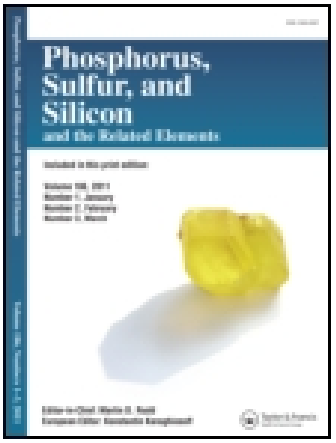

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Microwave-Assisted Synthesis of Some Novel Thiazolidinone and Thiohydantoin Derivatives of Isatins

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MICROWAVE-ASSISTED SYNTHESIS OF SOME NOVEL THIAZOLIDINONE AND THIOHYDANTOIN DERIVATIVES OF ISATINS

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A simple, rapid, and efficient method for the synthesis of some new thiazolidinone and thiohydantoin derivatives of isatins along with some Mannich bases has been achieved in excellent yield from indole-2,3-dione-3-thiosemicarbazone employing microwave irradiation.

Keywords Isatin; Mannich base; microwave; Schiff base; thiazolidinone; thiohydantoin

INTRODUCTION

Microwave-assisted organic synthesis has currently emerged as a fascinating and clean methodology in synthetic organic chemistry.[1] Isatin derivatives are endowed with a variety of biological activities such as antibacterial, antifungal, antiplasmodial, and anti-HIV activity.[2–5] Schiff and Mannich bases of 1*H*-indole-2,3-dione have been found to exhibit a broad spectrum of chemotherapeutic properties including antiviral, antitubercular, antifungal, and antibacterial activity.[6–9] An insight into the structure–activity relationships of isatins reveals a profound increase in the biological activities of *N*-Mannich bases and 3-thiosemicarbazones of 5-bromo-isatin.[10–15] The hydantoin structure motifs display a wide range of biological activities, such as antiarrhythmic, anticonvulsant, antiepileptic, antineuralgic, trigeminal neuralgia, and skeletal muscle relaxant activity.[16–18] Further, 4-thiazolidinones have been reported to be highly effective as antimicrobial, antiviral, anticancer, and thrombolytic drugs.[19,20] It may be anticipated that the combination of the thiazolidinone and thiohydantoin moieties placed at suitable positions of the isatin framework would remarkably enhance the biological activity. Taking this into consideration, an efficient and safe synthesis of some new indole systems containing the thiazolidinone and thiohydantoin moieties has been developed using microwave irradiation.

RESULTS AND DISCUSSION

A number of synthetic methods for the formation of Mannich and Schiff bases have been described during the past two decades, but they usually suffer from drawbacks such as

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harsh reaction conditions, lack of versatility, use of corrosive reagents, long reaction times, and tedious workup procedures. Therefore, the search for an easy and efficient method for the preparation of *N*-Mannich bases, thiohydantoins, and thiazolidinones is always desirable. With the current focus on green chemistry, carrying out organic synthesis under microwave irradiation is an important goal in clean synthesis. As a result, we report in this article a practical and efficient alternative for the synthesis of thiohydantoins, thiazolidinones, and *N*-Mannich bases by the use of microwave irradiation. In the present study, 1*H*-indole-2,3-dione **1a** and its 5-bromo derivative **1b** were reacted with thiosemicarbazide in ethanol containing a catalytic amount of glacial acetic acid in a household microwave oven at 160 W to give the thiosemicarbazone derivatives **2a** and **2b**, respectively. Compounds **2** were subsequently allowed to undergo a Mannich reaction using formaldehyde solution and morpholine, piperidine, or diethyl amine in ethanol to furnish the Mannich bases **3a–e** in good yields. The 2-(isatin-3-azino)-4-thiazolidinones **4a**,**b** were prepared by the reaction of **2a**,**b** with chloroacetic acid in ethanol containing anhydrous sodium acetate, whereas the 3-(isatin-3-imino)-2-thiohydantoins **5a**,**b** were obtained by the reaction of **2a**,**b** with chloroacetic acid in the presence of piperidine (Scheme 1). All products displayed IR spectra as well as ^{1}H and ^{13}C NMR spectra consistent with the assigned structures. The yields of the compounds **2–5** and their melting points are given in Table I.

