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Preparation and reactions of 4-iodobutyl pinacolborate. Synthesis of substituted alkyl and aryl pinacolboronates via 4-iodobutyl pinacolborate utilizing tetrahydrofuran as the leaving group

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ABSTRACT

Iodine reacts with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin), under ambient reaction conditions in THF, to form the iodoalkylborate species 2-(4-iodobutoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4-IboxBpin). Apparently, one-half equivalent of I_2 reacts with HBpin to form IBpin in pentanes, which in turn cleaves THF to form the 4-IboxBpin. Alkyl and aryl Grignard reagents, prepared under Barbier conditions, then react with 4-IboxBpin to form the corresponding alkyl and aryl pinacolboronates while reforming and liberating THF as the leaving group.

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Both arylboronic acids and arylboronates have widespread application over a range of synthetic and biological processes.[1] Among these are the use of boronic esters in cross-coupling reactions, such as palladium- and copper(II)-mediated processes.[2] Pinacolboronates have also garnished tremendous attention as coupling partners due to many factors, including their stability in many different reaction conditions as well as easy handling and purification. These compounds are often invaluable in the formation of complex structures and scaffolds of synthetic targets and used in stereospecific conversions to different functionalities.[3,4]

Many methods exist for the synthesis of boronic esters, both simple and functionalized, however each possesses drawbacks. The most established method for this is the use of an aryllithium or aryl Grignard reagent added to excess trialkylborate at −78 °C, with trimethyl-, triethyl-, or triisopropylborate being the most commonly used alkylborates.[5,6] Other methods have since been developed utilizing different boron sources, such as palladium- or copper-catalyzed borylation of arylhalides with bis(pinacolato)diboron (B_2pin_2), however only one Bpin moiety is incorporated into the product.[7] Borylation using other expensive transition metals, such as rhodium,[8] ruthenium,[9] and iridium[10] also exist, including processes utilizing aromatic C–H bond activation.[11] We were interested in developing a new method for the synthesis of pinacolboronates that can be carried out under ambient conditions using inexpensive reactants, such as Grignard reagents. Herein, we report the results of our study on the reactions of Grignard reagents with 2-(4-iodobutoxy)-4,4,5,5-tetramethyl-1,2,3-dioxaborolane [4-iodobutoxyBpin, (4-IboxBpin)] boron donor where tetrahydrofuran (THF) is extruded as the leaving group.

The most popular borate trapping method developed by Brown and Cole must be performed at −78 °C and does not work efficiently with Grignard reagents. Even 2-isopropoxy-4,4,5,5-tetramethyl-1,2,3-dioxaborolane (*i*PrO-Bpin) works well only with organometallic reagents when carried out at −78 °C and generates metal isopropoxide byproducts.[12] We sought to extend Brown–Cole boronate synthesis to include inexpensive and green Grignard reagents.

Since *i*PrO-Bpin reacts as a boron donor with organometallic reagents,[12] we wanted to test the use of 4-iodobutyl-4,4,5,5-tetramethyl-1,2,3-dioxaborolane in the borate trapping reaction with reagents such as organolithiums and Grignard reagents, preferably at 25 °C. To test the feasibility of this approach, we began exploring the reaction of I_2 and pinacolborane (HBpin). The reaction between I_2 and B-H containing compounds, such as dialkylborane and diaminoborane, have been used to cleave cyclic ethers through the intermediate formation of B-iodo derivatives.[13–15] We anticipated that the reaction between I_2 and HBpin in pentane would furnish IBpin, which in turn should be capable of cleaving the THF ring in a similar fashion. The resulting 4-iodobutylBpin compound could be a potential boron donor in borylation reactions, driven by the favorable recyclization of an iodobutoxide leaving group to the neutral THF molecule.

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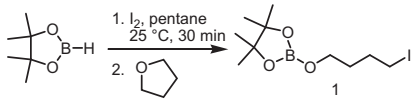
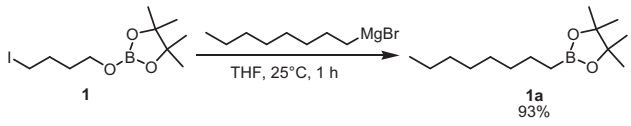
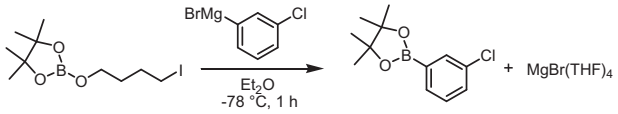


Figure 1. Synthesis of 4-IboxBpin (**1**).



Scheme 1. Reaction of **1** with preformed Grignard reagent.



