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A New Route to Prepare 6-Chloro-5-(2-chloroethyl)oxindole

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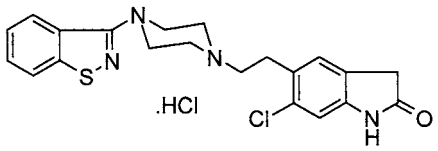
Abstract:
6-Chloro-5-(2-chloroethyl)oxindole, a key intermediate in the manufacturing of the antipsychotic drug, ziprasidone, has been synthesized by a new route. The salient features of the synthesis are (1) bis-dialkylation of 2,4-difluoro-5-chloronitrobenzene with sodium diethyl malonate, (2) decarboxylative hydrolysis to obtain the oxindole derivative, and (3) reduction and chlorination of acetic ester side chain.

Introduction

Ziprasidone hydrochloride[1] is a serotonin and dopamine antagonist, and effective as an antipsychotic drug. Ziprasidone does not increase the weight of the patient and therefore has a distinctive advantage. Many currently available antipsychotic drugs have the side effect of inducing significant weight gain, which is distressing and stigmatizing to patients and increases the risk of cardiovascular complications.[2] Ziprasidone is indeed a superior drug that was recently approved by the Food and Drug Administration of the United States.[3]



Ziprasidone.hydrochloride (1)

Previous Work. Ziprasidone was earlier prepared[4] by a route described in Scheme 1. The synthesis involves Wolf−Kishner reduction of 6-chloroisatin (**2**) to give 6-chlorooxindole (**3**). Subsequent treatment with chloroacetyl chloride and $AlCl_3$ under Freidel−Crafts conditions provided 5-chloroacetyl-6-chlorooxindole (**4**). The ketone functionality of **4** was reduced using triethylsilane in trifluoroacetic acid to produce 6-chloro-5-(2-chloroethyl)oxindole (**5**). The alkylation reaction between **5** and **6**[5] in the presence of Na_2CO_3 in water followed by salt preparation with aqueous hydrochloric acid gave ziprasidone hydrochloride.

This synthesis suffers from two limitations:

(a) The intermediate ω-chloroacetophenone derivative **4** is an irritant, and on large-scale manufacturing process it may pose handling difficulties.

(b) The use of triethylsilane reagent for reduction of the benzylic ketone is expensive.

New Route. On the basis of these limitations, we devised a new synthetic route for the key intermediate **5**, in which the ω-chloroacetophenone derivative **4** and the use of triethylsilane were circumvented.

The basic premise of our synthetic approach is based on S_NAr reaction of aromatic halides with a carbon nucleophile. For example, we had recently reported[6] that halogen atoms present at the ortho and para positions of nitrohalobenzenes can be conveniently displaced with the sodium salt of diethyl malonate to give aryl-substituted malonate esters in good yield. The meta-substituted nitrohalobenzene does not undergo such a substitution reaction. Therefore, our first choice was to conduct the substitution reaction of 2,4,5-trichloronitrobenzene (**7**) with an excess of the sodium salt of diethyl malonate in DMF. This reaction gave a 2:1 mixture of monoalkylated products (**8a** and **8b**), with a trace of dialkylated product (**10**).

Since fluorine is a better leaving group, particularly when activated by a nitro group,[7] we envisaged that 5-chloro-2,4-difluoronitrobenzene (**9**), easily obtainable from 2,4,5-trichloronitrobenzene (**7**) and activated KF in DMF,[8] would be an ideal precursor for dialkylation reactions. Indeed, the reaction of **9** with the sodium salt of diethyl malonate gave the dialkylated product **10**, as sole product. However, subsequent decarboxylative elimination of **10** turned out to be a difficult proposition. For instance, the decarboxylation of **10** under Krapcho's conditions (NaCl, H_2O, DMSO, 160 °C)[9] or with its modified conditions ($MgCl_2 \cdot 6H_2O$, DMA, 140 °C)[10] resulted in the formation of *m*-xylene (**11**) and toluene derivatives (**12**). Formation of these compounds was due to the bis(dealkoxycarbonylation) of diethyl malonate group under the influence of the electron-withdrawing nitro substituent. (Scheme 2).[6]

(1) *Drugs Future* **1994**, *19*, 560.
(2) Howard, H. R.; Seeger, T. F. Novel Antipsychotics. *Annu. Rep. Med. Chem.* **1993**, *28*, 39.
(3) Press release from Food and Drug Administration: Washington, DC, 2000.
(4) Lowe, J. A., III; Nagel, A. A. U.S. Patent 4,831,031; Bowles, P. U.S. Patent 5,206,366.
(5) Walinsky, S. W.; Fox, D. E.; Lambert, J. F.; Sinay, T. G. *Org. Process Res. Dev.* **1999**, *3*, 126.
(6) Gurjar, M. K.; Reddy, D. S.; Murugaiah, A. M. S. *Synthesis* **2000**, 1659.
(7) Zhu, J. *Synlett* **1997**, 133.
(8) (a) King, F. E.; Clark-Lewis, J. W. *J. Chem. Soc.* **1953**, 172. (b) Mason, J.; Milner, D. J. *Synth. Commun.* **1994**, *24*, 529. (c) Smyth, T. P.; Carey, A.; Hodnett, B. K. *Tetrahedron* **1995**, *51*, 6363.
(9) Krapcho, A. P. *Synthesis* **1982**, 805.
(10) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

