Rapid and Efficient Synthesis of 1*H*-Indol-2-yl-1*H*-Quinolin-2-ones

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Supporting Information

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate-hexane mixture as the eluent unless specified otherwise. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Water content (KF) was determined by Karl Fisher titration on a Metrohm 737 KF coulometer.

Preparation of 2-Chloro-3-{2-[5-(2-methoxy-ethoxy)-2-nitrophenyl]-vinyl}-quinoline (12). To a solution of 4.53 g (22.7 mmol) of 4-(2-methoxy-ethoxy)-1-nitrobenzene (**9**)¹ in 50 mL of THF at $-15\text{ }^{\circ}\text{C}$ was added dropwise 30 mL (30.0 mmol, 1M in ether) of (trimethylsilylmethyl) magnesium chloride at such a rate that the internal temperature did not rise above $-5\text{ }^{\circ}\text{C}$. After stirring for 30 min at $-5\text{ }^{\circ}\text{C}$, the solution was cannulated into 5.22 g (23.0 mmol) of DDQ in 10 mL of THF. The resulting mixture was stirred at rt for 2 h and quenched with 50 mL of 5% AcOH in water and 100 mL of isopropyl acetate. The layers were separated and the organic layer washed with 50 mL of

sat. NaHCO₃, 100 mL 1N NaOH, and 50 mL of water. The solvent was removed under reduced pressure and the residue (5.27 g, 81%) was used in the next step without further purification. The product could be purified over silica gel to give **10** as a clear oil: ¹H NMR (CDCl₃, 400 MHz) δ 0.05 (s, 9H), 2.63 (s, 3H), 3.46 (s, 3H), 3.77 (m, 2H), 4.16 (m, 2H), 6.60 (d, 1H, *J* = 2.7 Hz), 6.72 (dd, 1H, *J* = 9.2 and 2.7 Hz), 8.05 (d, 1H, *J* = 9.2 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ -1.36, 26.0, 59.4, 67.8, 70.8, 111.2, 116.1, 128.0, 141.1, 141.2, 162.1.

To a mixture of 5.27 g (18.6 mmol) of **10** and 3.56 g (18.6 mmol) of 2-chloro-3-quinolinecarboxaldehyde (**6a**) in 50 mL of isopropyl acetate was added 2.79 mL (2.79 mmol) of a 1M solution of TBAF in THF. The mixture was stirred at rt for 30 min and quenched with 20 mL of sat. NH₄Cl. The layers were separated and the organic layer washed with 20 mL of water. The solvent was removed under reduced pressure and the residue (6.51 g, 87%) was used in the next step without further purification. The product could be purified over silica gel to give **11** as a clear foam: ¹H NMR (CDCl₃, 400 MHz) δ 3.36 (s, 3H), 3.42 (m, 2H), 3.65 (m, 2H), 3.84 (br s, 1H), 4.01 (m, 2H), 5.43 (m, 1H), 6.77 (m, 2H), 7.51 (t, 1H, *J* = 8.1 Hz), 7.67 (t, 1H, *J* = 8.1 Hz), 7.75 (d, 1H, *J* = 8.1 Hz), 7.86 (m, 2H), 8.33 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 40.7, 59.2, 67.9, 70.6, 70.8, 113.3, 118.3, 127.3, 124.4, 127.5, 127.8, 128.0, 130.5, 135.6, 135.7, 136.4, 143.5, 146.9, 148.5, 162.0

To 5.90 g (14.65 mmol) of crude **11** in 75 mL of isopropyl acetate was added 2.50 mL (18.0 mmol) of TFAA and the solution stirred at rt for 1 h. To the resulting trifluoroacetate solution was added 6.70 g (44.0 mmol) of DBU and the mixture heated to 70 °C for 1 hour. The reaction mixture was cooled to rt, washed with 20 mL of water and

