Published in final edited form as:

Tetrahedron Lett. 2010 August 25; 51(34): 4482–4485. doi:10.1016/j.tetlet.2010.06.077.

Development of Practical Methodologies for the Synthesis of Functionalized Benzoboroxoles

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Abstract

2-Formylphenylboronic acids upon reaction with activated olefins such as acrylates, methyl vinyl ketone, and acrylonitrile, etc. provide functionalized benzoboroxoles. The corresponding homologated benzoboroxoles were synthesized via the reaction of 2-formylphenylboronic acids with α -bromomethylacrylates.

Keywords

Baylis-Hillman reaction; Benzoboroxoles; Barbier allylation

Introduction

Boronic acids and boronates are highly useful class of intermediates for cross-coupling and several other reactions in organic synthesis.¹ In medicinal chemistry, several boronic acid based molecules have been investigated as inhibitors of multiple enzymes.² However, in general, boron based molecules have been largely underutilized in modern medicinal chemistry research. The approval of drug bortezomib for the treatment of multiple myeloma has increased the enthusiasm for boronated molecules as a novel class of pharmaceutical compounds.³

Benzoboroxoles are cyclic hemiesters of phenylboronic acids.⁴ As compared to the corresponding acyclic boronic acids, benzoboroxoles exhibit high stability because of the presence of stable 5-membered ring. Although simple benzoboroxole **1** has been known for over 50 years, only recently great attention has been paid towards new applications of this structural unit in medicine (ex: **2–4**)⁵ (Figure 1).

Several benzoboroxoles have also been used as steroid conjugates for molecular imprinting, dyes, biosensors of α -hydroxy-carboxylic acids, and biocides for plastic biodegradation etc.⁶ Some of the benzoboroxoles have also been found to selectively complex with naturally occurring oligosaccharides to effect direct glycosidation of the sugars and used for the selective recognition of cell surface glycoconjugates.⁷

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Despite the surging applications of benzoboroxoles in various fields, the study of their synthesis and properties has been limited and the synthetic methods for rapid diversification of this novel structure are highly desired. The impressive application profile of these molecules and our interest⁸ in the synthesis of novel boronated molecules for medicinal chemistry prompted us to undertake the current project for the synthesis of functionalized benzoboroxoles. In this communication, we describe the development of two convenient and versatile protocols for the synthesis of densely functionalized benzoboroxoles based on Baylis-Hillman chemistry of 2-formylphenyl boronic acids.

Results and Discussion

Baylis-Hillman reaction is an important synthetic transformation that provides highly substituted allylic alcohols and amines in one step.⁹ The reaction is highly atom efficient and the product alcohols undergo a facile isomerization with a variety of nucleophiles to afford valuable synthons. We envisaged that the BH reaction of boronoaldehydes with electron-deficient olefins in the presence of tertiary amines like 1,4-diazabicyclo[2.2.2]octane (DABCO) should provide a wide variety of functionalized benzoboroxoles very easily. We also envisioned that allylic bromides derived from BH alcohols could provide further functionalized homologated benzoboroxoles upon Barbier type allylation. For the present study, we chose formylboronic acids **5a–c** as the electrophiles and several activated olefins such as methyl acrylate **6a**, phenyl acrylate **6b**, acrylonitrile **6c**, methyl vinyl ketone **6d**, and acrolein **8** as olefin partners. The initial reaction of aldehyde **5a** with 2 equiv of methyl acrylate in the presence of 10% DABCO was sluggish, and only a partial reaction took place to afford 20% of the benzoboroxole **7a** after 12 h. Prolonged continuation of the reaction for an additional 48 h did not improve the yield as well. However, complete consumption of the aldehyde was observed upon using stoichiometric amounts of DABCO, and benzoboroxole **7a** was obtained in 58% yield after silica gel column chromatography.¹⁰

