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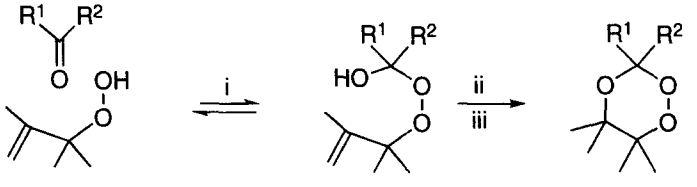
Versatility of the Cyclo-oxymercuriation Route to 1,2,4-Trioxanes[a]

A J Bloodworth*, Torsten Hagen, Karen A Johnson, Isabelle LeNoir and Chantal Moussy

Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ (UK)

Abstract: The versatility of the cyclo-oxymercuriation route to 1,2,4-trioxanes is illustrated by preparing new examples with heterocyclic, unsaturated and carbohydrate substituents and by post-cyclisation modification of the substituents including oxidative cleavage of alkene and reduction, condensation and Wittig olefination of carbonyl groups. © 1997, Published by Elsevier Science Ltd. All rights reserved.

Interest in the antimalarial drug artemisinin and peroxidic analogues remains high with attention recently being concentrated on probing the molecular mechanism of action.[1] Structure - activity studies play an important part in such an investigation and are much enhanced by versatile synthetic methods that support considerable structural variation. The cyclo-oxymercuriation route to 1,2,4-trioxanes involves the mercury(II)-induced cyclisation of hemiperoxyacetals derived from allylic hydroperoxides followed by reductive demercuriation. The versatility of the method has been illustrated in part by the successful use of several allylic hydroperoxides, notably 2,3-dimethylbut-1-en-3-yl hydroperoxide,[2,3] 1-phenylprop-2-enyl hydroperoxide,[4] 1-isopropylprop-2-enyl hydroperoxide,[5] 2-methylbut-2-enyl hydroperoxide,[5] and compounds CH_2=C(Ph)CH(OOH)CH_2OX (where X = H, CONHPh and Ac)[6] and of tin(IV) derivatives of allylic hydroperoxides.[5,7] Here, we demonstrate the versatility of the method in a complementary way by using one allylic hydroperoxide, namely 2,3-dimethylbut-1-en-3-yl hydroperoxide, with a variety of carbonyl compounds (R^1R^2CO) to prepare new 1,2,4-trioxanes that contain additional functionality. We also show that several functional group manipulations can be carried out whilst keeping the peroxide ring intact.

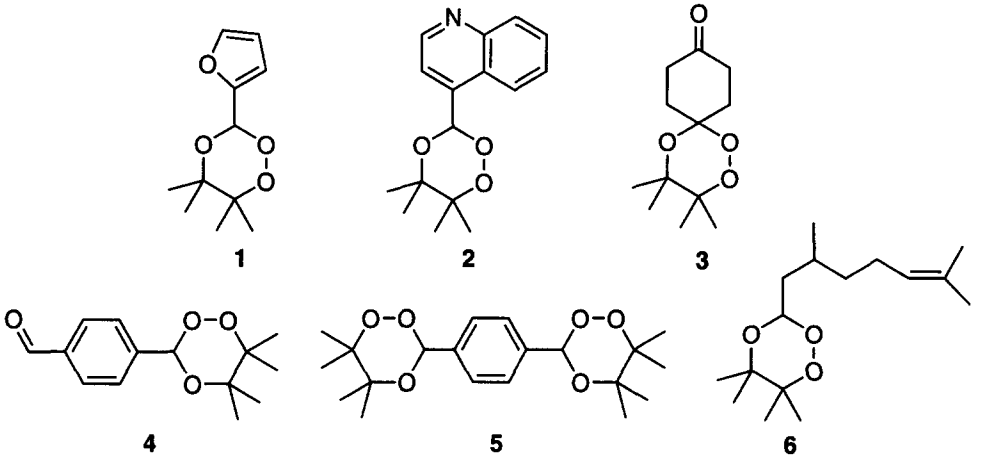


Scheme 1. *Reagents:* i, cat CF_3CO_2H; ii, $Hg(OAc)_2$, 6 mol% $HClO_4$; iii, $NaBH_4$, NaOH

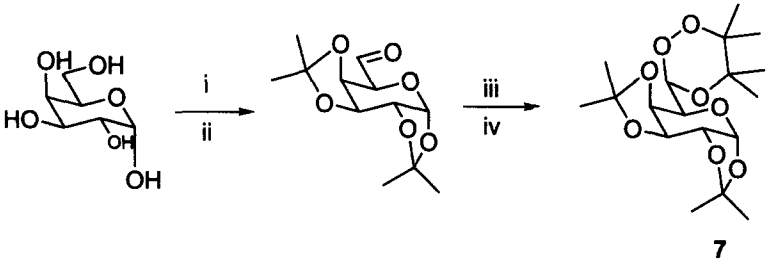
Previous examples of 1,2,4-trioxanes prepared from 2,3-dimethylbut-1-en-3-yl hydroperoxide (scheme 1) have been limited to those from reactions with formaldehyde,[3] aliphatic and aromatic aldehydes[2] and the symmetrical ketones acetone, cyclohexanone and adamantanone.[3] Using crude hydroperoxide (10 mmol) obtained by tetraphenylporphine - sensitised photo-oxygenation of 2,3-dimethylbut-2-ene with the appropriate

