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OPPI BRIEF

An Efficient Synthesis of the bis-Tetraazacyclodecane JM3100 Under PTC Conditions

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We now describe a facile synthesis of 1,4-bis((1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)benzene octahydrochloride **3** from 1, 4, 8, 11-tetrazacyclotetradecane **1** with dibromo-p-xylene **2** under phase transfer catalysis. The method gives good yields without protection and deprotection.

The chemistry of the tetraazacycloalkanes has undergone considerable development in the last years. Among their other properties, these macrocyclic polyamines are able to form stable complexes with transition metals, lanthanides, actinides, and other heavy metals.[1–4] The affinity and selectivity towards the metal ion can be tuned by varying the size of the macrocyclic core as well as the nature and the number of pendant coordinating arms on the nitrogen atoms. In addition, these molecules exhibit numerous biomedical applications. These were described as a new class of antiviral agents with potent inhibitory effects on HIV-1 and HIV-2 replication, along with high selectivity.[5–7]

Many methods have been devised for the synthesis of tetrazocyclodecanes and their functionalized derivatives, including high dilution techniques, use of metal cations as templates, protection/de-protection sequences and functionalization on either nitrogen or carbon atoms. A recent key step in this chemistry is the use of bis-aminal intermediates. [8–15]

Our new method avoids protection/de-protection sequences and is shown in *Scheme 1*. Compound **3** was synthesized from **1** with dibromo-p-xylene **2** under phase transfer conditions, using tetra-n-butyl ammonium bromide (TBAB), in good yield. The spectral and analytical data strongly supported the structure of **3** (see Experimental

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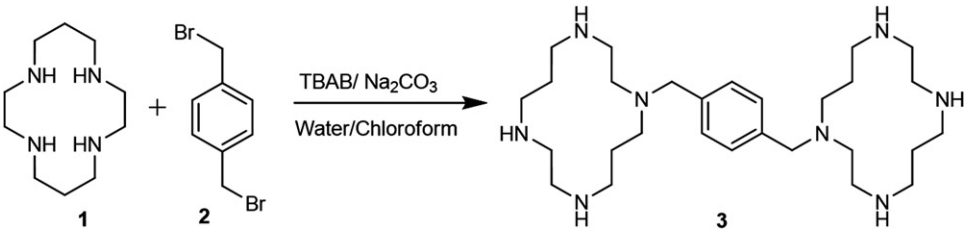

Scheme 1

Section). An efficient and convenient route has thus been developed with an overall yield of 92% with 99.6% purity. We expect this route may be scalable for synthesis.

Experimental Section

Melting points were uncorrected. Infrared spectra were obtained by using a Bruker WM-4(X) spectrometer 577 model. ^{1}H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded on a Bruker WM-400 spectrophotometer in $CDCl_3$ with tetramethylsilane as reference. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrophotometer. Elemental analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents were commercial grade, used without further purification. Purification of the synthesized compounds by column chromatography and thin-layer chromatography (TLC) was carried out by using alumina sheets purchased from Merck with ethanol as the moving phase.

Synthesis of 1,4-bis((1,4,8,11-Tetraazacyclotetradecan-1-yl)methyl)benzene octahydrochloride (3)

1,4,8,11-Tetraazacyclotetradecane **1** (0.205 mol) was dissolved in a mixture of water (160 mL) and chloroform (160 mL); sodium carbonate (0.205 mol) and α, α′-dibromo-p-xylene **2** (0.1mol) were added, followed by addition of 10% of TBAB catalyst (0.0205 mol). The solution was refluxed for 1-2 h, cooled to room temperature, poured into ice cold water and extracted with toluene (3x200 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a white solid **3**. The obtained solid material was dissolved in a minimum amount of dry methanol (250 mL) and dry HCl gas was gently passed through the solution to form a white precipitate which was filtered and dried to give **3** octahydrochloride.