The BH reaction of methyl acrylate with simple benzaldehyde typically takes more than a week. Even the reaction with 4-boronobenzaldehyde proved to be very sluggish and synthetically useful yield of the product alcohol was not obtained even after stirring the reaction for two weeks. The increased rate of reactivity with 2-boronobenzaldehyde **5a** could be attributed to the activation of carbonyl oxygen via coordination with proximal Lewis acidic boronic acid group. The reaction with boronoaldehydes **5b–c** was relatively slow presumably due to the electron donating capability of alkoxy group on the aromatic ring. The reaction took 5–7 days for completion and the product benzoboroxoles **7b–c** were obtained in 54% and 56% yield respectively. Similarly, the BH reaction of aldehydes **5a–c** with phenyl acrylate **6b** provided the corresponding benzoboroxoles **7d–f** in 41–45% yield (Scheme 1).

The BH reaction with acrylonitrile **6c** was facile with all the boronoaldehydes **5a–c** and the product benzoboroxoles **7g–i** were obtained in moderate to good yields. The reaction of aldehydes **5a–c** with methyl vinyl ketone **6d** provided the benzoboroxoles **7j–l** in 41–49% yield (Scheme 1).

Acrolein **8** is a sensitive monomer and undergoes rapid polymerization in the presence of amines, and generally is not considered to be a good BH substrate for unreactive aldehydes. Boronoaldehyde **5a** was found to be sufficiently reactive to afford the corresponding product **9** in 20% yield along with 60% of recovered starting material. Extended reaction time or excess quantities of acrolein did not help improve the yield of the product. The reaction was done in THF as the solvent at 0°C to minimize the polymerization of acrolein (Scheme 2).

After obtaining the benzoboroxoles **7a–l**, we carried out the allylation of bromides **12a–b** with boronoaldehydes **5a–c** under Barbier conditions. The requisite bromides **12a–b** were prepared in two steps starting from BH reaction of formaldehyde **10a** and acetaldehyde **10b** with methyl acrylate **6a** to afford the allylic alcohols **11a–b** followed by the treatment with HBr and H₂SO₄. Allylation of bromides **12a–b** with aldehydes **5a–c** in the presence of zinc and saturated ammonium chloride provided the homologated benzoboroxoles **13a–f** in good yields (Scheme 3).¹¹ In the case of BH bromide **12b** derived from acetaldehyde, as expected, the product benzoboroxoles **13d–f** were obtained in predominantly *syn* stereochemistry. The relative configuration was confirmed by single crystal X-ray analysis of **13d** (Figure 2).

Owing to the importance of several benzoboroxoles exhibiting significant antimicrobial activity, all the synthesized molecules have been tested for their efficacy as antibacterial and antifungal agents. We chose *Pseudomonas aeruginosa* (gram negative), *Streptococcus thermophilus* (gram positive) for anti-bacterial studies and *Candida albicans*, and *Aspergillus niger* as representative examples for anti-fungal evaluation. The microbial colonies were grown in Mueller Hinton broth at 37 ± 1 °C overnight. The microbial suspension was swabbed on to a Mueller Hinton agar plate. Twenty µL of the test dilution was added to sterile empty paper discs (10 mm) to achieve a final concentration of 5 & 1 µg/disc. Each disc was placed on the surface of agar plate. The plates were incubated at 37 ± 1 °C for 24–48 h. The antimicrobial activity was determined based on the zone of inhibition around the disc. The diameter of the zone was measured in millimeters. The antimicrobial activity was indicated by formation of inhibition zone compared against the standard disc. Unfortunately, none of them showed any significant zone inhibition at this concentration.

Conclusions

In conclusion, we have developed two convenient protocols based on Baylis-Hillman chemistry for practical synthesis of functionalized benzoboroxoles. These methodologies provide rapid diversification of the benzoboroxole scaffold and are highly amenable to scale-up. Some of these molecules were evaluated for their antibacterial and antifungal activities. The importance of benzoboroxoles in various fields, the paucity of synthetic procedures and the versatility of BH chemistry make the current procedures highly significant.

