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# Intermolecular Amidation of Quinoline *N*-Oxides with Arylsulfonamides under Metal-Free Conditions

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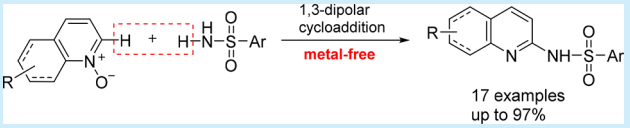
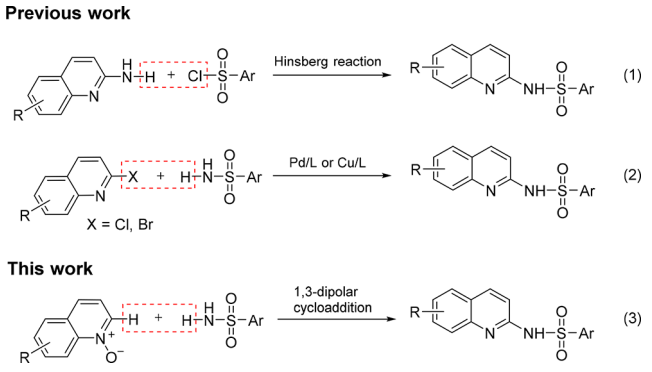
Supporting Information

**ABSTRACT:** An efficient method for the synthesis of *N*-(quinolin-2-yl)sulfonamides is described. The intermolecular amidation of quinoline *N*-oxides with sulfonamides proceeded smoothly in the presence of $PhI(OAc)_2$ and $PPh_3$ to afford *N*-(quinolin-2-yl)sulfonamides in satisfactory to excellent yields.




The *N*-(quinolin-2-yl)sulfonamide structural motifs have been frequently found in the frameworks of various pharmacologically active compounds and functional dyes.[1,2] Thus, the development of convenient and efficient methods for the synthesis of *N*-(quinolin-2-yl)sulfonamides is attracting considerable attention. Over the past years, two main methods have been developed for the synthesis of *N*-(quinolin-2-yl)sulfonamides. The most common method of synthesizing *N*-(quinolin-2-yl)sulfonamides is sulfonylation reactions of 2-amino-substituted quinolines with arylsulfonyl chlorides,[3] namely the Hinsberg reaction (Scheme 1, eq 1).[4] The second method involves the transition-metal-catalyzed cross-coupling of sulfonamides with halogenated quinolines (Scheme 1, eq 2).[5] Although these methods can be employed to synthesize *N*-(quinolin-2-yl)sulfonamides, these methods are limited by various factors, such as microwave radiation, high temperature, and the use of organic halides. In transition-metal-catalyzed reactions, specific ligands or Lewis acids are generally necessary because the ligating ability of heteroatoms can lead to catalyst deactivation; the electronic properties of specific ring positions can be unfavorable for elementary reactions.[6]

**Scheme 1. Synthesis of *N*-(Quinolin-2-yl)sulfonamides**




Recently, the nucleophilic addition of amines and amides to quinoline *N*-oxides has been considered as a common approach to synthesize 2-aminoquinolines.[7] However, the mixture of 2-aminoquinoline and 4-aminoquinoline is commonly obtained because of their poor 2,4-regioselectivity in these reactions. In addition, this type of the nucleophilic addition usually requires more nucleophilic amides. It is well-known that sulfonamides are difficult to use as nucleophiles for nucleophilic substitution reactions due to their poor nucleophilicity.[8] Therefore, the nucleophilic addition of sulfonamides to quinoline *N*-oxides for the synthesis of *N*-(quinolin-2-yl)sulfonamides remains a challenge.

In the course of our continuing research on the dehydrogenative reaction of amine *N*-oxide under metal-free conditions,[9] the intermolecular amidation of quinoline *N*-oxides with sulfonamides has been found to proceed in the presence of $PhI(OAc)_2$ and $PPh_3$ through 1,3-dipolar [3 + 3]-cycloaddition. A new type of 1,3-dipolar cycloaddition of quinoline *N*-oxides with sulfonamides should provide the following synthetic advantages: (1) overcome the extremely poor reactivity of sulfonamides as nucleophiles and (2) realize quinoline *N*-oxides as 1,3-dipoles to provide various *N*-(quinolin-2-yl)sulfonamides by cycloaddition.

In our initial studies, the intermolecular amidation of quinoline *N*-oxide (**1a**) with 4-methylbenzenesulfonamide (**2a**) was selected as a model reaction to optimize the reaction conditions. Table 1 summarizes the preliminary results.

