The synthesis of a series of diazatrichia-15-crown-5 and diazatrichia-16-crown-5 ligands containing two 8-hydroxyquinoline side arms are reported. The ligands were prepared by a two-step process. First, diazatrichiacrown ethers 11 and 12 were prepared by treating bis(a-chloroamide) 5 with various dimercaptans followed by reduction using a boron-THF complex. Hydroxymethyl-substituted macrocycle 12 was rearranged to hydroxy-substituted diazatrichia-16-crown-5 in refluxing aqueous HCl. Macroyclic diamines 11-13 were converted to either 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted diazatrichiacrown ethers 14-16 by a Mannich aminomethylation reaction or to 8-hydroxyquinolin-2-ylmethyl-substituted diazatrichiacrown ethers 17-19 by reductive amination using 8-hydroxyquinoline-2-carboxaldehyde.
Synthesis of Bis-8-Hydroxyquinoline-Armed Diazatrinthia-15-Crown-5 and Diazatrinthia-16-Crown-5 Ligands

by

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Synthesis of Bis-8-Hydroxyquinoline-Armed Diazatraithia-15-Crown-5 and Diazatraithia-16-Crown-5 Ligands

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Results and Discussion

Synthesis of Diazatraithia Crown Ethers. Secondary ring nitrogen atoms in crown ethers offer a convenient site for attachment of alkyl substituents. The crab-like synthesis of diazacrown ethers using the bis(α-chloroacetamide) provides a relatively high yield method to form macrocycles containing two secondary amine functions. In this regard, bis(α-chloroamide) 5 was treated with various dimercaptans in MeCN using a carbonate base to form macrocyclic diazatraithiadiamides 6-8 in good yields (Scheme 1). As expected, the larger 2:2 cycloaddition products, macrocyclic tetraamides 9 and 10, were also isolated in two cases in small yields. The NMR spectra of 9 and 10 were similar to those of 6 and 8, respectively. High dilution techniques helped minimize the production of these undesired by-products. Macrocyclic diazatraithia ligands 11 and 12 were prepared by reducing macrocyclic diamides 6 and 8, respectively, using a borane-THF complex. Initially, work up of the borane reduction products was done in refluxing 6 M HCl, but this process caused the formation of unexpected rearrangement and ring opened products as discussed below. Exposure to 6 M HCl at room temperature for a period of 10 minutes, along with extraction, was adequate for freeing the desired product from boron giving diazatraithia-18-crown-6 (11) and hydroxymethyl-substituted diazatraithia-15-crown-5 (12) in good yields.

The rearrangement product of 12 proved to be a new hydroxy-substituted diazatraithia-16-crown-5 (13) (Scheme 2). Ligand 13 is also of value in our research program. In an acid environment with heating, the protonated primary hydroxyl group from 12 becomes a leaving group when attacked by the neighboring ring sulfur atom. This leads to a charged epithio intermediate that is in turn attacked by water at the carbon atom most able to support a positive charge, forming 13. A minor product from this reaction resulted from the intramolecular attack by a neighboring ring nitrogen atom forming 13a in a very low-yield. A trace amount of another compound which has very similar properties to those of 13a was also observed. This material could be a result of the attack of the other ring nitrogen atom on the epithio intermediate.

Synthesis of 8-Hydroxyquinoline-substituted Ligands. Ligands 14-16 with the CHQ units attached at the CHQ 7-position were formed using Mannich reaction conditions as shown in Scheme 3. The best results were achieved by first forming the N,N'-bis(methoxymethyl)diazacrown ethers by stirring the diaza crowns in methanol and a slight excess of paraformaldehyde. After removal of methanol and addition of benzene to the mixtures, CHQ was added and the mixtures were refluxed. Benzene
proved to be a good reaction solvent since there were few side products. Products 14-16 were purified using radial chromatography.

Compounds 17-19 (Scheme 4) were obtained in good yields using a reductive amination procedure.\textsuperscript{1a,1b} Ligands 17-19 with the 8-hydroxyquinoline side arms attached at their 2-positions were more readily isolated than compounds 14-16 with CHQ units attached at their 7-positions.

References


Scheme 1. Syntheses of diazatrithiacrown ethers 11 and 12 containing two unsubstituted nitrogen atoms
Scheme 2. Rearranged crown ethers 13 and 13a

Scheme 3. Syntheses of 5-chloro-8-hydroxyquinolin-7-ylmethyl-substituted crown ethers via the Mannich reaction
Scheme 4. Syntheses of 8-hydroxy-quinolin-2-yilmethyl-substituted crown ethers via reductive amination