Facile Synthesis of Thiolariat Ethers or Crown Ethers Containing a Mercapto Group as a Side Arm

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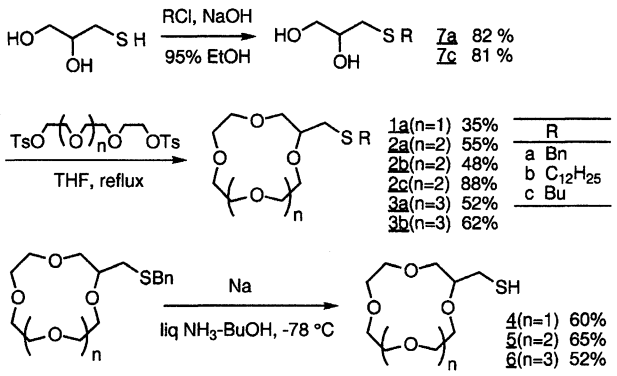
Cyclization reaction of S-substituted thioglycerol and oligoethylene glycol ditosylate gave thiolariat ethers in moderate yields. Mercaptomethyl crown ethers were obtained easily from benzylthiomethyl crown ethers by Na in liq. NH_3–BuOH.

Crown ethers containing a sulfur atom outside the ring have fascinating features for ion and molecular recognition.[1,2] For instance, thiolariat ethers **2**, crown ethers with a sulfide group as a side arm, exhibit remarkably high Ag^+ selectivity in solvent extraction.[3] Synergistic coordination of a crown ring and the sulfur atom in the side chain appears essential for such high selectivity. Crown ethers bearing a mercapto group as a side chain are considered to be key compounds in host-guest chemistry.[4,5] Crown ethers with two mercapto side chains have been reported to be an interesting enzyme model to synthesize peptides.[4] The crown ring works as a recognition site and the mercapto groups catalyze the reaction. The framework may be utilized for other enzyme models, because many reactions mediated by a mercapto group are known in biological systems.[6] In addition, these mercapto crowns can be used as precursors for various thiolariat ethers whose side chain contains a substituent unstable under basic cyclization reaction conditions. The mercapto crowns may also be useful for polymer-supported thiolariat ethers and for functionalization of surfaces of electrode and other solid materials. However, preparative methods for the sulfur-containing crown ethers described above have been laborious and tedious. Here we wish to report a simple and facile way to synthesize the lariat ethers **1**—**6** containing a sulfide or a mercapto side chain.

In a previous preparative method, thiolariat ethers were derived from 2,2-dimethyl-1,3-dioxolane-4-methanol in 7 steps via the corresponding mercaptomethyl crowns as intermediates.[3] However, the new route shown in Scheme 1 uses commercially available thioglycerol as a starting material; by this route, thiolariat ethers were obtained from the diols in 2 steps.[7] Alkyl halides or benzyl chloride was treated with thioglycerol to give *S*-alkylated diols **7a**, **7c** according to a similar method for **7b**.[8] Cyclization reaction was carried out by using the diols and oligoethylene glycol ditosylates in a THF suspension of NaH under reflux for 15



Scheme 1.

h. The crude thiolariat ethers thus obtained were purified by silica-gel flash column chromatography. Compared to thiolariat ethers **1** with a 12-crown-4 ring, 15-crown-5 and 18-crown-6 derivatives **2**, **3** were obtained in better yields, probably because of a template effect of Na^+ on the cyclization. Cleavage of the benzyl moiety of benzylthiomethyl crown ethers by the treatment of Na in liquid NH_3–BuOH at −78 °C for 0.5 h gave the corresponding mercaptomethyl crown ethers **4**, **5**, **6** in moderate yields. BuOH was necessary to dissolve thiolariat ethers **1a**, **2a**, **3a** completely in liq. NH_3, so that the reaction time was shortened significantly. The liq. NH_3–BuOH–Na system is useful and convenient, because conversion of chloromethyl crown ethers to mercaptomethyl ones by a usual thiourea method was not efficient: Much longer reaction time is required and the yield is low (ca. 30%), as reported before.[3] This procedure will be extended to preparation of crown ethers bearing several thiol side chains.

