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Synthesis of Oxindoles and Benzofuranones via Oxidation of 2-Heterocyclic BMIDAs

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Abstract: The synthesis of functionalized oxindoles and benzofuranones via oxidation of 2-BMIDA indoles and benzofurans, respectively, is described. Interconversion of boron species (BMIDA→BF₃K) was necessary to enable oxidation and overcome boronic acid stability issues associated with a difficult BMIDA hydrolysis. Overall, a robust process was developed that allowed access to a small library of oxindole and benzofuranone products and facilitated the step-efficient synthesis of biologically-active compounds containing the oxindole pharmacophore.

Keywords: Boron, oxidation, heterocycles, lactams, lactones

The oxindole motif is present in the core of numerous biologically active natural products as well as pharmaceuticals such as tenidap, coreulescine, and semaxanib (Figure 1). Consequently, numerous methods have been and continue to be developed to allow access to this privileged chemotype.

![Figure 1: Pharmaceutically relevant oxindoles.](image)

The most common synthetic approaches towards the oxindole framework forge the pyrrole nucleus either via disconnection at the amide C-N bond to provide a phenylacetic acid precursor, or at the C-3 position to afford an anilide precursor (Scheme 1a). Despite significant research, preparation of oxindoles beginning from the corresponding indole starting materials are comparatively limited, with oxidative methods often suffering from the problem of over-oxidation to deliver isatins (Scheme 1b). Hydrolysis of 2-oxy-indoles gives the corresponding oxindoles; however, this requires a pre-oxygenated indole as a starting material (Scheme 1c). We recently disclosed a one-pot synthesis of 2-heterocyclic BMIDA’s, which are bench stable, free flowing solids that can be stored indefinitely without degradation. Here we present the utility of 2-BMIDA indoles and benzofuranones as readily accessible precursors to oxindoles and benzofuranones, respectively, and the scope and limitations of this process (Scheme 1d).

![Scheme 1: Methods for the synthesis of oxindoles.](image)
a range of solvent/water mixtures and in the presence of base (Scheme 2 – see Supporting Information for full details).\textsuperscript{11}

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{Scheme2.png}
\caption{Attempted direct hydrolysis/oxidation of 2-BMIDA indole 1. PDB = protodeboronation.}
\end{figure}
\end{center}

Based on the base lability of BMIDA and the well studied slow or fast release of the parent boronic acid,\textsuperscript{10} we planned an \textit{in situ} hydrolysis of 1 to deliver 2 that would then be oxidized to deliver 3a. To our surprise, when using a base/oxidant system of NaOH/H\textsubscript{2}O\textsubscript{2} at room temperature (fast hydrolysis conditions), the BMIDA group remained intact, \textit{i.e.} no hydrolysis was observed, even in the presence of excess aq. NaOH. In an attempt to drive the hydrolysis step, the reaction was heated to 50 °C with increasing quantities of NaOH. However, while hydrolysis could be induced, these reactions returned the protodeboronated product 4 in quantitative yields in all cases, presumably due to the sensitivity of 2 under these reaction conditions. Attempting to temper the reaction conditions using a slow hydrolysis protocol with either K\textsubscript{2}PO\textsubscript{4} or K\textsubscript{2}CO\textsubscript{3} in the presence of H\textsubscript{2}O\textsubscript{2} returned starting material (1) only. Changing the oxidant to Oxone\textsuperscript{®} had a small positive effect – hydrolysis remained sluggish, requiring extended reaction times or elevated temperatures and although trace quantities of 3a were observed under these conditions, protodeboronation product 4 dominated along with degradation of 3a.

These initial investigations highlighted a compatibility issue between the conditions required to hydrolyze the BMIDA unit and the stability of the intermediate boronic acid (as well as the oxindole product). To overcome these issues, we postulated that a simple boron species interconversion process might be achieved under mild reaction conditions to deliver an organoboron derivative that could then be oxidized under conditions sufficiently mild to inhibit degradation of the organoboron intermediate or product. In particular, BMIDA species can be converted to the potassium organotrifluoroborate (BF\textsubscript{3}K) derivative under relatively mild reaction conditions\textsuperscript{12} and BF\textsubscript{3}K species can also be oxidized under mild conditions.\textsuperscript{13} However, BMIDA-BF\textsubscript{3}K interconversion on this template was unknown. Accordingly, we evaluated conversion of BMIDA 1 to the BF\textsubscript{3}K derivative 5.

