Macroheterocycles; XIV. A Convenient Synthesis of Azacrown Ether Derivatives via Aminomethylation

A. V. Bogatsky*, N. G. Lukyanenko, V. N. Pastushok

Physico-Chemical Institute, Academy of Sciences of Ukr. S.S.R., Odessa, Chernomorskaya doroga 86, 270080, U.S.S.R.

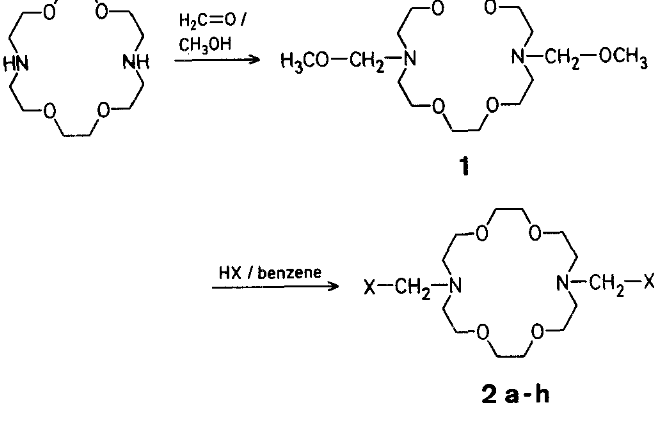
R. G. Kostyanovsky

Institute of Chemical Physics, Academy of Sciences of U.S.S.R., Moscow, Kosygina 4, 117977, U.S.S.R.

We have previously reported that diaza-18-crown-6 readily undergoes aminomethylation at carbon (Mannich reaction), nitrogen, and oxygen in 82-94% yield[1]. Analogous *N*-phosphonomethylations using formaldehyde and phosphoric acid (Kabachnik-Fields reaction) have been achieved with aza-18-crown-6[2] and 1,4,7-triazacyclononane[3] in 74% and 58% yield, respectively. In this case, introduction of a functional group into the side chain results in considerable changes in the binding properties[2,3] of the crown compounds.

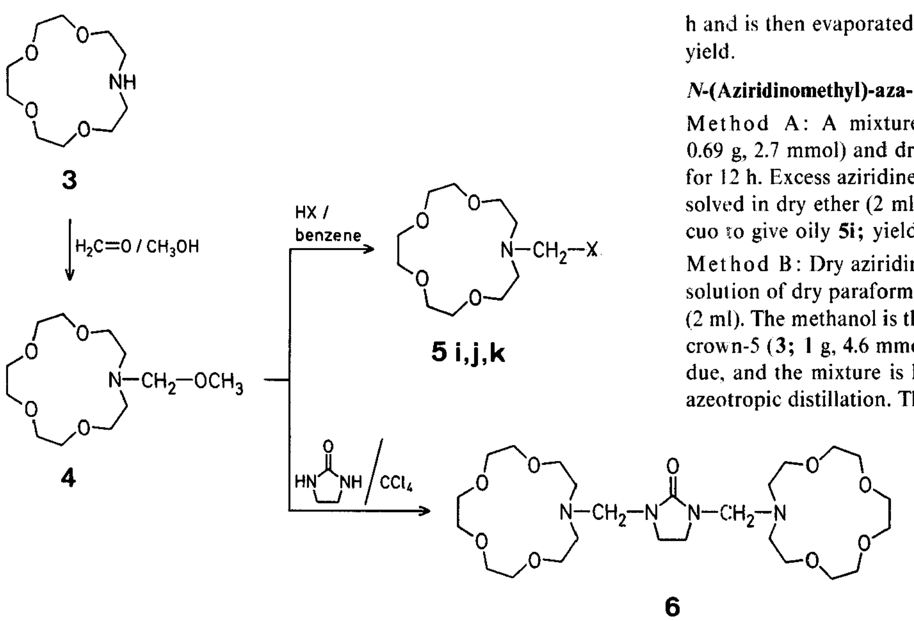
The formation of a diaminomethane derivative from one molecule of formaldehyde and two molecules of an azacrown ether is sterically hindered[1]. Instead, the reactions of 1,10-diaza-18-crown-6 and of aza-15-crown-5 (**3**) with formaldehyde and methanol afford *N,N'*-bis[methoxymethyl]-1,10-diaza-18-crown-6 (**1**) and *N*-(methoxymethyl)-aza-15-crown-5 (**4**) in 82 and 98% yields, respectively. The *N*-methoxymethyl derivatives **1** and **4** are reactive aminomethylating agents, as shown in the present report.

The reaction of *N,N'*-bis[methoxymethyl]-1,10-diaza-18-crown-6 (**1**) with imidazole, 4-butanelactam (2-oxopyrrolidine), and cyclic imides in dry benzene (20°C, 1-2 h) affords the *N,N'*-disubstituted diazacrown ethers **2** in high yields.



