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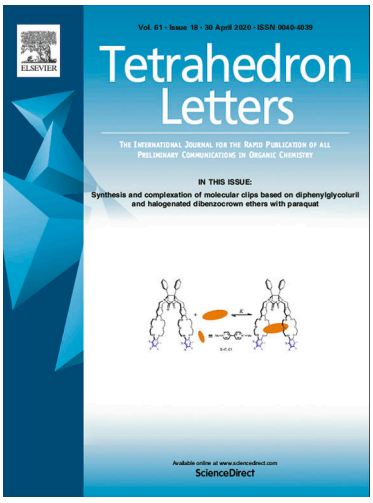

SO_2F_2-Mediated Deoxygenative C2-Sulfonylation of Quinoline N-Oxides with Sodium Sulfinates

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PII: S0040-4039(20)31085-6
DOI: https://doi.org/10.1016/j.tetlet.2020.152586
Reference: TETL 152586

To appear in: *Tetrahedron Letters*

Received Date: 24 August 2020
Revised Date: 10 October 2020
Accepted Date: 18 October 2020

Please cite this article as: Ai, C., Liao, X., Zhou, Y., Yan, Z., Lin, S., SO_2F_2-Mediated Deoxygenative C2-Sulfonylation of Quinoline N-Oxides with Sodium Sulfinates, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152586

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SO_2F_2-Mediated Deoxygenative C2-Sulfonylation of Quinoline N-Oxides with Sodium Sulfinates

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Sulfuryl fluoride

Metal-free

Oxidant-free

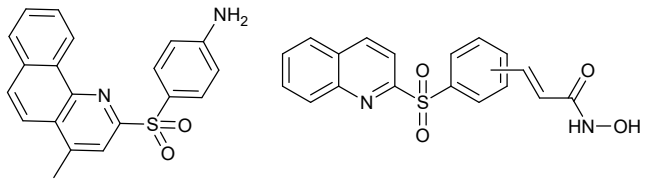
2-sulfonylquinolines

ABSTRACT

A mild and efficient method for deoxygenative C2-sulfonylation of quinoline N-Oxides in the presence of a base has been developed employing extremely inexpensive SO_2F_2 as an activator and sodium sulfinate as nucleophilic sulfonylation source. It is noteworthy that the reaction proceeded well under metal- and oxidant-free conditions to give a variety of 2-sulfonylquinolines in medium to good yields.

Introduction

In the past decades, C-H functionalization has become a highly attractive strategy for organic chemists, as it has been proved to be a powerful and versatile tool for installation of a series of functional groups through C-H bond activation.[1] By this approach the derivatization of quinolines at C2 or C8 position regioselectively can be realized in a relatively simple way.[2] *N*-heteroaromatic compounds with a sulfur moiety at side chain exhibit a broad range of physical, chemical and biological activities, and play important roles in agricultural, industrial and pharmaceutical chemistry (Fig. 1).[3] Traditionally, 2-sulfonyl



Antibacterial agents Antitumor agents

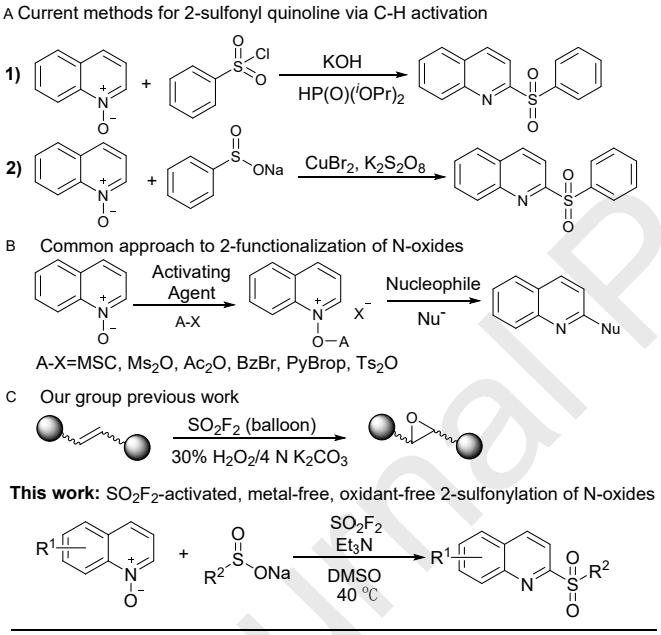
Fig 1. Examlpes of bioactive 2-sulfonylquinoline derivative molecules

