Electronic Supporting Information (ESI)

for

Synthesis of benzimidazole-fused 1,4-benzoazepines and benzosultams spiro-connected to a 2-oxindole core via a tandem epoxide-opening/$S_N$Ar approach

Abhijit Gogoi, Subhamoy Mukhopadhyay, Raju Chouhan, and Sajal Kumar Das*

Department of Chemical Sciences, Tezpur University, Napaam, Tezpur-784028, Assam, India

*Email: sajalkd@tezu.ernet.in

Table of Contents

1. Preparation of Compounds S2
   1.1. Preparation of spiro-epoxyoxindoles 1a–j S2
   1.2. Synthesis of 2-(2-fluoroaryl)benzoimidazoles 2a–h S2
   1.3. Preparation of N-arylbenzenesulfonamides 4a–d S4
2. X-Ray Crystallography S5
3. References S7
4. NMR Spectra of Compounds S8
1. Preparation of Compounds

1.1. Preparation of spiro-epoxyoxindoles 1a–j

Spiro-epoxyoxindoles 1a, 1b, 1c, 1e, 1f, 1g, 1h, 1i, and 1j are known compounds and were prepared by us following the reported procedures. Preparation of 1d is outlined in Scheme SI-1.

**Scheme SI-1: Synthesis of 1-allyl-5-fluorospiro[indoline-3,2'-oxiran]-2-one 1d**

![Scheme SI-1](image)

A mixture of trimethylsulfoxonium iodide (484 mg, 2.0 mmol, 1.0 equiv) and Cs2CO3 (1.3 g, 4.0 mmol, 2.0 equiv) in dry MeCN (10 mL) was stirred at 50 °C for 1 h under a nitrogen atmosphere. A solution of N-allyl-5-fluorisatin (410 mg, 2.0 mmol, 1.0 equiv) in dry MeCN (10 mL) was then added dropwise over 10 min. After 1 hour, the mixture was filtered through a pad of Celite and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: 15–35% EtOAc/hexanes) to afford 1d as a clear liquid; yield: 75% (329 mg). 1H NMR (400 MHz, CDCl3) δ 7.03 (td, J = 8.9, 2.6 Hz, 1H), 6.89–6.79 (m, 2H), 5.83 (ddt, J = 17.1, 10.6, 5.4 Hz, 1H), 5.32–5.23 (m, 2H), 4.38 (qdt, J = 16.3, 5.4, 1.6 Hz, 2H), 3.60 (d, J = 6.7 Hz, 1H), 3.42 (d, J = 6.7 Hz, 1H). 13C{1H} NMR (100 MHz, CDCl3) δ 171.2, 159.3 (d, J_C-F = 242.3 Hz), 140.2 (d, J_C-F = 2.1 Hz), 130.9, 124.5 (d, J_C-F = 8.4 Hz), 118.3, 116.7 (d, J_C-F = 23.6 Hz), 110.6 (d, J_C-F = 8.0 Hz), 110.3 (d, J_C-F = 25.5 Hz), 56.3 (d, J_C-F = 2.0 Hz), 54.4, 43.0. Anal. calcd. for C12H10FNO2: C, 65.75; H, 4.60; N, 6.39; found: C, 65.88; H, 4.65; N, 6.43.

1.2. Synthesis of 2-(2-fluoroaryl)benzoimidazoles 2a–h

2-(2-Fluoroaryl)benzoimidazoles 2a and 2c–g are known compounds and were prepared following known procedures. Scheme SI-2 outlines the preparation of 2-(2-fluoroaryl)benzoimidazoles 2b and 2h.
Scheme SI-2: Synthesis of 2-(2-fluoroaryl)benzoimidazoles 2b and 2h

2-(2-Fluorophenyl)-5,6-dimethyl-1H-benzo[d]imidazole (2b)

