Synthesis of Novel Spiro Thiazolotriazole Derivatives *via* 1,3-Dipolar Cycloaddition of Azomethine Ylide

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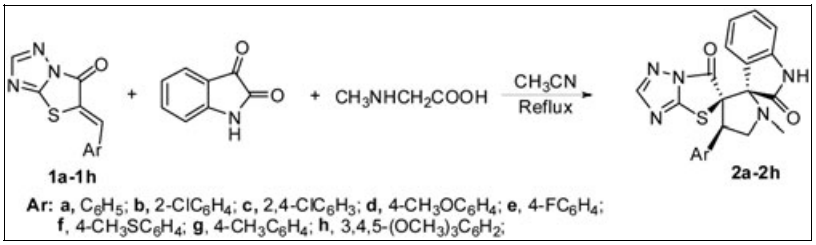

The 1,3-dipolar cycloaddition of azomethine ylide generated in situ from isatin and sarcosine to 5-arylmethylidene thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones afforded novel 1′-methyl-4′-aryldispiro [indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo[3,2-*b*][1,2,4]triazole]-2,6″ (1*H*)-diones in moderate yields. The structures of all the products were characterized thoroughly by NMR, infrared spectroscopy (IR), mass spectroscopy (MS) elemental analysis together with X-ray crystallographic analysis.

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INTRODUCTION

Thiazolotriazoles possess a broad spectrum of biological activities such as potent and selective COX-2 inhibitors [1], with pronounced antiinflammatory and analgesic activity [2].

The spiro pyrrolidine ring system is a frequently encountered structural motif in many pharmacologically relevant alkaloids, as typified by vincristine, vinblastine, and spirotryprostatins [3]. Intermolecular 1,3-dipolar cycloaddition reactions are considered one of the most convenient methods for the construction of a variety of complex pyrrolidine derivatives [4,5].

As part of our endeavor to synthesize novel heterocyclic system [6,7], we herein report the synthesis of a series of new spiro ipyrrolidine heterocycles containing thiazolo [3,2-*b*][1,2,4]triazole framework (Scheme 1).

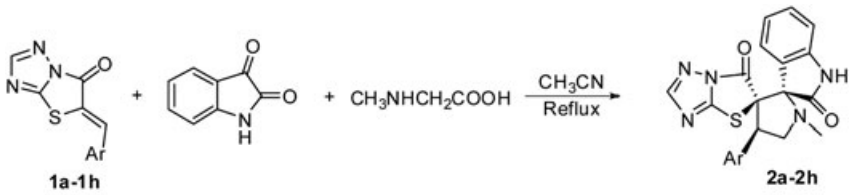
RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reaction of 5-arylmethylidene thiazolo[3,2-*b*] [1,2,4]triazol-6(5*H*)-ones **1** to the azomethine ylide generated *in situ* from isatin and sarcosine yield 1′-methyl-4′-aryldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo[3,2-*b*][1,2,4]triazole]-2,6″ (1*H*)-diones **2** (Scheme 2).

The structures of all compounds **2a–2h** were established by different spectroscopic techniques (NMR, IR, and MS) and elemental analysis. The IR spectrum of **2b** displayed $\nu_{C=O}$ at 1765.8 and 1691.3 cm^{-1}. The ^{1}H-NMR spectrum of **2b** revealed a singlet at δ 2.32 resulting from N—CH_3 (H-1), two triplet at δ 3.65 (J = 8.5) and 4.35 (J = 9.5) assignable to the protons of methylene (H-2) and one triplet at δ 5.08 (J = 8.5) corresponding to the proton of CH (H-3) in pyrrolidine ring. The presence of singlet at #δ 7.90 ppm corresponding to the proton of methylene (H-6). The singlet at δ 8.34 is in accord with the proton of NH in indole ring.

The ^{13}C-NMR spectrum of the product **2b** exhibited the presence of N—CH_3 carbon (C-1) at δ 35.36, carbonyl carbons at δ 165.99 (C-7) and 176.55 (C-8). The signal at δ 47.67 and 55.16 are assignable to the carbons of CH (C-3) and CH_2 (C-2), respectively, which existed in pyrrolidine ring (based on HMQC). The signal at δ 129.96 is in agreement with the carbon of C-6 in triazole ring. The signals at δ 78.63 and 79.01 represent the spiro carbon of C-4 and C-5, respectively. In the ^{1}H–^{13}C HMBC map of **2b** (Fig. 1), protons of H-2 and H-1 correlate with a spiro carbon C-5 (79.01 ppm), protons of CH (H-3) and CH_2 (H-2) exist in pyrrolidine ring correlate with the spiro carbon C-4 (78.63 ppm). The correlation of H-3 with C-7 indicates the carbon

Scheme 1



atom of carbonyl carbon (C-7) at 165.99 ppm. Further, the structure of 2g was confirmed by X-ray diffraction, supporting the structural assignments of all compounds made using spectroscopic methods. (Fig. 2) [8].

