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In Situ Generated Hypolodite Activator for the C2 Sulfonylation of Heteroaromatic *N*-oxides

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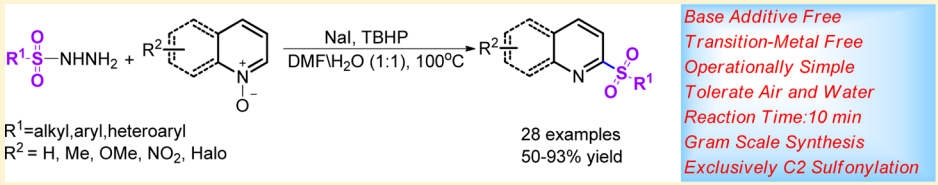
Supporting Information



ABSTRACT: A mild approach for direct C2 sulfonylation of heteroaromatic *N*-oxides with sulfonyl hydrazides affording 2-sulfonyl quinolines/pyridines has been developed. A variety of heteroaromatic *N*-oxides and sulfonyl hydrazides participate effectively in this transformation which uses hypoiodites (generated in situ from NaI and TBHP) as a means of substrate activators. In this reaction, the *N*-oxide plays a dual role, acting as a traceless directing group as well as a source of oxygen atom.

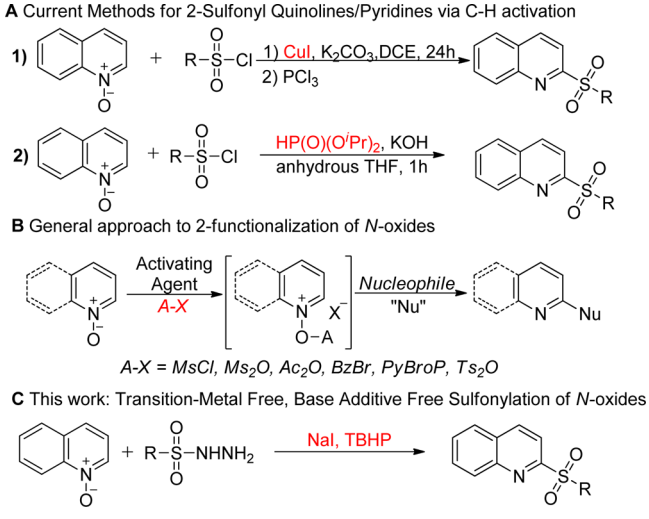
INTRODUCTION

The development of simple and environment friendly strategy for the formation of C−S bond is one of the fundamental challenges in synthetic organic chemistry community.[1] Recently, N-heteroaromatic compounds have been actively pursued in pharmaceuticals[2] and material sciences;[3] and C−S bonds attached to N-heteroaromatic compounds have been recognized, because N-heteroaromatic compounds containing a sulfur moiety are present in many biologically active compounds.[4] Thus, the synthesis of sulfonyl N-heteroaromatic compounds through N-heteroaromatic compounds modification by novel methods has attracted attention in medicinal and synthetic chemistry.[5] 2-Sulfonyl N-heteroaromatic compounds are generally synthesized by oxidation of the corresponding sulfides[6] or by alkylation of sulfinate salts.[7] Both methods suffer drawbacks: The ultimate starting materials are often 2-halopyridine, many of which are foul-smelling.

In 2013, Wu and Cui reported the first example of copper-catalyzed direct sulfonylation of quinoline/pyridine *N*-oxides via C−H activation. However, to realize the synthesis of the desired 2-sulfonyl quinolines/pyridines, a harsh reagent (PCl_3) was required to reduce the *N*-oxide products in this transformation (Scheme 1A, 1).[8] In 2015, Zhao and Chen described a transition metal-free one pot approach to selective synthesis of 2-sulfonyl quinolines/pyridines via H-phosphonate-mediated C−H activation (Scheme 1A, 2).[9] Despite substantial progress, the reaction is in need for base additives as well as strictly anhydrous reaction conditions. It is therefore important to develop a new method that can tolerate moisture or water.

Since the first example of regioselective C2 functionalization of *N*-oxides with *N*-phenylbenzimidoyl chlorides as the activators was developed by M. Henze in 1936,[10] considerable progress has been made in this area (Scheme 1B).[11] However, to the best of our knowledge, iodide-TBHP system (in situ generated hypoiodite), as an environmentally benign and inexpensive reagent that can be stored and handled in the laboratory using normal laboratory methods,[12] has not yet been employed as the activator. We therefore considered that iodine reagents might serve as both activating reagents and as reductants in the regioselective sulfonylation reaction, achieving a one-pot synthesis of 2-sulfonyl quinolines/pyridines. Herein we report the hypoiodite-mediated C−H activation of quinoline/pyridine *N*-oxides with sulfonyl hydrazides[13] for the direct synthesis of 2-sulfonyl quinolines/pyridines without assistance

Scheme 1. Functionalization of *N*-Oxides via C−H Activation



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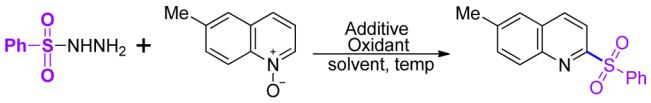
of transition-metal catalysts, base additives, or phosphorus additives (Scheme 1C).

RESULTS AND DISCUSSION

We initially chose benzenesulfonohydrazide (**1a**) as a model substrate to react with 6-methylquinoline *N*-oxide (**2a**) in the presence of iodine and *tert*-butyl hydroperoxide (TBHP, 70% in water) in acetonitrile at 80 °C under an air atmosphere. Much to our delight, the reaction proceeded to give access to the desired sulfonylation product **3a**, albeit with a low yield (40%, Table 1, entry 1). Encouraged by this result, we planned to employ different iodine regents, oxidants, and solvents to search for the optimal reaction conditions. Iodine regents, such as *n*-Bu_4NI, NaI, KI, and NIS could provide 13−52% yields (entries 2−5). NaI was superior to the others and proved to be the best catalyst (entry 3). No desired product was observed when phenyliodine bis(trifluoroacetate) (PIFA) or NaBr was used as a catalyst (entries 6−7). The optimization of various oxidants indicated that TBHP was the best choice, whereas the others like hydrogen peroxide (H_2O_2, 30% in water), benzoyl peroxide (BPO), *tert*-butyl peroxybenzoate (TBPB), $Na_2S_2O_8$, oxone, and O_2 were less effective (entries 8−13). Various solvents were then probed to promote the reaction, and the solvent mixture DMF/H_2O (1:1) was found to be particularly effective for this sulfonylation (see SI). In an attempt to improve the reaction efficiency, other reaction parameters were tested, including loading of NaI and TBHP, substrate ratio and concentration (see SI). After careful optimization, we found that adjusting the dosage of NaI to 2.0 equiv and substrate ratio to 1:2 (**1a**:**2a**) in the presence of 2.0 equiv of NaI in 1 mL DMF/H_2O (1:1) at 80 °C further facilitated the reaction process and afforded 81% yield of **3a** (see SI). Elevating the reaction temperature to 100 °C showed a positive result, with the starting material consumed completely in 5 min and the yield improved to 88% (entry 14). However, a continued increase in temperature to 120 °C had a negative impact on the reaction, resulting in fast decomposition of benzenesulfonohydrazide **1a** (entry 15).

