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Scalable Preparation of Benzimidazole Compounds

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Scalable Preparation of Benzimidazole Compounds

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Abstract: The preparation of benzimidazole compound **7**, an ORL-1 agonist, is described. The four-step procedure gave the compound **7** in 29% overall yield.

Keywords: Amination, benzimidazole, chlorination

Benzimidazole compound **7** was found to be a potent ORL-1 agonist in structure activity relationship (SAR) studies to prepare analgesic compounds through opioid receptors, especially the ORL1 receptor. The medicinal chemical synthetic route is shown in Scheme 1. Each step in the synthesis was further optimized to support an exploratory bulk campaign of the compound **7** as described. In a previous article we reported the optimal condition for the Strecker reaction, using TsOH as an acid to prepare α-aminonitrile **3** in good yield.[1] Herein, we report the results of our process research and scale-up to prepare the desired compound **7** from compound **3** (Scheme 2).

First, the nitrile group in **3** was displaced with PhMgBr.[2] During the addition of PhMgBr to a mixture of **3** in tetrahydrofuran (THF), the suspension gradually turned into a clear solution. Dimethoxyethane (DME) was the best

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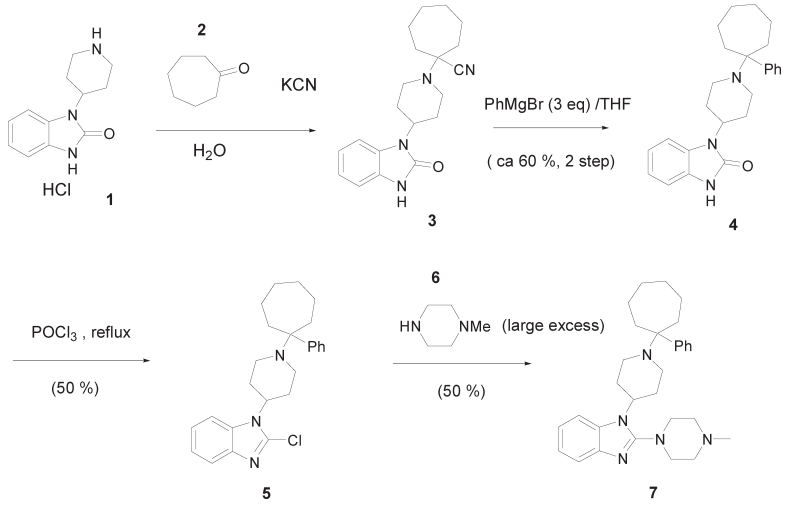
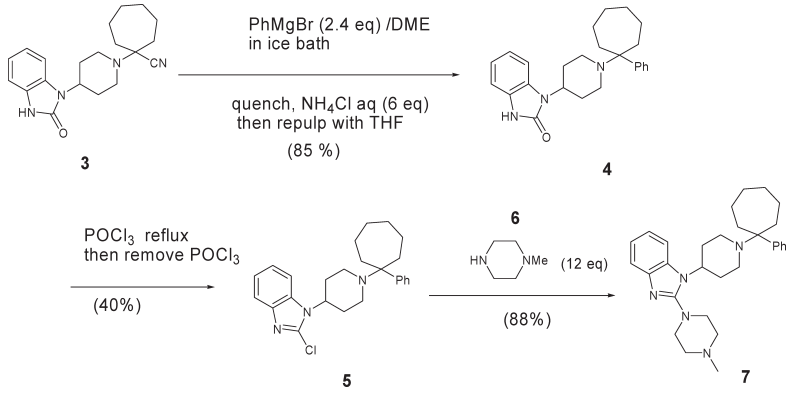


