One-Step Synthesis of Dihydroxyazacrown Ethers

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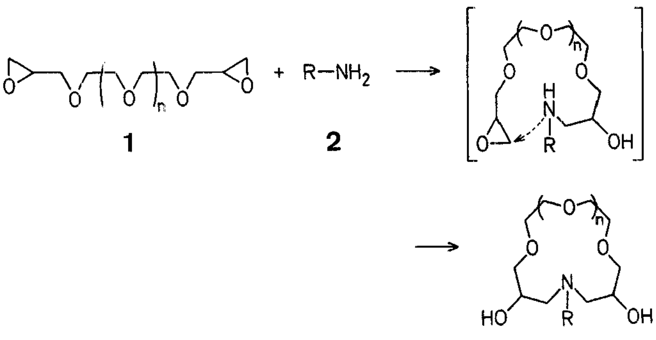
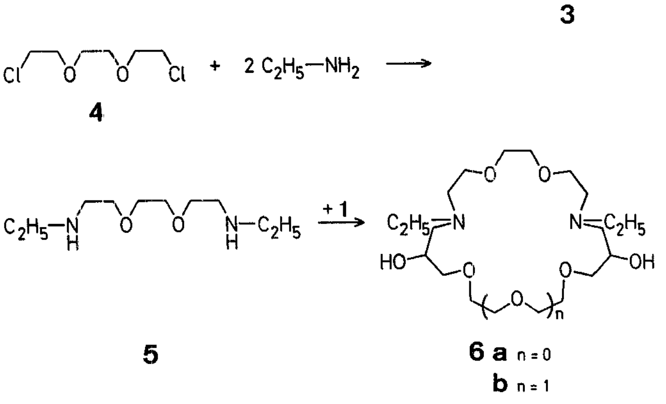
Bifunctional crown ethers such as diazacrown ethers are important as intermediates in the synthesis of cryptands and can be transformed into polymers including crown rings in the backbone by the reaction with appropriate bifunctional compounds[1-6]. Crown compounds having two functional groups outside the ring are also useful for the above purposes[7,8,9]. However, the syntheses of such compounds are rather complicated and simple methods for their preparation are desired. Earlier we have reported the synthesis of bis[aminomethyl]crown ethers[10]. We now describe a facile preparation of mono- and diazacrown ethers **3** and **6** bearing two hydroxy groups on the ring.





The reaction of oligoethylene glycol diglycidyl ethers **1** with primary amines **2** in an appropriate solvent gave the dihydroxyazacrown ethers **3** in moderate yield (Table 1). The G.L.C. pure compounds **3** were characterized by spectral analyses (Table 2).

The solvent plays an important role in this reaction and inexpensive protic solvents such as water and methanol were found to be most appropriate, in accordance with the observation that the ring-opening of oxiranes was accelerated in protic solvents[11]. On the other hand, in aprotic solvents such as benzene, dioxan, and trichloromethane, etc., the reaction hardly proceeded and **1** was recovered almost quantitatively.

As was expected, the yield was found to increase when the reaction was carried out in a dilute solution. No significant difference in the yields of **3** was observed for the different primary amines **2** used.

Although the yields were improved by using a slight excess of amine **2** (1.3-1.5 mol to one mol of **1**), the addition of a large excess of amine **2** (>3 mol) resulted in the reduction of yield due to formation of the by-product, bis[aminomethyl]oligoethylene glycols[10]. Generally the reaction was found to be rather slow at room temperature. The increase of temperature remarkably accelerated the reaction only in methanol without affecting the yield very much.

Dihydroxydiazacrown ethers **6** were prepared by the reaction of diglycidyl ethers **1** (n=0, 1) with 1,2-bis[2-(ethylamino)-ethoxy]ethane **(5)** (Table 3). The latter was obtained from 1,2-bis[2-chloroethoxy]ethane **(4)** and ethylamine.

