Pergamon

Tetrahedron Letters 40 (1999) 5147–5149

TETRAHEDRON LETTERS

Synthesis of heterobifunctional *p*-carborane derivatives. 3-[12-(Mercaptomethyl)-1,12-dicarba-*closo*-dodecaboran(12)-1-yl]propionic acid

István Ujváry † and Ronald J. Nachman *

USDA-ARS, Food Animal Protection Research Laboratory, 2881 F & B Road, College Station, TX 77845, USA

Received 15 April 1999; accepted 6 May 1999

Abstract

3-[12-(Mercaptomethyl)-1,12-dicarba-*closo*-dodecaboran(12)-1-yl]propionic acid (**1**) was prepared in six steps involving sequential dithiocarboxylation and hydroxypropylation of *p*-carborane as key transformations. Published by Elsevier Science Ltd.

Keywords: alkylation; carboranes; carboxylic acids and derivatives; lithiation; oxidation; thiols.

Carborane-containing substances, 1,2-dicarba-*closo*-dodecaborane derivatives in particular, have become important for use in boron neutron capture therapy of cancer.[1] Incorporating the highly hydrophobic carborane skeleton[2] imparts unusual lipophilicity that may extend the biological activity of mammalian peptide neurohormone analogs.[3] Such lipophilic effects may also enhance cuticular penetrability and prolong receptor binding of peptidomimetic insect hormone analogs incorporating a carboranyl mimic of phenylalanine.[4] The rigid boron-rich icosahedrane structure possesses unique physicochemical properties making it an interesting building block for nanotechnology.[5]

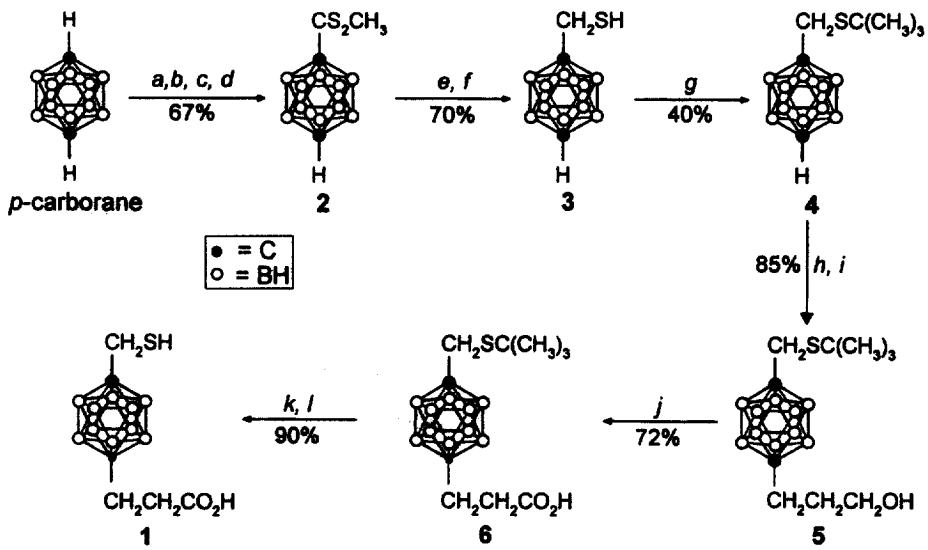
While sulfur-containing *o*-, *m*- and *p*-carboranes have been known for some time,[6] the chemistry of carboranes appended to a -CH_2SH group is a relatively unexplored area. 1-Mercaptomethyl-1,2-dicarba-*closo*-dodecaborane was recently described[7] but its synthesis involving the addition of decaborane to *t*-butyl propargyl sulfide precludes the preparation of related *m*- and *p*-carborane derivatives. During our studies on the potential agricultural application of carboranes,[4,8] we prepared various heterobifunctional derivatives of *p*-carborane including those containing a mercaptomethyl group. Such analogs could be elaborated, for instance, to methylsulfonate carboranyl analogs as replacements of the Tyr(SO_3H) residue, a critical component of the vertebrate gastrin/CCK and insect sulfakinin neuropeptide families.[9]

* Corresponding author. E-mail: nachman@acs.tamu.edu

† On leave from the Plant Protection Institute, Hungarian Academy of Sciences, H-1525 Budapest, P. O. Box 102, Hungary. E-mail: iujv@planta.nki.hu

0040-4039/99/$ - see front matter Published by Elsevier Science Ltd.
PII: S0040-4039(99)00886-2

This preliminary report describes the synthesis of millimolar quantities of 3-[12-(mercaptomethyl)-1,12-dicarba-*closo*-dodecaboran(12)-1-yl]propionic acid (**1**) (Scheme 1).[10]



