Solvent-Free Microwave-Assisted Synthesis of 1*H*-Indole-2, 3-dione Derivatives

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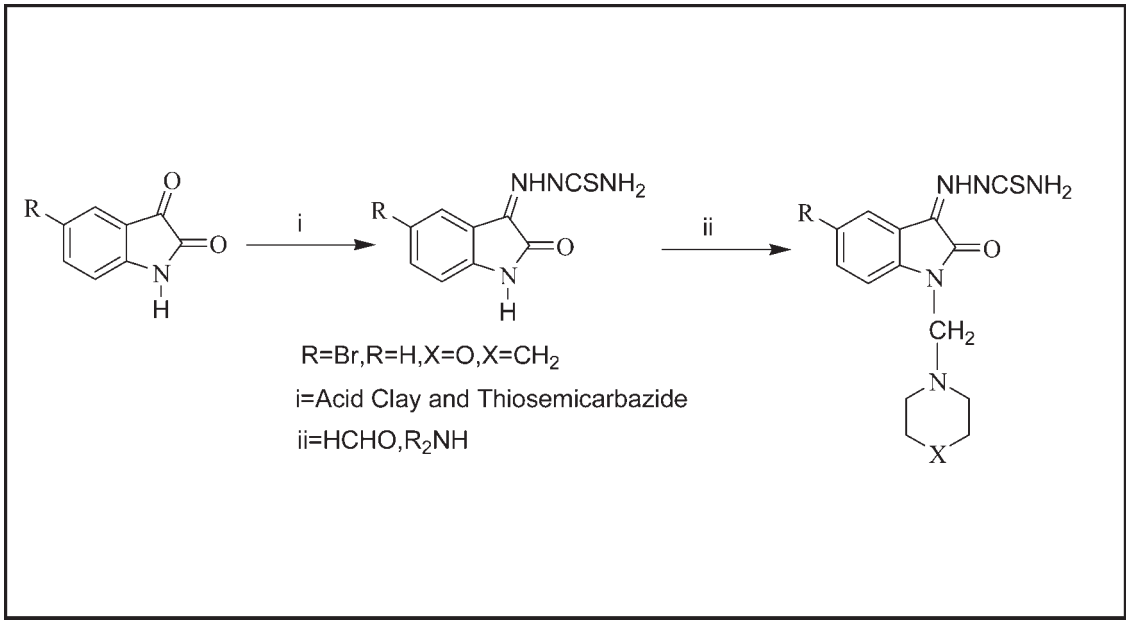

Microwave-assisted synthesis has been found to increase both reaction rates and yields *via* more efficient heating compared with standard thermal conduction. Dry reaction of isatins with thiosemicarbazide and their thiosemicarbazone with secondary amine on acid—washed K10 in microwave oven afforded isatin-3-thiosemicarbazones and N-Mannich bases in reasonably good yield. The chemical structures were confirmed by means of ^{1}H NMR, IR spectral data, and elemental analysis.

