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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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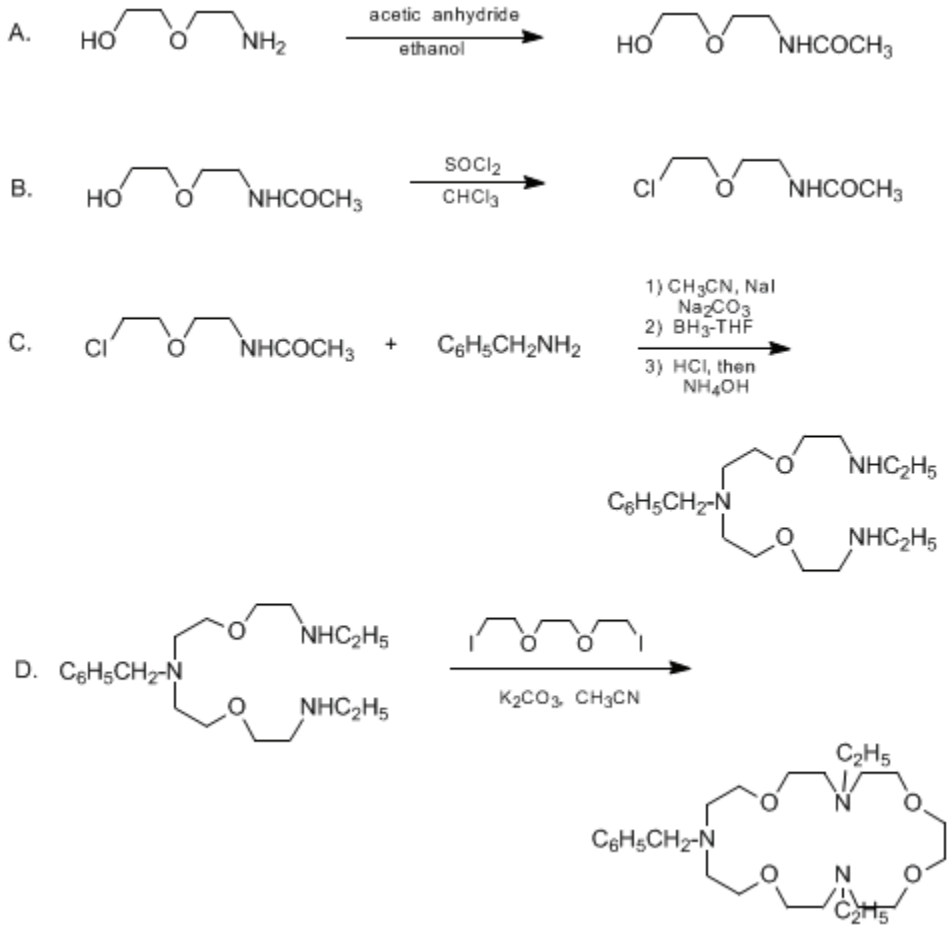
4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE (TRIAZA-21-CROWN-7)



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1. Procedure

A. *N-[2-(2-Hydroxyethoxy)ethyl]acetamide*. Into an oven-dried, 100-mL, three-necked, round-bottomed flask that contains a magnetic stirring bar, 25-mL addition funnel, condenser, and thermometer, is placed 15.75 g (0.15 mol) of 2-(2-aminoethoxy)ethanol (Note 1) in 20 mL of anhydrous ethanol (Note 2). Acetic anhydride (15.75 g, 0.154 mol) (Note 1) is slowly dripped into this stirring solution while the temperature is kept at or below 40°C. The resulting mixture is stirred under reflux for 15 min. The mixture is evaporated on a rotary evaporator to give a pale yellow oil that is distilled through a short path apparatus containing a 2-cm Vigreux column to give 20.3–21.5 g (92–97%) of product, bp 135–139°C/0.12 mm (Note 3).

