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## Highly Efficient Method for the Synthesis of 1,4-Phenylenedithioureas Under Solvent- and Catalyst-Free Conditions Promoted by Microwave Irridiation

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#### HIGHLY EFFICIENT METHOD FOR THE SYNTHESIS OF 1,4-PHENYLENEDITHIOUREAS UNDER SOLVENT- AND CATALYST-FREE CONDITIONS PROMOTED BY MICROWAVE IRRIDIATION

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#### **GRAPHICAL ABSTRACT**



**Abstract** A highly efficient method for the synthesis of 1,4-phenylenedithioureas promoted by microwave irridiation is reported. It is based on the nucleophilic addition reaction of 1,4-phenylenediisothiocyanate to aromatic amines under solvent- and catalyst-free conditions. The reaction has the advantages of short reaction time, good yields, and environmental acceptability.

**Keywords** Microwave irradiation; 1,4-phenylenediisothiocyanate; 1,4-phenylenedithioureas; solvent- and catalyst-free conditions

#### INTRODUCTION

Thioureas have attracted much attention by virtue of their bioactivities as pharmaceuticals and pesticides. Various thiourea derivatives and their metal complexes exhibit analgesic,<sup>[1]</sup> anti-HIV,<sup>[2]</sup> anti-viral,<sup>[3]</sup> analgesic,<sup>[4]</sup> and antinociceptive

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activity.<sup>[5]</sup> Recently, the activity of bisthioureas againt several representative pathogenic bacteria and fungi was investigated.<sup>[6]</sup> It can act as an organocatalyst<sup>[7,8]</sup> and bind anions by formation of multiple hydrogen bonds.<sup>[9]</sup> Until now, several methods for the preparation of phenylenedithioureas have been proposed.<sup>[10–14]</sup> The classical method for the preparation of phenylenedithioureas always involves many drawbacks and limitations such as poor yields, harsh reaction conditions,<sup>[15]</sup> and toxic reagents.<sup>[13,16,17]</sup> Therefore, the development of efficient and high-yielding methods for the synthesis of novel thioureas is of great importance in searching for bioactive molecules as well as in synthetic chemistry.

Microwave (MW) irradiation has proven to be a very efficient technique to accelerate different kinds of reactions.<sup>[17,18]</sup> The ability to rapidly heat reactions significantly above the boiling point of the solvent has resulted in dramatic decreases in reaction times and increases in reaction yields for a variety of chemical transformations.<sup>[19]</sup> Many of these reactions have been demonstrated to give good yields and to shorten reaction times under MW irradiation as compared to traditional heating methods.

#### **RESULTS AND DISCUSSION**

Based on this preliminary research, we proposed a new method by which the synthesis of 1,4-phenylenedithioureas was carried out under solvent- and catalyst-free conditions (Scheme 1). Greater yields and shorter reaction times were reached under MW-assisted conditions compared with conventional heating. It has the advantages of good yields, short reaction times, and environmental acceptability.

In our initial study, various reaction conditions including temperatures and solvents were tested for the synthesis of **3a** (Table 1). The reactions were carried out at temperatures ranging from  $10 \,^{\circ}$ C to  $70 \,^{\circ}$ C (Table 1). It was found that the yield of **3a** was improved (93%) and the reaction time was shortened (2 min) at  $60 \,^{\circ}$ C, whereas the yield plateaued at  $70 \,^{\circ}$ C (entry 6). Therefore,  $60 \,^{\circ}$ C was chosen as the optimized reaction temperature for all microwave-assisted reactions under study.

To compare the efficiency of MW irradiation with conventional heating procedures in organic solvents, 1,4-phenylenediisothiocyanate was heated with 2 equiv of 4-methyl benzenamine in organic solvents at  $60 \,^{\circ}$ C in an oil bath for 30 min. The results were summarized in Table 2. It was found that MW irridiation gave the best yield.