Table 1. Optimization of the Reaction Conditions[a]



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

entry	additive (equiv)	oxidant (equiv)	solvent	temp. (°C)	yield (%)[b]
1	I_2 (1.0)	TBHP (2.5)	CH_3CN	80	40
2	*n*-Bu_4NI (2.0)	TBHP (2.5)	CH_3CN	80	13
3	NaI (2.0)	TBHP (2.5)	CH_3CN	80	52
4	KI (2.0)	TBHP (2.5)	CH_3CN	80	52
5	NIS (2.0)	TBHP (2.5)	CH_3CN	80	24
6	PIFA (2.0)	TBHP (2.5)	CH_3CN	80	–
7	NaBr (2.0)	TBHP (2.5)	CH_3CN	80	–
8	NaI (2.0)	H_2O_2 (6)	CH_3CN	80	48
9	NaI (2.0)	BPO (1.75)	CH_3CN	80	28
10	NaI (2.0)	TBPB (1.75)	CH_3CN	80	19
11	NaI (2.0)	NaS_2O_8 (1.75)	CH_3CN	80	trace
12	NaI (2.0)	oxone (1.75)	CH_3CN	80	trace
13	NaI (2.0)	O_2	CH_3CN	80	26
14	**NaI (2.0)**	**TBHP (3)**	**DMF/H_2O (1:1)**	**100**	**88**

[a]Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.4 mmol), iodine regent, oxidant, solvent (2 mL) was stirred for 10 min at 80 °C. [b]Yield of **3a** was determined by HPLC on crude products. [c]1.75 equiv of **1a** was used. [d]2.25 equiv of **1a** was used. [e]1 mL DMF aqueous was used as the solvent. [f]3 mL DMF aqueous was used as the solvent.

Having identified the optimized reaction conditions, we subsequently explored the substrate scope (Table 2). A set of sulfonyl hydrazides including aromatic and aliphatic could efficiently sulfonylation of quinoline *N*-oxides to deliver the desired 2-sulfonyl quinolines **3** in moderate to high yields. Reactions of *m*-, *o*, and *p*-toluenesulfonyl hydrazides proceeded well, and almost equal yields were achieved, suggesting that the steric effect of substituents on aromatic rings is negligible (**3b**−**3d**). Arylsulfonyl hydrazides possessing either electron-donating (**3d**−**3f**) or electron-withdrawing substituents (**3g**−**3j**) were well tolerated in this sulfonylation, affording the desired products in moderate to excellent yields. The electron-donating substituted benzenesulfonylhydrazines showed superior reaction efficiency to that of the electron-withdrawing ones. This protocol was tolerant of synthetically valuable functional groups on the phenyl moiety (for example, alkoxy, fluoro, chloro, bromo and acetyl groups), which could allow an opportunity for further transformations. The sulfonylation process also occurred well with polycyclic and heteroaromatic sulfonyl hydrazides, affording the targeted compounds **3k**−**3m** in 52−85% yields. Besides the aromatic sulfonyl hydrazides, aliphatic sulfonyl hydrazides were also found to be suitable sulfonylation reagents for the standard conditions (**3n**−**3o**).

We next turned our attention to the scope of heteroaromatic *N*-oxides. To our delight, the current catalytic system was suitable for a wide range of substituted quinoline *N*-oxides (**3p**−**3ab**). No matter whether the N-heteroaromatic ring is substituted with either sterically hindered group, electron-donating (Me and OMe), or electron-withdrawing (Cl, Br, I and NO_2), all of them delivered the desired products in good to excellent yields (**3p**−**3z**). Notably, isoquinoline *N*-oxide and pyridine *N*-oxide could proceed efficiently and afford the corresponding products (**3aa** and **3ab**) in 71% and 72% yields, respectively. However, substituted pyridine *N*-oxides (**3ac** and **3ad**) failed to produce the desired products under the optimal reaction conditions

In order to prove the practicality of this approach, a gram-scale synthesis of the **3a** (1.703g, 86% yield) and **3t** (1862g, 89% yield) was performed, respectively, which suggested that such methodology could also be efficiently scaled up (Scheme 2).

To clarify the mechanism of the regioselective sulfonylation process, the following control experiments were performed. First, a radical trapping reagent (for example, TEMPO and BHT) had little effect on the reaction efficiency, suggesting that free radical intermediate is not involved in this reaction (Scheme 3a).[5a,c,e,f,14] Second, intermolecular kinetic isotope effects (KIE) were investigated with regard to the C(sp_2)−H/D bonds for the quinoline substrates. A clear KIE value of 1.0 was observed in a 1:1 mixture of quinoline *N*-oxide **2a** and quinoline-D *N*-oxide ([D_1]-**2a**) (Scheme 3b), indicating that the quinoline *N*-oxide C(sp_2)−H bond breaking might not be the rate-limiting step. Third, considering that this type of coupling reaction may involve the 2-iodoquinoline intermediate, generated from the regioselective C2-iodination, we attempted to treat **1a** with 2-iodo-6-methylquinoline *N*-oxides (**4a**) and 2-iodo-6-methylquinoline (**4a′**). However, no

