Synthesis of regioisomeric 3-(*N*-phenylpyrazolyl)indoles from comanic acid and phenylhydrazine

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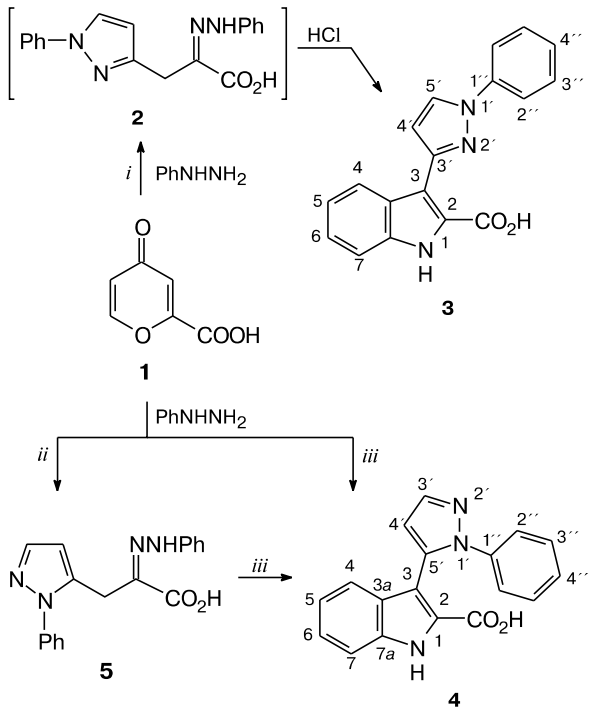
Synthesis of new indole derivatives receives much attention because the indole ring is an important structural unit of many natural alkaloids and biologically active compounds.[1] It is known that γ-pyrone reacts with phenylhydrazine to give 1-phenylpyrazol-5-ylacetaldehyde phenylhydrazone.[2] Recently,[3] we have demonstrated that a reaction of 6-(trifluoromethyl)comanic acid[4] with phenylhydrazine can yield phenylhydrazones of 1-phenyl-5-trifluoroacetonylpyrazole-3-carboxylic acid or 1-phenyl-3-trifluoroacetonylpyrazole-5-carboxylic acid, depending on the solvent nature.

In the present work, we found that the reaction of comanic acid **1** with phenylhydrazine hydrochloride in boiling dioxane leads (probably through the expected 3-(1-phenylpyrazol-3-yl)pyruvic acid phenylhydrazone **2**, which was not isolated) to indole **3** in 35% yield. Interestingly, heating of acid **1** with phenylhydrazine hydrochloride in AcOH—H_2O (2 : 1) gives isomeric indole **4** in 50% yield. In this case, intermediate pyrazole **5** was isolated in low yield (18%) when the reaction was carried out in water at ~20 °C. Reflux of compound **5** in AcOH—H_2O (2 : 1) in the presence of HCl for 1 h affords indole **4** in 67% yield (Scheme 1).

The structures of the products obtained were confirmed by data from elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and IR spectroscopy. The ^{1}H NMR spectrum of indole **4** shows doublets for the pyrazole H(3) and H(4) protons at δ 7.80 and 6.56 (J = 1.6 Hz), respectively. These chemical shifts agree well with the literature data[5] for its closest analog 3-(*N*-phenylpyrazol-5-yl)indole (δ: 7.75 (H(3)), 6.60 (H(4)), J = 2.0 Hz). In the spectrum of isomer **3**, the doublets for the H(5) and H(4) protons are shifted downfield to δ 8.61 and 7.24 (J = 2.5 Hz), respectively. This results from the planar conformation of the molecule and, along with the coupling constant, confirms the proposed structure.

To sum up, comanic acid and phenylhydrazine can be used as starting reagents for the synthesis of regioisomeric 3-(*N*-phenylpyrazolyl)indole-2-carboxylic acids. The latter are of interest for medicinal chemistry because the presence of hydrophilic substituents in drug molecules makes them more soluble in aqueous media, which usually enhances their pharmacological properties.

Scheme 1



i. Dioxane, Δ. *ii*. H_2O, 20 °C. *iii*. AcOH, H_2O, HCl.

