Synthesis of 3-Amino-1-carboxy-*o*-carborane and an Improved, General Method for the Synthesis of All Three C-Amino-C-carboxycarboranes

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Amino acids of the polyhedral carboranes have potential applications in boron neutron capture therapy and in other areas of bioorganic chemistry, but simple, general methods for their synthesis are nonexistent. A general method for synthesis of C-amino-C-carboxy derivatives of *o*-, *m*-, and *p*-carborane is reported, starting from their respective monoacids and proceeding through nucleophilic attack by an alcohol on the intermediate C-isocyanates. Deprotection of the resulting carbamates provides a simple method for access to the C-amines. Alternatively, the C-isocyanates can be isolated for further reactions. Carbonylation of the carbamates at the remaining carboranyl CH results in high-yield production of the carbamate-protected amino acid. Another related method for the high-yield preparation of the isomeric 3-amino-1-carboxy-*o*-carborane is also described which makes available for the first time all four reasonably accessible members of the series.

Introduction

Biomedical applications of the unique structural and chemical properties offered by polyhedral carboranes have received increasing attention over the past decade and require the investigation of synthetic methods for adding functional substituents to the carborane cage. In particular, the recent resurgence of interest in boron neutron capture therapy (BNCT) has created a need for heterobifunctional carborane derivatives bearing water-solubilizing groups whose deprotection chemistries can be efficiently manipulated.[1] Carboranes having dissimilar polar functional groups on the carbons or borons of the icosahedral cage might be water-soluble and possible tumor localizers in themselves, but could be even more important synthons for attachment to known tumor seekers such as porphyrins.[2] Additionally, the structural rigidity of the cage and its unique spatial and chemical features might be put to good use in peptidomimetic chemistry. Unfortunately, heterobifunctional carboranes are exceedingly rare in the chemical literature and general methods for their preparation are essentially nonexistent. We have recently reported the synthesis of three isomeric C-amino-C-carboxy members (Figure 1, compounds **1**−**3**) of the dicarbadodecahedral carborane family by three different routes.[3] In this work we report a single, better yielding general method applicable to all three amino acids, and a very efficient method for synthesis of a fourth isomer (**4**), the 3-amino-1-carboxy amino acid of *o*-carborane.

A general method for high-yield synthesis of amino acids **1**−**3** from commercially available precursors is desirable both to avoid different reaction conditions and starting materials for each and to increase the yields of valuable product, which varied from ∼70% for Boc-protected **1** to 87% for Boc-protected **3**. High-yield syntheses from readily available isotopically enriched precursors are particularly crucial in the preparation of ^{10}B enriched compounds for the ultimate use in BNCT. Currently, the only commercially available ^{10}B enriched starting materials for such compounds are *o*-carborane and decaborane ($B_{10}H_{14}$). As a consequence, we sought a general method starting with *o*-carborane since this compound can be thermally isomerized to *m*- and *p*-carborane should the need arise.

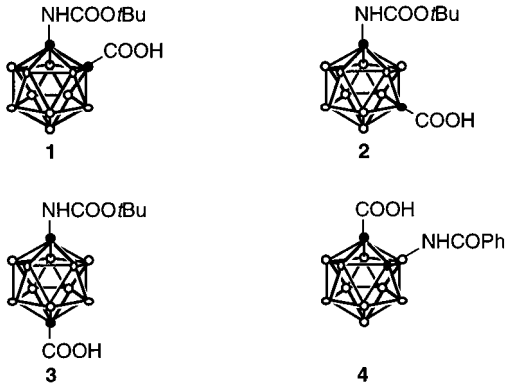

Figure 1. Structures of four isomeric N-protected carborane amino acids.

Experimental Section

Carboranes were purchased from either Astor Ltd. (Vancouver, Canada) or Dexsil Corp. (Hamden, CT) and were purified by sublimation before use. Anhydrous ether was purchased from Fisher and used as such. *n*-BuLi (1.6 M solution in hexane) and all other reagents and chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI). Flash chromatography was performed on Merck Silica gel 60 (230−400 mesh). Analytical thin-layer chromatography was carried out on Alltech silica gel plates, and 0.5% (w/v) $PdCl_2$ in 10% concentrated HCl/acetone solution was used as visualizing agent upon heating. All reactions were carried out under high-purity argon unless otherwise indicated. Melting points were determined on Fisher Johns melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 300 MHz and used tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were recorded at 75.5 MHz and used solvent as the internal standard.

