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tert-Butyl Hydroperoxide Mediated Cascade Synthesis of 3-Arylsulfonylquinolines

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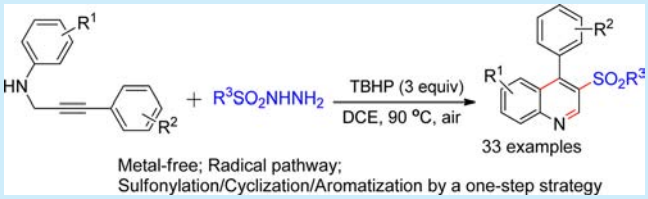
Supporting Information

ABSTRACT: 3-Arylsulfonylquinoline derivatives play important roles as pharmaceutical drugs. A new method for the synthesis of 3-arylsulfonylquinoline derivatives has been achieved through *tert*-butyl hydroperoxide mediated cycloaddition between *N*-propargyl aromatic amine derivatives and arylsulfonylhydrazides without the addition of any metals. This transformation offers a straightforward route to the formation of a C−S bond and quinoline ring in one step via a sulfonylation−cyclization−aromatization process.



Substituted quinoline derivatives are important in various research areas, such as in natural product synthesis and in medicinal chemistry.[1] A prominent example is quinine, an alkaloid found in plants.[1b] 4-Hydroxy-2-alkylquinolines are involved in antibiotic resistance.[2] Because of this importance, the quinoline moiety continues to attract the attention of organic chemists. Various methodologies have been described for the construction of quinoline skeletons.[3]

On the other hand, organosulfones are important intermediates in organic synthesis and have a wide application in the fields of agrochemicals, pharmaceuticals, and materials chemistry.[4] Examples of sulfones in pharmacology include dapsone, a drug formerly used as an antibiotic to treat leprosy, dermatitis herpetiformis, tuberculosis, or pneumocystis pneumonia. 3-(Phenylsulfonyl)quinoline derivatives are useful as central nervous system agents and are particularly useful as anti-obesity agents and for the treatment of hypertension.[5] However, the efficient synthesis of molecules bearing both a quinoline motif and a sulfonyl group is quite limited. In 2013, synthesis of 2-(arylsulfonyl)quinolone *N*-oxides from quinoline *N*-oxides and sulfonyl chlorides was presented by Cui's group.[6] In 2015, Chen et al. reported that H-phosphonate mediated sulfonylation of quinoline *N*-oxides directly led to a variety of 2-sulfonylquinolones.[7] These breakthroughs for the preparation of quinoline-based sulfones are highly efficient and compatible with a variety of functional groups. However, in Chen's method, the P(O)−H compound as an additive is used in excess, which is quite wasteful. Moreover, only quinolone derivatives were used as the starting materials.

Arylsulfonohydrazide is a cheap and stable sulfonyl species.[8] Combined use of *tert*-butyl hydroperoxide (TBHP) with transition metals[9] or iodine[10] to produce sulfonyl radicals from sulfonohydrazides has gained considerable momentum over the past few years, holding promise for defining new paradigms en route to S-containing organic compounds. It is still an attractive but challenging task to develop a metal-free, environmentally benign method to access other important sulfonated compounds in high yields from sulfonohydrazides.

Our continued interest in the construction of heterocyclic scaffolds via the difunctionalization of unsaturated compounds[11] prompted us to explore an environmentally benign method for the synthesis of 3-sulfonylquinolones from *N*-propargylaniline derivatives and arylsulfonohydrazides. This idea was first examined by using **1a** and 4-methylbenzenesulfonohydrazide ($TsNH_2NH_2$, **2a**) as reaction partners (Table 1). In the beginning, with 20 mol % of tetrabutylammonium iodide (TBAI) as the catalyst and 3.0 equiv of TBHP as the oxidant, the reaction of *N*-(3-phenyl-2-propynyl)aniline (**1a**)[12] with **2a** was performed in DCE at 90 °C under air conditions, affording the expected 4-phenyl-3-tosylquinoline (**3a**) in 79% yield (Table 1, entry 1).[10c−e,13] Other catalysts were also efficient for this reaction (entries 2−4). To our surprise, in the absence of any added catalyst, TBHP was chosen as the oxidant, and **3a** was obtained in 83% yield (entry 5). Other peroxides were also examined, such as di-*tert*-butylperoxide (DTBP), H_2O_2, and $K_2S_2O_8$, but TBHP exhibited the best efficiency (entries 6−8). Reaction yield was not improved by varying the TBHP concentration. Screening a few other solvents, such as DMSO, CH_3CN, and H_2O, revealed that DCE was the best choice (entries 9−11). However, the yield of product **3a** decreased when the temperature was decreased to 60 °C or increased to 100 °C (entries 12 and 13). The same yield was obtained when the reaction was conducted under a nitrogen atmosphere (entry

