

NOVEL AND CONVENIENT SYNTHESSES OF N-ALKYL-SUBSTITUTED TRIAZA- AND TETRAAZA-CROWN COMPOUNDS

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Abstract: A new short method to prepare N-alkyl-substituted triaza- and tetraaza-crown compounds in good overall yields by reacting the appropriate oligoazaoxadiazamine with allyloxymethyl-substituted triethylene glycol diiodide or diglycolyl dichloride (followed by reduction) is presented.

The aza-crown compounds have received considerable interest in recent years because of their ability to complex a variety of metal and organic cations and anions.¹⁻⁶ The diaza-crowns are also starting materials for the preparation of the cryptands.⁷ Silica gel-bound crown compounds have been prepared by reacting the corresponding allyloxymethyl-substituted crowns first with triethoxysilane followed by coating and heating the resulting crown-silane material on silica gel.⁸⁻¹⁰ Silica gel-bound diaza-18-crown-6 had a much greater affinity for heavy metal cations than silica gel-bound 18-crown-6.⁸ For example, log K values in water for the interaction of silica gel-bound 18-crown-6 for Cd^{2+} and Ag^+ were 0.39 ± 0.13 and 1.61 ± 0.09 , respectively, while log K values for the interaction of silica gel-bound N,N'-dibenzyl-diaza-18-crown-6 for the same two cations were 5.0 ± 0.2 and 8.2 ± 0.2 , respectively. These log K values are essentially the same as those for the unbound crowns for interaction with the same cations.

Although there are few data on the complexation of the polyaza-crown ligands with various metal ions, it is apparent that increasing the number of nitrogen atoms in the macroring increases the affinity of the ligand towards the heavy metal cations.¹¹ The log K values for the interaction of Zn^{2+} with diaza-18-crown-6, tetraaza-18-crown-6 and hexaaza-18-crown-6 are 4.31, 10.90 and 17.8, respectively. It is important to note that the log K values for the interaction of the N-alkyl-substituted polyaza-crowns with various cations were nearly the same as for the interaction of the unsubstituted polyaza-crowns with the same cations.¹¹ Thus, N-alkyl-substituted polyaza-crowns can be used for complexation purposes.

Previous methods for the synthesis of polyaza-crown compounds have used the "zip" reaction of an aminoalkyl-substituted cyclic lactam to increase the ring size¹² and either the method of Richman and Atkins¹³ or a modification of the Richman-Atkins procedure.¹⁻⁵ Each of

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these methods require many steps particularly in the formation of starting materials. The Richman-Atkins type reaction requires the use of methanesulfonyl, benzenesulfonyl or toluenesulfonyl groups to both protect and activate the amino nitrogens and additional steps to remove the sulfonyl moiety. In some cases, the attachment of various alkyl groups to the nitrogen atoms follows the removal of the sulfonyl blocking groups.¹⁴

We have developed a general synthetic strategy which allows the preparation of N-alkyl-substituted polyaza-crown compounds using only a few steps. Scheme 1 shows the synthesis of triaza-18-crown-6 (1) and triaza-21-crown-7 (2) compounds using our new procedure. Scheme 2 shows the synthesis of tetraaza-24-crown-8 (3), tetraaza-27-crown-9 (4 and 5) and tetraaza-30-crown-10 (6) compounds. All the new polyaza-crowns except 1 contain the allyloxymethyl group which will allow the attachment of these crowns to silica gel.^{8,9} The key in these synthetic schemes is the use of N-[2-(chloroethoxy)ethyl]acetamide (compound A, Schemes 1 and 2) to prepare triaza-synthon 7 and tetraaza-synthons 12-15. Details for the synthesis of triaza-crown 1 and tetraaza-crown 3 are given below.

Compound A was prepared by first reacting 2-(2-aminoethoxy)ethanol with acetic anhydride to produce N-[2-(2-hydroxyethoxy)ethyl]acetamide. This product was reacted with thionyl chloride to give A (bp 107-109/0.07 mm) in an 85% overall yield. It is important to note that the corresponding benzamide and sulfonamide compounds internally cyclize to form the corresponding morpholinyl amides.¹⁵ Benzylamine and 2.1 equivalents of A were reacted in refluxing toluene in the presence of anhydrous sodium carbonate using a Dean-Stark apparatus for 48 hours. The reaction mixture was filtered, evaporated and the residue was chromatographed on silica gel (isopropyl and ethyl alcohols) to isolate a 71% yield of the diamide product as a viscous liquid. The diamide was reduced by 2 equivalents of lithium aluminum hydride in THF in the usual manner to give a 73% yield of triamine 7, bp 148-150°C/0.2 mm. Triamine 7 and diglycolyl dichloride each in toluene were simultaneously added over a several hour period to toluene (well stirred) containing two equivalents of triethylamine at room temperature. The toluene solution was stirred for 24 hours, filtered and evaporated. The residue was chromatographed on alumina (toluene/ethanol: 20/1) to give a 62% yield of the cyclic diamide. The cyclic diamide was reduced in the usual manner by 2 equivalents of lithium aluminum hydride followed by purification by chromatography on alumina (toluene/ethanol: 50/1) to give a 74% yield of 1¹⁶ as an oil, NMR (δ): 1.05 (t, 6 H), 2.60 (q, 4 H), 2.7 (m, 12 H), 3.6 (m, 14 H), 7.4 (m, 5 H). The overall yield of 1 from benzylamine and A was 24%.

