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Synthesis of Ethyl Nicotinate-5-Boronic Acid Pinacol Ester and Its Application Toward Suzuki Coupling

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Abstract: A method for the synthesis and isolation of pure ethyl nicotinate-5-boronic acid pinacol ester has been described. This boronate ester was used to prepare C_2-C_5 heteroarylnicotinates in good yields.

Keywords: C_2-C_5 heteroarylnicotinates, cross-coupling reaction, ethyl nicotinate-5-boronic acid pinacol ester

Nicotinic acid (niacin or vitamine B_3) is omnipresent in all living cells and bioactive molecules and is used for the treatment of dyslipidemia.[1] In vivo, nicotinic acid is converted to nicotinamide, which in turn is a component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP).[2] Futhermore, in medicinal chemistry nicotinic acids can be used as surrogates of benzoic acids. Nicotinic acids form zwitterionic molecules,[3] which could possess different physical properties. These proprieties could affect their biological activities, thereby making them interesting synthetic targets.

Some bioactive molecules such as kinase inhibitors contain 5-heteroarylnicotinates in their structure.[4] These biaryls can be readily prepared from the Suzuki reaction using 5-bromonicotinates and the corresponding heteroaryl boronic acid or boronate.[5] However, in the case of 2-heteroarylboronate, only poor yields of the corresponding cross-coupling products are usually obtained with the main side reaction being protodeboronation.[6] Alternatively, C_2-C_5 heteroarylnicotinates

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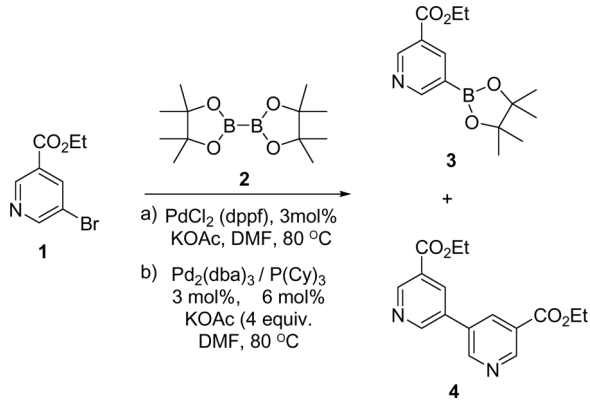
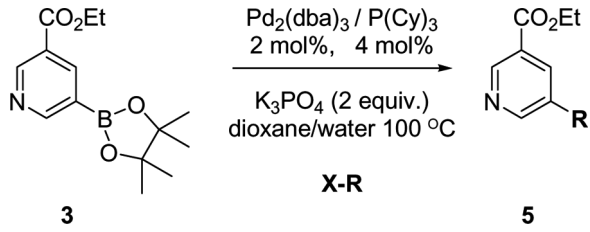


Scheme 1. Synthesis of ethyl nicotinate-5-boronic acid pinacol ester.

could derived from the Suzuki reaction of nicotinate-5-boronic acid or nicotinate-5-boronic acid pinacol ester with 2-halogenoheteroaryl. Nicotinate-5-boronic acid and the corresponding pinacol ester are both commercially available but extremely expensive. Futhermore, to the best of our knowledge there is no reported literature procedure for their synthesis and isolation.

Herein is presented our work on the synthesis and isolation of ethyl nicotinate-5-boronic acid pinacol ester, on a multiple-gram scale, and its application toward the synthesis of C_2-C_5 heteroarylnicotinates. Initially, the $PdCl_2$(dppf)-KOAc conditions[5] were employed for the palladium-catalyzed coupling reaction of ethyl 5-bromonicotinate **1** with bis(pinacolato)diboron **2** (Scheme 1, condition a). Unfortunately, under these conditions, after extractive workup, the crude ^{1}NMR analysis indicated that the desired boronate **3** was present as a minor component. The homocoupling product **4** as well as pinacol residues were observed as major products. In addition, all chromatographic attempts to isolate boronate **3** were unsuccessful because of its poor stability on silica gel. Subsequently,

