

Unexpected Products via Singlet Oxygen Oxygenation of Functionalized 5,6-Dihydro-1,4-oxathiins

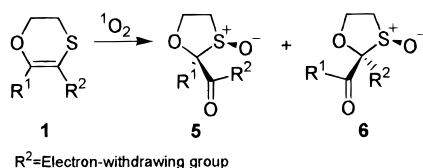
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ABSTRACT



Singlet oxygen oxygenation of 5,6-dihydro-1,4-oxathiins substituted at C-3 with an electron-withdrawing group leads stereoselectively to ketosulfoxides **5** and **6**, instead of the expected dicarbonyl compounds **3**. A mechanism involving an unprecedented intramolecular rearrangement of the corresponding dioxetanes **2** is proposed.

Singlet oxygen shows a diversity of reactions with different substrates and, over the past few decades, has been extensively used to introduce oxygenated functions into many organic molecules, often stereo- and regioselectively.¹ Considerable attention has also been focused on the mechanistic understanding of the interaction of singlet oxygen with organic compounds.¹ Following our interest in the singlet oxygen oxygenation of heterocycles,² we have now turned our attention to 5,6-dihydro-1,4-oxathiins **1**. This heterocyclic system is present in certain biologically active commercial products which are broadly used in agriculture as systemic fungicides,^{3a} and more recently, some derivatives have been found to exhibit antitumor and/or anti-HIV activity.^{3b} The

dye-sensitized photooxygenation of 2,3-diphenyl derivative **1a** at $-78\text{ }^\circ\text{C}$ has been reported.⁴ The reaction leads, via a [2 + 2] cycloaddition of singlet oxygen on the double bond, to a thermally unstable dioxetane intermediate **2a**, which undergoes the usual fragmentation to the dicarbonyl compound **3a** (Scheme 1).⁴

In this letter we report preliminary results on the reaction of singlet oxygen with the variously substituted 1,4-oxathiins **1b–e**.

The photooxygenation reactions of compounds **1b–e**⁵ were carried out in CH_2Cl_2 solutions at $-20\text{ }^\circ\text{C}$ using tetraphenylporphyrin as a sensitizer. Under these conditions, only compound **1e** afforded the corresponding dicarbonyl compound **3e**, whereas oxathiins **1b–d** led to unprecedented oxygenation products **5b** and **6b** (2:1 molar ratio), **5c** and **6c** (1:2 molar ratio), and **5d** and **6d** (3:1 molar ratio) (Scheme 1).⁶

(4) Handley, R. S.; Stern, A. J.; Schaap, A. P. *Tetrahedron Lett.* **1985**, 26, 3183.

(5) Compounds **1b–e** were readily prepared according to a literature procedure by *N*-bromosuccinimide-promoted ring expansion of the corresponding 1,3-oxathiolanes: Caputo, R.; Ferreri, C.; Guaragna, A.; Palumbo, G.; Pedatella, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1971.

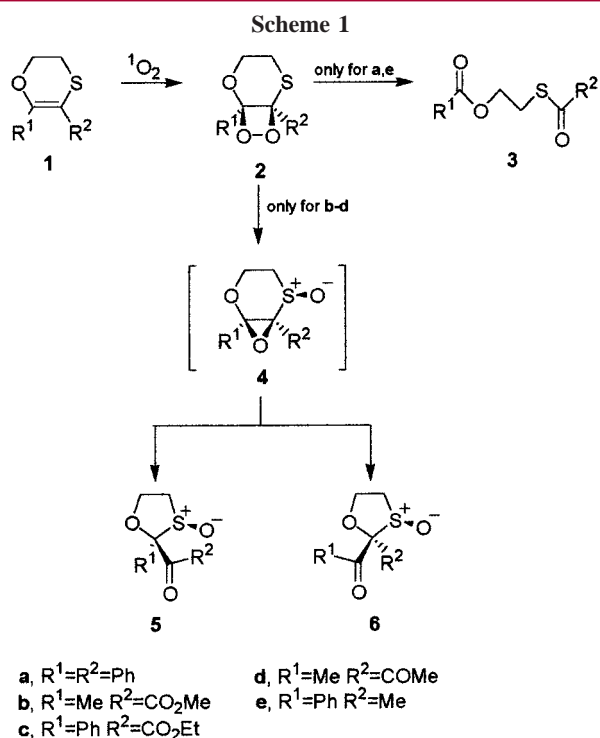
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(1) (a) Foote, C. S.; Clennan, E. L. In *Active Oxygen in Chemistry*; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Chapman & Hall: London, 1995; p 105. (b) *Singlet Oxygen*; Frimer, A. A., Ed.; CRC Press: Florida, 1985. (c) *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: London, 1979.

