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A Practical Synthesis of 1,4,7,10-Tetraaza-Cyclododecane, A Pivotal Precursor for MRI Contrast Agents

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A PRACTICAL SYNTHESIS OF 1,4,7,10-TETRAAZA-CYCLODODECANE, A PIVOTAL PRECURSOR FOR MRI CONTRAST AGENTS

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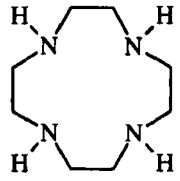
Abstract: A practical preparation of the versatile macrocycle 1,4,7,10-tetraazacyclododecane (cyclen) was developed starting from cheap and easily available starting materials as ethylenediamine and glyoxal.

In recent years, paramagnetic lanthanide(III) complexes have been the subject of extensive research due to their potential application as contrast agents in Magnetic Resonance Imaging (MRI). Gadolinium(III) complexes from the ligand DOTA

(1,4,7,10-tetraazacyclododecane-*N,N',N»,N'»*-tetraacetic acid) and DTPA (diethylenetriaminopentaacetic acid) were the first complexes entered into clinical practice and they represent the reference compounds for the development and evaluation of new contrast agents. Due to the higher thermodynamic and kinetic stability, $[Gd(DOTA)]^-$ is currently preferred to $[Gd(DTPA)]^{2-}$.[1]

The synthesis of DOTA was based on the alkylation of 1,4,7,10-tetraazacyclododecane (**1**, «cyclen») with chloroacetic acid, and hence this tetraazamacrocycle represents the key intermediate. Because of the well-known difficulties in performing macrocyclization reactions, many efforts have been devoted to the development of viable, economical and easily scaled-up synthetic routes to cyclen.



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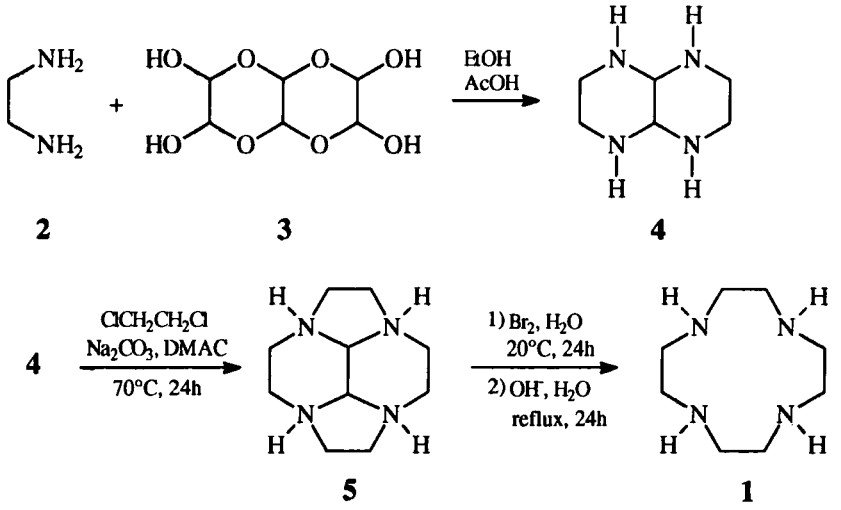
Apart from the Richman-Atkins protocol[2a-c] and subsequent improvements,[2d-e] the more recent and alternative approaches consist in a) reaction of triethylenetetramine with dithiooxamide to afford a tricyclic bis-amidine followed by double reductive ring expansion with DIBAL-H,[3] b) the condensation of triethylenetetramine with butanedione to afford a tricyclic bis-aminal which undergoes alkylation with 1,2-dibromoethane giving cyclen as protected bis-aminal derivative.[4]

The main drawback of these procedures is the use of triethylenetetramine which is commercially available at high purity levels at high prices whereas the use of the less expensive technical (60-70%) triethylenetetramine[5] requires purification steps. Furthermore, in the synthetic protocol involving dithiooxamide, the stench

hydrogen sulphide is obtained as byproduct and moisture-sensitive hydride reagent DIBAL-H is employed in the reductive step. Although conceptually straightforward, the implementation of such strategies in an efficient and practical manner constitutes a demanding challenge in synthetic methodology.

We wish to report here an efficient and economical route (Scheme 1) to cyclen which can be easily scaled-up and utilizes as starting materials ethylenediamine and glyoxal, which are both commercially available in pure form at low cost.

Scheme 1



The condensation of glyoxal and ethylenediamine was already described by Fuchs *et al.*[6] to afford decahydro-4a,8a-pyrazino[2,3-*b*]pyrazine **4** (or 1,4,5,8-tetraazadecalin) with a *trans* stereochemistry at the ring junction as ascertained by NMR data. In our hands, compound **4** was obtained as single diastereoisomer in 80% yield after crystallization from ethanol. The *trans* configuration depicted in structure **4** was assumed on the ^{1}H and ^{13}C-NMR parameters which completely match with those reported.[6]

As far as we know, the reactivity of compound **4** towards bis-electrophile reagents has never been reported in detail till now.[7a,b] We found that by reacting **4** with 1,2-dichloroethane in *N,N*-dimethylacetamide (DMAC) at 70°C for 24h the tetracyclic derivative **5** could be isolated in 75% yield after purification by column chromatography or vacuum sublimation. The yield of the alkylation step was strongly influenced by the temperature: below 70°C the reaction rate was very slow, requiring many days to reach a preparatively satisfying transformation. Conversely, working at 80°C or above, it was readily recognizable the extensive darkening of the reaction mixture, with the formation of polar coloured byproducts and concomitant decrease in isolated yield.[8] The stereochemistry of compound **5** was assigned *trans* considering that the absence of protic solvents either in the alkylation step or in the workup, should rule out any epimerization (*i.e.*, requiring an acid-catalyzed ring opening).[9]

The subsequent oxidation of **5** with molecular bromine in water to the corresponding bis-amidinium salt followed by alkaline hydrolysis gave the desired cyclen **1**.[7a]

In summary, the above sequence for the preparation of intermediate **5** is simple, efficient and allows an easy access to cyclen **1** in few high-yielding steps. It is worthwhile to observe that this protocol represents an improvement in the synthesis of **1** in terms of atom-economy,[10] highly desirable feature in the last years for the development of industrial preparations.

