SYNTHESIS OF 5-SUBSTITUTED 7-AZAOXINDOLES VIA PALLADIUM-CATALYZED REACTIONS

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Abstract - A synthesis of 5-substituted 1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-ones (5-substituted 7-azaoxindoles) via palladium-catalyzed Suzuki coupling, Stille coupling, and carbonylation reactions is described.

Azaoxindoles have attracted considerable interest in medicinal chemistry as a useful scaffold for generating potential drug molecules.\(^1\)\(^2\) During our effort in developing structure-activity relationships of oxindoles as c-Raf1 kinase inhibitors,\(^3\) we discovered that the oxindole ring core can be replaced by 7-azaoxindole.\(^4\)\(^5\) We knew from our earlier work on oxindoles that introduction of diverse substitutions at the 5-position led to improvement in their physical properties without sacrificing potency of their biological activities. Thus, we decided to also incorporate substitution at the 5-position of the 7-azaoxindole. Synthesis of 7-azaoxindole has been disclosed;\(^6\) however, on the onset of our program, synthesis of 5-substituted 7-azaoxindole was relatively unknown. Herein we report the synthesis of 5-substituted 7-azaoxindole via palladium-catalyzed coupling reactions that allow diverse modifications at the 5-position of the 5-bromo-7-azaoxindole (1).

Scheme 1

As outlined in Scheme 1, 3,3-dibromo-7-azaoxindole (2)\(^6\) was brominated in the presence of bromine and sodium bicarbonate solution in tert-butanol at pH 6.5-7 to give 3,3,5-tribromo-7-azaoxindole (3) in 98% yield.\(^7\) Facile reduction of 3 in the presence of excess zinc dust in a saturated ammonium chloride and
THF solution provided 1 in quantitative yield. Alternatively, compound (1) can be obtained via a two-step sequence from 7-azaindole (bromination and reduction) as reported by Viaud et al. in 80% overall yield.8

As shown in Scheme 2, palladium-catalyzed Suzuki, Stille and carbonylation reactions were employed to introduce substitution at the 5-position of 5-bromo-7-azaoxindole (1).9 Suzuki coupling reaction of 1 was carried out with PhB(OH)2 under several standard conditions such as [Pd(PPh3)4 or Pd(PPh3)2Cl2, Na2CO3, toluene/EtOH, reflux], [Pd(PPh3)4 or Pd(PPh3)2Cl2, Na2CO3, Et4NCl, MeCN, reflux], and [Pd(OAc)2, dppf, Et3N, DMF, 95 °C]. In all cases, the reactions were sluggish and incomplete, and only 0-5% product was obtained. The addition of LiCl was found to be crucial for the success of the Suzuki reaction. When LiCl (3 eqv.) was added to the reaction conditions [1, PhB(OH)2, Pd(PPh3)2Cl2, Na2CO3, LiCl, toluene/EtOH, 95 °C, 18 h], a complete Suzuki transformation was observed. As illustrated in Table 1, compound (4a) was obtained from 1 in 51% yield.

Scheme 2

Stille coupling reaction of 1 could be achieved with most tin reagents in 36-66% yield [RSnBu3, Pd(PPh3)2Cl2, Et4NCl, MeCN, 95 °C, 22 h].10 However, compounds (4g, 4h and 4i) were isolated in poor yield (23, 28 and 12% respectively), and we did not observe any product formation (4j and 4k) when electron deficient tin reagents such as 2-tributylstannylpyrazine and 5-tributylstannylpyrimidine were used (Entries 9 and 10).

Ester functionality at the 5-position of 1 can be readily incorporated via palladium-catalyzed carbonylation reaction in the presence of alcohol in 24-53% yield [ROH, 40 psi CO, Pd(OAc)2, dppp, Et3N, DMSO, 95 °C, 18 h]. High pressure and high temperature were required for the carbonylation
reaction of 1 because we did not observe any product formation when the reaction was carried out with an atmospheric pressure of carbon monoxide or when the reaction was carried out at room temperature.

Table I. Synthesis of 5-Sustituted 7-Azaoxindole via Palladium-Catalyzed Reactions.

