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Communications

Polymer-bound Boronate *via* the Solid Phase Coupling Reaction of Resin-bound Aryl Triflate with Diboron Pinacol Ester

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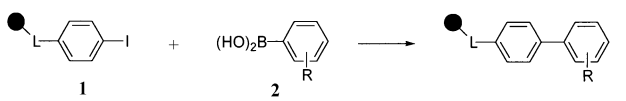
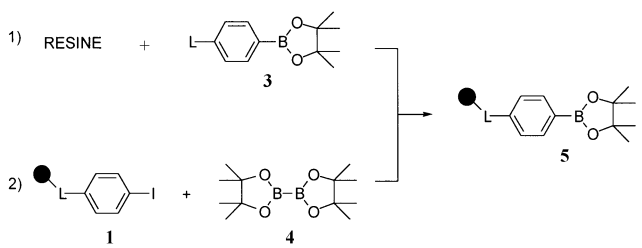
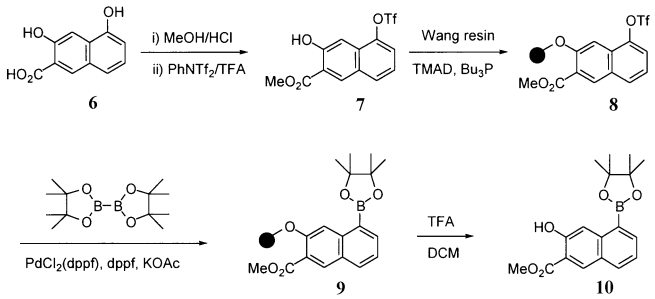
The generation of non-peptide small molecules by solid phase methods has proven to be a successful strategy in increasing the diversity of new pharmacologically active substance.[1] The Suzuki coupling reactions have been adapted to solid phase as a major tool for high-yielding carbon-carbon bond construction, coupling a resin-bound aryl halide **1** with a solution phase boronic acid **2** (Scheme 1).[2] However, due to the limited number of commercially available boronic acids, developing new methods of attaching the boron species to the resin in combinatorial chemistry has gained interest. A method to overcome this difficulty is to prepare the polymer-bound borates **5** which can follow a subsequent solid phase Suzuki coupling reaction with diverse aryl halides.[3] Two different methods for the polymer-bound borate have been reported so far as shown in Scheme 2: 1) attachment of each boron derivative **3** to the resin;[2c] 2) solid phase boron synthesis with the reaction of the diboron pinacol ester **4** to polymer-bound *p*-iodobenzamide **1**.[4] Therefore, it may be very meaningful to tether the borate into a different resin-bound substrates from aryl halide for more diversity. Herein we report the Pd (0) catalyzed coupling reaction of resin-bound aryl triflate **8** with diboron pinacol ester **4**, which is proven to give the polymer-bound arylboronate from aryl alcohol (Scheme 3). Generally, the aryl triflate was readily derived from the aryl alcohol with triflating agents.[7] This is a continuation of our ongoing efforts to develop the non-peptide protein tyrosine kinases (PTK) inhibitors.[5] For naphthyl boronic acid inhibitor libraries, we needed to develop the solid phase synthetic methods of resin-bound naphthyl boronate **9**. The starting material methyl-3-hydroxy-5-triflate-2-naphtholate **7** as an aryl triflate was prepared from a commercially available 3,5-dihydroxy-2-naphthoic acid **6** by the esterification and subsequent triflation with *N*-phenyltrifluoromethanesulfonimide.[6,7] Compound **7** was tethered to the Wang resin using the Mitsunobu reaction in 1,1-azobis(*N,N*-dimethylformamide) and tributylphosphine[8] to lead to the polymer **8**. The extent of loading of **7** on resin **8** was determined on the basis of elemental analysis, which showed 1.76% sulfur to be 92% loading



Scheme 1



Scheme 2



Scheme 3

yields. Introduction of boron functional group to triflate of solid support was performed with application of Miyauras conditions[9] {diboron pinacol ester, $PdCl_2$(dppf), dppf, KOAc} in dioxane at 80 °C for 24 hrs to furnish a solid phase boronate **9**.