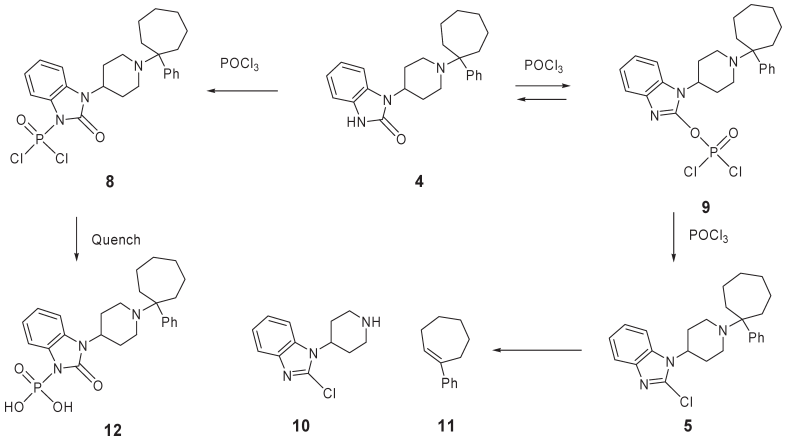
Scheme 1. Synthesis of compound **7**.

solvent, and in combination with a lower temperature during the addition of PhMgBr, gave **4** in the best yield. Five equivalents of a saturated aqueous NH_4Cl solution were needed to quench the reaction mixture and remove almost all of the Mg salts (0.2 w/w%). If this procedure was not followed, the next step of chlorination did not work well. (When 1.4 w/w% of Mg was present with compound **4**, the chlorination reaction did not go to completion and approximately 50% of **4** remained as determined by high performance liquid chromatography (HPLC) analysis.) Processing on this scale gave **4** in 85% yield (94% purity based on HPLC analysis) as a white solid after a reslurry in THF.

To prepare compound **5**, chlorination of **4** was accomplished with neat $POCl_3$ at reflux.[3] To isolate and purify compound **5**, excess $POCl_3$ was



Scheme 2. Conversion of compound **3** to compound **7**.

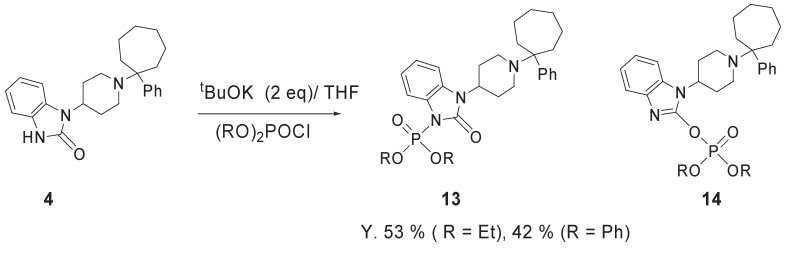


Scheme 3. Plausible mechanism of the reaction of **4** with $POCl_3$.

removed under reduced pressure to be a more effective process on a larger scale. Subsequent filtration through basic alumina helped to remove minor polar impurities. (These polar impurities were unknown.) Overall, this procedure provided **5** in 40% yield as a solid. The low yield for this step may be attributable to an unproductive side reaction with $POCl_3$ to form the undesired compound **8**, which could not be isolated or detected directly (Scheme 3). In addition, compound **8** seems to be converted to compound **12** after quenching the reaction with aq. NaOH, based on MS analysis. Support for this hypothesis comes from the reaction of **4** with chlorophosphonates, which gave only compound **13** instead of compound **14** (Scheme 4).[4] In addition, at a longer reaction time, compounds **10** and **11** which were generated from compound **5**, were observed by ^{1}H NMR and/or mass spectroscopy (MS) analyses. Therefore, on this scale, the optimal reaction time for this reaction was for 2 h.

Recently, the chlorination of hydroxypyridine derivatives using P_2O_5 and $^nBu_4NCl$ has been reported.[5] Unfortunately, this procedure failed to afford the desired product **5**.

For the final amination, 12 equiv. of 1-methylpiperazine (**6**) were needed to drive the reaction almost to completion.[3e] In the crude product, only trace



Scheme 4. Reaction of **4** with chlorophosphonates.

amounts of **4** were observed but they could be removed by a reslurry in hot isopropanol (IPA)/EtOH. (Residual solvent (CH_2Cl_2 and EtOAc) was not completely removed by a reslurry with IPA. Please see the experimental section.) After filtration and drying, the desired product **7** was obtained in 88% yield as a white solid. Based on HPLC analysis, only one unknown impurity (0.1%) was observed.

