



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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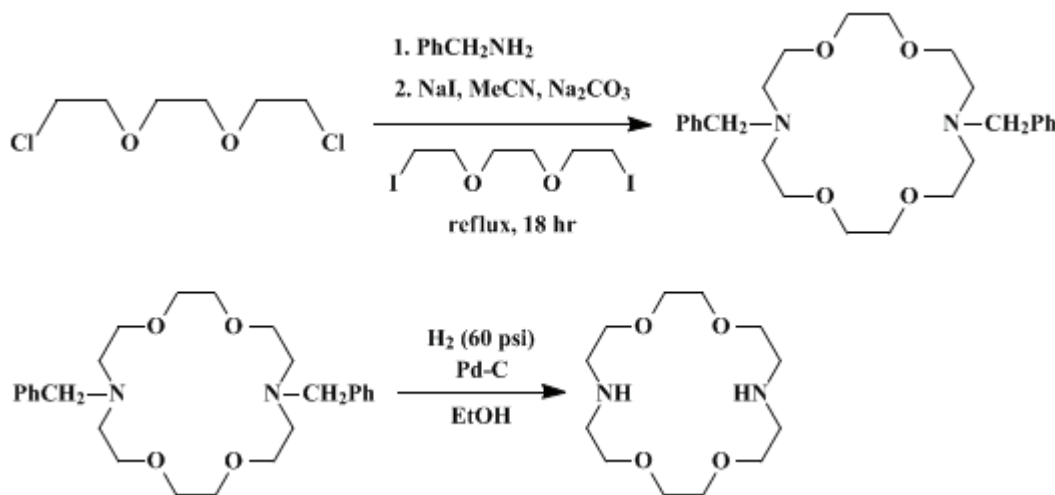
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Organic Syntheses, Coll. Vol. 8, p.152 (1993); Vol. 68, p.227 (1990).

4,13-DIAZA-18-CROWN-6

[1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane]



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1. Procedure

A. *1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane*. A solution of benzylamine (172 g, 1.6 mol) (Note 1) and 1,2-bis(2-chloroethoxy)ethane (18.7 g, 0.1 mol) (Note 2) is stirred and heated at 120°C for 28 hr. The reaction is cooled to room temperature, sodium hydroxide pellets (8.0 g, 0.2 mol) are added, and the mixture is heated at 120°C, with stirring, for 1 hr. The reaction is cooled and excess benzylamine is removed by vacuum distillation (Note 3) using a water aspirator (Note 4). The resulting oil is dissolved in chloroform (100 mL), filtered, and washed with water (50 mL) to remove salts. The organic phase is dried (Na₂SO₄) and concentrated under reduced pressure. Bulb-to-bulb distillation using a Kugelrohr apparatus (175–177°C, 0.2 mm) gives 27.9–31.2 g (85–95%) of 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane (Note 5) as a slightly yellow oil that is sufficiently pure to be used for the preparation of *N,N'*-dibenzyl-4,13-diaza-18-crown-6.

B. *N,N'*-Dibenzyl-4,13-diaza-18-crown-6. In a 3-L, round-bottomed flask fitted with a mechanical stirrer and an efficient reflux condenser are placed 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane (28.2 g, 86 mmol), 1,2-bis(2-iodoethoxy)ethane (39.3 g, 106 mmol) (Note 6), anhydrous sodium carbonate (45.3 g, 427 mmol), and sodium iodide (6.4 g, 43 mmol) in acetonitrile (1700 mL). The resulting solution is stirred mechanically (Note 7) and heated at reflux for 21 hr. The reaction is cooled, filtered, and concentrated under reduced pressure (Note 8). The crude solid is dissolved in a refluxing solution of acetone–dioxane (175 mL each) and allowed to crystallize in a freezer. The crystals (a mixture of sodium iodide and the sodium iodide complex of the product) are dried and taken up in 500 mL of water and 400 mL of chloroform. The phases are separated and the aqueous portion is extracted with chloroform (3 × 75 mL). The combined organic phases are dried (MgSO₄) and concentrated under reduced pressure. Recrystallization (hexanes, 500 mL, followed by absolute ethanol, 110 mL) affords 25.6–27.0 g (67–71%) of *N,N'*-dibenzyl-4,13-diaza-18-crown-6 as a white solid (mp 80–81°C): ¹H NMR (CDCl₃) δ: 2.82 (t, 8 H, NCH₂); 3.64 and 3.70 (t, s, s, 2 CH₂, OCH₂ and CH₂Ph); 7.37 (s, 10 H, Ar); IR (KBr) cm⁻¹: 2960, 2900, 2880, 1500, 1460, 1120, 1060, 1050, 750, 700 (Note 9) and (Note 10).

C. *4,13-Diaza-18-crown-6*. *N,N'*-Dibenzyl-4,13-diaza-18-crown-6 (25.0 g, 56 mmol) (Note 11), 10% Pd/C catalyst (1.0 g), and absolute ethanol (300 mL) are shaken in a Parr series 3900 hydrogenation apparatus at 60-psi hydrogen pressure and 25°C for 72 hr. The mixture is filtered through a pad of Celite and concentrated under reduced pressure. The yield of pure 4,13-diaza-18-crown-6 after

recrystallization (hexanes, 1 g/35 mL) is 13.5 g (91%). The white solid (mp 114–115°C) possesses physical properties identical to those previously reported:² ¹H NMR (CDCl₃) δ: 2.06 (bs, 2 H, NH); 2.72 (t, 8 H, CH₂N); 3.54 (s, 16 H, CH₂); IR (KBr) cm⁻¹: 3330.

