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A Microwave-Assisted Solid-State Synthesis and Characterization of Diheterocyclic Thioureas

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ABSTRACT: *In this study, a number of new diheterocyclic thioureas have been synthesized under microwave irradiation coupled with solvent-free condition, which proves to be simple and efficient. The structures of the prepared compounds are characterized by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectra.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:148–151, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20193

INTRODUCTION

It is now well known that, with the development of microwave ovens, solvent-free reactions have become easier due to their short reaction time, uniform heating, high yields, high efficiency, and convenient work-up conditions [1]. Meanwhile, it also leads to increase in safety and environmental aspects [2]. All these merits are in accordance with the green production's requests of energy saving and high efficiency [3]. Today, it has been widely used in a variety of organic reactions [4].

Heterocyclic thiourea compounds are known to exhibit antiviral [5], antituberculous [6], fungicidal [7], and herbicidal activities [8]. Some *N*-heterocyclic compounds (such as antipyrine) have been found to exhibit wide physiological activity [9]. Meanwhile, 4-aminoantipyrine is a versatile reagent, which has been extensively utilized in heterocyclic synthesis. It has been found that antipyrine and its derivatives possess antibacterial [10] and anti-inflammatory properties [11]. Some *N*-antipyrinyl compounds, such as *N*,*N*-diantipyrinyl thiourea and *N*-allyl-*N*′-antipyrinyl thiourea, could be used for extracting copper, silver, gold, and platinum and for determining the micropalladium [12]. Therefore, particularly intense interest has been directed toward their synthesis.

Recently, we prepared 4-antipyrinyl isothiocyanate [13–15] (Scheme 1) and studied the reaction of 4-antipyrinyl isothiocyanate and heterocyclic amines assisted by microwave. A series of diheterocyclic thioureas containing 4-antipyrinyl framework were obtained with excellent yields.

RESULTS AND DISCUSSION

As shown in Scheme 1, 4-antipyrinyl isothiocyanate **2** was prepared from the reaction of 4-aminoantipyrine with carbon disulfide and ethyl chlorocarbonate in the presence of triethylamine as a catalyst. The structure of compound **2** was confirmed by MS spectra-245 (M^+), elemental analysis, IR spectra (N=C=S, 2038 cm^{-1}), and ^{1}H NMR spectra (the signals of no NH protons).

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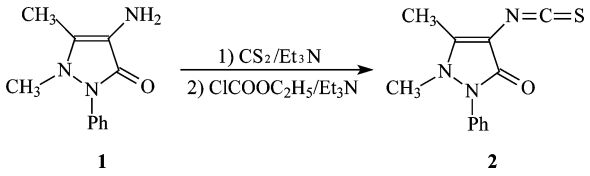


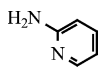
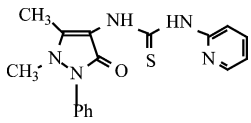
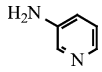
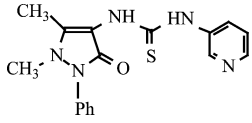
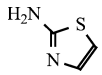
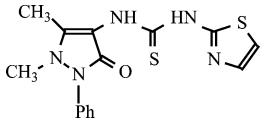
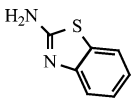
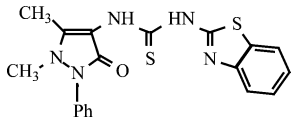
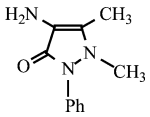
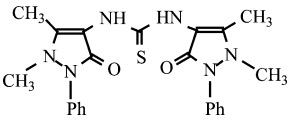
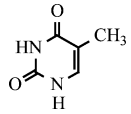
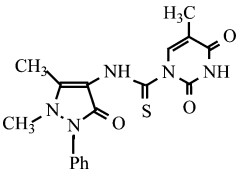
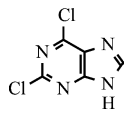
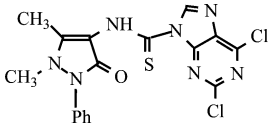
1 **2**