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{Scheme3.png}
\caption{Conversion of BMIDA 1 to BF\textsubscript{3}K 5.}
\end{figure}
\end{center}

A short survey of reaction conditions found that 1 could be quantitatively converted to 5 upon treatment with aq. KHF\textsubscript{2} in MeOH at 70 °C (Scheme 3a). In addition, 5 could be quantitatively converted to the desired oxindole product 3a using Oxone\textsuperscript{®}. Combining these two events proved to be straightforward (Table 1). Oxidation of intermediate 5 was found to be sluggish in MeOH; however, a solvent switch to acetone before addition of the oxidant was more effective (entry 1 vs. entry 2). A short optimization of reaction time and KHF\textsubscript{2} stoichiometry (entries 2-5) revealed that the overall two-step process could be completed in 6 hours using 5 equiv. of KHF\textsubscript{2} to facilitate conversion to 5, ultimately delivering 99% conversion to 3a. Interestingly, while oxidation of the intermediate BF\textsubscript{3}K 5 was facile with Oxone\textsuperscript{®}, NaBO\textsubscript{3} and H\textsubscript{2}O\textsubscript{2} were ineffective for oxidation of this intermediate (entries 6 and 7, respectively).

With optimum conditions in hand, the scope of the reaction was investigated by application to a range of substituted 2-BMIDA indole architectures (Scheme 4).

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{Scheme4.png}
\caption{Substrate scope of the oxidation process. Isolated yields. \textsuperscript{4}Determined by \textsuperscript{1}H NMR analysis.}
\end{figure}
\end{center}

The reaction was found to be tolerant of both electron-donating and electron-withdrawing groups (3g, 3h, 3l). Halogenated substrates were also effective, providing a synthetic handle for
further functionalization (3c, 3d, 3e, 3f). In addition, azaindoline 3j was delivered in moderate yield by NMR (42%) with the mass balance consisting of the product of protodeboronation. However, this product was found to be labile to hydrolysis on silica. The N-tosyl group could be replaced with a methyl unit but resulted in a decrease in yield of the corresponding oxindole (3b). Other N-protecting groups were not assessed. Lastly, in addition to oxindoles, the oxidation process was applicable to 2-BMIDA benzosfurans to allow access to benzofuranones in excellent yields (3k, 3l).

In keeping with our interests in medicinal chemistry, we sought to utilize the oxindole products as building blocks in the synthesis of biologically active molecules. In particular, the ubiquity of the oxindole motif in kinase drug discovery led us to target compounds of this class. First steps into derivatization of our oxindole products quickly identified an issue with deprotection of the N-tosyl. Specifically, the lactam was found to be readily hydrolyzed under both acidic and basic conditions. To the best of our knowledge, no methods exist for the deprotection of the unidentifiable mixture of products.

To limit exposure to basic reaction conditions, we evaluated several single-electron methods. Mg powder in MeOH resulted in solvolysis of 3a. Sml₂ conditions led to full consumption of the starting material within five minutes of addition; however, none of the desired oxindole was observed, delivering only an unidentified mixture of products. Fortunately, application of sodium naphthalenide at −78 °C provided clean conversion to the desired oxindole product in 90% isolated yield.

With effective conditions for the deprotection now available, we were able to prepare several biologically active products (Scheme 5 and 6). Both the natural product (±)-coerulescine and kinase inhibitor semaxanib could be quickly accessed through common oxindole 3a following tosyl deprotection (Scheme 5). From this common intermediate, condensation with commercially available pyrrole 7 afforded semaxanib in excellent yield, while C₃ alkylation followed by ring expansion enabled access to (±)-coerulescine in moderate overall yield. Although the dialkylation to form the cyclopropane proceeded with good conversion by NMR (ca. 60%), the desired spirocycle 8 was found to be highly unstable on silica, thereby limiting the yield of this process.

