One-pot synthesis of 1,3,4-oxadiazole-5-thioethers in water

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Abstract: An efficient and environmental-friendly one-pot procedure has been developed for the synthesis of 1,3,4-oxadiazole-5-thioethers by the reaction of acylhydrazine with carbon disulfide and organic halides or α, β-unsaturated carbonyl compounds. The reactions were carried out in water in the presence of potassium phosphate within 2–4 h to afford the expected products in excellent yields.

Keywords: 1,3,4-Oxadiazole-5-thioether; One-pot synthesis; Environmental-friendly; Aqueous medium; Acylhydrazine; Potassium phosphate

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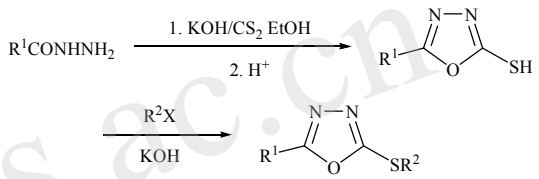
1. Introduction

1,3,4-Oxadiazole-5-thioether derivatives have recently been the object of deep investigation due to their different biological properties, such as anti-HIV[1], anticancer[2], antibacterial[3], antifungal[4], anticonvulsant[5], antihypertensive[6], analgetic, antipyretic, and anti-inflammatory[7] activities.

The classical synthetic method of 1,3,4-oxadiazole-5-thioether derivatives generally requires two steps (Scheme 1). Acylhydrazine is firstly reacted with carbon disulfide under strong basic conditions in organic solvents to form the corresponding intermediates 2-mercapto-1,3,4-oxadiazoles, and this isolated intermediates is then treated with organic halide to form the corresponding 1,3,4-oxadiazole-5-thioether product[1a,4b,8]. The drawbacks of this method include strong basic reaction conditions, long reaction time, and the use of expensive and harmful organic solvents. In order to overcome these problems, several improvements have been explored. Microwave-assisted technique was used to shorten the reaction time[1b], the solid-phase approach was used to simplify the purification of product[8b], and weak organic base was used instead of strong inorganic base to avoid side-reactions[3a,7c]. However, none of these methods were fully satisfied.



Scheme 1. Classical synthetic method of 1,3,4-oxadiazoline-5-thioether derivatives.

We have been focusing on the discovery and development of green synthetic methods for years, and have recently published[9] several papers on the reactions in water or organic solvent free system. As a continuation of our work, here we wish to report an efficient, one-pot synthesis of 1,3,4-oxadiazole-5-thioether derivatives in water.

2. Results and discussion

Initially, we examine whether the classical two-steps procedure could be carried out in one-pot. The preliminary result showed that acylhydrazine reacted with carbon disulfide, and then treated with benzyl chloride in one-pot did produce the desired product 1,3,4-oxadiazole-5-thioether (**2a**) in 85% yield, provided that the reaction was performed in DMF in the presence of potassium phosphate. After further screening several solvents, finally we found that water also worked effectively as the solvent for this reaction. Therefore, a green, one-pot synthesis of 1,3,4-oxadiazoline-5-thioether derivatives is now developed, because water is a nontoxic, cheap and readily available reaction medium.

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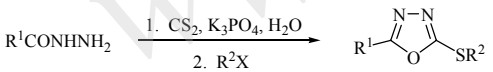
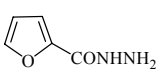
With the success of the one-pot procedure in hand, we then focused our attention on exploring the scope using a variety of acylhydrazines and alkyl halides (Table 1). In all cases studied, no matter whether the active organic halides which contained ester, nitrile, alkene, or the inactive organic halides, such as methyl iodide were used, the reactions proceeded smoothly to afford the desired products in good to excellent yields. Under these reaction conditions, the ether bond and unstable furan ring in acylhydrazines **1**, as well as various functional groups in the alkyl halide substrates were all stable. Moreover, if methyl acrylate was used instead of alkyl halide, the corresponding S-Michael addition product (**2u**) was obtained in 82% yield (entry 21).

Comparing to the previously reported methods, the advantages of our new method are obvious: (1) utilizing water as solvent; (2) one-pot procedure without intermediate isolation and purification; (3) simple operation; (4) high yields; (5) broadly applicable to various substrates. For example, compound **2v**, which showed considerable anticonvulsant activity[5a], was synthesized in ethanol for 7 h with 70% yield as reported in the two-step method in the literature. But by utilizing our one-pot procedure, it was synthesized in water with 84% yield, and the reaction was completed in 3 h.

