Diaza-2,2,8,8-tetramethyl-1,6,10-trioxaspiro[4.5]dec-3-ene **(6)** was synthesized. The single crystal X-ray structure shows that the 6-membered ring is in the chair conformation with the azo group in the axial position. Comparison of the ^{13}C NMR spectra of **6** in solution and in the solid state indicates that the preferred conformation in solution is also that with the azo group axial. Thus, although an alkoxy group normally occupies the axial position (the anomeric effect), the azo group outranks it insofar as the axial preference is concerned.

Thermolysis of 6 in benzene afforded N_2, acetone, the carbene dimer 2-(5',5'-dimethyl-1,3-dioxan-2-ylidene)-5,5-dimethyl-1,3-dioxane, and 2-hydroxy-5,5-dimethyl-1,3-dioxane from reaction of the carbene intermediate with adventitious water. Those products were taken as evidence for the intermediacy of the carbene, 5,5-dimethyl-1,3-dioxan-2-ylidene.

Keywords: Spirooxazoline, thermolysis, dialkoxycarbenes, dioxanes

Introduction

Dialkoxycarbenes are nucleophilic carbonyl group equivalents. They have been generated primarily in the four ways illustrated with Scheme 1. Thermolysis of 7,7-dialkoxynorbornadienes[1] in solution at about 140 ^{o}C causes cheletropic cycloreversion to a dialkoxycarbene and an arene but the process involves side reactions that may interfere with the isolation of carbene-derived products. Moreover, the synthesis of 7,7-dialkoxynorbornadienes with different alkoxy groups is not simple because the cyclopentadienone acetal precursor is usually prepared from hexachlorocyclopentadiene and an alcohol.[2] Photolysis of dialkoxy diazirines is an excellent method for generating dioxycarbenes for spectroscopic studies and for mechanistic work[3] but such diazirines must generally be used as dilute solutions as neat diazirines are explosive. Orthoformates have been used effectively at 140 ^{o}C as dialkoxycarbene precursors[4], but they are not suitable as sources of unsymmetric dialkoxycarbenes. 2,2-Dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines have a number of advantages. They are shelf stable in pure form but at 100-110 ^{o}C they afford primarily a dialkoxycarbene, N_2, and acetone, Scheme 2.[5] Moreover, symmetrically-and unsymmetrically-substituted 2,2-dialkoxy-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines can be prepared readily, as well as 2-alkoxy-2-aryloxy-and 2,2-diaryloxy oxadiazolines, by the exchange method.[5b, 6]

Given the utility of 2,2-dialkoxy-Δ^3-1,3,4-oxadiazolines as thermal precursors of dialkoxycarbenes, it was of interest to synthesize some spirocyclic analogues to investigate their structures. In this paper, we report the structure of an oxadiazoline, spiro-fused through C-2 to a six-membered ring. The system investigated (**6**) could have either a preference for the azo-axial conformation (**6a**) or the alkoxy-axial conformation (**6b**), Scheme 3. According to many studies of the anomeric effect[7], alkoxy substitutents have a preference for the axial position when the competition is with an alkyl group or with H. Although the source of the anomeric effect has been the subject of debate, it is clear that the more electron-withdrawing substituent, in systems that are sterically unbiased (eq [1]) adopts the axial position.[8] Based on that precedent, one would predict that the azo group (sigma *p*-phenylazo= 0.33)[9] would outrank an alkoxy group in terms of axial preference, in a system such as **6**, eq [2].