2. Notes

1. **Benzylamine** was obtained from Aldrich Chemical Company, Inc., and was used without further purification.
2. **1,2-Bis(2-chloroethoxy)ethane** was obtained from Eastman Kodak Company, and was used without further purification.
3. The excess **benzylamine**, recovered from the distillation step, can be reused if redistilled from **calcium oxide**.
4. If an efficient water aspirator is used (<20 mm), the **benzylamine** should distill between 60 and 70°C.
5. The product has the following spectral characteristics: ¹H NMR (CDCl₃) δ: 1.82 (s, 2 H, NH), 2.72 (t, 4 H, NCH₂), 3.58 (s and t, 8 H, CH₂), 3.72 (s, 4 H, benzyl), and 7.28 ppm (s, 10 H, Ar).
6. **1,2-Bis(2-iodoethoxy)ethane** was prepared as described by Kulstad and Malmsten.³ **1,2-Bis(2-chloroethoxy)ethane** (21.3 g, 0.114 mol) and **sodium iodide** (37.0 g, 0.247 mol) in **acetone** (55 mL) were heated at reflux while stirring magnetically during 3 days. The reaction mixture was allowed to cool and was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in **methylene chloride** (200 mL), washed with aqueous 10% **sodium thiosulfate** solution (2 × 100 mL), dried over **magnesium sulfate**, and evaporated under reduced pressure. The residual **methylene chloride** was removed by high-vacuum evaporation at ambient temperature and the resulting **1,2-bis(2-iodoethoxy)ethane** (40 g, 95%) was used without further purification. The proton NMR spectrum (δ, CDCl₃) is as follows: 3.25 (t, 4 H); 3.68 (s, 4 H); 3.78 (t, 4 H).
7. This reaction must be stirred vigorously (120–150 rpm using a 60-mm paddle) for best results.
8. The **acetonitrile** in this step can be reused without any further purification.
9. Wester and Voegtle⁴ reported mp 80°C.
10. When this reaction is run on twice the reported scale, the percent yield is the same.
11. The ***N,N'*-dibenzyl-4,13-diaza-18-crown-6** must be freshly recrystallized from absolute **ethanol** for the hydrogenolysis to proceed at a reasonable rate.

3. Discussion

During the past two decades, a relatively few macrocyclic polyethers have played central roles in numerous research programs. Examples are **18-crown-6**, **dibenzo-18-crown-6**, and **aza-15-crown-5**. **4,13-Diaza-18-crown-6** and its derivatives are compounds of considerable current interest despite the parent's high price and limited availability. **4,13-Diaza-18-crown-6** is a key compound in the study of two-armed macrocycles since it may readily be alkylated or acylated to afford a variety of symmetric, *N,N'*-disubstituted derivatives.

4,13-Diaza-18-crown-6 has been prepared in a variety of ways.^{2,3,5,6,7,8,9} Lehn first reported its preparation by reaction of **1,2-bis(2-aminoethoxy)ethane** with triglycolic acid dichloride, followed by **lithium aluminum hydride** or diborane reduction of the resulting bislactam.² Kulstead and Malmsten have condensed **1,2-bis(2-aminoethoxy)ethane** with **1,2-bis(2-iodoethoxy)ethane** to give **4,13-diaza-18-crown-6**.³ Recently, we have reported that a single-step reaction of **benzylamine** with **1,2-bis(2-iodoethoxy)ethane**, followed by hydrogenation of the resulting *N,N'*-dibenzyl-protected crown, gives **4,13-diaza-18-crown-6**.⁵ The latter, single-step cyclization reaction is more direct than the present procedure, but the yield is substantially lower and the manipulations are less convenient.

The method described here offers three advantages over the previously published procedures.^{2,3,5,6,7,8,9} First, the cyclization reaction does not require the use of high-dilution conditions in order to obtain satisfactory yields of product. This is a substantial improvement over the procedure of Lehn,² which requires large volumes of dry solvents and slow addition rates. Second, purification of all the intermediates is straightforward, involving either vacuum distillation using a Kugelrohr apparatus or recrystallization. This is an important advantage when the sequence is scaled up because it allows the preparation of large sample sizes in relatively short periods of time. We have prepared as much as 40 g of **4,13-diaza-18-crown-6** in less than 1 week. Third, the benzyl protecting groups are easily removed by

hydrogenolysis over H₂/Pd–C in [ethanol](#). Previous preparations of [4,13-diaza-18-crown-6](#) are more difficult because they involve the hydrolysis or reduction of *N*-tosyl protected nitrogens.^{5,6,7,8} We should also note that our own previously published,⁵ single-step preparation for *N,N*-disubstituted-4,13-diaza-18-crown-6 derivatives is more convenient than the present preparation because it involves a single-step reaction, but the yields are always inferior to those obtained using the present, multistep approach.

References and Notes

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Appendix

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

hexanes

N-tosyl

[ethanol](#) (64-17-5)

[acetonitrile](#) (75-05-8)

[sodium hydroxide](#) (1310-73-2)

[chloroform](#) (67-66-3)

[sodium carbonate](#) (497-19-8)

[sodium thiosulfate](#) (7772-98-7)

[acetone](#) (67-64-1)

[calcium oxide](#)

[sodium iodide](#) (7681-82-5)

[methylene chloride](#) (75-09-2)

[magnesium sulfate](#) (7487-88-9)

dioxane (5703-46-8)

benzylamine (100-46-9)

lithium aluminum hydride (16853-85-3)

18-Crown-6 (17455-13-9)

1,2-bis(2-chloroethoxy)ethane (112-26-5)

DIBENZO-18-CROWN-6 (14187-32-7)

4,13-Diaza-18-crown-6,
1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane (23978-55-4)

1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane (66582-26-1)

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

aza-15-crown-5

1,2-bis(2-aminoethoxy)ethane (929-59-9)

N,N'-dibenzyl-4,13-diaza-18-crown-6 (69703-25-9)