Controlled Formation of Acid-Pyridine Heterosynthon over Acid-Acid Homosynthon in 2-Anilinonicotinic Acids

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SUPPORT INFORMATION

Synthesis

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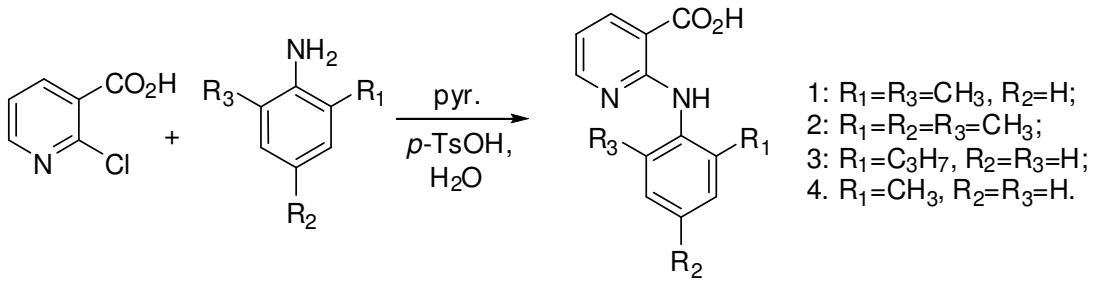
2-PNA analogs were synthesized according to a literature method,[1] shown as the following:



All starting materials and solvents were obtained from commercial sources and used as received.

Synthesis of 2-[(2,6-dimethylphenyl)amino]- 3-pyridinecarboxylic acid (**1**)

2-chloronictinic acid (5.0 g, 3.0 mmol), 2,6-dimethyl-aniline (4.0 g, 3.3 mmol), pyridine (2.5 mL, 3.2 mmol), and *para*-toluenesulfonic acid (*p*-TsOH) (1.3 g, 0.8 mmol) were added to a round-bottom flask with 40 mL of water. The resultant mixture was refluxed 36 hours. Solvents were removed under reduced pressure, and the resulting oily mixture was refluxed in a mixture of H_2O and ethyl acetate (EtOAc). The two layers were separated. Crystals formed in the EtOAc solution (0.9 g, yield%: 11.5).

^{1}H NMR (DMSO-d_6, 400 MHz) 9.43 (s, 1H), 8.16 (m, 2H), 7.09 (m, 3H), 6.70 (m, 1H), 2.10 (s, 6H); ^{13}C NMR (DMSO-d_6, 400 MHz) 169.3, 157.3, 153.3, 140.3, 136.9, 135.5, 127.8, 126.0, 112.5, 106.3, 18.3; mp: 180 °C; MS (EI) 242; IR (KBr) 3443 (s), 1701 (s), 1663 (s), 1636 (s), 1604 (s), 1586 (s), 1566 (s).

Synthesis of 2-(mesitylamino)nicotinic acid (**2**)

2-chloronictinic acid (7.3 g, 4.6 mmol), 2,4,6-trimethylaniline (6.6 g, 4.8 mmol), and pyridine (3.8 g, 4.8 mmol), and *p*-TsOH (1.2 g, 0.6 mmol) were added to a round-bottom flask with 20 mL of water.

The resulting mixture was refluxed overnight. The mixture was cooled to room temperature, and precipitate was recovered by filtration (3.7 g, yield%: 31.1).

^{1}H NMR (DMSO-d_6, 400 MHz) 13.28 (s, br, 1H), 9.34 (s, 1H), 8.13 (m, 2H), 6.90 (s, 2H), 6.67 (m, 1H), 2.24 (s, 1H), 2.05 (s, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) 169.3, 157.5, 153.3, 140.3, 135.2, 134.9, 134.2, 128.4, 112.4, 106.2, 20.5, 18.2; IR (KBr)3446 (s), 3250 (s), 2918 (w), 2405 (m), 1669 (s), 1600 (s), 1581 (s), 1504 (s); MS (EI) 256; mp: 270-275 °C.

*Synthesis of 2-[[2-(1-methylethyl)phenyl]amino]-3-pyridinecarboxylic acid (**3**)*

2-chloronictinic acid (11.1 g, 7.0 mmol), 2-isopropyl-aniline (10.3 g, 7.6 mmol), pyridine (6.0 mL, 7.6 mmol) and *p*-TsOH (1.5 g, 0.9 mmol) were added to a round-bottom flask with 40 mL of water. The resulting mixture was refluxed overnight. Solvents were removed under reduced pressure, and water and EtOAc were added to separate the mixture. After heating, two layers were obtained. Crystals formed in the EtOAc layer (5.0 g, yield%: 27.8).