Results and Discussion

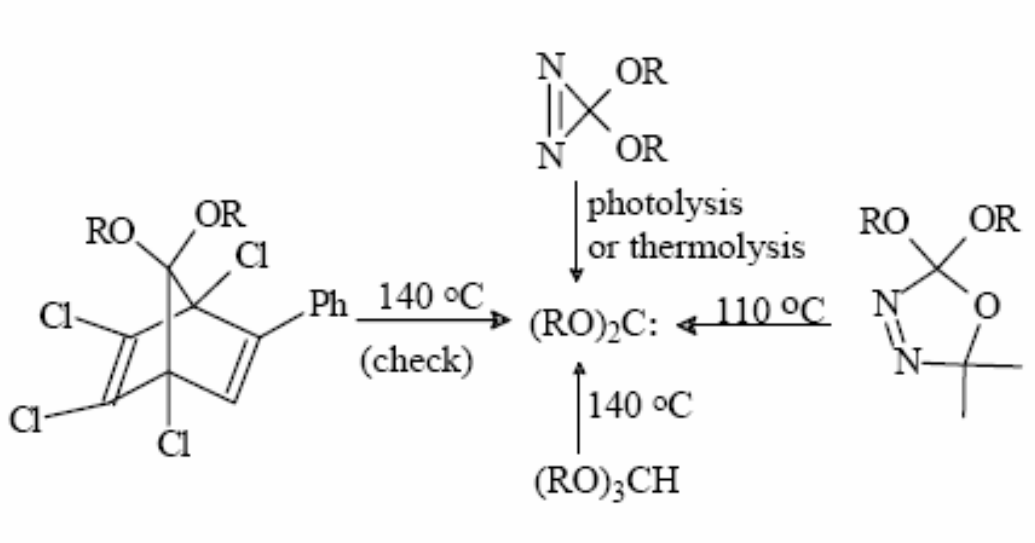
Oxadiazoline **6** was prepared according to Scheme 3. Transesterification of diethyl carbonate with 2,2-dimethyl-1,3-propanediol (**1**) gave carbonate **2**, which underwent hydrazinolysis to **3**. Condensation of **3** with acetone gave **4**, and oxidation[5b] of **4** with lead tetraacetate (LTA) in dichloromethane afforded a mixture containing **5**. Cyclization of **5** to **6** was accomplished with trifluoroacetic acid in dichloromethane, Scheme 3. The structure of **6** in the solid state was determined by means of single crystal X-ray diffraction. A gross feature of the structure is the chair-like geometry of the 6-membered ring and the axial position of the azo group of the 5-membered ring, Table 1. That geometry might reflect an inherent preference for the "azo axial" conformation in the solution from which the oxadiazoline had crystallized or it could be caused by lattice forces in the solid. In order to distinguish between the two possibilities, the ^{13}C NMR spectrum of solid **6** was acquired for comparison with the spectrum of **6** in solution. In that way it was possible to link the known structure in the solid state (X-ray), *via* the ^{13}C spectra of both the solid and the solution, to the probable conformation of **6** in solution.

Table 2 lists the solid-state and the solution-phase ^{13}C NMR spectra of **6** as well as the ^{1}H NMR spectrum of **6** in solution. . All signals in the spectrum of the solid were relatively sharp except those from C2 and C5, which are broadened by quadrupolar coupling to the azo nitrogens. Comparison of the ^{13}C data shows that the ^{13}C chemical shifts in the solid are very similar to those of **6** in chloroform solution; the average difference is only 0.6 δ. This result suggests that the conformations in the solid state and in solution are the same.

