Tetrahedron Letters,Vol.28,No.5,pp 523-526,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

PHENYLSULFENYL CHLORIDE/N,N-DIISOPROPYLETHYLAMINE: A USEFUL REAGENT FOR CYCLIC ETHER FORMATION (SULFENYLETHERIFICATION)

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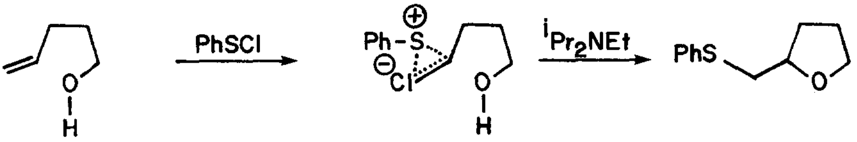
Summary: A general method for the formation of cyclic ethers and lactones is described. The procedure employs phenylsulfenyl chloride and N,N-diisopropylethylamine to generate an episulfonium ion intermediate from which the cyclic products arise by internal nucleophilic displacement.

Secondary metabolites containing cyclic ethers, particularly tetrahydrofuran rings, are widely dispersed in nature and thus there is considerable interest in devising viable synthetic methods for their construction.[1,2]

Recently, during the development of a procedure for the controlled epimerization of vinyl *tertiary*-alcohols we discovered that the norbornene-alcohol 19 afforded the functionalized oxetane 20 upon treatment of the lithium alkoxide with PhSCl at -78°C.[3] (Table, entry 8) It seemed likely that the oxetane arose *via syn* addition of a polarized sulfenate ester intermediate of type 4 to the double bond. However, 4 failed to form 3 at temperatures up to 80°C.[4] In contrast to this behaviour, we wish to report that intramolecular cyclization



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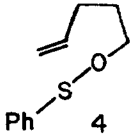

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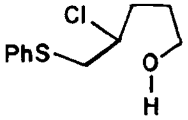

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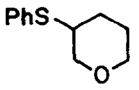

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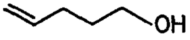
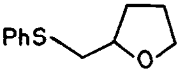
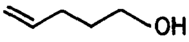
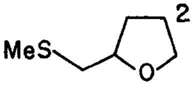
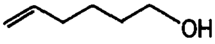
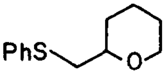
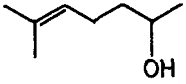
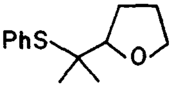
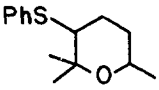
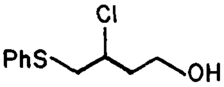
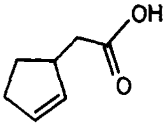
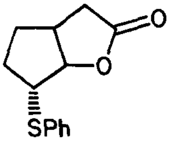
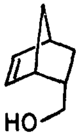
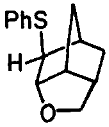
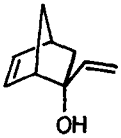
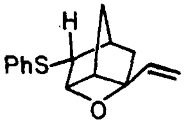
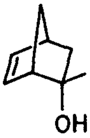
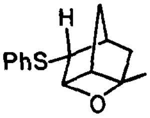
could be achieved in good yield when unsaturated alcohols (or acids) were treated with phenyl or methylsulfenyl chloride in acetonitrile at room temperature (21°C) followed by the addition of N,N-diisopropylethylamine. These studies compliment the recent report[2] which employed dimethyl(methylthio)sulfonium fluoroborate for this type of transformation and provide access to the sulfur analogue of selenium based methods for cyclic etherification and lactonization.[5-7]

The substituted tetrahydrofuran **3** was formed from **1** in 84% yield *via* the preferred 5-*exo-tet* cyclization of **2** (entry 1).[8,9] A 6-*endo-tet* ring closure to the pyran **6** was not observed, although six membered rings were formed exclusively when the alternative choice was a 7-*endo-tet* ring closure (entry 3). The more highly substituted olefin **10** (entry 4) gave a 1:1 mixture of the two cyclic ethers **11** and **12**. Cyclization did not occur to a simple oxetane with **13** (entry 5) but intermolecular attack by the chlorine nucleophile took precedence. As expected from related studies[10] the procedure also holds promise for sulfenyllactonization (entry 6) and for etherification in other more complex unsaturated systems (entry 7). The *trans* coupling constant (J = 2.5 Hz) between the *endo* and *exo* hydrogens established the stereochemistry of **18**.[11] Unfortunately the method does not appear to provide a general preparative entry into functionalized norborane-oxetanes of type **22**. An oxetane was not isolated from the reaction of **21** with PhSCl/$^{i}Pr_2NEt$ but instead a low yield (17%) of an unstable aldehyde (2-thiophenyl-(3-methyl-3-cyclopentenyl)ethanal) was obtained. However, **22** was the major product (20%, $J_{exo-exo}$ = 5.0 Hz) accompanied by the ring opened thio-aldehyde (14%) when the lithium alkoxide of **21** was reacted with phenylsulfenyl chloride. This sulfenate ester cycloaddition failed with **17** and thus requires a reactive norborane double bond in which the sulfenate ester is aligned in the correct geometry.

