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Application of Thiol–Olefin Co-oxygenation Methodology to a New Synthesis of the 1,2,4-Trioxane Pharmacophore

Paul M. O'Neill,*,† Amira Mukhtar,† Stephen A. Ward,‡ Jamie F. Bickley,† Jill Davies,‡ Mario D. Bachi,§ and Paul A. Stocks†

Department of Chemistry, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK, and Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

p.m.oneill01@liv.ac.uk

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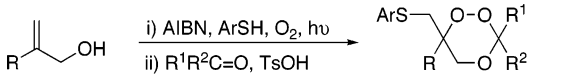
ABSTRACT

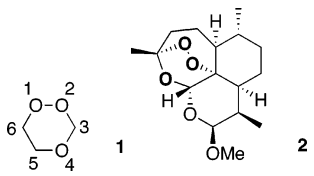


3a, R = Ph
3b, R = Me

4a-j, Ar=Ph, *p*-Cl-Ph

Thiol–olefin co-oxygenation (TOCO) of substituted allylic alcohols generates α-hydroxyperoxides that can be condensed in situ with various ketones to afford a series of functionalized 1,2,4-trioxanes in good yields. Manipulation of the phenylsulfenyl group in 4a allows for convenient modification to the spiro-trioxane substituents, and we describe, for the first time, the preparation of a new class of antimalarial prodrug.

The 1,2,4-trioxane pharmcophore **1** (Figure 1) is an important functional group in medicinal chemistry. It is found in the artemisinin class of antimalarials such as artemether **2** and artesunate, in which its reaction with heme (or free Fe(II)) generates cytotoxic radicals that cause parasite death.[1] More recently, artemisinin-derived 1,2,4-trioxane monomers and dimers have been shown to be potent inhibitors of cancer cell proliferation.[2] A disadvantage with the semisynthetic compounds described is that their production requires artemisinin as starting material. Artemisinin is extracted from the plant *Artemisia annua* in low yield, a fact that necessitates significant crop production. Therefore, there is much need for the development of new and improved approaches to the 1,2,4-trioxane functionality. Current literature methods for the synthesis of the 1,2,4-trioxane unit include the reaction of dioxetanes with carbonyls in the presence of Lewis acids,[3] acid-catalyzed cyclization of hydroxyperoxyacetals[4] with olefins and reactions of α-peroxy aldehydes with carbonyl



1 **2**

Figure 1. Numbering system of the basic 1,2,4-trioxane ring system **1** and the antimalarial 1,2,4-trioxane artemether **2**.

† University of Liverpool.
‡ Liverpool School of Tropical Medicine.
§ The Weizmann Institute of Science.

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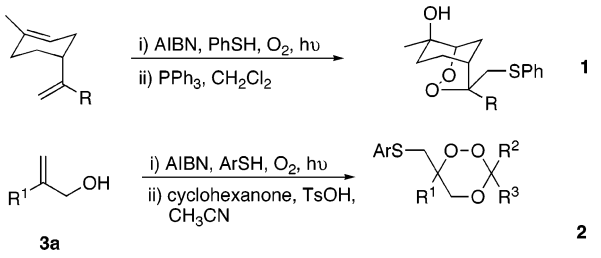
compounds.[5] All these routes provide the trioxane in moderate to low overall yields.

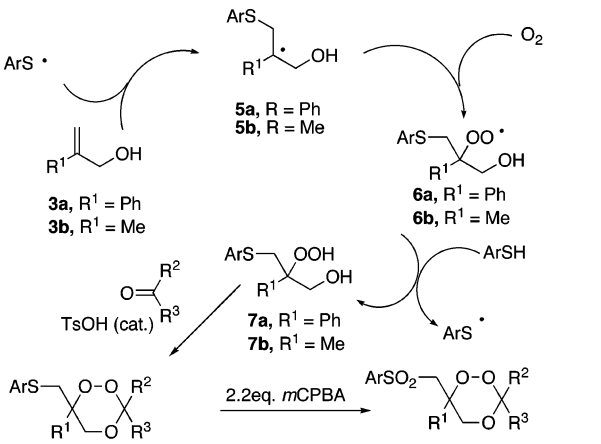
During the course of our recent work on the synthesis of new antimalarial endoperoxides, we utilized a thiol−olefin co-oxygenation (TOCO) reaction to generate bicyclic peroxides structurally related to yingzhaosu A (Scheme 1, reaction 1).[6] In this letter we describe how, by replacement of a terpene with an allylic alcohol, this methodology can be extended to a new synthesis of functionalized spiro 1,2,4-trioxanes by a simple one-pot procedure (Scheme 1, reaction 2).

