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Metal-free oxysulfenylation of alkenes with 1-(arylthio)pyrrolidine-2,5-diones and alcohols†

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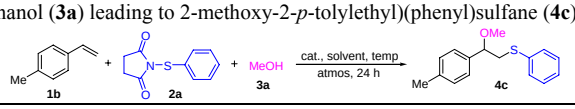
β-Alkoxy sulfides are widely used as the versatile building blocks in organic synthesis. Therefore, it is highly desirable to develop a convenient and efficient method for oxysulfenylation of alkenes. In this communication, an easy and efficient metal-free approach to *β*-alkoxy sulfides has been developed. The protocol uses readily available 1-(arylthio)pyrrolidine-2,5-diones and alcohols as the oxysulfenylating agents, chloroform as the solvent, no ligand, additive and exclusion of air were required. Therefore, the present method provides a useful strategy for synthesis of β-alkoxy sulfides.

Aryl sulfides are widely used in material sciences and biology, especially in the pharmaceutical area,[1] in which β-alkoxy sulfides act as the versatile building blocks in organic synthesis.[2] Recently, difunctionalization of alkenes causes much attention, and diverse molecules were prepared via this strategy under transition metal mediated and metal-free conditions,[3] so the difunctionalization method provides opportunity for oxysulfenylation of alkenes. In the sulfenylation of organic compounds, the sulfenylating agents are a key factor, and the common chemicals include disulfides,[4] sulfenamides,[5] sulfenyl halides,[6] sulfenate esters,[7] methyl(bismethylthio)sulfonium salts,[8] and dimethyl(methylthio)sulfonium salts.[9] Unfortunately, some of them are not readily prepared, and isolated and preserved, and some drawbacks occurred in oxysulfenylation of alkenes such as limited substrate scope, formation of byproducts unfriendly to the environment. Recently, Tian and co-workers have developed an interesting and efficient approach to β-alkoxy sulfides by using sulfonyl hydrazides in the presence of iodine.[10] 1-(Arylthio)pyrrolidine-2,5-diones are the readily available and handing arylthiating reagents.[11] Very recently, we have developed iron or boron-catalyzed C-H arylthiolation of phenols and arylamines with 1-(arylthio)pyrrolidine-2,5-diones.[12] It is known to all that a metal-free reaction is environmentally friendly and highly desirable because the protocol avoids residue of toxic transition metals in the products.[13] Herein, we report a simply and efficient metal-free oxysulfenylation of alkenes.

At first, reaction of 1-methyl-4-vinylbenzene (**1b**) with 1-(phenylthio)pyrrolidine-2,5-dione (**2a**) and methanol (**3a**) leading to 2-methoxy-2-*p*-tolylethyl)(phenyl)sulfane (**4c**) was applied as the model to screen reaction conditions including solvents, temperature and amount of alcohol under metal-free conditions (Table 1). To our delight, the reaction was successfully performed by using 5.0 equiv of methanol (relative to amount of **1b**) in the absence of catalyst in $CHCl_3$ at 80 °C, and the corresponding product **4c** was obtained in 52% yield (entries 1). When 10 equiv of methanol was used, a 93% yield was provided (entries 2). Reaction at a lower temperature led to a lower yield (entry 3). The similar yields were afforded when the reaction was carried out in the presence of 20.0 equiv of methanol or at higher temperature (entries 4 and 5). After screening of solvents (entries 6-14), we found that $CHCl_3$ was a suitable solvent. Several common catalysts were investigated (entries 15-19), and the results showed that yields were lower than the one under metal-free condition (entry 2). When air in the tube was displaced with nitrogen atmosphere, a 92% yield was provided (entry 20). Therefore, nitrogen atmosphere was not necessary for the reaction in the sealed Schlenk tube.