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1,2-Dicarba-*closo*-dodecaborane-1-carboxylic Acid (6). *o*-Carborane (**5**) (10.0 g, 69.4 mmol) was dissolved in ether (950 mL) at room temperature in a dry 1 L round-bottom flask equipped with a magnetic stir bar and cooled to −78 °C under argon atmosphere. To the stirred solution *n*-BuLi (48.0 mL, 76.8 mmol, 1.6 M in hexanes) was added slowly over 20 min, and stirring was continued for another 20 min at the same temperature. Dry ice (20−25 g) was crushed into small pieces and was added immediately to the reaction mixture, which was stirred for an additional 1 h and then warmed to room temperature. Excess ether was removed by rotary evaporator at room temperature. Water (300 mL) was added to the reaction product, and unreacted *o*-carborane was removed by extracting with hexanes (2 × 150 mL). The aqueous layer was acidified with 3 N HCl and the desired product extracted with hexanes (4 × 150 mL) from the acidified solution. Combined extracts were dried ($MgSO_4$) and concentrated to give 12.4 g (95%) of the desired *o*-carborane monocarboxylic acid (**6**): mp 150−151 °C [lit.[4] 150−151 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35−3.50 (br, B−H, 10H), 4.03 (s, 1H), 11.10 (1H, COOH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 56.71 (carborane CH), 67.57 (carborane C), 166.90 (COOH). IR (KBr): 3100−3400 (br, O−H), 3080 (carborane C−H), 2588 (B−H), 1723.8 (C═O) cm^{-1}.

1,2-Dicarba-*closo*-dodecaborane-1-carbonyl Chloride (7). Dry toluene (60 mL) and *o*-carborane monocarboxylic acid (**6**) (13.6 g, 72.6 mmol) were placed in a two-neck 100 mL round-bottom flask equipped with a short path distillation head and a side arm under an argon atmosphere. Phosphorus pentachloride (15.7 g, 75.5 mmol) was added through the side arm over a period of 1 h. The mixture was stirred for 30 min and toluene and phosphorus oxychloride were co-distilled off at 110 °C at atmospheric pressure. The flask was allowed to cool to room temperature after which the house vacuum was applied to remove any traces of volatile material. The flask and distillation head were wrapped with aluminum foil for insulation, and the house vacuum was replaced with a high-vacuum pump. The acid chloride product (**7**) was distilled under vacuum (5 mm, 120 °C) to give 14.0 g of pure acid chloride (93.4%): mp 39−40 °C [lit.[5] mp 39−41 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50−3.50 (br, 10 B−H), 4.12 (s, 1H, carborane C−H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 57.22 (carborane CH), 74.19 (carborane C), 164.45 (C═O).

1,2-Dicarba-*closo*-dodecaborane-1-isocyanate (8). Dry toluene (15 mL) and 1,2-dicarba-*closo*-dodecaborane-1-carbonyl chloride (**7**) (1.15 g, 5.56 mmol) were placed under an argon atmosphere into a two-neck 25 mL round-bottom flask equipped with a condenser. Excess trimethylsilyl azide (1.6 mL, 16 mmol) was added to the solution by syringe and the mixture refluxed under argon for 5 h. After cooling to room temperature, the condenser was replaced with a short path distillation head and toluene removed by distillation at atmospheric pressure. The product was then distilled under high vacuum (2 mm, 75−76 °C) to give 0.850 g of the isocyanate (**8**) (82.6%): mp 82−85.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20−3.50 (br, 10 B−H), 3.88 (s, 1H, carborane CH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 59.95 (carborane C−H), 62.51 (carborane C), 126.33 (N═C═O). IR (neat): 3067.1 (m, carborane C−H), 2587.8 (s, B−H), 2258.5 (s, N═C═O) cm^{-1}. HRMS for $C_3{}^{10}B_2{}^{11}B_8H_{11}NO$. Calcd: 184.1766. Found: 184.1759 (Δ = 3.8 ppm).

