Full Experimental and Spectral Details

Studies on the Synthesis of Indothiazinone and Its Derivatives via Direct 3-Acylation of Indole

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General Experimental

Unless otherwise noted, all reactions were performed under an argon atmosphere in oven-dried glassware. The starting materials and solvents were used as received from commercial suppliers without further purification. Thin layer chromatography was carried out using Merck silica gel 60 F₂₅₄ plates, and visualized with a combination of UV, *p*-anisaldehyde, and potassium permanganate staining. Flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm, 230-400 mesh). NMR spectra were recorded in deuterated solvents on a Bruker 500 (500 MHz for ¹H; 125 MHz for ¹³C) spectrometer. ¹H and ¹³C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), bd (broad doublet), dd (doublet of doublets), dt (doublet of triplets), or dq (doublet of quartets); the coupling constants are reported in hertz (Hz). High-resolution fast atom bombardment (EI) mass spectra were recorded using a JEOL JMS-700 mass spectrometer at the Daegu center of KBSI, Korea.

Experimental Procedures

Preparation of thiazole-3-carbonyl chloride solution

Thiazole-2-carboxylic acid was synthesized from 3-bromothiazole according to the reported procedure.^[7] To a stirred solution of thiazole-3-carboxylic acid (546.6 mg, 4 mmol) in dichloromethane (20 mL), oxalyl chloride (0.31 mL, 3.64 mmol) and a drop of N,N-dimethylamine were added subsequently at 0°C. After 30 min, the reaction temperature was elevated to rt. After completion of reaction, which was monitored with a generation of methyl ester in methanol on TLC, the resulting solution was used as is for direct 3-acylation of indole.

Synthesis of indothiazinone (**1**)

A solution of diethylaluminium chloride (25w% in dichloromethane, 1.5 mL, 3 mmol) was added to a stirred solution of indole (234.3 mg, 2 mmol) in dichloromethane (10 mL) at 0°C. After stirring 30 min, a solution of thiazole-3-carbonyl chloride above (0.2M in dichloromethane, 20 mL, 4 mmol) was added and stirred for 2h at 0°C. The resulting mixture was quenched with water, extracted with dichloromethane, and dried over anhydrous MgSO₄. Volatiles were removed under reduced pressure, and the residue was purified by SiO₂ flash chromatography to afford indothiazinone (**1**, 288 mg, 63%) as yellow solid.

(1-methyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**6**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (1 mL), DBU (0.06 mL, 0.4 mmol) and iodomethane (0.02 mL, 0.4 mmol) were added subsequently at 0°C and stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO₄. Volatiles were removed under reduced pressure, and the residue was purified by SiO₂ flash chromatography to afford (1-methyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**6**, 38.9 mg, 80%) as yellow solid.

(1-allyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**7**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (1 mL), DBU (0.06 mL, 0.4 mmol) and allyl bromide (0.03 mL, 0.4 mmol) were added subsequently at 0°C and

stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO_4 . Volatiles were removed under reduced pressure, and the residue was purified by SiO_2 flash chromatography to afford (1-allyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**7**, 49.7 mg, 93%) as yellow solid.

(1-benzyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**8a**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (1 mL), DBU (0.06 mL, 0.4 mmol) and benzyl bromide (0.05 mL, 0.4 mmol) were added subsequently at 0°C and stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO_4 . Volatiles were removed under reduced pressure, and the residue was purified by SiO_2 flash chromatography to afford (1-benzyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**8a**, 48.4 mg, 76%) as yellow solid.

(1-(4-methoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (**8b**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (1 mL), DBU (0.06 mL, 0.4 mmol) and 4-methoxybenzyl chloride (0.05 mL, 0.4 mmol) were added subsequently at 0°C and stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO_4 . Volatiles were removed under reduced pressure, and the residue was purified by SiO_2 flash chromatography to afford (1-(4-methoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (**8b**, 52.3 mg, 75%) as yellow solid.

(1-(3,4-dimethoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (**8c**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (0.5 mL), DBU (0.06 mL, 0.4 mmol) and 3,4-dimethoxybenzyl bromide (92.4mg, 0.4 mmol) in dichloromethane (0.5mL) were added subsequently at 0°C and stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO_4 . Volatiles were removed under reduced pressure, and the residue was purified by SiO_2 flash chromatography to afford (1-(3,4-dimethoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (**8c**, 30.3 mg, 40%) as yellow solid.