Scheme 1. Synthesis of *p*-carborane derivative **1**. (a) 1.05 equiv. *n*-BuLi, THF/hexane, −10°C, 1.5 h; (b) 0.2 equiv. CuBr+0.4 equiv. LiBr, THF, −15°C, 15 min; (c) 1.4 equiv. CS_2, −10°C, 90 min; (d) CH_3I, −15°C to rt, 1.5 h; (e) 1.05 mol equiv. BH_3–Me_2S, reflux, 1.5 h; (f) excess *cc.* HCl, reflux, 16 h; (g) excess isobutene, catalytic *cc.* H_2SO_4, CH_2Cl_2, rt, 52 h; (h) 1.05 equiv. *n*-BuLi, ethyl ether/hexane, 4 h, rt; (i) 1.2 equiv. oxetane, 0°C to rt, 12 h; (j) 3.0 equiv. pyridinium dichromate, DMF, 10°C, 10 h; (k) 1.0 equiv. $Hg(OAc)_2$, 1.87 equiv. anisole, trifluoroacetic acid, 0°C, 30 min, then solvent removal at reduced pressure; (l) 10 equiv. 2-mercaptoethanol, 70% acetic acid, 6 h, rt, aqueous workup

Facile monofunctionalization of *p*-carborane to the corresponding dithiocarboxylate was accomplished by analogy to the Cu(I)-catalyzed synthesis of dithioesters from lithiated aromatic compounds.[11] Thus, monolithiation of *p*-carborane[12] at −10°C followed by subsequent additions of CuBr/LiBr and an excess of CS_2 afforded the corresponding lithium carbodithioate. Addition of methyl iodide gave, after work-up and purification by column chromatography (silica gel, hexane), dithioester **2**.

The dithioester **2** was then reduced by BH_3–Me_2S in refluxing toluene[13] to afford thiol **3** after column chromatography (silica gel, hexane). Protection of thiol **3** as its *t*-butyl sulfide used standard conditions[14] and afforded compound **4** and some starting material after repeated purifications (silica gel, hexane).

Lithiation of sulfide **4** at room temperature followed by the addition of oxetane gave, after chromatography (silica gel, 0 to 10% EtOAc in hexane), alcohol **5** in good yield. The latter was oxidized by pyridinium dichromate in DMF[15] to the corresponding acid **6** after purification by chromatography (silica gel, 20% EtOAc in hexane).

Removal of the *t*-butyl protective group was achieved using mercuric acetate in trifluoroacetic acid.[16] Treatment of the resulting Hg(II)-salt with an excess of 2-mercaptoethanol and extractive purification gave the title product **1** after chromatography (silica gel, 20% EtOAc in hexane containing 0.1% acetic acid).

In conclusion, a heterobifunctional *p*-carborane derivative containing mercaptomethyl and carboxyethyl functionalities was prepared from *p*-carborane. The method used for the introduction of dithiocarboxylate group should be applicable to other carboranes as well.

Acknowledgements

The financial support of the Office of International Cooperation and Development of the US Department of Agriculture is gratefully acknowledged.