1-[((*tert*-Butyloxy)carbonyl)amino]-1,2-*closo*-dodecaborane (9). A mixture of 1,2-dicarba-*closo*-dodecaborane-1-carbonyl chloride (**7**) (2.51 g, 12.2 mmol) and trimethylsilyl azide (2.0 mL, 20 mmol) in dry toluene (25 mL) was refluxed for 1 h. After cooling to room temperature, *tert*-butyl alcohol (10 mL) was added by syringe and the mixture stirred for several minutes. It was again refluxed for 1 h. Excess toluene and *tert*-butyl alcohol were removed under reduced pressure with a rotary evaporator. The crude product was dissolved in ethyl acetate (100 mL) and washed with water. The ethyl acetate layer was separated, dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane: ethyl acetate, 90:10) to give 2.90 g of 1-(((*tert*-butyloxy)carbonyl)-amino)-1,2-dicarba-*closo*-dodecaborane (**9**) (92%): mp 136−138° C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43 (s, 9H), 1.40−3.50 (br, 10 B−H),4.60 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.09 (methyls), 61.29 (carborane CH), 79.75, 82.98, 151.60 (C═O) IR (KBr): 3333.1 (s, N−H), 3092.3 (s, carborane C−H), 2612.9, 2607.1, 2578.5, 2567.4 (s, B−H), 1702.9 (s, CO) cm^{-1}. LRMS (*m*/*z*): 258.2 (M − H), 202.2, 184.2, 154.2, 141.2, 57.1. HRMS for $C_7H_{21}{}^{10}B_2{}^{11}B_8NO_2$. Calcd: 259.3602. Found: HRMS $C_7H_{21}{}^{10}B_2{}^{11}B_8NO_2$−H. HRMS for $C_7H_{20}{}^{10}B_2{}^{11}B_8NO_2$. Calcd: 258.2497. Found: 258.2507 (Δ = 3.8 ppm).

1-[((*tert*-Butyloxy)carbonyl)amino]-1,2-dicarba-*closo*-dodecaborane-2-carboxylic acid (1). *n*-BuLi (4.20 mL, 6.73 mmol; 1.6 M in hexane) was slowly added to a stirred solution of 1-(((*tert*-butyloxy)-carbonyl)amino)-1,2-dicarba-*closo*-dodecaborane (**9**) (0.758 g, 2.92 mmol) in dry ether (30 mL) at room temperature. After stirring at room temperature for 10 min, the mixture was refluxed for 2 h. The resulting reaction mixture was cooled to −78 °C, and dry CO_2 was then added. The reaction mixture was allowed to warm to room temperature and quenched with saturated NaCl. Excess ether was removed under reduced pressure, water (100 mL) was added, and the mixture was extracted with hexanes (3 × 100 mL). The aqueous layer was acidified with 1% diluted HCl at 0 °C. Solid product was obtained upon filtration and dried to give 0.850 g of protected amino acid (**1**) (96%): mp 194−197 °C with sublimation. ^{1}H NMR (300 MHz, $CDCl_3$ + 2 drops of CD_3OD): δ 1.45 (s, 9H), 1.40−3.50 (br, 10H, B−H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.43, 82.12, 85.03, 85.90, 154.31, 163.64. IR (KBr): 3600−3000 (br, O−H), 2585.9 (s, B−H), 1684.4 (CO), 1647.3 (CO) cm^{-1}. HRMS for $C_8{}^{10}B_2{}^{11}B_8H_{21}N_1O_4$. Calcd: 303.2473. Found: HRMS $C_8{}^{10}B_2{}^{11}B_8H_{21}N_1O_4$−COOH. HRMS for $C_7{}^{10}B_2{}^{11}B_8H_{20}N_1O_2$. Calcd: 258.2497. Found: 258.2481 (Δ = 6.1 ppm).