[a]This paper is dedicated to Professor Waldemar Adam on the occasion of his 60th birthday.

aldehyde or ketone (20 mmol) and following the one-pot procedure,[2] the new 1,2,4-trioxanes **1**-**6**[8] were prepared. Purification was by column chromatography although HPLC was required to separate the mixture of **4** and **5** obtained from terephthaldehyde and reversed phase HPLC was needed to obtain a pure sample of **2**. Compounds **3**-**5** were white solids whereas the others were colourless oils. Yields were poor (6-12%) for the products derived from the heterocyclic and aromatic aldehydes, better (36%) for **3** and excellent (85%) for **6** which was isolated as a 1:1 mixture of diastereoisomers. It is important that, as anticipated from the relative reactivities of variously substituted alkenes towards oxymercuriation, the double bond of citronellal is unreactive under the cyclo-oxymercuriation conditions and so is retained in the product **6**. Compound **2** is interesting in that it contains the heterocyclic nucleus of the original antimalarial, quinine, fused to the peroxidic nucleus of artemisinin.

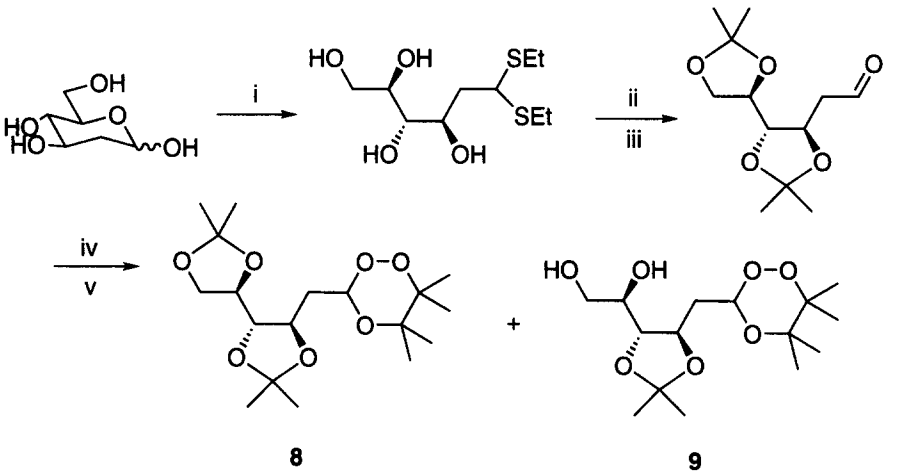


Much effort has gone into chemically modifying artemisinin to enhance its antimalarial properties. This has mainly involved reducing the lactone ring and derivatising the resultant lactol, dihydroartemisinin. As part of this approach, the preparation and activities of some carbohydrate derivatives have been reported.[9] Unlike these derivatives, compounds with the sugar moiety attached *directly* to the 1,2,4-trioxane ring can be prepared by the cyclo-oxymercuriation route. Thus, D-galactose was converted into the 1,2:3,4-diacetonide and oxidised with the Pfitzner-Moffatt reagent to give the corresponding C-6 aldehyde[10] which afforded the 1,2,4-trioxane **7**[8] in 32% yield as a 1:1 mixture of diastereoisomers (scheme 2).



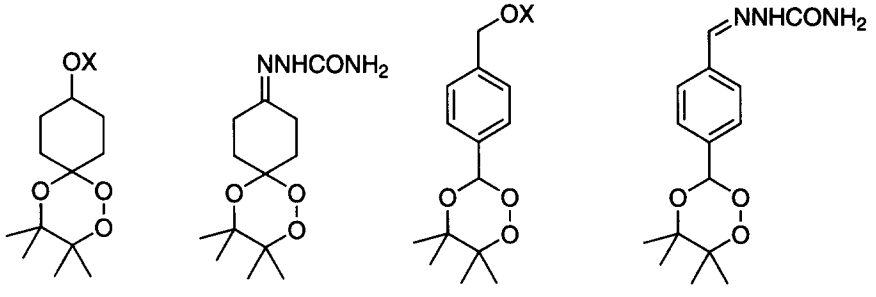
Scheme 2. *Reagents:* i, $Me_2C(OMe)_2$, cat 4-$MeC_6H_4SO_3H$; ii, DMSO,DCC; iii, $Hg(OAc)_2$, 6 mol% $HClO_4$; iv, $NaBH_4$, NaOH

In another example, 2-deoxy-D-glucose was converted into an open chain dithioacetal and thence into the 3,4:5,6-diacetonide aldehyde[11] used to prepare the sugar-1,2,4-trioxanes **8**[8] (20%) and **9**[8] (16%) (scheme 3), which were readily separated by column chromatography. Clearly, partial deprotection takes place under the cyclo-oxymercuriation-reduction conditions. Compounds **8** and **9** were isolated as 1:1 and 2:1 mixtures of diastereoisomers respectively.



