Synthesis of *N*-[Tris(hydroxymethyl)methyl]benzenecarboxamides: A Convenient Route to Polyhydroxylated Dendritic Cores

Bernadette A. Hernandez, Virginia Chang, Ignacio Villanueva, and Michael D. Heagy*

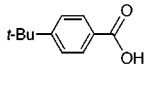
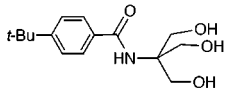
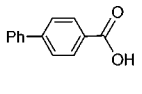
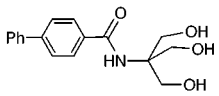
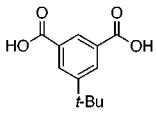
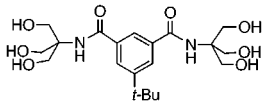
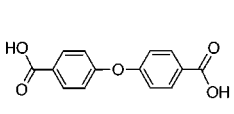
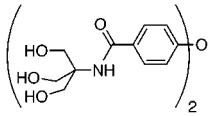
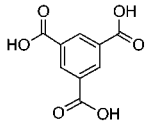
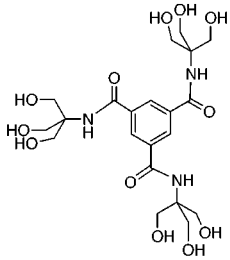
Department of Chemistry, New Mexico Institute of Mining & Technology, Socorro, New Mexico 87801

Received March 30, 1999

The past decade has witnessed an increased interest in the aromatic core component that derives the branching regions of dendritic wedges or dendrons.[1] Dendron construction methods currently use two broad strategies known as the "convergent synthetic route" and "divergent synthetic route" in the synthesis of dendrimers.[2] Among the number of dendron series reported, the poly(amido alcohol) class possess branch cells from three different branch cell reagents and feature radially oriented heterogeneous generations. The structural components that constitute the branching regions of these poly(amido alcohols) or arborol dendrimers have been typically generated from protected tris(hydroxymethyl)aminomethane (TRIS), while the core has been derived from an activated benzenecarboxylic acid.[3,4] A current limitation of the convergent synthetic approach with benzenecarbonyl chlorides is the requisite protection of hydroxyl functionality prior to formation of the amide bond, as mixtures of the adventitious aromatic ester are otherwise obtained. Others have recently reported synthetic limitations caused by sterically demanding protecting groups when attempting to construct a densely packed dendrimer.[5] Alternatively, the divergent synthetic route should allow the unprotected triol moiety to undergo proliferation toward the desired dendritic species. Used directly, and thereby avoiding the protection/deprotection steps, these branch cells may be used to anchor multiples of dendrons in the production of arborol dendrimers.

As a result of our research project that involves the synthesis of polydentate ligands as complex ceramic precursors for use in ceramic thin films,[6] we herein report a mild and convenient method to append tri-, hexa-, and nonadentate ligands about an aromatic core. This approach allows a variety of commercially available aromatic carboxylic acids to be transformed to their *N*-[tris(hydroxymethyl)methyl]carboxamides in one step. The selective activation of carboxylfunctions to form the TRIS carboxamides has been achieved using the pseudobase *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline or EEDQ.[7,8] The results are summarized in Table 1. Tridentate aromatic ligands have been produced from substituted benzoic acids (entries 1 and 2), hexadentate ligands from aromatic dicarboxylic acids (entries 3 and 4), and a nonadentate ligand from 1,3,5-benzenetricarboxylic acid (entry 5) with this peptide-coupling agent.

Table 1. Polydentate Aromatic Cores Obtained by EEDQ-Activated Coupling between TRIS and Aromatic Carboxylic Acids

entry	substrate	product	yield[a]
1			57%
2			72%
3			72%
4			57%
5			58%

[a] Isolated yield of analytically pure product

A stoichiometric amount of this acyl-transfer reagent upon dissolution in refluxing pyridine with aromatic carboxylic acids and TRIS delivers the desired carboxamides in moderate to good yields. Yields of these polydentate ligands are sufficient to allow for simple purifying procedures through recrystallization of the obtained crude solid. A general reaction scheme for the synthesis of these polyhydroxylated cores is outlined in Scheme 1.

In the case of carbodiimide-catalyzed coupling approaches to amide bond formation of the TRIS moiety, we mention Stoddart's use of DCC/HOBT as a successful coupling method between hydroxyl-protected TRIS and aromatic carboxylic acids.[3] In such studies, however, these reactions utilize the glycoside-protected version of

(1) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dentritic Molecules, Concepts, Syntheses, Perspectives*; VCH: Weinheim, 1996.

(2) Tomalia, D. A.; Durst, H. D. *Top. Curr. Chem.* **1993**, *165*, 193−313.

(3) Ashton, P. R.; Hounsell, E. F.; Jayaraman, N.; Nilsen, T. M.; Spencer, N.; Stoddart, J. F.; Young, M. *J. Org. Chem.* **1998**, *63*, 3429−3437.

(4) Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Jayaraman, N.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 732−735.