(2) Scarpati, R.; Iesce, M. R.; Cermola, F.; Guitto, A. *Synlett* **1998**, 17.

(3) (a) Cook, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 994. (b) Borkow, G.; Barnard, J.; Nguyen, T. M.; Belmonte, A.; Wainberg, M. A.; Parniak, M. A. *J. Virol.* **1997**, 71, 3023.



Both structures **5** and **6** were assigned on a spectroscopic basis. In particular, the ¹³C NMR spectra showed C-2 signals (δ 108.7–116.1) in the typical δ region for carbons bearing two heteroatoms and the IR exhibited strong absorption bands between 1055 and 1072 cm^{-1} (S=O stretching). X-ray crystallographic analysis of **5b** (Figure 1) and **6b** as 2,4-

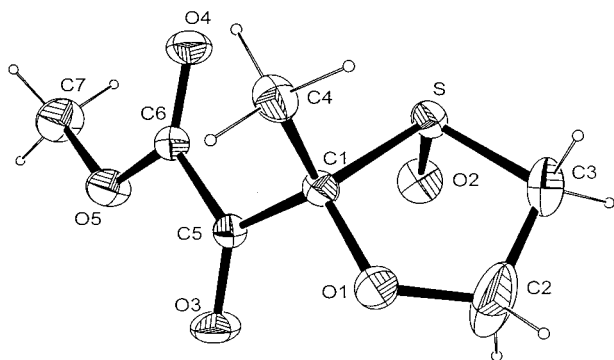


Figure 1. X-ray structure of **5b**.

dinitrophenylhydrazone derivative **7** (Figure 2) confirmed the assigned structures and highlighted the *cis* relationship between sulfoxide oxygen and the newly formed carbonyl function.⁷

All the attempts to detect either the stereoisomers of **5b–d** and **6b–d** or the expected dicarbonyl compounds **3b–d** were unsuccessful. The formation of compounds **5** and **6** cannot be accounted for by ene reaction¹ considering that (i)

oxathiins **1b,d** do not afford any traces of the corresponding ene products despite the presence of allylic hydrogens, and (ii) **1c**, which bears a phenyl group and cannot therefore undergo an ene reaction, leads to the same final product pattern.

The occurrence of singlet oxygenation was verified by carrying out the oxygenation of **1b** under different conditions, i.e., absence of light, exclusion of the sensitizer, addition of a quencher (DABCO; 1,4-diazabicyclo[2.2.2]octane). Evidence of a fairly unstable intermediate, which quickly decomposed to both **5b** and **6b**, was spectroscopically achieved from the oxygenation mixture of **1b** at -70°C in $\text{CDCl}_3/\text{CFCl}_3$.⁸ To this intermediate we tentatively assigned the structure **2b** on the basis of ¹H NMR data and, in particular, by comparing the value of Me singlet (δ 1.76) with those reported for methyl groups at bridgehead in fused dioxetanes.⁹

The different course of the oxygenation reactions of oxathiins **1** probably lies in the nature of the substituent at C-3. Indeed, only **1b–d** bearing electron-withdrawing groups lead to the unusual oxygenation products **5** and **6**.