Tenidap, a potent COX inhibitor, was efficiently synthesized in five steps from oxindole 3e (Scheme 6). Tosyl deprotection gave the free oxindole 9, which, upon treatment with phenyl chloroformate followed by ammonium carbonate, gave oxindole 10 in 73% yield. Condensation with 2-thiophencarboxyl chloride and subsequent exposure to ammonium carbonate afforded tenidap in excellent yield.

In conclusion, we have reported a novel method for the preparation of oxindoles from 2-BMIDA indoles. A boron species (BMIDA to BF₃·K) interconversion was used to overcome the instability of the intermediate indole 2-boronic acid towards the conditions required for hydrolysis of an unusually robust BMIDA species. The BF₃·K species was readily oxidized to the corresponding oxindole under mild conditions allowing one-pot access to oxindole products. The scope of the reaction was evaluated by application towards a series of substrates and further exemplified in the context of the synthesis of kinase inhibitors semaxanib and tenidap, and the natural product coerulescine.

The experimental section has no title; please leave this line here.

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**Scheme 5** Synthesis of semaxanib and (±)-coerulescine. Isolated yields.

**Scheme 6** Synthesis of tenidap. Isolated yields.

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**Table 2** Deprotection of N-Ts oxindole 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 M NaOH, 1,4-dioxane, rt</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1 M NaOH, 1,4-dioxane, rt</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1 M TBAF, THF, rt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Mg, MeOH, rt</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Sml₂, pyrrolidine, H₂O, rt</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Na, naphthalene, −78 °C</td>
<td>90</td>
</tr>
</tbody>
</table>

*Isolated yields.*

To limit exposure to basic reaction conditions, we evaluated several single-electron methods. Mg powder in MeOH resulted in solvolysis of 3a. Sml₂ conditions led to full consumption of the starting material within five minutes of addition; however, none of the desired oxindole was observed, delivering only an unidentified mixture of products. Fortunately, application of sodium naphthalenide at −78 °C provided clean conversion to the desired oxindole product in 90% isolated yield.

With effective conditions for the deprotection now available, we were able to prepare several biologically active products (Scheme 5 and 6). Both the natural product (±)-coerulescine and kinase inhibitor semaxanib could be quickly accessed through common oxindole 3a following tosyl deprotection (Scheme 5). From this common intermediate, condensation with commercially available pyrrole 7 afforded semaxanib in excellent yield, while C₃ alkylation followed by ring expansion enabled access to (±)-coerulescine in moderate overall yield. Although the dialkylation to form the cyclopropane proceeded with good conversion by NMR (ca. 60%), the desired spirocycle 8 was found to be highly unstable on silica, thereby limiting the yield of this process.

Tenidap, a potent COX inhibitor, was efficiently synthesized in five steps from oxindole 3e (Scheme 6). Tosyl deprotection gave the free oxindole 9, which, upon treatment with phenyl chloroformate followed by ammonium carbonate, gave oxindole 10 in 73% yield. Condensation with 2-thiophencarboxyl chloride and subsequent exposure to ammonium carbonate afforded tenidap in excellent yield.

In conclusion, we have reported a novel method for the preparation of oxindoles from 2-BMIDA indoles. A boron species (BMIDA to BF₃·K) interconversion was used to overcome the instability of the intermediate indole 2-boronic acid towards the conditions required for hydrolysis of an unusually robust BMIDA species. The BF₃·K species was readily oxidized to the corresponding oxindole under mild conditions allowing one-pot access to oxindole products. The scope of the reaction was evaluated by application towards a series of substrates and further exemplified in the context of the synthesis of kinase inhibitors semaxanib and tenidap, and the natural product coerulescine.

The experimental section has no title; please leave this line here.
All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Where necessary, purification was carried out according to standard laboratory methods. Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials. Room temperature was generally ca. 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer. Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution.

Normal phase flash chromatography was carried out using ZEPOP 60 HYD 40-63 μm silica gel. Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. 1H NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. 1H NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz.

IR (solid): 3060, 2924, 2855, 1698, 1614, 1496, 1470, 1370, 1249 cm⁻¹.

Prepared according to the general procedure from 6-chloro-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester (46 mg). Yield: 29 mg, 90%. White amorphous solid.