Table 1 Optimization of conditions on reaction of 1-methyl-4-vinylbenzene (**1b**) with 1-(phenylthio)pyrrolidine-2,5-dione (**2a**) and methanol (**3a**) leading to 2-methoxy-2-*p*-tolylethyl)(phenyl)sulfane (**4c**)[a]



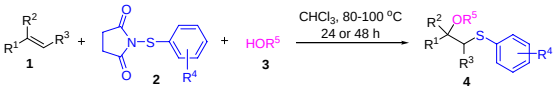
Entry	Cat.	Solvent	Temp (°C)	Yield (%)[b]
1[c]	-	$CHCl_3$	80	52
2	-	**$CHCl_3$**	**80**	**93**
3	-	$CHCl_3$	60	60
4[d]	-	$CHCl_3$	80	93
5	-	$CHCl_3$	100	93
6	-	CH_2Cl_2	80	90
7	-	DCE	80	89
8	-	Toluene	80	35
9	-	EtoAc	80	58
10	-	Dioxane	80	25
11	-	THF	80	70
12	-	CH_3CN	80	48
13	-	DMF	80	76

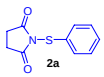
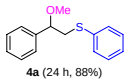
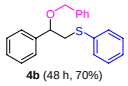
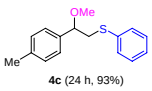
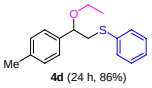
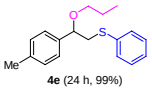
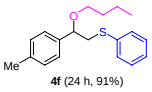
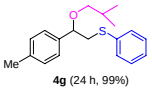
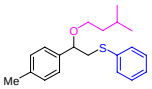
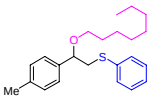
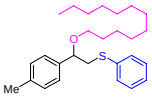
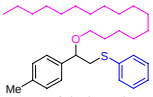
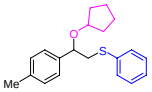
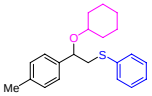
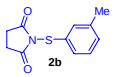
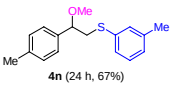
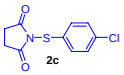
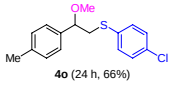
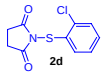
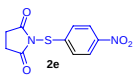
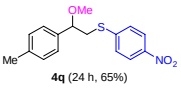
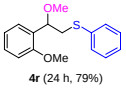
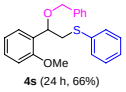
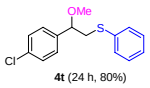
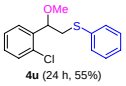
14	-	DMSO	80	82
15	$FeCl_3$	$CHCl_3$	80	87
16	$Cu(OAc)_2$	$CHCl_3$	80	28
17	CuCl	$CHCl_3$	80	56
18	$Pd(OAc)_2$	$CHCl_3$	80	30
19	$BF_3{\cdot}OEt_2$	$CHCl_3$	80	68
20[e]	-	$CHCl_3$	80	92

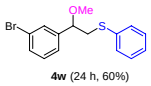
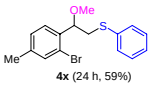
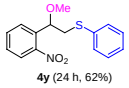
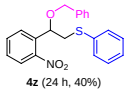
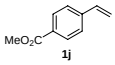
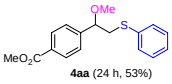
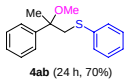
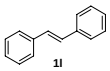
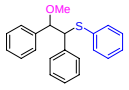
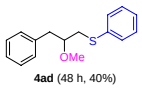
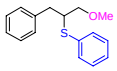
[a] Reaction conditions: 1-methyl-4-vinylbenzene (**1a**) (0.2 mmol), 1-(phenylthio)pyrrolidine-2,5-dione (**2a**) (0.3 mmol), methanol (**3a**) (2.0 mmol), anhydrous solvent (1.0 mL), temperature (60-100 °C), reaction time (24 h) in a sealed Schlenk tube. [b] Isolated Yield. [c] 5.0 equiv of MeOH was used. [d] 20.0 equiv of MeOH was used. [e] Nitrogen atmosphere.

