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Regioselective Mukaiyama hydroperoxysilylation of 2-alkyl- or 2-aryl-prop-2-en-1-ols: application to a new synthesis of 1,2,4-trioxanes

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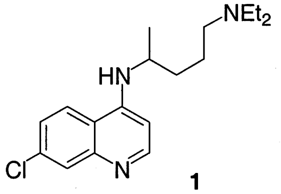
Abstract—Co(II)-mediated peroxysilylation of allylic alcohols **6** or **9** regioselectively provides peroxysilyl alcohols **7** and **10** in good yield. Reaction of these peroxysilyl alcohols with aldehydes or ketones provides target 1,2,4-trioxanes in good to excellent yields. The sequence of Markovnikov hydroperoxysilylation and subsequent reaction with a carbonyl compound can also be readily achieved in a one-pot procedure. Significantly, easily prepared trioxanes **11a** and **11b** have potent in vitro antimalarial activity versus chloroquine resistant K1 *Plasmodium falciparum*. © 2001 Elsevier Science Ltd. All rights reserved.

Malaria is one of the world's most deadly diseases and is becoming an increasingly serious problem as malaria parasites develop resistance to quinoline-containing drugs such as chloroquine (**1**). There is, therefore, considerable urgency to develop new classes of antimalarials.[1,2]

Artemisinin (**2**) (qinghaosu) is an unusual 1,2,4-trioxane which has been used clinically in China for the treatment of multidrug resistant *Plasmodium falciparum* malaria. The 1,2,4-trioxane pharmacophore is essential for biological activity and many synthetic derivatives have been prepared that contain this group. These include the 1,2,4-trioxane derivative fenozan BO-7 (**3**)[3] and the C-3-aryl 1,2,4-trioxanes (e.g. **4**, R = F).[4]

Although semi-synthetic analogues such as **3** and **4** have excellent antimalarial properties, the overall yields of analogues in both classes are low. As a result there is much need for the development of new and improved approaches to the antimalarial 1,2,4-trioxane pharmacophore. Literature methods for the synthesis of the 1,2,4-trioxane sub-unit include the reaction of dioxetanes with carbonyls in the presence of Lewis acids,[5] acid-catalysed cyclisation of hydroperoxyacetals[6] with olefins and reactions of α-peroxy aldehydes with carbonyl compounds.[7] All of these routes provide the trioxane in low overall yield.



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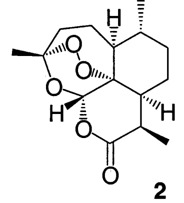

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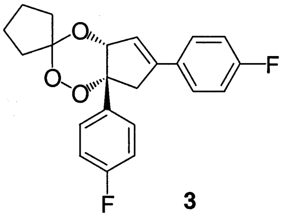

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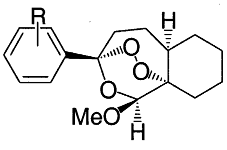

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For the synthesis of trioxanes of the type **5b**, reported literature methods involve acid-catalysed perhydrolysis (98% H_2O_2!) of epoxides followed by cyclisation of key peroxy alcohols **5a** with carbonyl partners (Scheme 1).[8]

In this paper, we report on a new, general and much milder approach to the synthesis of target trioxanes **5b**, which not only avoids the use of potentially hazardous hydrogen peroxide solutions but also enables trioxanes with potent activity in the nanomolar range, to be easily prepared in two simple chemical steps in a one-pot procedure.

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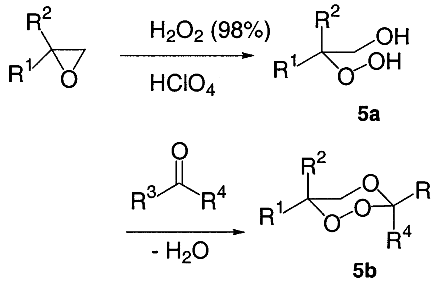
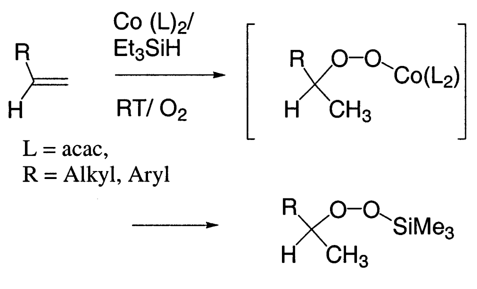


Scheme 1.