Scheme 1. 2,3-Dioxabicyclo[3.3.1] Nonane and 1,2,4-Trioxane Synthesis by Thiol−Olefin Co-oxygenation (TOCO)



Scheme 2 illustrates the mechanism for the TOCO/condensation reaction. Phenylthiyl radical, generated from thiophenol through initiation with AIBN/*hυ*, attacks the double bond of the allyl alcohol **3a** in a Markovnikov fashion to generate a tertiary carbon radical **5a**. This radical traps oxygen to form a peroxy radical **6a**. Radical hydrogen abstraction from thiophenol produces the α-hydroxyperoxide **7a** and regenerates phenylthiyl radical to propagate the reaction. The α-hydroxyperoxide was subsequently shown to undergo smooth condensation with cyclohexanone in the presence of a catalytic amount of tosic acid to generate the 1,2,4-trioxane **4a**.[7] Figure 2 depicts X-ray crystal structures for the trioxane **4d** and the sulfone generated from **4f**.

Scheme 2. Mechanism of the TOCO Reaction and Synthesis of Spiro-trioxanes



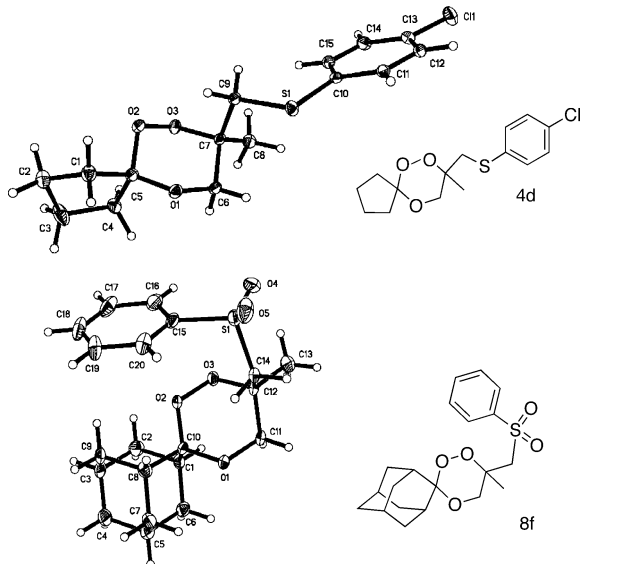


Figure 2. X-ray structures of sulfide trioxane **4d** and sulfone trioxane **8f**.

Application of the method described in Scheme 2 to various combinations of ketones and allylic alcohols afforded the series of spiro-trioxanes shown in Table 1. Considering the complex sequence of events that must occur to obtain the α-hydroxyperoxide intermediate and subsequent carbonyl

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(6) (a) Bachi, M. D.; Korshin, E. E. *Synlett* **1998**, 122 (b) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449. (c) For an earlier example of the TOCO reaction, see: Beckwith, A. L. J.; Wagner, R. D. *J. Org. Chem.* **1981**, 46, 3638.

(7) **Synthesis of 8-(4-Chloro-phenylsulfenylmethyl)-8-methyl-6,7,10-trioxa-spiro[4.5]decane (4d)**. A two-necked, 250 mL, round-bottomed flask was charged with a solution of 2-methyl-2-propen-1-ol (200 mg, 0.23 mL, 2.77 mmol) and AIBN (31 mg, 1.89 mmol) in acetonitrile (46 mL). The reaction vessel was flushed with oxygen for several minutes at 0 °C then stoppered and kept under a positive pressure of pure oxygen. The reaction mixture was vigorously stirred and UV irradiated (at 0 °C) using an externally mounted 100W BLAK-RAY UV lamp at a distance of 5−7 cm, with simultaneous addition of 4-chlorothiophenol (500 mg, 3.46 mol, 1.25 equiv) in acetonitrile (13 mL) over a period of 30 min. After completion of the addition, the reaction was left to continue stirring at 0 °C for 4−6 h or until consumption of starting materials (monitored by TLC). The reaction vessel was then cooled to −10 °C and flushed with nitrogen, and a solution of cyclopentanone (780 mg, 0.82 mL, 6.94 mmol) in dichloromethane (13 mL) was added, followed by catalytic amounts (ca. 15 mg) of tosic acid. The mixture was left stirring at −10 °C, and allowed to warm slowly to room-temperature overnight. Removal of the solvent in vacuo and purification by column chromatography yielded the endoperoxide (**4d**) as a white solid (391 mg, 46%). Full spectroscopic and compound characterization is contained in the Supporting Information. **Caution:** Since vapors of organic solvents may form explosive mixtures with oxygen in closed systems, all such reactions should be conducted behind safety shields. For safety precautions in working with peroxides, see reference 6b.

