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A convenient synthesis of the novel carboranyl-substituted tetrahydroisoquinolines: application to the biologically active agent for BNCT

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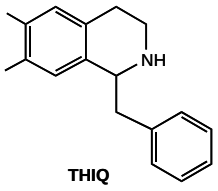
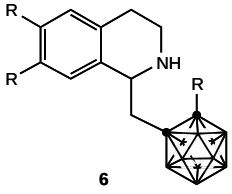
Abstract—A convenient method for *o*-carborane-substituted tetrahydroisoquinolines (THIQ) is described; in particular, compound **8c** accumulates in B-16 melanoma cells with a significantly high level although its cytotoxicity is significantly low.

Isoquinoline alkaloids, which are widely distributed in the plant and animal kingdoms, have received much attention because of their important biological activities.[1] For example, 1,2,3,4-tetrahydroisoquinolines present in the mammalian brain play a major role in the therapy of variety of neurological disorders.[2] In particular, 1-arylmethyl-1,2,3,4-tetrahydroisoquinoline (THIQ) has been reported to be a potent dopamine antagonists with respect to neuroleptic agents.[3] This property makes the tetrahydroisoquinoline carboranes promising candidates for delivering borons for the treatment of brain tumors. Our synthetic strategy was to use tetrahydroisoquinoline as a carrier for ^{10}B, the target molecules being the tetrahydroisoquinolines in which the boron functionality was present as a carborane, 1,2-dicarbadodecaborane, a icosahedron cage of ten boron atoms and two carbon atoms. The large number of boron atoms has a clear advantage for BNCT.[4] The synthetic utility and the potent pharmacological activity of tetrahydroisoquinolines have attracted the attention of synthetic chemists in recent years, and consequently, several efficient synthetic procedures have been explored.[5] A convenient method for the synthesis of these types of compounds is intramolecular cyclization, in which arylethylamines are activated towards electrophilic attack under acidic conditions by their reaction with aldehydes to form iminium ions.[6] Thus, the present study has demonstrated the feasibility of extending the known intramolecular cyclization of arylethylamine with the *o*-carboranylaldehyde or *o*-carboranylaldehyde diethyl acetal.

We herein report the synthesis of tetrahydroisoquinolines **6** and **8** in which the benzyl groups of THIQ are replaced by the *o*-carboranyl methyl unit. Compounds **6** and **8** are the first fully characterized boronated tetrahydroisoquinolines to be reported and contain one *o*-carborane cage covalently linked to the tetrahydroisoquinoline periphery.



THIQ



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The general synthetic strategy for the preparation of the starting materials used to prepare the reported *o*-carboranylacetaldehydes (**4**) relied on the methods developed by Rudolph.[7] The synthesis of **4** was accomplished in two steps (Scheme 1).

The synthesis was initiated by the monolithiation of the *o*-carborane derivatives (**1**). When *o*-carborane was reacted with an equimolar quantity of *n*-butyllithium in benzene, followed by its reaction with bromoacetaldehyde diethyl acetal (**2**), the *o*-carboranylacetaldehyde diethyl acetal (**3**) was formed in high yield (77%). The

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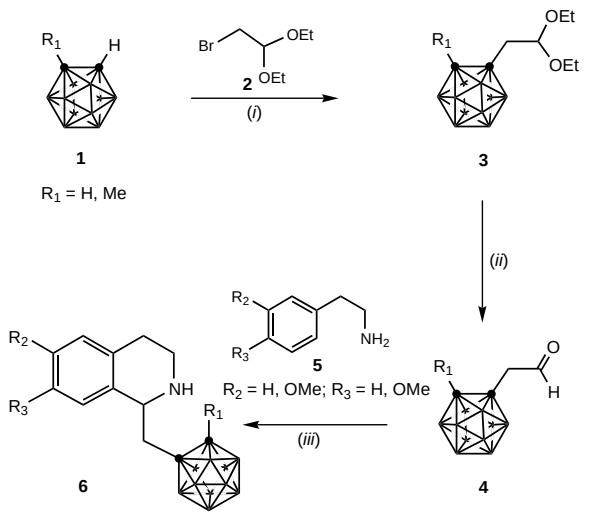


Scheme 1. Synthesis of **6**. *Reagents and conditions*: (i) Bu^{n}Li, benzene, 25°C; (ii) AcOH, HCl, 25°C; (iii) HCO_2H, reflux.

