Facile Preparation of Tetra(2-aminoethyl)methane and Tetra(3-aminopropyl)methane: Novel Tetravalent Monomers for Materials Synthesis

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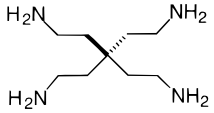
Introduction

Progress in the synthesis of dendritic molecules can hinge on the availability of appropriate multivalent initiator cores. Several cores which have served as scaffolds to construct four-directional dendrimers include the rigid, functionalized carbon core, 1,3,5,7-adamantanetetracarboxylic acid,[1a] and those that contain heteroatoms (e.g., tetraallylsilane[1a,2] and phosphonium- or ammonium-centered[1a] cores.) Early work using pentaerythritol,[1] tetra(3-bromopropyl)methane, methane tetra(3-propanoic acid), and tetra(carboxyethoxymethyl)-methane[1a] illustrated the value of the tetrafunctional methane motif in furnishing tetrahedrally symmetric dendrimers. Similar amine-tipped methane analogues, such as tetra(2-aminoethyl)methane (**1**) or the higher homologue (**2**), can extend this tetravalent growth strategy to include robust first generation amide linkers. These concerns meshed with our interests in the assembly of higher-dimensional, periodic, covalently linked organic materials,[3] and in this vein we have developed efficient syntheses of both tetraamines. Tetraamine **1** has been claimed in a patent,[4] but no preparative details were included, while **2** appeared to be unknown at the inception of this work.



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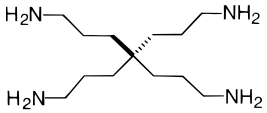

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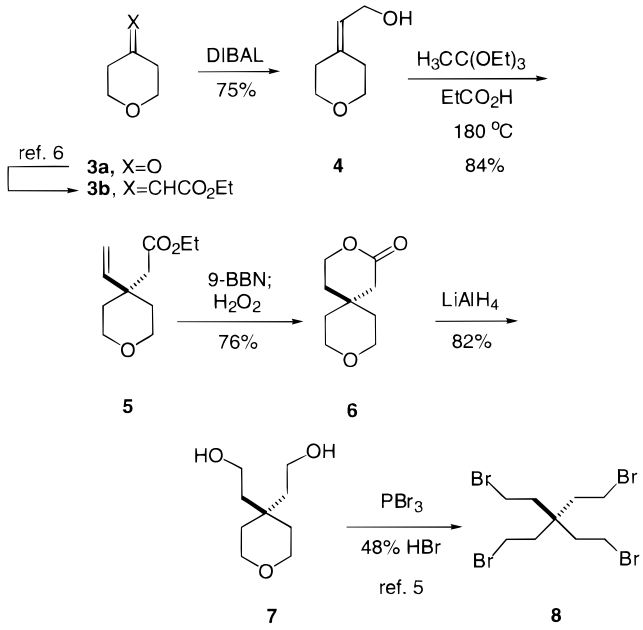
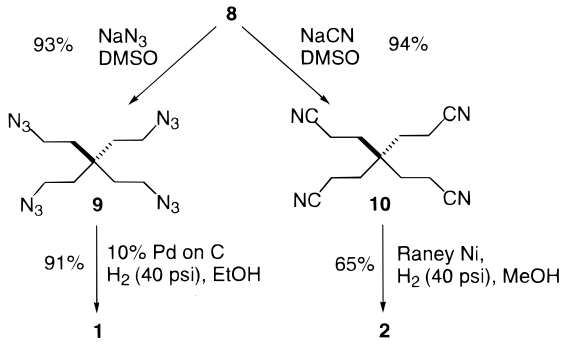
Results and Discussion

Both syntheses proceed through the key tetrabromide **8** (Scheme 1). This compound has been described by Newkome et al.,[5] but their reported synthesis requires a demanding Knoevenagel/Michael transformation on ketone **3a**, which is complicated by formation of variable quantities of unproductive byproduct. Our route skirts these difficulties by featuring a Johnson ortho ester Claisen rearrangement of alcohol **4** to fashion the central tetrasubstituted carbon in **8** following routine functional group manipulation.