IR (solid): 2924, 2857, 1768, 1610, 1595, 1424, 1372, 1333, 1236 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ 8.07-7.88 (m, 3H), 7.35 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 1.1 Hz, 2H), 3.52 (s, 2H), 2.43 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 172.7, 157.0, 145.6, 135.2, 133.8, 129.8, 112.7.

HRMS (TOF): m/z [M+H]+ calcd for C₁₂H₁₃NO₃S: 322.0305; found: 322.0304.

5-Fluoro-1-tosylindolin-2-one (3d)

Prepared according to the general procedure from (5-fluoro-1H-indol-2-yl)boronic acid, MIDA ester (44 mg). Yield: 28 mg, 92%. Off-white amorphous solid.

IR (solid): 3073, 2973, 2924, 2794, 1610, 1599, 1476, 1368 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ 8.06-7.93 (m, 2H), 7.88 (dd, J = 9.0, 4.5 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.04 (dd, J = 9.0, 2.8 Hz, 1H), 6.98-6.94 (m, 3H), 3.55 (s, 2H), 2.43 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 172.3, 145.9, 138.9, 135.0, 130.2, 129.8, 128.2, 128.0, 125.0, 124.9, 114.3, 35.9, 21.7.


5-Chloro-1-tosylindolin-2-one (3e)

Prepared according to the general procedure from (5-chloro-1H-indol-2-yl)boronic acid, MIDA ester (44 mg). Yield: 29 mg, 90%. White amorphous solid.

IR (solid): 2956, 2922, 1755, 1599, 1470, 1370, 1232 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.99-7.94 (m, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.36-7.29 (m, 3H), 7.22-7.19 (m, 1H), 3.55 (s, 2H), 2.43 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 172.0, 145.9, 138.9, 135.0, 130.2, 129.8, 128.6, 128.0, 125.0, 124.9, 114.3, 35.9, 21.7.

HRMS (NSI): m/z [M+H]+ calcd for C₁₂H₁₂ClNO₂S: 322.0299; found: 322.0302.

5-Bromo-1-tosylindolin-2-one (3f)

Prepared according to the general procedure from (5-bromo-1H-indol-2-yl)boronic acid, MIDA ester (51 mg). Yield: 24 mg, 66%. Light brown amorphous solid.

IR (solid): 2956, 2924, 2854, 1757, 1599, 1469, 1455, 1375 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 8.01-7.96 (m, 2H), 7.83 (d, J = 8.8 Hz, 1H), 7.51-7.46 (m, 1H), 7.39-7.33 (m, 3H), 3.58 (s, 2H), 2.45 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 171.4, 145.5, 138.9, 134.9, 131.0, 129.8, 128.6, 128.0, 125.0, 124.9, 114.8, 35.9, 21.7.


5-Methoxy-1-tosylindolin-2-one (3g)

Prepared according to the general procedure from (5-methoxy-1H-indol-2-yl)boronic acid, MIDA ester (46 mg). Yield: 28 mg, 88%. Light brown amorphous solid.

IR (solid): 2950, 2924, 2855, 1757, 1601, 1483, 1470, 1372 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ 8.79 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 6.85 (dd, J = 9.0, 2.4 Hz, 1H), 6.79 (s, 1H), 3.79 (s, 3H), 3.53 (s, 2H), 2.42 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 172.7, 157.0, 145.6, 135.2, 133.8, 129.8, 127.9, 124.9, 114.5, 113.2, 55.7, 36.5, 21.7.

HRMS (NSI): m/z [M+H]+ calcd for C₁₂H₁₃NO₃S: 318.0795; found: 318.0796.
1-Tosyl-5-(trifluoromethoxy)indolin-2-one (3h)
Prepared according to the general procedure from (1-tosyl-5-(trifluoromethoxy)-1H-indol-2-yl)boronic acid, MIDA ester (51 mg). Yield: 30 mg, 80%. Off-white amorphous solid. IR (solid): 3161, 1692, 1469, 1332 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.92 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 4.51 (s, 1H), 2.36 (s, 3H).

13C NMR (CDCl₃, 126 MHz): δ 172.8, 146.0, 139.8, 130.9, 129.8, 124.8, 121.0, 118.9, 118.2, 113.1, 21.7. Trifluoromethyl carbon not observed. 