Scheme 1. Reactions of 1,4-phenylenediisothiocyanate with aromatic amines.

#### SYNTHESIS OF 1,4-PHENYLENEDITHIOUREAS



Table 1. Influence of temperature and time on the reaction<sup>a</sup>

Entry	Temperature (°C)	Time (min)	Yield of <b>3a</b> (%) <sup><i>t</i></sup>
1	25	25	32
2	30	15	45
3	50	6	80
4	60	2	93
5	70	2	92
6	80	2	93

<sup>a</sup>The power of MWI was 300 W.

<sup>b</sup>Isolated yield based on 1,4-phenylenediisothiocyanate.

Under the optimal MW conditions (300 W, 60 °C), we then examined the generality of the reaction by using 1,4-phenylenediisothiocyanate with a series of aromatic amines. All the reactions proceeded smoothly to give the corresponding 1,4-phenylenedithioureas in good yields (75–93%). The results are summarized in Table 3. A good yield was obtained when the substrates were well mixed.

The results in Table 3 show that the reaction can be favorably applied to aromatic amines with either electron-withdrawing groups or electron-donating groups. Delicate electronic effects of amines on the reaction were observed: Those with electron-donating groups reacted more rapidly and gave better yields (entries 1, 2,

Table 2. Solvent encets on the reaction of 1 with 2a						
Entry	Amine	Solvent	Time (min)	Yield of <b>3a</b> (%) <sup><i>t</i></sup>		
1	Me NH <sub>2</sub>	THF	30	55		
2		EtOH	30	85		
3	Me NH <sub>2</sub>	CH3COOEt	30	71		
4	Me NH <sub>2</sub>	MW	2	93		

Table 2. Solvent effects on the reaction<sup>a</sup> of 1 with 2a

<sup>a</sup>Materials were heated up to 60 °C in organic solvents.

<sup>b</sup>Isolated yield based on 1,4-phenylenediisothiocyanate.

Table 3. The reactions between 1,4-phenylenediisothiocyanate and aromatic amines under microwave  $irradiation^{a}$ 



3a-3l

2a-2l

1

Entry	Amine	Product	Time (min)	Yield of <b>3</b> $(\%)^b$
1	Me NH <sub>2</sub>	<b>3</b> a	2	93
2	MeO NH <sub>2</sub>	3b	3	92
3	EtO-NH2	3c	2	91
4	F-NH2	3d	8	89
5	$Cl \longrightarrow NH_2$	3e	4	91
6	Br NH <sub>2</sub>	3f	3	92
7		3g	2	93
8	NH <sub>2</sub>	3h	2	92
9		3i	3	90
10		3j	9	84
11	H <sub>3</sub> C NH <sub>2</sub>	3k	1	94
12	NH <sub>2</sub>	31	18	86

<sup>a</sup>The power of MWI was 300 W at 60 °C.

<sup>b</sup>Isolated yield based on 1,4-phenylenediisothiocyanate.

7, and 11), whereas those with electron-poor groups on the benzene ring (entries 4, 10, and 12) required longer reaction times and gave poorer yields.

In conclusion, the present procedure provides an efficient methodology for the synthesis of 1,4-phenylenedithioureas. The notable advantages offered by the method are simple operation, fast and environmentally friendly reaction conditions, and good yields of products.

#### EXPERIMENTAL

The reaction was carried out in a Sineo MW reactor with a heat setting (Sineo Microwave Chemical Technology Co. Ltd. in Shang Hai). Melting points were determined with a XRC-1 micro-melting-point apparatus and were uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR were measured on a Bruker DPX-400 M spectrometer at 400 MHz and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts ( $\delta$ ) were expressed in parts per million (ppm) from TMS, and coupling constants *J* are given in hertz (Hz). High-resolution mass spectra (HRMS) were taken on a Waters Q-TofMS/MS spectrometer. Column chromatography was performed using silica gel (200–300 mesh, GF<sub>254</sub>). All reactions were monitored by thin-layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified before use.

