Synthesis of Indatraline Using a Suzuki Cross-Coupling Reaction and a Chemoselective Hydrogenation: A Versatile Approach

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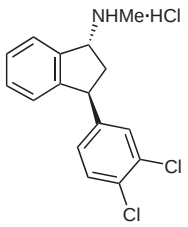
Received 16 April 2003

Abstract: Indatraline and its derivatives can be obtained in five steps from indanone by using a Suzuki cross-coupling reaction and a chemoselective hydrogenation catalyzed by Wilkinson's catalyst.

Key words: indatraline, indanone, Suzuki reaction, hydrogenation, Wilkinson's catalyst

The abuse of stimulants, such as methamphetamine and amphetamine, is a national and international[1] public health problem,[2] and a considerable number of adverse effects[3] derive from that abuse including the increased transmission of hepatitis and HIV/AIDS.[4,5] For this reason, selective dopamine reuptake inhibitors are currently being evaluated for their potential as substitution medications to treat cocaine and methamphetamine abuse.[6,7] Indanamines were found to have potencies as dopamine (DA) reuptake blockers[8] and it has been reported that indatraline **1** (LU 19-005) (Figure 1) is a potent psychoactive compound with high binding and inhibitory affinity for neuronal monoamine reuptake sites including the dopamine (DA) transporter and the serotonin (5-HT) transporter.[9,10] Studies on monkeys indicate that indatraline reduces cocaine self-administration[11] and that the (+)-(1*R*,3*S*) enantiomer is twenty times more efficient than the (–)-(1*S*,3*R*) enantiomer.[12]



Indatraline 1

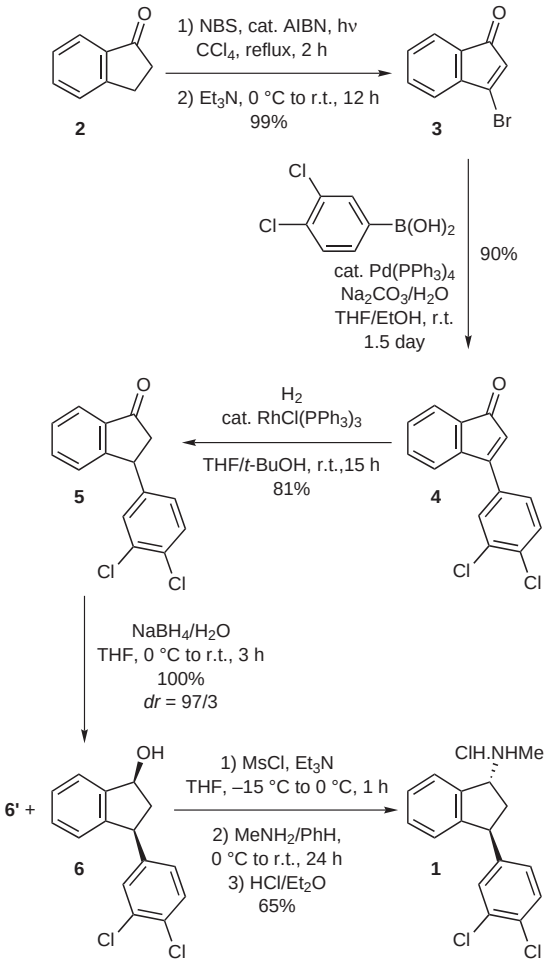
Figure 1

Several syntheses of indatraline have been reported, one of which is enantioselective and is related to the synthesis of (+)-indatraline,[13] while the others are racemic and have relied on classical resolution or chiral HPLC techniques to obtain enantiomerically pure material.[8,9] Here, we would like to report a short synthesis of racemic indatraline that relies on two key steps, a Suzuki cross-coupling reaction which employs commercially available boronic acids,[14] and a chemoselective hydrogenation performed in the presence of Wilkinson's catalyst.

