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Working with Hazardous Chemicals

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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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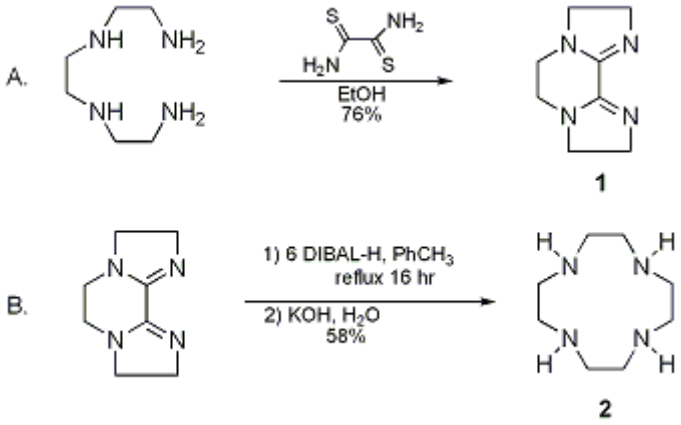
1,4,7,10-TETRAAZACYCLODODECANE



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Checked by Maya Escobar and Stephen F. Martin.

1. Procedure

Caution: Hydrogen sulfide (H_2S) is generated in Part A of this procedure. The reaction and associated operations must be carried out with provision for H_2S trapping in an efficient hood.

A. 2,3,5,6,8,9-Hexahydrodiimidazo[1,2-a:2',1'-c]pyrazine (**1**). A 500-mL, three-necked, round-bottomed flask is equipped with a 125-mL pressure-equalizing addition funnel, a Teflon-coated magnetic stirring bar, a fritted-gas dispersion tube (initially closed) connected to a nitrogen manifold , and a reflux condenser fitted with a nitrogen (N_2) inlet tube connected to the nitrogen manifold. The nitrogen manifold exit line is routed through two fritted-gas washing bottles charged with 30% aqueous sodium hydroxide (NaOH) in order to scrub H_2S evolved in the reaction (Note 1). The reaction flask is charged with 10.0 g (83.2 mmol) of dithiooxamide (Note 2) and 50 mL of absolute ethanol . A solution of 12.2 g (83.2 mmol) of triethylenetetramine (Note 3) in 50 mL of absolute ethanol is introduced into the reaction flask in one portion via the addition funnel. The magnetically stirred reaction mixture is heated at reflux for 4 hr under nitrogen with evolution of H_2S and ammonia (NH_3) (Note 4). The mixture is then cooled to room temperature and residual H_2S and NH_3 are purged from the reaction mixture for 3 hr by entrainment with nitrogen, which is bubbled through the submerged fritted-gas dispersion tube. Ethanol is removed by rotary evaporation, and the residue is dissolved in 150 mL of chloroform ($CHCl_3$). The insoluble material is removed by gravity filtration through a glass wool plug that is inserted in a short-stem glass funnel. $CHCl_3$ is then removed by rotary evaporation to give 14.0 g of crude product. This solid is taken up in 50 mL of boiling toluene , insoluble impurities are removed by filtration through a glass wool plug, and the flask and funnel are rinsed with a second 50-mL aliquot of boiling toluene (Note 5). The combined filtrates are concentrated to afford 13.4 g of light yellow crystalline product. Sublimation of this material (0.05 mm, 110°C) affords 10.4 g (76%) of pure (>99%) white product (Notes 6, 7, 8).