EXPERIMENTAL SECTION

Ethylenediamine, glyoxal trimer dihydrate, 1,2-dichloroethane and *N,N*-dimethyl acetamide were purchased from Aldrich and used without further purification. Aluminum oxide for chromatography (Brockmann activity I) was purchased from Merck and brought to the desired activity by addition of the proper amount of distilled water. Analytical TLC were conducted on aluminum oxide TLC purchased from Merck. Detection was accomplished by spraying with alkaline

$KMnO_4$ followed by heating to 80°C or by spraying with Dragendorff reagent. ^{1}H-NMR and ^{13}C-NMR were registered on a Bruker AC-200 spectrometer.

Decahydro-4a,8a-pyrazino[2,3-*b*]pyrazine (4)

In a 250 mL round-bottomed flask, glyoxal trimer dihydrate (**2**, 7.024 g, 33.3 mmol) was suspended in ethanol (70 mL) containing a small amount of glacial acetic acid (0.5 mL). Ethylenediamine (**3**, 13.4 mL, 200 mmol) was slowly introduced by a dropping funnel, maintaining the reaction temperature <10°C with an ice-bath. The reaction mixture was stirred for 15 min at 10°C after the addition, then brought to reflux for 30 min. Cooling to room temperature caused the separation of **4** as white crystals. Additional crops of **4** were obtained by concentration of mother liquors. The product was washed with cold ethanol and dried *in vacuo*. It could be recrystallized from small volumes of ethanol. Yield 11.351 g (80 %). M.p. 195-198°C (dec.). ^{1}H-NMR (D_2O, 200 MHz) 2.75 ppm m[4H], 2.84 ppm m[4H], 2.99 ppm s[2H]. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 46.73 ppm [CH_2], 75.03 ppm [CH]. ^{13}C-NMR (D_2O, 50.3 MHz) 44.76 ppm [CH_2], 73.07 ppm [CH].Anal. Calcd for $C_6H_{14}N_4$: C, 50.68; H, 9.92 ; N, 39.40. Found: C, 50.49; H, 10.11; N, 39.31.

Decahydro-2a,4a,6a,8a-tetraazacyclopent[*fg*]acenaphthylene (5)

In a 100 mL round-bottomed flask **3** (1.009 g, 7.092 mmol) was dissolved in *N,N*-dimethylacetamide (DMAC, 5 mL). Sodium carbonate (4.600 g, 43.4 mmol) and 1,2-dichloroethane (3.5 mL, 44.5 mmol) were added and the mixture heated to 70°C for 24h. After cooling. methylene chloride (20 mL) was added and the mixture filtered on Celite®. The filtrate was evaporated *in vacuo*. The oily residue was purified by column chromatography (Al_2O_3, Brockmann activity III, eluent CH_2Cl_2-CH_3OH 97/3). White, waxy solid. Yield 1.033 g (75 %). M.p. 91-92°C (lit.[11] 90-94°C). ^{1}H-NMR ($CDCl_3$) 2.40 ppm m[4H], 2.52 ppm m[4H], 2.75-2.86 ppm m[8H], 2.96 ppm s[2H]. ^{1}H-NMR (D_2O) 2.49 ppm m[4H], 2.63 ppm m[4H], 2.82 ppm m[4H], 2.91 ppm m[4H], 3.01 ppm s[2H]. ^{13}C-NMR ($CDCl_3$) 50.14

ppm [CH_2], 50.92 ppm [CH_2], 77.29 ppm [CH]. ^{13}C-NMR (D_2O, 50.3 MHz) 49.74 ppm [CH_2], 50.65 ppm [CH_2], 76.65 ppm [CH]. Anal. Calcd for $C_{10}H_{18}N_4$: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.61; H, 9.53; N, 28.72.

1,4,7,10-Tetraazacyclododecane (1)

In a round-bottomed flask, compound **5** (1.943 g, 10.0 mmol) was dissolved in distilled water (20 mL). Concd HCl was added until pH 6 and then bromine (1.60 ml, 31.1 mmol) was continuously dropped into the solution (slightly exothermic reaction). The reaction was stirred overnight at room temperature, then NaOH (12.0 g, 400 mmol) was portionwise added and the mixture was refluxed for 36h. After cooling, the reaction mixture was evaporated *in vacuo* and the residue was continuously extracted with toluene (100 ml) for 10h. The organic extracts were dried over K_2CO_3, filtered and concentrated *in vacuo*; from this solution, cyclen (**1**) precipitated as white powder; concentration of the mother liquors gave two further crops of **1** (total yield 1.121 g, 65 %). An analytical sample was recrystallyzed from toluene to give cyclen as white powder, m.p. 108-110°C (lit.[3] 103-107°C). Anal. Calcd for $C_8H_{20}N_4$: C, 55.78; H, 11.70; N, 32.52. Found: C, 55.61; H, 11.93; N, 32.29.

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8. Various attempts to isolate occasionally occurring yellow impurities were unsuccessful, due to the very tiny amount present in the product. However, the different colour of various batches of **5** influenced neither the product characteristics (m.p., spectra) nor the yields of the subsequent steps.

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