(5) Jayaraman, N.; Stoddart, J. F. *Tetrahedron Lett.* **1997**, *38*, 6767−6770.

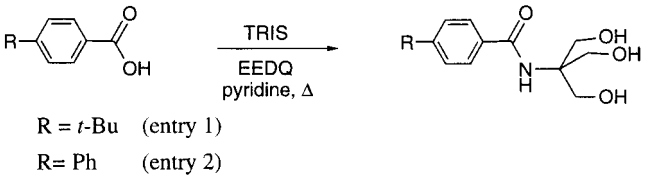
(6) Boyle, T. J.; Clem, P. G.; Rodriguez, M. A.; Tuttle, B. A.; Heagy, M. D. *J. Sol−Gel Sci. Technol.*, in press.

(7) Vaino, A. R.; Depew, W. T.; Szarek, W. A. *J. Chem. Commun.* **1997**, 1871−1872.

(8) Coupling agent used in the synthesis of peptides: (a) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651−1652 (b) Sundaram, P. V. *Biochem. Biophys. Res. Commun.* **1974**, *61*, 717−722. (c) Sipos, F.; Gaston, D. W. *Synthesis* **1971**, 321. (d) Yajima, H.; Kawatani, H. *Chem. Pharm. Bull.* **1971**, *19*, 1905−1913.

10.1021/jo990560k CCC: $18.00
Published on Web 08/17/1999

Scheme 1



R = *t*-Bu (entry 1)

R= Ph (entry 2)

TRIS, and this protocol proved unsuccessful in the course of our work involving the unprotected triol.

The experimental results described here demonstrate that the peptide-coupling agent, EEDQ, should be of considerable use in the preparation of dendritic cores derived from tris(hydroxymethyl)aminomethane (TRIS) branches in addition to the development of polydentate ligands. The absence of activated aromatic carboxylic acid cores in this synthesis alleviates the need to protect the triol functionality of the TRIS ligand prior to amide bond formation and allows a wide variety of commercially available aromatic cores to be used for the divergent synthesis of different dendrimer topologies. The application of EEDQ-activated coupling between TRIS and aliphatic carboxylic acids is currently under investigation in our laboratory.

Experimental Section

General Methods. Experiments were conducted under an atmosphere of nitrogen. All glassware was washed and dried with acetone. Pyridine was purchased from Fisher Scientific and distilled over calcium hydride. 4-Phenylbenzoic acid, 4-*tert*-butylbenzoic acid, 4,4′-oxybis(benzoic acid), 5-*tert*-butyl-1,3-benzenedicarboxylic acid, 1,3,5-benzenetricarboxylic acid, and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) were purchased from Acros Organics and used without further purification. Tris(hydroxymethyl)aminomethane (TRIS) was purchased from Aldrich Chemical Co. and used without additional purification.

Thin-layer chromatography (TLC) was performed using precoated hard layer silica gel plates and/or Whatman adsorption silica gel plates: 60 Å, F_{254}, 2.50 mm thickness. Visualization of the developed chromatographs was performed by UV absorbance and/or iodine vapor. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 300 MHz NMR. The chemical shifts for the ^{1}H spectra are reported in ppm on the δ scale from the tetramethylsilane (TMS) internal reference (0 ppm). Melting points are uncorrected. Elemental analyses were obtained from Sandia National Laboratory using a CHNS/O analyzer.

***N*-[Tris(hydroxymethyl)methyl]-4-*tert*-butylbenzenecarboxamide (Table 1, Entry 1).** 4-*tert*-Butylbenzoic acid (3.17 g, 17.78 mmol), TRIS (3.23 g, 26.66 mmol), EEDQ (8.80 g, 35.59 mmol), and 125 mL of pyridine were introduced to a 250 mL round-bottom flask, equipped with a Dean−Stark receiver and condenser. The reaction mixture was allowed to reflux overnight. The solution was concentrated via rotary evaporation and the remaining pyridine removed under vacuum. To this solid was added 40 mL of ethyl acetate and the slurry filtered to remove excess EEDQ. The solid was washed with water, and the crude product was recrystallized in dichloromethane to yield a white powder (2.85 g, 57%): mp 139−142 °C; ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.76 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 4.57 (t, J = 5.5 Hz, 3H), 3.77 (d, J = 5.5 Hz, 6H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 167.86, 154.54, 133.01, 127.69, 125.51, 63.11, 61.12, 35.14, 31.51; IR (KBr pellet) 2946.34, 1636.02, 772.08, cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24;, N, 4.98. Found: C, 63.72; H, 8.19; N, 5.09.