#### **General Procedure**

1,4-Phenylenediisothiocyanate was synthesized according to the literature.<sup>[20]</sup> 1,4-Phenylenediisothiocyanate (1 mmol) and aromatic amines (2 mmol) were well mixed in a mortar. The resulting mixture was then placed into the microwave reactor and heated to 60 °C (constant microwave irradiation at 300 W). The progress of the reaction was monitored by TLC (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH). After completion of the reaction, the reaction mixture was filtrated, washed with ethanol, and purified by column chromatography.

#### **Characterization Data for 3**

**1,4-Phenylene-bis[3-(4'-methylphenyl)thiourea]** (3a)<sup>[13]</sup>. White powder; mp 230–232 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.68 (s, 4H, NH), 7.42 (s, 4H, ArH), 7.35 (d, 4H, J=8.4Hz, ArH), 7.16 (d, 4H, J=8.4Hz, ArH), 2.29 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.0, 137.2, 136.3, 134.1, 129.3, 124.3, 124.2, 20.9.

**1,4-Phenylene-bis[3-(4'-methoxylphenyl)thiourea] (3b)**<sup>[13]</sup>. White powder; mp 218–220 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.55 (s, 2H, NH), 9.52 (s, 2H, NH), 7.41 (s, 4H, ArH), 7.31 (s, 4H, ArH), 6.89 (d, 4H, J = 6.4 Hz, ArH), 3.73 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.3, 157.0, 136.3, 132.6, 126.4, 124.2, 114.1, 55.7.

**1,4-Phenylene-bis**[**3-(4'-ethoxylphenyl)thiourea**] (**3c**)<sup>[13]</sup>. White powder; mp 226–228 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.59 (s, 2H, NH), 9.55 (s, 2H, NH), 7.411 (s, 4H, ArH), 7.32 (d, 4H, J=8.8 Hz, ArH), 6.89 (d, 4H, J=8.8 Hz,

ArH), 4.01 (q, 4H, J = 6.8 Hz, CH<sub>2</sub>), 1.32 (t, 6H, J = 6.8 Hz, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.3, 156.2, 136.3, 132.5, 126.3, 124.2, 114.6, 63.6, 15.1.

**1,4-Phenylene-bis[3-(4'-fluorophenyl)thiourea] (3d).** White powder; mp 232–235 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.71 (s, 4H, NH), 7.48–7.44 (dd, 4H,  $J_1 = 5.2$  Hz,  $J_2 = 8.8$  Hz, ArH), 7.42 (s, 4H, ArH), 7.16 (t, 4H, J = 8.8 Hz, ArH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.3, 160.8, 158.4, 136.2, 126.6, 124.3, 115.5. HRMS: calcd. for C<sub>20</sub>H<sub>16</sub>S<sub>2</sub>N<sub>4</sub>F<sub>2</sub> [M +Na<sup>+</sup>] 437.0682, found 437.0681.

**1,4-Phenylene-bis[3-(4'-chlorophenyl)thiourea]** (**3e**)<sup>[21]</sup>. White powder; mp 233–235 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.84 (s, 2H, NH), 9.82 (s, 2H, NH), 7.50 (d, 4H, J=8.0 Hz, ArH), 7.41 (s, 4H, ArH), 7.36 (d, 4H, J=8.0 Hz, ArH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.3, 155.8, 153.4, 137.2, 136.2, 126.2, 125.0, 124.4, 119.1, 116.9.

**1,4-Phenylene-bis[3-(4'-bromophenyl)thiourea] (3f)**<sup>[21]</sup>. White powder; mp 222–224 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.85 (s, 2H, NH), 9.83 (s, 2H, NH), 7.49 (d, 8H, J=8.4 Hz, ArH), 7.44 (s, 4H, ArH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  179.9, 139.4, 136.2, 131.6, 125.9, 124.3, 116.7.

