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THE SYNTHESIS OF NEW DIAZA-N-PIVOT LARIAT 15-CROWN-5 AND 18-CROWN-6 MACROCYCLES

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Abstract. Nine diaza-15-crown-5 and nine diaza-18-crown-6 macrocycles containing tertiary aminoalkyl and hydroxyalkyl side groups attached to one of the ring nitrogen atoms have been prepared in good yields. The ring closure step involved the reaction of a bis-secondary amine containing the tertiary aminoalkyl or hydroxyalkyl substituent with ethylene glycol bis-(2-iodoethyl)ether or diethylene glycol bis-(2-chloroethyl)ether plus sodium iodide. The starting tertiary aminoalkyl- or hydroxyalkyl-substituted bis-secondary amine was prepared by reacting N-[2-(2-chloroethoxy)ethyl]acetamide or its benzamide analogue with a primary amine.

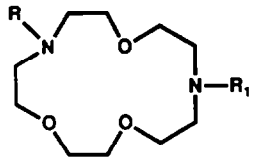
INTRODUCTION

The lariat crown ethers were designed to have enhanced cation binding properties.[1,2] These compounds have a side arm containing one or more extra donor groups. They also were prepared to mimic the dynamic complexation process shown by many natural macrocyclic ligands. The pivot group can be attached to either the macroring carbon or nitrogen atoms. Some of the carbon- and nitrogen-pivot lariat crown ethers exhibited increased cation binding abilities over the parent crown ethers, probably by further ligation of the cation by the side arm donor atoms.[3,4] In general, the complexing ability of lariat-crowns for alkali metal ions increases gradually with extending oxyethylene side arms. The side arms with amino donor atoms have increased affinity for soft heavy metal cations. An increased affinity for heavy metal ions has also been observed for cyclens containing amine side groups.[5,6]

Up to now, N-pivot lariat crown ethers with two or more ring nitrogen atoms have been difficult to prepare, particularly where the nitrogen atoms have different substituents.[7] The prior-art synthesis requires separate alkylation of each macroring nitrogen atom using an excess of the expensive aza-crowns. Our new building block method to prepare per-N-alkyl-substituted polyaza-crown ethers has been used to prepare aza-crowns with hydroxyalkyl-substituted side groups attached to one of the macroring nitrogen atoms.[8,9] These products are obtained because the ring closure reaction of a diiodide takes place on the two reactive secondary nitrogen atoms of the hydroxyalkyl-substituted bis-secondary amine.

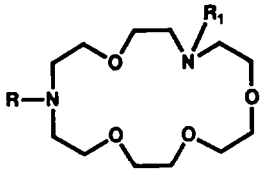
In this paper, we describe reactions to prepare two diaza-15-crown-5 and diaza-18-crown-6 ligands with hydroxyalkyl side groups attached to one of the macroring nitrogen atoms (Figure 1). We also have prepared diaza-15-crown-5 and diaza-18-crown-6 macrocycles with N,N-dimethyl- or N,N-diethylaminoalkyl and metholino-ethyl side arms attached to a macroring nitrogen atom by ring closure of the corresponding N,N-dimethyl-, N,N-diethylaminoalkyl- and morpholinoethyl-substituted bis-secondary amines (Figure 1).

Figure 1. New N,N'-Dialkyldiaza-N-Pivot Lariat Crown Ethers



$R_1 = C_2H_5$
1b, R = $(CH_2)_3N(C_2H_5)_2$
2b, R = $(CH_2)_2N(C_2H_5)_2$
3b, R = $(CH_2)_3N(CH_3)_2$
4b, R = $(CH_2)_2N(CH_3)_2$
5b, R = $(CH_2)_2OH$
6b, R = $(CH_2)_2O(CH_2)_2OH$
7b, R = $CH_2C_6H_5$
8b, R = $(CH_2)_2$Morpholine

