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Conversion of 1-Boc-indoles to 1-Boc-oxindoles

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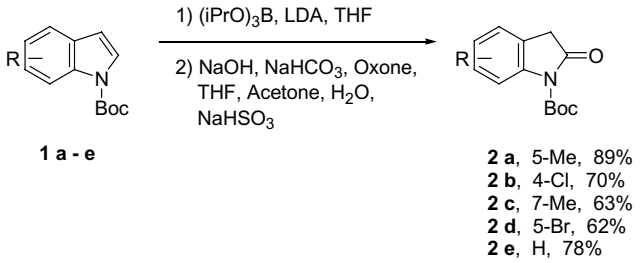
Abstract—A facile synthesis of substituted oxindoles **2** from the corresponding indole is described. The reaction, which proceeds through the 2-(indolyl) borate intermediate, is general and applicable to several indoles.

The oxindole ring is found in many natural products[1] and pharmaceutically active compounds.[2] While many methods exist for the construction of oxindoles from nonindole precursors,[3] fewer options exist for the conversion of indoles into the corresponding oxindoles. Methods for the oxidation of substituted indoles to yield their respective oxindoles are often multi-step procedures,[4] or involve an aqueous enzymatic system,[5] since straightforward oxidation of indole generally takes place at the electron rich 3-position.[6] Sometimes these methods require hydrogenation[7,8] to yield the desired oxindole. Recently we reported on an improved process to convert *N*-Boc protected indoles into 2-(indolyl) borates[9] and here we describe an extension of that chemistry to give substituted oxindoles in good yields.

Ozone® has been used to oxidize boronic acid and boronic esters to their corresponding alcohols.[10] A number of commercially available indoles were *N*-Boc protected under standard conditions (Scheme 1). The resulting *N*-Boc indoles were taken forward without further purification to yield the desired boronic acids after hydrolysis of the isopropylborate esters.[6] These acids were then oxidized to the desired oxindoles.[11] It is worth noting that the procedures were not optimized but consistently good yields were obtained. Additionally, protection of the 3-position on the indole was not necessary, which allowed for the two reactions to be simply run in one pot.

In conclusion, we have demonstrated a convenient and efficient protocol for the synthesis of substituted oxindoles. The method provides a convenient and rapid one-pot transformation of Boc-indoles to Boc-oxindoles employing an environmentally friendly oxidation.



Scheme 1.

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11. In a typical procedure, to a solution of *N*-Boc-5-methylindole **1a** (2.00 g; 8.65 mmol) in THF (10 mL) was added triisopropylborate (3.0 mL; 13.0 mmol). The solution was cooled to 0–5 °C and LDA (1.8 M, 11.2 mmol) was added over 1 h. After 30 min the reaction was quenched by the addition of 2 N HCl (15.6 mL, 31.1 mmol). The organic layer was separated, and washed with water (10 mL). To the organic layer was added acetone (20.0 mL), water (20.0 mL) followed by NaOH (0.519 g, 13.0 mmol), and $NaHCO_3$ (5.81 g, 69.2 mmol) then cooled to 0 °C. To the reaction mixture was added Oxone® (5.3 g, 8.62 mmol) in water (20 mL). The reaction was aged for 15–30 min and quenched with $NaHSO_3$. The product was partitioned into MTBE (20 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (20% EtOAc/hex) to give **2a** (1.90 g, 89% yield); mp 89.0–90.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.56 (1H, d, J = 8.6 Hz), 7.10–7.08 (2H, m), 3.68 (2H, s), 2.28 (3H, s), 1.55 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.0, 149.3, 138.6, 133.5, 128.3, 125.4, 124.6, 114.5, 83.7, 36.5, 28.2, 21.0; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.98; H, 6.94; N, 5.60.
Compound **2b** 1.50 g (70% yield); mp 100.0–101.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.65 (1H, d, J = 8.0 Hz), 7.34 (1H, t, J = 8.2, 8.2 Hz), 7.21 (1H, dd, J = 0.47, 0.66 Hz), 3.72 (2H, s), 1.56 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.6, 149.0, 142.2, 129.8, 129.4, 124.2, 123.5, 113.5, 84.3, 36.1, 28.1; Anal. Calcd for $C_{13}H_{14}ClNO_3$: C, 58.32; H, 5.27; N, 5.23. Found: C, 58.44; H, 5.24; N, 5.07.
Compound **2c** 1.34 g (63%yield); mp 65.0–66.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.13 (2H, t, J = 7.4, 10.3 Hz), 7.05 (1H, t, J = 7.42, 7.47 Hz), 3.76 (2H, s), 2.16 (3H, s), 1.55 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.2, 149.8, 139.6, 130.8, 125.7, 124.3, 122.5, 84.7, 36.4, 27.8, 19.2; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.96; H, 6.97; N, 5.64.
Compound **2d** 0.66 g (62% yield); mp 95.0–96.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.63 (1H, d, J = 8.5 Hz), 7.50–7.47 (2H, m), 3.75 (2H, s), 1.55 (9H, s); ^{13}C NMR (DMSO-d_6,100 MHz) δ 172.3, 149.1, 140.4, 130.7, 127.7, 127.5, 116.7, 116.4, 84.2, 36.4, 28.1; Anal. Calcd for $C_{13}H_{14}BrNO_3$: C, 50.02; H, 4.52; N, 4.49. Found: C, 50.19; H, 4.39; N, 4.42.
Compound **2e** 1.67 g, 78% yield); mp 66.0–67.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.68 (1H, d, J = 8.59 Hz), 7.30–7.27 (2H, m), 7.13 (1H, t, J = 7.46, 7.55 Hz), 3.72 (2H, s), 1.56 (9H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.9, 149.3, 141.0, 128.0, 124.8, 124.7, 124.4, 114.7, 83.9, 36.5, 28.2; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.74; H, 6.47; N, 5.89.