To a solution of 2-fluorobenzaldehyde 9a (993 mg, 8.0 mmol, 1.00 equiv) in EtOH (48 mL) was added NaHSO₃ (8.3 g, 80.0 mmol, 10.0 equiv) in H₂O (16 mL) and the resulting mixture was stirred at rt for 1 h. Next, 4,5-dimethylbenzene-1,2-diamine 8a (1.1 g, 8.0 mmol, 1.00 equiv) was added to it. The resulting mixture was refluxed for 4 h. The reaction mixture was allowed to cool to rt and ethanol was removed under reduced pressure. The resulting residue was dissolved in a mixture of EtOAc (50 mL) and H₂O (50 mL). The organic layer was separated, washed with brine (50 mL), and then dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: 5–20% EtOAc/hexanes) to afford 2b as a white solid (mp: 200–201 °C); yield: 75% (1.44 g). ¹H NMR (400 MHz, DMSO-d₆) δ 12.37 (s, 1H), 8.26 (t, J = 7.6 Hz, 1H), 7.75–7.19 (m, 5H), 2.35 (s, 6H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ 159.8 (d, J = 249.8 Hz), 146.0, 142.2, 134.2, 131.8 (d, J = 8.6 Hz), 130.5 (d, J = 2.9 Hz), 125.4 (d, J = 3.2 Hz), 118.9 (d, J = 11.5 Hz), 116.9 (d, J = 21.7 Hz), 112.3, 20.5. Anal. Calcd. for C₁₅H₁₃FN₂: C, 74.98; H, 5.45; N, 11.66; found: C, 75.17; H, 5.49; N, 11.69.

2-(5-Bromo-2-fluorophenyl)-5,6-dichloro-1H-benzo[d]imidazole (2h)

S3
The title compound was prepared from 5-bromo-2-fluorobenzaldehyde 9b (1.62 g, 8.0 mmol), 4,5-dichlorobenzene-1,2-diamine 8b (1.42 g, 8.0 mmol) and NaHSO₃ (8.3 g, 80.0 mmol, 10.0 equiv), following the procedure described for the preparation of 2b. The crude product was purified by silica gel column chromatography (eluent: 5–20% EtOAc/hexanes) to afford 2h as a white solid (mp: 239–240 °C); yield: 79% (2.27 g). ¹H NMR (400 MHz, DMSO-d₆): δ 12.96 (s, 1H), 8.33 (dd, J = 6.5, 2.6 Hz, 1H), 8.06–7.73 (m, 3H), 7.47 (dd, J = 11.0, 8.8 Hz, 1H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ 159.2 (d, J = 252.0 Hz), 147.9 (d, J = 2.6 Hz), 143.2, 135.4 (d, J = 8.8 Hz), 132.7 (d, J = 2.8 Hz), 126.0, 120.8, 119.8 (d, J = 12.9), 119.6 (d, J = 23.5 Hz), 117.3 (d, J = 3.1 Hz). Anal. Calcd. for C₁₃H₆BrCl₂FN₂: C, 43.37; H, 1.68; N, 7.78; found: C, 43.26; H, 1.72; N, 7.74.

2-(2-Fluoro-5-nitrophenyl)-1H-benzo[d]imidazole (2i)

![2i](image)

The title compound was prepared from 2-fluoro-5-nitrobenzaldehyde 9c (1.0 g, 5.9 mmol), o-Phenylenediamine 8c (0.64 g, 5.9 mmol) and NaHSO₃ (6.1 g, 59.0 mmol, 10.0 equiv), following the procedure described for the preparation of 2b. The crude product was purified by silica gel column chromatography (eluent: 5–20% EtOAc/hexanes) to afford 2h as a yellowish-white solid (mp: 201–203 °C); yield: 33% (0.80 g). ¹H NMR (400 MHz, DMSO-d₆) δ 12.88 (s, 1H), 9.04 (dd, J = 6.3, 3.0 Hz, 1H), 8.39 (dt, J = 9.0, 3.6 Hz, 1H), 7.76–7.71 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.31–7.24 (m, 2H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ 162.9 (d, J₁₃C-F = 261.1 Hz), 144.843, 144.841 (d, J₁₃C-F = 5.9 Hz), 143.4, 135.6, 127.3 (d, J₁₃C-F = 10.9 Hz), 126.0 (d, J₁₃C-F = 5.1 Hz), 124.0, 122.8, 119.751, 119.752 (d, J₁₃C-F = 14.1 Hz), 118.96 (d, J₁₃C-F = 24.7 Hz), 112.71. LRMS (ESI+)m/z calcd for C₁₃H₆FN₃O₂ [M+H]+: 258.1; found: 258.1 (100%). Anal. Calcd. for C₁₃H₈FN₃O₂: C, 60.70; H, 3.14; N, 16.34; found: C, 60.85; H, 3.20; N, 16.40.

