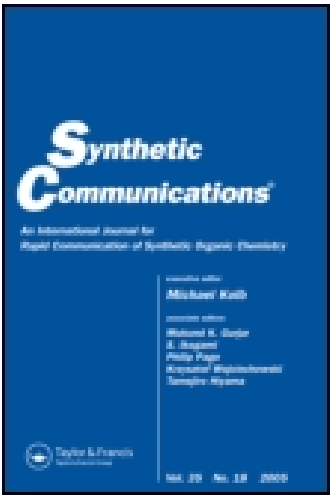

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Synthesis of Mono Protected 1,10-Diaza-18-Crown-6

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ABSTRACT

A synthetic procedure for the preparation of unsymmetrically protected 1,10-diaza-18-crown-6 has been elaborated. In contrast to previously published routes, no unprotected 1,10-diaza-18-crown-6 is needed as precursor and cheap bulk chemicals can be used.

Key Words: Azacrown ether; Macrocycle; Cyclization.

Crown ethers are widely used for recognition of alkali and ammonium cations. In contrast to regular crown ethers, aza crowns have the advantage of simplified functionalization due to their nucleophilic nitrogen atoms.

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Therefore, they have been used to generate ion channels,[1] lariat ethers,[2,3] fluorescence responsive sensors,[4] and cryptands.[5]

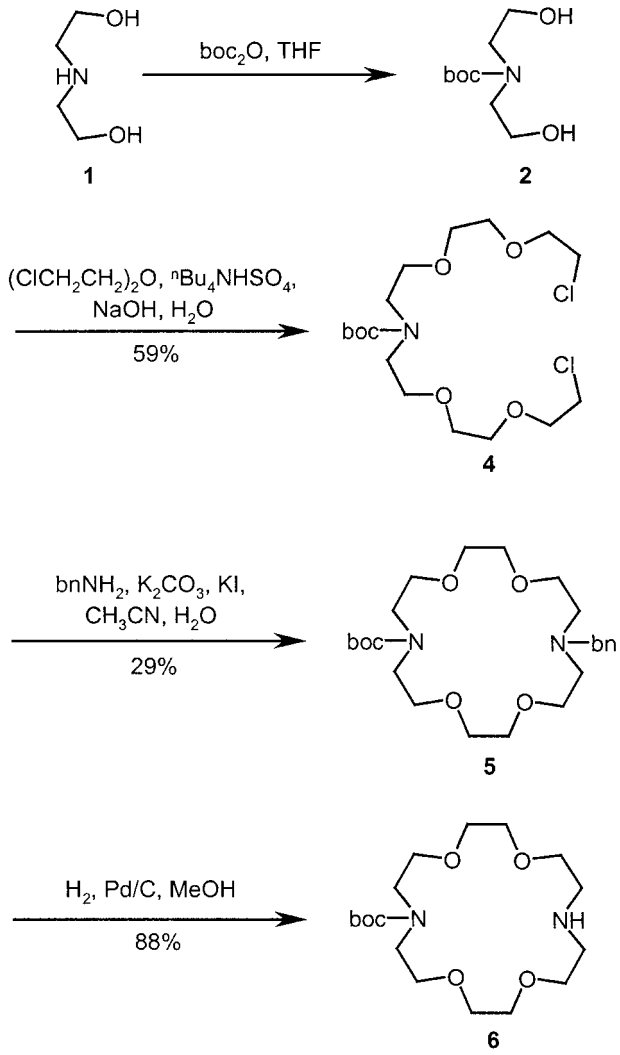
Diaza crown ethers offer even more possibilities to generate new crown-derived structures. Applicability is admittedly restricted by the similar reactivity of the crown nitrogens. Thus, fewer asymmetric, monosubstituted diaza crown ethers have been synthesized due to the imminent loss of reaction yield by the inevitable creation of the doubly substituted crown ether as well. Hall et al. have reported two ways to generate mono-*boc*-protected diaza crown ethers. Treatment of 1,10-diaza-18-crown-6 with 1 equivalent of *Boc*-anhydride generates the mono-*boc* derivative in 44% yield.[6] The other published route[7] starts off with the two-fold substituted 1,7-diaza-18-crown-6 followed by selective removal of one of the two *Boc*-groups by treatment with TFA and precipitation of the product. Although both routes are reliable, they still require a diaza-crown precursor that is not always commercially available or rather expensive as for 1,10-diaza-18-crown-6. As we needed protected diaza crown ethers, we investigated for a way to synthesize asymmetrically substituted diaza crown ethers by using cheaper bulk chemicals. We report herein the synthesis of mono-*boc*-protected 1,10-diaza-18-crown-6 in four steps, which is capable of generating the desired product at reasonable costs.