Table 1. Synthesis of Dihydroxyazacrown Ethers **3**

Product No.	n	R	Solvent	Reaction temp. [°C]	Reaction time [h]	Yield[a] [%]
3a	1	C_2H_5	H_2O	r.t.	50	36
3a	1	C_2H_5	CH_3OH/H_2O	r.t.	50	38
3b	2	C_2H_5	CH_3OH/H_2O	r.t.	50	35
3c	3	C_2H_5	CH_3OH/H_2O	r.t.	25	24
3d	1	H	H_2O	r.t.	50	12
3d	1	H	H_2O	r.t.	50	31[b]
3e	1	$HOCH_2CH_2$	H_2O	r.t.	50	34
3f	1	s-C_4H_9	CH_3OH	r.t.	50	29
3f	1	s-C_4H_9	CH_3OH	55°	3	31[c]
3f	1	s-C_4H_9	CH_3OH	55°	3	37[c,d]
3f	1	s-C_4H_9	CH_3OH	55°	3	18[c,e]
3f	1	s-C_4H_9	CH_3OH	55°	3	37[c,f]
3f	1	s-C_4H_9	CH_3OH	55°	7	49[f]
3f	1	s-C_4H_9	t-C_4H_9OH	55°	3	33
3g	2	s-C_4H_9	CH_3OH	r.t.	50	36
3h	1	n-$C_{10}H_{21}$	CH_3OH	r.t.	50	43
3h	1	n-$C_{10}H_{21}$	CH_3OH	reflux	2.5	38
3h	1	n-$C_{10}H_{21}$	$(CH_3)_2SO$	100°	3	6
3i	1	C_6H_5	CH_3OH	r.t.	100	48

[a] Yield of isolated product based on **1**.
[b] 1.5 Mol of amine **2** to 1 mol of diglycidyl ether **1**.
[c] Yield determined by G.L.C.
[d] 1.3 Mol of amine **2** to 1 mol of diglycidyl ether **1**.
[e] 3 Mol of amine **2** to 1 mol of diglycidyl ether **1**.
[f] Double the amount of solvents normally needed were used.

The method reported here provides a facile route to azacrown ethers having functional groups from commercially available sources.

Primary amines **2** and 1,2-bis[2-chloroethoxy]ethane **4** were obtained from Tokyo Kasei Kogyo Co., Ltd.; the mono- and diethyleneglycol diglycidyl ethers **1** (n=0, 1) from Nippon Oil and Fats Co., Ltd. Tri- and tetraethyleneglycol diglycidyl ether **1** (n=2, 3) were prepared from chloromethyloxirane and the corresponding oligoethylene glycol[10].

All compounds prepared were tested for their purity by G.L.C. (Shimadzu GC-8APF, 5% silicon OV-1 on 60-80 mesh Uniport KS, 2.6 mm × 2 m glass column, 230-270°C).

Dihydroxyazacrown Ethers 3; Typical Procedures:

Procedure A, (Table 1) at room temperature in solvents methanol or water or methanol/water:

14-Ethyl-12,16-dihydroxy-1,4,7,10-tetraoxa-14-azacycloheptadecane **(3b):**
Triethylene glycol diglycidyl ether [**1** (n=2); 2.6 g, 0.01 mol] is dissolved in methanol (50 ml), and 70% aqueous ethylamine (0.7 g, 0.01 mol) is added. After the mixture has been stirred for 50 h at room temperature, it is evaporated to dryness. The residue is distilled using a Kugelrohr apparatus to give **3b** as a yellowish viscous liquid; yield: 1.07 g (35%); b.p. 115-120°C/0.005 torr.

9,13-Dihydroxy-1,4,7-trioxa-11-azacyclotetradecane **(3d):**
Diethylene glycol diglycidyl ether [**1** (n=1); 2.2 g, 0.01 mol] is dissolved in water (50 ml), and 28% aqueous ammonia (1.2 g, 0.01 mol) is added to the solution. After the mixture has been stirred for 50 h at room temperature, the solvent is evaporated and the residue is distilled using a Kugelrohr apparatus to give **3d** as a colorless solid; yield: 0.55 g (12%); b.p. 105-110°C/0.005 torr.

