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Efficient Approach to 4-Sulfonamidoquinolines via Copper(I)-Catalyzed Cascade Reaction of Sulfonyl Azides with Alkynyl Imines‡

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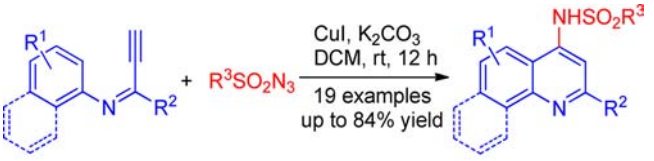
ABSTRACT



A novel and efficient approach to 4-sulfonamidoquinolines via copper-catalyzed cascade reaction of sulfonyl azides with alkynyl imines has been developed in which a 1,3-dipole cycloaddition/ketenimine formation/6π-electrocyclization/[1,3]-H shift cascade reaction was involved. Various 4-sulfonamidoquinolines were afforded in up to 84% yield for 19 examples. This synthetic strategy features with atom economy, concise steps, easy operation, and mild reaction conditions.

The structural motif of 4-aminoquinolines exists widely in both pharmaceutical molecules and natural products, which are exemplified by chloroquine (**A**), used as as an antimalaria agent,[1] and compound **B**, a natural product with antioxidant activity (Figure 1).[2] Consequently, developing mild and efficient access to polyfunctional 4-aminoquinolines is of great significance.

Conventionally, 4-aminoquinolines were synthesized by S_NAr reaction of 4-haloquinolines and primary amines. Elevated reaction temperature and tedious purification steps were often required in this procedure.[3] Palladium-catalyzed Buchwald–Hartwig amination reaction was proved to be a convenient alternative approach to 4-aminoquinolines from 4-haloquinolines in the past decade.[4]

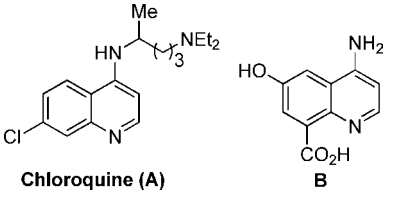


Figure 1. Two examples illustrating the importance of compounds with the 4-aminoquinoline moiety.

However, some 4-haloquinolines and their derivatives are not commercially available.

‡ Dedicated to Professor Irina Petrovna Beletskaya for her contribution to metal-catalyzed reactions.

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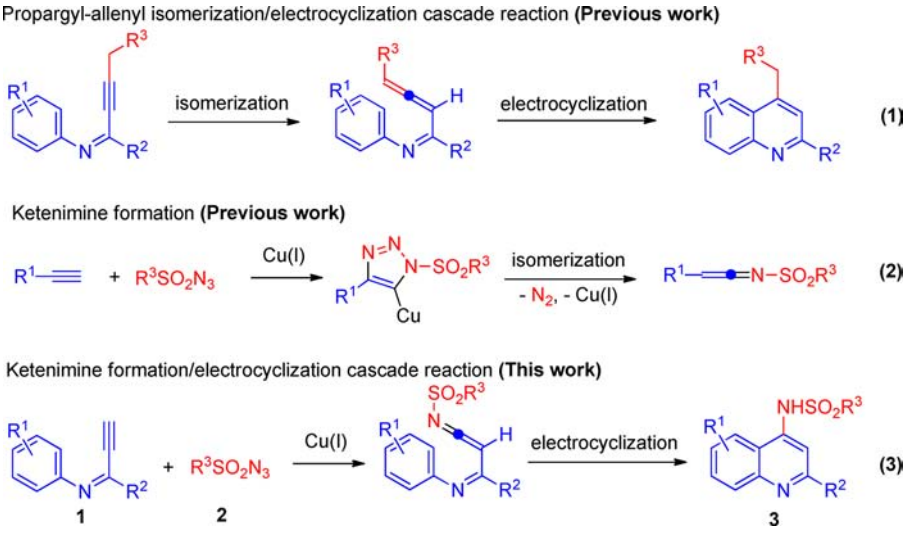
Scheme 1. Synthetic Route to 4-Sulfonamidoquinolines