Methyl 1,2-oxo-1-tosylindoline-5-carboxylate (3i)
Prepared according to the general procedure from (5-(methoxycarbonyl)-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester (48 mg). Yield: 22 mg, 62%. White amorphous solid. 

IR (solid): 3161, 2956, 2925, 2855, 1798, 1779, 1616, 1601, 1480, 1450, 1374 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.86 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.53 (s, 2H), 2.36 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 171.9, 165.8, 145.6, 143.6, 134.4, 130.2, 129.4, 127.6, 126.1, 125.5, 122.8, 112.8, 51.8, 35.3, 21.3.

HRMS (TOF): m/z [M+H]+ calcld for C₁₁H₁₀O₅S: 372.0517; found: 372.0527.

Benzofuran-2(3H)-one (3j)
Prepared according to the general procedure from benzofuran-2-ylboronic acid, MIDA ester (27 mg). Yield: 14 mg, 100%. White amorphous solid.

IR (solid): 3095, 2956, 2925, 2919, 1779, 1617, 1601, 1480, 1465, 1299 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ 7.66–7.59 (m, 4H), 7.08 (t, J = 7.5 Hz, 2H), 7.03 (d, J = 8.0 Hz, 1H), 3.66 (s, 2H).

13C NMR (CDCl₃, 101 MHz): δ 173.6, 154.2, 128.4, 124.1, 123.6, 122.6, 110.3, 32.5.

5-Fluorobenzofuran-2(3H)-one (3k)
Prepared according to the general procedure from 5-fluorobenzofuran-2-ylboronic acid, MIDA ester (29 mg). Yield: 15 mg, 98%. White amorphous solid.

IR (solid): 3081, 2958, 2926, 2855, 1796, 1634, 1610, 1483, 1400, 1388 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.07–6.82 (m, 3H), 3.69 (s, 2H).

13C NMR (CDCl₃, 500 MHz): δ 173.6, 159.4 (d, J_C-F = 242.5 Hz), 150.6, 124.4 (d, J_C-F = 9.5 Hz), 115.5 (d, J_C-F = 24.3 Hz), 112.2 (d, J_C-F = 25.6 Hz), 111.7 (d, J_C-F = 8.4 Hz), 33.5.

19F NMR (CDCl₃, 471 MHz): δ -58.21.


1-Tosyl-5-(trifluoromethoxy)indolin-2-one (3h)
Prepared according to the general procedure from 1-tosyl-5-(trifluoromethoxy)-1H-indol-2-yl)boronic acid, MIDA ester (51 mg). Yield: 30 mg, 80%. Off-white amorphous solid. IR (solid): 3200, 1701, 1684, 1671, 1527, 1437, 1357 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ 8.34 (s, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 1.76 (d, J = 3.0 Hz, 2H), 1.54 (d, J = 2.9 Hz, 2H).

13C NMR (CDCl₃, 101 MHz): δ 179.1, 140.6, 131.3, 126.7, 122.0, 118.6, 109.7, 27.4, 19.5.

HRMS (NSI): m/z [M+H]+ calcld for C₁₁H₁₁F₅O: 239.1179; found: 239.1177.

Spiro[cyclopropane-1,3'-indolin]-2'-one (8)
An oven dried flask was charged with oxindole (133 mg, 1 mmol, 1 equiv) before the addition of dry DMF (1.25 mL, 0.8 M) and dibormonethane (94 µL, 1.1 mmol, 1.1 equiv). The solution was then cooled to 0 °C before the addition of NaH (60% dispersion in mineral oil, 187 mg, 4.5 mmol, 4.5 equiv) portionwise over 20 min. The reaction mixture was then warmed to room temperature and stirred overnight before being quenched with H₂O (3 mL) and extracted with EtOAc (5 mL). The organics were then washed with H₂O (2 × 5 mL) and brine (2 × 5 mL). The organics were then passed through a hydrophobic frit and concentrated under vacuum before being purified (silica gel, 20-40% EtOAc/petroleum ether) to afford the desired product. Yield: 23 mg, 14%. Red/brown amorphous solid.