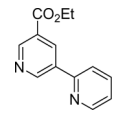
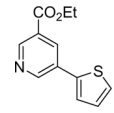
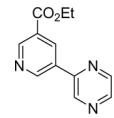
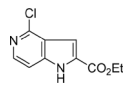
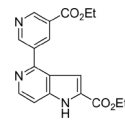
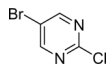
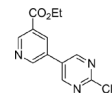
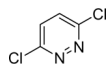
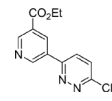
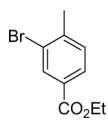
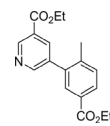


Scheme 2. Synthesis of C2-C5 heteroarylnicotinates.

we turned our attention to the $Pd_2(dba)_3$-tricyclohexylphosphine conditions[6] to examine a more efficient synthesis of the boronate **3**.

Under these conditions, less homocoupling product **4** was observed and in consequence less pinacol residues were formed. These conditions allowed us to reproducibly generate boronate **3** in 30% yield on a 10-g scale after recrystallization. The boronate **3** was then used to prepare a series of C_2-C_5 heteroarylnicotinates **5** in very good yields. Typically, 2-halogenoheteroaryls were treated with 1.5 equiv. of **3** in the presence of 2 mol% $Pd_2(dba)_3$, $P(Cy)_3$ (4 mol%), and K_3PO_4 in dioxane–water at 100 °C for 1 h (Scheme 2).[7] Examples of substrates (Table 1) utilized for the present study include 2-chloropyridine (entry 1), 2-bromothiophene (entry 2),

Table 1. Suzuki cross-coupling reaction of boronate **3** with 2-halgenoheteroaryls

Entry	Halogen	Entry	Coupling product	Yield (%)
1		**8**		92
2		**9**		85
3		**10**		55
4		**11**		62
5		**12**		57
6		**13**		77
7		**14**		84

2-chloropyrazine (entry 3), and 4-chloro-5-azaindole[8] (entry 4). In all cases, good yields of the corresponding coupling products were obtained (entries 8–11). The coupling reaction with substrate **4** provides access to 4-nicotinate-5-azaindoles (entry 11), which are poorly represented in the literature (some pyridoazaindoles are known kinase inhibitors).[9] The reaction was also performed on dihalogenoheterocycles such as 5-bromo-2-chloropyrimidine (entry 5) and 3,6-dichloropyridazine (entry 6) to afford cross-coupling products in good yields. Obviously, these conditions can also be applied on halogenoaryls as exemplified by entry 7.

In conclusion, an efficient method was described to prepare and isolate ethyl nicotinate-5-boronic-acid pinacol ester. This boronate can be used for palladium cross-coupling reactions with 2-halogenoheteroaryls to give access to the synthesis of C_2-C_5 heteroarylnicotinates in good yields.

EXPERIMENTAL

All chemicals were purchased from commercial suppliers and used without purification. NMR spectra were recorded on a Brucker 400 instrument. The ^{1}H and ^{13}C chemical shifts were obtained with DMSO-d_6, $CDCl_3$, or acetone-d_6 as solvents.

Ethyl Nicotinate-5-boronic Acid Pinacol Ester

A mixture containing bis(pinacolato)diboron (14.35 g, 56.5 mmol), $Pd_2(dba)_3$ (1.59 g, 1.74 mmol), tricyclohexylphosphine (0.97 g, 1.74 mmol), and potassium acetate (17.06 g, 174 mmol) in DMF (175 mL) was flushed with nitrogen for 15 min. Ethyl 5-bromonicotinate (10.00 g, 43.5 mmol) in DMF (25 mL) was added slowly to the previous mixture at 80 °C. After a period of 18 h at 80 °C, the reaction mixture was cooled at room temperature, and most of the DMF was evaporated under high vacuum. Ether was then added to the residue, and the mixture was washed with water. The organic phase was separated, dried over sodium sulphate, filtered, and evaporated under reduced pressure. Hexane was then added to the residue. The green-brown solid was removed by filtration. The filtrate was evaporated under reduced pressure. The product was dissolved in a minimum of acetone, and the resulting solution was cooled at 0 °C for 18 h. The solid was collected and washed with a minimum of cold acetone to provide 3.12 g (30%) of the desired boronate **3** as a grey solid. An analytical sample can be obtained by futher recrystallization in hexane to provide colorless clear crystals. Mp 93.5 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.40–1.43 (m, 15H), 4.43 (q, $J = 7.1$ Hz, 2H), 8.56 (t, $J = 1.9$ Hz, 1H, 9.01 (d, $J = 1.5$ Hz, 1H, 9.15 (d, $J = 2.3$ Hz, 1H; ^{13}C NMR (400 MHz, $CDCl_3$)