(1-(3,5-dimethoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (**8d**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (1 mL), DBU (0.06 mL, 0.4 mmol) and 3,5-dimethoxybenzyl bromide (92.4 mg, 0.4 mmol) were added subsequently at 0°C and stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO₄. Volatiles were removed under reduced pressure, and the residue was purified by SiO₂ flash chromatography to afford (1-(3,5-dimethoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (**8d**, 31.8 mg, 42%) as yellow solid.

1-(3-(thiazole-2-carbonyl)-1H-indol-1-yl)ethan-1-one (**9**)

To a stirred solution of NaH (60% in mineral, 12 mg, 0.3 mmol) in DMF (1 mL), a solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in DMF (1 mL) was added at 0°C. After stirring for 0.5 h, acetic anhydride (0.02 mL, 0.24 mmol) was added at the same temperature. The resulting mixture was stirred for 5 h at rt, and then quenched with water. The mixture was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous MgSO₄. Volatiles were removed under reduced pressure, and the residue was purified by SiO₂ flash chromatography to afford 1-(3-(thiazole-2-carbonyl)-1H-indol-1-yl)ethan-1-one (**9**, 35.3 mg, 65%) as yellow solid.

(1-benzoyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**10**)

To a stirred solution of indothiazinone (**1**, 45.7 mg, 0.2 mmol) in dichloromethane (1 mL), DBU (0.06 mL, 0.4 mmol) and benzoyl chloride (0.05 mL, 0.4 mmol) were added subsequently at 0°C and stirred overnight at rt. The resulting mixture was diluted with dichloromethane, washed with water and brine, and dried over anhydrous MgSO₄. Volatiles were removed under reduced pressure, and the residue was purified by SiO₂ flash chromatography to afford (1-benzoyl-1H-indol-3-yl)(thiazol-2-yl)methanone (**10**, 54.5 mg, 82%) as white solid.

Characterization Data

Indothiazinone (1)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.16 (d, 1H, $J = 3.15$ Hz), 8.78 (s, 1H), 8.56 (d, 1H, $J = 7.25$ Hz), 8.02 (d, 1H, $J = 3.05$ Hz), 7.64 (d, 1H, $J = 3.05$ Hz), 7.46 (m, 1H), 7.35 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 178.31, 170.28, 144.14, 136.48, 135.88, 126.80, 124.77, 124.08, 123.19, 122.72, 114.48, 111.43; HR-MS (EI+) calcd for $\text{C}_{12}\text{H}_8\text{N}_2\text{OS}$ $[\text{M}]^+$ 228.0357; found 228.0355.

(1-methyl-1H-indol-3-yl)(thiazol-2-yl)methanone (6)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.01 (s, 1H), 8.55 (m, 1H), 8.01 (d, 1H, $J = 3.05$ Hz), 7.62 (d, 1H, $J = 3.1$ Hz), 7.37 (m, 3H), 3.91 (s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 177.57, 170.68, 144.00, 140.41, 137.24, 127.78, 124.56, 123.72, 123.16, 122.87, 112.84, 109.76, 33.73; HR-MS (EI+) calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{OS}$ $[\text{M}]^+$ 242.0514; found 242.0513.

(1-allyl-1H-indol-3-yl)(thiazol-2-yl)methanone (7)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.05 (s, 1H), 8.56 (m, 1H), 8.03 (m, 1H), 7.63 (m, 1H), 7.36 (m, 3H), 6.06 (m, 1H), 5.33 (m, 1H), 5.22 (d, 1H, J = 34.2 Hz), 4.86 (d, 2H, J = 5.4 Hz); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 144.06, 139.58, 136.61, 131.98, 127.94, 124.59, 123.71, 123.20, 122.97, 118.72, 113.17, 110.28, 49.76; HR-MS (EI+) calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{OS}$ $[\text{M}]^+$ 268.0670; found 268.0668.

