Copper-catalyzed synthesis of 2-aminobenzothiazoles from 2-iodophenyl isocyanides, Potassium sulfide and amines

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1) General Information

NMR spectra of the products 3a-3v were obtained using Bruker Avance-500 instruments, calibrated to TMS (1H NMR spectra) and CD(H)Cl3 (13C NMR spectra) as the internal reference (0.00 ppm for 1H NMR spectra and 77.00 ppm for 13C NMR spectra). High-resolution massspectra. (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization). Reactions were monitored by thin-layer chromatography. Column chromatography (petroleum ether/ethyl acetate) was performed on silica gel(200-300 mesh).

2) Synthesis of Starting Materials Preparation of 1a-1j:

\[
\begin{align*}
\text{R} & \quad \text{HCOOH, Ac}_2\text{O} \\
\text{CH}_2\text{Cl}_2, \text{rt}, 2 \text{ h} & \quad \text{NHCHO} \\
\text{R} & \quad \text{PPh}_3, \text{I}_2, \text{Et}_3\text{N} \\
\text{CH}_2\text{Cl}_2, \text{rt}, 1 \text{ h} & \quad \text{NC}
\end{align*}
\]

General Procedure for the Synthesis of o-iodoformanilides\(^1\)

To formic acid (2.41 mL, 63.9 mmol) was added acetic anhydride (2.16 mL, 22.8 mmol) and the mixture was stirred at room temperature. After stirring for 10 min, to the mixture was added the solution of o-iodoaniline (3.99 g, 18.3 mmol) in CH2Cl2 (60 mL) and the mixture was stirred at room temperature. After stirring for 2 h, the mixture was concentrated under reduced pressure to give o-iodoformanilides (4.42 g, 98%) as a white solid.

General Procedure for the Synthesis of 2-iodophenyl isocyanides\(^2\)

To a stirred solution of formamide 1 (1.0 mmol) and I2 (381 mg, 1.5 mmol) in CH2Cl2 (3 mL) was added Ph3P (394 mg, 1.5 mmol), followed by the dropwise addition of Et3N (415 μL, 301 mg, 3 mmol). The mixture was stirred at r.t. until the consumption of the formamide was complete (TLC monitoring, typically 1 h), and then diluted with CH2Cl2 (10 mL) and washed with ice-cold sat. aq Na2S2O3 solution (10 mL). The aq phase was extracted with CH2Cl2 (2 × 10 mL). Each portion of the organic phase was sequentially washed with deionized H2O (10 mL) and brine (10 mL), dried over anhydrous Na2SO4, and filtered. The combined organic phase was concentrated under reduced pressure and purified by column chromatography (silica
gel, typically PE as the eluent) to give the corresponding 2-iodophenyl isocyanides

3) Typical Procedures

\[
\text{R}^1\text{N} = \text{Cu}(10 \text{ mol%}) \rightarrow \text{DMF, } 100 \, ^\circ\text{C}
\]

To a schlenk tube were added 2-iodophenyl isocyanides (0.3 mmol), K2S (3equiv), amines (0.3 mmol), CuCl (10 mol%), 1,10-Phen (20 mol%), and DMF (2 mL). the mixture was stirred at 100 °C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by TLC. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted in ethyl acetate, and washed with water. The aqueous phase was re-extracted with ethylacetate. The combined organic extracts were dried over Na2SO4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate as eluent to afford the desired product.

4) Characterization Data

2-(piperidin-1-yl)benzo[d]thiazole(3a): The product was purified by flash chromatography to give 62 mg (95%) as a white solid. 1H NMR (CDCl3, 500 MHz) \( \delta = 7.56 \) (d, \( J = 8.0 \) Hz, 1H), 7.53 (d, \( J = 8.5 \) Hz, 1H), 7.26 (t, \( J = 8.0 \) Hz, 1H), 7.03 (t, \( J = 7.5 \) Hz, 1H), 3.58 (s, 4H), 1.66 (s, 6H). 13C NMR (CDCl3, 125 MHz) \( \delta = 168.8, 152.8, 130.5, 125.8, 121.0, 120.5, 118.7, 49.5, 25.2, 24.1. \)

2-(pyrrolidin-1-yl)benzo[d]thiazole(3b): The product was purified by flash chromatography to give 60 mg (98%) as a yellow solid. 1H NMR (CDCl3, 500 MHz) \( \delta = 7.58 \) (t, \( J = 8.0 \) Hz, 2H), 7.27 (t, \( J = 7.5 \) Hz, 1H), 7.02 (t, \( J = 7.5 \) Hz, 1H), 3.54 (t, \( J = 6.5 \) Hz, 4H), 2.03-2.01 (m, 4H). 13C NMR (CDCl3, 125 MHz) \( \delta = 165.2, 153.0, 130.5, 125.8, 120.5(2\text{C}), 118.4, 49.4, 25.5. \)
N,N-diethylbenzo[d]thiazol-2-amine (3c): The product was purified by flash chromatography to give 58 mg (94%) as a colourless oil. $^1$H NMR (CDCl$_3$, 500 MHz) δ = 7.55 (t, $J = 8.0$ Hz, 2H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 3.57-3.52 (m, 4H), 1.26 (t, $J = 7.0$ Hz, 6H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ = 167.2, 153.2, 130.5, 125.7, 120.6, 120.4 118.4, 45.3, 12.8.