The first step is the transformation of indanone (**2**) to the 3-bromoindenone (**3**) in a one-pot sequence.[15] Indanone (**2**) was illuminated with a light bulb (75 Watts, visible light) in the presence of *N*-bromosuccinimide (2.1 equiv) and a catalytic amount of AIBN in refluxing CCl_4.[16] After 2 hours, triethylamine (3.5 equiv) was added at 0 °C and the reaction mixture was stirred at room temperature for 12 hours. This process provided 3-bromoindenone (**3**) in 99% yield. The transformation of **3** to 3-arylated indenone **4** was obtained by using a Suzuki cross-coupling reaction.[17] When **3** was treated with 3,4-dichlorophenylboronic acid (1.1 equiv) and with a catalytic amount of palladium tetrakistriphenylphosphine [$Pd(PPh_3)_4$, 0.05 equiv] in the presence of an aqueous saturated solution of Na_2CO_3 (3.0 equiv) in a degassed mixture of THF/EtOH (5/1) at room temperature for 1.5 days, compound **4** was isolated in 90% yield.[18] Chloride is certainly one of the most reducible atoms in transition metal-catalyzed hydrogenation processes[19] and, as a result, selective hydrogenation of the enone **4** in the presence of chloride atoms was delicate. However, chlorotris(triphenylphosphine)rhodium(I) catalyst (Wilkinson's catalyst, 0.04 equiv) in THF/*t*-BuOH (1/1)[20,21] showed good chemoselectivity, and hydrogenation of **4** under one atmosphere of hydrogen for 15 hours led to the known precursor of indatraline,[8,9,13] ketone **5**, in 81% yield. Ketone **5** was obtained in three steps in 72% yield.

Reduction of **5** with $NaBH_4$ (2.0 equiv, –5 °C to r.t.) in a mixture of THF/H_2O (10/1) gave a mixture of the *cis* and *trans* alcohols **6** and **6′** in quantitative yield and in a ratio of 97/3 in favour of the *cis*-isomer. After separation of the isomers,[22] the *cis*-isomer **6** was treated with triethylamine (4.0 equiv) in THF, and mesyl chloride was added (2.0 equiv, –15 °C to 0 °C) followed by a large excess of a 10% benzenic solution of methylamine. Slow warming of the reaction mixture to room temperature gave the free amine of indatraline as a pale yellow oil. Treatment of this oil with HCl in diethyl ether gave the salt as a pale yellow solid, which after recrystallization from ethyl EtOAc/EtOH (20/1) afforded indatraline (**1**)[9,13] in 65% yield for the three-step sequence (Scheme 1).

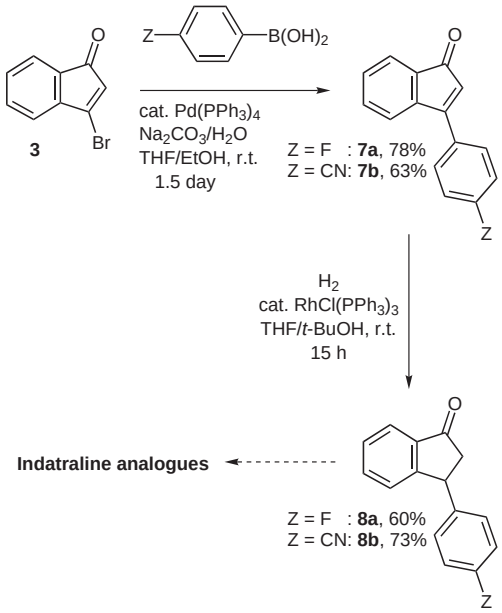
Synlett 2003, No. 10, Print: 05 08 2003.
Art Id.1437-2096,E;2003,0,10,1515,1517,ftx,en;G08403ST.pdf.



Scheme 1

Furthermore, 3-aryl-1-aminoindane in which the aryl group is substituted with functional groups sensitive to hydrogenation conditions, such as a fluorine or a cyano group, can be prepared. 3-(4-Fluorophenyl)indenone (**8a**) and 3-(4-cyanophenyl)indanone (**8b**) were prepared from 3-bromoindenone (**3**). When 3-bromoindenone (**3**) was treated under the Suzuki conditions [$Pd(PPh_3)_4$, Na_2CO_3/H_2O, THF/EtOH, r.t., 1.5 days) with 4-fluorophenylboronic acid and 4-cyanophenylboronic acid, compounds **7a** (78% yield) and **7b** (63% yield) were isolated. After hydrogenation of **7a** and **7b** with Wilkinson's catalyst (1 atm, 15 h), compounds **8a**[23] (60% yield) and **8b**[24] (73% yield) were respectively obtained (Scheme 2).

The synthesis of indatraline and the precursors of its analogues, such as **8a** and **8b**, demonstrates the versatility of our synthetic scheme. By combining the availability of arylboronic acids, which are used in the Suzuki cross-coupling reaction, with the chemoselectivity of the Wilkinson's hydrogenation, a great variety of 3-aryl-1-aminoindane derivatives can be prepared and tested for biological activity.



