Molecular Design and Synthesis of B-10 Carriers for Neutron Capture Therapy

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Molecular design and synthesis of B-10 carriers for neutron capture therapy

Yoshinori Yamamoto

Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Abstract · Several new synthetic methods for B-10 containing nucleoside derivatives have been developed. (1) The palladium-catalyzed coupling reaction of halogenated nucleoside derivatives with the aryltin compound having a boronic moiety proceeds chemoselectively at the C-Sn bond rather than the C-B bond to give boron-containing nucleoside derivatives. (2) The 1,2-addition reaction of the carbanions, generated from nucleoside derivatives, with aromatic aldehydes having boronic moiety gives boronated nucleoside derivatives bearing a hydroxy group. (3) The reaction of nucleoside derivatives having an acetylene group with decaborane produces carborane containing nucleosides. (4) Boron containing amino acid derivatives, which have both hydrophilic and liphophilic moiety, have been prepared. The cytotoxicity of the boron-containing biorelated compounds, and their application to neutron capture therapy are discussed.

INTRODUCTION

The theoretical attractiveness of neutron capture therapy (NCT) versus other radio- and chemotherapic approaches for the treatment of cancer is as appealing now as when first proposed by Locher (ref. 1). The interaction of boron-10 and thermal neutron produces intense, ionizing radiation that is confined to single or adjacent cancer cells.

$$^{10}B + {}^{1}n \longrightarrow {}^{7}Li + {}^{4}He + 2.4Mev$$

Since a practical method for production of highly purified thermal neutron has been accomplished, much attention has been paid to the design and synthesis of boron-10 (^{10}B) carriers that deliver adequate concentration of ^{10}B atoms to tumors (ref. 2).

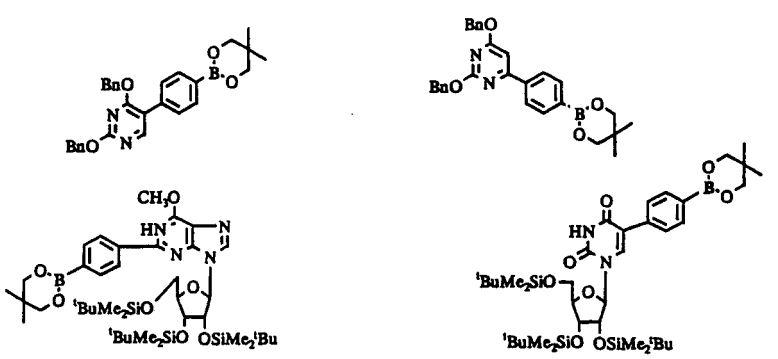
PREPARATION OF MONO-BORON CONTAINING CARRIERS

We have developed several new synthetic methods for B-10 containing bio-related molecules. (1) The palladium-catalyzed coupling reaction of halogenated nucleoside derivatives with the aryltin compound having a boronic moiety proceeded chemoselectively at the C-Sn bond rather than the C-B bond to give boron containing nucleoside derivatives in good yields (eq. 1) (ref. 3). The use of $Pd(PPh_3)_4$ as a catalyst, and use of a less polar solvent such as

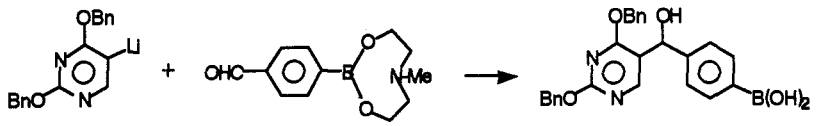
$$R\text{-}X + Bu_3Sn\text{-}Ar\text{-}B(OR^1)_2 \xrightarrow{Pd\ cat.} R\text{-}Ar\text{-}B(OR^1)_2 \qquad \text{eq 1}$$

toluene and of higher reaction temperature were essential to achieve the coupling. The use of acetonide and methoxymethyl group as the sugar protecting group, or the reaction without protection gave poor results. The sterically bulky t-butyldimethylsilyl group afforded the coupling products in much higher yields. The compounds prepared by the Pd-catalyzed coupling are shown in Scheme 1.

