Pergamon

Tetrahedron Letters, Vol. 38, No. 50, pp. 8753-8756, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10343-4

New Methods for the Synthesis of Oxy-Functionalized 1,2,4-Trioxanes and 1,2,4-Trioxepanes from Unsaturated Hydroperoxy Acetals

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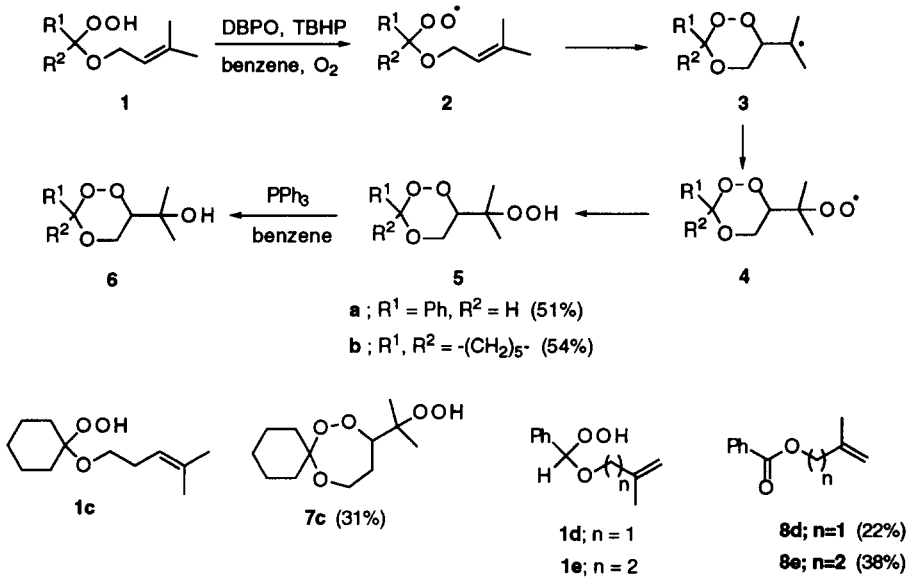
Abstract: Oxy-functionalized 1,2,4-trioxanes or 1,2,4-trioxepanes were produced by either autoxidation of the unsaturated hydroperoxy acetals **1**, or the acid-catalyzed cyclization of epoxy hydroperoxides **9** which were readily prepared from **1**. By the appropriate choice of cyclization procedure, the structures of the resulting cyclic peroxides could be efficiently controlled.

Recent investigations of the chemistry of the antimalarial drug artemisinin and other cyclic peroxides have focused attention on the mechanism of their mode of action.[1] Since structure-activity studies play an important part in such investigations, it is important that versatile synthetic methods, which produce compounds with considerable structural variation, should be available.[2] Electrophilic cyclization[3] or ozonolysis[4] of unsaturated hydroperoxy acetals **1** have been found to be convenient methods for the synthesis of functionalized 1,2,4-trioxanes and their homologues. We report herein that a variety of new oxy-functionalized cyclic peroxides can be prepared from identical or similar precursors. Thus, by appropriate choice of methodology, e.g. peroxyl radical cyclization of **1**, or cyclization *via* either carbocations or peroxyl anions of the derived epoxy hydroperoxides **9**, cyclic peroxides with varied ring sizes and substitution patterns can be prepared.

Autoxidation of unsaturated hydroperoxy acetals **1**, which has been extensively studied in connection with prostaglandin biosynthesis and polyalkene degradation,[5a] is virtually unexploited for the synthesis of 1,2,4-trioxanes and related compounds. Of the various possible reagents which could be used to generate the desired peroxyl radical by hydrogen abstraction, a combination of di-*t*-butyl peroxyoxalate (DBPO) and *t*-butyl hydroperoxide (TBHP)[6] was found to be highly effective. Thus, a solution of acetal hydroperoxide **1a** in benzene under dry oxygen (1 atm.), on treatment with DBPO (0.5 equiv.) and excess TBHP (5 equiv.) at room temperature, yielded the trioxane **5a** (a 7:3 mixture of the *cis*- and *trans*-isomers; 51% yield) after 8 h. (Scheme 1). Subsequent reduction of either of the stereoisomeric trioxanes **5a** with triphenylphosphine gave in each case the stereochemically defined 6-hydroxymethyl-substituted 1,2,4-trioxane **6a** almost quantitatively (NOE measurement). The related hydroperoxide **1b** was transformed into the trioxane **5b** in a similar fashion.[7] Thus, *exo*- cyclization of peroxyl radical **2** leading to the corresponding *tert*-alkyl radical **3** seems to occur very efficiently. With hydroperoxide **1c** as substrate, the anticipated 1,2,4-trioxepane derivative **7c** was obtained in 31% yield. This is, to our knowledge, the first example of formation of seven-membered cyclic peroxide by an intramolecular cyclization of peroxyl radical.[5b] However, treatment of hydroperoxides **1d** and **1e** with a mixture of DBPO and TBHP resulted in the isolation of the acyclic esters **8d** (22%) and **8e** (38%) respectively together with the unchanged starting materials (*ca.* 40%). In these cases, both the *exo*- and *endo*-cyclizations appear to be

