Iodobenzene-Promoted Pd-Catalysed ortho-Directed C–H Activation: The Synthesis of Benzothiazoles via Intramolecular Coupling

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Abstract A series of 2-aminobenzothiazoles were synthesized by a palladium-catalysed oxidative coupling with good yields (62–89%). Iodobenzene was found to be effective as an additive in this intramolecular C–S bond-formation reaction. The directing thiourea group attached to the aryl ring is essential for the activation of the ortho C–H bond.

Key words palladium, iodobenzene, C–H activation, synthesis, amino-benzothiazole

Benzothiazole derivatives represent an extensive group of heterocyclic compounds, several of which have already found application in the medical sphere as antitumor agents1 with selective growth inhibitory properties against human cancer cell lines and in agriculture as plant growth regulators (PGR).2 2-Aminobenzothiazoles can be obtained from human cancer cell lines and in agriculture as plant growth dominated by condensation reactions,3–7 or intramolecular through either intermolecular transformations, which are promoted Pd-catalysed synthesis of benzothiazoles via intramolecular coupling.

The initial study involved palladium-catalysed ortho-directed C–H activation for cross-coupling with iodobenzene. The model reaction we chose was the intermolecular oxidative coupling reaction between 1,1-dimethyl-3-phenyl-thiourea and iodobenzene. Gratifyingly, the intermolecular cross-coupling product was not detected, and the intramolecular cyclisation product (2-aminobenzothiazole) was furnished with a satisfactory yield of 81% (Scheme 1). The oxidative coupling product could not be obtained when no iodobenzene was present. Much less (23%) intramolecular cyclisation product was formed when the reaction was performed under nitrogen, revealing that atmospheric oxygen was the oxidant, and that iodobenzene was a necessary additive.

Encouraged by these results, we began to optimise the reaction conditions. First, a broad screening of copper and palladium catalysts revealed that copper salts were ineffective (Table 1, entries 1–3), but palladium catalysts, for example, PdBr₂, PdCl₂, Pd(OAc)₂ could catalyse the model reaction to give the cyclisation products with 64%, 69% and 81% isolated yields, respectively (Table 1, entries 5, 4 and 8). Various other additives, for example, pyridine, ethyldiisopro-pylamine, KF, CsF and LiCl (Table 1, entries 18–22) that might promote the model reaction were screened, but results showed that these additives were less active than iodobenzene in promoting the intramolecular cyclisation. The additive loading was also investigated, with the optimal additive loading being found to be 0.5 equiv, with 1.0 or 1.5 equiv not improving the yield significantly, and a lower loading (0.1 equiv relative to thiourea) resulted in the yield reducing to 65%.

Substituted iodobenzenes proved to be less reactive than iodobenzene (Table 1, entries 8, 16 and 17). A range of bases, such as NaH, CH₃ONa, NaOH, KOr-Bu, Cs₂CO₃, K₂CO₃, Na₂CO₃ and NEt₃ was surveyed and K₂CO₃ was found to be the most suitable base for this reaction (Table 1, entries 8–15). Solvent and temperature studies showed that DMSO was the best solvent (Table 1, entries 8, 23–25) and 100 °C was the optimal temperature (Table 1, entries 8, 26–28). Under the optimal reaction conditions, various substituted N-arylthioureas (1a–p) underwent cyclisation smoothly, providing the corresponding 2-aminobenzothiazoles (2a–p) in good yields. Substrate scope experiments revealed that arylthioureas bearing electron-withdrawing groups at the para- (1b–h), meta- (1l) and ortho- (1j, 1k) positions cyclised well, giving 73–89% isolated yields (Table 2, entries...
2–8, 9, 10–11). However, electron-donating p-MeO (1l), p-
Me (1m) substituents on the N-aryltiourea slowed the re-
action and decreased the yields (Table 2, entries 12, 13).
Presumably due to steric hindrance from the bulky alkylat-
ed amino group, the cyclisation yields of 2a, 2n and 2o de-
creased in turn, and substrate 1o and 1p, which bear two 
butyl groups on the nitrogen (Table 2, entries 15, 16), af-
forded the products in moderate yields (63% for 1o, 62% for 
1p).