EXPERIMENTAL

5-Arylmethylidene thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones **1** [9] were prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C. TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts and $CDCl_3$ was used as solvent. Elemental analysis was performed with an Elementar analyzer (varioEL II). MS was conducted with a Finnigan LCQ Advantage MAX mass spectrometer. IR spectra were recorded on a Perkin-Elmer spectrometer (Spectrum One). Melting points were measured with a Yanaco MP500 melting point apparatus and are uncorrected.

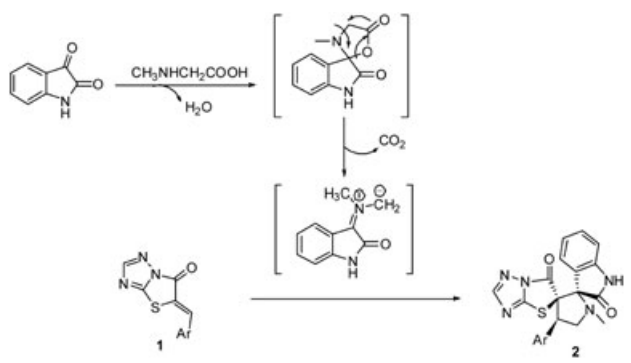
General procedure for the synthesis of 1′-methyl-4′-aryldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo[3,2-*b*][1,2,4]triazole]-2,6″ (1*H*)-diones (2a-2h). A mixture of 5-arylmethylidene thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones **1** (1 mmol), isatin (1 mmol), and sarcosine (1 mmol) in acetonitrile (60 mL) was refluxed for 36 h. Completion of the reaction was evidenced by TLC analysis using petroleum ether-ethyl acetate (3:1, *V/V*) as eluent. The solvent was evaporated under reduced pressure. The crude product was purified by silica gel (50 g) column chromatography using petroleum ether-ethyl acetate (3:1, *V/V*) as eluent to afford the corresponding **2**.

1′-Methyl-4′-phenyldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo[3,2-*b*][1,2,4]triazole]-2,6″ (1*H*)-dione (2a). White solid, yield 60%; mp: 201–203°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H), 3.67 (dd, J_1 = 8.0 Hz, J_2 = 9.5 Hz, 1H), 4.20 (t, J =9.5 Hz, 1H), 4.67 (dd, J_1 = 8.0 Hz, J_2 = 9.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.23–7.26 (m, 1H), 7.30–7.39 (m, 4H), 7.50 (d, J = 7.5 Hz, 2H), 7.86 (s, 1H), and 8.12 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 35.10, 52.84, 58.03, 79.23, 80.21, 110.33, 122.55, 123.85, 126.93, 128.35, 128.99, 130.97, 137.14, 141.96, 160.46, 163.30, 166.62, and 176.49; IR (KBr) *v*: 1766.9, 1743.8 cm^{-1}; ESI MS *m/z*: 404 $[M+H]^+$. Anal. calcd. for $C_{21}H_{17}N_5O_2S$: C 62.52, H 4.25, N 17.36; found C 62.42, H 4.21, N 17.15.

4′-(2-Chlorophenyl)-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo-[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2b). White solid, yield 58%; mp: 214–216°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.32 (s, 3H), 3.65 (t, J = 8.5 Hz, 1H), 4.35 (t, J =9.5 Hz, 1H), 5.08 (t, J = 8.5 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.23–7.28 (m, 2H), 7.34–7.41 (m, 3H), 7.90 (s, 1H), 7.91–7.92 (m, 1H), and 8.34 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz)δ: 35.36, 47.67, 55.16, 78.63, 79.01, 110.46, 121.97, 123.98, 126.95, 127.28, 129.26, 129.49, 129.96, 131.06, 135.16, 136.43, 142.16, 160.23, 163.51, 165.99, and 176.55; IR (KBr) *v*: 1765.8, 1691.3 cm^{-1}; MS (ESI) *m/z*: 438 $[M+H]^+$. Anal. calcd for $C_{21}H_{16}ClN_5O_2S$: C 57.60, H 3.68, N 15.99; found C 57.51, H 3.84, N 15.72.

