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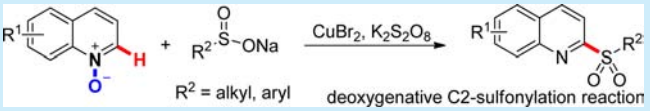
Cu-Catalyzed Deoxygenative C2-Sulfonylation Reaction of Quinoline *N*-Oxides with Sodium Sulfinate

Bingnan Du, Ping Qian, Yang Wang, Haibo Mei, Jianlin Han,* and Yi Pan*

School of Chemistry and Chemical Engineering, State Key laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China

Supporting Information

ABSTRACT: An unexpected Cu-catalyzed deoxygenative C2-sulfonylation reaction of quinoline *N*-oxides in the presence of radical initiator $K_2S_2O_8$ was developed that used sodium sulfinate as a sulfonyl coupling partner. The mechanism studies indicate that the reaction proceeds via Minisci-like radical coupling step to give sulfonylated quinoline with good chemical yields.

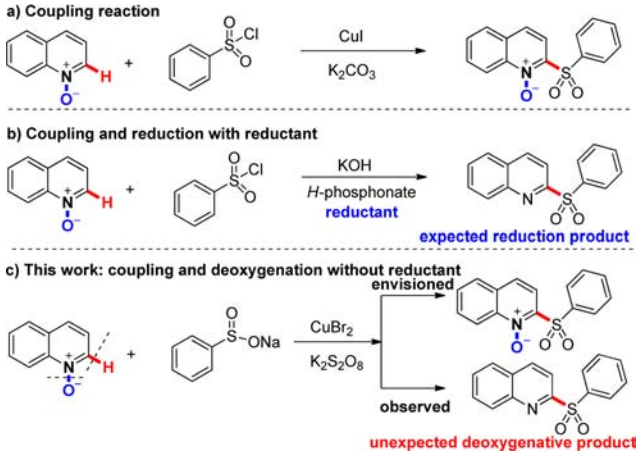


In the past decade, transition-metal-catalyzed C−H functionalization has received extensive attention in organic synthesis,[1] as it has been demonstrated to be a powerful and versatile tool for directly introducing new functionalities via C−H bond transformation with high atom economy. In the past few years, significant achievements have been made in the area of C−H bond functionalization of quinoline *N*-oxides with C2 or C8[2] position regioselectivities under transition-metal catalysis or metal-free conditions.[3] Among these reactions, most were catalytic reactions of quinoline *N*-oxides with C−H bond transformation resulting in substituted quinoline *N*-oxides.[4] The others were the deoxygenative functionalization reactions using reductants or additives, affording substituted quinolines as products.[5] On the other hand, in the presence of oxidants, the substituted quinoline *N*-oxides were found as products without the cleavage of N−O bonds.[6] To the best of our knowledge, the coupling reaction with the deoxygenation of quinoline *N*-oxides in the presence of oxidant has rarely been explored.[7]

Heterocyclic aromatic sulfone is recognized as a crucial class of scaffold in natural products, pharmaceuticals, and biologically active compounds.[8] In particular, quinoline sulfone compounds exhibited biological antibacterial activities and antiproliferative activity.[9] The previous report on the synthesis of these compounds was nucleophilic substitution reaction of halide with thiol, followed by the oxidation of thioether to the corresponding sulfone.[10] In 2013, the Wu group reported an efficient and concise protocol to synthesize sulfonylated quinoline *N*-oxides via copper-catalyzed C−H bond activation with aryl sulfonyl chlorides as the sulfonylation reagents (Scheme 1a).[11]

Recently, Li also developed an attractive method for the synthesis of sulfonylated quinoline from quinoline *N*-oxides and sulfonyl chlorides (Scheme 1b).[12] However, a stoichiometric amount of toxic *H*-phosphonate is required for the reduction of *N*-oxides. Very recently, the He group reported an approach for direct C2 sulfonylation of heteroaromatic N-oxides with sulfonyl hydrazides affording 2-sulfonyl quinolines/pyridines using NaI and TBHP as activators.[13] Based on our continued pursuit of Cu-catalyzed reactions and C−H bond activation,[14]

