Tetrahedron Letters,Vol.27,No.29,pp 3417-3420,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

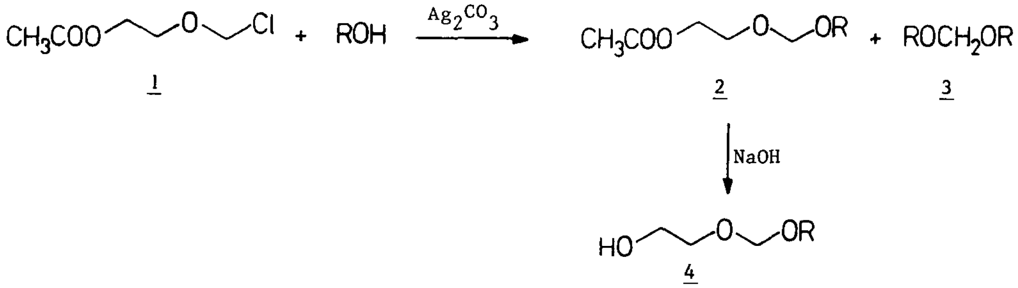
NOVEL REACTIVITY OF 2-(CHLOROMETHOXY)ETHYL ACETATE

David J. Aitken, Lilias Rees, Colin J. Suckling, and Hamish C.S. Wood
Department of Pure and Applied Chemistry, University of Strathclyde,
295, Cathedral Street, Glasgow G1 1XL, Scotland

Abstract: 2-(Chloromethoxy)ethyl acetate reacts with alcohols in the presence of silver carbonate to produce 2-(alkoxymethoxy)ethyl acetates and bis(alkoxy)methanes. A mechanism which involves neighbouring group participation of a chloromethyl ether oxygen atom is proposed to account for the formation of the latter products.

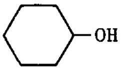
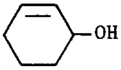
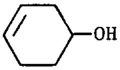
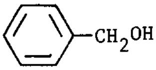
In recent years, 2-(chloromethoxy)ethyl acetate, 1[1] and other related compounds[2,3] have been used in the preparation of acyclic nucleoside analogues, several of which have potent anti-viral activity.[3] We have extended the synthetic applications of 1 to prepare O-glycoside fragments and in the course of our work have discovered a novel reaction of this compound.

Treatment of 1 with an alcohol and silver carbonate in dichloromethane produced not only the expected 2-(alkoxymethoxy)ethyl acetate, 2, but, in addition, significant amounts of the bis(alkoxy)methane, 3. For practical reasons it was found convenient in most cases to convert the acetate, 2, into the corresponding alcohol, 4, before isolation and characterisation of the reaction products (Scheme 1). Typical examples are presented in Table 1. Our preliminary experiments indicate that the analogous reaction using phenol instead of an aliphatic alcohol gives a mixture of products which is difficult to separate. Such a reaction may be complicated by an aromatic-ring substitution reaction.



Scheme 1

Table 1

Entry	Alcohol	Yield^{a,b} of 4,%	Yield^{a,b} of 3,%
1		28.0^{c}	25.2
2		24.9	14.8
3		26.1	28.1
4		42.9	15.2

a Isolated yields are quoted. Additionally, unreacted alcohol (c.30%) was recovered from the reaction.

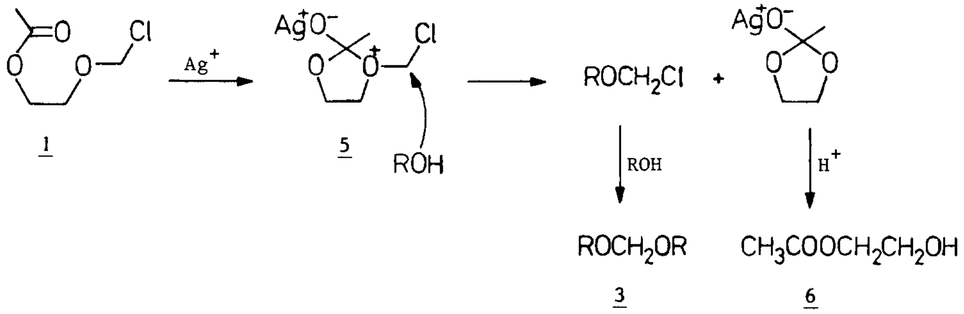
b All new compounds showed satisfactory spectroscopic and microanalytical data.

c Reaction products were separated without subsequent hydrolysis of the ester; this figure refers to yield of 2 .