Cascade reactions, which allow multiple transformations in a one-pot process, were recognized as an environmentally friendly and atom-economical strategy for building molecular complexity.[5] Several examples in constructing 4-aminoquinolines using this strategy have emerged. For example, the research groups of Schmidt,[6] Tverdomed,[7] Strekowski,[8] Luo,[9] and Rossi[10] have reported pioneering work on synthesis of 4-aminoquinolines and their derivatives from pyrazolium-3-carboxylates, 2-aminobenzonitriles, 2-(trifluoromethyl)anilines, *o*-oxazoline-substituted anilines, and *β*-(2-aminoaryl) α,*β*-ynones, respectively. Despite these notable advances in this area, some challenges still exist, such as the difficulty to access substrate, harsh reaction conditions, and inferior tolerance of functional groups. It continues to be an area of intense interest to develop new protocols to build such a valuable molecule from cheap and readily accessible starting materials by concise steps under milder reaction conditions.

A propargyl−allenyl isomerization/6*π*-electrocyclization cascade process has become an important synthetic method to access 4-substituted quinolines from alkynyl imines (Scheme 1, eq 1).[11] On the other hand, a copper-catalyzed 1,3-dipole cycloaddition/ring−chain isomerization/ketenimine formation cascade process was well developed by Chang, Wang, and other groups (Scheme 1, eq 2).[12] Considering the advancement of alkynyl imine chemistry and ketenimine chemistry, we envisioned that 4-sulfonamidoquinolines **3** could be synthesized via a cascade reaction of *N*-aryl alkynyl imines **1** with sulfonyl azides **2**. Moreover, the sulfonamide skeleton is often used in the design of pharmaceuticals.[13] Over 30 drugs containing *N*-arylsulfonamides are in clinical use as antibacterials,[14] non-nucleotide reverse transcriptase inhibitors,[15] antitumor agents,[16] and HIV-1 protease inhibitors.[17] Herein, we disclose a highly practical procedure to build 4-sulfonamidoquinolines in one step, in which a novel copper-catalyzed 1,3-dipole cycloaddition/ketenimine formation/6*π*-electrocyclization/[1,3]-H shift cascade reaction was involved (Scheme 1, eq 3). The reaction features mild reaction conditions and a general substrate scope.

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Table 1. Screening Reaction Parameters for the Cascade Reaction of *C*,*N*-Diphenyl Alkynyl Imine and Tosyl Azide Catalyzed by Copper(I)

