Date: 20-03-15 11:26:45



DOI: 10.1002/ejoc.201500156

Dithiooxamide as an Effective Sulfur Surrogate for Odorless High-Yielding Carbon–Sulfur Bond Formation in Wet PEG200 as an Eco-Friendly, Safe, and Recoverable Solvent

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Keywords: Synthetic methods / Green chemistry / Michael addition / Sulfur / Copper

In this study, we have employed dithiooxamide, a solid, odorless, and commercially available compound, as a sulfur surrogate for the preparation of dialkyl sulfides from available alkyl halides in high yields. This sulfur transfer agent was also used for a copper-catalyzed high-yielding preparation of diaryl sulfides from their available aryl halides and for

the preparation of thia-Michael adducts in high yields. All the reactions were performed under odorless conditions in wet PEG200 (PEG = polyethylene glycol), which is an ecofriendly, safe, and recoverable solvent. The protocols were easily applicable to large-scale operation.

Introduction

The carbon-sulfur bond is found in a great number of pharmaceuticals and biologically active molecules.^[1] Organosulfur compounds are employed in various clinical applications such as the treatment of cancer^[2] HIV,^[3,4] and Alzheimer's and Parkinson's diseases.^[5]

Conventional methods for the preparation of thioethers through the condensation of thiols with organic halides often require harsh reaction conditions such as strong bases and elevated temperatures. A number of protocols have been reported for the formation of aryl carbon-sulfur bonds by using palladium,^[6] nickel,^[7] cobalt,^[8] copper,^[9] and iron^[10] catalysts. Although the preparation of thioethers through the reaction of thiols with aryl halides is a common method, the direct use of the volatile, hazardous, and foulsmelling thiols, which are sometimes expensive and less available, particularly aryl thiols, makes these reactions potentially hazardous and less attractive towards large-scale operations. For this reason, other sulfur surrogates, instead of thiols, such as thiourea,^[11,12] potassium thiocyanate,^[13] potassium ethyl xanthogenate,^[14] potassium thioacetate,^[15] thioacetamide,^[16] aminothiourea,^[17] sodium hydrosulfide,^[18,19] elemental sulfur,^[20,21] and carbon disulfide^[22] have been introduced in recent years.

The other potential method for the formation of a carbon-sulfur bond involves a thia-Michael addition.^[23–27] A variety of odorless protocols for this method have been

reported to eliminate the difficulties that result from using thiols. Some examples involve the employment of thioiminium salts of thiols,^[28] dialkyl disulfides,^[29] 4,4-bis(alkyl-thio)but-3-en-2-ones^[30] and *S*-alkylisothiouranium salts as thiol equivalent precursors.^[31]

However, these methods also suffer from weaknesses, such as the need to prepare most of the reagents from thiols, the necessity of long reaction times, the use of strong bases, and the inaccessibility and price of some catalysts. Recently, we reported a one-pot method for the generation of C-S bonds by thia-Michael reactions using thiourea as the sulfur source, alkyl halides, and Michael acceptors.^[32] In the majority of the reported methods, organic solvents were used. At the present time, disposing of harmful organic solvents is one of the core concerns of the chemical industry. Organic solvents are not recyclable for the most part. They are toxic, flammable, and also expensive. Nevertheless, polyethylene glycols (PEGs) and their derivatives are recognized to be nontoxic, inexpensive, and readily available. In addition, they have negligible vapor pressures, are thermally stable, and are easily recoverable. By taking these points into consideration, it follows that PEGs are highly suitable media for safe and environmentally friendly chemical reactions.^[33] Performing chemical reactions in eco-friendly media has been a focus of ours in recent years. For this objective, we have reported reactions that are conducted in water,^[32,34–39] in polyethylene glycols,^[11,22b,40] and also in ionic liquids.^[41,42] Moreover, carbon-sulfur bond formation reactions that are conducted in eco-friendly media have also been of interest. We have described a one-pot odorless C-S bond formation reaction by using a Michael addition with thiourea and alkyl bromides in water^[32] or in wet polyethylene glycol^[40a] This protocol has also been applied to odorless thioarylations of alkyl bromides with

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500156.