Scheme 1 B-10 Carriers Prepared by Pd-catalyzed Coupling Reactions



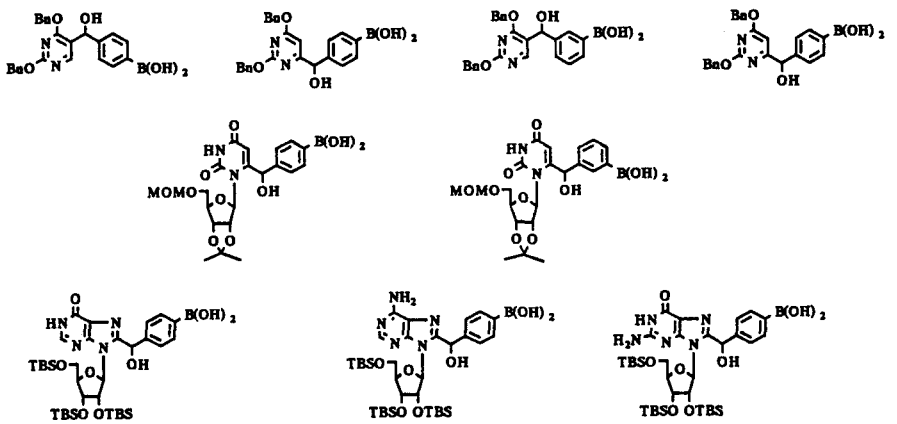
One of the most often used procedures for preparation of ^{10}B carriers is the direct reaction of the carbanions YLi with trialkyl borates (substitution reaction) (ref. 4). However, the desired coupling does not take place in certain cases. (2) We anticipated that the 1,2-addition of YLi to aldehyde group would proceed more readily and rapidly than the substitution reaction; YH=nucleoside derivatives. Actually, YLi reacted selectively with the aldehyde group in the presence of boronic groups, giving the boron containing biologically active compounds (eq. 2) (ref. 5). Here also,



eq 2

proper choice of the protective group of boronic acid was important for obtaining the coupling product in high yield. Use of N-methyldiethanolamine gave the best result. The compounds prepared by this method are shown in Scheme 2.

Scheme 2 **B-10 Carriers Prepared by Condensations via Aldehydes Having Boronic Moiety**

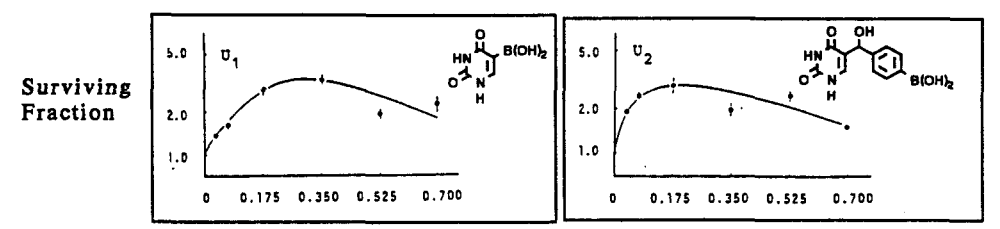


TOXICITY OF SOME CARRIERS

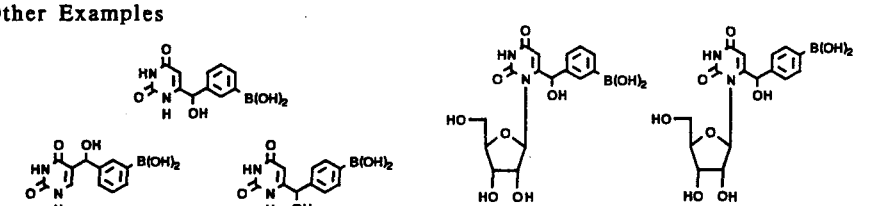
Toxicity of the above ^{10}B carriers toward HeLa-S3 cells was investigated by Prof. Ujeno's group at Kyoto University (ref. 6). Some of the results are shown in Scheme 3. As the drug concentration increased from 0 to 0.7×10^{-4}M in H_2O, the surviving fractions of U_1 and U_2 were always greater than 1.0. Accordingly, it is clear that the boronic acid derivatives (U_1 and U_2) are not toxic toward HeLa-S3 cells at the concentration of 0.7×10^{-4}M. Much concentrated solution could not be prepared because of low solubility of U_1 and U_2 in H_2O. However, the compounds having the sugar moiety, as shown in other examples, were very soluble in water. These compounds exhibited no toxicity toward HeLa-S3 cells even in much higher concentrations.

Scheme 3 **Toxicity of ^{10}B Carriers Toward HeLa-S3 Cells**

(Cooperative work with Prof. Ujeno, Dr. Akaboshi and Dr. Kitaoka)

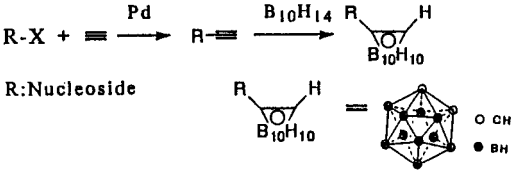


Other Examples

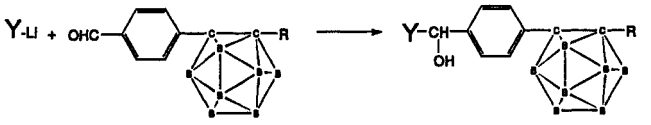


PREPARATION OF POLY-BORON CONTAINING CARRIERS

(3) We next examined the preparation of decaborane containing uridine and guanosine derivatives (ref. 7). It is known that the reaction of acetylenic derivatives with decaborane produces 1,2-dicarba-closo-dodecaborane (12) (ref. 8). Our strategy is shown in eq 3. The acetylene derivatives of nucleosides, derived from the palladium catalyzed coupling between acetylene and RX(R: nucleoside), were treated with $B_{10}H_{14}$ in the presence of CH_3CN, giving the desired products in good yields. The compounds prepared by this method are shown in Scheme 4. An application of the carbanion condensation method mentioned in eq 2 to the aldehyde having an ortho-carborane moiety was also examined (ref. 9). The reaction of YLi with the R-substituted aldehyde proceeded smoothly, giving the desired product (eq 4). If R was hydrogen, that is, if the un-substituted aldehyde was used, the condensation did not take place. Presumably, the hydrogen abstraction by YLi took place, giving polymerized materials. The compounds prepared by this procedure are also shown in Scheme 4.