Scheme 1



Scheme 2



Tetraazide **9** was prepared in excellent yield from **8** by treatment with NaN_3 in DMSO, although the potential explosiveness of this compound cautioned against isolation and purification of large batches in any single run (Scheme 2). Rather, the crude material was conveniently reduced to the tetraamine **1** through palladium-catalyzed hydrogenation. This tetraamine was isolated in pure form as the tetra-*N*-BOC derivative. The tetrabromide **8** also served as an effective precursor to tetranitrile **10** through similar displacement chemistry. Newkome et al. reported that tetranitrile **10** is available from **8** (78%) through cyanide displacement in acetonitrile.[7a] Substituting DMSO as solvent raised this yield to 94%. The homologated tetraamine **2** was prepared from **8** by Raney nickel catalyzed hydrogenation.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone under Ar immediately

(1) (a) *A Review of Dendritic Macromolecules*; Moorefield, C. N., Newkome, G. R., Ed.; Advances in Dendritic Macromolecules; JAI Press Inc.: Greenwich, CT, 1994; Vol. 1, pp 1−67 and references therein. (b) Kremers, J. A.; Meijer, E. W. *React. Funct. Polym.* **1995**, *26*, 137.

(2) Frey, H.; Lach, C.; Lorenz, K. *Adv. Mater.* **1998**, *10*, 279.

(3) Feldman, K. S.; Campbell, R. F.; Saunders: J. C.; Ahn, C.; Masters, K. M. *J. Org. Chem.* **1997**, *62*, 8814.

(4) Bolton, N.; Smith, W. N. U.S. Patent 4 906 703, 1990; *Chem. Abstr.* **1990**, *113*, 173672.

(5) Newkome, G. R.; Gupta, V. K.; Griffin, R. W.; Arai, S. *J. Org. Chem.* **1987**, *52*, 5480.

(6) Lammek, B.; Derdowska, I.; Rekowski, P. *Pol. J. Chem.* **1990**, *64*, 351.

(7) (a) Newkome, G. R.; Arai, S.; Fronczek, F. R.; Moorefield, C. N.; Lin, X.; Weis, C. D. *J. Org. Chem.* **1993**, *58*, 898. (b) Rice, L. M.; Sheth, B. S.; Zalucky, T. B. *J. Pharm. Sci.* **1971**, *60*, 1760.

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before use. Moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under Ar. Solvents for chromatography (Et_2O, EtOAc, CH_2Cl_2, hexane) were distilled from CaH_2 prior to use. Flash column chromatography was carried out under positive pressure using 32−63 μm silica gel and the indicated solvents. Melting points are uncorrected. Electron impact mass spectra (EIMS) were obtained at 50−70 eV. ESI spectra were generated in positive ion mode from an acetonitrile/water solution (50/50 v/v) containing 1% acetic acid. High resolution (accurate mass) MALDI spectra were generated in reflector mode using a mixture of peptides and matrix cluster peaks as internal references. High-resolution chemical impact mass spectra (CIMS) and FAB high-resolution mass spectra were obtained from the mass spectrometry laboratory at the University of Texas at Austin. Combustion analyses were performed by Midwest Microlab, Indianapolis, IN. ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information to establish purity for those compounds which were not subject to combustion analyses.

2-(Tetrahydropyran-4-ylidene)ethanol (4).[8] Ethyl (tetrahydropyran-4-ylidene)acetate **3b** (11.4 g, 67.1 mmol) was dissolved in 50 mL of THF and cooled to 0 °C. A solution of 1.0 M DIBALH in hexanes (148 mL, 148 mmol) was added dropwise, and once the addition was complete, the solution was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was slowly poured into ice-cold 1 M HCl (150 mL), and the resulting suspension was stirred until all of the salts had dissolved. This solution was extracted with chloroform, and the organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude oil was purified by silica gel chromatography using 30% EtOAc/hexanes as eluent to afford 6.4 g of alcohol **4** as a yellow oil (75%): IR ($CDCl_3$) 3472, 3600 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.92 (m, 4H), 3.67 (m, 4H), 4.14 (m, 2H), 5.44 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.6, 36.6, 57.8, 68.4, 69.1, 122.3, 138.0; MS *m*/*z* (relative intensity) 128 (M^+, 15).

