## A New Route to 5-Aryl and 5-Heteroaryl-2-pyrones via Suzuki Coupling of a 2-Pyrone-5-boronate ester

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**Abstract:** The synthesis of the 2-pyrone-5-boronate ester **5** is described along with its palladium-catalysed coupling reactions with a range of aryl and heteroaryl halides and triflates.

Key words: Suzuki coupling, palladium, boron, heterocycles, pyrone

The 2-pyrone unit is an important feature of a number of natural products which display a wide range of biological activity.<sup>1</sup> A number of simple 2-pyrones, including 5-phenyl-2-pyrone, have been investigated for their binding and inactivation of  $\alpha$ -chymotrypsin.<sup>2</sup> More recently, phenylsubstituted 2-pyrones have been shown to be potent HIV-1 protease inhibitors.<sup>3</sup> In addition to biological activity, 2pyrones have been used in the preparation of other ring systems. Reaction with ammonia is a well-established route to pyridones.<sup>4</sup> Diels-Alder reactions of 2-pyrones can lead to a variety of products depending on the dienophile and whether cycloaddition is followed by extrusion of carbon dioxide.<sup>4</sup> Cycloadditions not involving carbon dioxide extrusion have been utilised in the synthesis of shikimate-derived compounds<sup>5</sup> as well as in the synthesis of a tricylic portion of the gibberellic acids.<sup>6</sup> A recent paper reported the synthesis of 5-aryl-2-pyrones using a Suzuki coupling reaction of 5-bromo-2-pyrone and their subsequent Diels-Alder reactions.<sup>7</sup> As we have developed a new 2-pyrone-5-boronate ester and demonstrated its utility in the synthesis of bufadienolide-related steroids,<sup>8</sup> we wanted to explore the use of this reagent in the preparation of 5-aryl and 5-heteroaryl-2-pyrones.

In designing a suitable pyrone boron derivative for Suzuki coupling reaction, we were mindful of the ready cleavage of the pyrone ring under aqueous base conditions. Consequently, we turned our attention to preparing a 5-boronate ester substituted 2-pyrone as pinacol boronate esters have found use in palladium-catalysed coupling reactions.<sup>9</sup> In our hands, the best synthesis of 5-bromo-2-pyrone **3** involved photochemically-initiated bromination of 2-pyrone **1** to give the 5,6-dibromo-2-pyrone **2** followed by dehydrobromination using triethylamine to give **3** in 60% overall yield (Scheme 1). Masuda and co-workers have reported the coupling of pinacolborane **4** with a range of

Synlett 2003, No. 2, Print: 31 01 2003. Art Id. 1437-2096,E;2002,0,02,0253,0255,ftx,en;D26202ST.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0936-5214 aryl halides using Pd(0) catalysis.<sup>10</sup> Under the conditions reported by Masuda, reaction of **4** with 5-bromo-2-pyrone **3** gave little or no product. However, changing the catalyst to PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and carrying out the reaction in refluxing toluene gave the desired pinacolboronate **5** in 83% yield as a stable, crystalline solid.<sup>11</sup>





Reaction of 5 with a variety of aryl and heteroaryl halides and triflates was explored to define the usefulness of this boronate reagent (Table 1). All reactions were conducted using a slight excess of the boronate 5 in dry DMF as solvent, with PdCl<sub>2</sub>(dppf) as catalyst and using crushed potassium phosphate as base at 60 °C.12 As can be seen from entries 1-3, aryl bromides, iodides and triflates are all equally effective under these conditions giving rise to 5phenyl-2-pyrone in very good yield. Entry 4 demonstrates that benzene rings substituted with electron-withdrawing groups are also good substrates whilst entry 5 indicates that electron-donating substituents only lower the yield slightly. The attempted double coupling of 1,4-di-iodobenzene (entry 6) failed to give more than a trace of biscoupled product and instead the mono-coupled product was isolated in 70% yield. This is in contrast to the Stille coupling of 5-trimethylstannyl-2-pyrone with 1,4-di-iodobenzene reported by Meinwald in which a 68% yield of the bis-coupled product was obtained.<sup>13</sup> This could be caused by decomposition of the pyrone boronate during the reaction even though 2.2 molar equivalents were used. Boronate 5 reacted cleanly with 3-bromothiophene to give the coupled product in 82% yield (entry 7). Our interest in the free-radical chemistry of 2-haloindoles and subsequent carbon-carbon bond formation at the 2-position of indoles<sup>14</sup> prompted us to explore the Suzuki reaction of 5 with a range of 2-bromoindoles (entries 8-10). Reaction with N-phenylsulfonyl-2-bromoindole gave coupled product in 42% yield after purification. N-Unsubstituted

