Macroheterocycles; LVII.[1] Improved Synthesis of Azacrown Ethers with Phenolic Sidearms

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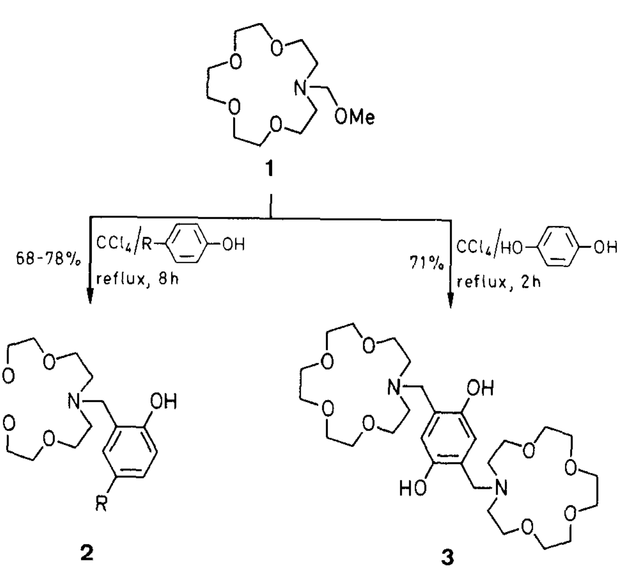
Azacrown ethers with phenolic sidearms are readily prepared by the reaction of *N*-(methoxymethyl)azacrown ethers with phenols.

Azacrown ethers bearing phenolic sidearms are powerful and selective cationic bindering agents for alkali, alkaline earth and some heavy metal cations and draw great attention as sensitive reagents for extraction spectrophotometry of these ions.[2-6] These compounds are usually prepared by alkylation of azacrown ethers with hydroxybenzyl halides.[2,7] In some cases the preliminary protection of phenol, hydroxyl[7] and other functional groups of the substituted hydroxybenzyl halides, which are able to interact alternatively with azacrown ethers is necessary. In most cases the substituted hydroxybenzyl halides are not readily available.

Here we report an improved one-step synthesis of azacrown ethers with phenolic sidearms by the reaction of the accessible *N*-(methoxymethyl)azacrown ethers[8,9] with phenols. This reaction is a special case of Mannich reaction.[8] As compared with the alkylation of azacrown ethers with 2-hydroxybenzyl halides, this method has at least two advantages: (i) the substituted phenols are readily available, and (ii) due to the electrophilic character of the reaction it is not necessary to protect the functional groups of the substituted phenols, sensitive to nucleophilic attack by the azacrown ether nitrogen.

The reaction of *N*-(methoxymethyl)aza-15-crown-5 (**1**)[8] and *N,N'*-bis(methoxymethyl)-4,13-diaza-18-crown-6 (**4**)[9] with the appropriate phenols proceeded very smoothly in refluxing carbon tetrachloride at heating and gave



