Synthesis of Sulfur and Nitrogen Analogues of Monooxo Crown Ethers

Kenji Matsushima

Department of Applied Chemistry, Faculty of Science and Technology,
Kinki University, Kowakae, Higashi-osaka,
Osaka, Japan 577

Yohji Nakatsuji, Norio Kawamura, and Mitsuo Okahara*

Department of Applied Chemistry, Faculty of Engineering,
Osaka University, Yamada-oka, Suita,
Osaka, Japan 565

Received May 29, 1985

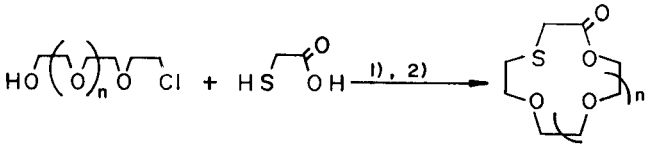
Sulfur or nitrogen analogues of monooxo crown ethers were prepared *via* intramolecular cyclization of the corresponding thia or aza oligoethylene glycol carboxylmethyl ethers by using benzenesulfonyl chloride in the presence of alkali metal carbonates.

J. Heterocyclic Chem., **23**, 255 (1986).

Crown ethers have been intensively synthesized in relation to the complexing abilities toward a variety of cations since 1967 [1]. As a lot of macrocyclic polyether-diester compounds (dioxo crown ethers) were prepared by Bradshaw *et al.* and some of them were clarified to have the specific cation selectivity ($K^+ > Ba^+$) similar to that for valinomycin, the importance of the modification of electron-donating group has been noticed [2]. Recently, we synthesized a variety of monooxo crown ethers and found that these compounds possessed the intermediate properties between normal crown ethers and dioxo crown ethers by measuring their stability constants toward alkali metal cations [3]. From this standpoint, we now describe the synthesis of sulfur and nitrogen analogues of monooxo crown ethers, which are desirable for soft cations.

3-Oxo monothia crown ethers **3** were prepared by the reaction of oligoethylene glycol monochloride **1** with thioglycolic acid **2** in basic conditions followed by cyclization using benzenesulfonyl chloride in the presence of alkali metal carbonate (Scheme 1). The use of strong base such as alkali metal *t*-butoxide was found to give a lot of undesirable by-products mainly based on intra- and intermolecular reactions of **1**. So, alkali metal carbonates were used as the base in the first step of this reaction and were found to be appropriate for suppressing the side reaction.

Scheme 1

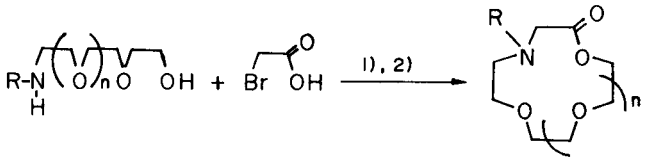


1 2 3

1) K_2CO_3 2) $PhSO_2Cl$ / M_2CO_3 / dioxane (M = K, Na)

N-Substituted 3-oxo monoaza crown ethers **6** were also prepared according to the procedure as shown in Scheme 2. *N*-(Polyoxyethylene)amine **4** as a starting material was prepared by alkylation of primary amine using **1** in the presence of sodium carbonate in about 80% yield according to the conventional method [4].

Scheme 2



4 5 6

1) M_2CO_3 2) M_2CO_3 / $PhSO_2Cl$ / dioxane (M = Na, K)

Table

Synthesis of Monooxo Crown Ethers

Compound	n	M	Yield (%) [a]
3a	2	Na	14
3b	3	Na	28
3c	4	K	18
6a	2	Na	9
6b	2	Na	12
6c	3	K	16

[a] Purified yield.

EXPERIMENTAL

The infrared spectra were obtained on a Hitachi 260-10 spectrometer. The mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV. The ^1H nmr spectra were taken at 100 MHz on a JEOL JNM-PS-100 spectrometer, using tetramethylsilane as the internal standard.

3-Oxo-1-thia-15-crown-5 (**3a**).