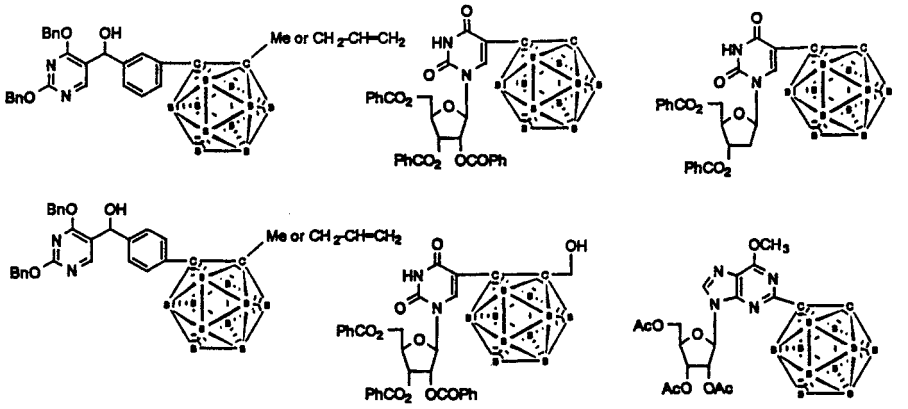


eq 3



eq 4

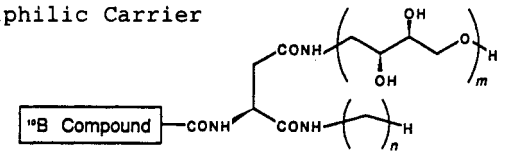
Scheme 4 B-10 Carriers Containing Carborane Structure



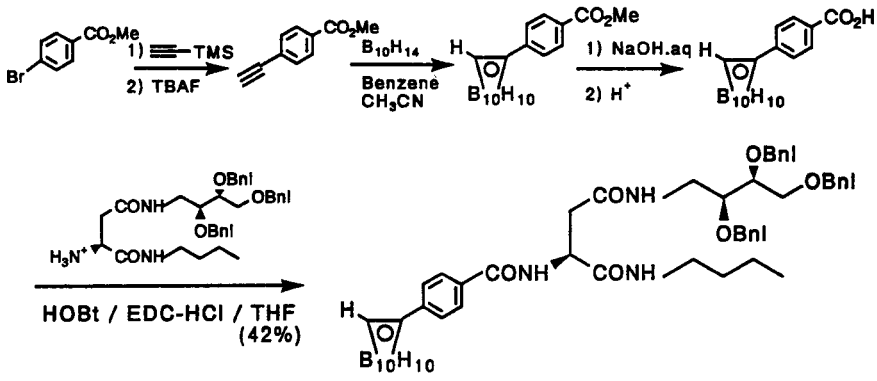
HYDROPHILICITY AND LIPOPHILICITY INVESTIGATION OF CARRIERS

Hydrophilic character is required for B-10 carriers in order to be delivered to cancer cells. On the other hand, lipophilic character is needed to penetrate cell membrane. According, an amphiphilic characteristic is essential for an ideal carrier. We intended to prepare such compounds, and a typical example is shown in Scheme 5 (ref. 10). The chain length of hydrocarbon part, and a liphophilic part, can be changed at will. The length of alcohol (after debenzylation) chain (a hydrophilic part) also can be changed. The two chains were combined via the amide bonds. The carrier is connected to the carborane moiety again via the amide bond.

An Amphiphilic Carrier

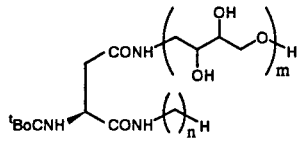


Scheme 5 Preparation of B-10 Carriers Having an Amphiphilic Character



The partition coefficient of the carriers (m=1 and n=4, or m=1 and n=8) was investigated. The result is shown in Scheme 6. When the length of lipophilic part increased, needless to say, the solubility to the organic solvents increased. The compound with m=1 and n=8 was soluble both in water and in organic solvents. So, we are now in a position to have an amphiphilic carrier.

Scheme 6 Control of Hydrophilicity/Lipophilicity



Partition Coefficient: Pow=Corg / Cwater

m	n	$CHCl_3$	C_6H_6	$C_8H_{17}OH$
1	4	0.061	0.022	1.5
1	8	0.44	0.29	

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