Diethanolamine **1** was converted into *N-Boc*-diethanolamine **2** by following a reported procedure.[8] Protected **2** was then substituted twice with 1,1′-dichloro ethyl ether **3** in a phase transfer reaction using nBu_4NHSO_4 as a phase transfer catalyst. The yield of **4** was 59%, whereas an attempted reaction with *N-Cbz*-diethanolamine under the same conditions was not successful at all. This is probably due to the lower stability against nucleophiles of a *Cbz* group compared to a *Boc* group. The crown ether precursor **4** was then cyclized with benzylamine to give the *Bn*- and *Boc*-protected diaza crown ether **5** with a 29% yield. Other amines can be used instead of benzylamine as long as they do not have functionalities that are vulnerable to nucleophilic attack. Deprotection of the benzyl group is easily performed with a 88% yield with dihydrogen and Pd/C as catalyst to form the mono-*Boc*-protected diaza crown ether **6**.

In summary, a way has been elaborated which gives unsymmetrically protected 1,10-diaza-18-crown-6 without the use of the unprotected crown ether but with cheap bulk chemicals.

EXPERIMENTAL

General. IR spectra: Bio-Rad FTS 3000 FT-IR. ^{1}H- and ^{13}C-NMR spectra: Bruker AC 250 or Bruker Avance 300; at 300 K; TMS as the internal



Scheme 1. Synthesis of mono-*Boc*-protected diaza crown ether **6**.

standard; s = singlet, bs = broad singlet, m = multiplet; the multiplicity of the ^{13}C signals was determined using the DEPT technique and is quoted as (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. Elemental analysis was carried out by the microanalytical laboratory, University of Regensburg. Commercially available reagents were used as received.

Thin-layer chromatography (TLC) was performed on alumina sheets (Merck KgaA, 20 × 20 cm, Silica gel 60 F_{254}).

Bis-{2-[2-(2-chloro-ethoxy)-ethoxy]-ethyl}-carbamic acid *tert*-butyl ester (4). Bis-(2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (**2**, 2.1 g, 10.2 mmol) was dissolved in 18 mL of 1,1′-dichlorodiethyl ether (**3**, 22 g, 154 mmol). The mixture was cooled to 0°C and 3.4 g (10 mmol) of nBu_4NHSO_4 and 18 mL of 50% NaOH aq. solution was added. After stirring for 2 d at room temperature, the mixture was diluted with 100 mL of H_2O and extracted with diethyl ether (100 mL). The aqueous phase was extracted twice with diethyl ether (50 mL). The combined organic phases were washed with H_2O (50 mL), dried over $MgSO_4$, and the solvent was evaporated in vacuum. The remaining 1,1′-dichlorodiethyl ether was distilled off prior to column chromatography on silica gel with PE/EE 70/30 → 60/40 (R_f (60/40) = 0.46). Compound **4** (2.54 g, 59%) was obtained as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 3.43–3.45 (m, 4 H), 3.57–3.67 (m, 16 H), 3.73–3.77 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (+), 42.7 (−), 47.6 (−), 47.8 (−), 69.7 (−), 69.9 (−), 70.3 (−), 70.4 (−), 70.7 (−), 71.4 (−), 79.6 (C_{quart}), 155.5 (C_{quart}).