IR (solid): 3166, 3122, 2917, 2842, 1686, 1617, 1565, 1554, 1539, 1463, 1455, 1340, 1316, 1204 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ 8.37 (s, 1H), 8.00 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.13 (dd, J = 7.6, 1.2 Hz, 1H), 7.05 (dd, J = 7.6, 1.1 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 5.98 (d, J = 2.5 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H).

13C NMR (CDCl₃, 101 MHz): δ 169.8, 137.0, 136.9, 132.6, 127.1, 126.6, 125.6, 123.6, 121.5, 117.4, 112.7, 111.8, 109.2, 13.9, 11.6.

HRMS (NSI): m/z [M+H]+ calcld for C₁₃H₁₈N₂O₃: 239.1179; found: 239.1177.
\(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.45 (s, 1H), 7.41 (d, \(J = 7.3\) Hz, 1H), 7.19 (d, \(J = 7.7, 1.2\) Hz, 1H), 7.04 (d, \(J = 7.6, 1.0\) Hz, 6.89 (d, \(J = 7.7\) Hz, 1H), 3.11–3.00 (m, 1H), 2.91 (s, 2H), 2.88–2.74 (m, 1H), 2.49 (s, 3H), 2.41 (sdd, \(J = 12.5, 7.7, 4.7\) Hz, 1H), 2.12 (dt, \(J = 12.9, 7.5\) Hz, 1H).

\(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 182.7, 140.1, 136.0, 127.8, 123.4, 122.9, 121.5, 116.7, 36.3.

HRMS (NSI): \(m/z\) [M+H]\(^+\) calc for C\(_{23}\)H\(_{18}\)N\(_2\): 321.0099; found: 321.0099.

**Phenyl 5-chloro-2-oxoindoline-1-carboxylate (10)**

Step 1: Phenyl 5-chloro-2-[(phenoxycarbonyl)oxy]-1H-indole-1-carboxylate.

To a flask charged with 5-chloro-2-oxindole (1 g, 6 mmol, 1 equiv) was added 20 mL dry THF followed by triethylamine (1.75 mL, 12.6 mmol, 2.1 equiv). The reaction mixture was stirred at 0 °C for 1 h. The resulting precipitate was then filtered and the filtrate was washed with THF (2×20 mL). The filtrate was then concentrated under vacuum to obtain a pink solid (20 mL), and dried by filtering and washing with THF to afford the desired product 10. Yield: 585 mg, 73% over two steps. White amorphous solid.

HRMS (NSI): \(m/z\) [M+H]\(^+\) calc for C\(_{21}\)H\(_{16}\)ClNO: 321.0099; found: 321.0099.

**Acknowledgment**

We thank the Carnegie Trust for a PhD studentship (CPS) and the EPSRC UK National Mass Spectrometry Facility at Swansea University for analyses.

**Supporting Information**

Optimization data, and \(^{1}\)H and \(^{13}\)C NMR spectra for all new compounds.

**References**


Initial screening of reaction conditions were based on a report from Hutton: Churches, Q. I.; Hooper, J. F.; Hutton, C. A. J. Org. Chem. 2015, 80, 5428.


Synthesis of Oxindoles and Benozfuranones via Oxidation of 2-Heterocyclic BMIDAs
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Contents

1. General

2. General Experimental Procedures

3. Compound Characterization Data
   4.1 Intermediates
   4.2 Products from Scheme 3
   4.3 Products from Scheme 4
   4.4 Products from Schemes 5 and 6

4. References

5. NMR spectra for intermediates and products
1. General
All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.1

1.1 Purification of Solvents
DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N₂ in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. Acetone, MeOH, CH₂Cl₂, Et₂O, EtOAc, MeCN, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

1.3 Experimental Details
Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials. The glassware was oven-dried (150 °C) and purged with N₂ before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally ca. 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

1.4 Purification of Products
Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

1.5 Analysis of Products
Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ¹⁹F NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. ¹¹B NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz. ¹H and ¹³C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 125 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with CDCl₃ referenced at 7.26 (¹H) and 77.0 ppm (¹³C) and DMSO-d₆ referenced at 2.50 (¹H) and 39.5 (¹³C). ¹¹B NMR spectra are referenced to BF₃•Et₂O. High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column. Analysis was performed using a gradient method, eluting with 5–80% MeCN/H₂O over 16 minutes at a flow rate of 2 mL/min. Samples for HPLC analysis were prepared through the addition of 2 mL of caffeine standard in MeCN to the completed reaction mixture. The resulting solution was then stirred before the removal of a 200 μL aliquot. The aliquot was diluted to 1 mL with MeCN. A 200 μL aliquot of the diluted solution was then filtered through cotton wool and further diluted with 800 μL MeCN and 500 μL H₂O for HPLC analysis against established conversion factors.
2. Optimization of Hydrolysis/Oxidation procedure

