One-Step Coupling of Tris(hydroxymethyl)aminomethane to Aliphatic and Aromatic Carboxylic Acids

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Received 9 December 1999; revised 19 April 2000

Abstract: A convenient and general method was established to append tri-, hexa-, and nonadentate ligands about an aromatic or aliphatic core. This approach allows a variety of commercially available carboxylic acids to be transformed to their *N*-tris(hydroxymethyl)methylcarboxamides in one step. The selective activation of the acid functionality to form the polyhydroxylated dendritic cores has been achieved using the acyl transfer agent *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ).

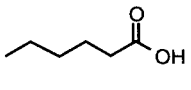
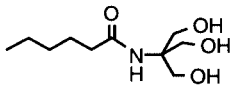
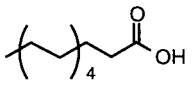
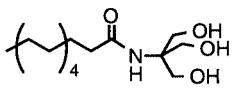
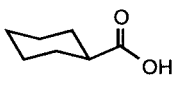
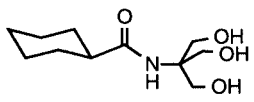
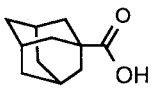
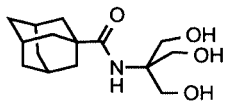
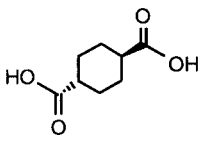
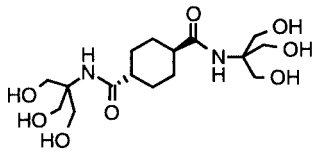
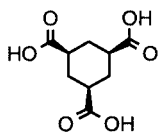
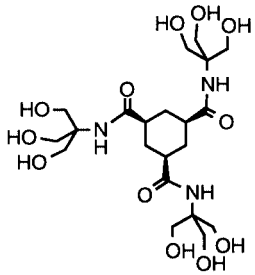
Key words: carboxylic acids, dendrimers, coupling, amides, ligands

Numerous methods exist to form carboxamides from carboxylic acids and simple primary amines.[1] Fewer reactions are known which can make this conversion in a single step. Generally, reactions of this type have been explored in the context of peptide synthesis through the use of such amino acid coupling reagents as, ethoxyacetylene,[2a] DCC,[2b,c] ketenimes,[2d] ynamines,[2e] and copper complexes.[2f] However, many of these methods give less than satisfactory results when the primary amine in question involves a sterically crowded, polyhydroxylated amine such as tris(hydroxymethyl)aminomethane, (TRIS). The importance of the TRIS group to dendrimer synthesis lies in its use as a 1 → 3 branching component in the poly(amido alcohols) class of arborol dendrimers.[3,4] Current methods towards appending TRIS to dendritic cores in a single step are limited as TRIS has slight solubility in polar aprotic solvents and forms adventitious mixtures of carboxylic esters when the carboxyl component is strongly activated as either the acyl halide or symmetrical anhydride.[5]

Since this amine is of current interest for TRIS connectivity in the generation of dendritic cores, as well as our project that utilizes the TRIS moiety for the production of polydentate ligands[6], we wish to report a convenient route towards the synthesis of such *N*-tris(hydroxymethyl)methylcarboxamides.[7] The selective conversion of either aliphatic or aromatic carboxylic acids to their corresponding TRIS carboxamides has been achieved in one step using the acyl-transfer reagent *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, (EEDQ)[8] (Scheme).

