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Sulfonylation of Quinoline *N*-Oxides with Aryl Sulfonyl Chlorides via Copper-Catalyzed C–H Bonds Activation

Zhiyong Wu,[†] Hongyu Song,[†] Xiuling Cui,*[,†,‡] Chao Pi,[†] Weiwei Du,[†] and Yangjie Wu*[,†]

Department of Chemistry, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou, 450052, P. R. China, and School of Biomedical Sciences, Engineenring Research Center of Molecular Medicine of Chinese Education Ministry, Xiamen Key Laboratory of Ocean and Gene Drugs, Institute of Molecular Medicine of Huaqiao University, Fujian, Xiamen, 361021, P. R. China

cuixl@zzu.edu.cn; wyj@zzu.edu.cn

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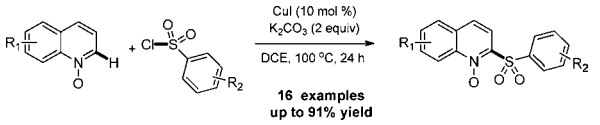
ABSTRACT



An efficient and concise one-pot protocol to synthesize sulfonylated quinoline *N*-oxides via copper-catalyzed C–H bond activation has been developed. Commercially available and less expensive aryl sulfonyl chlorides were used as the sulfonylation reagents. Various 2-aryl sulfonyl quinolines were obtained in up to 91% yields in chemo- and regioselective manners.

The heterocyclic aromatic sulfone skeleton has proven to be a useful building block in organic synthesis, medicinal chemistry, and natural products.[1] It exists widely in pharmaceutical molecules, such as enzyme inhibitors[2] and biological activity antagonists,[3] which are exemplified in Figure 1. Compound **a** was found to be a novel potent and highly selective HIV-1 non-nucleoside reverse transcriptase inhibitor.[4] Compounds **b** and **c** are potent and selective serotonin 5-HT6 receptor (5-HT6R) antagonists.[5]

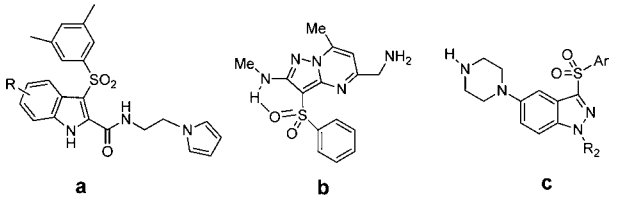


Figure 1. Examples illustrating the importance of heterocyclic aromatic sulfone.

The wide usefulness of compounds containing this skeleton has resulted in the development of synthetic methodologies to construct them. The conventional methods have typically involved a nucleophile substitution reaction of halide with thiol, followed by oxidation of the corresponding sulfide.[6] Recently, a "one step" protocol was explored from the cross-coupling of sulfinate salts with halides catalyzed by metal[7] or tetrabutylammonium chloride.[8] However, some halogenated heterocyclic aromatic compounds are not commercially available and are problematic to prepare. Therefore, a rapid, efficient, and

[†] Zhengzhou University.
[‡] Institute of Molecular Medicine of Huaqiao University.

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practical access to heteroaromatic sulfone compounds is highly desired from a synthetic practicality viewpoint.

Recently, significant progress has been made in transition-metal-catalyzed C−H bond functionalization.[9] Substantial growth in carbon−heteroatom bond formation based on the transition-metal-catalyzed C−H bond activation has been observed.[10] Nevertheless the development of effective C−S bond formation reactions is still underdeveloped compared to C−N[11] and C−O[12] bond formation. Until very recently, several representative examples were reported by Doi and Dong involving intra- and intermolecular reactions to generate the C−S bond.[13] Quinoline *N*-oxides are widely present in biologically active compounds,[14] and they are important intermediates for the syntheses of substituted quinoline as motifs in biologically active compounds.[15] Moreover, *N*-oxide could serve as a directing group and allow C−H functionalization to occur at the 2-position.[16] In our continuing effort to develop versatile C−X (X = C, O, S, N) bond formations based on metal-catalyzed C−H activation of quinoline *N*-oxides,[17] we embarked on the development of C−S bond formation. Herein, we disclose a highly practical procedure to build 2-aryl sulfonyl quinolines in one step from quinoline *N*-oxides with aryl sulfonyl chloride catalyzed by a cheap metal, copper.

