A NEW EFFICIENT SYNTHESIS OF 6-NITROQUIPAZINE

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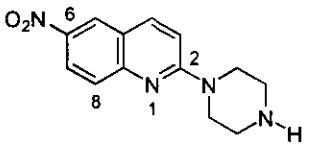
Abstract - A convenient and regioselective synthesis of 6-nitroquipazine from hydrocarbostyril in three steps is described. This synthetic route involved a nitration, a chlorination followed by aromatization, and an aromatic substitution reaction.

Our interest in developing new neurotransmitters, which have good affinity to serotonin transporter *in vivo*, has led us to synthesis of 6-nitroquipazine (**1**) derivatives. 6-Nitroquipazine has been known as one of the most potent and selective antagonist of 5-hydroxyltryptamine (Serotonin or 5-HT) transporter *in vitro*[1,2] and *in vivo*.[3,4] Recently, a comparative molecular field analysis (COMFA) and pharmacological evaluation of quipazine, one of arylpiperazine, with a subtype of serotonin receptor, 5-HT_3, were reported.[5,6]



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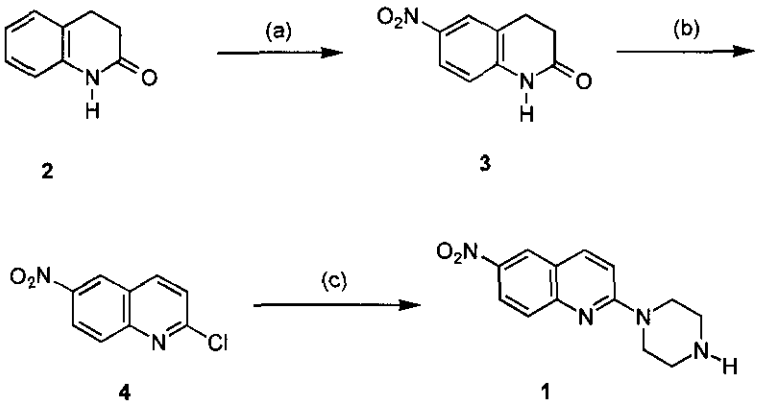
Even though 6-nitroquipazine has a good binding affinity toward 5-HT transporter, the studies of structure-activity relationship of its derivatives are not sufficient. Surprisingly, the regioselective synthesis of 6-nitroquipazine has not been reported. The only synthesis of 6-nitroquipazine itself was known as a patent by Hashimoto and Goromaru.[7] This process, however, was neither regioselective nor efficient. The final process of this patent is a non-regioselective nitration of quipazine and requires the isolation of the 6-nitro derivative from mixture of nitroquipazines. In our experiment, the direct nitration of quinaldine provided a

mixture of 5-, 6-, 8-nitroquinaldines in 71% yield with the ratio of 33:8:59 under the normal acidic nitration condition using conc. HNO_3/conc. H_2SO_4. Furthermore the synthetic route to 5-iodo-6-nitroquipazine reported by Mathis *et al.* is too inefficient and difficult to obtain the target molecule in good yield.[9-10] We now report a new regioselective and efficient synthesis of 6-nitroquipazine (**1**).

Synthesis of quinolines containing electron-withdrawing groups in the aryl ring was required for the preparation of biologically active compounds. Unfortunately, many of quinoline routes - Combes,[11] Conrad-Limpach,[12] Skraup,[13] Friedländer,[14] and Pfitzinger synthesis[15] - are largely affected by the nature of substituents, and electronic-withdrawing substituents are appreciably unfavorable for cyclization although electron-donating ones are preferable. In addition, there are limitations due to orientation of ring closure by either electron-donating or -withdrawing substitutents on the ring.

As shown in Scheme 1, 6-nitroquipazine was prepared by three steps from a commercially available starting material, hydrocarbostyril (**2**), in 82% yield.

Scheme 1. Synthesis of 6-Nitroquipazine from Hydrocarbostyril.



Reaction conditions: (a) conc. H_2SO_4, conc. HNO_3, -10 °C, 3 h; (b) DDQ, $POCl_3$, benzene, reflux, 3 h; (c) (i) 1-piperazinecarboxaldehyde, DMF, reflux, 2 h; (ii) 4 M H_2SO_4, 90 °C, 3 h.

This synthetic route involved a nitration of hydrocarbostyril, a chlorination and aromatization in the presence of dichlorodicyanobenzoquinone (DDQ) with $POCl_3$, and an aromatic displacement reaction with piperazine.

Nitration proceeded too fast to form a dinitrated side-product, 6,8-dinitrohydrocarbostyril under the normal acidic nitration conditions using conc. HNO_3/conc. H_2SO_4 with a desired mononitro

product, 6-nitrohydrocarbostyril in 60% yield. Dilution of the acids with water and lowering the reaction temperature to -10 °C improved the yield of mononitro product (**3**) to 90%. 6-Nitrohydrocarbostyril reacted with five equivalents of phosphorus oxychloride and one equivalent of chloranil in benzene to give 2-chloro-6-nitroquinoline (**4**) in 50% yield. But the yield was improved upto 96% when DDQ was used instead of chloranil. This process likely involves chlorination with $POCl_3$ and subsequent aromatization with DDQ. In order to confirm this aspect, the reaction was carried out under several different conditions. Upon treatment with only phosphorus oxychloride without DDQ, **4** was formed although in a low yield of 3% with consuming of all the starting material (**3**). On the other hand, when DDQ was used without $POCl_3$, 6-nitro-2-quinolone was not formed and only the starting material (**3**) was recovered. 6-Nitrohydrocarbostyril was treated with five equivalents of $POCl_3$ and 0.3, 0.4, 0.5, and 1.0 equivalents of DDQ in benzene to give 2-chloro-6-nitroquinoline (**4**) in 20, 37, 41, and 96% yields, respectively. 6-Nitroquipazine was obtained in 95% yield by aromatic nucleophilic substitution reaction of 2-chloro-6-nitroquinoline with five equivalents of 1-piperazinecarboxaldehyde in DMF under refluxing for 2 h, followed by refluxing with 4M H_2SO_4 for 1h to remove the carboxaldehyde protecting group.

