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Photooxygenation of 3-aryl-2-cyclohexenols: synthesis of a new series of antimalarial 1,2,4-trioxanes☆

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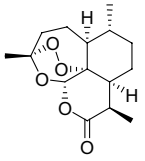
Abstract—Using easily accessible 3-aryl-2-cyclohexenols, a photooxygenation route for the preparation of bicyclic 1,2,4-trioxanes is reported. Several of these trioxanes have shown significant antimalarial activity against multidrug resistant *Plasmodium yoelii* in mice by the oral route.

Artemisinin **1**, since its isolation and characterization in the early 1970s from *Artemisia annua*, has been a subject of much investigation, not only due to its unique structure but also because of its potent antimalarial activity.[1] With the establishment of 1,2,4-trioxane as the antimalarial pharmacophore of artemisinin, various successful attempts have been made to prepare derivatives[1] as well as simple 1,2,4-trioxanes with varying orders of antimalarial activity.[2,3]



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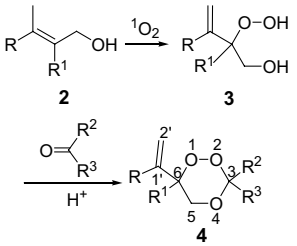
As a part of our endeavour to develop structurally simple synthetic substitutes of artemisinin, we earlier developed a new, convenient and high yielding method for the preparation of 1,2,4-trioxanes.[2h] Preparation of β-hydroxyhydroperoxides by photooxygenation of allylic alcohols and the acid-catalyzed condensation of the hydroperoxides with aldehydes or ketones are the key steps of this method (Scheme 1). Several monocyclic 1,2,4-trioxanes prepared using this procedure have shown promising antimalarial activity in vitro and in vivo.[4]

Using easily accessible 3-aryl-2-cyclohexenols we have explored the scope of this photooxygenation route for the preparation of bicyclic 1,2,4-trioxanes and report herein the synthesis of a new series of 1,2,4-trioxanes some of which show significant antimalarial activity against multidrug resistant *Plasmodium yoelii* in mice by the oral route. There are only a few reports on photooxygenation of allylic cyclohexenols,[5] and the hydroperoxides were isolated only in one study.[5c] This is the first report on the synthesis of trioxanes using β-hydroxyhydroperoxides derived from photooxygenation of cyclohexenols.

3-Aryl-2-cyclohexenones **5a**–**c**, prepared by a literature procedure,[6] were reduced with $NaBH_4$ in MeOH or



Scheme 1.

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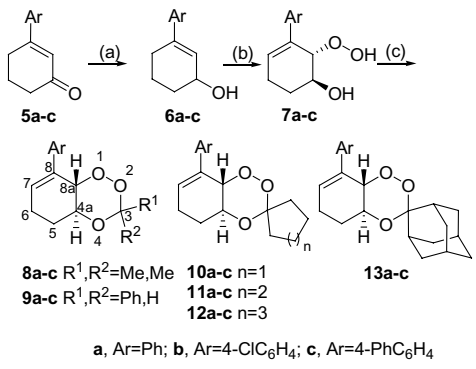
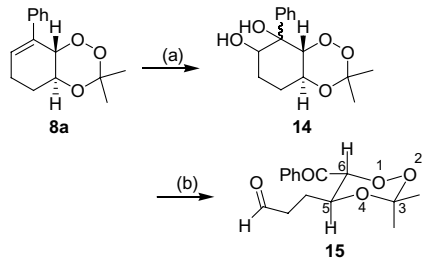
CH_2Cl_2–MeOH (2:1) to yield 3-aryl-2-cyclohexenols **6a–c** in 95–98% yields. No double-bond reduction was observed under these conditions.[7] Methylene blue sensitized photooxygenation of these 3-aryl-2-cyclohexenols **6a–c** in MeCN gave 2-hydroperoxy-3-aryl-3-cyclohexenols **7a–c** in 22–35% yields. Hydroperoxides **7a–c** on acid catalyzed condensation with acetone furnished trioxanes **8a–c** in 25–37% yields.[8,9] Similar condensation with benzaldehyde, cyclopentanone, cyclohexanone, cycloheptanone and 2-adamantanone furnished trioxanes **9a–c**, **10a–c**, **11a–c**, **12a–c** and **13a–c** in 28–37%, 16–26%, 19–21%, 12–16% and 17–24% yields, respectively[9] (Scheme 2).