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aryl halides in the presence of copper(I) iodide in wet PEG200.^[11]

In continuation of our interest in the introduction of new methods for odorless C–S bond formation in PEGs as environmentally friendly media, we herein report a one-pot synthetic route for the conversion of alkyl and aryl halides into their corresponding symmetrical sulfides by using dithiooxamide, a commercially available compound, as a solid, odorless sulfur surrogate in wet PEG200 (Scheme 1). We have also employed dithiooxamide to generate C–S bonds by thia-Michael addition reactions using benzyl halides (Br, Cl) and different Michael acceptors (Scheme 1; EWG = electron-withdrawing group).





ethyl acrylate, acrylamide

Scheme 1.

Results and Discussion

Initially, 1-iodoheptane was used as a model compound for preparation of the corresponding sulfide. The effects of varying the temperature, solvent, and base were then studied. According to the data presented in Table 1, the best results were obtained by using wet PEG200 as the solvent and NaOH as the base at a reaction temperature of 30– 35 °C (Table 1, Entry 2). Under these conditions, the desired 1,1-diheptyl sulfide was isolated in 85% yield along with 1,1-diheptyl disulfide in 15% isolated yield.

Under the optimized reaction conditions, NaOH (2 mmol), in wet PEG200 (0.15 mL of H_2O in 2 mL PEG200) at 30–35 °C, different alkyl halides (1 mmol) underwent the reaction with dithiooxamide (0.3 mmol) to give the corresponding symmetrical dialkyl sulfides. The desired products were obtained in moderate to excellent yields for a wide range of primary alkyl halides. The secondary alkyl halide cyclohexyl bromide gave dicyclohexyl sulfide in 40% isolated yield. Other results from this study are shown in Table 2. We have found that this method was also suitable for large-scale (100 mmol) procedures, which afforded the desired products in high yields.

Table 1. Optimization of the reaction between iodoheptane and di-thiooxamide. $^{\left[a\right] }$

	S	base,	(<i>n</i> -C ₇ H ₁₅ –) ₂ S	Α
<i>n</i> -C ₇ H ₁₅ I +	$H_2N \longrightarrow NH_2$		+	
	S	30-33 C	(<i>n</i> -C ₇ H ₁₅ -S) ₂	в

					, <u>E</u>
Entry	Base	Solvent	Time [h]	% Yield A ^[b]	% Yield B ^[c]
1 ^[d]	NaOH	PEG200	2	70	30
2	NaOH	PEG200	4	85	15
3	NaOH	CH ₃ CN	24	20	50
4	NaOH	DMF ^[e]	1	50	50
5	NaOH	CH_2Cl_2	24	_	_
6	NaOH	EtOAc	24	10	10
7	NaOH	toluene	24	_	_
8[f]	NaOH	H_2O	24	24	_
9[g]	NaOH	H_2O	24	24	10
10	Et ₃ N	PEG200	24	24	15
11	K_2CO_3	PEG200	4	4	10
12	NaHCO ₃	PEG200	24	24	10
13	КОН	PEG200	6	6	15
14	K_3PO_4	PEG200	4	4	10

[a] Reagents and conditions: iodoheptane (1 mmol), dithiooxamide (0.3 mmol), base (2 mmol), solvent (2 mL), and H₂O (0.15 mL) in the air. [b] Isolated yield of sulfide. [c] Isolated yield of disulfide. [d] The reaction was carried out at 50 °C. [e] DMF = N,N-dimeth-ylformamide. [f] The reaction was carried out in a mixture of H₂O (2 mL) and sodium dodecyl sulfate (SDS, 5 mol-%). [g] The reaction was carried out in the mixture of H₂O (2 mL) and Triton X100 (10 mol-%).

