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One-pot Synthesis of 2-Alkylthio-1,3,4-oxadiazole and *Bis*-(1,3,4-oxadiazole-2-yl)thio alkyl Derivatives from Acid Hydrazides and CS_2

MOHAMMAD SOLEIMAN-BEIGI[1,*], MOHAMMAD ALIKARAMI[2] and TAHEREH HOSSEINZADEH[3]

[1]Department of Chemistry, Faculty of Basic Science, Ilam University, P.O. Box 69315-516, Ilam, Iran
[2]Department of Chemistry, Ilam Branch, Islamic Azad University, Ilam, Iran
[3]Department of Chemistry, Faculty of Basic Science, Ilam University, Ilam, Iran

*Corresponding author: Fax: +98 841 2227022; E-mail: SoleimanBeigi@yahoo.com

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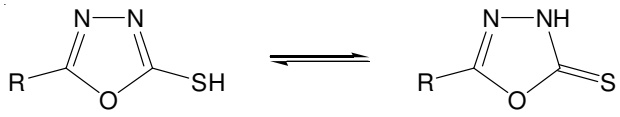
An efficient and one-pot method for synthesis of 2-alkylthio-1,3,4-oxadiazole derivatives in mild conditions is described. Some novel derivatives such as *bis*-1,3,4-oxadiazole analogs are also synthesized.

Key Words: One-pot method, 2-Alkylthio-1,3,4-oxadiazole derivatives, *Bis*-1,3,4-oxadiazole analogs, Acid hydrazides.

INTRODUCTION

Nowadays, one-pot multicomponent reactions have emerged as valuable tools in organic synthesis for reducing operative steps and enhancing synthesis efficiency[1-3]. 2-Alkythio derivatives of 1,3,4-oxadiazole-2-thiols (thiones) are an important class of five-member heterocyclic compounds which have attracted much attention due to their applications as key intermediates in organic and inorganic synthesis[4,5] and studies of biological activity[6-11].

Theoretical studies and investigations shown that 1,3,4-oxadiazole-2-thione derivatives are in equlibrium to their thiols tautomeric forms (**Scheme-I**)[12-14].



Scheme-I: Thiol-thione tautomerization of 1,3,4-oxadiazole-2-thione

Due to thiol-thione tautomeric equilibrium, their derivatives represent an important type of heterocyclic compound as key intermediates in the field of heterocyclic chemistry because of their potential multifunctional donor sites, *via* either exocyclic sulfur or endo cyclic nitrogen. Many methods are reported for N-alkylation or S-alkylation of 1,3,4-oxadiazole-2-thiones in different mediums which, 1,3,4-oxadiazole-2-thiones are generally used as the substrate after purification[15-25]. By far, the most common strategy for the synthesis of 1,3,4-oxadiazole-2-thiols involves the interaction of acid hydrazides with carbon disulfide in the presence of alcoholic potassium hydroxide[26-30]. Furthermore, in order to obtain pure 1,3,4-oxadiazole-2-thiols in the presence of a catalyst such as KOH, the reaction mixture should be neutralized because the parent compound of 1,3,4-oxadiazole-2-thiol has acidic character ($pK_a = 3.85$)[31]. This makes the procedure rather difficult and reduces the yield of the product.

In the past few years, catalyst-free and one-pot reactions have been noted as important routes for the development of organic synthesis methodologies due to their environmentally friendly properties and their economic advantages[32,33].

EXPERIMENTAL

All chemicals were purchased from Merck, Fluka and Aldrich chemical companies. Yields refer to isolated products. Melting points were determined by an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were obtained on a FT-IR Hartman-Bomen spectrophotometer as KBr disks. The ^1H NMR (400 and 300 MHz) and ^{13}C NMR (100 and 75 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solutions. Mass spectra were recorded on an Agilent Technology (HP) 5973 instrument (ionizing voltage 70 eV). Elemental analyses were done on a Carlo-Erba EA1110CHNO-S analyzer. The progress of the reaction was followed by TLC using silica-g el SIL G/ UV 254 plates. Products were characterized by comparing their physical and spectral data with those of the authentic samples.