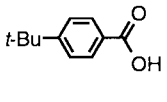
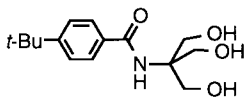
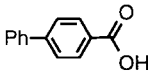
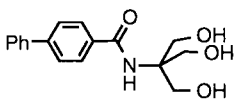
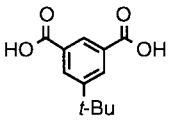
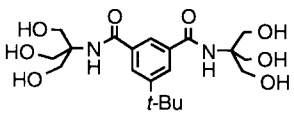
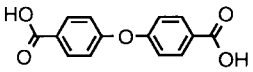
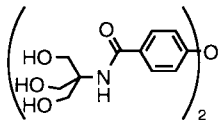
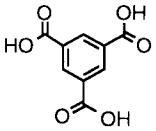
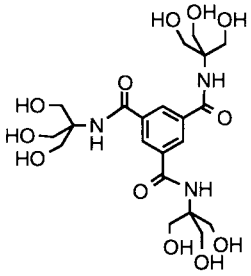
Using this method tridentate ligands have been produced directly from linear and cyclic aliphatic monocarboxylic acids (Table 1, Entries 1–4) and aromatic monocarboxylic acids (Table 2, Entries 1, 2). Hexadentate ligands were synthesized from cyclohexane dicarboxylic acid (Table 1, Entry 5) and aromatic dicarboxylic acids (Table 2, Entries 3, 4). Finally, two nonadentate ligands were produced from *cis*-1,3,5-cyclohexanetricarboxylic acid (Table 1, Entry 6) and 1,3,5-benzenetricarboxylic acid (Table 2, Entry 5) with this peptide-coupling agent.

Table 1 Polydentate Aliphatic Cores Obtained by EEDQ-activated Coupling between TRIS and Carboxylic Acids

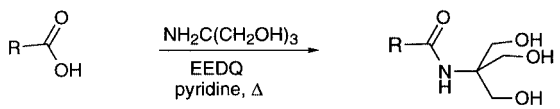
Entry	Substrate	Product	Yield[a] (%)
1			57
2			78
3			67
4			45
5			47
6			30

[a] Isolated yield of analytically pure product.

Table 2 Polydentate Aromatic Cores Obtained by EEDQ-activated Coupling between TRIS and Carboxylic Acids

Entry	Substrate	Product	Yield[a] (%)
1			57
2			72
3			72
4			57
5			58

The general reaction performed in this study where R represents either an aliphatic or aromatic group is shown in the Scheme. An equivalent amount of EEDQ upon dissolution in refluxing pyridine with mono-, di-, or tricarboxylic acids and TRIS delivers the desired carboxamides in moderate to good yields. Yields of these polyhydroxylated compounds are sufficient to allow for simple purifying procedures through recrystallization of the obtained crude solid. The byproducts of the reaction, quinoline, ethanol and CO_2 are all easily removed. For the removal of excess TRIS, water was required as the rinse solvent and, in certain cases, the moderate yields reported in Tables 1 and 2 were a consequence of enhanced water solubility of the final product.



Scheme

Single crystals of *N*-tris(hydroxymethyl)methyl-4-*tert*-butylbenzenecarboxamide (Table 2, Entry 3) were obtained and found to be suitable for X-ray structure analysis (Figure). As this compound was prepared for the eventual application in ceramic thin-film materials, the solid-state motif is of particular interest. Since aromatic compounds have a higher C:H ratio than aliphatic compounds, aromatics have a propensity to maximize van der Waals C,C interactions in the crystal lattice via close-packing of phenyl groups.[9] Due to the steric congestion introduced by the bulky *tert*-butyl groups as well as multiple hydrogen-bonding groups of the TRIS-triol, we were curious as to how this compound is arranged in the unit cell. The tridendate ligand shows an offset stacking arrangement of the *tert*-butylbenzene rings where the aromatic contact distance along the z-axis between phenyl rings was determined at 3.19 Å. This intermolecular distance along the z-axis lies within the narrow range (3.1 Å to 3.4 Å) typically observed between two phenyl groups in the solid state.

In summary, this method provides a convenient route to various aliphatic and aromatic TRIS carboxamides without side reactions, and thus obviates the need to protect hydroxylfunctionality prior to the amide-coupling reaction.[10,11] Such advantages in the use of EEDQ over DCC coupling conditions are possible since the reactive intermediate, a mixed anhydride forms slowly while its consumption by the amine is fast.[2e] Tables 1 and 2 indicate the versatility of this reaction and the yields obtained during this study. Lastly, the facility and mild conditions of the reaction make it suitable for large scale preparations.

