One-step Methods to Prepare Cryptands and Crowns Containing Reactive Functional Groups

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A one-step synthesis of cryptand [2.2.2] containing three methylenyl substituents in a 25% yield from the reaction of triethanolamine and 3-chloro-2-chloromethyl-1-propene is described. A similar cryptand was prepared in 56% yield by a two-step process. One-step syntheses of *N,N'*-hydroxyethyl-diaza-18-crown-6 and crown-6 compounds containing two alkene functional groups are also described.

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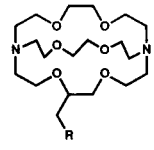
There is a growing interest in the preparation of functionalized macrocyclic compounds which can be bonded to solid supports such as silica gel [1]. We have been particularly interested in new methods to prepare functionalized crowns and cyclams in high yields in as few steps as possible. The silica gel-bound crowns and cyclams can be used to separate various metal cations [1-5].

The syntheses of cryptands and crowns are often tedious and time consuming with many steps [2]. Simple condensation reactions of two starting materials in a 2:2 ratio for a crown or a 3:2 ratio for a cryptand would be very attractive procedures. These methods would allow a one-pot synthesis of symmetrical macrocycles of differing sizes from simple starting materials. The appropriate template ion coupled with rigid starting materials could lead to desired products in high yields with only small amounts of by-products.

Cyclocondensations with 4:2 and 2:2 ratios of starting materials are those which are used most often for the template synthesis of cyclanediene macrocycles. Curtis first discovered that monocarbonyl compounds condensed with diamines to form cyclic compounds in ratios of 4:2 and 2:2 [6,7]. This rapid cyclization method also was used to form rigid crown ethers containing aromatic rings [8-12]. Generation of macrocycles by simultaneous Schiff base formation also has been studied. In some cases, the products were reduced to saturated ligands. These types of products were often obtained as by-products in the Stetter cycloaddition of diacid chlorides and diamines [13-16]. Flexible chains can form more cyclic products, including smaller rings. Thus, the formation of saturated crown ethers using a 2:2 ratio of starting materials gave low yields (5-30%) of the desired products unless a metal template ion was used [17-20]. In the preparation of the cryptands, the best results were obtained by 2:1 condensations of a diamine with two molecules of a dihalide rather than 3:2 cycloadditions since, in this case only four new bonds needed to be formed [21-26].

We now present several syntheses of mono- di- and trifunctionalized macrocyclic compounds by simple 3:2, 2:2 or 1:1 cycloadditions. Monofunctionalized cryptands, such as cryptands **1-3**, have been prepared by Montanari and Tundo [27] and also by Bartsch and his coworkers [28], in multiple steps. We have reported the synthesis of polyazacrowns and cyclams with substituent alkenyl [2,4], hydroxyalkyl [29] and secondary aminoalkyl [30] functional groups and with unsubstituted macroring nitrogen atoms [31].



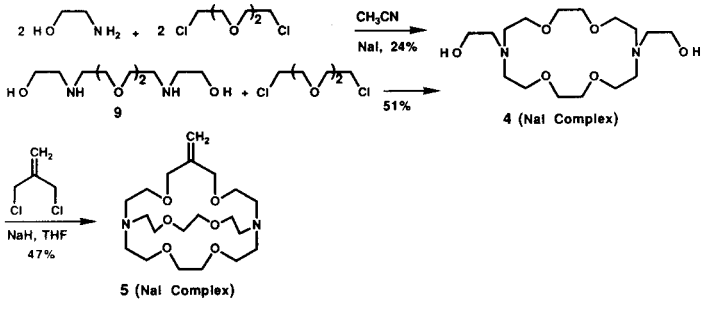
1. R = OC_6H_{13}
2. R = OH
3. R = $OCH_2CH=CH_2$

Results and Discussion.