indole (entry 9) also reacted in moderate yield whilst coupling with *N*-Boc-2-bromo-3-formylindole (entry 10) gave the cleanest reaction but again only a moderate yield of coupled product was isolated. It is likely that the sensitivity of the 2-bromoindoles used contributes to the lower yields obtained. Finally, an attempt to produce a dimeric 2-pyrone by coupling **5** with its precursor failed to give any coupled product (entry 11). Again, we believe this is due to side reactions of the pyrone ring under the basic conditions of the reaction.

Table 1 Suzuki Coupling Reactions of Boronate 5



As part of our studies on 2-pyrone substituted steroids related to bufadienolides, we were interested in reduction of the pyrone ring to the saturated lactone. To this end, compound  $\mathbf{6}$  (entry 5, in Table 1) was reacted with hydrogen at atmospheric pressure using 5% rhodium on alumina as catalyst (Scheme 2). Anisole derivative 7 (mp 95–97  $^{\circ}$ C) was isolated in 91% yield after purification. The Suzuki coupling of **5** with aromatic halides followed by hydrogenation provides a rapid and efficient way of introducing a valerolactone residue onto an aromatic ring.





In summary, we have shown that boronate **5** is a useful reagent for palladium-catalysed coupling reactions with aryl and heteroaryl halides and triflates. It allows the introduction of a 2-pyrone moiety into a wide variety of aromatic systems and the facility with which the pyrone can be reduced further adds to the utility of these products.

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- (11) **Preparation of(5)**: A mixture of 5-bromo-2-pyrone (13 g, 74 mmol), pinacolborane (16.2 mL, 14.7 g, 111 mmol), triethylamine (31 mL, 22.1 g, 222 mmol) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (1.56 g, 2.2 mmol) in dry tolune (100 mL) was heated to reflux under a N<sub>2</sub> atmosphere for 6 hours. After this time, TLC analysis showed no remaining 5-bromo-2-pyrone. The dark solution was filtered through a short plug of silica and this was further eluted with dichloromethane (250 mL). The solvent was removed under reduced pressure to give a dark crystalline solid. Flash column chromatography using dichloromethane as eluent gave the 2-pyrone-5-boronate **5** (13.6 g, 61.4 mmol, 83%) as a pale yellow crystalline solid, mp 91–93 °C. This material was used in all coupling reactions. An analytically pure sample with the same mp could be obtained as white crystals by sublimation at 0.7 mm

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(12) Typical procedure for Suzuki coupling: Phenyl triflate (50 mg, 0.22 mmol), 2-pyrone-5-boronate 5 (55 mg, 0.25 mmol), and PdCl<sub>2</sub>(dppf) (20 mg, 0.022 mmol) were dissolved in dry DMF (4 mL) under a N<sub>2</sub> atmosphere. Finely crushed K<sub>3</sub>PO<sub>4</sub> (180 mg, 0.82 mmol) was added to the DMF solution and this slurry was heated to 60 °C for 6 hours. The DMF was removed under reduced pressure to give a dark solid that was initially purified by dissolving in dichloromethane and filtering through a plug of silica,

followed by washing with dichloromethane (30 mL). The solvent was removed under reduced pressure to give a solid that was further purified by flash column chromatography (10% ethyl acetate in dichloromethane) to yield 5-phenyl-2-pyrone (30.2 mg, 0.172 mmol, 80%).  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 300 MHz) 6.38 (1 H, dd, J = 9, 1 Hz, H-3), 7.35 (5 H, m, aromatic-H), 7.56 (1 H, dd, J = 9, 3 Hz), 7.62 (1 H, dd, J = 3, 1 Hz);  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 75 MHz) 116.5, 120.6, 126.0, 128.4, 129.3, 133.5, 144.0, 148.3, 161.2; m/z 172 (M<sup>+</sup>, 90%), 144(38), 115(100), 89(12), 63(10). These data match those reported.<sup>7</sup>

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