Table 1. Trioxanes Synthesized via Intermolecular Trapping of the Hydroxyperoxide Products **7a** and **7b** of the TOCO Reaction with Cyclic Ketones

allylic alcohol	ketone	trioxane	yield %
3a	cyclohexanone	**4a**: R^1 = Ph; R^2 and R^3 = $(CH_2)_5$; Ar = Ph	68
3a	cyclopentanone	**4b**: R^1 = Ph; R^2 and R^3 = $(CH_2)_4$; Ar = Ph	54
3b	cyclohexanone	**4c**: R^1 = Me; R^2 and R^3 = $(CH_2)_5$; Ar = Ph	53
3b	cyclopentanone	**4d**: R^1 = Me; R^2 and R^3 = $(CH_2)_4$; Ar = *p*-Cl−Ph	46
3b	cyclobutanone	**4e**: R^1 = Me; R^2 and R^3 = $(CH_2)_3$; Ar = Ph	61
3b	adamantanone	**4f**: R^1 = Me; R^2CR^3 = adamantylidene; Ar = Ph	42
3b	4-*t*-Bu-cyclohexanone	**4g**: R^1 = Me; R^2CR^3 = 4-*t*-Bu-cyclohexylidene; Ar=*p*-Cl−Ph	80
3b	1,4-cyclohexadione	**4h**: R^1 = Me; R^2CR^3 = 4-oxocyclohexylidene; Ar= Ph	25
3b	cyclohexanone	**4i**: R^1 = Me; R^2 and R^3 = $(CH_2)_5$; Ar = *p*-Cl−Ph	55
3b	cyclododecanone	**4j**: R^1 = Me; R^2 and R^3 = $(CH_2)_{11}$; Ar = *p*-Cl−Ph	66

condensation, the overall sequence proceeds in good yield. Byproducts generated from oxidation of thiophenol are observed in very low yields.

Sulfide trioxanes (**4e**, **4f**, and **4j**) and the sulfones (**8d** and **8f**) were tested for antiparasitic activity versus chloroquine-resistant *Plasmodium falciparum* (Table 2). All of the

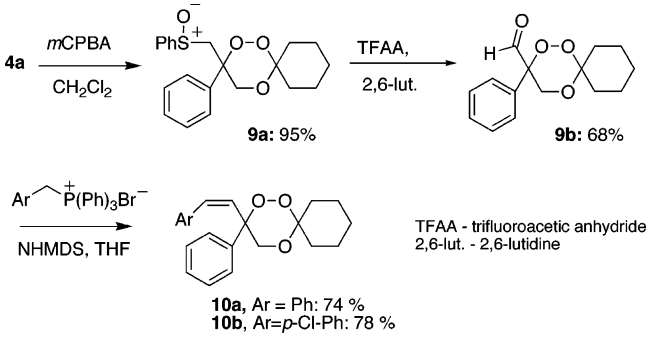
Table 2. In Vitro Antimalarial Activity of Spiro-trioxanes versus K1 *Plasmodium falciparum*[a]

trioxane	IC_{50} (nM) ± mean
4e	314 ± 68
4f	285 ± 54
4j	135 ± 53
8d	90 ± 33
8f	329 ± 42
artemether	4 ± 15
artemisinin	12 ± 20
chloroquine	210 ± 55

[a] **8d** and **8f** are the sulfones derived from **4d** and **4f** (see Table 1), respectively. Compounds were evaluated using the methods described in ref 1b.

analogues display moderate antimalarial activity, with the exception of trioxane **8d**, which exhibits good activity (90 nM). This compound is currently being examined for its in vivo antimalarial activity versus *Plasmodium berghei*.