Table 1. One-pot synthesis of 1,3,4-oxadiazole-5-thioethers **2** in water



1 **2**

Entry	Acylhydrazines	Halides	Product	*t* (h)	Yield (%)
1	$CH_3CONHNH_2$	$C_6H_5CH_2Cl$	**2a**	2.5	86[a]
2		CH_3I	**2b**	2.5	85[b]
3		n-BuBr	**2c**	3	89[a]
4		$ClCH_2COOC_2H_5$	**2d**	2.5	89[a]
5		CH_2=$CHCH_2Br$	**2e**	2.5	88[a]
6		4-NO_2-$C_6H_4CH_2Br$	**2f**	3.5	85[b]
7		3-NO_2-$C_6H_4CH_2Br$	**2g**	3.5	90[b]
8		4-MeO-$C_6H_4CH_2Br$	**2h**	2.5	91[b]
9		4-Cl-$C_6H_4CH_2Br$	**2i**	2.5	91[b]
10	$C_6H_5CONHNH_2$	$C_6H_5CH_2Cl$	**2j**	3	92[b]
11		CH_3I	**2k**	3	86[b]
12		n-BuBr	**2l**	3.5	93[a]
13		$ClCH_2COOC_2H_5$	**2m**	3	96[b]
14		CH_2=$CHCH_2Br$	**2n**	3	90[a]
15		4-NO_2-$C_6H_4CH_2Br$	**2o**	4	86[b]
16		3-NO_2-$C_6H_4CH_2Br$	**2p**	4	84[b]
17		4-MeO-$C_6H_4CH_2Br$	**2q**	3	91[b]
18		4-Cl-$C_6H_4CH_2Br$	**2r**	3.5	92[b]
19		$BrCH_2CH_2CN$	**2s**	3.5	87[b]
20		$C_6H_5CH_2Cl$	**2t**	3	84[b]
21	$C_6H_5CONHNH_2$	CH_2=$CHCO_2CH_3$	**2u**	3.5	82[b]
22	2-BnO-$C_6H_5CONHNH_2$	CH_3I	**2v**	3	84[b]

[a] Isolated yield(purified by column chromatography).
[b] Isolated yield(purified by recrystalization).

In conclusion, we have developed a convenient, environmental-friendly one-pot procedure for the synthesis of 1,3,4-oxadiazole-5-thioethers, by reacting acylhydrazines, carbon disulfide and alkyl halides in the presence of potassium phosphate in water.

3. Experimental

All reagents and solvents were obtained from commercial sources. Melting points were determined on an X4 microscope. ^{1}H NMR spectra were recorded on a VXR 300 (300 MHz) instrument. Elemental analyses were performed on a Vario EL III (Germany).

General procedure. A mixture of the correpsonding acylhydrazine (3 mmol), potassium phosphate (1.02 g, 3 mmol) and carbon disulfide (0.46 g, 6 mmol) in water (15 mL) was stirred at r.t. for 10 min. After refluxing for an additional 2 h, the organic halide or α, β-unsaturated carbonyl compound (3 mmol) was added. Stirring was continued at r.t. until the reaction was complete (monitored by TLC, about 0.5 – 1 h). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by recrystalization or column chromatography over silica-gel using ethyl acetate/petroleum ether as eluent, to afford the corresponding product.

2-Methyl-5-[(phenylmethyl)thio]-1,3,4-oxadiazole (2a)[7b]. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3), 4.44 (s, 2H, CH_2), 7.26 – 7.42 (m, 5H, C_6H_5).

2-Methyl-5-(methylthio)-1,3,4-oxadiazole (2b)[7b]. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H, CH_3), 2.71 (s, 3H, CH_3).

2-Methyl-5-(butylthio)-1,3,4-oxadiazole (2c). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* 7.2 Hz, CH_3), 2.39 (s, 3H, CH_3), 2.85 (t, 2H, *J* 6.9 Hz, CH_2), 4.14 – 4.21 (q, 2H, *J* 6.9 Hz, CH_2), 4.32 (t, 2H, *J* 7.2 Hz, SCH_2). Anal. Calcd for $C_7H_{12}N_2OS$: C, 48.74; H, 7.46; N, 16.37. Found: C, 48.81; H, 7.02; N, 16.26.

