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Letter

Dioxygen-Triggered Oxo-Sulfonylation of Hydrazones

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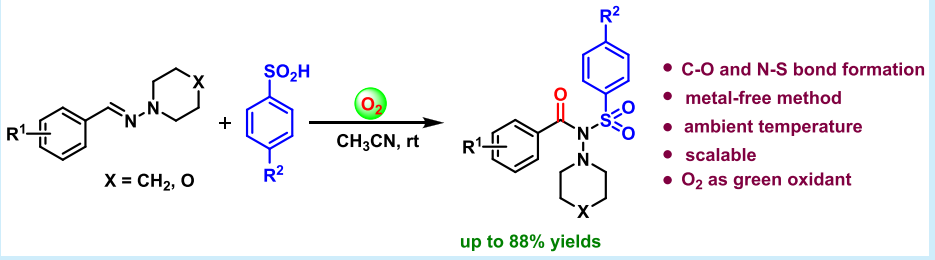

ABSTRACT: A simple and highly efficient method for the oxo-sulfonylation of aldehyde-derived hydrazones has been developed using sulfinic acid as a source of sulfonyl group and oxygen as a green oxidant under metal-free conditions at room temperature. The present C−O and N−S bond-forming difunctionalization strategy affords diversely functionalized *N*-acylsulfonamides in good yield. Experimental results suggest a radical mechanistic pathway of the present reaction.

Difunctionalization is a powerful and straightforward strategy for the introduction of two functional groups in a single reaction to synthesize highly functionalized organic compounds.[1] It has drawn the significant interest of the synthetic organic community due to its wide synthetic utility in chemical synthesis. Oxo-sulfonylation is an important approach for the difunctionalization of various types of systems to introduce oxo and sulfonyl groups.[2] In this context, alkenes and alkynes have been extensively studied for oxo-sulfonylation to form C−O and C−S bonds.[3] Although a number of strategies for the oxo-sulfonylation of alkenes and alkynes have been developed, the metal-free di-oxygen-triggered method is the most practical and efficient technique because oxygen is a readily available, nontoxic, and ecosustainable oxidant and reagent. Recently Lei and coworkers reported convenient dioxygen activation-mediated methods for the oxo-sulfonylation of alkenes and alkynes under transition-metal-free conditions.[4] Despite these significant achievements in the direct construction of C−O and C−S bonds, C−O and N−S bond-forming oxo-sulfonylation is rare and highly demanding.[5] It is worth mentioning that molecules with C−O and N−S bonds show great importance in medicinal chemistry.[6−9] We envisioned that the C═N group in hydrazone derivatives might be explored for oxo-sulfonylation to construct a moiety having consecutive O−C, C−N, and N−S bonds. To the best of our knowledge, there is no report on the oxo-sulfonylation of hydrazones for the synthesis of *N*-acylsulfonamides.

N-Acylsulfonamides are important carboxylic acid bioisosteres[6] that are present in a variety of currently marketed drugs and pharmacological tools, as shown in Figure 1.[7] A number of anti-hepatitis C drugs like beclabuvir,[8a] asunaprevir,[8a] danoprevir,[8b] and paritaprevir[8c] contain an *N*-acylsulfonamide

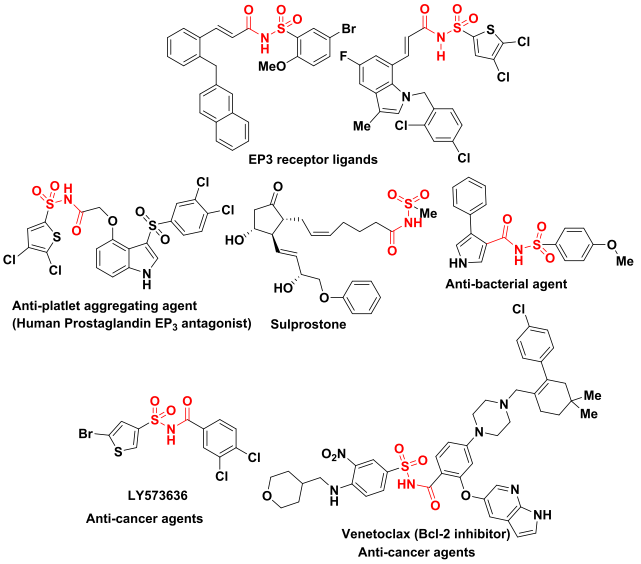

Figure 1. Some biologically active compounds containing the acyl sulfonamide moiety.