$R_1 = CH_2C_6H_5$
9b, R = $(CH_2)_3N(C_2H_5)_2$



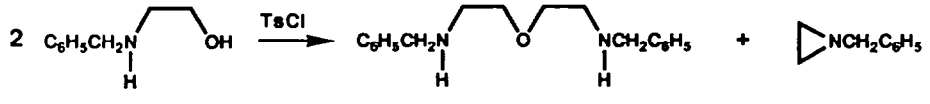
$R_1 = C_2H_5$
1c, R = $(CH_2)_3N(C_2H_5)_2$
2c, R = $(CH_2)_2N(C_2H_5)_2$
3c, R = $(CH_2)_3N(CH_3)_2$
4c, R = $(CH_2)_2N(CH_3)_2$
5c, R = $(CH_2)_2OH$
6c, R = $(CH_2)_2O(CH_2)_2OH$
7c, R = $CH_2C_6H_5$
8c, R = $(CH_2)_2$Morpholine

$R_1 = CH_2C_6H_5$
9c, R = $(CH_2)_3N(C_2H_5)_2$

RESULTS AND DISCUSSION

The starting diamines needed to prepare the 1,7-diaza-crowns are derivatives of 1,5-diamino-3-oxapentane. Only a few methods are reported for the preparation of the N,N'-dialkyl derivatives of the 1,5-diamino-3-oxapentane.[10] The most direct method was a 3-step synthesis from diglycolyl dichloride.[11] Our initial approach to prepare 1,5-bis-alkylamino-3-oxapentane was to use an Okahara process of forming ethers from alcohols in the presence of tosyl chloride. Condensation of 2-(N-alkylamino)ethanol with tosyl chloride gave mostly the N-alkylaziridine with only a 15% yield of the desired diaminoether (Scheme 1).

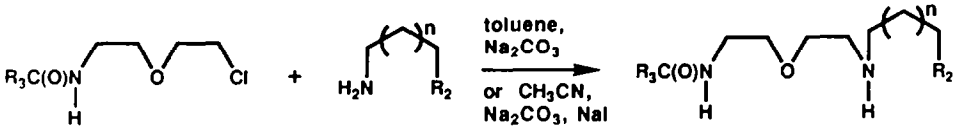
Scheme 1. Preparation of N,N'-Dibenzylamino-3-oxapentane



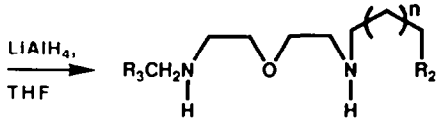
Even more interesting is the preparation of diamines with two different alkyl substituents. Boon reported a complicated method to prepare secondary diamines with different alkyl substituents on each nitrogen atom using a phenyl blocking group.[12] Our method to prepare the 1,5-bis-alkylamino-3-oxapentane with the same (benzyl) and different alkyl

substituents on each nitrogen atom is shown in Scheme 1 and 2. N-[2-(2-Chloroethoxy)ethyl]acetamide (11)[9,13] or its benzamide analogue (12)[9] were reacted with an excess of the appropriate primary amine using sodium carbonate as the base followed by reduction (Scheme 2). Building blocks 11 and 12 were reacted previously with a less than equal amount of a primary amine to prepare triamines capable of ring closure on the two end secondary amine units to form triaza-crowns.[9] The reactions shown in Scheme 2 were best carried out in toluene because the sodium chloride by-product was easy to remove. This was not possible for the preparation of diamine 4a because the starting amine had a boiling point close to that of toluene. In this case, the reaction was carried out in acetonitrile in the presence of sodium iodide which converted 11 to its more reactive iodo analogue. Often, the crude amide product was reduced without purification. The resulting bis-secondary amines were separated in 20-60% yields by distillation. The 2:2 adduct, 1,7,13-triaza-4,10-dioxatridecane, could be isolated as a higher boiling fraction. This method appears to be applicable for the synthesis of a variety of bis-secondary amines. Table I lists the yields and physical properties for the bis-secondary amines which we prepared.