N-heteroaromatic compounds are commonly synthesized by oxidation of corresponding sulfides or by alkylation of sulfinate salts.[4] Both methods suffer the following flaws: that the basic raw materials are often 2-halopyridines, and that most of which have a terrible odor.

In the past few years, significant achievements have been made for preparation of 2-sulfonylquinolines under transition-metal catalysis or metal-free conditions.[5] For instance, in 2015, Zhao and Chen developed a powerful strategy for the synthesis of sulfonylated quinolines from quinoline N-oxides and sulfonyl

chlorides via H-phosphonate-mediated C−H activation. [Scheme 1, A, 1)].[6] In 2016, the Han group reported an efficient and concise methodology to afford sulfonylated quinoline N-oxides via copper-catalyzed C-H activation with sodium sulfinate as the sulfonylation reagent [Scheme 1, A, 2)].[7] Meanwhile, the He group disclosed the hypoiodite-mediated C-H activation of quinoline N-oxides with sulfonyl hydrazides for direct synthesis of 2-sulfonyl quinolines. All the above reported methods are successful in conversion of quinoline *N*-oxides into the corresponding C2 sulfonylation products.[8] However, they still have disadvantages of using metal catalysis and oxidants, and requiring strictly anhydrous reaction conditions. Therefore, it is still a challenging task for chemists to develop mild, metal- and oxidant-free, and water-insensitive approaches for C2 sulfonylation of quinoline N-oxides.

Scheme 1. 2-functionalization of N-Oxides via C-H Activation

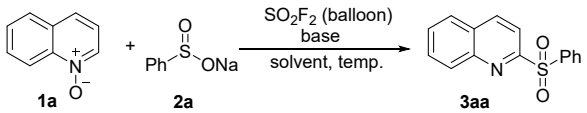


The development of C2 functionalization of N-oxide regioselectively can be traced back to 1936, in which M. Henze first achieved the target products with N-phenylbenzimidoyl chlorides as activator[9] (Scheme 1, B). On the other hand, sulfuryl fluoride gas (SO_2F_2) has been used as fumigant for a long time, and its application in organic synthesis only recently came into our eyes. In 2014, Sharpless revealed a new class of click chemistry based on sulfur(VI) fluoride exchange (SuFEx), which provides a fast and highly efficient way to effect chemical functionalization.[10] Sulfuryl fluoride is a cheap (0.1 US$ mol^{-1}) and stable reagent (currently, SO_2F_2 gas in a steel cylinder is commercially available in China). Since Sharpless' pioneering work on SuFEx-based click chemistry, sulfuryl fluoride has been widely used in other chemical conversion.[11] Very recently, Qin group reported a variety of SO_2F_2-mediated synthesis of chemical functional groups, including arylnitriles, ethenesulfonyl fluorides, arylcarboxylic acids, alkynes, and amides.[12] Meanwhile, our group recently reported an efficient SO_2F_2-mediated epoxidation of olefins with hydrogen peroxide (Scheme 1, C).[13] However, to the best of our knowledge, SO_2F_2 as an inexpensive reagent, has not yet been employed as an activator for deoxygenative C2 functionalization of quinoline N-oxides. Therefore, we envisioned that sulfuryl fluoride can serve as an activator and sodium sulfinate as a nucleophilic reagent to implement a one-pot synthesis of 2-sulfonyl quinolines. Herein, we report a metal- and oxidant-free, and mild SO_2F_2-mediated deoxygenative C2 sulfonylation of quinoline N-oxides.

