A New Synthesis of Cyclen (1,4,7,10-Tetraazacyclododecane)

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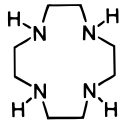
Cyclen (1,4,7,10-tetraazacyclododecane, **1**) is an important macrocyclic tetraamine that has been used extensively in metal complexation[1] and as a synthetic precursor to related pendant-armed[2] and bridged polydentate ligands,[3] some of which have biomedical applications.[4]



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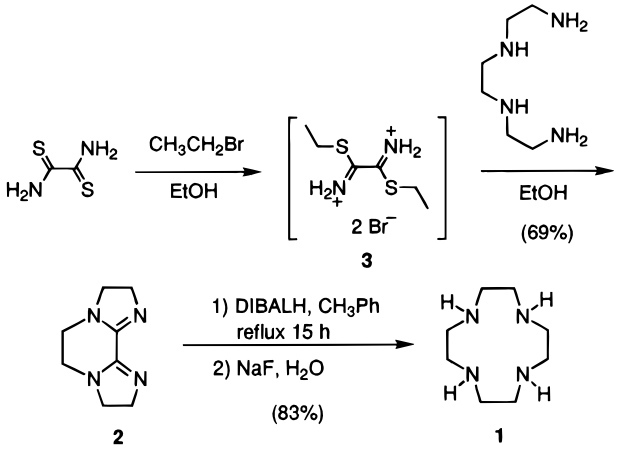
For many years, the best synthesis of **1** has been that based upon the general Stetter−Richman−Atkins method.[5−7] The procedure worked out by Richman and Atkins[5] involves medium-dilution macrocyclization of the disodium salt of tritosyldiethylenetriamine with N-tosyldiethanolamine ditosylate to give tetratosylcyclen, which is then detosylated with concentrated H_2SO_4. We have used a Kellogg-type Cs_2CO_3 variation[8] of this synthesis (for *in situ* deprotonation of tritosyldiethylenetriamine in the cyclization) with good success and Sherry and coworkers have employed K_2CO_3.[9] The disadvantages of this four-step route are (a) it is not "atom-economic",[10] i.e. it requires tosylations and subsequent detosylations; (b) the cyclization requires large amounts of dry DMF; and (c) it is labor intensive. The current high prices of cyclen[11] reflect the level of effort involved in its synthesis.

We have developed an efficient two-step synthesis of cyclen from triethylenetetraamine and dithiooxamide (Scheme 1).

Scheme 1



This route avoids, to a large extent, the above problems and also avoids the use of transition metal templates.[12] The key step of the new synthesis is the double reductive ring expansion of tricyclic bis-amidine **2** to cyclen (**1**) with DIBALH. Yamamoto and Maruoka discovered the highly regioselective reductive cleavage of amidines with DIBALH and reported ring expansion of bicyclic amidines to diazacycloalkanes (for example, the conversion of DBU to 1,5-diazacycloundecane).[13] Others have utilized this reaction for the synthesis of diazacycloalkanes,[14] but the reaction has not to our knowledge been extended to the reduction of bis-amidines of oxalic acid. Reduction of **2** (100 mg to 5 g scale) with DIBALH in refluxing toluene (15 h) gave good yields of crude (>90% purity) **1**, which was sublimed to >98% purity. No other purification step was necessary. The largest scale reaction run to date (see Experimental Section) gave an 83% yield of **1** after sublimation, and we see no reason why the reaction cannot be scaled up further.

Cyclen precursor **2** was prepared in 69% yield by S-alkylation of dithiooxamide with excess bromoethane[15] followed by reaction of the putative bis-thioimido ester salt **3** with triethylenetetraamine. The procedure was modeled upon that of Wang and Bauman, who prepared 2,2′-bi-2-imidazoline from ethylenediamine by an analogous reaction.[16] The only difficulty associated with the reaction is the production of byproduct ethanethiol (stench), which must be flushed from the reaction mixture and oxidized.[17]

In summary, the new synthesis affords cyclen (**1**) in two synthetic steps with an overall yield of 57%. No protecting groups are required and solvent requirements are modest in comparison to the Richman−Atkins syn-

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(11) Major specialty chemical suppliers' cyclen (**1**) prices: $213−290 (U.S.) per gram (March, 1996).

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(17) We have used commercial laundry bleach solution for this purpose, but even the resulting disulfide is very odoriferous. Professor Peter A. Petillo (University of Illinois), who has graciously checked our cyclen synthesis, used 30% aqueous H_2O_2 successfully, and we have subsequently found 15% aqueous H_2O_2 to work well in a related reaction.

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thesis.[5] The sequence can be regarded as involving a "permanent covalently-bound template"[12b] consisting of the two carbon unit that is introduced in the first step and ultimately converted to the new ethylene bridge of **1**. Additional methods for synthesis of **2** and related compounds are being actively investigated, as is the applicability of the approach presented here to the synthesis of other macrocyclic tetraamines.