Table 1 Optimization of Model Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>Cu(OAc)₂</td>
<td>Phi</td>
<td>K₂CO₃</td>
<td>DMSO</td>
<td>100</td>
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<tr>
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<td>K₂CO₃</td>
<td>DMSO</td>
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<td>Pd(dba)₂</td>
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<td>DMSO</td>
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<td>54</td>
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<tr>
<td>7</td>
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<td>K₂CO₃</td>
<td>DMSO</td>
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<tr>
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<td>Cs₂CO₃</td>
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<td>100</td>
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</table>

* Reaction conditions: 1a (1.0 mmol), catalyst (10% mmol), additive (0.5 equiv), base (1.0 equiv), O₂ (air), DMSO (2 mL) for 4–6 h.
   "Isolated yield."
**Table 2** Iodobenzene-Promoted Pd-Catalysed Synthesis of Benzothiazoles via an Intramolecular Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>4.0</td>
<td>81</td>
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<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
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<td>77</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>4.0</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
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</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>2i</td>
<td>4.0</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>2j</td>
<td>4.0</td>
<td>74</td>
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In summary, we have presented an iodobenzene-promoted Pd-catalysed synthesis of benzothiazoles via an intramolecular coupling. A series of 2-aminobenzothiazoles was synthesised by a palladium-catalysed oxidative coupling in good yields (62–89%). Iodobenzene was found to be an effective additive in this intramolecular C–S bond-formation reaction. A directing group (thiourea) attached to the aryl ring is essential for activation of the ortho C–H. This protocol is experimentally simple and shows broad substrate scope, affording the 2-aminobenzothiazoles, and could be attractive in the fields of medicinal chemistry and materials science.

All reactions were carried out in dried glassware with septa. All starting materials were purchased from commercial suppliers. DMSO was dried over molecular sieves. Yields refer to isolated compounds estimated to be >95% pure as determined by 1H NMR and capillary GC analysis.

**Typical Procedure for the Preparation of 2-Aminobenzothiazoles in the Presence of Iodobenzene and Palladium Diacetate**

1,1-Dimethyl-3-phenylthiourea (1.0 mmol), Pd(OAc)$_2$ (10% mmol), $K_2$CO$_3$ (1.0 mmol), iodobenzene (0.5 mmol) were placed in a dried tube equipped with a septum and magnetic stirrer bar, and DMSO (2 mL) was then added. The mixture was stirred at 100 °C and the reaction was followed by TLC until the starting material was consumed (ca. 4–6 h). The reaction was cooled to r.t., quenched with sat. NH$_4$Cl solution (5 mL) and then extracted with EtOAc (10 mL). The organic extract was dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography with a solvent system as described below to afford the desired product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
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<td><img src="image1" alt="Substrate 11" /></td>
<td><img src="image2" alt="Product 2k" /></td>
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</tr>
<tr>
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<td><img src="image3" alt="Substrate 12" /></td>
<td><img src="image4" alt="Product 2l" /></td>
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</tr>
<tr>
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<td><img src="image5" alt="Substrate 13" /></td>
<td><img src="image6" alt="Product 2m" /></td>
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<tr>
<td>14</td>
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<td><img src="image8" alt="Product 2n" /></td>
<td>4.0</td>
<td>79</td>
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<tr>
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<td><img src="image9" alt="Substrate 15" /></td>
<td><img src="image10" alt="Product 2o" /></td>
<td>4.0</td>
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<td>16</td>
<td><img src="image11" alt="Substrate 16" /></td>
<td><img src="image12" alt="Product 2p" /></td>
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<td>62</td>
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</table>

$^a$ Reaction conditions: 1 (1.0 mmol), catalyst (10% mmol), additive (0.5 mmol), base (1.0 mmol), O$_2$ (air), DMSO (2 mL) for 4–6 h.

$^b$ Isolated yield.
N,N-Dimethylbenzo[d]thiazol-2-amine (Table 2, entry 1, 2a)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give the target compound 2a (144 mg, 81%) as a dark-yellow solid; mp 82–84 °C.
1H NMR (400 MHz, CDCl 3): δ = 7.6 (t, J = 7.6 Hz, 2 H), 7.33 (t, J = 8.0 Hz, 1 H), 7.10 (t, J = 7.6 Hz, 1 H), 3.23 (s, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 168.77, 153.08, 131.01, 125.98, 120.96, 120.66, 110.72, 40.22.
HRMS (ESI): m/z calcd for C 18 H 18 N 2 S: 322.1242; found: 322.1246.