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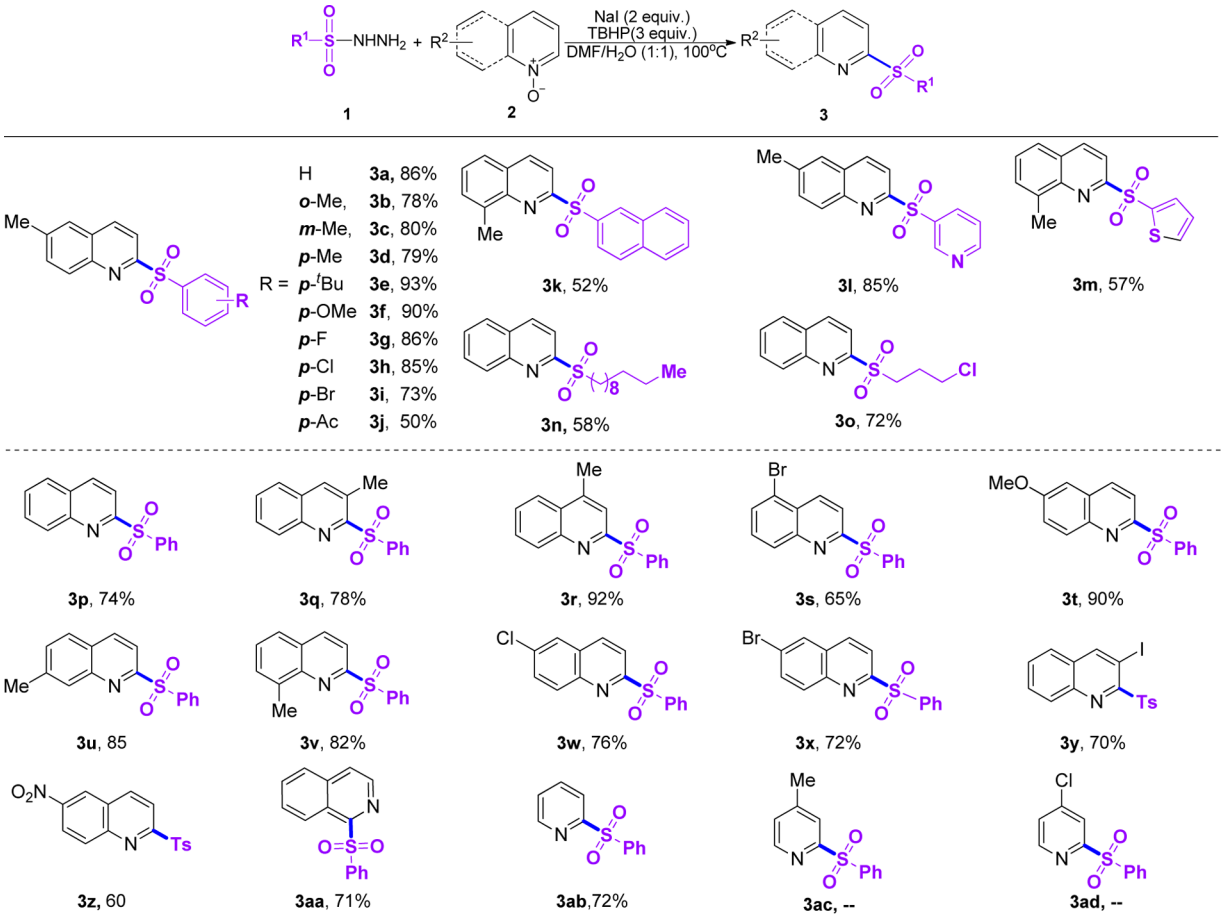
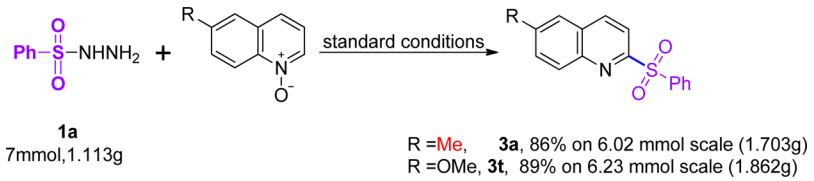
Table 2. Reaction Scope[a]



[a]Compound **1** (0.2 mmol) and **2** (0.4 mmol), NaI (0.4 mmol), TBHP (0.6 mmol, 70% in water). No reaction is denoted by "--".

Scheme 2. Gram-Scale Synthesis of 3a



formation of product **3a** was observed under the standard conditions (Scheme 3c). The decomposition of the sulfonyl hydrazide **1a** in the absence of **2a** gave the sulfonothioate **5a** and disulfide **6a** in 11 and 35% yields, respectively (Scheme 3d). However, the desired product **3a** was not obtained when **5a** or **6a** was treated under the standard conditions (Scheme 3e), suggesting that **5a** and **6a** might not be an intermediate in this reaction. Moreover, the effect of iodine was also investigated (Scheme 3f). When 2 equiv of $PhI(OAc)_2$ or IBX was employed instead of our catalytic system, no **3a** was obtained. In contrast, when NaIO generated in situ from I_2 and NaOH was used, the reaction gave target product **3a** in a 21% yield. This result clearly shows that the *N*-oxide of the substrate not only directs the remote C−H activation but also delivers an oxygen atom.

Based on these observations and previous literature reports,[11c,d,15] a mechanism can tentatively be proposed (Scheme 4). First, the oxidation of iodide with TBHP might produce I_2, which could be further oxidized in the same fashion to form the potential actual oxidant species hypoiodite ($[IO]^-$). Subsequently, nucleophilic addition reaction of $[IO]^-$ by quinoline *N*-oxide afforded the intermediate **A**. The sulfonyl nucleophile generated from base-accelerated decomposition of benzenesulfonohydrazide attacks α-carbon of intermediate **A**. The resulting intermediate **B** underwent deprotonation/aromatization to give the targeted product **3** and release of the unstable HIO_2, which undergo disproportionation to produce I_2 and IO_3^-.

CONCLUSIONS

In summary, for the first time, a NaI/TBHP-mediated direct C_2-sulfonylation of heteroaromatic *N*-oxides has been developed for the synthesis of 2-sulfonylquinolines/pyridines. This transition metal and base additive-free synthetic process works well with a wide range of heteroaromatic *N*-oxides and can be safely conducted on a gram scale. The features such as generality, high efficiency, short reaction time, and air- and moisture-insensitive reaction conditions make the present