^{1}H NMR (DMSO-d_6, 400 MHz) 13.48 (br, 1H), 10.20 (s, 1H), 8.28 (dd, 1H), 8.22 (dd, 1H), 7.91 (dd, 1H), 7.31 (dd, 1H), 7.18 (dt, 1H), 7.10 (dt, 1H), 6.80 (dd, 1H), 3.15 (m, 1H), 1.21 (d, 6H); ^{13}C NMR (DMSO-d_6, 400 MHz) 169.4, 156.5, 152.9, 140.5, 139.8, 136.4, 125.8, 125.3, 124.0, 113.4, 107.1, 27.6, 22.9; IR (KBr) 3446 (s), 2960 (w), 1654 (m), 1599 (m), 1583 (m), 1513 (m); MS (EI) 256; mp: 168-170 °C.

*Synthesis of 2-[(2-methylphenyl)amino]-3-pyridinecarboxylic acid (**4**)*

2-chloronicotinic acid (4.3 g, 2.7 mmol), 2-methylaniline (3.0 g, 2.8 mmol), pyridine (2.2 g, 2.8 mmol), and *p*-TsOH (1.5 g, 0.8 mmol) were added to a round-bottom flask with 20 mL water. The mixture was refluxed overnight. The solution was cooled to room temperature, and the yellow solid was recovered by filtration (5.7 g, yield%: 97.3).

^{1}H NMR (DMSO-d_6, 400 MHz) 10.27 (s, 1H), 8.36 (m, 1H), 8.26 (m, 2H), 7.19 (m, 2H), 6.97 (m, 1H), 6.84 (m, 1H), 2.29 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) 169.3, 155.9, 152.5, 140.8, 140.4, 138.2, 131.0, 127.9, 127.0, 121.5, 121.1, 114.0, 113.3, 107.6, 18.5; MS (EI): 228.

Crystal Growth

Crystal growth was carried out for each compound in organic solvents. Typically, a compound was dissolved in a given solvent to make a saturated solution at room temperature. Then the solution was set for slow evaporation until single crystals were harvested with solvent remaining or totally evaporated. All crystallization experiments were conducted in an unmodified atmosphere. An example is given as the following: 50 mg compound **1** was dissolved in 10 mL HPLC grade methanol in a glass vial at room temperature. The vial was sealed with perforated parafilm. Crystals were obtained as aggregated plates in about a week. Preliminary polymorph screening was performed for each compound. In the seven solvents (dimethylsulfoxide, ethyl acetate, *iso*-propanol, methanol, acetone, ethanol, dimethylformamide) used for compound **1**, two forms were obtained. **1b** was produced from ethanol, and **1a** was from the other solvents. For compound **2**, the crystal growth was complicated. In ether, acetone, *iso*-propanol, dimethylformamide, dimethylsufoxide, ethanol, acetic acid, acetonitrile, and water, **2a** was exclusively produced. In methanol, either pure **2a** or **2b** or concomitant polymorphs of both can be observed. In a mixture of 1:1 ratio methanol and water, concomitant polymorphs of **2a** and **2c** were harvested. In ethyl acetate, all three forms can be resulted, as individual pure form **2a**, or as concomitant polymorphs of **2a** and **2b** or **2a** and **2c**. Only one crystal form was prepared for compounds **3** and **4** in the solvents tested (methanol, acetone, acetonitrile, ethyl acetate, *iso*-propanol, dimethylformamide, ethanol for **3**, and methanol, ethanol, acetone, ethyl acetate, ether, acetonitrile, and dimethylsulfoxide for **4**). In addition, sublimation was also applied for crystal growth for compounds **1**, **2**, and **3**. No new forms were found for compound **3**. For compounds **1** and **2**, **1a** and **2a** were produced.

Crystal Structure Determination

Crystal structures of all the compounds were determined by single-crystal X-ray diffraction. Data collection for **1b** was carried out at 90K on a Bruker X8 Proteum diffractometer with CuKα radiation (λ = 1.54178 Å), and data for the other crystals were collected at 90K on a Nonius kappaCCD diffractometer with MoKα radiation (λ = 0.71073 Å).[2] Cell refinement and data reduction were done using SCALEPACK and DENZO-SMN.[3] Structure solution and refinement were carried out using the SHELXS97 and SHELXL97 program, respectively.[4, 5]

Conformational Search

A potential energy surface scan of τ_2 was performed for compound **1** with Gaussian 03 (Gaussian, Inc., Wallingford, CT). The molecule was optimized from various initial structures in order to identify the most stable conformation, which was then used for scanning the torsion angle with all bond lengths and bond angles fixed. B3LYP/6-311G(d, p) and B3LYP/6-311++G(d, p) were used for the structural optimization and conformational search, respectively.

References:

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