The reaction of **1a** with **2a**, PhI=O, and $PPh_3$ proceeded smoothly at 80 °C and produced the desired product **3a** with 43% yield (Table 1, entry 1). The use of $PhI(OTf)_2$ and PhI(OH)OTs as trivalent iodine compounds, instead of PhI=O, afforded the desired product in poor yields (5% and 24%, respectively; Table 1, entries 2 and 3). The desired reaction proceeded smoothly with $PhI(OAc)_2$ to yield 97% **3a** (Table 1, entry 4). No reaction was observed in the absence of a trivalent iodine compound (Table 1, entry 5). The solvents were screened by using $PPh_3$ as an additive (entries 4, 6–10). Nonpolar (toluene and 1,2-dichloroethane) and polar (dioxane,

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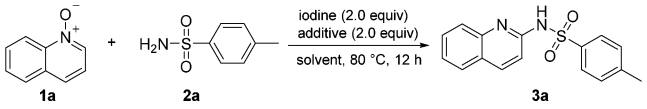
**Table 1. Optimization of Reaction Conditions**[a]




1a 2a 3a

| entry | iodine | additive | solvent | yield[b] (%) |
|---|---|---|---|---|
| 1 | PhI=O | $PPh_3$ | $CH_3CN$ | 43 |
| 2 | $PhI(OTf)_2$ | $PPh_3$ | $CH_3CN$ | 5 |
| 3 | PhI(OH)OTs | $PPh_3$ | $CH_3CN$ | 24 |
| 4 | $PhI(OAc)_2$ | $PPh_3$ | $CH_3CN$ | 97 |
| 5 | | $PPh_3$ | $CH_3CN$ | 0 |
| 6 | $PhI(OAc)_2$ | $PPh_3$ | toluene | 72 |
| 7 | $PhI(OAc)_2$ | $PPh_3$ | DCE | 64 |
| 8 | $PhI(OAc)_2$ | $PPh_3$ | dioxane | 59 |
| 9 | $PhI(OAc)_2$ | $PPh_3$ | acetone | 59 |
| 10 | $PhI(OAc)_2$ | $PPh_3$ | DMF | 84 |
| 11 | $PhI(OAc)_2$ | | $CH_3CN$ | 21 |

[a]Reaction conditions: quinoline *N*-oxide (**1a**) (1.0 mmol, 145 mg), sulfonamides **2a** (0.5 mmol, 85.0 mg), $PhI(OAc)_2$ (322 mg, 1.0 mmol), $PPh_3$ (262 mg,1.0 mmol), and $CH_3CN$ (2.0 mL), 80 °C, 12 h. [b]Isolated yield was provided.

acetone, DMF, and $CH_3CN$) solvents were examined. Among these solvents, $CH_3CN$ was the most effective (entry 4). However, the reaction of quinoline *N*-oxide with sulfonamide was performed in the absence of $PPh_3$ to produce **3a** with 21% yield (Table 1, entry 11).

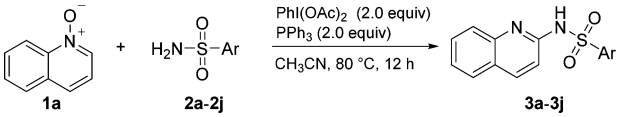
The reactions of sulfonamides **2a−j** with quinoline *N*-oxide were performed under optimized conditions. The results are summarized in Table 2. Good to excellent yields of *N*-quinolinesulfonamides **3a−f** were obtained from the reactions of sulfonamides **2a−f** (entries 1−6, 70%−97%). A relatively higher yield of *N*-(quinolin-2-yl)sulfonamide was synthesized from a sulfonamide bearing an electron-donating group on the benzene ring than that from a sulfonamide bearing an electron-withdrawing group on benzene ring (entries 1 and 4 vs entry 5).

The sulfonamide **2g** bearing an $-NH_2$ group on the benzene ring was also suitable for this reaction to produce 70% *N*-(quinolin-2-yl)sulfonamide **3g** (entry 7). The sulfonamides **2h** and **2i** that contain a halogen atom (Br or Cl) were also employed successfully to synthesize *N*-(quinolin-2-yl)-sulfonamides. The corresponding products **3h** and **3i** were obtained in 87% and 93% yields, respectively (entries 8 and 9). The reaction of 5-bromothiophene-2-sulfonamide (**2j**) was evaluated under the same conditions, and *N*-(quinolin-2-yl)sulfonamide **3j** was formed with 45% yield (entry 10).

