Cycloperoxyhalogenation: an Effective Route to 1,2-Dioxolanes

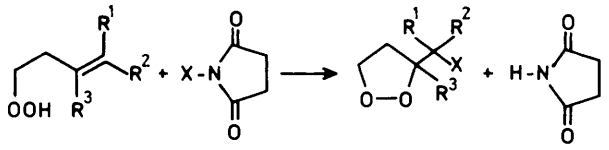
A. J. Bloodworth* and Richard J. Curtis

Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.

Alk-3-enyl hydroperoxides react with *N*-iodosuccinimide or *N*-bromosuccinimide to give iodo- or bromo-alkyl 1,2-dioxolanes with no (iodides) or partial (bromides) stereospecificity; stereospecific cyclization is achieved by using molecular halogen plus pyridine.

Iodocyclization has been increasingly exploited in the synthesis of oxygen- and nitrogen-containing heterocycles.[1] However, as far as we are aware, it has not been applied to the preparation of cyclic peroxides, which are synthetically challenging compounds of interest (i) as models for a growing number of recently isolated physiologically active natural products, (ii) as precursors of theoretically interesting reactive intermediates such as diradicals and radical ions, and (iii) as synthetic intermediates for the preparation of polyoxygenated compounds with stereochemical control at contiguous chiral centres. We report here preliminary results which show that iodocyclization and bromocyclization,[2] of unsaturated hydroperoxides provide an effective and, under appropriate conditions, stereospecific route to 1,2-dioxolanes.

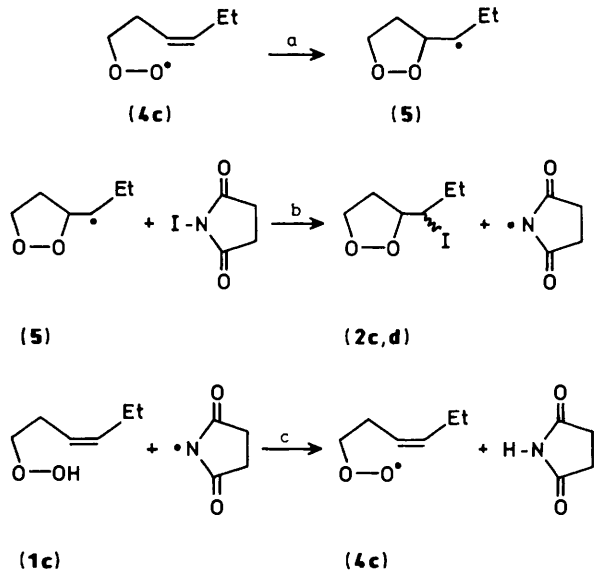
Treatment of unsaturated hydroperoxides (**1a—d**)[3] with 1 equiv. of *N*-iodosuccinimide (NIS) in dichloromethane at



(1) (2) X = I (3) X = Br

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = Me$
c; $R^1 = Et$, $R^2 = R^3 = H$
d; $R^1 = R^3 = H$, $R^2 = Et$

Scheme 1

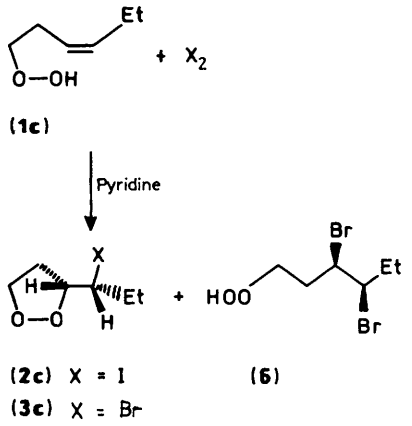


Scheme 2

room temperature for 0.5–3 h followed by washing with aqueous sodium thiosulphate and purification by silica chromatography afforded the 1,2-dioxolanes (**2**)† (Scheme 1) in unoptimised yields of 42—57%. As additional confirmation of structure, compound (**2b**) was prepared independently, by cycloperoxymercuriation[4] of hydroperoxide (**1b**) followed by iodinolysis.[5]

Similar reactions with *N*-bromosuccinimide (NBS) afforded the corresponding bromodioxolanes (**3a**),† (**3b**),[4] and (**3c,d**),[4]‡ but treatment of hydroperoxide (**1b**) with *N*-chlorosuccinimide failed to yield the chlorodioxolane.