**1,4-Phenylene-bis[3-(4'-iodophenyl)thiourea] (3g)**<sup>[21]</sup>. Light brown powder; mp 232–234 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.82 (s, 2H, NH), 9.79 (s, 2H, NH), 7.64 (d, 4H, J=8.4 Hz, ArH), 7.41 (s, 4H, ArH), 7.32 (d, 4H, J=8.4 Hz, Hz, ArH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  179.8, 139.8, 137.5, 136.2, 126.0, 124.3, 88.9.

**1,4-Phenylene-bis[3-(2'-methylphenyl)thiourea] (3h)**<sup>[22]</sup>. White powder; mp 230–232 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.63 (s, 2H, NH), 9.25 (s, 2H, NH), 7.42 (s, 4H, ArH), 7.26-7.22 (m, 4H, ArH), 7.19–7.14 (m, 4H, ArH), 2.23 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ 180.7, 138.2, 135.2, 130.8, 128.4, 126.5, 124.4, 18.3.

**1,4-Phenylene-bis[3-(2'-chlorophenyl)thiourea] (3i)**<sup>[23]</sup>. White powder; mp 148–150 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.99 (s, 2H, NH), 9.38 (s, 2H, NH), 7.62 (d,2H, J = 7.6 Hz, ArH), 7.50–7.39 (m, 6H, ArH), 7.33 (t, 2H, J = 7.6 Hz, Hz, ArH), 7.24 (t, 2H, J = 7.6 Hz, ArH).<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.6, 136.8, 136.2, 130.3, 130.1, 129.9, 127.86, 127.6, 124.4.

**1,4-Phenylene-bis[3-(3'-chloro-4'-fluorophenyl)thiourea]** (3j). White powder; mp 184–186 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.95 (s, 2H, NH), 9.84 (s, 2H, NH), 7.77 (d, 2H, J = 5.6 Hz, ArH), 7.42 (s, 4H, ArH), 7.38 (q, 4H, J = 8.8 Hz, ArH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  180.0, 138.9, 136.2, 128.7, 128.6, 125.6, 124.3. HRMS: calcd. for C<sub>20</sub>H<sub>14</sub>S<sub>2</sub>N<sub>4</sub>Cl<sub>2</sub>F<sub>2</sub> [M +Na<sup>+</sup>] 504.9903, found 504.9902.

**1,4-Phenylene-bis[3-(3',4'-dimethylphenyl)thiourea] (3k).** White powder; mp 182–184 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.59 (s, 4H, NH), 7.41 (s, 4H, ArH), 7.21 (s, 2H, ArH), 7.17 (d, 2H, J=8.0 Hz, ArH), 7.09 (d, 2H, J=8.4 Hz, ArH), 2.20 (s, 6H, CH<sub>3</sub>), 2.20 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  179.9, 137.4, 136.6, 136.3, 133.0, 125.5, 124.2, 121.9, 19.9, 19.3. HRMS: calcd. for C<sub>24</sub>H<sub>26</sub>S<sub>2</sub>N<sub>4</sub> [M +Na<sup>+</sup>] 457.1497, found 457.1496.

**1,4-Phenylene-bis[3-(\alpha-naphthyl)thiourea]** (31). White powder; mp 204–207 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.85 (s, 2H, NH), 9.75 (s, 2H, NH), 7.97 (s, 4H, ArH), 7.86 (s, 2H, ArH), 7.54–7.47 (m, 12H, ArH). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  181.6, 136.5, 135.5, 134.4, 130.4, 128.6, 127.1, 126.6, 126.5, 126.1, 125.8, 124.6, 123.5. HRMS: calcd. for C<sub>28</sub>H<sub>22</sub>S<sub>2</sub>N<sub>4</sub> [M +Na<sup>+</sup>] 501.1184, found 501.1184.

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