***N*-[Tris(hydroxymethyl)methyl]-4-phenylbenzenecarboxamide (Table 1, Entry 2).** 4-Phenylbenzoic acid (0.70 g, 3.55 mmol), TRIS (1.29 g, 10.66 mmol), EEDQ (1.32 g, 5.33 mmol), and 50 mL of pyridine were introduced to a 100 mL round-bottom flask, equipped with a Dean−Stark receiver and condenser. Pyridine was removed from the heterogeneous mixture by distillation and replaced with ethyl acetate. This mixture was placed in a fritted glass funnel and filtered to remove dissolved EEDQ. The remaining solid was washed with water to dissolve excess TRIS. The crude solid was vacuum filtered and dried. The product was crystallized from ethyl acetate (0.72 g, 72%): mp 147−148 °C; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 7.9 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.50 (t, J = 7.3 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 7.3 (s, 1H), 4.52 (t, J = 6.4 Hz, 3H), 3.83 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 168.7, 145.0, 140.8, 134.7, 129.9, 129.0, 128.8, 128.0, 127.8, 63.5, 63.4; IR (KBr pellet) 2946, 1641, 742 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.74; H, 6.50; N, 4.49.

***N*,*N*′-Bis[tris(hydroxymethyl)methyl]-5-*tert*-butyl-1,3-benzenedicarboxamide (Table 1, Entry 3).** 5-*tert*-Butyl-1,3-benzenedicarboxylic acid (1.44 g, 6.50 mmol), TRIS (3.93 g, 32.5 mmol), EEDQ (4.83 g, 19.50 mmol), and 50 mL of pyridine were introduced to a 100 mL round-bottom flask, equipped with a Dean−Stark receiver and condenser. The reaction mixture was allowed to reflux overnight. Pyridine was removed by distillation and replaced with methanol. The methanol solution was concentrated using a rotary evaporator and the crude solid recrystallized from 80:20 dichloromethane/methanol. The reaction afforded a white powder (1.99 g, 71.7%): mp 147−153 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (d, J = 4.9 Hz, 3H), 3.93 (d, J = 5.5 Hz, 12H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.4, 152.1, 135.1, 127.3, 122.9, 62.8, 61.4, 34.7, 30.2; IR (KBr pellet) 2959, 1646, 1049 cm^{-1}. Anal. Calcd for $C_{20}H_{32}N_2O_8$: C, 56.07; H, 7.54; N, 6.54. Found: C, 56.24; H, 7.44; N, 6.35.

Oxybis[*N*-tris(hydroxymethyl)methyl]-4,4′-benzenedicarboxamide (Table 1, Entry 4). Oxybis(benzoic acid) (5.0 g, 19.4 mmol), TRIS (14.07 g, 116.1 mmol), EEDQ (14.36 g, 58.1 mmol), and 150 mL of pyridine were introduced to a 250 mL round-bottom flask, equipped with a Dean−Stark receiver and condenser. The reaction mixture was stirred and allowed to reflux overnight. Pyridine was removed by distillation, replaced with ethanol, and evaporated under vacuum. The crude material was washed with three aliquots of ∼10 mL of acetone to dissolve the EEDQ excess. The remaining solid was recrystallized in water to eliminate the excess TRIS (5.13 g, 57%): mp 158−164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (d, J = 8.8 Hz, 4H), 7.28 (s, 2H), 7.11 (d, J = 8.5 Hz, 4H), 4.77 (t, J = 5.8 Hz, 6H), 3.68 (d, J = 5.8 Hz, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.03, 158.94, 131.22, 130.24, 118.77, 63.24, 60.97; IR (KBr pellet) 2880, 1627, 765 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_2O_9$: C, 56.89; H, 6.08; N, 6.03. Found: C, 56.21; H, 5.89; N, 5.75.

***N*,*N*′,*N*″-Tris[tris(hydroxymethyl)methyl]-1,3,5-benzenetricarboxamide (Table 1, Entry 5).** 1,3,5-Benzenetricarboxylic acid (2.0 g, 9.52 mmol), TRIS (10.37 g, 85.6 mmol), EEDQ (11.77 g, 47.60 mmol), and 150 mL of pyridine were introduced to a 250 mL round-bottom flask, equipped with a Dean−Stark receiver and condenser. The reaction mixture was stirred and allowed to reflux for 48 h. Pyridine was removed by distillation, and at least three-20 mL aliquots of acetone were used to dissolve the EEDQ excess. The crude solid was washed with hot water (removal of the excess TRIS) to afford a white powder (2.85 g, 57.6%): mp >300 °C;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (s, 3H), 7.54 (s, 3H), 4.73 (t, J = 5.8 Hz, 9H), 3.72 (d, J = 3 Hz, 18H), 3.32 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) 167.07, 135.93, 123.91, 63.52, 60.80; IR (KBr pellet) 2961, 1652, 801 cm^{-1}. Anal. Calcd for $C_{21}H_{33}N_3O_{12}$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.57; H, 6.37; N, 8.59.

Acknowledgment. Support has been provided by the Sandia University Research Project contract and the NSF-Western Alliance to Expand Student Opportunities (financial support to B.A.H). M.D.H wishes to thank Dr. Timothy J. Boyle, of the Sandia-Advanced Materials Laboratory for the collaborative effort that this project has initiated, Dr. Todd Alam from the Sandia National Laboratory for the use of their NMR facilities, and Ms. Dalia Diaz for assistance in the preparation of the aforementioned compounds.

JO990560K