A New Easy Method for the Synthesis of Cyclic Halogenoethers and Halogenolactones

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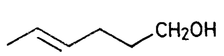
Oxidation of halogen salts with *m*-chloroperbenzoic acid in the presence of 18-crown-6 and of suitable hydroxy or carboxy alkenes leads readily to high yield production of cyclic halogenoethers or halogenolactones.

Cyclic halogenoethers and halogenolactones are of considerable inherent interest and synthetic utility.[1,2] We report a new route to these types of compounds, which is preparatively simple, fast, and leads to the desired products in good to excellent yields. Most procedures described hitherto employ either molecular halogen, *N*-halogeno reagents, such as

Table 1. Cyclic halogenoethers and halogenolactones.

Starting material	Product	(Yield)	Physical data[a,b,c]	Lit. ref. (yield)
(1)	**(2)**	X = I (95%)	m/z 226(M^+), 99 (base peak); δ 1.89 (3H, d)[d]	4[e]
		X = Br (91%)	δ 1.69 (3H, d)[d]	4[e]
		X = Cl (55%)	δ 1.47 (3H, d)[d]	5[e]
(3)	**(4)**	(75%)	δ identical to literature values	6 (17%)
(5)	**(6)**	X = I (70%)	m/z 226(M^+); δ 0.99 (3H, t), 1.59 (2H, m), 2.39 (2H, m), 3.90 (4H, m)	—
		X = Br (65%)	δ 0.99 (3H, t), 1.59 (2H, m), 2.34 (2H, m), 3.95 (4H, m)	7 (40—60%)
(7)	**(8)**	(80%)	m/z 111($M^+ - \text{Br}$, base peak); δ 3.75 (2H, m), 4.31 (1H, br. d), 4.54 (1H, d)	—
(9)	**(10)**	X = I (85%)	δ 5.21 (1H, d), 4.50 (1H, br. d); 1780 cm^{-1}; m.p. 37—38 °C (lit. 35—36 °C)	8 (95%)
		X = Br (78%)	m/z 204.206(M^+), 175.177, 125($M - \text{Br}$); δ 5.07 (1H, d), 4.45 (1H, br. d); 1780 cm^{-1}	—
(11) $[\alpha]_D$ −66.2°[f]	**(12)**	(75%)	δ 1.45 (3H, s), 1.71 (3H, d, J 2 Hz), 3.34 (2H, s), 4.35 (1H, d), 5.25 (1H, br. s);[g] $[\alpha]_D$ −17.7°	—
(13)	**(14)**	X = I (35%)	δ 1.20, 1.22 (9H, 2 × s), 4.24 (1H, m)[g]	—
		X = Br (30%)	δ identical to literature values	9 (34%)
(15)	**(16)**	X = I (92%)	m/z and δ identical to lit. values	10 (73%)
		X = Br (85%)	m/z 220, 218(M^+); δ 3.71 (3H, m), 4.51 (1H, d, J 6 Hz)[h]	—
		X = Cl (60%)	m/z 158(M^+); δ 3.61 (3H, m), 4.30 (1H, br. m)[h]	—
(17)	**(18)**	(86%)[i]	m/z 153($M^+ - 127$); δ 1.28 (3H, s), 1.91 (6H, s), 3.55 (1H, m), 4.89—5.38 (2H, m), 6.03 (1H, dd, J 14.3, 10 Hz)[j]	—

[a] Satisfactory elemental analyses were obtained for all new compounds which could be distilled without decomposition. [b] N.m.r. data are in $CDCl_3$. [c] No hydroxy group absorptions were observed in the i.r. spectra of the products. [d] *Cf.* ref. 11 for comparable differences between chemical shifts of methyl groups α to halogens. [e] No yield reported. [f] Rotation in ethanol. [g] N.m.r. spectrum comparable to that of bromine analogue (ref. 9). [h] N.m.r. spectrum of bromo and chloro compounds comparable to that of iodo analogue (ref. 10). [i] A 15 : 1 mixture of isomers. [j] N.m.r. data of major isomer.



