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Cleavage of Cyclic Ethers Including Oxetane and Oxolane with a Highly Nucleophilic Species of Phenylselenide Anion

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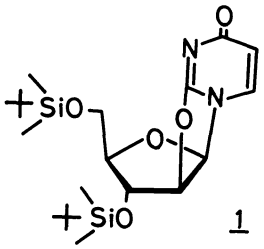
Phenylselenide anion generated from $(PhSe)_2$ and $LiAlH_4$ was found to be highly reactive to various types of cyclic ethers, providing a new method to prepare γ- and δ-phenylselenenyl alcohols from oxetane and oxolane, respectively.

Selenium-containing organic molecules have been known to be a useful synthon in synthetic chemistry.[1] In the field of nucleoside, however, interests regarding selenium seem to have been focused on preparing biologically active compound such as selenazofurin,[2] which contains selenium in its base moiety. Thus, only one report, wherein adenosine was converted to the corresponding 5'-deoxy-5'-(2-nitrophenyl)selenenyl derivative,[3] has been available so far for the selenenylation of the sugar moiety.

During the course of our studies on the use of organometallics for the synthetic purpose in nucleoside field,[4] we were in need of preparing uridine analogues containing phenylselenenyl group in the sugar moiety which might be useful for further modification. When the reported method,[3] a simple application of Grieco's procedure,[5] was used for the preparation of 5'-deoxy-5'-phenylselenenyluridine, uridine was completely recovered.[6] This failure and the anticipated difficulty to apply Grieco's procedure to nucleosidic secondary alcohols led us to examine the bond cleavage reaction of anhydrouridine derivatives with phenylselenide anion. In this communication, we would like to report that phenylselenide anion, when generated from $(PhSe)_2$ and $LiAlH_4$, reacts not only with anhydrouridine derivatives but also with simple oxetanes and even with oxolanes.

Although phenylselenide anion can be prepared from benzeneselenol and a base, reduction of $(PhSe)_2$ seems to be more practical in being able to avoid contact with the stench and toxicity of benzeneselenol. When 3',5'-bis-O-(t-butyldimethylsilyl)-O^2,2'-anhydro-1-(β-D-arabinofuranosyl)uracil (1) was treated with sodium benzeneselenolate, prepared from Na and $(PhSe)_2$ in THF,[7] an arabinofuranosyluracil derivative (2)[8] was the sole product after 7 h at room temperature. The desired phenylselenenylated product (3)[9] was obtained when the reaction was conducted with phenylselenide anion, prepared by $NaBH_4$ in EtOH-THF,[10] at refluxing temperature for 7 h. However, the yield of 3 was not satisfactory, being only 38%.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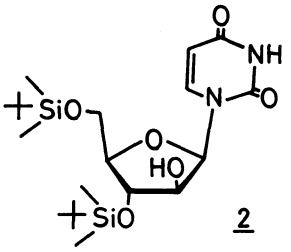
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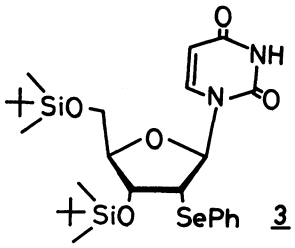
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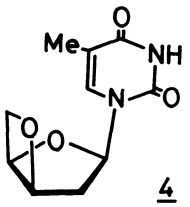
We found that the use of $LiAlH_4$ as the reducing agent for $(PhSe)_2$ gave a highly nucleophilic phenylselenide anion capable of effecting the smooth conversion of 1 to 3.[11] Thus, the anhydro bond cleavage of 1 with this reagent was carried out at room temperature overnight to furnish 3 in 97% yield.

Quite interestingly, a non-activated anhydro nucleoside 4 also underwent the ring cleavage under the same conditions to give 5 in 86% yield.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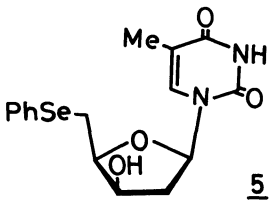
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These results encouraged us to examine the reaction with a 2',5'-anhydro-1-(β-D-arabinofuranosyl)uracil derivative 6[12] to see whether a more stable nucleosidic oxolane ring could be cleaved by the $(PhSe)_2/LiAlH_4$ to form the corresponding 5'-deoxy-5'-phenylselenenylated product 7. When the reaction of 6 was carried out under the above mentioned conditions, two products, 7 (13%) and 8 (18% based on the reagent used), were formed. Of particular interest was the formation of 8, since it clearly indicated that even a simple oxolane, THF, could react with this reagent. Replacement of THF by 1,4-dioxane enabled us to carry out the reaction of 6 at a higher temperature of 100 °C and, after 11 h, 7 was obtained in 44% yield without concomitant formation of products derived from the solvent.