20 mL of brine, and then concentrated to a volume of 40 mL at which point the product crystallized to give 4.55 g (81%) of nitrostyrene **12** as a yellow solid: mp 134-135 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 3.49 (s, 3H), 3.83 (m, 2H), 4.28 (m, 2H), 6.96 (dd, 1H, J = 9.1 and 2.7 Hz), 7.28 (d, 1H, J = 2.7 Hz), 7.42 (d, 1H, J = 16.0 Hz), 7.58 (t, 1H, J = 8.1 Hz), 7.71 (t, 1H, J = 8.1 Hz), 7.75 (d, 1H, J = 16.0 Hz), 7.85 (d, 1H, J = 8.1 Hz), 8.00 (d, 1H, J = 8.1 Hz), 8.13 (d, 1H, J = 9.1 Hz), 8.45 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 59.4, 68.2, 70.4, 114.1, 114.6, 127.5, 127.6, 127.9, 128.0, 128.4, 129.5, 130.8, 135.0, 135.6, 141.1, 147.3, 150.0, 162.8; Anal. Calcd. For $\text{C}_{20}\text{H}_{17}\text{ClN}_2\text{O}_4$: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.33; H, 4.19; N, 7.23.

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Preparation of 2-Chloro-3-[5-(2-methoxyethoxy)-1H-indol-2-yl]-quinoline

(13). Method A. A solution of 1.30 g (3.38 mmol) of **12** in 9 mL of $\text{P}(\text{OEt})_3$ was heated to 155 °C for 2 h and the solvent removed under reduced pressure to give 900 mg (76%) of **13** which could be used without further purification. The product could be purified over silica gel to give **13** as a yellow foam: ^1H NMR (CDCl_3 , 400 MHz) δ 3.46 (s, 3H), 3.79 (m, 2H), 4.17 (m, 2H), 6.86 (d, 1H, J = 1.6 Hz), 6.92 (dd, 1H, J = 8.8 and 2.4 Hz), 6.94 (d, 1H, J = 2.4 Hz), 7.29 (d, 1H, J = 8.8 Hz), 7.50 (t, 1H, J = 8.0 Hz), 7.65 (t, 1H, J = 8.4 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 8.4 Hz), 8.24 (s, 1H), 8.97 (br s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 59.2, 68.1, 71.4, 103.5, 104.8, 112.2, 114.5, 126.0, 127.1,

127.6, 128.2, 128.6, 130.7, 132.4, 133.5, 138.1, 146.4, 147.8, 153.7; Anal. Calcd. For $C_{20}H_{17}ClN_2O_2$: C, 68.09; H, 4.86; N, 7.94. Found: C, 68.10; H, 4.73; N, 7.94.

Method B: To a solution containing 1.50 g (3.90 mmol) of **12** in 7 mL of MeCN was added 52.5 mg (0.234 mmol) of $Pd(OAc)_2$ and 246 mg (0.936 mmol) of PPh_3 . The resulting mixture was heated at 70 °C under CO (6 atm) for 12 h. The resulting mixture was filtered over celite and concentrated under reduced pressure to afford 1.29 g (94%) of crude **13** which was identical to that prepared in Method A and sufficiently pure for use in the hydrolysis step.

Preparation of 3-[5-(methoxy-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (1). A mixture of 700 mg (1.98 mmol) of **13** in 10 mL of a 1:1 mixture of AcOH/water was heated at reflux for 3 hour during which the product crystallized from the reaction mixture. The solution was cooled to rt and filtered to give 650 mg (98%) of **1** as a yellow solid: mp 272-273 °C; 1H NMR ($(CD_3)_2SO$, 400 MHz) δ 3.31 (s, 3H), 3.66 (t, 2H, J = 4.6 Hz), 4.07 (t, 2H, J = 4.6 Hz), 6.77 (dd, 1H, J = 8.8 and 2.3 Hz), 7.05 (d, 1H, J = 2.2 Hz), 7.22 (m, 2H), 7.37 (d, 1H, J = 8.2 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.50 (t, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 7.6 Hz), 8.50 (s, 1H), 11.44 (br s, 1H), 12.20 (br s, 1H); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz) δ 58.6, 67.7, 71.1, 102.1, 102.8, 113.0, 115.4, 119.9, 122.8, 123.0, 128.2, 128.7, 130.4, 132.3, 134.2, 134.5, 137.9, 153.2, 161.1; Anal. Calcd. For $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.45; N, 8.38. Found: C, 71.58; H, 5.26; N, 8.28.

