Synthesis of quinoxaline derivatives via copper(I)-catalyzed cross-coupling reaction of 1,2-dihalobenzenes with N, N'-disubstituted ethane-1,2-diamines under ligand- and solvent-free conditions

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1. General Information

All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. All melting points are uncorrected. All starting substrates were prepared according to the known literatures. The NMR spectra were recorded in CDCl₃ on a 400 MHz instrument with TMS as internal standard. High-resolution mass spectra (HRMS) were obtained with a Q-TOF Premier (ESI). TLC was carried out with 0.2 mm thick silica gel plates (GF254). Visualization was accomplished by UV light. Column chromatography was hand packed with silica gel (200-300 mesh). All reactions were carried out in an over-dried Schlenk tube equipped with a magnetic stir bar.

2. General procedure for the synthesis of quinoxaline derivatives

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, CuI (0.05 mmol), 1,2-diiodobenzenes or 1,8-diiodonaphthalene (0.5 mmol) and DBU (1.0 mmol). The tube was placed under vacuum for twenty minutes and backfilled with N₂. Then N, N'-disubstituted-1,2-diamines (1.0 mmol) was added through a syringe. The reaction mixture was stirred at 110 °C for 24 h. The reaction was monitored by TLC. When 1,2-diiodobenzenes or 1,8-diiodonaphthalene consumed completely, the reaction was stopped and purified directly by column chromatography on silica gel to give the pure products (petroleum ether/EtOAc v/v = 10/1).

3. General Data

\[ \text{1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (1c)} \]
Brown oil; 63mg; 78% yield; \(^1\)H NMR (400M Hz, CDCl₃/TMS): \(\delta 6.70-6.69 \text{ (m, 2H)}\), \(\delta 6.56-6.54 \text{ (m, 2H)}\), \(\delta 3.34 \text{ (s, 4H)}\), \(\delta 2.88 \text{ (s, 6H)}\); \(^13\)C NMR (100M Hz, CDCl₃/TMS): \(\delta 136.84, 118.29, 110.76, 50.06, 39.37\).

\[ \text{1,4,6-trimethyl-1,2,3,4-tetrahydroquinoxaline (2c)} \]
Brown oil; 62mg; 70% yield; \(^1\)H NMR (400M Hz, CDCl₃/TMS): \(\delta 6.51-6.46 \text{ (m, 2H)}\), \(\delta 6.38 \text{ (s, 1H)}\), \(\delta 3.37-3.34 \text{ (m, 2H)}\), \(\delta 3.29-3.27 \text{ (m, 2H)}\), \(\delta 2.88 \text{ (s, 3H)}\), \(\delta 2.85 \text{ (s, 3H)}\), \(\delta 2.26 \text{ (s, 3H)}\); \(^13\)C NMR (100M Hz, CDCl₃/TMS): \(\delta 136.95, 134.66, 127.82, 118.26, 111.88, 111.18, 50.28, 50.22, 39.68, 39.22, 21.09\); HRMS (ESI): \(m/z \text{ calcd for C}_{11}H_{17}N_{2} \ [M+H]^+: 177.1392\), found: 177.1390.
6-isopropyl-1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (3c). Brown oil; 66mg; 65% yield; $^1$H NMR (400M Hz, CDCl3/TMS): $\delta$ 6.57 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, 1H), $\delta$ 6.50 (d, $J = 8.0$ Hz, 1H), $\delta$ 6.42 (d, $J = 2.0$ Hz, 1H), $\delta$ 3.37-3.35 (m, 2H), $\delta$ 3.31-3.29 (m, 2H), $\delta$ 2.85 (s, 3H), $\delta$ 2.82-2.77 (m, 1H), $\delta$ 1.25 (d, $J = 6.8$ Hz, 6H); $^{13}$C NMR (100M Hz, CDCl3/TMS): $\delta$ 138.98, 136.75, 134.93, 115.38, 110.91, 109.43, 50.28, 50.09, 39.59, 39.40, 33.81, 24.41; HRMS (ESI): m/z calcd for C$_{13}$H$_{21}$N$_2$ [M+H]$^+$: 205.1705, found: 205.1708.

6-(tert-butyl)-1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (4c). Brown oil; 70mg; 64% yield; $^1$H NMR (400M Hz, CDCl3/TMS): $\delta$ 6.72 (d, $J = 8.0$ Hz, 1H), $\delta$ 6.60 (s, 1H), $\delta$ 6.51 (d, $J = 8.0$ Hz, 1H), $\delta$ 3.36-3.32 (m, 4H), $\delta$ 2.92 (s, 3H), $\delta$ 2.87 (s, 3H), $\delta$ 1.33 (s, 9H); $^{13}$C NMR (100M Hz, CDCl3/TMS): $\delta$ 141.02, 136.37, 134.66, 114.65, 110.49, 108.48, 50.33, 50.03, 39.47, 34.19, 31.07; HRMS (ESI): m/z calcd for C$_{14}$H$_{23}$N$_2$ [M+H]$^+$: 219.1861, found: 219.1866.