6-Bromo-N,N-dimethylbenzo[d]thiazol-2-amine (Table 2, entry 2, 2b)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give the target compound 2b (198 mg, 77%) as a fawn solid; mp 109–112 °C.
1H NMR (400 MHz, CDCl 3): δ = 7.66 (s, 1 H), 7.40–7.33 (m, 2 H), 3.17 (s, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 168.81, 151.97, 132.61, 129.16, 123.11, 119.81, 113.20, 40.29.
HRMS (ESI): m/z calcd for C 19 H 17 BrN 2 S: 382.0993; found: 382.0999.

6-Nitro-N,N-dimethylbenzo[d]thiazol-2-amine (Table 2, entry 3, 2c)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to give the target compound 2c (169 mg, 76%) as a bright-yellow solid; mp 209–211 °C.
1H NMR (400 MHz, CDCl 3): δ = 8.44 (s, 1 H), 8.14 (d, J = 8.8 Hz, 1 H), 7.46 (d, J = 8.8 Hz, 1 H), 3.23 (s, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 172.03, 158.37, 141.34, 131.21, 122.62, 117.79, 117.24, 40.43.

6-Fluoro-N,N-dimethylbenzo[d]thiazol-2-amine (Table 2, entry 6, 2f)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give the target compound 2f (147 mg, 75%) as a white solid; mp 118–120 °C.
1H NMR (400 MHz, CDCl 3): δ = 7.40–7.37 (m, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 6.92 (t, J = 8.0 Hz, 1 H), 3.03 (6 H).
13C NMR (100 MHz, CDCl 3): δ = 168.33, 157.85 (d, J C–F = 7.6 Hz, 1 H), 149.34, 131.52 (d, J C–F = 10.6 Hz), 119.04 (d, J C–F = 8.6 Hz), 113.57 (d, J C–F = 23.5 Hz), 107.40 (d, J C–F = 26.8 Hz), 40.22.
HRMS (ESI): m/z calcd for C 19 H 15 F3N 2 S: 413.0966; found: 413.0969.

6-Chloro-N,N-diethylbenzo[d]thiazol-2-amine (Table 2, entry 7, 2g)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:4) to give the target compound 2g (209 mg, 87%) as a pale-yellow syrup.
1H NMR (400 MHz, CDCl 3): δ = 7.40 (s, 1 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.09 (d, J = 8.4 Hz, 1 H), 3.46–3.40 (m, 4 H), 1.16 (t, J = 7.2 Hz, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 167.37, 151.76, 131.72, 126.16, 125.63, 120.13, 119.04, 45.46, 12.82.
HRMS (ESI): m/z calcd for C 20 H 18 ClN 2 S: 363.1292; found: 363.1299.

6-Bromo-N,N-diethylbenzo[d]thiazol-2-amine (Table 2, entry 8, 2h)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:4) to give the target compound 2h (208 mg, 73%) as a pale-yellow syrup.
1H NMR (400 MHz, CDCl 3): δ = 7.63 (s, 1 H), 7.36–7.31 (m, 2 H), 3.54–3.49 (m, 4 H), 1.24 (t, J = 7.2 Hz, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 167.40, 152.09, 132.21, 129.00, 122.98, 119.58, 112.90, 45.58, 1.07.
HRMS (ESI): m/z calcd for C 21 H 17 BrN 2 S: 391.1006; found: 391.1009.

4-Bromo-N,N-diethylbenzo[d]thiazol-2-amine (Table 2, entry 9, 2i)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give the target compound 2i (188 mg, 73%) as a white solid; mp 116–118 °C.
1H NMR (400 MHz, CDCl 3): δ = 7.62 (s, 1 H), 7.32 (d, J = 8.4 Hz, 1 H), 7.06 (d, J = 8.4 Hz, 1 H), 3.08 (s, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 169.56, 154.61, 129.97, 123.55, 121.61, 119.41, 40.16.
HRMS (ESI): m/z calcd for C 21 H 16 BrN 2 S: 375.0792; found: 375.0794.