N,N-diisopropylbenzo[d]thiazol-2-amine (3d): The product was purified by flash chromatography to give 48 mg (68%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) δ = 7.56 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 4.01-3.93 (m, 2H), 1.41 (d, $J = 7.0$ Hz, 12H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ = 165.4, 153.0, 129.7, 125.5, 120.4, 120.0, 118.5, 50.8, 20.3.

4-(benzo[d]thiazol-2-yl)morpholine (3e): The product was purified by flash chromatography to give 62 mg (94%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) δ = 7.61 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 8.0$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 3.81 (t, $J = 8.0$ Hz, 1H), 3.60 (t, $J = 8.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ = 168.9, 152.4, 130.5, 126.0, 121.6, 120.7, 119.2, 66.2, 48.4.

2-(thiazolidin-3-yl)benzo[d]thiazole (3f): The product was purified by flash chromatography to give 55 mg (82%) as a yellow solid. mp: 105.3-107.1 °C. $^1$H NMR (CDCl$_3$, 500 MHz) δ = 7.61 (t, $J = 8.0$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 4.69 (s, 2H) 3.88 (t, $J = 6.0$ Hz, 2H), 3.15 (t, $J = 6.0$ Hz, 2H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ = 165.0, 152.1, 130.6, 126.1, 121.7, 120.8, 119.2, 52.6, 51.8, 30.6.
N-allyl-N-methylbenzo[d]thiazol-2-amine (3g): The product was purified by flash chromatography to give 58 mg (95%) as a colourless oil. 

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.57 (t, J = 7.5 \text{ Hz}, 2H), 7.28 (t, J = 8.0 \text{ Hz}, 1H), 7.05 (t, J = 7.5 \text{ Hz}, 1H), 5.90-5.82 (m, 1H), 5.26 (d, J = 7.5 \text{ Hz}, 1H), 5.23 (s, 1H), 4.12 (d, J = 5.5 \text{ Hz}, 2H), 3.14 (s, 3H). \(^1\)C NMR (CDCl\(_3\), 125 MHz) \(\delta = 168.4, 152.8, 131.8, 130.6, 125.9, 121.0, 120.5, 118.7, 117.9, 55.4, 37.6.\) HRMS (ESI) m/z calcd for \(\text{C}_{11}\text{H}_{13}\text{N}_{2}\text{S}^+\) (M+H)\(^+\) 205.07940, found 205.07928.

N-benzyl-N-methylbenzo[d]thiazol-2-amine (3h): The product was purified by flash chromatography to give 74 mg (97%) as a yellow solid. 

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.58 (t, J = 8.5 \text{ Hz}, 2H), 7.33-7.27 (m, 6H), 7.05 (t, J = 7.5 \text{ Hz}, 1H), 4.74 (s, 2H), 3.11 (s, 3H). \(^1\)C NMR (CDCl\(_3\), 125 MHz) \(\delta = 168.8, 153.0, 136.3, 130.8, 128.7, 127.6, 127.5, 125.9, 121.0, 120.6, 118.8, 56.4, 37.7.\)

N,N-dibenzylbenzo[d]thiazol-2-amine (3i): The product was purified by flash chromatography to give 84 mg (85%) as a yellow solid. 

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.59 (t, J = 8.0 \text{ Hz}, 2H), 7.34-7.27 (m, 11H), 7.08 (t, J = 7.5 \text{ Hz}, 1H), 4.74 (s, 4H). \(^1\)C NMR (CDCl\(_3\), 125 MHz) \(\delta = 169.0, 153.0, 136.2, 131.0, 128.7, 127.7, 127.6, 126.0, 121.2, 120.6, 119.0, 53.2.\)

2-(3,4-dihydroisoquinolin-2(1H)-yl)benzo[d]thiazole (3j): The product was purified by flash chromatography to give 78 mg (98%) as a white solid. 

