Tetrahedron Letters No. 46, pp 4029 - 4032, 1974. Pergamon Press. Printed in Great Britain.

FACILE SYNTHESES OF 12-CROWN-4[1a] AND 15-CROWN-5[1b]

Fred L. Cook, Thomas C. Caruso, Michael P. Byrne, Chauncey W. Bowers, Don H. Speck
and Charles L. Liotta*

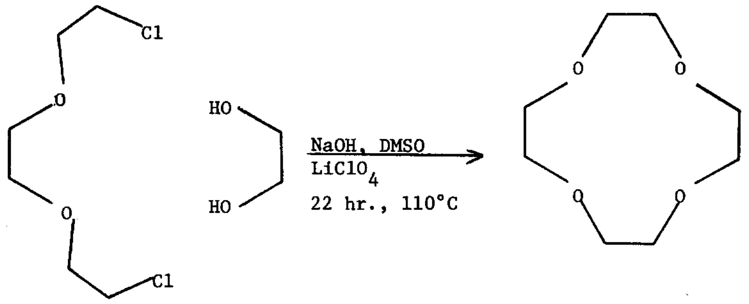
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

(Received in USA 10 September 1974; received in UK for publication 8 October 1974)

Since the pioneering work of Pederson on the preparation and properties of macrocylic polyethers ("crown" ethers)[2], there have been numerous reports of syntheses of a wide variety of oxygen, sulfur, and nitrogen containing crowns[3]. As a result of the work performed in our laboratories concerning the synthesis and purification of 18-crown-6[4], its ability to effectively complex potassium ions and solubilize potassium salts in non-polar and polar aprotic solvents[5], its utility as a phase transfer catalyst in synthesis ("naked" anions)[5], and its ability to form solid complexes with a variety of dipolar molecules (e.g. nitriles)[6], interest has developed in the utility of the lower crown homologues, 12-crown-4 and 15-crown-5. Based upon work reported for substituted derivatives, 12-crown-4 appears to be a good complexing agent for lithium ion, while 15-crown-5 appears to be a good complexing agent for sodium and potassium ions.[2c,7,8]

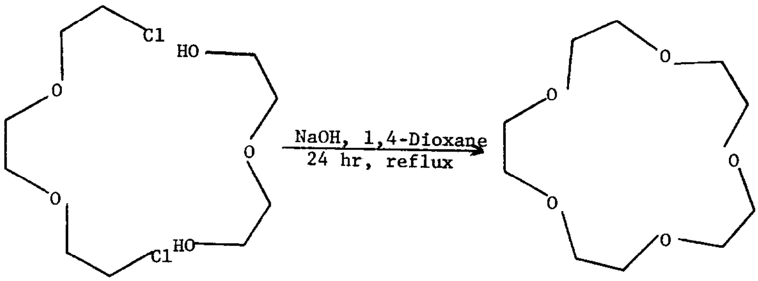
While several syntheses of substituted derivatives of 12-crown-4 and 15-crown-5[2c,8] have been reported, few syntheses of unsubstituted crowns have appeared. Dale and Kristiansen prepared 15-crown-5 in 20% isolated yield *via* a modified Williamson synthesis with triethylene glycol, diethylene glycol ditosylate and potassium *t*-butoxide in anhydrous benzene at reflux temperatures[3b,c]. This synthesis suffers from the commercial unavailibility of the ditosylate, the necessity for dry conditions, unsuccessful attempts to liberate the crown from the potassium tosylate complex by simple heating, and the necessity of using column chromatography for isolation of the free product. The unsubstituted 12-crown-4 has been synthesized by several workers[9-12], all using acid-catalyzed cyclic tetramerization of ethylene oxide. Dale and Kristiansen produced 12-crown-4 in this manner[11a], and found it to form a 1:1 complex with lithium cation.[11b] Stewart, Waddan and Borrows have published the only detailed isolation procedure to date for 12-crown-4, the product being obtained in low yield[9]. Dale and Kristiansen also attempted (unsuccessfully) to synthesize 12-crown-4 by the modified Williamson procedure mentioned above, isolating instead 24-crown-8[3b,c]. We now wish to report facile modified Williamson syntheses of 12-crown-4 and 15-crown-5 not requiring anhydrous conditions and with commercially available starting materials.