(1-benzyl-1H-indol-3-yl)(thiazol-2-yl)methanone (8a)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.14 (s, 1H), 8.58 (d, 1H, J = 7.9 Hz), 7.99 (d, 1H, J = 3.05 Hz), 7.62 (d, 1H, J = 3.05 Hz), 7.33(m, 6H), 7.19 (d, 2H, J = 6.95 Hz), 5.44 (s, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 177.80, 170.50, 144.10, 140.08, 136.71, 135.81, 129.03, 128.16, 128.02, 126.82, 124.67, 123.87, 123.26, 122.97, 113.33, 110.51, 51.16; HR-MS (EI+) calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OS}$ $[\text{M}]^+$ 318.0827; found 318.0826.

(1-(4-methoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (8b)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.12(s, 1H), 8.57(m, 1H), 8.00(d, 1H, J =3.1 Hz), 7.62(d, 1H, J =3.1Hz), 7.34(m, 2H), 7.29(m, 2H), 7.29(m, 1H), 7.15(m, 2H), 6.85(m, 2H), 5.37(s, 2H), 3.77(s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 177.70, 170.56, 159.49, 144.05, 139.93, 136.66, 128.32, 128.07, 127.75, 124.63, 123.80, 123.23, 122.95, 114.41, 113.20, 110.55, 55.32, 50.73; HR-MS (EI+) calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ $[\text{M}]^+$ 348.0932; found 348.0933.

(1-(3,4-dimethoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (8c)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.11(s, 1H), 8.57(d, 1H, $J=7.9\text{Hz}$), 8.00(d, 1H, $J=3.1$), 7.63(d, 1H, $J=3.1$), 7.35(m, 2H), 7.29(m, 1H), 6.81(d, 1H, $J=8\text{Hz}$), 6.75(d, 1H, $J=8.5$), 5.37(s, 2H), 3.85(s, 3H), 3.79(s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 177.75, 170.54, 149.47, 149.00, 144.05, 139.91, 136.75, 128.10, 128.04, 124.67, 123.83, 123.27, 122.96, 119.52, 113.23, 111.44, 110.52, 110.18, 55.96, 51.02, 29.72; HR-MS (EI+) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ $[\text{M}]^+$ 378.1038; found 378.1036.

(1-(3,5-dimethoxybenzyl)-1H-indol-3-yl)(thiazol-2-yl)methanone (8d)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.13(s, 1H), 8.57(d, 1H, $J=7.9\text{Hz}$), 8.00(d, 1H, $J=3.1\text{Hz}$), 7.62(m, 1H), 7.32(m, 3H), 6.35(m, 3H), 5.36(s, 2H), 3.71(s, 6H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 177.75, 170.51, 161.34, 144.04, 140.11, 138.19, 136.78, 127.96, 124.67, 123.90, 123.27, 122.94, 113.32, 110.49, 105.00, 99.57, 55.37, 51.19; HR-MS (EI+) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ $[\text{M}]^+$ 378.1038; found 378.1040.

1-(3-(thiazole-2-carbonyl)-1H-indol-1-yl)ethan-1-one (9)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.43 (s, 1H), 8.49 (m, 2H), 8.07 (d, 1H, $J = 3.05$ Hz), 7.71 (d, 1H, $J = 3.05$ Hz), 7.45 (m, 2H), 2.81 (s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 178.70, 169.10, 169.00, 144.52, 136.26, 135.64, 128.21, 126.39, 125.64, 125.43, 122.51, 117.82, 116.37, 23.97; HR-MS (EI+) calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ $[\text{M}]^+$ 270.0463; found 270.0465.

(1-benzoyl-1H-indol-3-yl)(thiazol-2-yl)methanone (10)

$^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.30 (s, 1H), 8.55 (m, 1H), 8.35 (m, 1H), 7.91 (d, 1H, $J=3.05$), 7.87 (m, 2H), 7.71 (m, 2H), 7.62 (m, 3H), 7.48 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ 178.90, 168.85, 168.78, 144.48, 138.49, 136.12, 133.27, 132.99, 129.92, 128.87, 128.48, 126.10, 125.56, 125.44, 122.62, 117.31, 115.94; HR-MS (EI+) calcd for $\text{C}_{19}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ $[\text{M}]^+$ 332.0619; found 332.0621.

¹H NMR and ¹³C NMR Spectra

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

¹H-NMR

¹³C-NMR

Reference

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