The reaction [heating] of *N*-(methoxymethyl)-aza-15-crown-6 (**4**) with aza-15-crown-5 (**3**) is sterically hindered so that the *N,N*-methylene-bis[azacrown ether] could not be obtained. On the other hand, compound **4** reacts readily with aziridine, 2-nitropropane, and 2,6-dimethylphenol to give the *N*- or *C*-aminomethylation products **5i, j, k** in good yields. Compound **5i** was also prepared in 94% yield by reaction of aza-15-crown-5 (**3**) with *N*-(hydroxymethyl)-aziridine according to Ref.[1]. The high yield of **5i** obtained from **4** can be rationalized by the fact that neither aza-15-crown-5 (**3**) nor aziridine[4] form symmetrical diaminomethanes. The reaction of compound **4** with 2-oxoimidazolidine affords the bis[azacrown ether] **6**.

Compounds **2**, **4**, **5**, and **6** were characterized by microanalysis as well as by mass-, I.R.-, and ^{1}H-N.M.R.-spectral data.



N,N'-Disubstituted 1,10-Diaza-18-crown-6 (2a-h); General Procedure:

A mixture of N,N'-bis[methoxymethyl]-1,10-diaza-18-crown-6 (prepared from 1,10-diaza-18-crown-6[5] according to Ref.[1]; **1**; 1 g, 2.9 mmol) and the *NH*-acidic compound (5.8 mmol) in absolute benzene (5 ml) is heated to reflux and then allowed to stand at 20°C for 1-2 h. Products **2c** and **2e** are isolated by suction. In the other cases, the mixture is filtered and the filtrate evaporated. Product **2h** is recrystallized from acetone.

N-(4-Hydroxy-3,5-dimethylbenzyl)-aza-15-crown-5 (5k):

This compound is prepared from *N*-(methoxymethyl)-aza-15-crown-5 (**4**; 0.268 g, 1.1 mmol) and 2,6-dimethylphenol (0.138 g, 1.1 mmol) following the above procedure.

N-(Methoxymethyl)-aza-15-crown-5 (4):

A solution of aza-15-crown-5[6] (**3**; 5 g, 22.8 mmol) in dry methanol (30 ml) is added to a stirred solution of dry paraformaldehyde (0.685 g, 22.8 mmol) in dry methanol (30 ml). The mixture is kept at 20°C for 12 h and is then evaporated in vacuo to give oily **4** in nearly quantitative yield.

N-(Aziridinomethyl)-aza-15-crown-5 (5i):

Method A: A mixture of *N*-(methoxymethyl)-aza-15-crown-5 (**4**; 0.69 g, 2.7 mmol) and dry aziridine (0.42 g, 9.7 mmol) is kept at 20°C for 12 h. Excess aziridine is then removed in vacuo. The residue is dissolved in dry ether (2 ml), the solution filtered, and evaporated in vacuo to give oily **5i**; yield: 0.68 g (94%).

Method B: Dry aziridine (0.19 g, 4.6 mmol) is added at −40°C to a solution of dry paraformaldehyde (0.137 g, 4.6 mmol) in dry methanol (2 ml). The methanol is then evaporated in vacuo, a solution of aza-15-crown-5 (**3**; 1 g, 4.6 mmol) in dry benzene (4 ml) is added to the residue, and the mixture is kept at 20°C for 3 h. Benzene is removed by azeotropic distillation. The residue is dissolved in dry ether (3 ml), the solution filtered, and the filtrate evaporated in vacuo to give oily **5i**; yield: 1.19 g (95%).

N-(2-Methyl-2-nitropropyl)-aza-15-crown-5 (5j):

N-(Methoxymethyl)-aza-15-crown-5 (**4**; 1.53 g, 6 mmol) is mixed with 2-nitropropane (0.746 g, 8 mmol) and the mixture allowed to stand at 20°C for 12 h. Then, pentane (2 ml) is added and the lower layer isolated and subjected to column chromatography on silica gel using chloroform/methanol (5/1) as eluent to give the oily product **5j**; yield: 1.72 g (89%).

N,N'-(2-Oxotetrahydroimidazol-1,3-diyldimethyl)-bis[aza-15-crown-5] (6):

A mixture of *N*-(methoxymethyl)-aza-15-crown-5 (**4**; 0.691 g, 2.6 mmol) and 2-oxotetrahydroimidazole (0.113 g, 1.3 mmol) in dry tetrachloromethane (5 ml) is refluxed for 3 h, cooled to room temperature, and filtered. The filtrate is evaporated to give the oily product **6**; yield: 0.68 g (95%).