group in their core structures. It is also present in many therapeutic agents,[9a] prostaglandin E receptor 3 (EP3)

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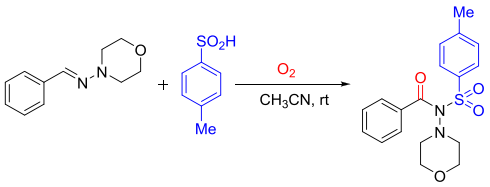
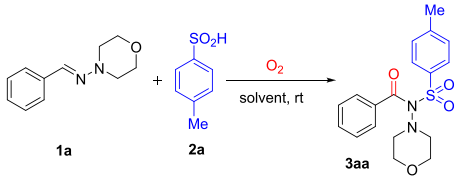
receptor antagonists,[9b] prostacyclin receptor agonists,[9c] and HCV NS5B polymerase allosteric inhibitors.[9d] Therefore, the development of novel and reliable synthetic methods for the synthesis of *N*-acylsulfonamides derivatives has gained significant interest of modern synthetic organic chemists.[10] Hydrazones are attractive synthetic intermediates in organic chemistry.[11] As a part of our ongoing research on hydrazones[12] and also considering the high importance of C−O and N−S bond forming reactions, herein we report a simple and straightforward method for the synthesis of *N*-acylsulfonamide derivatives through the oxo-sulfonylation of aldehyde-derived hydrazones using O_2 as a green oxidant[13] under metal-free conditions at ambient temperature (Scheme 1).

Scheme 1. Synthesis of *N*-Acylsulfonamide from Hydrazone



We examined the reaction taking (*E*)-*N*-morpholino-1-phenylmethanimine (**1a**) as a model substrate and 4-methylbenzenesulfinic acid (**2a**) as a sulfonylating agent. Initially the reaction was carried out in the presence of 1.5 equiv of **2a** under an O_2 atmosphere in 1,2-DCE at room temperature. Delightfully, *N*-morpholino-*N*-tosylbenzamide (**3aa**) was obtained in 65% yield after 10 h (Table 1, entry 1). In addition, a very low amount (12%) of benzaldehyde was formed in the reaction medium due to the hydrolysis of hydrazone. No further improvement of the reaction yield was found, even after 16 h. Encouraged by this initial result, the reaction was performed under different conditions for the further improvement of the reaction yield, and the results are summarized in Table 1. During screening of different solvents like 1,4-dioxane, CH_3CN, THF, toluene, EtOH, DMF, and DMSO for the present reaction (Table 1, entries 2−8), CH_3CN was found to be a better solvent for this transformation, affording the desired product **3aa** in 82% yield (Table 1, entry 3). The desired product was obtained in 47% yield under air (Table 1, entry 9). Next, the reaction was performed using different oxidants (1 equiv) such as $K_2S_2O_8$ and *tert*-butyl hydroperoxide (TBHP) under open air, but lower yields were observed (Table 1, entries 10 and 11). No significant increment of the reaction yield was found with increasing the loading of **2a** (2 equiv) and reaction temperature (80 °C), but a decrease in yield was obtained in the presence of 1 equiv of **2a** (Table 1, entries 12 and 13). Finally, the optimized reaction condition was achieved using 1.5 equiv of **2a** in CH_3CN at ambient temperature under an O_2 atmosphere for 10 h (Table 1, entry 3). Moreover, other sulfonylating agents like *p*-toluenesulfonyl chloride, sodium *p*-toluenesulfinate, and *p*-toluenesulfonic acid were not effective for this transformation under an O_2 atmosphere.

