A Rapid, Catalyst-Free, Three-Component Synthesis of Rhodanines in Water Using Ultrasound

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Abstract: A green, efficient, rapid, high-yielding, catalyst-free method for the synthesis of rhodanines in water using ultrasonic irradiation is described. The procedure is straightforward and the rhodanine products are isolated by simple filtration.

Key words: ultrasound, rhodanines, sonochemistry, carbon disulfide, catalyst-free

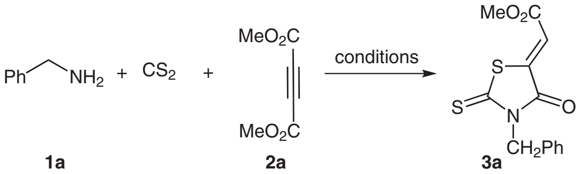
The use of water as a solvent has many advantages in organic processes and reactions, both in industry and in green chemistry applications. It is economical, non-toxic and environmentally friendly. The hydrophobic products produced when using water as the solvent are separable by extraction with an organic solvent.[1] Increasingly, ultrasound has been used in organic synthesis.[2] Compared with traditional methods, the use of ultrasound is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yields and shorter times under mild ultrasonic irradiation conditions.[2–5]

One of the main objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents.[6] Rhodanines, in particular, are known to possess a wide spectrum of biological activity including the inhibition of targets such as HCV NS3 protease[6] and β-lactamase.[7] As a part of our ongoing research on the synthesis of heterocyclic compounds with medicinal applications,[8] and based on our previous study on the synthesis of rhodanine,[9] we became interested in the development of a green and practical method to synthesize rhodanines of potential pharmacological and biological interest via sonochemistry.

Herein, we report a simple, efficient, one-pot method for the synthesis of rhodanine derivatives in high yields (86–94%) and in short times (3–5 minutes) using ultrasonic irradiation and water as the reaction medium.

In order to evaluate the efficiency of this method the synthesis of rhodanine **3a**, via reaction of dimethyl acetylenedicarboxylate (DMAD, **2a**), carbon disulfide (CS_2) and benzylamine (**1a**) as a model system, was carried out in water using ultrasonic irradiation (US) or high-speed stirring (HSS) (Table 1).

Table 1 Investigation of the Reaction Conditions for the Synthesis of Rhodanine **3a**[a]



Solvent	Method[b]	Yield (%)[c]
H_2O	**US**	**94**
H_2O[d]	US	92
H_2O	HSS	<10
H_2O[d]	HSS	<10
EtOH	US	90
EtOH–H_2O (1:1)	US	93
EtOH	HSS	<10
EtOH–H_2O (1:1)	HSS	<10
THF	US	91
THF	HSS	<10
MeCN	US	92
MeCN	HSS	<10

[a] Reaction conditions: DMAD (8 mmol), CS_2 (40 mmol), $BnNH_2$ (8 mmol), solvent (40 mL), 3 min.
[b] All reactions were run at 34–36 °C based on the internal temperature of the ultrasound-assisted reaction system. US = ultrasound; HSS = high-speed stirring.
[c] Yield of isolated product based on the starting alkyne.
[d] H_2O (10 mL) was used.

To our surprise, the one-pot, three-component synthesis of rhodanine **3a** in water as the solvent using ultrasonic irradiation was complete in three minutes, but the high-speed stirring method required a reaction time of one hour to go to completion (Figure 1).

We next investigated the effect of various solvents on the synthesis of rhodanine **3a** (model system) using ultrasonic irradiation and high-speed stirring. In each case reactions using the ultrasound method were complete within three minutes with the highest yield of 94% being obtained in