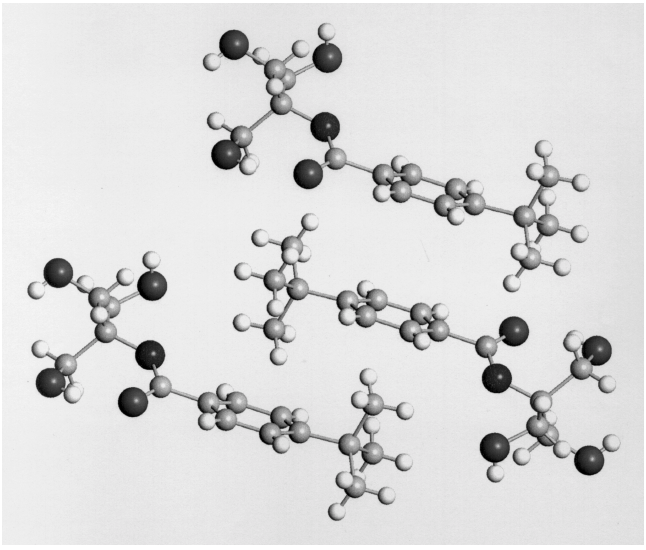


Figure X-Ray Structuere of *N*-tris(hydroxymethyl)methyl-4-*tert*-butylbenzenecarboxamide

All experiments were conducted under N_2. All glassware was washed with acetone and dried. TLC was performed using JT Baker pre-coated hard layer silica gel plates and/or Whatman adsorption silica gel plates: 60Å, F254, 2.50 mm thickness. ^1H and ^{13}C NMR

spectra were recorded on a JEOL Eclipse 300 MHz NMR. The chemical shifts for the ^{1}H spectra are reported in ppm on the δ scale from TMS internal reference. IR spectra were recorded on a Perkin-Elmer FT/IR-1710 spectrophotometer. Melting points are uncorrected. Elemental analyses were obtained from Sandia National Laboratory using a CHNS/O analyzer.

N-Tris(hydroxymethyl)methylhexanecarboxamides; General Procedure

The appropriate carboxylic acid (1.0 g, 8.6 mmol) and an equivalent amount of TRIS (2.08 g, 17.17 mmol), EEDQ (3.2 g, 12.9 mmol), and pyridine (50 mL) were introduced to a 100 mL round-bottom flask, equipped with a Dean–Stark receiver and condenser. The mixture was heated and allowed to reflux (5 h). The solution was concentrated by rotary evaporation and the remaining pyridine was removed under high vacuum. The remaining solid was washed and filtered with CH_2Cl_2 (5 mL) to extract excess EEDQ. The crude product was dissolved in H_2O and extracted with Et_2O (3 × 50 mL). Rotary evaporation of Et_2O solution yielded a white solid.

N-Tris(hydroxymethyl)methylhexanecarboxamide (Table 1, Entry 1)

Yield: 57%; mp 95–100 °C.

^{1}H NMR (300 MHz, CD_3COCD_3): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 1.3 (m, 4 H), 1.58 (m, 2 H), 2.25 (t, *J* = 7.4 Hz, 2 H), 3.6 (s, 6 H), 6.8 (s, 1 H).

^{13}C NMR (75 MHz, CD_3COCD_3): δ = 13.4, 22.3, 25.4, 31.2, 36.3, 62.4, 174.8.

IR (KBr): ν = 1602, 2922, 3273 cm^{-1}.

Anal. calcd for $C_{10}H_{21}NO_4$: C 54.78, H 9.65, N 6.38. Found: C 54.69, H 9.60, N 6.40.

N-Tris(hydroxymethyl)methyldodecanecarboxamide (Table 1, Entry 2)

Yield: 78%; mp 106–109 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 6.3 Hz, 3 H), 1.24 (s, 16 H), 1.47 (m, 2 H), 2.12 (t, *J* = 7.2 Hz, 2 H), 3.51 (d, *J* = 5.8 Hz, 6 H), 4.75 (t, *J* = 5.8 Hz, 3 H), 7.08 (s, 1 H).

