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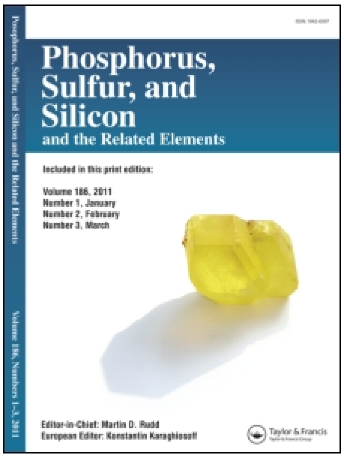

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An Environmentally Benign Method for the Synthesis of Symmetrical *N, N*'-Disubstituted Thioureas in a Water Medium

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An Environmentally Benign Method for the Synthesis of Symmetrical *N,N*′-Disubstituted Thioureas in a Water Medium

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An environmentally benign method for the synthesis of symmetrical N,N′*-disubstituted thioureas in a water medium using poly(ethylene glycol)-400 (PEG-400) as a catalyst and a microwave as a heating source is described. Diaryl- and dialkyl-thioureas efficiently are synthesized by the reactions of thiourea with a variety of amines. This protocol has advantages of (a) no use of hazardous reagents and volatile organic solvents, (b) a rapid reaction rate, (c) a high yield, and (d) a simple work-up procedure.*

Keywords Environmentally benign; microwave irradiation; *N,N*′-disubstituted thiourea; PEG-400; water medium

INTRODUCTION

Thioureas are of importance in medicinal chemistry due to their biological activities, e.g., anti-HIV,[1] antituberculosis[2] and antiarrhythmic activities,[3] and in connection with biomimetic models.[4] Thioureas are valuable building blocks for the synthesis of five- and six-membered heterocycles.[5]

Treatment of 2 equivalents of a primary or secondary amine with thiophosgene is the easiest and most general method of making symmetrical disubstituted thioureas.[6] However, this method is hazardous due to the toxic properties of thiophosgene. Hence, numerous

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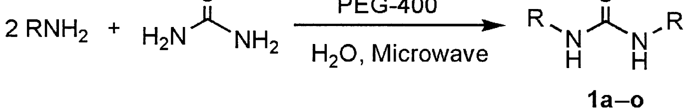
alternative methods have been developed for the synthesis of symmetrical thioureas avoiding the use of thiophosgene. Thus, symmetrical thioureas are formed by (i) either the direct[7] or catalyzed[8] reaction of carbon disulfide and amines; (ii) the reaction of carbodiimides with hydrogen sulfide;[9] (iii) the reaction of 2-chloropyridinium salts with sodium trithiocarbonate and amines;[10] or (iv) the reaction of 1,1′-thiocarbonyldiimidazole with amines.[11] However, these methods still suffer from the following practical limitations: the use of flammable and volatile organic solvents, harsh reaction conditions, poor yields, and many side reactions.

Organic reactions in an aqueous medium have been the subject of considerable attention in terms of achieving more environmentally friendly synthetic transformations.[12] In an effort to develop aqueous reactions, in this article, we wish to report an environmentally friendly aqueous method suitable to symmetrical *N*,*N*′-diaryl and dialkyl substituted thioureas, which utilizes an industrial commodity chemical thiourea as a starting material, inexpensive PEG-400 as a catalyst, and microwave irradiation as a heating source.

