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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 provide functionalized benzoboroxoles. The corresponding homologated benzoboroxoles were synthesized via the reaction of 2-formylphenylboronic acids with α-bromomethylacrylates.

1. Introduction

Boronic acids and boronates are highly useful classes 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 a stable five-membered ring. Although simple benzoboroxole **1** has been known for over 50 years, only recently great attention has been paid toward the new applications of this structural unit in medicine (e.g., **2–4**)[5] (Fig. 1).

Several benzoboroxoles have also been used as steroid conjugates for molecular imprinting, dyes, biosensors of α-hydroxy-carboxylic acids, 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 are used for the selective recognition of cell surface glycoconjugates.[7]

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 interest[8] 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 Letter, we describe the development of two convenient and versatile protocols for the synthesis of densely functionalized benzoboroxoles based on Baylis–Hillman chemistry of 2-formylphenylboronic acids.

2. 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

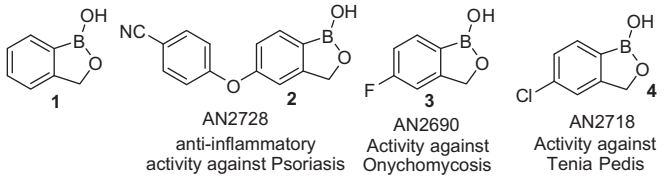

Figure 1. Functionalized benzoboroxoles.

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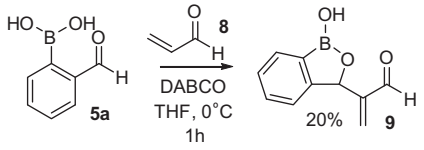
reaction of boronoaldehydes with electron-deficient olefins in the presence of tertiary amines like 1,4-diazabicyclo[2.2.2] octane (DABCO) should provide a wide variety of functionalized benzoboroxoles very easily. We also envisioned that allylic bromides derived from BH alcohols could provide further 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 a synthetically useful yield of the product alcohol was not obtained even after stirring the reaction mixture for two weeks. The increased rate of reactivity with 2-boronobenzaldehyde **5a** could be attributed to the activation of the carbonyl oxygen via coordination with a proximal Lewis acidic boronic acid group. The reaction with boronoaldehydes **5b–c** was relatively slow presumably due to the electron-donating capability of the alkoxy group on the aromatic ring. The reaction took 5–7 days for the 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).

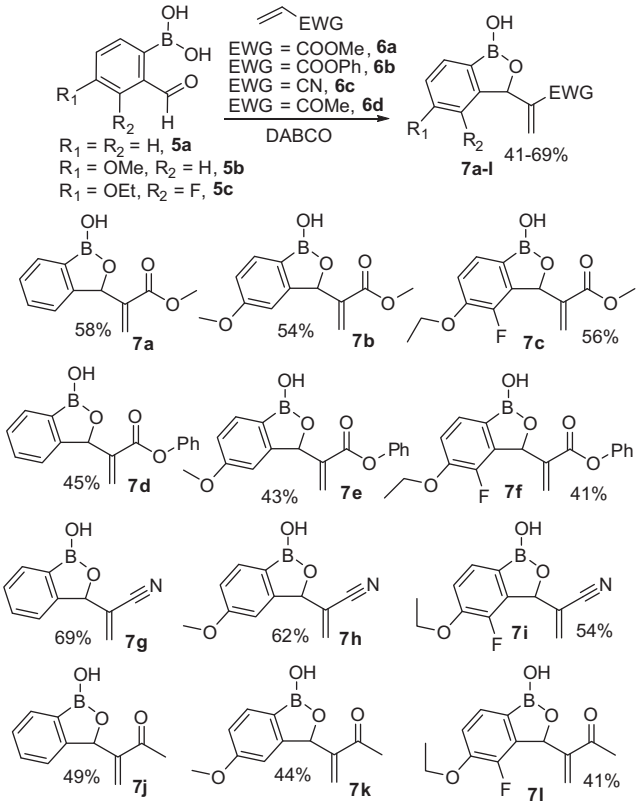
The BH reaction with acrylonitrile **6c** was facile with all the boronoaldehydes **5a–c** and the product benzoboroxoles **7g–i** were obtained in moderate to good yields. The reaction of aldehydes **5a–c** with methyl vinyl ketone **6d** provided the benzoboroxoles **7j–l** in 41–49% yield (Scheme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