δ 14.32, 24.85, 61.38, 84.55, 125.66, 143.12, 153.02, 158.82, 165.38, Anal. Calcd. for $C_{14}H_{20}BNO_4$: C, 60.68; H, 7.27; N, 5.05. Found: C, 60.48; H, 7.09; N, 4.86.

Typical Procedure: Synthesis of Ethyl 2,3′-Bipyridine-5′-carboxylate (entry 8)

A mixture of boronate (0.50 g, 1.80 mmol), 2-chloropyridine (entry 1) (0.14 g, 1.26 mmol), $Pd_2(dba)_3$ (0.02 g, 0.02 mmol), and tricyclohexylphosphine (0.01 g, 0.04 mmol) in dioxane (5.0 mL) was degased. An aqueous solution (1.0 mL) of K_3PO_4 (0.58 g, 2.53 mmol) was added to the previous mixture and heated at 100 °C under nitrogen. After a period of 18 h, the reaction was cooled and partitioned between ethyl acetate (20 mL) and pH 5 aqueous KH_2PO_4 (20 mL). The organic phase was washed three times with the $KHPO_4$ solution. The organic phase was separated, dried over sodium sulphate, filtered, and evaporated under reduced pressure. The title compound (entry 8) was purified by flash chromatography (60% ethyl acetate in hexane) to provide 264 mg (92% yield) of a white solid, which was recrytallized in hexane. Mp 80.5 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.44 (t, $J = 7.2$ Hz, 3H), 4.46 (q, $J = 7.1$ Hz, 2H), 7.47 (ddd, $J = 1.0$, 4.8, 7.5 Hz, 1H), 7.97 (dt, $J = 1.8$, 7.8, 15.5 Hz, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 8.77 (ddd, $J = 1.0$, 4.8, 6.3 Hz, 1H), 8.99 (t, $J = 2.1$ Hz, 1H), 9.18 (d, $J = 2.0$ Hz, 1H), 9.49 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.31, 61.57, 120.76, 123.26, 136.34, 134.63, 135.08, 137.12, 150.20, 150.81, 151.73, 153.81, 165.21. Anal. calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.26; H, 5.24; N, 12.17.

Ethyl 5-(2-Thienyl)nicotinate (Entry 9)

Mp 63.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.43 (t, $J = 7.1$ Hz, 3H), 4.45 (q, $J = 7.1$ Hz, 2H), 7.25 (dd, $J = 3.7$, 5.1 Hz, 1H), 7.66 (dd, $J = 1.0$, 5.1 Hz, 1H), 7.72 (dd, $J = 1.0$, 3,6 Hz, 1H), 8.48 (t, $J = 2.1$ Hz, 1H), 9.05 (d, $JJ = 1.9$ Hz, 1H), 9.12 (d, $JJ = 2.3$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl3) δ 14.31, 61.64, 124.98, 126.39, 126.71, 128.45, 130.28, 133.65, 139.22, 149.21, 150.24, 165.12. Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.59; H, 4.96; N, 5.76.

Ethyl 5-Pyrazin-2-ylnicotinate (Entry 10)

Mp 95.5 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.44 (t, $J =$ 7.1 Hz, 3H), 4.47 (q, $J = 7.1$ Hz, 2H), 8.71 (d, $J = 2.4$ Hz, 1H), 8.79 (dd, $J = 1.6$, 2.3 Hz, 1H), 9.01 (t, $J =$ 2.1 Hz, 1H), 9.24 (d, $J = 2.0$ Hz, 1H), 9.39

(d, $J =$ 1.4 Hz, 1H), 9.54 (d, $J =$ 2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.30, 61.76, 126.58, 131.89, 135.14, 142.14, 144.25, 144.62, 149.49, 151.52, 151.63, 164.87. Anal. calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.15; H, 4.75; N, 18.10.

