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Letter

Molecular Iodine Catalyzed Hydroxysulfenylation of Alkenes with Disulfides in Aerobic Conditions

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 $\begin{array}{c} Ar & S & \downarrow & Un \\ R^2 & R^1 \\ metal-free catalysis \\ air as oxidant \\ both aryl and aliphatic alkenes \\ 24 examples \end{array}$

up to 86% isolated vield

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Abstract An environmentally friendly and efficient strategy has been developed for preparing β -hydroxy sulfides by a molecular-iodine-catalyzed radical reaction. This reaction involves hydroxysulfenylation of alkenes with disulfides in aqueous solution. Air is used as the oxidant without any additives. Control experiments indicated that the oxygen atom of products might come from O₂. Both aryl alkenes and aliphatic alkenes were well tolerated in this transformation and afforded the corresponding products in moderate to high yields.

Key words hydroxysulfenylation, hydroxy sulfides, iodine catalysis, green chemistry

β-Hydroxy sulfides have found widespread use as convenient intermediates for the construction of biologically active heterocycles,¹ pharmaceuticals,² and natural products.³ Consequently, numerous synthetic methods have been reported for the preparation of these compounds. The classical approaches for accessing these compounds involves the ring opening of epoxides with thiols.⁴ Alternatively, the thiol–oxygen co-oxidation reaction of alkenes is another useful method.⁵ Despite their great success, these methods involve the use of large excesses of fetid, sensitive, and toxic thiols, possibly hindering their widespread application. Thus, an efficient way for building these useful structures without generating obnoxious odors remains an attractive prospect.

In the past decade, methods for the use of disulfides instead of thiols have been developed for the preparation of β -hydroxy sulfides.⁶ Among these, the oxidative sulfidation of alkenes with disulfides has attracted considerable attention. Alkene dihydroxysulfenylation can efficiently introduce a C–O bond and a C–S bond in one step from simple starting materials. For example, Movassagh and Navidi⁷ reported a Zn/AlCl₃-catalyzed one-pot synthesis of β -hydroxy sulfides from various styrenes and disulfides (Scheme 1a). Yadav and co-workers⁸ disclosed a metal-free radical pathway to afford β -hydroxy sulfides by using Rongalite (HOCH₂SO₂Na·2H₂O) as a promoter under aerobic conditions (Scheme 1b). Recently, Yan and co-workers⁹ reported a HBr/H₂O₂-mediated sulfidation of styrenes, leading to β hydroxy sulfides (Scheme 1c). Although these methods provide efficient routes to β -hydroxy sulfides, most of them have drawbacks, such as the use of toxic catalysts or excessive use of promoters or oxidants. Furthermore, these methods are generally focused exclusively on terminal aryl alkenes, whereas aliphatic alkenes are inert toward these transformations. Therefore, an environmentally friendly and efficient process for preparing such motifs remains highly desirable.





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As a classical nonmetallic-element-catalyzed process, molecular-iodine-catalyzed oxidation represents a recent advance in terms of environmental sustainability and cost effectiveness.¹⁰ The Peddinti group¹¹ recently developed a regioselective synthesis of β -hydroxy sulfides from terminal styrenes and thiophenols by using iodine; however, DMSO was used as the oxidant in this reaction. As an ideal oxidant, molecular oxygen is clean, nontoxic, and environmentally sustainable. In this context, we describe the development of an environmentally friendly and efficient method for an aerobic molecular-iodine-catalyzed hydroxysulfenylation of both aryl and aliphatic alkenes with disulfides to generate β -hydroxy sulfides (Scheme 1d).