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2-Chloro-4-[5-(2-methoxy-ethoxy)-2-nitrobenzyl]-1,4-dihydro-quinolin-3-carboxaldehyde (14). White solid: mp 147-147 °C; ^1H NMR (CDCl_3 , 400 MHz) δ 2.96 (dd, 1H, $J = 12.8$ and 6.5 Hz), 3.47 (s, 3H), 3.51 (dd, 1H, $J = 12.8$ and 6.5 Hz), 3.77 (t, 2H, $J = 4.7$ Hz), 4.11 (m, 2H), 4.52 (t, 1H, $J = 6.5$ Hz), 6.64 (d, 1H, $J = 2.6$ Hz), 6.75-6.88 (m, 4H), 6.98 (t, 1H, $J = 7.5$ Hz), 7.17 (t, 1H, $J = 7.5$ Hz), 7.89 (d, 1H, $J = 9.2$ Hz), 9.72 (s, 1H); ^{13}C NMR (CD_2Cl_2 , 100 MHz) δ 38.1, 41.0, 59.4, 68.5, 71.3, 108.9, 113.9, 115.4, 118.7, 124.6, 125.3, 127.8, 128.1, 129.5, 136.8, 137.0, 140.9, 143.7, 145.2, 162.2; Anal. Calcd. For $\text{C}_{20}\text{H}_{19}\text{ClN}_2\text{O}_5 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 58.33; H, 4.89; N, 6.80. Found: C, 58.54; H, 4.51; N, 6.75.

23a

Preparation of 2-Methoxy-3-{2-nitro-5-(2-piperidin-1-yl-ethoxy)-phenyl}-vinyl}-quinoline (23a). To a solution of 15.0 g (108 mmol) of 4-nitrophenol in 75 mL of DMF was added 45.0 g (326 mmol) of solid K_2CO_3 followed by 19.9 g (108 mmol) of 1-(2-chloroethyl)piperidine hydrochloride. The resulting mixture was heated to 50 °C for 2 h, cooled to rt, and diluted with 250 mL of water and 250 mL of EtOAc. The layers were

separated and the organic layer washed with 250 mL of brine and dried over MgSO_4 . The solvent was removed under reduced pressure and the product was recrystallized from EtOAc/hexane to give 19.7 g (73%) of **20a** as a colorless solid: mp 65-66 °C (lit.² mp 66 °C); ^1H NMR (CDCl_3 , 400 MHz) δ 1.38 (m, 2H), 1.53 (m, 4H), 2.43 (m, 4H), 2.72 (t, 2H, $J = 6.0$ Hz), 4.11 (t, 2H, $J = 6.0$ Hz), 6.88 (d, 2H, $J = 9.3$ Hz), 8.10 (d, 2H, $J = 9.3$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 24.1, 26.0, 55.1, 57.6, 67.0, 114.6, 125.8, 141.4, 164.01; Anal. Calcd. For $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.42; H, 7.28; N, 11.19.

To a solution of 7.50 g (30 mmol) of **20a** in 60 mL of THF at -15 °C was added dropwise 39 mL (39 mmol, 1M in ether) of (trimethylsilylmethyl) magnesium chloride at such a rate that the internal temperature did not rise above -5 °C. After stirring for 30 min at -5 °C, the solution was cannulated into 40 mL of 1N aqueous iodine and stirred for 2 h at rt. The mixture was diluted with 150 mL of isopropyl acetate and the layers were separated. The organic layer was washed with 75 mL of water. The solvent was removed under reduced pressure and the residue (**21a**, 8.47 g, 84%) was used in the next step without further purification.