Scheme 2

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(18) **Typical Experiment for the Suzuki Reaction**: A solution of the β-bromoindenone **3** (4.18 g, 20 mmol) and 3,4-dichlorophenyl-boronic acid (4.2 g, 22 mmol) in THF (100 mL) containing absolute EtOH (20 mL) and H_2O (20 mL) was degased with argon for 20 min. Na_2CO_3 (6.36 g, 60 mmol) and $Pd(PPh_3)_4$ (1.16 g, 1 mmol) were added to this solution. The resulting mixture was vigourously stirred at r.t. for 1.5 d under an argon atmosphere and then diluted with CH_2Cl_2 (250 mL). The reaction mixture was washed with H_2O (2 × 100 mL) and the aqueous layer extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (60/40 petroleum ether/CH_2Cl_2) to give the β-arylindenone **4** as a yellow solid (4.95 g, 90% yield): Mp 148–150 °C. IR: 1700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.74 (d, *J* = 2.0 Hz, 1 H), 7.63–7.25 (6 H), 6.01 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 121.2 (CH), 123.1 (CH), 123.9 (CH), 126.6 (CH), 129.1 (CH), 129.6 (CH), 131.1 (CH), 131.9 (C), 132.9 (C), 133.1 (CH), 133.4 (C), 134.6 (C), 143.3 (C), 160.1 (C), 196.3 (C). MS (EI): *m*/*z* (rel. int.) = 274 (86) [M^+], 239 (100), 211 (28), 176 (73).

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(21) **Typical Experiment for the Wilkinson Hydrogenation:** $(PPh_3)_3RhCl$ (0.122 g, 0.132 mmol) was added to a solution of β-arylindenone **4** (0.91 g, 3.3 mmol) in THF/*t*-BuOH (1/1, 24 mL) under an argon atmosphere. The resulting solution was saturated with hydrogen and stirred under one atmosphere of hydrogen overnight at r.t. The reaction mixture was filtered through a short pad of alumina and washed thoroughly with EtOAc. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (90/10 petroleum ether/EtOAc) to provide β-arylindenone **5** as a colorless solid (0.74 g, 81% yield): Mp 113–115 °C. IR: 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.82 (d, *J* = 7.7 Hz, 1 H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.45 (t, *J* = 7.4 Hz, 1 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 7.30–7.20 (2 H), 6.96 (dd, *J* = 8.3, 2.1 Hz, 1 H), 4.55 (dd, *J* = 8.1, 3.8 Hz, 1 H), 3.23 (dd, *J* = 19.2, 8.1 Hz, 1 H), 2.62 (dd, *J* = 19.2, 3.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 204.8 (C), 156.4 (C), 143.9 (C), 136.7 (C), 135.3 (CH), 132.9 (C), 131.1 (C), 130.9 (CH), 129.6 (CH), 128.3 (CH), 126.9 (CH), 126.6 (CH), 123.6 (CH), 46.4 (CH_2), 43.5 (CH). MS (EI): *m/z* (rel. int.) = 276 (100) [M^+], 241 (77), 212 (25), 178 (60).

(22) Separated by flash chromatography on silica gel (70/30 petroleum ether/EtOAc).

(23) **Compound 8a:** Mp 116–118 °C. IR 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.81 (d, *J* = 7.6 Hz, 1 H), 7.59 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.25 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.14–6.93 (4 H), 4.57 (dd, *J* = 8.0, 3.8 Hz, 1 H), 3.23 (dd, *J* = 19.3, 8.1 Hz, 1 H), 2.64 (dd, *J* = 19.3, 3.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 205.5 (C), 161.8 (d, *J* = 245 Hz, CF), 157.6 (C), 139.4 (C), 136.7 (C), 135.1 (CH), 129.1 (CH), 129.0 (CH), 128.0 (CH), 126.7 (CH), 123.4 (CH), 115.9 (CH), 115.6 (CH), 46.9 (CH_2), 43.7 (CH). MS (EI): *m/z* (rel. int.) = 226 (100) [M^+], 197 (30), 183 (28).

(24) **Compound 8b:** Mp 108–110 °C. IR: 2230, 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.83 (d, *J* = 7.7 Hz, 1 H), 7.67–7.56 (3 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.30–7.20 (3 H), 4.67 (dd, *J* = 8.1, 3.8 Hz, 1 H), 3.27 (dd, *J* = 19.2, 8.2 Hz, 1 H), 2.64 (dd, *J* = 19.2, 3.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 204.5 (C), 156.2 (C), 149.1 (C), 136.7 (C), 135.3 (CH), 132.7 (2 CH), 128.4 (3 CH), 126.6 (CH), 123.7 (CH), 118.5 (C), 111.0 (C), 46.2 (CH_2), 44.3 (CH). MS (EI) *m/z* (rel. int.) = 233 (100) [M^+], 204 (30), 190 (22).