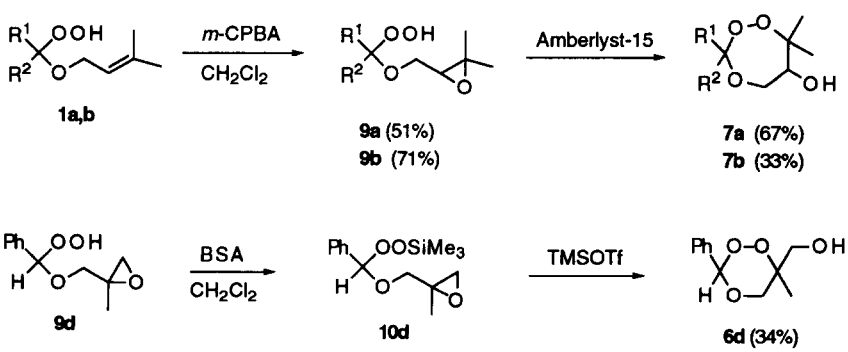
disfavoured; the formation of acyclic esters **8d** and **8e** would be consistent with the respective putative secondary peroxyl radicals participating in Russell termination processes.[8]

Scheme 1



Given the significant limitations of the peroxyl radical cyclization process, the acid-catalyzed cyclization of the related epoxy hydroperoxides **9** was examined (Scheme 2).[5a] Epoxidation of the acetal peroxides **1** with *m*-chloroperbenzoic acid afforded the corresponding epoxy hydroperoxides **9** in good to moderate yield. Reaction of **9** with Amberlyst-15[9] in CH_2Cl_2 proceeded smoothly at rt. For example, when a solution of **9a** (224 mg) in CH_2Cl_2 (30 mL) was treated with of Amberlyst-15 (50 mg) at rt for 45 h, 1,2,4-trioxepane **7a** was obtained in 67% yield (*ca.* 1:1 mixture of the *cis*- and *trans*-isomers). Similarly, **9b** was converted into **7b**.[10] From **9d**, however, the corresponding trioxane **6d** was obtained in 30% yield. Alternatively, trimethylsilylation of the hydroperoxyl group of **9d**, followed by treatment with TMSOTf[11] also gave the same trioxane **6d**. Thus,

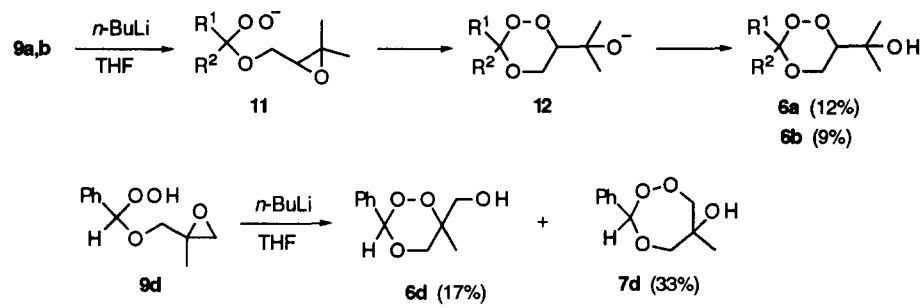
Scheme 2



these cyclizations must proceed *via* intramolecular displacement at the more highly substituted oxirane ring carbon in each case, suggesting that the respective intermediates must have a high degree of carbocationic character.[5b]

In contrast, it was expected that peroxyl anions such as **11** (Scheme 3) derived from epoxy hydroperoxides **9** should undergo cyclization predominantly by nucleophilic attack at the less hindered position of the oxirane ring thereby providing an entry to the cyclic peroxides having alternative ring sizes to those obtained from acid-catalyzed cyclizations (Scheme 2).