Scheme I



Preparation of 12-Crown-4[1a] (Scheme I). Into a 250 ml, 3-neck, round bottom flask equipped with an internal thermometer, reflux condenser and magnetic stirring bar was added 70 ml of DMSO and 9.25 g. (0.23 mole) of NaOH (98% pellets). After stirring for 5 minutes, 24.58 g. (0.23 mole) of anhydrous lithium perchlorate (City Chem. Corp.) was added in one portion.[13a] The mixture attained a milky appearance and warmed to ca 60°C while being stirred for 10 minutes. A solution of 6.21 g. (0.10 mole) of ethylene glycol (Fisher) in 15 ml of DMSO was added to the flask and the resulting mixture was stirred at ambient temperature for 15 minutes. A solution of 18.73 g. (0.10 mole) of 1,8-dichloro-3,6-dioxaoctane (Eastman) in 15 ml of DMSO was then added in a thin stream from a dropping funnel. The system was heated at 110°C[15] for 22 hours with stirring. The solution was cooled, filtered, and the filtrate was added to 500 ml of distilled water. The water solution was extracted with four-200 ml aliquots of chloroform, the combined extracts dried over anhydrous magnesium sulfate, the salt filtered, and the $CHCl_3$ removed by rotary evaporation (aspirator pressure). Distillation under vacuum gave 2.33 g. (13.2%) of hygroscopic 12-crown-4:[16,17] b.p. 67-70°C at 0.5 mm Hg (Lit.[9] b.p. 118-119°C at 15 mm Hg); ir (neat, NaCl plates) 2925, 1465, 1365, 1280, 1250, 1130, 1100, 1095, 920 cm^{-1}.[17] ^{1}H-nmr ($CDCl_3$, external TMS/$CDCl_3$) 3.65 ppm (sharp singlet) ^{13}C-nmr ($CDCl_3$, internal TMS, proton decoupled) 70.621 ppm; mass spectra m/e (relative %): 176 (magnified, $P^{\oplus}$), 133 (30%), 89 (94%), 87 (56%), 73 (70%), 59(57%), 45 (100%); elemental analysis, calculated for $C_8H_{16}O_4$: %C = 54.53, %H = 9.15; found: %C = 54.31, %H = 9.15.

Scheme II



Preparation of 15-Crown-5 (Scheme II). Into a 3-liter, 3-neck flask, equipped with a mechanical stirrer and reflux condenser, was added 500 ml of 1,4-dioxane[13b] and 79.5 g. (0.75 mole) of diethylene glycol (Aldrich). A solution of 60 g. (1.50 mole) of NaOH (98% pellets) was added to the flask while stirring. Immediately a heavy, white precipitate formed and the flask warmed slightly. The mixture was allowed to stir at ambient temperature for ca. 20 minutes. A solution of 140 g. (0.75 mole) of 1,8-dichloro-3,6-dioxaoctane (Eastman) in 100 ml of dioxane was added to the flask, and the mixture refluxed for 24 hours. The solution was cooled, filtered and the bulk of the solvent was removed by rotary evaporation (aspirator pressure). The residue was again filtered, and the filtrate was dissolved in 500 ml of methylene chloride. The solution was dried over anhydrous $MgSO_4$, filtered, and the CH_2Cl_2 removed by rotary evaporation (aspirator pressure). The residue was distilled under vacuum to give 23.4 g. (14.2%)[18a] of 15-crown-5[17] b.p. range collected[18b] 100°-135°C at 0.2 mm Hg; ir[17] (CCl_4, 0.1 mm NaCl cell) 2875, 1445, 1350, 1280, 1250, 1185, 975, 925 cm^{-1}; ^{1}H-nmr (CCl_4 internal TMS standard) 3.58 ppm (sharp singlet); ^{13}C-nmr ($CDCl_3$ internal TMS, proton decoupled) 70.621 ppm; mass spectra m/e (relative %): 220 (magnified, $P^{\oplus}$), 133 (74%), 89 (100%), 87 (66%), 73(75%), 59 (60%), 45 (78%); elemental analysis, calculated for $C_{10}H_{20}O_5$: %C = 54.52, %H = 9.17: found: %C = 54.39, %H = 9.18.

Reference and Notes

1. a) 1,4,7,10-Tetraoxacyclododecane; b) 1,4,7,10,13-Pentaoxacyclopentadecane.

2. a) C. J. Pedersen, J. Amer. Chem. Soc., 89(26), 7017 (1967); b) ibid, 92(2), 386 and 391(1970); c) For reviews on crown ether chemistry, see: 1) C. J. Pedersen and H. K. Frensdorff, Angew. Chem. Int. Ed. Engl., 11, 16 (1972); 2) J. J. Christensen, D. T. Eatough, and R. M. Izatt, Chem. Rev., 74(3), 351 (1974).