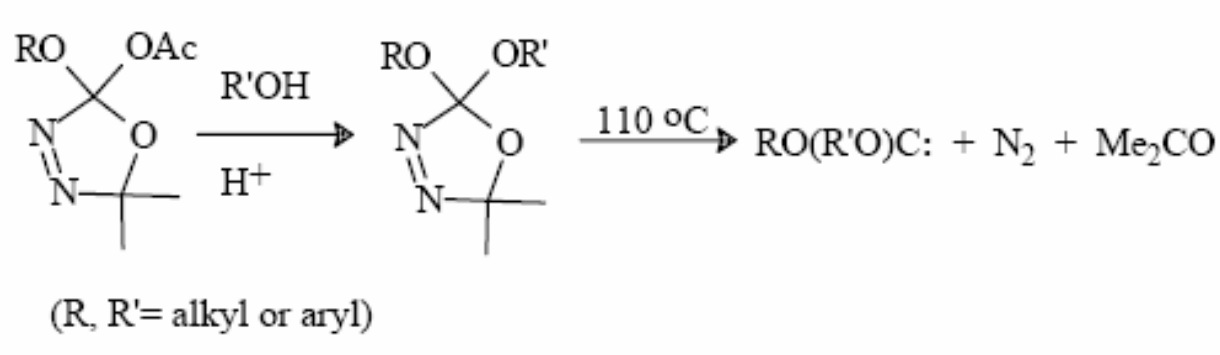
Although the axial azo bond (N4-C5) appears at first glance to be longer than the other azo bond (C2-N3), just as the axial C-aryl bonds of the system in Eq. [1] were longer than the equatorial C-aryl bonds,[8] the uncertainties mean that the difference is not significant.

Reactions of 6 -Thermolysis of **6** in benzene-d_6 at 100 ^{o}C was followed by ^{1}H NMR spectroscopy, with toluene as internal standard for integration. Depletion of **6** followed the first order rate law; $k = 1.19 \times 10^{-5}$ s^{-1} at 100 ºC, from 15 data points to 88 % of completion.

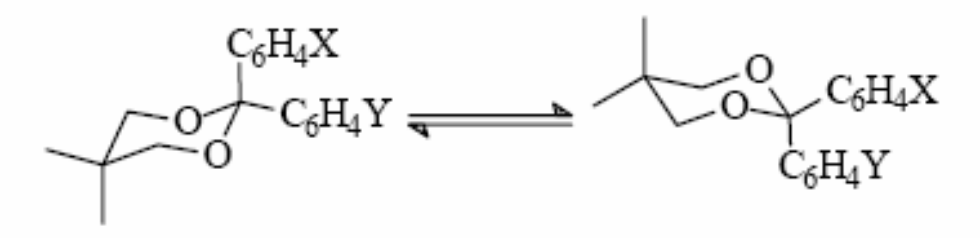
Analysis by GC showed that there were two major products, which could be separated by preparative GC to afford a pure sample of carbene dimer (**9**, 28%) and a sample of hemi orthoester **10** (*ca.* 22%), contaminated with **9**. The hemi orthoester must be derived from capture of the carbene **8** by adventitious water, Scheme 5. Those two products were taken as evidence for the fragmentation of **6** to acetone, N_2, and 5,5-dimethyl-1,3-dioxan-2-ylidene (carbene **8**).