Procedure B, at elevated temperatures (Table 1) in methanol or *t*-butyl alcohol or dimethyl sulfoxide:

11-Decyl-9,13-dihydroxy-1,4,7-trioxa-11-azacyclotetradecane **(3h):**
To refluxing methanol (30 ml) are added simultaneously dropwise diethylene glycol diglycidyl ether [**1** (n=1); 2.2 g, 0.01 mol] in methanol (10 ml) and decylamine (1.6 g, 0.01 mol) in methanol (10 ml) during 0.5 h with stirring. After the addition, the reaction is continued for 2 h, the methanol is evaporated, and the residue distilled using a Kugelrohr apparatus to give **3h** as a yellowish viscous liquid; yield: 1.42 g (38%); b.p. 155-160°C/0.005 torr.

Table 2. Characterization of Dihydroxyazacrown Ethers **3a-i**

Product No.	b.p. [°C]/ torr[a]	n_D^{20} or m.p. [°C]	Molecular formula[b]	I.R. (Neat) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	M.S. (70 eV) m/e (rel. intensity %)
3a	105-110°/0.005	1.4865	$C_{12}H_{25}NO_5$ (263.3)	3360, 2860, 1450, 1350, 1250, 1130	1.04 (t, 3H, J=8 Hz); 2.4-2.9 (m, 6H); 3.04 (s, 2H); 3.5-4.0 (m, 14H)	263 (M^+, 14.0); 248 (6.0); 246 (8.0); 115 (37.0); 100 (100); 72 (68.4); 58 (92.6)
3b	115-120°/0.005	1.4834	$C_{14}H_{29}NO_6$ (307.4)	3410, 2880, 1460, 1360, 1260, 1120	1.04 (t, 3H, J=7 Hz); 2.5-2.9 (m, 6H); 3.23 (s, 2H); 3.4-4.0 (m, 18H)	307 (M^+, 10.8); 292 (9.8); 260 (13.1); 218 (14.7); 128 (23.8); 114 (28.8); 102 (35.5); 89 (30.3); 72 (100); 68 (90.2)
3c	145-150°/0.02	1.4824	$C_{16}H_{33}NO_7$ (351.4)	3340, 2870, 1450, 1350, 1250, 1120	1.02 (t, 3H, J=7 Hz); 2.4-2.8 (m, 6H); 3.3-4.0 (m, 24H)	351 (M^+, 9.0); 336 (8.7); 304 (15.9); 128 (30.5); 116 (41.9); 100 (51.4); 72 (100); 58 (89.5)
3d	105-110°/0.005	49-54°	$C_{10}H_{21}NO_5$ (235.3)	3360, 3300, 2865, 1450, 1350, 1250, 1120, 875	2.6-3.2 (m, 4H); 3.25 (s, 3H); 3.5-4.0 (m, 14H)	235 (M^+, 11.2); 218 (18.7); 192 (16.7); 118 (59.6); 104 (26.7); 87 (35.5); 44 (100)
3e	140-145°/0.005	1.5014	$C_{12}H_{25}NO_6$ (279.3)	3360, 2870, 1460, 1355, 1250, 1130	2.5-3.1 (m, 6H); 2.78 (s, 1H); 3.4-4.1 (m, 16H); 3.77 (s, 2H)	279 (M^+, 1.6); 248 (100); 174 (40.0); 100 (40.3); 73 (39.2)

Table 2. (Continued)