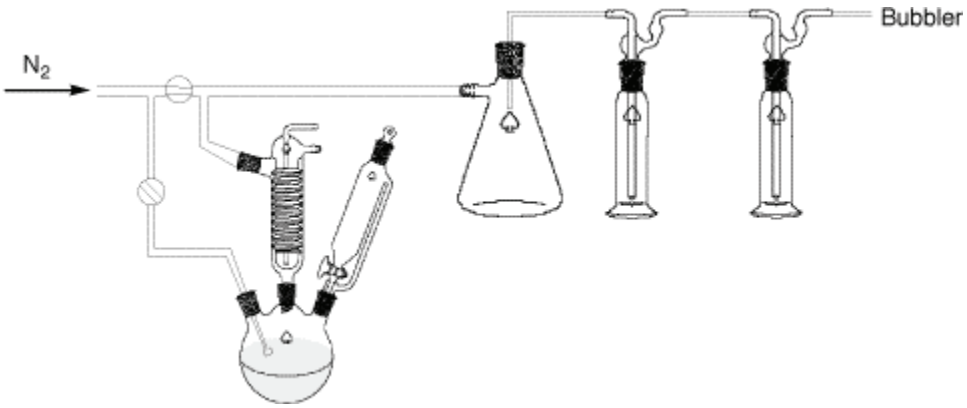
B. 1,4,7,10-Tetraazacyclododecane (**2**). A 1-L, three-necked, round-bottomed flask charged with 8.96 g (54.6 mmol) of 2,3,5,6,8,9-hexahydrodiimidazo[1,2-a:2',1'-c]pyrazine is equipped with a reflux condenser fitted with nitrogen inlet tube, a 500-mL pressure-equalizing addition funnel, and a Teflon-coated magnetic stirring bar. The system is flushed with N_2 prior to cannulation of 218 mL (327 mmol) of 1.5 M diisobutylaluminum hydride (DIBAL-H) in toluene (Note 9) to the addition funnel. The reaction flask is cooled in an ice/water (H_2O) bath and the DIBAL-H solution is added to the reaction flask with stirring over 5 min. The reaction mixture is heated at reflux under nitrogen for 16 hr (Note 10). The reaction flask is again cooled in an ice/H_2O bath prior to the addition of 200 mL of toluene .

Excess DIBAL-H is quenched by the cautious dropwise addition of 20 mL of 3 M aqueous potassium hydroxide (KOH) solution. When gas evolution ceases, 350 mL of 3 M aqueous KOH is added in one portion and the two-phase mixture is transferred to a separatory funnel (Notes 11, 12). The phases are separated and chipped ice is added to the aqueous phase, which is further extracted with ice-cold $CHCl_3$(12 × 150 mL). The combined organic extracts are dried over sodium sulfate (Na_2SO_4), filtered, and the solvents are removed by rotary evaporation to afford 6.19 g of white crystalline solid. Sublimation (0.05 mm, 90°C) of this material gives 5.44 g (58%) of product **2** (>98% purity by NMR; Notes 13, 14, 15).

2. Notes

1. The nitrogen manifold (Tygon tubing is suitable) is connected as follows, in this order: (a) nitrogen source, (b) T-connector to fritted-gas dispersion tube with shutoff valve or clamp, (c) shutoff valve or clamp (enables nitrogen to be routed through fritted-gas dispersion tube when closed and dispersion tube is opened), (d) T-connector to nitrogen inlet tube on reflux condenser, (e) safety flask, (f) gas washing bottle #1, (g) gas washing bottle #2, and (h) mineral oil exit bubbler (See Figure 1).

Figure 1



2. Dithiooxamide was purchased from Fluka Chemical Corp.
3. Triethylenetetramine was purchased from Aldrich Chemical Company, Inc. , as a hydrate. Anhydrous triethylenetetramine must be used in this procedure. The anhydrous tetraamine was obtained by azeotropic distillation of water (Dean-Stark trap, 3 days) from a solution of 125 g of the commercial hydrate in 150 mL of toluene . Analysis by ^{1}H NMR verified the removal of water, and no further purification was necessary.
4. Dithiooxamide dissolved to give a homogeneous orange solution soon after the initiation of heating.
5. The hot filtration must be carried out quickly to avoid crystallization of product. This step can be omitted, but a second sublimation may then be necessary to obtain product of sufficient purity for reduction to cyclen.
6. Compound **1** has the following physical and spectroscopic properties: mp 148-150°C (lit[2] mp 150-151°C); ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 3.26 (s, 4 H), 3.35 [apparent t (XX' of AA'XX'), 4 H, J_{appar} = 9.6], 3.86 [apparent t (AA' of AA'XX'), 4 H, Jappar = 9.6] ; ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ: 45.3, 52.1, 53.9, 155.4 ; IR (KBr) cm^{-1}: 1629 (C=N); MS (EI) 164.15 (M)+; Anal. Calcd for $C_8H_{12}N_4$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.38; H, 7.55; N, 34.22.
7. Bisamidine **1** is hydrolyzed in water (in minutes to hours depending upon purity). While it is not necessary to handle **1** in a dry atmosphere, it is prudent to store it in a desiccator.
8. The checkers found that when the reaction was conducted on 1/2 scale, significantly lower yields (55 - 70% before sublimation) were obtained.
9. DIBAL-H in toluene (1.5 M) was purchased from Aldrich Chemical Company, Inc.
10. The submitters found that a small scale (0.4 g of **1**) reaction with 5 equivalents of DIBAL-H at reflux for 8 hr afforded product in 94% crude yield. However, these conditions gave incomplete reduction and a lower yield when the reaction was scaled up to 10 g of **1**. Therefore, the number of equivalents of DIBAL-H was increased to 6 and the reaction was run for 16 hr.
11. A small amount of solid remains undissolved, but this tends to be distributed in the aqueous phase,