In our initial study, we chose bis(4-chlorophenyl) disulfide (**1a**) and styrene (**2a**) as our model substrates. To our delight, we obtained a 62% yield of the desired product **3a** in the presence of I₂ in MeCN–H₂O (3:1, v/v) at 40 °C under air after two hours (Table 1, entry 1). To obtain an optimum yield, we screened a wide variety of oxidants. O₂ gave a low yield of the desired product; instead, more than 50% of diphenyl disulfide was obtained (entry 2). H₂O₂ and K₂S₂O₈ as oxidants also showed negative effects, giving only trace amounts of the desired product (entries 3 and 4). Consequently, the reaction was carried out on the open air. A study of the reaction temperature showed that 60 °C was the best choice, and the yield of the corresponding product

Table 1 Optimization of the Reaction Conditions^a

	s.	Ĵ,	oxidant,	Dxidant, I2	
CI_	S S	~ + Ph	solver		30
	Ia	2	a		54
Entry	Catalyst (mol%)	Oxidant	Temp (°C)	Solvent	Yield ^ь (%)
1	I ₂ (20)	air	40	MeCN-H ₂ O	62
2	I ₂ (20)	O ₂	40	MeCN-H ₂ O	32
3	I ₂ (20)	$H_2O_2^c$	40	MeCN-H ₂ O	trace
4	I ₂ (20)	$K_2S_2O_8{}^c$	40	MeCN-H ₂ O	trace
5	I ₂ (20)	air	r.t.	MeCN-H ₂ O	40
6	I ₂ (20)	air	60	MeCN-H ₂ O	82
7	I ₂ (20)	air	80	MeCN-H ₂ O	74
8	I ₂ (20)	air	60	MeOH-H ₂ O	55
9	I ₂ (20)	air	60	DMSO-H ₂ O	25
10	I ₂ (20)	air	60	$MeCN-H_2O^d$	82
11	I ₂ (20)	air	60	H ₂ O	trace
12	I ₂ (30)	air	60	MeOH-H ₂ O	80
13	I ₂ (10)	air	60	MeOH-H ₂ O	43

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), solvent/ H_2O = 3:1 (2 mL), 2 h.

^d MeCN/H₂O = 1:1.

3a increased to 82% (entry 6). The choice of solvent had a significant impact on the reaction: MeOH–H₂O (3:1, v/v) and DMSO–H₂O (3:1, v/v) afforded lower yields (entries 8 and 9).When the ratio of MeCN to H₂O was 1:1, a similar yield was obtained to that under the model condition (entry 10). However, only trace amount of the desired product was obtained in water (entry 11). Finally, the effect of the amount of the catalyst was also checked. Increasing the amount of I₂ to 30 mol% led to a similar yield (entry 12), whereas decreasing the amount of I₂ resulted in a significantly lower yield (entry 13). Thus, the optimal experimental conditions were established as follows: disulfide **1** (1 equiv), alkene **2** (2.0 equiv), and I₂ (20 mol%) as catalyst in a 1:1 (v/v) mixture of MeCN and H₂O (2 mL) under ambient conditions.

With the optimal condition in hand, we examined the scope and generality of the present method.¹³ As shown in Scheme 2. diverse arvl alkenes 2 bearing a variety of substituents were employed to react with diaryl disulfides 1 under the optimized reaction conditions to give the corresponding products **3a-k** smoothly in moderate to high yields (52-86%). The electronic properties of substituents on the aryl rings of alkene had a slight influence on the reaction, but both electron-donating and electron-withdrawing substituents gave satisfactory results (3g-j). Steric hindrance in the alkene had a significant effect, and aryl alkenes with para-, meta-, or ortho-chloro substituents were successfully converted into the corresponding products **3d-f** in yields of 80, 72, and 51%, respectively. Note that, α, α -disubstituted alkenes **21–n** were suitable for this protocol. The α , β -substituted alkenes **20** and **2p** also participated in this reaction, but gave only moderate yields, probably due to steric hindrance. Furthermore, aliphatic alkenes such as cyclohexene (2q), 4-methylpent-1-ene (2r), and 4bromobut-1-ene (2s) also showed good tolerance in this reaction and afforded the corresponding β -hydroxy sulfides **3q-s** in moderate yields. In addition, the regioselectivity toward the cyclohexene product **3q** was examined; a NOESY NMR showed that the regioisomer of the products is *trans*, and the relative configuration of **3q** is shown in Scheme 2.