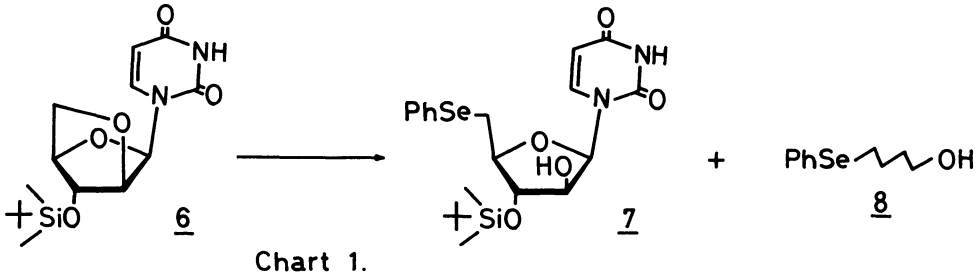


Chart 1.

Since allylic and homoallylic alcohols are of growing synthetic importance and since they can be readily prepared from suitably substituted phenylselenenyl alcohols upon selenoxide fragmentation, we finally investigated the reactions of simple oxetanes and oxolanes with the $(PhSe)_2/LiAlH_4$.[13] The results are summarized in Table 1.

As can be seen from the Table, oxetanes react smoothly at room temperature (entries 1-3) to give the corresponding γ-phenylselenenylpropanol, while ring-

Table 1. The reaction of cyclic ethers with the $(PhSe)_2/LiAlH_4$[a)]

Entry	Substrate	Temp/°C	Time/h	Product	Yield/%
1	Trimethylene oxide	r.t.	18	$HO(CH_2)_3SePh$	89
2	2-Methyloxetane	r.t.	18	$HOCHMe(CH_2)_2SePh$	60
3	3-Methyl-3-oxetanemethanol	r.t.	18	$HOCH_2CMe(CH_2OH)CH_2SePh$	80
4	Tetrahydrofuran	r.t.	18	$HO(CH_2)_4SePh$	8
5	Tetrahydrofuran	60	24	$HO(CH_2)_4SePh$	39
6	Tetrahydrofuran	100	11	$HO(CH_2)_4SePh$	87
7	Tetrahydrofurfuryl alcohol	100	11	$HOCH(CH_2OH)(CH_2)_3SePh$	84
8	7-Oxabicyclo[2.2.1]heptane	100	11	trans-4-Phenylselenenylcyclohexanol	92
9	2,5-Dimethyltetrahydrofuran	100	11	——	—

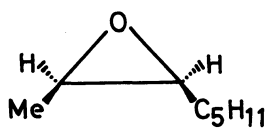
a) All reactions were carried out in 1,4-dioxane by using the reagent prepared as described in Ref. 13.

opening of oxolanes is sluggish at ambient temperature and requires heating at 100 °C. The presence of a hydroxyl group does not pose any problem (entries 3 and 7), though the reaction conditions are mild enough that O-t-butyldimethylsilyl group is adequate for protection (the reaction of 6), if necessary. The results of α-substituted oxetane (entry 2) and oxolane (entry 7), as well as the formation of 5 and 7, suggest that this reaction may occur through an S_N2-like process, the ring-opening taking place by nucleophilic attack at the less substituted carbon.

The reaction of 7-oxabicyclo[2.2.1]heptane, an α,α'-disubstituted oxolane, gave a cyclohexanol with the introduced phenylselenenyl group in trans-orientation (entry 8). On the other hand, the use of 2,5-dimethyltetrahydrofuran (entry 9) resulted in complete recovery of the starting material, indicating that nucleophilic attack of this reagent to α,α'-disubstituted oxolane is possible only when the molecule is activated by its ring strain.

The present results constitute the first examples of cleaving oxetanes and oxolanes with phenylselenide anion and have an additional appeal since the resulting products could serve as precursors of γ-unsubstituted allylic or δ-unsubstituted homoallylic alcohols.

