

Photooxidation of Methylthiopyrans into Thiopyran Carboxaldehydes in Carbon Tetrachloride

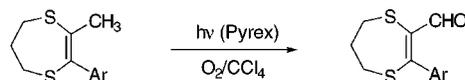
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ABSTRACT

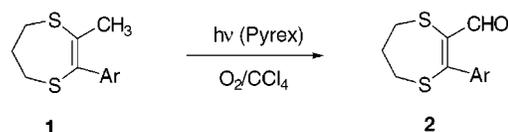


Methylthiopyrans are converted into the corresponding carboxaldehydes via a simple and efficient oxidation by oxygen in carbon tetrachloride. The reaction is not a radical chain process. The proposed mechanism involves photoinduced electron transfer from the starting thiopyran to solvent (CCl_4) followed by a series of events depicted in Scheme 1. The critical feature of the mechanism is that formation of superoxide ($\text{O}_2^{\cdot-}$) is avoided, preventing direct oxidation of sulfur atoms.

Benzylic photooxidations in the presence of electron-transfer (ET) sensitizers often provide a useful alternative to catalytic oxidation of methyl-substituted aromatics into aldehydes.¹ Potentially, the advantage of such photo ET-based reactions over catalytic processes should be obvious for organosulfur substrates that are capable of poisoning the catalyst. Most commonly, however, photooxidation of sulfides and other S^{II} organic species with oxygen is directed at the sulfur atom, leading to higher oxidation states of sulfur and/or C–S bond cleavage.² Although generation of cation-radicals derived from an organosulfur compound is usually a simple and efficient process, the limited choice of end results diminishes the synthetic appeal of such reactions. Recently, we have been focusing our research efforts on the development of synthetically useful methods in which the generated sulfur-centered cation-radical is facilitating chemical changes in the molecule, besides S oxidation or C–S bond cleavage. Previously, we reported a photo-ET-induced C–C bond

cleavage in hydroxyalkyl dithianes and its relevance to the development of photoremovable protecting groups for carbonyls.³ We now report our findings on photo-ET-induced oxidation of the methyl group in substituted thiopyrans into a carbonyl, which is a rare example of a sulfide moiety surviving a photooxidation in the presence of molecular oxygen.

We have found that irradiation (Pyrex filter) of 2-methyl-3-phenyl-5,6-dihydro-1,4-dithiopyran (**1a**) in CCl_4 in the presence of oxygen furnished aldehyde **2a** as the major product.⁴ Under nitrogen atmosphere no reaction occurred.



Ar = (a) C_6H_5 ; (b) $p\text{-C}_6\text{H}_4\text{-Me}$; (c) $p\text{-C}_6\text{H}_4\text{-OMe}$; (d) $p\text{-C}_6\text{H}_4\text{-F}$;
(e) $\alpha\text{-naphthyl}$; (f) $p\text{-C}_6\text{H}_4\text{-COOMe}$; (g) $p\text{-C}_6\text{H}_4\text{-CN}$

We then synthesized a series of 3-aryl-substituted 2-methyl-1,4-dithiopyrans **1** and studied their photooxidation into

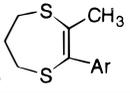
(3) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924–9931.

(4) All photooxidations were carried out with a medium-pressure Hg UV source in Pyrex tubes with bubbling oxygen. A 10 mM amount of **1a–g** in carbon tetrachloride was used, and irradiations were carried out until complete conversion of the starting material was achieved.

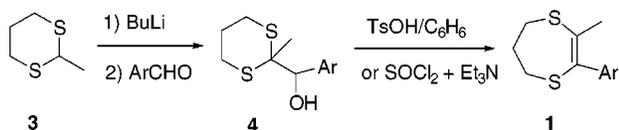
(1) Julliard, M.; Galadi, A.; Chanon, M. *J. Photochem. Photobiol., A: Chem.* **1990**, *54*, 79–90 and references therein. (b) Santamaria, J.; Iroundi, R. *Tetrahedron Lett.* **1991**, *32*, 4291–4.

(2) Most notably, such ET-initiated cleavages are used for photochemical deprotection of dithioacetals: (a) Schmittel, M.; Levis, M. *Synlett* **1996**, 315–316. (b) Tanemura, K.; Dohya, H.; Imamura, M.; Suzuki, T.; Horaguchi, T. *Chem. Lett.* **1994**, 965–8. (c) Kamata, M.; Murakami, Y.; Tamagawa, Y.; Kato, M.; Hasegawa, E. *Tetrahedron* **1994**, *50*, 12821–8. (d) Epling, G. A.; Wang, Q. *Tetrahedron Lett* **1992**, *33*, 5909–12. (e) Epling, G. A.; Wang, Q. *Synlett* **1992**, 335–6.