RESULTS AND DISCUSSION

Synthesis of *N,N*′-Diphenylthiourea Using Different Catalysts

In the course of our investigation, we selected the synthesis of *N*,*N*′-diphenylthiourea by reaction of thiourea with aniline as a model reaction. When the mixture of 2 equiv. of aniline and 1 equiv. of thiourea was refluxed in water at 100°C for 24 h, no reaction product was formed (entry 1, Table I). However when the reaction was catalyzed by 2% equiv. of different catalysts, *N*,*N* ′-diphenylthiourea was obtained in varying yields: *β*-Cyclodextrin (*β*-CD) as a supramolecular catalyst for this reaction gave 26% yield (entry 2, Table I); Sodium *n*-dodecylsulfonate as a micellar catalyst gave 51% yield (entry 3, Table I); some quaternary ammonium salts as phase transfer catalysts also gave moderate yields (entries 4–6, Table I). In contrast, PEG-400 as a catalyst afforded the highest yield (entry 7, Table I). Subsequent tests confirmed that PEG-400 was the most efficient catalyst for the synthesis of *N*,*N*′-diphenylthiourea in water medium (Scheme 1).



SCHEME 1

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TABLE I Synthesis of *N,N′*-Diphenylthiourea in a Water Medium Using Different Catalysts

Entry	Catalyst	Time (h)	Yield (%)
1	None	24	0
2	β-CD	24	26
3	n-$C_{12}H_{25}SO_3Na$	24	51
4	$(n\text{-}C_4H_9)_4NBr$	24	37
5	$(n\text{-}C_4H_9)_4NI$	24	49
6	n-$C_{16}H_{33}N(CH_3)_3Br$	24	56
7	PEG-400	24	80

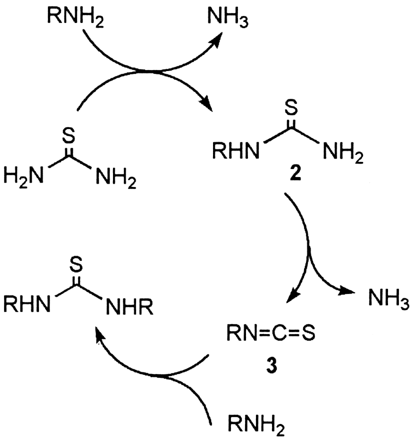
PEG-400 Catalyzed Synthesis of *N,N′*-Disubstituted Thiourea Under Microwave Irradiation

We found that the PEG-400 catalyzed synthesis of *N*,*N′*-diphenylthiourea in water could be accelerated efficiently by microwave irradiation. A reaction could be completed within 2 min at 650W microwave power to afford the product in a 94% yield. Therefore, we extended this protocol to other symmetrically disubstituted thioureas.

The mixture of 2 equiv. of primary aromatic amines and 1 equiv. of thiourea was irradiated in water for 2 min to give symmetrical diaryl thioureas **1a–j** in 77–97% yields after cooling to room temperature and filtration (Scheme 1, Table II). The symmetrical di(thiazol-2-yl) thiourea (**1k)** was obtained under a similar condition in an 87% yield. The reactions of 2 equiv. of primary aliphatic amines with 1 equiv. of thiourea could be completed within much shorter time (30 s) to afford the corresponding products in high yields (93–96%) (**1m–o)**. It is noteworthy to mention that this procedure is efficiently applicable to all primary amines to produce *N*,*N′*-disubstituted thioureas in very high selectivity. No side reactions were observed.

Hypothesized Mechanism for the Synthesis of Symmetrically Disubstituted thioureas

A plausible reaction mechanism for the title reactions is illustrated in Scheme 2. Thiourea reacts with one molecule of amine, librating one molecule of ammonia, and is transformed to monosubstituted thiourea **2**. Subsequently, the monosubstituted thiourea is converted to an isothiocyanate **3** with the loss of another molecule of ammonia. Then the



SCHEME 2

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isothiocyanate reacts with another amine molecule to produce *N*,*N*′-disubstituted thiourea.

In conclusion, we have successfully developed an environmentally friendly method that can be applicable to diaryl- and dialkyl-substituted thioureas. This method utilizes industrial-commodity primary amines and thiourea as starting materials, inexpensive PEG-400 as a catalyst, microwave as a heating source, and water as the reaction medium. This protocol has advantages of (a) not using flammable and volatile organic solvents of rapid reaction rate, (b) high yield, and (c) a simple work-up procedure.

