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# An efficient synthesis of dithiocarbamates under ultrasound irradiation in water

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**Abstract** Multicomponent reactions with ultrasonic activation have been used as a simple, rapid, atom economic, and green method for the synthesis of dithiocarbamate derivatives in water. The one-pot, three-component condensation of primary and secondary amines with carbon disulfide and unsaturated carbonyl compounds or alkyl halides under ultrasonic irradiation was developed as a green and fast protocol for the rapid high-yielding preparation of dithiocarbamates in water.

**Keywords** Carbon disulfide · Dithiocarbamate · Multicomponent reaction · Water chemistry · Ultrasonic irradiation

## Introduction

Most chemical manufacturing industries and chemistry laboratories use electricity generated from coal for heating purposes and organic solvents which are responsible for environmental pollution. In view of this, attempts have been made to use alternate energy sources and green reaction media in organic synthesis and industry. In this context the use of water as an alternate greener reaction medium [1-5] has gained popularity, offering environmentally clean technology by improving product yields and

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selectivities, enhancing product recovery, and minimizing the production of waste at source. On the other hand, ultrasound is widely used for improving the traditional reactions that involve expensive reagents, strongly acidic conditions, long reaction times, high temperatures, unsatisfactory yields, and incompatibility with other functional groups [6–9].

Organic dithiocarbamates are valuable synthetic intermediates which are found in a variety of biologically active compounds [10]. Functionalization of the carbamate moiety offers an attractive method for the generation of derivatives, which may have interesting medicinal and biological properties [11]. For these reasons, the synthesis of dithiocarbamate derivatives with different substitution patterns at the thiol chain has become a field of increasing interest in synthetic organic chemistry during the past few years.

Among the numerous methods for the synthesis of dithiocarbamate derivatives, condensation of amines with isothiocyanate, thiophosgene, or its derivatives constitutes the most widely accepted general method [12, 13]. Despite the toxicity of these reagents, their use remains inevitable because of the importance of dithiocarbamates in the biological field and organic synthesis. Therefore, safer, nontoxic, and user-friendly one-pot procedures for the synthesis of dithiocarbamates have been developed recently [14–31].

## **Results and discussion**

During the course of our study aimed at improving the ecocompatibility of certain organic processes, we have been particularly interested in the synthesis of dithiocarbamates in water and solvent-free conditions to develop environmentally benign reactions [32–37]. Herein, we wish to report an efficient preparation of dithiocarbamate derivatives from the one-pot reaction of amines, carbon disulfide, and unsaturated enones or alkyl halides in water under ultrasound irradiation.





Table 1 Ultrasound-assisted, one-pot preparation of dithiocarbamates in water





Entry	Michael acceptor	Amine	Yield <sup>a</sup> /%	Ref.
1	Methyl acrylate	1a	88	
2	Methyl acrylate	1b	90	[15]
3	Methyl acrylate	1c	90	[16]
4	Methyl acrylate	1d	80	[16]
5	Methyl acrylate	1 <b>f</b>	75	[18]
6	Methyl acrylate	1g	78	[18]
7	Acrylonitrile	<b>1</b> a	90	[18]
8	Acrylonitrile	1b	88	[18]
9	Acrylonitrile	1c	80	[18]
10	Acrylonitrile	1d	75	[15]
11	Acrylonitrile	1h	78	[20]
12	Methyl vinyl ketone	<b>1</b> a	95	[18]
13	Methyl vinyl ketone	1b	88	[18]
14	Methyl vinyl ketone	1d	85	[15]
15	Methyl vinyl ketone	1e	92	[18]
16 <sup>b</sup>	Benzylideneacetone	1a	74	[15]
17 <sup>b</sup>	Benzylideneacetone	1b	68	[18]
18 <sup>b</sup>	Benzylideneacetone	1c	78	[18]
19	Methyl methacrylate	1b	76	[15]
20	Methyl methacrylate	1c	70	[18]

<sup>a</sup> Isolated yields

<sup>b</sup> Reaction time 15 min

First, we embarked upon a series of experiments to establish the optimum conditions. First findings showed that the three-component reaction of 2 mmol pyrrolidine with 2 mmol methyl acrylate and 3 mmol carbon disulfide in 2 cm<sup>3</sup> water under ultrasound irradiation for 10 min was an excellent reaction condition and dithiocarbamate **3** was obtained in 90% yield (Scheme 1).

