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THE USE OF PhSeCl IN THE SYNTHESIS OF CYCLIC ETHERS

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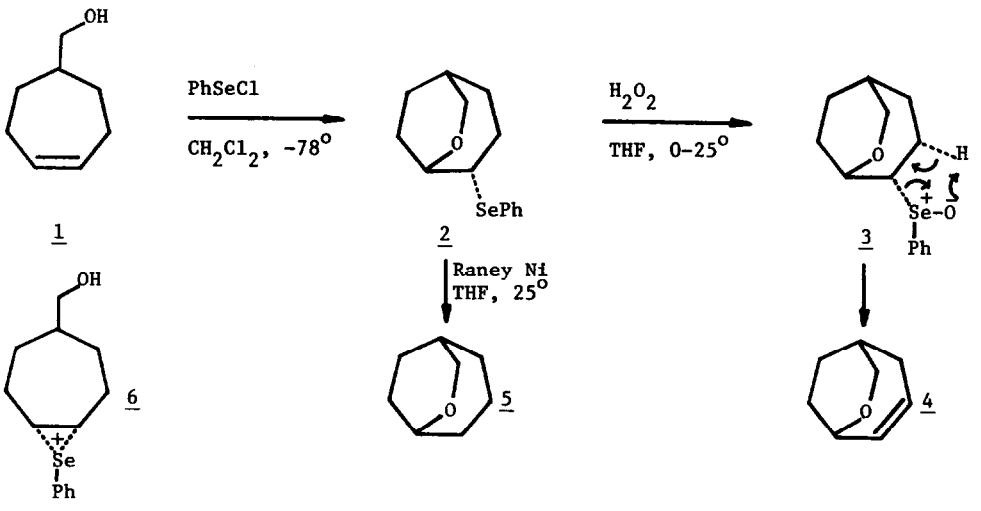
Our recent introduction of certain selenium reagents to induce cyclization reactions efficiently and under extremely mild conditions,[1] opened up a variety of promising avenues for the synthesis of heterocycles. We now wish to report the use of PhSeCl in the synthesis of cyclic ethers, materials of considerable importance in synthesis, particularly in the area of natural products. This new methodology which takes advantage of the high electrophilicity of PhSeCl and the recently developed and synthetically useful chemistry of the phenylseleno group[1,2,3] is illustrated in Scheme I. 4-Cycloheptene-1-methanol (1),[4] on treatment with PhSeCl (1.1 equiv) in CH_2Cl_2 at -78° afforded, after column chromatography, (SiO_2; CH_2Cl_2) the phenylselenoether 2[5] in 95% yield as a colorless oil, NMR ($CDCl_3$; 220 MHz) τ 2.52 (m,2H,Ph), 2.80 (m,3H,Ph), 6.04 (m,1H,-OC<u>H</u>-), 6.16 and 6.35 (doublets,J=4Hz,1H each,-OC<u>H</u>$_2$-), 6.47 (m,1H,-SeC<u>H</u>-), 7.70-8.50 (m,9H,-C<u>H</u>$_2$- and -C<u>H</u>-). Oxidation of the phenylseleno group of 2 with 30% hydrogen peroxide[2,3]