Scheme 1. Synthesis of 2-Sulfonyl Quinoline *N*-Oxide and Quinoline



herein we report a new strategy to access quinoline sulfone compounds via $CuBr_2$- and $K_2S_2O_8$-promoted reaction between sodium sulfinates and quinoline *N*-oxides (Scheme 1c). Notably, the reaction promoted by $K_2S_2O_8$ afforded the unexpected deoxygenative C2-sulfonylation[15] product instead of the envisioned sulfonylated quinoline *N*-oxide.

Based on the previous reports,[4,5] we initiated the reaction with quinoline *N*-oxide **1a** and sodium *p*-toluenesulfinate **2a**. To our surprise, an unexpected deoxygenative product 2-(toluene-4-sulfonyl)quinoline **3aa** was found with $CuBr_2$ as catalyst (entry 1, Table 1). Although only 11% chemical yield was obtained, this unusual result still inspired us to optimize this reaction by using other copper catalysts. Several copper salts (entries 2−6) were screened; however, no improvement was found. The results showed $CuBr_2$ was the best choice for this transformation. Further optimization was carried out with

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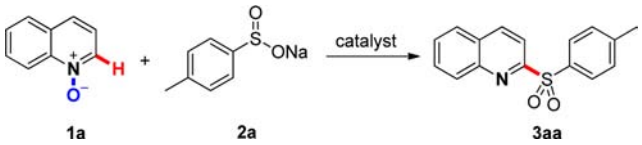
Table 1. Optimization of the Reaction Conditions[a]