Ethyl (4-Ethenyl-4-tetrahydropyran-4-yl)acetate (5). 2-(Tetrahydropyran-4-ylidene)ethanol **4** (6.25 g, 48.8 mmol), propionic acid (0.22 g, 2.9 mmol), and triethyl orthoacetate (55.4 g, 340 mmol) in a heavy-walled Pyrex tube equipped with a Teflon valve were purged with Ar and evacuated at −196 °C. This reaction flask was placed into a 200 °C oil bath for 36 h. At that time, the vessel was cooled to room temperature, and the reaction solution was poured into 50 mL of EtOAc and ca. 20 g of silica gel. The slurry was stirred for 2 h and then evaporated to dryness. The **5**-impregnated silica gel was loaded onto a silica gel column and chromatographed with 30% EtOAc/hexanes as eluent to afford 8.16 g of ester **5** as a colorless oil (84%): IR ($CDCl_3$) 1725 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, J = 7.12 Hz, 3H), 1.75 (m, 4H), 2.37 (s, 2H), 3.68 (m, 4H), 4.09 (q, J = 7.13 Hz, 2H), 5.05 (dd, J = 17.7, 1.0 Hz, 1H) and 5.23 (dd, J = 10.9, 1.0 Hz, 1H), 5.80 (dd, J = 11.0, 17.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 35.6, 37.0, 46.3, 60.0, 64.0, 114.9, 142.8, 170.9; HRMS (+CI) calcd for $C_{11}H_{18}O_3$ (MH^+) 199.1334, found 199.1340.

3,9-Dioxaspiro[5.5]undecan-2-one (6). Ethyl (4-vinyl-4-tetrahydropyran-4-yl)acetate (**5**) (3.56 g, 18.0 mmol) was dissolved in 150 mL of THF, cooled to 0 °C, and treated dropwise with 0.5 M 9-BBN in THF (72 mL, 36 mmol). The reaction flask was held at 5 °C for 72 h. A solution of 3 N NaOH (15 mL, 45 mmol) was added dropwise at 0 °C followed by addition of 30% H_2O_2 (149 mL) via addition funnel. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, poured into water, and extracted with chloroform (3 × 150 mL). The combined organic layers were washed with a 1:1 solution of brine and saturated sodium thiosulfate. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a yellow oil. This oil was purified by silica gel chromatography with 30% EtOAc/hexanes to 70% EtOAc/hexanes as eluent to afford 2.33 g of 3,9-dioxaspiro[5.5]undecan-2-one (**6**) as a pale yellow oil (76%): IR ($CDCl_3$) 1731 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (m, 4H), 1.84 (m, 4H), 2.48 (s, 2H), 3.69 (m, 4H), 4.36 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.5, 33.4, 37.3, 41.4, 63.2, 171.0. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.28; H, 8.18.

4,4-Bis(2-hydroxylethyl)pyran (7). 3,9-Dioxaspiro[5.5]-undecan-2-one (**6**) (0.85 g, 5.0 mmol) was dissolved in 10 mL of Et_2O and treated with a solution of 1.0 M $LiAlH_4$ in Et_2O (15.0 mL, 15.0 mmol). The resulting suspension was stirred at room temperature for 3 h. The reaction mixture was worked up by sequential addition of 0.38 mL of H_2O, 0.38 mL of 15% NaOH, and 1.14 mL of H_2O. The white suspension was stirred for 3−4 h, filtered, and washed with copious amounts of Et_2O. The filtrate was concentrated in vacuo to give 0.71 g of **7** as a viscous, colorless oil (82%). Spectral data for **7** matched those reported by Newkome et al.[5]

3,3-Bis(2-azidoethyl)pentane-1,5-diazide (9). 3,3-Bis(2-bromoethyl)pentane-1,5-dibromide (**8**) (177 mg, 0.40 mmol), prepared from **7** as described by Newkome,[5] was added to a freshly made solution of 0.5 M NaN_3 in DMSO (116 mg of NaN_3 in 3.5 mL of DMSO, 1.77 mmol). The reaction solution was stirred at room temperature for 3.5 h and then poured slowly into 5 mL of water and allowed to stir for 2 h. The solution was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with water (3×) and then with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 109 mg of tetraazide **9** as a yellow oil (93%): IR ($CDCl_3$) 2100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59 (t, J = 7.5 Hz, 8H), 3.34 (t, J = 7.5 Hz, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.0, 36.3, 46.5; MS (+ESI) *m*/*z* (relative intensity) 315 (MNa^+, 40); HRMS calcd for $C_9H_{16}N_{12}$ 315.1519, found 315.1495.

