Tetrahedron Letters,Vol.30,No.51,pp 7191-7194,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

BORON-10 CARRIERS FOR NCT. A NEW SYNTHETIC METHOD VIA CONDENSATION WITH ALDEHYDES HAVING BORONIC MOIETY

Yoshinori Yamamoto*, Toshiya Seko, FengGuang Rong, and Hisao Nemoto
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Summary: Several boron-10 containing nucleoside derivatives for neutron capture therapy were synthesized by using 1,2-addition reaction of the carbanions, generated from nucleoside derivatives, with aromatic aldehydes having boronic moiety.

Recently, much attention has been paid to boron-10 neutron capture therapy (^{10}B-NCT)[1~7]. The combination of ^{10}B and thermal neutron produces 2.4 MeVmol^{-1} enough to destroy the tumor cells as shown in equation 1.

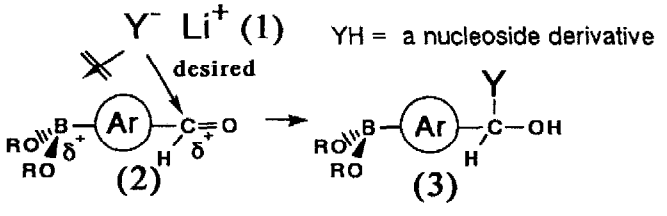
$$^{10}B + {}^{1}n \longrightarrow {}^{4}He + {}^{7}Li + 2.4\ MeV \quad (eq.\ 1)$$

^{10}B NCT is now in the stage of phase III. Since selective production of thermal neutron has been achieved recently[8], one of the unsolved problems is development of new ^{10}B carriers which deliver adequate concentration of ^{10}B atoms to tumors. In order to significantly increase physiological selectivity for tumors relative to dodecaborane derivatives[9] (a second generation compound), several third generation compounds such as ^{10}B-containing acetylcholine[2], nucleosides[3,4] and amino acids[5,6,7], have been synthesized in recent years.

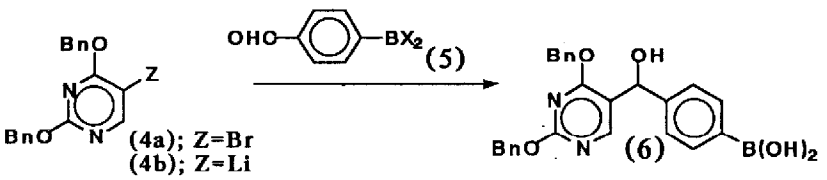
Until now, most of organoboron compounds have been used as synthetic reagents[10], and thus the carbon-boron bond is cleaved at the final stage of synthetic transformation. For the present purpose, the carbon-boron bond has to be kept stable in the final target molecule. One of the most often used procedures for preparation of ^{10}B carriers is the direct reaction of the carbanions (Y-Li$^+$, (1)), derived from the fragment of carriers, with trialkyl borates[4] (eq 2).

$$Y\text{-}Li^{+}\ (1) + B(OR)_3 \longrightarrow Y\text{-}B(OR)_2 \quad (eq.\ 2)$$

However, the desired coupling does not take place in certain cases, since the nuceophilicity of certain carbanions is not strong enough[11] or the carbon-boron bond of the product is not stable enough to be isolated[12]. We report a new general method to prepare boron containing biologically active compounds. We anticipated that the 1,2-addition of (1) to aldehyde group would proceed more readily and rapidly than the substitution of trialkyl borates with (1). If this would be the case and (1) would react selectively with the aldehyde group of (2) even in the presence of another electrophilic center, the desired ^{10}B carriers (3) may be obtained in high yields (Scheme 1). We first attempted the reaction of aryllithium (4b) with several protected 4-formylphenylboronic acids[13] (Table 1, entries a-c).



Scheme 1



Entry	a	b	c	d	e[a]
X_2					
	(5a)	(5b)	(5c)	(5d)	(5e)
Yield(%)	17	50	52	77	7

Table 1

a: DME/THF=1/1 was used as a solvent since (5e) is insoluble in THF.

The desired 1,2-adduct (6) was obtained in low yield along with several byproducts when catechol was used as the protective group of dihydroxyboryl group (entry a). The yield was enhanced with 1,3-diol protecting groups. (entries b and c). Use of N-methyldiethanolamine gave the best result (entry d). It is considered that the vacant orbital of boron atom is occupied with the lone pair electrons of nitrogen atom, preventing the nucleophilic attack to boron atom[14]. However, use of N-diethanolamine resulted in very low yield[15] (entry e).

