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An Alternative Synthesis of 2-Chloro-5-Hydroxypyridine: A Key Component of the Non-Opioid Analgesic Agent ABT-594

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AN ALTERNATIVE SYNTHESIS OF 2-CHLORO-5-HYDROXYPYRIDINE: A KEY COMPONENT OF THE NON-OPIOID ANALGESIC AGENT ABT-594

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Abstract: The synthesis of the biologically useful synthon 2-chloro-5-hydroxypyridine from 3-iodo-6-chloropyridine is described.

(*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) (**1**) has recently been reported as a potent, orally active, non-opiate analgesic agent which acts through neuronal nicotinic acetylcholine receptors (nAChR).[1,2] ABT-594 has antinociceptive properties 30-100 times more potent than morphine[3] in animal pain models and been recommended as an attractive candidate for further evaluation as an analgesic agent for the management of pain states, which might avoid the withdrawal effects associated with opioid analgesics. The crucial 2-chloro-5-oxypyridine moiety, an important structural component for potent biological activity of ABT-594 and related structures, has been incorporated by coupling of 2-chloro-5-hydroxypyridine (**2**) with appropriately N-protected alcohols.[2,3] The 2-chloro-5-hydroxypyridine **2** has been prepared in 53% yield by a two-step prrocedure from 5-amino-2-chloropyridine **3**, available from Aldrich Chemical (5g, $107), by substitution of the derived 5-diazonium ion by hydroxyl.

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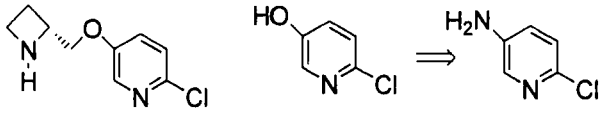
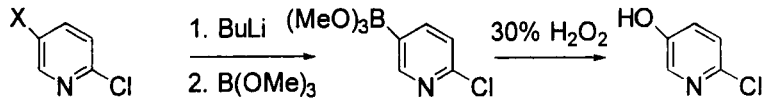


1 2 3

We desired an alternative convenient and efficient route to pyridine **2**, which has the advantage of reduced cost. According to the procedure of Ogura and coworkers[4] and of Clayton and Regan,[5] 2-chloro-5-iodopyridine (**4a**) was prepared from 2-aminopyridine (Aldrich, 500g, $58.20) in two steps in 60% (75% and 80%) overall yield (lit.[4,5] 50%). The 2-chloro-5-iodopyridine **4a** can be converted chemoselectively via trapping of the derived organolithium derivative[6] **4b** with trimethyl borate[7] to the boronic ester **5**, which is directly oxidized in situ using 30% hydrogen peroxide to give 2-chloro-5-hydroxypyridine (**2**) in 66% isolated yield.



4a X = I
4b X = Li

5 **2**

Experimental

Chromatography was obtained using Janssen Chimica Silica gel (particle size 0.06-0.2 mm). ^{1}H NMR spectra were recorded at 300 MHz .

2-Chloro-5-Hydroxypyridine (2). Solid 2-chloro-5-iodo-pyridine[4,5] (1.116 g, 5 mmol) was placed in a 3-neck 100mL round bottom flask with a gas inlet adapter and stirrer. The contents were evacuated and placed under argon, THF (15 mL) was added, and the solution was cooled to –78 °C by dry ice/acetone bath. A 2.02 M solution of BuLi/cyclohexane (2.75 mL, 5.55 mmol) was added by syringe over a 20 min period. An exotherm was noted and the color changed from light yellow to orange. Stirring was continued an additional 20 min at –78 °C. Next, trimethyl borate (99.99+%) (0.62 mL, 5.55 mmol) was added by syringe over 20 min with vigorous stirring. Upon completion of the addition, the reaction was warmed to –10 °C and maintained at this temperature for 45 min using an ice/salt bath. The color changed to deep yellow. Chilled (15 °C) glacial acetic acid (0.43 mL, 7.5 mmol) was added at once followed by the dropwise addition of 30% hydrogen peroxide (0.75 mL, 5.5 mmol) over a 10 min period. Throughout the addition the temperature did not exceed 0 °C. After addition the mixture was allowed to warm to room temperature and was stirred an additional 30 min before quenching with distilled water (10 mL). The organic layer was extracted with $CHCl_3$ (2 x 20 mL) and the combined extracts were dried with magnesium sulfate, filtered, and solvent was removed in *vacuo* to provide a brown oil (798 mg). Addition of CH_2Cl_2 left a yellow green solid (205 mg), which was filtered and the residue was chromatographed (hexane:ethyl acetate, 4:1) to afford crystalline product **2** (227 mg, 67.1 %), R_f = 0.53 (2:1 hexane/ethyl acetate), mp 150-153 °C (lit.[8] 152-159 °C; ^{1}H NMR (CD_3OD) δ 7.23 (2H, m), 7.87 (m, 1H).

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