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

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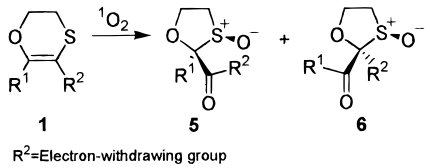
ABSTRACT



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 °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 °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]

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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.

(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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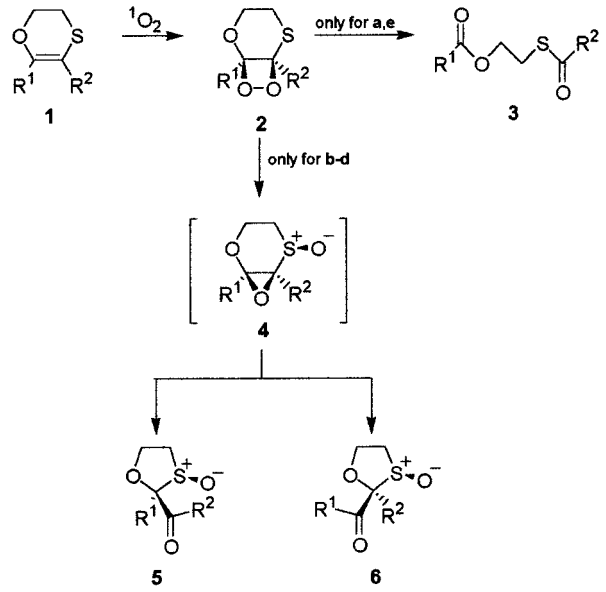
Scheme 1



Both structures **5** and **6** were assigned on a spectroscopic basis. In particular, the ^{13}C 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-

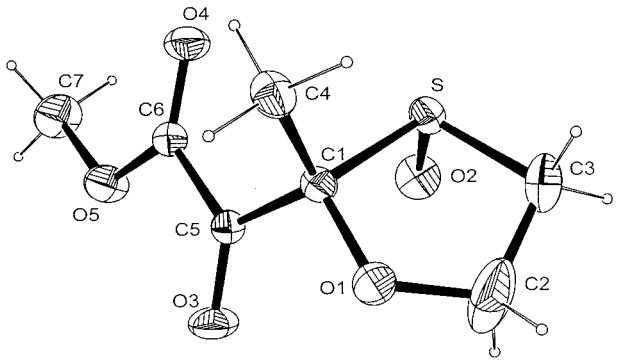


Figure 1. X-ray structure of **5b**.

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 reaction[1] 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 $CDCl_3$/$CFCl_3$.[8] To this intermediate we tentatively assigned the structure **2b** on the basis of ^{1}H 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**), ^{1}H 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 ^{1}H NMR spectra of crude mixtures. **5b**: Mp 126−128 °C (from CH_2Cl_2/hexane); IR ($CHCl_3$) 1737 (s), 1055 (s) cm^{-1}; ^{1}H 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); ^{13}C 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 ($M^+ - COCO_2CH_3$). **6b**: Oil; IR ($CHCl_3$) 1742 (s), 1072 (s) cm^{-1}; ^{1}H 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); ^{13}C 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 ($M^+ - COCH_3$), 147 ($M^+ - CO_2CH_3$).

(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 Kα radiation, λ (Mo Kα) = 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**: $C_7H_{10}O_5S$, MW = 206.2, monoclinic $P2_1$, a = 6.794(2) Å, b = 9.948(2) Å, c = 13.386(2) Å, β = 91.18(2)°, V = 904.5(4) Å^3, Z = 4, D_{calcd} = 1.51 g cm^{-3}, μ(Mo Kα) = 3.45 cm^{-1}, $R(F)$ = 0.033 for 2575 observed independent reflections (θ_{max} = 27°) and 234 parameters. Crystal data for **7**: $C_{13}H_{14}N_4O_8S$, MW = 386.4, triclinic P_{-1}, a = 9.238(2) Å, b = 12.246(2) Å, c = 15.723(2) Å, α = 82.87(1)°, β = 77.15(2)°, γ = 72.02(2)°, V = 1646.5(6) Å^3, Z = 4, D_{calcd} = 1.56 g cm^{-3}, μ(Mo Kα) = 2.50 cm^{-1}, $R(F)$ = 0.056 for 3424 observed independent reflections (θ_{max} = 26.5°) and 469 parameters.

(8) The oxygenation was carried out as above at −70 °C in $CDCl_3$/$CFCl_3$. The ^{1}H 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**: ^{1}H 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 ^{13}C 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.

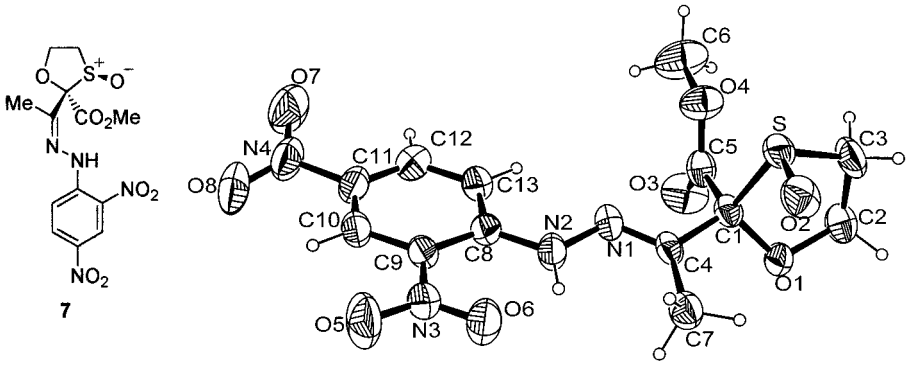


Figure 2. Chemical and X-ray structures of **7** and the 2,4-dinitrophenylhydrazone of **6b**.

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 oxygen[10] 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.

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 products[3] 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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(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.; Hadjiarapoglou, 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.

(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.