\(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta = 7.60 (d, J = 8.0 \text{ Hz}, 2H), 7.30 (t, J = 7.5 \text{ Hz}, 1H), 7.24-7.16 (m, 4H), 7.07 (t, J = 7.5 \text{ Hz}, 1H), 4.80 (s, 2H), 3.85 (t, J = 6.0 \text{ Hz}, 2H), 3.00 (t, J = 6.0 Hz,
$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 168.0, 152.7, 134.2, 132.4, 130.4, 128.5, 126.8, 126.5, 126.3, 125.9, 121.1, 120.6, 118.9, 49.5, 46.1, 28.7.

**N-methyl-N-phenylbenzo[d]thiazol-2-amine (3k):**

The product was purified by flash chromatography to give 40 mg (56%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.62 (d, $J$ = 8.0 Hz, 1H), 7.47 (t, $J$ = 8.0 Hz, 1H), 7.45-7.40 (m, 4H), 7.33 (t, $J$ = 7.5 Hz, 1H), 7.29 (t, $J$ = 7.5 Hz, 1H) 7.06 (t, $J$ = 7.5 Hz, 1H), 3.63 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 168.2, 152.5, 145.7, 131.1, 129.9, 127.4, 125.9, 125.8, 121.7, 120.4, 119.1, 40.4.

**N-methyl-N-(p-tolyl)benzo[d]thiazol-2-amine (3l):**

The product was purified by flash chromatography to give 52 mg (68%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.61 (d, $J$ = 8.0 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.29-7.23 (m, 5H), 7.04 (t, $J$ = 7.0 Hz, 1H), 3.60 (s, 3H), 2.39 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 168.5, 152.6, 143.2, 137.5, 131.1, 130.5, 125.9, 125.8, 121.5, 120.4, 119.0, 40.4, 21.1.

**2-(3,4-dihydroquinolin-1(2H)-yl)benzo[d]thiazole (3m):**

The product was purified by flash chromatography to give 54 mg (68%) as a white solid. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.87 (d, $J$ = 8.0 Hz, 1H), 7.66 (d, $J$ = 8.0 Hz, 1H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.32 (t, $J$ = 8.0 Hz, 1H), 7.22 (t, $J$ = 8.0 Hz, 1H), 7.15 (d, $J$ = 7.0 Hz, 1H), 7.12 (t, $J$ = 7.5 Hz, 1H), 7.07 (t, $J$ = 7.5 Hz, 1H), 4.07 (t, $J$ = 6.0 Hz, 2H), 2.78 (t, $J$ = 6.0 Hz, 2H), 2.06-2.01 (m, 2H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 166.6, 151.6, 140.3, 130.8, 130.2, 129.0, 126.6, 125.9, 124.2, 122.3, 121.1, 120.5, 119.5, 49.3, 27.3, 23.4.
6-methyl-2-(piperidin-1-yl)benzo[d]thiazole (3n): The product was purified by flash chromatography to give 56 mg (80%) as a yellow solid. 

$\text{^1H NMR (CDCl}_3, 500 \text{ MHz)} \delta = 7.42 (d, J = 8.5 \text{ Hz, 1H}), 7.37 (s, 1H), 7.07 (d, J = 8.5 \text{ Hz, 1H}), 3.57 (s, 4H), 2.37 (s, 3H), 1.67 (s, 6H).$ 

$\text{^13C NMR (CDCl}_3, 125 \text{ MHz)} \delta = 168.3, 150.7, 130.6, 130.6, 126.9, 120.6, 118.3, 49.5, 25.2, 24.2, 21.1.$

![Image](image)

6-methoxy-2-(piperidin-1-yl)benzo[d]thiazole (3o): The product was purified by flash chromatography to give 66 mg (89%) as a white solid. 

$\text{^1H NMR (CDCl}_3, 500 \text{ MHz)} \delta = 7.44 (d, J = 8.5 \text{ Hz, 1H}), 7.13 (d, J = 2.5 \text{ Hz, 1H}), 7.07 (dd, J = 9.0 \text{ Hz, 2.5 Hz, 1H}), 3.80 (s, 3H), 3.55 (s, 4H), 1.67 (s, 6H).$ 

$\text{^13C NMR (CDCl}_3, 125 \text{ MHz)} \delta = 167.6, 154.7, 147.1, 131.6, 119.2, 113.3, 105.2, 55.8, 49.6, 25.2, 24.2.$

![Image](image)

N,N-dimethyl-2-(piperidin-1-yl)benzo[d]thiazol-6-amine (3p): The product was purified by flash chromatography to give 68 mg (87%) as a green solid. mp: 113.6-114.2 °C. 