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INTRODUCTION

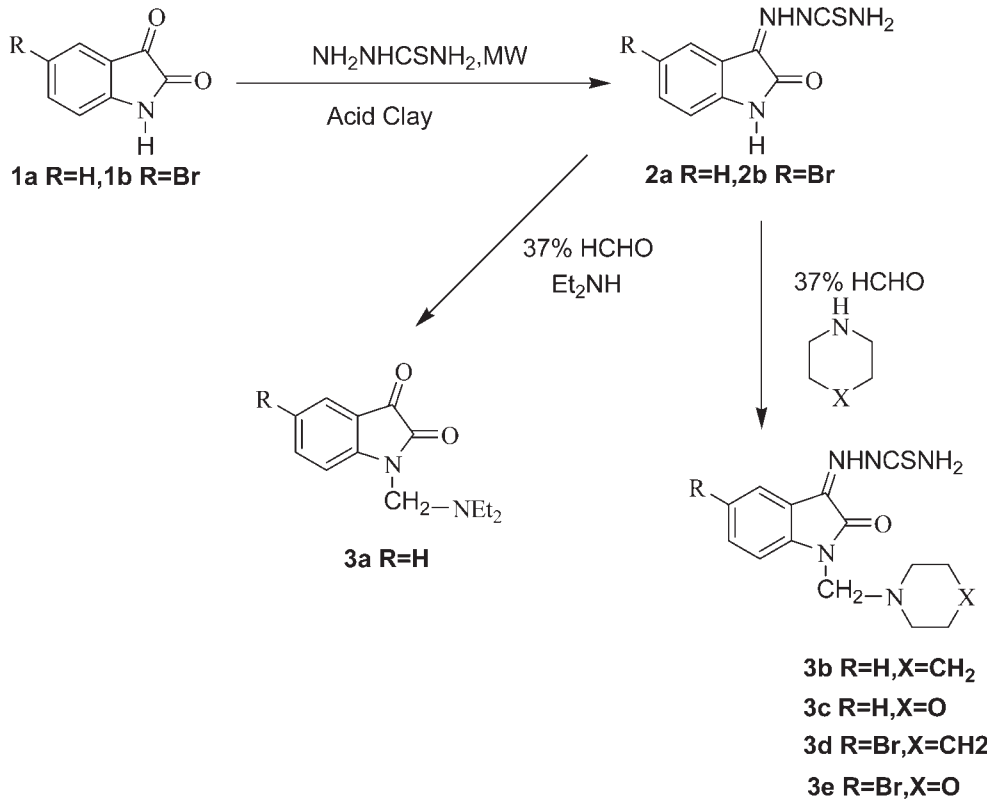
Microwave-assisted organic synthesis is a fascinating and quickly growing area in synthetic organic chemistry [1a–e]. This new synthetic technique is based on the observation that some reactions proceed much faster and with higher yields under microwave irradiation compared with conventional heating. In many cases reactions that normally require many hours at reflux temperature under classical conditions can be completed within a few minutes or even seconds in a microwave oven. The microwave-assisted chemical transformations have become important because of several advantages over the conventional thermal reactions.

Solvent-free chemical synthesis has received much attention recently [2a–e]. Solvent-free processes are not only environmentally benign but also economical [3]. Because a solvent is not required, toxic wastes can be minimized or eliminated, and so the cost of solvent and waste treatment is reduced. Furthermore, operational simplicity is an attractive feature. Recent advances in this area include, for example, aldol and related reactions [4a–f].

In view of the growing need for green chemistry for a cleaner environment and the ever increasing contribution of acidic solid surfaces, especially Montmorillonite clay, we have now developed a general, solvent-free synthesis of Schiff and Mannich bases of isatin.

Montmorillonite clay with its large surface area and high Bronsted and Lewis acidity has emerged as an environmentally benign solid acid catalyst, replacing many hazardous acid catalysts in organic synthesis and reactions, both in laboratory and industry.

Scheme 1



Isatin (1*H*-indole-2,3-dione) derivatives [5a–d] are reported to manifest a variety of biological activities like antibacterial, antifungal, antiplasmodial, and anti-HIV [6–8]. In recent years, Schiff and Mannich bases of 1*H*-indole-2,3-dione are found to exhibit broad-spectrum chemotherapeutic properties such as antiviral [9], anti-TB [10–12], antifungal, anticancer [13,14], anti-protozoal [15], muscle relaxant [16], and antibacterial [17–20]. An insight into the structure activity relationships of isatin reveals that N-Mannich bases and 3-thiosemicarbazones of 5-bromo-isatin are reported to have a profound increase in their biological activities [21–29]. In view of the above, it was thought worthwhile to exploit the use of MW irradiation for the synthesis of some potent bioactive Mannich and Schiff base of isatin.