Scheme 3. *Reagents:* i, EtSH, HCl; ii, $Me_2C(OMe)_2$, cat 4-$MeC_6H_4SO_3H$; iii, $HgCl_2$,$CaCO_3$; iv, $Hg(OAc)_2$, 6 mol% $HClO_4$; v, $NaBH_4$, NaOH

It was possible to modify the functional groups in the substituents of compounds **3**, **4** and **6** to afford further novel 1,2,4-trioxanes. Thus, reduction of the carbonyl groups using *ethanolic* sodium borohydride (rather than the aqueous reagent used to prepare **3** and **4**) afforded alcohols **10** and **13**,[8] which by reaction with phenyl isocyanate were converted into the corresponding *N*-phenylcarbamates **11**[8] and **14**.[8] Alternatively, condensation with semicarbazide hydrochloride gave the semicarbazones **12**[8] and **15**.[8]



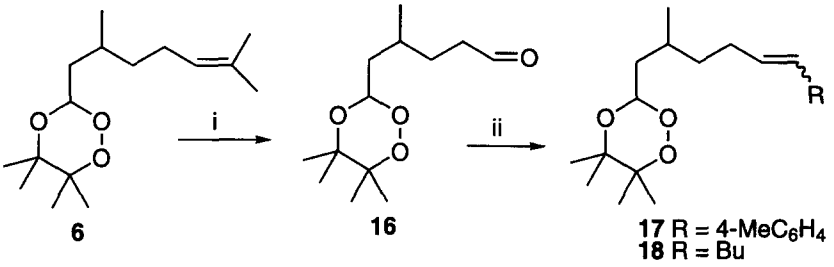
10 X = H
11 X = CONHPh

12

13 X = H
14 X = CONHPh

15

Under more testing conditions, the citronellal derivative **6** underwent oxidative cleavage of the double bond to give aldehyde **16**[8] which by Wittig olefination gave the new alkenyl 1,2,4-trioxanes **17**[8] and **18**[8] (scheme 4).



Scheme 4. *Reagents:* i, $NaIO_4$, 1 mol% OsO_4; ii, $RCH_2PPh_3^+ Br^-$, BuLi

The new 1,2,4-trioxanes **1-5** and **7-15** were evaluated[12] for antimalarial activity *in vitro* against *p. falciparum* and IC_{50} values ranged from 30 ng ml^{-1} to 70 μg ml^{-1}.

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REFERENCES AND NOTES

1. Posner, G.H.; Tao X.L.; Cumming, J.N.; Klinedinst, D.; Shapiro, T.A. *Tetrahedron Lett.*, **1996**, 37, 7225; Jefford, C.W.; Vicente, M.G.H.; Jacquier, Y.; Favarger, F.; Mareda, J.; Millassonschmidt, P.; Brunner, G.; Burger, U. *Helv. Chim. Acta*, **1996**, 79, 1475; Posner, G.H.; Park, S.B.; Gonzalez, L.; Wang, D.; Cumming, J.N.; Klinedinst, D.; Shapiro, T.A.; Bachi, M.D. *J. Am. Chem. Soc.*, **1996**, 118, 3537; Avery, M.A.; Fan, P.; Karle, J.M.; Bonk, J.D.; Miller, R.; Goins, D.K. *J. Med. Chem.*, **1996**, 39, 1885; Wu, W-M.; Yao, Z-J.; Wu, Y-L.; Jiang, Y-F.; Chen, H-B.; Shan, F.; Li, Y. *Chem. Commun.*, **1996**, 2213 and references therein.
2. Bloodworth, A.J.; Shah, A. *J. Chem. Soc., Chem. Commun.*, **1991**, 947.
3. Anderson, J.E.; Bloodworth, A.J.; Shah, A. *J. Chem. Soc., Perkin Trans. 2*, **1993**, 1927.
4. Bloodworth, A.J.; Tallant, *N.A. J. Chem. Soc., Chem. Commun.*, **1992**, 428.
5. Anderson, J.E.; Bloodworth, A.J.; Cai, J.; Davies, A.G.; Tallant, N.A. *J. Chem. Soc., Chem. Commun.*, **1992**, 1689.
6. Bloodworth, A.J.; Johnson, K.A. *Tetrahedron Lett.*, **1994**, 35, 8057.
7. Cai, J.; Davies, A.G. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3383.
8. All new peroxides had consistent ^1H and ^{13}C NMR spectra and satisfactory C and H analyses and/or high resolution mass spectra and gave positive peroxide tests with acidic iron(II) thiocyanate.
9. Lin, A.J.; Li, L.; Andersen, S.L.; Klayman, D.L. *J. Med. Chem.*, **1992**, 35, 1639; Ramu, K.; Baker, J.K. *J. Med. Chem.*, **1995**, 38, 1911.
10. Horton, D.; Nakadate, M.; Tronchet, J.M.J. *Carbohydr. Res.*, **1968**, 7, 56.
11. Rokach, J.; Wang, S. *Tetrahedron Lett.*, **1994**, 35, 6239.
12. Kirby, G.C.; Warhurst, D.C. unpublished work; full details will be published elsewhere.

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