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A Modular Synthesis of 4-Aminoquinolines and [1,3] N-to-C Rearrangement to Quinolin-4-ylmethanesulfonamides

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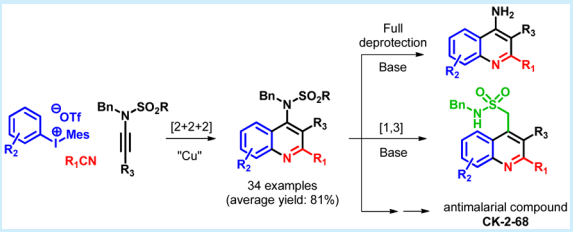
Supporting Information

ABSTRACT: A copper-catalyzed regiocontrolled three-component reaction afforded diversified 4-aminoquinolines using nitriles, diaryliodoniums, and ynamides. The C7-substituted regioisomers were formed regioselectively when *meta*-substituted phenyliodonium salts were used. [1,3] N-to-C rearrangement of the products to quinolin-4-ylmethanesulfonamides and simultaneous deprotection of benzyl and sulfonamide group were newly developed. Finally, antimalarial CK-2-68 was successfully prepared.



Malaria remains a serious parasitic infection with high mortality rates.[1] 4-Aminoquinolines are known as potent antimalarial drugs;[2] however, some drugs such as chloroquine and amodiaquine have posed resistance and toxicity problems.[3] Although promising structural analogues such as isoquine have received much attention,[4] the limited number of systematic synthetic approaches[5] to diversify 4-aminoquinolines may have hindered the advent of new drugs.[6] Additionally, as shown in Figure 1, the group at the C7 position has important effects on

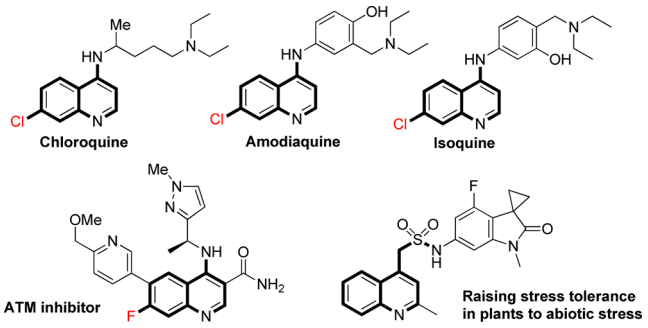


Figure 1. Important 4-aminoquinolines and quinolin-4-ylmethanesulfonamide.

the association strength of hematin and pK_a of the quinoline nitrogen for antiplasmodial activities.[7] Other biological activities, such as ATM (ataxia telangiectasia mutated) and HER (human epidermal growth factor receptor) inhibition, have been found for functionalized 4-aminoquinoline structures as well.[8] On the other hand, sulfonamide derivatives exhibit a broad range of biological activities and are used as antibacterial drugs, antiviral agents, and antifungal agents since sulfa drugs have been developed as synthetic antibiotics.[9] Especially, quinolin-4-ylmethanesulfonamides are also known to exhibit the stress tolerance in plants to abiotic stress.[10]

A regioselective multicomponent reaction strategy would provide atom economy, efficiency, diversity, and step economy for the systematic synthesis of heterocycles.[11] In this regard, we were interested in ynamides[12] and investigated the three-component annulation of a nitrile (**A**), diaryliodonium salt (**B**),[13] and ynamide (**C**).[14] To date, two-component cyclizations have been reported to provide quinazolines (2**A**+**B**);[15] 2,4-diaminopyridines (**A**+2**C**),[16] 4-aminopyrimidines (2**A**+**C**),[17a,b] 3-aminoisoquinolines (**A**+**C**),[17b] and 2-aminopyridines (**A**+**C**);[17c] and 1-amino-dihydronaphthalenes (**B**+**C**).[18] Therefore, three-component annulation may lead to the mixture of N-heterocycles due to their possible combinations. In the case of simple alkynes, however, quinolines have been successfully prepared by the Chen group.[19a] Recognizing the amphoteric property of ynamide as electrophile and nucleophile[12] and Chen's previous work,[19a,i] we hypothesized that if copper-catalyzed arylation of a nitrile with a diaryliodonium salt[15,19] is fast enough, nucleophilic addition with an ynamide and subsequent cyclization could proceed smoothly to afford a 4-aminoquinoline.[20] Furthermore, regioselective formation of C-7 substituted products would be expected from the proper substituent interaction using *m*-substituted phenyliodonium salts.[21] Herein, we introduce a modular [2 + 2 + 2] cycloaddition allowing systematic functionalization of 4-aminoquinolines and [1,3] N-to-C rearrangement to provide quinolin-4-ylmethanesulfonamides by base treatment (Scheme 1). In comparison, in the metal-free approaches developed by the Movassaghi[20a] and Bräse groups,[20b] two components condensed to give 4-aminoquinolines in moderate yields with no singly *meta*-substituted amides.