General procedure for synthesis of 2-alkylthio-5-aryl-1,3,4-oxadiazole derivatives: A mixture of acid hydraizde

(1.0 mmol) and carbon disulfide (3.0 mmol) in DMF (2.0 mL) was stirred for 15 min at room temperature, the mixture of reaction then was heated at 70 ºC for appropriated time until complete ring closure (4 h). After cooling to room temperature, alkyl halide (1.2 mmol) and Et_3N (4 mmol) were added to mixture of reaction and stirred again at room temperature until completion of reaction as monitored by TLC (ethyl acetate: *n*-hexane (1:2). Then the solvent was evaporated *in vacuo* and the crude product was purified by preparative TLC (silica gel, eluent EtOAc:*n*-hexane 1:2) to obtain pure product.

Ethyl-[5-(4-chlorophenyl)-1,3,4-oxadiazol)-2-ylthio] acetate (Table-2, entry 2): m.p. 85-86 ºC[34]. IR (KBr, ν_{max}, cm^{-1}): 1736, 1602, 1200, 1088. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H, $-CH_3$), 4.12 (s, 2H, $-SCH_2$), 4.27 (q, *J* = 7.2 Hz, 2H, $-OCH_2$), 7.49 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.94 (d, *J* = 8.4 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.09, 34.40, 62.45, 121.92, 127.96, 129.47, 138.03, 163.23, 165.25, 167.30.

2-(Methylthio)-5-(4-methylphenyl)-1,3,4-oxadiazole (Table-2, entry 6): m.p. 50-51 ºC. IR (KBr, ν_{max}, cm^{-1}): 1611, 1477, 1087. ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, $-CH_3$), 2.78 (s, 3H, Ar-CH_3), 7.30 (d, *J* = 8.1, 2H, Ar-H), 7.90 (d, *J* = 8.1, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.66, 21.63, 120.87, 126.61, 129.72, 142.17, 164.3, 165.60.

2-(Ethylylthio)-5-phenyl-1,3,4-oxadiazole (Table-2, entry 8): m.p. 46-48 ºC. IR (KBr, ν_{max}, cm^{-1}): 1605, 1086. ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (t, *J* = 7.6 Hz, 3H, $-CH_3$), 3.33 (q, 2H, *J* = 7.6 Hz, $-SCH_2$), 7.52 (m, 3H, Ar-H), 8.02 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.76, 27.04, 123.68, 126.61, 129,01, 131.57, 164.33, 165.66. MS (EI, 70 eV): m/z (%) = 206 (95), 178 (42), 145 (67), 105 (100), 77 (84). Anal. calcd. for $C_{10}H_{10}N_2OS$: C, 58. 23; H, 4.89; N, 13.58. Found: C, 58. 10; H, 4.97; N, 13.70.

2-(Allylthio)-5-(4-chlorophenyl)-1,3,4-oxadiazole (Table-2, entry 9): m.p. 59-61 ºC. IR (KBr, ν_{max}, cm^{-1}): 1640, 1603, 1087. ^1H NMR (300 MHz, $CDCl_3$): δ 3.93 (d, *J* = 8.0 Hz, 2H, $-SCH_2$), 5.23 (d, *J* = 9.9, 1H, C=CH), 5.40 (d, *J* = 15.9, 1H, C=CH), 6.01 (m, 1H, CH=C), 7.47 (d, *J* = 6.7, 2H, Ar-H), 7.94 (d, *J* = 6.7, 2H, Ar-H). ^{14}C NMR (75 MHz, $CDCl_3$): δ 35.25, 119.89, 122.10, 127.90, 129.43, 131.61, 137.89, 163.99, 165.02. MS (EI, 70 eV): m/z (%) 252 (28), 179 (18), 139 (100), 115 (51), 82 (54). Anal. calcd. for $C_{11}H_9N_2OSCl$: C, 52. 28; H, 3.59; N, 11.08. Found: C, 52. 11; H, 3.37; N, 11.22.

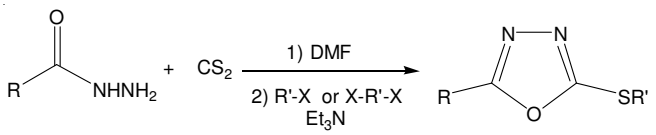
2-(Benzylthio)-5-phenyl-1,3,4-oxadiazole (Table-2, entry 11): m.p. 92-94 ºC. IR (KBr, ν_{max}, cm^{-1}): 1613, 1585 1087. ^1H NMR (400 MHz, $CDCl_3$): δ 4.54 (s, 2H, $-SCH_2$), 7.27-7.99 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.85, 123.60, 126.67, 128.14, 128.84, 129.06, 129.20, 131.68, 135.64, 163.89, 165.84. MS (EI, 70 eV): m/z (%) 268 (12), 206 (76), 178 (30), 145 (63), 105 (100), 91 (45), 77 (85). Anal. calcd. for $C_{15}H_{12}N_2OS$: C, 67. 14; H, 4.51; N, 10.44. Found: C, 67. 31; H, 4.77; N, 10.21.