RESUTS AND DISCUSSION

In the present study, 1*H*-indole-2,3-dione and its 5-bromo derivative (**1a**,**1b**) were allowed to react with thiosemicarbazide in the presence of a catalytic amount of acid clay under microwave irradiation at 160 W to give thiosemicarbazone derivatives (2a/2b) in reasonably good yield. The resulting products 2a/2b was subsequently made to undergo Mannich reaction using formaldehyde solution and morpholine/piperidine/secondary amine to furnish the desired product **3a–e** in excellent yields (Scheme 1). All the products displayed IR and ^{1}H NMR spectra consistent with their assigned structures. The physical data and yield of the products are given in Table 1. For the synthesis of thiosemicarbazone, we initially attempted the dry reaction of isatin with thiosemicarbazide on montmorrillonite K^{10} clay (Bronsted acidity: Hamett acidity function, $H_0 = -5.5$ to -5.9) at room temperature and also under microwave irradiation; however, the reaction was extremely sluggish. To overcome this difficulty, we utilized the fact that washing of this clay with mineral acids increases its acidity sharply ($H_0 = -6$ to -8) [30]. Indeed acid-treated clay has been previously used for a few reactions [31]. Therefore, we washed montmorrillonite K_{10} clay with concentrated HCl, which, after usual work-up, furnish what we designate ''acid clay.'' It was found to be devoid of any free acid and chloride ions. We next used this acid-clay in the targeted reactions and achieved success.

Table 1

Yield and physical data of the products.

Product	R	Formula	Time		Yield[a] (%)		Mp (°C)
			MW[b] (min)	Conventional (h)	MW	Conventional	
2a	H	$C_9H_8N_4SO$	4	5	88	75	244–245
2b	Br	$C_9H_7N_4SOBr$	4	5	92	80	271–272
3a	H	$C_{14}H_{19}N_5OS$	4	4	93	84	132–134
3b	H	$C_{15}H_{19}N_5OS$	5	4	92	83	178–179
3c	H	$C_{14}H_{17}N_5O_2S$	5	4	94	88	212–213
3d	Br	$C_{15}H_{18}N_5OSBr$	4	4	92	82	216–217
3e	Br	$C_{14}H_{16}N_5O_2SBr$	5	4	94	80	230–231

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

CONCLUSION

The use of MWI provides an efficient, clean, and quick methodology for the synthesis of various 1*H*-indole-2,3-dione derivatives with greater yields than the previously reported conventional methods.

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 spectra were run on a Jeol AL 300 FTNMR spectrometer and the chemical shifts are expressed as δ ppm using TMS as internal reference. Elemental analyses were performed on Exeter Analytical Inc. ''Model CE-440 CHN analyzer. All commercially available chemicals were purchased from E. Merck and Aldrich.

General procedure for the preparation for 2a/2b

Microwave-assisted Method. A mixture of isatin/5-bromoisatin (1a/1b, 0.01 mol), thiosemicarbazide (0.011 mol), and catalytic amount of acid clay contained in an Erlenmeyer flask was introduced in to a Le Chef domestic microwave oven and was irradiated for 4 min at 160 W. After completion of the reaction (as monitored by TLC), the mixture was extracted with dichloromethane (3 × 20 mL), the solvent was evaporated and the solid obtained was recrystallized with ethanol and dried to afford the product 2a/2b.

Conventional Method. A solution of thiosemicarbazide (0.011 mol) in ethanol (10 mL) was added to a solution of isatin/5-bromoisatin (1a/1b) (0.01 mol) in ethanol (20 mL). After addition of a drop of acetic acid, the mixture was refluxed on a water bath for 5 h. The product formed after cooling was collected by filtration and washed with ethanol or recrystallized from ethanol.