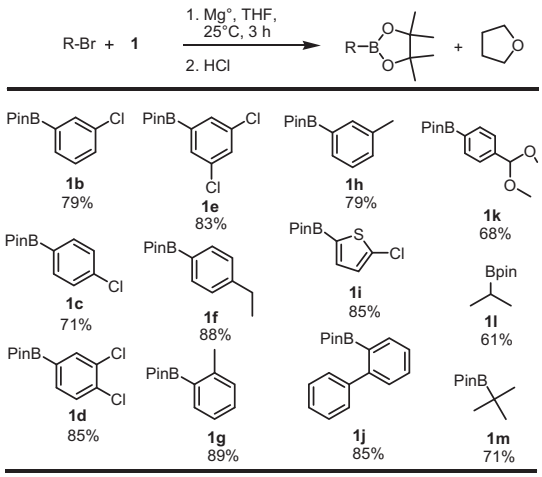
Scheme 2. Addition of ArMgBr to 4-iodobutylBpin in Et_2O.

To test this, we began with the addition of HBpin to a solution of I_2 in pentane, producing a dark purple solution. After 30 min of stirring, THF was added and the solution decolorized over 3 h at 25 °C. Analysis of the product by MS, ^1H, ^{13}C, and ^{11}B NMR spectroscopy indicated the formation of 4-4-iodobutylBpin (**1**, 4-IboxBpin) (Fig. 1).[16]

We then studied the potential of **1** as a boron donor by reacting it with various Grignard reagents. Thus, addition of *n*-octylmagnesium bromide in THF to **1** at 25 °C afforded *n*-octylBpin in high yield (Scheme 1).

To check the generality of this methodology and the leaving group capability of iodobutoxide, we carried out the reaction of **1** with Grignards prepared under Barbier conditions. First, 4-IboxBpin was synthesized as described above in toluene and neat **1** was isolated by the evaporation of toluene and any excess THF under reduced pressure. Its ^1H NMR spectrum indicated that no residual THF was present. Anhydrous diethyl ether (Et_2O) was then added, followed by dropwise addition of 3-chlorophenylmagnesium bromide in Et_2O at −78 °C to quantitatively trap the liberated THF. The reaction was stirred for 3 h, producing a white precipitate. An ^1H NMR spectrum of the isolated precipitate in D_2O showed the presence of THF, stemming from the release and subsequent cyclization of iodobutoxide (Scheme 2).[17]

Table 1
Synthesis of haloaryl pinacolboronates via 4-IboxBpin under Barbier conditions



After removal of the precipitate and subsequent aqueous workup, the corresponding 3-chlorophenyl pinacolboronate was confirmed as the product. Encouraged by this result, we tested this system with a range of aryl and haloaryl substrates (Table 1).[18]

In summary, we have developed a method for synthesizing alkyl and aryl pinacolboronates under Barbier conditions in good to excellent yields. Through the course of this work, we discovered a novel boron electrophile, 4-IboxBpin, synthesized via the ring opening of THF by IBpin. 4-IboxBpin reacts readily with alkyl and aryl Grignard reagents formed under Barbier conditions to produce the corresponding alkyl and aryl pinacolboronates while extruding THF as a leaving group. This is a significant improvement to older synthetic methods as this reaction is performed at room temperature, utilizes inexpensive and green Grignard reagents, and liberates neutral THF instead of a basic alkoxide group.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.033.

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16. *General procedure for the synthesis of compound* **1**: To a mixture of anhydrous pentane (8 mL) and I_2 (0.254 g, 1.0 mmol) under Ar was added neat pinacolborane (0.29 mL, 2.0 mmol) dropwise over 1 min to provide a dark purple solution. The mixture was stirred at 25 °C for 30 min. Anhydrous THF (0.16 g, 2.0 mmol) was then added dropwise over 1 min with constant stirring at 25 °C. The reaction was complete after 3 h, producing a clear solution, and confirmed by the disappearance of pinacolborane starting material (δ +27.7, d, J = 173.9 Hz) and the appearance of a singlet at +30.6 ppm via ^{11}B NMR. Brine (1 mL) was then added. The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford compound **1**. Clear oil; 97% yield (0.632 g). ^1H NMR (500 MHz, $CDCl_3$) δ 3.88 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 7.0 Hz, 2H), 1.90 (m, 2H), 1.67 (m, 2H), 1.22 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 81.5, 62.3, 30.9, 28.5, 23.3, 5.3. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +22 (s). HRMS (ESI): m/z calcd for $C_{10}H_{20}BIO_3$ 326.0550, found 326.0548.
17. For ^1H NMR spectra, see Supplementary data.
18. *General procedure for the synthesis of compounds* **1a–1m**: The following procedure is representative. To a solution containing 4-IboxBpin (0.651 g, 2.0 mmol) and anhydrous THF (8 mL) under Ar, Mg turnings (0.048 g, 2.0 mmol) were added. The corresponding halide reagent (2.0 mmol) was then introduced dropwise over 5 min with constant stirring at 25 °C. The reaction was complete after 3 h, as evidenced by the disappearance of 4-IboxBpin (δ +21.6) via ^{11}B NMR. 1 M HCl (3 mL) was then added to the reaction flask and left to stir for 5 min. The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford the corresponding pinacolboronate.