



Oxysulfonylation

Oxysulfonylation of Alkenes with Sulfonyl Hydrazides under Transition-Metal-Free Conditions

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Abstract: A novel method to synthesise β -keto sulfones is demonstrated by Brønsted acid promoted oxysulfonylation of alkenes with sulfonyl hydrazides under transition-metal-free

conditions. The reaction selectively affords structurally diverse $\beta\text{-keto}$ sulfones in good to excellent yields in a 9:1 mixture of acetonitrile/water.

Introduction

Alkenes as versatile and readily available building blocks are frequently employed in a broad range of chemical transformations.^[1] Among these transformations, 1,2-difunctionalization of carbon-carbon double bonds is one of the most powerful methods for the introduction of functional groups into target compounds.^[2] In this regard, the oxysulfonylation of alkenes has emerged as an ideal strategy for the synthesis of β -keto sulfones, which are very versatile compounds in organic chemistry because of their biological properties^[3] and widespread synthetic applications.^[4] While recent years have witnessed a number of reports on the construction of β -keto sulfones,^[5,6] most of them require transition-metal catalysts, expensive reagents, relatively complicated or harsh reaction conditions, and have only narrow substrate scopes. Therefore, a new general, convenient, green and sustainable approach for the oxysulfonvlation of alkenes is still necessary.

Sulfonyl hydrazides are readily accessible, and they have been employed to form hydrazones and heterocycles, which have versatile applications in organic chemistry.^[7] Moreover, sulfonyl hydrazides can be utilized as aryl sources through the cleavage of their carbon–sulfur bonds,^[8] and as sulfenylating agents through the cleavage of their sulfur–nitrogen bonds.^[9] In contrast, the reports that sulfonyl hydrazides are utilized as sulfonyl source are very few. Recently, Wang and co-workers described a synthesis of β -keto sulfones using sulfonyl hydrazides as sulfonyl sources.^[10] However, a toxic heavy metal catalyst is used, and the efficiency of the method is rather poor. Herein we report an efficient and green synthesis of β -keto sulfones by trifluoroacetic acid catalyzed oxysulfonylation of alkenes with sulfonyl hydrazides and dioxygene in a 9:1 mixture of acetonitrile/water [Equation (1)].

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Results and Discussion

Initially, treatment of benzenesulfonyl hydrazide (**1a**) with styrene (**2a**; 1.5 equiv.) and 10 mol-% of trifluoroacetic acid in nitromethane under air at 70 °C led to the formation of β -keto sulfone **3a** in 40 % yield (Table 1, Entry 1). Control experiments indicated that dioxygen is essential for the desired reaction, and a slightly better yield (46 %) was obtained from the reaction with dioxygen under normal pressure (Table 1, Entries 2 and 3).

Table 1. Optimization of the reaction conditions.[a]

PhSC	₂ NHNH ₂ +	Ph ·	catalyst, oxidant	
1a		2a		3a
Entry	Catalyst	Oxidant	Solvent	Yield [%] ^[b]
1	CF₃COOH	air	MeNO ₂	40
2	CF ₃ COOH	none	MeNO ₂	0
3	CF₃COOH	O ₂	MeNO ₂	46
4	CF ₃ COOH	0 ₂	dioxane	31
5	CF ₃ COOH	O ₂	toluene	0
6	CF ₃ COOH	0 ₂	MeCN	65
7	CF ₃ COOH	0 ₂	1,2-dichloroethane	27
8	CF ₃ COOH	O ₂	water	trace
9	CF₃COOH	O ₂	DMSO	49
10	CF₃COOH	O ₂	EtOH	53
11	CF₃COOH	02	MeCN/H ₂ O (9:1)	81
12	H_2SO_4	O ₂	MeCN/H ₂ O (9:1)	56
13	HCI	O ₂	MeCN/H ₂ O (9:1)	62
14	TsOH	O ₂	MeCN/H ₂ O (9:1)	70
15	tartaric acid	O ₂	MeCN/H ₂ O (9:1)	48
16	benzoic acid	0 ₂	MeCN/H ₂ O (9:1)	32
17 ^[c]	CF ₃ COOH	0 ₂	MeCN/H ₂ O (9:1)	70

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol-%), solvent (2.0 mL), oxidant (if any, 1 atm), 70 °C, 15 h. [b] Isolated yields. [c] CF₃COOH (5 mol-%).

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To improve the yield, we screened a range of common solvents and found that the use of acetonitrile led to the formation of β -keto sulfone **3a** in 65 % yield (Table 1, Entries 4–10). To our delight, the use of a 9:1 mixture of MeCN/H₂O dramatically enhanced the yield up to 81 % (Table 1, Entry 11). Replacment of trifluoroacetic acid by a few other Brønsted acids led to much lower yields (Table 1, Entries 12–15). Further efforts to decrease the amount of trifluoroacetic acid resulted in a lower yield (Table 1, Entry 17).

Encouraged by our preliminary findings, we investigated the substrate scope for the oxysulfonylation of sulfonyl hydrazides with styrene (**2a**). In the presence of 10 mol-% of trifluoroacetic acid and dioxygen under normal pressure, a range of arene-, and heteroarenesulfonyl hydrazides smoothly reacted with styrene to give structurally diverse β -keto sulfones in good to excellent yields (Table 2, Entries 1–9). It is noteworthy that either an electron-withdrawing or an electron-donating group was introduced into the β -keto sulfone product by employing an arene-sulfonyl hydrazide bearing such a group on the aromatic ring. Furthermore, alkanesulfonyl hydrazids also could smoothly react with styrene (**2a**) to give the corresponding β -keto sulfone **3***j*, and as expected, lower yields were obtained for the oxysulfonylation of styrene with less reactive sulfonyl hydrazides (Table 2, Entry 10).