References

1. (a) 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. (b) Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 950–984.
2. Fauchère, J. L.; Do, K. Q.; Jow, P. Y. C.; Hansch, C. *Experientia* **1980**, *36*, 1203–1204.
3. See for example: Escher, E.; Guillemette, G.; Leukart, O.; Regoli, D. *Eur. J. Pharmacol.* **1980**, *66*, 267–272.
4. Nachman, R. J.; Teal, P. E. A.; Radel, P. A.; Holman, G. M.; Abernathy, R. L. *Peptides* **1996**, *17*, 747–752.
5. Schöberl, U.; Magnera, T. F.; Harrison, R. M.; Fleischer, F.; Pflug, J. L.; Schwab, P. F. H.; Meng, X.; Lipiak, D.; Noll, B. C.; Allured, V. S.; Rudalevige, T.; Lee, S.; Michl, S. *J. Am. Chem. Soc.* **1997**, *119*, 3907–3917.
6. For an early overview see: Grimes, R. N. *Carboranes*; Academic Press: New York, 1970; for recent works see: Viñas, C.; Cirera, M. R.; Teixidor, F.; Kivekäs, R.; Sillanpää, R.; Llibre, J. *Inorg. Chem.* **1998**, *37*, 6746–6750 and references cited therein.
7. Plešek, J.; Heømánek, S. *Coll. Czech., Chem. Commun.* **1979**, *44*, 2769–2771.
8. Oros, G.; Ujváry, I.; Nachman, R. J. *Amino Acids* **1999**, *17*, in press.
9. Nachman, R. J.; Holman, G. M.; Haddon, W. F.; Ling, N. *Science* **1986**, *234*, 71–73.
10. Analytical data for compounds **1–6**. ^{1}H and ^{13}C NMR spectra were obtained at 300.1 and 75.5 MHz, respectively. Compound **2**: mp 62–63°C; ^{1}H NMR ($CDCl_3$) δ 1.1–3.6 (broad, 11H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 22.7, 61.3, 93.7, 221.4; IR ($CHCl_3$) ν 2612 (s), 1414 (w), 1175 (m), 1093 (m), 970 (w) cm^{-1}; MS (EI) *m/z* calcd for $C_4H_{14}B_{10}S_2$ [M$^+$]: 234, observed: 234, 219, 188, 141 (within the boron cluster envelopes). Compound **3**: thick redish oil; ^{1}H NMR ($CDCl_3$) δ 1.2–3.1 (br, 11H), 1.57 (t, *J*=9.1 Hz, 1H), 2.70 (d, *J*=9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.3, 58.5, 84.4; IR ($CHCl_3$) ν 2610 (s), 1420 (w), 1280 (m), 1067 (m), 910 (w) cm^{-1}; MS (EI) *m/z* calcd for $C_3H_{14}B_{10}S$ [M$^+$]: 190, observed: 190, 154 (within the boron cluster envelopes). Compound **4**: mp 38–39°C; ^{1}H NMR ($CDCl_3$) δ 0.95–3.1 (br, 11H), 1.16 (s, 9H), 2.63 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 30.5, 35.7, 43.0, 58.5, 82.4; IR ($CHCl_3$) ν 2960 (m), 2610 (s), 1960 (br), 1460 (w), 1365 (w), 1265 (w), 1165 (m), 1070 (m) cm^{-1}; MS (EI) *m/z* calcd for $C_7H_{22}B_{10}S$ [M$^+$]: 246, observed: 246, 231, 190 (within the boron cluster envelopes). Compound **5**: mp 77–78°C; ^{1}H NMR (C_6D_6) δ 0.90–3.40 (br, 10H), 0.95 (s, 9H), 1.53 (m, 4H), 2.64 (s, 2H), 2.92 (t, *J*=6.1 Hz, 2H); ^{13}C NMR (C_6D_6) δ 30.4, 32.8, 34.5, 35.2, 42.7, 61.3, 78.1, 80.0; IR ($CHCl_3$) ν 3010 (w), 2960 (br), 2885 (w), 2610 (s), 1460 (w), 1365 (m), 1160 (m), 1060 (m), 1035 (m), 915 (w) cm^{-1}; MS (EI) *m/z* calcd for $C_{10}H_{28}B_{10}OS$ [M$^+$]: 305, observed: 305, 289, 247, 230 (within the boron cluster envelopes). Compound **6**: mp 128–129°C; ^{1}H NMR ($CDCl_3$) δ 0.90–3.20 (br, 10H), 1.17 (s, 9H), 1.92 (m, 2H), 2.18 (m, 2H), 2.65 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 30.5, 31.8, 33.4, 34.8, 43.1, 77.2, 77.6, 177.6; IR ($CHCl_3$) ν 2970 (s), 2940 (s), 2900 (w), 2865 (w), 2610 (s), 1717 (s), 1460 (m), 1420 (m), 1365 (m), 1295 (w), 1160 (m), 1030 (w) cm^{-1}; MS (EI) *m/z* calcd for $C_{10}H_{26}B_{10}O_2S$ [M$^+$]: 318, observed: 318, 303, 263 (within the boron cluster envelopes). Compound **1**: mp 155–156°C; ^{1}H NMR (C_6D_6) δ 1.10–3.40 (br, 10H), 1.11 (t, *J*=9.2 Hz, 1H), 1.76 (t, *J*=7.8 Hz, 2H), 1.89 (t, *J*=7.8 Hz, 2H), 2.16 (d, *J*=9.2 Hz, 2H), 9.30 (br, 1H); ^{13}C NMR (C_6D_6) δ 31.3, 32.0, 33.5, 78.1, 80.3, 178.0; IR ($CHCl_3$) ν 3010 (w), 2610 (s), 1715 (s), 1425 (w), 1280 (w), 1020 (w), 916 (w) cm^{-1}; MS (FAB) *m/z* calcd for $C_6H_{18}B_{10}O_2S$ [M$^+$]: 264.3, observed: 264.2 (within the boron cluster envelopes).
11. Verkruijsse, H. D.; Brandsma, L. *J. Organomet. Chem.* **1987**, *332*, 95–98.
12. *p*-Carborane was obtained from Boron Biologicals Inc., Raleigh, NC, USA.
13. Jabre, I.; Saquet, M.; Thuillier, A. *J. Chem. Res. (M)* **1990**, 756–784.
14. Callahan, F. M.; Anderson, G. W.; Paul, R.; Zimmerman, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 201–207.
15. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
16. Nishimura, O.; Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576–1585.