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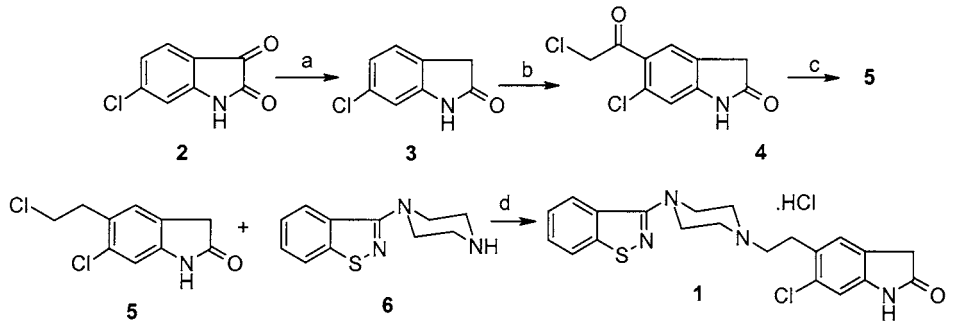
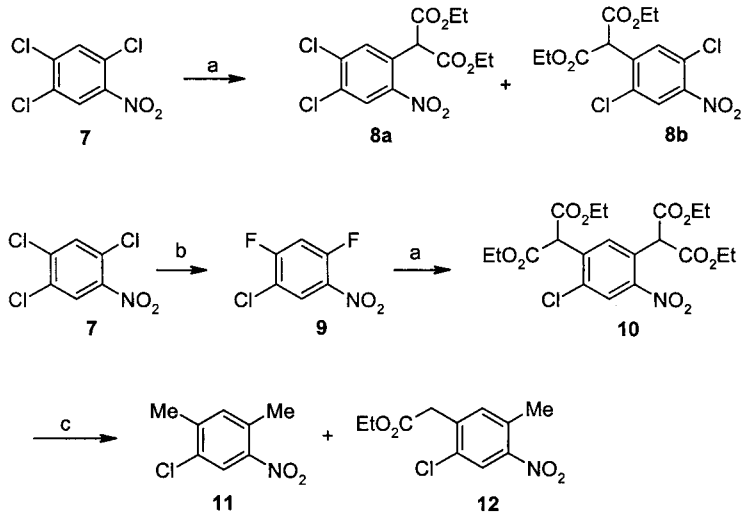
Scheme 1[a]



[a] *Reagents and Conditions:* a) NH_2NH_2, EtOH. b) $ClCH_2COCl$, $AlCl_3$, CH_2Cl_2. c) Et_3SiH, CF_3CO_2H. d) (i) Na_2CO_3, H_2O. (ii) HCl, H_2O

Scheme 2[a]



[a] *Reagents and Conditions:* a) $Na^+CH^-(CO_2Et)_2$, DMF, 100 °C, 12 h. b) KF, cetrimide, DMF, 125 °C, 12 h. c) NaCl, H_2O, DMSO, 160 °C, 12 h or $MgCl_2 \cdot 6H_2O$, DMA, 140 °C, 7 h.

The formation of these byproducts, **11** and **12**, prompted us to modify the reaction conditions. The hydrolysis of aryl malonate derivative (**10**) was carried out by refluxing with 6 N HCl and glacial acetic acid which provided the requisite derivative **13.** It was converted into the dimethyl ester **14** using thionyl chloride in methanol and fully characterized by analytical and spectroscopic methods.

Subsequent hydrogenation of the nitro group in **14** was carried out with Raney nickel in acetic acid to provide the oxindole derivative **15** in excellent yield. Reduction of **15** with $LiBH_4$ prepared in situ and catalytic $B(OMe)_3$ in refluxing THF provided[11] the alcohol **16** which was converted into 6-chloro-5-(2-chloroethyl)oxindole **5** by two methods. **16** was first converted into the tosylate derivative **17**, which on exposure to LiCl in DMF provided the target molecule **5**: mp 222 °C, lit.[4] mp 210−211 °C. Alternatively, conversion of alcohol **16** into the chloro derivative **5** was effected in one step with triphenylphosphine in refluxing CCl_4 (Scheme 3).