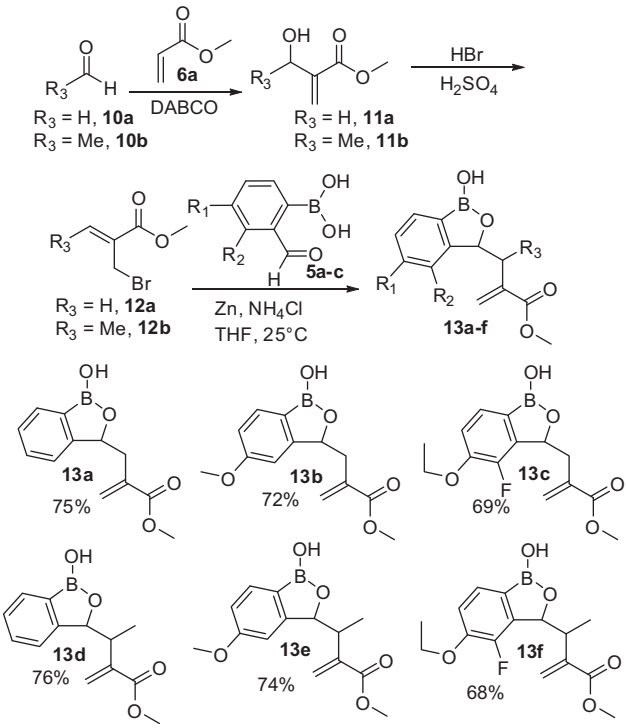
After obtaining the benzoboroxoles **7a–l**, we carried out the allylation of bromides **12a–b** with boronoaldehydes **5a–c** under Barbier conditions. The requisite bromides **12a–b** were prepared in two steps starting from BH reaction of formaldehyde **10a** and acetaldehyde **10b** with methyl acrylate **6a** to afford the allylic alcohols **11a–b** followed by the treatment with HBr and H_2SO_4. 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** (Fig. 2).



Scheme 2. Reaction of β-boronoaldehydes with acrolein.



Scheme 1. Baylis–Hillman reaction of β-boronoaldehydes.



Scheme 3. Synthesis of homologated benzoboroxoles.

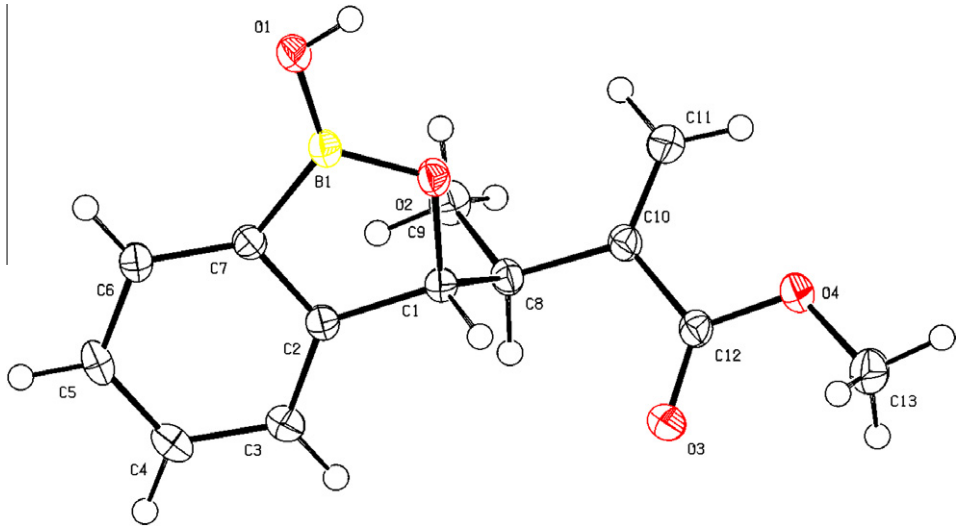


Figure 2. X-ray crystal structure of **13d**.

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 antibacterial studies and *Candida albicans*, and *Aspergillus niger* as representative examples for antifungal 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 microliters of the test dilution were added to sterile empty paper discs (10 mm) to achieve a final concentration of 5 and 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 the formation of an inhibition zone compared against the standard disc. Unfortunately, none of them showed any significant zone inhibition at this concentration.

3. Conclusions

In conclusion, we have developed two convenient protocols based on Baylis–Hillman chemistry for the 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

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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 was quenched with dilute HCl and worked up with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), 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; $C_{12}H_{13}BO_4$ requires: C, 60.60; H, 5.09); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 NH_4Cl (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 ($MgSO_4$), 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; $C_{12}H_{13}BO_4$ requires: C, 62.11; H, 5.65); ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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%).