4′-(2,4-Dichlorophenyl)-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thia-zolo[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2c). White solid, yield 50%; mp: 222–223°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H), 3.65 (t, J = 8.5 Hz, 1H),

Scheme 2



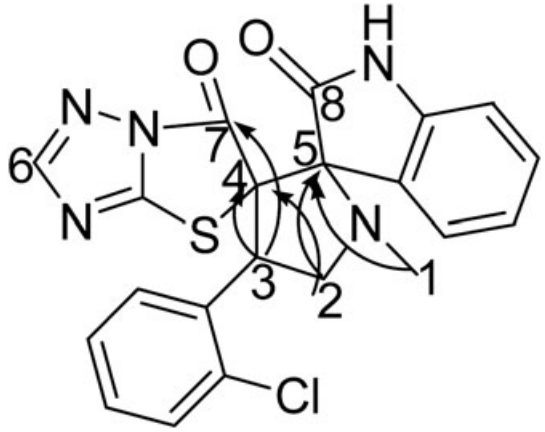


Figure 1. Partial HMBC diagram of **2b**.

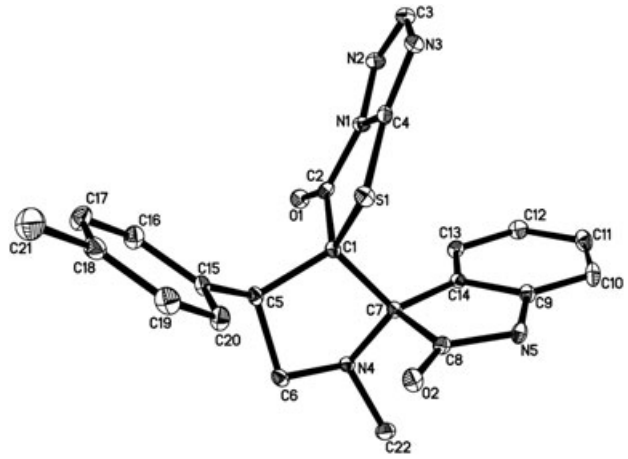


Figure 2. ORTEP diagram of **2g** (H atoms have been omitted for clarity).

4.27 (t, J =9.5 Hz, 1H), 5.03 (t, J = 8.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.24–7.27 (m, 1H), 7.34–7.39 (m, 3H), 7.85 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), and 8.16 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 35.32, 47.21, 55.21, 78.34, 78.95, 110.51, 121.78, 124.06, 126.91, 127.62, 129.31, 130.96, 131.16, 133.82, 134.53, 136.96, 142.07, 160.32, 163.27, 165.83, and 176.37; IR (KBr) v: 1765.0, 1711.0 cm^{-1}; MS (ESI) m/z: 472 $[M+H]^+$. Anal. calcd for $C_{21}H_{15}Cl_2N_5O_2S$: C 53.40, H 3.20, N 14.83; found C 53.75, H 3.51, N 14.92.

4′-(4-Methoxyphenyl)-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiaz-olo[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2d). White solid, yield 53%; mp : 231–233°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.29 (s, 3H), 3.64 (dd, J_1 = 8.0 Hz, J_2 = 9.5 Hz, 1H), 3.81 (s, 3H), 4.14 (t, J = 9.5 Hz, 1H), 4.63 (dd, J_1 = 8.0 Hz, J_2 = 9.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.5 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 7.23–7.27 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.86 (s, 1H), and 7.96 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 35.05, 52.23, 55.23, 58.13, 79.12, 80.60, 110.23, 114.19, 122.57, 123.80, 126.88, 129.17, 130.88, 131.19, 141.84, 159.39, 160.39, 163.31, 166.66, and 176.39; IR (KBr) v: 1761.1, 1718.7 cm^{-1}; MS(ESI) m/z: 434 $[M+H]^+$. Anal. calcd for $C_{22}H_{19}N_5O_3S$: C 60.96, H 4.42, N 16.16; found C 61.25, H 4.68, N 16.40.