1-[((*tert*-Butyloxy)carbonyl)amino]-1,7-*closo*-dodecaborane-7-carboxylic Acid (2). This compound was prepared in a fashion similar to the *ortho* isomer: mp 192−194 °C. ^{1}H NMR (300 MHz, $CDCl_3$ + 2−3 drops of CD_3OD): δ 0.88−3.80 (br, 11H, B−H) 1.45 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 27.11, 29.22, 81.25, 88.40, 94.31, 154.09, 168.43. IR (KBr): 3600−2400 (br, O−H), 2619.9 (B−H), 1696.8, 1628.9 cm^{-1}. LREI$^+$ (*m*/*e*): 303.3 (M$^+$), 273.2, 248.2, 233.2, 215.2, 187.2, 170.2, 158.2, 143.2, 126.1, 98.1, 57.1. HRMS for $C_8H_{21}{}^{10}B_2{}^{11}B_8N_1O_4$. Calcd: 303.2473. Found: 303.2420 (Δ = 17.4 ppm). Anal. Calcd for $C_8H_{21}B_{10}N_1O_4$: C, 31.67; H, 6.98; N, 4.62. Found: C, 31.06; H, 7.09; N, 4.42.

1-[((*tert*-Butyloxy)carbonyl)amino]-1,12-*closo*-dodecaborane-12-carboxylic Acid (3). This compound was prepared in a fashion similar to the *ortho* isomer: mp 178−180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10−3.5 (br, B−H), 1.30 (s, 9H). ^{13}C NMR (75.5 MHz, CD_3OD): δ 28.27, 75.35, 81.43, 90.07, 153.93, 165.69. IR (KBr): 2400−3600 (br, O−H), 2930.3, 2860.0, 2620.4 (B−H), 1721.2 (C═O), 1457.1, 1375.4, 1285.2 cm^{-1}. LRMS (*m*/*z*): 303.2 (M$^+$), 247.2, 203.2, 186.2, 157.2, 142.2, 125.1, 114.1, 57.1. HRMS for $C_8H_{21}{}^{10}B_2{}^{11}B_8N_1O_4$. Calcd: 303.2473. Found: 303.2491 (Δ = 5.9 ppm). Anal. Calcd for $C_8H_{21}B_{10}N_1O_4$: C, 31.67; H, 6.98; N, 4.62. Found: C, 31.82; H, 6.89; N, 4.81.

1-Amino-12-[(benzyloxy)carbonyl]-1,12-dicarba-*closo*-dodecaborane (11). A mixture of 1-(((*tert*-butyloxy)carbonyl)amino)-1,12-dicarba-*closo*-dodecaborane-12-carboxylic acid (**3**) (0.600 g, 1.98 mmol) and benzyl bromide (0.415 g, 2.42 mmol) in acetonitrile (50 mL) in the presence of Cs_2CO_3 (0.700 g, 2.14 mmol) was refluxed for 18 h. Excess acetonitrile was removed under reduced pressure to afford clean benzyl ester (**10**) in quantitative yield. The doubly protected amino acid (**10**) was then treated with trifluoroacetic acid (4 mL) in dichloromethane (10 mL) and stirred for 24 h. After evaporation of the solvent, the salt was taken into ethyl acetate (50 mL) and treated with triethylamine (2 mL) and water (10 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. Crude product was purified through a short silica gel column using a hexane/ethyl acetate/triethylamine mixture (95:5:1) as the eluent to afford free amine (**11**) (0.541 g) in 93% yield: mp 75−76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30−3.8 (br, 10H), 3.56 (s, 2H, NH), 5.03 (s, 2H), 7.20−7.50 (m, 5H). HRMS for $C_{10}{}^{10}B_2{}^{11}B_8H_{19}O_2N_1$. Calcd: 293.2418. Found: 293.2392 (Δ = 8.8 ppm).