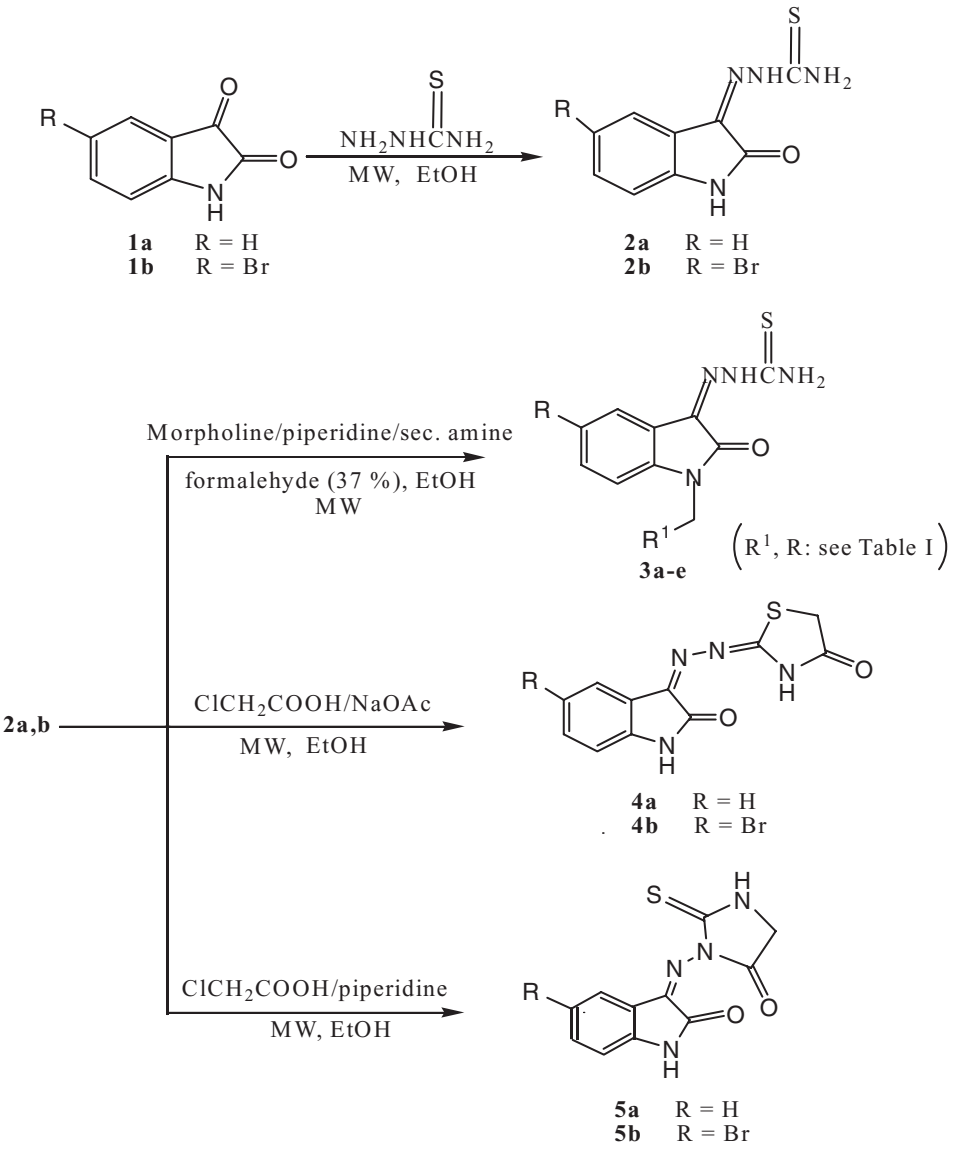
EXPERIMENTAL

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a Jasco FT/IR-5300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained with a JEOL AL 300 FTNMR spectrometer, and the chemical shifts are given in ppm using TMS as internal reference. All commercially available chemicals were purchased from Merck and Aldrich.

Table I Yields and physical data of compounds **2–5**

Compound	R	R^1	Formula	MW[a] Time (min)	Yield[b] (%)	Mp (°C)
2a	H	—	$C_9H_8N_4SO$	4	75	240
2b	Br	—	$C_9H_7N_4SOBr$	4	80	255
3a	H	$N(C_2H_5)_2$	$C_{14}H_{19}N_5OS$	4	87	130
3b	H		$C_{15}H_{19}N_5OS$	5	85	180
3c	H		$C_{14}H_{17}N_5O_2S$	5	90	210
3d	Br		$C_{15}H_{18}N_5OSBr$	4	84	215
3e	Br		$C_{14}H_{16}N_5O_2SBr$	5	82	230
4a	H	—	$C_{11}H_8N_4O_2S$	9	90	210
4b	Br	—	$C_{11}H_7N_4O_2SBr$	7	85	245
5a	H	—	$C_{11}H_8N_4O_2S$	8	92	225
5b	Br	—	$C_{11}H_7N_4O_2SBr$	7	80	260

[a]Irradiation at 160 W.
[b]Isolated yield.