The method is straightforward and can be readily conducted as follows: Phenylsulfenyl chloride [prepared from sulfuryl chloride (0.24 mL, 2.96 mmol) and diphenyldisulfide (0.634 g, 2.90 mmol) in dry acetonitrile (10 mL) containing dry pyridine (2 drops)] was added dropwise to a magnetically stirred solution of 4-penten-1-ol (0.50 g, 5.81 mmol) in dry acetonitrile (10 mL) maintained in a nitrogen atmosphere at room temperature (21°C). Stirring was continued for 0.5 h after addition was complete, a solution of N,N-diisopropylethylamine (1.20 mL, 6.89 mmol) in acetonitrile (5 mL) was added, and the reaction mixture stirred for a further 0.5 h. The reaction mixture was concentrated under reduced pressure, extracted with ether (50 mL), the combined ether extracts washed with water (3 x 50 mL), saturated aqueous ammonium chloride (2 x 25 mL), dried, filtered, concentrated, and the product purified by chromatography (silica gel, 5% ethyl acetate/*n*-hexane) to give 2-phenylthiomethyltetrahydrofuran (**3**) (0.94 g, 84%).

These results are consistent with the initial formation of an episulfonium ion intermediate of type **2**[12] which is displaced by the internal oxygen nucleophile, although in unfavourable cases direct attack by chlorine can also compete to give Markovnikov addition products of type **5**. Recently Williams and Phillips have reported an alkylation-solvolysis

TABLE

Entry	Reactant	Reagent	Product	Isolated Yield
1	 1	PhSCl $^{i}Pr_2NEt$	 3	84%
2	 1	MeSCl $^{i}Pr_2NEt$	 7	86%
3	 8	PhSCl $^{i}Pr_2NEt$	 9	85%
4	 10	PhSCl $^{i}Pr_2NEt$	 11 1 : 1  12	84%
5	 13	PhSCl $^{i}Pr_2NEt$	 14	97%
6	15 	PhSCl $^{i}Pr_2NEt$	16  cf.,2,10	84%
7	17 	PhSCl $^{i}Pr_2NEt$	18 	83%
8	19 	BuLi PhSCl	20 	60%
9	21 	BuLi PhSCl	22 	20%

route to substituted tetrahydrofurans *via* sulfonium and oxonium ion intermediates.[13] The sulfur functionality is generally useful for further synthetic manipulations. Thus after oxidation of the sulfur moiety it may be reductively removed, alkylated at the adjacent carbon, or eliminated to give a substituted alkene, depending upon the ultimate synthetic objective. These features and the simplicity of this cyclization method should facilitate its extended use in synthesis.

Acknowledgements: We are grateful to Memorial University of Newfoundland and the Natural Sciences and Engineering Research Council of Canada for financial support of this research, and B. Gregory for high resolution mass spectra.

REFERENCES AND NOTES

1. Ting, P.C.; Bartlett, P.A. *J. Am. Chem. Soc.*, 1984, *106*, 2668.
2. O'Malley, G.J.; Cava, M.P. *Tetrahedron Lett.*, 1985, *26*, 6159.
3. Brown, W.L.; Fallis, A.G. *Tetrahedron Lett.*, 1985, *26*, 607.
4. Recently Edstrom and Livinghouse described the addition of methyl benzenesulfenate to alkenes in the presence of Lewis acids followed by arene annulation *via* the resulting episulfonium ion. (Edstrom, E.D.; Livinghouse, T. *J. Am. Chem. Soc.*, 1986, *108*, 1334) Treatment of **4** with either boron trifluoride etherate or silica gel afforded the tetrahydrofuran **3** (~50% yield) accompanied by the alcohol **1** from hydrolysis of **4**. This transformation holds synthetic potential and merits further study but at present is less satisfactory as a preparative procedure than the method described above and failed with the sulfenate ester derived from **17** under Lewis acid conditions.
5. Nicolaou, K.C.; Lysenko, Z. *Tetrahedron Lett.*, 1977, *1257*.
6. Clive, D.L.J.; Chittattu, G.; Curtis, N.J.; Kiel, W.A.; Wong, C.K. *J. Chem. Soc. Chem. Commun.*, 1977, *725*.
7. Nicolaou, K.C.; Petasis, N.A., *Selenium in Natural Products Synthesis*, Cis Inc. Philadelphia, 1984.
8. Baldwin, J.E. *J. Chem. Soc. Chem. Commun.*, 1976, *734*.
9. Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. *J. Org. Chem.*, 1977, *42*, 3846.
10. Nicolaou, K.C.; Lysenko, Z. *J. Chem. Soc. Chem. Commun.*, 1977, *293*; Kimura, R.; Ichihara, A.; Sakamura, S. *Syn.*, 1979, *516*.
11. Nicolaou, K.C.; Magolda, R.L.; Sipio, W.J.; Burnette, W.E.; Lysenko, Z.; Joullie, M.M. *J. Am. Chem. Soc.*, 1980, *102*, 3784.
12. Smit, W.A.; Zefirov, N.S.; Bodrikov, I.V., 'Chemistry of Episulfonium Ions and Mechanism of Ad_E-Reactions of Alkenes with Sulfenyl Derivatives', in *Organic Sulfur Chemistry*, R. Kh. Freidlina; A.E. Skorva (ed.), Pergamon Press, Oxford, 1981.
13. Williams, D.R.; Phillips, J.G. *Tetrahedron*, 1986, *42*, 3013.

(Received in USA 14 October 1986)