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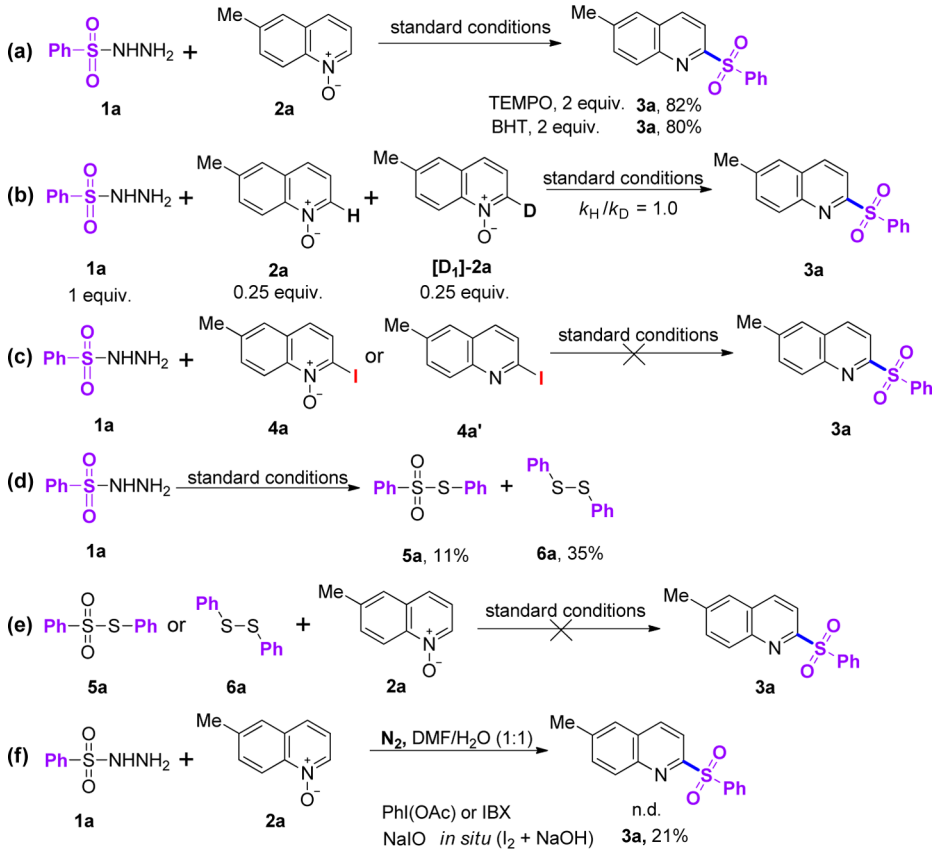
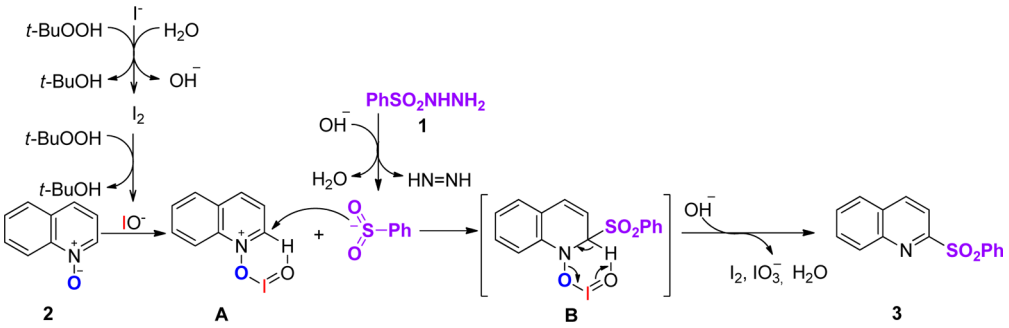
Scheme 3. Control Experiments



Scheme 4. Proposed Reaction Mechanisms



method an attractive alternative for the preparation of 2-sulfonylquinolines/pyridines.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all commercial materials and solvents were used without further purification. Column chromatography was performed using silica gel (100−200 mesh) as the stationary phase. All reactions were monitored by thin-layer chromatography (TLC). NMR spectra were recorded with 400 MHz spectrometers for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$ for ^{1}H and ^{13}C NMR. Multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dq (doublet of quartets), q (quartet), or m (multiplet). IR spectra were recorded on a FT-IR spectrometer, and only major peaks are reported in cm^{-1}. High-resolution mass spectra were taken with GCT-TOF instrument with EI or ESI source.

General Procedure for the Synthesis of 3. A solution of heteroaromatic *N*-oxide (0.2 mmol), sulfonyl hydrazide (0.4 mmol), NaI (60 mg, 0.4 mmol), and TBHP (70%, 77 mg, 0.6 mmol) in DMF/water (1:1) (4 mL) was stirred under an air atmosphere at 100 °C for a desired time (monitored by TLC). After the reaction was finished, the mixture was added to 5 mL water and extracted with ethyl acetate (3 × 5 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was separated on a silica gel column with petroleum ether/ethyl acetate (1/5) as the eluent to get product **3**.

Kinetic Isotope Effect. A 1:1 mixture of **2a** and the deuterated substrate [**D$_1$**]-**2a** was subjected to the standard reaction condition for 3 min. The GC-MS analysis of 6-methylquinoline *N*-oxide **2a** and 6-methylquinoline-D *N*-oxide ([**D$_1$**]-**2a**) quinoline *N*-oxide in residual material reveals a nearly equal mixture of isotopes, corresponding to an intermolecular KIE of K_H/K_D = 1.1.

*6-Methyl-2-(phenylsulfonyl)quinolone (**3a**).* White solid, mp 150−152 °C, yield: 86% (48.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.24 (d, J = 5.0 Hz, 1H), 8.15 (d, J = 10.0 Hz, 1H), 8.12 (d, J = 10.0 Hz, 2H), 8.04 (d, J = 10.0 Hz, 1H), 7.59 (d, J = 10.0 Hz, 2H), 7.57 (d, J =

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10.0 Hz, 1H), 7.51 (t, J = 5.0 Hz, 2H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 21.8, 117.8, 126.4, 128.9, 129.0, 130.0, 133.4, 133.6, 137.8, 139.4, 139.7, 146.1, 157.1; IR (KBr) ν_{max} 2960, 1302, 1260, 1132, 803, 604 cm^{-1}; HRMS (ESI): M + H^+ found 284.0750; $C_{16}H_{14}NO_2S$ requires 284.0754.

*6-Methyl-2-(o-tolylsulfonyl)quinoline (**3b**)*. White solid, mp 144−145 °C, yield: 78% (46.3 mg). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.30 (d, J = 10.0 Hz, 1H), 8.27 (d, J = 10.0 Hz, 1H), 8.12 (d, J = 10.0 Hz, 1H), 7.99 (d, J = 10.0 Hz, 1H), 7.63 (s, 1H), 7.59 (d, J = 10.0 Hz, 1H), 7.48 (t, J = 5.0 Hz, 1H), 7.41 (t, J = 5.0 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 2.54 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 20.7, 21.8, 117.8, 126.40, 126.46, 129.0, 130.0, 130.5, 132.4, 133.3, 133.8, 137.3, 137.7, 139.0, 139.7, 145.8, 157.2; IR (KBr) ν_{max} 2926, 1302, 1168, 816, 707, 605, 574 cm^{-1}; HRMS (ESI): M + H^+ found 298.0908; $C_{17}H_{16}NO_2S$ requires 298.0910.

*6-Methyl-2-(m-tolylsulfonyl)quinoline (**3c**)*. White solid, mp 143−144 °C, yield: 80% (47.5 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 4.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 21.3, 21.8, 117.9, 126.1, 126.4, 128.9, 129.1, 130.0, 133.3, 134.4, 137.8, 139.2, 139.3, 139.6, 146.1, 157.2; IR (KBr) ν_{max} 2920, 1320, 1166, 820, 698, 612, 465 cm^{-1}; HRMS (ESI): M + H^+ found 298.0908; $C_{17}H_{16}NO_2S$ requires 298.0910.