Although oxirane approach to allylic alcohols is well known,[14)] our survey of the literature revealed that the availability of γ-unsubstituted allylic alcohols by this approach was quite limited due to the formation of two regioisomers during the cleavage of an oxirane such as 9.[15,16)]



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References

1) K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, Chemica Scripta, 8A, 9 (1975); D. Liotta, Acc. Chem. Res., 17, 28

(1984).
2) P. C. Srivastava and R. K. Robins, J. Med. Chem., 26, 445 (1983); B. M. Goldstein, F. Takusagawa, H. M. Berman, P. C. Srivastava, and R. K. Robins, J. Am. Chem. Soc., 107, 1394 (1985).
3) H. Takaku, T. Nomoto, and K. Kimura, Chem. Lett., 1981, 1221.
4) H. Tanaka, H. Hayakawa, and T. Miyasaka, Tetrahedron, 38, 2635 (1982); H. Tanaka, H. Hayakawa, S. Iijima, K. Haraguchi, and T. Miyasaka, ibid., 41, 861 (1985); H. Hayakawa, H. Tanaka, and T. Miyasaka, ibid., 41, 1675 (1985); H. Tanaka, H. Hayakawa, K. Obi, and T. Miyasaka, Tetrahedron Lett., 26, 6229 (1985); H. Tanaka, M. Hirayama, M. Suzuki, T. Miyasaka, A. Matsuda, and T. Ueda, Tetrahedron, 42, 1971 (1986); H. Tanaka, H. Hayakawa, K. Obi, and T. Miyasaka, ibid., 42, 4187 (1986); H. Hayakawa, H. Tanaka, K. Obi, M. Itoh, and T. Miyasaka, Tetrahedron Lett., 28, 87 (1987); H. Hayakawa, H. Tanaka, N. Itoh, M. Nakajima, T. Miyasaka, K. Yamaguchi, and Y. Iitaka, Chem. Pharm. Bull., 35, 2605 (1987).
5) P. A. Grieco, S. Gilman, and M. Nishizawa, J. Org. Chem., 41, 1485 (1976).
6) Uridine was treated with PhSeCN (3 equiv.) and Bu_3P (3 equiv.) in pyridine at room temperature overnight.
7) D. Liotta and H. Santiesteban, Tetrahedron Lett., 1977, 4369.
8) We are presently trying to trap an intermediate leading to the formation of 2.
9) Satisfactory spectral data (^{1}H-NMR, MS, and UV) and elemental analyses have been obtained for all new compounds involved in the present study.
10) D. Liotta, W. Markiewicz, and H. Santiesteban, Tetrahedron Lett., 1977, 4365.
11) Disappearance of the yellow color was used as a criterion of determining the stoichiometry of the two reactants. A typical procedure for the reaction of anhydrouridine derivatives is as follows. A yellow solution of $(PhSe)_2$ (0.8 mmol) in THF (3 ml) was treated with $LiAlH_4$ (0.6 mmol) under positive pressure of dry Ar to give a colorless suspension within 10 min. To this, a THF (3 ml) solution of 1 (0.5 mmol) was added and the mixture was stirred overnight at room temperature. Quenching with 10% aqueous AcOH followed by chromatographic purification through a silica gel column (benzene:EtOAc = 20:1) gave 3 as crystals (mp 143-145 °C).
12) K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, J. Chem. Soc., Chem. Commun., 1984, 108.
13) A typical procedure for the reaction of simple cyclic ethers is as follows. A yellow solution of $(PhSe)_2$ (3.2 mmol) in 1,4-dioxane (12 ml) was treated with $LiAlH_4$ (2.4 mmol) under positive pressure of dry Ar. A colorless suspension resulted after ca. 2 h. To this, THF (2 mmol) was added and the mixture was stirred at 100 °C for 11 h. Quenching with 10% AcOH followed by chromatographic purification through a silica gel column ($CHCl_3$) gave 4-phenylselenenylbutanol as a viscous oil.
14) K. B. Sharpless and R. F. Lauer, J. Am. Chem. Soc., 95, 2697 (1973).
15) J. Rémion, W. Dumont, and A. Krief, Tetrahedron Lett., 1976, 1385.
16) D. L. J. Clive, Tetrahedron, 34, 1049 (1978).

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