Scheme 2. Preparation of bis-Secondary Amine Starting Materials (1a-9a)



11, $R_3 = CH_3$
12, $R_3 = C_6H_5$



$R_3 = CH_3$
1a, $R_2 = (C_2H_5)_2N$, n = 1
2a, $R_2 = (C_2H_5)_2N$, n = 0
3a, $R_2 = (CH_3)_2N$, n = 1
4a, $R_2 = (CH_3)_2N$, n = 0
5a, $R_2 = OH$, n = 0
6a, $R_2 = O(CH_2)_2OH$, n = 0
7a, $R_2 = C_6H_5$, n = -1
8a, R_2 = morpholine, n = 0

$R_3 = C_6H_5$
9a, $R_2 = (C_2H_5)_2N$, n = 1

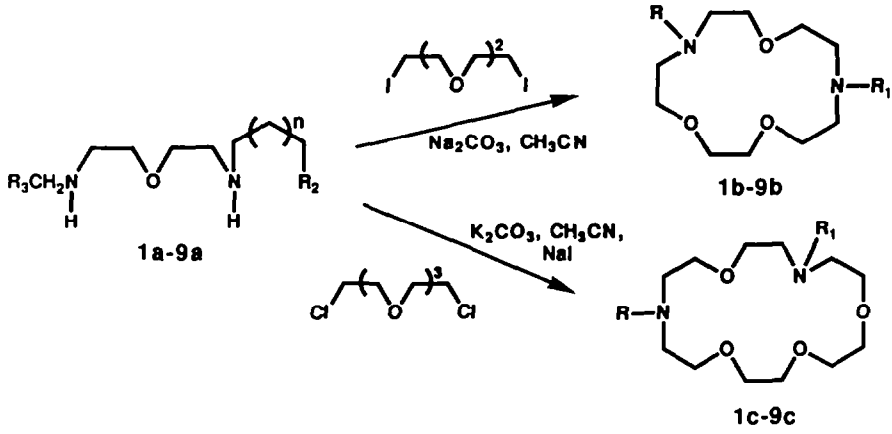
The macrocycles were prepared by reacting either 1,2-bis-(iodoethoxy)ethane (for macrocyles 1b-9b) or diethylene glycol bis-(2-chloroethyl)ether (for 1c-9c) with the appropriate bis-secondary amine in acetonitrile using sodium or potassium carbonate as the base (Scheme 3). In the case of the dichloride, sodium iodide was added to in situ convert it to the diiodide which is much more reactive. 1,2-Bis-(chloroethoxy)ethane plus sodium iodide could be used to form 1b-9b instead of the corresponding diiodide. Our best results were

Table I. Yields and Properties of the bis-Secondary Amine Starting Materials (Scheme 2)