Though formation of both *cis* and *trans* fused trioxanes is possible, all the trioxanes isolated appeared to be single isomers by ^1H and ^{13}C NMR.[9] Also based on coupling constants it was not possible to assign unambiguously the stereochemistry. So an indirect approach was adopted. Thus trioxane **8a** was treated with catalytic OsO_4 and 70% *t*-butyl hydroperoxide (TBHP) in the presence of triethylbenzylammonium acetate ($Et_3BnNOAc$) to give diol **14**.[10] This diol appeared as a mixture of two isomers on TLC but homogeneous by ^1H NMR. In the ^1H NMR spectrum of **14** H-8a appeared as a doublet at 4.19 ppm with $J = 9.4$ Hz, indicating that the stereochemistry at the ring junction is *trans*. This was further confirmed by $Pb(OAc)_4$ mediated cleavage of trioxane **14** to monocyclic trioxane **15**. In the ^1H NMR spectrum of **15** H-6 appeared as a doublet at 5.20 ppm with $J = 9.6$ Hz, confirming the *trans* stereochemistry. Since NMR spectra of all the trioxanes were similar it is assumed that the stereochemistry at the ring junction in all these trioxanes is *trans*. Also the ^1H NMR spectra of these trioxanes deserves further comments. In the ^1H NMR spectrum of **8a** (as well as all the other trioxanes), although signals for each proton were easily assigned, most of the signals appeared as multiplets and H-8a in particular gave rise to a very complex pattern. Thus H-8a which would be expected to be either a doublet (coupling with only H-4a) or at the most a doublet of doublets (direct coupling with H-4a and allylic coupling with H-7) appeared as a seven-line pattern. The 2D NMR (^1H–^1H COSY) spectrum of **8a** revealed that H-8a was not only coupling with H-4a and H-7, but also with the C-6 protons (Scheme 3).



Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1 h; (b) O_2, *hv*, methylene blue, MeCN, 0 °C, 18 h; (c) aldehyde/ketone, concd HCl (cat.), CH_2Cl_2, 0 °C, 3–6 h.



Scheme 3. Reagents and conditions: (a) OsO_4 (cat.), 70% TBHP, $Et_3BnNOAc$, Me_2CO, rt, 2 d, 64%; (b) $Pb(OAc)_4$, PhH, rt, stir, 1 h, 84%.

Table 1. In vivo antimalarial activity results of trioxanes against *Plasmodium yoelii* in mice by the oral route[a]

Compound	Dose (mg/kg/day)	% Suppression on day 4[b]
10c	96	96.2
11c	96	98.5
12c	96	100.0
13b	96	96.3
β-Arteether	48	100.0

[a] See Ref. 11.

[b] Percent suppression = $[(C - T)/C] \times 100$; where C = parasitaemia in the control group, and T = parasitaemia in the treated group.

These trioxanes were subjected to in vivo antimalarial activity against multidrug-resistant *P. yoelii* in mice at a dose of 96 mg/kg by the oral route.[11] Trioxanes **10c**, **11c**, **12c** and **13b** showed more than 95% suppression of parasitaemia at this dose (Table 1). As can be seen in Table 1, trioxane **12c** was the most active of the series. It shows complete suppression of parasitaemia on day 4.

In conclusion, we have developed a photooxygenation route for the preparation of *trans*-fused bicyclic 1,2,4-trioxanes. Stereoselective photooxygenation of 3-aryl-2-cyclohexenols and acid catalyzed condensation of *trans*-2-hydroperoxy-3-aryl-3-cyclohexenols with aldehydes and ketones are the key steps of this method. Several new trioxanes prepared by this method have shown significant antimalarial activity against multidrug resistant *P. yoelii* in mice by the oral route.