A procedure for the preparation of polymer-bound boronate **9**: To a Schlenk flask under argon was added resin **8** (290 mg), bis(pinacolato) diboron (213 mg, 0.84 mmol) **4**, $PdCl_2$(dppf) (23 mg, 28 mmol), dppf (18 mg, 32 mmol), and KOAc (206 mg, 2.1 mmol). The solid mixture was heated at 50 °C for 24 hrs under vacuum (2 torr) to degas and dry, then dioxane (10 mL) was added. The reaction mixture was heated at 85 °C for 24 hrs, transferred to a peptide filter flask, rinsed with dioxane, MeOH, DMF vortexing for 30 min, and dichloromethane, and dried under vacuum to give the resin **9**. To determine the amount of loading of above 2 steps solid phase reaction on Wang resin, resin **9** was stirred in 1 : 1 TFA/dichloromethane (8 mL) for 20 min, filtered, and rinsed with dichloromethane. The combined filtrate was evaporated to give the crude product. Column chromatography with dichloromethane as an eluent provided 25 mg of product, 2-carbomethoxy-5-dioxaborolanyl-3-hydroxynaphthalene **10** (52% yield). TLC (dichloromethane) $Rf = 0.58$. ^{1}H NMR (300 MHz, $CDCl_3$) d 10.44 (1H, s), 8.47 (1H, s), 8.29 (1H, s), 8.11(1H, d, $J = 7.0$ Hz), 7.88 (1H, d, $J = 8.1$ Hz), 7.31 (1H, dd, $J = 7.0$, 8.1 Hz), 4.03 (3H, s), 1.41 (12H, s); MS (FAB) m/e 328 (M).

In conclusion, an efficient solid phase reaction to obtain polymer-bound boronate from aryl alcohol *via* aryl triflate has been developed. This scheme will be applied to the synthesis of combinatorial libraries of naphthyl boronic acids.

Acknowledgment. Spectroscopic analyses were performed in the Korea Basic Science Institute.

References

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3. Commercial database showed the availability of more than five thousands of aryl halides versus two hundreds, often much more expensive, boronic acids and esters.
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6. Procedure for the preparation of **7**: 3,5-Dihydroxy-2-naphthoic acid **6** (0.5 g, 4.45 mmol) was dissolved in anhydrous MeOH pre-saturated with HCl (g) (50 mL). This solution was heated at reflux for 48 hrs. The MeOH was removed in vacuum followed by sonication and concentration from ether (3x) to remove trace HCl. The product was purified with a short path silica gel column (EtOAc) yielding 0.49 g (2.25 mmol; 92 %) of ester. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (1H, s), 10.12 (1H, s), 8.35 (1H, s), 7.48 (1H, s), 7.38 (1H, d, $J = 8.0$ Hz), 7.14 (1H, dd, $J = 8.0$, 7.0 Hz), 6.87 (1H, d, $J = 7.0$ Hz), 3.91 (3H, s); MS (EI) m/e 218 (M). Ester (0.94 g, 4.31 mmol) was suspended in anhydrous CH_2CH_2 (20 mL) and cooled in an ice water bath. *N*-phenyltrifluoromethanesulfonimide (1.69 g, 4.74 mmol) was added to the reaction solution followed by dropwise addition of TEA (0.72 mL, 5.17 mmol) slowly added dropwise resulting in a brown solution. The reaction mixture was stirred at 0 °C for 1 hr, then the cooling bath was removed and the reaction was stirred at room temperature for additional 2 hrs. The dichloromethane was removed in vacuum. A short path silica gel column was used to isolate pure product **7** (1.40 g, 4.00 mmol, 93%) with dichloromethane as a waxy cream colored solid. ^{1}H NMR (300 MHz, DMSO-d_6) d 10.76 (1H, s), 8.53 (1H, s), 8.09 (1H, d, $J = 8.0$ Hz), 7.66 (1H, d, $J = 8.0$ Hz), 7.43 (1H, dd, $J = 8.0$, 8.0 Hz), 7.30 (1H, s), 3.90 (3H, s); MS (EI) m/e 350 (M).
7. For the triflation, see: Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607-4610.
8. To a peptide filter flask under argon were added triflate **7** (0.50 g, 1.43 mmol), 1,1-azobis(*N,N*-dimethylformamide) (246 mg, 1.43 mmol), Wang resin (243 mg, 0.14 mmol), and 1 : 1 tetrahydrofuran/dichloromethane (10 mL). Tributylphosphine (146 mL, 1.43 mmol) was added dropwise with syringe. The reaction mixture was shaken overnight at room temperature, filtered, rinsed with tetrahydrofuran (2x) and dichloromethane (2x), and dried under vacuum. See: Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789-3792.
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