Comp	R_2	Method	Yield % (overall)	bp (°C/mm)	^{1}H NMR spectra (δ)
1a	$(CH_3CH)_2N$ (n = 1)	A	28	88-93/0.095	0.88 (t, 6H), 0.98 (t, 3H), 1.15-1.30 (b, 2H), 1.42-1.60 (m, 2H), 2.30-2.45 (m, 6H), 2.50 (t, 4H), 2.65 (t, 4H), 3.42 (t, 4H)
2a	$(CH_3CH_2)_2N$ (n = 0)	A	35	77-83/0.12	0.90 (t, 6H), 1.01 (t, 3H), 1.5 (b, 1H), 2.36-2.80 (m, 15H), 3.48 (t, 4H)
3a	$(CH_3)_2N$ (n = 1)	A	59	71-75/0.12	1.02 (t, 3H), 1.20-1.40 (b, 2H), 1.48-1.62 (m, 2H), 2.12 (s, 6H), 2.22-2.6 (m, 6H), 2.70 (t, 4H), 3.48 (t, 4H)
4a	$(CH_3)_2N$ (n = 0)	B	24	62-67/0.10	0.95 (t, 3H), 1.3-1.65 (b, 2H), 2.05 (s, 6H), 2.2 (t, 2H), 2.52-2.72 (m, 8H), 3.45 (t, 4H)
5a	HO (n = 0)	C	61	94-98/0.10	1.03 (t, 3H), 2.55 (q, 2H), 2.63-2.76 (m, 8H), 3.35-3.60 (m, 7H)
6a	$HOCH_2CH_2O$ (n = 0)	C	38	125-130/0.12	1.00 (m, 3H), 1.5 (b, 2H), 2.55-2.80 (m, 8H), 3.32-4.00 (m, 11H)
7a	C_6H_5 (n = -1)	A	23	105-110/0.13	1.00 (t, 3H), 1.5 (b, 2H), 2.55 (q, 2H), 2.62-2.78 (m, 4H), 3.4-3.5 (m, 4H), 3.70 (s, 2H), 7.13-7.25 (m, 5H)
8a	morpholinyl (n = 0)	A	42	103-108/0.085	1.03 (t, 3H), 1.50 (b, 2H), 2.32-2.48 (m, 6H), 2.62-2.83 (m, 8H), 3.50 (t, 4H), 2.66 (t, 4H)
9a	$(CH_2CH)_2N$ (n = 1)	A	53	145-148/0.13	1.00 (t, 6H), 1.52-1.68 (m, 4H), 2.38-2.82 (m, 12H), 3.48-3.57 (m, 4H), 3.78 (s, 2H), 7.2-7.35 (m, 5H)

obtained when either dichloride was heated with sodium iodide in acetonitrile in the presence of potassium carbonate before the addition of the appropriate diamine. This latter addition was done at room temperature. The ring closure reaction gave yields of 50% or better in almost all cases. The products were isolated by column chromatography. Macrocycles 1b-9b and 1c-9c are listed in Table II along with their MS and ^{1}H NMR spectra. Satisfactory elemental analyses were obtained for all new macrocyclic ligands.

Scheme 3. Preparation of Macrocycles



EXPERIMENTAL SECTION

Infrared (IR) spectra were obtained on a Perkin-Elmer FT 1600 spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Varian Gemini 200 spectrometer in deutereochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Starting materials were purchased from Aldrich, Fluka, SIGMA, Lancaster Synthesis and Pfaltz and Bauer chemical companies. N-[2-(2-Chloroethoxyl)ethyl]acetamide (11) and N-[2-(2-Chloroethoxy)ethyl]benzamide (12) were prepared as reported.[9] Compound 12 was recrystallized from ethyl ether, m.p. 46-47°C (lit. value 43-47°C[14]).

Preparation of 1,5-diamino-3-oxapentane derivatives (1a-9a) (Scheme 2). Method A. A mixture of 19 g (0.115 mol) of 11 (or 26.2 g of 12 for 9a), 200 ml of toluene, 14 g (0.132 mol) of anhydrous sodium carbonate and 0.18 mol of the appropriate substituted amine was added to a flask equipped with a Dean-Stark trap. In the case of amine 3a, 11 was dropped into the mixture over a 5-h period. The stirred mixture was refluxed for 48 h, cooled to room temperature and filtered. The solid was washed twice with methylene chloride. The combined solvents were evaporated under reduced pressure. A solution of the residue in 100 ml of THF was slowly dropped into a stirred mixture of 100 ml of THF and 4 g of lithium aluminum hydride at 0-5°C. The resulting mixture was refluxed for 24 h and then cooled. Aqueous 5% sodium hydroxide (10 ml) was very slowly dropped into the stirred mixture at 0-5°C. After standing for 2 h, the mixture was filtered and the solid was washed several times with THF. The filtrate was evaporated under reduced pressure and the residue was distilled twice through a short column under reduced pressure. The yields, boiling points, and ^{1}H NMR data for monoadduct diamines 1a-3a and 7a-9a are listed in Table I. In addition, 2:2 adduct by-products were obtained for further investigation.

