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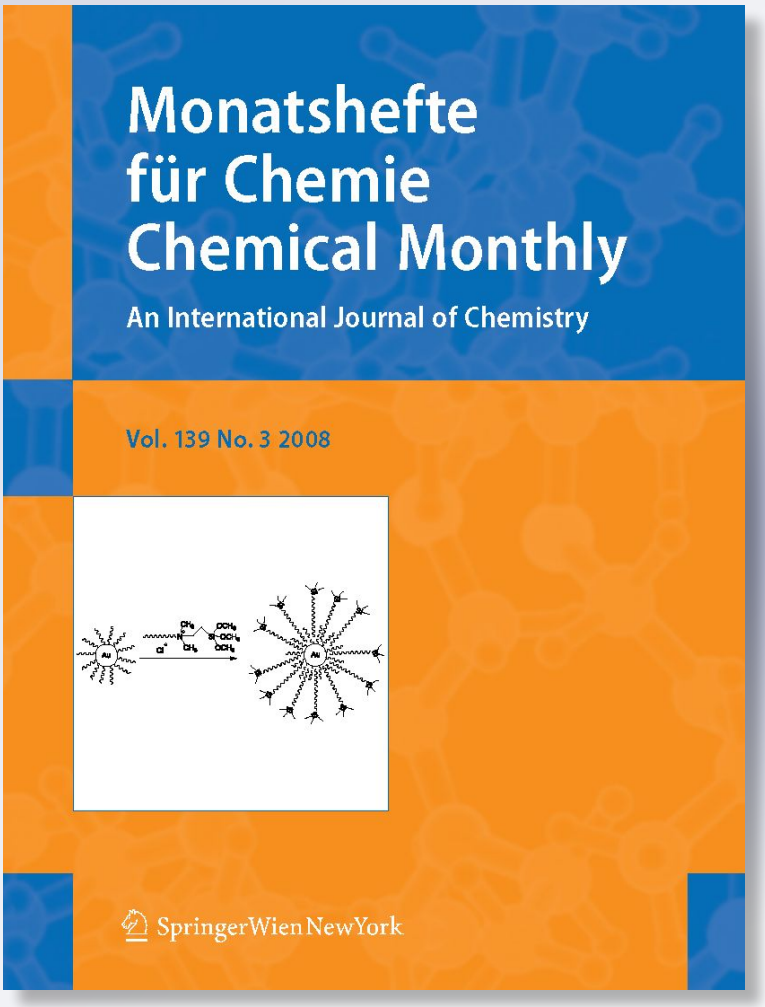

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ORIGINAL PAPER

Microwave-assisted synthesis of symmetrical and unsymmetrical *N*,*N*′-disubstituted thioureas and ureas over MgO in dry media

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Abstract Under mild microwave irradiation conditions a variety of symmetrical and unsymmetrical *N*,*N*′-disubstituted thioureas and ureas were prepared via the reaction of *N*-monosubstituted hydroxylamines with isocyanate and isothiocyanate derivatives over MgO under solvent-free conditions. This new method afforded satisfactory results with good yields, short reaction time, and simplicity in the experimental procedure.

Keywords *N*-Monosubstituted hydroxylamines · Isocyanate · Isothiocyanate · Microwave irradiation · Solvent-free

Introduction

Green chemistry has been attracting great interest from chemists because of the potential environmental benefits of using such methods. A number of procedures involving new eco-friendly reagents and catalysts, selected media such as water, supercritical fluids, ionic liquids, solvent-free reactions, non-classical modes of activation such as ultrasound or microwaves are now recommended for green chemistry. There are several advantages of performing organic reactions in a solventless system such as short reaction time, increased safety, and economic advantages from the absence of solvent [1]. Recently, microwave irradiation (MWI) has become an established tool in organic synthesis [2–4], because of the rate enhancements, higher yields, and often improved selectivity with respect to conventional reaction conditions. In addition, solvent-free MWI processes are also clean and efficient; moreover, the use of organic or inorganic solid supports has received increased attention [5, 6].