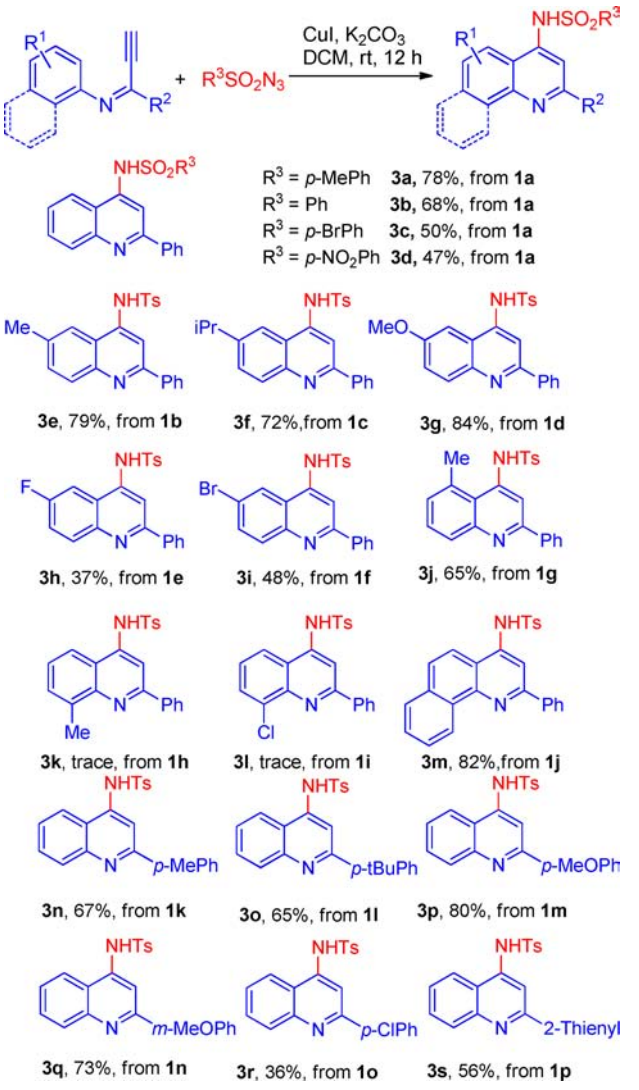
entry	Cu(I)	solvent	base	yield[a] (%)
1	CuI (0.05)	1,4-dioxane	Et_3N	30
2	CuI (0.05)	THF	Et_3N	25
3	CuI (0.05)	toluene	Et_3N	29
4	CuI (0.05)	chloroform	Et_3N	35
5	CuI (0.05)	DCM	Et_3N	38
6	CuI (0.05)	DMF	Et_3N	<5
7	CuI (0.05)	MeCN	Et_3N	<5
8	CuI (0.05)	DCM	pyridine	<5
9	CuI (0.05)	DCM	K_2CO_3	78
10	CuI (0.05)	DCM	$KHCO_3$	75
11	CuI (0.05)	DCM	Na_2CO_3	49
12	CuI (0.05)	DCM	Cs_2CO_3	15
13[b]	CuI (0.05)	DCM	K_2CO_3	77
14[c]	CuI (0.05)	DCM	K_2CO_3	78
15	CuI (0.01)	DCM	K_2CO_3	67
16	CuBr (0.05)	DCM	K_2CO_3	66
17	CuCl (0.05)	DCM	K_2CO_3	65

[a] Isolated yield based on *C*,*N*-diphenyl alkynyl imine **1a**. [b] At 40 °C. [c] 1.5 equiv of **2a** was used. THF = tetrahydrofuran.

To the best of our knowledge, this is the first report regarding the successful synthesis of 4-substituted quinolines bearing a sulfonamide group in one step at room temperature.

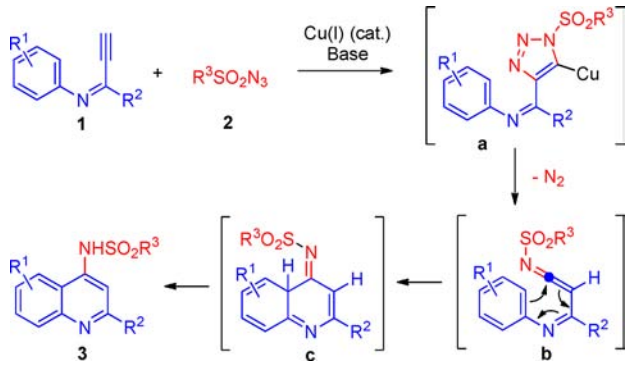
The reaction of *C*,*N*-diphenyl alkynyl imine **1a** (0.5 mmol) with tosyl azide **2a** was initially chosen as a model reaction in the presence of CuI (5 mol %) and 1.5 equiv of Et_3N in 1,4-dioxane (2 mL) under N_2 atmosphere at room temperature. The reaction was monitored by TLC. The starting material **1a** was consumed within 15 min, and a pale product **3a** immediately precipitated and was isolated in 30% yield (Table 1, entry 1). The structure of **3a** was identified to be 4-methyl-*N*-(2-phenyl-4-quinolinyl)benzenesulfonamide by NMR spectra. Inspired by this result, the various reaction parameters were valued, including solvents, bases, temperature, and copper(I) salts. The results are listed in Table 1. The solvents were tested first (entries 1−5). Dichloromethane (DCM) gave the highest yield (38%, entry 5). Polar solvents, such as *N*,*N*-dimethylformamide (DMF) (entry 6) and MeCN (entry 7), made the reaction more complicated, and only a trace amount of product was detected. Pyridine instead of Et_3N as base led to a trace amount of product (entry 8). Interestingly, the yields increased obviously when inorganic bases, such as K_2CO_3, $KHCO_3$, and Na_2CO_3, except Cs_2CO_3, were used instead of Et_3N (entries 9−12). K_2CO_3 could give 78% yield (entry 9). The reaction was not obviously improved by elevating the reaction temperature (entry 13 vs entry 9) and the loading of **2a** (entry 14 vs entry 9). When the catalyst loading was reduced to 1 mol % (entry 15) or the other copper salts, such as CuBr and CuCl, were used as a catalyst (entries 16 and 17), the yield decreased in some extent. Finally, the optimized reaction conditions were eventually identified as **1a** (0.5 mmol), 1.1 equiv of **2a**, 5 mol % of CuI, and 1.5 equiv of K_2CO_3 in 2 mL of DCM under N_2 atmosphere at room temperature.