2	a	b	c	d
R	H	Me	CHO	NO_2

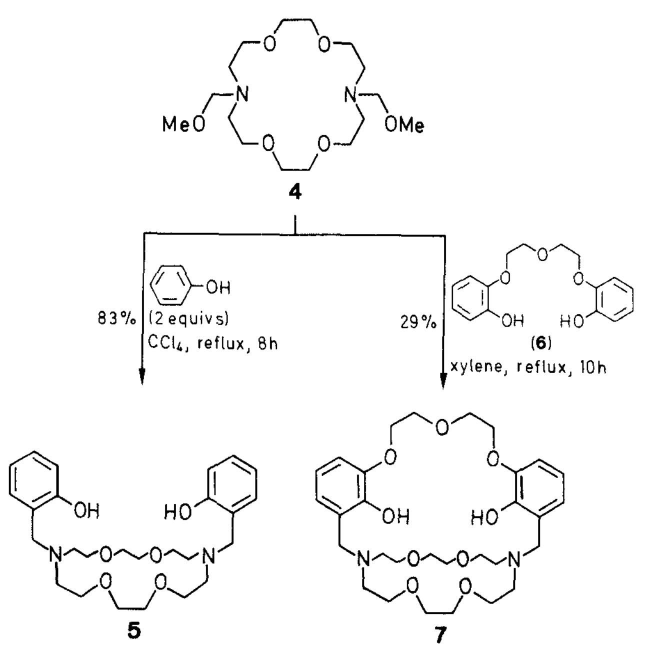


Table. Compounds **2a–d**, **3**, **5**, **7** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)	^{1}H-NMR ($CDCl_3$/HMDS) δ, J(Hz)	MS (70 eV) m/z (%)
2a	78	oil	$C_{17}H_{27}NO_5$ (325.4)	2.73 (t, 4H, J = 5.5), 3.47–3.83 (m, 18H), 6.57–7.00 (m, 4H), 8.1 (br s, 1H)	325 (M$^+$, 4)
2b	74	oil	$C_{18}H_{29}NO_5$ (339.4)	2.00 (s, 3H), 2.70 (t, 4H, J = 5.5), 3.37–3.73 (m, 18H), 6.43–6.80 (m, 3H)	339 (M$^+$, 11)
2c	68	oil	$C_{18}H_{27}NO_6$ (353.4)	2.83 (t, 4H, J = 5,8), 3.50–3.93 (m, 18H), 6.73–7.73 (m, 3H), 9.70 (s, 1H)	353 (M$^+$, 16)
2d	73	oil	oil[1]	2.82 (t, 4H, J = 6.0), 3.51–3.90 (m, 18H), 6.67–8.10 (m, 3H)	370 (M$^+$, 30)
3	71	95–96	$C_{28}H_{48}N_2O_{10}$ (572.7)	2.70 (t, 8H, J = 5.5), 3.40–3.76 (m, 36H), 6.07 (s, 2H)	572 (M$^+$, 6)
5	83	122	120–122[6]	2.82 (t, 8H, J = 5.6), 3.62–3.80 (m, 20H), 6.50–7.42 (m, 8H), 10.00 (br s, 2H)	474 (M$^+$, 12)
7	29	oil	$C_{30}H_{44}N_2O_5$ (576.7)	2.61 (t, 8H, J = 5.6), 3.33–3.66 (m, 20H), 3.83–4.19 (m, 8H), 6.46–6.67 (m, 6H)	576 (M$^+$, 25)

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[a] Satisfactory microanalysis obtained: C ±0.29, H ±0.30, N +0.32.

the crown ethers **2**, **3** and **5** in good yields (68–83%). This reaction can be used for the synthesis of cryptands with endocyclic phenolic groups, which is demonstrated for the cryptand **7**. The cryptand was obtained in 29% yield at the reaction of diazacrown ether **4** with bisphenol **6** in xylene at boiling. Use of carbon tetrachloride in this reaction reduces the yield of **7**.

Compounds **2**, **3**, **5**, **7** were characterized by microanalyses, mass and ^{1}H-NMR spectral data (Table).

N-Substituted 1,4,7,10-Tetraoxa-13-azacyclopentadecanes 2a–d: General Procedure:

A mixture of *N*-(methoxymethyl)aza-15-crown-5 (**1**;[7] 263 mg, 1 mmol) and the appropriate phenol (1 mmol) in CCl_4 (20 mL) is refluxed for 8 h. After removing the solvent under reduced pressure, the pure products **2a–d** are isolated by chromatography on alumina (eluent: $CHCl_3$/benzene, 1:2).

13,13′-[2,5-Dihydroxy-1,4-benzenediylbis(1,4,7,10-tetraoxa-13-azacyclopentadecane)] (3):

A mixture of azacrown ether **1** (526 mg, 2 mmol) and hydroquinone (110 mg, 1 mmol) is refluxed in (20 mL) CCl_4 for 2 h. Isolation of the pure product is similar to the above procedure.

7,16-Bis(2-hydroxyphenylmethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (5):

A mixture of diazacrown ether **4**[8] (350 mg, 1 mmol) and phenol (188 mg, 2 mmol) is refluxed in CCl_4 (20 mL) for 8 h. The solvent is removed under reduced pressure and the product is isolated by chromatography on alumina (eluent: $CHCl_3$/benzene, 1:2).

Cryptand 7:

A mixture of diazacrown ether **4** (350 mg, 1 mmol) and 2,2′-[oxy bis(ethyleneoxy)diphenol (290 mg, 1 mmol) in xylene (100 mL) is refluxed for 10 h. After removing the solvent under reduced pressure, the cryptand **7** is isolated by chromatography on alumina (eluent: $CHCl_3$/hexane, 2:1).

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