We initiated our investigation on the model reaction of quinoline *N*-oxides with *p*-tolylsulfonyl chloride to optimize the critical reaction parameters (Table 1). To our delight, the direct C_2-sulfonylation took place in the presence of $Pd(OAc)_2$ (10 mol %) and K_2CO_3 (2 equiv) in toluene under air, affording compound **3a** in 47% yield (entry 1, Table 1). Compound **3a** was identified by 1D and 2D NMR spectra. Inspired by this result, various catalysts, such as $PdCl_2$, $Pd(PhCN)_2Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(TFA)_2$, CuI, CuCl, and CuBr, were screened (entries 1−8, Table 1). 10 mol % CuI provided product **3a** in the highest yield (73%, entry 8, Table 1). A 41% yield was obtained in the absence of catalyst (entry 9, Table 1). It was found that the solvent played a crucial role in this transformation. Among the solvents examined (toluene, dioxane, C_2H_5OH, NMP, DMAc, CH_3CN, DME, DCE, DMA, and DMF, entries 10−18, Table 1), DCE was the best, affording **3a** in 91% yield (entry 18, Table 1). The base also played an important role in the reaction. No product was detected in the absence of any base (entry 26, Table 1). K_2CO_3 was superior to other bases, such as Na_2CO_3, $NaHCO_3$, $KHCO_3$, Cs_2CO_3, CsF, KOAc, and Et_3N (entry 18 vs entries 19−25, Table 1). The yield decreased to 79% when the catalyst loading was reduced to 5 mol % from 10 mol % (entry 27, Table 1). After surveying a variety of catalysts, bases, solvents, and catalyst loadings, we found that the combination of 10 mol % of CuI and 2 equiv of K_2CO_3 in DCE at 100 °C for 24 h served as the

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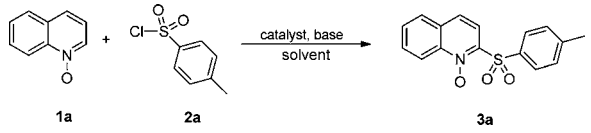
optimal conditions for this transformation. These results indicated that this transformation was facile and practical, as it did not require the use of strong bases, an expensive catalyst, and the rigorous exclusion of air.

Table 1. Direct 2-Sulfonylation of Quinoline *N*-Oxide with *p*-Tolylsulfonyl Chloride[a]



1a 2a 3a

entry	catalyst	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	K_2CO_3	toluene	47
2	$PdCl_2$	K_2CO_3	toluene	60
3	$Pd(PPh_3)_2Cl_2$	K_2CO_3	toluene	55
4	$Pd(PhCN)_2Cl_2$	K_2CO_3	toluene	61
5	$Pd(TFA)_2$	K_2CO_3	toluene	N.R.
6	CuCl	K_2CO_3	toluene	72
7	CuBr	K_2CO_3	toluene	62
8	CuI	K_2CO_3	toluene	73
9	–	K_2CO_3	toluene	41
10	CuI	K_2CO_3	dioxane	N.R.
11	CuI	K_2CO_3	DMF	N.R.
12	CuI	K_2CO_3	NMP	N.R.
13	CuI	K_2CO_3	DMAc	N.R.
14	CuI	K_2CO_3	CH_3CN	N.R.
15	CuI	K_2CO_3	DMA	N.R.
16	CuI	K_2CO_3	DME	N.R.
17	CuI	K_2CO_3	C_2H_5OH	N.R.
18	**CuI**	**K_2CO_3**	**DCE**	**91**
19	CuI	$KHCO_3$	DCE	23
20	CuI	Na_2CO_3	DCE	58
21	CuI	$NaHCO_3$	DCE	31
22	CuI	Cs_2CO_3	DCE	81
23	CuI	CsF	DCE	<5
24	CuI	KOAc	DCE	38
25	CuI	Et_3N	DCE	<5
26	CuI	–	DCE	N.R.
27	CuI	K_2CO_3	DCE	79[c]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), catalyst (10 mol %) and base (2 equiv), solvent (3 mL), under air, 100 °C, 24 h, sealed tube. [b] Isolated yields. [c] Catalyst (5 mol %).