In conclusion, a concise four-step synthesis to prepare the compound **7** has been developed. This proceeded in 29% overall yield and did not require column chromatography for purification.

EXPERIMENTAL

NMR (1H, 13C) spectra were obtained using JMN-GX270, JEOL. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. HPLC (High Performance Liquid Chromatography) was recorded on Alliance 2960, Waters. MS (Mass Spectroscopy) was recorded on Automass 1, JEOL.

Compound 4

Over 1.5 h, 1.0 M PhMgBr in THF (4.8 L, 4.8 mol, Aldrich) was added to a mixture of **3** (676 g, 2.0 mol)[1] and DME (3.4 L, 5.0 vol) in an ice bath. During the addition, the mixture turned into a solution, the internal temperature rose to ca. 7°C, and then solids appeared. This mixture was heated at 50°C for 2 h (HPLC result of aliquot showed that the ratio between **4** and **3** was ca 10:1). After cooling, 1.5 M aq. NH_4Cl solution (prepared by NH_4Cl, 642 g; and H_2O, 8 L) was added gradually over 1 hr to the reaction mixture. The addition was exothermic and the final pH of the aqueous layer was ca. 9–10. Hexane (7.5 L, 11 vol) was added and the mixture was stirred at rt for 2 h. The precipitated solids were collected by filtration, and the obtained solid was washed with H_2O (1.5 L) and hexane (1.5 L) and then dried in a vacuum oven (70°C, 24 h) to afford crude **4** (744 g, 96%, **4**:**3** = ca. 10:1 based on HPLC analysis).

A mixture of crude **4** (1.22 kg) in THF (6.1 L, 5.0 vol) was heated at reflux for 2 h. After cooling, the mixture was filtered, and the solids were washed with THF (3 L) and hexane (1 L) and then dried in a vacuum oven (70°C, 3 days) to give **4** (1.1 kg, total 85%) as a white solid. By HPLC analysis, the material is 94% pure and contains ca. 5.6% of **3** and/or **1** as well as 0.4% unknown impurities. Ash analysis: ca. 0.2 w/w%.

HPLC condition: 210 nm, column; Kromasil, eluent; CH_3CN/0.3% $HClO_4$ = 40:60, 1 mL/min; ^{1}H NMR (270 MHz, d-DMSO): δ 10.80 (brs, 1H), 7.55–7.45 (m, 2H), 7.40–7.30 (m, 2H), 7.25–7.15 (m, 2H), 7.02–6.92 (m, 3H), 4.10–3.95 (m, 1H), 2.95–2.80 (m, 2H), 2.30–1.90 (m, 8H), 1.80–1.35 (m, 10H). MS m/z 389: IR (KBr) 3394, 1697 cm^{-1}.

Compound 5

A mixture of **4** (200 g, 513 mmol) and $POCl_3$ (1.0 L, 10.7 mol) was stirred at 110°C for 2 h under N_2. After cooling to 60°C, excess $POCl_3$ was removed by distillation under reduced pressure (80 mmHg then 60 mm Hg). The residue was cooled and dissolved in anhydrous CH_2Cl_2 (2.0 L). The resulting solution was added, with vigorous stirring, to a 2 N aq. NaOH (6.5 L) solution at such a rate as to maintain the temperature at 10 to 15°C. After the addition was complete, the mixture was neutralized by the careful addition of 2 N aq.HCl (1.1 L), then CH_2Cl_2 (2.8 L) and water (1.2 L). The resulting mixture was stirred at rt for 1 h and after settling, the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1.5 L × 2). The combined organic phases were dried over Na_2SO_4 (3.7 kg) and filtered through a Celite pad® (500 g). Basic alumina (900 g) was added to the filtrate and it was concentrated. The residue was dried under vacuum for 1 h. EtOAc (8.5 L) was then added and the resulting mixture was stirred for 1 hr at rt then filtered through a Celite pad® (800 g). The filtrate was concentrated, and the residue was dissolved in isopropyl ether (IPE) (10 L). The solvent was removed (ca. 5.5 L) by distillation at normal pressure, and a precipitate had appeared. This reaction mixture was cooled gradually to rt and filtered to give 62.8 g (30%) of colorless crystalline **5**. The filtrate was concentrated and the residue was recrystallized from IPE with the same procedure described previously to give 19.9 g (10%, 40% total) of **5**.