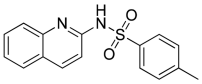
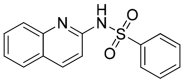
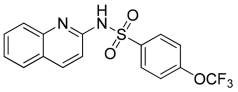
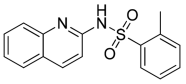
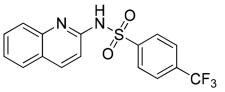
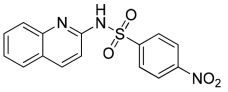
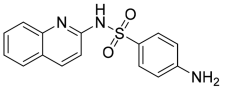
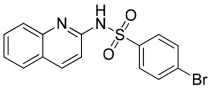
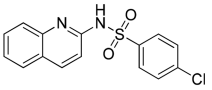
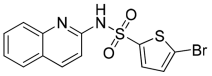
Good preliminary results encouraged us to examine the scope of this reaction for various quinoline *N*-oxides under the optimized reaction conditions; the results are summarized in Table 3. The reaction of quinoline *N*-oxides **1b−e** with sulfonamide **2a** produced **3k−n** in satisfactory yields (Table 2, entries 1−4). The relatively low yield of **3m** was attributed to the steric effect of the 8-methyl group in quinoline *N*-oxide substrate (entry 3). Low yield (55%) was also observed in the reaction of **1f** bearing a bromo on quinoline (entry 5).

To extend the scope of this reaction, isoquinoline *N*-oxide (**1h**) and 2-phenylpyridine *N*-oxide (**1g**) were employed to react with **2a** under the optimized conditions. The results are shown in Scheme 2. The reaction of **1h** with **2a** proceeded smoothly to produce sulfonamide **3p** in 94% yield (Scheme 2, eq 4). New product **3p** was identified by means of its NMR, IR,

**Table 2. Amidation of Quinoline *N*-Oxide with Benzenesulfonamide Derivatives under Metal-Free Conditions**[a]




1a 2a-2j 3a-3j

| entry | Ar of amide **2** | product **3** | | yield (%)[b] |
|---|---|---|---|---|
| 1 | **2a**: 4-MePh |  | **3a** | 97 |
| 2 | **2b**: Ph |  | **3b** | 86 |
| 3 | **2c**: 4-$CF_3O$Ph |  | **3c** | 87 |
| 4 | **2d**: 2-MePh |  | **3d** | 90 |
| 5 | **2e**: 4-$CF_3$Ph |  | **3e** | 70 |
| 6 | **2f**: 4-$NO_2$Ph |  | **3f** | 83 |
| 7 | **2g**: 4-$NH_2$Ph |  | **3g** | 70 |
| 8 | **2h**: 4-BrPh |  | **3h** | 87 |
| 9 | **2i**: 4-ClPh |  | **3i** | 93 |
| 10 | **2j**:  |  | **3j** | 45 |

[a]Reaction conditions: quinoline *N*-oxide (**1a**) (1.0 mmol, 145 mg), sulfonamides **2a−j** (0.5 mmol), $PhI(OAc)_2$ (322 mg, 1.0 mmol), $PPh_3$ (262 mg, 1.0 mmol), and $CH_3CN$ (2.0 mL), 80 °C, 12 h. [b]Isolated yield was provided.

and HRMS data and X-ray structure (Figure 1).[10] A test on **1g** with sulfonamide **2a** was also carried out. However, the yield of sulfonamide **3q** was only 19% (Scheme 2, eq 5). This low yield was not improved when the reaction temperature and time were increased or large amounts of $PhI(OAc)_2$ and $PPh_3$ were added.

Control experiments were conducted to gain insights into the mechanism of this type of amidation reactions. *N*-(4-Methylphenylsulfonyl) imino-phenyl-$\lambda^3$-iodane (**A**) was synthesized via the reaction of **2a** with $PhI(OAc)_2$ with 90% yield to verify the proposed mechanism of the present method (Scheme 3). Subsequently, the 1,3-dipolar [3 + 3]-cycloaddition reaction



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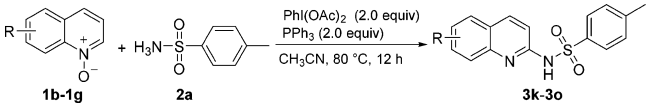
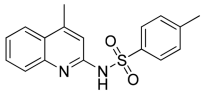
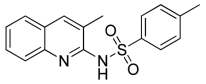
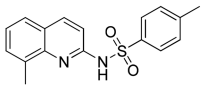
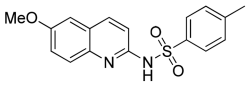
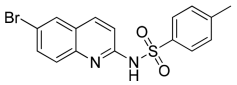
**Table 3. Amidation of Quinoline *N*-Oxide Derivatives with 4-Methylbenzenesulfonamide under Metal-Free Conditions**[a]