We began the screening using CuCl and PhI(Mes)OTf in EtOAc at 75 °C for 3 h with molecular sieves (MS) 4 Å to prevent hydrolysis of the intermediate nitrillium salt (Table 1). Ynamides and diaryliodonium salts were prepared according to known methods.[14c,22] During the optimization, no 3-aminoisoquinoline side product was detected. In the absence of CuCl,

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Scheme 1. Regiocontrolled Modular Syntheses of 4-Aminoquinolines and [1,3] N-to-C Rearrangement to Quinolin-4-ylmethanesulfonamides

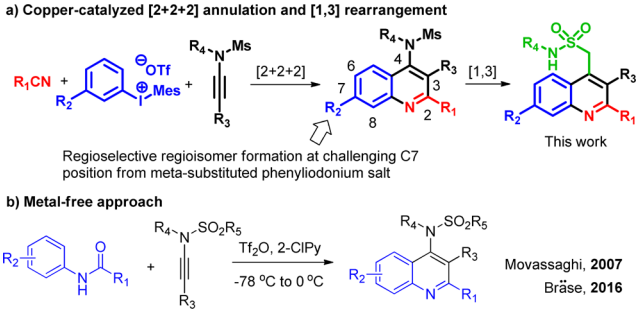
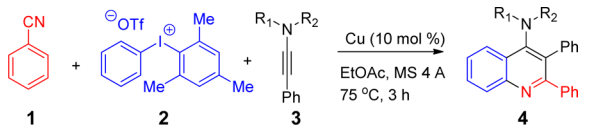


Table 1. Optimization of Reaction Conditions[a]



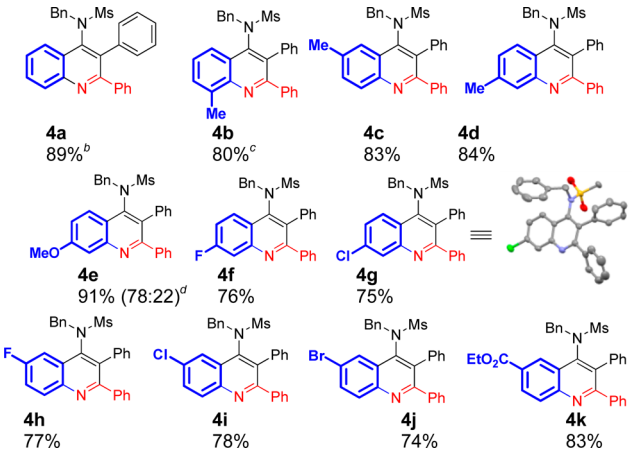
entry	Cu	R^1-N-R^2	1:2:3	yield (%)[b]
1	–	Me-N-Ms	1.5:1.0:1.5	NR[c]
2	CuCl	Me-N-Ms	1.5:1.0:1.5	31[c]
3	CuCl	Me-N-Ms	1.2:1.3:1.0	51 (39[c])
4	CuCl	Me-N-Ms	1.0:1.2:1.3	62 (52,[d] 12[e])
5	CuI	Me-N-Ms	1.0:1.2:1.3	35
6	$Cu(OAc)_2$	Me-N-Ms	1.0:1.2:1.3	55
7	$CuPF_6$[f]	Me-N-Ms	1.0:1.2:1.3	51
8	CuTC	Me-N-Ms	1.0:1.2:1.3	69
9	CuTC	Ph-N-Ms	1.0:1.2:1.3	75
10	CuTC	Allyl-N-Ms	1.0:1.2:1.3	77
11	CuTC	**Bn-N-Ms**	**1.0:1.2:1.3**	**95**
12	CuTC	Bn-N-CO_2Et	1.0:1.2:1.3	42
13[d]	CuTC	Oxazolidone	1.0:1.2:1.3	36
14	CuTC	Ph-N-Boc	1.0:1.2:1.3	<5