<table>
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<tr>
<th>Entry</th>
<th>Product</th>
<th>R</th>
<th>Reagent</th>
<th>Procedure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>25&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>C</td>
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<sup>a</sup> Typical procedures are provided in the experimental procedure session. Procedure A is the Suzuki reaction, Procedure B is the Stille reaction, and Procedure C is the carbonylation reaction.  
<sup>b</sup> Satisfactory spectroscopic data were obtained for all products.  
<sup>c</sup> Compound (4d) was isolated from 4c during silica gel column chromatography purification.

In conclusion, we have developed facile procedures of introducing diverse substitutions at the 5-position of the readily available 5-bromo-7-azaoxindole (1) via palladium-catalyzed Suzuki coupling, Stille coupling and carbonylation reactions.

**EXPERIMENTAL**

Melting points were determined on a Mel-temp II apparatus and are uncorrected. Proton NMR spectra were obtained with a VARIAN Unity Plus NMR spectrophotometers at 300 or 400 MHz. IR spectra were obtained with a Bruker DuraScope Vector 22. MS spectra were recorded on a Micromass Platform II mass spectrometers using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization...
(ESI). Microanalysis data were obtained from Atlantic MicroLab, Inc. in Georgia, U.S.A. Organic solvents and reagents were purchased and used without further purification. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon or nitrogen. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi rotatory evaporator. Analytical TLC was carried out on precoated plates (Merck Silica Gel 60 F-254), and spots were visualized with UV light. Column chromatography was performed on Merck Silica gel 60 (230-400 mesh) with stated solvent system under pressure.

5-Phenyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4a)

To a stirred mixture of 1 (213 mg, 1.0 mmol) and PhB(OH)_2 (183 mg, 1.5 mmol) in toluene (6 mL) and EtOH (6 mL) were added 1 M Na_2CO_3 (2.5 mL, 2.5 mmol), LiCl (127 mg, 3.0 mmol) and Pd(PPh_3)_2Cl_2 (35 mg, 0.05 mmol) under N_2. The reaction mixture was heated to reflux at 95 °C for 18 h. The reaction mixture was diluted with CHCl_3 (50 mL) and washed with brine (20 mL). The aqueous layer was thoroughly extracted with CHCl_3. The combined organic layers were dried, filtered and evaporated. The resulting product was purified by column chromatography (eluent: ethyl acetate/hexane, 1/1) to provide 4a (108 mg, 51.4%) as a yellow solid: mp 207-209 °C (decomp) (EtOAc). IR (Neat) ν: 3170, 1714, 1619, 1588, 1443, 1305, 1206, 892, 751, 696 cm⁻¹. ^1H NMR (DMSO-d_6) δ: 11.04 (s, 1H), 8.32 (s, 1H), 7.83 (s, 1H), 7.60 (d, 2H, J = 7.4 Hz), 7.44 (t, 2H, J = 7.4 Hz), 7.32 (t, 1H, J = 7.4 Hz), 3.58 (s, 2H). ^13C NMR (DMSO-d_6) δ: 176.54, 158.44, 144.89, 138.31, 130.97, 130.53, 129.72, 127.98, 127.00, 121.41, 113.17, 91.01, 87.67, 35.80. MS (-ve APCI): 209 (M-H).

Anal. Calcd for C_13H_10N_2O + 0.25H_2O: C, 72.71; H, 4.93; N, 13.05. Found: C, 72.72; H, 4.93; N, 12.95.

5-Phenylethynyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4b)

To a stirred mixture of 1 (213 mg, 1.0 mmol) in MeCN (4 mL) were added phenylethynyltributyltin (0.42 mL, 1.2 mmol), Et_4NCl hydrate (166 mg, 1.0 mmol), and Pd(PPh_3)_2Cl_2 (35.1 mg, 0.05 mmol) under N_2. The reaction mixture was heated to reflux at 95 °C for 22 h. The reaction mixture was diluted with Et_2O (100 mL) and washed with 2M KF solution (20 mL). The aqueous layer was thoroughly extracted with Et_2O. The combined organic layers were dried, filtered and evaporated. Trituration of the product with Et_2O provided 4b (155 mg, 66%) as a yellow solid: mp 195-197 °C (Et_2O). IR (Neat) ν: 3142, 3052, 1719, 1697, 1618, 1465, 1312, 1230, 750 cm⁻¹. ^1H NMR (DMSO-d_6) δ: 11.23 (s, 1H), 8.25 (d, 1H, J = 1.6 Hz), 7.68 (s, 1H), 7.51-7.53 (m, 2H), 7.39-7.42 (m, 3H), 3.57 (s, 2H). ^13C NMR (DMSO-d_6) δ: 176.39, 158.59, 158.72, 150.00, 134.51, 131.93, 129.46, 122.92, 121.38, 113.17, 91.01, 87.67, 35.80. MS (-ve APCI): 233 (M-H). Anal. Calcd for C_15H_10N_2O: C, 76.91; H, 4.93; N, 11.96. Found: C, 75.66; H, 4.56; N, 11.23.