After having the optimized reaction conditions, we investigated the scope for oxysulfenylation of alkenes (**1**) with 1-(arylthio)pyrrolidine-2,5-diones (**2**) and alcohols (**3**). For alkenes **1a-j**, styrenes containing electron-donating groups exhibited higher reactivity than those containing electron-withdrawing groups on the phenyl ring. 1-(Prop-1-en-2-yl)benzene (**1k**) also gave 70% yield (entry 28). The oxysulfenylation of styrenes exhibited high regioselectivity (entries 1-28) because formation of benzylic carbonium ion was favorable in Scheme 1. For internal alkene **1l**, its reactivity was inferior to terminal alkenes (entry 29). 1-Allylbenzene (**1m**) afforded two isomers (**4ad** and **4ad'**) for the difference of addition position (entry 30). Reaction of 3,4-dihydro-2*H*-pyran (**1n**) with 1-(phenylthio)pyrrolidine-2,5-dione (**2a**) and methanol (**3a**) gave **4ae** in 41% yield with a pair of diastereoisomers appearing (ratio = 1.7: 1) (see NMR in Supporting Information) (entry 31). For 1-(arylthio)pyrrolidine-2,5-diones (**2**), **2a** displayed higher reactivity than **2b-e**. For example, 1.5 equiv of **2a** was required when **2a** was used as the sulfenylating agent, but 2.5 equiv of **2a-e** had to be added in order that the reactions completed with **2b-e** as the sulfenylating agents. For alcohols (**3**), the secondary alcohols (entries 12 and 13) showed slightly weak reactivity than the primary alcohols, so extension of time and elevation of temperature were required. The oxysulfenylation of alkenes (**1**) with 1-(arylthio)pyrrolidine-2,5-diones (**2**) and alcohols (**3**) could tolerate some functional groups including C-Cl bond (entries 15, 16, 20 and 21), nitro (entries 17 and 25), ester (entry 27), ether (entries 18 and 19), C-Br bond (entries 22 and 23), and *O*-heterocycle (entry 31).

Table 2 Oxysulfenylation of alkenes (**1**)[a]

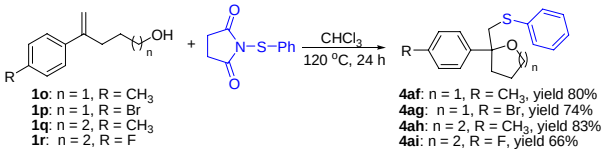


Entry	1	2	4 (Time, Yield[b])
1			 4a (24 h, 88%)
2	**1a**	**2a**	 4b (48 h, 70%)
3		**2a**	 4c (24 h, 93%)
4	**1b**	**2a**	 4d (24 h, 86%)
5	**1b**	**2a**	 4e (24 h, 99%)
6	**1b**	**2a**	 4f (24 h, 91%)
7	**1b**	**2a**	 4g (24 h, 99%)
8	**1b**	**2a**	 4h (24 h, 98%)
9	**1b**	**2a**	 4i (24 h, 95%)
10	**1b**	**2a**	 4j (24 h, 79%)
11	**1b**	**2a**	 4k (24 h, 85%)
12[c]	**1b**	**2a**	 4l (48 h, 73%)
13[c]	**1b**	**2a**	 4m (48 h, 64%)
14	**1b**	 2b	 4n (24 h, 67%)
15	**1b**	 2c	 4o (24 h, 66%)
16	**1b**	 2d	 4p (24 h, 73%)
17	**1b**	 2e	 4q (24 h, 65%)
18	 1c	**2a**	 4r (24 h, 79%)
19	**1c**	**2a**	 4s (24 h, 66%)
20	 1d	**2a**	 4t (24 h, 80%)
21	 1e	**2a**	 4u (24 h, 55%)