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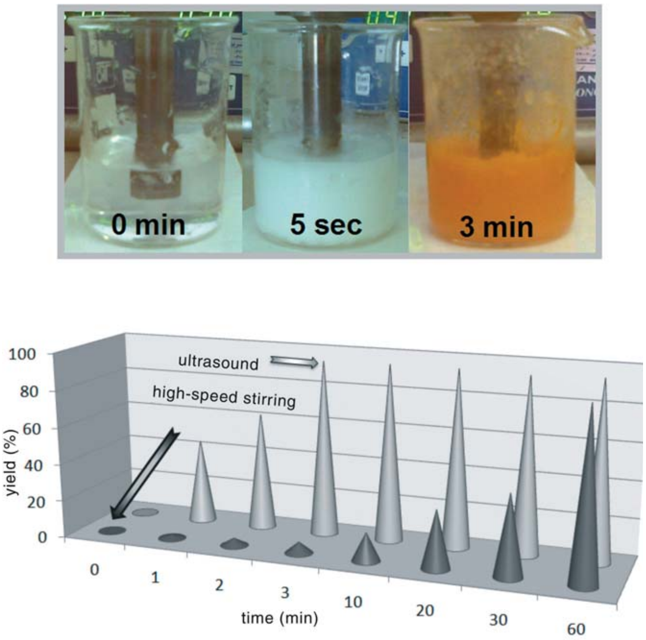
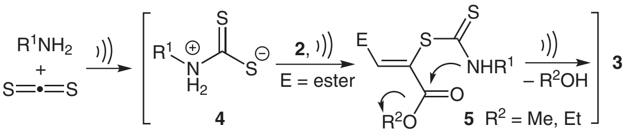


Figure 1 Comparison of the reaction time for the synthesis of rhodanine **3a** in water using ultrasound and high-speed stirring

water. However, the yields of rhodanine **3a** using the high-speed stirrer method were less than 10% after three minutes reaction time regardless of the solvent employed. Decreasing the volume of water (10 mL) had a negligible effect on the reaction yield under ultrasonic conditions (Table 1). As the reaction was complete within three minutes using the ultrasound method, and based on green chemistry criteria and the straightforward workup, we selected water as the solvent for further studies.

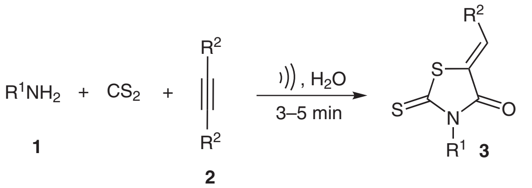
The scope of this sonochemical method for the synthesis of other rhodanine derivatives using the optimized conditions was studied (Table 2). In each case good to excellent yields of products were obtained which lend support to the specific effects of ultrasound. It should be noted that this procedure showed some limitations with aromatic or hindered amines, with enaminones being obtained as the main products.[10]

The proposed mechanism for the sonochemical synthesis of rhodanines **3** is shown in Scheme 1. It is conceivable that reaction between the amine and carbon disulfide initially forms dithiocarbamate **4**.[9,11–13] This species undergoes addition of the negatively charged sulfur to the alkyne **2** to afford intermediate vinyl dithiocarbamate **5**. Finally, intramolecular cyclization of **5** yields the rhodanine **3**.



Scheme 1 Proposed mechanism for synthesis of rhodanines **3**

Table 2 Synthesis of Rhodanines in Water Using Ultrasound[a]



Product	R^1	R^2	Time (min)	Yield (%)[b]
3a	$PhCH_2$	CO_2Me	3	94
3b	$4\text{-}ClC_6H_4CH_2$	CO_2Me	4	93
3c	$2\text{-}ClC_6H_4CH_2$	CO_2Me	4	91
3d	$2\text{-}ClC_6H_4CH_2$	CO_2Et	4	92
3e	PhCH(Me)	CO_2Me	3	92
3f	*i*-Bu	CO_2Me	5	88
3g	allyl	CO_2Me	5	90
3h	*i*-Pr	CO_2Me	5	86

[a] Reaction conditions: amine (1 mmol), alkyne (1 mmol), CS_2 (5 mmol), H_2O (5 mL).

[b] Yield of isolated product based on the starting alkyne.

In conclusion, we have described a simple, green, rapid, ultrasound-mediated and catalyst-free procedure for the synthesis of rhodanine derivatives in high yields. The reaction is performed under neutral conditions by simple mixing of the starting materials and the products were isolated by straightforward filtration. The product rhodanines are of potential pharmacological and biological interest.

All reagents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. A multiwave ultrasonic generator (Sonicator 3000; Misonix Inc., Farmingdale, NY, USA), equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 20 kHz with a maximum power output of 600 W, was used for ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. The reactions were performed in open vessels.

Rhodanines 3a–h; General Procedure

To a mixture of a primary amine (1 mmol) and CS_2 (5 mmol) in H_2O (5 mL) was added the appropriate alkyne (1 mmol). The resulting mixture was subjected to ultrasonic irradiation for 3–5 min using a high-density ultrasonic probe. After completion of the reaction as indicated by TLC, the mixture was filtered, the orange residue washed with H_2O and then dried to afford the rhodanine. All the products are known[9] and were characterized by comparison of their IR spectra and physical data with those of authentic samples.

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