# A New One-Pot Synthesis of Double-Armed Ionizable Crown Ethers Using the Mannich Reaction

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## Introduction

Double-armed crown ethers have been widely studied as mimics of biological ionophores.[1] Some of the azacrown ethers **1** with two ionizable arms exhibit favorable complexing abilities toward many divalent metal ions.[2] For example, the chromogenic crown ether **1h** is known to be a good selective reagent for the determination of calcium ion concentration in blood serum.[3] However, the syntheses of various azacrown ethers **1** have been limited since crown ethers analogous to **1** were obtainable only by treatment of the appropriate benzylic halides or carboxylic acid derivatives with 4,13-diaza-18-crown-6 (**2**)[3,4] or *N*,*N*′-bis(methoxymethyl)-4,13-diaza-18-crown-6 with appropriate substituted phenols.[5] In this paper, we report a new one-pot method for syntheses of the double-armed crown ethers **1** from 4,13-diaza-18-crown-6 (**2**) and substituted phenols **3** (Scheme 1).

## Results and Discussion

The yields are good for **1a**−**f**, although the yields drop as strongly electron-withdrawing substituents are added, as in **1g**,**h**. The low yield of **1h** is attributed to the poor solubility of **3h** in benzene as well as the relatively weak nucleophilicity of **3h** and its anion. Although the reaction mechanism for our methodology is believed to be the same as that of the usual Mannich reaction,[6] our reaction is quite sensitive to the particular solvent were used. For example, the substitution of anhydrous ethanol for benzene reduced the yields of **1a** and **1c** to 5% and 17%, respectively. This result underscores the fact that the selection of the right solvent is crucial for the successful synthesis of the Mannich base via this method.

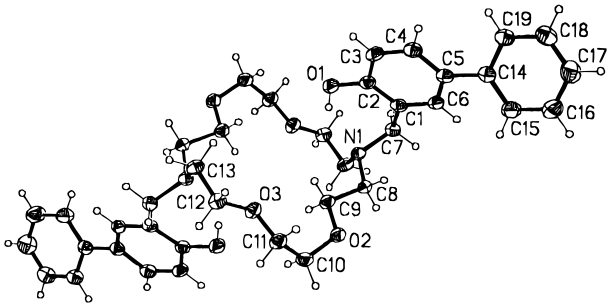
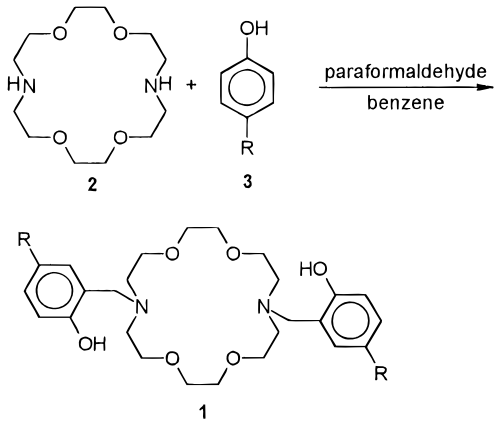



**Figure 1.** ORTEP drawing of **1b**.

**Scheme 1. Preparation of 1**




**1a** R=$OCH_3$ **1e** R=Cl
**1b** R=phenyl **1f** R=F
**1c** R=$CH_3$ **1g** R=CN
**1d** R=$C(CH_3)_3$ **1h** R=$NO_2$

Crystals of **1b**, **1c**, and **1f** suitable for single-crystal structural determination[7] were obtained by recrystallization from *n*-hexane and ethyl acetate mixture. The crystal structures of **1b**,**c**,**f** reveal that the hydroxyl groups on both sidearms point to the center of azacrown ring from opposite sides of the ring. This suggests that the preferred conformations of **1b**,**c**,**f** may be ideal for axial complexation with a central guest cation.[4b,d,8] (ORTEP drawings of **1b** and **1f** are given in Figures 1 and 2, respectively. That of **1c** is available as supporting information.)

Additional host−guest chemistry studies of **1b**,**d**,**f**,**g** are underway at this time, with results to be published.

