A Highly Efficient Procedure for 3-Sulfenylation of Indole-2-Carboxylates

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General. All starting materials, solvents and reagents were obtained from Aldrich Chemical Company (St. Louis, MO, USA) and used without further treatment. ^{1}H NMR spectra were obtained on a Varian INOVA spectrometer using $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard or DMSO-d_6 as the solvent and DMSO as the internal standard. MS spectra were obtained on a Micromass Platform LC mass spectrometer. The experiments were conducted in the positive ion mode. Elemental analysis was conducted by Quantitative Technologies Inc.

General Procedure for Sulfenylation of Indole-2-carboxylates.

To a cooled solution of *N*-chlorosuccinimide (1.2 eq) in dichloromethane (8 mL/mmol) at -78°C, the appropriate thiol (1.2 eq) was added. The reaction was warmed to 0°C over 15 minutes and a solution of the appropriate indole-2-carboxylate (1 eq) in dichloromethane (2 mL/mmol) was added. The reaction was stirred at 0°C for 1 hour, then concentrated under reduced pressure. The residue was suspended in H_2O (6 mL/mmol) and stirred for 1 hour. The solid was filtered and recrystallized from EtOAc/hexanes to yield the desired product.

3-(3-Chloro-propylsulfanyl)-5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid methyl ester (entry 2, Table 1): Prepared by the sulfenylation method described above from 3-chloro-1-propanethiol and 5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid methyl ester to provide the desired ester (86%). 400 MHz

^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, *J* = 9.0 Hz), 7.21 (d, 1H, *J* = 2.4 Hz), 7.04 (dd, 1H, *J* = 9.0, 2.4 Hz), 3.98 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H), 3.65 (t, 2H, *J* = 6.4 Hz), 2.94 (t, 2H, *J* = 6.8 Hz), 1.91 (m, 2H). MS *m/z* 328, 330 (M+1).

5-Methoxy-1-methyl-3-phenylsulfanyl-1*H*-indole-2-carboxylic acid methyl ester (entry 3, Table 1): Prepared by the sulfenylation method described above from thiophenol and 5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid methyl ester to provide the desired ester (99%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.46 (d, 2H, *J* = 7.1 Hz), 7.14 (m, 5H), 6.95 (s, 1H), 4.01 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H). MS *m/z* 328 (M+1).

5-Methoxy-1-methyl-3-p-tolylsulfanyl-1*H*-indole-2-carboxylic acid amide (entry 4, Table 1): Prepared by the sulfenylation method described above from 4-methylthiophenol and 5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid amide to provide the desired amide (96%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.37 (d, 1H, *J* = 8.9 Hz), 7.08 (s, 1H), 7.02 (m, 4H), 4.16 (s, 3H), 3.80 (s, 3H), 2.26 (s, 3H). MS *m/z* 327 (M+1).

3-Benzylsulfanyl-5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid amide (entry 5, Table 1): Prepared by the sulfenylation method described above from benzyl mercaptan and 5-methoxy-1-methyl-1*H*-indole-2-carboxylic acid amide to provide the desired amide (91%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.31 (d, 1H, *J* = 9.6 Hz), 7.18 (m, 2H), 7.02 (m, 4H), 4.08 (s, 3H), 3.89 (s, 2H), 3.83 (s, 3H). MS *m/z* 327 (M+1). Anal. Calc'd for $C_{19}H_{20}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; Found: C, 66.03; H, 5.57; N, 8.23.

5-Methoxy-3-(2-methoxycarbonyl-ethylsulfanyl)-1*H*-indole-2-carboxylic acid methyl ester (entry 7, Table 2): Prepared by the sulfenylation method described above from methyl 3-mercaptopropionate and 5-methoxy-indole-2-carboxylic acid methyl ester to provide the desired ester (94%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 1H, *J* = 9.0 Hz), 7.20 (d, 1H, *J* = 2.4 Hz), 7.01 (dd, 1H, *J* = 9.0, 2.4 Hz), 3.88 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 3.09 (t, 2H, *J* = 7.3 Hz), 2.51 (t, 2H, *J* = 7.3 Hz). MS *m/z* 324 (M+1).

