Supplementary Material

N,N-Dialkyl-\( N' \)-Chlorosulfonyl Chloroformamidines in Heterocyclic Synthesis. Part XIV. Synthesis and Reactivity of the New Benzo[4,5]imidazo[1,2-b][1,2,6]thiadiazine Ring System

Dylan Innes,\(^A\) Michael V. Perkins,\(^A\) Andris J. Liepa,\(^B\) and Craig L. Francis\(^B,C\)

\(^A\)School of Chemical and Physical Sciences, Flinders University, Bedford Park, SA 5042, Australia.

\(^B\)Biomedical Synthetic Chemistry Group, CSIRO, Clayton, Vic. 3168, Australia.

\(^C\)Corresponding author. Email: craig.francis@csiro.au

S1 Synthesis of dichlorides 1a-c
S1-S3 Synthesis and spectral data for benzimidazole derivatives 4, 8, 11, 13, and 16
S3-S4 Crystal structures for compounds 6c, 6d, and 15b
S5-S9 \(^1\)H NMR and \(^13\)C NMR spectra for benzimidazol-2-ylacetonitriles 4b-d
S10-S24 \(^1\)H NMR and \(^13\)C NMR and \(^19\)F NMR spectra for benzimidazo-thiadiazines 6
S25-S26 \(^1\)H NMR and \(^13\)C NMR spectra for ethyl benzimidazol-2-yl-acetate 8
S27-S32 \(^1\)H NMR and \(^13\)C NMR spectra for ethyl benzimidazo-thiadiazine carboxylates 9
S33 \(^1\)H NMR spectrum for 2-(4-chlorophenacyl)benzimidazole 11
S34-S35 \(^1\)H NMR and \(^13\)C NMR spectra for 4-chlorophenyl benzimidazo-thiadiazine 12
S36-S37 \(^1\)H NMR and \(^13\)C NMR spectra for 2-tosylmethyl-benzimidazole 13
S38-S48 \(^1\)H NMR and \(^13\)C NMR spectra for tosyl benzimidazo compounds 14 and 15
S49-S51 \(^1\)H NMR, \(^13\)C NMR and \(^19\)F NMR spectra for trifluoromethyl-benzimidazole 16
S52-S57 \(^1\)H NMR, \(^13\)C NMR and \(^19\)F NMR spectra for trifluoromethyl benzimidazo-pyrimidines 19 and 20
S58-S59 \(^1\)H NMR and \(^13\)C NMR spectra for 2-methyl benzimidazo compounds 22 or 23
S60-S67 \(^1\)H NMR and \(^13\)C NMR spectra for \(N5\)-alkyl substituted benzimidazo-thiadiazines 26
S68-S69 \(^1\)H NMR and \(^13\)C NMR spectra for \(N5\)-acyl substituted benzimidazo-thiadiazine 28
S70-S71 \(^1\)H NMR and \(^13\)C NMR spectra for 4,5-dimethyl benzimidazo-thiadiazine 29
Synthesis of dichlorides 1a-c

The dichlorides 1a-c were prepared from sulfonyl chloride and the corresponding dialkyl cyanamide as previously described (Scheme S1).[6]

\[
\begin{align*}
\text{R}_2\text{N} & \equiv \text{N} \quad \text{SO}_2\text{Cl}_2 \quad \rightarrow \quad \text{R}_2\text{N} \equiv \text{N} \quad \text{SO}_2\text{Cl}_2 \\
\text{N} & \quad \text{Cl} \\
1 & \quad \text{R}_2\text{N} \\
\text{Me}_2\text{N} & \quad 1\text{a} \\
\text{Et}_2\text{N} & \quad 1\text{b} \\
\text{N} & \quad 1\text{c}
\end{align*}
\]

Scheme S1

Synthesis of benzimidazole derivatives 4.

