Tetrahedron Letters No. 44, pp 4273 - 4276.
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0040-4039/78/1029-4273$02.00/0

NEW SYNTHESIS OF N-ALKYL MONOAZA CROWN ETHERS

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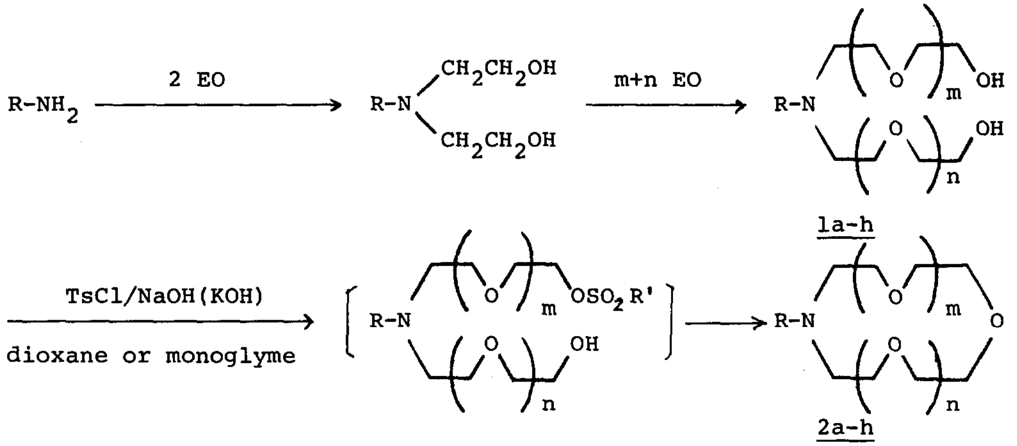
The macrocyclic aminopolyethers have been reported to have complexing ability with alkali cations1) and soft metallic cations such as Ag^+, Cu^{2+} 2,3) as well as with primary and secondary alkylammonium salts4). They are also known to be useful as self-solvating bases5), phase-transfer catalysts6,7) and Micelle-forming amphiphilic compounds8). Although various types of azacrown ethers have recently been reported2,9-19), most of them were synthesized via reactions of several steps and their yields are generally low because of synthetic difficulties. Furthermore, to our knowledge, no systematic investigation has been done on the synthesis and properties of N-alkyl monoaza crown ethers which are the simplest members among the macrocyclic aminopolyethers.

We have recently reported a new general method for the synthesis of substituted and unsubstituted crown ethers via monotosylated polyethylene glycols formed *in situ*20).

We have now found that this method is conveniently applicable for the preparation of N-alkyl monoaza crown ethers. Thus, N,N-di(polyoxyethylene)alkylamines with suitable ethylenoxy units (1a-h) can be easily converted to the corresponding N-alkyl monoaza crown ethers (2a-h) by treatment with equimolar quantities of p-toluene sulfonyl chloride and excess alkali metal hydroxides in an aprotic solvent.



R: CH_3, C_2H_5, C_4H_9, CH_2=$CHCH_2$, m, n: 0 - 5

R': CH_3-C_6H_5

For example, N,N-di(polyoxyethylene)ethylamine 1c (R=C_2H_5, m+n=3, bp: 148-150°C/ 0.2 mmHg, 2.6g, 0.01 mol) and p-toluenesulfonyl chloride (1.9g, 0.01 mol) were dissolved in 20 ml of dioxane and the solution was added dropwise to a suspension of powdered sodium hydroxide in dioxane (1.65g/40 ml) at room temperature over a period of three hours. After the addition was complete, the reaction product was filtered and the remained solid was washed with dichloromethane (10 ml X 3). Upon removing the solvent *in vacuo* from the combined solution, a viscous liquid (4.0g) was obtained. It was pyrolyzed using a kugelrohr distillation apparatus under reduced pressure to afford N-ethyl monoaza 15-crown-5 (2c) as a colorless liquid. Yield: 2.47g (75%). IR (neat, cm^{-1}): 2880s, 1460w, 1350m, 1300w, 1250w, 1200w, 1120s, 980w, and 930w. MS (m/e): 247 (M^+), 232, 166, 114, 100, 73, 58 and 45. NMR (CCl_4, δ): 1.00 (t, 3H), 2.52 (q, 2H), 2.60 (t, 4H), 3.52 (s+t, 16H). Analysis for $C_{12}H_{25}NO_4$: Found; C: 57.95, H: 10.24, N: 5.68, Calcd.; C: 58.27, H: 10.19, N: 5.66.