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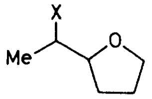

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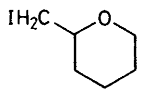

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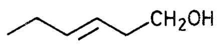

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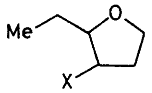

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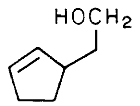

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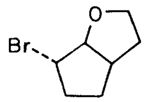

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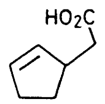

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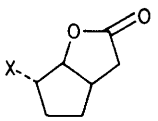

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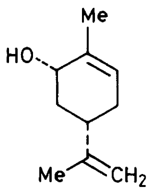

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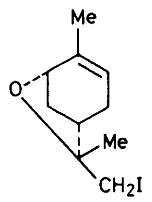

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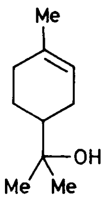

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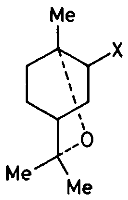

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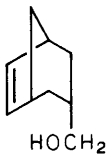

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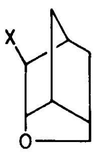

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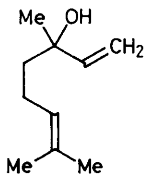

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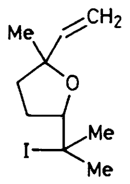

(18)

N-bromosuccinimide or, in the case of lactones, thallium containing reagents.[1—3]

In a typical reaction hex-4-en-1-ol (**1**) (10 mmol), 18-crown-6 (1 mmol), and sodium iodide (50 mmol) were stirred in CH_2Cl_2 (25 ml) at room temperature for 5 min. The mixture was cooled to 0 °C and a solution of *m*-chloroperbenzoic acid (11 mmol) in CH_2Cl_2 (20 ml) was added dropwise with stirring over 5 min. The reaction mixture was vigorously stirred for an additional 5 min, and was then worked up. The reaction product was purified by medium pressure liquid chromatography on a silica column (elution with 1 : 99, diethyl ether to petroleum b.p. 60—80 °C), to yield 2-(1-iodoethyl)-tetrahydrofuran (**2**) in a 95% yield. The products of a number of parallel reactions are described in Table 1. In the preparation of cyclic chloroethers the addition of the peracid has to be made over a longer period (30—45 min) with powerful stirring.

The reactions above described do not take place in the absence of a crown ether. Although 18-crown-6 is generally used with potassium salts, in the present reactions the sodium salts led to a higher yield.

No epoxide formation is observed under the conditions described above even in the presence of double bonds which do not participate in the reaction. In those cases where isomers can be formed on the olefinic carbons participating in the reaction we observe the formation of mainly one isomer, presumably owing to the expected *anti* addition to the double bond generally accepted for this type of reaction.

We assume that the halide anion is oxidized by the peroxy acid to a positive halogen species (possibly forming an acyl hypohalite) which attacks the double bond leading to a halonium ion; *anti* cyclization by suitably placed alcoholic or carboxylic groups leads to cyclic ethers or lactones. The suggested ready formation of a positive halogen species should make possible the introduction of various new synthetic methodologies.

Received, 3rd April 1984; Com. 473

References

1 *E.g.* for halogenolactones: P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, 1978, **100**, 3950; M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, 1979, **8**, 171; A. R. Chamberlin, M. Dezube, P. Dussault, and M. C. McMills, *J. Am. Chem. Soc.*, 1983, **105**, 5819; P. Kočovský and R. Tureček, *Tetrahedron*, 1983, **39**, 3621; S. Batmangherlich, A. H. Davidson, and G. Procter, *Tetrahedron Lett.*, 1983, **24**, 2889.

2 *E.g.* for halogenoethers: R. A. Johnson, F. H. Lincoln, J. L. Thomson, E. G. Nidy, S. A. Mizsak, and U. Axen, *J. Am. Chem. Soc.*, 1977, **99**, 4184; N. Whittaker, *Tetrahedron Lett.*, 1977, 2805; E. J. Corey, I. Szekely, and C. S. Shiner, *ibid.*, 1977, 3529; S. D. Rychnovsky and P. A. Bartlett, *J. Am. Chem. Soc.*, 1981, **103**, 3963; M. Khan, M. Hashmi, F. Ahmad, and S. M. Osman, *J. Chem. Soc., Chem. Commun.*, 1983, 1057.

3 R. C. Cambie, K. S. Ng, P. S. Rutledge, and P. D. Woodgate, *Aust. J. Chem.*, 1979, **32**, 2793.

4 L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1950, 1707.

5 A. Lebouc, *Bull. Soc. Chim. Fr.*, 1974, 1559.

6 J. W. Lown and A. V. Joshua, *Can. J. Chem.*, 1977, **55**, 122.

7 H. Normant, *C. R. Acad. Sci.*, 1948, **226**, 1734.

8 R. K. Hill and A. G. Edwards, *Tetrahedron*, 1965, **21**, 1501; J. D. Fissekis and B. A. Markert, *J. Org. Chem.*, 1966, **31**, 2945.

9 F. Bellesia, R. Grandi, U. M. Pagnoni, and R. Trave, *J. Chem. Soc., Perkin Trans. 1*, 1979, 851.

10 P. J. Kropp, P. R. Worsham, R. I. Davidson, and T. H. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 3972.

11 L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon Press, Oxford, 1969, p. 164.