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6-Hydroxymethyl-1,2,4,-trioxanes and Derivatives : An Alternative 1,2,4-Trioxane Synthesis from β'γ'-Unsaturated β-Hydroxyhydroperoxides

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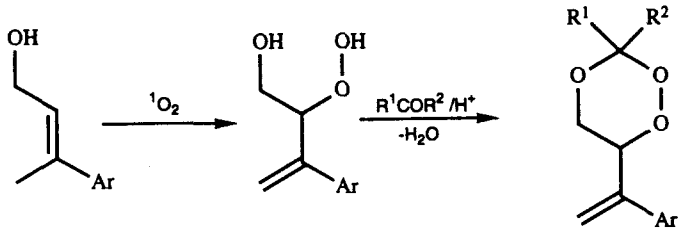
Abstract: Allylic hydroperoxides CH_2:C(Ph)CH(OOH)CH_2OX (X = H, CONHPh, Ac), from regiospecific photooxygenation of allylic alcohols CH_3C(Ph):$CHCH_2$OX, form hemiperoxyacetals with aldehydes or ketones which upon cyclisation with mercury(II) trifluoroacetate then reduction with sodium borohydride diastereoselectively afford 1,2,4-trioxanes with $XOCH_2$ substituents at C-6.

Synthetic routes to 1,2,4-trioxanes have received much attention recently because of the antimalarial properties of the naturally occurring example artemisinin[1]. The first reported preparation of a 1,2,4-trioxane involved the acid-catalysed condensation of a β-hydroxyhydroperoxide with a ketone[2]. This route was unattractive and little used as long as the sole source of the hydroperoxide component was the ring-opening of epoxides with concentrated hydrogen peroxide[2,3]. However, the regiospecific photooxygenation of allylic alcohols provides β-hydroxyhydroperoxides much more conveniently and Singh has exploited this to prepare 6-α-arylvinyl-1,2,4-trioxanes (**3**) which are antimalarial *in vitro*[4] and *in vivo*[5].

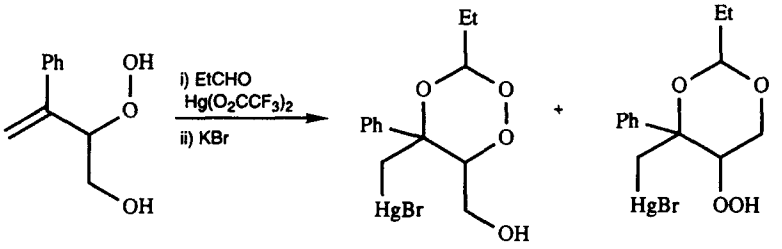


1 **2** **3**

We have shown that allylic hydroperoxides with a terminal double bond readily afford 1,2,4-trioxanes via the cyclooxymercuriation of derived hemiperoxyacetals[6]. Accordingly, we have now applied the cyclooxymercuriation method to hydroperoxides **2** with the aim of obtaining novel 1,2,4-trioxanes with different exocyclic functionality to that in compounds **3**. To succeed in this it has proved necessary to modify the cyclooxymercuriation conditions. Also, in the process of optimising the yield of 1,2,4-trioxanes we have investigated the hitherto unknown photooxygenation of an allylic carbamate and observed regiospecificity parallel to that of the parent alcohol. Herein we present our preliminary results.

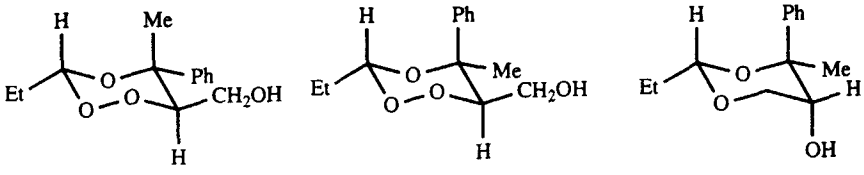
3-Phenylbut-2-en-1-ol (**1**, Ar = Ph) was prepared by lithium aluminium hydride reduction of ethyl 3-phenylbut-2-enoate, itself obtained by $POCl_3$ dehydration of the Reformatsky alcohol from acetophenone and ethyl bromoacetate. The product contained about 25% of the non-conjugated isomer ethyl 3-phenylbut-3-enoate, but this was unaffected by the subsequent photooxygenation conditions and was readily removed chromatographically from the resultant 3-phenyl-2-hydroperoxybut-3-en-1-ol (**2**, Ar = Ph). Modified conditions (tetraphenylporphine sensitiser, dichloromethane, 400W sodium lamp) allowed us to obtain **2**(Ar = Ph) in higher yield (66%) and shorter reaction time (3h) than those reported by Singh[4].

The usual conditions (mercury(II) acetate, perchloric acid catalyst)[6] for cyclooxymercuriation of hemiperoxyacetals derived from allylic hydroperoxides failed when applied to a mixture of **2**(Ar = Ph) and propanal. However, treatment with mercury(II) trifluoroacetate gave, after anion exchange, a 41% yield of a 2:3:3 mixture of three compounds which were identified by NMR spectroscopy as two diastereoisomers of the desired 1,2,4-trioxane **4** and a single diastereoisomer of the 1,3-dioxane **5**.



