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Suzuki Reaction of a Diarylborinic Acid: One-Pot Preparation and Cross-Coupling of Bis(3,5-dimethylphenyl)borinic Acid

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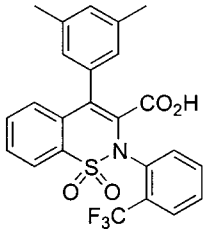
Abstract:

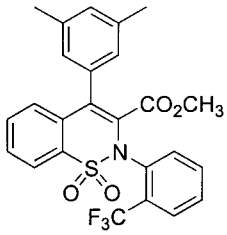
3,5-Dimethylphenylmagnesium bromide reacts with triisopropyl borate to give 3,5-dimethylphenylboronic acid and bis(3,5-dimethylphenyl)borinic acid. Conditions were found which allowed the clean preparation of bis(3,5-dimethylphenyl)borinic acid, which was coupled with a vinyl triflate using Suzuki cross-coupling conditions. Both aryl groups were efficiently transferred from boron in the Suzuki step.

Introduction

Endothelin receptor antagonists have generated considerable interest as pharmaceutical agents due to the involvement of endothelin in conditions such as pulmonary hypertension, congestive heart failure, and renal failure.[1] PD 0182783 (**1**) is a potent endothelin A antagonist which was considered for the treatment of pulmonary hypertension.[2] Early toxicological studies required the rapid synthesis of 3 kg of **1**. After briefly exploring Negishi-type cross-coupling strategies utilizing an arylzincate,[3] the Suzuki cross-coupling reaction[4] was investigated to form the penultimate methyl ester **2**.[5]



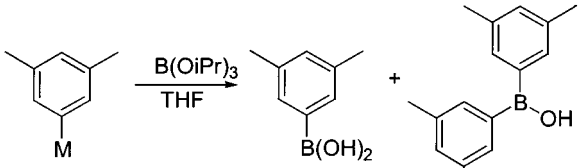
1



2

Although 3,5-dimethylphenylboronic acid **4** is commercially available, its high cost prompted the investigation into the preparation of **4** from 3,5-dimethylphenylmagnesium bromide **3a** and triisopropyl borate.[4a]

Table 1. **Formation of arylboronic acid 4 and diarylborinic acid 5**



3a (M=MgBr)
3b (M=Li)

4 **5**

entry	SM	$B(OiPr)_3$ (equiv)	temp. (°C)	ratio **4**:**5**[a]
1	**3a**	1.2	−55 to rt	1:2.4
2	**3a**	2.0	−55 to rt	2.5:1
3	**3b**	1.2	−70 to rt	2.3:1
4	**3a**	0.6	−5 to rt	1:40

[a] Ratios determined by HPLC analysis (area%)

Results and Discussion

Addition of Grignard reagent **3a** to a THF solution of triisopropyl borate at −55 °C, followed by a water quench, resulted in a mixture of the desired arylboronic acid **4** and another product which was determined by LC/MS[6] to be diarylborinic acid **5**. Although triisopropyl borate has been shown in the literature to minimize multiple boron additions relative to trimethyl borate,[7] it was difficult to prevent the formation of the diarylborinic acid in this case. Even with the use of two equivalents of triisopropyl borate, a 2.5:1 ratio of arylboronic acid **4** to diarylborinic acid **5** was formed (Table 1, Entry 2). Replacing the aryl Grignard with the aryllithium species **3b** derived from *n*-BuLi treatment of the aryl bromide at −70 °C resulted in a 2.3:1 ratio of arylboronic acid **4** to diarylborinic acid **5** (Table 1, Entry 3). When 0.6 equiv of triisopropyl borate was used at −5 °C (Table 1, entry 4), diarylborinic acid **5** was produced almost exclusively. This eliminated the need for cryogenic reaction conditions, simplifying equipment requirements for scale-up. Although diarylborinic acid **5** could be prepared cleanly, it was isolated as an oil, which crystallized on storage at 5 °C. Diarylborinic acids are known to be difficult to crystallize;[8] therefore, we hoped to utilize it without isolation. While arylboronic acids are typically isolated prior to use in the Suzuki reaction, this process often results in lost yield and analytical difficulties due to varying amounts of anhydride formation.

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(4) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576(1−2)*, 147−168.

(5) The direct cross-coupling of aryl Grignard **3a** with triflate **6** was not investigated. Geissler, H. Transition Metal-catalyzed Cross Coupling Reactions. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; pp 158−183.

(6) Column: YMC ODS-AQ (4.6 × 150 mm, 5 μm); mobile phase: 80:20 MeOH:0.1% formic acid; conditions: 1.0 mL/min flow, 220 nm detection; *RT* = 8.8 min, APCI(−): 283.1 (M + $HCOO^-$), 237.1 (M − H).

(7) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316−1319.