5-(1-Ethoxyvinyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4c)
This compound was prepared from 1 according to the method used for the product (4b). The expected derivative (4c) was obtained after purification by column chromatography (eluent: ethyl acetate/hexane, 1/1) in 55% yield as a yellow solid; mp 138-140 °C (decomp) (EtOAc). IR (Neat) ν: 3094, 2974, 2836, 2724, 1720, 1615, 1478, 1327, 1223, 1150, 1053 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.09 (s, 1H), 8.32 (s, 1H), 7.76 (s, 1H), 4.71 (s, 1H), 4.27 (s, 1H), 3.90 (q, 2H, J = 7 Hz), 3.58 (s, 2H), 1.36 (t, 3H, J = 7 Hz). ¹³C NMR (DMSO-d₆) δ: 176.61, 159.11, 157.61, 143.69, 129.27, 126.49, 120.78, 82.97, 63.66, 35.90, 14.99. MS (+ve ESI): 205 (M+H). Anal. Calcd for C₁₁H₁₂N₂O₂: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.13; H, 5.96; N, 13.51.

5-Acetyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4d)

This compound was prepared from 1 according to the method used for the product (4c). The expected derivative (4d) was obtained after purification by column chromatography (eluent: ethyl acetate/hexane, 1/1) in 25% yield as a yellow solid: mp 118-220 °C (decomp) (EtOAc). IR (Neat) ν: 3152, 3081, 2959, 2887, 1713, 1672, 1610, 1453, 1300, 1226, 1145 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.41 (s, 1H), 8.72 (d, 1H, J = 1.6 Hz), 7.97 (s, 1H), 3.60 (s, 2H), 2.52 (s, 3H). ¹³C NMR (DMSO-d₆) δ: 196.74, 176.85, 162.45, 149.76, 131.03, 127.76, 121.38, 35.78, 27.21. MS (-ve APCI): 175 (M-H). Anal. Calcd for C₉H₈N₂O₂: C, 61.36; H, 4.58; N, 15.90. Found: C, 60.84; H, 4.67; N, 15.81.

4-(2-Oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)benzenesulfonamide (4e)

This compound was prepared from 1 according to the method used for the product (4b). The expected derivative (4e) was obtained after purification by column chromatography (eluent: ethyl acetate/hexane, 1/1) in 29% yield as a white solid: mp 273-275 °C (decomp) (EtOAc). IR (Neat) ν: 3350, 3245, 2975, 2821, 2765, 1714, 1626, 1312, 1150 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.12 (s, 1H), 8.41 (d, 1H, J = 2 Hz, 1H), 7.91 (d, 1H, J = 2 Hz, 1H), 7.85 (d, 1H, J = 8.8 Hz, 2H), 7.81 (d, 1H, J = 8.8 Hz, 2H), 7.36 (s, 2H), 3.60 (s, 2H). MS (-ve ESI) 290 (M+H). Anal. Calcd for C₁₃H₁₁N₃O₃S: C, 53.97; H, 3.83; N, 14.52. Found: C, 53.97; H, 3.85; N, 14.55.

5-(2-Furyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4f)

This compound was prepared from 1 according to the method used for the product (4b). The expected derivative (4f) was obtained after purification by column chromatography (eluent: ethyl acetate/hexane, 1/1) in 36% yield as a peach solid: mp 219-220 °C (EtOAc). IR (Neat) ν: 3082, 1704, 1602, 1424, 1306, 1217 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.09 (s, 1H), 8.40 (d, 1H, J = 1.8 Hz), 7.84 (s, 1H), 7.72 (d, 1H, J = 1.8 Hz), 6.89 (d, 1H, J = 3.5 Hz), 6.57 (dd, 1H, J = 3.3 and 1.8 Hz), 3.58 (s, 2H). ¹³C NMR (DMSO-d₆) δ: 176.41, 158.20, 151.75, 143.43, 142.10, 127.88, 121.60, 121.56, 112.69, 105.84, 35.93. MS (+ve APCI): 201 (M+H). Anal. Calcd for C₁₁H₈N₂O₂: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.61; H, 4.13; N, 13.91.

