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Iodine-catalyzed three-component oxysulfenylation of alkenes with sulfonyl hydrazides and alcohols†

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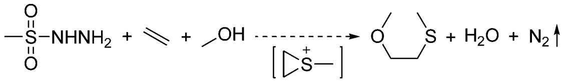
An unprecedented three-component oxysulfenylation reaction of alkenes with sulfonyl hydrazides and alcohols has been developed in the presence of 20 mol% iodine to give a range of structurally diverse β-alkoxy sulfides in good to excellent yields.

Among many of the synthetic transformations of alkenes, 1,2-difunctionalization of carbon–carbon double bonds constitutes one of the most powerful methods for the introduction of functional groups into target compounds. In this regard, the oxysulfenylation of alkenes has emerged as an ideal strategy for the synthesis of β-alkoxy sulfides, which serve as versatile building blocks in chemical synthesis.[1] While several types of sulfenylating agents, such as sulfenyl halides,[2] sulfenamides,[3] sulfenate esters,[4] disulfides,[5] dimethyl(methylthio)sulfonium salts,[6] and methyl(bismethylthio)sulfonium salts,[7] have been identified for the two- and three-component oxysulfenylation of alkenes, many of them are not amenable to preparation and handling. Moreover, previously reported oxysulfenylation reactions of alkenes frequently require excess sulfenylating agents, suffer from a narrow substrate scope, and/or yield byproducts unfriendly to the environment. Thus, it would be highly desirable to explore new sulfenylating agents for the oxysulfenylation of alkenes, particularly in a three-component manner, which would exhibit higher efficiency relative to the sequential synthesis of the same targets by conventional bimolecular reactions.[8]

As part of our efforts in exploring new chemistry of hydrazine derivatives,[9] we recently reported the use of sulfonyl hydrazides as sulfenylating agents in a sulfenylation reaction of indoles.[9b] A few months later Singh and co-workers reported a hydrothiolation reaction of terminal alkynes and a sulfenylation reaction of organic halides with sulfonyl hydrazides.[10] In contrast to many other sulfenylating agents, sulfonyl hydrazides are readily accessible solids and compatible with moisture. Prompted by this background together with our interest in developing new multicomponent reactions,[11] we envisioned that simple sulfonyl hydrazides could act as sulfenylating agents to attack alkenes to form thiiranium ion (episulfonium ion) intermediates, which would be opened up by external alcohols to yield β-alkoxy sulfides (eqn (1)).[1] Importantly, the proposed three-component oxysulfenylation reaction of alkenes with sulfonyl hydrazides and alcohols was expected to generate water and molecular nitrogen as environmentally benign byproducts.[9b]



(1)

To test our hypothesis, sulfonyl hydrazide **1a**, styrene (**2a**), and ethanol (**3a**) were subjected to our previously reported conditions for the sulfenylation of indoles, that is, with iodine as the catalyst in ethanol at 70 °C.[9b] While the desired three-component reaction proceeded to give β-alkoxy sulfide **4a** as a single regioisomer, the yield was only 34% (Table 1, entry 1). To improve the yield, we screened a range of common organic solvents and found that the use of 1,2-dichloroethane led to the formation of β-alkoxy sulfide **4a** as a single regioisomer in 88% yield (Table 1, entry 7). Nevertheless, the yield decreased dramatically when replacing iodine with *N*-iodosuccinimide (NIS)[12] or Bu_4NI, reducing the catalyst loading, or decreasing the temperature (Table 1, entries 9–12).

Under the optimized reaction conditions, a range of aryl- and alkylsulfonyl hydrazides smoothly reacted with arylethenes and alcohols to give structurally diverse β-alkoxy sulfides in good to excellent yields with extremely high regioselectivity (Table 2). It is noteworthy that both electron-withdrawing and electron-donating groups were successfully introduced into the aromatic rings of the products by employing the sulfonyl hydrazides or the arylethenes bearing such groups. While primary and secondary alcohols could serve as suitable oxygen

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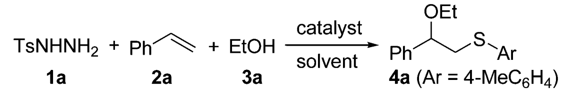
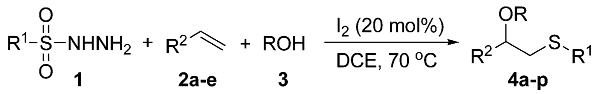
Table 1 Optimization of reaction conditions[a,b]



Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Yield[c] (%)
1	I_2 (20)	EtOH	70	34
2	I_2 (20)	DMSO	70	0
3	I_2 (20)	DMF	70	0
4	I_2 (20)	MeCN	70	Trace
5	I_2 (20)	EtOAc	70	Trace
6	I_2 (20)	Dioxane	70	79
7	I_2 (20)	DCE	70	88
8	I_2 (20)	Toluene	70	82
9	NIS (40)	DCE	70	67
10	Bu_4NI (40)	DCE	70	Trace
11	I_2 (10)	DCE	70	51
12	I_2 (20)	DCE	50	47

[a] Reaction conditions: sulfonyl hydrazide **1a** (0.20 mmol), alkene **2a** (0.24 mmol), alcohol **3a** (50 μL), catalyst (20 or 40 mol%), solvent (0.50 mL), 70 or 50 °C (oil bath), 16 h. [b] In all cases compound **4a** was obtained as a single regioisomer. [c] Isolated yield.

