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Synthesis of New Azacrown and Azathiacrown Ethers Using a Hypervalent Sulfur-Containing Tetraazapentalene as a Ring-Building Block

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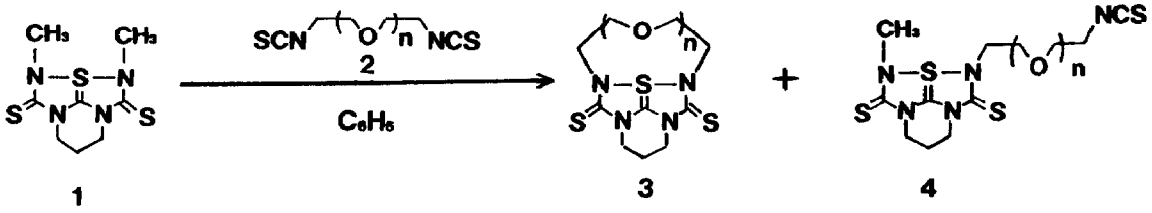
Abstract: *New azacrown and azathiacrown ethers (5a-c and 7), incorporating two thiourea moieties, were synthesized from the hypervalent sulfur-containing tetraazapentalene (1) and diisothiocyanate derivatives of oligoethylene glycols and from 1 and 3,6,9-trithia-1,11-undecanediisothiocyanate, respectively, by cyclization and then desulfurization.*

Recently, we have reported that the tetraazapentalene derivative, 2,3-dimethyl-6,7-dihydro-5H-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazacyclopent[cd]indene-1,4(2H,3H)-dithione(**1**)[1], reacts with alkyl- and arylisothiocyanates or isocyanates to give new N-alkyl and N-arylsubstituted tetraazapentalene derivatives[2] by replacement of the isothiocyanate moiety of **1** and that the hypervalent sulfur of **1** can be removed by treatment with $NaBH_4$[3] and CF_3COOH[4] to give the perhydropyrimidine and perhydropyrimidin-2-one derivatives, respectively. More recently, these reactions have been applied to the synthesis of rigid macrocycles[5] from **1**, p-xylylenediisothiocyanate, and diamines. These findings led us to explore the synthesis of flexible macrocycles using **1** as a ring-building block. We now report a convenient method for preparing new azacrown and azathiacrown ethers (**5a-c** and **7**) from **1** and diisothiocyanate derivatives of oligoethylene glycols (**2a-c**) and from **1** and 3,6,9-trithia-1,11-undecanediisothiocyanate, respectively.

The typical procedure for the cyclization reaction is as follows. A solution of 3,6,9-trioxa-1,11-undecanediisothiocyanate[6] (**2a**) (213 mg, 0.77 mmol) in benzene (30 cm^3) was added to a solution of **1** (200 mg, 0.77

mmol) in benzene (40 cm^3) with stirring at room temperature. The mixture was refluxed for 48 h and then evaporated. Chromatography of the residue on silica gel with CH_2Cl_2-AcOEt (9:1) gave tetraazapentalene crown ether (**3a**) and monosubstituted tetraazapentalene derivative (**4a**) together with recovery of **1** (Scheme 1). The other products were not detected in this reaction. Similar treatment of **1** with diisocyanates **2b,c** gave **3b,c** and **4b,c**. The structures of **3a-c**[7] and **4a-c** were determined by their IR, ^1H NMR and FAB mass spectra and elemental analyses. The yields of **3a-c** depended on the number of the $-CH_2OCH_2-$ unit of **2**.