4′-(4-Fluorophenyl)-1′-methyldispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo-[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2e). White solid, yield 52%; mp : 199–200°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H), 3.67 (dd, J_1 = 8.0 Hz, J_2 = 9.5 Hz, 1H), 4.13 (t, J =9.5 Hz, 1H), 4.65 (dd, J_1 = 8.0 Hz, J_2 = 9.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 7.03–7.07 (m, 3H), 7.24–7.27 (m, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.49 (dd, J_1 = 5.5 Hz, J_2 = 8.5 Hz, 2H), 7.87 (s, 1H), and 7.92 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 34.99, 52.04, 58.19, 79.13, 80.02, 110.27, 115.74, 115.90, 122.38, 123.86, 126.88, 130.97, 131.77, 131.83, 132.90, 132.92, 141.82, 160.46, 163.03, 166.43, and 176.32; IR (KBr) v: 1767.7, 1705.2 cm^{-1}; MS (ESI) m/z: 422 $[M+H]^+$. Anal. calcd for $C_{21}H_{16}FN_5O_2S$: C 59.85, H 3.83, N 16.62; found C 59.97, H 3.90, N 16.53.

1′-Methyl-4′-[4-(methylthio)phenyl]dispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]th-iazolo[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2f). White solid, yield 56%; mp : 198–199°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.29 (s, 3H), 2.48 (s, 3H), 3.65 (t, J = 9.0 Hz, 1H), 4.15 (t, J = 9.5 Hz, 1H), 4.61 (t, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.22–7.25 (m, 3H), 7.37 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.87 (s, 1H), and 8.09 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz)δ: 15.46, 35.03, 52.37, 57.93, 79.18, 80.18, 110.34, 122.47, 123.80, 126.57, 126.86, 130.45, 130.93, 133.68, 138.87, 141.95, 160.42, 163.18, 166.51, and 176.57; IR (KBr) v: 1764.5, 1712.0 cm^{-1}; MS(ESI) m/z: 450 $[M+H]^+$. Anal. calcd for $C_{22}H_{19}N_5O_2S_2$: C 58.78, H 4.26, N 15.58; found C 58.40, H 4.46, N 15.71.

1′-Methyl-4′-(4-methylphenyl)dispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazol-o[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2g). White solid, yield 59%; mp : 207–208°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H), 2.34 (s, 3H), 3.64 (dd, J_1 = 8.0 Hz, J_2 = 9.0 Hz, 1H), 4.18 (t, J = 9.5 Hz, 1H), 4.64 (dd, J_1 = 8.0 Hz, J_2 = 10.0 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 7.02–7.05 (m, 1H), 7.14–7.18 (m, 2H), 7.23–7.27 (m, 1H), 7.38 (d, J = 8.0 Hz, 3H), 7.86 (s, 1H), and 8.33 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 21.17, 35.12, 52.57, 58.02, 79.28, 80.36, 110.41, 122.61, 123.81, 126.93, 129.44, 129.67, 130.95, 134.08, 138.16, 142.08, 160.43, 163.35, 166.65, and 176.77; IR (KBr) v: 1715.7, 1654.2 cm^{-1}; MS(ESI) m/z: 418 $[M+H]^+$. Anal. calcd for $C_{22}H_{19}N_5O_2S$: C 63.29, H 4.59, N 16.78; found C 63.55, H 4.30, N 16.50.

1′-Methyl-4′-(3,4,5-trimethoxyphenyl)dispiro[indole-3,2′-pyrrolidine-3′,5″-[1,3]thiazolo[3,2-*b*][1,2,4]triazole]-2,6″(1*H*)-dione (2h). White solid, yield 52%; mp : 224–225°C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.28 (s, 3H), 3.68 (t, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 6H), 4.11 (t, J = 9.5 Hz, 1H), 4.54 (t, J = 8.5 Hz, 1H), 6.79 (t, J =8.0 Hz, 3H), 7.03 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), and 8.01 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 35.07, 52.81, 56.18, 58.65, 60.90, 79.24, 80.26, 107.02, 110.39, 122.41, 123.81, 126.65, 131.01, 133.11, 137.61, 141.92, 153.46, 160.46, 163.49, 166.78, and 176.37; IR (KBr) v: 1761.7, 1713.2 cm^{-1}; MS(ESI) m/z: 494 $[M+H]^+$. Anal. calcd for $C_{24}H_{23}N_5O_5S$: C 58.41, H 4.70, N 14.19; found C 58.82, H 4.83, N 14.25.

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