6-fluoro-1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (5c). Brown oil; 66mg; 73% yield; $^1$H NMR (400M Hz, CDCl3/TMS): $\delta$ 6.40 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), $\delta$ 6.31 (dt, $J_1 = 2.8$ Hz, $J_2 = 8.0$ Hz, 1H), $\delta$ 6.24 (dd, $J_1 = 2.8$ Hz, $J_2 = 11.2$ Hz, 1H), $\delta$ 3.40-3.37 (m, 2H), $\delta$ 3.22-3.20 (m, 2H), $\delta$ 2.91 (s, 3H), $\delta$ 2.89 (s, 3H); $^{13}$C NMR (100M Hz, CDCl3/TMS): $\delta$ 158.44, 156.12, 138.17, 138.07, 132.86, 111.00, 110.90, 102.37, 102.15, 98.18, 97.91, 50.05, 49.85, 39.96, 39.03. HRMS (ESI): m/z calcd for C$_{10}$H$_4$FN$_2$ [M+H]$^+$: 181.1141, found: 181.1149.

1,4-dimethyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxaline (6c)$^2$. Brown oil; 78mg; 68% yield; $^1$H NMR (400M Hz, CDCl3/TMS): $\delta$ 6.94 (d, $J = 8.0$ Hz, 1H), $\delta$ 6.65 (s, 1H), $\delta$ 6.47 (d, $J = 8.0$ Hz, 1H), $\delta$ 3.43-3.40 (m, 2H), $\delta$ 3.33-3.31 (m, 2H), $\delta$ 2.91 (s, 3H), $\delta$ 2.89 (s, 3H); $^{13}$C NMR (100M Hz, CDCl3/TMS): $\delta$ 139.14, 136.19, 126.73, 124.05, 119.57, 119.26, 118.94, 118.60, 115.73, 115.69, 115.65, 115.60, 108.89, 106.67, 106.63, 106.60, 106.56, 49.60, 49.25, 39.30, 39.04.
1,4-dimethyl-6-(trifluoromethoxy)-1,2,3,4-tetrahydroquinoxaline (7c). Brown oil; 81mg; 66% yield; $^1$H NMR (400M Hz, CDCl$_3$/TMS): δ 6.50 (d, $J$ = 8.0 Hz, 1H), δ 6.40 (d, $J$ = 8.0 Hz, 1H), δ 6.33 (s, 1H), δ 3.38-3.36 (m, 2H), δ 3.30-3.28 (m, 2H), δ 2.86 (s, 3H), δ 2.85 (s, 3H); $^{13}$C NMR (100M Hz, CDCl$_3$/TMS): δ141.78, 137.44, 135.27, 124.71, 122.17, 119.64, 117.08, 110.01, 109.56, 103.83, 49.77, 49.58, 39.50, 39.11; HRMS (ESI): m/z calcd for C$_{11}$H$_{14}$F$_3$N$_2$O [M+H]$^+$: 247.1058, found: 47.1057.

5,7-dichloro-1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (8c). Brown oil; 84mg; 73% yield; $^1$H NMR (400M Hz, CDCl$_3$/TMS): δ 6.69 (d, $J$ = 2.4 Hz, 1H), δ 6.53 (d, $J$ = 2.0 Hz, 1H), δ 3.27-3.25 (m, 2H), δ 3.08-3.06 (m, 2H), δ 2.97 (s, 3H), δ 2.72 (s, 3H); $^{13}$C NMR (100M Hz, CDCl$_3$/TMS): δ 142.50, 130.67, 129.08, 128.90, 117.03, 109.53, 48.80, 43.60, 43.23, 39.16; HRMS (ESI): m/z calcd for C$_{10}$H$_{13}$Cl$_2$N$_2$ [M+H]$^+$: 231.0456, found: 231.0455.

1,4-diethyl-1,2,3,4-tetrahydroquinoxaline (9c). Brown oil; 20mg; 21% yield; $^1$H NMR (400M Hz, CDCl$_3$/TMS): δ 6.63 (m, 2H), δ 6.57 (m, 2H), δ 3.35-3.29 (m, 8H), δ 1.15 (t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (100M Hz, CDCl$_3$/TMS): δ 135.23, 117.70, 111.10, 46.61, 45.48, 10.53.

1,4-dimethyl-1,2,3,4-tetrahydronaphtho[1,8-ef][1,4]diazepine (11c). Yellow solid; Mp: 113-115 °C; 69mg; 65% yield; $^1$H NMR (400M Hz, CDCl$_3$/TMS): δ 7.27-7.26 (m, 4H), δ 6.68 (t, $J$ = 4.0 Hz, 2H), δ 3.35 (s, 4H), δ 3.01 (s, 6H); $^{13}$C NMR (100M Hz, CDCl$_3$/TMS): δ 149.29, 136.92, 125.84, 123.69, 120.55, 110.16, 57.55, 42.21.

1,4-diethyl-1,2,3,4-tetrahydronaphtho[1,8-ef][1,4]diazepine (12c). Yellow solid; Mp: 120-124 °C; 24mg; 20% yield; $^1$H NMR (400M Hz, CDCl$_3$/TMS):
δ 7.23-7.19 (m, 4H), δ 6.69 (d, $J = 6.4$ Hz, 2H), δ 3.39-3.33 (m, 8H), δ 1.27 (t, $J = 7.0$ Hz, 6H); $^{13}$C NMR (100M Hz, CDCl$_3$/TMS): δ 148.86, 137.25, 125.69, 123.61, 120.00, 110.94, 53.98, 47.42, 29.86, 12.93; HRMS (ESI): $m/z$ calcd for C$_{16}$H$_{21}$N$_2$ [M+H]$^+$: 241.1705, found: 241.1701.

4. Copies of NMR spectra
5. Reference