Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6309–6312

TETRAHEDRON LETTERS

One-pot synthesis of non-symmetric tetraoxanes with the H_2O_2/MTO/fluorous alcohol system☆

Jernej Iskra,[a] Danièle Bonnet-Delpon[b,*] and Jean-Pierre Bégué[b]

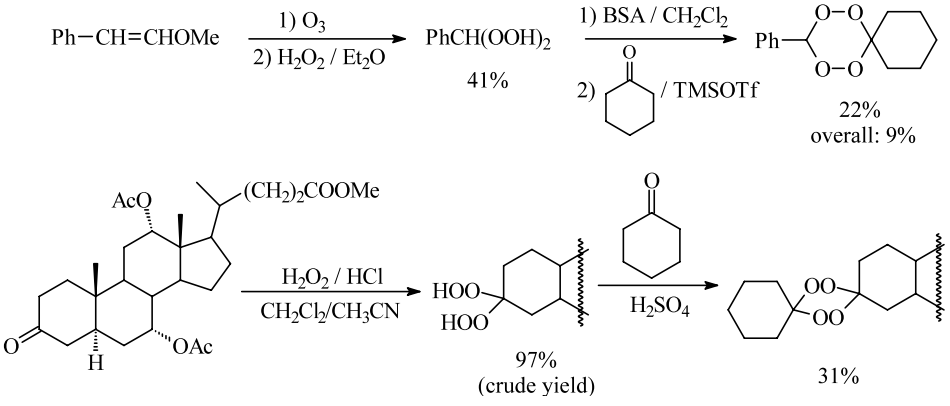
[a]*Laboratory of Organic and Bioorganic Chemistry, 'Jozef Stefan' Institute, Jamova 39, Slovenia*
[b]*BIOCIS UPRES-A 8079, Faculté de Pharmacie, Université Paris-Sud, Chatenay-Malabry, France*

Received 21 May 2003; revised 13 June 2003; accepted 14 June 2003

Abstract—1,2,4,5-Tetraoxanes, potent antimalarial drugs, were selectively synthesized in fluorous alcohols (2,2,2-trifluoroethanol–TFE and 1,1,1,3,3,3-hexafluoro-2-propanol–HFIP). A use of these solvents enabled for the first time a one-pot synthesis of non-symmetric tetraoxanes in good yields from simple ketones and aldehydes with 2 equiv. of 30% hydrogen peroxide and 0.1 mol% of methyltrioxorhenium (MTO).

Artemisinin and its semisynthetic derivatives represent a new class of antimalarials, active against *Plasmodium falciparum*, a chloroquine-resistant parasite, which causes several million deaths per year worldwide.[1,2] They contain an endoperoxide functional group as the pharmacophore and several types of synthetic cyclic peroxides were established to have good antimalarial activity.[3] Among them, dispiro-1,2,4,5-tetraoxanes **2** (7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecanes) exhibit remarkable antimalarial activity. They are structurally simple and easily prepared by acid-catalyzed condensation of substituted cyclohexanones and hydrogen peroxide.[4–8] However, until now representatives of this group of compounds were structurally very limited and good yields of symmetric tetraoxanes **2** could be achieved only in some cases.[6,9,10]

Bearing in mind that symmetric tetraoxanes **2** are limited in number, non-symmetric tetraoxanes would offer more opportunity for selective incorporation of various functional groups on the tetraoxane scaffold. Very recently two methods have been reported for the synthesis of mixed tetraoxanes. They are multi-step procedures with isolation of the explosive dihydroperoxide intermediate (Scheme 1).[11]



Scheme 1.

☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)01472-2

* Corresponding author. Tel.: +33-146835739; fax: +33-146835740; e-mail: daniele.bonnet-delpon@cep.u-psud.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01472-2

An easy, safe and efficient route to mixed tetraoxanes would give strong impetus to find candidates with good activity and determine their structure/activity relationship and their mode of action against malarial parasites. A one-pot procedure for synthesis of mixed tetraoxanes would demand quantitative conversion of the starting ketone to a *gem*-dihydroperoxide under neutral conditions with no excess of hydrogen peroxide, followed by addition of a second carbonyl compound and acid to promote cyclization. We envisaged that H_2O_2/MTO/fluorous alcohol could be a good system, since we, among others, have shown that fluorous alcohols, trifluoroethanol (TFE) and hexafluoropropanol, (HFIP) can activate both H_2O_2[12] and methyltrioxorhenium[13] for oxidation and epoxidation reactions, while nucleophile oxirane ring opening reactions exhibit remarkable selectivity.[14]