Scheme 3



Consistent with this expectation, treatment of the epoxy hydroperoxide **9a** with *n*-BuLi (1 equiv.) at rt for 15 h gave the expected trioxane **6a** as the sole isolable cyclic peroxide, albeit in low yield (12%); unchanged **9a** (32%) was also recovered. It is worth noting that in the corresponding acid-catalyzed cyclization of **9a**, the trioxepane **7a** was obtained exclusively. The reaction of **9b** under the same conditions gave **6b** (9%) together with the unreacted **9b** (54%). From **9d**, trioxepane **7d** (33%)[12] was the major product isolated, together with a small amount of trioxane **6d** (17%) (Scheme 3). As noted above, our previous attempt to prepare **7d** from **1d** by the peroxyl radical cyclization method had failed. Cerium hydroxide-mediated cyclization, which had been shown to be effective for the synthesis of 1,2-dioxanes,[2b] was unsuccessful with the epoxy hydroperoxides **9**; only decomposition was observed.

In conclusion, we have succeeded in developing three alternative methods for the synthesis of oxy-functionalized 1,2,4-trioxanes and 1,2,4-trioxepanes from either unsaturated hydroperoxy acetals or the corresponding epoxy hydroperoxides as appropriate. These methods seem to be complementary to each other and enable the preparation of a variety of new cyclic peroxide derivatives.

Acknowledgement. This work was supported in part by a Grant-in Aid for Scientific Research on Priority Areas (09270212) from the Ministry of Education, Science, Culture and Sports of Japan. We thank British Council (Tokyo) for the award of travel grant to M. N. and K. J. M. and also a grant for graduate students to Y. U.

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7. **Trioxane 5b:** m. p. 102-103 °C (ethyl acetate); ^{1}H NMR δ 1.25 (s, 3 H), 1.29 (s, 3 H), 1.3-2.2 (m, 10 H), 3.79 (dd, *J* = 3.3 x 10.2 Hz, 1 H), 4.05 (dd, *J* = 10.2 x 11.9 Hz, 1 H), 4.49 (dd, *J* = 3.3 x 11.9 Hz, 1 H), 7.80 (s, 1 H); ^{13}C NMR δ 20.70 (q), 21.46 (q), 22.23, 22.28, 25.45, 29.24, 34.20, 58.53 (t), 82.16 (s), 82.28 (d), 102.75 (s). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.93; H, 8.74.
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10. **Trioxepane 7b**: a colorless oil; ^{1}H NMR δ 1.20 (s, 3 H), 1.3-2.2 (m, 10 H), 1.38 (s, 3 H), 2.97 (d, *J* = 11.5 Hz, 1 H)(O*H*), 3.29 (dd, *J* = 11.5 x 3.6 Hz, 1 H)(C*H*OH), 3.61 (dd, *J* = 3.6 x 12.2 Hz, 1 H), 4.14 (d, *J* = 12.2 Hz, 1 H); ^{13}C NMR δ 21.73 (q), 22.40 (q), 22.59, 22.99, 25.21, 31.47, 33.57, 61.44 (t), 74.34 (d), 85.18 (s), 106.65 (s). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.68; H, 8.77.
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12. **Trioxepane 7d:** an oil; ^{1}H NMR δ 1.16 (s, 3 H), 3.39 (s, 1 H), 3.82 (dd, *J* = 2.0x11.9 Hz, 1 H), 3.9-4.1 (m, 1 H), 4.16 (d, *J* = 7.6 Hz, 1 H), 4.21 (d, *J* = 9.6 Hz, 1 H), 5.99 (s, 1 H), 7.3-7.6 (m, 5 H; ^{13}C NMR δ 19.89 (q), 72.44 (s), 73.59 (t), 85.39 (t), 104.96 (d), 126.25, 128.36, 129.11, 136.44. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.84. Found: C, 62.80; H, 6.66.

(*Received in UK* 13 *August* 1997; *revised* 8 *October* 1997; *accepted* 10 *October* 1997)