Supporting Information

New Access to 2,3-Disubstituted Quinolines through Cyclization of o-Alkynylisocyanobenzenes

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Experimental

General. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-2000 spectrometer (300 MHz for ^{1}H NMR) at ambient temperature. ^{1}H NMR data are reported as follows: chemical shift in ppm downfield from tetramethylsilane (in δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz), and integration. ^{13}C chemical shift are reported in ppm downfield from tetramethylsilane (in δ). All ^{13}C spectra were obtained with complete proton decoupling. High resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer.

Solvents were distilled from the indicated drying agents: THF (Na/benzophenone); methanol (Mg/I_2); Et_2O (Na/benzophenone); diethylamine (CaH_2); triethylamine (CaH_2); DMF (CaH_2).

o-Iodoaniline (TCI), trimethylsilylacetylene (TCI), phosphorous oxychloride (Wako), potassium carbonate (Wako), and diethyl malonate (Aldrich) were used as received.

Copper(I) iodide was purified by recrystallization from saturated aqueous NaI before use.[1]

Tetrakis(triphenylphosphine)palladium(0),[2] dichlorobis(triphenylphosphine)nickel(II),[3] and acetic formic anhydride[4]

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[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals* (third edition); Pergamon; Oxford; 1988; p.322.
[2] Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
[3] Venanzi, L. M. *J. Chem. Soc.* **1958**, 719.

were prepared according to literature methods.

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring.

Representative method for preparation of *o*-alkynylisocyanobenzenes 3. **Synthesis of 2-(trimethylsilylethynyl)-1-isocyanobenzene (3a).** To a mixture of $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) and CuI (58 mg, 0.30 mmol) in DMF (5 mL) were added 2-iodoaniline (**1**) (6.6 g, 30 mmol), trimethylsilylacetylene (5.1 mL, 36 mmol), and diethylamine (25 mL) at room temperature. The mixture was stirred at room temperature for 6 h. To the mixture was added hydrochloric acid (0.5 M, 60 mL). After extraction with ether, the organic phase was washed with saturated sodium bicarbonate and dried over sodium sulfate. Filtration followed by evaporation of the solvent gave 2-(trimethylsilylethynyl)aniline (**2a**) (5.8 g, quant.). The material was used for the next step without further purification.

2-(Trimethylsilylethynyl)aniline (**2a**) (2.4 g, 12.7 mmol) was dissolved in THF (50 mL). To this was added acetic formic anhydride (1.0 mL, 15.3 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 12 h. Evaporation of the volatile material gave 2-(trimethylsilylethynyl)formanilide (2.8 g, quant.). The material was used for the next step without further purification.

To a mixture of the formanilide (2.67 g, 12.3 mmol) and triethylamine (8.60 mL, 62 mmol) in THF (40 mL) was added phosphorous oxychloride (1.37 mL, 14.7 mmol) dropwise at 0°C over 15 min. The mixture was stirred at 0°C for 2 h. To the mixture was added saturated aqueous sodium bicarbonate (50 mL) at 0°C. Extraction with ethyl acetate followed by column chromatography on Florisil (hexane : ether = 3 : 1) afforded **3a** (2.28 g, 93%) as blackish yellow oil. The compound **3a** is known in the literature (Ref. 8 in the main text).

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[4] Krimen, L. I. *Org. Synth.* Vol. VI, p.8. Muramatsu, I.; Murakami, M.; Yoneda, T.; Hagitani, A. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 244.

General method for the reaction of 3 with methanol giving 4a-e. A solution of 2-alkynylisocyanobenzene (0.50 mmol) in methanol (0.5 mL) was stirred for 20 h at 50°C. After evaporation of the solvent, the residue was purified by column chromatography on silica gel or bulb-to-bulb distillation. Only for the preparation of **4a**, potassium carbonate (69 mg, 0.50 mmol) was also used.

3-*t*-Butyl-2-methoxyquinoline (4b). The compound was isolated by column chromatography on silica gel (hexane : ether = 1 : 1). ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 4.11 (s, 3H), 7.34 (t, J = 8.1 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.3, 34.2, 52.9, 123.8, 125.5, 126.4, 127.3, 128.6, 133.8, 134.3, 145.0, 161.3. IR (neat) 2968, 1744, 758 cm^{-1}. Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.38; H, 7.87; N, 6.47.