With the optimized reaction conditions in hand, the scope of substrates was examined. The results were summarized in Figure 2. A series of functional groups on the phenyl ring of sulfonyl chlorides were tested. Both the electron-donating and -withdrawing groups were compatible. The products were isolated in 61−91% moderate to excellent yields (**3a**−**3i**, Figure 2). Generally, the reaction efficiency was slightly sensitive to the electronic property of the sulfonyl chlorides. Electron-donating compared to electron-withdrawing groups gave slightly higher yields. The quinoline *N*-oxide derivatives with electron-donating methyl groups at the 4- and 6-positions smoothly underwent sulfonylation at the 2-position with arenesulfonyl chlorides (**3j**−**3o**, Figure 2). This catalytic system was also applied to isoquinoline *N*-oxide. However, C_4-substituted product **3p** was obtained in 88% yield (Scheme 1). No products were afforded when *N*-oxides derived from pyrazine, pyrimidine, 1-methyl-imidazole, pyridine, and their derivatives were utilized as the substrate.

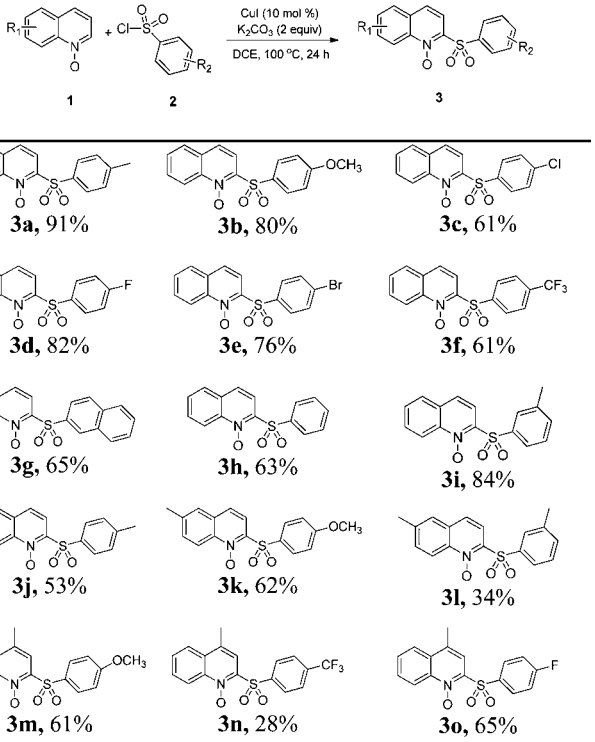
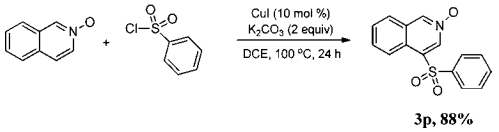


Figure 2. Copper-catalyzed sulfonylation of quinoline *N*-oxides. Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), CuI (10 mmol %), K_2CO_3 (0.4 mmol), DCE (3 mL), under air, 100 °C, 24 h, sealed tube. Isolated yields.

Scheme 1. Copper-Catalyzed Sulfonylation of Isoquinoline *N*-Oxide



A plausible reaction mechanism was outlined according to the literature and reaction results in Scheme 2. First, the CuI electrophilic attack at the 2-carbon of the quinoline *N*-oxides afforded intermediate **A**.[18] The following oxidative addition of arene sulfonyl chloride to the intermediate

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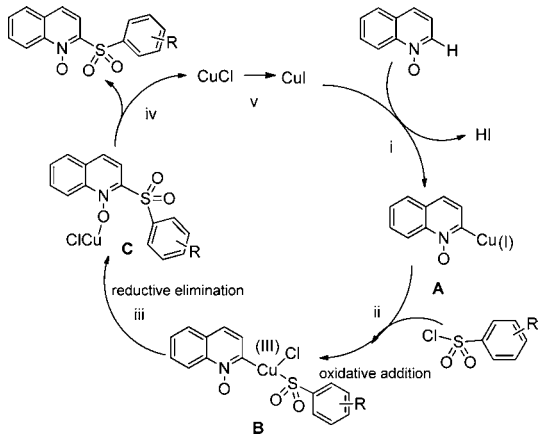
Scheme 2. Plausible Reaction Mechanism



A formed the Cu(III) intermediate **B**.[19] Then, the intermediate **B** produced intermediate **C** with coordination of the copper atom with the oxygen atom of *N*-oxide. Finally, the intermediate **C** provided the target product as well as CuCl. Then CuCl underwent an anion exchange process and regenerated the CuI to finish the catalytic cycle.

In conclusion, an efficient approach for the direct C_2-sulfonylation of quinoline *N*-oxides has been developed based on a copper-catalyzed C−H bond activation. This novel method provides easy access to sulfonylated heterocyclic compounds using commercially available, inexpensive aryl sulfonyl chlorides as the sulfonylation reagents and cheap copper as the catalyst.

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Supporting Information Available. Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.