Coupling of Amino Carboranes to Carboxylic Acid Containing Substrates

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The reactivity of the known amino carboranes $1-H_2NCH_2-1,2-C_2B_{10}H_{11}$ and $7-H_3N-7-CB_{10}H_{12}$ with carboxylic acid containing substrates was investigated. The reactions studied using the coupling reagent, 1,1'-carbonyldiimidazole, resulted in the preparation of a series of amides in moderate to high yield. The relative importance of this type of research resides in the fact that it allows the introduction of amino acids in close contact with the carborane cage. These compounds can constitute a new generation of substrates useful in boron neutron capture therapy. Our emphasis lies in the development of suitable synthetic schemes allowing the preparation of this type of compound. Experimental details and analytical data supporting the formulation of the prepared compounds are reported.

Introduction

Research dealing with the introduction of functionalized molecules as substituents in close contact with carborane cages has received considerable attention in recent years.¹ Interest in exploring the preparation of this type of compound is owed to the potential use of the synthesized compounds in boron neutron capture therapy (BNCT).² The traditional synthetic method used for the introduction of functionalized side chains into an o-carborane cage relies in the reaction of decaborane (14) with the suitable alkyne.³ This approach, albeit efficient, it is somewhat limited, resulting from the incompability of certain functional groups with the precursor decaborane (14) cage.⁴ Certain alkynes are known to be incompatible, resulting from unwanted side reactions with the decaborane (14) precursor. Those include alkynes which contain amines, alcohols, ketones, and carboxylic acids as part of the side chain.⁴ Therefore, alkynes bearing these functional groups cannot be used in the preparation of functionalized o-carborane cages.

The approach used in this paper is the functionalization of the known carboranes $1-H_2NCH_2-1,2-C_2B_{10}H_{11}$ and $7-H_3N-7-CB_{10}H_{12}$, which are conveniently prepared by the methods of Soloway and Knoth outlined below.^{5,6}

 $B_{10}H_{14} + HC ≡ CCH_2N(CO)_2C_6H_4 \rightarrow 1-C_6H_4(CO)_2NCH_2-1,2-C_2B_{10}H_{11} (1)$ 1-C₆H₄(CO)₂NCH₂-1,2-C₂B₁₀H₁₁ + NaBH₄ →

 $1-H_2NCH_2-1, 2-C_2B_{10}H_{11}$ (2)

$$B_{10}H_{14} + 2NaCN \rightarrow Na_2B_{10}H_{13}CN$$
 (3)

$$Na_2B_{10}H_{13}CN + H^+ \rightarrow 7-H_3N-7-CB_{10}H_{12}$$
 (4)

Equations 1 and 2 were used in the preparation of the aminomethyl *o*-carborane, and eqs 3 and 4 delineate the preparation of the amino monocarbon carborane. Furthermore, the preparation of these compounds is carried out in a single-pot reaction, without need of isolating the intermediates.

These compounds where chosen because of their ease of preparation and purification. In addition, the yield obtained from

 ⁽a) Hariharan, J. R.; Wyzlic, I. M.; Soloway, A. H. Polyhedron 1995, 14, 823-825.
(b) Hawthorne, M. F. Angew. Chem., Int. Ed. Engl. 1993, 32, 950-984.
(c) Kane, R. R.; Dreschel, K.; Hawthorne, M. F. J. Am. Chem. Soc. 1993, 115, 8853-8854.
(d) Paxton, R. J.; Beatty, R. G.; Varadarajan, A.; Hawthorne, M. F. Bioconjugate Chem. 1992, 3, 241-247.
(e) Hawthorne, M. F.; Varadarajan, A.; Knobler, C. B.; Chakrabarti, S.; Paxton, R. J.; Beatty, B. G.; Curtis, F. L. J. Am. Chem. Soc. 1990, 112, 5365-5366.
(f) Hawthorne, M. F. Pure Appl. Chem. 1991, 63, 327-334.
(g) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. Chem. Rev. 1998, 98, 1515-1562.
(h) Yang, W.; Barth, R. F.; Adams, D. M.; Soloway, A. H. Cancer Res. 1997, 57, 4333-4339.
(i) Kabalka, G. W. Expert Opin. Ther. Pat. 1998, 8, 545-551.
(j) Hawthorne, M. F. Mol. Med. Today 1998, 4, 174-181.