Ethyl 5-(5-Azaindol-4-yl)nicotinate (Entry 11)

Mp 216.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (t, $J =$ 7.1 Hz, 3H), 3.93 (s, 3H), 4.42 (q, $J =$ 7.1 Hz, 2H), 7.47 (s, 1H), 7.51 (d, $J =$ 5.8 Hz, 1H), 8.48 (d, $J =$ 5.8 Hz, 1H), 8.80 (t, $J =$ 2.0 Hz, 1H), 9.19 (d, $J =$ 2.0 Hz, 1H), 9.42 (d, $J =$ 2.1 Hz, 1H); ^{13}C NMR (400 MHz, acetone-d_6) δ 14.58, 52.73, 61.87, 107.07, 108.10, 121.76, 126.39, 129.96, 135.23, 136.49, 142.11, 143.22, 149.49, 150.30, 153.15, 161.61, 165.07. Anal. calcd. for $C_{17}H_{15}N_3O_4$: C, 62.71; H, 4.61; N, 12.91. Found: C, 62.27; H, 4.56; N, 12.62.

Ethyl 5-(2-Chloropyrimidin-5-yl)nicotinate (Entry 12)

Mp 146.4 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.42 (t, $J =$ 7.1 Hz, 3H), 4.55 (q, $J =$ 7.1 Hz, 2H), 8.70 (t, $J =$ 2.1 Hz, 1H), 9.20 (s, 2H), 9.23 (d, $J =$ 2.4 Hz, 1H), 9.24 (d, $J =$ 2.0 Hz, 1H); ^{13}C NMR (400 MHz, acetone-d_6) δ 14.27, 62.01, 126.85, 128.92, 129.27, 135.18, 151.07, 151.28, 157.54, 161.55, 164.49. Anal calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94. Found: C, 54.58; H, 3.79; N, 15.67.

Ethyl 5-(6-Chloropyridazin-3-yl)nicotinate (Entry 13)

Mp 108.2 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.44 (t, $J =$ 7.1 Hz, 3H), 4.47 (q, $J =$ 7.1 Hz, 2H), 8.01 (d, $J =$ 9.0 Hz, 1H), 8.48 (d, $J =$ 9.0 Hz, 1H), 9.03 (t, $J =$ 2.1 Hz, 1H, 9.28 (d, $J =$ 2.0 Hz, 1H), 9.53 (d, $J =$ 2.2 Hz, 1H); ^{13}C NMR (400 MHz, acetone-d_6) δ 13.61, 61.40, 126.60, 127.46, 129.12, 131.26, 134.86, 151.51, 151.68, 156.02, 156.44, 164.44). Anal. calcd. for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94. Found: C, 54.95; H, 3.77; N, 15.67.

Ethyl 5-[5-(Methoxycarbonyl)-2-methylphenyl]nicotinate (Entry 14)

Mp 70.8 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.41 (t, $J =$ 7.2 Hz, 3H), 2.37 (s, 3H), 3.93 (s, 3H), 4.44 (q, $J =$ 7.2 Hz, 2H), 7.46 (d, $J =$ 7.6, 1H), 7.96 (d, $J =$ 7.6 Hz, 1H), 8,01 (s, 1H), 8.30 (t, $J =$ 2.0, 1H), 8.83 (d, $J =$ 2.0 Hz, 1H), 9.18 (d, $J =$ 2.0 Hz, 1H); $_{13}$C NMR (400 MHz, $CDCl_3$) δ 14.28, 20.31, 52.24, 61.64, 125.96, 127.38, 130.01, 130.18, 131.798,

135.98, 136.33, 137.10, 141.56, 149.71, 153.06, 165.13, 166.77. Anal. calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.98; H, 5.49; N, 4.50.

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