Synthesis of THIQ Derivatives as Potential Boron Neutron Capture Therapy Agents: N-Functionalized *o*-Carboranylmethyl Benzopiperidines

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Abstract: A method for synthesizing *o*-carborane substituted tetrahydroisoquinolines containing a polar functional group such as sulfonic or phosphoric acid on the nitrogen atom of the piperidine ring, starting from *N*-(2-arylethyl)sulfamic acid or 2-arylethylamidophosphate, is described. In vitro studies showed that the desired compounds **7a** and **10b** accumulate to high levels in B-16 melanoma cells despite low cytotoxicity.

Key words: BNCT, *o*-carborane, tetrahydroisoquinoline, 2-arylethylamine, iminium ion

o-Carborane is a stable, lipophilic molecule that resembles benzene in terms of reactivity and bulkiness.[1] Its remarkable thermal and chemical stability makes it a unique candidate molecule for use in several specialized applications in the fields of materials science, coordination compounds, and radiopharmaceuticals. The medicinal chemistry of *o*-carborane, which contains ten boron atoms, gives it a clear advantage for use in boron neutron capture therapy (BNCT).[2] BNCT was first proposed as a potential cancer therapy in 1936, but its successful application in the treatment of cancer patients still presents a challenge in medical research.[3] A major challenge in designing boron-containing drugs for BNCT of cancer is the selective delivery of ^{10}B to the tumor as well as water solubility.[4]

Previously, we synthesized 1,2,3,4-tetrahydro isoquinolines (THIQ, **2**), *s*-triazines (**3**) and piperidines (**4**) containing the *o*-carborane unit as potential BNCT agents (Figure 1).[5] Among these compounds, THIQ (**2**) derivatives exhibited promising results in that they showed significantly greater boron uptake compared to boron phenylalanine (BPA). However, the water solubility of compounds **2** needs to be improved if they are to be used as BNCT agents. Our promising preliminary results led us to investigate the possibility of developing water-soluble THIQ derivatives.

It has been suggested that the addition of sulfonic or phosphoric acid functionalities to molecules will increase their water-solubility in biological systems. Therefore, in the present study we synthesized the THIQ derivatives **7**, **9**, and **13** containing sulfonic or phosphoric acid moieties on the nitrogen atom of the piperidine ring, and tested the accumulation of selected molecules in vitro (Scheme 1).

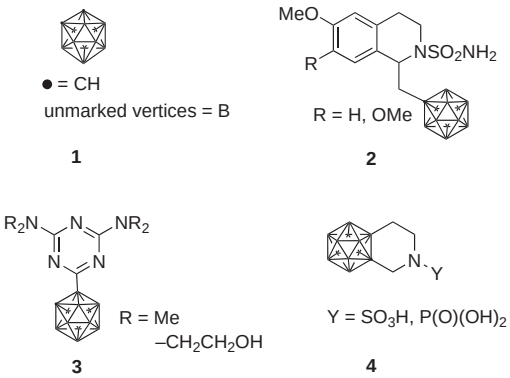

Figure 1 BNCT agents developed in our laboratory including 1,2,3,4-tetrahydro isoquinolines (THIQ, **2**), *s*-triazines (**3**), and piperidines (**4**).

The starting sulfamic acid **6** and phosphates **8** and **12** were prepared by treating chlorosulfonic acid or diethyl chlorophosphate with the corresponding 2-arylethylamines **5** and **11** at room temperature for 3 hours in dichloromethane, according to established synthetic protocols.[6] The starting acetal **15** was obtained in 95% yield by direct reaction of lithio-*o*-carborane with chloroacetaldehyde diethyl acetal by the Rudolph method as shown in Scheme 2.[7]

Intramolecular cyclization of starting materials **6**, **8**, or **12** with acetal **15** proceeding through an iminium ion intermediate in formic acid (96% in H_2O) gave the desired products **7**, **9** and **13** in 42–70% yield. In these processes, an electron-withdrawing substituent was introduced on the nitrogen of **5** and **11** to increase the electrophilicity of the iminium intermediate.[8] Deethylation of **9** and **13** by treatment with hydrogen bromide in acetic acid afforded the free acids **10** and **14** in 42–45% yield.[9]