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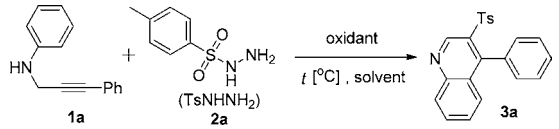
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst[b]	oxidant (equiv)	solvent	t (°C)	yield[c] (%)
1	TBAI	TBHP (3)	DCE	90	79
2	KI	TBHP (3)	DCE	90	76
3	$FeCl_3$	TBHP (3)	DCE	90	60
4	$Cu(OAc)_2$	TBHP (3)	DCE	90	55
5		**TBHP (3)**	**DCE**	**90**	**83**
6		DTBP (3)	DCE	90	18
7		H_2O_2 (3)	DCE	90	trace
8		$K_2S_2O_8$ (3)	DCE	90	42
9		TBHP (3)	DMSO	90	46
10		TBHP (3)	CH_3CN	90	74
11		TBHP (3)	H_2O	90	trace
12		TBHP (3)	DCE	60	58
13		TBHP (3)	DCE	100	78
14[d]		TBHP (3)	DCE	90	83
15[e]		TBHP (3)	DCE	90	82

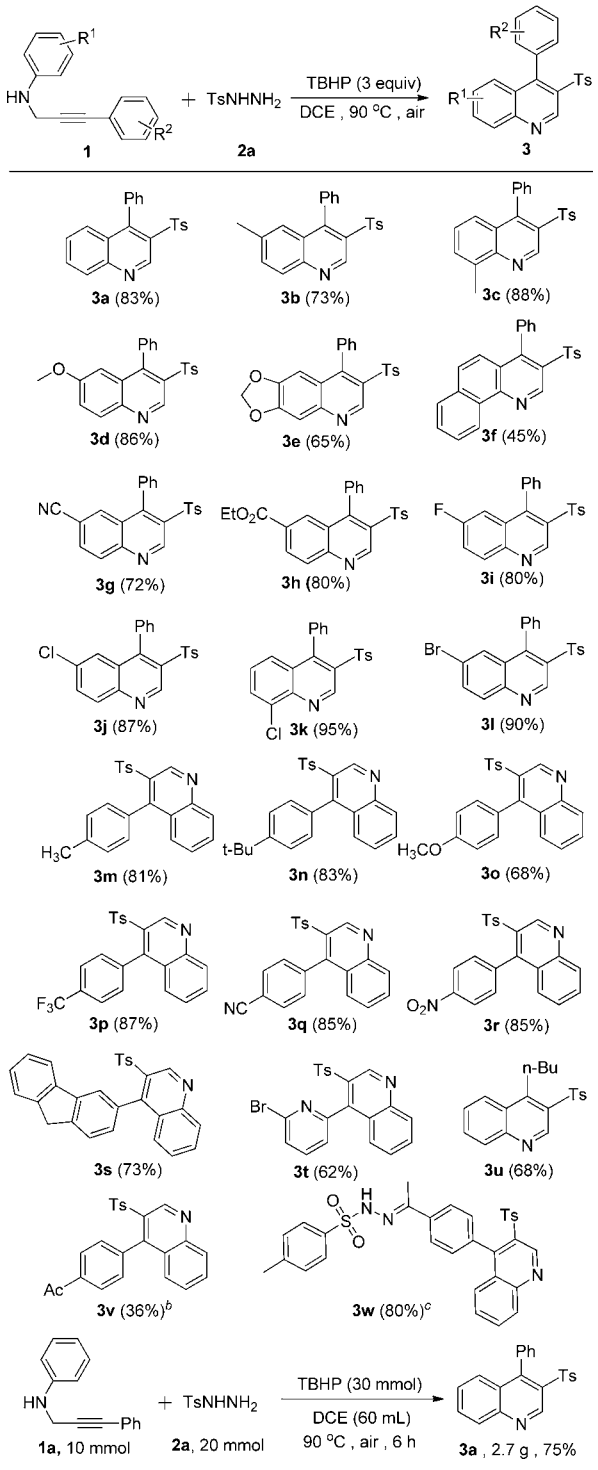
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), and oxidant (3 equiv) in solvent (2.5 mL) at 90 °C with stirring under air for 5 h. Oil bath. [b]Catalyst (20 mol %). [c]Yield of isolated product. [d]Under nitrogen. [e]**2a** (0.6 mol).