Scheme 2. Copper(I)-Catalyzed Cascade Synthesis of 4-Sulfonamidoquinolines from Alkynyl Imines and Sufonyl Azides



With the optimized reaction conditions in hand, the generality and scope of the substrates were examined as shown in Scheme 2. First, we investigated the various sulfonyl azides **2a**−**d**. Electron-rich sulfonyl azides favored this transformation. Tosyl azide **2a** gave the best result, 78% yield. Then the effect of different substitutes on the *N*-aromatic moiety was studied. The evident electronic and steric effects were observed. Electron-donating groups in the *para* positions on the *N*-aryl ring gave higher yields than those of electron-withdrawing groups (**3e**−**g** vs **3h**, **3j**). The *m*-methyl substrate **1g** gave 20:1 regioisomeric products in 65% yield. The major product was proved to be 4-methyl-*N*-(2-phenyl-5-methyl-4-quinolinyl)benzenesulfonamide **3j** by NMR spectra. Only a trace amount of the corresponding products (**3k**,**l**) were detected, probably due to the substituents at the 8-position of the naphthyl ring,

Scheme 3. Proposed Mechanistic Pathway



which blocked the 6π-electrocyclization process. It is worth noting that *N*-(1-naphthyl)alkynyl imine **1j** could proceed well and gave the desired product **3m** in 82% yield under the optimal conditions. In addition, the substituted scope on imine carbon was also examined. Electron-rich substituents on the imine carbon led to higher yields than that of an electron-deficient substituents (**3n**−**q** vs **3r**). The thienyl-substituted substrate **1p** also could give the corresponding product **3s** in moderate yield (56%).

A possible reaction mechanism was proposed according to the literature and the results obtained (Scheme 3). First, the reaction of alkynyl imine **1** with sulfonyl azide **2** catalyzed by copper gave the triazole intermediate **a**, which isomerized to form the ketenimne intermediate **b**.[12] The intramolecular 6π-electrocyclization occurred and provided the intermediate **c**. The following [1,3]-H shift process gave the final product 4-sulfonamidequinoline **3**.

In summary, we have developed an efficient approach to a variety of 4-sulfonamidoquinolines in one step, which features a novel copper-catalyzed cascade reaction under mild reaction conditions. *N*-Phenyl alkynyl imines successfully underwent 1,3-dipole cycloaddition/ketenimine formation/6π-electrocyclization/[1,3]-H shift cascade reactions with sulfonyl azides catalyzed by cheap copper salt at room temperature. The desired products were provided in moderate to good yields.

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Supporting Information Available. Synthesis procedure, characterization, and ^{1}H NMR and ^{13}C NMR spectra of products **1a**−**p** and **3a**−**j**,**m**−**s**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.