^{13}C NMR (75 MHz, CD_3COCD_3): δ = 14.5, 22.7, 25.9, 29.5, 31.9, 36.4, 61.4, 62.8, 174.4.

IR (KBr): ν = 1620, 2919, 3284 cm^{-1}.

Anal. calcd for $C_{16}H_{33}NO_4$: C 63.34, H 10.96, N 4.60. Found: C 63.44, H 10.71, N 4.72.

N-Tris(hydroxymethyl)methylcyclohexanecarboxamide (Table 1, Entry 3)

Yield: 67%; mp 165–170 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.34 (m, 5 H), 1.79 (m, 5 H), 2.25 (m, 1 H), 3.72 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.4, 25.6, 29.5, 45.5, 61.8, 178.9.

IR (KBr): ν = 1646, 2919, 3284 cm^{-1}.

Anal. calcd for $C_{11}H_{21}NO_4$: C 57.40, H 8.75, N 6.08. Found: C 57.26, H 8.95, N 6.15.

N-Tris(hydroxymethyl)methyl-1-adamantanecarboxamide (Table 1, Entry 4)

Yield: 45%; mp 193–195 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.7 (m, 12 H), 1.97 (s, 3 H), 3.49 (s, 6 H), 4.9 (br, s, 3 H), 6.39 (s, 1 H).

^{13}C NMR (75 MHz, pyridine-d_5): δ = 28.5, 36.8, 39.7, 40.8, 58.4, 64.7, 180.6.

IR (KBr): ν = 1514, 2906, 3377 cm^{-1}.

Anal. calcd for $C_{15}H_{25}NO_4$: C 63.58, H 8.89, N 4.94. Found: C 63.01, H 8.70, N 5.58.

trans-*N*,*N*'-Bis[tris(hydroxymethyl)methyl]-1,4 cyclohexanedicarboxamide (Table 1, Entry 5)

Yield: 47%; mp 238–239 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.31 (m, 4 H), 1.74 (d, *J* = 7.2 Hz, 4 H), 2.18 (s, 2 H), 3.51 (d, *J* = 5.5 Hz, 12 H), 4.75 (t, *J* = 5.8 Hz, 6 H), 7.05 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.2, 36.8, 64.7, 70.7, 76.5, 169.7.

IR (KBr): ν = 1601, 1648, 2922, 3320 cm^{-1}.

Anal. calcd for $C_{16}H_{30}N_2O_8$: C 50.79, H 7.99, N 7.40. Found: C 50.90, H 7.90, N 7.45.

cis-*N*,*N*',*N*"- Tris[tris(hydroxymethyl)methyl]-1,3,5-cyclohexanetricarboxamide (Table 1, Entry 6)

Yield: 30%; mp 198–204 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.4 (m, 3 H), 1.75 (m, 3 H), 2.3 (m, 3 H), 3.52 (s, 18 H), 4.75 (br, s, 9 H), 7.0 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 32.5, 61.2, 62.5, 176.2.

IR (KBr): ν = 1648, 2922, 3406 cm^{-1}.

Anal. calcd for $C_{21}H_{39}N_3O_{12}$: C 47.99, H 7.48, N 7.99. Found: C 47.10, H 7.48, N 7.30.

N-Tris(hydroxymethyl)methyl-4-*tert*-butylbenzenecarboxamide (Table 2, Entry 1)

Yield: 57%; mp 139–142 °C.

^{1}H NMR (400 MHz, CD_3COCD_3): δ = 1.32 (s, 9H), 3.77 (d, *J* = 5.5 Hz, 6H), 4.57 (t, *J* = 5.5 Hz, 3H), 7.33 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, CD_3SOCD_3): δ = 31.5, 35.1, 61.1, 63.1, 125.5, 127.7, 133.0, 154.5, 167.8.

IR (KBr): ν = 772, 1636, 2946 cm^{-1}.