Experimental

Tetrahydrofuran was distilled from sodium diphenylketyl just before use. IR spectra were obtained on a Hitachi 270-50 spectrophotometer. NMR spectra were recorded on a Varian Gemini-200 (200 MHz for ^1H and 50 MHz for ^{13}C) and a

JEOL α-500 (125 MHz for ^{13}C) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Spectral data of 12-crown-4 and 15-crown-5 derivatives **1**, **2**, **4**, **5** are identical to those of the authentic samples prepared by a previous method.[3)]

***S*-Alkylated Diols 7.** Compounds **7a,c** were prepared according to Lawson's method for synthesis of **7b** with slight modification.[8)] For example, to a solution of NaOH (6.94 g, 0.165 mol) in 95% EtOH was added first thioglycerol (12.0 ml, 0.144 mol) and then benzyl chloride (16.6 ml, 0.144 mol) under nitrogen. After stirring for 4 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was mixed with water (50 ml), extracted with CH_2Cl_2 (50 ml× 3). The organic layer was dried over anhydrous $MgSO_4$, concentrated in vacuo, and then purified by molecular distillation under reduced pressure (185—190 °C/3 mmHg, 1 mmHg=133.322 Pa) to give **7a**[9)] in 82% yield as a colorless oil. *S*-Alkylated diol **7c**[10)] was also synthesized in a similar way.

7c: ^1H NMR (200 MHz; $CDCl_3$) δ=0.92 (3H, d, J=7.0 Hz), 1.3—1.7 (4H, m), 2.5—2.8 (6H, m), 3.1—3.3 (1H, br), 3.5—3.7 (1H, m), 3.7—3.9 (2H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=13.70, 22.01, 31.84, 32.16, 35.88, 65.63, 70.17.

Thiolariat Ether 2c. A solution of tetraethylene glycol ditosylate (8.44 g, 16.8 mmol) in THF (25 ml) was added dropwise to a mixture of diol **7c** (2.52 g, 15.4 mmol) and NaH (55% in oil, 1.64 g, 37.5 mmol) in THF (45 ml) at room temperature. The mixture was refluxed for 15 h, and then concentrated in vacuo. To the residue thus obtained was added water (20 ml), followed by extraction with CH_2Cl_2 (20 ml×3). The organic layer was washed with water, dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by a silica-gel flash column using ethyl acetate to give thiolariat ether **2c** in 88% yield as a colorless oil. Thiolariat ethers **1**, **2a**, **2b**, **3** were prepared in a similar way, although three times as much as THF was used in the case of **2c**.

1a: IR (neat) 2866, 1954, 1724, 1601, 1494, 1454, 1349, 1291, 1247, 1107, 995, 949, 878, 771, 751, 703 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=2.58 (2H, d, J=5.3 Hz), 3.57—3.80 (15H, m), 3.77 (2H, s, SCH_2Ar), 7.15—7.39 (5H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=32.55, 37.06, 69.95, 70.94, 71.00, 71.17, 72.98, 79.31, 127.52, 128.82, 129.36, 138.79. Found: m/z 312.1406. Calcd for $C_{16}H_{24}O_4S$: M, 312.1395.

2a: IR (neat) 3060, 3028, 2860, 1700, 1600, 1496, 1454, 1354, 1292, 1252, 1140, 988, 942, 876, 860, 838, 770, 702 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=2.56 (2H, d, J=5.8 Hz), 3.57—3.78 (19H, m), 3.76 (2H, s, SCH_2Ar), 7.22—7.35 (5H, m); ^{13}C NMR (200 MHz; $CDCl_3$) δ=33.04, 37.11, 70.42, 70.67, 70.74, 70.95, 71.09, 71.21, 72.90, 79.52, 127.34, 128.83, 129.36, 138.79. Found. m/z 356.1623. Calcd for $C_{18}H_{28}O_5S$: M, 356.1657.

2b: IR (neat) 2923, 2853, 1466, 1348, 1292, 1253, 1127, 985, 941, 870, 839, 722 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=0.88 (3H, t, J=6.3 Hz), 1.26 (18H, s), 1.50—1.65 (2H, m), 2.55 (2H, t, J=7.5 Hz), 2.65 (2H, d, J=5.7 Hz), 3.60—3.85 (19H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=14.18, 22.79, 29.00, 29.37, 29.47, 29.67, 29.76, 29.86, 32.05, 33.21, 34.08, 70.44, 70.68, 70.75, 70.80, 70.95, 71.10, 71.28, 72.92, 79.78. Found: m/z 434.3070. Calcd for $C_{23}H_{45}O_5S$: M, 434.3066.