Conclusions

We have developed a new route to an advanced intermediate (**5**) for the antipsychotic drug, ziprasidone, which avoids both the irritant intermediate (**4**) and the use of triethylsilane.

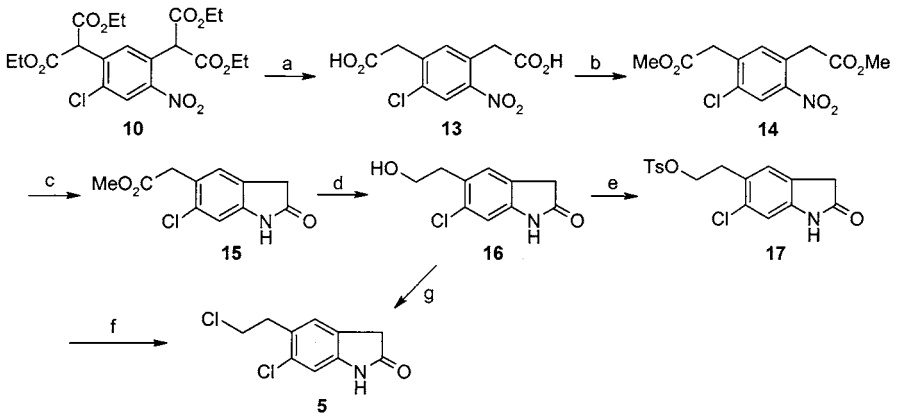
Experimental Section

General Methods. Starting materials and reagents were purchased from Aldrich, Fluka, or Lancaster and used as received. TLC was performed on precoated silica gel plates (E-Merk, 60 F_{254}) and visualized by UV irradiation or spraying with anisaldehyde or phosphomolybdic acid stains followed by charring on a hot plate. NMR spectra were recorded on Bruker spectrometers (AC 200, MSL 300) with TMS as an internal standard. IR spectra were obtained from Perkin-Elmer 16 PC-FTIR spectrophotometer. EI mass spectra were recorded on Finngan MAT-1020. Combustion data were recorded on Elmentar-Vario-EL (Heraeus Company Ltd., Germany). Melting points were measured on Buchi 535 melting point apparatus.

5-Chloro-2,4-difluoronitrobenzene (9). Toluene was distilled from the mixture of potassium fluoride (38.2 g, 657 mmol), cetrimide (5.94 g, 17.6 mmol), DMF (250 mL), and dry toluene (100 mL) to remove traces of moisture. 2,4,5-Trichloronitrobenzene (**7**) (50.0 g, 220 mmol) was added and heated at 125 °C for 12 h under N_2. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2-

(11) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *Inorg. Chem.* **1981**, *20*, 4454.

Scheme 3[a]



[a] *Reagents and Conditions:* a) 6 N HCl, AcOH, reflux, 18 h. b) $SOCl_2$, MeOH, rt, 4 h. c) Raney Ni, H_2 (45 psi), AcOH, rt, 3 h. d) $LiBH_4$, $B(OMe)_3$, THF, reflux, 18 h. e) TsCl, Et_3N, DMAP, CH_2Cl_2, reflux, 5 h. f) LiCl, DMF, 50 °C. g) TPP, CCl_4, THF, reflux, 3 h.

SO_4), and evaporated to give a residue, which was distilled under vacuo to provide **9** (23.5 g, 55%), bp = 83 °C at 0.5 Torr, lit. bp = 85 °C at 0.5 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.18 (t, 1 H, J = 9.2 Hz), 8.24 (t, 1 H, J = 7.4 Hz).

Tetraethyl 4-Chloro-6-nitro-1,3-benzenedimalonate (10). Sodium diethyl malonate (52.0 g, 285 mmol) and **9** (20.0 g, 103 mmol) in DMF (125 mL) were heated at 100 °C for 12 h. The reaction mixture was cooled and acidified with 10% dilute HCl. Water was added to the reaction, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The crude product **10** (46.0 g, 94%) was used directly in the next reaction. A small portion of the crude product was chromatographed on silica gel with ethyl acetate−petroleum ether (1:5) as eluent to give pure **10**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (t, 12 H, J = 7.27 Hz), 4.28 (m, 8 H), 5.21 (s, 1 H), 5.27 (s, 1 H), 7.70 (s, 1 H), 8.15 (s, 1 H); IR (Nujol) 1715 cm^{-1}; MS (m/z) 473 [M$^+$].

4-Chloro-6-nitro-1,3-benzenediacetic Acid (13). A mixture of **10** (46.0 g, 97 mmol), 6 N HCl (125 mL) and glacial acetic acid (125 mL) was heated under reflux for 18 h, cooled and concentrated in vacuo to provide a solid which was recrystallised from ethyl acetate−light petroleum to give **13** (24.0 g, 90%): mp = 193−194 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 3.9 (s, 2 H), 4.10 (s, 2 H), 7.60 (s, 1 H), 8.15 (s, 1 H); IR (Nujol) 1685 cm^{-1}. Anal. Calcd for $C_{10}H_8ClNO_6$: C, 43.90; H, 2.95; N, 5.12. Found: C, 44.14; H, 2.92; N, 4.94.

