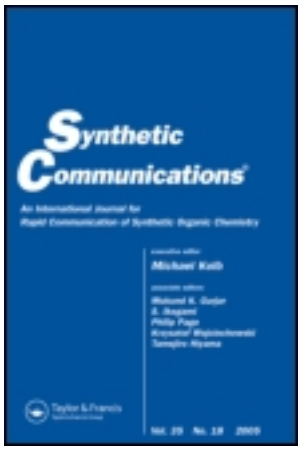

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Preparation of Ethyl 5-Iodo-1*H*-indole-2-carboxylate

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ABSTRACT

A facile, two step procedure for the preparation of ethyl 5-iodo-1*H*-indole-2-carboxylate (**1**) from commercially available ethyl 1*H*-indole-2-carboxylate is described herein, employing a regioselective *C*3, *C*5-bisiodination followed by zinc-mediated *C*3-dehalogenation.

Key Words: Indole; Regioselective halogenation; Dehalogenation.

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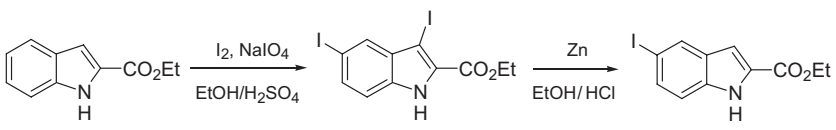
In the course of a recent drug discovery program, we required access to 5-substituted indole-2-carboxylic acids or esters. While several are commercially available, our requirements for wide structural diversity led us to engage 5-halo derivatives in metal-catalyzed cross coupling reactions. While ethyl 5-bromo-1*H*-indole-2-carboxylate is available, we were surprised to discover that a synthesis of the more reactive and versatile 5-iodo-1*H*-indole-2-carboxylate (**1**) was absent from the literature.[1] We have therefore devised a simple, direct route to **1** from commercially available ethyl 1*H*-indole-2-carboxylate (Sch. 1).

Iodination of indoles is known to proceed regioselectively at *C*3 under relatively mild conditions.[2] However, further halogenation of the benzo portion of the indole moiety has often resulted in mixtures of halogenation products, which vary depending on the reaction conditions employed.[3] Recent work by Erra-Balsells and coworkers on the chlorination,[4,5] bromination[6] and iodination[7] of carbazoles and β-carbolines, and by Billimoria and Cava on the regioselective *C*3,*C*5-dibromination of indolo[1,2-*c*]quinazoline,[8] provided precedent for regioselective bishalogenation of indole-2-carboxylate derivatives. In fact, upon treatment with in situ generated periodic acid ($I_2/NaIO_4/H_2SO_4$/EtOH/reflux),[9] ethyl indole-2-carboxylate (**2**) was regioselectively *C*3,*C*5-bishalogenated to provide diiodide **3** in quantitative yield after workup. The structure of **3** was confirmed by ^{1}H NMR nOe correlations (see Experimental section). The reaction was found to proceed sequentially; initial treatment resulted in immediate *C*3-iodination, which was followed by *C*5-iodination upon heating in ethanol over the next 90 min. Other attempts at bisiodination (i.e., NIS or I_2/H_2SO_4) provided only *C*3-monoiodination, leaving the benzo portion of the indole unfunctionalized.[10]

In order to access the desired compound **1**, selective dehalogenation of **3** was investigated. *C*3-Protonation of indoles is facile under strongly acidic conditions,[11] and this process was exploited by Murakami and colleagues to affect the selective *C*3-protodebromination of substituted ethyl 3-bromoindole-2-carboxylates using LiBr in aqueous acid, with



Scheme 1.