Scheme 1

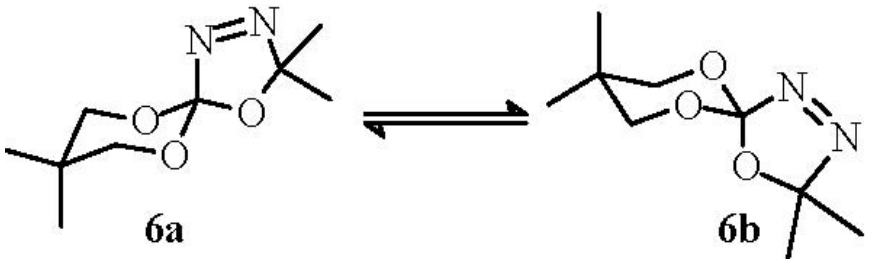


Scheme 2

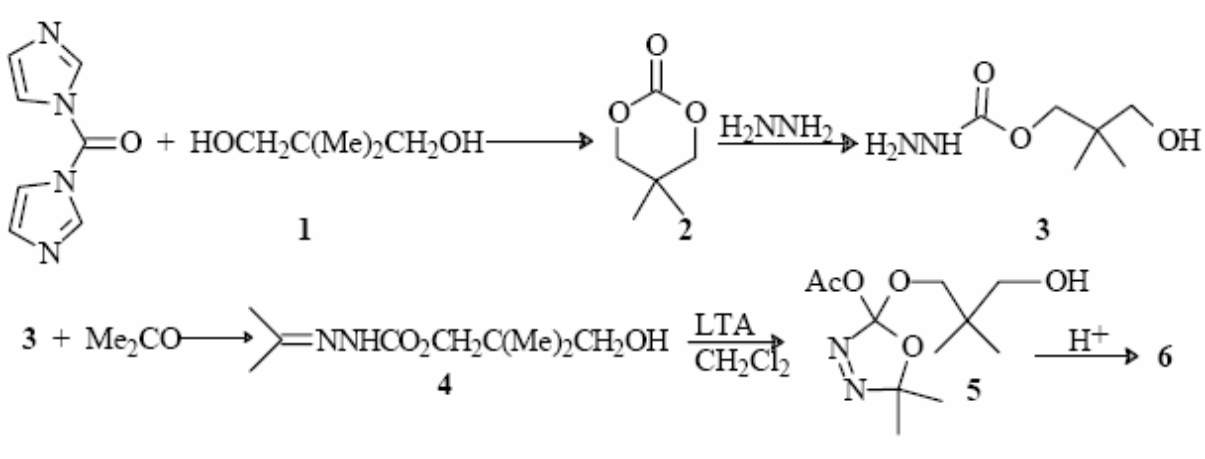


Eqn. 1

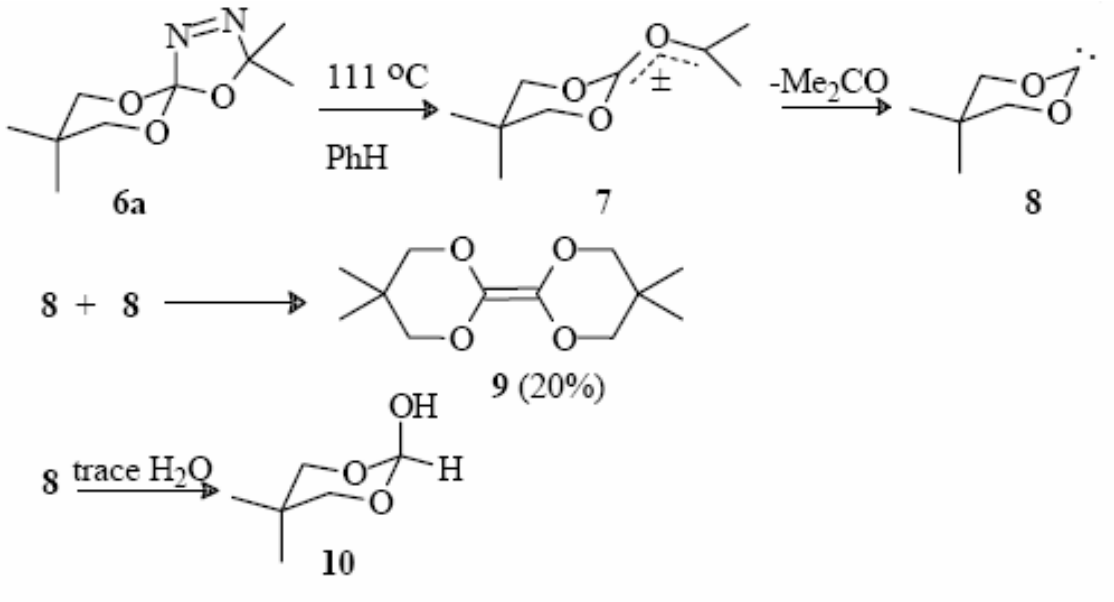
(the aryl group with an electron-withdrawing *p*-substituent(X) adopted the axial position)