Results and discussion

Our study started with the reaction of quinoline N-oxide (**1a**) and sodium benzenesulfinate (**2a**) under a SO_2F_2 atmosphere. Much to our delight, in the presence of Et_3N as a base, at room temperature for 16 h, the reaction smoothly proceeded to give the desired sulfonylation product **3aa** in a moderate yield (Table 1, entry 1). Encouraged by this result, we screened other solvents for the optimal conditions. DMF and dioxane showed negative effects just providing **3aa** in 36% and 30% yields, respectively (Table 1, entries 2-3). It is noteworthy that just trace 4-sulfonylquinoline was detected in these reactions. Further optimization of various bases was carried out, including Et_3N, DBU, DIPEA, K_2CO_3, Cs_2CO_3 and base-free (Table 1, entries 4-8). Results showed that Et_3N as a base exhibited higher efficiency compared with the others. Meanwhile, the best outcome of the reaction was observed when slightly elevating the reaction temperature to 40°C (Table 1, entry 9) with the formation of **3aa** in 82% yield.

Table 1. Optimization of the reaction conditions[a]



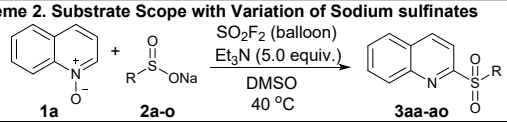
1a 2a 3aa

entry	solvent	base	temp.	yield[b]
1	DMSO	Et_3N	RT	60%
2	DMF	Et_3N	RT	36%
3	dioxane	Et_3N	RT	30%
4	DMSO	—	RT	13%
5	DMSO	DBU	RT	54%
6	DMSO	DIPEA	RT	20%
7	DMSO	Cs_2CO_3	RT	22%
8	DMSO	K_2CO_3	RT	25%
9	**DMSO**	**Et_3N**	**40 °C**	**82%**

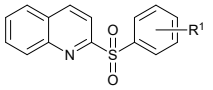
[a]Reaction conditions:**1a** (0.3 mmol), **2a** (0.9 mmol),1.5 mmol of base, 2.5 mL of solvent ,under SO_2F_2 atmosphere (using a balloon combined with syringe needle), at room temperature for 16 h.
[b]isolated yield.

With the optimum conditions (Table 1, entry 9) in hand, we subsequently explored the substrate scope. A set of sodium sulfinates including aromatic and aliphatic sulfinates were evaluated in the reactions with quinoline N-oxide (**1a**). Results are shown in Scheme 2. Reactions of o-methyl, p-methyl, p-methoxy, and p-tert-butyl benzenesulfinates proceeded well to furnish corresponding products (**3ab**-**3ae**). That o-substituted sulfinates gave a relatively low yield suggests steric factor has a negative effect on the conversion of starting material. Halogen (-F, -Br, -Cl) on the benzene ring of benzenesulfinates could be tolerated well, all affording targeted products in over 70% yields (**3af**-**3ah**). Fortunately, benzenesulfinates containing electron-withdrawing groups were also suitable substrates and produced desired compounds (**3ai**-**3ak**) in acceptable yields ranging from 48%-64%. When sodium thiazole sulfonate used, a good yield was received (**3kl**). In the end, besides the aromatic sulfinates, several aliphatic sulfinates were smoothly converted to desired products in 70%, 65%, and 71% yields, respectively (**3am**, **3an**, **3ao**).