3-Cyclohexyl-2-methoxyquinoline (4c). The compound was isolated by column chromatography on silica gel pretreated with triethylamine (hexane : ether = 3 : 1). ^{1}H NMR ($CDCl_3$) δ 1.28-1.53 (m, 5H), 1.79-1.84 (m, 1H), 1.88-1.92 (m, 2H), 1.98-2.02 (m, 2H), 2.88-3.02 (m, 1H), 4.12 (s, 3H), 7.36 (t, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.79 (s, 1H), 7.85 (t, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.3, 26.8, 32.7, 37.3, 53.4, 123.8, 125.7, 126.7, 127.0, 128.4, 132.1, 133.5, 144.9, 160.8. IR (neat) 2940, 1742, 760 cm^{-1}. Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.91; H, 8.09; N, 5.79.

2-Methoxy-3-(methoxymethyl)quinoline (4d). The compound was isolated by bulb-to-bulb distillation (110-135°C/0.15 mmHg). ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 4.10 (s, 3H), 4.57 (s, 2H), 7.37 (t, J = 8.1 Hz, 1H), 7.59 (t, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 53.4, 58.6, 69.3, 122.7, 124.0, 125.2, 126.9, 127.4, 129.0, 135.5, 145.8, 160.0. IR (neat) 2992, 1750, 762 cm^{-1}. HRMS Calcd. for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0948.

2-Methoxy-3-phenylquinoline (4e). The compound was isolated by column chromatography on silica gel pretreated with triethylamine (hexane : ether =

10 : 1). ^{1}H NMR ($CDCl_3$) δ 4.17 (s, 3H), 7.39-7.71 (m, 7H), 7.79 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.02 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 53.6, 124.2, 125.5, 126.5, 126.9, 127.4, 127.7, 128.2, 129.3, 129.4, 136.8, 138.0, 145.9, 159.8. IR (neat) 3068, 2760, 1740 cm^{-1}. Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.89; H, 5.70; N, 5.75.

General method for the reaction of 3 with diethylamine giving 5a-f. A mixture of 2-alkynylisocyanobenzene (1.0 mmol) and diethylamine (5 mL) was stirred for 24 h at room temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

2-Diethylamino-3-trimethylsilylquinoline (5a). For the synthesis of this compound, the reaction was carried out in the presence of potassium carbonate (0.5 mmol) under otherwise identical conditions. The compound was isolated by column chromatography on silica gel (hexane : EtOAc = 5 : 1). ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.25 (broad, 6H), 3.40 (broad, 4H), 6.84 (d, J = 7.8 Hz, 1H), 6.89 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 0.0, 12.3, 15.0, 39.5, 45.5, 96.3, 104.6, 116.3, 121.0, 121.8, 129.4, 133.4, 152.8, 154.8. IR (neat) 2980, 2156, 1745, 760 cm^{-1}. Anal. Calcd. for $C_{16}H_{24}N_2Si$: C, 70.53; H, 8.88; N,10.28. Found: C, 70.82; H, 9.03; N, 10.35.

3-*t*-Butyl-2-diethylaminoquinoline (5b). The compound was isolated by column chromatography on Florisil (ether). ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 6H), 1.54 (s, 9H), 3.10 (broad, 4H), 7.43 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 8.10 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8, 31.2, 48.4, 76.6, 125.4, 126.9, 127.2, 127.7, 128.3, 135.0, 141.2. IR (neat) 2976, 1748, 760 cm^{-1}. Anal. Calcd. for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N,10.93. Found: C, 79.84; H, 9.67; N, 10.73.

3-Cyclohexyl-2-diethylaminoquinoline (5c). The compound was isolated by column chromatography on silica gel pretreated with triethylamine (hexane : EtOAc = 5 : 1). ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 6.9 Hz, 6H), 1.41-1.45 (m, 5H),

1.80-1.92 (m, 5H), 2.90-3.02 (m, 1H), 3.28 (q, *J* = 6.9 Hz, 4H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.84 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.3, 25.7, 26.3, 27.2, 27.5, 34.5, 38.1, 46.2, 124.0, 126.0, 126.7, 127.5, 128.1, 134.2, 137.4, 145.5, 161.0. IR (neat) 2980, 1740, 760 cm^{-1}. Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.80; H, 9.38; N, 9.84.

2-Diethylamino-3-(methoxymethyl)quinoline (5d). The compound was isolated by column chromatography on silica gel pretreated with triethylamine (hexane : EtOAc = 10 : 1).^{1}H NMR ($CDCl_3$) δ 1.19 (t, *J* = 6.9 Hz, 6H), 3.39 (q, *J* = 6.9 Hz, 4H), 3.48 (s, 3H), 4.56 (s, 2H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.2, 45.0, 58.3, 71.0, 123.7, 124.9, 126.0, 127.2, 127.3, 128.9, 137.1, 146.5, 159.5. IR (neat) 2976, 1750, 770 cm^{-1}. HRMS Calcd. for $C_{15}H_{20}N_2O$: 244.1576. Found: 244.1572.