5,6-Dimethylbenzimidazole 4b[7] was prepared following published procedures,[7,8] in which 4,5-dimethyl-1,2-diaminobenzene 5b was heated with ethyl cyanoacetate. However, attempts to employ this procedure for preparation of the 5,6-dihalogenated derivatives 4c and 4d[9] were unsuccessful, requiring the use of the relatively more reactive 2-cyanoacetimidic acid ethyl ester.[10]

\[
\begin{align*}
\text{H} & \quad 4\text{a} \\
\text{Me} & \quad 4\text{b} \\
\text{Cl} & \quad 4\text{c} \\
\text{F} & \quad 4\text{d}
\end{align*}
\]

2-(5,6-Dichloro-1H-benzo[d]imidazol-2-yl)acetonitrile 4c

A stirred mixture of 4,5-dichlorobenzene-1,2-diamine 5c (1.0 g, 5.7 mmol) and 2-cyanoacetimidic acid ethyl ester hydrochloride[9] (1.1 g, 7.6 mmol) in CH$_2$Cl$_2$ (30 mL) was heated at reflux overnight. The reaction mixture was cooled to room temperature and the precipitate was collected, washed with water and purified by column chromatography. Elution with 60% EtOAc in hexanes provided the title compound 4c (0.63 g, 49%) as a white solid; mp 200 °C dec.; (Found: [M + H]$^+$ 225.9935; C$_9$H$_6$Cl$_2$N$_3$, requires [M + H]$^+$ 225.9939); $^1$H NMR (600 MHz, DMSO-$d_6$ + 1 drop conc. HCl) 7.98 (2H, s, Ar H), 4.64 (2H, s, CH$_2$). $^{13}$C NMR (150 MHz, DMSO-$d_6$ + 1 drop conc. HCl) 147.63, 134.85, 126.92, 116.46, 115.31, 18.20.

2-(5,6-Difluoro-1H-benzo[d]imidazol-2-yl)acetonitrile 4d[9]

A mixture of 4,5-difluorobenzene-1,2-diamine 5d (195 mg, 1.4 mmol) and 2-cyanoacetimidic acid ethyl ester hydrochloride[10] (250 mg, 1.7 mmol) in CH$_2$Cl$_2$ (7 mL) was stirred at 40 °C overnight. After cooling, the precipitate was collected, washed with water and with CH$_2$Cl$_2$ (3 × 10 mL) to give the title
compound \textit{4d} (184 mg, 70\%) as a tan solid; mp 202–203 °C (lit\cite{9} 210–212 °C); \textit{Found: [M + H]\textsuperscript{+} 194.0525; C\textsubscript{9}H\textsubscript{6}N\textsubscript{3}F\textsubscript{2} requires [M + H]\textsuperscript{+} 194.0530}; \textit{1H NMR} (400 MHz, DMSO-\textit{d}\textsubscript{6}) 7.62 (2H, t, \(J\text{ 10.9 Hz, ArH}\)), 4.37 (2H, s, CH\textsubscript{2}); \textit{13C NMR} (150 MHz, DMSO-\textit{d}\textsubscript{6} + 1 drop conc. HCl) 149.56 (d, \(J\text{ 17.0 Hz, ArH}\)), 147.93 (d, \(J\text{ 17.0 Hz}\)), 146.54, 128.86 (t, \(J\text{ 6.1 Hz}\)), 114.76, 103.37 (dd, \(J\text{ 17.0, 7.2 Hz}\), 17.94.

\textit{Ethyl 2-(1H-benzo[d]imidazol-2-yl)acetate} \textit{8} \textsuperscript{[8]}

