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Supplementary Material

Low Temperature Calorimetry of 3-Fluoro-5-(3-pyridinyloxy) Benzenamine and N-[3-Fluoro-5-(3-Pyridinyloxy)Phenyl]-N'-3-Pyridinyl Urea

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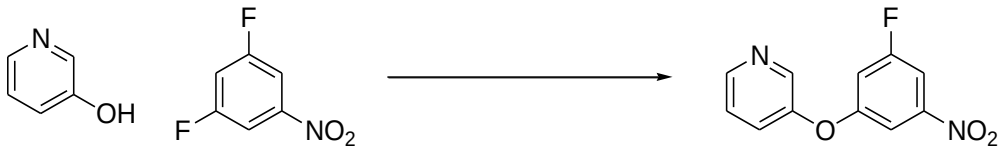
Step 1: Synthesis of 3-(3-Fluoro-5-nitrophenoxy) pyridine

A mixture of 3-hydroxypyridine (11.9 g, 126 mmol, 1.0 equiv), 3,5-difluoronitrobenzene (20.0 g, 126 mmol, 1.0 equiv) and potassium carbonate (34.8 g, 252 mmol, 2.0 equiv) in dry N,N-dimethylformamide (200 mL) was heated to 100 °C overnight. The reaction was allowed to cool to room temperature, and the solvent was removed in vacuo. The mixture was diluted with EtOAc and water, and the layers were separated. The organic layer was washed twice with water. The combined aqueous layers were extracted once with EtOAc and the combined organic layers were washed once with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel chromatography (50% EtOAc/hexanes) provided the title compound as a yellow oil (14.1 g, 48%).

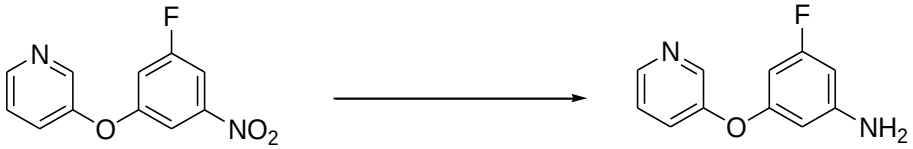


Supplementary Figure 1. Synthesis of 3-(3-Fluoro-5-nitrophenoxy) pyridine.

Step 2: Synthesis of 3-fluoro-5-(3-pyridinyloxy) benzenamine

To a 0°C suspension of 3-(3-Fluoro-5-nitrophenoxy)pyridine (6.0 g, 25.6 mmol, 1.0 equiv) in 1:1:MeOH:conc.HCl (200 mL) was added Fe powder (5.69 g, 100 mmol, 4.0 equiv) as a solid portion-wise. After stirring at 0 °C for 30 min, the reaction was allowed to warm to room temperature and stirred for 1.5 h. The MeOH was then removed in vacuo, and the PH of the resulting mixture was adjusted to 10 by the addition 50% aq. NaOH. The aqueous suspension was then extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield the aniline as an orange solid which was used without further purification (3.15 g, 61%).

LCMS (ES, m/z) 205.0 [M + H]+.1H NMR (300 MHz, DMSO-d6) -ppm 8.38-8.50 (m, 2H), 7.42-7.51 (m, 2H), 6.10-6.14 (d, J = 12 Hz, 1H), 6.00 (s, 2H), 5.63 (s, 2H).



Supplementary Figure 2. Synthesis of 3-fluoro-5-(3-pyridinyloxy) benzenamine.

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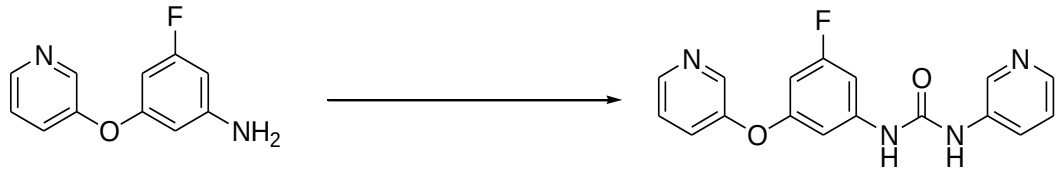
Step 3: Synthesis of N-[3-fluoro-5-(3-pyridinyloxy) phenyl]-N'-3-pyridinyl urea

To a solution of triphosgene (145 mg, 0.49 mmol, 0.40 equiv) in dry DCM (2.0 mL) was added via cannula a solution of 3-aminopyridine (93 mg, 0.98 mmol, 1.0 equiv) and DIPEA (375 uL, 2.15 mmol, 2.2 equiv) in dry DCM (2.0 mL) over 10 min. The solution was allowed to stir for an additional 10 minutes. A solution of 3-fluoro-5-(3-pyridinyloxy) benzenamine (200 mg, 0.98 mmol, 1.0 equiv) in dry DCM (2.0 mL) was then added to the resulting mixture via cannula over 10 min. The reaction mixture was stirred for an additional 30 min, and the resulting solution was diluted with EtOAc and saturated. aq. NaHCO3. The layers were separated, and the organic layer was washed twice with saturated. aq. $NaHCO_3$. The combined aqueous layers were extracted once with EtOAc, and the combined organic layers were washed once with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel chromatography (50 EtOAc/hexanes) furnished the title compound as a white solid.

LCMS (ES, m/z) 325.1 [M + H]+.1H NMR (400 MHz,DMSO-d6) - ppm 9.17 (s,1H), 8.91 (s,1H), 8.57 (d, J = 2.5 Hz,1H), 8.43-8.49 (m, 2H), 8.21 (dd, J = 4.7, 1.4 Hz, 1 H), 7.91 (ddd, J = 8.3, 2.6, 1.5 Hz, 1H), 7.58 (ddd, J = 8.4, 2.8 1.4 Hz, 1H), 7.49 (dd, J = 8.4, 4.6 Hz, 1H), 7.32 (dd, J = 8.3, 4.7 Hz, 1H), 7.20 (dt, J = 11.3, 2.1 Hz, 1H), 6.93 (s, 1H), 6.59 (dt, J = 9.9, 2.3 Hz, 1H).



Supplementary Figure 3. Synthesis of N-[3-fluoro-5-(3-pyridinyloxy) phenyl]-N'-3-pyridinyl urea.

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