22	 **1f**	**2a**	 **4v** (24 h, 64%)
23	 **1g**	**2a**	 **4w** (24 h, 60%)
24	 **1h**	**2a**	 **4x** (24 h, 59%)
25	 **1i**	**2a**	 **4y** (24 h, 62%)
26	**1i**	**2a**	 **4z** (24 h, 40%)
27[c]	 **1j**	**2a**	 **4aa** (24 h, 53%)
28[d]	 **1k**	**2a**	 **4ab** (24 h, 70%)
29[d]	 **1l**	**2a**	 **4ac** (24 h, 44%)
30[d]	 **1m**	**2a**	 **4ad** (48 h, 40%)  **4ad'** (48 h, 25%)
31[d]	 **1n**	**2a**	 **4ae** (24 h, 41%)

[a] Reaction conditions: without exclusion of air, alkene (**1**) (0.2 mmol), 1-(arylthio)pyrrolidine-2,5-dione (**2**) (0.3 mmol for entries 1-13, 18-26 and 28-31; 0.5 mmol for entries 14-17; 0.6 mmol for entry 27), alcohol (**3**) (4.0 mmol for entry 27; 2.0 mmol for the others), dry $CHCl_3$ (1.0 mL), temperature (80 °C), reaction time (24 or 48 h) in a sealed Schlenk tube. [b] Isolated yield. [c] **T**emperature (140 °C). [d] Temperature (100 °C).

We attempted the synthesis of furans and pyrans containing SPh by using the present method. As shown in Scheme 1, sulfenylation of **1o-r** with **2a** was performed well at 120 °C, and the target products (**4af-ai**) were obtained in 66-83% yields.

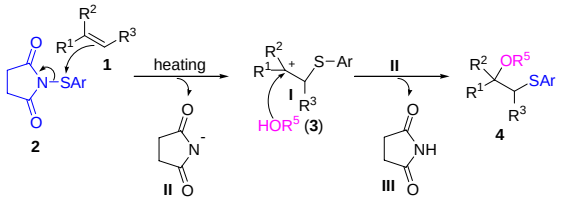


1o: n = 1, R = CH_3
1p: n = 1, R = Br
1q: n = 2, R = CH_3
1r: n = 2, R = F

4af: n = 1, R = CH_3, yield 80%
4ag: n = 1, R = Br, yield 74%
4ah: n = 2, R = CH_3, yield 83%
4ai: n = 2, R = F, yield 66%

Scheme 1 Synthesis of compounds **4af-ai** by using the present method.

A possible mechanism on the oxysulfenylation of alkenes is proposed in Scheme 2 according to the results above and the previous references.[4a,10,12] Treatment of alkene (**1**) with 1-(arylthio)pyrrolidine-2,5-dione (**2**) leads to carbonium ion intermediate **I** leaving **II** under heating condition, and electrophilic attack of alcohol (**3**) to **I** provides the target product (**4**) freeing succinimide (**III**).



Scheme 2 Possible mechanism for the oxysulfenylation of alkenes.

In summary, we have developed an easy, efficient and practical oxysulfenylation of alkenes, and the *β*-alkoxy sulfides were obtained in moderate to good yields. The protocol uses readily available 1-(arylthio)pyrrolidine-2,5-diones and alcohols as the oxysulfenylating reagents, no catalyst, ligand and additive were necessary, and the method can tolerate wide functional groups. Therefore, the present method will find wide application in synthesis of *β*-alkoxy sulfides.

Experimental section

General procedure for synthesis of compounds 4a-ai. A 25 mL Schlenk tube was charged with a magnetic stirrer, alkene (**1**) (0.2 mmol), 1-(arylthio)pyrrolidine-2,5-dione (**2**) (0.3 mmol for entries 1-13, 18-26 and 28-31; 0.5 mmol for entries 14-17; 0.6 mmol for entry 27 in Table 2), alcohol (**3**) (4.0 mmol for entry 27; 2.0 mmol for the others) and $CHCl_3$ (1.0 mL) were added to the tube. The tube was sealed, and the mixture was stirred at 80-140 °C till the reaction completed (TLC determination). The resulting mixture was cooled to room temperature, the solvent was removed by a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ ethyl acetate as eluent to give the desired target product (**4**).

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Notes and references

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