A Friedländer Approach for the Incorporation of 6-Bromoquinoline into Novel Chelating Ligands

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Supporting Information:

Experimental Section

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Absorption spectra were recorded with a Perkin-Elmer λ-3B spectrophotometer. Luminescence studies were made with dilute (1×10^{-5} M) solutions at room temperature using a Perkin-Elmer LS-50B spectrofluorometer. Absorption and emission maxima were reproducible to within ±2 nm. NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Tetrahydroacridone **7**[1] and 4-*tert*-butyl-2,6-diacetylpyridine (**18b**)[2] were prepared according to published procedures. Elemental analyses were performed by Quantitative Technologies Inc., P. O. Box 470, Whitehouse, NJ 08888. Emission quantum yields were determined by relative actinometry.[3] The procedure involves the measurement of the integrated emission profile (I) and absorbance (A) of an unknown sample and a reference compound. The quantum yield of the sample (ϕ) is then determined by using

$$\phi = \phi_R(I/I_R)(n/n_R)^2(A_R/A)$$

where n is the refractive index of the solvent, and ϕ_R, n_R and A_R all refer to the reference compound. The reference used in this work was anthracene in EtOH ($\phi = 0.27$)[4] at 298 K. The refractive index of the mixture CH_2Cl_2-MeOH (99:1) was assumed to be the same as that of CH_2Cl_2 ($n = 1.424$). The refractive index for EtOH is 1.360.

5-Bromo-2-nitrobenzaldehyde (5)

The 3-bromobenzaldehyde (18.5 g, 0.10 mol) was added during 20 min to a stirred mixture of HNO_3 (10.0 mL) and concentrated sulfuric acid (120 mL) in ice bath. After 3 h stirring at room temperature, the solution was poured onto ice (400 mL) and the precipitate was collected by filtration, washed with H_2O and dried over P_2O_5. The crude product was recrystallized from hexane to afford 5-bromo-2-nitrobenzaldehyde as pale yellow needle-like crystals (10.46 g, 45%), mp 63-66 °C (lit[5] mp 61-62 °C).

2-Amino-5-bromobenzaldehyde (6)

To a hot, stirred solution of $Na_2S_2O_4$ (26.0 g, 0.15 mol) and Na_2CO_3 (12.8 g, 0.12 mol) in H_2O (500 mL) was added slowly a solution of 5-bromo-2-nitrobenzaldehyde (6.20 g, 27 mmol) in MeOH (100 mL) over 25 min. The solution was then refluxed for 2 h and cooled to 0 °C. The precipitate was collected by filtration, washed with H_2O and MeOH to afford **6** (0.99 g). The filtrate was extracted with Et_2O and the Et_2O solution was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to afford additional **6** for a total yield of 1.70 g (32 %): mp 74-76 °C; ^{1}H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.58 (d, 1H, J = 2.4 Hz), 7.37 (dd, 1H, J = 9.0 Hz, 2.4 Hz), 6.57 (d, 1H, J = 8.7 Hz), 6.12 (b, 2H).

6-bromo-2-(2'pyridyl)-quinoline (10)

To a mixture of **6** (524 mg, 2.62 mmol) and 2-acetylpyridine (322 mg, 266 mmol) in absolute ethanol (25 mL) under Ar was added, dropwise, saturated ethanolic KOH (4 mL), and the mixture was refluxed overnight. After cooling, the precipitate was collected by filtration, washed with EtOH (2 × 5 mL) and dried under reduced pressure. Compound **10** was obtained as pale yellow crystals (488 mg, 65%): mp 122-3 °C; ^{1}H NMR ($CDCl_3$) δ 8.74 (d, 1H, J = 5.1 Hz), 8.63 (d, 1H, J = 8.1 Hz), 8.59 (d, 1H, J = 8.7 Hz), 8.20 (d, 1H, J = 8.7 Hz), 8.05 (d, 1H, J = 9.0 Hz),

8.02 (d, 1H, J = 2.1 Hz), 7.89 (dt, 1H, J = 7.8 Hz, 1.8 Hz), 7.80 (dd, 1H, J = 9.0 Hz, 2.1 Hz), 7.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.3, 154.7, 148.0, 145.3, 136.0, 134.7, 131.9, 130.4, 128.5, 128.2, 123.1, 120.7, 119.5, 118.7; LC-MS (m/z): 287.2 (M +2).