3-(2-*tert*-Butoxycarbonylamino-ethylsulfanyl)-5-methoxy-1*H*-indole-2-carboxylic acid methyl ester (entry 8, Table 2): Prepared by the sulfenylation method described above from (2-mercapto-ethyl)-carbamic acid *tert*-butyl ester and 5-methoxy-indole-2-carboxylic acid methyl ester to provide the desired ester (97%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.39 (d, 1H, *J* = 8.9 Hz), 7.15 (d, 1H, *J* = 2.6 Hz), 6.99 (dd, 1H, *J* = 8.9, 2.6 Hz), 3.90 (s, 3H), 3.81 (s, 3H), 3.09 (t, 1H, *J* = 7.2 Hz), 2.98 (m, 2H), 2.77 (t, 2H, *J* = 7.0 Hz), 2.49 (s, 9H). MS *m/z* 381 (M+1).

3-*m*-Tolylsulfanyl-1*H*-indole-2-carboxylic acid ethyl ester (entry 9, Table 2): Prepared by the sulfenylation method described above from 3-methylthiophenol and indole-2-carboxylic acid ethyl ester to provide the desired ester (81%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.49 (d, 1H, *J* = 8.3 Hz), 7.39 (d, 1H, *J* = 8.3 Hz), 7.28 (t, 1H, *J* = 7.6 Hz), 7.05 (m, 2H), 6.92 (s, 1H), 6.86 (d, 1H, *J* = 7.6 Hz), 6.77 (d, 1H, *J* = 7.6 Hz), 4.27 (q, 2H, *J* = 7.1 Hz), 2.14 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). MS *m/z* 312 (M+1).

3-(3-Methoxy-phenylsulfanyl)-1*H*-indole-2-carboxylic acid ethyl ester (entry 10, Table 2): Prepared by the sulfenylation method described above from 3-methoxythiophenol and indole-2-carboxylic acid ethyl ester to provide the desired ester (76%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.51 (d, 1H, *J* = 8.3 Hz), 7.41 (d, 1H, *J* = 8.3 Hz), 7.29 (m, 1H), 7.08 (m, 2H), 6.64 (d, 1H, *J* = 7.8 Hz), 6.55 (m, 2H), 4.28 (q, 2H, *J* = 7.1 Hz), 3.60 (s, 3H), 1.21 (t, 3H, *J* = 7.1 Hz). MS *m/z* 328 (M+1). Anal. Calc'd for $C_{18}H_{17}NO_3S$ C, 66.03; H, 5.23; N, 4.28; Found: C, 65.69; H, 5.07: N, 4.20.

3-(3-Bromo-phenylsulfanyl)-1*H*-indole-2-carboxylic acid ethyl ester (entry 11, Table 2): Prepared by the sulfenylation method described above from 3-bromothiophenol and indole-2-carboxylic acid ethyl ester to provide the desired ester (64%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.53 (d, 1H, *J* = 8.3 Hz), 7.46 (d, 1H, *J* = 8.1 Hz, 1H), 7.33 (td, 1H, *J* = 7.6, 1.1 Hz), 7.26 (m, 1H), 7.13 (m, 3H), 7.01 (m, 1H), 4.28 (q, 2H, *J* = 7.1 Hz), 1.20 (t, 3H, *J* = 7.08 Hz). MS *m/z* 376, 378 (M+1).

3-(4-Bromo-phenylsulfanyl)-5-fluoro-1*H*-indole-2-carboxylic acid methyl ester (entry 13, Table 2): Prepared by the sulfenylation method described above from 4-bromothiophenol and 5-fluoro-indole-2-

carboxylic acid methyl ester to provide the desired ester (51%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.51 (dd, 1H, *J* = 9.0, 4.6 Hz), 7.36 (d, 2H, *J* = 8.5 Hz), 7.17 (td, 1H, *J* = 9.0, 2.4 Hz), 7.07 (dd, 1H, *J* = 9.0, 2.4 Hz), 6.96 (d, 2H, *J* = 8.5 Hz), 3.81 (s, 3H). MS *m/z* 380, 382 (M+1). Anal. Calc'd for $C_{16}H_{11}BrFNO_2S$: C, 50.54; H, 2.92; N, 3.68; Found: C, 50.74; H, 2.56; N, 3.68.

