Tetrahedron Letters, Vol.31, No.28, pp 4029-4032, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF POLYHEDRAL BORANE DERIVATIVES HAVING A CARBOXY GROUP

Koichiro Nagasawa* and Masayuki Narisada
Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka 553, Japan

Summary: Polyhedral borane derivatives having a carboxy group were synthesized by the reaction of $Na_2{}^{10}B_{12}H_{11}SH$ with $Br(CH_2)_nCOOR$ in KOH and DMSO. ^{10}B-Containing polylysine and γ-globulin are also described.

Boron neutron capture therapy (BNCT) requires the delivery of considerable amounts of B-10 atoms into the targeted malignant tissue. Recently, the synthesis of boron-containing compounds that show affinity for a wide variety of tumors has been attempted by many investigators.[1,2] For such usage, the boron-carbon bond must be sufficiently stable in the final target molecule. We now report the synthesis of new polyhedral borane derivatives having a carboxy group which forms stable bonds with amino groups in the target molecules.

Polyhedral borane was modified by the following route.

$$\underset{\mathbf{1}}{Na_2{}^{10}B_{12}H_{11}SH} + \underset{\mathbf{2}}{Br(CH_2)_nCOOR} \xrightarrow[DMSO]{KOH} Na_2{}^{10}B_{12}H_{11}S(CH_2)_nCOOR \xrightarrow{(CH_3)_4NCl} \underset{\mathbf{3}}{[(CH_3)_4N]_2{}^{10}B_{12}H_{11}S(CH_2)_nCOOR} \quad \text{(eq. 1)}$$

$$\mathbf{3} \xrightarrow[CH_3OH]{NaOH} [(CH_3)_4N]_2{}^{10}B_{12}H_{11}S(CH_2)_nCOOH \xrightarrow[CsOH]{\text{ion exchange}} \underset{\mathbf{4}}{Cs_2{}^{10}B_{12}H_{11}S(CH_2)_nCOOH} \quad \text{(eq. 2)}$$

Table 1

Compound	3a	3b	3c[a]
n	2	2	1
R	CH_3	C_2H_5	C_2H_5
Yield (%)	78.4	70.8	12.5
Procedure	(A)	(A)	(B)

a This compound was prepared by an alternate route (procedure B).

The general procedure (A) is as follows: $Na_2{}^{10}B_{12}H_{11}SH$[3-5] (1) (1.1 g) was stirred in 140 ml absolute dimethylsulfoxide (DMSO) with 2.9 g of crushed potassium hydroxide. Next, 8.56 g of methyl 3-bromopropionate (2a) in 5 ml of DMSO was added over a period of 20 min from a dropping funnel. After 22 h, the reaction mixture was concentrated under vacuum. The resulting solid was resolved in a small amount of water and followed by addition of aqueous solution of tetramethylammonium chloride (1.13 g). The pale purple product was filtered off and the filtrates were recrystallized from acetonitrile-ether. **3a** was obtained. The yield was 1.6 g (78.4%). Similarly, **3b** was obtained from the reaction of 1 with ethyl 3-bromopropionate (**2b**) in good yield (70.8%) as shown in Table 1.

Stoochnoff et al.[6] have reported the use of sodium hydride/methyl halide in tetrahydrofuran at room temperature for the methylation of alcohols. During the course of our study, we used this method to prepare **3c** (n = 1, R = C_2H_5) in DMSO (procedure B).

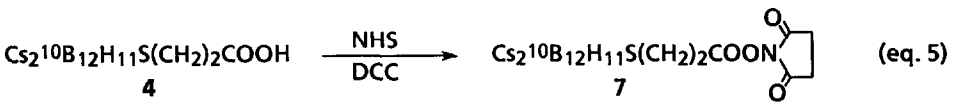
$$[(CH_3)_4N]_2{}^{10}B_{12}H_{11}SH + NaH \longrightarrow \underset{\mathbf{5}}{[(CH_3)_4N]_2{}^{10}B_{12}H_{11}SNa} \qquad \text{(eq. 3)}$$

$$\mathbf{5} + BrCH_2COOC_2H_5 \longrightarrow \underset{\mathbf{6}}{[(CH_3)_4N]_2{}^{10}B_{12}H_{11}SCH_2COOC_2H_5} \qquad \text{(eq. 4)}$$

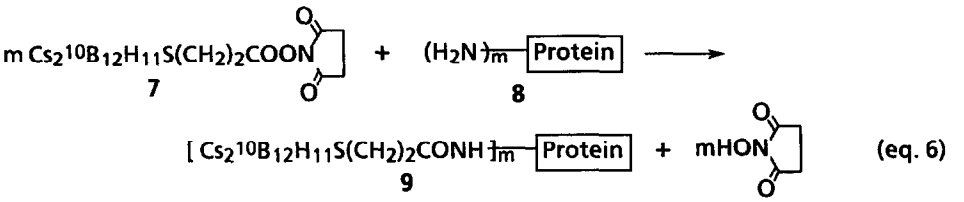
In the alternate procedure (B), $[(CH_3)_4N]_2{}^{10}B_{12}H_{11}SH$ (644 mg) in 15 ml of dimethylformamide (DMF) was added dropwise under stirring to the suspension containing 160 mg of commercially available oil-coated sodium hydride (NaH content was about 60%) in 3 ml of DMF. Hydrogen gas evolved during the addition. The temperature of the reaction mixture was gradually increased to 40-50°C. After hydrogen gas evolution ceased, the reaction mixture was cooled to room temperature and 334 mg of ethyl bromoacetate, $BrCH_2COOC_2H_5$, dissolved in 4 ml of DMF was added dropwise over 2 h. The brown precipitate was filtered off and the filtrates were reduced to a solid under vacuum. To the resulting solid dissolved in 10 ml of distd water, 440 mg of tetramethylammonium chloride in 3 ml of distd water was added. After the filtration, the resulting precipitate was recrystallized from acetonitrile-ethanol. The yield was 110 mg (12.5%). The mother liquor of the reaction was neutralized with dil H_2SO_4 and evaporated to dryness. After washing from ethanol, the resulting solid was recrystallized from H_2O-C_2H_5OH which was identified as $[(CH_3)_4N]_2{}^{10}B_{12}H_{11}SCH_2COONa$ by comparison with the authentic sample. The yields obtained with this method, though very low, are reasonable when one considers that the hydrolysis of ester was conducted in strong basic solution.