5-(3-Pyridinyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4g)
This compound was prepared from 1 according to the method used for the product (4b). The expected derivative (4g) was obtained after purification by column chromatography (eluent: ethyl acetate/hexane, 1/1) in 23% yield as a yellow solid: mp 257-258 °C (decomp) (EtOAc). IR (Neat) ν: 3009, 1713, 1626, 1464, 1218 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.13 (s, 1H), 8.84 (d, 1H, J = 1.2 Hz), 8.52 (d, 1H, J = 4.4 Hz), 8.39 (s, 1H), 8.03 (d, 1H, J = 8.0 Hz), 7.91 (s, 1H), 7.44 (dd, 1H, J = 8.0 and 4.8 Hz), 3.60 (s, 2H). ¹³C NMR (DMSO-d₆) δ: 176.49, 159.00, 149.02, 147.92, 145.21, 133.91, 131.00, 127.44, 124.58, 121.63, 36.01. MS (+ve APCI): 212 (M+H). Anal. Calcd for C₁₂H₉N₃O: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.04; H, 4.35; N, 19.78.

5-(2-Thienyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4h)
This compound was prepared from 1 according to the method used for the product (4b). The expected derivative (4h) was obtained after purification by column chromatography (eluent: ethyl acetate/hexane, 1/1) in 28% yield as a yellow solid: mp 249-250 °C (EtOAc). IR (Neat) ν: 3071, 1704, 1615, 1589, 1305, 1221, 681 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.12 (s, 1H), 8.38 (s, 1H), 7.86 (s, 1H), 7.55 (d, 1H, J = 5.0 Hz), 7.49 (d, 1H, J = 3.6 Hz), 7.15 (dd, 1H, J = 5.0 Hz and 3.6 Hz), 3.63 (s, 2H). ¹³C NMR (DMSO-d₆) δ: 176.42, 158.41, 143.51, 141.11, 129.86, 129.17, 125.97, 124.80, 124.11, 121.76, 35.96. MS (+ve APCI): 217 (M+H). Anal. Calcd for C₁₁H₈N₂OS: C, 61.09; H, 3.73; N, 12.95; S, 14.83. Found: C, 60.8; H, 3.81; N, 12.73; S, 14.82.

5-(3-Thienyl)-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (4i)
This compound was prepared from 1 according to the method used for the product (4b). The expected derivative (4i) was obtained after trituration with MeOH in 12% yield as a yellow solid: mp 235-237 °C (MeOH). IR (Neat) ν: 3093, 2918, 1706, 1615, 1591, 1305, 1221, 681 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.03 (s, 1H), 8.48 (d, 1H, J = 1.8 Hz), 7.90 (m, 1H), 7.83 (s, 1H), 7.63 (dd, 1H, J = 5.0 and 3.0 Hz), 7.54 (dd, 1H, J = 5.0 and 1.1 Hz), 3.58 (s, 2H). ¹³C NMR (DMSO-d₆) δ: 176.49, 157.97, 144.29, 139.33, 130.34, 127.98, 126.47, 125.92, 121.41, 120.82, 35.96. MS (-ve APCI): 215 (M-H). Anal. Calcd for C₁₁H₈N₂OS: C, 61.09; H, 3.73; N, 12.95. Found: C, 60.91; H, 3.80; N, 12.83.