Anal. Calcd for $C_{15}H_{23}O_4N$: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 2, Entry 2)

Yield: 72%; mp 147–148 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.83 (d, *J* = 6 Hz, 6 H), 4.52 (t, *J* = 6.4 Hz, 3 H),), 7.3 (s, 1 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.50 (t, *J* = 7.3 Hz, 2 H), 7.73 (d, *J* = 8.8 Hz, 2 H), 7.77 (d, *J* = 8.6 Hz, 2 H), 7.9 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, CD_3COCD_3): δ = 63.4, 63.5, 127.8, 128.0, 128.8, 129.0, 129.9, 134.7, 140.8, 145.0, 168.7.

IR (KBr): ν = 742, 1641, 2946 cm^{-1}.

Anal. calcd for $C_{17}H_{19}O_4N$: 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 2, Entry 3)

Yield: 72%; mp 147–153 °C.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.38 (s, 9 H), 3.93 (d, *J* = 5.5 Hz, 12 H), 8.03 (d, *J* = 4.9 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 30.2, 34.7, 61.4, 62.8, 122.9, 127.3, 135.1, 152.1, 169.4.

IR (KBr): ν = 1049, 1646, 2959 cm^{-1}.

Anal. calcd for $C_{20}H_{32}N_2O_4$: 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 2, Entry 4)
Yield: 57%; mp 158–164 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.68 (d, *J* = 5.8 Hz, 12 H), 4.77 (t, *J* = 5.8 Hz, 6 H), 7.11 (d, *J* = 8.5 Hz, 4 H), 7.28 (s, 2 H), 7.86 (d, *J* = 8.8 Hz, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 60.9, 63.2, 118.8, 130.2, 131.2, 158.9, 167.0.

IR (KBr): ν = 765, 1627, 2880 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 2, Entry 5)**
Yield: 58%; mp >300 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.32 (s, 4 H), 3.72 (d, *J* = 3 Hz, 18 H), 4.73 (t, *J* = 5.8 Hz, 9 H), 7.54 (s, 3 H), 8.26 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 60.8, 63.5, 123.9, 135.9, 167.1.

IR (KBr): ν = 801, 1652, 2961 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.

X-Ray Structure Determination of *N*-Tris(hydroxymethyl)methyl-4-*tert*-butylbenzenecarboxamide (Table 2, Entry 1)
A colorless crystal was mounted on a thin glass fiber using fluorolube. The crystal, which was mounted from a pool of silicone oil, was immediately placed under a liquid N_2 stream on a Bruker AXS diffractometer. The lattice parameters were optimized from a least-squares calculation on 106 carefully centered reflections. Lattice determination and data collection were carried out using SMART Version 5.054 software. The compound, $C_{15}H_{22}NO_4$, crystallizes in triclinic space group P-1; a = 6.2515(9), b = 8.6633(12), c = 14.045(2) Å, β = 91.186(3)°. At Z = 2, V = 740.84(18) Å^3 and FW = 280.34 the calculated density is ρ = 1.257 Mg/m^3. The structure was solved by means of direct methods using SHELXTL 5.1 software. A total number of 4679 reflections were collected at 168(2)K. R_{int} = 0.016(3) MoKα radiation (λ = 0.71073 Å), μ = 0.091 mm^{-1} no absorption correction. 3241 reflections with $I>2\sigma(I)$ were used in the final full-matrix least squares process. The final refinement included anisotropic thermal parameters on all non-hydrogen atoms and converged to R1 = 0.0518 and ($R2_w$ = 0.1423, $w = 1/\sigma^2$ F). Hydrogen atoms were fixed in positions of ideal geometry and refined within the XSHELL software. These idealized hydrogen atoms had there isotropic temperatures fixed at 1.2 or 1.5 times the equivalent isotropic U of the C atoms they were bonded prior to the final refinement.

Acknowledgement

Support for this project was provided by the Sandia-University Research Project contract. M.D.H. wishes to thank Ms. Sara C. Vick and Dr. Mark A. Rodriguez for obtaining the crystal structure data and Dr. Timothy J. Boyle of the Advanced Materials Laboratory for the collaborative effort that this project has initiated.

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Article Identifier:
1437-210X,E;2000,0,10,1435,1438,ftx,en;M03699SS.pdf