^{(2) (}a) Cai, J.; Soloway, A. H.; Barth, R. F.; Adams, D. M.; Hariharan, J. R.; Wyzlic, I. M.; Radcliffe, K. J. Med. Chem. 1997, 40, 3887-3896. (b) Rong, F.-G.; Soloway, A. H.; Ikeda, S.; Ives, D. H. Nucleosides Nucleotides 1997, 16, 379-401. (c) Yang, W.; Barth, R. F.; Rotaru, J. H.; Moeschberger, M. L.; Joel, D. D.; Nawrocky, M. M.; Goodman, J. H.; Soloway, A. H. Int. J. Radiat. Oncol., Biol., Phys. 1997, 37, 663–672. (d) Barth, R. F.; Yang, W.; Rotaru, J. H.; Moeschberger, M. L.; Joel, D. D.; Nawrocky, M. M.; Goodman, J. H.; Soloway, A. H. Cancer Res. 1997, 57, 1129-1136. (e) Srivastava, R. R.; Singhaus, R. R.; Kabalka, G. W. J. Org. Chem. 1997, 62, 4476-4478. (f) Miura, M.; Gabel, D.; Oenbrink, G.; Fairchild, R. G. Tetrahedron Lett. 1990, 31, 2247-50. (g) Sjoeberg, S.; Hawthorne, M. F.; Wilmouth, S.; Lindstroem, P. Eur. J. Chem. **1995**, *1*, 430-5. (i) Kim, Y. S.; Kane, R. R.; Beno, C. L.; Romano, S.; Mendez, G.; Hawthorne, M. F. Tetrahedron Lett. 1995, 36, 5147-50. (j) Chen, C.-J.; Kane, R. R.; Primus, F. J.; Szalai, G.; Hawthorne, M. F.; Shively, J. E. Bioconjugate Chem. 1994, 5, 557-64. (k) Drechsel, K.; Lee, C. S.; Leung, E. W.; Kane, R. R.; Hawthorne, M. F. Tetrahedron Lett. 1994, 35, 6217-20. (1) Kane, R. R.; Drechsel, K.; Hawthorne, M. F. J. Am. Chem. Soc. 1993, 115, 8853-4. (m) Hosmane, N. S.; Franken, A.; Zhang, G.; Srivastava, R. R.; Smith, R. Y.; Spielvogel, B. F. Main Group Met. Chem. **1998**, 21, 319–324. (n) Spielvogel, B. F. Phosphorus, Sulfur Silicon Relat. Elem. 1994, 87, 267-276. (o) Goudgaon, N. M.; El-Kattan, Y. A.; Xia, X.; McAtee, J.; Soria, J.; Wey, S.-J.; Liotta, D. C.; Schinazi, R. F. Nucleosides Nucleotides 1997, 16, 2133-2150. (p) Fulcrand-El Kattan, G.; Lesnikowski, Z. J.; Yao, S.; Tanious, F.; Wilson, W. D.; Schinazi, R. F. J. Am. Chem. Soc. 1994, 116, 7494-7501. (q) Fulcrand-El Kattan, G.; Goudgaon, N. M.; Ilksoy, N.; Huang, J.-T.; Watanabe, K. A.; Sommadossi, J.-P.; Schinazi, R. F. J. Med. Chem. 1994, 37, 2583-2588. (r) Goudgaon, N. M.; Fulcrand El-Kattan, G.; Schinazi, R. F. Nucleosides Nucleotides 1994, 13, 849-880. (s) Lesnikowski, Z. J.; Schinazi, R. F. J. Org. Chem. 1993, 58, 6531-6534. (t) Ghaneolhosseini, H.; Tjarks, W.; Sjoberg, S. Tetrahedron 1998, 54, 3877-3884. (u) Ghaneolhosseini, H.; Tjarks, W.; Sjoberg, S. Tetrahedron **1997**, 53, 17519–17526. (v) Tjarks, W.; Gabel, D. J. Med. Chem. **1991**, 34, 315–319. (w) Ketz, H.; Tjarks, W.; Gabel, D. Tetrahedron Lett. 1990, 31, 4003-4006.

these reactions is reasonable, allowing the exploration of the chemistry of these compounds in multigram quantities.

Recent developments in the preparation of compounds suitable for use in BNCT suggest the feasibility of this approach.⁷ The introduction of amino acid functionalities into the o-carborane cage has been demonstrated by us, as well as other groups, as a reasonable approach for the syntheses of compounds which are potential candidates for use in BNCT.⁷ Coupling of carborane cages with biomolecules, such as simple peptides, amino acids, barbiturates, monoclonal antibodies, immunoproteins, phthalocyanines, and porphyrins, is currently being investigated in the preparation of compounds suitable for BNCT.^{7a,e,f,8} This article presents our synthetic methodology, based on coupling of amino-containing carboranes with substrates containing carboxylic acids. This is accomplished by using the coupling reagent 1,1'-carbonyldiimidazole as a means of preparing an amide linkage between the carborane cage and the substrate. We have used this approach in the coupling of aminomethyl o-carborane and the amino monocarbon carborane

