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CONVENIENT SYNTHESES OF N-[2-(2-HYDROXYETHOXY)ETHYL]-SUBSTITUTED POLYAZA-CROWN ETHERS AND CYCLAMS WITHOUT THE NEED FOR A HYDROXY BLOCKING GROUP

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Abstract: Short three or four step syntheses of N-[2-(2-hydroxyethoxy)ethyl]-substituted polyaza-crowns and cyclams without the need for a hydroxy blocking group are presented. Cyclization of a hydroxy-substituted diamine took place on the two amine nitrogen atoms because sodium carbonate does not ionize the hydroxy group.

There is an increasing number of applications for macrocyclic ligands that contain additional functional groups (i.e., acids, alcohols, amines, alkenes, etc.) which allow extra binding of the ligand to a cation[1-3] or allow attachment to biomolecules[4], polymers[5-8] and silica gel.[9-11] The silica gel-bound crowns allow the separation of metal ions from aqueous solutions and have application for the purification of waste waters.[11-13]

Aza-crowns and cyclams which have side chains containing a functional group or have one secondary amine group in the macroring would have important applications. In contrast to the synthesis of poly-N-functionalized aza-crown ethers or cyclams containing the same functional group on each ring nitrogen atom, which can easily be prepared by reacting the unsubstituted macrocycle with an excess of alkylating agent[14,15], the synthesis diaza- or polyaza-crowns and cyclams with one N-functionalized group requires a more selective synthetic procedure. In principle, side chains containing an appropriate functional group can be attached before or after cyclization or the functional group can be produced by a separated chemical process after cyclization such as reduction of a cyano group.[16-18] Another method was used by Krespan which utilized oxetane which was selectively ring-opened under acidic conditions to give the diol.[19] Up to now, the most important aza-crown macrocycles with a hydroxy function were prepared where one starting material had a blocked (THP, benzyl or allyl) hydroxy function. The blocking group was removed in the last step.[5,8,10,21-25] Hydroxy functionalized macrocycles are important because they may be easily incorporated into synthetic polymers.[5-8,20,25] Any synthetic method that provides easier access (no blocking, fewer steps, etc.) to this class of compounds is therefore of great interest. With the aza-crowns and cyclams, the N-hydroxyalkyl group was also attached after cyclization.[26] A few aza-crowns with hydroxy groups attached directly to a ring carbon atom have been synthetized

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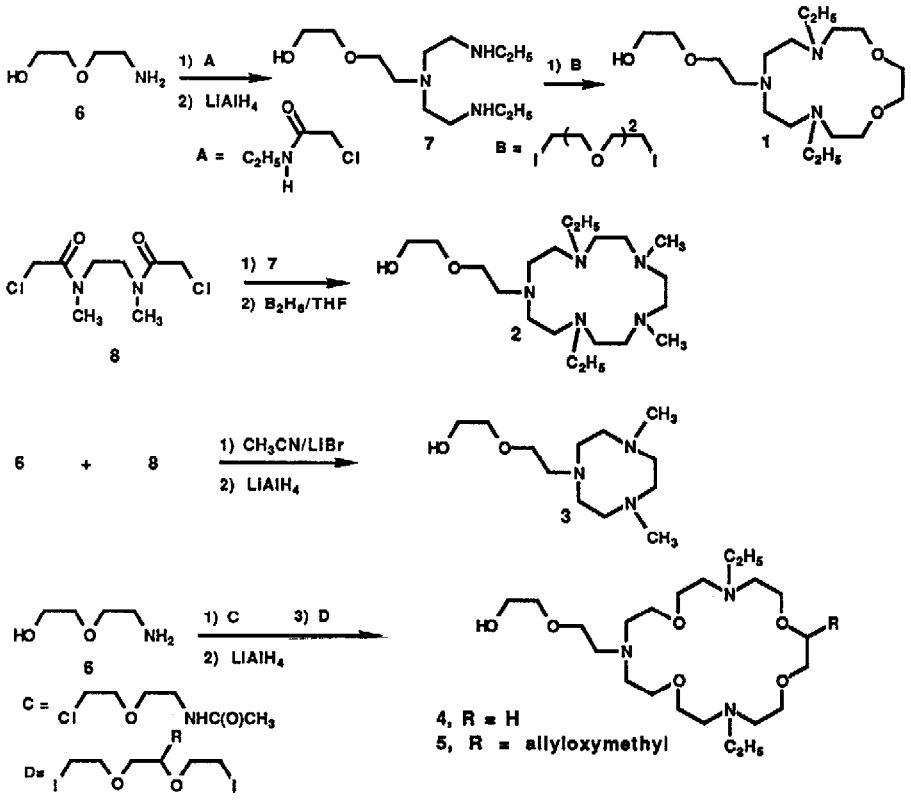
Scheme I. Synthesis of N-[2-(2-Hydroxyethoxy)ethyl]-Substituted Aza-Crowns and Cyclams