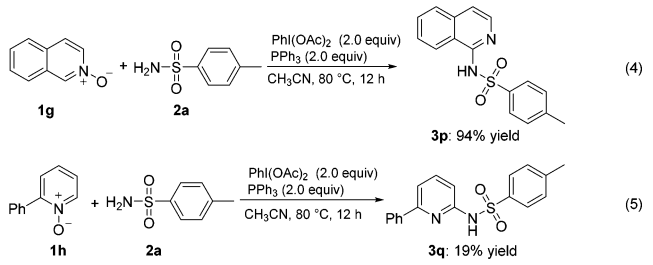



1b-1g 2a 3k-3o

| entry | R of *N*-oxide **1** | product **3** | | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1b**: 4-Me |  | **3k** | 88 |
| 2 | **1c**: 3-Me |  | **3l** | 80 |
| 3 | **1d**: 8-Me |  | **3m** | 70 |
| 4 | **1e**: 6-MeO |  | **3n** | 80 |
| 5 | **1f**: 6-Br |  | **3o** | 55 |

[a]Reaction conditions: quinoline *N*-oxide derivatives **1b−g** (1.0 mmol), 4-methylbenzenesulfonamide (0.5 mmol, 85.0 mg), $PhI(OAc)_2$, (1.0 mmol 322 mg), and $PPh_3$ (1.0 mmol, 262 mg) in $CH_3CN$ (2.0 mL) at 80 °C for 12 h. [b]Isolated yield.

**Scheme 2. Amidation of Isoquinoline *N*-Oxide and 2-Phenylpyridine *N*-Oxide with 4-Methylbenzenesulfonamide**



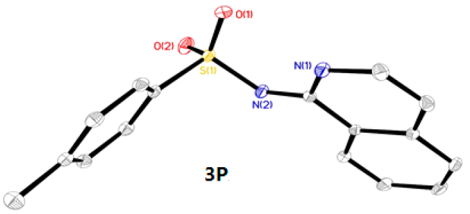
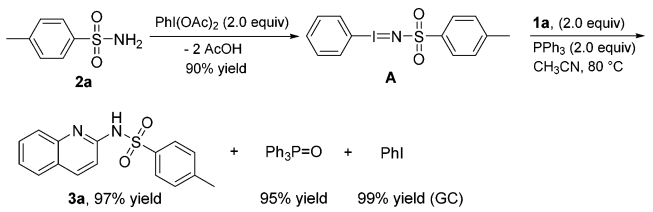




**Figure 1.** X-ray structure of **3p**.

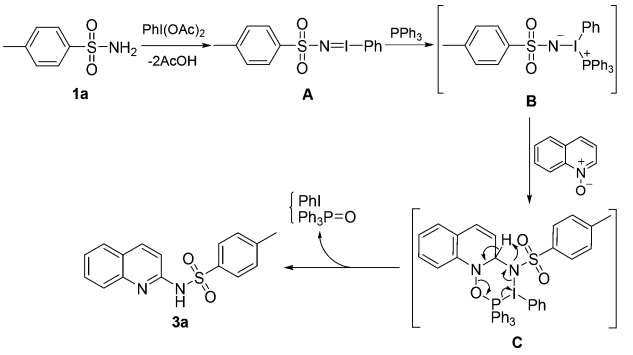
**Scheme 3. Control Experiment**




of **A** with quinoline *N*-oxide and $PPh_3$ was carried out to produce **3a**, $Ph_3P$ = O, and PhI in almost the same yield (97% isolated yield vs 95% isolated yield vs 99% GC yield).

Scheme 4 shows the proposed mechanism for the 1,3-dipolar [3 + 3]-cycloaddition reaction of quinoline *N*-oxides with

**Scheme 4. Schematic of the Proposed Mechanism**




sulfonamides $PhI(OAc)_2$ and $PPh_3$. The reaction of **2a** with $PhI(OAc)_2$ proceeded to produce tolylsulfonyl imino iodo arene (**A**).[11] After $PPh_3$ was added to **A**, intermediate **B** was generated. The 1,3-dipolar [3 + 3]-cycloaddition reaction of quinoline *N*-oxides with intermediate **B** may have occurred to generate the six-membered intermediate **C**; the ring-opening reaction then proceeded to yield the desired product **3a**.