## Experimental Section

**General.** To a solution of 4,13-diaza-18-crown-6 (**2**, 100 mg, 0.381 mmol) and paraformaldehyde (28 mg, 0.93 mmol) in dry benzene (4 mL) was added the corresponding substituted phenol **3** (0.91 mmol) at rt. The resulting mixture was then heated and held at reflux for 18−22 h. The solvent was removed *in vacuo*, and the crude products were purified by flash chromatography.[9] All the spectral data of products are in accordance with the assigned structures of **1a**−**g**. Data for $^1$H NMR (300 MHz), $^{13}$C

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(7) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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(9) Silica gel (230−400 mesh) was deactivated by ∼2% triethylamine in eluent solution (40−70% of ethyl acetate in hexane).

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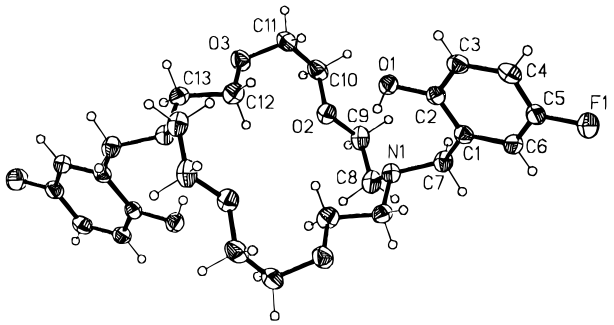


**Figure 2.** ORTEP drawing of **1f**.

**Table 1. Yields and Melting Points of Products 1**

| product | yield (%)[a] | mp,[b] °C (lit. mp) |
|---|---|---|
| 1a | 87 | 134−135 (134−135)[5d] |
| 1b | 91 | 151−152 |
| 1c | 85 | 114−115 (118−120)[5d] |
| 1d | 70 | 173−174 |
| 1e[5e] | 77 | 117−118 |
| 1f | 75 | 135−136 |
| 1g | 50 | 160−161 |
| 1h | 15 | 163−164 (164−165)[3] |

[a] Yields are based on isolated, purified products. [b] Melting points are not corrected.

NMR (75.48 MHz), and $^{19}$F NMR (282 MHz, $CFCl_3$ as an internal standard) were obtained in $CDCl_3$ solvent. High-resolution mass spectra of **1** were obtained by chemical ionization in the positive mode. The yields and melting points of products **1** are summarized in Table 1.

**1a**: $^1$H NMR $\delta$ 2.85 (t, $J$ = 5.1 Hz, 8H), 3.58 (s, 8H), 3.64 (t, $J$ = 5.1 Hz, 8H), 3.71 (s, 6H), 3.77 (s, 4H), 6.55−6.72 (m, 6H); $^{13}$C NMR $\delta$ 53.8, 55.8, 58.7, 69.0, 70.8, 113.7, 114.8, 116.8, 123.0, 151.7, 152.5; HRMS calcd for $C_{28}H_{43}N_2O_8$ $(M + H)^+$ 535.3019, found 535.2984.

**1b**: $^1$H NMR $\delta$ 2.94 (t, $J$ = 5.1 Hz, 8H), 3.64 (s, 8H), 3.71 (t, $J$ = 5.1 Hz, 8H), 3.92 (s, 4H), 6.92 (d, $J$ = 8.4 Hz, 2H), 7.24−7.55 (m, 14H); $^{13}$C NMR $\delta$ 53.7, 58.6, 68.8, 70.8, 116.7, 122.4, 126.4, 126.6, 127.5, 128.6, 132.1, 141.0, 157.5; HRMS calcd for $C_{38}H_{47}N_2O_6$ $(M + H)^+$ 627.3434, found 627.3436.

**1c**: $^1$H NMR $\delta$ 2.21 (s, 6H), 2.83 (t, $J$ = 5.4 Hz, 8H), 3.59 (s, 8H), 3.64 (t, $J$ = 5.4 Hz, 8H), 3.74 (s, 4H), 6.68−6.95 (m, 6H); $^{13}$C NMR $\delta$ 20.4, 53.6, 58.6, 69.1, 70.7, 116.0, 122.1, 128.0, 129.0, 129.2, 155.5; HRMS calcd for $C_{28}H_{42}N_2O_6$ $(M^+)$ 502.3043, found 502.3036.