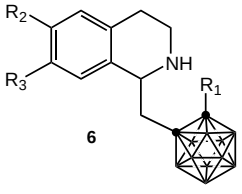
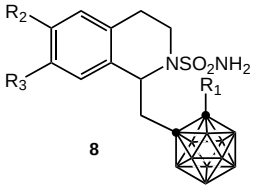
resultant diethyl acetal (**3**) was hydrolyzed with acetic acid in the presence of concentrated HCl to give the corresponding aldehyde (**4**) in good yield (71%). With this *o*-carboranylacetaldehyde (**4**) now available, the Pictet–Spengler reaction (intramolecular cyclization) with the arylethylamine (**5**) was investigated as a route to the target compounds **6** (Scheme 1).[8] Intramolecular cyclization of the arylethylamine with aldehyde proceeds under reflux conditions; this method of heterocyclic ring formation was investigated as a route to the target compounds. Thus, this condensation was finally achieved in 41–58% yield by refluxing the mixture of **4** and **5** in a formic acid solution (Table 1). In this case, no color change was observed and the disappearance of the starting material was detected by TLC after 12 h of vigorous stirring at refluxing temperature. By replacing *o*-carboranylacetaldehyde (**4a**) with 1-methyl-*o*-carboranylacetaldehyde (**4b**), the cyclization generated the corresponding product in moderate yield. In particular, acidic reaction conditions were advantageous in obtaining the target because the *o*-carborane cage was relatively stable under such conditions.[9]

Identification of all isolated products **6** was accomplished with the aid of infrared, ^{1}H and ^{13}C NMR, and elemental analysis. The NMR data for these structurally similar molecules are in accord with their formulations. Such an assignment was further assumed by comparison of the NMR data for similar compounds reported in the literature.[3]

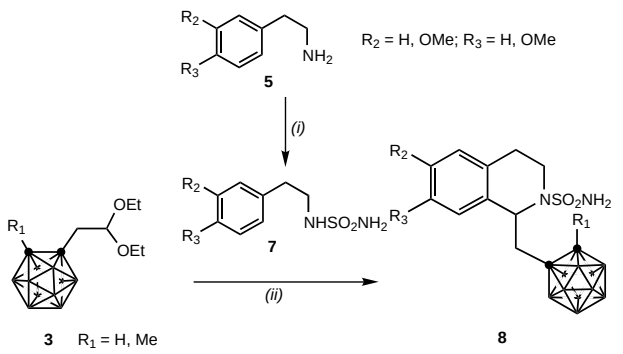
As an extension of these studies, the reaction of the aminosulfonyl functionalized arylamine (**7**) with *o*-carboranylacetaldehyde diethyl acetal (**3**) was investigated in order to evaluate the effect of placing a sulfonyl group on the amine functionality. It has been noted that the sulfamide moiety is widely represented in many natural products and plays an important role in biological activities.[10] The approach we had in mind for the synthesis of the aminosulfonyl tetrahydroisoquinoline skeleton was based on our previous success involving the α-sulfamidoalkylation procedure[11] outlined in Scheme 2.

The requisite aminosulfonyl functionalized arylamines (**7**) could be conveniently prepared by aminosulfonylation of the nitrogen atom of **5** according to established synthetic protocols.[12] When the sulfamide (**7**) was treated with acetal **3**, the cyclized 2-aminosulfonyl-1-(*o*-carboran-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (**8**) was obtained in 70–87% yield. In this case, the cyclization to **8** is faster and the reaction is nearly complete in 6 h at room temperature while the cyclization to **6** required an overnight reflux. Having the sulfonyl group in the arylamine undoubtedly facilitates cyclization of the initially formed iminium ion. The aforementioned synthesis of **6** is plagued by the harsh experimental

Table 1. Reaction conditions and yield of products **6**[13] and **8**[14]

	Entry	Product	R_1	R_2	R_3	Reaction conditions		Yield (%)[a]
						Temp.	Time (h)	
	1	**6a**	H	OMe	H	Reflux	12	41.2
	2	**6b**	Me	OMe	H	Reflux	12	47.7
	3	**6c**	H	OMe	OMe	Reflux	12	55.4
	4	**6d**	Me	OMe	OMe	Reflux	12	57.7
	5	**8a**	H	OMe	H	rt	6	71.1
	6	**8b**	Me	OMe	H	rt	6	70.3
	7	**8c**	H	OMe	OMe	rt	6	81.0
	8	**8d**	Me	OMe	OMe	rt	6	87.0

[a] Isolated yield.



Scheme 2. Synthesis of **8**. *Reagents and conditions*: (i) $(H_2N)_2SO_2$, H_2O, reflux; (ii) HCO_2H, 25°C.

conditions necessary for ring closure that limit their use with precursor compounds containing sensitive functional group such as *o*-carborane. Thus, the cyclization procedure outlined in Scheme 2 represents an efficient and mild approach toward this important class of nitrogen heterocycles.