Prepared by a literature procedure\cite{11}. Thus, acetyl chloride (1 mL, 14 mmol) was added dropwise to a stirred solution of benzimidazole acetonitrile \textit{4a} (500 mg, 3.18 mmol) in EtOH (8 mL) at 0 °C. The reaction mixture was heated at reflux for 2 h, cooled to room temperature and the remaining solvent removed \textit{in vacuo}. The hydrochloride salt was dissolved in water and neutralised with a saturated solution of NaHCO\textsubscript{3}. Extraction with CH\textsubscript{2}Cl\textsubscript{2} (3 × 20 mL) provided the title compound \textit{8} (605 mg, 93\%) as a brown solid; mp 106–108 °C (lit.\cite{8} 128.5–129.5 °C); \textit{1H NMR} (600 MHz, DMSO-\textit{d}\textsubscript{6}) 7.56–7.48 (2H, m, ArH), 7.20–7.12 (2H, m, ArH), 4.13 (2H, q, \(J\text{ 7.1 Hz, CH}2\textCH3\)), 3.97 (2H, s, ArCH\textsubscript{2}), 1.20 (3H, t, \(J\text{ 7.1 Hz, CH}2\textCH3\)); \textit{13C NMR} (150 MHz, DMSO-\textit{d}\textsubscript{6}) 168.72, 147.75, 138.71, 121.54, 114.75, 60.81, 35.10, 14.03.

\textit{2-(1H-Benzimidazol-2-yl)-1-(4-chlorophenyl)ethan-1-one} \textit{11} \textsuperscript{[12]}

Prepared by a literature procedure\cite{12} using acetonitrile as solvent in the first step with the modification of heating the tri-benzoylated intermediate in \(n\)-BuOH at 110 °C for 2 h rather than in 2-propanol at reflux. The title compound \textit{11} (60\% yield) was obtained as a bright yellow solid; mp 225–228 °C (lit.\cite{12} 226–228 °C). \textit{1H NMR} (600 MHz, DMSO-\textit{d}\textsubscript{6}) 12.32 and 12.24 (1H, 2 x br s, NH), 8.09 (0.30H, d, \(J\text{ 8.5 Hz, ArH}\)), 7.87 (1.6H, d, \(J\text{ 8.5 Hz, ArH}\)), 7.64 (0.32H, d, \(J\text{ 8.6 Hz, ArH}\)), 7.51 (1.6H, d, \(J\text{ 8.6 Hz, ArH}\)), 7.56 and 7.37 (2H, 2 x m, H-4,7), 7.15–7.18 (2H, m, H-5,6), 6.03 (1H, \(s\), C=CH-C=O), 4.67 (0.41H, \(s\), CH\textsubscript{2}).
A solution of 2-chloromethylbenzimidazole (0.57 g, 3.4 mmol) and sodium p-toluenesulfinate (1.6 g, 9 mmol) in freshly distilled DMSO (20 mL) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with brine (4 × 50 mL) to remove the DMSO and excess sulfinate salts. The organic phase was dried (Na₂SO₄), and the solvent was removed in vacuo to provide the title compound 13 (0.81 g, 83%) as a tan solid; mp 206–208 °C (lit.[13] 202 °C); ¹H NMR (600 MHz, DMSO-­d₆) 12.63 (1H, br. s, NH), 7.65 (2H, d, J 8.0 Hz, ArH), 7.53 (2H, dd, J 6.2, 2.9 Hz, ArH), 7.40 (2H, d, J 8.0 Hz, ArH), 7.18 (2H, dd, J 6.2, 2.9 Hz, ArH), 4.94 (2H, s, CH₂), 2.39 (3H, s, CH₃); ¹³C NMR (150 MHz, DMSO-d₆) 144.68, 142.52, 135.80, 129.75, 127.93, 122.09, 55.84, 21.09.

3-(1H-Benzimidazol-2-yl)-1,1,1-trifluoropropan-2-one

Prepared by a literature procedure.[15] The title compound 16 (300 mg, 44%) was obtained as a white powder; mp 280–282 °C (lit.[15] 279–280 °C dec.); ¹H NMR (600 MHz, DMSO-d₆) 12.68 (2H, br s, 2 x NH), 7.51 (2H, br s, ArH), 7.25–7.22 (2H, m, ArH), 5.41 (1H, s, C=CH₂COF₃); ¹³C NMR (150 MHz, DMSO-d₆) 167.96 (q, J 30.5 Hz), 151.94, 130.30, 123.13, 118.83 (q, J 288.9 Hz), 111.70 (m), 71.69; ¹⁹F (565 MHz MHz; DMSO-d₆) −74.48.