1 **3** **4**

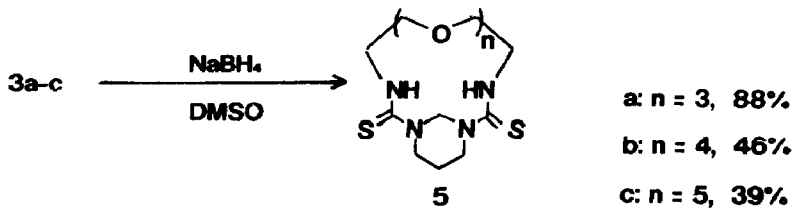
a: n = 3, 74% **a**: n = 3, 4%

b: n = 4, 56% **b**: n = 4, 14%

c: n = 5, 44% **c**: n = 5, 11%

Scheme 1

The ring opening of the tetraazapentalene skeleton of **3a-c** was carried out using $NaBH_4$. A typical procedure is as follows. A large excess (10 molar equiv.) of $NaBH_4$ was added under argon to a solution of **3a** (100 mg, 0.256 mmol) in DMSO (30 cm^3) at room temperature. The mixture was stirred for 15 h, poured into aqueous HCl, neutralized with aqueous KOH, and then extracted with $CHCl_3$. After removal of $CHCl_3$ under reduced pressure, the residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (4:1) to give azacrown ether (**5a**) in a high yield (Scheme 2). Compounds **5b,c** were obtained in moderate yields under similar conditions. The structures of **5a-c** were determined by their ^1H NMR[8] and FAB mass spectra[8]



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a: n = 3, 88%

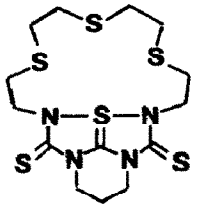
b: n = 4, 46%

c: n = 5, 39%

Scheme 2

and elemental analyses. In the ^{1}H NMR spectra of **5a-c**, the characteristic singlet signals due to the methylene protons (NC*H*$_2$N) at 2-position appeared at δ = 5.34-5.66.

This synthetic method was applied to the synthesis of azathiacrown ether. When the reaction of **1** with 3,6,9-trithia-1,11-undecanediisothiocyanate was carried out in benzene at 50°C for 45 h, tetraazapentalene thiacrown ether (**6**) was isolated in 45% yield. The reaction of **6** with NaBH$_4$ under the conditions being similar to the cases of **3a-c** gave azathiacrown ether (**7**), incorporating two thiourea moieties, in 57% yield. The structures of **6**[7] and **7**[8] were established by their spectral data and elemental analyses. Further investigations concerning the scope of the present reaction are now in progress.



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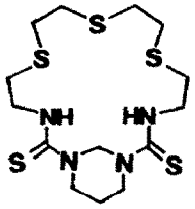

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7. Characteristic analytical data: **3a**, mp 199-200°C (decomp); ^{1}H NMR ($CDCl_3$) δ =2.36 (quint, 2H, $NCH_2CH_2CH_2N$, J=6.0 Hz), 3.56-3.68 (m, 8H, 2X

OCH_2CH_2O), 3.73 (t, 4H, 2X OCH_2CH_2N, J=4.6 Hz), 3.98 (t, 4H, 2X OCH_2CH_2N, J=4.6 Hz), 4.40 (t, 4H, $NCH_2CH_2CH_2N$, J=5.8 Hz); Anal. Calcd for $C_{14}H_{22}N_4O_3S_3$: C, 43.06; H, 5.68; N, 14.35. Found: C, 42.90; H, 5.67; N, 14.36. **3b**, mp 154.5-155.5°C (decomp); ^{1}H NMR($CDCl_3$) δ=2.37 (quint, 2H, $NCH_2CH_2CH_2N$, J=5.8 Hz), 3.62-3.71 (m, 12H, 3X OCH_2CH_2O), 3.81 (t, 4H, 2X OCH_2CH_2N, J=4.9 Hz), 3.93 (t, 4H, 2X OCH_2CH_2N, J=4.9 Hz), 4.40 (t, 4H, $NCH_2CH_2CH_2N$, J=6.1 Hz); Anal. Calcd for $C_{16}H_{26}N_4O_4S_3$: C, 44.22; H, 6.03; N, 12.89. Found: C, 44.16; H, 6.03; N, 13.02. **3c**, mp 124.5-125.5°C (decomp); ^{1}H NMR($CDCl_3$) δ=2.36 (quint, 2H, $NCH_2CH_2CH_2N$, J=6.0 Hz), 3.63-3.70 (m, 16H, 4X OCH_2CH_2O), 3.76 (t, 4H, 2X OCH_2CH_2N, J=5.5 Hz), 3.98 (t, 4H, 2X OCH_2CH_2N, J=5.8 Hz), 4.41 (t, 4H, $NCH_2CH_2CH_2N$, J=5.8 Hz); Anal. Calcd for $C_{18}H_{30}N_4O_5S_3$: C, 45.17; H, 6.32; N, 11.70. Found: C, 45.00; H, 6.12; N, 11.65. **6**, mp 202-203°C (decomp); ^{1}H NMR($CDCl_3$) δ=2.38 (quint, 2H, $NCH_2CH_2CH_2N$, J=6.0 Hz), 2.81-2.90 (m, 8H, 2X SCH_2CH_2S), 2.95 (t, 4H, 2X SCH_2CH_2N, J=6.7 Hz), 3.96 (t, 4H, 2X SCH_2CH_2N, J=6.4 Hz), 4.41 (t, 4H, $NCH_2CH_2CH_2N$, J=5.8 Hz); Anal. Calcd for $C_{14}H_{22}N_4S_6$: C, 38.33; H, 5.05; N, 12.77. Found: C, 38.07; H, 5.07; N, 12.65. All FAB mass spestra were measured by using m-nitrobenzyl alcohol (NBA) as a matrix. **3a**, m/z 391 ($M+H^+$); **3b**, m/z 435 ($M+H^+$); **3c**, m/z 479 ($M+H^+$); **6**, m/z 439 ($M+H^+$).