2.1 General procedure for optimization reactions.

A 10 mL microwave vial was charged with \( \text{N-tosylindole-2-BMIDA} \) (43 mg, 0.1 mmol, 1 equiv) before the addition of solvent (0.4 mL, 0.25 M) and base (x equiv). To the resulting solution was added oxidant (x equiv). The reaction mixture was stirred at \( X \) °C for \( X \) h before being quenched with sodium metabisulfite (10 mg). The reaction mixtures were then analyzed by reverse phase HPLC against established conversion factors.

2.2 \( \text{H}_2\text{O}_2 \) optimization

Carried out according to the general procedure using 30% w/v \( \text{H}_2\text{O}_2 \) (0.2 mL, 2.5 mmol, 25 equiv) for 1 hr.

<table>
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<tr>
<th>Entry</th>
<th>Base (vol/mass)</th>
<th>Base equiv</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Conversion %</th>
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2.3 Oxone optimization

Carried out according to the general procedure for 24 hr.

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<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Conversion %</th>
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<td>THF</td>
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<tr>
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<td>3 (64 mg)</td>
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<td>THF</td>
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<td>THF</td>
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<td>60</td>
<td>MeCN</td>
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<tr>
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<td>2.5 (77 mg)</td>
<td>3 (64 mg)</td>
<td>70</td>
<td>MeCN</td>
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<tr>
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<td>MeCN</td>
<td>15</td>
</tr>
<tr>
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<td>2.5 (77 mg)</td>
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<td>MeCN</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>10 (307 mg)*</td>
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<td>50</td>
<td>THF</td>
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</tr>
<tr>
<td>9</td>
<td>10 (307 mg)*</td>
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<td>70</td>
<td>THF</td>
<td>4</td>
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</table>

* Oxone was added to the reaction as a solution in 2 mL H\(_2\)O
4. Compound characterization data

Synthesis of starting materials.
Compounds 1a, b, c, f, g, h, i and l were synthesized according to ref 7. Compounds 1d and j were purchased from commercial suppliers and used as received.

Synthesis of (5-chloro-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester 1e

To an oven dried 50 mL flask was added N-(2-iodo-4-chlorophenyl)-4-methylbenzenesulfonamide (1.02 g, 2.5 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (540 mg, 3 mmol, 1.2 equiv), Pd(PPh₃)₂Cl₂ (35 mg, 0.05 mmol, 2 mol%), CuI (48 mg, 0.25 mmol, 10 mol%), Cu(OAc)₂ (136 mg, 0.75 mmol, 30 mol%), and K₂PO₄ (530 mg, 2.5 mmol, 1 equiv). The flask was then sealed and purged with N₂ before addition of DMF (20 mL, 0.125 M). The reaction mixture was then heated to 30 °C for 4 h before being heated to 55 °C for a further 14 h. The reaction mixture was allowed to cool to room temperature before the solution was then dried and concentrated under reduced pressure before being diluted with EtOAc (10 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as an off-white solid (790 mg, 69%).

υmax (solid): 2972, 1763, 1599, 1526, 1448, 1340, 1295 cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 8.12 (d, J = 9.0 Hz, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 1.7 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.05 (s, 1H), 4.47 (d, J = 17.5 Hz, 2H), 4.23 (d, J = 17.5 Hz, 2H), 2.95 (s, 3H), 2.33 (s, 3H).

¹³C NMR (DMSO-d₆, 101 MHz): δ 169.1, 145.5, 136.9, 134.7, 131.1, 130.0, 128.0, 126.6, 125.0, 120.9, 120.8, 115.8, 64.3, 49.4, 21.0. Carbon bearing boron not observed.

¹¹B NMR (DMSO-d₆, 128 MHz): δ 10.38.