14). Moreover, the yield did not increase when 3 equiv of **2a** was added (entry 15). After optimization of the reaction conditions, we established a metal-free, environmentally benign route for the formation of 3-tosylquinolines (entry 5).

With the optimal conditions in hand, the generality of the method was explored, and the results are summarized in Scheme 1. First, the substitution pattern on the aromatic ring of the aniline group was explored (R^1; Scheme 1). Electron-donating groups on the aromatic ring produced the corresponding 3-tosylquinolines in good yields (**3b**−**3f**). Electron-withdrawing groups (CN, COOMe) on the benzene ring were also investigated and smoothly converted into products **3g** and **3h** in 72 and 80% yields, respectively. Halogen atoms such as fluoro, chloro, and bromo on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **3i**−**3l** in good to excellent yields, which could allow for further synthetic transformations. The structure of **3k** was confirmed by single-crystal X-ray analysis (Figure 1). Substrates bearing electron-donating (methyl, *tert*-butyl, and methoxy) or electron-withdrawing (CF_3, CN, and NO_2) groups on the benzene ring that is directly bound to the triple bond (R^2; Scheme 1) all produced the desired products in satisfactory yields, suggesting that the substituted groups did not have a significant influence on the reaction (**3m**−**3w**). In addition, aliphatic alkyne was also examined, and the desired product **3u** was obtained in good yield. To demonstrate the practical application of this method, *N*-3-phenylpropargyl aniline (**1a**, 10 mmol) was employed in a gram-scale reaction and delivered **3a** in 75% yield.

Next, the reactions of various arylsulfonohydrazides with **1a** were examined (Scheme 2). This reaction was also compatible with halogen substituents on the aromatic ring of arylsulfonohydrazides. Thus, benzenesulfonohydrazide, 4-fluorobenzenesulfonohydrazide, 4-chlorobenzenesulfonohydrazide, and 4-bromobenzenesulfonohydrazide reacted with **1a** to give products **5a**−**5d** in 81−73% yields. Electron-withdrawing (NO_2 and CF_3)

Scheme 1. Synthesis of 3-Tosylquinoline Derivatives[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), and TBHP (3 equiv) in DCE (2.5 mL) at 90 °C with stirring under air for 5 h. [b]R^1 = H, R^2 = Ac, **2a** (0.2 mmol). [c]R^1 = H, R^2 = Ac, **2a** (0.6 mmol).

substrates led to the formation of products **5e**−**5g** in good yields. Various arylsulfonohydrazides with electron-donating substituents were investigated; the corresponding products were obtained in 75−65% yields (**5h**−**5j**). The reaction of methylsulfonylhydrazine with **1a** under standard conditions led to a complicated mixture, and a trace amount of the product was obtained.