*6-Methyl-2-tosylquinoline (**3d**)*. White solid, mp 144−146 °C, yield: 79% (46.9 mg). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.26(d, J = 10.0 Hz, 1H), 8.15 (d, J = 5.0 Hz, 1H), 8.07 (d, J = 10.0 Hz, 1H), 8.03 (d, J = 10.0 Hz,2H), 7.61 (d, J = 5.0 Hz, 2H), 7.33 (d, J = 10.0 Hz, 2H), 2.55 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 21.6, 21.8, 117.7, 126.4, 128.9, 129.0, 129.7, 130.0, 133.3, 136.4, 137.8, 139.6, 144.6, 146.1, 157.4; IR (KBr) ν_{max} 2962, 1319, 1260, 1128, 792, 700, 607 cm^{-1}; HRMS (ESI): M + H^+ found 298.0895; $C_{17}H_{16}NO_2S$ requires 298.0896.

*2-((4-tert-Butylphenyl)sulfonyl)-6-methylquinoline (**3e**)*. White solid, mp 201−202 °C, yield: 93% (63.1 mg). ^1H NMR(400 MHz, $CDCl_3$) δ: 8.17 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 12.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 20.7, 30.0, 34.2, 116.9, 125.1, 125.3, 127.7, 127.9, 129.0, 132.2, 135.3, 136.7, 138.5, 145.1, 156.3, 156.5; IR (KBr) ν_{max} 2962, 1319, 1261, 1096, 797, 647, 614 cm^{-1}; HRMS (ESI): M + H^+ found 340.1378; $C_{20}H_{21}NO_2S$ requires 340.1380.

*2-((4-Methoxyphenyl)sulfonyl)-6-methylquinoline (**3f**)*. White solid, mp 140−142 °C, yield: 90%, (53.6 mg). ^1H NMR (400 MHz,$CDCl_3$) δ: ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 3H), 7.52 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 3.75 (s, 3H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 20.7, 54.6, 113.3, 116.6, 125.3, 127.8, 128.9, 129.6, 130.1, 132.2, 136.7, 138.4, 145.0, 156.6, 162.7; IR (KBr) ν_{max} 2961, 1593, 1497, 1260, 1100, 801, 590 cm^{-1}; HRMS (ESI): M + H^+ found 314.0857; $C_{17}H_{16}NO_3S$ requires 314.0860.

*2-((4-Fluorophenyl)sulfonyl)-6-methylquinoline (**3g**)*. White solid, mp 105−106 °C, yield: 86%, (51.7 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 3H), 8.03 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 8.0 Hz, 2H), 2.54 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 20.7, 115.3 (d, J_{C-F} = 22.5 Hz), 116.5, 125.4, 127.9, 128.9, 130.8 (d, J_{C-F} = 9.6 Hz,), 132.4, 134.1, 136.9, 138.8, 145.0, 155.9, 164.8(J_{C-F} = 254.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ:-103.5. IR (KBr) ν_{max} 2922, 1584, 1323, 1229, 1134, 821, 682, 587 cm^{-1}; HRMS (ESI): M + H^+ found 302.0644; $C_{16}H_{13}FNO_2S$ requires 302.0646.

*2-((4-Chlorophenyl)sulfonyl)-6-methylquinoline (**3h**)*. White solid, mp 121−122 °C, yield: 85% (51.3 mg). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.31 (d, J = 10.0 Hz, 1H), 8.18 (d, J = 10.0 Hz, 1H), 8.10 (d, J = 10.0 Hz, 2H), 8.06 (d, J = 5.0 Hz, 1H), 7.65 (d, J = 5.0 Hz, 2H), 7.53 (d, J = 10.0 Hz, 2H), 2.59 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 21.8, 117.6, 126.4, 129.0, 129.3, 129.9, 130.5, 133.5, 137.7, 137.9, 139.9, 140.4, 146.1, 156.8; IR (KBr) ν_{max} 2998, 1637, 1357, 1100, 860, 567 cm^{-1}; HRMS (ESI): M + H^+ found 318.0362; $C_{16}H_{13}ClNO_2S$ requires 318.0364.

*2-((4-Bromophenyl)sulfonyl)-6-methylquinoline (**3i**)*. Yellow solid, mp 123−124 °C, yield: 73%, 52.6 mg. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.0 Hz, 1H), 8.07 (m, J = 8.0 Hz, 1H), 7.95 (d, J = 12.0 Hz, 1H), 7.91 (d, J = 12.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 21.8, 117.6, 126.4, 128.8, 129.0, 129.1, 129.9, 130.5, 132.3, 133.5, 137.9, 138.3, 139.9, 146.1, 156.7; IR (KBr) ν_{max} 2984, 1567, 1300, 1179, 825, 512 cm^{-1}; HRMS (ESI): M + H^+ found 361.9857; $C_{16}H_{13}BrNO_2S$ requires 361.9859.

*2-((4-Acetylphenyl)sulfonyl)-6-methylquinoline (**3j**),*. White solid, mp 174−176 °C, yield: 50%, (32.5 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 2H), 2.62 (s, 3H), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 20.8, 25.9, 116.7, 125.4, 125.5, 127.7, 128.3, 128.9, 131.2, 132.6, 136.9, 139.0, 139.6, 142.1, 155.5, 196.8; IR (KBr) ν_{max} 2925, 1688, 1320, 1260, 1159, 820, 675 cm^{-1}; HRMS (ESI): M + H^+ found 326.0843; $C_{18}H_{16}NO_3S$ requires 326.0845.

*8-Methyl-2-(naphthalen-2-ylsulfonyl)quinoline (**3k**)*. White solid, mp 137−139 °C, yield: 52% (34.6 mg). ^{1}HNMR (500 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 8.45 (q, J = 10.0 Hz, 2H), 8.10 (d, J = 10.0 Hz, 1H), 8.06 (d, J = 10.0 Hz, 1H), 8.01 (d, J = 10.0 Hz, 1H), 7.95 (d, J = 5.0 Hz, 1H), 7.88 (d, J = 10.0 Hz,1H), 7.58−7.65 (m, 4H); 2.54 (s, 3H); $^{13}C\{^1H\}$ NMR(125 MHz,$CDCl_3$) δ: 20.7, 117.8, 123.7, 126.4, 127.5, 127.9, 128.9, 129.2, 129.5, 130.0, 130.7, 132.1, 133.4, 135.3, 137.8, 139.7, 146.1, 157.2; IR (KBr) ν_{max} 3858, 3637, 2901, 1636, 1297, 679 cm^{-1}; HRMS (ESI): M + H^+ found 334.0895; $C_{20}H_{16}NO_2S$ requires 334.0896.

*6-Methyl-2-(pyridin-3-ylsulfonyl)quinoline (**3l**)*. White solid, mp 156−157 °C, yield: 85% (48.2 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.25 (s, 1H), 8.74 (d, J = 4.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 12.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 12.0 Hz, 2H), 7.42 (dd, J = 8.0, 4.0 Hz, 1H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 20.8, 116.3, 122.6, 125.4, 128.0, 128.8, 132.6, 134.8, 135.7, 137.0, 139.1, 145.0, 148.9, 152.9.,155.4; IR (KBr) ν_{max} 2961, 1568, 1376, 1165, 1081, 1020, 798, 600 cm^{-1}; HRMS (ESI): M + H^+ found 285.0704; $C_{15}H_{13}N_2O_2S$ requires 285.0706.