Thiourea and urea derivatives are important synthetic intermediates for amidines or guanidines [7]. Thioureas have also been used as neutral receptors for various anions [8] and natural product mimics. There are many methods for the preparation of disubstituted ureas [9–14] and thioureas [15–19] including condensation of amine hydrochlorides with potassium thiocyanate [20]. The most direct approach involves interaction of carbon disulfide with primary amines [9]. However, this reaction is often associated with several by-products depending on the reaction conditions employed [9]. To the best of our knowledge, there are no reports on the use of *N*-substituted hydroxylamines in the reaction with isothiocyanate and isocyanate derivatives for the synthesis of the related *N*,*N*′-disubstituted thioureas and ureas.

In continuation of our work in studying organic reactions in ionic liquids, water, or solventless systems as a green reaction medium [21–27], we wish to report here the synthesis of symmetrical and unsymmetrical *N*,*N*′-disubstituted thioureas and ureas from the reaction of *N*-substituted hydroxylamines with isothiocyanate and isocyanate derivatives over MgO as basic solid support in a solventless system under MWI (Scheme 1).

Results and discussions

In a pilot experiment, *N*-methylhydroxylamine (**2a**) and phenylisothiocyanate (**1a**) were mixed with excess of MgO

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Scheme 1

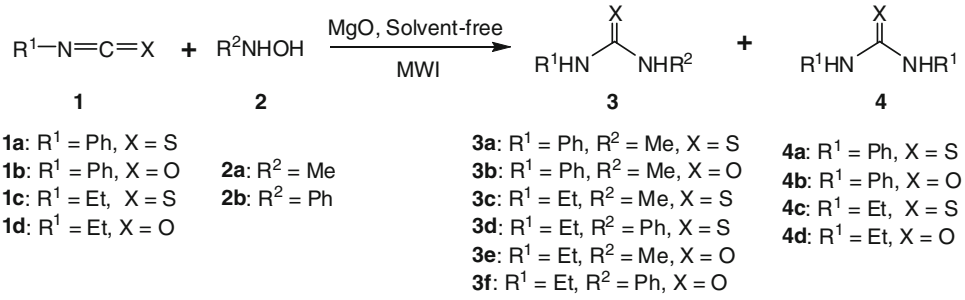


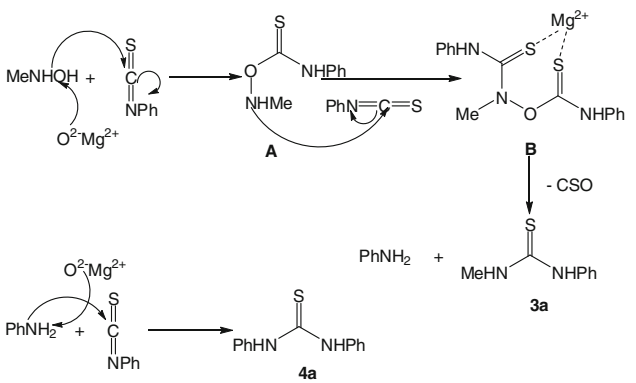
Table 1 Microwave-assisted synthesis of thioureas and ureas over MgO in solventless system

Entry	Reactant **1**	Reactant **2**	MWI or thermal heating	Time/min	Product **3**, yield[a]/%	Product **4**, yield[a]/%
1	**1a**	**2a**	MWI	3	**3a** (76)	**4a** (9)
2	**1a**	**2b**	MWI	4.5	–	**4a** (81)
3	**1b**	**2a**	MWI	3.5	**3b** (75)	**4b** (8)
4	**1b**	**2b**	MWI	3	–	**4b** (78)
5	**1c**	**2a**	MWI	3.5	**3c** (71)	**4c** (13)
6	**1c**	**2b**	MWI	4	**3d** (76)	**4c** (12)
7	**1d**	**2a**	MWI	3.5	**3e** (74)	**4d** (10)
8	**1d**	**2b**	MWI	4	**3f** (72)	**4d** (9)
9	**1a**	**2a**	MWI (neat conditions)	60	**3a** (22)	–
10	**1c**	**2a**	MWI (neat conditions)	60	**3c** (23)	–
11	**1a**	**2a**	Thermal heating	300	**3a** (25)	–
12	**1c**	**2a**	Thermal heating	300	**3c** (21)	–