In our first attempt at the preparation of a monofunctionalized cryptand, we prepared **3** using different starting materials. Bartsch and his coworkers reacted 1,10-diaza-18-crown-6 with the dimesylate derivative of 4-(allyloxymethyl)-3,6-dioxa-1,8-octanediol to form **3** [28]. We found that the corresponding allyloxymethyl-substituted diiodide gave a 22% higher yield of cryptand **3**. However, our procedure required an additional step to convert Bartsch's dimesylate to the diiodide. Methylenyl-substituted cryptand **5** was prepared by two pathways (Scheme I). The bis-hydroxyethyl-substituted diaza-crown **4** was prepared by two procedures as shown. The reaction of available 1,2-bis-(2-chloroethanoxy)ethane with ethanolamine in the presence of sodium iodide (to effect *in situ* conversion of the dichloride to the diiodide) gave a 24% yield of **4** as the sodium iodide complex. The diaza-crown 4-complex was first prepared in a 28% yield by Gokel and his coworkers by the same 2:2 condensation process utilizing 1,2-bis-(2-iodoethoxy)ethane [32]. The crown 4-complex was prepared in a 51% yield by reacting either 1,2-bis-(2-chloroethoxy)ethane and sodium iodide or its diiodo analogue with 6,9-dioxa-3,12-diazatetradecane-1,14-diol (**9**) (Scheme I). The reaction of **4** with 3-chloro-2-chloromethyl-1-propene gave the sodium iodide complex of cryptand **5** in a 47% yield. The overall three-step yield of **5** was about 20%. We considered preparing cryptand **5** by first preparing methylenyl-substituted diaza-19-crown-6 [33] and reacting this with 1,2-bis-(2-iodoethoxy)ethane. The diaza-19-crown-6 was prepared in low yields in our laboratory so

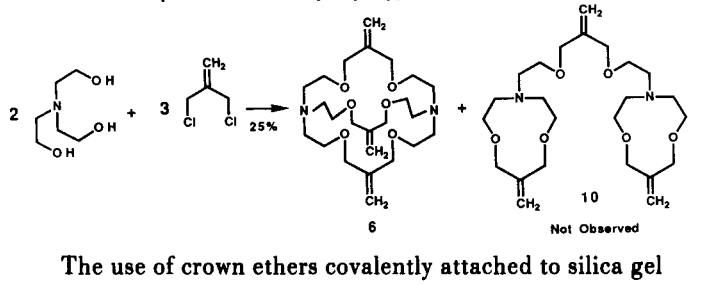
we did not pursue this synthetic process for the preparation of **5**. Compound **5** and its hydroxymethyl analog was prepared by Tomoi and his coworkers in a 6% overall yield in multiple steps [33-36].

Scheme I. Preparation of Bis-Hydroxyethyldiaza-Crown (4) and Methylenylcryptand [2.2.2] (5)



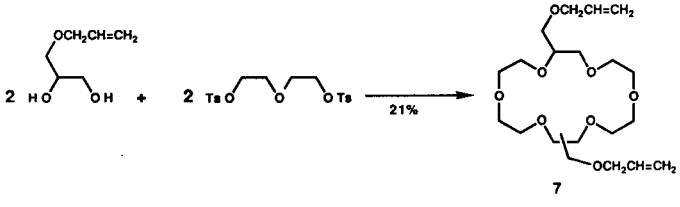
Tris-methylenyl-substituted cryptand [2.2.2] (**6**) was prepared in a 25% yield by the one-step 3:2 cyclization procedure shown in Scheme II. The 25% yield was for one step. The process was not optimized. Bis-10-crown-3 **10** (see Scheme II) could be a product of this reaction. This by-product would have the same molecular weight and elemental analysis as **6**. We do not believe that **10** was one of the products of this reaction. The ^{1}H nmr spectrum of **10** would be different from that of **6**. Compound **10** would have two types of ^{1}H nmr signals for the methylenyl hydrogen atoms ($C=CH_2$). The signal for these protons located on the 10-membered rings would differ from that of the methylenyl hydrogen atoms on the open chain portion of the molecule. There would also be two peaks corresponding to the CH_2 units next to the two types of methylenyl groups in **10**. The ^{1}H nmr spectrum for **6** clearly had sharp singlets for those two types of hydrogen atoms. Therefore, compound **10** was not detected in the reaction (Scheme II). Triethanolamine [37] and 3-chloro-2-chloromethyl-1-propene are inexpensive starting materials making this an important new synthesis of a potentially useful cryptand.

