Molecular Iodine-Catalyzed Benzylic sp$^3$ C–H Bond Amination for Synthesis of 2-Arylquinazolines from 2-Aminobenzaldehyde, 2-Aminobenzophenone and 2-Aminobenzyl Alcohol

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General Information

All chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC) with a flame ionization detector (FID) with a capillary column (30 m × 0.25 mm × 0.25 μm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. GC-MS (Rtx-17, 30 m × 25 mm ID, film thickness (df = 0.25 μm) (column flow 2 mL min⁻¹, 80 °C to 240 °C at 10 °C min⁻¹ rise) was used for the mass analysis of the products. Products were purified by column chromatography on 100-200 mesh silica gel. The ¹H NMR spectras were recorded on 400 MHz and 500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The ¹³C NMR spectras were recorded on 100 MHz and 125 MHz and Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (J) values were reported in hertz (Hz). Splitting patterns of proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet) in ¹H NMR spectroscopic analysis. The products were confirmed by GCMS, ¹H and ¹³C NMR spectroscopy analysis.

General procedure for the synthesis of 2-arylquinazolines (3)

An oven dried 25 mL round bottom flask was charged with 2-aminobenzaldehyde/2-aminobenzoketone (1, 0.5 mmol) or 2-aminobenzyl alcohol (4a, 0.5 mmol) with benzylamine (2, 1.5 mmol) and molecular iodine (10 mol%). It was then stirred at 130 °C for 3-15 h under oxygen balloon. The reaction was monitored by TLC. After the completion of reaction, reaction mixture was cooled to room temperature. The obtained crude product was further purified by column chromatography.

Optimization study for the reaction of 2-aminobenzophenone with benzylamine

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</table>

*Reaction Conditions: 2-aminobenzophenone (1d, 0.5 mmol), benzylamine (2a, 1.5 mmol). *GC yield.
Analytical data

$^1$H NMR, $^{13}$C NMR and GC-MS analytical data of compounds (3)

6-chloro-2-(4-methoxyphenyl)quinazoline (3b)

Yellow solid; mp 168–170 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.32 (s, 1H), 8.54–8.52 (m, 2H), 7.95 (d, $J$ = 9.0 Hz, 1H), 7.85 (d, $J$ = 2.1 Hz, 1H), 7.77 (dd, $J$ = 9.0, 2.3 Hz, 1H), 7.02 (d, $J$ = 8.4 Hz, 2H), 3.88 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.0, 161.1, 159.4, 149.3, 135.0, 132.2, 130.2, 130.1, 125.8, 123.7, 114.0, 55.4; GCMS (EI, 70 eV): m/z (%): 270 (M, 100), 272 (M+2, 33), 255 (24), 227 (14), 192 (10).

6-chloro-2-(4-fluorophenyl)quinazoline (3c)

Pale yellow solid; m.p. 190–192 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.35 (s, 1H), 8.61–8.57 (m, 2H), 7.99 (d, $J$ = 1.20 Hz, 1H), 7.88 (d, $J$ = 4.0 Hz, 1H), 7.82–7.80 (m, 1H), 7.18 (t, $J$ = 8.5 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.0, 163.5, 160.3, 159.5, 149.1, 135.2, 132.8, 130.7, 130.6, 130.3, 125.8, 123.9, 115.7, 115.5; GCMS (EI, 70 eV): m/z (%): 258 (M, 100), 260 (M+2, 33), 231 (38), 196 (27), 179 (15).

2-phenylquinazoline (3d)

Yellow solid; mp 100–102 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.45 (s, 1H), 8.61–8.59 (m, 2H), 8.07 (d, $J$ = 8.4 Hz, 1H), 7.91–7.86 (m, 2H), 7.58 (t, $J$ = 7.5 Hz, 1H), 7.54–7.47 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.05, 160.5, 150.8, 138.02, 134.1, 130.6, 128.6, 128.56, 127.3, 127.12, 123.6; GCMS (EI, 70 eV): m/z (%): 206 (M, 100), 179 (44), 103 (20).