2c: IR (neat) 2920, 2864, 1466, 1350, 1292, 1252, 1144, 1118, 986, 942, 872, 840 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=0.91 (3H, t, J=7.1 Hz), 1.25—1.65 (4H, m), 2.56 (2H, t, J=7.5 Hz), 2.65 (2H, d, J=5.8 Hz), 3.55—3.90 (19H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=13.74, 22.04, 31.89, 32.87, 34.02, 70.43, 70.69, 70.75, 70.95, 71.10, 71.25, 72.93, 79.78. Found: m/z 322.1797. Calcd for $C_{15}H_{30}O_5S$: M, 322.1814.

3a: IR (neat) 3060, 3028, 2868, 1690, 1496, 1454, 1352, 1296, 1248, 1128, 992, 948, 848, 768, 702 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=2.57 (2H, d, J=5.8 Hz), 3.57—3.78 (23H, m), 3.76 (2H, s, SCH_2Ar), 7.20—7.33 (5H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=32.56, 37.07, 69.96, 70.82, 70.91, 71.06, 72.95, 79.11, 127.36, 128.84, 129.36, 138.78. Found: m/z 400.19489. Calcd for $C_{20}H_{32}O_6S$: M, 400.19196.

3b: IR (neat) 2922, 2852, 1739, 1618, 1463, 1455, 1350, 1295, 1249, 1122, 990, 947, 869, 760, 722, 664 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=0.88 (3H, t, J=6.3 Hz), 1.26 (18H, s), 1.47—1.65 (2H, m), 2.54 (2H, t, J=7.5 Hz, $-SCH_2-$), 2.65 (2H, d, J=5.5 Hz, $-SCH_2-$), 3.60—3.92 (23H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ=14.12, 22.69, 28.90, 29.27, 29.35, 29.55, 29.61, 29.64, 29.66, 29.72, 31.92, 33.11, 33.45, 69.78, 70.63, 70.66, 70.72, 70.81, 70.84, 70.87, 72.78, 79.19. Found: m/z 478.33281. Calcd for $C_{20}H_{32}O_6S$: M, 478.33395.

Mercaptomethyl 18-Crown-6 6. Liquid ammonia (ca. 50 ml) was trapped at −78 °C in a reactor containing a solution of benzylthiomethyl crown ether **3a** (187 mg, 0.467 mmol) in 1-butanol (1.0 ml). After a clear solution was obtained by stirring, Na (370 mg, 16 mmol) was added to the mixture at −78 °C. The blue reaction mixture was stirred for 0.5 h at −78 °C under nitrogen, and then ammonium chloride was added to quench the reaction. Liquid ammonia was removed by bubbling N_2. The residue was acidified with concd HCl (10 ml), extracted with CH_2Cl_2 (20 ml×3, 10 ml×10). The organic layer was concentrated in vacuo, and purified by a silica-gel flash column using CH_2Cl_2–methanol (10 : 1, v/v) as eluent to give **6** in 52% yield as a pale yellow oil.

4: IR (neat) 2866, 2555 (SH), 1964, 1727, 1633, 1454, 1349, 1296, 1249, 1110, 994, 946, 878, 725 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=1.67 (1H, t, J=8.5 Hz), 2.61—2.79 (2H, m), 3.52—3.90 (15H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=26.16, 70.00, 71.01, 71.18, 72.19, 80.37; MS m/z 222 (M^+).[11)]

5: IR (neat) 2865, 2553 (SH), 1968, 1718, 1636, 1454, 1351, 1294, 1250, 1123, 986, 940, 853, 732, 702 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ=1.56 (1H, t, J=8.3 Hz), 2.60—2.78 (2H, m), 3.51—3.92 (19H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=26.67, 70.60, 70.66, 70.78, 71.06, 71.38, 72.32, 80.82. Found: m/z 266.1178. Calcd for $C_{11}H_{22}O_5S$: M, 266.1188.

6: IR (neat) 2865, 2553 (SH), 2360, 2342, 2241, 1964, 1727, 1644, 1470, 1454, 1351, 1296, 1250, 1110, 989, 948, 841, 731 cm^{-1} ^1H NMR (200 MHz; $CDCl_3$) δ=1.56 (1H, t, J=8.3 Hz), 2.61—2.79 (2H, m), 3.56—3.78 (23H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ=25.86, 69.79, 70.78, 70.88, 70.98, 72.14, 80.28. Found: m/z 310.1445. Calcd for $C_{13}H_{26}O_6S$: M, 310.1450.

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