Table 2. Oxysulfonylation of sulfonyl hydrazides with styrene (2a).^[a]

RSO ₂ NHNH ₂	+ Ph CF ₃ CO HeCN/ O ₂ (1 a	OH (10 mol-%) H ₂ O (9:1) tm), 70 °C, 15 h	
1	2a		3
Entry	1 , R	3	Yield [%] ^[b]
1	1a , Ph	3a	81
2	1b , 4-MeC ₆ H ₄	3b	83
3	1c , 4-MeOC ₆ H ₄	Зc	71
4	1d , 4-AcNHC ₆ H ₄	3d	72
5	1e , 4-FC ₆ H ₄	3e	74
6	1f, 4-CIC ₆ H ₄	3f	79
7	1g , 4-BrC ₆ H ₄	3g	70
8	1h, 2-naphthyl	3h	77
9	1i, 2-thienyl	3i	71
10	1j , Me(CH ₂) ₇	Зј	60

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), CF₃COOH (10 mol-%), MeCN/H₂O (9:1; 2.0 mL), O₂ (1 atm), 70 °C, 15 h. [b] Isolate yields.

A few other types of alkenes were examined in oxysulfonylation reactions with benzenesulfonyl hydrazide (**1a**) under the standard reaction conditions. Generally, reactions of arylethenes bearing electron-withdrawing groups (Cl, Br and CN) or electron-donating groups (Me and OMe) with benzenesulfonyl hydrazide proceeded smoothly and afforded the corresponding products in good to excellent yields (Table 3, Entries 1–7). 1-Vinylnaphthalene and 2-vinylnaphthalene both reacted well to afford the corresponding β -keto sulfones in good yields (Table 3, Entries 8–9). Nevertheless, the oxysulfonylation reaction was not applicable to less reactive alkylethenes such as 1octene (Table 3, Entry 10). Table 3. Oxysulfonylation of benzenesulfonyl hydrazide (1a) with alkenes.^[a]

PhSO ₂ NHNH ₂	+ 🖉 R	CF ₃ COOH (10 mol-% <u>MeCN/H₂O (9:1)</u> O ₂ (1 atm), 70 °C, 15	⁶⁾ 0 0 → R S Ph
1a	2		3
Entry	2 , R	3	Yield [%] ^[b]
1	2b , 4-MeC _e	;H ₄ 3k	81
2	2c , 4-MeOC	₆ H ₄ 3I	60
3	2d , 4-ClC ₆	H ₄ 3m	85
4	2e , 4-BrC ₆	H ₄ 3n	82
5	2f , 4-NCC ₆	H ₄ 30	59
7	2h , 2-ClC ₆	H ₄ 3p	79
8	2i , 1-napht	hyl 3q	70
9	2j , 2-napht	hyl 3r	67
10	2k ,CH ₃ (CH	₂) ₅ 3s	0

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), CF₃COOH (10 mol-%), MeCN/H₂O (9:1; 2.0 mL), O₂ (1 atm), 70 °C, 15 h. [b] Isolate yields.

It is known that the generation of sulfonyl radicals is initiated by oxidation of sulfonyl hydrazides to give diazenes in the presence of dioxygen.^[11] Therefore, the reaction mechanism may be a radical pathway. When a stoichiometric amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyl oxyl, a well-known radicalcapturing species) was added to this reaction mixture, no reaction took place at all [Equation (2)]. This control experiment supports the aforementioned hypothesis.



According to our experimental results and the generally accepted mechanism for sulfonyl radical formations from sulfonyl hydrazides,^[12] we propose the following reaction pathway for the trifluoroacetic acid catalyzed oxysulfonylation reaction of alkenes and sulfonyl hydrazides. As shown in Scheme 1, it is presumed that the generation of sulfonyl radicals **7** is initiated by oxidation of sulfonyl hydrazides to give diazene **5** in the



Scheme 1. Proposed reaction pathways.





presence of dioxygen and trifluoroacetic acid. Thereafter, addition of sulfonyl radical **7** to alkenes produces the reactive alkyl radical **8**, which can be trapped by dioxygen under the present conditions and forms the peroxy radical **9**. Finally, this peroxy radical **9** couples with an HOO[•] species, produces tetroxide **10**, which decomposes, and furnishes product **3**.

Conclusions

We have developed an efficient and green method to synthesise β -keto sulfones from alkenes and sulfonyl hydrazides. In the presence of 10 mol-% of trifluoroacetic acid, a range of alkenes smoothly underwent oxysulfonylation with sulfonyl hydrazides and dioxygen in a 9:1 mixture of acetonitrile/water to give structurally diverse β -keto sulfones in moderate to excellent yields. Studies of the detailed mechanism of this process and its application are ongoing.

Experimental Section

General Procedure for the Oxysulfonylation of Alkenes with Sulfonyl Hydrazides: To a solution of sulfonyl hydrazide 1 (0.20 mmol) in MeCN/H₂O (9:1; 2.0 mL), under oxygen (1 atm) at room temperature, were added alkene 2 (0.30 mmol) and TFA (2.2 mg, 0.020 mmol). The mixture was stirred at 70 °C for 20 h, cooled to room temperature, and directly purified by preparative thin layer chromatography on silica gel, eluting with petroleum ether/ethyl acetate (10:1 to 3:1), to give compound **3**.

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