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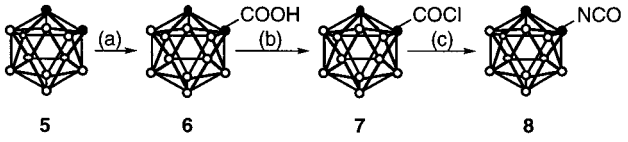
3-Amino-1,2-dicarba-*closo*-dodecaborane (12). A 500 mL three-neck round-bottom flask was charged with *o*-carborane (**5**) (10.0 g, 69.4 mmol) and a stir bar under argon atmosphere. Liquid ammonia (350 mL) was collected in the same flask using a dry ice−acetone ammonia condenser. Sodium metal (3.35 g, 145 mmol, 2.09 equiv) was added slowly through a side arm over 30 min At the end of the addition of the sodium metal, the ammonia solution turned a deep blue color due to excess sodium metal. Potassium permanganate (24.0 g, 145 mmol) was added slowly through the side arm using a protective blast shield and stirred for another 2 h. (**CAUTION**: This reaction is potentially explosive and should be carried out with protection and without delay after the 2 h stirring time. In one instance where the reaction was left unoxidized overnight, a violent explosion took place, destroying the apparatus.) To destroy excess sodium in the reaction mixture, *tert*-butyl alcohol (20 mL) was then added cautiously followed by 50% aqueous *tert*-butyl alcohol (20 mL) and then by water (10 mL). Excess ammonia was allowed to evaporate. MnO_2 was filtered through a Buchner funnel with the aid of ethyl acetate (500 mL). The ethyl acetate solution was dried over sodium sulfate, and solvents were removed under reduced pressure. The crude product was taken into 5 N HCl (100 mL) and stirred overnight. Unreacted *o*-carborane was extracted from the acidic solution with hexanes and the aqueous solution neutralized with 2 N NaOH solution to provide pure 3-amino-1,2-dicarba-*closo*-dodecaborane (**12**) as a white solid (9.27 g, 84%): mp 214−216 °C [lit.[6] 218−219 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1−3.56 (br, B−H, 10H), 4.32 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 58.51. IR (KBr): 3474, 3411 (NH), 3063 (cage C−H), 2580 (B−H) cm^{-1}. Mass LREI (*m*/*z*): 159.2, 142.2. HRMS for $C_2{}^{10}B_2{}^{11}B_8H_{13}N_1$. Calcd: 159.2051. Found: 159.2051 (Δ = 0 ppm).

3-(Benzoylamino)-1,2-dicarba-*closo*-dodecaborane (13). Benzoyl chloride (2.18 g, 15.5 mmol) was added over 5 min via syringe to a solution of 3-amino-*o*-carborane (**12**) (2.00 g, 12.6 mmol) in CH_2Cl_2 (50 mL), pyridine (2.31 g, 27.5 mmol, excess), and a catalytic amount of 4-DMAP (60 mg) at room temperature. After the addition was complete, the reaction mixture was stirred for another 2 h. The solvent was removed, and residue was dissolved in ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ and then with water. The crude product was passed through silica gel to obtain 3.05 g of white crystalline-protected amine product (**13**) (92%): mp 182−183 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.00−3.5 (br, B−H, 9H), 4.90 (s, 2H), 7.31−7.92 (m, 5H). ^{13}C (acetone-d_6, 75.5 MHz): δ 57.38, 128.38, 129.06, 132.64, 135.08, 171.04. IR (KBr): 3291.2 (N−H), 3079.8 (C−H), 3054.9 (carborane CH), 2613, 2563 (B−H), 1655.9 (C═O) cm^{-1}. LREI (*m*/*z*): 262.4, 105.1, 77.1. HRMS for $C_9{}^{10}B_2{}^{11}B_8H_{17}NO$ (HRMS $C_9{}^{10}B_2{}^{11}B_8H_{17}NO$−H). Calcd: 262.2235. Found: 262.2227 (Δ = 3.0 ppm). Anal. Calcd for $C_9{}^{10}B_2{}^{11}B_8H_{17}NO$: C, 40.72; H, 6.46; N, 5.28. Found: C, 40.64; H, 6.75; N, 5.20.