3-(1-Phenyl-1*H*-pyrazol-3-yl)-1*H*-indole-2-carboxylic acid (3). Freshly distilled phenylhydrazine (0.25 g, 2.3 mmol), acid **1** (0.14 g, 1.0 mmol), and three drops of conc. HCl were added to anhydrous dioxane (6 mL). The reaction mixture was refluxed for 3 h, whereupon water (6 mL) was added. The resulting oily phase slowly crystallized with time. The crystalline precipitate was filtered off and recrystallized from AcOH—H_2O (2 : 1). The yield was 0.08 g (35%), m.p. 270 °C. Found (%): C, 71.10; H, 4.42; N, 14.01. $C_{18}H_{13}N_3O_2$. Calculated (%): C, 71.28; H, 4.32; N, 13.85. IR, ν/cm^{-1}: 3330, 3281, 1667, 1598. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.18 (t, 1 H, H(5) J = 7.6 Hz); 7.24 (d, 1 H, H(4′), J = 2.5 Hz); 7.33 (t, 1 H, H(4′′), J = 8.2 Hz); 7.35 (t, 1 H, H(6), J = 7.8 Hz); 7.51 (d, 1 H, H(7), J = 8.3 Hz);

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7.57 (t, 2 H, H(3´´), H(5´´), J = 7.8 Hz); 7.94 (d, 2 H, H(2´´), H(6´´), J = 7.9 Hz); 8.30 (d, 1 H, H(4), J = 8.2 Hz); 8.61 (d, 1 H, H(5´), J = 2.5 Hz); 11.93 (s, 1 H, NH); 13.6—13.9 (br.s, 1 H, CO_2H).

3-(1-Phenyl-1*H*-pyrazol-5-yl)-1*H*-indole-2-carboxylic acid (4). *Method A*. Three drops of conc. HCl and phenylhydrazone **5** (0.1 g, 0.31 mmol) were added to a 2 : 1 mixture (4 mL) of AcOH and water. The resulting suspension was refluxed for 1 h to complete homogenization and cooled. The crystals that formed were filtered off, washed with water, and dried. The yield was 0.05 g (67%), m.p. 275 °C.

Method B. Acid **1** (0.15 g, 1.1 mmol) and phenylhydrazine hydrochloride (0.34 g, 2.4 mmol) were added to a 2 : 1 mixture (4 mL) of AcOH and water. The reaction mixture was refluxed for 4 h and then cooled to ~20 °C. The crystalline product that formed was filtered off, washed with water, dried, and recrystallized from AcOH—H_2O (1 : 1). The yield was 0.16 g (50%). Found (%): C, 71.05; H, 4.39; N, 13.77. $C_{18}H_{13}N_3O_2$. Calculated (%): C, 71.28; H, 4.32; N, 13.85. IR, ν/cm^{-1}: 3310, 3280, 1666, 1597, 1498. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 6.56 (d, 1 H, H(4´), J = 1.6 Hz); 7.07 (t, 1 H, H(5), J = 7.6 Hz); 7.13—7.30 (m, 6 H, H(6), Ph); 7.32 (d, 1 H, H(4), J = 8.2 Hz); 7.47 (d, 1 H, H(7), J = 8.2 Hz); 7.80 (d, 1 H, H(3´), J = 1.6 Hz); 12.02 (s, 1 H, NH); 12.6—13.2 (br.s, 1 H, CO_2H). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 110.0 (C(4´)), 110.3 (C(3)), 113.2 (C(7)), 120.6 (C(6)), 121.3 (C(5)), 123.7 (C(2″)), 125.4 (C(4)), 126.4 (C(5´)), 127.1 (C(4″)), 127.7 (C(2)), 129.0 (C(3″)), 135.5 (C(3*a*)), 136.3 (C(1″)), 140.2 (C(7*a*)), 140.8 (C(3´)), 162.2 (CO_2H).

2-(Phenylhydrazono)-3-(1-phenyl-1*H*-pyrazol-5-yl)propionic acid (5). Freshly distilled phenylhydrazine (0.25 g, 2.3 mmol) and acid **1** (0.15 g, 1.1 mmol) were added to water (3 mL). The reaction mixture was stirred and kept at 20 °C for 18 h. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from AcOH—H_2O (1 : 1, 12 mL). The yield was 0.06 g (18%), m.p. 215 °C. Found (%): C, 67.30; H, 5.12; N, 17.27. $C_{12}H_{10}N_2O_3$. Calculated (%): C, 67.49; H, 5.03; N, 17.49. IR, ν/cm^{-1}: 3024, 1664, 1601, 1580, 1497. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 4.01 (s, 2 H, CH_2); 5.94 (d, 1 H, H(4), J = 1.6 Hz); 6.87 (t, 1 H, H(4´), J = 7.4 Hz); 7.23 (t, 2 H, H(3´), H(5´), J = 7.8 Hz); 7.32 (d, 2 H, H(2´), H(6´), J = 8.1 Hz); 7.42 (t, 1 H, H(4″), J = 7.8 Hz); 7.46 (d, 1 H, H(3), J = 1.6 Hz); 7.54 (t, 2 H, H(3″), H(5″), J = 7.8 Hz); 7.65 (d, 2 H, H(2″), H(6″), J = 7.9 Hz); 10.15 (s, 1 H, NH); 11.6—12.2 (br.s, 1 H, CO_2H).

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