Selected spectroscopic properties of the piperidine rings and carborane units of **7**, **9**, **10**, **13** and **14** are given in Table 1. Compounds **7**, **9**, **10**, **13**, and **14** showed absorption bands in the infrared spectrum at 2583–2606 cm^{-1} characteristic of vibrations of the B–H group.[10] Diagnostic signals of compounds **7**, **9**, **10**, **13** and **14** were observed at δ = 4.09–4.78 ppm in the ^1H NMR spectra and

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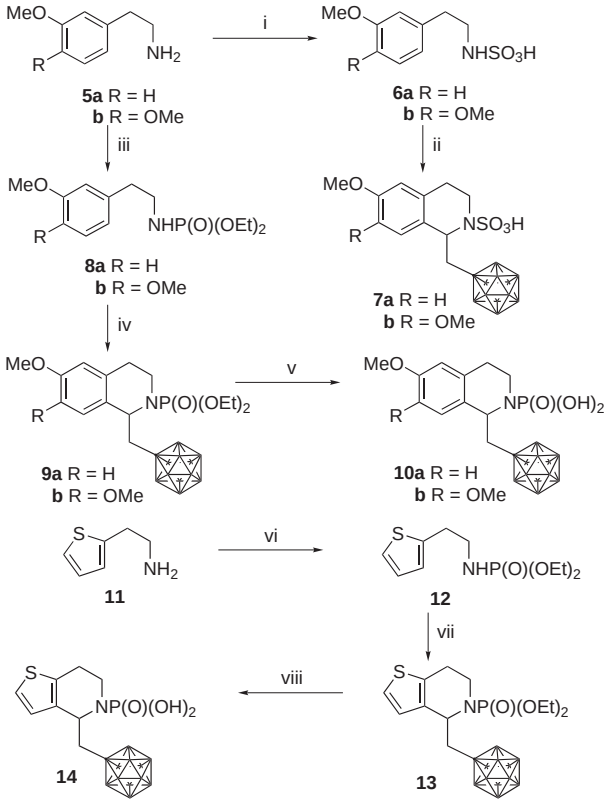
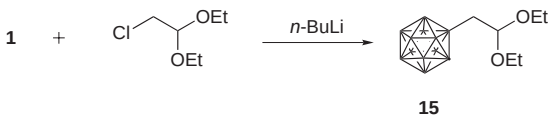


Scheme 1 *Reagents and conditions:* (i) $ClSO_3H$, $CHCl_3$, 0–5 °C; (ii) **15**, CH_2Cl_2, r.t.; (iii) $ClP(O)(OEt)_2$, $CHCl_3$, 0–5 °C; (iv) **15**, CH_2Cl_2, r.t.; (v) *c*-HBr, AcOH, r.t.; (vi) $ClP(O)(OEt)_2$, $CHCl_3$, 0–5 °C; (vii) **15**, CH_2Cl_2, r.t.; (viii) *c*-HBr, AcOH, r.t.

at δ = 54.1–54.6 ppm in the ^{13}C NMR spectra for the methine (C-1) unit furnished by the acetal **15**. The methine unit signals at δ = 4.51–4.56 ppm in the ^{1}H NMR spectra of the starting acetal **15** move downfield upon



Scheme 2 Synthesis of *o*-carboranyl acetal **15**.

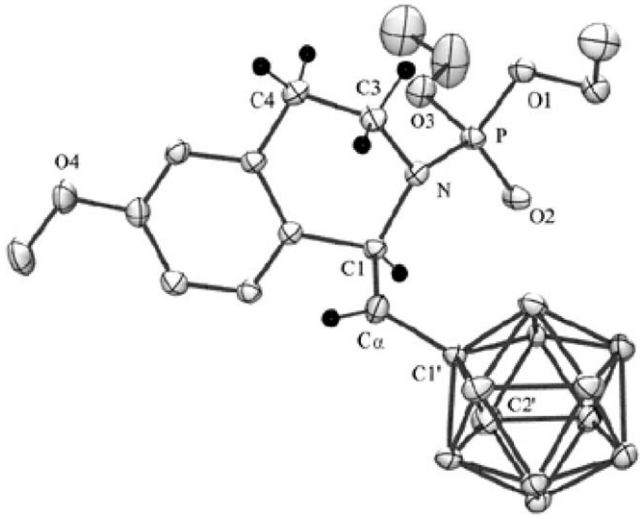
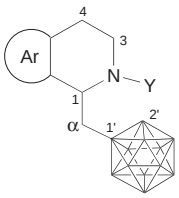


Figure 2 Molecular structure of **9b** with thermal ellipsoids drawn at the 30% level.