3,3-Bis(2-cyanoethyl)pentane-1,5-cyanide (10). 3,3-Bis-(2-bromoethyl)pentane-1,5-dibromide (**8**) (1.0 g, 2.3 mmol) and KCN (2.07 g, 32.0 mmol) were combined and dissolved in 70 mL of DMSO and allowed to stir at room temperature for 12 h. The reaction mixture was poured into 100 mL of water and stirred for 2 h. The solution was extracted with EtOAc (3 × 50 mL). The organic layer was washed with water (3×) and then dried over Na_2SO_4, filtered, concentrated, and dried in vacuo to afford 560 mg of **10** as white crystals (94%). Spectral data for **10** matched those reported by Newkome et al.[7a]

Tetra(2-aminoethyl)methane (1). A solution of 3,3-bis(2-azidoethyl)pentane-1,5-diazide (**9**) (160 mg, 0.55 mmol) in 5 mL of absolute ethanol was combined with 10% palladium on carbon (16 mg, 0.1 mmol) in a hydrogenation vessel. The reaction mixture was hydrogenated at 40 psi hydrogen pressure at room temperature for 24 h. The suspension was filtered through Celite, and the filtrate was concentrated and dried in vacuo to give 94 mg of **1** as a viscous yellow oil (91%): IR (neat) 3295, 3354 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.39 (t, 8H), 2.63 (m, 8H); ^{13}C NMR (50 MHz, CD_3OD) δ 36.9, 37.2, 41.2; MS (+ESI) *m*/*z* (relative intensity) 189 (MH^+, 16); HRMS calcd for $C_9H_{24}N_4$ 189.2079, found 189.2086.

Derivatization of 1. Tetraamine **1** (20 mg, 0.106 mmol) and an excess of di-*tert*-butyl dicarbonate (140 mg, 0.638 mmol) were dissolved in CH_2Cl_2 (5 mL) under Ar and heated to reflux. After 3 days, the reaction mixture was cooled to room temperature, acidified with concentrated HCl, and allowed to stir for 3 h. The solution was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with water. The organic layer was dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. The crude product was purified by silica gel chromatography with 30% EtOAc/hexanes as eluent to afford 26 mg of the tetra-*tert*-butyl carbamate as a white solid (42%): mp 128−130 °C; IR ($CDCl_3$) 1705, 3457 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 and 1.47 (s and t, $-CH_3$ and $-CH_2$-, 44H), 3.11 (m, 8H), 4.68 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 35.7, 35.8, 36.6, 79.2, 156.0; HRMS (+MALDI) calcd for $C_{29}H_{56}N_4O_8$ (M + Na) 611.3996, found 611.3998. Anal. Calcd $C_{29}H_{56}N_4O_8$: C, 59.16; H, 9.59; N, 9.52. Found: C, 58.83; H, 9.40; N, 9.37.

Tetra(3-aminopropyl)methane (2). A suspension of tetranitrile (**10**) (100 mg, 4.4 mmol) in 5 mL of MeOH was mixed with a 50% slurry of Raney nickel (W2-type) in water in a hydrogenation vessel. The tetranitrile was hydrogenated at 40 psi hydrogen pressure for 48 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated and dried in vacuo to give 70 mg of **2** as an amorphous white solid (65%): mp 84−86 °C; IR ($CDCl_3$) 3624, 3659 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.24 (m, 8H), 1.37 (m, 8H), 2.60 (m, 8H), 2.97 (m, 8H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.2, 34.7, 37.6, 43.4; MS (+ESI)

(8) Kyo, S.; Tanaka, H.; Renge, T. Jpn Patent 09 706, 1978; *Chem. Abstr*. **1978**, *89*, 42408.

m/*z* (relative intensity) 245 (MH^+, 100); HRMS calcd for $C_{13}H_{32}N_4$ 245.2705, found 245.2694. Copies of ^1H and ^{13}C NMR of the tetra HCl salt of **2** in DMSO-d_6 are included in the Supporting Information.

Acknowledgment. We thank the National Science Foundation (CHE9727305) for financial support.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for **1**, **2** (neutral and ·4HCl), **5**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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