A mixture of tetraethylene glycol monochloride (**1**) (n = 2) (8.5 g, 0.04 mole), thioglycolic acid (**2**) (4.2 g, 88%, 0.04 mole), and potassium carbonate (5.6 g, 0.04 mole) was heated at 100-107° for 3.5 hours with stirring. Dioxane (200 ml) and sodium carbonate (4.3 g, 0.04 mole) were added to the mixture. To the stirred mixture was added dropwise benzenesulfonyl chloride (7.2 g, 0.04 mole) in dioxane (20 ml) over a 2 hour period at 70° and the mixture was further stirred for 3 hours at that temperature. After cooling to room temperature, the insoluble matter was removed by filtration. The filtrate was evaporated under reduced pressure to give a viscous brown liquid (10.6 g). This residue was thermolyzed in a Kugelrohr apparatus under reduced pressure (~225°/0.04 Torr) to give a yellowish liquid (2.15 g). Water (25 ml) was added to the liquid and washed with hexane (25 ml x 2). The aqueous layer was extracted with dichloromethane (25 ml). After evaporating the dichloromethane, the residue was further purified by distillation in Kugelrohr under reduced pressure (105-110°/0.02 Torr) to give a pale yellow oil (1.36 g, 14%). The analytical data of **3a** were as follows: ir (neat): 2880 (s), 1735 (s, ν C=O), 1450 (m), 1350 (m), 1280 (s), 1130 (s), 1040 (w), 935 (m), and 850 cm^{-1} (w); ms: (m/e) 250 (M^+, 42), 162 (27), 144 (23), 119 (31), 118 (51), 100 (40), 89 (31), 87 (33), 86 (67), 75 (22), 73 (35), 60 (20), 46 (32), 45 (100), 43 (39), and 42 (27); nmr (carbon tetrachloride): δ 2.73 (t, 2H), 3.22 (s, 2H), 3.40-3.80 (m, 12H), and 4.20 (t, 2H).

Anal. Calcd. for $C_{10}H_{18}SO_5$: C, 47.98; H, 7.25; S, 12.81. Found: C, 47.76; H, 7.28; S, 12.69.

3-Oxo-1-thia-18-crown-6 (**3b**).

This compound had bp 120-124°/0.03 Torr (Kugelrohr apparatus); ir (neat): 2880 (s), 1740 (s, ν C=O), 1455 (m), 1360 (m), 1290 (s), 1130 (s), 1040 (w), 945 (m), and 860 cm^{-1} (w); ms: (m/e) 294 (M^+, 29), 144 (30), 119 (33), 118 (40), 100 (33), 89 (36), 87 (42), 86 (69), 73 (31), 45 (100), and 43 (35); nmr (carbon tetrachloride): δ 2.76 (t, 2H), 3.32 (s, 2H), 3.50-3.80 (m, 16H), and 4.22 (t, 2H).

Anal. Calcd. for $C_{12}H_{22}SO_6$: C, 48.96; H, 7.53; S, 10.89. Found: C, 49.07; H, 7.59; S, 10.59.

3-Oxo-1-thia-21-crown-7 (**3c**).

This compound had bp 135-140°/0.03 Torr (Kugelrohr apparatus); ir (neat): 2870 (s), 1730 (s, ν C=O), 1450 (m), 1350 (m), 1290 (s), 1120 (s), 1035 (w), 945 (m), and 850 cm^{-1} (w); ms: (m/e) 338 (M^+, 15), 144 (24), 119 (27), 118 (43), 100 (25), 89 (39), 87 (43), 86 (50), 73 (37), 45 (100), and 43 (34); nmr (carbon tetrachloride): δ 2.75 (t, 2H), 3.24 (s, 2H), 3.45-3.75 (m, 20H), and 4.22 (t, 2H).

Anal. Calcd. for $C_{14}H_{26}SO_7$: C, 49.69; H, 7.74; S, 9.47. Found: C, 49.59; H, 7.81; S, 9.21.

N-(Polyoxyethylene)amine (**4**).

Compound **4** was prepared from primary amine (0.15 mole) and **1** (0.05 mole) in the presence of sodium carbonate (0.053 mole) at 120° for 3-4 hours according to a known method [4].

N-(Tetraoxyethylene)phenylamine (**4a**).

This compound was obtained in a yield of 80%, bp 175-180°/0.04 Torr (Kugelrohr apparatus).

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.38; H, 8.77; N, 5.31.

N-(Tetraoxyethylene)hexylamine (**4b**).

This compound was obtained in a yield of 82%, bp 150-155°/0.04 Torr (Kugelrohr apparatus).

Anal. Calcd. for $C_{14}H_{31}NO_4$: C, 60.62; H, 11.27; N, 5.05. Found: C, 60.30; H, 11.32; N, 4.97.

N-(Pentaethylene)phenylamine (**4c**).

This compound was obtained in a yield of 82%, bp 190-195°/0.04 Torr (Kugelrohr apparatus).