3-(2-Methoxy-phenylsulfanyl)-5-fluoro-1*H*-indole-2-carboxylic acid methyl ester (entry 14, Table 2): Prepared by the sulfenylation method described above from 2-methoxythiophenol and 5-fluoro-indole-2-carboxylic acid methyl ester to provide the desired ester (48%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.51 (dd, 1H, *J* = 9.0, 4.4 Hz), 7.16 (td, 1H, *J* = 9.3, 2.7 Hz), 7.00 (m, 3H), 6.64 (td, 1H, *J* = 7.6, 1.5), 6.36 (dd, 1H, *J* = 7.6, 1.5 Hz), 3.83 (s, 3H), 3.79 (s, 3H). MS *m/z* 332 (M+1).

General Procedure for the Amide Coupling (7): 5-Methoxy-indole-2-carboxylic acid (1eq) was suspended in acetonitrile (3.5 mL/mmol). CDI (1.1eq) was added and the mixture was heated to reflux for one hour. A mixture of the appropriate amine (1eq) and DBU (1.05eq) in acetonitrile (2 mL/mmol) was stirred at room temperature for 25 minutes, then added to the indole mixture. The reaction was heated to reflux overnight. The mixture was cooled and poured into ice water (15 mL/mmol) and then filtered to yield the desired amide.

5-Methoxy-1*H*-indole-2-carboxylic acid (2-mercapto-ethyl)-amide (7a): Prepared by the amide coupling method described above from 5-methoxy-indole-2-carboxylic acid and cysteamine hydrochloride to yield the desired amide (89%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 1H, *J* = 8.7 Hz), 7.05 (d, 1H, *J* = 2.2 Hz), 6.97 (dd, 1H, *J* = 8.7, 2.2 Hz), 6.79 (s, 1H), 3.85 (s, 3H), 3.67 (m, 2H), 2.81 (dt, 2H, *J* = 8.5, 6.3 Hz), 1.44 (t, 1H, *J* = 8.5 Hz). MS *m/z* 251 (M+1).

5-Methoxy-1*H*-indole-2-carboxylic acid (2-mercapto-2-methyl-propyl)-amide (7b): Prepared by the amide coupling method described above from 5-methoxy-indole-2-carboxylic acid and 1-amino-2-methyl-propane-2-thiol to yield the desired amide (95%). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 1H, *J* = 9.0 Hz),

7.07 (d, 1H, *J* = 2.4 Hz), 6.97 (dd, 1H, *J* = 9.0, 2.4 Hz), 6.85 (d, 1H, *J* = 2.5 Hz), 3.85 (s, 3H), 3.55 (d, 2H, *J* = 6.2 Hz), 1.70 (s, 1H), 1.43 (s, 6H). MS *m/z* 279 (M+1).

3-Methoxy-7,8-dihydro-6*H*,10*H*-5-thia-8,10-diaza-benzo[*a*]azulen-9-one (8a): Prepared by the sulfenylation method described above from 5-methoxy-1*H*-indole-2-carboxylic acid (2-mercapto-ethyl)-amide to provide the desired cyclic product (75%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.33 (d, 1H, *J* = 8.9 Hz), 6.97 (d, 1H, *J* = 8.9 Hz), 6.93 (s, 1H), 3.84 (s, 3H), 3.78 (m, 2H), 3.23 (m, 2H). MS *m/z* 249 (M+1).

3-Methoxy-6,6-dimethyl-7,8-dihydro-6*H*,10*H*-5-thia-8,10-diaza-benzo[*a*]azulen-9-one (8b): Prepared by the sulfenylation method described above from 5-methoxy-1*H*-indole-2-carboxylic acid (2-mercapto-2-methyl-propyl)-amide to provide the desired cyclic product (60%). 400 MHz ^{1}H NMR (DMSO-d_6) δ 8.29 (t, 1H, *J* = 6.0 Hz), 7.29 (d, 1H, *J* = 8.7 Hz), 6.86 (m, 2H), 3.74 (s, 3H), 3.17 (d, 2H, *J* = 6.0 Hz), 1.37 (s, 6H). MS *m/z* 277 (M+1).