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

entry	oxidant	solvent (2 mL)	yield (%)
1	O_2	1,2-DCE	65
2	O_2	1,4-dioxane	nr
3	**O_2**	**CH_3CN**	**82**
4	O_2	THF	58
5	O_2	toluene	37
6	O_2	EtOH	nr
7	O_2	DMF	10
8	O_2	DMSO	nr
9	air	CH_3CN	47
10	$K_2S_2O_8$ (1 equiv)	CH_3CN	58
11	TBHP (1 equiv)	CH_3CN	52
12	O_2	CH_3CN	61[b], 79[c]
13	O_2	CH_3CN	57[d]

[a]Reaction conditions: 0.2 mmol of **1a**, 1.5 equiv of **2a** in the presence of O_2 in 2 mL of solvent at room temperature for 10 h. [b]Reaction was carried out using 1 equiv of **2a**. [c]Reaction was carried out using 2 equiv of **2a**. [d]Stirred at 80 °C.

After getting the optimized reaction conditions, we explored the substrate scope of the present reaction by varying the substituents of the hydrazone derivatives, and the results are summarized in Scheme 2. Benzaldehyde-derived 4-morpholinyl hydrazone containing electron-donating substituents like −Me and −OMe at the C-4 position of the phenyl ring successively reacted with 4-methylbenzenesulfinic acid (**2a**) to provide the desired products in good yield (**3ba** and **3ca**). Moreover, the structure of 4-methyl-*N*-morpholino-*N*-tosylbenzamide (**3ba**) was confirmed by the single-crystal X-ray analysis. Halogen-substituted (−F, −Cl, and −Br) hydrazone derivatives gave satisfactory yields of the products (**3da**−**fa**). The reaction showed good tolerance toward a variety of electron-withdrawing substituents like −CN and $-NO_2$ (**3ga** and **3ha**). Hydrazone derivatives of 4-hydroxybenzaldehyde and benzo[*d*][1,3]dioxole-5-carbaldehyde (**1i** and **1j**) also participated in the present reaction to furnish the desired products in good yield (**3ia** and **3ja**). *N*-Morpholino-1-(naphthalen-2-yl)-methanimine (**1k**) also reacted very well (**3ka**). 1-Piperidinyl hydrazones of different substituted benzaldehydes gave the desired products in good yield under the optimized reaction conditions (**3la**−**oa**). However, benzylidenehydrazine (**1p**), *N*,1-diphenylmethanimine (**1q**), and 1-cyclohexyl-*N*-morpholinomethanimine (**1r**) failed to produce the desired products under the present reaction conditions. Hydrazones of 1-methyl-1-phenylhydrazine produced benzamides under the optimized reaction conditions (**4a**−**d**). In that case, the desired *N*-acylsulfonamides were not formed. This may be due to the steric crowding between the sulfonyl group and the methyl/phenyl group of hydrazone. However, we were unable to cleave the morpholino or piperidine group of the desired products. To show the practical applicability of this present protocol, the gram-scale reaction was also performed in the usual laboratory setup by taking (*E*)-*N*-morpholino-1-phenylmethanimine (**1a**) on a 5 mmol scale. The reaction afforded the corresponding *N*-morpholino-*N*-tosylbenzamide (**3aa**) in 77% yield.

Subsequently, we explored the present reaction by investigating the different substituents of arylsulfinic acid (**2**). Simple benzenesulfinic acid, 4-methoxy, and 4-chloro benzenesulfinic acid smoothly reacted with (*E*)-*N*-morpholino-1-phenylmethanimine (**1a**) to produce the corresponding