making filtration at this stage unnecessary.
12. Originally,[2] a NaF/H_2O workup was used. Soxhlet extraction of the solids generated in the work-up was required to obtain good yields of crude **2**. The present aqueous KOH work-up simplifies the procedure and gives comparable or better yields of crude **2**.
13. Compound **2** has the following physical and spectroscopic properties: mp 105-107°C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 2.69 (s, 16 H), 2.16 (br s, 4 H) ; ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ: 46.11 . ^{1}H NMR relative integrations are consistent with anhydrous **2**. There has been much confusion in the literature concerning the mp of **2**. Stetter and Mayer[3] originally reported mp 35°C. Buøen, et al. reported mp 119-120°C.[4] Zhang and Busch subsequently reported mp 36-38°C.[5] Aldrich and Fluka list melting point ranges of 110-113°C (97%) and 105-110°C (=97%) respectively in their catalogs. The submitter's mp range for **2** (calibrated thermometer) is lower than that reported in reference 4, but is consistent with the mp range of sublimed material (no detectable impurities by high S/N NMR) that they have prepared by the Richman-Atkins procedure[6] (mp 105-109°C).
14. The checkers have found it necessary to perform as many as twelve extractions with cold chloroform to obtain the product from the aqueous solution.
15. The submitters obtained yields as high as 88% at scale.

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 title compound, **2**,[3] ("cyclen") and its derivatives are important ligands,[7] some of which have biomedical applications[8] (for example, as ligand components of MRI contrast agents). Cyclen is commercially available, but expensive.[9]

This procedure is a modification of the method originally reported by Weisman and Reed.[2] In the first reaction of the two-step sequence (Step A), a two-carbon, permanent, covalently-bound template[10] is introduced by way of dithiooxamide to convert triethylenetetramine to tricyclic bisamidine **1**. Step A is analogous to the synthesis of 2,2'-bi-2-imidazoline reported by Forssell in 1891.[11] Step B is a double reductive ring expansion, which converts the two amidine (template) carbons of bisamidine **1** to a -CH_2CH_2- unit of **2**. The reaction is conceptually based upon Yamamoto and Maruoka's highly regioselective DIBAL-H reduction of bicyclic amidines to ring-expanded cyclic diamines.[12]

The advantages of this procedure are: (a) it is short and relatively efficient (44-68% overall yield), (b) it is atom-economic,[13] (c) starting materials are readily available, (d) purifications are simple, and (e) it permits preparation of moderate quantities of product with modest effort. The disadvantages are the production of hydrogen sulfide *(highly toxic)* in Step A and the required use of DIBAL-H, an active hydride reducing agent. However, the former can be efficiently trapped and the latter can be handled safely at the reported scale.

There are alternative methods for preparation of cyclen. Since the mid-1970's, the standard method for preparation of cyclen has been based upon the general Stetter-Richman-Atkins synthesis of macrocyclic polyamines,[6], [14] a medium-dilution cyclization approach that uses tosyl protection of nitrogen. The cyclen syntheses developed by Richman and Atkins[6] (5 steps) and related modifications[2], [15] (4 steps), while very reliable, are still labor-intensive sequences that suffer from atom economy and solvent requirement problems. These problems are largely overcome by the shorter approach documented here. Three additional syntheses of **2** have recently appeared in the literature.[16] [17] [18] The syntheses (each 3 steps) rely upon carbon templating for preorganization, subsequent cyclization, and final template removal. Such an approach may prove superior for large scale production of **2**, since active hydride reducing agents are avoided. However, the procedure reported here is very satisfactory for the laboratory-scale preparation of **2**.