Further characteristic feature of N-methyldiethanolamine is following; mixing of N-methyldiethanolamine and a dihydroxyboryl compound in THF at room temperature followed by concentration of the solvent gave the corresponding protected boronic derivatives within several minutes, which were subsequently used in the 1,2-addition reaction without further purification. This protection group was removed in aqueous NH_4Cl within a minute. The protected (5d) and (7) are soluble in many organic aprotic solvents like THF, dichloromethane and chloroform, while either 3- or 4-formylphenylboronic acid is not soluble well in the solvents. Thus, the temporary attachment of N-methyldiethanolamine is a convenient method[16] for the protection of dihydroxyboryl group from the nucleophilic attack.

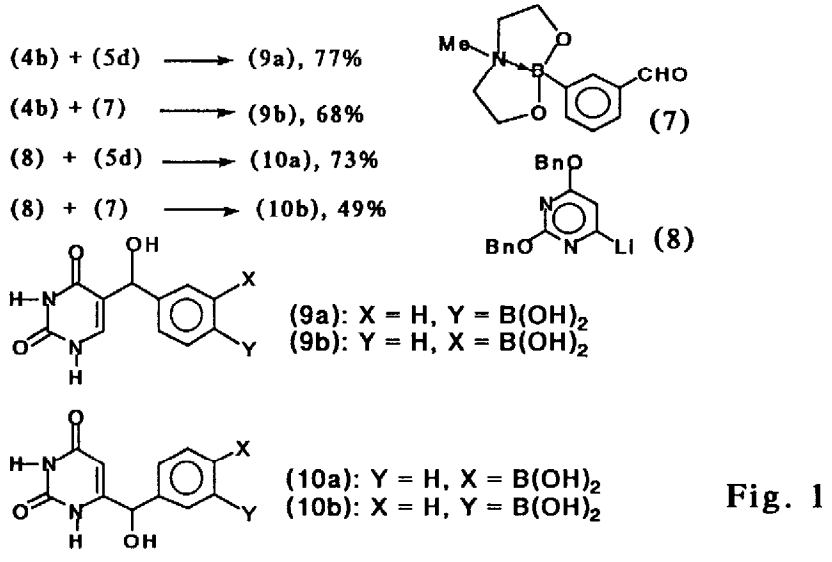


Fig. 1

General procedure is following: a solution of (5d) (1 mmol) was added to the aryllithium (4b), prepared from (4a) (2 mmol) with butyllithium (1.98 mmol)[4] in THF at -85°C. The reaction mixture was stirred for 30 min at -85°C and quenched with aqueous ammonium chloride solution. The desired product (6) was isolated by column chromatography on silica gel. The deprotection reaction of benzyl groups in (6) with palladium on carbon under hydrogen atmosphere in methanol gave (9a)[17] in quantitative yield. Quite similarly, the reaction of (4b) with (7) followed by deprotection produced (9b)[18] in 68% yield. Furthermore, the present method could be applied to the reaction of (8); (10a)[19] and (10b)[20] were obtained from (5d) and (7), respectively, in good to allowable yields (Fig. 1).

We next examined whether the present method could be applicable to more complex molecules or not. The reactions of the carbanions bearing sugar groups, (11)[21], (12a)[22], (12b)[22], and (13)[22], with the boron containing aldehydes proceeded smoothly to give the desired nucleosides (14) ~ (16)[23] in reasonable to good yields (Fig. 2). The C-C bond formation reaction, the boron containing aldehyde-organolithium condensation method, is operationally very simple, and possesses wide applicability compared to the previous direct method. We are now in a position to prepare systematically a number of boron containing nucleosides, and hence to elucidate the relation between activity to ^{10}B-NCT and molecular structure.