Table 2. Yields and Physical Properties of 15-Crown-5 (1b-9b) and 18-Crown-6 (1c-9c) Macrocycles[a] (Scheme 3, Figure 1)

Comp	Yield (%)	Chromatography Eluant Solvents Toluene:Ethanol	MS (m/e)	^{1}H NMR spectra (δ)
1b	72	40:1	359,342,331,273, 245,182(100), 157,100	0.88-1.04 (m, 9H), 1.42-1.62 (m, 2H), 2.25-2.78 (m, 18H), 3.45-3.68 (m, 12H)
2b	71	60:1	345,259(100), 245,231,114,86	0.83-0.96 (m, 9H), 2.3-2.5 (m, 10H), 2.56-2.70 (m, 8H), 3.35-3.55 (m, 12H)
3b	21	40:1	331,273,259, 229,205,160, 141, 85(100)	0.96 (t, 3H), 1.47-1.64 (m, 2H), 2.25 (s, 6H), 2.35-2.55 (m, 6H), 2.60-2.78 (m, 8H), 3.43-3.68 (m, 12H)
4b	49	40:1	317,272,259(100), 243,203,140	1.01 (t, 3H), 2.20 (s, 6H), 2.30-2.90 (m, 14H), 3.48-3.74 (m, 12H)
5b	52	50:1	290,273,259(100), 245,229,176,160,	1.04 (t, 3H), 2.52-2.80 (m, 12H), 3.38-3.72 (m, 14H), 3.98 (b, 1H).
6b	81	50:1	334,303,273,259 (100),228,162, 114, 102	1.00 (t, 3H), 2.53 (q, 2H), 2.62-2.80 (m, 10H), 3.46-3.68 (m, 18H), 4.30 (b, 1H)
7b	62	100:1	336,305,291,275, 245(100),222, 155,100	0.99 (t, 3H), 2.55 (q, 2H), 2.65-2.84 (m, 8H), 3.48-3.70 (m, 14H), 7.14-7.32 (m, 5H)
8b	67	45:1	359,259(100), 245,144,114,100	1.05 (t, 3H), 2.38-2.81 (m, 18H), 3.50-3.72 (m, 16H)
9b	80	60:1	421,335,277,208, 164,113,86(100)	1.00 (t, 6H), 1.50-1.68 (m, 2H), 2.32-2.51 (m, 8H), 2.64-2.82 (m, 8H), 3.50-3.65 (m, 14H), 7.17-7.34 (m, 5H)
1c	33	50:1	403,374,317,303 273,182,113,86 (100), 72	0.9-1.02 (m, 9H), 1.48-1.63 (m, 2H), 2.3-2.6 (m, 10H), 2.71 (t, 8H), 3.5-3.65 (m, 16H)
2c	44	70:1	389,303(100), 259,188,100,86	0.82-0.95 (m, 9H), 2.34-2.70 (m, 18H), 3.38-3.60 (m, 16H)
3c	33	40:1	375,317,303,287, 259,190,154,141,	0.97 (t, 3H), 1.47-1.65 (m, 2H), 2.26 (m, 6H), 2.40-2.58 (m, 6H), 2.64-2.78 (m,

			85(100)	8H), 3.48-3.68 (m, 16H)
4c	47	45:1	361,303(100), 259,247,188,158, 114,100	1.06 (t, 3H), 2.24 (s, 6H), 2.41 (q, 2H), 2.55-2.87 (m, 12H), 3.53-3.80 (m, 16H)
5c	62	40:1	334,317,303,289, 259,188,137,107 (100)	1.01 (t, 3H), 2.50-2.68 (m, 12H), 3.45-3.80 (m, 18H), 4.00 (b, 1H)
6c	73	40:1	378,347,303,259, 137,107,63(100)	1.03 (t, 3H), 2.59 (q, 2H), 2.71-2.88 (m, 10H), 3.52-3.80 (m, 22H), 4.10 (b, 1H)
7c	72	100:1	380,349,335,289, 259,190,164,91 (100)	0.97 (t, 3H), 2.53 (q, 2H), 2.63-2.77 (m, 8H), 3.42-3.68 (m, 18H), 7.13-7.28 (m, 5H)
8c	55	45:1	403,303(100), 289,259,188,114, 100	1.00 (t, 3H), 2.39-2.83 (m, 18H), 3.50-3.74 (m, 20H)
9c	68	60:1	465,379,275,252, 182,113,86(100)	0.94 (t, 6H), 1.43-1.62 (m, 2H), 2.26-2.50 (m, 8H), 2.60-2.78 (m, 8H), 3.40-3.75 (m, 18H), 7.12-7.29 (m, 5H)