4-Nitro-N,N-dimethylbenzo[d]thiazol-2-amine (Table 2, entry 10, 2j)
The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give the target compound 2j (166 mg, 74%) as a brown solid; mp 199–201 °C.
1H NMR (400 MHz, CDCl 3): δ = 7.98 (d, J = 8.4 Hz, 1 H), 7.74 (d, J = 7.6 Hz, 1 H), 7.02 (t, J = 8.0 Hz, 1 H), 3.24 (s, 6 H).
13C NMR (100 MHz, CDCl 3): δ = 171.10, 147.23, 138.66, 135.14, 125.80, 122.49, 119.42, 40.29.
HRMS (ESI): m/z calcd for C 19 H 14 N 4 O 2 S: 440.0949; found: 440.0949.
4-Chloro-\(N,N\)-dimethylbenzo[\(d\)]thiazol-2-amine (Table 2, entry 11, 2k)

The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:3) to give the target compound 2k (188 mg, 89%) as a white solid; mp 95–96 ºC.

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.41\) (d, \(J = 8.0\) Hz, 1 H), 7.26 (d, \(J = 8.0\) Hz, 1 H), 6.90 (t, \(J = 7.6\) Hz, 1 H), 3.12 (s, 6 H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 168.80, 150.21, 132.34, 126.18, 122.98, 121.18, 119.14, 40.15\).

HRMS (ESI): \(m/z\) calcd for C\(_{12}\)H\(_{12}\)N\(_2\)S: 262.1504; found: 262.1497.

6-Methoxy-\(N,N\)-dimethylbenzo[\(d\)]thiazol-2-amine (Table 2, entry 12, 2l)

The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to give the target compound 2l (148 mg, 71%) as a pale-yellow solid; mp 90–92 ºC.

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.43\) (d, \(J = 7.6\) Hz, 1 H), 7.09 (s, 1 H), 8.85 (d, \(J = 4.0\) Hz, 1 H), 3.75 (s, 3 H), 3.10 (s, 6 H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 167.43, 154.66, 147.22, 131.86, 119.06, 113.49, 110.23, 55.87, 40.21\).

HRMS (ESI): \(m/z\) calcd for C\(_{11}\)H\(_{10}\)N\(_2\)O: 208.0670; found: 208.0682.

\(N,N\)-6-Methylbenzo[\(d\)]thiazol-2-amine (Table 2, entry 13, 2m)

The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:1) to give the target compound 2m (126 mg, 73%) as a red-brown solid; mp 96–98 ºC.

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.43\) (d, \(J = 8.0\) Hz, 1 H), 7.09 (d, \(J = 4.0\) Hz, 1 H), 6.85 (d, \(J = 8.8\) Hz, 1 H), 3.76 (s, 3 H), 3.10 (s, 6 H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 168.25, 150.92, 131.06, 130.61, 127.11, 120.72, 118.34, 40.19, 21.21\).

HRMS (ESI): \(m/z\) calcd for C\(_{12}\)H\(_{10}\)N\(_2\)S: 206.0721; found: 208.0729.

\(N,N\)-Diethylbenzo[\(d\)]thiazol-2-amine (Table 2, entry 14, 2n)

The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:4) to give the target compound 2n (163 mg, 79%) as a pale-yellow syrup.

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.59\) (t, \(J = 8.0\) Hz, 2 H), 7.26 (t, \(J = 7.2\) Hz, 1 H), 7.01 (t, \(J = 7.6\) Hz, 1 H), 3.57–3.51 (m, 4 H), 1.26 (t, \(J = 7.2\) Hz, 6 H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 167.30, 130.24, 125.93, 120.88, 120.56, 118.45, 45.54, 12.87\).

HRMS (ESI): \(m/z\) calcd for C\(_{12}\)H\(_{12}\)N\(_2\): 208.0885; found: 208.0885.

\(N,N\)-Dibutylbenzo[\(d\)]thiazol-2-amine (Table 2, entry 15, 2o)

The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:10) to give the target compound 2o (165 mg, 63%) as a colourless viscous oil.

\(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.54\) (t, \(J = 8.0\) Hz, 2 H), 7.25 (t, \(J = 8.0\) Hz, 1 H), 7.01 (t, \(J = 8.0\) Hz, 1 H), 3.48 (t, \(J = 8.0\) Hz, 4 H), 1.70–1.63 (m, 4 H), 1.42–1.33 (m, 4 H), 0.96 (t, \(J = 8.0\) Hz, 6 H).

\(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 167.90, 153.06, 130.52, 125.82, 120.71, 120.47, 118.51, 51.05, 29.64, 20.15, 13.96\).

HRMS (ESI): \(m/z\) calcd for C\(_{14}\)H\(_{14}\)N\(_2\): 262.1504; found: 262.1497.