Eqn. 2

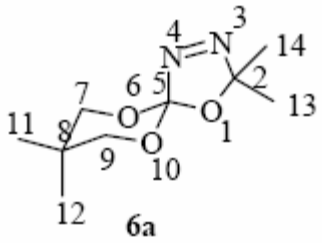


Scheme 3



Scheme 4

Table1. Selected Geometric Features of **6a**



6a

Bond lengths (Å)		Bond Angles (°)	
01-C2	1.435(3)	O1-C2-N3	104.3(2)
C2-N3	1.482(4)	C2-N3-N4	111.3(2)
N3-N4	1.238(3)	N3-N4-C5	109.6(2)
N4-C5	1.499(4)	N4-C5-O1	106.3(2)
C5-O6	1.384(2)	C5-O6-C7	114.5(2)
O6-C7	1.454(3)	O6-C7-C8	110.6(2)
C7-C8	1.517(3)	C7-C8-C9	105.8(2)
C8-C9	1.517(3)	C8-C9-O10	110.6(2)
C9-O10	1.454(3)	C9-O10-C5	114.5(2)
O10-C5	1.384(2)	O10-C5-O6	114.0(2)

Table 2. NMR Spectra of **6**[a,b]

$\delta^{13}C$ (25 MHz, solid state)	$\delta^{13}C$ (50 MHz, $CDCl_3$)	$\delta^{1}H$ (200 MHz, $CDCl_3$)
20.4 (C11 or C12)	21.7 (C11 or C12)	0.98 (s, 3H, 11-CH_3 or 12-CH_3)
22.7 (C12 or C11)	22.5 (C12 or C11)	1.22 (s, 3H, 12-CH_3 or 11-CH_3)
24.7 (C13, C14)	24.5 (C13, C14)	1.52 (s, 6H, 13,14-CH_3)
30.4 (C8)	29.7 (C8)	3.74 (d, ^2J= -11.1 Hz, 2H)
75.1 (C7, C9)	74.9 (C7, C9)	4.25 (d, ^2J= -11.1 Hz, 2H)
121.5 (C2)	119.8 (C2)	
134.3 (C5)	133.5 (C5)	

[a] The structure and the numbering system are shown in Table 1. [b] ^{15}N NMR (50.69 MHz, $CDCl_3$, ref. CH_3NO_2) δ: 70.05, 90.02.

Experimental Section

3-Hydroxy-2,2-dimethylpropoxy)carbonyl hydrazone of acetone (**4**).

Reaction of 1,1′-carbonyldiimidazole (3.51 g, 0.022 mol) with 2,2-dimethyl-1,3-propanediol (1.85 g, 0.021 mol) gave **2**[10] as a crystalline solid, mp 88-93 °C (benzene/petroleum ether). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.11 (s, 6H), 4.06 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.2, 28.5, 77.6, 148.3; MS (EI) *m/z*: 131 (M+H, 15), 86 (11), 71 (38), 56 (100); MS (CI, NH_3) *m/z*: 148 (M+ NH_4, 100).

Hydrazinolysis of **2** (2.86 g, 0.022 mol) in 70 mL of dichloromethane by stirring for 2h with hydrazine hydrate (7.1 mL, 0.15 mol), removal of the water layer, and evaporation of the solvent gave **3** (81 %) as white crystals, mp 68-70 °C; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.86 (s, 6H), 3.25 (s, 2H), 3.91 (s, 2H), 5.66 (s, br, 1H), 6.61 (s, br, 1H); ^{13}C NMR (50 MHz, CDCl3) δ: 21.5, 37.0, 67.9, 70.5, 159.7; MS (CI, NH_3) *m/z*: 180 (M+ NH_4, 48); HRMS *m/z*: calcd for $C_6H_{15}N_2O_2$ 163.1082, found 163.1092.

Reaction of **3** with acetone gave **4** as a viscous liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.87 (s, 6H), 1.83 (s, 3H), 1.99 (s, 3H), 3.28 (s, 2H), 3.98 (s, 2H), 7.96 (s, br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.5, 21.6, 25.3, 36.7, 68.3, 71.0, 152.0; HRMS *m/z*: calcd for $C_9H_{19}N_2O_3$ 203.1395 found 203.1414.