1.3. Preparation of N-arylenzenesulfonamides 4a–d

N-arylenzenesulfonamides 4a, 4c, and 4d are known compounds and were prepared following known procedures.¹⁰-¹² Scheme SI-3 outlines the preparation of N-phenylbenzenesulfonamid 4b.
Scheme SI-3: Synthesis of N-phenylbenzenesulfonamide 4b

![Scheme SI-3](image)

2,5-Difluoro-N-phenylbenzenesulfonamide (4b)

To a solution of aniline 11 (96 mg, 1.0 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 mL) were successively added pyridine (237 mg, 3.0 mmol, 3.0 equiv) and 12 (212 mg, 1.0 mmol, 1.0 equiv) at 0 °C and the resulting mixture was stirred at rt for overnight. It was quenched by adding 1N HCl (5 mL) and then diluted with CH$_2$Cl$_2$ (15 mL). The organic layer was separated, washed with brine (10 mL), and then dried over anhydrous Na$_2$SO$_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: 5–20% EtOAc/hexanes) to afford 4b as white solid; yield: 78% (253 mg). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57–7.53 (m, 1H), 7.30–7.13 (m, 7H, merged with CDCl$_3$ peak), 6.89 (s, 1H). $^{13}$C{(^1)H} NMR (100 MHz, CDCl$_3$) δ 157.8 (dd, $J = 248.4, 2.6$ Hz), 154.7 (dd, $J = 250.4, 2.9$ Hz), 135.3, 129.5, 128.0 (dd, $J = 16.2, 6.9$), 126.2, 122.0 (dd, $J = 24.0, 8.8$ Hz), 121.7, 118.3 (dd, $J = 24.2, 7.9$ Hz), 117.8 (d, $J = 26.9$ Hz). Anal. calcd. for C$_{12}$H$_9$F$_2$NO$_2$S: C, 53.53; H, 3.37; N, 5.20; found: C, 53.66; H, 3.32; N, 5.26.

2. X-Ray Crystallography

- **The methods to cultivate the crystals of products 2h and 2k:**

  For compound 3c:

  Compound 3c (10 mg) was dissolved in hexanes/EtOAc = 3:1 (2 mL) in a 10 mL RB flask and the resultant solution was kept in the fume hood at room temperature for 3 days.

  For compound 5a:

  Product 5a (10 mg) was dissolved in hexane/EA = 3:1 (2 mL) in a 10 mL RB flask and the resultant solution was kept in the fume hood at room temperature for 2 days.
• **X-ray crystallography**: X-ray reflections were collected on a Bruker APEX-II, CCD diffractometer using Mo Kα (λ = 0.71073 Å) radiation. Data reduction was performed using Bruker SAINT Software. Structure was solved in Olex2-1.5- alpha software using ShelXT settings and refined using ShelXL-2014 settings with anisotropic displacement parameters for non-H atoms. A check of the final CIF file using PLATON did not show any missed symmetry. The crystallographic parameters for the structure are summarized in table SI-2.

• **Crystal data parameters for compound 3c and 5a**

Table SI-1: The crystallographic parameters for compound 3c and 5a

<table>
<thead>
<tr>
<th>Crystal Data</th>
<th>3c</th>
<th>5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula unit</td>
<td>C_{23} H_{16} Br N_{3} O_{2}</td>
<td>C_{28} H_{22} N_{2} O_{4} S</td>
</tr>
<tr>
<td>Formula wt.</td>
<td>446.30</td>
<td>482.53</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>T [K]</td>
<td>296</td>
<td>296</td>
</tr>
<tr>
<td>a [Å]</td>
<td>8.8245(7)</td>
<td>11.3157(15)</td>
</tr>
<tr>
<td>b [Å]</td>
<td>12.584(1)</td>
<td>17.700(3)</td>
</tr>
<tr>
<td>c [Å]</td>
<td>17.0500(14)</td>
<td>12.6167(18)</td>
</tr>
<tr>
<td>α [°]</td>
<td>78.499(2)</td>
<td>90</td>
</tr>
<tr>
<td>β [°]</td>
<td>83.899(2)</td>
<td>111.045(4)</td>
</tr>
<tr>
<td>γ [°]</td>
<td>89.971(2)</td>
<td>90</td>
</tr>
<tr>
<td>Volume [Å³]</td>
<td>1844.4(3)</td>
<td>2358.4(6)</td>
</tr>
<tr>
<td>Space group</td>
<td>P -1</td>
<td>P 1 21/c 1</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ρ_{calc} (g/cm³)</td>
<td>1.607</td>
<td>1.359</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
<td>2.255</td>
<td>0.176</td>
</tr>
<tr>
<td>Reflns. Collected</td>
<td>6438</td>
<td>4390</td>
</tr>
<tr>
<td>Observed reflns.</td>
<td>5657</td>
<td>2284</td>
</tr>
<tr>
<td>R₁ [I&gt;2σ(I), wR₂]</td>
<td>0.0455, 0.1131</td>
<td>0.0489, 0.1285</td>
</tr>
<tr>
<td>GOF</td>
<td>1.065</td>
<td>0.918</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Instrument</td>
<td>Bruker APEX-II</td>
<td>Bruker APEX-II</td>
</tr>
<tr>
<td>X-ray</td>
<td>MoK(\alpha;\lambda=0.71073)</td>
<td>MoK(\alpha;\lambda=0.71073)</td>
</tr>
<tr>
<td>CCDC Reference No.</td>
<td>2263545</td>
<td>2270204</td>
</tr>
</tbody>
</table>