Dimethyl 4-Chloro-6-nitro-1,3-benzenediacetate (14). Thionyl chloride (3 mL, 5.5 mmol) was added dropwise to a solution of **13** (15.0 g, 55 mmol) in methanol (150 mL). The reaction mixture was stirred at room temperature for 4 h, rendered neutral with sodium bicarbonate solution, and then concentrated to remove excess of methanol. The residue was extracted with ethyl acetate, washed with brine, dried (anhydrous Na_2SO_4), and evaporated. The solid residue was recrystallized from methanol to give **14** (15.7 g, 95%): mp = 107−108 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.70 (s, 3 H), 3.75 (s, 3 H), 3.85 (s, 2 H), 3.95 (s, 2 H), 7.30 (s, 1 H), 8.20 (s, 1 H); IR (Nujol) 1724 cm^{-1}. Anal. Calcd for $C_{12}H_{12}ClNO_6$: C, 47.78; H, 4.01; N, 4.64. Found: C, 47.64; H, 3.95; N, 4.68.

Methyl 6-Chloro-(2-oxindol-5-yl)acetate (15). A solution of **14** (16 g, 53 mmol) in acetic acid (80 mL) containing 1.6 g of Raney nickel was hydrogenated at 45 psi for 3 h. After the catalyst was filtered, acetic acid was distilled to afford solid which was recrystallized from 2-propanol to afford pure **15** (12 g, 94%): mp = 191−192 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 3.48 (s, 2 H), 3.67 (s, 3 H), 3.77 (s, 2 H), 6.96 (s, 1 H), 7.27 (s, 1 H), 10.72 (s, 1 H); IR (Nujol) 1722, 1676 cm^{-1}. Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.85. Found: C, 55.08; H, 4.17; N, 5.84.

6-Chloro-5-(2-hydroxyethyl)-2-oxindole (16). A mixture of sodium borohydride (4.74 g, 125 mmol) and lithium bromide (10.87 g, 125 mmol) in THF (150 mL) was refluxed for 16 h with vigorous stirring. Oxindole ester **15** (15.0 g, 62.6 mmol) and $B(OMe)_3$ (0.7 mL, 6.2 mmol) were added, and refluxing continued for 18 h. The reaction mixture was concentrated and acidified with 3 N sulphuric acid and solid filtered to afford **16** (10 g, 75%): mp = 178−179 °C; IR (Nujol) 1716 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 2.70−2.90 (m, 2 H), 3.40 (s, 2 H), 3.60−3.77 (m, 2 H), 6.85 (s, 1 H), 7.17 (s, 1 H), 9.3 (br s, 1 H); EI MS (m/z) 211 [M$^+$]. Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.63; H, 4.97; N, 6.39.

6-Chloro-5-(2-chloroethyl)-2-oxindole (5). Method A. A mixture of **16** (10.8 g, 51 mmol), TsCl (11.7 g, 61.4 mmol), triethylamine (11 mL), and DMAP (0.2 g) in CH_2Cl_2 (200 mL) was refluxed for 5 h and concentrated, and the residue was passed through a silica gel pad (30% ethyl acetate in hexane) to obtain **17** (16.0 g, 85%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3 H), 3.02 (t, 2 H, J = 4.3 Hz), 3.43 (s, 2 H), 4.21 (t, 2 H, J = 4.3 Hz), 6.83 (s, 1 H), 7.01 (s, 1 H), 7.27 (d, 2 H, J = 6.5 Hz), 7.67 (d, 2 H, J = 6.5 Hz), 9.10 (s, 1 H).

17 (16 g, 43.7 mmol) and LiCl (18.54 g, 437 mmol) in DMF (80 mL) were heated at 50 °C for 8 h, diluted with water, and extracted with diethyl ether. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was filtered through silica gel column with EtOAc−light petroleum (1:1) as eluent to give **5** (9.55 g, 95%): mp = 222 °C, lit.[4] mp = 210−211 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 3.15 (t, 2 H, J = 7.1 Hz), 3.45 (s, 2 H), 3.77

(t, 2 H, $J = 7.1$ Hz) 6.93 (s, 1 H), 7.28 (s, 1 H), 9.95 (br s, 1 H); EI MS (*m*/*z*) 231 [M + 1]

Method B. A mixture of **16** (1.4 g, 6.6 mmol), triphenylphosphine (2.6 g, 9.9 mmol) in THF (17 mL) and CCl_4 (3 mL) was refluxed for 3 h and concentrated. The residue was purified on silica gel as described above to give **5** (1.48 g, 97%).

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