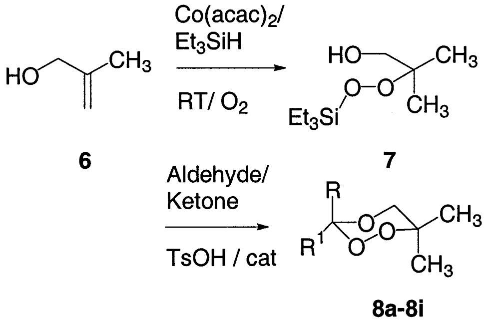


Scheme 2.

Our approach makes use of the highly regioselective 'Markovnikov' reaction of alkenes with molecular oxygen (O_2), triethylsilane and Co(acac)$_2$ as catalyst to give triethylsilyl peroxides in high yield (Scheme 2).[9–11] We reasoned that the use of 2-substituted allylic alcohols (e.g. **6**), in this reaction, would lead to key triethylsilyl protected peroxyalcohols required for reaction with an appropriate carbonyl compound. Oh has recently shown that hydroperoxysilylation of cinnamyl alcohol gives a peroxysilyl alcohol, which is a precursor of the seven-membered 1,2,4-trioxepane system.[12] However, to date, there have been no reports of the use of the 'Mukaiyama–Isayama' hydroperoxysilylation procedure for the synthesis of trioxanes of the general structure **5b**.

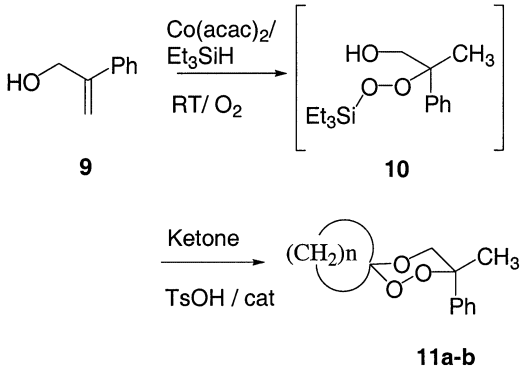
We were pleased to find that under the conditions of Mukaiyama and Isayama [Co(acac)$_2$, Et$_3$SiH, O$_2$, RT], commercially available 2-methyl-2-propen-1-ol (**6**) was readily converted to 2-triethylsilylperoxy-2-methylpropan-1-ol (**7**) in 60% yield (Scheme 3). The alcohol **7** was purified by silica gel chromatography and was accompanied by minor amounts of the corresponding diol, which presumably arises via Co(II)-mediated reduction of the peroxysilyl alcohol.[9]

Alcohol **7** was smoothly coupled with a range of carbonyl substrates. Yields were generally good for the formation of target trioxanes (Table 1, 40–90%) using aldehydes (entries 1–5) or ketones (entries 6–9). For the preparation of trioxanes **8f–i**, separate purification of **7** was not required and a one-pot peroxysilylation/cyclisation using crude **7** and an appropriate ketone gave the target trioxanes in good yield after flash column chromatography.



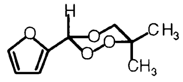
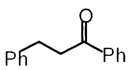
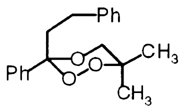
Scheme 3.

Based on these observations, we decided to investigate other alcohol substrates. Peroxysilylation of 2-phenylprop-2-en-1-ol (**9**) under standard conditions followed by addition of cyclopentanone or cyclohexanone provided target 1,2,4-trioxanes **11a** and **11b** in 42 and 54% overall yield following chromatography (Scheme 4 and Table 2).



Scheme 4.

Table 1. Synthesis of 1,2,4-trioxanes

	Carbonyl compound	Product	Yield (%)
1	Benzaldehyde	**8a** (R=H, R^1=Ph)	65[13]
2	*p*-Fluorobenzaldehyde	**8b** (R=H, R^1=*p*-F-Ar)	90[14]
3	*p*-Nitrobenzaldehyde	**8c** (R=H, R^1=*p*-NO$_2$-Ar)	40
4	*p*-Phenylbenzaldehyde	**8d** (R=H, R^1=*p*-Ph-Ph)	73
5	Furfuraldehyde	 **8e**	65
6	Cyclohexanone	**8f** (R, R^1=-CH$_2$(CH$_2$)$_3$CH$_2$-)	53[a]
7	Acetophenone	**8g** (R=Me, R^1=Ph)	50[a]
8	*p*-Fluoroacetophenone	**8h** (R=Me, R^1=*p*-F-Ar)	42[a]
9		 **8i**	40[15]

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[a] Yields are for a one-pot procedure.