2-((5-(4-Chlorophenyl)-1,3,4-oxadiazole-2-yl)thio)acetic acid (Table-2, entry 12): m.p. 148-150 ºC. IR (KBr, ν_{max}, cm^{-1}): 3200-2400, 1736, 1610. ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 2H, $-SCH_2$), 7.47 (d, *J* = 8.43 Hz, 2H, Ar-H), 7.86 (d, *J* = 8.45 Hz, 2H, Ar-H), 13.02 (s, 1H, COOH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.30, 121.04, 127.71, 129.58, 138.64, 160.65, 163.96, 178.0. Anal. calcd. for $C_{10}H_8N_2O_3S$: C, 50. 84; H, 3.41; N, 11.86. Found: C, 51. 08; H, 3.67; N, 12.04.

1,2-*Bis*((5-phenyl-1,3,4-oxadiazole-2-yl)thio) ethane (Table-2, entry 13): m.p. 122-125 ºC. IR (KBr, ν_{max}, cm^{-1}): 1604, 1087. ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 4H, $-CH_2$), 7.55 (m, 6H, Ar-H), 8.04 (m, 4H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.54, 124.60, 126.51, 128,01, 131.55, 164.03, 165.60. MS (EI, 70 eV): m/z (%) 382 (62), 205 (100), 145 (42), 105 (41), 77 (57). Anal. calcd. for $C_{19}H_{17}N_4O_2S_2$: C, 57. 41; H, 4.31; N, 14.10. Found: C, 57. 21; H, 4.57; N, 13.88.

RESULTS AND DISCUSSION

These issues have prompted us to investigate the synthesis of 2-alkylthio-1,3,4-oxadiazole in one-pot and mild solution conditions from acid hydrazides and carbon disulfide. In this work, we have explored an one-pot method for chemoselective synthesis of 2-alkylthio-1,3,4-oxadiazole derivatives from acid hydrazides (**Scheme-II**).



Scheme-II

To optimize reaction conditions, reaction of benzhydrazide and CS_2 at catalyst-free condition in DMF was studied as model reaction. The reaction mixture was stirred for 0.5 h in room temperature, then the temperature was increased to 70 ºC for 3.5 h. After completion of reaction, ethyl iodide we added to mixture of reaction at room temperature in the presence of some different bases as the results are presented in Table-1.

TABLE-1
SEEKING THE SUITABLE BASE FOR THE ONE-POT SYNTHESIS OF 2-ETHYLTHIO-5-PHENYL-1,3,4-OXADIAZOLE FROM BENZHYDRAZIDE IN 6 h

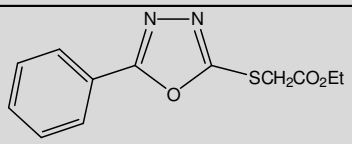
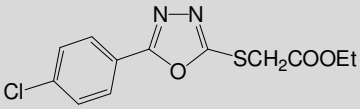
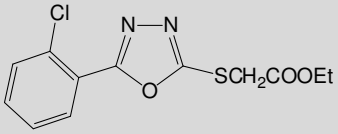
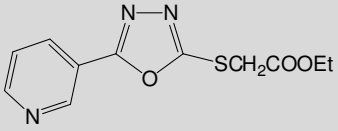
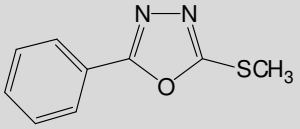
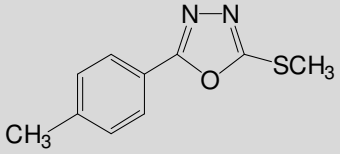
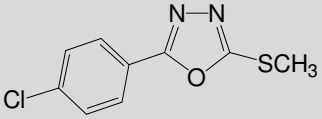
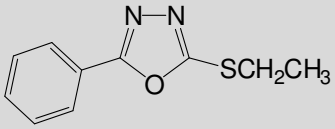
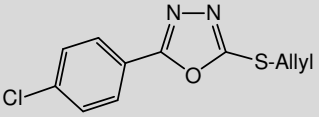
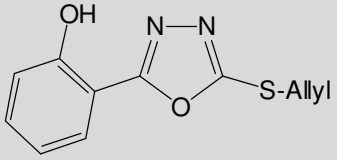
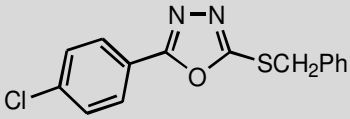
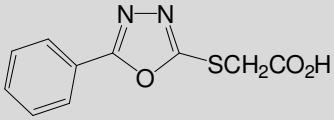
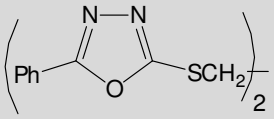
Entry	Base	Yield (%)[a]
1	None	–
2	KF/Al_2O_3	43
3	TBAH[b]	68
4	KOH	21
5	NaOH	11
6	Et_3N	98
7	DABCO	80