SCHEME 1

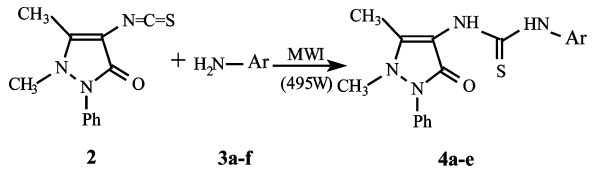
A number of different amines were chosen to assess the scope of the reaction. The synthetic results are presented in Table 1. Generally speaking, this reaction gives very good yields with primary amines allowing us to obtain the corresponding thiourea as the only product.

The synthesis of diheterocyclic thioureas **4a–e** was readily achieved according to the following solvent-free procedure (Scheme 2). Heterocyclic amine **3a–e** and 4-antipyrinyl isothiocyanate **2** was mixed thoroughly in a mortar, which was then placed into a household microwave oven and then irradiated for the specified time under solvent-free condition. When the reaction was placed in a focused microwave oven, several experiments were performed at various powers and irradiation times in order to find the most appropriate conditions. As shown by the results in Table 1, the use of focused microwave irradiations without solvent gave high yields under very mild conditions in a short reaction

TABLE 1 Reaction Time, Melting Point, and Yields of Diheterocyclic Thioureas **4**

Entry	*Amine (**3**)*	*Product (**4**)*	*Irradiation Time (min)*	*Melting Point (°C)*	*Yield (%)*
a			15	248–250	90
b			5[a]	212–214	98
c			15	216–218	90
d			15	224–226	95
e			10	245–247	98
f			40	–	0
g			40	–	0

[a]Irradiation power: 300 W.



2 **3a-f** **4a-e**

SCHEME 2

time (5–15 min). The reaction was monitored by TLC.

It was observed that in the case of 2-aminopyridine **3a** and 3-aminopyridine **3b**, the corresponding thioureas (**4a, 4b**) were obtained with different rates; 3-aminopyridine reacted faster than 2-aminopyridine, which show a regular chemical behavior according to the nucleophilic activity of the amino group, that is, in the addition reaction, amines with high nucleophilic activity can accelerate the reaction, while those with low nucleophilic activity result in longer reaction time. It is also noteworthy that in the case of cytosine and 6-chloro-2-purinamine, the corresponding thioureas were obtained with very long time and low yield, probably for their low nucleophilic activity and very high melting point (>300°C), which seemed no synthetic utility in these conditions.

The simplicity of the experimental procedures renders this method particularly attractive. In a similar way, we have also studied the addition of **2** to the secondary heterocyclic amines 5-methyluracil **3f** and 2,6-dichloropurine **3g** in the same reaction conditions. However, we did not obtain the desired compounds and the starting materials were recovered unchanged. The reaction seems to be very sensitive to steric effects. Therefore, the scope of this reaction seems to be limited to the primary heterocyclic amines.

In conclusion, we have developed a very simple, efficient, and environment-friendly methodology for the synthesis of diheterocyclic thioureas. This methodology works under solvent-free conditions assisted by microwave irradiation and affords in very high yields the corresponding products, which require no organic solvent, catalyst, and complicated instruments. No by-product is formed during the reaction. The reaction works very well for primary heterocyclic amines, while some low nucleophilic with very high melting point amines and sterically hindered secondary amines in general cannot be used. The structures of the prepared compounds were characterized by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectra. And more detailed work about the application of the thioureas in analytical chemistry and physiological activity is in progress in our laboratory.

EXPERIMENTAL

Melting points were determined with a Kofler micromelting point apparatus and were uncorrected. IR was recorded on a FTS-40 spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, using TMS as internal standard and DMSO-d_6 as solvent. Chemical shifts (δ) were expressed in ppm downfield from internal standard TMS. Elemental analyses were performed on PE-2400 CHN elemental analyzer. The experiment was carried out with Galanz microwave oven (750 W).