SCHEME I

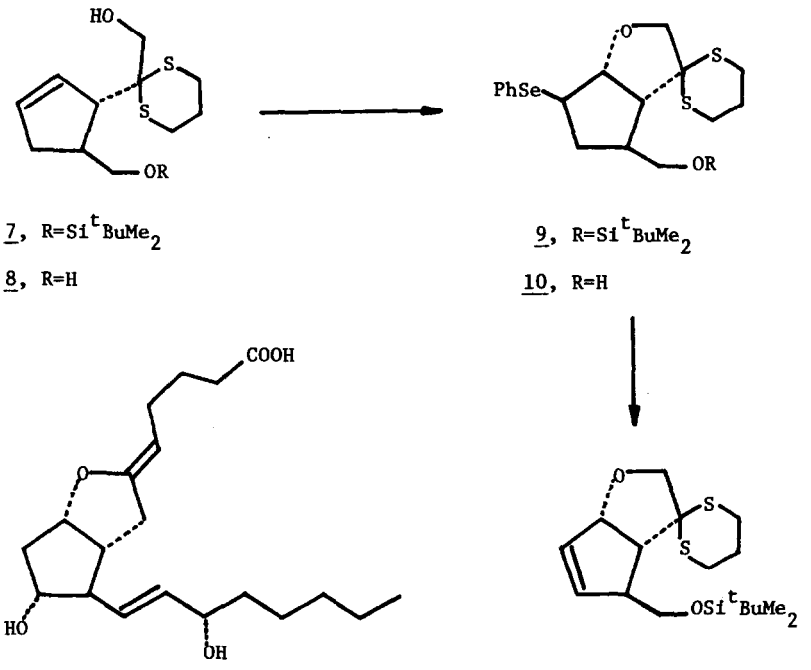


(1.5 equiv) in THF at 0-25° afforded, via the selenoxide 3 by syn elimination, the allylic ether 4 in 87% yield, m.p. 60-61° (sublimed), NMR ($CDCl_3$, 220 MHz) τ 4.04 and 4.21 (mulitplets, 1H each, olefinic), 5.85 (m,1H,-OCH-), 5.98 and 6.14 (multiplets, 1H each,-OCH_2-), 7.30-8.35 (m,7H,-CH_2-and-CH-). Reductive removal of the phenylseleno group by Raney Nickel[6] in THF at 25° proceeded cleanly to furnish the bicyclic saturated ether 5 in 94% yield, purified by sublimation, m.p. 119-120°, NMR ($CDCl_3$, 220 MHz) τ 5.96 (m,1H,-OCH-), 6.05 and 6.25 (broad doublets,J=4.5Hz,1H each,-OCH_2-), 7.80-8.50 (m,11H,-CH_2-and-CH-).

This facile cyclization reaction presumably proceeds via a reactive intermediate such as 6, formed by the initial attack of PhSeCl on the double bond, followed by ring closure resulting from an internal nucleophilic attack by the hydroxyl group. The stereochemistry of the phenylselenoether 2 is tentatively assigned and is based on mechanistic considerations.

The generality and applicability of this new etherification reaction in complex and sensitive cases was tested by the conversion of the unsaturated alcohols 7 and 8 to their corresponding ethers. Reaction of 7[7] with PhSeCl (1.1 equiv) in CH_2Cl_2 at -78° produced rapidly the 5-membered ring ether 9, isolated by column chromatography (SiO_2; CH_2Cl_2) in 86% yield, m.p. 76-77° (pentane). The structure of 9 was based on its NMR spectrum, ($CDCl_3$, 220 MHz) τ 2.45 (m,2H,Ph), 2.74 (m,3H,Ph), 5.26 (dd,J=3,2Hz,1H,-OCH-), 5.79 and 6.06 (doublets, J=4Hz,1H each,-OCH_2-), 6.22 (dd,J=4.5,2Hz,1H,-SeCH-), 6.43 (m,2H,-CH_2OSi-), 7.16 (m,4H), 7.27 (t,J=3Hz,1H), 7.64 (m,2H), 8.00 (m,2H), 8.30 (m,1H)(-CH_2-and-CH-), 9.10 [s,9H,-Si(CCH_3)$_3$], 9.93 [s,6H,-Si(CH_3)$_2$] and its transformation (1.5 equiv. H_2O_2 in THF at 0°-25°; 75%) to the unsaturated ether 11, NMR ($CDCl_3$, 220 MHz) τ 4.10 and 4.30 (multiplets,1H each, olefinic), 4.68 (m,1H,-OCH-), 5.90 and 6.43 (doublets,J=4Hz,1H each,-OCH_2-), 6.47 (d,J=3Hz,2H,-CH_2OSi-), 6.72 (m,1H), 7.15 (m,5H), 7.98 (m,2H)(-CH_2-and--CH-), 9.12 [s,9H,-Si-C(CH_3)$_3$], 9.95 [s,6H,-Si(CH_3)$_2$].

An interesting observation was made when the diol 8[7] was subjected to the cyclization reaction as described above. Thus, on exposure to PhSeCl, the ether 10 was formed exclusively in 90% yield, NMR ($CDCl_3$, 220 MHz) τ 2.47 (m,2H,Ph), 2.74 (m,3H,Ph), 5.24 (dd,J=3,2Hz,1H,-OCH-), 5.78 and 6.05 (doublets, J=4Hz,1H each,-OCH_2-), 6.20 (dd,J=4.5,2Hz,1H,-SeCH-), 6.37 (m,2H,-CH_2OH), 7.50 (s,1H,OH), 7.12 (m,4H), 7.54 (m,2H), 8.00 (m,2H) and 8.30 (m,1H) (-CH_2-and-CH). Silylation[8] of 10 gave a material chromatographically and spectroscopically identical to 9, establishing the skeletal structure assigned to 10.



7, R=Si^{t}BuMe$_2$

8, R=H

9, R=Si^{t}BuMe$_2$

10, R=H

12

11

The mildness and high efficiency of the reactions described, leading to cyclic ethers of various types make this new methodology an attractive way of approaching complex naturally occurring substances containing this functionality. For example, the potential of this method in the construction of the recently discovered prostacyclin (PGX)(12),[9,10] a major factor in blood platelet aggregation, and/or analogues and isomers of it, is obvious.[11]

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11. This work was financially supported by the University of Pennsylvania.