Acknowledgements

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8. Typical procedure for the preparation of trioxanes: To a precooled solution (0 °C) of hydroperoxide (**7a**–**c**, 1 equiv) and aldehyde or ketone (5–6 equiv) in CH_2Cl_2 was added concentrated HCl (4–5 drops) and the solution stirred at 0 °C for 3–6 h. The reaction mixture was poured over satd aq $NaHCO_3$ and extracted with CH_2Cl_2. Standard workup gave the crude trioxane, which was chromatographed over silica gel (60–120 mesh) using EtOAc–hexane (1:99) as eluent to furnish the pure trioxane.
9. Selected characteristic data. Hydroperoxide **7a**: IR (neat, cm^{-1}) 3354; ^1H NMR (200 MHz, $CDCl_3$): δ 1.70–1.88 (m, 1H), 1.95–2.09 (m, 1H), 2.30 (m, 2H), 2.60 (br s, 1H, OH), 4.36 (m, 1H), 4.82 (m, 1H), 6.18 (t, 1H, J = 3.4 Hz), 7.32 (m, 5H), 8.43 (br s, 1H, OOH); FAB-MS (*m*/*z*) 207 $[M+H]^+$. Trioxane **8a**: mp 88–89 °C; IR (KBr, cm^{-1}) 1605; ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.66 (s, 3H), 1.76–1.98 (m, 2H), 2.40 (m, 2H), 4.18 (m, 1H), 5.15 (m, 1H), 5.89 (m, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.14 (q), 25.21 (t), 25.85 (t), 26.41 (q), 70.67 (d), 82.76 (d), 104.67 (s) 127.13 (2 × d), 127.76 (d), 128.52 (3 × d), 135.03 (s), 137.05 (s); FAB-MS (*m*/*z*) 247 $[M+H]^+$; HR EIMS (*m*/*z*) calcd for $C_{22}H_{26}O_3$ 246.1256 $(M)^+$, found 246.1263. Trioxane **9a**: mp 135–136 °C; IR (KBr, cm^{-1}) 1597; ^1H NMR (200 MHz, $CDCl_3$): δ 2.01–2.17 (m, 2H), 2.47 (m, 2H), 4.16 (m, 1H), 5.42 (m, 1H), 5.95 (m, 1H), 6.31 (s, 1H), 7.23–7.40 (m, 8H), 7.49–7.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.24 (t), 25.55 (t), 77.90 (d), 82.61 (d), 105.70 (d) 127.22 (2 × d), 127.46 (2 × d), 127.87 (d), 128.81 (2 × d), 128.87 (3 × d), 130.39 (d), 134.56 (s), 134.86 (s), 136.94 (s); FAB-MS (*m*/*z*) 295 $[M+H]^+$. Trioxane **11a**: IR (neat, cm^{-1}) 1600; ^1H NMR (200 MHz, $CDCl_3$): δ 1.46–1.65 (m, 9H), 1.75–1.99 (m, 2H), 2.24–2.45 (m, 3H), 4.22 (m, 1H), 5.17 (m, 1H), 5.88 (m, 1H), 7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.71 (t), 22.82 (t), 25.24 (t), 25.95 (t), 25.99 (t), 29.90 (t), 35.72 (t), 69.78 (d), 82.93 (d), 104.88 (s), 127.10 (2 × d), 127.71 (d), 128.54 (3 × d), 135.19 (s), 137.15 (s); FAB-MS (*m*/*z*) 287 $[M+H]^+$. Trioxane **13a**: mp 138–140 °C; IR (KBr, cm^{-1}) 1604; ^1H NMR (200 MHz, $CDCl_3$): δ 1.55–2.19 (m, 15H), 2.40 (m, 2H), 2.97 (br s, 1H), 4.18 (m, 1H), 5.18 (m, 1H), 5.88 (m, 1H), 7.30 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 25.30 (t), 26.03 (t), 27.65 (2 × d), 30.08 (d), 33.48 (t), 33.74 (t), 33.81 (t), 34.11 (t), 37.18 (d), 37.66 (t), 69.18 (d), 82.81 (d), 106.91 (s), 127.10 (2 × d), 127.67 (d), 128.56 (2d), 128.66 (d), 135.35 (s), 137.28 (s); FAB-MS (*m*/*z*) 339 $[M+H]^+$; HR EIMS (*m*/*z*) calcd for $C_{22}H_{26}O_3$ 338.1882 $(M)^+$, found 338.1851. Trioxane **14**: mp 146–148 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.67 (s, 3H), 1.69–2.10 (m, 4H), 2.68 (s, 1H, OH), 3.90 (dd, 1H, J = 10.6, 4.8 Hz), 4.19 (d, 1H, J = 9.4 Hz), 4.47 (ddd, 1H, J = 11.2, 9.4, 4.2 Hz), 7.30–7.51 (m, 5H); ^1H NMR (200 MHz, $CDCl_3/D_2O$): δ 1.32 (s, 3H), 1.67 (s, 3H), 1.69–2.10 (m, 4H), 3.90 (dd, 1H, J = 10.6, 4.8 Hz), 4.19 (d, 1H, J = 9.4 Hz), 4.47 (ddd, 1H, J = 11.2, 9.4, 4.2 Hz), 7.30–7.51 (m, 5H); FAB-MS (*m*/*z*) 281 $[M+H]^+$. Trioxane **15**: IR (neat, cm^{-1}) 1688; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.64 (s, 3H), 1.69–1.96 (m, 2H), 2.61 (m, 2H), 4.40 (td, 1H, J_t = 9.6 Hz, J_d = 3.0 Hz), 5.20 (d, 1H, J = 9.6 Hz), 7.50 (t, 2H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.2 Hz), 8.05 (d, 2H, J = 7.2 Hz), 9.76 (t, 1H, J = 1.2 Hz); FAB-MS (*m*/*z*) 279 $[M+H]^+$.
10. A slight modification of the Sharpless' procedure was used: Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063–2066.
11. The in vivo efficacy of compounds was evaluated against *Plasmodium yoelii* (MDR) in the Swiss mice model. The colony of bred Swiss mice (25 ± 1 g) were inoculated with 1×10^6 parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0 to 3, in two divided doses daily. The drug dilutions were prepared in groundnut oil, so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg) in 0.1 mL and administered orally for each dose. Parasitaemia level were recorded from thin blood smears between days 4–28.[12] Mice treated with β-arteether served as a positive control.
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