Scheme II. Preparation of Methylenylcryptand [2.2.2] (6)



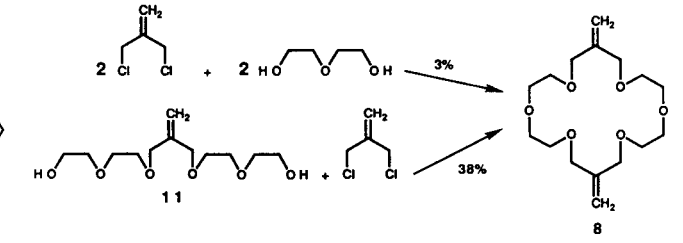
The use of crown ethers covalently attached to silica gel for the separation of metal cations [1,3,5] necessitates a convenient and low-cost method to prepare these crowns. The initial method for attaching the crown to silica gel was by a hydrosilylation reaction of an allyloxymethyl-substituted 18-crown-6 with triethoxy silane followed by coating and heating the crown-triethoxysilane on silica gel. Compound **7** which possesses two allyloxymethyl substituents, was prepared in a reasonable yield (21%) by a 2:2 cycloaddition reaction of commercially available allyloxymethylethylene glycol and the ditosylate derivative of ethylene glycol (Scheme III). This is a relatively inexpensive method to prepare this important material. The product of this reaction was found also to contain products of 1:1, 3:3 and 4:4 cycloadditions, namely, allyloxymethyl-9-crown-3, trialkyloxymethyl-27-crown-9, and tetraallyloxymethyl-36-crown-12. These products were observed in the gc-ms analysis of the crude reaction mixture. The desired 18-crown-6 product (**7**) was isolated first by alumina chromatography followed by distillation.

Scheme III. Preparation of Bis-Allyloxymethyl-18-Crown 6 (7)



Bis-methylenyl-substituted 20-crown-6 (**8**) was prepared in only 3% yield by the 2:2 cyclization reaction of 3-chloro-2-chloromethy-1-propene and diethylene glycol (Scheme IV). However, a two-step process using these same ingredients gave a 20% overall yield of **8**. In the first step, an excess of ethylene glycol was reacted with the dichloride to form **11**. This glycol was then reacted with the dichloride to produce **8**. We suspect that the very poor yield of **8** by a 2:2 cycloaddition was a result of the fact that 20-crown-6 compounds form weak complexes with metal cations so that there would be a low template effect. Higher yields for this cycloaddition may be possible if the more reactive ditosylate starting material were used. 18-Crown-6 (**7**), on the other hand, forms strong complexes with metal cations and the 2:2 cycloaddition reaction gave a better yield.

Scheme IV. Preparation of Bis-Methylenyl-Crown-6 (8)



A 3:2 cycloaddition to form a cryptand (such as **6**) at moderate yields can be important because this one-step reaction results in a compound which is difficult to prepare by other methods.

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Perkin Elmer FT 1600

spectrometer. The proton nuclear magnetic resonance (^{1}H nmr) spectra were determined on a Varian Gemini 200 spectrometer using deuteriochloroform. Elemental analyses were determined by MHW Laboratories, Phoenix, Arizona. Molecular weights were determined by the electron impact method on a Finnegan 8430 High Resolution Mass Spectrometer. All starting materials were used as purchased except for **9** which was prepared as reported [38] and **11** which was prepared as follows:

8-Methylenyl-3,6,10,13-tetraoxapentadecane-1,15-diol (**11**).