To a mixture of 8.47 g (25.2 mmol) of **21a** and 4.71 g (25.2 mmol) of 2-methoxy-3-quinolinecarboxaldehyde (**6b**)³ in 75 mL of dry isopropyl acetate (KF = 120 ug/mL) was added 3.78 mL (3.78 mmol) of a 1M solution of TBAF in THF. The mixture was stirred at rt for 30 min and quenched with 75 mL of sat. NH_4Cl . The layers were separated and the organic layer washed with 75 mL of water. The mixture was azeotropically dried to a final volume of 75 mL and a KF of 110 ug/mL. To the solution was added 6.34 g (30.2 mmol) of TFAA and the mixture stirred at rt for 1 h. To the

resulting trifluoroacetate solution was added 11.5 g (75.6 mmol) of DBU and the mixture heated to 70 °C for 1 hour. The reaction mixture was cooled to rt, washed with 75 mL of water and 75 mL of brine, and then concentrated under reduced pressure. The residue was passed over a plug of silica gel eluting first with EtOAc and then with 1:1 EtOAc/acetone to give 7.09 g (65%) of **23a** as a clear oil: ¹H NMR (CDCl₃, 400 MHz) δ 1.46 (m, 2H), 1.63 (m, 4H), 2.53 (m, 4H), 2.81 (t, 2H, *J* = 6.0 Hz), 4.15 (s, 3H), 4.23 (t, 2H, *J* = 6.0 Hz), 6.88 (dd, 1H, *J* = 9.1 and 2.7 Hz), 7.23 (d, 1H, *J* = 2.7 Hz), 7.32 (d, 1H, *J* = 16.2 Hz), 7.39 (t, 1H, *J* = 8.0 Hz), 7.60 (t, 1H, *J* = 8.0 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 16.2 Hz), 8.07 (d, 1H, *J* = 9.1 Hz), 8.21 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 24.2, 26.0, 53.8, 55.3, 57.7, 66.9, 113.8, 121.8, 124.5, 125.4, 126.9, 127.5, 127.6, 127.7, 127.8, 129.8, 135.0, 136.3, 141.1, 146.2, 160.0, 162.7; Anal. Calcd. For C₂₅H₂₇N₃O₄: C, 69.27; H, 6.28; N, 9.69. Found: C, 68.91; H, 6.21; N, 9.43.

Preparation of 3-[5-(2-piperidin-1-yl-ethoxy)-1H-indol-2-yl]-1H-quinolin-2-one (2). Method A: A solution of 1.35 g (3.11 mmol) of **23a** in 8 mL of P(OEt)₃ was heated to 155 °C for 2 h and the solvent removed under reduced pressure to give 790 mg (63%) of **24a**. The residue was re-dissolved in 25 mL of MeOH and 2.6 mL of 6N HCl was added and the resulting mixture heated at reflux for 4 h, cooled to rt, and concentrated under reduced pressure. The resulting residue was neutralized with sat.

NaHCO₃ and the product filtered to give 760 mg (63%) of **2** as a yellow solid: mp 276 °C (decomp); ¹H NMR ((CD₃)₂SO, 400 MHz) δ 1.37 (m, 2H), 1.50 (m, 4H), 2.44 (m, 4H), 2.65 (t, 2H, *J* = 5.7 Hz), 3.29 (br s, 1H), 4.05 (t, 2H, *J* = 5.7 Hz), 6.71 (dd, 1H, *J* = 8.6 and 2.1 Hz), 7.02 (s, 1H), 7.20 (m, 2H), 7.34 (m, 2H), 7.47 (t, 1H, *J* = 8.2 Hz), 7.68 (d, 1H, *J* = 8.2 Hz), 11.4 (br s, 1H), 12.1 (br s, 1H); ¹³C NMR ((CD₃)₂SO, 100 MHz) δ 24.4, 26.1, 54.9, 58.1, 66.5, 102.1, 102.9, 112.9, 113.4, 115.3, 19.9, 122.8, 123.0, 128.2, 128.7, 130.4, 132.3, 134.1, 134.5, 137.9, 153.2, 161.1; Anal. Calcd. For C₂₄H₂₅N₃O₂·H₂O: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.39; H, 6.41; N, 10.41.

Method B: To a solution containing 2.50 g (5.80 mmol) of **23a** in 25 mL of MeCN was added 78.1 mg (0.348 mmol) of Pd(OAc)₂ and 365 mg (1.39 mmol) of PPh₃. The resulting mixture was heated at 70 °C under CO (6 atm) for 12 h. The resulting mixture was filtered over celite and concentrated under reduced pressure to afford 2.05 g (88%) of crude **24a**. Hydrolysis of **24a** was accomplished as in Method A to give 1.95 g of **2**.