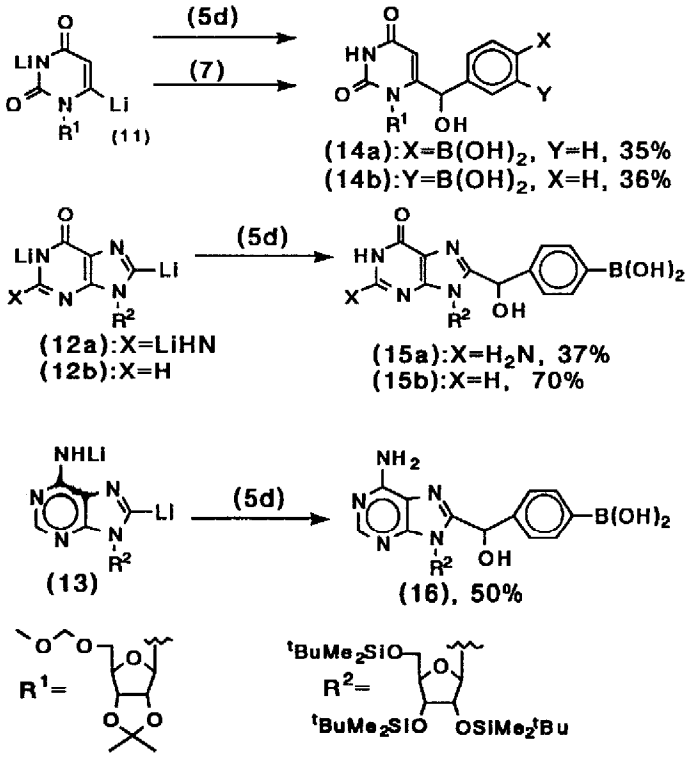


Fig. 2

References and Notes

1) Y. Yamamoto, *Kagaku*, 1986, **41**, 774; A. H. Soloway, *"Progress in Boron Chemistry"* , **1**, 203
2) B. F. Spielvogel, F. U. Ahmed, A. T. Mcphail, *J. Am. Chem. Soc.*, 1986, **108**, 3824.
3) T. K. Laio, E. G. Podrebarac, C. C. Cheng, *J. Am. Chem. Scc.*, 1964, **86**, 1869.
4) R. F. Schinazi, W. H. Prusoff, *J. Org. Chem.*, 1985, **50**, 841.
5) D. H. Kinder, M. M. Ames, *J. Org. Chem.*, 1987, **52**, 2452.
6) D. S. Matteson, K. M. Sadhu, G. E. Leinhard, *J. Am. Chem. Soc.*, 1981, **103**, 5241.
7) B. F. Spielvogel, L. Wojnowich, M. K. Das, A. T. McPhail, K. D. Hargrave, *J. Am. Chem. Soc.*, 1976, **98**, 5702.
8) T. Kobayashi, and K. Kanda, *Radiation Research*, 1982, **91**, 77; T. Kobayashi, and K. Kanda, *Nuclear Instruments and Methods*, 1983, **204**, 525.
9) F. Alam, A. H. Soloway, J. E. McGuire, R. F. Barth, W. E. Carey and D. Adams, *J. Med. Chem.* 1985, **28**, 522.
10) For example, H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, 'Organic Synthesis via Boranes', Wiley, New York 1975.
11) The coupling reaction of the carbanions **(11)**, **(12a)**, **(12b)** and **(13)** with tributyl borate did not take place. The coupling takes place only with the carbanion of **(4b)**[4] in 87% yield.
12) The reaction of **(8)** with tributyl borate gave very labile boron containing compound[4].
13) p- and m-Formylphenylboronic acids were prepared from p- and m-bromobenzaldehyde, respectively, according to a modified method of the reported procedure; H. R. Synder, A. J. Reedy, W. J. Lennarz, *J. Am. Chem. Soc.*, 1958, **80**, 835.
14) W. Kliegel, S. J. Rettig, J. Trotter, *Can. J. Chem.*, 1988, **66**, 1091.
15) In entry e, the proton on the nitrogen atom would be deprotonated by the base to form the nitrogen anion, resulting in complex mixtures. Similarly, several unidentified by-products were obtained in entry a.
16) In contrast, diethanolamine forms stable complex with dihydroxyboryl group, and thus the deprotection condition is not mild. See reference 5.
17) ^{13}C-NMR (67.75 MHz, DMSO-d_6) δ 163.1, 150.9, 145.6, 137.7, 133.7, 125.4, 116.1, 67.7. (The signal of carbon attached to boron atom was too weak to be observed.)
18) ^{13}C-NMR (67.75 MHz, DMSO-d_6) δ 163.3, 151.2, 142.6, 137.8, 133.7 (br, weak, -C-B(OH)$_2$), 132.8, 132.4, 128.5, 126.9, 116.3, 67.6.
19) ^{13}C-NMR (67.75 MHz, DMSO-d_6) δ 164.1, 158.6, 151.4, 142.6, 134.0, 125.6, 96.1, 70.6. (The signal of carbon attached to boron atom was too weak to be observed.)
20) ^{13}C-NMR (67.75 MHz, DMSO-d_6) δ 164.6, 159.1, 151.8, 140.2, 134.5 (br, weak, -C-B(OH)$_2$), 134.1, 132.9, 129.0, 127.6, 96.5, 71.1
21) H. Tanaka, H. Hayakawa, T. Miyasaka, *Chem. Pharm. Bull.*, 1981, **29**, 3565.
22) H. Hayakawa, K. Haraguchi, H. Tanaka, T. Miyasaka, *Chem. Pharm. Bull.*, 1987, **35**, 72.
23) Each compound **(14)** ~ **(16)** was obtained as a mixture of ~1:1 diastereomers.

(Received in Japan 13 October 1989)