- (3) (a) Kutal, C. R.; Owen, D. A.; Todd, L. J. Inorg. Synth. 1968, 11, 19–23. (b) Heying, T. L.; Ager, J. W., Jr.; Clark, S. L.; Mangold, D. L.; Goldstein, H. L.; Hillman, M.; Pollack, R. J.; Szymanski, J. W. Inorg. Chem. 1963, 2, 1089–1092. (c) Fein, M. M.; Grafstein, D.; Paustian, J. E.; Bobinski, J.; Liechstein, B. M.; Mayes, N.; Schwartz, N. N.; Cohen, M. S. Inorg. Chem. 1963, 2, 1115–1119. (d) Zakharkin, L. I.; Stanko, V. I.; Brattsev, V. A.; Chapovskii, Yu. A.; Klimova, A. I.; Oxlobystin, O. Yu.; Ponomarenko, A. A. Dokl. Akad. Nauk SSSR 1964, 155, 1119–1122. (e) Dupont, J. A.; Hawthorne, M. F. J. Am. Chem. Soc. 1973, 86, 1643. (f) Paxson, T. E.; Callahan, K. P.; Hawthorne, M. F. Inorg. Chem. 1973, 12, 708–709. (g) Fein, M. M.; Bobinski, J.; Mayes, N.; Schwartz, N.; Cohen, M. S. Inorg. Chem. 1963, 2, 1111–1115.
- (4) The Chemistry of Boron and Its Compounds; Muetterties, E. L., Ed.; John Wiley & Sons: New York, 1967.
- (5) Wilson, G. J.; Anisuzzaman, A. K. M.; Alam, F.; Soloway, A. H. Inorg. Chem. 1992, 31, 1955–1958.
- (6) (a) Knoth, W. H.; Little, J. L.; Lawrence, J. R.; Scholer, F. R.; Todd, L. J. *Inorg. Synth.* **1968**, *11*, 33–41. (b) Knoth, W. H. *J. Am. Chem. Soc.* **1967**, *89*, 1274.
- (7) (a) Wyzlic, I. M.; Tjarks, W.; Soloway, A. H.; Perkins, D. J.; Burgos, M.; O'Reilly, K. P. *Inorg. Chem.* **1996**, *35*, 4541–4547. (b) Arterburn, J. B.; Wu, Y.; Quintana, W. *Polyhedron* **1996**, *15*, 4355–4359. (c) Wu, Y.; Carroll, P. J.; Kang, S. O.; Quintana, W. *Inorg. Chem.* **1997**, *36*, 4753–4761. (d) Wu, Y.; Carroll, P. J.; Quintana, W. *Polyhedron* **1998**, *17*, 3391–3407. (e) Kahl, S. B.; Kasar, R. A. J. Am. Chem. Soc. **1996**, *118*, 1223–1224. (f) Varadarajan, A.; Hawthorne, M. F. Bioconjugate Chem. **1991**, *2*, 242–253.
- (8) (a) Wellman, F.; Gabel, D. Proc. First Int. Symp. Neutron Capture Ther. (Brookhaven Nat. Lab.) 1983, BNL 51730, pp 276-80. (b) Sweet, F.; Kao, M. S.; Williams, A.; Khachatrian, L.; Wessels, B.; Kirsch, J. Proc. First Int. Symp. Neutron Capture Ther. (Brookhaven Nat. Lab.) 1983, BNL 51730, pp 323-30. (c) Kahl, S. B. Proc. First Int. Symp. Neutron Capture Ther. (Brookhaven Nat. Lab) 1983, BNL 51730, pp 294-303. (d) Hechter, O.; Schwartz, I. L. Proc. First Int. Symp. Neutron Capture Ther. (Brookhaven Nat. Lab.) 1983, BNL 51730, pp 197-206. (e) Spielvogel, B. F.; Das, M. K.; McPhail, A. T.; Onan, K. D.; Hall, I. H. J. Am. Chem. Soc. 1980, 102, 6343-6344. (f) Spielvogel, B. F.; Wojnowich, L.; Das, M. K.; McPhail, A. T. J. Am. Chem. Soc. 1976, 98, 5702-5703. (g) Feakes, D. A.; Shelly, K.; Knobler, C. B.; Hawthorne, M. F. Proc. Natl. Acad. Sci. 1994, 91, 3029-3033. (h) Beatty, B. G.; Paxton, R. J.; Hawthorne, M. F.; William, L. E.; Richard-Dickson, K. J.; Do, T.; Shively, J. E.; Beatty, J. D J. Nucl. Med. 1993, 34, 1294-1302. (i) Shelly, K.; Feakes, D. A.; Hawthorne, M. F.; Schmidt, P. G.; Krisch, T. A.; Beaver, W. F. Proc. Natl. Acad. Sci. 1992, 89, 9039-9043. (j) Hawthorne, M. F.; Varadarajan, A.; Paxton, R. J.; Beatty, B. G.; Curtis, C. L. Progress in Neutron Capture Therapy for Cancer; Allen, B. J., Moore, D. E., Harrington, B. V., Eds.; Plenum Press: New York, 1992; p 277. (k) Varadarajan, A.; Sharkey, R. M.; Goldenberg, D. M.; Hawthorne, M. F. Bioconjugate Chem. 1991, 2, 102-110. (1) Schinazi, R. F.; Prussoff, W. H. Tetrahedron Lett. 1978, 50, 4981-4984. (m) Schinazi, R. F.; Prussoff, W. H. J. Org. Chem. 1985, 34, 841-847. (n) Matalka, K. Z.; Barth, R. F.; Staubus, A. E.; Moeschberger, M.; Coderre, J. A. Advances in Neutron Capture Therapy; Soloway, A. H., Barth, R. F., Carpenter, D. E., Eds.; Plenum Press: New York, 1993; pp 249-52. (o) Coderre, J. A.; Glass, J. D.; Fairchild, R. G.; Roy, U.; Cohen, S.; Fand, I. Cancer Res. 1987, 47, 6377-6383.

with simple amino acids, such as glycine, alanine, and phenylalanine, in a simple and clear-cut manner. The methodology employed is simple, straightforward, and efficient, as demonstrated by the reaction yield of the products obtained. Additionally, the reactivity of $7-H_3N-7-CB_{10}H_{12}$ with substrates containing carbonyl groups was enhanced, when compared to the previous report by Jenilek and co-workers, in which reactions with this type of compound resulted in isolation of product only under forcing conditions.⁹ The reactions described in this paper were carried out at room temperature.

This paper constitutes a continuation of our work in this area, detailing the interest of development of synthetic pathways for the preparation of boron-containing compounds bearing organic recognition elements, crucial for success in BNCT.