In the same manner, the reaction of 1d (R=C_2H_5, m+n=4, bp: 160-165°C/0.12 mmHg, 4.9g, 0.016 mol) with p-toluenesulfonyl chloride (3.0g, 0.016 mol) and potassium hydroxide (3.6g, 0.064 mol) in 100 ml dioxane gave N-ethyl monoaza 18-crown-6 (2d, R=C_2H_5, m+n=4) in 60% yield. IR (neat, cm^{-1}): 2880s, 1460w, 1350m, 1300w, 1250w, 1200w, 1120s, 980w and 930w. MS (m/e): 291 (M^+), 276, 260, 116, 114, 100, 89, 73, 58 and 45. NMR (CCl_4, δ): 1.00 (t, 3H), 2.54 (q, 2H), 2.64 (t, 4H), 3.48 (t, 4H), 3.54 (s, 16H). Analysis for $C_{14}H_{29}NO_5$: Found; C: 57.29, H: 10.19, N: 4.78, Calcd.; C: 57.69, H: 10.05, N: 4.81.

Similar treatment of adduct 1i (R=CH_3, m+n=2) with p-toluenesulfonyl chloride in the presence of sodium hydroxide afforded a small amount of the corresponding monoaza 12-crown-4 2i (R=CH_3, m+n=2), indicating the template effect was not effective in this case. Results of the synthesis of other monoaza 15- and 18-crown ethers are summarized in Table 1.

Synthesis of N-Alkyl Monoaza Crown Ethers[a,b)]

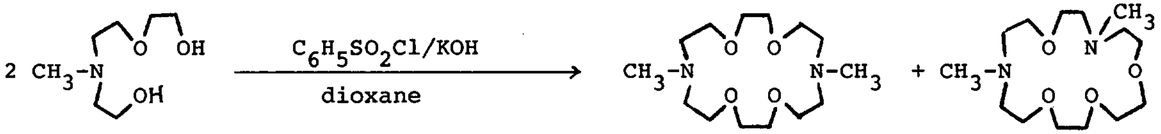
	Starting material R	m+n	Product	Yield (%)	MS (m/e)[c]	NMR (CCl_4, δ)
1a	CH_3	3	N-Methyl-monoaza-15-crown-5 (2a)	45	233(M^+), 202, 146, 114, 102, 100, 88, 59, 58, 57, $\underline{44}$.	2.28(s, 3H), 2.60(t, 4H), 3.52(s+t, 16H)
1b	"	4	N-Methyl-monoaza-18-crown-6 (2b)	55	277(M^+), 246, 114, 102, 100, 88, 86, 59, 58, 57, $\underline{44}$.	2.26(s, 3H), 2.58(t, 4H), 3.52(s+t, 20H)
1e	C_4H_9	3	N-Butyl-monoaza-15-crown-5 (2e)	58	275(M^+), 273, $\underline{232}$, 202, 144, 114, 100, 98, 86, 84, 56, 45	0.94(t, 3H), 1.40(m, 4H), 2.54(t, 2H), 2.78 (t, 4H), 3.70(s+t, 16H)
1f	"	4	N-Butyl-monoaza-18-crown-6 (2f)	67	319(M^+), $\underline{286}$, 246, 100, 86, 45	0.90(t, 3H), 1.40(m, 4H), 2.40(t, 2H), 2.62 (t, 4H), 3.52(s+t, 20H)
1g	CH_2=$CHCH_2$	3	N-Allyl-monoaza-15-crown-5 (2g)	48	259(M^+), 232, 230, 128, 114, 112, 85, 84, $\underline{70}$, 56, 45	2.70(t, 4H), 3.14(d, 2H), 3.64(s+t, 16H), 5.20(m, 2H), 5.80(m. 1H)
1h	"	4	N-Allyl-monoaza-18-crown-6 (2h)	40	303(M^+), 276, 274, 232, 128, $\underline{70}$, 56, 45	2.66(t, 4H), 3.10(d, 2H), 3.52(s+t, 20H), 5.18(m, 2H), 5.74(m, 1H)

a) Reaction condition: TsCl/NaOH(1a, 1e and 1g), KOH(others)/Dioxane

b) IR spectra are almost the same as that of 2c, 2d. Elementary analyses agreed within ± 0.4% of the calculated values for all compounds.

c) The main fragment ion peaks are recorded. The underlined peaks are base peaks.

On the other hand, from the reaction of adduct 1j (R=CH_3, m+n=1) in the analogous reaction condition (benzenesulfonyl chloride/KOH/dioxane), a mixture of dimeric compounds, N,N'-dimethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane and N,N'-dimethyl-1,7-diaza-4,10,13,16-tetraoxacyclooctadecane was obtained as a colorless liquid in 24% yield. MS (m/e): 290 (M^+), 259, 229, 146, 132, 100, 88, 72 and 58. NMR (CCl_4, δ): 2.26 (s, 6H), 2.58 (t, 8H), 3.45-3.60 (s+t, 16H).



Acknowledgment: The authors wish to thank Prof. Daniel Swern, Temple University, for revision and helpful advices.

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(Received in Japan 22 July 1978)