Ethyl 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (5a)
To a mixture of 1 (213 mg, 1.0 mmol) in DMSO (1 mL) and EtOH (2 mL) in Parr bomb were added Et₃N (0.31 mL, 2.25 mmol), Pd(OAc)₂ (33.7 mg, 0.15 mmol), and 1,4-(bisdiphenylphosphino)propane (dppp) (61.9 mg, 0.15 mmol). Carbon monoxide gas (40 psi) was applied and the reaction mixture was vigorously stirred and heated at 95 °C for 18 h. The reaction mixture was diluted with Et₂O (50 mL) and washed with water (10 mL). The aqueous layer was thoroughly extracted with Et₂O. The combined organic layers were dried, filtered and evaporated. Trituration of the crude product with MeOH yielded 5a (53 mg, 25.7%) as a tan solid: mp 218-220 °C (MeOH). IR (Neat) ν: 3013, 2998, 2831, 1702, 1622, 1405, 1288, 1256, 1150, 1021, 775 cm⁻¹. ¹H NMR (DMSO-d₆) δ: 11.39 (s, 1H), 8.62 (s, 1H), 7.95 (s,
1H), 4.27 (q, 2H, J = 7 Hz), 3.59 (s, 2H), 1.28 (t, 3H, J = 7 Hz).  $^{13}$C NMR (DMSO-d$_6$) δ: 176.80, 165.64, 162.57, 149.51, 132.29, 121.34, 120.33, 61.35, 35.81, 14.83.  MS (-ve APCI): 205 (M-H).  Anal. Calcd for C$_{10}$H$_{10}$N$_2$O$_3$: C, 53.57; H, 5.39; N, 12.49.  Found: C, 53.84, H, 5.10; N, 12.11.

**Isobutyl 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (5b)**

This compound was prepared from 1 according to the method used for the product (5a). The expected derivative (5b) was obtained after trituation with MeOH in 53% yield as a yellow solid: mp 148-150 °C (MeOH).  IR (Neat) υ: 3109, 2964, 2848, 1712, 1618, 1407, 1282, 1247, 1145, 778 cm$^{-1}$;  $^1$H NMR (DMSO-d$_6$) δ: 11.41 (s, 1H), 8.65 (s, 1H), 7.97 (s, 1H), 4.03 (d, 2H, J = 6.5 Hz), 3.61 (s, 2H), 1.99 (m, 1H), 0.94 (d, 6H, J = 6.5 Hz).  MS (-ve APCI): 177 (M-C$_4$H$_9$).  Anal. Calcd for C$_{12}$H$_{14}$N$_2$O$_3$: C, 61.53; H, 6.02; N, 11.96.  Found: C, 61.86; H, 6.28; N, 11.50.

**Benzyl 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (5c)**

This compound was prepared from 1 according to the method used for the product (5a). The expected derivative (5c) was obtained after trituation with MeOH in 24% yield as an off-white solid: mp 176-178 °C (MeOH).  IR (Neat) υ: 3098, 3041, 2832, 1735, 1702, 1626, 1446, 1372, 1259, 1211, 1145 cm$^{-1}$.  $^1$H NMR (DMSO-d$_6$) δ: 11.43 (s, 1H), 8.67 (d, 1H, J = 1.8 Hz), 7.99 (s, 1H), 7.46-7.35 (m, 5H), 5.32 (s, 2H), 3.60 (s, 2H).  $^{13}$C NMR (DMSO-d$_6$) δ: 176.80, 165.52, 162.88, 149.71, 136.75, 132.36, 129.21, 128.82, 128.64, 121.45, 120.06, 66.77, 35.98.  MS (-ve APCI): 177 (M-C$_4$H$_7$).  Anal. Calcd for C$_{15}$H$_{12}$N$_2$O$_3$: C, 67.16; H, 4.51; N, 10.44.  Found: C, 67.20; H, 4.57; N, 10.39.

**ACKNOWLEDGEMENTS**

We thank Dr. Lee Kuyper for providing helpful discussion.

**REFERENCES AND NOTES**


11. 4-(Tributyltin)benzenesulfonamide was prepared as follows: A mixture of 1 g (4.2 mmol) of 4-bromobenzenesulfonamide, 3.65 g (6.3 mmol) of bis(tributyltin), and 0.046 g of Pd(PPh₃)₄ in MeCN (25 mL) and toluene (3 mL) was heated to reflux for 18 h. After cooling to rt, the reaction mixture was diluted with ethyl acetate (10 mL) and the excess bis(tributyltin) was removed via separatory funnel. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (hexane/ethyl acetate, 2/1) to afforded 4-(tributyltin)benzenesulfonamide (970 mg, 52%) as a pale yellow oil. ¹H NMR (DMSO-d₆) δ: 7.73 (d, 2H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.0 Hz), 7.28 (s, 2H), 1.48 (m, 6H), 1.26 (m, 6H), 1.07 (m, 6H), 0.82 (t, 9H, J = 7.3 Hz). ¹³C NMR (DMSO-d₆) δ: 147.81, 144.50, 137.22, 125.24, 29.21, 27.33, 14.20, 9.96. MS (-ve ES): 445 (M-H).