Experimental Section

All experiments were carried out under purified dry nitrogen. Solvents were dried and freshly distilled under reduced pressure prior to use. NMR spectra: Gemini 200 (Varian); ¹H NMR, standard (CH₃)₄Si; ¹³C NMR, standard (CH₃)₄Si. Unity 400 (Varian); ¹¹B NMR, standard, external BF₃•OEt₂ in C₆D₆. IR spectra were recorded on a Perkin-Elmer 1700 in the range 200–4000 cm⁻¹.

 $1-H_2NCH_2-1,2-C_2B_{10}H_{11}^5$ and $7-H_3N-7-CB_{10}H_{12}^6$ were prepared according to the literature procedure. 1,1'-Carbonyldiimidazole, benzoic acid, *N-t*-BOC alanine, *N-t*-BOC glycine, *N-t*-BOC phenylalanine, and other reagents used in the syntheses of these compounds were obtained commercially and used without further purification (Aldrich).

General Synthesis of 1-Amidomethyl-1,2-dicarba-closo-dodecaborane (12) Derivatives. In a typical reaction, a solution of THF (3 mL) containing 0.5 mmol of the desired carboxylic acid was added to 0.5 mmol of 1,1'-carbonyldiimidazole and the resulting solution stirred at room temperature for 30 min. A solution consisting of 0.5 mmol of 1-aminomethyl-1,2-dicarba-closo-dodecaborane (12) and 0.2 mL of pyridine was added to this solution, and stirring was continued overnight. The resulting white solid, pyridinium chloride, was filtered off and the solvent and excess pyridine removed under reduced pressure, leaving a residue that was dissolved in a minimum amount of methylene chloride and separated by silica gel chromatography, using ethyl acetate as the eluant. The characterization data for each compound synthesized using this general procedure are summarized below.

1-C₆H₅CONHCH₂-1,2-C₂B₁₀H₁₁ (1). Yield: 0.106 g (76%), mp 202–4 °C. ¹H NMR (acetone- d_6): δ (ppm) 4.21 (2H, d, J = 6.6 Hz), 4.69 (1H, bs), 7.49 (3H, m), 7.89 (2H, m), 8.62 (1 H, bs). ¹³C NMR (acetone- d_6): δ (ppm) 45.47 (CH₂), 62.04 (carborane C), 77.33 (carborane C), 128.31, 129.47, 132.82, 134.56 (aromatic), 168.31 (C= O). ¹¹B NMR (acetone- d_6): δ (ppm, J) 2.59 (1B, 147 Hz), -0.61 (1B, 146 Hz), -4.79 (2B, 161 Hz), -6.41 (2B, coupling constant could not be reliably calculated because of overlap). FT-IR (cm⁻¹): 3432 (s, NH), 3308 (m, NH), 3048 (w, CH), 2576 (s, BH), 1644 (s, C=O), 1552 (m), 1492 (w), 1428 (w), 1312 (w), 1020 (w), 800 (w), 724 (w), 692 (w).MS: m/z 279 (M⁺, 5.9%), 105, (M⁺ – NHCH₂C₂B₁₀H₁₁, 100%), 77 (M⁺ – O=CNHCH₂C₂B₁₀H₁₁, 53.7%).

1-(*N*-*tert*-**BOC**-alanyl)amidomethyl-*o*-carborane (2). Yield: 0.140 g (81%), mp 165–8 °C. ¹H NMR (acetone- d_6): δ (ppm) 1.29 (3H, d, J = 7.2 Hz), 1.49 (9H, s), 4.05 (3H, m), 4.56 (1H, bs), 6.31 (1H, bs), 8.04 (1H, bs). ¹³C NMR (acetone- d_6): δ (ppm) 18.03 (CHCH₃), 28.84 (C(CH₃)₃), 44.76 (CH₂), 51.53 (CHCH₃), 61.64 (carborane C), 77.03 (carborane C), 79.96 (C(CH₃)₃), 156.84 (*t*-BOC C=O), 174.87 (amide C=O). ¹¹B NMR (acetone- d_6): δ (ppm, J) 2.20 (1B, 146 Hz), 0.69 (1B, 145 Hz), -4.77 (2B, 158 Hz), -6.43 (2B, coupling constant could not be reliably calculated because of overlap), -7.94 (4B, coupling constant could not be reliably calculated because of overlap). FT-IR (cm⁻¹): 3380 (m, NH), 3300 (m, NH), 3064 (w, CH), 2984 (w, CH), 2592 (s, BH), 1696 (s, C=O), 1648 (m, C=O), 1524 (s, C=O), 1456

⁽⁹⁾ Jelinek, T.; Plesek, J.; Hermanek, S.; Stibr, B. Collect. Czech. Chem. Commun. 1985, 50, 1376–1382.

(w), 1420 (w), 1392 (w), 936 (w), 868 (w), 840 (w), 788 (w), 728 (w), 664 (w), 628 (w).