[a] Isolated yields after recrystallization

and irradiated by microwave to obtain *N*-methyl-*N*′-phenylthiourea (**3a**) in 76% yield and *N*,*N*′-diphenylthiourea (**4a**) as a minor product in less than 10% yield (Table 1). By this method, other isocyanates and isothiocyanates with *N*-(phenyl and methyl)hydroxylamines gave satisfactory results (Table 1, entries 2–8). In order to exhibit the catalytic effect of MgO, the condensation of *N*-methylhydroxylamine with two isothiocyanates (**1a** and **1c**) was studied in the absence of MgO under MWI conditions. It was found that MgO was more effective, and very poor yield of the corresponding thioureas were isolated in these conditions (Table 1, entries 9–10). In the absence of MWI, the reactions proceeded in longer reaction times at 80 °C in lower yields in comparison with MWI conditions (Table 1, entries 11–12). So MWI can shorten the reaction time and also assist the reaction process effectively. We conducted these reactions on a 25-mmol scale and found that they underwent a smooth transformation to the thiourea and urea derivatives in good yields. Thus, the present procedure is amenable to scaling up. Optimization of the reaction conditions was studied with different molar ratios of MgO and under different microwave powers. The best ratio was found to be 200 mol% of MgO under 200-W microwave power. Increasing the power of microwave decreases the yields of the products.

A plausible mechanism for the formation of the selected products **3a** and **4a** over MgO is outlined in Scheme 2. Intermediate **A** apparently results from the initial nucleophilic attack of *N*-methylhydroxylamine on phenylisothiocyanate in the presence of MgO as base catalyst. Subsequent nucleophilic addition of intermediate **A** to another phenylisothiocyanate yields the intermediate **B**, which fragments to CSO, aniline, and **3a** as a major product. The fragmentation of **B** perhaps accrued in the



Scheme 2

presence of water or oxygen present in the open reaction vessel under MWI. The compound *N*,*N*′-diphenylthiourea (**4a**) was obtained from the nucleophilic attack of aniline on unreacted phenylisothiocyanate in very low yield.

Conclusion

Under solvent-free conditions, microwave-assisted synthesis of symmetrical and unsymmetrical *N*,*N*′-disubstituted thioureas and ureas over MgO can be achieved from *N*-monosubstituted hydroxylamines and isocyanates and isothiocyanates efficiently. The advantages of this protocol are mild reaction conditions, short reaction times, simple work-up procedure, absence of organic solvent, and good yields. Therefore, we believe that the new synthetic method reported here constitutes an environmentally greener and safer process than existing approaches.

Experimental

All reagents were purchased from Merck and used without further purification. NMR spectra of samples in $CDCl_3$ solution were measured using a Bruker Avance AC-400 instrument (^{1}H at 400 MHz and ^{13}C at 100 MHz). Mass spectra were recorded on a Platform II (Micromass, Manchester, UK) quadrupole mass spectrometer fitted with an electrospray interface. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer. Melting points were measured in open glass capillaries using a Stuart melting point apparatus. Microwave experiments were conducted in a Milestone MicroSYNTH apparatus.

General procedure for the preparation of thioureas and ureas over MgO under MWI

Isocyanate and isothiocyanate derivatives (20 mmol) and *N*-monosubstituted hydroxylamine (20 mmol) were added to 10 cm^3 acetone containing 1.61 g MgO (40 mmol) and stirred for 10 min at room temperature. After evaporation of acetone the mixture was subjected to MWI at 200 W for a few minutes (depending on the reactants, see Table 1). The completion of reaction was monitored by TLC using EtOAc/petroleum 1:2 as eluent. After completion of the reaction, the mixture was cooled to room temperature and extracted with ether or ethyl acetate. The extracts were concentrated on a rotary evaporator and the crude mixture was purified by silica gel (Merck 230–240 mesh) column chromatography using a 1:2 ethyl acetate/*n*-hexane mixture as eluent to give pure products **3a**–**3f** and **4a**–**4d**, which were characterized by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and IR), elemental analysis, and by comparison of their melting points with those reported in the literature (Table 2).

Table 2 Melting points of products

Product	M.p./°C	Lit. m.p./°C
3a	95.5–99	92 [28]
3b	146–147	148–149 [29]
3c	87–89	54 [30]
3d	91–93	98 [31]
3e	99–102	54–55 [29]
3f	95.7–97	94–95 [32]
4a	152–154	153–154 [11]
4b	229–233	232 [11]
4c	77–78.5	78 [12]
4d	111–113	112 [33]

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