Preparation of (2-Methoxyethyl)-(2-{3-[2-(2-methoxy-quinolin-3-yl)-vinyl]-4-nitrophenoxy}-ethyl-N-methylamine (23b). To a solution of 20.5 g (230 mmol) of *N*-(2-methoxyethyl)methylamine in 400 mL of acetonitrile was added 95.0 g (687 mmol) of solid K₂CO₃ followed by 39.2 g (234 mmol) of ethyl bromoacetate. The resulting slurry was heated to reflux for 2 h, cooled to rt, and filtered. The solvent was removed under reduced pressure and the residue dissolved in MTBE, washed with 100 mL of brine, and

dried over MgSO_4 . The solvent was concentrated under reduced pressure to afford 40.3 g (100%) of the crude product (ethyl [(2-methoxyethyl)-*N*-methylamino]acetate which was used in the next step without further purification.

To a slurry of 8.73 g (230 mmol) of LAH in 250 mL of THF was added dropwise 40.3 g (230 mmol) of the above ester in 100 mL of THF. After the addition was complete, the reaction mixture was heated to reflux for 1 h and cooled to 0 °C. To the solution was carefully and sequentially added 10 mL of water, 10 mL of 2N NaOH, and 20 mL of water. The inorganic solids were filtered over celite and the filtrate diluted with 100 mL of EtOAc and dried over MgSO_4 . The solvent was removed under reduced pressure to afford 30.6 g (100%) of crude 2-[(2-methoxyethyl)-*N*-methylamino]-ethanol which was used in the next step without further purification.

To a solution of 16 mL of thionyl chloride at 0 °C was carefully added 30.6 g (230 mmol) the above alcohol. The dark mixture was heated to 50 °C for 1 h at which point 40 mL of ethanol was added. The reaction mixture was allowed to cool to rt and concentrated under reduced pressure and used directly in the next step without further purification.

To a solution of 21.0 g (151 mmol) of 4-nitrophenol in 100 mL of DMF was added 62.6 g (453 mmol) of K_2CO_3 and the above crude chloride from the above reaction. The resulting mixture was heated at 50 °C for 6 h and stirred for 12 h at rt. To the mixture was added 500 mL of water and 500 mL of EtOAc. The layers were separated and the organic layer washed with 250 mL of water, 250 of brine, and was dried over MgSO_4 . The solvent was removed under reduced pressure to give 30.0 g (78%) of *N*-(2-methoxyethyl)-*N*-methyl-[2-(4-nitrophenoxy)-ethyl]-amine **20b** as a clear oil: ^1H NMR (CDCl_3 , 400 MHz) δ 2.42 (s, 3H), 2.71 (t, 2H, $J = 5.5$ Hz), 2.91 (t, 2H, $J = 5.8$ Hz), 3.37

(s, 3H), 3.51 (t, 2H, $J = 5.5$ Hz), 4.18 (t, 2H, $J = 5.8$ Hz), 6.97 (d, 2H, $J = 9.2$ Hz), 8.20 (d, 2H, $J = 9.2$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 43.4, 56.3, 57.3, 58.9, 67.1, 70.6, 114.6, 125.9, 141.5, 163.9.

To a solution of 10.2 g (40.1 mmol) of **20b** in 150 mL of THF at -15 °C was added dropwise 52 mL (52.0 mmol, 1M in ether) of (trimethylsilylmethyl) magnesium chloride at such a rate that the internal temperature did not rise above -5 °C. After stirring for 30 min at -5 °C, the solution was cannulated into 55 mL of 1N iodine solution and stirred for 2 h at rt. The mixture was diluted with 200 mL of isopropyl acetate and the layers were separated. The organic layer was washed with 150 mL of water. The solvent was removed under reduced pressure and the residue (**21b**, 11.1 g, 81%) was used in the next step without further purification.

