Facile Synthesis of Monoaza Crown Ethers

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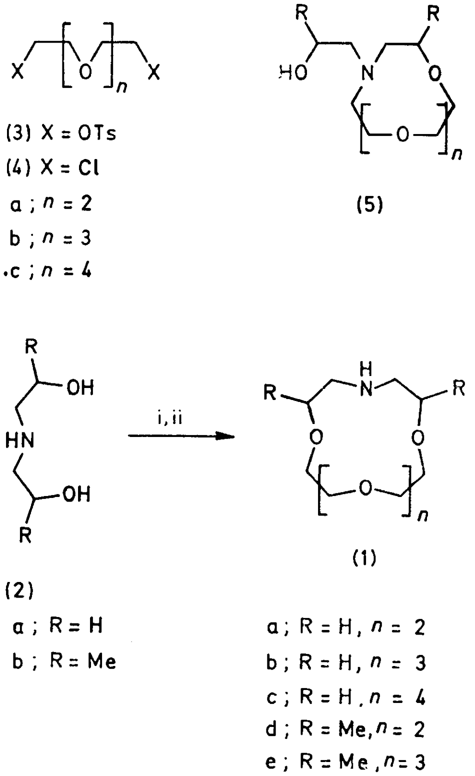
Summary A facile one-step synthesis of monoaza crown ethers by treatment of dialkanolamines with oligoethylene glycol di(toluene-*p*-sulphonates) or dichlorides in Bu^tOM–Bu^tOH (M = Na, K) is described.

Recently, we have reported some crown ethers with functional groups[1,2] which are important as intermediates in the synthesis of bis-crown compounds or crown ether polymers. Also, the monoaza crown ethers (**1**), which themselves are reactive crown ethers, can readily be transformed into various derivatives[3] and immobilized on a polymer backbone. Although it is obvious that the reaction of the dialkanolamines (**2**) with the oligoethylene glycol di(toluene-*p*-sulphonates) (**3**) or dichlorides (**4**) is the simplest way to obtain these compounds, the possibility of unfavorable *N*-alkylation has prevented use of this method. Thus, previous syntheses of these compounds were rather laborious, because they required deprotection of the substituent of the *N*-substituted monoaza crown ethers, which were prepared by the reaction between *N*-substituted diethanolamines [*N*-(tolyl-*p*-sulphonyl)-,[4] *N*-benzyl-[5] or *N*-trityl-diethanolamine,[6] *etc.*] and oligoethylene glycol di(toluene-*p*-sulphonates). Although the amino-group of diethanolamine is more reactive towards alkylating agents than the hydroxy-group in neutral or mildly basic conditions, *O*-alkylation is expected to be more predominant than *N*-alkylation in basic conditions, which generate the alkoxide. We have found that the *N*-unsubstituted monoaza crown ethers can be obtained in satisfactory yields from accessible dialkanolamines, such as diethanolamine or diisopropanolamine, by controlling the reaction conditions without protection of the amino-group.



(3) X = OTs
(4) X = Cl
a ; n = 2
b ; n = 3
c ; n = 4

(5)

(2)
a ; R = H
b ; R = Me

(1)
a ; R = H, n = 2
b ; R = H, n = 3
c ; R = H, n = 4
d ; R = Me, n = 2
e ; R = Me, n = 3

OTs = toluene-*p*-sulphonate

Scheme. *Reagents*, i, M, Bu^tOH (M = Na or K); ii, Compounds (**3**) or (**4**), Bu^tOH, dioxan, 40—60 °C.

For example, diethanolamine (**2a**) (3·15 g) and sodium metal (2·07 g) were dissolved in t-butanol (250 ml), and triethylene glycol di(toluene-*p*-sulphonate) (**3a**) (13·7 g) in dioxan (150 ml) was added in drops to the solution during 3 h, at 40 °C. After the addition, the reaction was continued for 1 h, then the reaction mixture was filtered and the solvent was evaporated off. Water (25 ml) was added to the residue and the solution was extracted once with hexane to remove hexane-soluble materials and then extracted several times with dichloromethane. The dichloromethane extracts were combined, the solvent was evaporated off, and the residue was distilled (kugelrohr) to give a white solid (3·19 g), b.p. 80—85 °C/0·02 Torr, m.p. 23—26 °C. This product, which gave almost a single

TABLE

Crown ether	Glycol derivative	Template atom (M)	Yield[a] (%)
(**1a**)	(**4a**)	Na	37
(**1b**)[b]	(**3b**)	K	61
(**1b**)	(**4b**)	K	35
(**1c**)[c]	(**3c**)	K	35
(**1d**)[d,e]	(**3a**)	Na	33
(**1e**)[d,f]	(**3b**)	K	34

[a] Crude isolated yield. [b] Further purified by recrystallization from hexane, white crystals, m.p. 49—51 °C (lit.,[4] 49—51 °C). [c] Clear liquid; *m/e* 307 (M^+); δ(CDCl$_3$) 2·64 (s, 1 H), 2·79 (t, 4 H), and 3·56—3·80 (s + m, 24 H). [d] A mixture of stereoisomers. [e] Clear liquid; *m/e* 247 (M^+); δ(CDCl$_3$) 1·05—1·22 (m, 6 H), 2·59 (s, 1 H), 2·42—2·80 (m, 4 H), and 3·40—3·84 (s + m, 14 H). [f] White waxy solid; *m/e* 291 (M^+); δ(CDCl$_3$) 1·06—1·22 (m, 6 H), 2·54 (s, 1 H), 2·38—2·83 (m, 4 H), and 3·37—3·89 (s + m, 18 H).

peak by g.l.c. analysis, was identified as monoaza 15-crown-5 (**1a**) from its spectral data (crude yield, 45%). Furthermore, the sodium thiocyanate complex was obtained by treating compound (**1a**) with sodium thiocyanate in acetone–hexane, followed by thermolysis to give the pure product (yield 20%), m.p. 30—32 °C (lit.,[4] 27—30 °C). Other monoaza crown ethers were obtained in almost the same manner and were purified by the appropriate means. The results are shown in the Table.

The reactions of oligoethylene glycol dichlorides (**4**), which are not so reactive as the di(toluene-*p*-sulphonates) (**3**), were carried out at 60 °C. The yields were lower than obtained from compounds (**3**) because of the formation of open-chain oligomers. However, the formation of another possible isomer, the *N*-(2-hydroxyalkyl)monoaza crown ethers (**5**), was not observed in the reactions investigated. On the other hand, when di-isopropanolamine (**2b**) was treated with compounds (**3**), the yields of the monoaza crown ethers were somewhat lower and the main by-product was oligoethylene glycol di-t-butyl ether. The t-butoxy-anion could competitively attack the toluene-*p*-sulphonate in the case of the less reactive s-alkoxy-anion.[7]

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