Scheme 1

Synthesis of Compounds 2: General Procedure

Isatin/5-bromoisatin **1a/1b** (0.01 mol) and thiosemicarbazide (0.011 mol) were introduced into a 100 mL conical flask containing ethanol (15 mL) and a few drops of glacial acetic acid. The reaction mixture was irradiated in an LG domestic microwave oven for 4 min at 160 W and was subsequently allowed to cool at room temperature. The mixture was filtered and washed with water (10 mL), and the resulting precipitate was recrystallized from ethanol (2 mL) to afford compounds **2**.

Synthesis of Compounds 3: General Procedure

To a stirred suspension of isatin/5-bromo isatin **2a/2b** (2 mmol) and formaldehyde solution (37%, 0.5 mL) in absolute ethanol (10 mL) in a 100 mL conical flask, a mixture of morpholine/piperidine/*N,N*-diethylamine (2 mmol) was added dropwise. The reaction mixture was then introduced into the microwave oven and was irradiated for 4–5 min at 160 W. The course of the reaction was monitored by TLC. The resulting mixture was allowed to stand overnight, and the resulting solid product was filtered and washed with petroleum ether (10 mL) to furnish pure compounds **3a**–**e**.

Synthesis of Compounds 4: General Procedure

A mixture of **2a/2b** (0.01 mol), chloroacetic acid (0.015 mol), and anhydrous sodium acetate (0.15 g) was placed in a 100 mL conical flask containing ethanol (10 mL) and was irradiated in the microwave oven at 160 W for 7–9 min. After the reaction was complete (TLC), the mixture was allowed to cool to room temperature. The resulting solid was filtered, washed with water (10 mL), and recrystallized from ethanol (2 mL) to provide compounds **4a**,**b**.

Synthesis of Compounds 5: General Procedure

A mixture of **2a/2b** (0.01 mol), chloroacetic acid (0.01 mol), and piperidine (1.5 mL) in a 100 mL conical flask containing ethanol (10 mL) was introduced into the microwave oven. The reaction mixture was initially irradiated for 30 sec at 160 W. After a break for 1 min and cooling to room temperature, it was again irradiated for 7–8 min. The solid product obtained was filtered, washed with water (10 mL), and recrystallized from ethanol (2 mL) to afford compounds **5a**,**b**.

Data

1*H*-Indole-2,3-dione-3-thiosemicarbazone (2a). Mp: 240°C (lit.[21] 247–249°C); IR (KBr): υ = 3425, 3238, 1682, 1611, 1130 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ = 12.45 (s, 1H), 11.18 (s, 1H), 9.02 (s, 1H), 8.67 (s, 1H), 7.65 (dd, J = 1.6 Hz, J = 7.9, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.08 (t, J = 8.4 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), ^{13}C NMR (DMSO-d$_6$): δ = 108, 112.2, 116, 120, 129, 137, 155, 162 (C=O/C=S), 176 (C=O/C=S).

5-Bromo-1*H*-indole-2,3-dione-3-thiosemicarbazone (2b). Mp: 255°C; IR (KBr): υ = 3430, 3230, 1690, 1133 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ = 12.47 (s, 1H), 11.17 (s, 1H), 9.02 (s, 1H), 8.68 (s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.41 (t, J = 8.5 Hz, 1H), 7.12 (m, 1H); ^{13}C NMR (DMSO-d$_6$): δ = 108.3, 112.5, 117.6, 121.9, 131.4, 140.0, 156.5, 164 (C=O/C=S), 175 (C=O/C=S).

***N*^{1}-Diethylaminomethyl-indole-2,3-dione-3-thiosemicarbazone (3a).** Mp: 130°C (Lit.[22] 135°C); IR (KBr): υ = 3436, 3240, 1670, 1140 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ = 12.11 (s,1H), 9.06 (s, 1H), 8.68 (s, 1H), 7.73 (dd, J = 1.8 Hz, J = 7.5 Hz, 1H), 7.45 (m, 1H), 7.17 (m, 1H), 7.20 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 2.65 (q, J = 6.8 Hz, 4H), 1.08 (t, J = 6.9 Hz, 6H); ^{13}C NMR (DMSO-d$_6$): δ = 16.6 (CH$_3$), 39.5 (CH$_2$), 61.7 (N-CH$_2$-N), 108, 112, 118.5, 121.8, 132, 140, 157, 163 (C=O/C=S), 175 (C=O/C=S).

***N*^{1}-Piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3b).** Mp: 180°C (lit.[22] 177–178°C); IR (KBr): υ = 3427, 2925, 1700, 1162 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ = 12.36 (s, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 7.71 (dd, J = 1.6 Hz, J = 7.8 Hz, 1H), 7.41 (m, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.17 (m, 1H), 4.47 (s, 2H), 2.54 (t, J = 4.8 Hz,

4H), 1.46 (m, 4H), 1.33 (m, 2H), ^{13}C NMR (DMSO-d_6): δ = 24.2, 25.8, 39.6 (CH_2), 62.5 (N-CH_2-N), 107.8, 112.5, 117, 121, 130.5, 140, 155, 162 (C=O/C=S), 177 (C=O/C=S).