8. **5a**: ^{1}H NMR($CDCl_3$) δ =1.88 (quint, 2H, $NCH_2CH_2CH_2N$, J=6.0 Hz), 3.60-3.66 (m, 8H, 2X OCH_2CH_2O), 3.75 (t, 4H, 2X OCH_2CH_2NH, J=4.9 Hz), 3.87-3.93 (m, 4H, 2X OCH_2CH_2NH), 4.02 (t, 4H, $NCH_2CH_2CH_2N$, J=6.1 Hz), 5.52 (s, 2H, NCH_2N), 7.03 (brs, 2H, 2X OCH_2CH_2NH); **5b**: ^{1}H NMR($CDCl_3$) δ=1.84 (quint,2H, $NCH_2CH_2CH_2N$, J=5.8 Hz), 3.63-3.69 (m, 16H, 4X CH_2OCH_2), 3.98-4.03 (m, 4H, 2X OCH_2CH_2NH), 4.22 (t, 4H, $NCH_2CH_2CH_2N$, J=5.8 Hz), 5.34 (s, 2H, NCH_2N), 7.33 (brs, 2H, 2X OCH_2CH_2NH); **5c**: ^{1}H NMR($CDCl_3$) δ=1.82 (quint, 2H, $NCH_2CH_2CH_2N$, J=5.7 Hz), 3.59-3.67 (m, 16H, 4X OCH_2CH_2O), 3.73 (t, 4H, 2X OCH_2CH_2NH, J=4.9 Hz), 3.86-3.91 (m, 4H, 2X OCH_2CH_2NH), 4.01 (t, 4H, $NCH_2CH_2CH_2N$, J=5.5 Hz), 5.66 (s, 2H, NCH_2N), 7.34 (brs, 2H, 2X OCH_2CH_2NH); **7**: ^{1}H NMR($CDCl_3$) δ=1.85 (quint, 2H, $NCH_2CH_2CH_2N$, J=5.8 Hz), 2.71-2.81 (m, 8H, 2X SCH_2CH_2S), 2.87 (t, 4H, 2X SCH_2CH_2NH, J=6.7 Hz), 3.84-3.91 (m, 4H, 2X SCH_2CH_2NH), 4.02-4.13 (brs, 4H, $NCH_2CH_2CH_2N$), 5.65 (s, 2H, NCH_2N), 7.35 (brs,2H, 2X, SCH_2CH_2NH). All FAB spectra were measured by using NBA as a matrix. **5a**: m/z 363 ($M+H^+$); **5b**: m/z 407 ($M+H^+$); **5c**: m/z 451 ($M+H^+$); **7**: m/z 411 ($M+H^+$).

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