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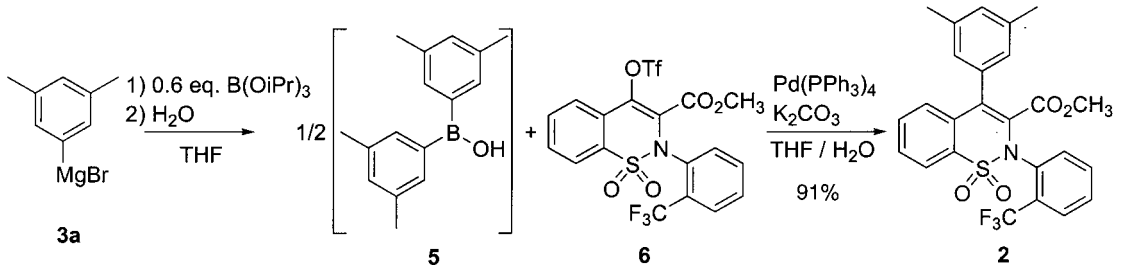
Scheme 1



With a convenient method of preparing diarylborinic acid **5**, we focused on using this compound in the Suzuki reaction. Sodium tetraarylborates have been used in the Suzuki reaction,[9] demonstrating the feasibility of multiple aryl transfers from boron, although the synthetic utility of diarylborinic acids in the Suzuki reaction has not been thoroughly explored. The reaction of 1 equiv of diarylborinic acid **5** with 2 equiv of vinyl triflate **6** proceeded in 91% yield, with each boron atom delivering two aryl groups (Scheme 1). The by-products of the diarylborinic acid-forming reaction appeared to have no adverse effects when carried into the coupling step. By avoiding the isolation of the diarylborinic acid,[10] we increased overall yield and used the readily accessible diarylborinic acid **5**.

In conclusion, conditions have been developed which allow the one-pot preparation and cross-coupling of bis(3,5-dimethylphenyl)borinic acid, giving excellent yields of coupled product. Furthermore, bis(3,5-dimethylphenyl)-borinic acid participated well in the Suzuki reaction, efficiently transferring two aryl groups from boron. This method increased overall yield by using the diarylborinic acid without isolation, eliminated the need for cryogenic conditions, and increased atom economy.

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received, with the exception of vinyl triflate **6**, which was prepared by reported methods.[2] ^{1}NMR spectra were recorded at 200 MHz, using tetramethylsilane as the internal reference in $CDCl_3$. ^{13}C NMR spectra were recorded at 50 MHz in $CDCl_3$. Melting points were uncorrected.

Isolation and Characterization of Bis(3,5-dimethylphenyl)borinic Acid 5. To a dry flask was added triisopropyl borate (2.2 g, 11.6 mmol) and THF (10 mL). This solution was cooled to −5 °C, and 3,5-dimethylphenylmagnesium bromide (40 mL, 20 mmol, 0.5 M in THF) was added, maintaining a temperature of less than 0 °C. After stirring for 1 h at −5 °C, the reaction mixture was allowed to warm to room temperature and quenched with HCl (25 mL, 1 M soln). The organic layer was separated and washed with water (25 mL), and the solvent was removed in vacuo. The resulting oil was purified by filtration through silica gel using 4% ethyl acetate in hexane as the eluent. A clear, colorless oil (2.0 g, 42%) was obtained which solidified on storage at 5 °C, mp 71.5−73.0 °C. ^{1}H NMR δ 7.41 (s, 4 H), 7.16 (s, 2 H), 5.78 (bs, 1 H), 2.36 (s, 12 H). ^{13}C NMR δ 137.4, 132.9, 132.6, 21.5. Anal. Calcd for $C_{16}H_{19}BO$: C, 80.70; H, 8.04. Found: C, 80.40; H, 8.04. FTIR (neat) 3446, 2917, 1597, 1324, 1210 cm^{-1}.

One-Pot Preparation of Methyl Ester 2. To a dry 50 L reactor was added triisopropyl borate (564 g, 3.0 mol) and THF (5 L). This solution was cooled to −5 °C, and 3,5-dimethylphenylmagnesium bromide (10 L, 5.0 mol, 0.5 M in THF) was added, maintaining a temperature of less than 0 °C. After stirring for 1 h at −5 °C, the reaction mixture was allowed to warm to room temperature. Water (11 L, nitrogen purged) was added followed by potassium carbonate (1.4 kg, 10.0 mol), triflate **6** (2.3 kg, 4.3 mol), and $Pd(PPh_3)_4$ (17 g, 14.7 mmol). The reaction mixture was heated to 50 °C for about 4 h. Trithiocyanuric acid (17 g, 95.9 mmol) and ethyl acetate (7.5 L) were then added, and the mixture was stirred for about 1 h. The lower aqueous layer was removed, and the organic layer was washed with HCl (9.5 L, 2 M solution) and water (10 L). Following vacuum distillation to a volume of about 5−10 L, 2-propanol (32 L) was added, and the vacuum distillation was continued until a volume of about 25 L remained. This slurry was heated to 80 °C to dissolve solids, and then slowly cooled to −5 °C. Following vacuum filtration, the cake was washed with 2-propanol (2.5 L) and 4:1 2-propanol:water (2.5 L). After drying overnight in a vacuum oven at 50 °C, 1.91 kg (91%) of product **2** was obtained, mp 173.1−174.2 °C. ^{1}H NMR δ 7.93−7.88 (m, 1 H), 7.75−7.71 (m, 1 H), 7.60−7.45 (m, 5 H), 7.28−7.23 (m, 1 H), 7.05 (s, 1 H), 6.98 (s, 2 H), 3.31 (s, 3 H), 2.35 (s, 6 H). ^{13}C NMR δ 162.4, 137.7, 134.3, 133.8, 133.7, 133.5, 132.4, 132.0, 131.0, 130.0, 129.7, 129.6, 129.1, 129.0, 127.8, 127.64, 127.56, 125.5, 121.9, 120.0, 51.9, 21.1. Anal. Calcd for $C_{25}H_{20}F_3NO_4S$: C, 61.59; H, 4.14; N, 2.87. Found: C, 61.50; H, 4.13; N, 2.83. FTIR (melt) 1738, 1351, 1314, 1181, 1127, 1115 cm^{-1}.

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