Macroheterocycles; XXXIX.[1] A Convenient Synthesis of Polyaza-oxa Cryptands

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A convenient procedure is proposed for the synthesis of cryptands by the alkylation of bis-*N*-(2-tosylaminoethyl)diaza-crown ethers with dibromides in the two-phase system: aqueous sodium hydroxide/toluene.

Cryptands are usually prepared by acylation of diazacrown ethers with diacid chlorides under high dilution conditions followed by reduction of the resulting macrobicyclic diamides.[2] Recently, this procedure has been adopted for the synthesis of cryptands consisting in the alkylation of *N,N'*-dimethyldiazacrown ethers with dihalides under high pressure and subsequent demethylation of quaternary cryptands.[3] Some other procedures for the preparation of cryptands are described.[4] However, all of them are performed under anhydrous conditions, which complicates the large-scale preparation of cryptands.

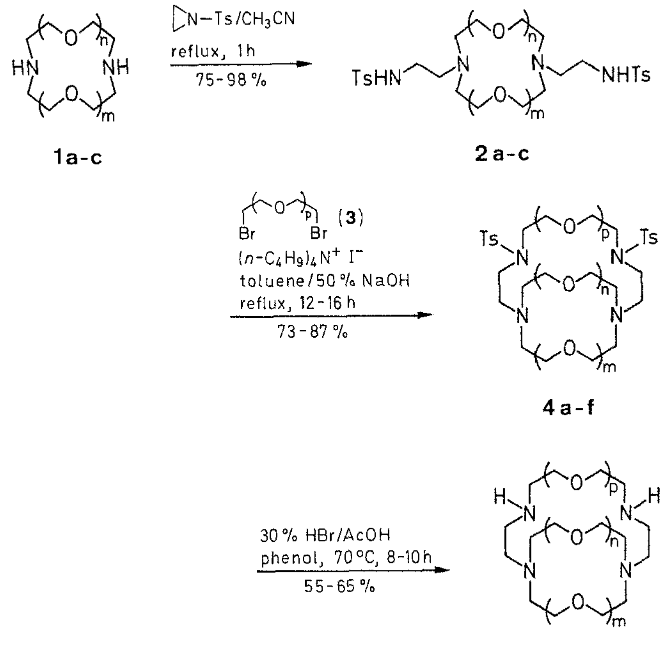

Table. Diaza-crown ethers **2**, Cryptants **4**, **5**

Product	n	m	p	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H-NMR (CDCl$_3$/TMS)[b] δ, *J* (Hz)	MS (70 eV)[c] *m/z* (M$^+$)
2a	1	1	–	91	165–167	$C_{26}H_{40}N_4O_6S_2$	2.31 (s, 6H, CH$_3$); 2.50 (m, 12H, NCH$_2$); 2.80 (m, 4H, CH$_2$NTs); 3.55 (t, 8H, *J* = 5.5, OCH$_2$); 6.75 (m, 2H, NH); 7.40 (m, 8H, C$_6$H$_4$)	568
2b	1	2	–	75	66–67	$C_{28}H_{44}N_4O_7S_2$	2.20 (s, 6H, CH$_3$); 2.43 (m, 12H, NCH$_2$); 2.70 (m, 4H, CH$_2$NTs); 3.35 (m, 12H, OCH$_2$); 5.70 (m, 2H, NH); 7.33 (m, 8H, C$_6$H$_4$)	612
2c	2	2	–	98	112–115	$C_{30}H_{48}N_4O_8S_2$	2.30 (s, 6H, CH$_3$); 2.50 (m, 12H, NCH$_2$); 2.80 (m, 4H, CH$_2$NTs); 3.41 (m, 16H, OCH$_2$); 5.87 (m, 2H, NH); 7.41 (m, 8H, C$_6$H$_4$)	656
4a	1	1	1	81	60–63	$C_{30}N_{46}N_4O_7S_2$	2.33 (s, 6H, CH$_3$); 2.40 (m, 12H, CH$_2$N); 3.31 (m, 20H, OCH$_2$, CH$_2$NTs); 7.00 (m, 8H, C$_6$H$_4$)	638
4b	1	1	2	73	oil	$C_{32}H_{50}N_4O_8S_2$	2.33 (s, 6H, CH$_3$); 2.43 (m, 12H, NCH$_2$); 3.33 (m, 24H, OCH$_2$, CH$_2$NTs); 7.00 (m, 8H, C$_6$H$_4$)	682
4c	1	2	1	87	oil	$C_{32}H_{50}N_4O_8S_2$	2.33 (s, 6H, CH$_3$); 2.63 (m, 12H, CH$_2$N); 3.40 (m, 24H, OCH$_2$, CH$_2$NTs); 7.4 (m, 8H, C$_6$H$_4$)	682
4d	1	2	2	83	oil	$C_{34}H_{54}N_4O_9S_2$	2.30 (s, 6H, CH$_3$); 2.67 (m, 12H, CH$_2$N); 3.45 (m, 28H, OCH$_2$, CH$_2$NTs); 7.43 (m, 8H, C$_6$H$_4$)	726
4e	2	2	1	87	oil	$C_{34}H_{54}N_4O_9S_2$	2.33 (s, 6H, CH$_3$); 2.60 (m, 12H, CH$_2$N); 3.40 (m, 28H, OCH$_2$, CH$_2$NTs); 7.33 (m, 8H, C$_6$H$_4$)	726
4f	2	2	2	84	48–50	$C_{36}H_{58}N_4O_{10}S_2$	2.37 (s, 6H, CH$_3$); 2.67 (m, 12H, CH$_2$N); 3.67 (m, 32H, OCH$_2$, CH$_2$NTs); 7.35 (m, 8H, C$_6$H$_4$)	770
5a	1	1	1	60	oil	$C_{16}H_{34}N_4O_3$	2.20 (s, 2H, NH); 2.75 (m, 20H, CH$_2$N); 3.41 (m, 12H, OCH$_2$)	330
5b	2	2	1	65	oil	$C_{20}H_{42}N_4O_5$	2.30 (s, 2H, NH); 2.60 (m, 20H, CH$_2$N); 3.47 (m, 16H, OCH$_2$)	418
5c	1	2	2	55	oil	$C_{20}H_{42}N_4O_5$	2.53 (m, 20H, CH$_2$N); 3.50 (m, 22H, OCH$_2$, NH)	418