Table 2. Synthesis and antimalarial activity of trioxanes **11a** and **11b**

	Ketone (R)	Product	Yield (%)	IC_{50} versus K1 *P. falciparum* (nM)
1	Cyclopentanone	**11a** $n=4$	42^{16}	94.9
2	Cyclohexanone	**11b** $n=5$	54^{17}	135.1
				Chloroquine 276.2
				Artemether 9.2
				Artemisinin 14.2

Antimalarial testing, versus the chloroquine resistant K1 strain in vitro, revealed that easily prepared trioxanes, **11a** and **11b**, have potent antimalarial activity: trioxane **11a** is only six-fold less potent than the structurally more complex natural product artemisinin and represents an excellent lead for further studies.

In summary, this paper describes a new approach to 1,2,4-trioxanes **5b** which is superior to existing routes in terms of convenience and overall yield. The chemistry should be applicable to the cost-effective synthesis of many new trioxane-containing drug candidates for biological screening.

Acknowledgements

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13. Compound **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (2H, m, Ar), 7.38 (3H, m, Ar), 6.03 (1H, s, $C\underline{H}$), 3.82 (2H, dd, $J=24.6$, 11.4 Hz, $C\underline{H}_2$), 1.62 (3H, s, $C\underline{H}_3$), 1.14 (3H, s, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.70, 129.98, 128.54, 127.09, 104.01, 77.41, 73.70, 22.43, 21.83; ν_{max} (Nujol mull): 2978.2 (C–H), 1455.9 (Ar), 1088.7 (C–O) cm^{-1}; MS *m*/*z*, found 194.09445. $C_{11}H_{14}O_3$ requires 194.09428; found: C, 68.17; H, 7.31; requires C, 68.02; H, 7.26%.
14. Compound **8b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (2H, m, Ar), 7.09 (2H, m, Ar), 6.01 (1H, s, $C\underline{H}$), 3.83 (2H, dd, $J=25.1$, 11.3 Hz, $C\underline{H}_2$), 1.62 (3H, s, $C\underline{H}_3$), 1.15 (3H, s, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.77 ($^1J_{CF}=247.3$ Hz), 130.69 ($^4J_{CF}=2.9$ Hz), 129.09 ($^3J_{CF}=8.0$ Hz), 115.49 ($^2J_{CF}=21.7$ Hz), 103.29, 77.40, 73.70, 22.40, 21.81; ν_{max} (Nujol mull): 2978.5 (C–H), 1455.4 (Ar), 1085.6 (C–O) cm^{-1}; MS *m*/*z*, found 212.08492. $C_{11}H_{13}FO_3$ requires 212.08487; found: C, 62.47; H, 6.26; requires C, 62.26; H, 6.17%.
15. Compound **8i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.05 (10H, m, Ar), 3.55 (2H, dd, J = 37.4, 11.1 Hz, $C\underline{H}_2$), 2.69 (2H, m, $C\underline{H}_2$), 2.09 (2H, m, $C\underline{H}_2$), 1.60 (3H, s, $C\underline{H}_3$), 0.93 (3H, s, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.71, 139.38, 128.35, 127.99, 127.27, 125.89, 105.10, 77.14, 67.83, 29.05, 22.60, 22.17; ν_{max} (Nujol mull): 2923.3 (C–H), 1458.1 (Ar), 1064.4 (C–O) cm^{-1}; MS *m*/*z*, found 298.15794. $C_{19}H_{22}O_3$ requires 298.15689; found: C, 76.44; H, 7.49; requires C, 76.48; H, 7.43%.
16. Compound **11a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (5H, m, Ar), 4.01 (2H, brm, $C\underline{H}_2$), 1.93–0.90 (11H, brm); MS *m*/*z*, found 235.13393. $C_{14}H_{19}O_3$ $[M+H]^+$ requires 235.13342; found: C, 71.88; H, 7.94; requires C, 71.77; H, 7.74%.
17. Compound **11b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (5H, m, Ar), 4.21 (2H, brm, $C\underline{H}_2$), 1.86–0.92 (13H, brm); ν_{max} (Nujol mull): 2923.9 (C–H), 1452.5 (Ar), 1094.3 (C–O) cm^{-1}; MS *m*/*z*, found 249.14971. $C_{15}H_{21}O_3$ $[M+H]^+$ requires 249.14907; found: C, 72.70; H, 8.18; requires C, 72.55; H, 8.12%.