To a mixture of 11.1 g (32.6 mmol) of **21b** and 6.10 g (32.6 mmol) of 2-methoxy-3-quinolinecarboxaldehyde (**6b**) in 100 mL of isopropyl acetate was added 4.90 mL (4.90 mmol) of a 1M solution of TBAF in THF. The mixture was stirred at rt for 30 min and quenched with 100 mL of sat. NH_4Cl . The layers were separated and the organic layer washed with 100 mL of water. The mixture was azeotropically dried to a final volume of 100 mL and a KF of 124 $\mu\text{g/mL}$. To the solution was added 8.31 g (39.5 mmol) of TFAA and the mixture stirred at rt for 1 h. To the resulting trifluoroacetate solution was added 15.2 g (100 mmol) of DBU and the mixture heated to 70 °C for 1 hour. The reaction mixture was cooled to rt, washed with 100 mL of water and 100 mL of brine, and then concentrated under reduced pressure. The residue was passed over a plug of silica gel eluting first with EtOAc and then with 1:1 EtOAc/acetone to give 10.5 g (74%) of **23b** as a clear oil: ^1H NMR (CDCl_3 , 400 MHz) δ 2.43 (s, 3H), 2.73 (t, 2H, $J = 5.5$ Hz), 2.93 (t,

2H, $J = 5.9$ Hz), 3.37 (s, 3H), 3.53 (t, 2H, $J = 5.5$ Hz), 4.16 (s, 3H), 4.21 (t, 2H, $J = 5.9$ Hz), 6.80 (dd, 1H, $J = 9.1$ and 2.7 Hz), 7.22 (d, 1H, $J = 2.7$ Hz), 7.32 (d, 1H, $J = 16.2$ Hz), 7.38 (dt, 1H, $J = 8.4$, 6.9, and 1.1 Hz), 7.60 (dt, 1H, $J = 8.4$, 6.9, and 1.1 Hz), 7.75 (dd, 1H, $J = 8.4$ and 1.1 Hz), 7.82 (d, 1H, $J = 8.4$ Hz), 7.91 (d, 1H, $J = 16.2$ Hz), 8.07 (d, 1H, $J = 9.1$ Hz), 8.22 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 43.4, 53.8, 56.4, 57.4, 59.0, 67.1, 70.7, 113.8, 121.8, 124.5, 125.4, 127.0, 127.5, 127.6, 127.7, 127.8, 129.8, 134.9, 136.3, 141.1, 146.2, 159.9, 162.6; Anal. Calcd. For $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.62; H, 6.11; N, 9.59.

Preparation of 3-(5-{2-[methyl-(2-methoxyethyl)-amino]-ethoxy}-1H-indol-2-yl)-1H-quinolin-2-one (3). Method A: A solution of 5.50 g (12.6 mmol) of **23b** in 25 mL of $\text{P}(\text{OEt})_3$ was heated to 155 °C for 2 h and the solvent removed under reduced pressure to afford 2.91 g (57%) of crude **24b**. The residue was re-dissolved in 35 mL of MeOH and 10.5 mL of 6N HCl was added and the resulting mixture heated at reflux for 4 h, cooled to rt, and concentrated under reduced pressure. The resulting residue was neutralized with sat. NaHCO_3 and the product filtered to give 2.81 g of **3** as a yellow solid: mp 204-205 °C; ^1H NMR ($(\text{CD}_3)_2\text{SO}$, 400 MHz) δ 2.27 (s, 3H), 2.58 (t, 2H, $J = 5.8$ Hz), 2.74 (t, 2H, $J = 5.6$ Hz), 3.20 (s, 3H), 3.40 (t, 2H, $J = 5.6$ Hz), 4.01 (t, 2H, $J = 5.8$ Hz), 6.71 (dd, 1H, $J = 8.8$ and 2.4 Hz), 7.02 (d, 1H, $J = 2.4$ Hz), 7.18 (s, 1H), 7.22 (d,

1H, $J = 8.1$ Hz), 7.33 (d, 1H, $J = 8.8$ Hz), 7.35 (d, 1H, $J = 8.8$ Hz), 7.46 (t, 1H, $J = 8.1$ Hz), 7.69 (d, 1H, $J = 8.1$ Hz), 8.47 (s, 1H), 11.4 (br s, 1H), 12.1 (br s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 43.4, 56.8, 57.1, 58.5, 66.8, 70.8, 102.2, 102.9, 113.0, 113.4, 115.4, 120.0, 122.8, 123.0, 128.2, 128.7, 130.5, 132.4, 134.2, 134.6, 138.0, 153.2, 161.1; Anal Calcd. For $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.47; H, 6.19; N, 10.37.