Microwave Irradiation Synthesis of Diheterocyclic Thioureas **4a–e**

A mixture of heterocyclic amine (1 mmol) and 4-antipyrinyl isothiocyanate **2** was mixed thoroughly in a mortar. The mixture was then placed into a household microwave oven and then irradiated for the specified time under solvent-free condition (495 W or 300 W). The end of the reaction was monitored by TLC. After the reaction was completed, the crude products were recrystallized from ethanol, and dried in vacuum to yield the pure products.

N-(4-Antipyrinyl)-N′-(2-pyridyl) Thiourea **4a** [14]. White crystals; IR (KBr) ν: 3218, 3175, 3105, 3037, 2997, 1687 (C=O), 1631, 1603, 1539, 1487, 1293 (C=S), 788, 752, 698 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 8.28–7.09 (m, 9H, ArH), 10.94 (s, 1H, N—H), 12.52 (s, 1H, N—H). Anal. Calcd for $C_{17}H_{17}N_5OS$: C, 60.14; H, 5.05; N, 20.63; Found: C, 60.25; H, 5.09; N, 20.51.

N-(4-Antipyrinyl)-N′-(3-pyridyl) Thiourea **4b** [15]. White powder; IR (KBr) ν: 3260, 3230, 3105, 3046, 2933, 1633 (C=O), 1601, 1580, 1565, 1531, 1295 (C=S), 761, 713 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.22 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 8.59–7.33 (m, 9H, ArH), 9.12 (s, 1H, N—H), 9.79 (s, 1H, N—H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.85, 36.57, 123.97, 125.03, 127.53, 130.00, 130.09, 136.00, 137.58, 146.47, 147.05, 162.58 (C=O), 183.08 (C=S). Anal. Calcd for $C_{17}H_{17}N_5OS$: C, 60.14; H, 5.05; N, 20.63; Found: C, 60.16; H, 5.00; N, 20.75.

N-(4-Antipyrinyl)-N′-(2-thiazole) Thiourea **4c**. Pale yellow crystals; IR (KBr) ν: 3225, 3202, 3102, 2993, 1643 (C=O), 1599, 1562, 1493, 1290 (C=S),

746, 700 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 8.54–7.08 (m, 7H, ArH), 9.80 (s, 1H, N—H), 11.96 (s, 1H, N—H). Anal. Calcd for $C_{15}H_{15}N_5O_2S_2$: C, 52.15; H, 4.38; N, 20.27; Found: C, 52.10; H, 4.42; N, 20.35.

N-(4-Antipyrinyl)-N′-(2-benzothiazole) Thiourea **4d** [14]. White crystals; IR (KBr) ν: 3225, 3196, 3105, 3062, 3003, 1648 (C=O), 1603, 1567, 1524, 1302 (C=S), 764, 752, 697 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 7.90–7.27 (m, 9H, ArH), 10.09 (s, 1H, N—H), 12.37 (s, 1H, N—H). Anal. Calcd for $C_{19}H_{17}N_5OS$: C, 62.79; H, 4.71; N, 19.27; Found: C, 62.75; H, 4.75; N, 19.22.

N,N′-Diantipyrinyl Thiourea **4e**. Pale yellow crystals; IR (KBr) ν: 3270 (N—H), 3110, 3030, 2981, 1662 (C=O), 1631 (C=C), 1595, 1532, 1497, 1298 (C=S), 763, 701 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 7.51–7.29 (m, 9H, ArH), 8.79 (s, 2H, 2N—H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.00, 36.75, 120.50, 124.68, 127.22, 130.03, 130.31, 136.30, 163.09 (C=O), 184.47 (C=S). Anal. Calcd for $C_{23}H_{24}N_6O_2S$: C, 61.59; H, 5.39; N, 18.74; Found: C, 61.65; H, 5.45; N, 18.63.

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