3,4-Diaza-2,2,8,8-tetramethyl-1,6,10-trioxaspiro[4.5]dec-3-ene (**6**).

A solution of acetone (2,2-dimethyl-3-hydroxypropoxy)carbonyl hydrazone (0.808 g, 4.0 mmol) in 5 mL of dichloromethane was dropped during one hour into a stirred, ice-cooled solution of lead tetraacetate (4.43 g, 100 mmol) in dichloromethane (25 mL). After the addition, the ice bath was removed and stirring was continued for two days. The solution was filtered through Celite, washed four times with 5% aqueous $NaHCO_3$ (25 mL), and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was dissolved in CH_2Cl_2 (20 mL) containing trifluoroacetic acid (0.01 mL). After 90 minutes the cyclization reaction, monitored by TLC, was complete. The solution was washed with 5% aqueous NaOH and dried over $MgSO_4$. Evaporation of the solvent left a residue that was chromatographed on silica (Chromatotron, 10% EtOAc in hexanes) to afford **6** as a pale yellow solid in 31% yield; mp 120-121 ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.21 (s, 3H), 1.52 (s, 6H), 3.74 (d, ^2J= -11 Hz, 2H); 4.23 (d, ^2J= -11 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.8, 22.6, 24.6, 29.8, 75.0, 119.8, 133.6; MS (CI, NH_3) *m/z*: (218, M+ NH_4, 17), 193 (34), 148 (100), 131 (66).

Thermolysis of 6.

A solution of **6** (318 mg. 11.6 mmol) in benzene (15 mL) was degassed by means of three freeze/pump/thaw cycles and the tube was sealed. The tube was heated at 110 ºC for 72 h. Cumene (17 μL. 0.12 mmol) was added as internal standard and yields were estimated from the GC trace.

2-Hydroxy-5,5-dimethyl-1,3-dioxane (10).

This compound was isolated by preparative GC in about 21% yield. The column (6′x 4mm i.d.) was packed with 3% OV-17, the eluting gas was helium at 40 mL min^{-1}, and the temperature was programmed from 83 to 255 ºC at 7º min^{-1}. The data that could be gathered came from ^{1}H NMR analysis of a sample slightly contaminated with **9**. ^{1}H NMR (200 MHz, C_6D_6) δ: 1.02 (s, 3H), 1.76 (s, 3H), 3.13 (d, ^2J= -10.6 Hz, 2H), 3.81(d, ^2J= -10.6 Hz, 2H), 5.97 (s, 1H).

Carbene dimer (9).

Isolated by preparative GC (conditions above) in 28% yield; ^{1}H NMR (300 MHz, C_6D_6) δ: 0.67 (s, 12H), 3.43 (s, 8H); ^{13}C NMR (75 MHz, C_6D_6) δ: 21.9, 31.0, 78.4, 136.7; MS (EI) *m/z*: 229 (M+H, 4), 191 (8), 161 (13), 132 (32), 115 (92), 69 (100), 56 (78). MS (HR) *m/z*: calcd for $C_{12}H_{21}O_4$ (M+H): 229.1439, found: 229.1453.

Crystal Structure

A Nicolet P3 diffractometer with MoKα radiation (λ= 0.71069 Å) was used to collect the data at 193K, from an orthorhombic crystal of dimensions 0.15x 0.25x 0.25 mm. The space group was P *cmn* No-62; *a*= 6.288(1), *b*= 9.452(2), and *c*= 17.769(4) Å; V= 1055.7(4) Å^3. The number of reflections collected was 1722 of which 739 were independent. R_{int} was 0.0160 and the final values of R_1, R_2 were 0.0449 and 0.0459. Some additional X-ray data are in the Supporting Information.

Acknowledgements

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Supporting Information

Additional details of the crystal and molecular structures determined by means of single crystal X-ray diffraction.

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