3-(Benzoylamino)-1-(hydroxycarbonyl)-1,2-*closo*-dodecaborane (4). *n*-BuLi (3.00 mL, 4.80 mmol; 1.6 M in hexane) was added slowly to a stirred solution of 3-(benzoylamino)-1,2-dicarba-*closo*-dodecaborane (**13**) (0.500 g, 1.91 mmol) in dry ether (75 mL) at −78 °C and then warmed to reflux temperature. After stirring at reflux temperature for 90 min, the reaction mixture was cooled to −78 °C. Crushed dry CO_2 was then added and the mixture allowed to warm to room temperature. The reaction was quenched with saturated NaCl and extracted with CH_2Cl_2 followed by acidification with 50% diluted HCl at 0 °C and saturated with solid NaCl. The solid product was filtered off to give 0.400 g of pure benzoyl-protected amino acid (**4**) (85%): mp 174−175 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1−3.6 (br, B−H), 5.22 (s, 1H), 7.26−7.77 (m, Ar−H, 5H). ^{13}C (acetone-d_6, 75.5 MHz): δ 57.24, 59.86, 127.32, 127.75, 129.89, 133.59, 134.86, 160.52, 170.62. IR (KBr): 3600−3000 (br, O−H), 3322 (N−H), 3092 (carborane C−H), 2613 (s, B−H), 1730 (C═O), 1600 (Ar) cm^{-1}. HRMS for $C_{10}{}^{10}B_2{}^{11}B_8H_{17}NO_3$. Calcd: 306.2133. Found: $C_{10}{}^{10}B_2{}^{11}B_8H_{17}NO_3$−H, 306.2132. Anal. Calcd for $C_{10}B_{10}H_{17}NO_3$: C, 39.08; H, 5.58; N, 4.56. Found: C, 39.95; H, 5.71; N, 4.51.

3-Amino-1-(hydroxycarbonyl)-1,2-*closo*-dodecaborane Hydrochloride (14). 3-(*N*-Benzoylamino)-1-(hydroxycarbonyl)-1,2-*closo*-dodecaborane (**13**) (4.09 g, 13.0 mmol) was added to 6 N HCl (20 mL) and heated at reflux for 36 h. The reaction mixture was cooled to 0 °C, and the precipitated benzoic acid was filtered off. The filtrate was concentrated to dryness to afford 2.61 g of the hydrochloride (**14**) (92%) as a pale yellow solid: mp 260 °C (dec.). ^{1}H NMR (acetone-d_6, 300 MHz): δ 1−3.6 (br, B−H), 4.81 (s, 1H), 6.28 (s, 1H). Mass LREI (*m*/*z*): 202.4, 173.2, 159.2, 149.0, 132.0, 115.1. IR (KBr): 2800−3600 (br, O−H), 2538 (B−H), 1674 (C═O) cm^{-1}.

Scheme 1



Reagents: (a) (i) n-BuLi, -78° C; (ii) CO_2; (iii) H^+; (b) PCl_5/ toluene/Δ; (c) $(CH_3)_3SiN_3$/toluene/Δ

Results and Discussion

The general reaction sequence began with a carborane C-monocarboxylic acid, as shown in Scheme 1 with *o*-carborane (**5**). The monoacid (**6**) is an important reactive synthon in its own right and has been prepared by monolithiation of (**5**) in benzene followed by carbonylation with CO_2 with quite variable yields of the desired product (**6**), usually contaminated with some diacid.[4] Reaction of the monolithio derivative with CO_2 in diethyl ether or THF generally gives only the diacid and unreacted starting material, probably through a disproportionation reaction. However, by carrying out the lithiation in diethyl ether at −78 °C under high-dilution conditions, the monoacid (**6**) can be obtained in reproducibly high yields (≥90%) even on a 10 g scale. Preparation of the monoacids of *m*- and *p*-carborane, the precursors of amino acids **2** and **3**, by this method is similarly successful and efficient.