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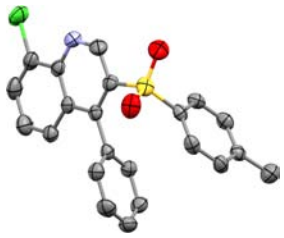
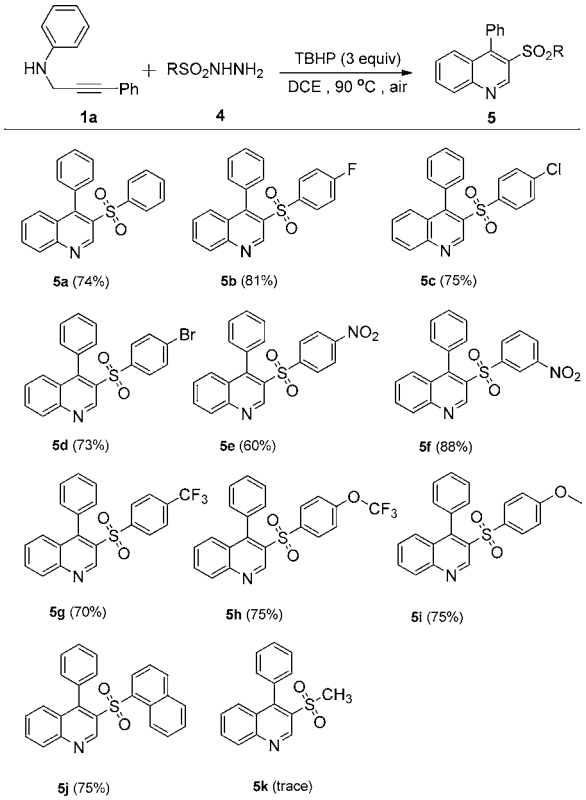


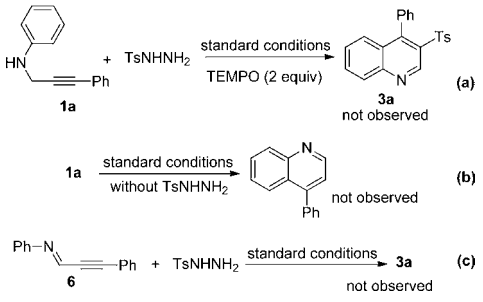
Figure 1. X-ray structure of **3k**.

Scheme 2. Scope of the Sulfonylation of *N*-3-Phenylpropargylaniline

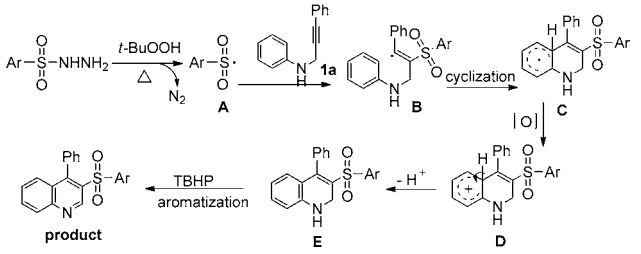


To gain insights into the mechanistic pathway, a series of control experiments were conducted. A radical scavenger, such as TEMPO, could completely restrain the reaction, thus suggesting that the radical processes might be involved (Scheme 3a). In the absence of benzenesulfonohydrazide (**2a**), the transformation could not proceed to provide 4-phenylquinolone (Scheme 3b). When $TsNH_2NH_2$ was treated with 1 equiv of *N*-(3-phenylprop-2-yn-1-ylidene)aniline (**6**) under the optimized reaction conditions, no desired product was observed, illustrating that **6** might not be an intermediate in this process (Scheme 3c). On the basis of these experimental results and previous mechanistic studies, a plausible mechanism is proposed, as shown in Scheme 4.

Scheme 3. Experiments for the Mechanistic Study



Scheme 4. Tentative Mechanistic Pathway



The reaction of sulfonylhydrazide with TBHP generates sulfonyl radical **A**, which then goes through intermolecular addition onto alkyne **2** to produce alkenyl radical **B**. Followed by the intramolecular attack of radical **B** on the pendant benzene ring subsequently provides radical **C**. Oxidation of **C** produces the corresponding cyclohexadienyl cation **D**, which undergoes deprotonation to yield the sulfonated 1,2-dihydroquinoline **E**. Finally, intermediate **E** ultimately aromatizes to afford the sulfonated quinoline.

In summary, we have developed an efficient protocol for the preparation of various 3-arylsulfonylquinolines via TBHP-mediated sulfonylation−cyclization−aromatization of various *N*-propargyl aromatic amine derivatives with arylsulfonylhydrazides without the addition of any metals. The TBHP oxidant system can be regarded as a metal-free, cost-effective, and environmentally benign system. Given that a wide range of substrates can be utilized for the cascade annulation, this simple protocol may provide a general approach to 3-arylsulfonylquinoline frameworks that are important in medicinal chemistry and catalytic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00198.

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3a**-**3w** and **5a**−**5j** (PDF)

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

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Notes

The authors declare no competing financial interest.

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