IR (NaCl): $\bar{\nu}$ (cm^{-1}) = 2968 (m), 2869 (m), 1692 (s), 1463 (m), 1410 (m), 1366 (m), 1294 (m), 1244 (m), 1146 (s), 1121 (s), 1064 (m), 972 (w), 920 (w), 865 (w), 747 (w), 667 (w).

MS (CI-MS, NH_3): e/z (%) = 418 (64, MH^+), 379 (58, $M + NH_4^+ - C_4H_8$), 362 (83, $MH^+ - C_4H_8$), 318 (100, $MH^+ - C_4H_8 - CO_2$), 180 (31).

$C_{17}H_{33}Cl_2NO_6$: calcd.: C, 48.81; H, 7.95; N, 3.35; Cl, 16.95; found: C, 48.59; H, 7.53; N, 3.20; Cl, 16.76.

16-Benzyl-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane-7-carboxylic acid *tert*-butyl ester (5). Bis-{2-[2-(2-chloro-ethoxy)-ethoxy]-ethyl}-carbamic acid *tert*-butyl ester (**4**, 160 mg, 0.38 mmol) was dissolved in 5 mL of acetonitrile with 50 μL of H_2O. Benzylamine (44 μL, 43 mg, 0.4 mmol), KI (133 mg, 0.8 mmol), and K_2CO_3 (552 mg, 4 mmol) were added and the suspension was refluxed for 2 d. After cooling to room temperature, the mixture was filtered over Celite and the remaining solids were washed with $CHCl_3$. Evaporation of the combined organic phases gave an oil that was purified by column chromatography (silica, EE/EtOH 20/1 → 10/1, R_f(10/1) = 0.23). Compound **5** (50 mg, 29%) was obtained as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 2.84 (bs, 4 H), 3.49–3.53 (m, 4 H), 3.51–3.62 (m, 16 H), 3.71 (bs, 2 H), 7.23–7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (+), 48.0 (−), 48.1 (−), 53.6 (−), 59.9 (−), 70.0 (−), 70.5 (−), 70.7 (−), 70.8 (−), 79.5 (C_{quart}), 127.1 (+), 128.3 (+), 129.0 (+), 136.3 (C_{quart}), 155.5 (C_{quart}).

IR (NaCl): $\bar{\nu}$ (cm^{-1}) = 3482 (bw), 2926 (m), 2868 (m), 1693 (s), 1456 (m), 1409 (m), 1364 (m), 1289 (m), 1246 (m), 1152 (s), 1122 (s), 927 (w), 736 (w), 698 (w). MS (ESI-MS, CH_2Cl_2/MeOH + 10 mmol/l NH_4OAc): e/z (%) = 475 (25, $M + Na^+$), 453 (100, MH^+).

1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7-carboxylic acid *tert*-butyl ester (6). 16-Benzyl-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane-7-carboxylic acid *tert*-butyl ester (**5**, 50 mg, 0.11 mmol) was dissolved in 20 mL of MeOH and 10% Pd/C were added. The mixture was pressurized with 10 bar H_2 over 2 d at 50°C. The solvent was evaporated after removal of the catalyst by filtration through Celite. Compound **6** (35 mg, 88%) was obtained as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.84–2.87 (m, 4 H), 3.48–3.51 (m, 4 H), 3.59–3.65 (m, 16 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (+), 47.5 (−), 48.0 (−), 49.1 (−), 69.6 (−), 69.9 (−), 70.2 (−), 70.7 (−), 79.5 (C_{quart}), 155.5 (C_{quart}).

IR (NaCl): $\bar{\nu}$ (cm^{-1}) = 3491 (bw), 2976 (m), 2871 (m), 1692 (s), 1460 (m), 1411 (m), 1364 (m), 1289 (m), 1246 (m), 1150 (s), 1120 (s), 773 (w).

MS (ESI-MS, CH_2Cl_2/MeOH + 10 mmol/l NH_4OAc): e/z (%) = 363 (100, MH^+).

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