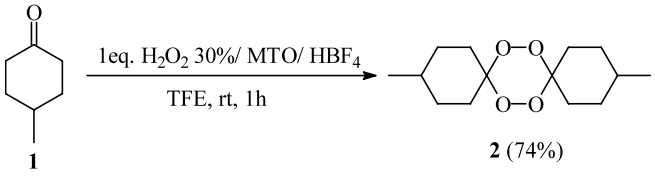
We tested the usefulness of fluorous alcohols in the synthesis of tetraoxane in the case of 4-methyl cyclohexanone, which is known to provide mainly hexaoxonane instead of the tetraoxane.[9] After reaction of **1** with 1 equiv. H_2O_2 30%, 0.1 mol% MTO and 1 equiv. of acid (HBF_4 in ether) in TFE, tetraoxane **2** was the only product formed as determined by its characteristic signal in ^1H NMR spectra at 3.1 ppm[15] and was isolated in 74% yield (Scheme 2). No formation of the hexaoxonane was observed. Similar reaction in ethanol yielded complex reaction mixture that contained 20% of tetraoxane.

Using similar reaction conditions, aliphatic ketones (e.g. 5-nonanone) did not react. In the same way, benzaldehyde **3a** reacted and tetraoxane **4a** was the sole reaction product, while aliphatic aldehyde **3b** yielded a complex reaction mixture. By replacing TFE by HFIP, the reaction was successful and the corresponding tetraoxane **4b** was obtained in 86% yield (Scheme 3). However, there was no reaction with 5-nonanone even in HFIP.

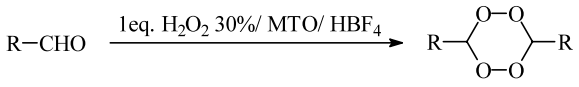
In the next step, we were interested in the possible synthesis of a *gem*-dihydroperoxide using the same oxidative system. If the reaction was performed in the absence of an acid catalyst, we could hope to prevent the cyclization process. Reaction of **1** with 2 equiv. of 30%H_2O_2/0.1 mol% MTO/TFE was followed by TLC and after 2 h of stirring only trace amounts of starting ketone remained. After a work-up procedure, 4-methyl-1,1-dihydroperoxycyclohexanone **5** was obtained as the major product and its structure was determined by a comparison of NMR spectra (Scheme 4).[11b]

A clean preparation of mixed tetraoxanes using the H_2O_2/MTO/TFE oxidative system could be envisaged, since first, conversion of a carbonyl compound to a *gem*-dihydroperoxide could be obtained with no excess of H_2O_2, and second, the acid-catalyzed conversion of the ketone to tetraoxane was selective. We thus proceeded towards the one-pot synthesis of mixed tetraoxanes by first oxidizing the most reactive carbonyl compound to a *gem*-dihydroperoxide, followed by the addition of the less oxidizable carbonyl compound in the presence of acid.

A solution of ketone **1**/2 equiv. H_2O_2 30%/0.1 mol% MTO in TFE (0.5 M) was stirred for 2 h at room temperature, then 2 equiv. of 5-nonanone were added, followed by the addition of 1 equiv. of HBF_4. The reaction mixture was stirred for an additional hour, and after the usual work-up procedure, mixed tetraoxane **6a** was obtained as the major reaction product, accompanied by a small amount of symmetric tetraoxane **2** (**6a**:**2** = 15:1). Product **6a** was easily separated from the starting ketones by column chromatography and purified by crystallization, yielding 64% of mixed tetraoxane **6a** (Scheme 5). When the more oxidizable 4-*tert*-butylcyclohexanone was taken as the second carbonyl



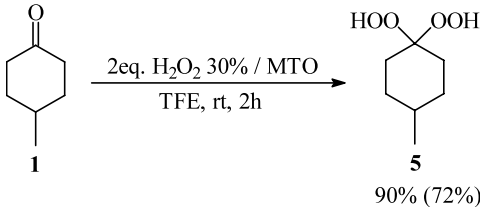
Scheme 2.