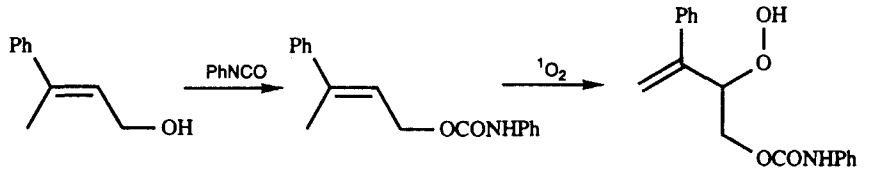
2 (Ar=Ph) **4** **5**

Reductive demercuriation of the mixture with basic sodium borohydride afforded 1,2,4-trioxane **6** (2 diastereoisomers; **6a** major) and 1,3-dioxane **7** which were separated by HPLC. The structures shown were deduced mainly from NOE measurements, consistent results being obtained from both the mercury-free compounds **6** and **7** and the parent organomercurials **4** and **5**. The preferential formation of these diastereoisomers of the 1,2,4-trioxane is readily accounted for whether the cyclooxymercuriation is kinetically or thermodynamically controlled since the transition states are expected to be strongly product-like. In both isomers the bulky groups at C-3 and C-6 are equatorial in the favoured conformation and little steric discrimination can be expected between the CH_2HgBr and phenyl groups.



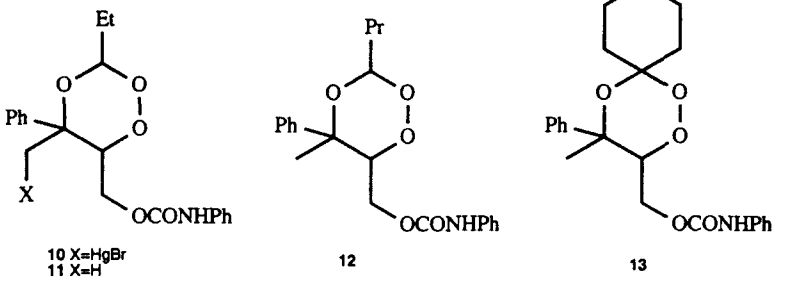
6a **6b** **7**

Clearly the alcohol group of the β-hydroxyhydroperoxide competes with the hydroperoxide group for addition to the aldehyde and cyclooxymercuriation of the resultant hemiacetal gives rise to the unwanted 1,3-dioxane **5**. To avoid this, while at the same time introducing a group which might enhance antimalarial activity[7], we converted the alcohol **1** (Ar = Ph) into the corresponding N-phenylcarbamate **8** (80%) and thence by photooxygenation into the allylic hydroperoxide **9** (70%). As far as we are aware the photooxygenation of allylic carbamates has not been reported before, but our results indicate that the carbamate group is just as effective here as the hydroxyl group in directing the incoming singlet oxygen regiospecifically to the nearest carbon atom of the double bond. This is noteworthy in that Adam and Nestler report that trialkylsilyloxyl, methoxyl and acetoxyl are markedly less regioselective than hydroxyl in related photooxygenations[8].



1 (Ar=Ph) **8** **9**

Cyclooxymercuriation of **9** under parallel conditions to those used for the parent β-hydroxyhydroperoxide **2**(Ar = Ph) gave the *N*-phenylcarbamate analogue (**10**) of 1,2,4-trioxane **4**. No side products were formed now and the yield (54%) of 1,2,4-trioxane was more than double that from the parent alcohol. Three diastereoisomers of **10** were detected in the ratio of 3:3:1. Not surprisingly, the two major isomers had the same configurations as those of the diastereoisomers of **4** (*cf.* **6a** and **6b**). This was shown unambiguously by identity with the products of independent synthesis from **4** and phenyl isocyanate. Borohydride reduction afforded the mercury-free 1,2,4-trioxanes **11** in good yield.

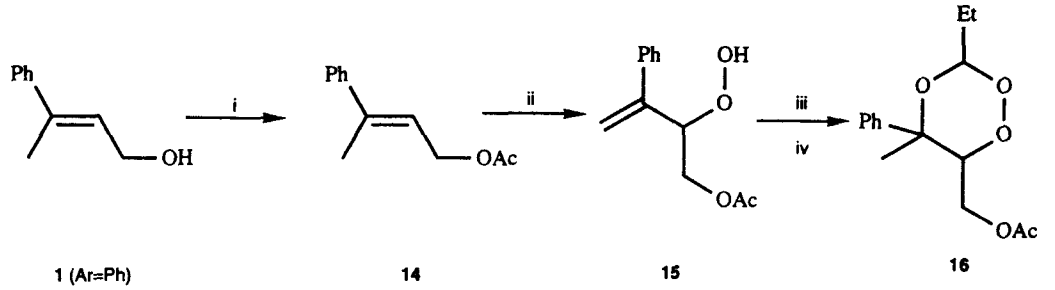


10 X=HgBr
11 X=H **12** **13**

Other 1,2,4-trioxanes were prepared from hydroperoxide **9** without isolating the intermediate mercuriated compounds. The dichloromethane solution from the reaction of butanal, **9** and mercury(II) trifluoroacetate was simply washed with aqueous sodium bicarbonate to remove the trifluoroacetic acid released in the oxymercuriation, then cooled and treated with ice-cold basic sodium borohydride in the usual way. The

resultant 1,2,4-trioxane **12** was isolated after purification by column chromatography in a yield of 37%; as with the ethyl analogue **11**, three diastereoisomers were obtained which were separated by HPLC. By the same procedure the spiro compound **13** was prepared from cyclohexanone in 36% yield showing that the method works with ketones as well as aldehydes.

It proved possible also to carry out parallel chemistry with the related allylic acetate **14**, 1,2,4-trioxane **16** (3 diastereoisomers in the ratio 3:2:2) being isolated in a yield of 35% from the derived hydroperoxide **15**.



1 (Ar=Ph) **14** **15** **16**

Reagents: i) AcOH, DCC, DMAP ii) $^1O_2$ iii) EtCHO, $Hg(O_2CCF_3)_2$ iv) $NaBH_4$, NaOH

By variation of the starting allylic alcohol and the O-protecting group it should prove possible to use this method to prepare a large range of 1,2,4-trioxanes with α-oxyalkyl substituents at C-6.

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