*8-Methyl-2-(thiophen-2-ylsulfonyl)quinoline (**3m**)*. White solid, mp 147−148 °C, yield: 57%, (32.9 mg); ^1H NMR (500 MHz, $CDCl_3$) δ:8.35 (d, J = 10.0 Hz, 1H), 8.19 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 5.0 Hz, 1H), 7.71 (d, J = 5.0 Hz, 1H), 7.62 (d, J = 5.0 Hz, 1H), 7.54 (t, J = 5.0 Hz, 1H), 7.14 (t, J = 5.0 Hz, 1H), 2.75 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 17.6, 116.3, 125.5, 127.5, 129.0, 130.2, 131.0, 135.2, 138.5, 138.8, 143.8, 145.8, 156.9; IR (KBr) ν_{max} 2963, 2361, 1261, 1095, 801, 649, 604 cm^{-1}; HRMS (ESI): M + H^+ found 290.0316; $C_{14}H_{12}NO_2S_2$ requires 290.0318.

*2-(Dodecylsulfonyl)quinoline (**3n**)*. White solid, mp 168−169 °C, yield: 58%, (41.8 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, J = 8.0 Hz, 1H), 8.02 (t, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 3.13−3.05 (m, 1H), 2.95−2.87 (m, 1H), 1.89−1.81 (m, 1H), 1.58−1.47 (m, 1H), 1.38−1.26 (m, 2H), 1.13 (s, 16H), 0.78 (t, J = 4.0 Hz, 3H); $^{13}C\{^1H\}$ NMR(100 MHz, $CDCl_3$) δ:13.1, 20.9, 21.6, 27.6, 28.1, 28.3, 28.4, 28.5, 30.8, 53.9, 114.7, 126.7, 127.0 127.1, 128.2, 129.7, 137.2, 146.4, 164.0. IR (KBr) ν_{max} 2923, 1592, 1470, 1044, 840, 752, 632 cm^{-1}; HRMS (ESI): M + H^+ found 262.2160; $C_{21}H_{32}NO_2S$ requires 362.2162.

*2-((3-Chloropropyl)sulfonyl)quinoline (**3o**)*. White solid, mp 151−152 °C, yield: 72%, (38.7 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.46 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 3.69−3.76 (m, 4H), 2.33−2.40 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 25.6, 42.8, 49.2, 116.9, 127.9, 129.2, 129.4, 130.1, 131.3, 139.0, 147.1, 156.6; IR (KBr) ν_{max} 3877, 3751, 3612, 2901, 1613, 649, 427 cm^{-1}; HRMS (ESI): M + H^+ found 270.0362; $C_{12}H_{13}ClNO_2S$ requires 270.0364.

*2-(Phenylsulfonyl)quinoline (**3p**)*. White solid, mp 160−161 °C, yield: 74%, (39.8 mg); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, J = 12.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.07 (t, J = 8.0 Hz, 3H), 7.79 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H),

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7.52 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 116.7, 126.7, 127.8, 128.01, 128.07, 128.2, 129.3, 129.9, 130.0, 132.7, 137.7, 138.1, 146.4, 157.0; IR(KBr) ν_{max} 2925, 1321, 1165, 1129, 1020, 756, 639 cm^{-1}; HRMS (ESI): M + H^+ found 270.0595; $C_{15}H_{12}NO_2S$ requires 270.0597.

*3-Methyl-2-(phenylsulfonyl)quinoline (**3q**).* White solid, mp 146−148 °C, yield: 78%, (44.1 mg). ^1H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 5.0 Hz, 3H), 7.90 (d, J = 5.0 Hz, 1H), 7.78 (d, J = 5.0 Hz, 1H), 7.71−7.65 (m, 2H), 7.60(q, J = 5.0 Hz, 3H), 2.90 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 18.8, 126.7, 128.5, 128.6, 129.0, 129.1, 129.4, 129.8, 129.9, 133.5, 138.8, 139.8, 144.6, 156.9; *IR (KBr)* ν_{max} 3049, 1588, 1364, 527, 501, 416 cm^{-1}; HRMS (ESI): M + H^+ found 284.0738; $C_{16}H_{14}NO_2S$ requires 284.0740.

*4-Methyl-2-(phenylsulfonyl)quinoline (**3r**).* White solid, mp 145−146 °C, yield: 92% (52.1 mg). ^1H NMR (400 MHz, $CDCl_3$) δ:8.06 (t, J = 8.0 Hz, 3H), 7.96 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 2.70 (s, 3H); $^{13}C\{^1H\}$ NMR(100 MHz,$CDCl_3$) δ:18.1, 117.1, 122.8, 127.7, 127.92, 127.95, 128.0, 129.5, 130.0, 132.6, 138,2, 146.1, 146.9, 156.6; IR (KBr) ν_{max} 2962, 1312, 1110, 777, 687, 622 cm^{-1}; HRMS (ESI): M + H^+found 284.0753; $C_{16}H_{14}NO_2S$ requires 284.0754.

*5-Bromo-2-(phenylsulfonyl)quinoline (**3s**).* yellow solid, mp 180−182 °C, yield: 65% (45.0 mg): ^1H NMR (400 MHz, $CDCl_3$) δ: 8.69 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 3H), 7.85 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0, 1H), 7.54 (d, J = 8.0, 1H), 7.47 (t, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 117.8, 120.8, 127.3, 128.11, 128.15, 129.2, 130.1, 131.7, 132.9, 137.6, 137.7, 147.0, 157.9; IR (KBr) ν_{max} 2961, 1507, 1328, 1284, 1078, 812, 684 cm^{-1}; HRMS (ESI): M + H^+ found 347.9701; $C_{15}H_{11}BrNO_2S$ requires 347.9703.

*6-Methoxy-2-(phenylsulfonyl)quinoline (**3t**).* White solid, mp 147−149 °C, yield: 90% (53.8 mg), ^1H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 12.0 Hz, 1H), 8.06 (t, J = 8.0 Hz, 3H,), 7.98 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 4.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 54.7, 103.5, 117.2, 123.3, 126.7, 127.8, 128.0, 128.3, 129.4, 130.8, 132.5, 135.8, 142.6, 158.8; IR (KBr) ν_{max} 2926, 1316, 1166, 1073, 1024, 802, 601 cm^{-1}; HRMS (ESI): M + H^+ found 300.0701; $C_{16}H_{14}NO_3S$ requires 300.0703.

