

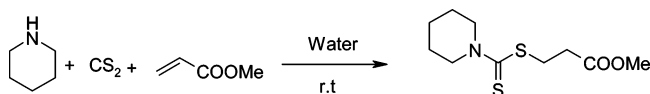
## One-Pot Synthesis of Dithiocarbamates Accelerated in Water

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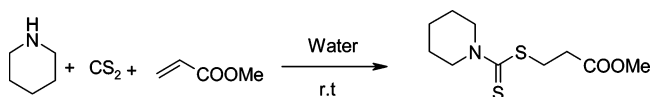


Highly efficient one-pot reactions of amines and carbon disulfide with  $\alpha,\beta$ -unsaturated compounds were carried out in water under a mild and green procedure with high yields.

The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvents but also because water exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents. Thus, development of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.<sup>1</sup>

Organic dithiocarbamates are valuable synthetic intermediates,<sup>2</sup> which are ubiquitously found in a variety of biologically active compounds.<sup>3</sup> Functionalization of the carbamate moiety offers an attractive method for the generation of derivatives, which may constitute interesting medicinal and biological properties.<sup>3</sup> Furthermore, diarylalkyl thioureas have merged as one of the promising nonvanilloid TRPV1 antagonists, possessing excellent therapeutic potentials in pain regulation<sup>4</sup> and human CB1 and CB2 cannabinoid receptor affinity.<sup>5</sup> For these reasons, the synthesis of dithiocarbamate derivatives with different substitution patterns at the thiol chain has become a

## SCHEME 1. Synthesis of Dithiocarbamate



field of increasing interest in synthetic organic chemistry during the past few years.

In fact, few methods for the synthesis of dithiocarbamate derivatives have been reported in the literature, and among them, reactions of amines with costly and toxic reagents, such as thiophosgene and isothiocyanate, have been reported as the general routes.<sup>6</sup> Direct thiocarboxylation of amines with carbon monoxide and sulfur to form urea derivatives has also been reported.<sup>7</sup> Recently, a one-pot reaction of amines with carbonyl sulfide, alkyl halides, or  $\alpha,\beta$ -unsaturated compounds also has been developed.<sup>8</sup> However, these reactions require very toxic reagents and harmful organic solvents such as DMF, DMSO, and methanol in the presence of a catalyst.

With the increasing interest in developing environmentally benign reactions, the atom-economic catalytic processes, or reactions without using any catalyst, and the use of green solvents are ideal processes in organic chemistry. As a continuation of our research devoted to the development of green organic chemistry by using water as the reaction medium or by performing organic transformations under solvent-free conditions,<sup>9</sup> herein we report an efficient, novel, and entirely green procedure for the Michael-type addition of dithiocarbamate to  $\alpha,\beta$ -unsaturated compounds in water without using catalyst at room temperature. The results of the present work show the desired product in excellent yield (Scheme 1).

To study the Michael reaction in water, we tested the reaction of piperidine, methyl acrylate, and carbon disulfide as a simple model substrate and the results are shown in Table 1. It was found that simple mixing of amine (5 mmol), carbon disulfide (8 mmol), and methyl acrylate (6 mmol) gave the desired product in high yields in water without any catalyst at room temperature.

After optimizing the conditions, we next examined the generality of these conditions to other substrates using several amines and  $\alpha,\beta$ -unsaturated compounds. The results are summarized in Table 1. A variety of  $\alpha,\beta$ -unsaturated carbonyl compounds or nitriles such as methyl acrylate, acrylonitrile, methyl vinyl ketone, and cyclohexenone underwent 1,4-addition with a wide range of aliphatic, aromatic, primary, secondary, and hindered amines in water at room temperature to give the

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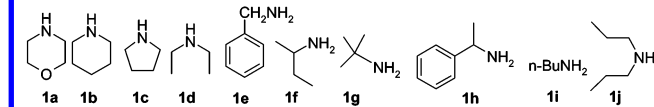
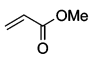