3. a) R. N. Greene, Tetrahedron Letters, No. 18, 1793 (1972); b) J. Dale and P. O. Kristiansen, J. Chem. Soc. Chem. Comm., 670 (1971); c) J. Dale and P. O. Kristiansen, Acta Chem. Scand., 26, 1471 (1972); d) C. J. Pedersen, J. Org. Chem., 36, 354 (1971); e) J. E. Richmann and T. J. Atkins, J. Amer. Chem. Soc., 96, 2268 (1974); f) L. A. Ochrymowycz, C. P. Mak and J. D. Michner, J. Org. Chem., 39, 2079 (1974).

4. a) 1,4,7,10,13,16-Hexaoxacyclooctadecane; b) G. W. Gokel, D. J. Cram, H. P. Harris, C. L. Liotta, and F. L. Cook, J. Org. Chem., 39, 0000 (1974); c) Organic Syntheses, submitted for publication.

5. a) C. L. Liotta, and H. P. Harris, First Fall Organic Conference, Cape Cod, Mass., Oct. 1, 1973, Abstract No. 5; b) J. Amer. Chem. Soc., 95, 2250 (1971); C. L. Liotta, H. P. Harris, et al., Tetrahedron Letters, No. 25, 2417 (1974); d) F. L. Cook, C. W. Bowers, and C. L. Liotta, J. Org. Chem., 39, 0000 (1974).

6. F. L. Cook, H. P. Harris, T. R. Henson, W. C. Tincher, and C. L. Liotta, J. Org. Chem., submitted for publication.

7. a) H. Lardy, Fed. Proc. Fed. Amer. Soc. Exp. Biol., 27, 1278 (1968); b) H. K. Frensdorff, J. Amer. Chem. Soc., 93, 600 (1971); c) C. J. Pedersen, Fed. Proc. Fed. Amer. Soc. Exp. Biol., 27, 1305 (1968); d) Professor R. A. Bartsch, private communication.

8. a) J. Smid, Angew. Chem. Int. Ed. Engl., 11, 112 (1972); b) H. Lardy, Fed. Proc. Fed. Amer. Soc. Exp. Biol., 27, 1278 (1968); c) R. J. Katnik and J. Schaefer, J. Org. Chem., 33, 384 (1968).

9. a) D. G. Stewart, D. Y. Waddan, and E. T. Borrows, Brit. Pat. 785, 229 (1957); b) Chem. Abstr., 52, 5038 h (1958).

10. K. H. Burg, H. P. Hermann, and H. Rehling, *Makromol. Chem.*, *111*, 181 (1968)

11.a)J. Dale, G. Borgen, and K. Daasvatn, Norw. Pat. Application (1973); b) F. A. L. Anet, J. Dale, *et al.*, *Acta Chem. Scand.*, *27*, 3395 (1973); c) J. Dale, *Tetrahedron*, *30*, 1683 (1974).

12.a)B. K. T. Leong, T.O.T. Ts'o, and M. B. Chenoweth, *Toxicol. Appl. Pharmacol.*, *27 (2)*, 342 (1974); b) *Chem. Abstr.*, *81*, 34056k (1974).

13.a)A run performed as detailed but without LiClO$_4$ gave no product. From the work of Chastrette *et al.* on the beneficial template effect of LiClO$_4$ acid-catalyzed condensation cyclization of furan and acetone, LiClO$_4$ appeared to be the most logical choice of lithium salt for the synthesis reported.[14] Identical runs to that detailed with LiOH·H$_2$O also gave no product, as did analogous runs with LiClO$_4$ in THF instead of in DMSO.
b)Other systems using THF or DMSO as solvents or using KOH instead of NaOH proved to be less satisfactory.

14.a)M. Chastrette and F. Chastrette, *J. Chem. Soc. Chem. Comm.*, 534 (1973); b) M. Chastrette, F. Chastrette, and J. Sabadie, *Organic Synthesis, Prep. No. 1407*, submitted for publication (1974).

15. Raising the temperature of the glycol-base solution to 110°C before addition of the chloride did not affect the yield.

16. A trace of DMSO in the final product was eliminated by redistillation.

17. Infrared analysis showed water to be present in the isolated product, probably in the form of the hydrate. The water was removed by allowing the crown to stir over molecular sieve adsorbent under nitrogen for *ca.* 12 hours.

18.a)NMR analysis showed that a fraction collected from 90-100°C at 0.2 mm Hg also contained some crown, but consisted mainly of triethylene glycol. b) Slow, careful redistillation of the product gave a constant boiling point of 78°C at 0.05 mm Hg.