Method B: To a solution containing 1.50 g (3.43 mmol) of **23b** in 20 mL of MeCN was added 46.2 mg (0.206 mmol) of $\text{Pd}(\text{OAc})_2$ and 216 mg (0.823 mmol) of PPh_3 . The resulting mixture was heated at 70 °C under CO (6 atm) for 12 h. The resulting mixture was filtered over celite and concentrated under reduced pressure to afford 1.28 g (92%) of crude **24b**. Hydrolysis of **24b** was accomplished as in Method A to give 1.20 g of **3**.

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Preparation of 3-(5-Methoxy-1H-indol-2-yl)-1H-pyridin-2-one (27). To a solution of 4.00 g (16.7 mmol) of 3-trimethylsilylmethyl-4-nitro-anisole (**21c**)³ in 75 mL of isopropyl acetate was added 2.30 g (16.7 mmol) of **25**⁴ followed by 2.50 mL (2.50 mmol) of a 1M solution of TBAF in THF. The mixture was stirred at rt for 30 min and quenched with 50 mL of sat. NH_4Cl . The layers were separated and the organic layer washed with 30 mL of water. The organic layer was azeotropically dried to a final volume of 75 mL and a KF of 107 ug/mL. To the solution was added 4.21 g (20.0 mmol) of TFAA and the mixture stirred at rt for 1 h. To the resulting trifluoroacetate solution

was added 7.63 g (50.1 mmol) of DBU and the mixture was heated to 70 °C for 1 h. The reaction mixture was cooled to rt, washed with 75 mL of water and 75 mL of brine, and then concentrated under reduced pressure. The residual solid was suspended in 25 mL of MTBE and filtered to give 3.08 g (64%) of 2-methoxy-3-[2-(5-methoxy-2-nitrophenyl)-vinyl]-pyridine as a yellow solid: mp 106-107 °C; ¹H NMR (CDCl₃, 400 MHz) δ 3.92 (s, 3H), 4.02 (s, 3H), 6.85 (dd, 1H, *J* = 9.1 and 2.7 Hz), 6.91 (dd, 1H, *J* = 7.4 and 5.0 Hz), 7.14 (d, 1H, *J* = 2.7 Hz), 7.21 (d, 1H, *J* = 16.2 Hz), 7.77 (d, 1H, *J* = 16.2 Hz), 7.82 (dd, 1H, *J* = 7.4 and 1.5 Hz), 8.05 (d, 1H, *J* = 9.1 Hz), 8.10 (d, 1H, *J* = 1.5 Hz), 8.11 (d, 1H, *J* = 1.5 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 53.5, 55.9, 113.1, 117.1, 120.0, 126.8, 127.3, 127.6, 135.4, 136.3, 141.0, 146.5, 161.2, 163.2; Anal. Calcd. For C₁₅H₁₄N₂O₅: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.85; H, 4.59; N, 9.62.

To a solution containing 1.50 g (5.24 mmol) of the above styrene in 20 mL of MeCN was added 71.0 mg (0.314 mmol) of Pd(OAc)₂ and 330 mg (1.26 mmol) of PPh₃. The resulting mixture was heated at 70 °C under CO (6 atm) for 12 h. The resulting mixture was filtered over celite and 1.5 mL of conc. HCl was added. The solution was heated to reflux for 12 h and the product was filtered to give 1.04 g (83%) of **27** as a yellow solid: mp 300 °C (decomp); ¹H NMR ((CD₃)₂SO, 400 MHz) δ 3.74 (s, 3H), 6.37 (m, 1H), 6.72 (m, 1H), 7.00 (m, 2H), 7.40 (m, 2H), 8.06 (m, 1H), 11.35 (br s, 1H), 12.06 (br s, 1H); ¹³C NMR ((CD₃)₂SO, 100 MHz) δ 55.7, 100.2, 101.6, 106.3, 112.3, 112.8, 121.9, 128.7, 131.8, 134.2, 135.3, 135.8, 154.0, 161.1; Anal. Calcd. For C₁₄H₁₂N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.62; H, 4.79; N, 11.50.