General procedure for the preparation of 3a–e

Microwave-assisted Method. The mixture of 2a/2b (2 mmol), formaldehyde solution (37%, 0.5 mL), and morpholine/piperidine/*N*,*N*-diethyl amine (2 mmol) was introduced into the microwave oven and was irradiated for 4–5 min at 160 W, while monitoring the course of reaction by TLC. The resulting mixture was extracted with dichloromethane (3 × 20 mL) and washed with petroleum ether. After evaporation of dichloromethane, pure solid 3a–e was obtained.

Conventional Method. To a suspension of 2a/2b (0.002 mol) in absolute ethanol (20 mL), 37% formaldehyde solution (0.5 mL) and morpholine/piperidine/*N*,*N*-diethyl amine (2 mmol) were added dropwise with vigorous stirring. After combining all reagents, the reaction mixture was stirred with gentle refluxing for 4 h. The solid product was collected by filtration and washed with petroleum ether to obtain pure product 3a–3e.

1H-Indole-2,3-dione-3-thiosemicarbazone(2a). (69%) Mp 240–241°C (lit. [23] 239–241°C); IR (KBr): 3425 (N-Hstr of indole), 3238 (N-Hstr of thiosemicarbazone moiety), 1682 (C=Ostr), 1130 (C=Sstr), ^{1}H NMR (DMSO-d_6):δ 12.45 (s, NH of thiosemicarbazone moiety), 11.18 (s,1H-NH proton of indole nucleus), 9.02 (s, 2H NH_2 of thiosemicarbazone moiety), 7.65 (d, 1H-C_7-H of indole nucleus), 7.35 (dd 1H C_6-H proton), 7.08 (dd, 1HC_5-H proton), 6.91 (d, 1HC_4-H proton). Anal Calcd. for $C_9H_8N_4OS$ (220.27) C, 49.03; H, 3.61; N, 25.42. Found: C, 48.97; H, 3.60; N, 25.28.

5-Bromo-1H-indole-2,3-dione-3-thiosemicarbazone (2b). Yield (73%); Mp 271–272°C; IR (KBr): 3430 (N-Hstr of indole nucleus), 3230 (N-Hstr of thiosemicarbazone moiety), 1690 (C=Ostr), 1133 (C=Sstr); ^{1}H NMR (DMSO-d_6): δ 12.47 (s, 1H-NH of thiosemicarbazone moiety), 11.17 (s, 1H NH proton of indole nucleus), 9.02 (s, 1H NH_2 of thiosemicarbazone moiety), 7.74 (d, 1HC_4-H proton), 7.41 (dd, 1H C_6-H proton), 7.12 (d, 1H C_7-H of indole nucleus). Anal Calcd. for $C_9H_7BrN_4OS$ (299.14) C, 36.10; H, 2.34; N,18.72. Found: C, 36.08; H, 2.30; N, 18.74.

N^1-Diethylaminomethyl-indole-2,3-dione-3-thiosemicarbazone (3a). Yield (75%); Mp 132–134°C (Lit. 135°C) [24]; IR (KBr): 3436 (N-Hstr of indole), 3240 (N-Hstr of thiosemicarbazone moiety), 1670 (C=Ostr), 1140 (C=Sstr); ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H NH of thiosemicarbazone moiety), 9.06 (s, 2H NH_2 of thiosemicarbazone moiety), 7.73 (d, 1H C_7-H proton), 7.45 (dd, 1H C_6-H proton), 7.17 (dd, 1H C_5-H proton), 7.20 (d, 1H C_4-H proton), 4.52 (s, 2H N-CH_2-N proton), 2.65 (q, 4H), 1.08 (t, 6H). Anal Calcd. for $C_{14}H_{19}N_5OS$ (305.63) C, 55.08; H, 6.23; N, 22.95. Found: C, 54.76; H, 6.17; N, 22.88.

