1,2,4-Trioxane *versus* 1,2-Dioxolane Formation in the Mercury(II) Acetate-mediated Cyclisation of Hemiperoxyacetals Derived from Allylic Hydroperoxides

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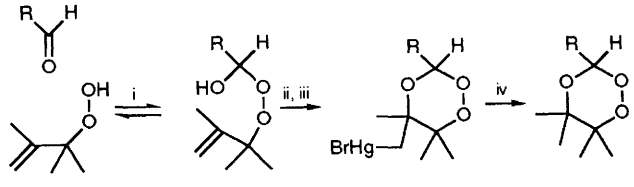
Upon treatment with mercury(II) acetate and perchloric acid catalyst, hemiperoxyacetals derived from 1-phenylprop-2-enyl hydroperoxide afford 3,5,6-trisubstituted 1,2,4-trioxanes with high diastereoselectivity whereas those derived from 3-phenylprop-2-enyl hydroperoxide yield only 3-phenyl-4-mercurio-1,2-dioxolane.

Synthetic routes to 1,2,4-trioxanes continue to attract intense interest because of the potential antimalarial activity of this class of cyclic peroxides.[1,2] Recently we described a new approach to the preparation of 1,2,4-trioxanes based on the mercury(II) acetate-mediated cyclisation of hemiperoxyacetals derived from an allylic hydroperoxide (Scheme 1).[2]

The discovery[3] that some of our products are active *in vitro* against chloroquine-resistant *Plasmodium falciparum* has encouraged us to develop the method further. Thus, we have now extended the reactions with 2,3-dimethylbut-3-en-2-yl hydroperoxide (Scheme 1) to ketones and isolated several hexaalkyl 1,2,4-trioxanes.[3] In the course of investigating the applicability of the method to other allylic hydroperoxides we have discovered and report here (*i*) a useful method for separating an allylic hydroperoxide with a terminal double bond from its non-terminal isomer, (*ii*) a high degree of diastereoselectivity in the formation of 3,5,6-trisubstituted 1,2,4-trioxanes and (*iii*) an isomer-dependent chemospecificity for 1,2-dioxolane *versus* 1,2,4-trioxane formation.

The previously unknown 3-phenylprop-2-enyl (cinnamyl) and 1-phenylprop-2-enyl hydroperoxides were obtained as a mixture† from the perhydrolysis of cinnamyl chloride (Scheme 2). Products with isomer ratios (**1**:**2**) of 85:15 (reagent A) or 40:60 (reagent B) were obtained in yields of 10 and 65% respectively. The isomers could not be separated by simple column chromatography, but a pure sample of the secondary alkyl hydroperoxide **2** (21%) was readily obtained by treating a solution of the mixture in dichloromethane with mercury(II) acetate. This converted the cinnamyl hydroperoxide into 4-acetoxymercurio-3-phenyl-1,2-dioxolane **3** while leaving isomer **2** unaffected; separation was then straightforward. Cinnamyl hydroperoxide could be regenerated from the mercurial by anion exchange to give the corresponding organomercury(II) bromide **3**′, followed by treatment with an equimolar amount of dilute hydrochloric acid.



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

$$PhCH{=}CH{-}CH_2Cl \rightarrow \underset{\mathbf{1}}{PhCH{=}CH{-}CH_2OOH} + \underset{\mathbf{2}}{CH_2{=}CH{-}CH(Ph)OOH}$$

Scheme 2 *Reagents*: (A) 30% H_2O_2, NaOH, MeOH; or (B) 85% H_2O_2 in Et_2O ($MgSO_4$ dried), $AgBF_4$

† All new peroxides had consistent ^1H and ^{13}C NMR spectra and, except for the 1,2,4-trioxanes derived from chloral, satisfactory C and H analyses.