$\text{^1H NMR (CDCl}_3, 500 \text{ MHz)} \delta = 7.42 (d, J = 8.5 \text{ Hz, 1H}), 6.98 (s, 1H), 6.79 (d, J = 8.5 \text{ Hz, 1H}), 3.52 (s, 4H), 2.90 (s, 6H), 1.65 (s, 6H).$ 

$\text{^13C NMR (CDCl}_3, 125 \text{ MHz)} \delta = 166.7, 146.5, 144.8, 132.1, 118.9, 113.0, 104.8, 49.5, 41.6, 25.2, 24.2.$ 

HRMS (ESI) m/z calcd for C$_{14}$H$_{20}$N$_3$S$^+$ (M+H)$^+$ 262.13724, found 262.13724.

![Image](image)

6-fluoro-2-(piperidin-1-yl)benzo[d]thiazole (3q): The product was purified by flash chromatography to give 57 mg (81%) as a yellow solid. 

$\text{^1H NMR (CDCl}_3, 500 \text{ MHz)} \delta = 7.44 (dd, J = 9.0 \text{ Hz, 4.5 Hz, 1H}), 7.28 (dd, J = 8.0 \text{ Hz, 2.5Hz, 1H}), 6.98 (td, J = 9.0 \text{ Hz, 2.5 Hz, 1H}), 3.56 (s, 4H), 1.68 (s, 6H).$ 

$\text{^13C NMR (125 MHz, CDCl}_3) \delta: 168.4 (d, J = 1.6 Hz), 157.9 (d, J = 238.3 Hz), 149.3, 131.3 (d, J = 10.5 Hz), 119.0 (d, J = 8.5 Hz), 113.4 (d, J = 23.5 Hz), 107.2 (d, J = 27.0 Hz), 49.5, 25.2, 24.1.$

![Image](image)
6-chloro-2-(piperidin-1-yl)benzo[d]thiazole(3r): The product was purified by flash chromatography to give 63 mg (83%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta = 7.52$ (s, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 7.21 (dd, $J = 9.0$ Hz, 2.0 Hz, 1H), 3.57 (s, 4H), 1.68 (s, 6H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta = 168.8$, 151.5, 131.8, 126.2, 125.9, 120.2, 119.3, 49.6, 25.2, 24.1. HRMS (ESI) m/z calcd for C$_{12}$H$_{14}$ClN$_2$S$^+$ (M+H)$^+$ 253.05607, found 253.05609.

6-bromo-2-(piperidin-1-yl)benzo[d]thiazole(3s): The product was purified by flash chromatography to give 76 mg (85%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta = 7.67$ (s, 1H), 7.36 (s, 2H), 3.58 (s, 4H), 1.69 (s, 6H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta = 168.8$, 151.9, 132.3, 129.0, 123.0, 129.0, 119.8, 113.2, 49.6, 25.3, 24.1.

2-(piperidin-1-yl)-6-(trifluoromethyl)benzo[d]thiazole(3t): The product was purified by flash chromatography to give 40 mg (47%) as a yellow solid. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta = 7.82$ (s, 1H), 7.55 (d, $J = 8.5$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 3.63 (s, 4H), 1.71 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 170.2$, 155.5, 130.7, 125.7, 123.1 (q, $J = 3.6$ Hz), 122.6 (q, $J = 32.3$ Hz), 118.3, 117.9 (q, $J = 3.9$ Hz), 49.7, 25.3, 24.1.

5-chloro-2-(piperidin-1-yl)benzo[d]thiazole(3u): The product was purified by flash chromatography to give 45 mg (60%) as a yellow solid. mp: 88.2-89.3 oC. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta = 7.49$ (s, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 6.99 (dd, $J = 8.5$ Hz, 2.0 Hz, 1H), 3.58 (s, 4H), 1.68 (s, 6H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta = 169.7$, 154.0, 131.6, 128.8, 121.1, 121.0, 118.6, 49.6, 25.2, 24.1. HRMS (ESI) m/z calcd for C$_{12}$H$_{14}$ClN$_2$S$^+$ (M+H)$^+$ 253.05607, found 253.05609.
5-methoxy-2-(piperidin-1-yl)benzo[4]thiazole(3v): The product was purified by flash chromatography to give 58 mg (78%) as a yellow solid. mp: 102.6-103.6 °C. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 7.40 (d, $J$ = 8.5 Hz, 1H), 7.10 (s, 1H), 6.67 (dd, $J$ = 8.5 Hz, 2.5 Hz, 1H), 3.81 (s, 3H), 3.57 (s, 4H), 1.67 (s, 6H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ = 170.1, 158.9, 154.1, 122.0, 120.7, 109.6, 103.0, 55.4, 49.5, 25.2, 24.2. HRMS (ESI) m/z calcd for C$_{13}$H$_{17}$N$_2$OS$^+$ (M+H)$^+$ 249.10561, found 249.10562.

5) References

6) Scanned $^1$H NMR and $^{13}$C NMR Spectra of All New Compounds