Table 2. One-pot conversion of alkyl halides into their corresponding symmetrical dialkyl sulfides.^[a]

		NaOH, PEG200, H ₂ O	→ R ^{S.}	`R
		30–35 °C	i.	IX.
Entry	RX	Product	Time [h]	Yield [%] ^[b]
1	PhCH ₂ Br	(PhCH ₂) ₂ S (1a)	0.5	100
2	PhCH ₂ Cl	(PhCH ₂) ₂ S (1a)	1	95
3	4-MeC ₆ H ₄ CH ₂ Cl	(4-MeC ₆ H ₄ CH ₂) ₂ S (1b)	1	93
4	4-BrC ₆ H ₄ CH ₂ Br	(4-BrC ₆ H ₄ CH ₂) ₂ S (1c)	0.5	100
5	$n-C_7H_{15}I$	$(n-C_7H_{15})_2S$ (1d)	3	90
6	$n-C_8H_{17}I$	$(n-C_8H_{17})_2S$ (1e)	3	87
7	n-C ₈ H ₁₇ Br	$(n-C_8H_{17})_2S$ (1e)	4	85
8	$n-C_{10}H_{21}Br$	$(n-C_{10}H_{21})_2S$ (1f)	6	83
9	PhCH ₂ CH ₂ Br	(PhCH ₂ CH ₂) ₂ S (1g)	4	85
10	$n-C_3H_7I$	$(n-C_{3}H_{7})_{2}S$ (1h)	1.5	87

[a] The reaction was carried out in the presence of dithiooxamide and NaOH in wet polyethylene glycol 200 (PEG200) at 30-35 °C in the air. [b] Isolated yield.

The proposed mechanism for the reaction of alkyl halides with dithiooxamide is presented in Scheme 2.

We have also extended our studies to the preparation of symmetrical diaryl sulfides, which are a more difficult task. To optimize the conditions, we studied the reaction of iodobenzene with dithiooxamide and K_2CO_3 in the presence of different amounts of CuI in wet PEG200 at 120 °C under an inert atmosphere in a sealed tube (Table 3, Entry 4). Un-

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Table 3. The effect of different catalyst loadings on the reaction of iodobenzene with dithiooxamide. $^{[a]}$



Entry	CuI [mol-%]	Time [h]	% Yield C ^[b]	% Yield D ^[b]
1	10	24	60	20
2	15	10	75	25
3	20	10	75	25
4 ^[c]	15	6	95	trace

[a] Reagents and conditions: iodobenzene (1 mmol), dithiooxamide (1 mmol), K_2CO_3 (2 mmol), CuI (15 mol-%), PEG200 (2 mL), and H_2O (0.15 mL).[b] Isolated yield. [c] The reaction was performed in a sealed tube.

Table 4. Screening different bases, solvents, and copper catalysts for the reaction of iodobenzene with dithiooxamide.^[a]



Entry	Base	Solvent	Catalyst	% Yield $\mathbf{C}^{[b]}$	% Yield D ^[b]
1	K ₂ CO ₃	PEG200	CuI	95	trace
2	Et ₃ N	PEG200	CuI	40	40
3	NaOH	PEG200	CuI	85	15
4	Cs_2CO_3	PEG200	CuI	80	20
5	K ₃ PO ₄	PEG200	CuI	90	10
6	_	PEG200	CuI	20	_
7	K_2CO_3	toluene	CuI	_	_
8	K_2CO_3	DMSO ^[c]	CuI	80	10
9	K_2CO_3	DMF	CuI	75	15
10	K_2CO_3	H_2O	CuI	_	_
11	K_2CO_3	PEG200	CuCl	65	10
12	K_2CO_3	PEG200	$Cu(OAc)_2$	50	15
13	K_2CO_3	PEG200	CuCl ₂	60	10
14	K_2CO_3	PEG200	CuNO ₃	60	15
15	K ₂ CO ₃	PEG200	-	_	_

[a] Reagents and conditions: iodobenzene (1 mmol), dithiooxamide (1 mmol), base (2 mmol), PEG200 (2 mL), H_2O (0.15 mL), and catalyst (15 mol-%) at 120 °C in a sealed tube. [b] Isolated yield. [c] DMSO = dimethyl sulfoxide.