6-Bromo-3,3'-dimethylene-2,2'-biquinoline (11)

To a mixture of **6** (130 mg, 0.65 mmol) and tetrahydroacridone **8** (126 mg, 0.64 mmol) in absolute EtOH (10 mL) under Ar was added, dropwise, saturated ethanolic KOH (1 mL), and the mixture was heated at reflux for 4 h. After cooling, the solvent was evaporated and the residue was purified by chromatography on silica gel, eluting with EtOAc-petroleum ether (1:1), to afford **11** as a white solid (205 mg, 88%): mp 251-253 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 9.0 Hz), 8.07 (s, 1H), 7.96 (m, 2H), 7.81-7.69 (m, 3H), 7.56 (t, 1H, J = 7.5 Hz), 3.25 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 152.8, 152.0, 148.3, 146.9, 135.1, 133.8, 133.7, 132.8, 132.7, 132.6, 131.1, 129.6, 129.4, 129.0, 128.6, 127.7, 127.0, 121.5, 28.8, 28.6. Anal. Calcd. For $C_{20}H_{13}N_2Br$: C, 66.50; H, 3.60; N, 7.76. Found: C, 66.23; H, 3.30; N, 7.51.

6,6'-Dibromo-3,3'-dimethylene-2,2'-biquinoline (12)

To a mixture of **6** (500 mg, 2.5 mmol) and 1,2-cyclohexanedione (**8**, 137 mg, 1.22 mmol) in absolute EtOH (10 mL) under Ar was added, dropwise, saturated ethanolic KOH (1 mL), and the mixture was heated at reflux for 4 h. After cooling, the precipitate was collected by filtration, washed with EtOH (2 x 5 mL), H_2O (2 x 5 mL) and EtOH (2 x 5 mL) and dried under reduced pressure. Compound **12** was obtained as a pale yellow solid (361 mg, 68%): mp 297-299 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 2H, J = 8.7 Hz), 8.01 (s, 2H), 7.98 (d, 2H, J = 2.1 Hz), 7.79 (dd, 2H, J = 9.0 Hz, 2.1 Hz), 3.28 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 146.7, 134.2, 133.7, 133.1, 132.6, 129.7, 129.1, 121.9, 120.1, 28.6. Anal. Calcd. For $C_{20}H_{12}N_2Br_2$: C, 54.57; H, 2.73; N, 6.37. Found: C, 54.52; H, 2.58; N, 6.27.

2,2'-Di(2''-pyridyl)-6,6'-biquinoline (13)

A solution of $NiCl_2$ (72 mg, 0.555 mmol), and PPh_3 (578 mg, 2.21 mmol) in DMF (6 mL) was heated at 50 °C with stirring under Ar for 0.5 h. The resulting blue suspension was treated with Zn dust (36 mg, 0.550 mmol) to produce a red-brown suspension; after 3 h a solution of **10** (158 mg, 0.555 mmol) in DMF (3 mL) was added and the mixture stirred overnight. After cooling, the reaction mixture was filtered and the solid was combined with KCN (0.7 g) in MeOH-H_2O (1:1, 20 mL) and heated at reflux. After filtration, the product was recrystallized from $CHCl_3$ to give **13** as a grey blue solid (60 mg, 27%): mp > 300 °C; ^{1}H NMR ($CDCl_3$): δ 8.77 (d, 1H, J = 4.5 Hz), 8.70 (d, 1H, J = 7.8 Hz), 8.64 (d, 1H, J = 8.7 Hz), 8.40 (d, 1H, J = 8.7 Hz), 8.33 (d, 1H, J = 8.7 Hz), 8.22 (d, 1H, J = 1.8 Hz), 8.17 (dd, 1H, J = 8.7 Hz, 2.1 Hz), 7.92 (dt, 1H, J = 7.8 Hz, 1.8 Hz), δ 7.40 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 155.3, 148.1, 146.4, 137.5, 135.9, 129.4, 128.1, 127.4, 125.0, 124.7, 123.0, 120.8, 118.4, 111.6; LC-MS (m/z): 412.3 (M^+ + 2).

6,6'-bi(3,3'-dimethylene-2,2'-biquinoline) (14)