N^1-Morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3c). Mp: 210°C (lit.[22] 215–216°C); IR (KBr): υ = 3447, 3206, 2852, 1692, 1149 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 12.38 (s, 1H), 9.05 (s, 1H), 8.71 (s, 1H), 7.73 (dd, J = 1.8 Hz, J = 7.8 Hz, 1H), 7.42 (m, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.15 (m, 1H), 4.49 (s, 2H), 3.54 (br s, 4H), 2.58 (br s, 4H); ^{13}C NMR (DMSO-d_6): δ = 50.9 (CH_2), 61.8 (N-CH_2-N), 64.4 (CH_2), 107.7, 112.8, 117.5, 121, 130.3, 140, 158.2, 162 (C=O/C=S), 177.5 (C=O/C=S).

5-Bromo-N^1-piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3d). Mp: 215°C; IR (KBr): υ = 3447, 2933, 1695, 1112 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 12.37 (s, 1H), 9.06 (s, 1H), 8.69 (s, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.45 (m, 1H), 7.28 (d, J = 8.2 Hz, 1H), 4.48 (s, 2H), 2.52 (t, J = 4.5 Hz, 4H), 1.46 (m, 4H), 1.34 (m, 2H), ^{13}C NMR (DMSO-d_6): δ = 24.5, 25.6, 39.5 (CH_2), 61.2 (N-CH_2-N), 107.2, 112.5, 118, 121.2, 130.7, 140, 158.7, 163 (C=O/C=S), 177 (C=O/C=S).

5-Bromo-N^1-morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3e). Mp: 230°C; IR (KBr): υ = 3440, 2925, 1691, 1145 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 12.39 (s, 1H), 9.05 (s, 1H), 8.68 (s, 1H), 7.80 (d, J = 2.4, 1H), 7.47 (m, 1H), 7.30 (d, J = 8.2 Hz, 1H), 4.50 (s, 2H), 3.54 (br s, 4H), 2.56 (br s, 4H); ^{13}C NMR (DMSO-d_6): δ = 49.5 (CH_2), 61.6 (N-CH_2-N), 64.3 (CH_2), 107.6, 112.5, 117.9, 122, 130.7, 140, 159, 163 (C=O/C=S), 176.5 (C=O/C=S).

2-(Isatin-3-azino)-4-thiazolidinone (4a). Mp: 210°C; IR (KBr): υ = 3260, 1675, 1467, 1129 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 12.46 (s, 1H), 11.18 (s, 1H), 7.66 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.37 (m, 1H), 7.10 (m, 1H), 6.93 (d, J = 8.5 Hz, 1H), 3.30 (s, 2H); ^{13}C NMR (DMSO-d_6): δ = 41.5, 151 (thiazolidinone), 109, 111.3, 116, 122.8, 129, 142, 155, 165 (C=O), 174 (C=O).

5-Bromo-2-(isatin-3-azino)-4-thiazolidinone (4b). Mp: 245°C; IR(KBr): υ = 3272, 1690, 1484, 1136 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 12.45 (s, 1H), 11.19 (s, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.41 (m, 1H), 7.13 (m, 1H), 3.29 (s, 2H); ^{13}C NMR (DMSO-d_6): δ = 41.5, 151 (thiazolidinone), 109, 110.8, 116, 122.8, 129.8, 142, 155.7, 165 (C=O), 175.2 (C=O).

3-(Isatin-3-imino)-2-thiohydantoin (5a). Mp: 225°C; IR(KBr): υ = 3269, 1675, 1467, 1127 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 12.26 (s, 1H), 11.29 (s, 1H), 7.80 (dd, J = 1.6 Hz, J = 8.5 Hz, 1H), 7.47 (m, 1H), 6.86 (m, 1H), 6.77 (d, J = 8.7 Hz, 1H), 3.32 (s, 2H); ^{13}C NMR (DMSO-d_6): δ = 57.5 (thiohydantoin), 108, 112, 116.5, 122.7, 126, 143, 154, 163 (C=O/C=S), 171.5 (C=O/C=S), 179 (C=O/C=S).

5-Bromo-3-(isatin-3-imino)-2-thiohydantoin (5b). Mp: 260°C; IR(KBr): υ = 3274, 1693, 1485, 1137; ^{1}H NMR (DMSO-d_6): δ = 12.27 (s, 1H), 11.28 (s, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.51 (m, 1H), 6.89 (m, 1H), 3.34 (s, 2H); ^{13}C NMR (DMSO-d_6): 57.3 (thiohydantoin), 107.8, 112, 117, 122.5, 126.2, 143, 154.2, 162 (C=O/C=S), 172 (C=O/C=S), 180 (C=O/C=S).

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