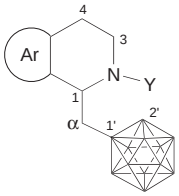
cyclization. To authenticate the assignments of the piperidine framework made on the basis of NMR spectral data, an X-ray structural study of **9b** was undertaken to confirm the basic structure shown in Figure 2.

Table 1 Summary of Selected Physical and Spectral Properties of the Piperidines **7**, **9**, **10**, **12**, **13**, and **14**



Entry	Compd	Y	Mp (°C)[a]	Yield (%)[b] IR (BH, cm^{-1})	NMR (^{1}H/^{13}C) C(1)	C(3)	C(4) C(α)		C(1′)	C(2′)
1	**7a**	SO_3H	123–125	54 2583	4.74–4.77 (m) 54.5	3.45–3.54 (m) 41.8	3.00–3.13 (m) 39.5 24.9		64.0	4.82 (br s) 72.6
2	**7b**	SO_3H	170–177	70 2589	4.58–4.63 (m) 54.6	3.35–3.42 (m) 42.0	2.98 (dd), 3.09 (dd) 40.1	2.83–2.95 24.3	64.6	5.33 (br s) 73.7
3	**9a**	P(O)(OEt)	133–135	42 2604	4.09 (dd), 4.67 (dd) 53.4	3.11–3.22 (m), 3.49 (ddd) 42.9	2.97–3.05 (m) 36.6	2.88–2.93 (m) 26.7	63.2	5.49 (br s) 72.8

Table 1 Summary of Selected Physical and Spectral Properties of the Piperidines **7**, **9**, **10**, **12**, **13**, and **14** (continued)



Entry	Compd	Y	Mp (°C)[a]	Yield (%)[b] IR (BH, cm^{-1})	NMR ($^1H/^{13}C$) C(1)	C(3)	C(4)	C(α)	C(1′)	C(2′)
4	**9b**	P(O)(OEt_2	145–147	45 2591	4.65 (dd) 53.6	3.10 (m), 3.50 (ddd) 42.8	2.89–2.91 (m) 36.8	2.46–2.51 (m) 25.9	63.1	5.46 (br s) 72.9
5	**10a**	P(O)(OH_2	291–294	42 2583	4.61–4.69 (m) 54.5	3.12–3.17 (m) 41.7	2.93–3.05 (m) 40.7 25.9		64.8	54.0 (br s) 74.2
6	**10b**	P(O)(OH_2	295–296	45 2591	4.59–4.63 (m) 54.6	3.35–3.42 (m) 41.6	2.99 (dd), 3.15 (dd) 39.8	2.84–2.96 24.8	64.9	5.44 (br s) 74.3
7	**13**	P(O)(OEt_2	106–107	48 2606	4.77 (dd) 52.3	3.07–3.18 (m), 3.55–3.61 (m) 42.0	2.82 (dd), 2.95–3.03 (m) 37.4	2.51–2.63 (m) 23.7	63.1	5.55 72.6
8	**14**	P(O)(OH_2	270–270	42 2591	4.69–4.78 (m) 41.4	2.91–3.12 (m) 54.5	2.50–2.80 (m) 40.8 21.9		64.8	5.34 (br s) 74.1

[a] Melting points are uncorrected.
[b] Purified yields

Contrary to our expectation, the water solubility of the tested samples was not improved. However, in an in vitro study, compounds **7a** and **10b** were found to accumulate markedly in B-16 melanoma cells (Table 2).

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Table 2 Cytotoxicity (IC_{50}) and Boron Uptake

Entry	Compd	B-16[a]		Boron uptake[b]	
		μg/mL	M	μg B/10^6 cells	± SD
1	**7a**	18	4.33×10^{-5}	0.41	0.047
2	**10b**	18	4.33×10^{-5}	1.00	0.098
BPA				0.083	0.012

[a] B-16: B-16 melanoma cell.
[b] Boron uptake by B-16 cells was determined using the ICP-AES method.[11] Briefly, cells were cultured in Falcon dishes (ϕ 90 mm) until they had grown to fill the dishes (ca. 3.0×10^6 cells/dish). Cells were then incubated for 3 h with Eagle-MEM medium containing one of the test compounds (boron concentration: 10.8 ppm). At 3 h, the cells were washed three times with PBS (–) and processed for the determination of the boron concentration by ICP-AES. Each experiment was carried out in triplicate.

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