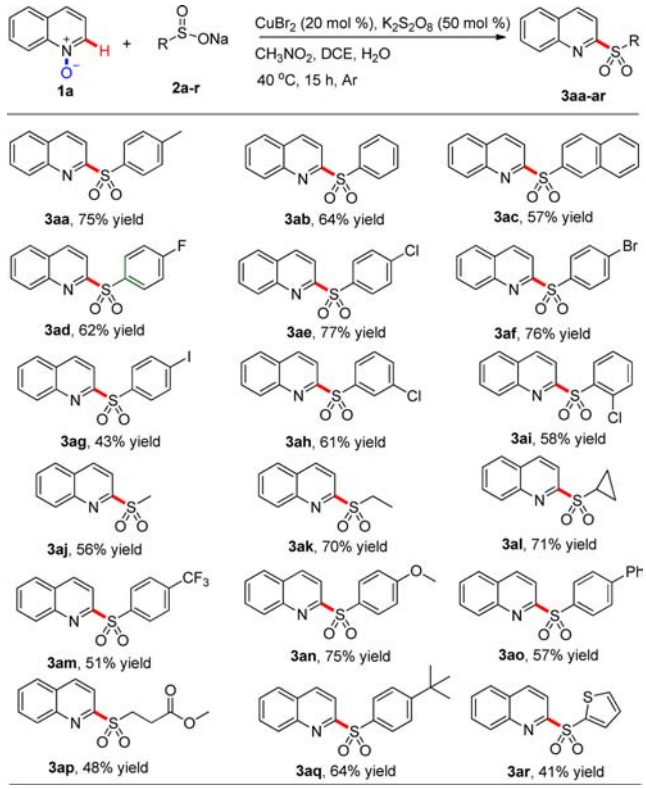


1a 2a 3aa

entry	catalyst	additive	solvent	yield[b] (%)
1	$CuBr_2$		DMF	11
2	CuI		DMF	<5
3	CuBr		DMF	9
4	CuCl		DMF	6
5	$Cu(OAc)_2$		DMF	<5
6	$Cu(OTf)_2$		DMF	<5
7	$CuBr_2$		DMA	13
8	$CuBr_2$		DCE	33
9	$CuBr_2$		dioxane	17
10	$CuBr_2$		toluene	<5
11	$CuBr_2$		CH_3NO_2	37
12	$CuBr_2$		DMSO	<5
13	$CuBr_2$		CH_3CN	11
14	$CuBr_2$		CH_3NO_2/DCE[c]	51
15	$CuBr_2$	$K_2S_2O_8$	CH_3NO_2/DCE	70
16	$CuBr_2$	$Na_2S_2O_8$	CH_3NO_2/DCE	68
17	$CuBr_2$	I_2	CH_3NO_2/DCE	62
18	$CuBr_2$	BQ[d]	CH_3NO_2/DCE	41
19	$CuBr_2$	O_2	CH_3NO_2/DCE	45
20[e]	$CuBr_2$	$K_2S_2O_8$	CH_3NO_2/DCE	75
21[e]		$K_2S_2O_8$	CH_3NO_2/DCE	14

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), catalyst (20 mol %), solvent (4 mL) in a flask under argon balloon for 15 h at 40 °C. [b]Isolated yield based on **1a**. [c]Volume ratio = 3:1. [d]Benzoquinone. [e]0.1 mL of H_2O was added.

Scheme 2. Substrate Scope with Variation of Sodium Sulfinate[a,b]



[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), $CuBr_2$ (20 mol %), $K_2S_2O_8$ (50 mol %), DCE (1 mL), CH_3NO_2 (3 mL), and H_2O (0.1 mL) under argon balloon at 40 °C for 15 h. [b]Isolated yield based on **1a**.

the use of various solvents (entries 7−13), and it was found that DCE (33% yield, entry 8) and CH_3NO_2 (37% yield, entry 11) gave observable improvements. Surprisingly, the yield was increased to 51% when a combination of CH_3NO_2 and DCE with a volume ratio of 3:1 was employed as cosolvent (entry 14). Encouraged by the positive result and based on the observed conversion of sulfinate into a sulfonyl group in this process, additional oxidants were investigated to improve the efficiency. We were pleased to find that the yield was increased to 70% with the addition of $K_2S_2O_8$ (entry 15). Other oxidants (entries 16−19), including $Na_2S_2O_8$, iodide, BQ, and oxygen, were also examined, and the results disclosed that $K_2S_2O_8$ was the best choice. We were glad to find that an addition of 0.1 mL of H_2O gave a slight promotion of yield to 75% (entry 20), which is mainly because the addition of water could increase the solubility of the catalyst and $K_2S_2O_8$. It is essential for the use of copper catalyst, as the reaction gave a very poor yield in the absence of copper catalyst (entry 21). Thus, the optimized reaction conditions were identified as 20 mol % of $CuBr_2$, 0.5 equiv of $K_2S_2O_8$, a 3:1 mixture of CH_3NO_2 and DCE as the cosolvent, and 0.1 mL of H_2O at 40 °C under argon atmosphere for 15 h.

With the optimal reaction conditions in hand, we turned our attention to the substrates scope for this transformation. Several sodium sulfinates were evaluated in the reaction with quinoline *N*-oxide **1a** (Scheme 2). As shown in Scheme 2, a wide range of sodium sulfinates, bearing aryl, alkyl, and cycloalkyl groups, could work well in this reaction, affording the corresponding reduction product 2-sulfonyl quinoline **3aa** with up to 77% chemical yields. Generally, sulfinates containing electron-donating groups performed better than substrates with electron-withdrawing groups (**3aa**, **3an** vs **3ad**, **3am**). Halogen groups on the aromatic ring of sodium benzenesulfinates also could be well tolerated in the Cu-catalyzed reaction, giving the desired product in moderate to good yields (**3ad**−**ai**). Fortunately, the reaction with iodo-substituted sodium benzenesulfinates also proceeded smoothly, resulting in the desired product with 43% yield (**3ag**). We can also find that *o*-substituted sodium benzenesulfinates gave lower yields (**3ae** vs **3ai**), mainly because of the steric hindrance. Moreover, alkyl sodium sulfinates could also be suitable substrates and gave a moderate to good yield (**3aj**−**al**). It is noteworthy that sodium sulfinate with an easily transferred group showed good reactivity (cyclopropyl **3al** and ester **3ap**) and afforded the desired product with 71% and 48% yield, respectively. Finally, a heterocyclic sulfinate, sodium thiophene-2-sulfinate **2r**, has been used in this reaction and was converted into the corresponding product **3ar** in 41% yield. The chemical structure of the obtained product has been confirmed by X-ray analysis of **3aa** (see the SI), which confirms that the N−O bond cleavage occurs during the reaction.