A mixture of 0.5 g (21 mmoles) of sodium hydride and 20 ml of diethylene glycol was stirred at 60° until the evolution of hydrogen gas ceased. 3-Chloro-2-chloromethyl-1-propene (1.25 g, 10 mmoles) was added at 60-70° and the mixture was stirred at 120° for 3 hours. The product was distilled to give 1.35 g (51%) of **11** as an oil, bp 140-145°/0.01 mm; ^{1}H nmr (δ) 3.2 (b, 2 H), 3.7 (m, 16 H), 4.1 (s, 4 H), 5.2 (s, 2 H).

Allyloxymethylcryptand[2.2.2] (**3**).

The procedure of Bartsch and his coworkers [28] to prepare **3** was followed except 0.95 g (2.2 mmoles) of 4-allyloxymethyl-1,8-diiodo-3,6-dioxaoctane [2] was used instead of the corresponding dimesylate. The remainder of the reactants included 0.53 g (2 mmoles) of 1,7,10,16-tetraoxa-4,13-diazacyclooctane, 3 g of anhydrous sodium carbonate (instead of *n*-butyl lithium), 0.1 g of sodium iodide and 80 ml of acetonitrile. The crude reaction product was purified by aluminium chromatography (toluene/ethanol:10/1) to give 0.4 g (46%) of **3**. The spectral properties of **3** were the same as those reported [28].

1,10-Bis-(2-hydroxyethyl)-4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (**4**) (Scheme I).

Method A.

The procedure of Gokel and his coworkers [32] to prepare **4** was followed except that 37.4 g (0.2 mole) of 1,2-bis-(2-chloroethoxy)ethane and 70 g of sodium iodide were used instead of the 1,2-bis-(2-iodoethoxy)ethane. The sodium iodide complex of **4** (12 g, 24%) was isolated, mp 126° (lit value 131° [32,39]); ms m/z 350.

Anal. Calcd. for $C_{16}H_{34}N_2O_6NaI$: C, 38.40; H, 6.85. Found: C, 38.46; H, 7.00.

Method B.

A mixture of 14.16 g (0.06 mole) of **9**, 23.0 g (0.06 mole) of 1,2-bis-(2-iodoethoxy)ethane and 60 g of anhydrous sodium carbonate was stirred and refluxed in 500 ml of acetonitrile for 36 hours. The mixture was cooled, filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (chloroform/ethanol:20/1). The appropriate product was recrystallized from THF to give 15.2 g (51%) of **4** which had the same physical properties as reported above. When 1,2-bis-(2-chloroethoxy)-ethane and sodium iodide was used instead of the diiodide analog, a yield of 32-41% of **4** was realized.

Methylenylcryptand[2.2.2] (**5**) (Scheme I).

Macrocycle **4** (5 g, 0.01 mole) was added to 250 ml of THF containing 0.5 g of sodium hydride and the mixture was refluxed for 2 hours in an Argon atmosphere. 3-Chloro-2-chloromethyl-1-propene (1.25 g, 0.01 mole) in 50 ml of THF was slowly added to the above stirred and refluxing solution and the resulting mixture was refluxed an addition 18 hours. The mixture was filtered hot and the residue was washed with hot THF. The organic solvents were evaporated and the residue was chromatographed on alumina using chloroform/acetonitrile:32/1 and 10/1 as eluants. The resulting solid was recrystallized (THF) to give 2.6 g (47%) of **5**, mp 230; ^{1}H nmr: (δ) 2.65 (m, 12 H), 3.6 (m, 20 H), 4.2 (s, 4 H), 5.2 (s, 2 H); ms m/z 402.

Anal. Calcd. for $C_{20}H_{38}O_6N_2NaI$: C, 43.46; H, 6.90; N, 5.06. Found: C, 43.48; H, 6.93; N, 5.07.

Tris-Methylenylcryptand[2.2.2] (**6**) (Scheme II).