Anal. Calcd. for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.17; H, 8.95; N, 4.54.

N-Phenyl-3-oxo-1-aza-15-crown-5 (**6a**).

A mixture of **4a** (10.0 g, 0.037 mole), bromoacetic acid (**5**) (5.6 g, 0.04 mole), and sodium carbonate (5.35 g, 0.05 mole) was heated at 120° for 4 hours with stirring. Dioxane (200 ml) and sodium carbonate (4.3 g, 0.04 mole) were added to the mixture. To the mixture was added dropwise benzenesulfonyl chloride (7.2 g, 0.04 mole) in dioxane (20 ml) over a 2 hour period at 70° and the mixture was further stirred for 2 hours at that temperature. After cooling to room temperature, the insoluble matter was removed by filtration. The filtratewas evaporated under reduced pressure to give a brown liquid (14.0 g). This residue was continuously extracted with hexane to give a crude product of **6a** (3.43 g). The crude product was purified by silica gel column chromatography (hexane/acetone) to give a pale yellow oil (1.02 g, 9%). The analytical data of **6a** were as follows: ir (neat): 3040 (w), 2880 (s), 1755 (s), 1735 (s), 1605 (s), 1510 (s), 1455 (w), 1390 (m), 1355 (m),1285 (w), 1255 (w),1190 (s), 1140 (s), 1045 (m), 990 (w), 940 (m), 870 (w), 755 (s), and 700 cm^{-1} (s); ms: (m/e) 310 (M+1, 19), 309 (M^+, 100), 162 (34), 149 (21), 146 (20), 132 (19), 120 (26), 119 (28), 106 (39), 105 (49), 104 (22), 91 (38), 77 (26), and 45 (22); nmr (carbon tetrachloride): δ 3.35-3.85 (m, 14H), 4.05-4.25 (s + m, 4H), 6.45-6.70 (m, 3H), and 7.00-7.20 (m, 2H).

Anal. Calcd. for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.94; H, 7.63; N, 4.66.

N-Hexyl-3-oxo-1-aza-15-crown-5 (**6b**).

This compound had ir (neat): 2940 (s), 2880 (s), 1745 (s, ν C=O), 1470 (m), 1355 (m), 1300 (w), 1260 (w), 1180 (s), 1130 (s), and 945 cm^{-1} (m); ms: (m/e) 317 (M^+, 23), 246 (100), 202 (90), 126 (22), 114 (62), 100 (25), 43 (33), and 42 (29); nmr (deuteriochloroform): δ 0.88 (t, 3H), 1.10-1.16 (m, 8H), 2.68 (t, 2H), 2.88 (t, 2H), 3.50-3.80 (s + m, 14H), and 4.28 (t, 2H).

Anal. Calcd. for $C_{16}H_{31}NO_5$: C, 60.54; H, 9.84; N, 4.41. Found: C, 60.46; H, 9.82; N, 4.40.

N-Phenyl-3-oxo-1-aza-18-crown-6 (**6c**).

This compound had ir (neat) 3060 (w), 3040 (w), 2880 (s), 1750 (s, ν C=O), 1600 (s), 1510 (s), 1460 (m), 1395 (m), 1360 (m), 1255 (m), 1190 (s), 1130 (s), 1040 (m), 995 (m), 950 (m), 860 (w), 760 (s), and 695 cm^{-1} (s); ms: (m/e) 354 (M+1, 22), 353 (M^+, 100), 162 (38), 120 (37), 106 (38), 105 (52), 91 (30), and 45 (26); nmr (carbon tetrachloride): δ 3.45-3.80 (m, 18H), 4.10-4.30 (s + m, 4H), 6.45-6.70 (m, 3H), and 7.00-7.23 (m, 2H).

Anal. Calcd. for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.87; H, 7.89; N, 4.13.

REFERENCES AND NOTES

[1] C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).

[2] J. S. Bradshaw, R. E. Asay, S. L. Baxter, P. E. Fore, S. T. Jolley, J. D. Lamb, G. E. Maas, M. D. Thompson, R. M. Izatt and J. J. Christensen, *Ind. Eng. Chem., Prod. Res. Rev.*, **19**, 86 (1980), and the references cited therein.

[3] K. Matsushima, N. Kawamura, Y. Nakatsuji and M. Okahara, *Bull. Chem. Soc. Japan*, **55**, 2181 (1982).

[4] P.-L. Kuo, M. Miki, I. Ikeda and M. Okahara, *J. Am. Oil Chem. Soc.*, **57**, 227 (1980).