Table 1

Entry	1 (Ar), 	Irrad time	Product	Yield, %
1	1a (C ₆ H ₅ -)	1 hr	2a	45
2	1b (p-CH ₃ C ₆ H ₄ -)	1 hr	2b	46
3	1c (p-CH ₃ OC ₆ H ₄ -)	1 hr	2c	72
4	1d (p-FC ₆ H ₄ -)	3 hr	2d	45
5	1e (α-naphthyl-)	12 hr	2e	36
6	1f (p-CH ₃ O ₂ CC ₆ H ₄ -)	12 hr	2f	< 5
7	1g (p-NCC ₆ H ₄ -)	12 hr	2g	< 5

carboxaldehydes **2** in carbon tetrachloride. As is evident from Table 1, most of the substrates we studied gave the corresponding aldehydes. Although the isolated yields of the aldehydes were moderate, the experimental simplicity and the mere fact that after irradiation the CCl₄ solution contains >90% (by NMR) of the product greatly enhances the preparative value of the method. Dithiepins **1** are easily available from 2-methyl-1,3-dithiane **3** via the Corey–Seebach dithiane–carbonyl adducts **4**⁵ with subsequent dehydration accompanied by ring expansion.



Mechanistically significant results were obtained with *p*-methoxycarbonyl (**1f**) and *p*-cyano (**1g**) species. These dithiepins carrying an electron-withdrawing substituent were virtually unreactive.

To rule out any radical *chain* process we ran a cross-experiment by irradiating a mixture of approximately 30% of (reactive) compound **1a** and 70% of (unreactive) cyano-substituted **1g**. The production of **2a** had slowed, and no **2g** was observed. If anything, abstraction of a hydrogen atom from the methyl group in **1g** is expected to be faster than it is in the unsubstituted **1a**. However, we did not detect any **2g** in the reaction mixture.

Finally, a thermal reaction of **1a–g** in the presence of radical initiators (AIBN or dibenzoyl peroxide) did not produce any amount of **2**.

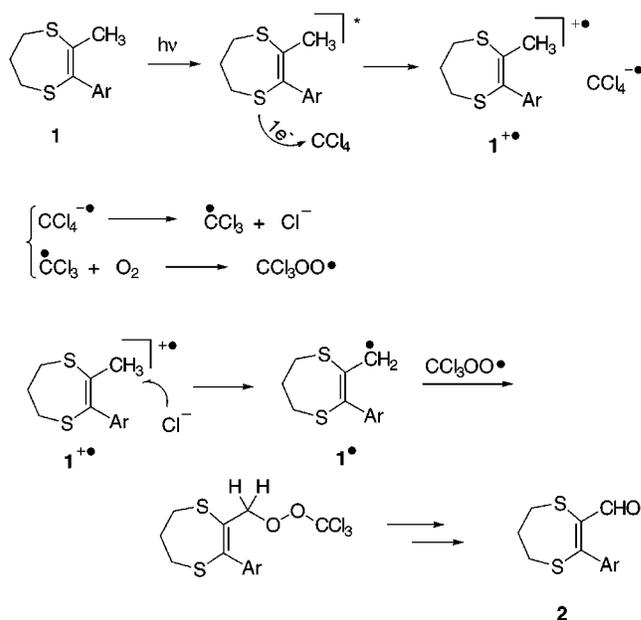
We also ran the oxidative photolysis in the presence of methylene blue and detected no aldehyde formation. This ruled out the involvement of singlet oxygen in the photo-oxidation.

(5) For a review, see: Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357–402.

Our fluorescence quenching experiments show that CCl₄ does quench the fluorescence of compounds **1** in degassed acetonitrile solutions.

Although the precise mechanism of this reaction is still under investigation, our experimental observations led us to the following mechanistic rationale (see Scheme 1). Carbon

Scheme 1



tetrachloride does not absorb light above the Pyrex filter cutoff, and therefore, it is the substrate **1** that is the primary light absorbing species, with the λ_{max} ranging from 305 to 350 nm. After the initial excitation, single electron transfer occurs from the excited methylthiopyran moiety to a molecule of solvent producing a cation-radical/anion-radical pair, {**1**^{•+}/CCl₄^{•-}}. It is well established that CCl₄^{•-} is unstable and falls apart into chloride anion and trichloromethyl radical,⁶ which is then intercepted by O₂. In a detailed kinetic study, Alfassi and Mosseri⁷ had demonstrated that in carbon tetrachloride CCl₃[•] reacts with molecular oxygen with $k_2 \approx 1.12 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. The rate is not diffusion controlled, but a relatively high estimated oxygen concentration (approximately 12 mM in CCl₄ with partial oxygen pressure 1 atm⁸) makes this pathway quite plausible in our case. **1**^{•+} is then deprotonated by Cl⁻, and **1**[•] radical recombines with CCl₃O₂[•], undergoes O–O bond cleavage, and produces the final aldehyde **2**. Judging by the experimental and theoretical data accumulated in the literature, cation-radicals (e.g., of toluenes or methyl-substituted naphthalenes) are generally found to be superacids. For example, Arnold reported the pK_a of the