With the optimal reaction conditions in hand, we investigated the generality and scope of the one-pot, threecomponent reaction with a variety of aliphatic amines and various electron-deficient olefins. A variety of  $\alpha$ , $\beta$ -unsaturated compounds such as methyl acrylate, acrylonitrile, methyl vinyl ketone, methyl methacrylate, and benzylideneacetone underwent 1,4-addition with a wide range of aliphatic amines like *n*-butylamine, benzylamine, pyrrolidine, piperidine, dipropylamine, and diethylamine to give the corresponding dithiocarbamates in high yields. The results are summarized in Table 1. In general, all the





Table 2 Ultrasound-assisted, one-pot reaction of amines, carbon disulfide, and alkyl halides in water

syntheses were performed under mild reaction conditions and showed short reaction times, good selectivity, and the absence of by-products.

We next examined the feasibility of utilizing the current strategy for the one-pot synthesis of dithiocarbamates from amines, carbon disulfide, and alkyl halides under the same reaction conditions (Scheme 2). In fact, treatment of a wide variety of alkyl halides with aliphatic amines and carbon disulfide at room temperature affords satisfactory to good yields of a variety of dithiocarbamates **5**, mainly in very short reaction times (10 min). The results are summarized in Table 2. Alkyl chlorides, bromides, and iodides are equally effective and no marked difference was observed in terms of reaction time and yield.

	RR'NH + R" <sup>^</sup> X 1 4 ) X = I, Br, Cl			))))))), 10 m 64-90%	CS <sub>2</sub> , water RR'N 5 64-90%				
H	H N	H N	NH	CH <sub>2</sub> NH <sub>2</sub>	NH <sub>2</sub>	H <sub>2</sub> N	NH <sub>2</sub>		
1a	1b	1c	1d	1e	1f	1g	1h		
Entry		Alky	yl halide		Amine			Yield <sup>a</sup> /%	Ref.
1		Ben	zyl chloride		1a			80	[15]
2	Benzyl chloride				1b			84	[19]
3	Benzyl chloride				1c			90	[19]
4	Benzyl chloride			1f			76	[15]	
5		Ben	zyl chloride		1g			72	[19]
6		Ben	zyl chloride		1h			70	[23]
7		3-Cl	hlorobenzyl cl	hloride	1a			85	[23]
8		3-Cl	hlorobenzyl cl	hloride	1b			80	[19]
9		3-Cl	hlorobenzyl cl	hloride	1c			88	[19]
10	3-Chlorobenzyl chloride			1d			76	[14]	
11	3-Chlorobenzyl chloride			1e			68	[19]	
12	Allyl chloride			1a			74	[15]	
13	Allyl chloride			1b			72	[15]	
14	Allyl chloride			1c			80	[14]	
15	Allyl chloride			1d			64	[15]	
16	Methyl bromoacetate			1a			92	[30]	
17		Met	hyl bromoace	tate	1b			80	[22]
18		Met	hyl bromoace	tate	1c			84	[22]
19	Methyl iodide				1b			86	[19]
20		Met	hyl iodide		1c			80	[19]

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In summary, we have developed a mild and fast procedure for the synthesis of various dithiocarbamates with excellent yields in water under ultrasonic irradiation. This simple procedure is greener and less laborious in terms of isolation and purification than those using isothiocyanates. Furthermore, the ultrasound-assisted procedure requires short reaction times, is catalyst-free, low cost, and affords efficient selectivity, which makes this method a useful and attractive strategy in view of economic and environmental advantages.

## Experimental

<sup>1</sup>H NMR spectra (500 MHz) and <sup>13</sup>C NMR spectra (125 MHz) were recorded using CDCl<sub>3</sub> or DMSO- $d_6$  as solvents. Chemical shifts are expressed in ppm downfield from TMS. Melting points were recorded on a Büchi 535 melting point apparatus. All starting materials are commercially available and were used without further purification. Water and other solvents were distilled before used. Sonication was performed in a Hielscher ultrasonic device (Vial Tweeter at UIS250v) with Sonotrode LS24d5 and Ampitude 80.

#### General procedure

A mixture of  $0.16 \text{ cm}^3$  pyrrolidine (2 mmol),  $0.18 \text{ cm}^3$ carbon disulfide (3 mmol), and 0.18 cm<sup>3</sup> methyl propenoate (2 mmol) in 2 cm<sup>3</sup> water was sonicated at room temperature for 10 min in a beaker surrounded by a water bath for cooling. The reaction mixture was allowed to stand for 10 min at room temperature and then the solid dithiocarbamate product was collected, washed with ethanol or diethyl ether, and dried in air. The reaction products were obtained in high purity in most cases, and did not require further purification by recrystallization or column chromatography. In a few cases the aqueous mixture was extracted with 10 cm<sup>3</sup> diethyl ether or ethyl acetate, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed under reduce pressure to give the desired products. All compounds are known and IR and <sup>1</sup>H NMR spectra were found to be identical to those described in Refs. [14–31].

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