1-(*N***-***tert***-BOC**-glycinyl)amidomethyl-*o*-carborane (3). Yield: 0.160 g (97%), mp 60–2 °C. ¹H NMR (acetone-*d*₆): δ (ppm) 1.43 (9H, s), 3.71 (2H, d, *J* = 5.9 Hz), 4.03 (2H, d, *J* = 6.7 Hz), 4.54 (1H, bs), 6.45 (1H, bs), 8.10 (1H, bs). ¹³C NMR (acetone-*d*₆): δ (ppm) 27.87 (C(CH₃)₃), 43.88 (CH₂), 60.74 (carborane C), 76.16 (carborane C), 79.07 (C(CH₃)₃), 156.46 (*t*-BOC C=O), 170.79 (amide C=O). ¹¹B NMR (acetone-*d*₆): δ (ppm) 2.27 (1B, 146 Hz), -0.70 (1B, 144 Hz), -4.82 (2B, 160 Hz), -6.45 (2B, coupling constant could not be reliably calculated because of overlap). FT-IR (cm⁻¹): 3317 (s, NH), 3060 (w, CH), 2982 (w, CH), 2590 (s, BH), 1677 (s, C=O), 1523 (s, C=O), 1455 (w), 1426 (w), 1393 (w), 1284 (w), 1252 (w), 1164 (m), 1078 (w), 1047 (w), 1022 (w), 944 (w), 861 (w), 787 (w), 725 (w), 664 (w), 609 (w).

 $1- (N\mbox{-}tert\mbox{-}BOC\mbox{-}phenylalanyl) amidomethyl-\mbox{-}o\mbox{-}carborane$ (4). Yield: 0.185 g (88%), mp 106–8 °C. ¹H NMR (acetone- d_6): δ (ppm) 1.35 (9H, s), 2.89-3.19 (2H, m), 3.86 (4.16 (2H, m)), 4.29 (1H, m), 4.46 (1H, bs), 6.31 (1H, d, J = 7.1 Hz), 7.26 (5H, s), 8.10 (1H, bs). ¹³C NMR (acetone-*d*₆): δ (ppm) 27.84 (C(CH₃)₃), 37.40 (CH₂), 43.99 (CH₂), 56.39 (CH), 60.59 (carborane C), 75.95 (carborane C), 79.09 (C(CH₃)₃), 126.71, 128.46, 129.45, 137.80 (aromatic), 155.87 (t-BOC C=O), 172.72 (amide C=O). ¹¹B NMR (acetone- d_6): δ (ppm) 2.22 (1B, 145 Hz), -0.67 (1B, 144 Hz), -4.76 (2B, 159 Hz), -6.42 (2B, coupling constant could not be reliably calculated because of overlap), -7.91 (4B, coupling constant could not be reliably calculated because of overlap). FT-IR (cm⁻¹): 3316 (s, NH), 3064 (w, CH), 2980 (w, CH), 2592 (s, BH), 1680 (s, C=O), 1520 (m, C=O), 1456 (w), 1392 (w), 1368 (w), 1300 (w), 1248 (w), 1164 (m), 1080 (w), 1044 (w), 1020 (w), 864 (w), 728 (w), 700 (w).

General Syntheses of $[Et_3NH]^+[7-ROOCNH-7-CB_{10}H_{12}]^-$. A solution of the desired carboxylic acid (0.67 mmol) was dissolved in 5 mL of THF. To this solution 0.67 mmol of 1,1'-carbonyldiimidazole was added, and the resulting solution was stirred at room temperature for 30 min. A solution containing 0.67 mmol of 7-H_3N-7-CB_{10}H_{12} and 0.3 mmol of triethylamine was added to the 1,1'-carbonyldiimidazole/ carboxylic acid solution and stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in 15 mL of ethyl acetate, washed with water (3 portions of 5 mL), and dried over magnesium sulfate. The ethyl acetate fraction was removed under reduced pressure, and the resulting solid was redissolved in dry ethyl acetate and chromatographed in a silica gel column. The analytical data obtained from the pure compounds separated in this fashion is presented below.

[Et₃NH]⁺**[7-C₆H₅CONH-7-CB₁₀H₁₂]**⁻ (**5**). Yield: 0.093 g (39%), colorless oil. ¹H NMR (acetone-*d*₆): δ (ppm) -3.02 (2H, bs), 1.39 (9H, t, *J* = 7.3 Hz), 3.42 (6H, q, *J* = 7.3 Hz), 7.46 (4H, m), 7.81 (1H, m), 8.00 (1H, bs). ¹³C NMR (acetone-*d*₆): δ (ppm) 9.62 (CH₃), 48.21 (CH₂), 63.27 (carborane C), 128.15, 129.41, 132.03, 136.61 (aromatic), 169.53 (C=O). ¹¹B NMR (acetone-*d*₆): δ (ppm) 1.61 (1B, 134 Hz), -4.98 (4B, 140 Hz), -18.47 (2B, 117 Hz), -21.79 (1B, 138 Hz), -27.69 (2B, 140 Hz). FT-IR (cm⁻¹): 3404 (m, NH), 3148 (w), 3008 (s, CH), 2800 (w, CH), 2712 (w), 2536 (s, BH), 1696 (w), 1632 (s, C=O), 1576 (w), 1520 (m), 1484 (w), 1396 (w), 1284 (m), 1280 (w), 1160 (w), 1128 (w), 1000 (w), 736 (w), 730 (m), 648 (w), 552 (w).