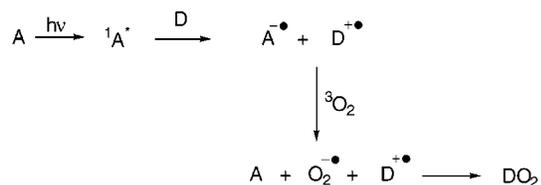
(6) Chateaufneuf, J.; Luszyk, J.; Ingold, K. U. *J. Org. Chem.* **1990**, *55*, 1061–1065 and references therein.

(7) Alfassi, Z. B.; Mosseri S. *J. Phys. Chem.* **1984**, *88*, 3296–3300.

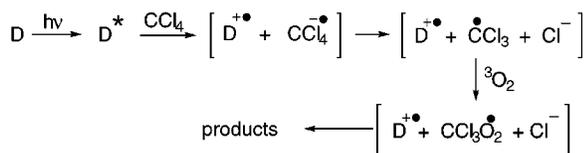
(8) Battino, R. *Solubility Data Series: Vol. 7, Oxygen and Ozone*; Pergamon: Oxford, England, 1981.

toluene cation-radical in acetonitrile to be -12 .⁹ This would argue that chloride anion is an adequate base for deprotonating $1^{+\bullet}$. We cannot entirely rule out a mechanism in which 1^\bullet radical reacts with O_2 , as long as the resulting hydroperoxide radical is not involved in chain propagation (as a possibility, it can be “capped” by CCl_3^\bullet radical). To reiterate, our cross-irradiation experiment with **1a** and **1g** seems to have ruled out radical hydrogen abstraction from the methyl group in the starting dithiepin.

In contrast to the data reported in the literature on ET-sensitized oxidations of methyl-substituted aromatic compounds into corresponding aldehydes,¹ our attempt to convert **1a** into **2a** upon ET-sensitization with 1,4-dicyanonaphthalene (DCN) in acetonitrile with bubbling oxygen failed. Although **1a** was slowly consumed, no trace of aldehyde **2a** was detected in the reaction mixture by NMR or GC-MS analysis. Failure of DCN-sensitized oxidation to produce the aldehyde in the dithiepin case can be explained in terms of Foote’s classic scheme for photosensitized oxygenation of sulfides via a *non-singlet-oxygen* mechanism:¹⁰

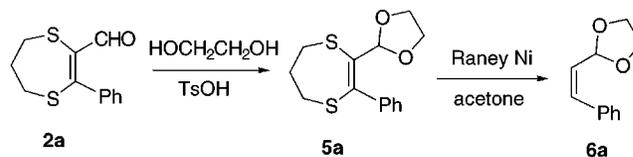


A critical feature of this mechanistic scheme is that the initially formed anion-radical of the ET-sensitizer immediately reduces triplet oxygen into superoxide. The reactions where $D^{+\bullet}$ is an organosulfur cation radical then always result in $O_2^{\bullet-}$ nucleophilic attack at sulfur, leading to S-oxidation. On the contrary, our scheme utilizes an excited donor and a unique acceptor, which falls apart before it has a chance to reduce O_2 :



As a result, at no time does the reaction mixture contain an oxygen nucleophile capable of attacking the S-atom in $D^{+\bullet}$ directly. In our view, $CCl_3O_2^\bullet$ is too electrophilic to react with the cation-radical.

In addition to an easy synthetic approach to thioheterocyclic carboxaldehydes, one of the possible synthetic applications of this reaction could be simple and efficient synthesis of cis α,β -unsaturated aldehydes, which we illustrate here using **2a** as a starting material.¹¹



In conclusion, we have uncovered a novel photooxidation of methylthiepins into carboxaldehydes that features an extremely simple experimental procedure. The unique aspect of the mechanism is that after the initial electron transfer there is no species of appreciable reducing potential present in the reaction mixture. The partition between $CCl_4^{\bullet-}$ reducing molecular oxygen or decomposing into trichloromethyl radical and chloride anion favors the latter, thus preventing superoxide formation, which in turn precludes the undesirable S-directed oxidation.

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Supporting Information Available: 1H and ^{13}C NMR spectra for compounds **1a–g**, **2a–e**, and **4a–g** and mass spectra for compounds **2a–e**. This material is available free of charge via the Internet at <http://pubs.acs.org>

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