[a]All macrocycles gave satisfactory elemental analyses.

Method B. A mixture of 19 g (0.115 mol) of **11**, 200 ml of acetonitrile, 21.5 g (0.203 mol) of anhydrous sodium carbonate, 18 g (0.12 mol) of sodium iodide and 15.9 g (0.18 mol) of N,N-dimethylethylene diamine was refluxed for 48 h; then cooled to room temperature and filtered. The solid was washed twice with 100 ml of chloroform. The filtrate and chloroform mixture was evaporated under reduced pressure. Water (70 ml) and then 70 ml of chloroform were added to dissolve and transfer the residue to an extraction funnel. After shaking thoroughly, the chloroform was separated and the aqueous solution was extracted three times with chloroform (200, 120 and 80 ml). The combined chloroform extracts were dried over anhydrous sodium sulfate. The drying agent was filtered and washed with chloroform. Thesolvent was evaporated and the amide was reduced as in Method A. The yield, boiling point, and ^{1}H NMR data for **4a** are listed in Table I.

Method C. The amounts of starting materials including ethanolamine or 2-(2-aminoethoxy)ethanol and apparatus were the same as in Method A except that the Dean-Stark trap was not used. For the preparation of diamine **5a**, **11** dissolved in toluene was dropped into the mixture over a 5-h period. The intermediate amides for the preparation of diamines **5a** and **6a** were separated by distillation (b.p. 175-185°C/0.13 mm and 194-200°C/0.11 mm respectively). The overall yields and other properties for **5a** and **6a** are listed in Table I.

General Procedure for the synthesis of crowns 1b-9b (Scheme 3). A mixture of 6 mmol of the appropriate bis-secondary amine (**1a-9a**), 2.35 g (6.35 mmol) of 1,2-bis-(2-iodoethoxy)ethane, 200 ml of acetonitrile, 0.1 of g sodium iodide and 15 g (0.14 mol) of anhydrous sodium carbonate was stirred under reflux for 24 h. The cooled mixture was filtered and the solid was washed with chloroform. The solvent was removed under reduced pressure. Chloroform (200 ml) was added to the residue to dissolve the product. After shaking, the suspended solid was filtered and the filtrate was washed with 50 ml of chloroform. The combined organic layers were evaporated to give a yellow oil which was purified by chromatography on neutral alumina using toluene/ethanol as the eluant and light yellow oil

products (1a-9a) were obtained after the solvent was evaporated. The yields and other properties are listed in Table II. Satisfactory elemental analyses was obtained for all macrocycles.

General Procedure for Synthesis of Macrocycles 1c-9c (Scheme 3). A mixture of 1.5 g (6.5 mmol) of diethyleneglycol bis-(2-chloroethyl)ether, 180 ml of acetonitrile, 2.92 g (19.5 mmol) of sodium iodide and 15 g (0.109 mol) of anhydrous potassium carbonate was stirred under reflux for 12-24 h. A solution of 6 mmol of the appropriate diamine 1a-9a in 30 ml of acetonitrile was added to the cooled reaction mixture. The resulting mixture was stirred under reflux for 24-48 h. Compounds 1c-9c were obtained as above for 1b-9b to give light yellow oil products. The yields and other properties are listed in Table II. Satisfactory elemental analyses was obtained for all macrocycles.

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