Table 5. One-pot preparation of symmetrical diaryl sulfides by using aryl halides (X = I or Br) and dithiooxamide in wet polyethylene glycol (PEG200) at 120 °C.^[a]



[a] Isolated yield. [b] The reactions were carried out by using 1.3 mmol of dithiooxamide.

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	Table 6	. Com	parison o	of the	results f	for the	thioeth	nerification	of iod	lobenzene	by usin	g dithi	ooxamide	versus	other	sulfur	source
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Entry	Solvent	<i>T</i> [°C]	Catalyst [mol-%]	Base	Sulfur source	Time [h]	Yield [%]
1	PEG200	120	CuI (15)	K ₂ CO ₃ (2 mmol)	dithioxamide (1 mmol)	6	95 ^[a]
2	PEG200	120	CuI (15)	K_2CO_3 (2 mmol)	dithiooxamide (0.5 mmol)	6	50 ^[a]
3	PEG200	120	CuI (15)	K_2CO_3 (2 mmol)	thiourea (1 mmol)	6	38 ^[a]
4	PEG200	120	CuI (15)	K_2CO_3 (2 mmol)	thioacetamide (1 mmol)	6	50 ^[a]
5	DMSO	130	nano CuO (5)	KOH (2 mmol)	potassium thiocyanate (1.5 mmol)	20	94 ^[15]
6	DMSO	120	CuI (10)	Cs_2CO_3 (3 mmol)	thioacetamide (1 mmol)	24	83[16]
7	DMSO	120	$Cu(OAC)_2 \cdot H_2O(5)$	K_2CO_3 (1 mmol)	aminothiourea (0.6 mmol)	12	94 ^[17]
8	PEG400	150	CuI (10)	K_3PO_4 (2 mmol)	Na_2S (0.5 mmol)	24	98 ^[43]
9	1,4-dioxane	100	$Pd_2dba_3^{[b]}(2)$	Cs_2CO_3 (1.4 mmol)	thiourea (0.6 mmol)	18	80 ^[44]

[a] Reactions were performed in our laboratories. [b] dba = dibenzylideneacetone.

der these conditions, the formation of the disulfide byproduct **D** was reduced drastically.

To further optimize the reaction, the effect of different bases, solvents, and amounts of copper catalyst were examined. The results show that the reaction proceeded to give the highest yield of diphenylsulfide (95%) by employing dithiooxamide (1 mmol) as the sulfur source, wet PEG200/ H_2O (2 mL/0.15 mL) as the reaction medium, K_2CO_3 (2 mmol) as the base, and CuI (15 mol-%) as the catalyst in a sealed tube at 120 °C (Table 4, Entry 1).

Under these optimized conditions, iodobenzene and the other aryl iodides that contain an electron-donating or electron-withdrawing group at the *para* position produced the desired diaryl sulfides in good to excellent yields (Table 5, Entries 1–5, 8 and 9). Thioetherification of sterically hindered aryl iodides such as 1-iodonaphthalene and 2-iodotoluene afforded the desired products in excellent yields (Table 5, Entries 6 and 7). The thioetherification of aryl bromides that contain electron-withdrawing groups was also studied. These reactions proceeded well and provided good yields under the above-mentioned conditions (Table 5, Entries 10–12).

This protocol was easily adapted to scaled up reactions. As an example, iodobenzene (50 mmol) was converted into diphenyl sulfide in a high isolated yield (90%).

To show the merits of this method over some of the other reported protocols for the thioetherification of aryl halides, we compared thioetherification reactions of iodobenzene by using dithiooxamide with those of previously reported sulfur surrogates (Table 6). The comparisons clearly demonstrate the advantage of using dithiooxamide over other sulfur surrogates. As is evident from the results, the thioetherification of aryl halides by using dithiooxamide can occur in shorter reaction times in some cases (Table 6, Entries 1–4).