Recently, we have reported the synthesis of hydrocarbostyril as a major product in 90% yield by the Beckmann rearrangement of 1-indanone oxime using $AlCl_3$ *via* tosylate at from -40 °C to room temperature.[16] While the yield of the Beckmann rearrangements of α-tetralone was higher than 65%, that of 1-indanone was only 20%, when polyphosphoric acid was used at 110-120 °C for 10 min.

EXPERIMENTAL

Materials and methods. ^1H NMR and ^{13}C NMR spectra were obtained on a Gemini-200 (200 MHz, Varian) and are reported in ppm downfield from internal tetramethylsilane. Solvents and reagents were purchased from the following commercial sources: Aldrich, Kanto, Acris. Analytical TLC was performed with Merck silica gel F-254 glass-backed plates. Visualization was achieved by phosphomolybdic acid (PMA) spray reagent, iodine, or UV illumination. Flash chromatography was performed according to Still[17] using Woelm silica gel (0.040-0.063 mm). MS were obtained on HP590 GC/MS 5972 MSD spectrometer.

6-Nitro-3,4-dihydro-2(1*H*)-quinolinone (3). After hydrocarbostyril (1.00 g, 6.70 mmol) was dissolved in 20 mL of conc. H_2SO_4, 5 mL of water was slowly added to the solution at -10 °C. 61% HNO_3 (0.50 mL, 6.70 mmol) was added to the well-stirred solution dropwise at -10 °C.

After the reactants were stirred for 10 min in a cooling bath, the reaction mixture was quenched by adding 50 mL of cold water carefully at rt. The resulting mixture was extracted with ethyl acetate (30 mL × 5). The combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. The 1.17 g (90%) of 6-nitrohydrocarbostyril (**3**) and 0.065 g (5%) of 8-nitrohydrocarbostyril were obtained by flash chromatography (CH_2Cl_2), both as pale yellow crystals: mp, 210.5-211.0 °C (EtOAc); IR (KBr) 3485, 3225, 3090, 2915, 1675, 1590, 1500, 1330 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 8.09 (br s, 2H), 6.94 (d, J = 9.4 Hz, 1H), 3.09 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 141.6, 141.3, 122.5, 122.3, 122.2, 113.8, 28.2, 23.3; MS (EI) m/z (relative intensity) 192 (M^+, 100), 164 (50), 134 (32), 117 (43), 91 (31), 77 (27). Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.45; H, 4.58; N, 14.70.

2-Chloro-6-nitroquinoline (4). To a solution of **3** (0.30 g, 1.56 mmol) and DDQ (0.35 g, 1.56 mmol) in 5 mL of benzene was added dropwise $POCl_3$ (0.71 mL, 7.8 mmol) at rt. The mixture was refluxed at 90 °C for 3 h, and then quenched by adding 20 mL of cold water. The mixture was neutralized with 4N NaOH, and extracted with ethyl acetate (20 mL × 3). The combined extracts were dried over sodium sulfate, and evaporated under reduced pressure. 2-Chloro-6-nitroquinoline (**4**, 0.31 g, 96%) was obtained by flash chromatography (10% EtOAc/hexane) as pale yellow crystals: mp, 235.5-236.5 °C (EtOAc); IR (KBr) 3450, 3100, 3060, 1620, 1530, 1490, 1340 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.79 (d, J = 2.6 Hz, 1H), 8.51 (dd, J = 9.2, 2.6 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 152.6, 148.3, 144.5, 140.8, 128.8, 125.0, 123.9, 123.3, 123.0; MS (EI) m/z (relative intensity) 208 (M^+, 72), 162 (39), 150 (42), 127 (100), 100 (23), 74 (22). Anal. Calcd for $C_9H_5N_2O_2Cl$: C, 51.92; H, 2.42; N, 13.43. Found: C, 51.99; H, 2.42; N, 13.14.

6-Nitroquipazine (1). To a solution of **4** (0.44 g, 2.10 mmol) in 15 mL of DMF was added dropwise 1-piperazinecarboxaldehyde (0.53 mL, 4.20 mmol) at rt. The mixture was heated for 2 h at 110 °C, and cooled to rt. 4 M H_2SO_4 (40 mL, 160.00 mmol) was added to the mixture. The mixture was heated at 90 °C for additional 3 h, and then quenched by adding 30 mL of cold water, and basified with 4 N NaOH. The resulting precipitate was filtered and washed with water and hexane. The filtrate was dried in oven overnight to give 6-nitroquipazine (**1**, 0.52 g, 95%): mp, 181-183 °C (EtOAc); IR (KBr) 3330, 2940, 3010, 2620, 1490, 1320 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.46 (d, J = 2.2 Hz, 1H), 8.23 (dd, J = 9.0, 2.2 Hz, 1H), 7.90 (d, J = 9.4 Hz, 1H), 7.60 (d, J = 9.4 Hz, 1H), 7.01 (d, J = 9.2 Hz, 1H), 3.79 (m, 4H), 2.98 (m, 4H), 2.08 (br s, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ 157.0, 149.9, 140.2, 137.0, 125.4, 122.6, 121.9, 119.4, 109.2, 44.3, 44.1.

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