[a] Satisfactory microanalysis obtained: C ±0.27, H ±0.17, N ±0.12. TLC analysis (neutral Al_2O_3, benzene, $CHCl_3$, *i*-PrOH, 8 : 5 : 0.1).

[b] Recorded on a Tesla BS-467 spectrometer.

[c] Obtained on a Varian-MAT 112 spectrometer.

We have previously shown the synthesis of aza-crown ethers under phase-transfer conditions.[5] As an extension of this procedure we report here a convenient preparation of novel cryptands with two nitrogen atoms in one of the bridges.

The reaction of diaza-12-crown-4 **1a**, diaza-15-crown-5 **1b** or diaza-18-crown-6 **1c** with *N*-tosylaziridine[6] in acetonitrile results in bis-*N*-2-tosyl amino ethyl diaza-crown ethers **2a–c**. Cryptands **4a–f** were obtained in good yields by the reaction of bis-sulphonamides **2a–c** with dibromides in a two-phase system consisting 50 % aqueous sodium hydroxide, toluene and tetra-*n*-butylammonium iodide as phase transfer catalyst. In the absence of the catalyst cryptands **4** are not formed.

The catalytic activity of the quaternary ammonium salts is decreased in the sequence: $(n\text{-}C_4H_9)_4N^+I^- \approx (n\text{-}C_4H_9)_4N^+Br^- > (n\text{-}C_4H_9)_4N^+Cl^- > (n\text{-}C_4H_9)_4N^+HSO_4{}^- > (C_2H_5)_3CH_2C_6H_5N^+Cl$. The high catalytic activity of tetra-*n*-butylammonium iodide and tetra-*n*-butylammonium bromide is perhaps due to their thermal stability in the alkali medium.[7]

The tosyl groups in **4** may be readily removed with hydrogen bromide in glacial acetic acid as shown by the synthesis of cryptands **5a–c**. Compounds **2**, **4**, **5** are characterized by microanalysis, mass- and ^{1}H-NMR spectra.

Bis-*N*-(2-tosylaminoethyl)diaza-crown ethers 2: General Procedure:
N-Tosylaziridine[6] (0.05 mol) in dry CH_3CN (120 mL) is added dropwise for an h to the refluxing solution of diazacrown ether **1**[5] (0.025 mol) in CH_3CN (120 mL) under nitrogen. After removal of the solvent under reduced pressure diaza crown ethers **2a–c** are purified by recrystallization from EtOH.

Bis-*N*-tosylcryptands 4; General Procedure:
Diaza-crown ether **2** (0.01 mol) and the corresponding dibromide **3** (0.01 mol) are added to the refluxing mixture of Bu_4NI (1 g, 2.7 mmol) in toluene (200 mL) and 50% aq. NaOH (100 mL). The vigorously stirred mixture is heated under reflux for 12–16 h. The organic layer is separated and dried ($MgSO_4$). The solvent is evaporated and the crude product is purified by column chromatography on neutral alumina. Elution with benzene/$CHCl_3$/*i*-PrOH (8:5:0.1) gives the product, cryptand **4**.

Cryptands 5; General Procedure:
Cryptand **4** (4.5 mmol), 30% HBr in glacial AcOH (25 g) and phenol (2.5 g, 26.5 mmol) are combined and stirred at 70°C for 8–10 h. The solution is poured into dry Et_2O (200 mL), the residual precipitate is dissolved in a minimum volume of water, basified with solid NaOH (to pH 10) and extracted with $CHCl_3$ (5 × 50 mL). The resultant extract is dried ($MgSO_4$), and the solvent is removed under reduced pressure. The cryptand **5** is obtained as a residue.

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