[a]Isolated yields; [b]tetra *n*-butyl ammonium hydroxide (25 % in water)

As shown in Table-1, this procedure dose not proceeds properly at the presence of strong bases such as KF/Al_2O_3, KOH, NaOH and TBAH (Table-1, entries 2-5). Furthermore, no product was observed in the base-free condition (Table-1, entry 1). While at the presence of organo bases such as Et_3N and DABCO, 2-ethylthio-5-phenyl-1,3,4-oxadiazole was obtained in high yields (Table-1, entries 6 and 7). Herein, Et_3N was selected as suitable and accessible base.

To test the generality of this procedure in optimized conditions, we have examined the reaction of acid hydrazides with CS_2 and a variety kind of alkyl halides such as alkyl,

TABLE-2
ONE-POT SYNTHESIS OF 2-ALKYLTHIO-5-ARYL-1,3,4-OXADIAZOLE FROM ACID HYDRAZIDES IN THE PRESENCE OF Et_3N

Entry	R-	R'X	Product	Time (min)	Yield (%)[a]
1	C_6H_5	$BrCH_2CO_2Et$		120	96
2	4-Cl-C_6H_4	$BrCH_2CO_2Et$		50	95
3	2-Cl-C_6H_4	$BrCH_2CO_2Et$		50	90
4	3-NC_5H_4	$BrCH_2CO_2Et$		60	75
5	C_6H_5	CH_3I		90	87
6	4-CH_3-C_6H_4	CH_3I		50	71
7	4-Cl-C_6H_4	CH_3I		40	86
8	C_6H_5	CH_3CH_2I		45	98
9	4-Cl-C_6H_4	CH_2=$CHCH_2Br$		40	97
10	2-OH-C_6H_4	CH_2=$CHCH_2Br$		50	75
11	C_6H_5	$PhCH_2Cl$		40	75
12	4-Cl-C_6H_4	$ClCH_2CO_2H$		55	72
13	C_6H_5	$BrCH_2CH_2Br$		70	93

[a]Isolated yield.

α-halo acid and ester, benzyl and allyl, as results are shown in Table-2.

When benzhydrazide was treated with alkyl halides under optimized reaction conditions, corresponding products were obtained in good to excellent yields (Table-2, entries 1, 5, 8 and 11). Similarly, reactions of aryl substituted acid hydrazides (*para*-methyl, *para*-chloro, *ortho*-chloro and *ortho*-hydroxy aryl acid hydrazides) with methyl iodide (Table-2, entries 6 and 7), α-bromo ester (Table-2, entries 2 and 3), α- chloro acid (Table-2, Entry 12) and allyl bromide (Table-2, entries 9 and 10) gave the products in high yields (71-97 %). In addition, from treating of 3-nicotinic hydrazide acid as a hetroaryl acid hydrazide with α-bromo ester (Table-2, entry 4) corresponded product was yielded very well.

The procedure, was also examined for synthesis of *bis*-1,3,4-oxadiazole compounds *via* reaction of benzhydrazde (2 mmol), carbond disulfide (3 mmol) and 1,2-dibromoethane (1 mmol) in optimal reaction conditions (Table-2, entry 13).

Conclusion

In summary, we have developed an one-pot and efficient method for the synthesis of 2-alkylthio-5-aryl-1,3,4-oxadiazole from acid hydrazides as substrate. Some of products are new and containing effective functional groups such as allyl, benzyl, acid and esters which they increase the volubility of products as intermediates in synthesis chemistry and biological activities. One-pot protocol, chemoselectivity, short reaction times, high yield, mild conditions, ease and safe handling are the main advantages of this method.

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