N-methylpyrrole as a bromine scavenger.[12] In an effort to extend this methodology to the protodeiodination of **3**, we subjected **3** to analogous conditions (LiI/*N*-methylpyrrole/H_2SO_4/AcOH, reflux). Disappointingly, the extreme reaction conditions that were required resulted in polymerization and poor yields of **1**. Tashiro and Fukata have shown that selective reductive dehalogenation of iodo- and bromo-substituted phenols occurs with zinc powder in the presence of aqueous acid.[13] Taken with the work of Murakami,[12] this precedent prompted us to subject **3** to acidic, reductive conditions to effect *C*3-deiodination. Under standard reductive conditions (powdered zinc/HCl/EtOH/ambient temperature), a clean transformation ensued to produce **1** with no detectable *C*5-deiodination. Thus, over two steps, a 57% isolated yield of crystalline **1** was obtained from ethyl indole-2-carboxylate.[14]

A simple two-step procedure involving regioselective *C*3,*C*5-bisiodination of ethyl 1*H*-indole-2-carboxylate, followed by *C*3-selective reductive dehalogenation readily provides access to the previously unreported ethyl 5-iodo-1*H*-indole-2-carboxylate (**1**). In addition to the high regioselectivity achieved in the halogenation reaction, this method also opens the potential for using the *C*3-iodide as a blocking group that can be easily removed under mild reductive conditions.[15]

EXPERIMENTAL

Ethyl 3,5-diiodo-1*H*-indole-2-carboxylate (3). To a stirring solution of ethyl-1*H*-indole-2-carboxylate (5.00 g, 26.4 mmol, 1.0 equiv.) in 50 mL of absolute EtOH was added I_2 (6.71 g, 26.4 mmol, 1.0 equiv.), $NaIO_4$ (2.83 g, 13.2 mmol, 0.50 equiv.) and H_2SO_4 (2.94 mL, 52.8 mmol, 2.0 equiv.). The vessel was heated to reflux for 90 min, cooled to ambient temperature and poured into saturated aqueous Na_2SO_3. The mixture was extracted three times with EtOAc and the combined organic extracts were washed once with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to provide the titled compound **3** (11.7 g, 100%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.27 (br s, 1H), 7.93 (s, 1H), 7.62 (dd, $J = 8.5$, 0.9 Hz, 1H), 7.18 (d, $J = 8.5$ Hz, 1H), 4.46 (q, $J = 7.1$ Hz, 2H) and 1.48 (t, $J = 7.1$ Hz, 3H) ppm; m/z (ES^+) = 441.8 (MH^+). ^{1}H-NMR nOe studies were performed to confirm the structural assignment of compound **3**. Irradiations of the proton resonances at 9.27 and 7.18 ppm showed nOe enhancements to the resonances at 7.18 and 7.62 ppm, respectively, confirming the *C*5 location of the iodo group.

Ethyl 5-iodo-1*H*-indole-2-carboxylate (1). To a stirring suspension of **3** (11.7 g, 26.4 mmol, 1.0 equiv.) in 250 mL of EtOH was added

concentrated aqueous hydrogen chloride (22.0 mL, 264 mmol). Zinc dust (26.9 g, 410 mmol) was added portionwise over 90 min. After stirring for 30 min, the mixture was diluted with water and extracted four times with EtOAc. The combined extracts were washed once with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was crystallized thrice from EtOAc/hexanes (1.60 g, 1.20 g and 0.710 g), which provided a total of 3.51 g of the title product. The remaining mother liquor was concentrated in vacuo and purified by flash chromatography (0% to 8% ethyl acetate in hexanes) to provide an additional 1.24 g of the titled compound (combined yield of **1**: 4.75 g, 57%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.98 (br s, 1H), 8.04 (d, $J = 1.0$ Hz, 1H), 7.56 (dd, $J = 8.7$, 1.6 Hz, 1H), 7.21 (d, $J = 8.8$ Hz, 1H), 7.12 (d, $J = 1.9$ Hz, 1H), 4.41 (q, $J = 7.2$ Hz, 2H) and 1.42 (t, $J = 7.2$ Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.9, 135.9, 133.8, 131.6, 130.2, 128.4, 114.0, 107.7, 61.5, and 14.6 ppm. Anal. calcd. for $C_{11}H_{10}INO_2$: C, 41.93; H, 3.20; N, 4.45; Found: C, 41.88; H, 2.97; N, 4.28. Exact mass calculated for $C_{11}H_{10}INNaO_2$: 337.9648; Found: 337.9649 (ESI, M + Na).

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