References
Additional Crystal Structures

**Figure S1.** ORTEP diagrams of 6c and 6d. A molecule of DMSO is omitted from the crystal structure of 6d for clarity.

**Figure S2.** ORTEP diagram of 15b.
$^1$H NMR spectrum for 4b (600 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 4c (600 MHz; DMSO-$d_6$ + 1 drop conc. HCl)
$^{13}$C NMR spectrum for 4c (150 MHz; DMSO-$d_6$ + 1 drop conc. HCl)
$^1$H NMR spectrum for 4d (400 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 4d (150 MHz; DMSO-$d_6$ + 1 drop conc. HCl)
$^1$H NMR spectrum for 6a (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6a (150 MHz; 55 °C; DMSO-$d_6$)
$^1$H NMR spectrum for 6b (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6b (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 6c (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6c (100 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 6d (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6d (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 6e (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6e (100 MHz; 55 °C; DMSO-$d_6$)
$^1$H NMR spectrum for **6f** (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6f (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 6g (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 6g (150 MHz; DMSO-$d_6$)
$^{19}$F NMR spectrum for 6g (565 MHz, DMSO-$d_6$)
$^1$H NMR spectrum for 8 (600 MHz; DMSO-$d_6$)
$^{13}\text{C}$ NMR spectrum for 8 (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 9a (600 MHz; DMSO-$d_6$)
\(^{13}\)C NMR spectrum for 9a (150 MHz; DMSO-\(d_6\))
$^1$H NMR spectrum for 9b (600 MHz; DMSO-$d_6$)
$^{13}$C NMR for spectrum 9b (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 9c (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 9c (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 11 (600 MHz; DMSO-$d_6$)

~20%  ~80%
$^1$H NMR spectrum for 12 (600 MHz; DMSO-\textit{d}_6)
$^{13}$C NMR spectrum for 12 (150 MHz; DMSO-$d_6$)

![Chemical Structure Image]

S35
$^1$H NMR spectrum for 13 (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 13 (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 14a (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 14a (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 14a (600 MHz; CDCl₃)
$^{13}$C NMR spectrum for 14a (150 MHz; CDCl$_3$)
HMQC NMR spectrum for **14a** (600 × 150 MHz; CDCl₃)
$^1$H NMR spectrum for 15a (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 15a (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 14b (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 14b (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for $15b$ (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 15b (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 16 (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 16 (150 MHz; DMSO-$d_6$)
$^{19}$F NMR spectrum for 16 (565 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 19 (600 MHz; DMSO-d$_6$)
$^{13}$C NMR spectrum for 19 (150 MHz; DMSO-$d_6$)
$^{19}$F NMR spectrum for 19 (565 MHz, DMSO-$d_6$)
$^1$H NMR spectrum for 20 (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for **20** (150 MHz; 60 °C; D1 = 5s; DMSO-$d_6$)
$^{19}$F NMR spectrum for 20 (565 MHz, DMSO-$d_6$)
$^1$H NMR spectrum for 22/23 (600 MHz; CDCl$_3$)

or
$^{13}$C NMR spectrum for 22/23 (150 MHz; CDCl$_3$)

or

or
$^1$H NMR spectrum for 26a (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 26a (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 26b (600 MHz; CDCl$_3$)
$^{13}$C NMR spectrum for 26b (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 26c (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for $26c$ (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 26d (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 26d (150 MHz; DMSO-$d_6$)
$^1$H NMR spectrum for 28 (600 MHz; DMSO-$d_6$)
$^{13}$C NMR spectrum for 28 (150 MHz; DMSO-$d_6$)
1H NMR spectrum for 29 (600 MHz; CDCl3)
$^{13}$C NMR spectrum for 29 (150 MHz; CDCl$_3$)