B. *N-[2-(2-Chloroethoxy)ethyl]acetamide*. N-[2-(2-Hydroxyethoxy)ethyl]-acetamide (20.58 g, 0.14 mol) in 30 mL of chloroform (Note 4) is placed in an oven-dried, 250-mL, three-necked, round-bottomed flask that contains a magnetic stirring bar, pressure-equalizing dropping funnel, condenser that is connected by a polyethylene tube to a glass funnel, and a thermometer (Note 2). The flask is cooled in an ice bath and the glass funnel is immersed in a beaker of water. Thionyl chloride (28 g, 0.24 mol) (Note 1) in 25 mL of chloroform is added dropwise to the stirring mixture at 10–15°C. The mixture is then stirred at room temperature for 30 min and under reflux for 20 min (Note 5). It is

immediately cooled to 30°C and the solvent and excess thionyl chloride are removed on a rotary evaporator (Note 6). The residue is immediately distilled through an 8-cm Vigreux column using an oil bath (Note 7) to give 17–18 g (73–77%) (Note 8) of N-[2-(2-chloroethoxy)ethyl]acetamide, bp 105–108°C/0.1 mm (Note 3).

C. *9-Benzyl-3,9,15-triaza-6,12-dioxaheptadecane*. A mixture of 17.5 g (0.105 mol) of N-[2-(2-chloroethoxy)ethyl]acetamide, 200 mL of acetonitrile (Note 9), 22 g (0.21 mol) of anhydrous sodium carbonate (Note 10), 16.5 g (0.11 mol) of sodium iodide (Note 1) and (Note 11) and 5.35 g (0.05 mol) of benzylamine (Note 1) is added to an oven-dried, 250-mL, three-necked flask that contains a magnetic stirring bar and condenser. The mixture is refluxed for 48 hr, cooled to room temperature and filtered under vacuum. The solid in the filter is washed twice with 70-mL portions of methylene chloride (Note 12). The combined filtrate and methylene chloride mixture are evaporated on a rotary evaporator until all of the solvents are removed. The residue is dissolved in 70 mL of water and transferred to an extraction funnel. The aqueous solution is extracted with three 200-mL portions of methylene chloride (Note 12). The combined methylene chloride extracts are dried over anhydrous magnesium sulfate (Note 13). The mixture is filtered under vacuum and the solid is washed with 100 mL of methylene chloride. The solvents are evaporated on a rotary evaporator. The residue is dissolved in 80 mL of tetrahydrofuran (Note 14) and transferred to a dropping funnel equipped with an anhydrous calcium sulfate drying tube. This solution is slowly dripped into 300 mL of cold, stirring 1 N borane-THF (Note 1) and (Note 15) in an oven-dried, 1-L, one-necked, round-bottomed flask containing a magnetic stirring bar. The addition funnel is removed, a condenser equipped with an anhydrous calcium sulfate drying tube is connected, and the stirring mixture is refluxed for 16 hr. The mixture is cooled and 20 mL of distilled water is slowly dripped into it from a dropping funnel (Note 16). The solvents are then removed on a rotary evaporator. The residue is cooled in an ice water bath and 300 mL of aqueous 18% hydrochloric acid (Note 17) is slowly added to the stirring mixture. The resulting mixture is stirred for 16 hr, first at room temperature, and then warmed until the solvent just reaches the boiling point. The solution is cooled and the solvents are completely removed on a rotary evaporator. To the residue is added 50 mL of water. The aqueous mixture is stirred (Note 18) and filtered under vacuum. The solid is washed with 15 mL of water, and 150 mL of ammonium hydroxide (Note 19) is added to the filtrate (Note 2). The resulting solution is extracted three times with 300-mL portions of chloroform (35 g of sodium chloride is added to the aqueous solution before the third extraction). The chloroform layers are combined and dried over anhydrous magnesium sulfate. The solution is filtered under vacuum, the solid is washed with 50 mL of chloroform, and the solvent is removed on a rotary evaporator. The residue is distilled slowly through a short path apparatus that contains a 2-cm Vigreux column to give 11.6–12.6 g (69–75%) of 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane as a light yellow oil, bp 144–152°C/0.085 mm (Note 3).