*7-Methyl-2-(phenylsulfonyl)quinoline (**3u**).* White solid, mp 144−145 °C, yield: 85% (48.0 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 3H), 7.86 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 4.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H),7.40 (d, J = 8.0 Hz, 1H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 20.8, 115.8, 125.9, 126.2, 126.7, 127.9, 128.0, 128.1, 130.5, 132.6, 137.2, 138.2, 140.6, 146.7, 156.9; IR (KBr) ν_{max} 2962, 1322, 852, 719, 686, 587 cm^{-1}; HRMS (ESI): M + H^+ found 284.0752; $C_{16}H_{14}NO_2S$ requires 284.0754.

*8-Methyl-2-(phenylsulfonyl)quinoline (**3v**).* White solid, mp 106−107 °C, yield: 82% (46.4 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, J = 8.0 Hz, 1H), 8.11(t, J = 8.0 Hz, 3H), 7.60 (d, J = 8.0 Hz, 1H), 7.55−7.41 (m, 5H), 2.57 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 17.4, 116.7, 125.5, 128.83, 128.89, 129.0, 129.4, 130.9, 133.6, 138.4, 138.8, 138.9, 146.3, 157.1; IR (KBr) ν_{max} 3018, 2916, 1477, 1468, 1302, 517 cm^{-1}; HRMS (ESI): M + H^+ found 284.0752; $C_{16}H_{14}NO_2S$ requires 284.0754.

*6-Chloro-2-(phenylsulfonyl)quinoline (**3w**).* White solid, mp 173−174 °C, yield 76% (46.0 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 12.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 12.0, 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 118.6, 126.3, 129.12, 129.17, 129.4, 131.9, 132.1, 133.9, 135.3, 137.8, 138.8, 145.8, 158.4; IR (KBr) ν_{max} 2947, 1531, 1301, 927, 816, 501 cm^{-1}; HRMS (ESI): M + H^+ found 304.0205; $C_{15}H_{11}ClNO_2S$ requires 304.0208.

*6-Bromo-2-(phenylsulfonyl)quinoline (**3x**).* Yellow solid, mp 180−182 °C, yield: 72% (49.8 mg). ^1H NMR (500 MHz,$CDCl_3$) δ: 8.26 (d, J = 10.0 Hz, 1H), 8.20 (d, J = 5.0 Hz, 1H), 8.12 (d, J = 10.0 Hz, 2H), 8.01 (s, 1H), 7.98 (d, J = 15.0 Hz, 1H), 7.80 (dd, J = 9.5 Hz, 7.0 Hz, 1H), 7.59 (t, J = 10.0 Hz, 1H), 7.53 (t, J = 10.0 Hz, 2H); ^{13}C NMR(125 MHz, $CDCl_3$) δ: 118.6, 123.6, 129.1, 129.2, 129.7, 131.6, 133.9, 134.6, 137.7, 138.8, 145.9, 158.5; IR (KBr) ν_{max} 2910, 1743, 1307, 1139, 814, 690 cm^{-1}; HRMS (ESI): M + H^+ found 347.9701; $C_{15}H_{11}BrNO_2S$ requires 347.9703.

*3-Iodo-2-tosylquinoline (**3y**).* White solid, mp 138−139 °C, yield: 70% (57.2 mg). ^1H NMR (500 MHz, $CDCl_3$) δ:8.88 (s, 1H), 8.00 (d, J = 10.0 Hz, 2H), 7.92 (d, J = 10.0 Hz, 1H), 7.75 (t, J = 10.0 Hz, 2H), 7.67 (t, J = 10.0 Hz, 1H), 7.39 (d, J = 10.0 Hz, 2H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 21.7, 79.9, 126.3, 129.3, 129.82, 129.85, 130.0, 130.1, 131.2, 134.5, 144.7, 144.8, 150.5, 156.3; IR (KBr) ν_{max} 2927, 1687, 1301, 1064, 738, 641 cm^{-1}; HRMS (ESI): M + H^+ found 409.9718; $C_{16}H_{13}INO_2S$ requires 409.9720.

*6-Nitrophenyl-2-tosylquinoline (**3z**).* White solid, mp 170−171 °C, yield: 60% (39.4 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 3H), 2.59 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 17.5, 116.6, 125.6, 128.9,129.13, 129.17, 130.9, 131.1, 132.1, 137.9, 138.3, 138.9,146.4, 156.7 ;IR (KBr) ν_{max} 3078, 2907, 1666, 1301, 1051, 723 cm^{-1}; HRMS (ESI): M + H^+ found 329.0603; $C_{16}H_{13}N_2O_4S$ requires 329.0605.

*1-(Phenylsulfonyl)isoquinoline (**3aa**).* White solid, mp 159−161 °C, yield: 71% (38.2 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.07 (d, J = 4.0 Hz, 1H), 8.33 (d, J = 4.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 4.0 Hz, 1H), 7.69 (t, J = 4.0 Hz, 3H), 7.56 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 123.3, 124.0, 124.2, 126.5, 127.8, 128.1, 128.2, 130.1, 132.6, 136.7, 138.0, 139.5, 155.9; IR (KBr) ν_{max} 1496, 1298, 1139, 1081, 720, 684, 591 cm^{-1}; HRMS (ESI): M + H^+ found 270.0581; $C_{15}H_{12}NO_2S$ requires 270.0583.

*2-(Phenylsulfonyl)pyridine (**3ab**).* White solid, mp 95−96 °C, yield: 72%, (31.5 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, J = 4.0 Hz, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 3H), 7.18 (d, J = 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR(100 MHz, $CDCl_3$) δ: 117.3, 123.6, 123.8, 127.8, 128.10, 128.13, 130.1, 137.1, 148.7; IR (KBr) ν_{max} 3052, 1574, 1419, 1088, 837, 788 cm^{-1}; HRMS (ESI): M + H^+ found 220.0439; $C_{11}H_{10}NO_2S$ requires 220.0441.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00475.

^1H and ^{13}C NMR spectra of compounds **3a−3ab** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chatgilialoglu, C.; Asmus, K.-D. *Sulfur-Centered Reactive Intermediates in Chemistry and Biology*; Plenum Press: New York, 1990. (b) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press, Oxford, 1993. (c) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1995. (d) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008.

DOI: 10.1021/acs.joc.6b00475
J. Org. Chem. 2016, 81, 4981−4987

(2) (a) *Pharmaceutical Chemistry. Drug Synthesis*; Roth, H. J., Kleemann, A., Eds.; Prentice Hall Europe: London, 1988; Vol. *1*, p 407. (b) Jones, G. In *Comprehensive Heteroaromatic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon Press: Oxford, 1996; Vol. *5*, p 167. (c) Graul, A.; Castaner, J. *Drugs Future* **1997**, *22*, 956. (d) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 4th ed.; Thieme: Stuttgart, Germany, 2001. (e) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039. (f) Boaen, N. K.; Hillmyer, M. A. *Chem. Soc. Rev.* **2005**, *34*, 267. (g) Wellington, K.; Plosker, G. L. *Drugs* **2002**, *62*, 1539. (h) Rajiv Dua, S. S.; Sonwane, S. K.; Srivastava, S. K. *Adv. Biol. Res.* **2011**, *5*, 120. (i) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(3) (a) *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH, Weinheim, 1998. (b) Hang, X.-C.; Fleetham, T.; Turner, E.; Brooks, J.; Li, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6753−6756.