Experimental Section

General. Reactions were run under nitrogen with stirring. Triethylenetetraamine (>97%) and dithiooxamide were purchased from Fluka. All other reagents and solvents were obtained from Aldrich.

1,4,7,10-Tetraazacyclododecane, Cyclen (1). DIBALH (160 mL of 1.5 M solution in toluene, 240 mmol) was added over 1 h to a slurry of **2** (4.93 g, 30.0 mmol) in dry toluene (160 mL) and then refluxed for 15 h. The mixture was then cooled to 0 °C, NaF (40.2 g, 960 mmol) and water (13.0 mL, 722 mmol) were added in alternating small portions with stirring, and the slurry was allowed to warm to rt. Solids were removed by vacuum filtration and washed with $CHCl_3$ (5 × 50 mL). Filtrate and washings were combined and dried (Na_2SO_4), and solvents were removed to yield 2.40 g of **1** (>98% purity by ^{1}H NMR). Soxhlet extraction of the reaction solids with toluene for 24 h, drying, and toluene removal yielded an additional 2.55 g of crude **1** (>90% purity). Combined crude product was sublimed (120 °C, 0.05 Torr) to yield 4.32 g (83%) of **1** (>98% purity by ^{1}H and ^{13}C NMR; mp 103−107 °C). Slower resublimation (65 °C, 0.02 Torr; 94% recovery) gave **1** of even greater purity according to NMR (mp 103−107 °C, Lit.[18] mp 119−120 °C).[19] ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.69 (s, 16H), 1.92 (s, 4H); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ 46.1. A mixed melting point (mp 103−109 °C) of resublimed product and authentic pure sublimed **1** prepared by the Richman−Atkins procedure (mp 105−109 °C) further confirmed the identity of product.[19]

2,3,5,6,8,9-Hexahydrodiimidazo[1,2-*a*:2′,1′-*c*]pyrazine (2). Bromoethane (19.0 mL, 257 mmol) was added in one portion to a suspension of dithiooxamide (5.15 g, 42.9 mmol) in absolute EtOH (19 mL). The slurry was heated to 60 °C for 4 h and then cooled to rt. The reaction flask was equipped with a short-path distillation head, and excess bromoethane and EtOH were removed by vacuum distillation (water aspirator) until 2−3 mL of liquid remained. EtOH (18 mL) was added, and the mixture was again concentrated by vacuum distillation. The nitrogen manifold exit line was then routed through a fritted gas washing bottle charged with aqueous (household) bleach solution.[17] EtOH (10 mL) was added to the reaction flask, followed by triethylenetetraamine (6.27 g, 42.9 mmol), followed by EtOH (10 mL). The solution was stirred at rt for 30 min and then at 80 °C for 20 min. Ethanethiol (stench) was then purged from the solution by entrainment with N_2, which was bubbled through the reaction mixture (fritted gas dispersion tube) into the bleach-filled gas washing bottle. After 15 h, the reaction mixture was concentrated to 2−3 mL by short-path vacuum distillation (40 °C, water aspirator). (A dry-ice cooled trap was used to assure that any residual ethanethiol was trapped; the trap was subsequently cleaned with bleach solution.[17]) Toluene (50 mL) was then added, undissolved solids were removed by filtration, the filtrate was concentrated, and resultant crude **2** was recrystallized from hot toluene (hot filtration necessary) to give 5.83 g of yellow solid (mp 146−149 °C). A second recrystallization from toluene gave 4.86 g (69%) of off-white **2** (mp 149−150 °C). This material was shown by NMR to be pure enough (>98%) for subsequent conversion to cyclen. If desired, it can be further purified by sublimation (100 °C, 0.01 Torr): white solid; mp 150−151 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.26 (s, 4H), 3.35 (apparent t (XX′ of AA′XX′), 4H, J_{appar}= 9.6Hz), 3.86 (apparent t (AA′ of AA′XX′), 4H, J_{appar} = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 90.56 MHz) δ 45.3, 52.1, 53.9, 155.4; IR (KBr) 1629 cm^{-1} (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. (Note: **2** is unstable toward hydrolysis and should be stored in a desiccator.)

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(19) There has been a great deal of confusion about the mp of **1** in the literature. Stetter and Mayer[20] originally reported mp 35 °C. Buøen *et al.* reported mp 119−120 °C.[18] Aldrich and Fluka list melting point ranges of 110−113 °C (97%) and 105−110 °C (≥97%) repectively in their catalogs. Confusing matters further, Zhang and Busch[21] subsequently reported mp 36−38 °C. Our mp range for **1** (calibrated thermometer) is lower than that reported in ref 18, but is consistent with the mp range of sublimed material (no detectable impurities by high S/N NMR) we have prepared by the Richman−Atkins method (mp 105−109 °C). ^{1}H NMR relative integrations of the material reported in this note are consistent with anhydrous **1**.

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