A solution of $NiCl_2$ (95 mg, 0.74 mmol) and triphenylphosphine (770 mg, 2.93 mmol) in DMF (6 mL) was heated at 50 ^{o}C with stirring under Ar for 0.5 h. The resulting blue suspension was treated with Zn dust (37 mg, 0.567 mmol) to produce a red-brown suspension. After 0.5 h, a solution of **11** (200 mg, 0.554 mmol) in DMF (3 mL) was added and the mixture was stirred overnight and then evaporated to dryness. MeOH (50 mL) and KCN (0.7 g) in H_2O (2 mL) were added and the mixture was sonicated for 1 h. The precipitate was collected by filtration and purified by chromatography on alumina, eluting with CH_2Cl_2 followed by CH_2Cl_2-CH_3OH (100:1). Recrystallization from CH_2Cl_2-hexane gave **14** as a yellow solid (121 mg, 77%): mp > 300 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.60 (d, 2H, J = 9.3 Hz), 8.50 (d, 2H, J = 8.7 Hz), 8.16 (m, 6H), 8.10 (s, 2H), 7.82 (d, 2H, J = 8.1 Hz), 7.74 (t, 2H, J = 7.8 Hz), 7.58 (t, 2H, J = 7.8 Hz), 3.31 (s, 8H). MALDI-TOF MS (m/z) 563.011 (M^+ + 1). Anal. Calcd. For $C_{40}H_{26}N_4 \bullet CH_2Cl_2$: C, 76.12; H, 4.33; N, 8.66. Found: C, 76.72; H, 4.07; N, 8.63.

6-(2-Methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline

To a pressure tube were added compound **11** (100 mg, 0.277 mmol), 2-methyl-3-butyn-2-ol (0.055 mL, 0.568 mmol), [$Pd(PPh_3)_4$] (30 mg, 0.019 mmol) and *n*-propylamine (15 mL). Ar was bubbled through the solution for 5 min and the vessel then closed and heated at 70-80 ^oC for 2 days. After cooling to room temperature, the mixture was evaporated to dryness. The residue was purified by chromatography on alumina, eluting with EtOAc. Evaporation of the solvent gave 6-(2-methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline as a pale yellow solid (100 mg, 98%): mp 240 ^oC (dec); ^1H NMR ($CDCl_3$) δ 8.47 (d, 1H, J = 9.3 Hz), 8.39 (d, 1H, J = 9.0 Hz), 8.10 (s, 1H), 8.01 (s, 1H), 7.89 (d, 1H, J = 1.5 Hz), 7.82 (d, 1H, J = 8.1 Hz), 7.71 (m, 2H), 7.57 (t, 1H, J = 7.5 Hz), 3.27 (s, 4H), 1.67 (s, 6H).

6-Ethynyl-3,3'-dimethylene-2,2'-biquinoline (15)

A solution of 6-(2-methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline (100 mg, 0.275 mmol) in toluene (20 mL) was treated with powdered NaOH (183 mg, 4.58 mmol) and the reaction mixture was refluxed for 4 h. After cooling, $CHCl_3$ (100 mL) was added and the mixture was washed with H_2O (2 x 70 mL) and dried over $MgSO_4$. The solvent was evaporated to afford **15** (78 mg, 93%): mp 188 ^oC (dec); ^1H NMR ($CDCl_3$) δ 8.46 (d, 1H, J = 8.4 Hz), 8.40 (d, 1H, J = 9.0 Hz), 8.10 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 7.82 (d, 1H, J = 7.8 Hz), 7.74 (m, 2H), 7.57 (t, 1H, J = 7.8 Hz), 3.27 (s, 4H), 3.24 (s, 1H); GC-MS (m/z): 306.2 (M^+).

6,6'-di-(2-Methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline

Following the procedure described for 6-(2-methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline, a mixture of compound **12** (200 mg, 0.457 mmol), 2-methyl-3-butyn-2-ol (0.443 mL, 4.57 mmol), [$Pd(PPh_3)_4$] (53 mg, 0.046 mmol) and *n*-propylamine (15 mL) provided a material which was purified by chromatography on alumina, eluting with EtOAc followed by EtOAc-CH_3OH (100:1) to afford 6,6'-di(2-methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline as a pale yellow solid (198 mg, 97%): mp 273 ^oC (dec); ^1H NMR ($CDCl_3$) δ 8.38 (d,

2H, J = 8.7 Hz), 7.99 (s, 2H), 7.87 (d, 2H, J = 1.2 Hz), 7.69 (dd, 2H, J = 8.7, 1.5 Hz), 3.27 (s, 4H), 1.67 (s, 12H).

6,6'-Diethynyl-3,3'-dimethylene-2,2'-biquinoline (17)

A solution of 6,6'-di(2-methyl-3-butyn-2-ol)-3,3'-dimethylene-2,2'-biquinoline (100 mg, 0.224 mmol) in toluene (20 mL) was treated with powdered NaOH (300 mg, 7.50 mmol) and the reaction mixture was heated at reflux for 4 h. After cooling, $CHCl_3$ (100 mL) was added and the mixture was washed with H_2O (2 x 70 mL), dried over $MgSO_4$, and the solvent evaporated to afford **17** (70 mg, 94%): mp 183 ^oC (dec); ^1H NMR ($CDCl_3$) δ 8.39 (d, 2H, J = 8.7 Hz), 8.03 (s, 2H), 7.97 (d, 2H, J = 1.5 Hz), 7.76 (dd, 2H, J = 9.0, 1.5 Hz), 3.26 (s, 4H), 3.24 (s, 2H); GC-MS (m/z): 330.1 (M^+).