N,N'-Dimethylethylenediamine was reacted with 2.2 equivalents of compound A as above to give a 58% yield of the diamide which was purified by chromatography on silica gel (ethanol then methanol). The diamide is the 2:1 reaction product. About 25% of a mono amide (the 1:1 product) was also isolated. This monoamide was also reduced and used to prepare triaza-crown compounds. The diamide was reduced by lithium aluminum hydride in the usual manner to give tetraamine 12 (72%), bp 126-129°C/0.075 mm. Tetraamine 12 was reacted with 1.1 equivalents of compound C^{10,17} in acetonitrile in the presence of potassium and sodium carbonates and sodium iodide¹⁹ to give 3¹⁶ (48%) as a liquid which was purified on alumina (toluene/ethanol: 50:1); NMR (δ): 1.05 (t, 6 H), 2.35 (s, 6 H), 2.6 (t, 12 H), 2.75 (t, 8 H), 3.45-3.75 (m, 19 H), 5.1-5.35 (3 peaks, 2 H), 5.9 (m, 1 H). The overall yield of 3 from A and N,N'-dimethylethylenediamine was 20%.

References and Notes

1. E. Graf and J.M. Lehn, Helv. Chim. Acta, **64**, 1040 (1981).
2. B. Dietrich, M.W. Hosseini, J.M. Lehn and R.B. Session, Helv. Chim. Acta, **66**, 1262 (1983).
3. M.W. Hosseini, J.M. Lehn and M.P. Mertes, Helv. Chim. Acta, **66**, 2444 (1983).
4. J. Comarmand, P. Plumere, J.M. Lehn, Y. Agrus, R. Louis, R. Weiss, O. Kahn and J. Margenstern-Badarau, J. Am. Chem. Soc., **104**, 6330 (1982).
5. M.W. Hosseini, J.M. Lehn, L. Maggiora, K.B. Mertes and M.P. Mertes, J. Am. Chem. Soc., **109**, 537 (1987).
6. A. Kumar, S. Mageswaran and I.O. Sutherland, Tetrahedron, **42**, 3291 (1986).
7. J.M. Lehn, Accts Chem. Res., **11**, 49 (1978).
8. J.S. Bradshaw, R.M. Izatt, J.J. Christensen, K.E. Krakowiak, B.J. Tarbet, R.L. Bruening and S. Lifson, J. Incl. Phenom., submitted.
9. J.S. Bradshaw, R.L. Bruening, K.E. Krakowiak, B.J. Tarbet, M.L. Bruening, R.M. Izatt and J.J. Christensen, J. Chem. Soc., Chem. Commun., in press.
10. J.S. Bradshaw, K.E. Krakowiak, R.L. Bruening, B.J. Tarbet, P.B. Savage and R.M. Izatt, J. Org. Chem., in press.
11. R.M. Izatt, J.S. Bradshaw, S.A. Nielsen, J.D. Lamb, J.J. Christensen and D. Sen, Chem. Rev., **85**, 271 (1985).
12. U. Kramer, H. Schmid, A. Guggisberg and M. Hesse, Helv. Chim. Acta, **62**, 811 (1979).
13. J.E. Richman and T.J. Atkins, J. Am. Chem. Soc., **96**, 2268 (1974).
14. F.P. Schmidtchen, J. Org. Chem., **51**, 5161 (1986).
15. C.J.M. Stirling, J. Chem. Soc., 3676 (1962).
16. Satisfactory elemental analyses, molecular weights by MS, and IR and NMR spectra were obtained for all new triaza- and tetraaza-crown compounds.
17. Compound C was prepared by exchanging the mesylate groups of the dimesylate derivative of allyloxymethyl-substituted triethylene glycol¹⁸ by iodo groups using sodium iodide in acetone.
18. D.A. Babb, B.P. Czech and R.A. Bartsch, J. Heterocyclic Chem., **23**, 609 (1986).
19. A mixture of sodium and potassium carbonates was used in order to insure that the appropriate cations needed for a template in closing the large macrocycles were present. It is possible that two cations are needed as templates for very large macrocycles. Sodium iodide has been reported to give higher yields when using a diiodo compound for ring closure.²⁰
20. V.J. Gatto, K.A. Arnold, A.M. Viscariello, S.R. Miller, C.R. Morgan and G.W. Gokel, J. Org. Chem., **51**, 5373 (1986).

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