We have proposed a mechanism that involves a catalytic cycle for the thioetherification reaction of aryl halides with dithiooxoamide catalyzed by CuI (Scheme 3). The first step is an oxidative addition, in which Cu inserts into the aryl halide bond to form complex **X**. The reaction then proceeds by an attack of the dithiooxamide on complex **X** to produce **Y**, from which the elimination of CuI generates **Z**. Upon hydrolysis, **Z** produces a thiolate moiety and 2-amino-2-

thiooxoacetamide. The generated thiolate ion may undergo an oxidative addition reaction followed by an elimination reaction with the aryl organocopper intermediate, which has been formed in situ by the reaction of the aryl halides with CuI.



Scheme 3. A plausible reaction mechanism for thioarylation reaction of aryl halides with dithiooxamide catalyzed by CuI.

We have also studied the reaction of methyl vinyl ketone with benzyl bromide as a model for a thia-Michael addition reaction. The optimized reaction was achieved by combining benzyl bromide (1 mmol) with dithiooxamide (1 mmol) in wet PEG200 (2 mL) and heating the resulting mixture at 80 °C. Methyl vinyl ketone (1 mmol) and NaHCO₃ (1.5 mmol) were then added, and the resulting mixture was stirred at 50 °C for the appropriate reaction time to give the desired Michael adduct in 85% isolated yield. By using these optimized conditions, the reactions of a series of different benzyl halides (Br, Cl) and n-decyl bromide with electron-deficient olefins were investigated. The reactions proceeded well to produce the desired thia-Michael adducts in good to excellent isolated yields. The results of this study are shown in Table 7. A mechanistic pathway for the thia-Michael addition reaction with dithiooxamide is presented in Scheme 4. It is worthy of mention that the workup for all reactions presented herein proceeded under almost odorfree conditions.

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Table 7. One-pot thia-Michael addition reaction of benzyl halides (X = Br or Cl) and *n*-decyl bromide with dithiooxamide and electron-deficient alkenes in wet PEG $200.^{[a]}$

EWG = methyl vinyl ketone, acrylonitrile, ethyl acrylate, acrylamide



[[]a] Isolated yield.



Scheme 4. A proposed pathway for the thia-Michael addition reaction of benzyl halides with electron-deficient olefins in the presence of dithiooxamide.

Conclusions

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In summary, we have herein presented a new application for dithiooxamide, a solid, odorless, commercially available compound, for use in the efficient preparation of dialkyl and diaryl sulfides in high yields from their available alkyl and aryl halides. Dithiooxamide can also be used in the preparation of thia-Michael adducts in high yields. All reactions were performed in wet PEG200 as an eco-friendly, safe, and recoverable solvent that is free of foul-smelling thiols. These protocols can be easily applied to large-scale operations, and we believe this method is a highly useful and practical addition to the available protocols for the generation of organosulfur compounds.

Experimental Section

General Methods: All chemicals were prepared in our laboratory or purchased from Merck, Fluka or Acros Chemical Companies and used without further purification. The ¹H NMR spectroscopic data were recorded with a Bruker Avance DPX 250 MHz spectrometer, and the ¹³C NMR spectroscopic data were recorded with a 62.9 MHz spectrometer. CDCl₃ was used as the NMR solvent with TMS as the internal standard. Mass spectra were obtained at 70 eV. The progress of the reactions were monitored by using silica gel analytical sheets or by GC analysis using a 3 m column packed with a DC-200 stationary phase.