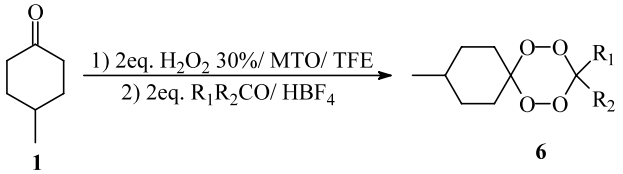
3a: R = Ph: TFE, rt, 1h: **4a** (77%)

3b: R = C_7H_{15}: HFIP, rt, 1h: **4b** (86%)

Scheme 3.



Scheme 4.



6a: $R_1 = R_2 = C_4H_9$ (64%)

6b: $R_1 = CH_2—CH_2$, $R_2 = CH_2—CH_2$ CH-*t*Bu (45%)

6c: $R_1 = C_7H_{15}$, $R_2 = H$ (62%)

6d: R_1 = Ph, R_2 = H (54%)

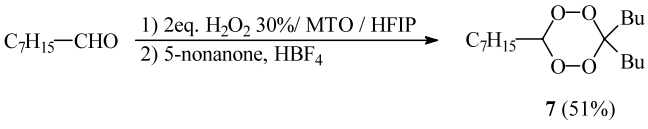
Scheme 5.

compound, reaction was less selective, since besides the mixed tetraoxane, both symmetric ones were formed in small quantities. Nevertheless **6b** was obtained in 45% yield after crystallization. Aliphatic as well as aromatic aldehydes could also be used for the cyclization, as may be seen in Scheme 5.

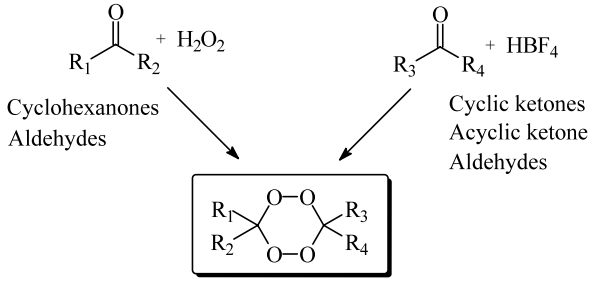
Having established that the H_2O_2/MTO/fluorous alcohol oxidative system quantitatively converts aldehydes into symmetrical tetraoxanes with only 1 equiv. of 30% H_2O_2 and 0.1 mol% of MTO, we tried to extrapolate to the synthesis of mixed tetraoxanes with the basic carbonyl unit of an aldehyde and the secondary one of an aliphatic ketone. Reaction was performed with octanal and 2 equiv. of H_2O_2 and 0.1 mol% of MTO in HFIP (rt, 1 h) followed by the addition of 2 equiv. of 5-nonanone and 1 equiv. of HBF_4 (rt, 1 h). Again, mixed tetroxane **7** was obtained in 51% isolated yield after column chromatography and crystallization (Scheme 6).

Conclusion. The use of the H_2O_2/MTO/fluorous alcohol system enables for the first time a one-pot and selective synthesis of non-symmetric tetraoxanes in good yields. Therefore isolation of the intermediate product, the *gem*-dihydroperoxide, is no longer necessary, representing a great improvement because of its unstable and explosive nature. The use of fluorous alcohols as solvents brings further advantages: the use of an excess of H_2O_2 is no longer required, the amount of catalyst is low (0.1 mol%), and finally, the cyclization step is highly selective since formation of trimeric cyclic peroxides (hexaoxonanes) was completely avoided, tetraoxanes being the only reaction products (Scheme 7).

Available tetraoxanes as a group of compounds were so far structurally limited. However, with this new method it is now possible to synthesize structurally diverse tetraoxanes and consequently selectively manipulate peroxide functionality. This will give a strong impetus to research on these antimalarials, and on their structure/activity relationship.



Scheme 6.



Scheme 7.

Supporting information. Experimental procedures and full characterization for compounds **2**, **4**, **5**, **6** and **7**.

Acknowledgements

This research was supported by the European Community Human Potential Programme Marie Curie Individual Fellowship (J.I.) under contract number HPMF-CT-1999-00097 and GDR Parasitology. We are grateful to Dr. Dusan Zigon and Dr. Bogdan Kralj for MS measurements and Michèle Ourévitch for the help with NMR spectra.