^{1}H NMR (270 MHz, $CDCl_3$): δ 7.71–7.63 (m, 2H), 7.61–7.47 (m, 2H), 7.39–7.18 (m, 5 H), 4.43–4.26 (m, 1H), 3.10–2.92 (m, 2H), 2.45–2.20 (m, 4H), 2.15–2.00 (m, 4H), 1.90–1.67 (m, 4H), 1.65–1.40 (m, 6H).

Compound 7

A mixture of 1-methylpiperazine (**6**) (420 mL, 3.8 mol) and **5** (129 g, 316 mmol) was stirred at 120°C for 28 h under N_2. The reaction mixture was allowed to cool to 60°C. At this point, a precipitate had formed and the mixture was diluted with EtOAc (2 L), then cooled to rt. With vigorous stirring, the reaction mixture was poured into a mixture of 0.33 N aq. NaOH (3.1 L), EtOAc (1 L) and CH_2Cl_2 (0.5 L). After settling, the two layers were separated, washed with dilute aq. NaCl solution, dried over Na_2SO_4 (500 g) and filtered. The filtrate was concentrated, and the residue was diluted with CH_2Cl_2 (0.5 L) and EtOAc (2 L). The resulting solution was warmed at 60°C, and the solvent was removed by distillation. After distilation (ca. 600 mL), a precipitate formed. The mixture was cooled to rt and stirred under N_2 for 2 days. The precipitate was collected by filtration, and the solid was washed with EtOAc (0.3 L) and dried under reduced pressure at rt for 18 h to give **7** (120 g) as a white solid. A small amount (~1%) of **5** could also be detected by HPLC analysis.

Purification

A mixture of crude **7** (189 g) and 2-propanol (0.5 L) was stirred at 50°C for 5 h and at rt for 14 h under N_2. The precipitated solids were collected by filtration and dried under reduced pressure at 50°C for 3.5 h.

For further purification, a mixture of **7** (184 g) in 2-propanol (1 L) and EtOH (0.5 L) was stirred at 50°C for 12 h under N_2. Similar treatment gave the desired product **7** (176 g, total 88%) as a white solid.

TLC: Rf = 0.22, CH_2Cl_2/MeOH = 10/1, silica-gel plate Merck 60F254, mp 182.8–183.5°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62–7.60 (m, 1H), 7.52 (d, 2H, J = 7.8 Hz), 7.50 (m, 1H), 7.34 (t, 2H, J = 7.9 Hz), 7.22 (t, 1H, J = 7.2 Hz), 7.15–7.12 (m, 2H), 4.10–4.03 (m, 1H), 3.24 (t, 4H, J = 4.9 Hz), 3.00 (d, 2H, J = 10 Hz), 2.61 (like br.s, 4H), 2.37 (s, 3H), 2.23 (t, 2H, J = 11 Hz), 2.14–2.06 (m, 4H), 1.79–1.76 (m, 2H), 1.68 (d, 2H, J = 11 Hz), 1.62–1.50 (m, 8H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 148.1, 141.9, 133.2, 127.8, 127.1, 126.1, 121.2, 120.9, 118.5, 111.6, 65.9, 54.8, 54.7, 51.2, 46.7, 46.1, 35.0, 31.2, 30.5, 24.5. IR (KBr) 2936, 2795, 1522, 1456, 1400, 1286, 1254, 1136, 1011 cm^{-1} HRFAB-MS (m/z) found 472.3446 $(M+H)^+$ calcd. 472.3434 (for $C_{30}H_{42}N_5$). Anal. Calcd. for $C_{30}H_{41}N_5$: C, 76.39; H, 8.76; N, 14.85. Found: C, 76.33; H, 8.74; N, 14.84.

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