**1d**: $^1$H NMR $\delta$ 1.25 (s, 18H), 2.86 (t, $J$ = 5.4 Hz, 8H), 3.59 (s, 8H), 3.66 (t, $J$ = 5.4 Hz, 8H), 3.80 (s, 4H), 6.72−7.17 (m, 6H); $^{13}$C NMR $\delta$ 31.6, 33.9, 53.6, 59.0, 69.0, 70.8, 115.6, 121.4, 125.4, 125.6, 141.6, 155.4; HRMS calcd for $C_{34}H_{54}N_2O_6$ $(M^+)$ 586.3982, found 586.3974.

**1e**: $^1$H NMR $\delta$ 2.83 (t, $J$ = 5.1 Hz, 8H), 3.58 (s, 8H), 3.63 (t, $J$ = 5.1 Hz, 8H), 3.75 (s, 4H), 6.72 (d, $J$ = 8.7 Hz, 2H), 6.93 (d, $J$ = 2.1 Hz, 2H), 7.08 (dd, $J$ = 8.7, 2.7 Hz, 2H); $^{13}$C NMR $\delta$ 53.7, 58,0, 68.8, 70.7, 117.6, 123.4, 123.9, 128.4, 128.5, 156.6; HRMS calcd for $C_{26}H_{36}N_2O_6Cl_2$ $(M^+)$ 542.1950, found 542.1934.

**1f**: $^1$H NMR $\delta$ 2.82 (t, $J$ = 5.4 Hz, 8H), 3.58 (s, 8H), 3.64 (t, $J$ = 5.4 Hz, 8H), 3.75 (s, 4H), 6.65−6.74 (m, 4H), 6.82 (dt, $J$ = 8.6, 2.9 Hz, 2H); $^{13}$C NMR $\delta$ 53.7, 58.2, 68.9, 70.7, 114.8 (d, $J$ = 17.5 Hz), 115.1 (d, $J$ = 18.0 Hz), 116.9 (d, $J$ = 7.7 Hz), 123.3 (d, $J$ = 6.6 Hz), 153.8, 155.9 (d, $J$ = 234.3 Hz);$^{19}$F NMR $\delta$ −126.6 (m, 2F); HRMS calcd for $C_{26}H_{37}N_2O_6F_2$ $(M + H)^+$ 511.2620, found 511.2606.

**1g**: $^1$H NMR $\delta$ 2.86 (t, $J$ = 5.1 Hz, 8H), 3.60 (s, 8H), 3.67 (t, $J$ = 5.1 Hz, 8H), 3.85 (s, 4H), 6.84 (d, $J$ = 8.7 Hz, 2H), 7.28 (d, $J$ = 1.5 Hz, 2H), 7.45 (dd, $J$ = 8.7, 2.1 Hz, 2H); $^{13}$C NMR $\delta$ 53.7, 57.8, 68.6, 70.8, 101.8, 117.2, 119.4, 123.4, 132.5, 133.2, 162.5; HRMS calcd for $C_{28}H_{37}N_4O_6$ $(M + H)^+$ 525.2713, found 525.2692.

**1h**: $^1$H NMR $\delta$ 2.90 (t, $J$ = 5.1 Hz, 8H), 3.59 (s, 8H), 3.66 (t, $J$ = 5.1 Hz, 8H), 3.93 (s, 4H), 6.85 (d, $J$ = 9.0 Hz, 2H), 7.95 (d, $J$ = 3.0 Hz, 2H), 8.07 (dd, $J$ = 9.0, 3.0 Hz, 2H); $^{13}$C NMR $\delta$ 53.8, 58.0, 68.6, 70.8, 116.6, 122.5, 124.8, 125.3, 140.0, 164.8; HRMS calcd for $C_{26}H_{37}N_4O_{10}$ $(M + H)^+$ 565.2510, found 565.2512.

**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for **1a**−**h**, $^{19}$F NMR spectrum for **1f**, and ORTEP drawing for **1c** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version on the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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