[Et₃NH]⁺[7-(CH₃)₃COOCNH(CH₃)CHCONH-7-CB₁₀H₁₂]⁻ (6). Yield: 0.140 g (58%), mp 83–85 °C. ¹H NMR (acetone- d_6): δ (ppm) -3.31 (2H, bs), 1.25 (1H, d, J = 7.0 Hz), 1.41 (9H, s), 1.44 (9H, t, J = 7.3 Hz), 3.44 (6H, q, J = 7.3 Hz), 4.07 (1H, t, J = 6.6 Hz), 6.18 (1H, bs), 7.53 (1H, bs). ¹³C NMR (acetone- d_6): δ (ppm) 8.68 (CH₂CH₃), 18.00 (CHCH₃), 27.76 (C(CH₃)₃), 47.13 (CH₂CH₃), 50.19 (CHCH₃), 61.10 (carborane C), 78.74 (C(CH₃)₃), 155.15 (*t*-BOC, C=O), 174.16 (amide C=O). ¹¹B NMR (acetone- d_6): δ (ppm) 1.50 (102 Hz), -5.21 (4B, coupling constant could not be calculated because of overlap), -18.56 (2B, J = 94 Hz), -21.97 (1B, J = 132 Hz), -27.86 (2B, J =137 Hz). FT-IR (cm⁻¹): 3388 (m, NH), 3312 (m, NH), 2984 (w, CH), 2804 (w, CH), 2732 (w), 2536 (s, BH), 1700 (s, C=O), 1644 (m, C= O), 1072 (w), 1036 (w), 980 (w), 896 (w), 836 (w), 788 (w), 740 (w). **[Et₃NH]**⁺**[7-(CH₃)₃COONHCH₂CONH-7-CB₁₀H₁₂]**⁻ (7). Yield: 0.162 g (59%), mp 156–8 °C. ¹H NMR (acetone- d_6): δ (ppm) –3.27 (2H, bs), 1.42 (9H, s), 1.43 (9H, t, J = 7.3 Hz), 3.44 (6H, q, J = 7.3Hz), 3.68 (2H, d, J = 5.0 Hz), 7.47 (1H, s), 8.58 (1H, bs). ¹³C NMR (acetone- d_6): δ (ppm) 9.50 (CH₂CH₃), 28.63 (C(CH₃)₃), 48.06 (CH₂-CH₃), 61.78 (carborane C), 79.68 (C(CH₃)₃), 156.82 (*t*-BOC C=O), 171.56 (amide C=O). ¹¹B NMR (acetone- d_6): δ (ppm) 1.52 (1B, 125 Hz), -5.24 (4B, 132 Hz), -18.50 (2B, 111 Hz), -21.94 (1B, 137 Hz), -27.82 (140 Hz). FT-IR (cm⁻¹): 3412 (s, NH), 2984 (m, CH), 2812 (w), 2736 (w), 2536 (s, BH), 1684 (s, C=O), 1520 (m, C=O), 1476 (w), 1448 (m), 1392 (w), 1368 (w), 1288 (w), 1252 (w), 1164 (m), 1040 (m), 992 (w), 944 (w), 852 (w), 784 (w), 708 (w), 648 (w).

[Et₃NH]⁺[7-(CH₃)₃COONH(CH₂C₆H₅)CHCONH-7-CB₁₀H₁₂]⁻ (8). Yield: 0.233 g (70%), mp 78–81 °C. ¹H NMR (acetone- d_6): δ (ppm) -3.20 (2H, bs), 1.34 (9H, s), 1.42 (9H, t, J = 7.3 Hz), 2.85–3.08 (2H, m), 3.42 (6H, q, J = 7.3 Hz), 4.28 (1H, m), 6.02 (1H, bs), 7.22 (5H, m), 7.53 (1H, s). ¹³C NMR (acetone- d_6): δ (ppm) 8.75 (CH₂CH₃), 27.74 (C(CH₃)₃), 38.52 (CH₂), 47.31 (CH₂CH₃), 55.93 (CH), 61.40 (carborane C), 78.75 (C(CH₃)₃), 126.49, 128.25, 129.61, 137.85 (aromatic), 155.20 (*t*-BOC C=O), 172.53 (amide C=O). ¹¹B NMR (acetone- d_6): δ (ppm) 1.53 (1B, J = 122 Hz), -5.21 (4B, 119 Hz), -18.52 (2B, 111 Hz), -21.94 (1B, 137 Hz), -27.80 (2B, J = 138 Hz). FT-IR (cm⁻¹): 3397 (m, NH), 2983 (m, CH), 2809 (w), 2734 (w), 2530 (s, BH), 1699 (s, C=O), 1645 (s, C=O), 1498 (m), 1471 (w), 1456 (w), 1393 (w), 1366 (w), 1249 (w), 1162 (m), 1081 (w), 1039 (w), 961 (w), 892 (w), 835 (w), 778 (w), 754 (w), 703 (w), 646 (w), 502 (w).

Cleavage of t-BOC Group. The *t*-BOC protected carborane (0.4 mmol) was stirred at room temperature in a mixture of ethanol (3 mL) and 12.0 M HCl (1.0 mL, 12 mmol) for 8 h. To the resulting solution, 20 mL of ethanol was added and then evaporated under reduced pressure, while keeping the temperature below 30 °C. The product obtained was a while solid, for which the analytical data are presented below.