**Figure SI-1.** ORTEP diagram of 3c with 50% probability ellipsoid.

**Figure SI-2.** ORTEP diagram of 5a with 40% probability ellipsoid.
3. References


NMR Spectra of Compounds
$\text{H NMR (400 MHz, CDCl}_3\text{) spectrum of compound 1d.}$

$\text{C}^{13}\text{H NMR (100 MHz, CDCl}_3\text{) spectrum of compound 1d.}$
$^1$H NMR (400 MHz, DMSO-$d_6$) spectrum of compound 2b.

$^{13}$C{$_1^1$H} NMR (100 MHz, DMSO-$d_6$) spectrum of compound 2b.
$^{1}$H NMR (400 MHz, DMSO-$d_6$) spectrum of compound 2h.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 2h.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 2i.

$^{13}$C{^1}H NMR (100 MHz, CDCl$_3$) spectrum of compound 2i.
$^{1}H$ NMR (400 MHz, CDCl$_3$) spectrum of compound 4b.
$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 4b.

$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3a

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3a
$^{1}$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3b.

$^{13}$C($^{1}$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3b.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3c.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3c.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3d.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3d.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3e.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3e.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3f.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3f.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3g.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3g.
$^{1}H$ NMR (400 MHz, CDCl$_3$) spectrum of compound 3h.

$^{13}C$($^{1}H$) NMR (100 MHz, CDCl$_3$) spectrum of compound 3h.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3i.

$^{13}$C{H} NMR (100 MHz, CDCl$_3$) spectrum of compound 3i.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3j.

$^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) spectrum of compound 3j.
$^{1}H$ NMR (400 MHz, CDCl$_3$) spectrum of compound 3k.

$^{13}C\{^1H\}$ NMR (100 MHz, CDCl$_3$) spectrum of compound 3k.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3l.

$^{13}$C{^1}H NMR (100 MHz, CDCl$_3$) spectrum of compound 3l.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3m.

$^{13}$C$^1$H NMR (100 MHz, CDCl$_3$) spectrum of compound 3m.
$^{1}H$ NMR (400 MHz, CDCl$_3$) spectrum of compound 3n.

$^{13}C{(^1H)}$ NMR (100 MHz, CDCl$_3$) spectrum of compound 3n.
1H NMR (400 MHz, CDCl3) spectrum of compound 3o.

13C{1H} NMR (100 MHz, CDCl3) spectrum of compound 3o.
H NMR (400 MHz, CDCl₃) spectrum of compound 3p.

13C(1H) NMR (100 MHz, CDCl₃) spectrum of compound 3p.
H NMR (400 MHz, CDCl₃) spectrum of compound 3q.

13C{¹H} NMR (100 MHz, CDCl₃) spectrum of compound 3q.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3r.

$^{13}$C{H} NMR (100 MHz, CDCl$_3$) spectrum of compound 3r.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3s.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3s.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3t.

$^{13}$C\{H\} NMR (100 MHz, CDCl$_3$) spectrum of compound 3t.
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3u.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) spectrum of compound 3u.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5a.

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of compound 5a.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5b

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of compound 5b.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5c

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of compound 5c
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5d

$^{13}$C$\{^1$H$\}$ NMR (100 MHz, CDCl$_3$) of compound 5d
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5e

$^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) of compound 5e.
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5f

$^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) of compound 5f
^1H NMR (400 MHz, CDCl$_3$) of compound 5g

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of compound 5g
$^1$H NMR (500 MHz, CDCl$_3$) of compound 5h

$^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) of compound 5h