(6) General Procedure. Each 0.02 M solution of **1b–e** (0.5 mmol) in dry CH_2Cl_2 in the presence of tetraphenylporphyrin (1.8×10^{-3} mmol) was irradiated at -20°C with a halogen lamp (General Electric, 650 W). During irradiation, dry oxygen was bubbled through the solution. When the reactions were complete [90 min (180 min for **1e**), ¹H NMR] and after removal of the solvent, the residues from **1b**, **1c**, and **1e** were chromatographed on silica gel TLC (eluting with ethyl acetate) and gave **5b** (47%) and **6b** (23%), **5c** (15% with a purity of 70%) and **6c** (30%), and **3e** (90%), respectively. All attempts to isolate **5d** and **6d** by TLC failed since they decompose on contact with chromatographic adsorbents; therefore, the yield (85%) refers to the crude oxygenation mixture. Partial chromatographic alteration was also observed for **5b,c** and **6b,c** whose isolated yields were lower than those estimated from ¹H NMR spectra of crude mixtures. **5b**: Mp 126–128 $^\circ\text{C}$ (from CH_2Cl_2 /hexane); IR (CHCl_3) 1737 (s), 1055 (s) cm^{-1} ; ¹H NMR (400 MHz, CDCl_3) δ 1.87 (s, 3H), 2.82 (ddd, $J = 13.3, 11.4, 7.2$ Hz, 1H), 3.21 (m, 1H), 3.93 (s, 3H), 4.55–4.75 (m, 2H); ¹³C NMR (100 MHz, CDCl_3) δ 20.6 (q), 53.0 (t), 53.3 (q), 70.3 (t), 108.7 (s), 160.3 (s), 188.5 (s); MS (EI) m/z 207 (MH^+), 119 ($\text{M}^+ - \text{COCO}_2\text{CH}_3$). **6b**: Oil; IR (CHCl_3) 1742 (s), 1072 (s) cm^{-1} ; ¹H NMR (400 MHz, CDCl_3) δ 2.40 (s, 3H), 3.15–3.35 (m, 2H), 3.82 (s, 3H), 4.69 (m, 1H), 5.00 (m, 1H); ¹³C NMR (100 MHz, CDCl_3) δ 28.7 (q), 53.2 (t), 53.7 (q), 72.0 (t), 110.5 (s), 165.2 (s), 198.7 (s); MS (EI) m/z 207 (MH^+), 163 ($\text{M}^+ - \text{COCH}_3$), 147 ($\text{M}^+ - \text{CO}_2\text{CH}_3$).

(7) Both structures **5b** and **7** were resolved and refined following a common procedure: data were collected on an Enraf-Nonius MACH3 diffractometer using a graphite-monochromated Mo K α radiation, λ (Mo K α) = 0.7093, $T = 293$ K, structures were resolved by direct methods and refined by full-matrix (on F) least-squares cycles. All non-hydrogen atoms were refined anisotropically, whereas the H atoms were included in the last refinement cycles as idealized contributions. The weighting scheme was $w^{-1} = [\sigma^2(F_o) + (0.02 F_o)^2 + q]$ where σ was derived from counting statistics and $q = 1$ for **5b** and $q = 0.2$ for the 2,4-dinitrophenylhydrazone **7**, respectively. In both structures, the asymmetric unit contains two independent molecules. Crystal data for **5b**: $\text{C}_7\text{H}_{10}\text{O}_5\text{S}$, MW = 206.2, monoclinic $P2_1$, $a = 6.794(2)$ Å, $b = 9.948(2)$ Å, $c = 13.386(2)$ Å, $\beta = 91.18(2)^\circ$, $V = 904.5(4)$ Å³, $Z = 4$, $D_{\text{calcd}} = 1.51$ g cm^{-3} , $\mu(\text{Mo K}\alpha) = 3.45$ cm^{-1} , $R(F) = 0.033$ for 2575 observed independent reflections ($\theta_{\text{max}} = 27^\circ$) and 234 parameters. Crystal data for **7**: $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_5\text{S}$, MW = 386.4, triclinic $P-1$, $a = 9.238(2)$ Å, $b = 12.246(2)$ Å, $c = 15.723(2)$ Å, $\alpha = 82.87(1)^\circ$, $\beta = 77.15(2)^\circ$, $\gamma = 72.02(2)^\circ$, $V = 1646.5(6)$ Å³, $Z = 4$, $D_{\text{calcd}} = 1.56$ g cm^{-3} , $\mu(\text{Mo K}\alpha) = 2.50$ cm^{-1} , $R(F) = 0.056$ for 3424 observed independent reflections ($\theta_{\text{max}} = 26.5^\circ$) and 469 parameters.

(8) The oxygenation was carried out as above at -70°C in $\text{CDCl}_3/\text{CFCl}_3$. The ¹H NMR spectrum of a sample, recorded at this temperature before the completion of the reaction, showed the presence of **2b** in addition to **1b**, **5b**, and **6b**: ¹H NMR (400 MHz) δ 1.76 (s, Me), 2.92* (m, CH_2S), 3.96 (s, OMe) and 4.51* (m, CH_2O) [* partially overlapped with the signals of the other products]. It was not possible to obtain a satisfactory ¹³C NMR spectrum, owing to the low concentration of **2b**.

(9) See for example: Burns, P. A.; Foote, C. S. *J. Am. Chem. Soc.* **1974**, *96*, 4339. Adam, W.; Ahrweiler, M.; Sauter, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 80.