D. *4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane* (*triaza-21-crown-7*). A mixture of 10 g (0.03 mol) of 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane and 600 mL of acetonitrile (Note 9) is placed in an oven-dried, 1-L, three-necked, round-bottomed flask equipped with a condenser, an efficient mechanical stirrer and a rubber septum. Argon gas is flushed through the flask using a needle through the septum before and during the reaction. To the above mixture, while stirring at room temperature, is added 50 g (0.36 mol) of anhydrous powdered potassium carbonate (Note 20) and the mixture is stirred for 15 min; then 11.5 g (0.031 mmol) of 1,2-bis(2-iodoethoxy)ethane (Note 1) is added. The resulting mixture is stirred under reflux for 24 hr. The cooled mixture is filtered under vacuum and the solid is washed with 100 mL of acetonitrile. The solvent is removed from the filtrate on a rotary evaporator. Methylene chloride (160 mL) (Note 12) is added to the residue and the resulting mixture is stirred (Note 18). The mixture is filtered under vacuum and the solid is washed with two 20-mL portions of methylene chloride (Note 12). The combined organic layers are evaporated on a rotary evaporator to give a brown oil. The oil is purified by chromatography on 300 g of alumina (Note 21) using 1000 mL of toluene/ethanol: 50:1 as the eluant. The first 120–150 mL of eluant is removed. The remainder of the eluant is evaporated in a rotary evaporator to give 9.6–10 g (72–75%) of the triaza-21-crown-7 as a light yellow oil (Note 22),(Note 23),(Note 24).

2. Notes

1. 2-(2-Aminoethoxy)ethanol, acetic anhydride (99+%), thionyl chloride (99+%), benzylamine (99%),

1,2-bis(2-iodoethoxy)ethane (98%), anhydrous sodium iodide (99+%) and borane-tetrahydrofuran complex (1.0 M solution in tetrahydrofuran) were purchased from Aldrich Chemical Company, Inc. and were used without further purification.
2. The reaction must be carried out in an efficient hood.
3. The IR and NMR spectra in reference [3] were consistent with the proposed structure.
4. Chloroform ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.
5. The reaction also can be carried out at room temperature for 48 hr.
6. A rotary evaporator that has a safety flask in the vacuum line was used. The water bath temperature was not higher than 50°C.
7. The submitters prefer to use an oil bath rather than a heating mantle because control of pot temperature is essential so that no polymers can form. There is a loss of vacuum at the beginning of the distillation because of various gases in the product.
8. The yield from a seven times larger reaction was 85%.[3]
9. Acetonitrile ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.
10. Sodium carbonate (anhydrous A.C.S. certified) distributed by Fisher Scientific was used.
11. In reference [3], xylene was used as the solvent instead of acetonitrile and sodium iodide was not used. The yield in that case was lower.
12. Methylene chloride ("Chrom Pure") manufactured by American Burdick & Jackson (distributed by American Scientific Products) was used.
13. Magnesium sulfate (anhydrous, powder) distributed by EM Science was used.
14. Tetrahydrofuran (HPLC quality), manufactured by Mallinckrodt Inc., was used.
15. When fresh lithium aluminum hydride was used instead of the borane-tetrahydrofuran complex,[3] the reduction gave low yields and the product was more difficult to purify.
16. The first drops of water are added very slowly because the reaction causes considerable foaming.
17. Analytical reagent grade hydrochloric acid, manufactured by Mallinckrodt Inc., was used for the preparation of the 18% solution.
18. The mixture was stirred until the solid was completely suspended.
19. Analytical reagent grade ammonium hydroxide (NH_3 = 29.6%), manufactured by Mallinckrodt Inc., was used.
20. "Baker Analyzed" reagent grade potassium carbonate (anhydrous, granular) was used.
21. Activated, neutral, 150 mesh alumina (Brockman 1 standard grade), sold by Aldrich Chemical Company, Inc., was used in a 5-cm diameter column for the purification of the triaza-crown. Alumina TLC plates (Aluminum oxide 60_{F254} neutral (Type E), manufactured by E. Merck, distributed by EM Science) were used to monitor the purification process (toluene/ethanol = 20:1, using iodine as an indicator).
22. The product is nearly 98% pure as determined by GC using a Carlo Erba 5160 Mega instrument, flame ionization detection, with H_2 as the carrier gas (50 cm/sec). The column was a 10-m × 200-μm i.d. fused silica column coated at a 0.15-μm film thickness with SE-33 (methyl silicone). The split injector was kept at 300°C, the detector at 280°C, and the column at 230°C. The product gave the correct elemental analysis and has the following spectral properties: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.0 (t, 6 H), 2.55 (m, 4 H), 2.72 (m, 12 H), 3.6 (m, 18 H), 7.35 (m, 5 H); IR (neat) cm^{-1}: 2860, 1440, 1340, 1110; MS (20 eV) m/e 160, 275, 336, 451 (100%).
23. The crown can be distilled under high vacuum in a short path distillation apparatus using an oil bath, bp 188–190°C/0.05 mm.
24. The product should be stored under argon at 0°C in a dark bottle to prevent decomposition.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here illustrates a new "building block" method for the preparation of per-N-alkyl-substituted polyaza-crown compounds.[3,4,5] The key building block, N-[2-(2-chloroethoxy)ethyl]