The next step in the general method was conversion of the C-monoacid into the C-monoisocyanate, as with **6** into **8**. This was carried out by the procedure of Washburne and Peterson in which an acid chloride is treated with trimethylsilyl azide in refluxing toluene.[7] This Curtius rearrangement of carborane 1-carbonyl azide gave an essentially quantitative yield of 1-isocyanato-*o*-carborane (**8**) in solution as indicated by thin-layer chromatography and ^{13}C NMR. Scobie and Threadgill have reported a similar in situ generation of isocyanate (**8**) and its reaction with 1 and 2° alcohols to form carbamates,[8] and Quintana and co-workers have reported that even 1-(isocyanatomethyl)-*o*-carborane is too reactive to permit direct characterization.[9] In contrast, we found this interesting and useful isocyanate can be isolated in high yield by removal of the solvent and vacuum distillation of the resulting oil to give a white crystalline solid. Evidence of the highly electrophilic nature of this compound is revealed by its ^{13}C spectrum. The highly deshielded isocyanate carbon has a chemical shift value of 126.33 ppm as compared to 123.59 ppm for 1-(isocyanatoethyl)-*o*-carborane and 123.11 ppm for 1-(isocyanatopropyl)-*o*-carborane.[9]

When this modified Curtius reaction was carried out with added *tert*-butyl alcohol, the intermediate isocyanate collapsed into a Boc-protected amine such as **9**, which can then be subjected to further transformations as illustrated in Scheme 2.

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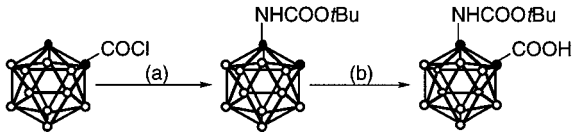
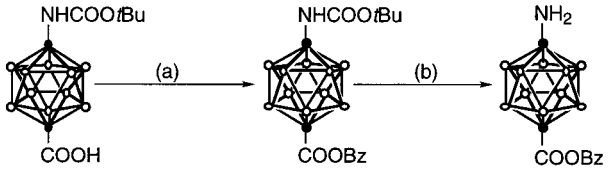
Scheme 2



Reagents: (a) $(CH_3)_3SiN_3/\Delta/t$-BuOH; (b) (i) n-BuLi; (ii) CO_2; (iii) H^+

Scheme 3



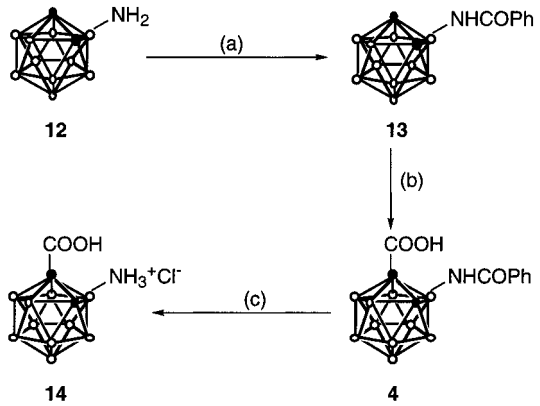
Reagents: (a) $Cs_2CO_3/PhCH_2Br/CH_3CN/\Delta$; (b) (i) TFA/CH_2Cl_2; (ii) TEA/CH_2Cl_2

For example, a carboxyl group was added to the remaining unsubstituted carborane carbon by treatment of the Boc-amine with *n*-butyllithium followed by CO_2 resulting in protected amino acid **1**. The overall yield of **1** from *o*-carborane (**5**) using this procedure was ≥90%, and the method was equally applicable to the synthesis of *m*-carborane (yield = 92%) and *p*-carborane (yield = 94%) Boc-protected amino acid derivatives of **2** and **3**, respectively. The physical and spectral properties of these Boc-protected amino acids were identical to those previously reported by us.[3] By replacing *tert*-butyl alcohol with 9-fluorenylmethanol, the corresponding Fmoc-protected amines are also available and, in principle, should be convertible into the Fmoc-protected amino acids by similar processes.

By straightforward manipulation of protecting groups, as in Scheme 3, the N-protected *p*-amino acid (**3**) was readily converted to the C-protected free amine (**11**). Treatment of **3** with Cs_2CO_3 followed by benzyl bromide gave doubly protected amino acid **10** whose amine group was exposed by removal of the Boc group with trifluoroacetic acid to give the desired free amine **11**. Through the use of solution-phase coupling techniques, homopolymers of **3** with 2, 3, 6, and 12 carborane cages have been prepared and will be described elsewhere. Due to the significantly decreased base strength of the amine, attempts to prepare similar homopeptide polymers of **1** have been unsuccessful.