Ethyl 2-(5-methyl-1,3,4-oxadiazol-2ylthio)acetate (2d)[7b]. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* 7.2 Hz, CH_3), 2.52 (s, 3H, CH_3), 4.04 (s, 2H, SCH_2), 4.21 – 4.28 (q, 2H, *J* 6.9 Hz, COCH_2).

2-Methyl-5-(2-propen-1-ylthio)-1,3,4-oxadiazole (2e)[7b]. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$):

δ 2.51 (s, 3H, CH_3), 3.86 (d, 2H, J 6.9 Hz, SCH_2), 5.19 (d, 1H, J 10.2 Hz, CH_2=), 5.36 (d, 1H, J 10.2 Hz, CH_2=), 5.91 – 6.05 (m, 1H, CH=).

2-Methyl-5-{[(4-nitrophenyl)methyl]thio}-1,3,4-oxadiazole (2f)[11b]. Colorless crystal; mp: 123 – 124 ºC (lit. mp: 124 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 4.50 (s, 2H, SCH_2), 7.63 (d, 2H, J 9.0 Hz, C_6H_4), 8.18 (d, 2H, J 9.0 Hz, C_6H_4).

2-Methyl-5-{[(3-nitrophenyl)methyl]thio}-1,3,4-oxadiazole (2g)[11b]. Colorless crystal; mp: 87 – 90 ºC (lit. mp: 90 – 91 ºC).^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 4.51 (s, 2H, SCH_2), 7.51 (t, 1H, J 7.5 Hz, C_6H_4), 7.82 (d, 1H, J 7.5 Hz, C_6H_4), 8.16 (d, 1H, J 7.5 Hz, C_6H_4), 8.31 (s, 1H, C_6H_4).

2-Methyl-5-{[(4-Methoxyphenyl)methyl]thio}-1,3,4-oxadiazole (2h)[11b]. Colorless crystal; mp: 40 – 42 ºC (lit. mp: 41 – 42 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.41 (s, 2H, SCH_2), 6.84 – 6.88 (m, 2H, C_6H_4), 7.31 – 7.36 (m, 2H, C_6H_4).

2-Methyl-5-[(p-chlorobenzyl)thio]-1,3,4-oxadiazole (2i)[11b]. Colorless crystal; mp: 54 – 56 ºC (lit. mp: 57 – 59 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 4.50 (s, 2H, SCH_2), 7.63 (d, 2H, J 8.7 Hz, C_6H_4), 8.18 (d, 2H, J 8.7 Hz, C_6H_4).

2-Phenyl-5-[(phenylmethyl)thio]-1,3,4-oxadiazole (2j) [11c]. Colorless crystal; mp: 95 – 97 ºC (lit. mp: 98 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.53 (s, 2H, SCH_2), 7.30 – 7.35 (m, 3H, C_6H_5), 7.45 – 7.53 (m, 5H, C_6H_5), 7.98 – 8.01 (m, 2H, C_6H_5).

2-Phenyl-5-(methylthio)-1,3,4-oxadiazole (2k)[11c]. Colorless crystal; mp: 37 – 38 ºC (lit. mp: 39 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79 (s, 3H, SCH_3), 7.46 – 7.55 (m, 3H, C_6H_5), 8.00 – 8.04 (m, 2H, C_6H_5).

2-Phenyl-5-(butylthio)-1,3,4-oxadiazole (2l)[11e]. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H, J 7.5 Hz, CH_3), 1.44 – 1.56 (m, 2H, CH_2), 1.78 – 1.86 (m, 2H, CH_2), 3.30 (t, 3H, J 7.5 Hz, SCH_3), 7.57 – 7.59 (m, 3H, C_6H_5), 8.05 – 8.07 (m, 2H, C_6H_5).

Ethyl 2-(5-phenyl-1,3,4-oxadiazol-2-ylthio)acetate (2m)[11d]. Colorless crystal; mp: 82 – 83 ºC (lit. mp: 71 – 72 ºC).^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, 3H, J 7.2 Hz, CH_3), 4.12 (s, 2H, SCH_2), 4.23 – 4.30 (dd, 2H, J 7.2 Hz, CH_2), 7.47 – 7.56 (m, 3H, C_6H_5), 7.99 – 8.03 (m, 2H, C_6H_5).

2-Phenyl-5-(2-propen-1-ylthio)-1,3,4-oxadiazole (2n)[11f]. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (d, 2H, J 7.2 Hz, SCH_2), 5.24 (d, 1H, J 16.5 Hz, CH_2=), 5.40 (d, 1H, J 16.5 Hz, CH_2=), 5.98 – 6.09 (m, 1H, CH=), 7.47 – 7.53 (m, 3H, C_6H_5), 7.99 – 8.02 (m, 2H, C_6H_5).