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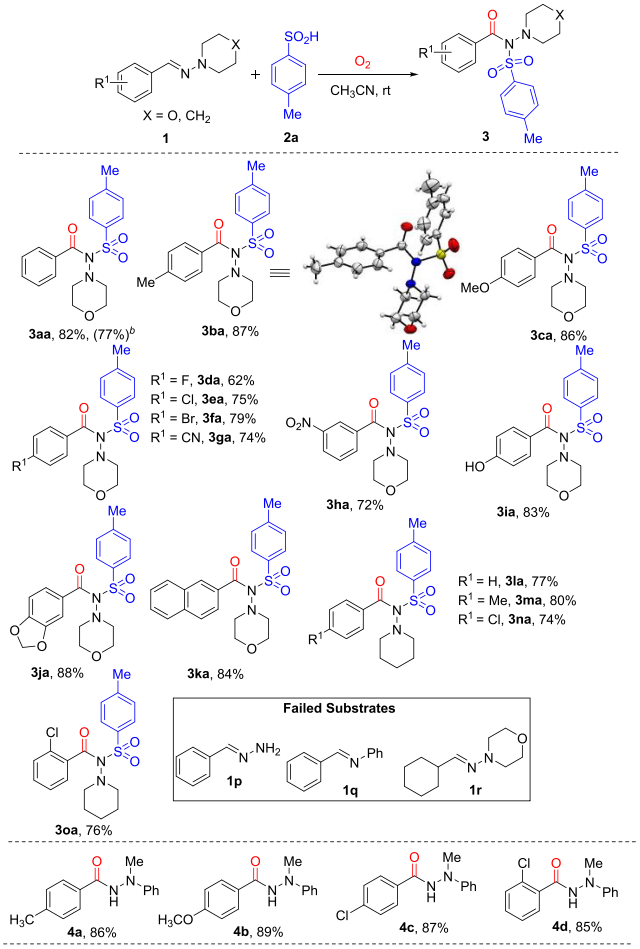
Scheme 2. Substrate Scope of the Present Method[a]

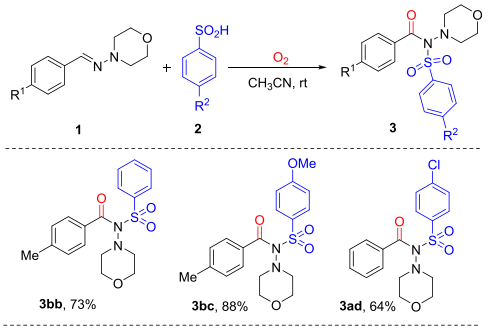


[a]Reaction conditions: 0.2 mmol of **1**, 1.5 equiv of **2a** in the presence of O_2 in 2 mL of CH_3CN at room temperature for 10 h. [b]5 mmol scale.

sulfonylated products (**3bb**, **3bc**, and **3ad**) in moderate to good yield (Scheme 3).

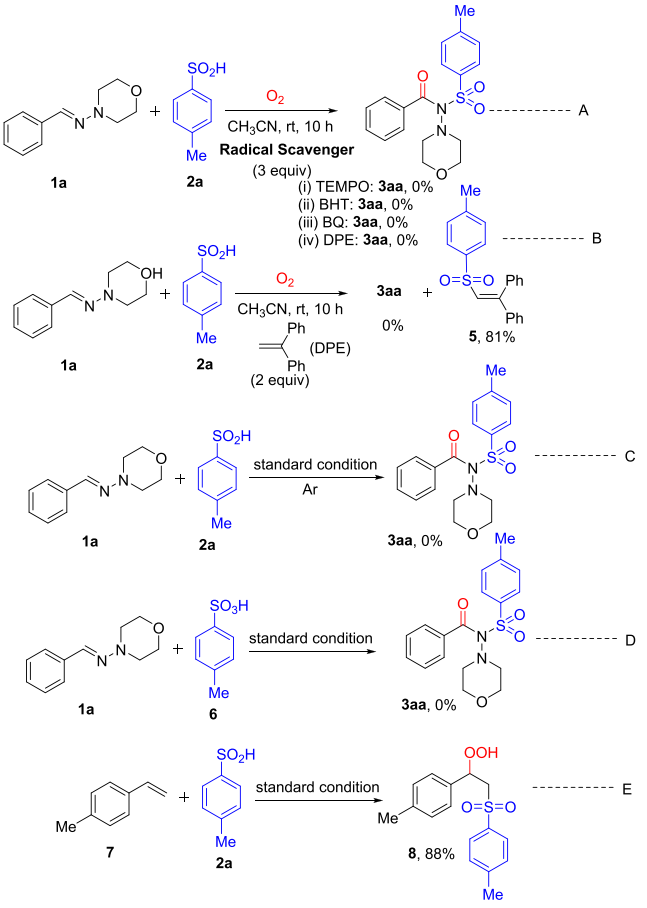
A few control experiments were carried out to propose the plausible mechanistic pathway of the reaction (Scheme 4). The present reaction did not proceed at all in the presence of radical scavengers like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), 1,4-benzoquinone (BQ), and 1,1-diphenylethylene (DPE) (Scheme 4, eq A), indicating the radical pathway of the reaction. Moreover, the formation of sulfonyl trapping product **5** with 1,1-diphenylethylene strongly suggests the radical mechanism (Scheme 4, eq B). The reaction did not take place under an argon atmosphere, which implies that the molecular O_2 might be responsible for oxygenation (Scheme 4, eq C). However, we were unable to perform the $^{18}O_2$ experiment under our present laboratory setup. Moreover, oxo-sulfonylation did not occur using sulfonic acid (**6**) (Scheme 4, eq D). This result suggests that the reaction did not proceed through the formation of sulfonic acid from sulfinic acid via aerial oxidation. 4-Methylstyrene (**7**) formed 1-((2-hydroperoxy-2-(*p*-tolyl)-ethyl)sulfonyl)-4-methylbenzene (**8**) under the present reaction conditions (Scheme 4, eq E). This result supports the formation of intermediate **C**.