EXPERIMENTAL

General Procedure for Symmetrical *N,N*′-Disubstituted Thioureas Under Microwave Irradiation

To a solution of thiourea (0.76 g, 10 mmol) dissolved in H_2O (0.5 mL), primary amines (20 mmol) and PEG-400 (0.08 g, 0.2 mmol) were added. Then the mixture was placed in a modified microwave oven and subjected to microwave irradiation at a power of 650 W for 2 min or 30 s (Table II). After the reactions were complete, the resulting mixture was cooled to room temperature, and the products were isolated either by filtration and washing with water (**1a**, **1b**, **1d**, **1f**, **1h**, **1i**, **1j** **1l**, and **1o**), or by extraction with EtOAc (3 × 20 mL) and concentration under reduced pressure (**1c**, **1e**, **1g**, **1k**, **1m**, and **1n**). Analytical samples were obtained by recrystallization from EtOH or EtOAc.

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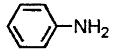
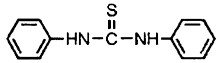
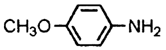
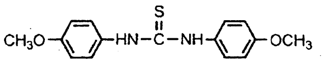
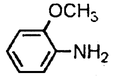
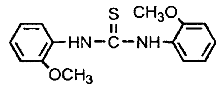
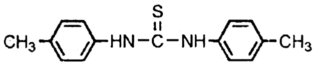
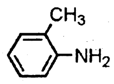
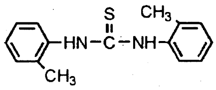
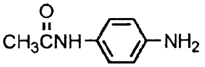
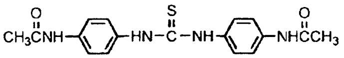
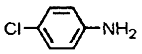
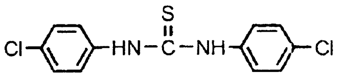
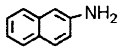
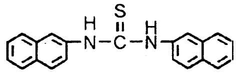
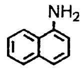
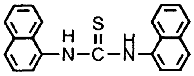
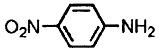
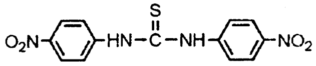
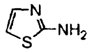
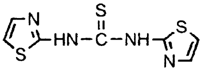
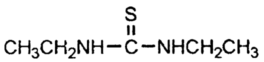
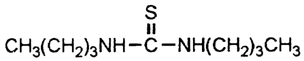
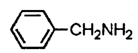
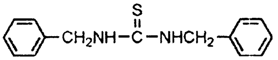
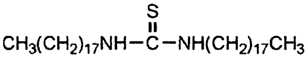
TABLE II Synthesis of Symmetrically Disubstituted Thioureas in a Water Medium Under MW Irradiation

Entry	Amine	Disubstituted thiourea[a]	Time	Yield (%)[b]
1a			2 min	94
1b			2 min	97
1c			2 min	86
1d			2 min	96
1e			2 min	77
1f			2 min	94
1g			2 min	93
1h			2 min	92
1i			2 min	90
1j			2 min	84
1k			2 min	87
1l	$CH_3CH_2NH_2$	 $CH_3CH_2NH-\overset{S}{\overset{\parallel}{C}}-NHCH_2CH_3$	30 s	96
1m	$CH_3(CH_2)_3NH_2$	 $CH_3(CH_2)_3NH-\overset{S}{\overset{\parallel}{C}}-NH(CH_2)_3CH_3$	30 s	96
1n			30 s	95
1o	$CH_3(CH_2)_{17}NH_2$	 $CH_3(CH_2)_{17}NH-\overset{S}{\overset{\parallel}{C}}-NH(CH_2)_{17}CH_3$	30 s	93

[a] All products were identified by ^1H NMR, IR, and elemental analyses and in comparison with authentic samples.

[b] Yields refer to the isolated products.

All products were identified by ^{1}H NMR, IR, and elemental analyses, and m.p. and were compared with authentic samples.

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