N^1-Piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3b). Yield (77%); Mp 178–179°C (lit. 177–178°C) [24];

IR (KBr): 3427 (N-Hstr of indole), 2925 (N-Hstr of thiosemicarbazone moiety), 1700 (C=Ostr), 1162 (C=Sstr); ^{1}H NMR (DMSO-d_6): δ 12.36 (s, 1H NH of thiosemicarbazone moiety), 9.06 (s, 1H NH_2 of thiosemicarbazone moiety), 7.71 (d 1H C_7-H proton), 7.41 (dd, 1H C_6-H proton), 7.26 (d, 1H C_4-H proton), 7.17 (dd, 1H C_5-H proton), 4.47 (s, 2H N-CH_2-N proton), 2.54 (t, 4H), 1.46 (m, 4H), 1.33 (m, 2H). Anal Calcd. for (319.14) $C_{14}H_{17}N_5OS$ C, 52.64; H, 5.33; N, 21.93. Found: C, 52.43; H, 5.37; N, 20.96.

N^1-Morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone (3c). Yield (68%); Mp 212–213°C: (lit. 215 216°C) [24] IR (KBr): 3447 (N-Hstr of indole), 3206 (N-Hstr of thiosemicarbazone moiety), 1692 (C=Ostr), 1149 (C=Sstr); ^{1}H NMR (DMSO-d_6): δ 12.38 (s, 1H NH of thiosemicarbazone moiety), 9.05 (s, 1H NH_2 of thiosemicarbazone moiety), 7.73 (d, 1H C_7-H proton), 7.42 (dd, 1H C_6-H proton), 7.27 (d, 1H C_4-H proton), 7.15 (dd, 1H C_5-H proton), 4.49 (s, 2H N-CH_2-N proton), 3.54 (br s, 4H), 2.58 (br s, 4H). Anal Calcd. for $C_{15}H_{19}N_5OS$ (317.26) C, 56.76; H, 5.99; N, 22.07. Found C, 56.74; H, 6.03; N, 22.11.

5-Bromo-N^1-piperidin-1-ylmethyl-indole-2,3-dione-3-thiosemicarbazone(3d). Yield (64%); Mp 216–217°C IR (KBr): 3447 (N-Hstr of indole), 2933 (N-Hstr of thiosemicarbazone moiety), 1695 (C=Ostr), 1112 (C=Sstr), ^{1}H NMR (DMSO-d_6): δ 12.37 (s, 1H NH of thiosemicarbazone moiety), 9.06 (s, 1H NH_2 of thiosemicarbazone moiety), 7.78 (dd, 1H C_4-H proton), 7.45 (dd, 1H C_6-H proton), 7.28 (d, 1H C_7-H proton), 4.48 (s, 2H N-CH_2-N proton), 2.52 (t, 4H), 1.46 (m, 4H), 1.34 (m, 2H). Anal Calcd. for $C_{14}H_{16}BrN_5O_2S$ (397.25) C, 42.30; H, 4.05; N, 17.63. Found C, 42.62; H, 4.05; N,17.60.

5-Bromo-N^1-morpholin-4-ylmethyl-indole-2,3-dione-3-thiosemicarbazone(3e). Yield (71%); Mp 230–231°C IR (KBr): 3440 (N-Hstr of indole), 2925 (N-Hstr of thiosemicarbazone moiety), 1691 (C=Ostr), 1145 (C=Sstr), ^{1}H NMR (DMSO-d_6): δ 12.39 (s, 1H NH of thiosemicarbazone moiety), 9.05 (s, 1H NH_2 of thiosemicarbazone moiety), 7.80 (dd, 1H C_4-H proton), 7.47 (dd, 1H C_6-H proton), 7.30 (d, 1H C_7-H proton), 4.50 (s, 2H N-CH_2-N proton), 3.54 (br s, 4H), 2.56 (br s, 4H). Anal Calcd. for $C_{15}H_{18}BrN_5OS$ (395.31) C, 45.55; H, 4.56; N, 17.72. Found C, 45.88; H, 4.63; N, 17.63.

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