References

1. Malaria Foundation International, http://www.malaria.org.
2. (a) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73–79; (b) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167–174; (c) Wu, Y. K. *Acc. Chem. Res.* **2002**, *35*, 255–259.
3. McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601–636.
4. (a) Dong, Y. X.; Matile, H.; Chollet, J.; Kaminsky, R.; Wood, J. K.; Vennerstrom, J. L. *J. Med. Chem.* **1999**, *42*, 1477–1480; (b) Vennerstrom, J. L.; Fu, H. N.; Ellis, W. Y.; Ager, A. L.; Wood, J. K.; Andersen, S. L.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 3023–3027; (c) Vennerstrom, J. L.; Ager, A. L.; Andersen, S. L.; Grace, J. M.; Wongpanich, V.; Angerhofer, C. K.; Hu, J. K.; Wesche, D. L. *Am. J. Trop. Med. Hyg.* **2000**, *62*, 573–578; (d) Vennerstrom, J. L.; Dong, Y. X.; Andersen, S. L.; Ager, A. L.; Fu, H. N.; Miller, R. E.; Wesche, D. L.; Kyle, D. E.; Gerena, L.; Walters, S. M.; Wood, J. K.; Edwards, G.; Holme, A. D.; McLean, W. G.; Milhous, W. K. *J. Med. Chem.* **2000**, *43*, 2753–2758.
5. Jefford, C. W.; Boukouvalas, A. J. J. *Synthesis* **1988**, 391–393.
6. Kim, H. S.; Shibata, Y.; Wataya, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M. *J. Med. Chem.* **1999**, *42*, 2604–2609.
7. McCullough, K. J.; Wood, J. K.; Bhattacharjee, A. K.; Dong, Y. X.; Kyle, D. E.; Milhous, W. K.; Vennerstrom, J. L. *J. Med. Chem.* **2000**, *43*, 1246–1249.
8. (a) Opsenica, D.; Pocsfalvi, G.; Juranic, Z.; Tinant, B.; Declercq, J. P.; Kyle, D. E.; Milhous, W. K.; Solaja, B. A. *J. Med. Chem.* **2000**, *43*, 3274–3282; (b) Todorovic, N. M.; Stefanovic, M.; Tinant, B.; Declercq, J. P.; Makler, M. T.; Solaja, B. A. *Steroids* **1996**, *61*, 688–696.
9. Dong, Y. X.; Vennerstrom, J. L. *J. Org. Chem.* **1998**, *63*, 8582–8585.
10. Ito, Y.; Yokoya, H.; Umehara, Y.; Matsuura, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2407–2408.
11. (a) Kim, H. S.; Tsuchiya, K.; Shibata, Y.; Wataya, Y.; Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1867–1870; (b) Solaja, B. A.; Terzic, N.; Pocsfalvi, G.; Gerena, L.; Tinant, B.; Opsenica, D.; Milhous, W. K. *J. Med. Chem.* **2002**, *45*, 3331–3336.

12. (a) Ravikumar, K. S.; Zhang, Y. M.; Bégué, J. P.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **1998**, 2937–2940; (b) Legros, J.; Crousse, B.; Bourdon, J.; Bonnet-Delpon, D.; Bégué, J. P. *Tetrahedron Lett.* **2001**, *42*, 4463–4466; (c) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 248–250; (d) ten Brink, G.-J.; Vis, J. M.; Arends, I. W. C. E.; Sheldon, R. A. *Tetrahedron* **2002**, *58*, 3977–3983; (e) Neimann, K.; Neumann, R. *Org. Lett.* **2000**, *2*, 2861–2863; (f) Berkessel, A.; Andreae, M. M. *Tetrahedron Lett.* **2001**, *42*, 2293–2295; (g) Berkessel, A.; Andreae, M. R. M.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4481–4484; (h) de Visser, S. P.; Kaneti, J.; Neumann, R.; Shaik, S. *J. Org. Chem.* **2003**, *68*, 2903–2912.
13. (a) Iskra, J.; Bonnet-Delpon, D.; Bégué, J. P. *Tetrahedron Lett.* **2002**, *43*, 1001–1003; (b) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 821–822.
14. Iskra, J.; Bonnet-Delpon, D.; Bégué, J. P. *Eur. J. Org. Chem.* **2002**, 3402–3410.
15. Dong, Y. X.; Vennerstrom, J. L. *J. Heterocycl. Chem.* **2001**, *38*, 463–466.