without a hydroxy blocking group.[27-29] In those cases, an epichlorohydrin[29] or 1,3-dibromo-2-propanol[27] was used to give the hydroxy-containing aza-crown but with only moderate yields. A multiple atom spacer between the crown and the functional group is necessary in any application where the functional group is used to attach the crown to a solid support so that the attached crown can interact with large molecules.[30,31] We now present a simple and general strategy to prepare N-monohydroxyalkyl-substituted aza-crowns and cyclams using unblocked 2-(2-aminoethoxy)ethanol (6) and readily available amino compounds as the starting materials. This design allows the synthesis of N-hydroxyalkyl-substituted aza-crown ethers or cyclams in only a few steps in contrast to the method previously reported.[5,8,21,25] Scheme 1 shows the synthesis of N-[2-(2-hydroxyethoxy)ethyl]triaza-15-crown-5 (1), 15-cyclam-5 (2) and 9-cyclam-3 (3) where the hydroxy group is five atoms removed from the ring and includes an additional oxygen donor atom. Scheme 1 also shows the synthesis of two triaza-21-crown-7 compounds (4,5) with the same functionalized side chain. We found that the synthetic method

used to prepare similar macrocycles which were previously reported[32], was applicable to some functionalized macrocycles. Our procedure does not require a blocking group on the hydroxy function because the sodium carbonate base does not remove the proton from the pendant hydroxy group and amines are better nucleophiles than the alcohols.

The key intermediate for the synthesis of 1 and 2, hydroxytriamine 7, was obtained from the reaction of commercially available 6 and 2.05 equivalents of commercially available N-ethylchloroacetamide in acetonitrile in the presence of sodium carbonate at reflux temperature. The reaction mixture was filtered, evaporated and the residue was chromatographed on silica gel (isopropyl alcohol). The diamide was reduced by 2 equivalents of lithium alumina hydride in the usual manner to give a 51% overall yield of triamine 7; b.p. 108-112°C/0.01 mm; NMR(δ): 1.1 (t, 6H), 1.8 (broad, 3H), 2.65 (m, 14H), 3.6 (m, 6H). Triamine 7 and 1,8-diodo-3,6-dioxaoctane (B) were refluxed in acetonitrile in the presence of sodium carbonate and sodium iodide for 24 hours. The reaction mixture was filtered, evaporated and the residue was chromatographed on neutral alumina (toluene/ethanol:20/1) to give a 68% yield of 1[33] as an oil, NMR (δ): 1.0 (t, 6H), 2.55 (q, 4H), 2.75 (m, 15H), 3.55 (m, 14H).

Compound 7 was reacted with compound 8 (prepared by reacting chloroacetyl chloride with N,N'-dimethylethylenediamine)[34] in acetonitrile in the presence of sodium carbonate for 24 hours at reflux temperature to give a cyclic diamide which was purified by chromatography on silica gel (methanol). The diamide was reduced by B_2H_6·THF in THF in the usual manner to give a 60% yield of cyclam 2[33], which was passed through a column containing Amberlite 410 followed by chromatography on neutral alumina (toluene/ethanol:10/1); NMR (δ): 1.0 (t, 6H), 2.20 (s, 6H), 2.55 (m, 27H), 3.6 (m, 6H). Compounds 6 and 8 were reacted in acetonitrile in the presence of sodium carbonate and lithium bromide at reflux temperature for 24 hours. The reaction mixture was filtered, evaporated and the residue was chromatographed on neutral alumina (isopropyl alcohol) and reduced by lithium aluminum hydride in THF or B_2H_6·THF in the usual manner to give a 40% overall yield of cyclam 3[31] as an oil, b p. 98°-101°C/0.01 mm; NMR (δ): 2.15 (s, 6H), 2.35 (m, 14H), 3.80 (m, 7H).

Two lariat crowns (4 and 5) were prepared from 6 by our published method[32] using N-[2-(2-chloroethoxy)ethyl]acetamide (C) followed by reduction with lithium aluminum hydride to form triamine 9. Compound 9 was ring closed with B or 1,8-diodo-4-allyloxymethyl-3,6-dioxaoctane.[10] These crowns were purified by column chromatography on neutral alumina (toluene/ethanol:50/1) to give 45% of 4[33] and 42% of 5[33] as oils; NMR (δ) for 4: 1.0 (t, 6H), 2.7 (m, 19H), 3.5 (m, 22H); NMR (δ) for 5: 1.05 (t, 6H), 2.70 (m, 19H), 3.70 (m, 23H), 4.0 (d, 2H), 5.25 (m, 2H), 5.9 (m, 1H).

Compounds 6-9 are excellent synthons for a variety of monohydroxy functionalized polyaza-crowns and cyclams. Only three examples of the monohydroxy-containing polyaza-crowns and two examples of the cyclams are shown here. Other monofunctionalized aza-crowns and cyclams are being prepared in our laboratory using similar procedures and closing the ring not only with the dihalides shown above but also with 1,3-diodo-2-hydroxypropane and using derivatives of 1,3-diamino-2-propanol.

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