Table 2 Three-component oxysulfenylation of arylethenes with sulfonyl hydrazides and alcohols[a,b]

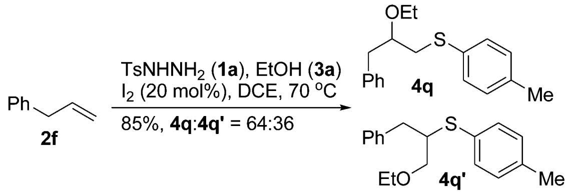


Entry	1, R^1	2a–e, R^2	3, R	4a–p	Yield[c] (%)
1	**1a**, 4-MeC_6H_4	**2a**, Ph	**3a**, Et	**4a**	88
2	**1b**, Ph	**2a**, Ph	**3a**, Et	**4b**	85
3	**1c**, 4-$MeOC_6H_4$	**2a**, Ph	**3a**, Et	**4c**	71
4	**1d**, 4-FC_6H_4	**2a**, Ph	**3a**, Et	**4d**	82
5	**1e**, 4-BrC_6H_4	**2a**, Ph	**3a**, Et	**4e**	74
6	**1f**, 4-IC_6H_4	**2a**, Ph	**3a**, Et	**4f**	76
7	**1g**, 3-$O_2NC_6H_4$	**2a**, Ph	**3a**, Et	**4g**	61
8	**1h**, 2,5-$Cl_2C_6H_3$	**2a**, Ph	**3a**, Et	**4h**	75
9	**1i**, 2-naphthyl	**2a**, Ph	**3a**, Et	**4i**	72
10	**1j**, $(CH_2)_7Me$	**2a**, Ph	**3a**, Et	**4j**	91
11	**1a**, 4-MeC_6H_4	**2b**, 4-ClC_6H_4	**3a**, Et	**4k**	90
12	**1a**, 4-MeC_6H_4	**2c**, 4-NCC_6H_4	**3a**, Et	**4l**	63
13	**1a**, 4-MeC_6H_4	**2d**, 2-naphthyl	**3a**, Et	**4m**	81
14	**1a**, 4-MeC_6H_4	**2e**, 1-naphthyl	**3a**, Et	**4n**	85
15	**1a**, 4-MeC_6H_4	**2a**, Ph	**3b**, ^{n}Bu	**4o**	94
16	**1a**, 4-MeC_6H_4	**2a**, Ph	**3c**, ^{i}Pr	**4p**	77

[a] Reaction conditions: sulfonyl hydrazide **1** (0.20 mmol), alkene **2** (0.24 mmol), alcohol **3** (50 μL), iodine (20 mol%), DCE (0.50 mL), 70 °C (oil bath), 16 h. [b] No regioisomer was detected by ^{1}H NMR spectroscopic analysis of the crude product. [c] Isolated yield.

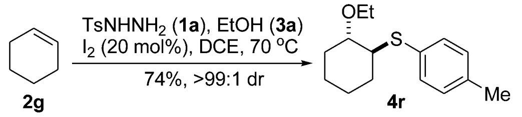
nucleophiles, the reaction was not applicable to bulky alcohols such as *tert*-butyl alcohol probably because of steric hindrance. As demonstrated by the results summarized in Table 2, the reaction tolerated a variety of functional groups such as alkoxy, fluoro, chloro, bromo, iodo, nitro, and nitrile groups.

A few other types of alkenes were examined in their three-component oxysulfenylation with sulfonyl hydrazides and alcohols under the standard reaction conditions. In sharp contrast to arylethenes, poor regioselectivity was observed in the reaction with alkylethenes. For example, the iodine-catalyzed oxysulfenylation of alkene **2f** with sulfonyl hydrazide **1a** and ethanol (**3a**) gave a 64 : 36 mixture of β-alkoxy sulfides **4q** and **4q′** (eqn (2)).

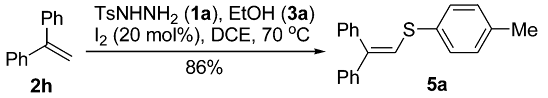


(2)

While the three-component reaction failed to proceed with acyclic 1,2-disubstituted and more highly substituted alkenes, such as (*E*)-stilbene and 2-methyl-1-phenyl-1-propene, cyclohexene (**2g**) was demonstrated to serve as a suitable substrate (eqn (3)). Moreover, the desired product, β-alkoxy sulfide **4r**, was obtained in 74% yield as a single stereoisomer with *trans* configuration. This result lends substantial support to the generation of a thiiranium ion intermediate during the reaction (see below). In contrast, the reaction with 1,1-diphenylethene (**2h**) did not give the corresponding β-alkoxy sulfide at all under the same conditions. Instead, another reaction pathway was established to give vinyl thioether **5a** in 86% yield (eqn (4)).