2-(3-methoxyphenyl)quinazoline (3i)

Yellow solid; mp 82–84 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.45 (s, 1H), 8.21–8.16 (m, 2H), 8.08 (d, $J$ = 8.4 Hz, 1H), 7.93–7.89 (m, 2H), 7.62–7.58 (m, 1H), 7.43 (t, $J$ = 8.0 Hz, 1H), 7.06–7.03 (m, 1H), 3.94 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.7, 160.4, 160.0, 150.7, 139.5, 134.1, 129.6, 128.7, 127.3, 127.1, 123.7, 121.1, 117.3, 112.9, 55.5; GCMS (EI, 70 eV): m/z (%): 236 (M, 100), 207 (45), 179 (25), 103 (18).

2-(thiophen-2-yl)quinazoline (3n)

Yellow solid; mp 135–137 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.32 (s, 1H), 8.13 (dd, $J$ = 4.0, 1.2 Hz, 1H), 7.98 (d, $J$ = 8.9 Hz, 1H), 7.86–7.82 (m, 2H), 7.55–7.49 (m, 2H), 7.17 (dd, $J$ = 5.0, 3.7 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.5, 157.8, 150.6, 143.8, 134.3, 129.9, 129.2, 128.4, 128.1, 127.2, 127.0, 123.3; GCMS (EI, 70 eV): m/z (%): 212 (M, 100), 185 (29), 141 (10), 76 (7).

6,8-dibromo-2-(4-fluorophenyl)quinazoline (3p)

Yellow solid; mp 216–218 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.30 (s, 1H), 8.69–8.65 (m, 2H), 8.27 (d, $J$ = 4.0 Hz, 1H), 8.02 (d, $J$ = 4.0 Hz, 1H), 7.22–7.17 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.3, 165.2, 163.8, 161.0, 159.9, 147.0, 140.2, 133.3, 131.1, 131.05, 128.8, 125.4, 124.9, 120.2, 115.9, 115.6; GCMS (EI, 70 eV): m/z (%): 384 (M+2, 48), 382 (M, 100), 380 (52), 355 (25), 274 (10), 195 (23).

2,4-diphenylquinazoline (3q)
White solid; m.p. 117–119 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.69 (d, $J = 8.1$ Hz, 2H), 8.15 (d, $J = 8.4$ Hz, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.89–7.85 (m, 3H), 7.60–7.58 (m, 3H), 7.54–7.47 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 168.3, 160.2, 138.2, 137.7, 133.5, 130.5, 130.2, 129.9, 129.2, 128.7, 128.5, 127.0, 121.7; GCMS (EI, 70 eV): m/z (%): 282 (M, 65), 281 (100), 203 (8), 178 (8), 151 (6), 141 (7), 77 (8).

6-chloro-2,4-diphenylquinazoline (3r)

White solid; m.p. 193–195 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.70–8.68 (m, 2H), 8.12–8.10 (m, 2H), 7.88 (dd, $J = 6.4$, 3.0 Hz, 2H), 7.83 (dd, $J = 9.0$, 2.2 Hz, 1H), 7.65–7.62 (m, 3H), 7.55–7.53 (m, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.6, 160.5, 150.5, 137.8, 137.1, 134.5, 132.6, 130.9, 130.8, 130.2, 130.1, 128.8, 128.7, 128.6, 125.80, 122.2; GCMS (EI, 70 eV): m/z (%): 318 (M+2, 46), 316 (M, 82), 315 (92), 283 (20), 281 (100), 178 (13), 151 (14), 140 (14), 77 (12).

References:

1. Wang, H.; Chen, H.; Chen, Y.; Deng, G. –J. Org. Biomol. Chem. 2014, 12, 7792. (Reference for compounds 3a, 3e, 3f, 3g, 3h, 3m)


Copies of $^1$H NMR, $^{13}$C NMR and GC-MS spectras

$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 6-chloro-2-(4-methoxyphenyl)quinazoline (3b)
$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 6-chloro-2-(4-fluorophenyl)quinazoline (3c)
$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 2-phenylquinazoline (3d)
$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 2-(3-methoxyphenyl)quinazoline (3i)
$^{1}H$ NMR, $^{13}C$ NMR and GC-MS spectra of 2-(thiophen-2-yl)quinazoline (3n)
$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 6,8-dibromo-2-(4-fluorophenyl)quinazoline (3p)
$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 2,4-diphenylquinazoline (3q)
$^1$H NMR, $^{13}$C NMR and GC-MS spectra of 6-chloro-2,4-diphenylquinazoline (3r)