HRMS: exact mass calculated for [M+H]⁺ (C₂₀H₁₉ClN₂O₆SB) requires m/z 461.0749, found m/z 461.0766.

Synthesis of (5-methoxy-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester 1g

To an oven dried 5 mL microwave vessel was added N-(2-iodo-4-methoxyphenyl)-4-methylbenzenesulfonamide (202 mg, 0.5 mmol, 1 equiv), ethynyl boronic acid, MIDA ester (109 mg, 0.6 mmol, 1.2 equiv), Pd(PPh₃)₂Cl₂ (7 mg, 0.01 mmol, 2 mol%), CuI (9.5 mg, 0.05 mmol, 10 mol%), Cu(OAc)₂ (27.2 mg, 0.15 mmol, 30 mol%), and K₂PO₄ (106 mg, 0.5 mmol, 1 equiv). The vessel was then capped and purged with N₂ before addition of DMF (4 mL, 0.125 M). The reaction mixture was then heated to 30 °C in a sand bath for 4 h before being heated to 55 °C for a further 14 h. The vessel was allowed to cool to room temperature, vented, and decapped. The solution was then dried and concentrated under reduced pressure before being diluted with EtOAc (20 mL) and washed with water (2 × 40 mL) and brine (2 × 40 mL). The organics were then dried and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 40-70% EtOAc/petroleum ether) to afford the title compound as a white solid (150 mg, 66%).
$\nu_{\text{max}}$ (solid): 2960, 2926, 2855, 1763, 1532, 1464, 1340, 1299 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 8.01 (d, $J = 9.1$ Hz, 1H), 7.86 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 2.5$ Hz, 1H), 7.00–6.94 (m, 2H), 4.46 (d, $J = 17.5$ Hz, 2H), 4.23 (d, $J = 17.4$ Hz, 2H), 3.76 (s, 3H), 2.96 (s, 3H), 2.33 (s, 3H).

$^{13}$C NMR (DMSO-$d_6$, 101 MHz): $\delta$ 168.9, 155.8, 144.9, 134.8, 132.9, 130.5, 129.6, 126.3, 121.6, 114.9, 114.0, 103.3, 64.0, 55.2, 49.2, 20.8. Carbon bearing boron not observed.

$^{11}$B NMR (DMSO-$d_6$, 128 MHz): $\delta$ 10.33.

HRMS: exact mass calculated for $[\text{M+NH}_4]^+$ ($\text{C}_{21}\text{H}_{25}\text{BN}_3\text{O}_7\text{S}$) requires $m/z$ 474.1505, found $m/z$ 474.1497.

5. References

6. NMR and HRMS spectra for intermediates and products

$^1$H NMR of 1e

$^{13}$C NMR of 1e
$^{11}$B NMR of 1e

$^1$H NMR of 1g
$^{13}$C NMR of 1g

$^{11}$B NMR of 1g
$^1$H NMR of 3a

$^{13}$C NMR of 3a
$^1$H NMR of 3b

13C NMR of 3b
$^1$H NMR of 3c

$^{13}$C NMR of 3c
$^1$H NMR of 3d

$^{13}$C NMR of 3d
$^1$H NMR of 3e

$^{19}$F NMR of 3d
$^{13}$C NMR of 3e

$^1$H NMR of 3f
$^{13}$C NMR of 3f

$^1$H NMR of 3g
$^{13}$C NMR of 3g

$^1$H NMR of 3h
$^{13}$C NMR of 3h

$^{19}$F NMR of 3h
$^1$H NMR of 3i

$^{13}$C NMR of 3i
$^{13}$C NMR of 3l

$^{19}$F NMR of 3l
$^1$H NMR of 6

$^{13}$C NMR of 6
$^1$H NMR of semaxanib

$^{13}$C NMR of semaxanib
$^{1}H$ NMR of 8

![1H NMR Spectrum of 8]

$^{13}C$ NMR of 8

![13C NMR Spectrum of 8]
$^1$H NMR of (±) coerulescine

(±) coerulescine

$^{13}$C NMR of (±) coerulescine
$^1$H NMR of 9

$^{13}$C NMR of 9
$^1$H NMR of tenidap

$^{13}$C NMR of tenidap