For the 2-aminosulfonyl tetrahydroisoquinolines **8**, elemental analyses confirmed the proposed formulation for this compound. The ^1H and ^{13}C NMR data, as well as the IR spectrum of these compounds, provided further confirmation of their identity. The final structural proof of **8b** was also obtained by an X-ray analysis, which has been performed on the crystals of **8b** (Fig. 1). The crystal structure corresponds well with the conformation and configuration derived from the NMR. All three regions, i.e. aryl, heterocyclic ring, and tethered *o*-carboranylmethyl group of **8b**, can be clearly assigned. The crystal structure of **8b** confirms that the heterocyclic ring exists in a half-chair conformation with an axial aminosulfonyl *N*-substituent and pseudo-axial accessory *o*-carborane cage held in a nearly perpendicular orientation relative to the fused ring system. The methylene-chain is not in a fully extended conformation but is nonetheless oriented such that the aminosulfonyl unit is held remote from the carborane fragment.

In conclusion, we have developed a general and versatile method for the preparation of tetrahydroisoquinolines flanked with an *o*-carborane unit at position 1. The intramolecular cyclization of arylethylamine is therefore, demonstrated to be a mild process which has great potential in medicinal chemistry for joining chemically sensitive targeting moieties to pharmacophores for BNCT. Furthermore, it is proved by in vitro study that compound **8c** accumulates highly into B-16 melanoma cells although it has low cytotoxicity (Table 2). The construction of alternative, more polar substituents on tetrahydroisoquinoline is now under active investigation.

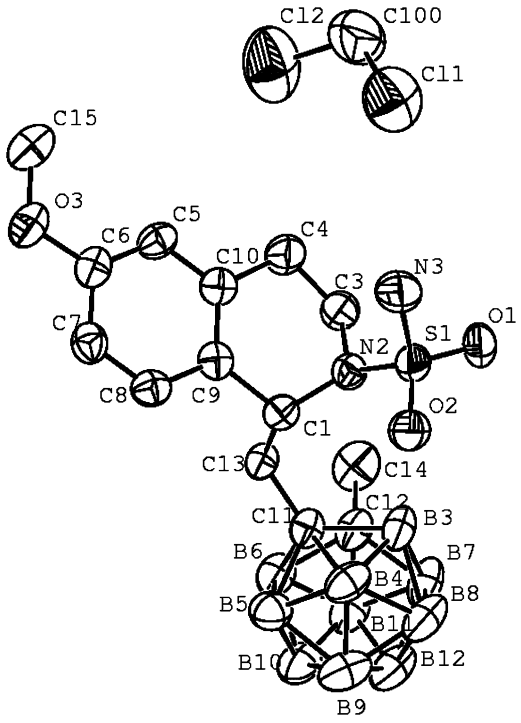


Figure 1. ORTEP drawing of compound **8b**.

Supplementary information

Electronic supplementary information (ESI) available: experimental details and spectral data for **6** and **8**, crystal data for **8b** (CCDC 161946), and growth inhibition of various tumor cell lines and boron incorporation into B-16 melanoma cell of **6** and **8**.

Acknowledgements

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Table 2. Cytotoxicity toward B-16 and boron incorporation

Compound	Cytotoxicity IC_{50} (M)	Administration		Boron incorporation (μg B/10^6 cells)[a]
		(M)	(μg B/mL)	
8c	2.2×10^{-5}	2.2×10^{-5}	40[b]	1.6±0.25
BPA·HCl	8.6×10^{-3}	1.0×10^{-3}	10.8	0.14±0.021

[a] B-16 cells were incubated for 3 h at 37°C with the medium containing the boron compound (1.0×10^{-4} M; 10.8 ppm B).
[b] The concentration for administration was 1.0×10^{-3} M (10.8 ppm B).

