Synthesis of 1,2,4-Trioxanes *via* Intramolecular Oxymercuriation

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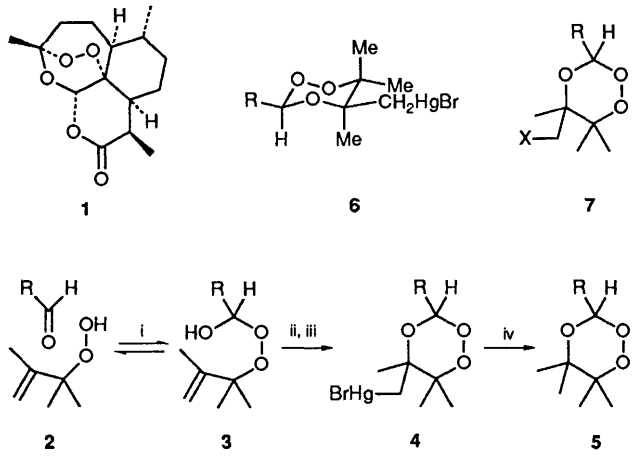
3-Alkyl- and 3-aryl-5,5,6,6-tetramethyl-1,2,4-trioxanes **5** are prepared by reduction of the corresponding 5-bromomercuriomethyl compounds **4** obtained, after anion exchange, by intramolecular oxymercuriation of the hemiperacetals **3** formed from aldehydes and 2,3-dimethylbut-1-en-3-yl hydroperoxide **2**; a 'one pot' procedure omitting the anion exchange and isolation of the organomercury(II) bromide **4** may be used.

Since it became clear that the antimalarial activity of the plant extract qinghaosu **1**[1] is associated with the peroxide moiety it contains, much effort has gone into developing new preparative routes to 1,2,4-trioxanes.[2] We now report the first application of intramolecular oxymercuriation to this synthetic problem. The new method described here utilises readily available starting materials, is easy to carry out, gives good yields, and is potentially very general.

The three-step sequence used to convert allylic hydroperoxide **2** into the 1,2,4-trioxanes **5** is shown in Scheme 1. Hydroperoxide **2** was obtained by tetraphenylporphine-sensitised photooxygenation of 2,3-dimethylbut-2-ene[3] and the crude product, still containing sensitiser, could be used without deleterious effect. The oxymercuriations (5–20 mmol scale) were complete in 1–3 h as judged by the time taken for all the mercury(II) acetate to dissolve, but there were no adverse effects if the reactions were allowed to run overnight. For the aliphatic aldehydes, the organomercury(II) bromides **4**,† obtained after anion exchange,[4] were readily purified by column chromatography (SiO_2, CH_2Cl_2) and were isolated in yields of 35–62%. The reductions[4] proceeded in over 90% yield with little or no side-products, and the 3-alkyl-1,2,4-trioxanes (**5**, R = alkyl)† were purified by column chromatography (SiO_2, CH_2Cl_2) followed by bulb-to-bulb distillation under reduced pressure. For the aromatic aldehydes, however, the crude organomercury(II) bromides **4** contained appreciable amounts of starting aldehyde which could not be removed by simple column chromatography.

† All new 1,2,4-trioxanes gave satisfactory C and H analyses and positive peroxide tests with acidic iron(II) thiocyanate.



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

We have shown that the three steps of the synthesis can be carried out consecutively in the same reaction vessel. In this 'one pot' procedure, the anion exchange was omitted and the solution of organomercury(II) acetate in dichloromethane was treated with NaOH (2 mol dm^{-3}) before commencing the reduction. By reducing the aromatic compounds with ethanolic rather than aqueous $NaBH_4$, the unreacted aldehydes present were converted into the corresponding alcohols which were readily removed by chromatography (SiO_2, CH_2Cl_2), thereby allowing the 3-aryl-1,2,4-trioxanes (**5**, R = aryl)† to be purified. The 'one pot' method is fast and convenient, avoids handling the intermediate organomercurial and gives better overall yields of the mercury-free 1,2,4-trioxanes **5**.

Consistent with the proposed structures, the organomercurials **4** were each obtained as a pair of diastereoisomers and the isomerism was removed by reduction. For each organomercurial **4** there was a predominant isomer (80–90%) which presumably has the *cis* configuration, since this can adopt a conformation **6** with both R and CH_2HgBr groups equatorial.

The presence of the 1,2,4-trioxane ring in compounds **4** and **5** was confirmed by the ^{13}C NMR signals observed for the ring-carbon atoms at δ 94–99 (C-3), 80–84 (C-6) and 75–79 (C-5), and by the ^1H NMR signals of appropriate multiplicity observed for the CHR proton at δ 5.0–5.5 (R = alkyl) or 6.3–6.8 (R = aryl). The spectra of the organomercurials **4** additionally showed characteristic signals for the CH_2HgBr group at δ_C 45–46 [$^1J(^{199}Hg)$ *ca.* 1550 Hz] and δ_H 2.0–2.3 (AB pattern with the downfield doublet showing long range coupling to the *gem* methyl group).

Halogenodemercuriation of compounds **4** should make available the corresponding halogen-containing 1,2,4-trioxanes (**7**, X = halogen). We have confirmed the efficacy of this route by preparing 5-bromomethyl-3,5,6,6-tetramethyl-1,2,4-trioxane (**7**, R = Me, X = Br) in 90% yield by brominolysis of the corresponding organomercurial in dichloromethane.

We are currently investigating the scope of the method with respect to both the unsaturated hydroperoxide and the multiply bonded acceptor which together afford the substrate for mercury(II)-induced cyclisation. We envisage the possibility not only of preparing 1,2,4-trioxanes with a wide range of substituents at the 3-, 5- and 6-positions, but also of preparing larger rings and rings with nitrogen atoms incorporated at the 4-position.

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