[Et₃NH]⁺[7-H₂NCH₂CONH-7-CB₁₀H₁₂][−] (9). Yield: 0.133 g (97%), mp 72–4 °C. ¹H NMR (CD₃CN): δ (ppm) –3.27 (2H, bs), 1.28 (9H, t, *J* = 7.1 Hz), 3.12 (6H, q, *J* = 7.1 Hz), 3.62 (2H, s), 7.55 (1H, s), 7.64 (2H, bs), 9.25 (1H, bs). ¹³C NMR (CD₃CN): δ (ppm) 9.25 (CH₂CH₃), 41.59 (CH₂), 47.43 (CH₂CH₃), 61.70 (carborane C), 166.97 (C=O). ¹¹B NMR (CD₃CN): δ (ppm) 1.74 (1B, coupling constant could not be calculated because of overlap), –5.19 (4B, coupling constant could not be calculated because of overlap), –18.35 (2B, coupling constant could not be calculated because of overlap), –21.91 (1B, *J* = 129 Hz), –27.90 (2B, 135 Hz). FT-IR (cm⁻¹): 3376 (m, NH), 2984 (m, CH), 2532 (s, BH), 1668 (s, C=O), 1472 (w), 1400 (w), 1268 (w), 1160 (w), 1120 (w), 1040 (w), 984 (w), 900 (w), 836 (w), 756 (w), 708 (w), 648 (w).

[Et₃NH]⁺[7-H₂N(CH₂C₆H₅)CHCONH-7-CB₁₀H₁₂]⁻ (10). Yield: 0.165 g (95%), mp 107–110 °C. ¹H NMR (CD₃CN): δ (ppm) –3.29 (2H, bs), 1.28 (9H, t, J = 7.0 Hz), 3.10 (8H, m), 4.06 (1H, bs), 6.79 (2H, bs), 7.34 (5H, s), 9.25 (1H, bs). ¹³C NMR (CD₃CN) δ (ppm) 9.11 (CH₂CH₃), 37.95 (CH₂), 47.22 (CH₂CH₃), 53.30 (CH), 61.71 (carborane C), 128.39, 129.71, 130.87, 135.09 (aromatic), 168.87 (C=O). ¹¹B NMR (CD₃CN): δ (ppm) 1.80 (1B, coupling constant could not be calculated because of overlap), -5.16 (4B, coupling constant could not be calculated because of overlap), -21.88 (1B, J = 125 Hz), -27.89 (2B, J = 131 Hz). FT-IR (cm⁻¹): 3608 (sh, NH), 3376 (m, NH), 2984 (m, CH), 2684 (sh, BH), 2536 (s, BH), 1668 (s, C=O), 1588 (w), 1496 (w), 1472 (w), 1392 (m), 1260 (w), 1184 (w), 1160 (w), 1036 (w), 1012 (w), 988 (w), 960 (w), 836 (w), 808 (w), 756 (w), 648 (w), 624 (w), 576 (w), 552 (w), 488 (w).

Results and Discussion

The preparation of amido-containing carboranes was accomplished via the coupling reaction of 1-H₂NCH₂-1, 2-C₂B₁₀H₁₁, and 7-H₃N-7-CB₁₀H₁₂ with carboxylic-containing substrates in the presence of 1,1'-carbonyldiimidazole. The advantage of this reaction lies in the fact that it allows the use of protected amino acids as a substrate, as demonstrated by the reactions with *N*-*t*-BOC protected alanine, glycine, and phenylalanine. In addition,



Figure 1. Preparation of amido-containing carboranes.



Figure 2. Deprotection of N-t-BOC group.

deprotection of the carborane-bound amino acid is accomplished in a simple manner, resulting in high yield of the free aminocontaining carborane amide.

Previous examples of the preparation of related compounds relied on high-temperature reactions, which lead to either a low yield of the desired compounds or decomposition of the reagents prior to reaction.⁹ The methodology outlined in this paper results in the formation of carborane-containing amino acids, linked via an amide bond, leaving a free amino group once the N-t-BOC protective group is removed, which in principle could be coupled to other amino acids or small peptides in the same manner.

The rationale of using boron-containing compounds having at least 10 boron atoms is that no isotopic enhancement to the active ¹⁰B compound is necessary to achieve relevant concentrations of ¹⁰B within cells. It has been estimated that for BNCT to be effective a mean concentration of uptake should be around 30 μ g of ¹⁰B per gram of tumor.¹⁰ This translates to approximately 3.0 μ mol of ¹⁰B present. In *p*-boronophenylalanine, for example, to supply this amount of ¹⁰B, 3.05 mmol of unenriched *p*-boronophenylalanine is needed. In contrast, to supply the necessary amount of ¹⁰B with **1**, this value decreases to 0.42 mmol, a significant reduction. This is not to say that completely enriched compounds obtained from ¹⁰B₁₀H₁₄ are not needed, but this process can be time consuming and expensive. Furthermore, the stability of the o-carborane cage and of substituted 7-RNH $-CB_{10}H_{12}^{-}$ salts is another attractive feature of this approach. No special precautions have to be taken in storing these compounds once synthesized, since they are air and moisture stable, unlike some other boron-containing compounds that can degrade under analogous conditions.

The advantage of the synthetic protocol used for the syntheses of the compounds delineated is the direct use of the amino carboranes, instead of other derivatives such as isocyanatecontaining carboranes, which has been used in an analogous fashion.⁷ This approach results in reducing the synthetic steps needed for incorporation of the amino acid into the carborane unit. The result is the isolation of the targeted compounds in less time, using reagents which are stable without the need of special precautions, just as it is true for isocyanato carboranes.⁷

The characterization of the compounds prepared in this study was achieved by using ¹H, ¹¹B, ¹³C NMR techniques, IR, and mass spectrometry for compound 1. For the carboranes derived from 1-aminomethyl-o-carborane, the ¹¹B NMR was analogous for all the compounds studied. It consisted of five peaks having relative intensities 1:1:2:2:4 between approximately -8.00 and

⁽¹⁰⁾ Bond, V. P.; Laster, B. H.; Wielopolski, L. Radiation Res. 1995, 141, 287 - 293.