We had envisaged that the reactions would proceed *via* iodonium and bromonium ions and thereby lead to stereospecific cyclizations. However, hydroperoxides (**1c**) and (**1d**) each gave the same, *ca.* 1:1, mixture of diastereoisomeric iodides (**2c,d**). Independent experiments showed that neither



Scheme 3

starting hydroperoxides nor product iodides underwent isomerization under the reaction conditions. Thus, a common intermediate is indicated in the iodocyclizations. We suggest that these reactions proceed by a free radical chain mechanism with the propagation steps (illustrated for the *cis*-isomer) in Scheme 2. Initiation, which probably involves electron transfer from the hydroperoxide to the NIS, provides the peroxyl radical (**4**) which is known[3] to cyclize to alkyl radical (**5**). The same radical (**5**) will arise from the *trans*-hydroperoxide.

Mixtures of diastereoisomeric dioxolanes were also produced in the corresponding NBS reactions, but *cis*-hydroperoxide (**1c**) gave predominantly (*ca.* 75%) the *threo*-isomer and *trans*-hydroperoxide (**1d**) gave mainly (*ca.* 80%) the *erythro*-isomer, the stereochemistries being identified by comparison of ^{13}C n.m.r. data with those for authentic *threo*-bromide prepared from (**1c**) by cycloperoxymercuriation and brominolysis in pyridine.[4]‡ We take this to indicate that stereospecific *trans*-addition *via* bromonium ion here competes with the free radical chain process, presumably because of a smaller rate constant for reaction of alkyl radical (**5**) with NBS compared with that for reaction with NIS (Scheme 2, step b).[6] Support for this interpretation came from experiments in which 5—20 mol% of the efficient radical trap galvinoxyl was included in the reaction mixture. The galvinoxyl was consumed within *ca.* 5 min, and t.l.c. showed that only one bromodioxolane was produced during this period, whereas both were obtained when galvinoxyl was absent.

Stereospecific cyclization was achieved by treating the hydroperoxides (**1c**) and (**1d**) with molecular iodine or bromine in dichloromethane in the presence of 1 equiv. of pyridine (*e.g.* Scheme 3). However, in the bromine reaction the major product (*ca.* 60 mol%) was the corresponding dibromohydroperoxide (**6**). Nevertheless, this represents an attractive route since the two products are readily separated chromatographically and the alternative stereospecific synthesis of (**3**), by treating the cycloperoxymercurial with bromine in pyridine,[4] in our hands is problematical and gives low yields. The iodocyclization was accompanied by the formation of a small amount of an unidentified compound which was again easily removed by chromatography. There was no evidence of reduction of the hydroperoxide by iodide since the corresponding alcohol yielded 2-ethyl-3-iodotetrahydrofuran upon treatment with iodine and pyridine, yet this was not obtained in the hydroperoxide reaction.

Experiments with pent-4-enyl hydroperoxide indicate that halogenocyclization is much less successful for preparing 1,2-dioxanes, since the corresponding tetrahydrofurans were

† All new compounds had satisfactory elemental analyses and mass spectra and ^{1}H and ^{13}C n.m.r. spectra consistent with the proposed structures.

‡ Although our n.m.r. data for (**3c,d**) agree numerically with those of Porter *et al.*,[4] we find that the assignments to *erythro*- and *threo*-configurations must be interchanged.

obtained as the major products, possibly through the intervention of *gem*-dialkylperoxonium ions.[7]

We thank the S.E.R.C. and Interox Chemicals Ltd. for financial support through a CASE studentship.

Received, 6th October 1988; Com. 8/03989E

References

1 Recent examples include: Y. G. Kim and J. K. Cha, *Tetrahedron Lett.*, 1988, **29**, 2011; M. Labelle, H. E. Morton, Y. Guindon, and J. P. Springer, *J. Am. Chem. Soc.*, 1988, **110**, 4533; P. A. Hunt, C. May, and C. J. Moody, *Tetrahedron Lett.*, 1988, **29**, 3001.

2 Isolated examples of cycloperoxybromination have been reported: L. A. Paquette, R. V. C. Carr, and F. Bellamy, *J. Am. Chem. Soc.*, 1978, **100**, 6764; E. Bascetta and F. D. Gunstone, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2207.

3 N. A. Porter, M. O. Funk, D. Gilmore, R. Isaac, and J. Nixon, *J. Am. Chem. Soc.*, 1976, **98**, 6000.

4 J. R. Nixon, M. A. Cudd, and N. A. Porter, *J. Org. Chem.*, 1978, **43**, 4048.

5 A. J. Bloodworth, K. J. Bowyer, and J. C. Mitchell, *J. Org. Chem.*, 1986, **51**, 1790.

6 A. G. Davies, B. P. Roberts, and J. M. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1972, 2221.

7 A. J. Bloodworth, T. Melvin, and J. C. Mitchell, *J. Org. Chem.*, 1988, **53**, 1078.