2-Phenyl-5-{[(4-nitrophenyl)methyl]thio}-1,3,4-oxadiazole (2o)[11a]. Colorless crystal; mp: 144 – 145 ºC (lit. mp: 145 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (s, 2H, SCH_2), 7.47 – 7.54 (m, 3H, C_6H_5), 7.67 – 7.70 (d, 2H, J 8.7 Hz, C_6H_5), 7.96 – 7.99 (dd, 2H, J 1.8 Hz, J 7.5 Hz, C_6H_4), 8.19 – 8.22 (dd, 2H, J 1.8 Hz, J 7.5 Hz, C_6H_4).

2-Phenyl-5-{[(3-nitrophenyl)methyl]thio}-1,3,4-oxadiazole (2p). Colorless crystal; mp: 123 – 124 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.59 (s, 2H, SCH_2), 7.51 – 8.31 (m, 9H, C_6H_5, C_6H_4). Anal. Calcd. for $C_{15}H_{11}N_3O_3S$: C, 57.75; H, 3.80; N, 13.59. Found: C, 57.50; H, 3.54; N, 13.41.

2-Phenyl-5-{[(4-methoxyphenyl)methyl]thio}-1,3,4-oxadiazole (2q)[11a]. Colorless crystal; mp: 116 – 117 ºC (lit. mp: 119 – 120 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 4.50 (s, 2H, SCH_2), 6.86 (d, 2H, J 8.7 Hz, C_6H_4), 7.39 (d, 2H, J 8.7 Hz, C_6H_4), 7.51 (m, 3H, C_6H_5), 7.98 – 8.01 (dd, 2H, J 1.5 Hz, J 7.8 Hz, C_6H_5).

2-Phenyl-2-{[(4-chlorophenyl)methyl]thio}-1,3,4-oxadiazole (2r)[11a]. Colorless crystal; mp: 112 – 113 ºC (lit. mp: 113 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.48 (s, 2H, SCH_2), 7.30 – 8.00 (m, 9H, C_6H_5, C_6H_4).

3-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-propanenitrile (2s)[11g]. Colorless crystal; mp: 82 – 83 ºC (lit. mp: 84 – 86 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (t, 2H, J 6.9 Hz, CH_2), 3.54 (t, 2H, J 6.9 Hz, SCH_2), 7.48 – 7.58 (m, 3H, C_6H_5), 8.00 – 8.04 (m, 2H, C_6H_5).

2-(2-Furanyl)-5-[(phenylmethyl)thio]-1,3,4-oxadiazole (2t). Colorless crystal; mp: 76 – 77 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52 (s, 2H, SCH_2), 6.59 (s, 1H, C_4H_3O), 7.10 (s, 1H, C_4H_3O), 7.26 –7.46 (m, 5H, C_6H_5), 7.63 (s, 1H, C_4H_3O). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.84; H, 4.24; N, 10.83. Found: C, 60.45; H, 3.90; N, 10.85.

Methyl 3-(5-phenyl-1,3,4-oxadiazol-2-ylthio) propanoate (2u). Colorless crystal; mp: 77 – 78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, 2H, J 7.2 Hz, CH_2), 3.74 (s, 3H, CH_3), 4.45 (t, 2H, J 7.2 Hz,

SCH_2), 7.47 – 7.91 (m, 5H, C_6H_5). Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.74; H, 4.34; N, 11.13. Found: C, 54.53; H, 4.58; N, 10.63.

2-[2-(Phenylmethoxy)phenyl]-2-(methylthio)-1,3,4-oxadiazole (2v)[5a]. Colorless crystal; mp: 78 – 79 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, OCH_3), 5.23 (s, 2H, SCH_2), 7.05 – 7.96 (m, 9H, C_6H_5, C_6H_4).

Acknowledgments

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水相一锅煮合成1,3,4-噁二唑-5-硫醚类化合物

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摘要: 此文报道了由酰肼, 二硫化碳及卤代烃或α, β-不饱羰基化合物在水相中一锅煮反应合成1,3,4-噁二唑-5-硫醚类化合物的方法。该方法具有高效、反应条件温和、操作简单、适用范围广和环境友好等优点。

关键词: 1,3,4-噁二唑-5-硫醚; 一锅煮合成; 环境友好; 水相; 酰肼; 磷酸钾