In summary, we developed a new method to synthesize *N*-quinolinesulfonamides via 1,3-dipolar [3 + 3]-cycloaddition reactions by quinoline *N*-oxides, sulfonamides, $PhI(OAc)_2$, and $PPh_3$. The new method is applicable to various quinoline N-oxide substrates and sulfonamides; hence, this methodology could be used to synthesize organic substances, particularly in the context of biologically active target molecules and pharmaceutical research areas. Further investigations are underway to apply this methodology in organic compound synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02922.

Experimental procedures and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Jacobsen, J. A.; Fullagar, J. L.; Miller, M. T.; Cohen, S. M. *J. Med. Chem.* **2011**, *54*, 591−602. (b) Galiana-Rosello, C.; Bilbao-Ramos, P.; Auxiliadora Dea-Ayuela, M.; Rolon, M.; Vega, C.; Bolas-Fernandez, F.; Garcia-Espana, E.; Alfonso, J.; Coronel, C.; Eugenia Gonzalez-Rosende, M. *J. Med. Chem.* **2013**, *56*, 8984−8998. (c) Nair, S. K.; Matthews, J. J.; Cripps, S. J.; Cheng, H. M.; Hoffman, J. E.; Smith, C.; Kupchinsky, S.; Siu, M.; Taylor, W. D.; Wang, Y.; Johnson, T. O.; Dress, K. R.; Edwards, M. P.; Zhou, S.; Hosea, N. A.; LaPaglia, A.; Kang, P.; Castro, A.; Ermolieff, J.; Fanjul, A.; Vogel, J. E.; Rejto, P.; Dalvie, D.; Bioorg. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2344−2348.

(2) (a) Lee, J. W.; Jung, H. S.; Kwon, P. S.; Kim, J. W.; Bartsch, R. A.; Kim, Y.; Kim, S.-J.; Kim, J. S. *Org. Lett.* **2008**, *10*, 3801−3804. (b) Hong, J. H.; Lee, S.; Jung, H. S.; Lee, K. B.; Kim, J. S. *Bull. Korean Chem. Soc.* **2010**, *31*, 3391−3394.

(3) (a) Hultquist, M. E.; Germann, R. P.; Webb, J. S.; Wright, W. B.; Roth, B.; Smith, J. M.; Subbarow, Y. *J. Am. Chem. Soc.* **1951**, *73*, 2558−2566. (b) Kokatla, H. P.; Yoo, E.; Salunke, D. B.; Sil, D.; Ng, C. F.; Balakrishna, R.; Malladi, S. S.; Fox, L. M.; David, S. A. *Org. Biomol. Chem.* **2013**, *11*, 1179−1198.

(4) Hinsberg, O. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2962−2965.

(5) Baffoe, J.; Hoe, M. Y.; Toure, B. B. *Org. Lett.* **2010**, *12*, 1532−1535.

(6) Shen, Q. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734−7735.

(7) (a) Yin, J. J.; Xiang, B. P.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554−4557. (b) Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341−1344.

(8) (a) Martinez-Asencio, A.; Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **2010**, *51*, 325−327. (b) Qu, P. P.; Sun, C. L.; Ma, J.; Li, F. *Adv. Synth. Catal.* **2014**, *356*, 447−459.

(9) (a) Xu, Z. W.; Yu, X. Q.; Feng, X. J.; Bao, M. *J. Org. Chem.* **2012**, *77*, 7114−7118. (b) Xu, Z. W.; Yu, X. Q.; Feng, X. J.; Bao, M. *Beilstein J. Org. Chem.* **2012**, *8*, 1564−1568.

(10) The structural assignment was based on the analysis of the $^{1}$H and $^{13}$CNMR spectra. The product of **3p** was further identified by determining its X-ray structure; the crystallographic data are available in the Supporting Information.

(11) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744−6746. (b) Brandt, P.; Sodergren, M. J.; Andersson, P. G.; Norrby, P. O. *J. Am. Chem. Soc.* **2000**, *122*, 8013−8020. (c) Wu, Q.; Hu, J.; Ren, X. F.; Zhou, J. R. *Chem. - Eur. J.* **2011**, *17*, 11553−11558. (d) Yoshimura, A.; Luedtke, M. W.; Zhdankin, V. V. *J. Org. Chem.* **2012**, *77*, 2087−2091.



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