The desired polyhedral borane carboxylic acid (**4**) was readily obtained by the hydrolysis of **3a**, **3b** and **3c** in alcoholic sodium hydroxide at room temperature. The resulting aqueous solution was converted to its acid form by passage through a cation exchange resin [Amberlite IR-120(H^+)]. It was taken to pH 7.0 with 1 N CsOH aqueous solution. Cs salt, **4a** (n = 2) was obtained in 70.4% yield (eq. 2). **4b** (n = 1) was obtained from the hydrolysis of **3c** (n = 1, R = C_2H_5) in a similar way.

Many attempts to conduct the reaction of the carboxy group of a chemotherapeutic agent with the amino group of proteins have been reported.[7-15] As an example, we tried the synthesis of ^{10}B-containing polylysine and mouse IgG by the method described above. The reactions of the polyhedral boranes having a carboxy group with an amino group on the protein proceeded smoothly to give the desired boron-protein compounds.



(eq. 5)



(eq. 6)

Protein: Polylysine (MW ≃ 15,000)
Mouse IgG (MW ≃ 150,000)

Table 2

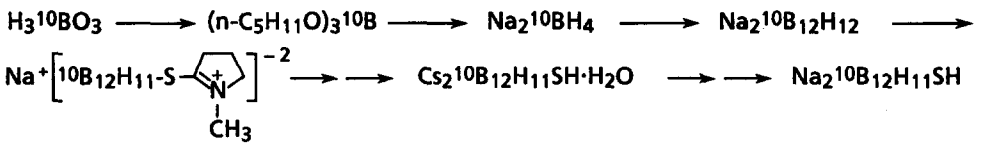
Protein (A)	^{10}B Compound (B)	Reaction mol ratio (A/B)	Conjugate number of ^{10}B atoms per protein molecule[b]
Mouse IgG[a]	4a (n = 2)	1 : 2000	867.7
Polylysine	4a (n = 2)	1 : 68	135.5

a Commercial product.
b ^{10}B was determined by a calorimetric method.[16]

The reaction of 4a with excess of N-hydroxysuccinimide (NHS) in the presence of N,N'-dicyclohexylcarbodiimide (DCC) yielded the boronated ester 7. This ester reacted easily to give ^{10}B-containing proteins (9) as shown in Table 2.

REFERENCES AND FOOTNOTES

1) H. Hatanaka and K. Seto, Nippon Rinsho, Suppl., 1988, **46**, 104.
2) H. Hatanaka, Boron-Neutron Capture Therapy for Tumors (ed. by H. Hatanaka), 1986, 1.
3) $Na_2{}^{10}B_{12}H_{11}SH$ (1) was prepared according to the method as described previously[4] and some oxidation products of 1 were investigated.[5]



4) a) T. Yoshizaki, I. Ikeuchi and K. Nagasawa, Proc. 2nd Int. Symp. on Neutron Capture therapy, 1986, 394. b) M. Komura, K. Aono, K. Nagasawa and S. Sumimoto, Chem. Express, 1987, **2**, 173.

5) a) K. Nagasawa and K. Aono, Book of Abstracts on the Meeting of 1989 International Chemical Congress of Pacific Basin Societies. Part 2, No. 438. b) K. Nagasawa, Y. Ikenishi and Y. Nakagawa, J. Organomet. Chem., in press.

6) B. A. Stoochnoff and N. L. Benoiton, Tetrahedron Lett., 1973, 21.

7) T. Takahashi, U. Fujii, H. Nariuchi and G. Fujii, Oncologia, 1987, **20**, 93.

8) F. Alam, A. H. Soloway, J. E. McGuire, R. F. Barth, W. E. Carey and D. Adams, J. Med. Chem., 1985, **28**, 522.

9) R. F. Barth, F. Alam, A. H. Soloway, D. M. Adams and Z. Steplewski, Hybridoma, 1986, **5**, 43.

10) P. N. Kulkarni, A. H. Glair and T. I. Ghose, Cancer Res., 1981, **41**, 2700.

11) J. Carlsson, H. Drevin and R. Axen, Biochem. J., 1978, **173**, 723.

12) W. B. Stason, M. Vallotton, E. Haber, Biochim. Biophys. Acta, 1967, **133**, 582.

13) R. F. Barth, N. Mafune, F. Alam, D. M. Adams, A. H. Soloway, G. E. Makroglou, O. A. Oredipe, T. E. Blue and Z. Steplewski, Strahlenther. Onkol., 1989, **165**, 142.

14) K. K. Matthay, T. D. Heath and D. Papahadjopoulos, Cancer Res., 1984, **44**, 1880.

15) Y. Hashimoto, Farumashia, 1985, **21**, 1213.

16) I. Ikeuchi and T. Amano, Chem. Pharm. Bull., 1972, **26**, 2619.

(Received in Japan 14 March 1990)