Then, several quinoline *N*-oxides were explored as substrates by reaction with sodium *p*-toluenesulfinate **2a** (Scheme 3). *o*-, *m*- and *p*-methyl-substituted quinoline *N*-oxides could all work well in the reaction, giving the desired product in good yields (**3ba**−**da**). The reactions of halogen group substituted quinoline *N*-oxide also proceeded well to give slightly lower yields (**3ea**−**ga**). Finally, isoquinoline *N*-oxide **1i** was used as

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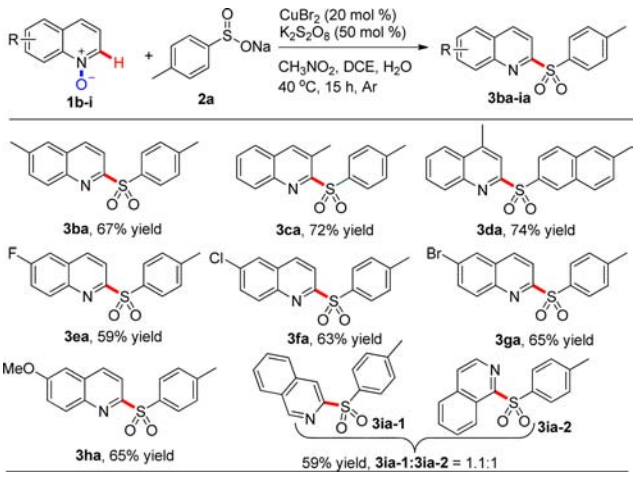
Scheme 3. Substrate Scope with Variation of Quinoline *N*-Oxide[a,b]

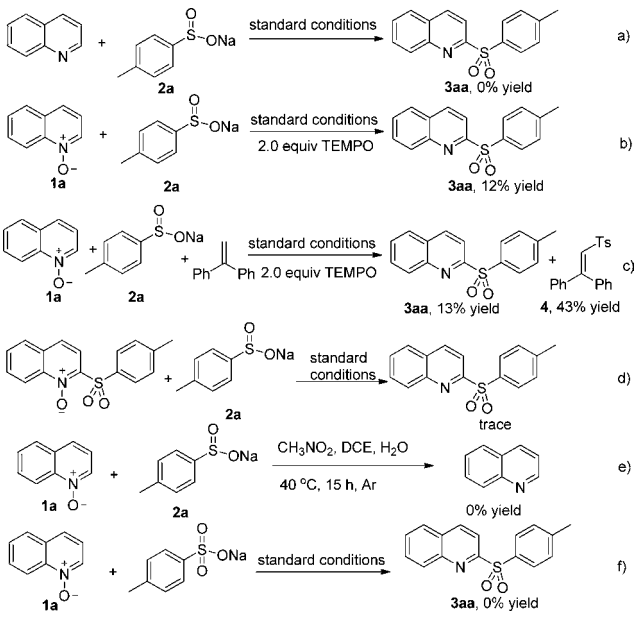


[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.5 mmol), $CuBr_2$ (20 mol %), $K_2S_2O_8$ (50 mol %), DCE (1 mL), CH_3NO_2 (3 mL) and H_2O (0.1 mL) under argon balloon at 40 °C for 15 h. [b]Isolated yield based on **1**.

the reactant to investigate the regioselectivity. The results disclose that the reaction showed no evident regioselectivity, and both two positions adjacent to N−O group were sulfonylated with the ratio of 1:1.1 (**3ia**). Fortunately, these two isomers **3ia** can be relatively easy obtained by using routine column chromatography.