Triethanolamine (6 g, 0.04 mole) in 100 ml of DMF was added dropwise to 100 ml of DMF containing 3.5 g (0.15 mole) of sodium hydride. The mixture was warmed to 80° until hydrogen gas ceased to evolve. The mixture was cooled to 0° and 7.5 g (0.06 mole) of 3-chloro-2-chloromethyl-1-propene in 20 ml of DMF was added. The resulting mixture was stirred overnight at room temperature and at 65° −75 for 24 hours. The solvent was filtered and evaporated. Water (20 ml) was added to the residue and the resulting mixture was extracted twice with 60 ml portions of chloroform. The choroform extracts were evaporated and the residue purified by alumina chromatography (acetonitrile/ethanol:50/1) and then on a short silica gel column (methanol and ammonia) to give 2.1 g (25%) of **6** as an oil which slowly solidified to a low mp solid; ^{1}H nmr: (δ) 2.75 (t, 12 H), 3.5 (t, 12 H), 4.05 (s, 12 H), 5.15 (2, 6 H); ms m/z 454.

Anal. Calcd. for $C_{24}H_{42}O_6N_2$: C, 63.41; H, 9.31. Found: C, 63.32; H, 9.29.

2,11(or 12)-Bis-allyloxymethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (**7**) (Scheme III).

3-Allyloxy-1,2-propanediol (6.6 g, 0.05 mole) was slowly added to 150 ml of DMF containing 3 g of sodium hydride. This mixture was warmed to 70° for 1 hour, cooled and 20.7 g (0.05 mole) of diethylene glycol ditosylate was added to it. The mixture was stirred at room temperature for 60 hours. Ethanol (2 ml) was then added and the solvents were evaporated under high vacuum (1 mm). The residue was dissolved in 20 ml of water and the water was extracted three times with 50 ml portions of chloroform. The combined chloroform solutions were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was chromatographed on alumia using toluene/ethanol:100/1 and 50/1 as eluants. The residue was distilled to give 2.1 g (21%) of **7**, bp 176-184°/0.05 mm; ^{1}H nmr: (δ) 3.6 (m, 26 H), 4.0 (d, 4 H), 5.1 (m, 4 H), 5.9 (m, 2 H); ms m/z 404. A gc-ms analysis of the crude product showed material at m/z 202, 404, 606 and 808 corresponding to the 1:1, 2:2, 3:3 and 4:4 cycloaddition products. The other products were not further isolated or identified.

Anal. Calcd. for $C_{20}H_{36}O_8 \cdot 0.5H_2O$: C, 58.09; H, 9.01. Found: C, 57.87; H, 8.97.

9,19-Dimethylenyl-1,4,7,11,14,17-hexaoxacycloeicosane (**8**) (Scheme IV).

Method A. (2:2 Cyclization).

Diethylene glycol (4.24 g, 0.04 mole) was slowly added to a stirred mixture of 2.3 g of sodium hydride in 150 ml of DMF. This mixture was stirred at 80° until hydrogen gas ceased to be evolved. This mixture was cooled and 5.3 g (0.042 mole) of 3-chloro-2-chloromethyl-1-propene was added. The resulting mixture was stirred at 80° for 16 hours and evaporated. The residue was

chromatographed on alumina (toluene/ethanol:200/1) to give 0.3 g (3%) of **8** as an oil; ^{1}H nmr (δ): 3.6 (m, 16 H), 4.1 (s, 8 H), 5.15 (s, 4 H); ms m/z 316.

Anal. Calcd. for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92. Found: C, 60.57; H, 8.78.

Method B.

Sodium hydride (0.3 g) was added to 1 g (3.8 mmoles) of **11** in 100 ml of THF. The mixture was stirred for 30 minutes at 50°. 3-Chloro-2-chloromethyl-1-propene (0.47 g, 3.8 mmoles) was added to the cooled solution and the mixture was stirred under reflux for 16 hours. Ethanol (0.5 ml) was then added and the cooled mixture was filtered and evaporated under reduced pressure. The residue was treated as above to give 0.45 g (38%) of **8** having the same physical properties as reported above.

Acknowledgement.

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