2.50 ppm. This spectrum is extremely similar to those reported for monosubstituted carboranes containing urea linkage, based on $1-O=C=N-(CH_2)_n-1,2-C_2B_{10}H_{11}$ (n = 1, 3), which the reported compounds are related.⁷

The ¹H and ¹³C NMR data were more informative, since it showed the presence of all the types of hydrogen and carbon atoms expected for the compounds having the proposed formulation. Of particular interest is the presence of the *N*-*t*-BOC carbonyl group, indicating that under the reaction conditions this protective group was unreactive, allowing the preparation of the targeted compound in high yield. For compound **1**, the mass spectral data showed the parent ion at m/z = 279, which corresponds to the proposed formulation of this compound. Furthermore, sequential losses of NHCH₂C₂B₁₀H₁₁ and O=CNHCH₂C₂B₁₀H₁₁ indicated that the proposed formulation of **1** was correct. The IR spectrum was informative as much as it clearly showed the presence of N–H, C–H, B–H, and C=O stretches associated with this molecule.

Because of the similarities of the ¹¹B NMR spectra for compounds 1-4, the characteristic ¹H and ¹³C NMR signals indicating the presence of the proper functional groups, and the IR spectra of these compounds, which confirmed the presence of N–H, C–H, B–H, and C=O groups, the identity of these compounds was established. Figure 1 details the synthetic route employed in the preparation of these compounds.

We also explored the chemistry of the known amino carborane, 7-H₃N-7-CB₁₀H₁₂, using the same synthetic strategy for the o-carborane-containing compounds. One of the reasons for this study is the fact that previous attempts of using this compound directly as a reagent, involving reaction of the amino group, was found to happen only under forcing conditions and longer reaction times.9 For example, reaction of 7-H₃N-7-CB₁₀H₁₂ with chloroacetic acid, resulting in the formation of 7-HOOCCH₂NH₂-7-CB₁₀H₁₂, a boronated glycine derivative, was accomplished in 29% yield in boiling ethanol after 48 h.9 An analogous compound, 7-C₆H₅CONH₂-7-CB₁₀H₁₂, a benzamide carborane, was isolated in 55% yield by performing the reaction in boiling ethyl acetate, also for 48 h.9 The yield obtained for compounds 5-8, reported here, ranged from a low of 38% to a high of 70%, and the reaction conditions were much milder than those employed in the report of Jenilek and coworkers.9

The deprotection of the *N*-*t*-BOC group was carried out by the established synthetic protocol for protected amino groups having this protecting group, Figure 2.¹¹ The reaction was

essentially complete after 8 h, resulting in the quantitative recovery of the free amino group. The yield obtained for compounds 9 and 10 was 97% and 95%, demonstrating the synthetic utility of this procedure. Characterization of these compounds was accomplished by ¹H, ¹¹B, and ¹³C NMR as well as the FT-IR spectra for both compounds. The disappearance of the carbonyl signal in the ¹³C NMR and on the IR spectra indicated that transformation to the free amine was accomplished. Also disappearing from the ¹H and ¹³C NMR was the signals attributed to the *tert*-butyl group of the *N*-*t*-BOC protective group. The ¹¹B NMR indicated that the monocarbon carborane cage survived the reaction intact, as the similarities between the spectra of 9 and 10 to those of its precursors molecules corroborate.

The reactivity exhibited by these amino carboranes with N-t-BOC protected amino acids under coupling reaction conditions using the readily available coupling reagent 1,1'-carbonyldiimidazole and subsequent deprotection of the N-t-BOC group demonstrates the synthetic utility of this approach. Of particular interest is the fact that the amino carborane 1-H₂NCH₂-1,2- $C_2B_{10}H_{11}$ was more reactive than 7-H₃N-7-CB₁₀H₁₂, as demonstrated by the reaction yield obtained from comparable reactions. This is undoubtedly a result of the higher nucleophilic character of the amino group on the o-carborane derivative. This follows the trend observed earlier in 7-H₃N-7-CB₁₀H₁₂ by Jenilek and co-workers,⁹ which could couple this carborane, under nucleophilic conditions, to other substrates only under forcing conditions. Nonetheless, the coupling reagent 1,1'carbonyldiimidazole demonstrated that it can enhance the reactivity of this compound and allow reactions to proceed at room temperature with reaction yields ranging from low to moderate (40-70%). The low nucleophilicity of this carborane can be owed to the closeness of the amino group to the cage and the fact that the carborane cage is negatively charged, reducing the nucleophilicity of this compound when compared to the o-carborane derivative.

Having demonstrated that this approach results in the preparation of amino acid substituted carboranes, the door is opened to the extension of this methodology to peptides, taking advantage of the reactions described here. We are continuing the research in this area, and the results will be reported in the future.

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^{(11) (}a) Nudelman, A.; Bechor, Y.; Falb, E.; Fisher, B.; Wexler, B.; Nudelman, A. Synth. Commun. 1998, 28, 471–4. (b) Peptides: Synthesis, Structures and Applications; Gutte, B., Ed.; Academic Press: San Diego, CA, 1995.