Table. Characteristics of Azacrown-Ethers (**2**, **4**, **5**, **6**) prepared

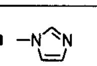
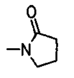
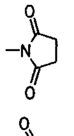
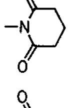
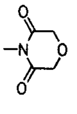
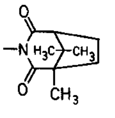
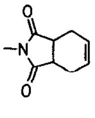
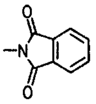
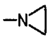
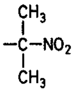
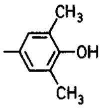
Prod-uct	X	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	M.S. *m/e*	^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm]
2 a		96	97°	$C_{20}H_{34}N_6O_4$ (422.5)	422	2.48 (t, 8H); 3.33 (m, 16H); 4.78 (s, 4H); 6.62 (s, 4H); 7.18 (s, 2H)
2 b		95	50°	$C_{22}H_{40}N_4O_6$ (456.6)	457	2.07 (m, 8H); 2.68 (t, 8H); 3.48 (m, 16H); 3.48 (m, 4H); 4.00 (s, 4H)
2 c		90	143-145°	$C_{22}H_{36}N_4O_8$ (484.5)	484	2.62 (s, 8H); 2.82 (t, 8H); 3.54 (m, 16H); 4.43 (s, 4H)
2 d		99	86°	$C_{24}H_{40}N_4O_8$ (512.6)	512	1.78 (m, 4H); 2.53 (t, 8H); 2.83 (t, 8H); 3.52 (m, 16H); 4.73 (s, 4H)
2 e		86	117-118°	$C_{22}H_{36}N_4O_{10}$ (516.5)	516	2.83 (t, 8H); 3.53 (m, 16H); 4.23 (s, 8H); 4.78 (s, 4H)
2 f		92	oil[c]	$C_{34}H_{56}N_4O_8$ (648.8)	649	0.93 (s, 12H); 1.15 (s, 6H); 1.95 (m, 8H); 2.65 (m, 2H); 2.85 (t, 8H); 3.57 (m, 16H); 4.75 (m, 4H)
2 g		99	125-126°	$C_{30}H_{44}N_4O_8$ (588.7)	589	2.28 (m, 8H); 2.70 (t, 8H); 3.50 (m, 16H); 4.37 (s, 4H); 5.78 (m, 4H)

Table. (Continued)

Prod-uct	X	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	M.S. *m/e*	¹H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm]
2h		87	128–130°	$C_{30}H_{36}N_4O_8$ (580.6)	581	2.88 (t, 8H); 3.57 (m, 16H); 4.65 (s, 4H); 7.72 (m, 8H)
4	–	98	oil	$C_{12}H_{25}NO_5$ (263.3)	263	2.90 (t, 4H); 3.02 (s, 3H); 3.60 (m, 16H); 4.05 (s, 2H)
5i		95	oil	$C_{13}H_{26}N_2O_4$ (274.2)	274	1.08 (m, 2H); 1.63 (m, 2H); 2.93 (t, 4H); 3.08 (s, 2H); 3.55 (m, 16H)
5j	 $-C(CH_3)_2-NO_2$	89	oil	$C_{14}H_{28}N_2O_6$ (320.2)	320	1.45 (s, 6H); 2.72 (t, 4H); 2.95 (s, 2H); 3.45 (m, 16H)
5k		97	oil	$C_{19}H_{31}NO_5$ (353.6)	354	2.15 (s, 6H); 2.70 (t, 4H); 3.46 (s, 2H); 3.58 (m, 16H); 4.55 (m, 1H); 6.77 (m, 2H)
6	–	95	oil	$C_{25}H_{48}N_4O_9$ (548.7)	549	2.65 (t, 4H); 3.45 (m, 32H); 3.45 (s, 4H); 3.90 (s, 4H)

[a] The purity of all products was determined by G.L.C. (1.5 m column, Chromosorb G/NAW, 7% OV-17) and was not less than 97%.

[b] Satisfactory microanalyses were obtained: C, ±0.30; H, ±0.32; N, ±0.36.

[c] $[\alpha]_D$: +5.52° (*c* 4.9, ethanol).

Received: May 9, 1983

---

* Address for correspondence.

[1] A. V. Bogatsky, N. G. Lukyanenko, V. N. Pastushok, R. G. Kostyanovsky, *Dokl. Akad. Nauk SSSR* **265**, 619 (1982); *C. A.* **97**, 216146 (1982).

[2] K. Nita, M. Takagi, K. Ueno, *Chem. Lett.* **1982**, 571.

[3] Y. M. Polikarpov et al., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 1669; *C. A.* **98**, 46001 (1983).

[4] R. G. Kostyanovsky, V. F. Bystrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1962**, 1488; *C. A.* **58**, 4401 (1963).

[5] B. Dietrich, J. M. Lehn, J. P. Sauvage, *Tetrahedron Lett.* **1969**, 2885.
J. M. Lehn, *U. S. Patent* 3888877 (1970), Scherico Ltd.; *C. A.* **74**, 100134 (1971).
S. Kulstad, L. A. Malmsten, *Acta Chem. Scand.* [B] **33**, 469 (1979).
G. W. Gokel, D. M. Dishong, R. A. Schultz, V. J. Gatto, *Synthesis* **1982**, 1005, 1007.

[6] H. Maeda, Y. Nakatsuji, M. Okahara, *J. Chem. Soc. Chem. Commun.* **1981**, 471.