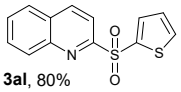
Scheme 2. Substrate Scope with Variation of Sodium sulfinates



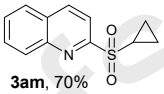
1a 2a-o 3aa-ao



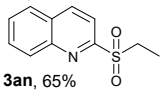
R¹= H **3aa**, 82%; p-Me **3ab**, 78%; o-Me **3ac**, 58%; p-^{t}Bu **3ad**, 65%; p-OMe **3ae**, 64%; p-F **3af**, 72%; p-Cl **3ag**, 73%; p-Br **3ah**, 75%; p-CF_3 **3ai**, 64%; p-NO_2 **3aj**, 48%; m-NO_2 **3ak**, 63%



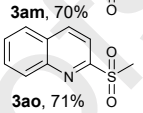
3al, 80%



3am, 70%



3an, 65%

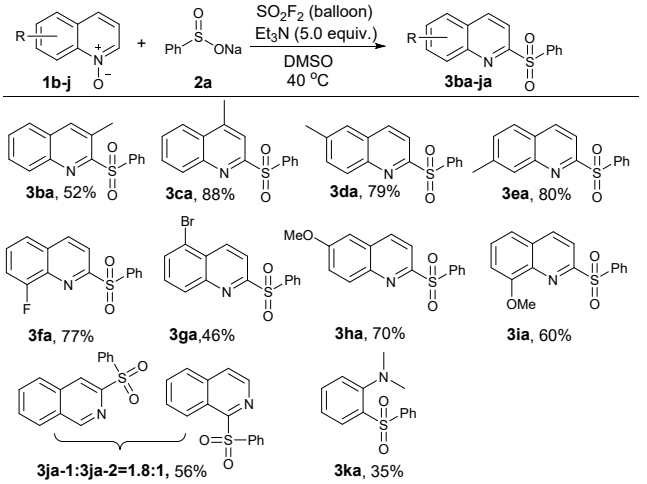


3ao, 71%

[a]General conditions: **1a** (0.3 mmol), **2** (0.9 mmol),1.5 mmol of Et_3N, under SO_2F_2 atmosphere (using a balloon combined with syringe needle), for 16 h at 40°C. [b]isolate yields

On the other hand, the compatibility of the functional groups on the quinoline N-oxides were also tested in the reaction. As shown in Scheme 3, using sodium benzenesulfinate (**2a**) as the model substrate, a wide range of substituted quinoline N-oxides were smoothly transformed to diverse sulfonyl-decorated quinolines. 3-, 4-, 6-, 7-methyl-substituted quinoline N-oxides worked well in the reactions, providing the desired products in medium to good yields. Obviously, the lower yield of 3-methyl quinoline N-oxide might be due to steric hindrance. Halogen-substituted quinoline N-oxides were also tolerated to give the corresponding products (**3fa**-**3ga**) in 46% and 77% yields, respectively. Meanwhile, methoxy-substituted quinoline N-oxides produced sulfonylated quinolines in medium yields (**3ha**-**3ia**). Subsequently, isoquinoline N-oxide **1i** was used as a substrate to examine the regioselectivity, and the results demonstrated that the reaction showed no obvious selectivity. Finally, we tried the reaction of N,N-dialkylaniline N-oxide with sodium benzenesulfinate, and a 35% yield of **3ka** was obtained.

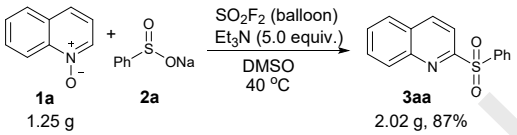
Scheme 3. Substrate Scope with Variation of N-Oxides



[a]General conditions: **1** (0.3 mmol), **2a** (0.9 mmol),1.5 mmol of Et_3N, 2.5 mL of DMSO, under SO_2F_2 atmosphere (using a balloon combined with syringe needle), for 16 h at 40°C. [b]isolated yields