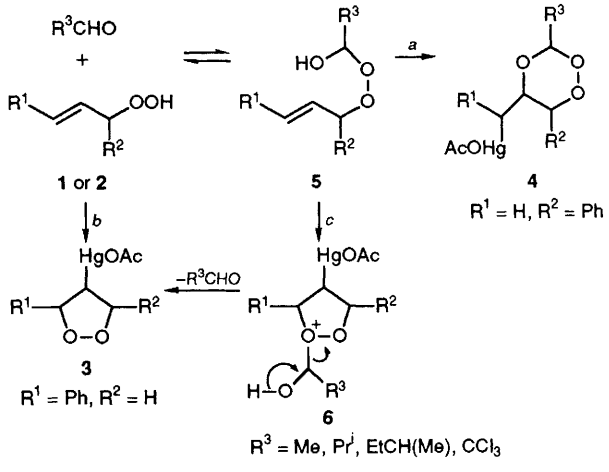
Each isomer was subjected to the conditions (Scheme 1[2]) previously successful in yielding mercuriated 1,2,4-trioxanes. Isomer **2** afforded 40–50% yields of 3,5,6-trisubstituted 1,2,4-trioxanes **4** (Scheme 3, path *a*) but cinnamyl hydroperoxide **1** gave only the 1,2-dioxolane **3**.‡

Attempts to alter the product obtained from isomer **1** by carrying out the reaction at −20 °C with mercury(II) trifluoroacetate were unsuccessful. ^1H NMR studies showed that for a given aldehyde the extent of hemiperoxyacetal formation (typically 75–100%) is very similar for the two hydroperoxides, showing that this is not the origin of the divergent reaction pathways.

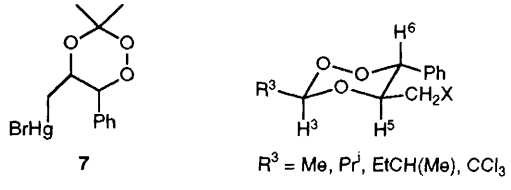
Our results do not permit us to choose between the various ways to explain why 1,2-dioxolane rather than 1,2,4-trioxane is obtained from cinnamyl hydroperoxide. However, it is worth pointing out that the reaction does not necessarily involve free cinnamyl hydroperoxide (Scheme 3, path *b*), since 1,2-dioxolane **3** could alternatively arise directly from hemiperoxyacetal **5** *via* the peroxonium ion[4] **6** (Scheme 3, path *c*).

By using a large excess of acetaldehyde (*ca.* 20 mol equiv.) the yield of 1,2,4-trioxane (**4**′, R^3 = Me) was increased from 42 to 70%. Under similar conditions, the 1,2,4-trioxane **7**† (40%) was obtained from acetone.

Reduction of the mercuriated 1,2,4-trioxanes **4**′ with sodium borohydride[2] cleanly afforded the corresponding 3-alkyl-5-methyl-6-phenyl-1,2,4-trioxanes **8**† (50–75%).



Scheme 3 *Reagents*: $Hg(OAc)_2$, 6 mol% $HClO_4$



‡ The cyclic peroxides were isolated after anion exchange as the corresponding organomercury(II) bromides **3**′ and **4**′.†

Every ring carbon atom of the new 1,2,4-trioxanes (**4′** and **8**) is a chiral centre, but the products were obtained with high diastereoselectivity, the major isomer ranging from 84% (R^3 = Me) to >97% [R^3 = Pr^i, EtCH(Me)§] of the mixture. The major isomer has the chair conformation shown with all three substituents equatorial, as revealed by the large (9 Hz) H^5–H^6 coupling constant for each peroxide and the ^1H and ^{13}C chemical shifts of the 3-methyl group in the R^3 = Me compound. The latter were respectively upfield and downfield of the corresponding values for the next most abundant isomer which differs only in having an axial 3-methyl group.

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§ The major product from 2-methylbutanal was obtained as a 1 : 1 mixture of diastereoisomers because of the additional exocyclic chiral centre.

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