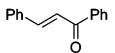

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**TABLE 1. One-Pot Preparation of Dithiocarbamate in Water without Using Any Catalyst**

$\text{RR'NH} \quad 1 + \text{CS}_2 + \text{CH}_2=\text{CHX} \xrightarrow[\text{r.t., 5-18 h}]{\text{Water}} \text{RR'N}=\text{C}(\text{S})\text{CH}_2\text{CHX} \quad 3$							
X = CN, COOMe, COR, CONH <sub>2</sub>							
							
entry	Michael acceptor	amines	yield (%)	entry	Michael acceptor	amines	yield (%)
1		1a	62	26		1a	57
2		1b	90	27		1b	80
3		1c	96	28		1c	83
4		1d	96	29		1d	94
5		1e	80	30		1e	79
6		1f	83	31		1f	56
7		1g	90	32		1h	75
8		1h	80	33		1i	76
9		1i	88	34		1j	78
10		1j	78				
11		1a	55	35 <sup>a</sup>		1b	70
12		1b	90	36		1c	60
13		1c	82	37		1d	74
14		1d	84				
15		1e	80			1b	76
16		1f	85			1c	70
17		1g	70			1d	68
18		1h	74				
19		1i	79	38 <sup>b</sup>			
20		1j	80	39			
				40			
23 <sup>a</sup>		1b	60				
24 <sup>a</sup>		1c	55				
25 <sup>a</sup>		1d	62				

<sup>a</sup> Reaction was carried out at 60 °C. <sup>b</sup> 5 mmol cyclohexanone or chalcone was used.

corresponding  $\beta$ -amino esters, ketones, and nitriles in high yields.

Generally, secondary amines such as pyrrolidine, piperidine, and diethylamine show higher yields compared with the primary amines. Primary amines such as benzylamine, *n*-butylamine, and *sec*-butylamine and hindered amines such as *tert*-butylamine undergo efficient addition with Michael acceptors to give only the monoadducts in high yields. Furthermore, cyclic  $\alpha,\beta$ -unsaturated ketones such as cyclohexenone and chalcone reacted readily under these reaction conditions and gave the corresponding 1,4-adducts in good yields.

The role of water as the reaction medium and its mechanism are still not clear. Despite the low solubility of amines and Michael acceptors in water, the Michael reaction is accelerated in water and proceeds efficiently at ambient temperature. This

one-pot reaction might take place at the interface of organic substrates with water in a heterogeneous system. Vigorous stirring is required for the success of this reaction.

In summary, we have described a novel, highly efficient, and entirely green protocol for one-pot preparation of dithiocarbamates in water. This protocol avoids the use of basic and highly toxic organic solvents, such as DMF or DMSO, and catalysts by playing the dual role of water as a solvent and a promoter. Furthermore, the procedure offers several advantages including catalyst-free, improved yields, cleaner reactions, and simple experimental procedures, which make it a useful and attractive strategy in multicomponent reactions in combinational chemistry. In addition, easy workup has been realized without using any organic solvents. When the products were solid or insoluble in water, the pure products were obtained with direct evaporation of unreacted material under reduced pressure. No extraction or column chromatography separation was necessary in some cases. At the end, the simplicity of this procedure is one of the advantages of the present protocol.

## Experimental Section

**General Procedure for the One-Pot Reaction of Amines, CS<sub>2</sub>, and  $\alpha,\beta$ -Unsaturated Olefins in Water.** To a mixture of carbon disulfide (8 mmol) was added a Michael acceptor (6 mmol) in water (10 mL) and an amine (5 mmol), and the reaction mixture was stirred at room temperature under vigorous magnetic stirring for 5–18 h. Then, the organic materials were extracted with diethyl ether or ethyl acetate (2  $\times$  10 mL). The combined organic phases were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the desired products. The residue was purified by flash column chromatography or crystallized from ethanol or diethyl ether to give the corresponding product.

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**Supporting Information Available:** Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra and CHN analyses for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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