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13. Compound **6a**: Yield 41.2%; mp 131–133°C; IR (KBr) 3326, 3070, 2586 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.49–2.51 (m, 2H), 2.70–2.80 (m, 1H), 2.98–3.10 (m, 1H), 3.28 (m, 1H), 3.90–3.37 (m, 1H), 3.39 (m, 1H), 3.70 (s, 3H), 3.79–3.83 (m, 1H), 5.18–5.31 (m, 1H), 6.66–6.68 (m, 1H), 6.77–6.79 (m, 1H), 7.08–7.11 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 26.9, 38.0, 41.8, 55.1, 56.7, 62.3, 73.8, 110.8, 112.7, 113.5, 128.3, 134.8, 153.8 ppm.
    Compound **6b**: Yield 47.7%; mp 131°C; IR (KBr) 3350, 2581 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.28 (s, 3H), 2.48–2.51 (m, 2H), 2.73–2.82 (m, 1H), 3.09–3.16 (m, 1H), 3.27–3.33 (m, 1H), 3.49–3.58 (m, 1H), 3.71 (s, 3H), 3.78–3.85 (m, 1H), 4.84 (m, 1H), 6.70–6.71 (m, 1H), 6.79–6.80 (m, 1H), 7.03–7.12 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 22.8, 26.0, 37.9, 45.5, 55.1, 56.8, 76.7, 77.0, 111.6, 112.8, 113.6, 128.5, 135.4, 158.3 ppm.
    Compound **6c**: Yield 55.4%; mp 183–185°C; IR (KBr) 3425, 2586, 3082 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.49–2.51 (m, 2H), 2.62–2.67 (m, 1H), 2.74–2.82 (m, 1H), 2.95–3.04 (m, 1H), 3.28 (s, 1H), 3.44–3.55 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 3.88–3.97 (m, 1H), 5.15–5.30 (m, 1H), 6.66 (s, 1H), 6.68 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 26.2, 38.7, 41.6, 55.4, 55.6, 56.7, 62.3, 73.7, 110.4, 112.1, 125.7, 127.6, 147.5, 148.2 ppm.
    Compound **6d**: Yield 57.7%; mp 179–181°C; IR (KBr) 3215, 2581 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.16 (s, 3H), 2.50–2.52 (m, 2H), 2.57–2.67 (m, 1H), 2.70–2.79 (m, 1H), 3.00–3.10 (m, 1H), 3.51–3.60 (m, 1H), 3.79–3.89 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.95–5.02 (m, 1H), 6.49 (s, 1H), 6.55 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 23.6, 26.3, 39.5, 41.1, 55.5, 55.6, 76.8, 76.9, 110.4, 112.1, 125.6, 127.5, 147.5, 148.2 ppm.
14. Compound **8a**: Yield 71.1%; mp 108°C; IR (KBr) 3425, 3285, 3082, 2586, 2561, 1348, 1161 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.38–2.39 (m, 2H), 2.75–2.79 (m, 1H), 2.97–3.02 (m, 1H), 3.06–3.23 (m, 1H), 3.36 (s, 1H), 3.36–3.48 (m, 1H), 3.70 (s, 3H), 4.73–4.76 (m, 1H), 6.63–6.64 (m, 1H), 6.73–6.81 (m, 1H), 6.94 (s, 2H), 7.03–7.05 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ 24.4, 38.2, 42.4, 55.0, 56.8, 60.6, 73.7, 112.6, 113.3, 127.1, 128.4, 136.8, 158.9 ppm.
    Compound **8b**: Yield 70.3%; mp 120°C; IR (KBr) 3352, 3273, 2583, 1359, 1116 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.04 (s, 3H), 2.39–2.50 (m, 2H), 2.55–2.65 (m, 1H), 2.96–3.06 (m, 1H), 3.15–3.24 (m, 1H), 3.43–3.53 (m, 1H), 3.71 (s, 3H), 4.92–4.94 (m, 1H), 6.68–6.69 (m, 1H), 6.75–6.80 (m, 1H), 6.79 (br s, 2H), 7.05–7.08 (m, 1H) ppm ; ^{13}C NMR (DMSO-d_6): δ 24.8, 24.9, 38.4, 41.8, 54.9, 55.0, 76.6, 77.1, 112.5, 113.4, 128.1, 128.2, 135.3, 158.1 ppm.
    Compound **8c**: Yield 81.0%; mp 210–212°C; IR (KBr) 3339, 3244, 3068, 2579, 1358, 1161 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.51 (m, 2H), 2.55–2.61 (m, 1H), 2.73–2.91 (m, 1H), 2.96–3.18 (m, 1H), 3.35 (s, 1H), 3.45–3.50 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 4.72 (m, 1H), 6.63 (s, 1H), 6.68 (s, 1H), 6.90 (s, 2H) ppm; ^{13}C NMR (DMSO-d_6): δ 2.37, 38.2, 41.8, 55.4, 55.6, 56.7, 60.7, 73.7, 110.5, 111.9, 125.4, 126.7, 147.1, 147.8 ppm.
    Compound **8d**: Yield 87.0%; mp 228–230°C; IR (KBr) 3335, 3244, 2579, 1348, 1141 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.12 (s, 3H), 2.44–2.55 (m, 1H), 2.50–2.54 (m, 2H), 2.93–3.01 (m, 1H), 3.07–3.19 (m, 1H), 3.46–3.50 (m, 1H), 3.72 (s, 1H), 3.74 (s, 3H), 4.88 (m, 1H), 6.65 (s, 1H), 6.67 (s, 1H), 6.73 (br s, 2H) ppm; ^{13}C NMR (DMSO-d_6): δ 22.8, 24.0, 38.4, 41.3, 54.9, 55.4, 55.5, 76.8, 77.1, 110.3, 112.0, 125.7, 127.5, 147.0, 147.9 ppm.