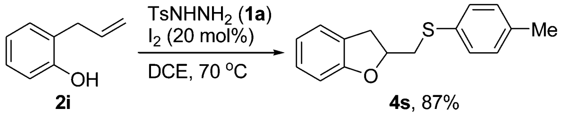


(3)



(4)

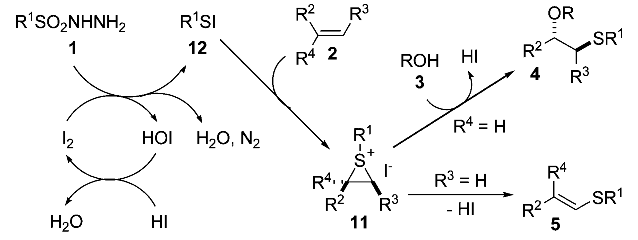
When the alkene was tethered with a hydroxy group, the corresponding oxysulfenylation proved to be useful for the formation of a functionalized heterocycle. For example, 2-allylphenol (**2i**) was treated with sulfonyl hydrazide **1a** and 20 mol% iodine to give 2,3-dihydrobenzofuran **4s** in 87% yield (eqn (5)).



(5)

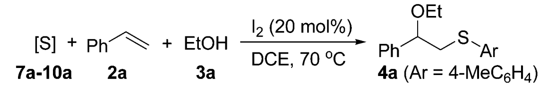
In sharp contrast, treatment of TsNHNHCOPh (**6a**), an *N′*-substituted sulfonyl hydrazide, with styrene (**2a**), ethanol (**3a**), and 20 mol% iodine did not give β-alkoxy sulfide **4a** at all. This result suggests that the $NHNH_2$ group is essential for the sulfonyl hydrazide to serve as an effective sulfenylating agent in the three-component oxysulfenylation reaction.

Sulfonyl hydrazide **1a** was demonstrated by previous studies to decompose in ethanol to give disulfide **7a**, sulfonothioate **8a**, sulfinic acid **9a**, and sulfinate ester **10a** (eqn (6)).[9b] Each of these decomposition products of sulfonyl hydrazide **1a** was treated with styrene (**2a**), ethanol (**3a**), and 20 mol% iodine, and β-alkoxy sulfide **4a** was obtained in a yield ranging from 0 to 40%, which is much lower than that for the corresponding reaction with sulfonyl hydrazide **1a** (88%, Table 2, entry 1). These results indicate that it is unlikely for such decomposition



Scheme 1 Proposed major reaction pathway.

products of sulfonyl hydrazide **1a** to serve as major intermediates leading to β-alkoxy sulfide **4a**.



7a-10a	**4a** (Ar = 4-MeC$_6$H$_4$)
7a, ArSSAr	28%
8a, ArSO$_2$SAr	40%
9a, ArSO$_2$H	Trace
10a, ArSO$_2$Et	0%

(6)

According to the above experimental results and previous relevant studies,[1,5h,9b] we propose the major reaction pathway depicted in Scheme 1 for the iodine-catalyzed three-component oxysulfenylation of alkenes with sulfonyl hydrazides and alcohols. Sulfonyl hydrazide **1** reacts with iodine to yield sulfenyl iodide **12**,[9b] electrophilic addition of which to alkene **2** gives thiiranium ion **11**.[5h,13] Subsequently, ring-opening of thiiranium ion **11** ($R^4 = H$) with alcohol **3** results in the formation of β-alkoxy sulfide **4**, and the regioselectivity is determined by the steric and electronic properties of the R^2 and R^3 groups.[1,5h] When a 1,1-disubstituted alkene serves as the substrate, thiiranium ion **11** ($R^3 = H$) is bulky and prefers to eliminate HI to give vinyl thioether **5**. In these steps, iodine has been converted to HOI and HI, the two of which react to give water and regenerate iodine to continue the catalytic cycle.

In summary, we have developed, for the first time, an efficient three-component oxysulfenylation reaction of alkenes with sulfonyl hydrazides and alcohols. In the presence of 20 mol% iodine, a range of aryl- and alkylsulfonyl hydrazides smoothly reacted with alkenes and alcohols to give structurally diverse β-alkoxy sulfides in good to excellent yields. It is noteworthy that the reaction tolerated a variety of functional groups such as alkoxy, fluoro, chloro, bromo, iodo, nitro, and nitrile groups and that water and molecular nitrogen were generated as environmentally benign byproducts. Moreover, a plausible major reaction pathway involving thiiranium ion intermediates has been proposed for the three-component oxysulfenylation reaction.

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12 The reaction mixture turned purple, and it suggested that iodine was generated from NIS.

13 Electrospray ionization (ESI) mass spectrometric analysis of the iodine-catalyzed reaction mixture of sulfonyl hydrazide **1a**, styrene (**2a**), and ethanol (**3a**) permitted us to assign thiiranium ion **11a** (R^1 = 4-MeC$_6$H$_4$, $R^2 = R^3 = H$, R^4 = Ph) according to the high resolution mass data [HRMS (ESI) calcd for $C_{15}H_{15}S^+$ 227.0889, found 227.0890].