Tetrahedron Letters, Vol. 33, No. 49, pp. 7489-7490.1992
Printed in Great Britain

00404039192 $5.00 + .00
Pergamon Press Ltd

A General, Convenient Way to Carborane-Containing Amino Acids for Boron Neutron Capture Therapy

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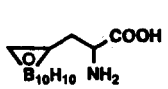
Abstract: A general, convenient procedure for the synthesis of carborane-containing amino acids in good yield has been developed. The synthesis of *o*-carboranylalanine 1. O-(*o*-carboran-1-ylmethyl)-tyrosine 2 and p-(*o*-carboran-1-yl)-phenylalanine 3 is reported.

p-Boronophenylalanhte (p-BPA)[1] is the first boron-containing amino acid that has been used in treatment of melanoma by means of Boron Neutron Capture Therapy (BNCT).[2] However, them is only a single boron atom in this amino acid and the structure appears to be metabolically unstable. This is rationale for the synthesis of carborane-containing analogues (10 boron atoms) of aromatic amino acids, which from metabolic studies with related compounds, might be highly resistant to oxidative changes.

In this letter! we describe a new, convenient procedure to previously synthesized *o*-carboranylalanine 1[3] (70% total yield) and two new boron-containing amino acids, O-(*o*-carboran-1-ylmethyl)-tyrosine 2 (77% total yield) and p-(*o*-carboran-1-yl)-phenylalanine 3 (71% total yield).



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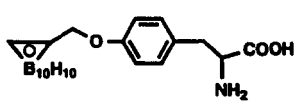

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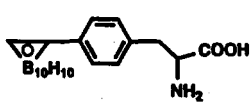
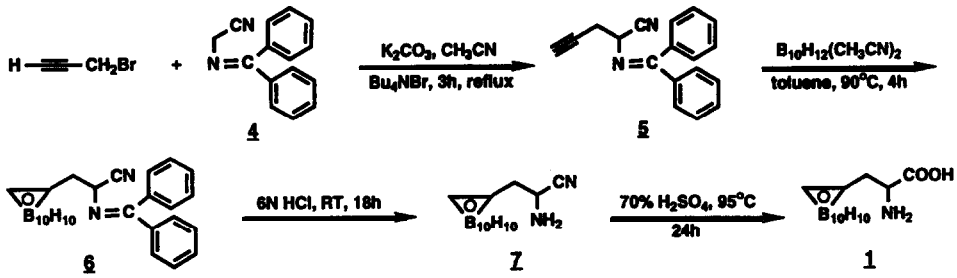


3

o-Carboranylalanine 1 is a potential analogue of phenylalanine and might be useful for BNCT. The dimensions of the cage am only slightly larger than space occupied by a benzene ring rotating about its C(l)-C(4) axis, and its two carbon atoms participate in the delocalized bonding.‘.

The synthesis of 1 involves a phase transfer alkylation[4] of commercially available N-(diphenylmethylene)aminoacetonitrile, 4. with propargyl bromide to yield monoalkylated product 5. Boronation of 5 with a decaborane-acetonitrile complex followed by the partial hydrolysis of the alkylated Schiff' s base, 6, with 6N HCl affords the aminonitrile 7. In order to hydrolyze the cyano function stronger acidic conditions (70% H_2SO_4, 95°C, 24h) are required to obtain *o*-carboranylalanine, 1.



The same procedure has also been applied to the synthesis of O-(*o*-carboran-1-ylmethyl)-tyrosine, 2 and p-(*o*-carboran-1-yl)-phenylalanine, 3. The corresponding carborane-containing p-substituted-benzyl bromides have been used in alkylating 4, followed by acid hydrolysis to produce the corresponding amino acids. This procedure yields a racemic mixture of the carboranecontaining amino acids and these are now beiig separated into their enantiomers for biological evaluation.

In summary, a practical method for the synthesis of carborane-containing amino acids, has been reported. This procedure can be used for the synthesis of the other boron-containing amino acids that might be potentially useful in treatment of cancer by means of BNCT.

Acknowledgement: This research has been supported by the U.S. Department of Energy grant DE-FG02-90ER60972 and contract DE-AC02-76CH000616 and the National Cancer Institute of the U.S. Public Health Service R01 CA 538%.

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5. ***o*-Carboranylalanine (1):** m.p. 205-208°C(dec.); MS (FAB+, 3-NBA) 232 (M+ H)+; Anal. Calcd for $C_5H_{17}NO_2B_{10}$: C. 25.96; H, 7.41; N, 6.06; B, 46.77. Found: C. 25.78: H. 7.30: N. 5.99; B, 46.50. ^{1}H NMR (MeOH-d4) δ: 1.1-3.4 (br, m, 10H, B-H); 2.64, 3.09 (d of AB_q, 2H, -CH_2-, J_{AB} =16.0, Jax = 5.4, J_{AX} = 5.6); 3.67 (t, 1Hx, -CH-, J = 5.3): the proton bonded to carbon atom of carborane cage is bidden under the OH-signal from the solvent.
6. **O-(*o*-Carboran-1-ylmethyl)-tyrosine (2): m.p. 196-197°C;** MS (FAB+, 3-NBA) 338 (M + H)+; Anal. Calcd for $C_{12}H_{23}B_{10}NO_3$: C, 42.71; H, 6.87; N, 4.15; B, 32.04. Found: C. 42.45: H, 6.77; N, 4.00; B. 31.91. ^{1}H NMR (MeOH-d4) δ: 1.1-3.3 (br, m, 10H, B-H); 2.97, 3.23 (d of AB_q, 2H, -CH_2-CH-, J_{AB} = 14.6, Jax = 8.4, J_{AX} = 4.5): 3.73 (dd, 1Hx, -CH-CH_2-); 4.51 (s, 2H, -CH_2-O-); 6.92, 7.24 (2d, 4H, H-aromat., J = 8.6); the proton bonded to carbon atom of carborane cage is hidden under the OH-signal from the solvent.
7. **p-(*o*-Carboran-1-yl)-phenylalanine** (3): m.p. 200-200°C; MS (FAB+, 3-NBA) 308 (M + H)+; Anal. Calcd for $C_{11}H_{21}NO_2B_{10}$: C. 42.98; H, 6.89: N.4.56; B, 35.17. Found: C. 42.68; H, 6.67; N, 4.41: B, 35.20. ^{1}H NMR (MeOH-d4) δ: 1.2-3.3 (br, m, 10H, B-H); 3.04.3.27 (d of AB_q, 2H, -CH_2-, J_{AB} = 14.5. J_{BX} = 8.3, J_{AX} = 4.7); 3.78 (dd. 1Hx,-CH-CH_2-); 5.11 (br, s, 1H, $C_{carborane}$-H); 7.32.7.53 (2d, 4H, H-aromat., J = 8.4).

(Received in USA 30 July 1992; accepted 9 September 1992)