To investigate the origin of the bis(alkoxy)methanes, 3, a control experiment was carried out in which an alcohol, silver carbonate and dichloromethane were mixed in the absence of 1. No bis(alkoxy)methane was formed, thus it is unlikely that such material can have arisen in our reactions by the double nucleophilic displacement reaction of a solvent molecule, as has been observed under basic phase-transfer conditions.[4] It was concluded, therefore, that 1 was the source of the acetal carbon atom of 3.

We have established that 2 is a terminal product of the reaction, thus it appears that nucleophilic substitution at the chloromethyl ether carbon of 1 is not favoured after cleavage of the carbon-chlorine bond. We have no unequivocal evidence of the mechanism, but it is probable that the silver ion converts 1 into a reactive, cyclic oxonium intermediate, 5 (Scheme 2). Ethylene glycol monoacetate, 6, has been detected in crude reaction products, which is consistent with the proposed mechanism.

Neighbouring group participation of ether oxygen in which a cyclic oxonium intermediate is formed has been well documented[5] for solvolysis rate enhancements and rearrangements of alkoxyalkyl esters and alkoxyacyl chlorides. The reaction mechanism proposed here for the formation of bis(alkoxy)methanes represents, to our knowledge, the first example of neighbouring group participation of a chloromethyl ether oxygen, and is of particular interest in view of the ease with which such compounds normally undergo straightforward nucleophilic substitution.



Scheme 2

Typical Procedure

To a stirred solution of alcohol, (22.5 mmol), in dichloromethane, (65 ml), was added active 4A molecular sieves, (c. 1 g), and silver carbonate, (8.0 g, 29 mmol), followed by 1 (3.43 g, 22.5 mmol). This mixture was kept at ambient temperature in the dark for 24-48 h, after which time it was filtered and stripped of solvent. The resulting oil was distilled *in vacuo* to remove the volatile fractions containing unreacted alcohol and **6**. The residue was dissolved in methanol and treated with an equivalent volume of 0.5 M aq. sodium hydroxide solution. This mixture was heated under reflux for 2 h, cooled, diluted with water and extracted with ether. The extracts were evaporated to leave an oil which, after chromatography on silica gel, yielded the two major products 3 and 4. These materials were further purified by distillation *in vacuo*.

Acknowledgement

One of us (DJA) thanks the Carnegie Trust for the Universities of Scotland for the award of a Scholarship.

References

1. L. Yu. Tychinskaya and V.L. Florent'ev, Bioorg. Khim., 1978, 4, 1461; M. Ya. Karpeiskii, S.M. Mikhailov, A.S. Tsieminya, A.A. Ziederman, I.M. Kravchenko, M. Yu. Lidak and R.A. Zhuk, Khim. Geterosikl. Soedin., 1980, 1541; W.O. Foye, J.M. Kauffman and Y. HoKim, J. Heterocycl. Chem., 1982, 19, 497; L. Colla, R. Busson, E. DeClerq and H. Vanderhaeghe, Eur. J. Med. Chem.-Chim. Ther., 1982, 17, 569; Z. Kazimierczuk, R. Stolarski and D. Shugar, Acta Biochim. Pol., 1984, 31, 33.
2. H.J. Schaeffer, S. Gurwara, R. Vince and S. Bittner, J. Med. Chem., 1971, 14, 367; J.R. Barrio, J.D. Bryant and G.E. Keyser, J. Med. Chem., 1980, 23, 572; A.C. Schroeder, R.G. Hughes, Jr. and A. Bloch, J. Med. Chem., 1981, 24, 1078; J.L. Kelley, J.E. Kelsey, W.R. Hall, M.P. Krochmal and H.J. Schaeffer, J. Med. Chem., 1981, 24, 753; H.M. Abrams, L. Ho and S.H. Chu, J. Heterocycl. Chem., 1981, 18, 947; A. Parkin and M.R. Harnden, J. Heterocycl. Chem., 1982, 19, 33; M.J. Robins and P.W. Hatfield, Can. J. Chem., 1982, 60, 547.
3. H.J. Schaeffer, L. Beauchamp, P. de Miranda, G.B. Elion, D.J. Bauer and P. Collins, Nature, 1978, 272, 583; T.A. Krenitsky, W.W. Hall, P. de Miranda, L.M. Beauchamp, H.J. Schaeffer and P.D. Whiteman, Proc. Natl. Acad. Sci. USA, 1984, 81, 3209; M.J. Robins, P.W. Hatfield, J. Balzarini and E. DeClerq, J. Med. Chem., 1984, 27, 1486.
4. E.V. Dehmlov and J. Schmidt, Tetrahedron Lett., 1976, 95.
5. B. Capon, Quart. Rev., 1964, 18, 45; B. Capon and S.P. McManus in "Neighbouring Group Participation", Plenum Press, New York, 1976, p. 125-194.

(Received in UK 8 May 1986)