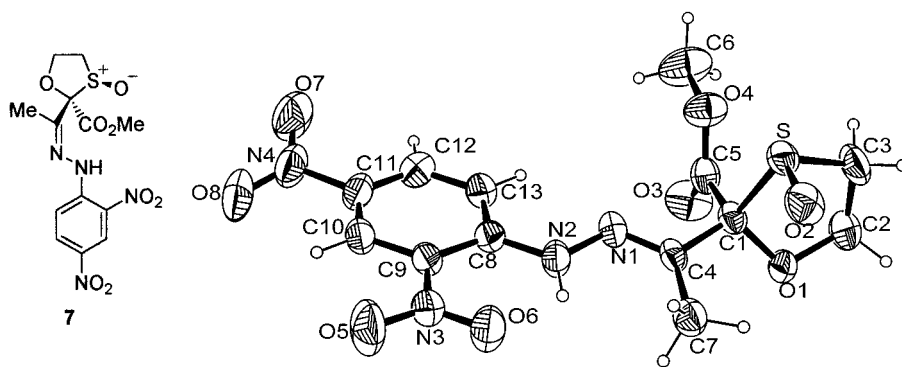


Figure 2. Chemical and X-ray structures of **7** and the 2,4-dinitrophenylhydrazone of **6b**.

In our opinion, the usual O–O and C–C bond cleavage of dioxetanes **2b–d** does not occur in the presence of electron-withdrawing groups, whose nature increases the electron demand by the O–O peroxide bond. This probably enables an intramolecular nucleophilic attack by the neighboring sulfur atom on oxygen¹⁰ and the formation of the sulfoxide epoxides **4b–d**, according to the mechanism proposed by Adam.^{11,12} The rearrangement via either sulfur or oxygen migration may well explain how the final compounds **5b–d** and **6b–d** were obtained.¹³

To the best of our knowledge, sulfoxide epoxides such as **4** have not been previously reported, and attempts to obtain evidence of their formation have been unsuccessful.

(10) An intramolecular nucleophilic attack of nitrogen at O–O bond has recently been observed in the thermal decomposition of the dioxetanes of 2-(*o*-aminophenyl)-4,5-dihydrofurans: Matsumoto, M.; Murakami, H.; Watanabe, N. *Chem. Commun.* **1998**, 2319.

(11) It is reported that intermolecular reactions of dioxetanes with divalent sulfur nucleophiles lead to epoxides: Adam, W.; Heil, M. *J. Am. Chem. Soc.* **1992**, *114*, 5591.

(12) The hypothesis that the oxygen transfer occurs via perepoxides seems unlikely. These ionic intermediates, which have been occasionally evidenced as precursors to dioxetanes and related epoxides,¹ would give oxygen transfer to electrophilic agents as sulfoxides (Schaap, A. P.; Recher, S. G.; Faler, G. R.; Villasenor, S. R. *J. Am. Chem. Soc.* **1983**, *105*, 1691) or sulfenate and sulfinate esters (Clennan, E. L.; Chen, M.-F.; Xu, G. *Tetrahedron Lett.* **1996**, *37*, 2911). The sulfide moiety in 1,4-oxathiane ring is a nucleophilic site and it is expected to undergo electrophilic oxidation.^{3a}

(13) Rearrangements of labile epoxides to carbonyl compounds are well documented. See for examples: (a) Adam, W.; Hadjijarapoglou, L.; Wang, X. *Tetrahedron Lett.* **1991**, *32*, 1295. (b) Baylon, C.; Hanna, I. *Tetrahedron Lett.* **1995**, *36*, 6475. (c) Katritzky, A. R.; Xie, L.; Serdyuk, L. *J. Org. Chem.* **1996**, *61*, 7564.

Further mechanistic investigations on this novel and highly stereoselective intramolecular rearrangement of dioxetanes **2** are currently in progress.

It is noteworthy that oxathiin **1b** is closely related to biologically active products³ and these preliminary observations provide useful information when investigating the photolytic fate of these molecules in the environment.¹⁴

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Supporting Information Available: Spectral data for compounds **5c**, **6c**, and **3e** and for the mixture of **5d** and **6d**, and experimental procedure for hydrazone **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) The degradative action of combined light, oxygen, and sensitizer on pesticides (Tsao, R.; Eto, M. In *Aquatic and Surface Photochemistry*; Helz, G. R., Zepp, R. G., Crosby, D. G., Eds.; Lewis: London; 1994; p 163) and drugs (*Drugs: Photochemistry and Photostability*; Albini, A., Fasani, E., Eds.; The Royal Society of Chemistry: Cambridge, UK; 1998) is well-known.