acetamide and its benzamide analog,[3] allows the preparation of a variety of tri- and tetraamino compounds capable of ring closure reactions to form a variety of polyaza-crowns.[3,4] Polyaza-crowns containing a secondary amine side chain (mono lariat ether),[5] a hydroxyalkyl side chain,[6] and very large polyaza-crowns (30–36 ring members)[3] have been prepared using these procedures. The triaza-18-crown-6 analog was prepared in an overall yield of 25% by treating 9-benzyl-3,9,15-triaza-6,12-dioxaheptadecane with 3-oxapentanedioyl dichloride followed by reduction.[3,4]

The procedures previously used to prepare N-peralkylated polyaza-crowns required the use of nitrogen protecting groups that must subsequently be removed and the alkyl groups added.[7,8,9,10,11] These added steps greatly reduced the overall yields of the polyaza-crowns. Polyaza-crowns are important for complexing certain "soft" heavy metals,[12,13,14,15,16] and anions,[17,18,19,20] and as enzyme mimics in certain biological systems.[21] It is important to note that the N-peralkylated polyaza-crowns have about the same affinity for metal cations as the unsubstituted aza-crowns.[15] We have prepared 26 new N-peralkylated polyaza-crowns using this new method.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (Triaza-21-crown-7)

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

iodine (7553-56-2)

toluene (108-88-3)

ammonium hydroxide (1336-21-6)

xylene (106-42-3)

sodium iodide (7681-82-5)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

benzylamine (100-46-9)

borane (7440-42-8)

aluminum oxide (1344-28-1)

Tetrahydrofuran,
THF (109-99-9)

lithium aluminum hydride (16853-85-3)

argon (7440-37-1)

1,2-bis(2-iodoethoxy)ethane (36839-55-1)

4-BENZYL-10,19-DIETHYL-4,10,19-TRIAZA-1,7,13,16-TETRAOXACYCLOHENEICOSANE

TRIAZA-21-CROWN-7

N-[2-(2-Hydroxyethoxy)ethyl]acetamide,
N-[2-(2-Hydroxyethoxy)ethyl]-acetamide (118974-46-2)

2-(2-aminoethoxy)ethanol (929-06-6)

N-[2-(2-Chloroethoxy)ethyl]acetamide (36961-73-6)

9-Benzyl-3,9,15-triaza-6,12-dioxaheptadecane (118974-42-8)

triaza-18-crown-6

3-oxapentanedioyl dichloride (21062-20-4)

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