To clarify the reaction mechanism, some control experiments were carried out (Scheme 4). When quinoline, instead of

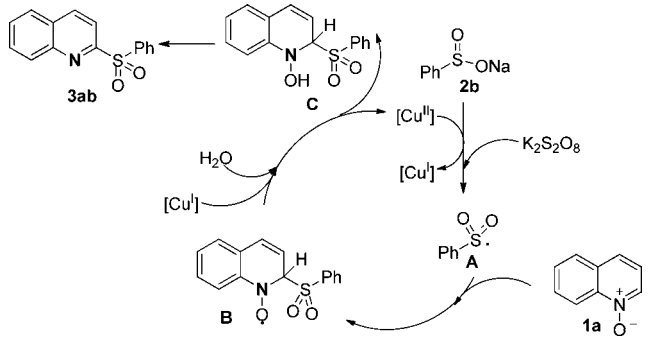
Scheme 4. Control Experiments



quinoline *N*-oxide, was used as the reactant under the standard conditions, no desired 2-sulfonyl quinoline was found, which indicates that the *N*-O group plays an important role in the transformation (Scheme 4a). Moreover, addition of a radical scavenger 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) to the reaction mixture will suppress this reaction (Scheme 4b), suggesting the possibility of a radical nature of this process. Then, 1,1-diphenylethylene (DPE) (DPE:**1a** = 1:1) was added into the reaction mixture of **1a** and **2a**. The formation of product **3aa** was suppressed, and the DPE coupling product **4** was obtained with 43% yield. This result further indicates the current system is a radical process (Scheme 4c). To clarify which species participates in the reduction of product, a reaction of 2-(toluene-4-sulfonyl)quinoline *N*-oxide with sodium *p*-toluenesulfinate was carried out under the standard conditions (Scheme 4d). Almost no desired product was found, which indicates the reaction does not undergo a sequence of sulfonylation and deoxygenation. We then added excess sodium *p*-toluenesulfinate in the reaction system in the absence of $CuBr_2$ and $K_2S_2O_8$ to examine whether sodium *p*-toluenesulfinate is the reducing agent (Scheme 4e). However, the experimental evidence indicates that sodium *p*-toluenesulfinate cannot reduce the quinoline *N*-oxide **1a** to quinoline. Finally, we used sodium *p*-toluenesulfonate instead of sodium *p*-toluenesulfinate as the sulfonyl precursor (Scheme 4f). However, no desired product was obtained, which implies that *p*-toluenesulfinate rather than *p*-toluenesulfonate acts as reactive species in this transformation.

On the basis of the results obtained above and the previous literature,[4,5] a plausible mechanism via Minisci-like radical coupling step for this deoxygenative sulfonation reaction was proposed in Scheme 5. In the initial step, sodium sulfinate **2b** is

Scheme 5. Proposed Mechanism



oxidized by Cu(II) or $K_2S_2O_8$ to form a sulfinate radical **A** via SET.[16] Then, the intermediate **A** reacts with quinoline *N*-oxide **1a** through a Minisci-like reaction to generate intermediate **B**.[17] Radical **B** is rapidly seized by Cu(I) to give hydroxylamine intermediate **C**, which is converted into the final product **3ab** through elimination of water and regenerates Cu(II) for the next cycle.

To conclude, an unexpected Cu-catalyzed deoxygenative C2-sulfonylation reaction of quinoline *N*-oxides in the presence of $K_2S_2O_8$ was developed. This reaction was carried out under mild conditions, which provides an easy pathway for the preparation of bioactive 2-sulfonyl quinolines with soldium sulfinate as a sulfonyl precursor. The mechanism studies indicate that the reaction proceeds via a Minisci-like radical-coupling step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02289.

Experimental procedures, full spectroscopic data for compounds **3** and **4**, X-ray analysis of **3aa**, and ^1H and ^{13}C NMR spectra (PDF)

X-ray data for **3aa** (CIF)

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: hanjl@nju.edu.cn.
*E-mail: yipan@nju.edu.cn.

Notes

The authors declare no competing financial interest.

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