References and Notes

1. Department of Chemistry, University of New Hampshire, Durham, NH 03824
2. (a) Weisman, G. R.; Reed, D. P. *J. Org. Chem.* **1996**, *61*, 5186; (b) *Correction: J. Org. Chem.* **1997**, *62*, 4548.
3. Stetter, H.; Mayer, K.-H. *Chem. Ber.* **1961**, *94*, 1410.
4. Buøen, S.; Dale, J.; Krane, J. *Acta Chem. Scand. Ser. B* **1984**, *B38*, 773.
5. Zhang, R.; Busch, D. H. *Inorg. Chem*. **1993**, *32*, 4920.
6. (a) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268; (b) Atkins, T. J.; Richman, J. E.; Oettle, W. F. *Org. Synth., Coll. Vol. VI* **1988**, 652.
7. (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. "Aza-Crown Macrocycles"; *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Series Ed.,Wiley: New York, 1993; Vol. 51; (b) Dietrich, B.; Viout, P.; Lehn, J.-M. "Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry"; VCH: Weinheim, 1993.
8. (a) Parker, D. In "Crown Compounds"; Cooper, S. R., Ed.; VCH: New York, 1992; (b) Jurisson, S.; Berning, D.; Jia, W.; Ma, D. *Chem. Rev*. **1993**, *93*, 1137.
9. Major specialty chemical suppliers' cyclen (**2**) prices: $214-290 (U.S.) per gram (1997); $236-295 per gram (2000) except that one supplier lowered the price to $3 per gram!
10. Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375.
11. Forssell, G. *Chem. Ber.* **1891**, *24*, 1846.
12. Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186.
13. Trost, B. M. *Science* **1991**, *254*, 1471.
14. Stetter, H.; Roos, E.-E. *Chem. Ber.* **1954**, *87*, 566.
15. (a) Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem*. **1984**, *49*, 110; (b) Chavez, F.; Sherry, A. D. *J. Org. Chem*. **1989**, *54*, 2990.
16. (a) Sandnes, R. W.; Vasilevskis, J.; Undheim, K.; Gacek, M. (Nycomed Imaging A/s, Norway) PCT Int. Appl. WO 96 28,432, 19 Sept 1996; *Chem. Abstr.* **1996**, *125:*301031c; (b) Sandnes, R. W.; Gacek, M.; Undheim, K. *Acta Chem. Scand.* **1998**, *52*, 1402.
17. Athey, P. S.; Kiefer, G. E.; (Dow Chem. Co. USA): U.S. Patent 5,587,451, 24 Dec 1996; *Chem. Abstr.* **1997**, *126*, 144300r.
18. Hervé, G.; Bernard, H.; Le Bris, N.; Yaouanc, J.-J.; Handel, H.; Toupet, L. *Tetrahedron Lett.* **1998**, *39*, 6861.

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

1,4,7,10-Tetraazacyclododecane (9); (294-90-6)

Hydrogen sulfide: HIGHLY TOXIC (8,9); (7783-06-4)

2,3,5,6,8,9-Hexahydrodiimidazo[1,2-a:2',1'-c]pyrazine:
Diimidazo[1,2-a:2',1'-c]pyrazine, 2,3,5,6,8,9-hexahydro- (13); (180588-23-2)

Dithiooxamide:
Ethanedithioamide (9); (79-40-3)

Triethylenetetramine (8);
1,2-Ethanediamine, N,N'-bis(2-aminoethyl)- (9); (112-24-3)

Chloroform: HIGHLY TOXIC. CANCER SUSPECT AGENT: (8);
Methane, trichloro- (9); (67-66-3)

Diisobutylaluminum hydride:

Aluminum, hydrodiisobutyl- (8);
Aluminum, hydrobis(2-methylpropyl)- (9); (1191-15-7)