Scheme 3. Substrate Scope of Sulfinic Acids[a]



[a]Reaction conditions: 0.2 mmol of **1**, 1.5 equiv of **2** in the presence of O_2 in 2 mL of CH_3CN at room temperature for 10 h.

Scheme 4. Control Experiments



On the basis of the control experimental results and literature reports,[4] a tentative mechanistic pathway is proposed in Scheme 5. Initially, 4-methylbenzenesulfinic acid generates an oxygen-centered sulfonyl radical **I** in the presence of molecular O_2, which resonates with sulfonyl radical **II**.[4] Next, the addition of sulfonyl radical (**II**) takes place at the iminium nitrogen center of (*E*)-*N*-morpholino-1-phenylmethanimine (**1a**) to form the intermediate **A**. Subsequently, intermediate **A** reacts with dioxygen to form intermediate **B**, which is subsequently converted to intermediate **C** via the hydrogen radical abstraction from sulfinic acid (**2a**).[4] Finally, the desired product *N*-morpholino-*N*-tosylbenzamide (**3aa**) is formed through the elimination of water from the intermediate **C**.

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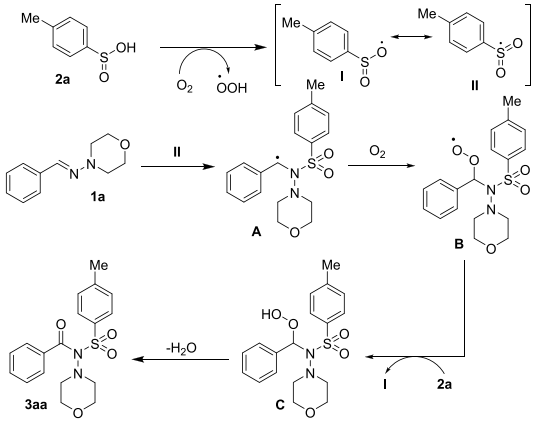
Scheme 5. Plausible Mechanistic Pathway



In summary, we have developed an environmentally friendly oxo-sulfonylation strategy for the synthesis of *N*-acylsulfonamide derivatives from aldehyde-derived hydrazones using sulfinic acid as a source of sulfonyl group under an O_2 atmosphere. The present difunctionalization strategy shows a newer way of formation of C−O and N−S bonds in a single operation. Mild and metal-free reaction conditions, the use of dioxygen as a nontoxic oxidant, and the availability of the starting material and ambient temperature make this protocol very efficient and practical. To the best of our knowledge, this is the first oxo-sulfonylation protocol of the hydrazone moiety. We believe that this unique protocol holds significant potential for the synthesis of valuable *N*-acylsulfonamides in chemical and pharmaceutical industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00759.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1985106 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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