The scope of the diaryl disulfide was also investigated. Diaryl disulfides **2t**-**x** with substituents such as fluoro, chloro, methyl, or bromo were suitable for the present reaction conditions, affording the desired products **3t**-**x** in moderate to good yields. The electronic effect of the substituents had a significant influence on the reaction, and bis(4fluorophenyl) disulfide gave a relatively low yield (52%) of **3w**, whereas bis(4-cyanophenyl) disulfide (**1y**) was inert toward this transformation. Diethyl disulfide (**1z**) was not suitable for this transformation.

To gain insight into the mechanism, we performed several control experiments. First, a radical trapping experiment was conducted by employing (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), and only an 11% yield of the desired product was obtained (Scheme 3a), indicating that

ОН

^b Yield of isolated product.

^c Two equivalents.

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Scheme 2 Substrate scope of the reaction. *Reagents and conditions*: **1** (0.5 mmol), **2** (1 mmol), I₂ (20 mol%), 1:1 MeCN-H₂O (2 mL), under open air, 2 h, 60 °C. Isolated yields are reported. NR = no reaction.

the reaction might involve a radical pathway. Next, when the reaction carried out without O_2 , only a trace amount of **3a** was obtained (Scheme 3b), The reaction was completely inhibited when the reaction was carried out in the absence of H₂O (Scheme 3c). Furthermore, when H₂O was replaced by $H_2^{18}O$ under the standard conditions, product **3a** with no ^{18}O label was detected (Scheme 3d). These results suggested that the oxygen atom in the product does not originate from H_2O , but probably comes from O_2 .

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On the basis of these control experiments and previous reports,^{8,9} we propose the plausible mechanism for the present reaction shown in Scheme 4. Initially, I₂ active the disulfide ArSSAr 1 to give the intermediate ArS–I (I).¹¹ This liberates radical ArS[•] (II) and an iodine free radical.¹¹ Subsequent addition of II to alkene 2 generates radical III, which reacts with molecular oxygen to give the peroxy radical IV.^{5h} Reaction between intermediates III and IV then affords radical V,¹² which reacts with the iodine free radical and abstracts one hydrogen atom from H₂O to form the desired product **3** and the catalyst I₂.



Scheme 4 The proposed mechanism

In summary, we have developed an environmentally friendly and effective molecular-iodine-catalyzed reaction for the preparation of β -hydroxy sulfides in aqueous solution.¹³ This reaction uses disulfides instead of fetid, sensitive, and toxic thiols. Importantly, air is used as the oxidant without any additive. Furthermore, H₂¹⁸O isotope experiment indicated that the oxygen atom of the products comes from O₂. Moreover, both terminal aryl alkenes, α, α -substi-

tuted aryl alkenes, α , β - substituted aryl alkenes, and aliphatic alkenes are tolerated well in this transformation to give the corresponding products in moderate to high yields, thereby providing a potential route for both academic and industrial applications.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690163.

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(13) β-Hydroxy Sulfides 3; General Procedure A 20 mL reaction vessel equipped with a magnetic stirring bar was charged with the appropriate disulfide 1 (0.5 mmol), alkyne 2 (1 mmol), I₂ (20 mol%), and 1:1 MeCN-H₂O (2 mL), and the mixture was stirred under air at 60 °C for 2 h. Surplus I_2 was quenched with sat. aq $Na_2S_2O_3$, and the mixture was extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexanes–EtOAc (4:1)].

2-[(4-Chlorophenyl)thio]-1-(4-fluorophenyl)ethanol (3b)

Colorless oil; yield: 101.5 mg (72%); ¹H NMR (400 MHz, CDCl₃): δ = 7.51–7.16 (m, 6 H), 7.10–7.04 (m, 2 H), 4.86–4.71 (m, 1 H), 3.50–3.09 (m, 2 H), 2.81–2.53 (m, 1 H). ¹³C NMR (101 MHz, CDCl₃): δ = 163.7, 161.3, 137.7, 133.4, 133.1, 131.7, 129.3, 127.53, 115.5, 71.2, 44.3. ¹⁹F NMR (376 MHz, CDCl₃): δ = –114.0. ESI-MS: *m/z* = 283 [M + 1]⁺. Anal. Calcd for C₁₄H₁₂CIFOS: C, 59.47; H, 4.28. Found: C, 59.30; H, 4.39.