Yield 92% with 99.6% purity, free base mp 131-132°C, lit mp 129-131°C;[16] HCl salt mp 240.0-245.5°C, lit mp 232°C.[7]

Free Base IR (cm^{-1}): 3417, 3283, 2937, 2817, 1645, 1531, 1464, 751; ^{1}H NMR (400 MHz, $CDCl_3$) 7.28 (s, 4H), 4.08 (s, 4H), 3.36 (bb, 8H), 3.26 (bb, 8H), 3.18-3.17 (m, 4H), 2.59-2.59 (m, 16H),179-1.68 (m, 4H), 1.58-1.48 (m,4H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.4, 29.6, 47.9, 48.1, 49.2, 50.10, 50.4, 51.2, 52.2, 54.9, 58.3, 129.2. 137.2. HRMS (M + 1): Calcd for C_{28} $H_{55}N_8$, 502.78196; Found (HRMS (M + 1)), 503.44962.[7] (See *Figure 1*)

Anal. Calcd for C_{28} $H_{55}N_8$: C, 66.75; H, 11.00; N, 22.24. Found: C, 66.85; H, 10.81; N, 22.19.

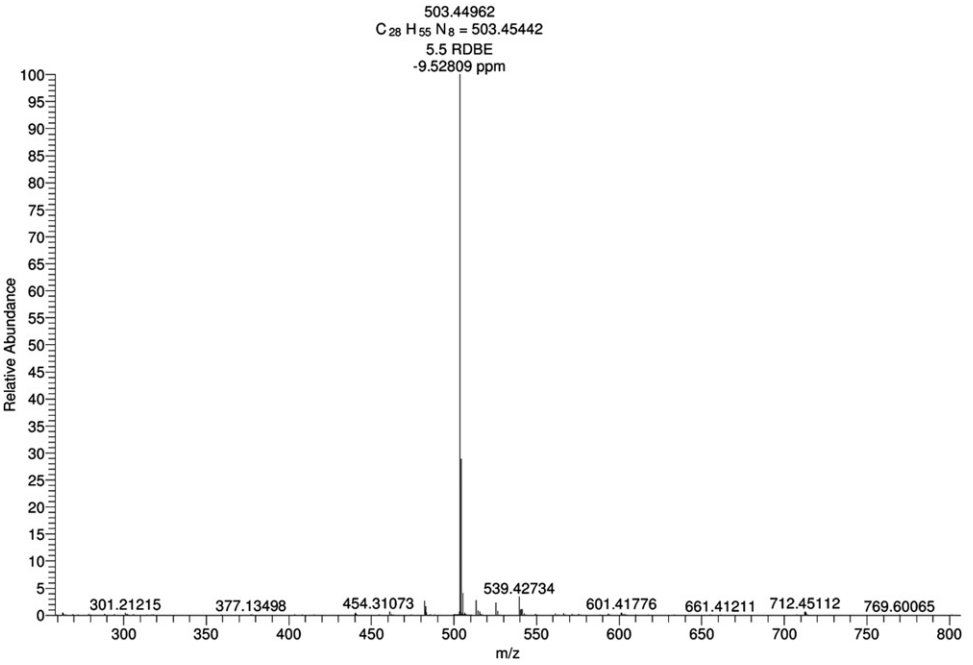

Figure 1. HRMS of bis-Tetraazacyclodecane JM3100.

HPLC Analysis

We used an HPLC equipped with ultraviolet spectrophotometer as detector, an auto sampler and a Zorbaxeclips plus C18 3.5 µm (100 mm ×4.6mm) column. Mobile phase A: we dissolved 6.32 g of sodium perchlorate and 1.73 g of 1-octane sulfonic acid sodium salt anhydrous in 1000 mL of water, then adjusted the pH to 2.00 ± 0.05 with diluted perchloric acid (10%). Mobile phase B: We mixed acetonitrile and the buffer (the same used in Mobile phase A) in the ratio of 95:5 v/v, flow rate 1.0 ml/min; column temperature 35 °C ±5 °C; wavelength 210 nm and run time 55 min. Gradient: 0 min: 84% A, 16% B; 5 min: 74% A, 26% B; 30 min: 57% A, 43% B; 32 min: 70% A, 93% B; 35 min: 70% A, 93% B; 36 min: 84% A, 16% B; 55 min: 84% A, 16% B; UV detection at 210 nm; flow rate: 1.0 mL/min; column oven temperature: 25 °C .

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