Ligand 16

To a pressure tube were added **11** (67 mg, 0.186 mmol), **15** (52 mg, 0.17 mmol), [$Pd(PPh_3)_4$] (20 mg, 0.017 mmol) and *n*-propylamine (20 mL). Ar was bubbled through the solution for 5 min and the vessel was closed and heated at 70-80 ^oC for 2 days. After cooling to room temperature, the yellow precipitate was filtered, washed with water, CH_3OH and CH_2Cl_2 and dried to give a first crop of **16** (40 mg). The filtrate was evaporated and the residue was purified by chromatography on alumina eluting with CH_2Cl_2-CH_3OH (100:1). After evaporation of the solvent, the product was further purified by recrystallization from CH_2Cl_2-hexane to give a second crop of **16** (31 mg, total yield 71%), mp > 300 ^oC; ^1H NMR ($CDCl_3$): δ 8.47 (d, 2H, J = 2.1 Hz), 8.44 (d, 2H, J = 2.7 Hz), 8.10 (s, 2H), 8.07 (m, 4H), 7.85 (m, 4H), 7.74 (t, 2H, J = 7.8 Hz), 7.58 (t, 2H, J = 7.8 Hz), 3.29 (s, 8H). Anal. Calcd. For $C_{42}H_{26}N_4 \bullet CH_2Cl_2 \bullet H_2O$: C, 74.89; H, 4.35; N, 8.13. Found: C, 74.12; H, 3.92; N, 8.06.

2,6-Di-(6'-Bromoquinol-2'-yl)-4*t*-butyl-pyridine (19)

To a mixture of 4-*tert*-butyl-2,6-diacetylpyridine (219 mg, 1.0 mmol) and 2-amino-5-bromobenzaldehyde (400 mg, 2.0 mmol) in absolute ethanol (8 mL) under Ar was added saturated ethanolic KOH (1 mL) dropwise, and the mixture was refluxed for 4 h. After cooling, the precipitate was collected by filtration, washed with EtOH, H_2O and EtOH and dried under reduced pressure. The white solid (480 mg) was recrystallized from $CHCl_3$-hexane and ligand **19** was obtained as pale yellow crystals (310 mg, 57%): mp 257-258 °C; ^{1}H NMR ($CDCl_3$): δ 8.86 (d, 1H, J = 8.7 Hz), 8.00 (s, 1H), 8.24 (d, 1H, J = 8.7 Hz), 8.13 (d, 1H, J = 9.0 Hz), 8.05 (d, 1H, J = 2.4 Hz), 7.83 (dd, 1H, J = 9.0 Hz, 2.1 Hz), 1.56 (s, 9H). GC-MS (*m/z*): 548.1 (M^+ + 1). Anal. Calcd for $C_{27}H_{21}N_3Br_2$ (%): C 59.25, H 3.87, N 7.71; found: C 59.49, H 3.46, N 7.44.

6,6'-Biquinoline (20)

A solution of $NiCl_2$ (304 mg, 2.31 mmol) and PPh_3 (2.44 g, 9.28 mmol) in DMF (15 mL) was heated to 50 ^{o}C with stirring under Ar for 0.5 h. The resulting blue suspension was treated with Zn dust (150 mg, 2.31 mmol) to produce a red-brown suspension; after 0.5 h a solution of 6-chloroquinoline in DMF (5 mL) was added, and the mixture stirred overnight. The mixture was poured into amonia solution (2 M, 100 mL) and extracted with dichloromethane (3 × 80 mL). The organic layer was washed with water (3 × 50 mL), dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate-petroleum ether (1:1 and 2:1). After evaporation of the solvent, the residue was recrystallized from hexane to afford a white solid (220 mg, 74%): mp 179-181 °C (lit.[6] mp 180-182 °C); ^{1}H NMR ($CDCl_3$) δ 8.96 (dd, 2H, J = 4.2, 1.5 Hz), 8.26 (t, 4H, J = 8.4 Hz), 8.15 (s, 2H), 8.12 (dd, 2H, J = 8.7, 1.8 Hz), 7.48 (dd, 2H, J = 8.4, 4.5 Hz).

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