Product No.	b.p. [°C]/ torr[a]	n_D^{20} or m.p. [°C]	Molecular formula[b]	I.R. (Neat) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]	M.S. (70 eV) *m/e* (rel. intensity %)
3f	110-115°/0.02	1.4856	$C_{14}H_{29}NO_5$ (291.4)	3470, 2960, 2880, 1475, 1370, 1350, 1255, 1135	0.88 (d, 6H, J=6 Hz); 1.73 (septet, t, 1H, J=6 Hz, 7 Hz); 2.22 (d, 2H, J=7 Hz); 2.4-2.9 (m, 4H); 2.90 (s, 2H); 3.4-4.0 (m, 14H)	291 (M$^+$, 2.2); 248 (100); 204 (7.6); 174 (29.2); 100 (22.5); 86 (7.5); 45 (13.7)
3g	130-135°/0.01	1.4826	$C_{16}H_{33}NO_6$ (335.4)	3430, 2950, 2850, 1470, 1365, 1350, 1255, 1125	0.86 (d, 6H, J=6 Hz); 1.71 (septet, t, 1H, J=6 Hz, 7 Hz); 2.23 (d, 2H, J=7 Hz); 2.4-2.9 (m, 4H); 3.3-4.0 (m, 20H)	335 (M$^+$, 1.5); 295 (14.4); 292 (100); 218 (31.8); 144 (12.0); 100 (8.9)
3h	155-160°/0.005	1.4812	$C_{20}H_{41}NO_5$ (375.6)	3400, 2930, 2850, 1465, 1350, 1250, 1125, 720	0.87 (t, 3H, J=7 Hz); 1.1-1.6 (m, 15H); 2.4-3.0 (m, 6H); 3.10 (s, 2H); 3.4-4.0 (m, 14H)	375 (M$^+$, 6.2); 248 (100); 174 (26.7); 170 (29.4); 100 (73.3)
3i	150-155°/0.001	42-44°	$C_{16}H_{25}NO_5$ (311.4)	3350, 3030, 2920, 2850, 1600, 1510, 1440, 1345, 1245, 1125, 750, 700	3.3-3.9 (m, 18H); 3.9-4.2 (m, 2H); 6.6-6.9 (m, 3H); 7.0-7.3 (m, 2H)	311 (M$^+$, 78.5); 163 (78.2); 120 (100); 106 (51.5); 105 (97.0); 91 (23.9); 77 (19.1)

[a] Kugelrohr distillation.

[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.18, N ±0.23.

Table 3. Synthesis of Dihydroxydiazacrown Ethers **6a, b**

Product No.	n	Yield[a] [%]	b.p. [°C]/ torr[b]	n_D^{20}	Molecular formula[c]	I.R. (Neat) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]	M.S. (70 eV), *m/e* (rel. intensity %)
6a	0	30	135-140°/0.01	1.4869	$C_{18}H_{38}N_2O_6$ (378.5)	3420, 2870, 1455, 1350, 1250, 1120	1.05 (t, 6H, J=7 Hz); 2.5-3.0 (m, 12H); 3.4-4.1 (m, 20H)	377 (M$^+$−1, 2.2); 231 (22.8); 218 (51.1); 146 (63.6); 144 (45.6); 115 (43.2); 86 (62.1); 72 (100)
6b	1	22	150-155°/0.002	1.4866	$C_{20}H_{42}N_2O_7$ (422.6)	3300, 2860, 1450, 1350, 1120	1.04 (t, 6H, J=7 Hz); 2.5-3.0 (m, 12H); 3.3-3.8 (m, 20H); 3.8-4.0 (m, 2H); 4.13 (s, 2H)	421 (M$^+$−1, 3.3); 262 (59.0); 231 (99.5); 188 (35.3); 146 (69.3); 115 (68.9); 86 (75.0); 72 (100)

[a] Yield of isolated product.

[b] Kugelrohr distillation.

[c] Satisfactory microanalyses obtained: C ±0.26, H ±0.21, N ±0.14.

1,2-Bis[2-(ethylamino)-ethoxy]ethane (5):

To a 70% solution of aqueous ethylamine solution (387 g, 6.0 mol) containing 99% sodium carbonate (48.2 g, 0.45 mol) is added 99% 1,2-bis[2-chloroethoxy]ethane (**4**; 56.7 g, 0.3 mol). The mixture is stirred for 17 h at 50°C and evaporated to dryness. Methanol (200 ml) is added to the residue and the insoluble salts are removed by filtration. After evaporation of methanol, the residue is distilled to give **5** as a yellowish liquid; yield: 40.2 g (66%); b.p. 60-63°C/0.005 torr.

8,17-Diethyl-6,19-dihydroxy-1,4,11,14-tetraoxa-8,17-diazacycloeicosane (6a); Typical Procedure:

Ethylene glycol diglycidyl ether [**1** (n=0); 1.7 g, 0.01 mol] is dissolved in methanol (50 ml), and 1,2-bis[2-(ethylamino)-ethoxy]ethane (**5**; 2.0 g, 0.01 mol) is added to the solution. After the mixture has been stirred for 50 h at room temperature, the solvent is evaporated and the residue is distilled using a Kugelrohr apparatus to give **6a** as a yellow liquid; yield 1.12 g (30%); b.p. 135-140°C/0.01 torr.

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