

SYNTHESIS AND X-RAY CRYSTAL STRUCTURE OF A STABLE α -CHLOROXYETANE

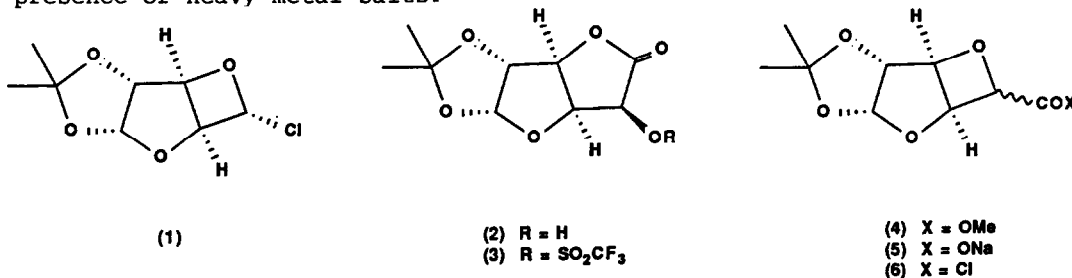
G. W. J. Fleet,^a J. C. Son,^a J. M. Peach^a and T. A. Hamor^b

^aDyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY
^bChemical Crystallography Laboratory, 9, Parks Road, Oxford OX1 3PD

The Barton modification of the Hunsdiecker reaction is the key step in the preparation of 3,5-anhydro-5R-chloro-1,2-O-isopropylideneoxylofuranose (1), a stable α -chlorooxetane.

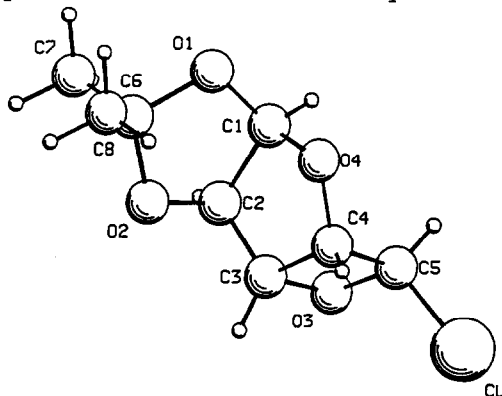
In model studies directed towards the synthesis of oxetane nucleosides, the potential of nucleophilic displacement reactions of α -halooxetanes by nucleoside bases is being evaluated.¹ α -Halooxetanes, other than multihalosubstituted derivatives, are generally described as unstable compounds.² This paper reports the preparation of 3,5-anhydro-5R-chloro-1,2-O-isopropylideneoxylofuranose (1), a stable α -chlorooxetane, by the Barton modification of the Hunsdiecker reaction.

Esterification of the protected lactone (2) with trifluoromethane sulphonic anhydride, followed by treatment of the resulting triflate (3) with potassium carbonate in methanol, yields the epimeric oxetane carboxylic esters (4);³ this ring contraction may readily be performed on a 10 g scale to produce (4) in an overall yield of 68% from the alcohol (2). The esters (4) are rapidly hydrolysed at room temperature by aqueous sodium hydroxide in methanol to give the epimeric sodium salts (5). All attempts to prepare the chlorooxetane (1), or the corresponding bromo compound, by the Hunsdiecker reaction⁴ - including the use of other heavy metal salts such as mercury⁵ and lead⁶ - were completely unsuccessful; it is clearly undesirable to attempt to prepare α -haloethers in the presence of heavy metal salts.



Recently, the formation of carbon radicals by the mild pyrolysis of mixed anhydrides derived from carboxylic acids and suitable thiohydroxamic acids (such as N-hydroxypyridine-2-thione) has been demonstrated to be an exceptionally powerful synthetic procedure;⁷ the thermal decomposition of such anhydrides in tetrachloromethane or bromotrichloromethane produces the corresponding nor-chlorides or bromides in good to excellent yields.⁸ Accordingly, the sodium salts (5) were converted to the corresponding acid chlorides (6) by treatment with oxalyl chloride which were added to a refluxing suspension of the sodium

salt of N-hydroxypyridine-2-thione in tetrachloromethane. The crude product was purified by flash chromatography to give 3,5-anhydro-5R-chloro-1,2-O-isopropylideneoxylofuranose (1), m.p. 62°-63°C, $[\alpha]^{20} +92^\circ$ (c, 1.14 in CHCl_3) in 27% yield from the methyl esters (4) [18% overall yield from (2)].⁹



Crystal structure of 3,5-anhydro-5R-chloro-1,2-O-isopropylideneoxylofuranose (1)

The structure of (1) was consistent with spectroscopic and microanalytical data obtained and was confirmed by X-ray crystallography.¹⁰ The crystal structure of (1) shows that the oxetane ring is planar with chlorine atom occupying the exo site of C-5; the C-Cl bond length of 1.772(4)Å is normal for chlorine bonded to sp^3 hybridised carbon.¹¹

This paper reports the first crystal structure of, and describes the preparation of, a highly functionalised chiral stable α -chlorooxetane; we are currently attempting to determine the scope of this reaction and to optimise the yields for the synthesis of this class of stable α -haloethers.¹²

REFERENCES

1. G. W. J. Fleet, J. C. Son, K. Vogt, J. M. Peach and T. A. Hamor, Tetrahedron Lett., 1988, 29, accompanying paper.
2. S. Searles in Comprehensive Heterocyclic Chemistry, (ed. W. Lwowski), Vol. 7, p. 390, Oxford, 1984.
3. G. N. Austin, G. W. J. Fleet, J. M. Peach, K. Prout and J. C. Son, Tetrahedron Lett., 1987, 28, 4741.
4. R. G. Johnson and R. K. Ingham, Chem. Rev., 1956, 56, 219; C. V. Wilson, Org. Reactions, 1957, 7, 332.
5. J. C. Cristol and W. C. Firth, J. Org. Chem., 1961, 26, 280.
6. D. D. Tanner, G. C. Gidley, N. Das, J. E. Rowe and A. Potter, J. Am. Chem. Soc., 1984, 106, 5261.
7. D. H. R. Barton, D. Bridon, I. Fernandez-Picot and S. Z. Zard, Tetrahedron, 1987, 43, 2733 and references cited therein.
8. D. H. R. Barton, D. Crich and W. B. Motherwell, Tetrahedron, 1985, 41, 3901.
9. When the same sequence of reactions was performed with bromotrichloromethane as the solvent for the final step, the 5-bromo analogues of (1) were isolated as an epimeric mixture which could not be separated by flash chromatography.
10. Data for (1): ^1H NMR (CDCl_3) δ 1.40 (3H, s), 1.43 (3H, s), 4.77 (1H, d), 5.05 (1H, d), 5.45 (1H, d), 5.96 (1H, d) and 6.24 (1H, d). ^{13}C NMR (CDCl_3) δ 27.09 (q), 27.83 (q), 82.76 (d), 85.50 (d), 85.91 (d), 98.75 (d), 108.99 (d) and 114.67 (s). m/z (CI, NH_3): 224 ($\text{M}+\text{NH}_4^+$, 2%), 113 (100%).
11. The details of the crystal structure of (1) will be given in a full paper.
12. We acknowledge an SERC postdoctoral fellowship (to JCS). TAH was on leave from Department of Chemistry, University of Birmingham, UK. We are grateful to Drs. Myers, Newton and Wallis of Glaxo Group Research for help in this project.