2-Diethylamino-3-phenylquinoline (5e). The compound was isolated by column chromatography on silica gel (hexane : ether = 5 : 1).^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 6.9 Hz, 6H), 3.33 (q, *J* = 6.9 Hz, 4H), 7.31-7.66 (m, 7H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.82 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 12.7, 44.1, 123.3, 124.7, 127.0, 127.1, 128.0, 128.6, 129.0, 129.1, 138.8, 140.9, 146.6, 158.3. IR (neat) 2980, 1740, 760 cm^{-1}. Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.51; H, 7.32; N, 9.95.

3-(1-Cyclohexenyl)-2-diethylaminoquinoline (5f). The compound was isolated by column chromatography on silica gel pretreated with triethylamine (hexane : ether = 5 : 1).^{1}H NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 6H), 1.69-1.79 (m, 4H), 2.18-2.28 (m, 2H), 2.30-2.38 (m, 2H), 3.54 (q, *J* = 7.2 Hz, 4H),5.86-5.96 (m, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.0, 22.1, 22.9, 25.7, 27.4, 43.6, 122.9, 124.6, 125.0, 126.8, 126.9, 128.5, 131.6, 137.0, 139.4, 146.4, 157.5. IR (neat) 2976, 1760, 770 cm^{-1}. Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.45; H, 8.67; N, 9.81.

Synthesis of 2-Diethylaminoquinazoline (7) (eq 2). A mixture of 2-isocyanobenzonitrile (**6**) (126 mg, 1.0 mmol), diethylamine (1 mL), and potassium carbonate (138 mg, 1.0 mmol) was stirred for 18 h at room temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1, pretreated with triethylamine) to give **7** (201 mg, quant.). The CAS number for **7**: [48149-11-7].

Synthesis of 2,9-dimethoxy-1,10-phenanthroline (9) (eq 3). According to the general procedure for the synthesis of methoxyquinolines, the title compounds was prepared from **8** (40 mg, 0.13 mmol), potassium carbonate (17 mg, 0.13 mmol), and methanol (1.0 mL) at room temperature. The title compound was isolated by column chromatography on silica gel (ether). ^{1}H NMR ($CDCl_3$) δ 4.28 (s, 6H), 7.08 (d, J = 9.0 Hz, 2H), 7.61 (s, 2H), 8.08 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 53.3, 113.5, 123.4, 125.2, 139.1, 143.1, 162.8. IR (neat) 2940, 1718, 848 cm^{-1}. HRMS Calcd. for $C_{14}H_{12}N_2O_2$: 240.0899. Found: 240.0903.

Procedure for the cross-coupling reaction of 4a with Grignard reagents (eq 4). To a mixture of $NiCl_2(PPh_3)_2$ (131 mg, 0.20 mmol) and a Grignard reagent (4.0 mmol) in ether (2 mL) was added **1a** (318 mg, 2.0 mmol) at room temperature. The mixture was stirred under reflux for 4 days. To the mixture was added water. The organic material was extracted with ether. Column chromatography on silica gel afforded the corresponding coupling product. The CAS number for **10a**: [91-63-4]; for **10b**: [24667-94-5].

Synthesis of diethyl (3-*t*-butylquinolin-2-yl)malonate (11). To a suspension of NaH (48 mg, 2.0 mmol) in THF (2.0 mL) was added diethyl malonate (0.33 mL, 2.2 mmol) dropwise at room temperature. The mixture was stirred for 10 min. To this was added 2-(*t*-butylethynyl)isocyanobenzene (**3b**) (182 mg, 1.0 mmol) at room temperature. The mixture was stirred at room

temperature for 40 h. Extractive workup followed by column chromatography on silica gel (hexane : ether = 1:1) afforded the title compound (298 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 6H), 1.51 (s, 9H), 4.18-4.36 (m, 4H), 5.56 (s, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.9, 31.1, 34.3, 59.6, 61.7, 126.7, 127.3, 127.4, 128.9, 129.1, 133.4, 141.2, 145.9, 153.1, 168.1. IR (nujol) 2944, 1756, 770 cm^{-1}. Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.81; H, 7.15; N, 3.78.