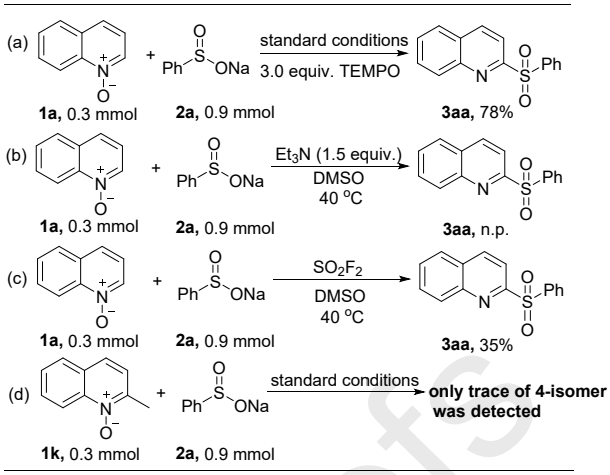
In order to demonstrate the practicality of this method, a gram-scale reaction was performed under standard conditions. As shown in Scheme 4, 1.25 g of quinoline N-oxide (**1a**) afforded 2.02 g of 2-sulfonyl quinoline (**3aa**) in 87% yield, which proved that this method can be applicable in organic synthesis.

Scheme 4. Gram-Scale synthesis of 2-sulfonylquinoline



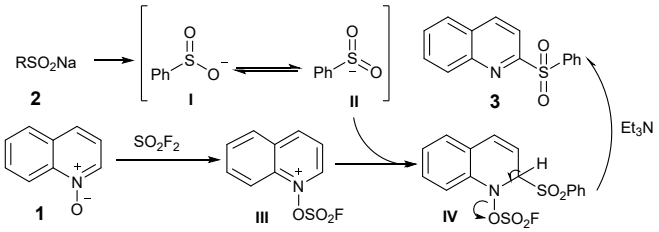
To explore the reaction mechanism, some control experiments were carried out (Scheme 5). First, a radical trapping reagent (TEMPO) had little influence on the reaction efficiency, proving that the reaction is not involved in free radical intermediate [Scheme 5, (a)]. Subsequently, no sulfonylation occurred between quinoline N-oxide (**1a**) and sodium benzenesulfinate (**2a**) without SO_2F_2 indicating SO_2F_2 plays a key role in the reaction [Scheme 5, (b)]. When the reaction was performed in the absence of a base, a low yield was obtained [Scheme 5, (c)]. It confirmed that base greatly promoted the transformation. Finally, treatment of 2-methylquinoline N-oxide under standard reaction conditions could not afford the 2-sulfonylation product and only trace of 4-sulfonylation product can be detected, which proved the sulfonylation of quinoline N-oxide regioselectively occurred at C2 position [Scheme, (d)].

Scheme 5. Control Experiments



On the basis of the mechanism investigation in previous literature[14] and the above experiment observations, a plausible mechanism was proposed as shown in Scheme 6. At first, tautomerization of sulfinate anion **I** exists in equilibrium S-centered anion **II**. Meanwhile, SO_2F_2 as an activator was attacked by the oxygen atom of quinoline N-oxide to form intermediate **III**. Then the C2 of the intermediate **III** was nucleophilically attacked by sulfonyl anion **II** and gives an intermediate **IV**, which subsequently suffer rearomatized to form 2-sulfonylquinoline **3**.

Scheme 6. Plausible Mechanism



Conclusions

In conclusion, we have reported the SO_2F_2-mediated deoxygenative sulfonylation of quinoline N-oxides under metal- and oxidant-free conditions with sodium sulfinates via C-H bond activation. SO_2F_2 was used as an activator to promote the synthesis of a variety of substituted 2-sulfonylquinolines. One distinct advantage of this method is that by-products derived from the use of SO_2F_2 is water-soluble anions SO_4^{2-} and F^- which can be easily removed by aqueous work-up operation.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21362022) and The Natural Science Foundation of Jiangxi Province (No. 20192BAB203006) for financial support.

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Supplementary Material

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submitted along with the manuscript and graphic files to the appropriate editorial office.

High lights

1. SO_2F_2 was used as an efficient activator for C-2 sulfonylation of quinoline *N*-oxides.
2. Low-cost (around 1 US dollar/kg) and environmentally benign SO_2F_2 was used.
3. The method possesses broad substrate scope.
4. Metal- and Oxidant-free conditions are the other two advantages.

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SO_2F_2-Mediated Deoxygenative C2-Sulfonylation of Quinoline N-Oxides with Sodium Sulfinates

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