(4) (a) Bartholow, M. Top 200 Drugs of 2011. *Pharmacy Times*. http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011 (accessed on January 9, 2013). (b) For a list of top drugs by year, see: http://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster (accessed on January 9, 2013). (c) Drews, J. *Science* **2000**, *287*, 1960.

(5) (a) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343−7348. (b) Katrun, P.; Mueangkaew, C.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. *J. Org. Chem.* **2014**, *79*, 1778−1785. (c) Chen, Z.-Z.; Liu, S.; Hao, W.-J.; Xu, G.; Wu, S.; Miao, J.-N.; Jiang, B.; Wang, S.-L.; Tu, S.-J.; Li, G. *Chem. Sci.* **2015**, *6*, 6654−6658. (d) Zuo, J.; Wu, Z.-J.; Zhao, J.-Q.; Zhou, M.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 634−640. (e) Zhang, M.; Xie, P.; Zhao, W.; Niu, B.; Wu, W.; Bian, Z.; Pittman, C. U.; Zhou, A. *J. Org. Chem.* **2015**, *80*, 4176−4183. (f) Wen, J.; Wei, W.; Xue, S.; Yang, D.; Lou, Y.; Gao, C.; Wang, H. *J. Org. Chem.* **2015**, *80*, 4966−4972.

(6) (a) Furukawa, N.; Ogawa, S.; Matsumura, K.; Fujihara, H. *J. Org. Chem.* **1991**, *56*, 6341−6348. (b) Trankle, W. G.; Kopach, M. E. *Org. Process Res. Dev.* **2007**, *11*, 913−917. (c) Xue, F.; Wang, D.; Li, X.; Wan, B. *J. Org. Chem.* **2012**, *77*, 3071−3081.

(7) (a) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696−2700. (b) Maloney, K. M.; Kuethe, J. T.; Linn, K. *Org. Lett.* **2011**, *13*, 102−105. (c) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226−6229.

(8) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. *Org. Lett.* **2013**, *15*, 1270−1273.

(9) Sun, K.; Chen, X.-L.; Li, X.; Qu, L.-B.; Bi, W.-Z.; Chen, X.; Ma, H.-L.; Zhang, S.-T.; Han, B.-W.; Zhao, Y.-F.; Li, C.-J. *Chem. Commun.* **2015**, *51*, 12111−12114.

(10) Henze, M. *Ber. Dtsch. Chem. Ges. B* **1936**, *69*, 1566−1568.

(11) (a) Hayashi, E.; Shimada, N. *Yakugaku Zasshi* **1977**, *97*, 1345−1352. (b) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554−4557. (c) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792−795. (d) Londregan, A. T.; Burford, K.; Conn, E. L.; Hesp, K. D. *Org. Lett.* **2014**, *16*, 3336−3339. (e) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. *Org. Lett.* **2014**, *16*, 1840−1843. (f) Chen, X.; Cui, X.; Yang, F.; Wu, Y. *Org. Lett.* **2015**, *17*, 1445−1448. (g) Vamos, M.; Cosford, N. D. P. *J. Org. Chem.* **2014**, *79*, 2274−2280. (h) Chen, Y.; Huang, J.; Hwang, T.-L.; Chen, M. J.; Tedrow, J. S.; Farrell, R. P.; Bio, M. M.; Cui, S. *Org. Lett.* **2015**, *17*, 2948−2951. (i) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 2384−2391. (j) Lawler, R. G.; Tabit, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 5671−5672.

(12) (a) Wu, X.-F.; Gong, J.-L.; Qi, X. *Org. Biomol. Chem.* **2014**, *12*, 5807−5817. (b) Liu, D.; Lei, A. *Chem. - Asian J.* **2015**, *10*, 806−823. (c) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376−1379. (d) Chen, S.; Xu, Y.; Wan, X. *Org. Lett.* **2011**, *13*, 6152−6155. (e) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331−5334. (f) Huang, J.; Li, L.-T.; Li, H.-Y.; Husan, E.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 10204−10206. (g) Lee, E.; Ryu, T.; Park, Y.; Park, S.; Lee, P. H. *Adv. Synth. Catal.* **2013**, *355*, 1585−1596. (h) Yang, Z.; Hao, W.-J.; Wang, S.-L.; Zhang, J.-P.; Jiang, B.; Li, G.; Tu, S.-J. *J. Org. Chem.* **2015**, *80*, 9224−9230. (i) Zhu, Y.-L.; Jiang, B.; Hao, W.-J.; Qiu, J.-K.; Sun, J.; Wang, D.-C.; Wei, P.; Wang, A.-F.; Li, G.; Tu, S.-J. *Org. Lett.* **2015**, *17*, 6078−6081.

(13) Friedman, L.; Litle, R. L.; Reichle, W. R. *Org. Synth.* **1960**, *40*, 93−95.

(14) (a) Yu, W.; Hu, P.; Fan, Y.; Yu, C.; Yan, X.; Li, X.; Xu, X. *Org. Biomol. Chem.* **2015**, *13*, 3308−3313. (b) Tang, Y.; Zhang, Y.; Wang, K.; Li, X.; Xu, X.; Du, X. *Org. Biomol. Chem.* **2015**, *13*, 7084−7090. (c) Yotphan, S.; Sumunnee, L.; Beukeaw, D.; Buathongjan, C.; Reutrakul, V. *Org. Biomol. Chem.* **2016**, *14*, 590−597. (d) Singh, R.; Allam, B. K.; Singh, N.; Kumari, K.; Singh, S. K.; Singh, K. N. *Org. Lett.* **2015**, *17*, 2656−2659. (e) Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, *48*, 12240−12242. (f) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Suo, Y.; Wang, H. *Chem. Commun.* **2013**, *49*, 10239−10241. (g) Qiu, J.-K.; Hao, W.-J.; Wang, D.-C.; Wei, P.; Sun, J.; Jiang, B.; Tu, S.-J. *Chem. Commun.* **2014**, *50*, 14782−14785. (h) Wei, W.; Wen, J.; Yang, D.; Guo, M.; Wang, Y.; You, J.; Wang, H. *Chem. Commun.* **2015**, *51*, 768−771. (i) Rong, G.; Mao, J.; Yan, H.; Zheng, Y.; Zhang, G. *J. Org. Chem.* **2015**, *80*, 4697−4703.

(15) Bering, L.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 3134−3137.

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