A Facile High-Yield Synthesis of [^{10}B]-8-Dihydroxyboryl Harmine, a Potential Agent for Boron Neutron Capture Therapy

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The resurgence of interest in Boron Neutron Capture Therapy (BNCT) as a treatment for malignant lesions has resulted in the synthesis of numerous boron compounds as candidates for clinical use. BNCT is a selective radiotherapy using boron-10 which absorbs thermal neutrons and releases high Linear Energy Transfer (LET) alpha particles by ^{10}B (n, α) ^{7}Li reaction. The alpha radiation kills cells in the range of 5-9 μm from the site of the α generation. Therefore, it is theoretically possible to kill tumor cells without affecting adjacent healthy tissues, if ^{10}B-compounds could be selectively delivered. Boron analogues of amino acids constitute a topic of major importance, and also peptides, antibodies, nucleosides and nucleotides [1], etc. In spite of the promising results with p-boronophenylalanine (BPA) and $B_{12}H_{11}SH^{2-}(Na^{+})$ (BSH), which presently attract considerable clinical interest, they display far from optimal selectivity for cancer cells.

The anatomical distribution of [^{3}H]Harmalas binding sites was determined by quantitative autoradiography in rat brain slices [2]**.** They have a well know brain distribution, so these compounds, labeled with ^{10}B are potential agents for BNCT. A general synthetic method has been developed for the rapid and efficient production of boronated Harmine.

Results And Discussion

Iodination

The methods for iodination have been used previously for indolealkylamine [4] and phenethylamines [4] using thallium trifluoroacetate as specific oxidizing agent of molecular iodine for iodination of aromatic compounds [5].

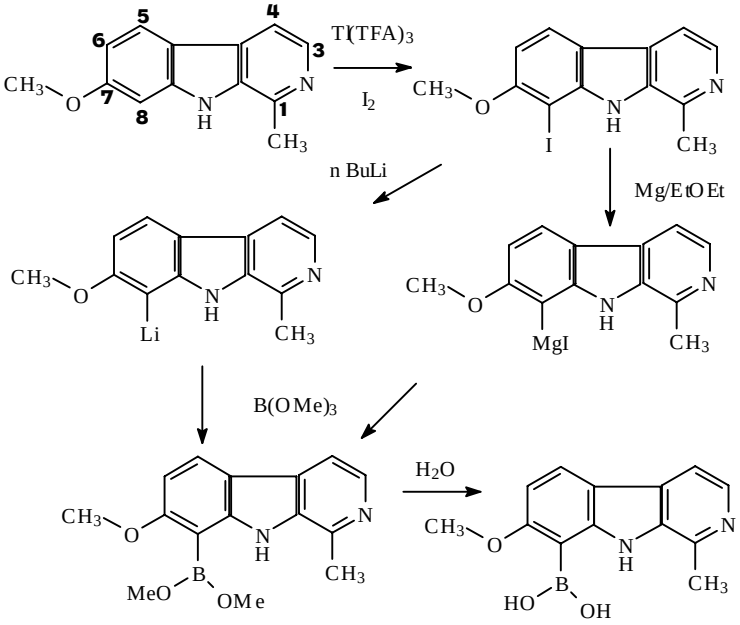
Boronation

We used the condensation of the Grignard reagent from 8-I-Harmine with trimethylborate. This method was previously used [6] for preparation of phenol from phenylbromide and trimethylborate with formation of phenylboronic acid as intermediate and for preparation of boronic analogue of cho-

line [7]. An alternative synthesis previously used for preparation of boronic analogues of nucleosides and nucleic bases [8-11] consist in treating the halogenated substrate with n-buthyllithium in THF followed by addition of trimethylborate at –86ºC. Trimethylborate was prepared by standard procedures [12] from 95% ^{10}B-enriched or natural isotope abundance boric acid and methanol and recovered from the formed azeotrope.

Summary and Conclusions

We have described a method for preparation of [^{10}B]-enriched-8-dihydroxyborylharmine (III) and characterized it by their spectral properties (MS, IR and NMR). This compound is a potential BNCT agent.



Scheme 1. Synthesis of boronated harmine.

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