Acknowledgments

We thank the College of Liberal Arts and Sciences, Rowan University, and Department of Chemistry and Biochemistry University of Minnesota Duluth for the facilities and funding. Partial support for this work was also provided by research grants from the National Institutes of Health (CA129993) (VRM), Whiteside Institute for Clinical Research (VRM), and Rowan University Non-Salary Financial Support Grants (NSFSG) (SCJ). We thank Dr. Victor G. Young, Jr. (University of Minnesota X-ray Crystallographic Laboratory) for providing the crystal structure.

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10. Representative procedure for the preparation of benzoboroxoles **7a–l**: To a stirred suspension of 2-boronobenzaldehyde **5a** (0.3 g, 2.0 mmol) and methyl acrylate **6a** (0.7 mL, 8.0 mmol) was added DABCO (224 mg, 2.0 mmol) and stirred for 2 days at room temperature. Upon completion (TLC), the reaction mixture was quenched with dilute HCl and worked up with ethyl acetate (3 × 10 mL). The combined organic layers were dried (MgSO₄), concentrated *in vacuo*, and purified via silica gel column chromatography (hexane:ethyl acetate, 3:1) to obtain 0.25 g (58%) of benzoboroxole **7a** as a white powder. *mp*: 91–93°C, (Found: C, 60.62%; H, 5.25%; C₁₂H₁₃BO₄ requires: C, 60.60%; H, 5.09%); ¹H NMR (400 MHz, CDCl₃): δ 9.45 (s, 1H), 7.70–7.72 (m, 1H), 7.40–7.44 (m, 1H), 7.25–7.35 (m, 2H), 6.16 (s, 1H), 5.93 (s, 1H), 5.79–5.80 (m, 1H), 3.67 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 166.2, 155.5, 140.6, 131.5, 131.2, 128.1, 126.6, 122.3, 79.3, 52.5; ESI-MS: 217 [(M–H)⁺, 100%].
11. Representative procedure for the preparation of benzoboroxoles **13a–f**: To a stirred suspension of 2-boronobenzaldehyde **5a** (0.3 g, 2.0 mmol) and zinc (0.19 g, 3.0 mmol), in 4.0 mL THF was added methyl α-bromomethylacrylate **12a** (0.72 g, 4.0 mmol), and saturated NH₄Cl (1 mL) and stirred overnight at room temperature. Upon completion (TLC), the reaction mixture was filtered over celite, and worked up with water and ethyl acetate (3 × 10 mL). The combined organic layers were dried (MgSO₄), concentrated *in vacuo*, and purified via silica gel column chromatography (hexane:ethyl acetate, 3:1) to obtain 0.35 g (75%) of benzoboroxole **13a** as a viscous liquid. (Found: C, 62.01%; H, 5.52%; C₁₂H₁₃BO₄ requires: C, 62.11%; H, 5.65%); ¹H NMR (400 MHz, CDCl₃): δ 9.24 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.41–7.45 (m, 1H), 7.29–7.36 (m, 2H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.69 (d, *J* = 1.2 Hz, 1H), 5.26 (dd, *J* = 4.0, 8.4 Hz, 1H), 3.64 (s, 3H), 2.89 (dd, *J* = 8.4, 14.4 Hz, 1H), 2.39 (dd, *J* = 8.4, 14.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 156.8, 136.9, 131.2, 131.1, 128.2, 127.9, 122.2, 79.1, 52.5, 39.2; ESI-MS: 231 (M–H)⁺, 189 (100%).

Figure 1.
Functionalized Benzoboroxoles

Figure 2.
X-ray Crystal Structure of **13d**

Scheme 1.
Baylis Hillman reaction of β -Boronoaldehydes

Scheme 2.
Reaction of β -Boronoaldehydes with Acrolein

Scheme 3.
Synthesis of Homologated Benzoboroxoles