Scheme 3. Synthesis of Chalcone Prodrugs **8a** and **8b**

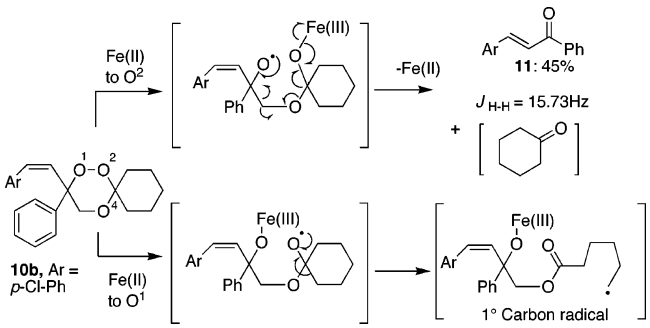


In addition to providing facile access to the trioxane pharmacophore, the TOCO/carbonyl condensation protocol generates a methylthiophenyl group in the resulting trioxane. This functionality has proven to be useful for further manipulation of the structure to generate chemically diverse groups. Scheme 3 illustrates the synthesis of a formyl-substituted trioxane (**9b**) via thiol oxidation using stoichiometric *m*CPBA followed by exposure of the sulfoxide **9a** to Pummerer conditions.[8] The resultant carbonyl group in **9b** readily undergoes numerous condensation and nucleophilic substitution reactions, imparting a high degree of structural flexibility to a pharmacophore that is of great interest in current medicinal chemistry.

For example, Wittig reactions on **9b** provide vinyl-substituted trioxane analogues **10a** and **10b** in excellent yields (Scheme 3).

These analogues are of interest since they have been shown to liberate chalcones in biomimetic Fe(II) degradation reactions (Scheme 4). Chalcones have recently attracted a

Scheme 4. Fe(II)-Mediated Trioxane Degradation



great deal of interest as antimalarial parasite cysteine protease inhibitors. Several chalcone derivatives, including licochalcone A and synthetic analogues, have been shown to possess

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good activity both in vitro and in vivo.[9,10] Despite the promising antimalarial activities of chalcone derivatives, a potential concern with this class of drug is that they might be expected to react with host proteins, thereby causing toxicity. In line with this, researchers have shown that in vitro, licochalcone A readily reacts with sulfur-based biological nucleophiles.[11] Therefore, a masked prodrug-based approach to delivering the chalcone selectively to the parasite would be desirable. Using $FeCl_2 \cdot 4H_2O$ as a mimic of heme iron(II), we carried out ferrous-mediated degradation of trioxane **10b** and obtained as a major product the chalcone, **11**. Scheme 4 outlines two pathways of ferrous-mediated degradation of **10b**. Association of oxygen 2, top half of Scheme 4, with Fe(II) generates an oxyl radical that can fragment to generate the observed chalcone in a yield of 45%. During the iron degradation process, it was noted that isomerization of the double bond occurs to provide the thermodynamically more stable trans isomer ($J_{H-H} = 15.8$ Hz for a trans-substituted chalcone versus $J_{H-H} = 11.9$ Hz for a cis-substituted chalcone).

Double-bond isomerization has also been noted by Meunier and co-workers in their biomimetic degradation studies on the cis-configured endoperoxide antimalarial artflene.[12]

An alternative pathway to a primary carbon-centered radical is also possible from **10b** via association of the endoperoxide oxygen 1 with Fe(II) followed by ester bond formation and C−C cleavage, and we are currently using spin trapping techniques to trap these postulated radical intermediates.[13]

The results of our preliminary biomimetic ferrous-mediated decomposition reactions are significant, since in theory, similar ferrous-mediated chalcone release within the iron-rich parasite food vacuole should be accompanied by concomitant cytotoxic radical generation. Thus, these endoperoxide systems may have the capacity to hit the malaria parasite through two distinctive mechanisms, namely, free-radical-mediated damage and cysteine protease inhibition.[14] The application of these new "trioxane" systems as endoperoxide cysteine protease inhibitor (ECPI) prodrugs will be the focus of future work in this area.

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Note Added after ASAP Posting. The footnote of Table 2 was unclear and compound numbering in the paragraph below Table 2 was incorrect in the version posted ASAP July 28, 2004; the corrected version was posted ASAP August 4, 2004.

Supporting Information Available: Experimental details and characterization data, including ^1H and ^{13}C NMR and MS data and combustion analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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