Synthesis of Diheptyl Sulfide as a Typical Procedure (1d): Iodoheptane (0.16 mL, 1 mmol) was added to a flask that contained dithiooxamide (0.036 g, 0.3 mmol) and NaOH (0.08 g, 2 mmol) in PEG200 (2 mL) and H₂O (0.15 mL). The mixture was stirred at 30-35 °C with a magnetic stir bar. The progress of the reaction was monitored by TLC or GC analysis for the consumption of iodoheptane (3 h). To isolate the product, the mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 × 3 mL). The

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combined organic phases were dried with Na₂SO₄, filtered, and concentrated to yield the crude product, which was further purified by column chromatography on silica gel (petroleum ether) to provide 1,2-diheptyl sulfide (1d, 90% yield) as a colorless oil. ¹H NMR (250 MHz, CDCl₃): $\delta = 2.43$ (t, J = 7 Hz, 4 H), 1.56–1.47 (m, 4 H), 1.26–1.21 (m, 16 H), 0.8 (t, J = 6.5 Hz, 6 H) ppm. ¹³C NMR (62.5 MHz, CDCl₃): $\delta = 32.1$, 31.7, 29.7, 28.9, 22.5, 14.0 ppm.

Synthesis of Diphenyl Sulfide as a Typical Procedure (2a): To a glass tube that contained CuI (0.028 g, 15 mol-%), K₂CO₃ (0.276 g, 2 mmol), and dithiooxamide (0.12 g, 1 mmol) in wet PEG200 (0.15 mL of H₂O in 2 mL PEG200) was added iodobenzene (0.11 mL, 1 mmol). The glass tube was sealed under vacuum, placed in an oil bath at 120 °C, and stirred for the appropriate reaction time (6 h for 2a). Upon completion of the reaction, the tube was cooled to room temperature and then opened. The reaction mixture was diluted with H₂O (5 mL), and the resulting mixture was extracted with EtOAc (4 × 10 mL). The combined extracts were dried anhydrous Na₂SO₄ and concentrated. The crude organic product was purified by column chromatography on silica gel (petroleum ether) to give diphenyl sulfide (2a, 95% yield) as a yellow oil. ¹H NMR (250 MHz, CDCl₃): δ = 137.0, 129.1, 127.5, 127.1 ppm.

Synthesis of 4-(Benzylthio)butan-2-one (3a) as a Typical Procedure for Thia-Michael Adduct Formation: A mixture of benzyl bromide (0.12 mL, 1 mmol), dithiooxamide (0.12 g, 1 mmol), and PEG200 (2 mL) was heated at 80 °C for 30 min. NaHCO₃ (0.126 g, 1.5 mmol) and methyl vinyl ketone (0.084 mL, 1 mmol) were added to mixture, which was then heated at 50 °C for 30 min. The mixture was diluted with water (3 mL), and the resulting mixture was extracted with ethyl acetate (3 × 3 mL). The combined extracts were dried and concentrated to give the crude residue, which was further purified by silica gel chromatography (petroleum ether/EtOAc, 10:1) to provide 4-(benzylthio)butan-2-one (**3a**, 85% yield) as a colorless oil. ¹H NMR (250 MHz, CDCl₃): δ = 7.31–7.21 (m, 5 H), 3.71 (s, 2 H), 2.69–2.59 (m, 4 H), 2.10 (s, 3 H) ppm. ¹³C NMR (62.9 MHz, CDCl₃): δ = 206.7, 138.2, 128.8, 128.5, 127.0, 43.2, 36.6, 30.0, 25.1 ppm.

Acknowledgments

The authors thank the National Elite Foundation of Iran for a grant (BN048) and also the Shiraz University Research Council for support of this work.

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Received: February 1, 2015 Published Online: ■ 1 Da

FULL PAPER

Dithiooxamide has been employed as a sulfur surrogate for the generation of C–S bonds in high yields by using alkyl and aryl halides. This method was also used for the preparation of thia-Michael adducts in high yields. All of the reactions were performed in wet PEG200 (PEG = polyethylene glycol) under odorless conditions.



Carbon-Sulfur Bond Formation

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Dithiooxamide as an Effective Sulfur Surrogate for Odorless High-Yielding Carbon–Sulfur Bond Formation in Wet PEG200 as an Eco-Friendly, Safe, and Recoverable Solvent

Keywords: Synthetic methods / Green chemistry / Michael addition / Sulfur / Copper

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