The modified Curtius reaction to the carbamate-protected amine procedure also provides an extremely convenient method for the preparation of C-monoaminocarboranes by simple acid deprotection of the Boc-protected amine intermediate. For example, treatment of **9** with trifluoroacetic acid in CH_2Cl_2 produced 1-amino-*o*-carborane in nearly quantitative yield. C-amino-*o*- and *m*-carboranes have previously been synthesized from the acyl azides[10] and by reduction of the nitroso analogues with $Al_2Cl_3H_3$,[11] but our procedure is much more convenient and gives much higher yields. In principle, it could also be extended to the preparation of homologous (aminoalkyl)-carboranes by using the corresponding alkyl acids, a more convenient method than one recently described which requires the preparation of carboranyl phthalimides.[12]

Scheme 4



Reagents: (a) PhCOCl/pyridine/DMAP; (b) (i) n-BuLi/ether/Δ; (ii) CO_2; (iii) H^+; (c) HCl/Δ

We then turned our attention to the synthesis of **4**, which required a different strategy, as B-carboxy derivatives of *o*-carborane are unknown. The obvious starting material was 3-amino-*o*-carborane (**12**). Minor modifications of the procedure of Zakharkin et al. gave the desired amine in >90% on a 10 g scale.[13] At room temperature, this compound slowly undergoes degradation (presumably by intermolecular amine-promoted cage opening) but is stable indefinitely when stored at −10 °C. Scheme 4 illustrates its conversion into protected amino acid (**4**).

Since the N−H protons of **12** can be removed with *n*-BuLi, it was necessary to first protect the amine function. Conversion into the *N*-benzoyl amide (**13**) was accomplished in nearly quantitative yield by treatment of **12** with benzoyl chloride at room temperature in CH_2Cl_2 in the presence of pyridine and 4-(dimethylamino)pyridine (DMAP). Alternatively, the Boc amine was prepared through reaction of **12** with di-*tert*-butyl dicarbonate with a catalytic amount of DMAP in *tert*-butyl alcohol. Addition of the carboxyl function to one of the two equivalent cage carbons was then readily accomplished by lithiation (2.2 equiv in ether) and carbonylation in ether. Yields of N-protected amino acid **4** were routinely in the 90−95% range. Removal of the benzoyl group in refluxing 6 N HCl gave a ≥90% yield of the amino acid hydrochloride (**14**). A similar reaction sequence applied to the Boc-protected derivative also gave the corresponding N-protected amino acid (not shown), but in this case the yields were quite variable and never exceeded 50%.

Unlike its C-amino acid cousin (**1**), the amine group of **4** (obtained by treatment of **14** with base) exhibits behavior typical of a normal aliphatic amine nucleophile, and we are actively exploring its application as a conformationally constrained *β*-amino acid as well as attaching it to tumor seeking molecules for BNCT applications. Also in contrast to amino acids **1**−**3**, amino acid **4** exists as a pair of enantiomers which can be resolved by diastereomeric salt formation. Reports of these applications will be made at an appropriate time.

In conclusion, we have developed a new, high-yielding and general method for the preparation of C-amino-C-carboxycarboranes and a straightforward method for gaining access to one the most interesting amino acids of the series, 3-amino-1-carboxy-*o*-carborane. These new methods allow for the first time an extensive exploration of the chemistries of these important molecules. The reaction sequences also make available for

(10) Zakharkin, L. I.; Kalinin, V. N. *Zh. Obshch. Khim.* **1965**, *35*, 1882−1884.
(11) Zakharkin, L. I.; Zhigareva, G. G. *Zh. Obshch. Khim.* **1975**, *45*, 1293−1301.
(12) Wilson, J. G.; Anisuzzamen, A. K. M.; Soloway, A. H. *Inorg. Chem.* **1992**, *31*, 1955−1958.
(13) Zakharkin, L. I.; Kalinin, V. N.; Gedymin, V. V.; Dzarasova, G. S. *J. Organomet. Chem.* **1969**, *16*, 371−379.

characteriztion and reaction the 1-isocyanato-*o*-carborane and provide facile, high-yielding routes to the three isomeric C-monoamines of the dodecaboranyl carborane series.

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