28

Preparation of 3-(5-Methoxy-1H-indol-2-yl)-1H-pyridin-2-one (28). To a solution of 2.81 g (9.10 mmol) of 3-trimethylsilylmethyl-4-nitro-anisole (**21c**)³ in 22 mL of isopropyl acetate was added 1.50 g (10.9 mmol) of **26**⁴ followed by 1.80 mL (1.80 mmol) of a 1M solution of TBAF in THF. The mixture was stirred at rt for 30 min and quenched with 20 mL of sat. NH₄Cl. The layers were separated and the organic layer washed with 15 mL of water. The organic layer was azeotropically dried to a final volume of 25 mL and a KF of 125 ug/mL. To the solution was added 2.24 g (10.7 mmol) of TFAA and the mixture stirred at rt for 1 h. To the resulting trifluoroacetate solution was added 4.16 g (27.3 mmol) of DBU and the mixture was heated to 70 °C for 1 h. The reaction mixture was cooled to rt, washed with 50 mL of water and 50 mL of brine, and then concentrated under reduced pressure. The residual solid was suspended in 25 mL of MTBE and filtered to give 1.06 g (41%) of 2-methoxy-6-[2-(5-methoxy-2-nitrophenyl)-vinyl]-pyridine as a yellow solid: mp 77-78 °C; ¹H NMR (CDCl₃, 400 MHz) δ 3.94 (s, 3H), 4.01 (s, 3H), 6.67 (d, 1H, *J* = 8.7 Hz), 6.90 (dd, 1H, *J* = 9.1 and 2.8 Hz), 6.95 (m, 2H), 7.17 (m, 1H), 7.56 (t, 1H, *J* = 7.8 Hz), 8.09 (d, 1H, *J* = 9.1 Hz), 8.25 (d, 1H, *J* = 15.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 53.2, 55.9, 110.8, 113.0, 113.5, 116.1, 127.6, 128.4, 132.5, 135.8, 138.9, 141.4, 152.1, 163.1, 163.7; Anal. Calcd. For C₁₅H₁₄N₂O₄: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.55; H, 4.55; N, 9.52.

To a solution containing 600 mg (2.10 mmol) of the above styrene in 10 mL of MeCN was added 28.3 mg (0.126 mmol) of Pd(OAc)₂ and 132 mg (0.504 mmol) of

PPh₃. The resulting mixture was heated at 70 °C under CO (6 atm) for 12 h. The resulting mixture was filtered over celite and 1.0 mL of conc. HCl was added. The solution was heated to reflux for 12 h and the product was filtered to give 412 mg (82%) of **28** as a yellow solid: mp 308 °C (decomp); ¹H NMR ((CD₃)₂SO, 400 MHz) δ 3.76 (s, 3H), 6.53 (d, 1H, *J* = 8.8 Hz), 6.82 (dd, 1H, *J* = 8.8 and 2.4 Hz), 7.05 (d, 1H, *J* = 2.3 Hz), 7.11 (d, 1H, *J* = 7.2 Hz), 7.30 (m, 1H), 7.34 (d, 1H, *J* = 8.8 Hz), 7.69 (t, 1H, *J* = 7.2 Hz), 9.23 (br s, 1H), 11.81 (s, 1H); ¹³C NMR ((CD₃)₂SO, 100 MHz) δ 55.8, 102.2, 103.3, 106.3, 113.1, 114.9, 115.0, 128.6, 131.6, 133.3, 141.4, 143.0, 154.4, 163.1; Anal. Calcd. For C₁₄H₁₂N₂O₂: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.60; H, 4.81; N, 11.52.

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