[a]Reaction conditions: Cu (10 mol %), MS 4 Å, EtOAc (0.15 M), 75 °C, 3 h. [b]NMR yield. [c]Under 0.4 M. [d]Ph_2IOTf. [e]Ph_2IPF_6. [f]$[Cu(CH_3CN)_4]PF_6$ was used.

the desired reaction did not occur, as expected (entry 1). We experimented with various ratios of the three starting materials (**1**, **2**, and **3**) at a concentration of 0.4 M. Yields were not satisfactory when **2** or **3** was used as the limiting reagent (entries 2 and 3). However, the yield increased to 51% when the concentration was decreased to 0.15 M (entry 3). The yield increased further to 62% upon setting **1** as the limiting reagent. The use of Ph_2IOTf and Ph_2IPF_6, however, decreased the yield to 52% and 12%, respectively (entry 4). Screening of the copper catalysts revealed that CuTC (copper(I) thiophene-2-carboxylate) provided the highest yield, 69% (entries 5–8). Then, we tested the effect of the N-substituents of the ynamides on the yield because their reactivities are known to be related to the functional groups.[23] To our delight, the yield increased gradually to 95% upon changing the methyl group to a phenyl, allyl, and benzyl (Bn) group (entries 9–11). Careful monitoring of the reaction with the Bn-substituted ynamide revealed that the reaction was complete to give **4a** within 20 min. When a carbamate group was utilized, yields decreased sharply. Substrates with ethyl carbamate and oxazolidone gave 42% and 36% yields, respectively, presumably owing to weak nucleophilicity (entries 12–13). A Boc-protected ynamine gave almost no desired product (entry 14).

With the optimum ynamide and conditions in hand, we focused on the reaction regioselectivity and substrate compatibility of the diaryliodonium salts (Scheme 2). *o*- and

Scheme 2. Substrate Scope of Ar(Mes)IOTf[a]



[a]Standard reaction conditions: nitrile/iodonium salt/ynamide = 1.0:1.2:1.3, nitrile (0.2 mmol), CuTC (10 mol %), MS 4 Å, EtOAc (0.15 M), 75 °C, 40 min. [b]Yield at 1 mmol scale [c]Reaction time was 7 h. [d]Yield of combined regioisomers and regioisomeric ratio determined by GC in the parentheses.

p-Me-substituted iodonium salts gave the desired products in good yields (**4b–c**). *m*-Me substituted iodonium salt afforded a single regioisomeric product (**4d**). However, two-electron-releasing methoxy and amino groups strongly activate the benzene ring toward electrophilic attack at the *o*-position, giving an inseparable mixture of **4e** (78:22). In particular, when electron-withdrawing *m*-F- and *m*-Cl-substituted iodonium salts were used, the single C7-substituted isomers (**4f–g**) were obtained. This indicates that not only the steric but also the electronic properties seem to be of influence on the regioselectivity.[21] The structure was confirmed by X-ray analysis of **4g**.[24] And all *p*-halogen- and ester-substituted iodonium salts provided the desired products (**4h–k**).[25]

Next, we screened the scope of ynamides and nitriles (Scheme 3). Regardless of their electronic and steric properties, most of the substrates afforded desired products with good to excellent yields.[25] Thiophene-substituted ynamide and alkyl nitriles gave slightly lower yields (**4u** and **4af**). **4m**, **4o**, and **4q** were isolated with almost equal amounts of atrop-diastereomeric mixtures, while a single product **4l** was produced. A tosyl substrate gave a lower yield (**4a** vs **4ah**).

Then, we investigated deprotection conditions and found unexpected simultaneous deprotection of benzyl and sulfonamide group with KO*t*-Bu under an Ar atmosphere, where base may induce elimination to form imine.[26] A 40% yield of fully deprotected product **5a** was improved to 88% when changing Ms to the Ts group. The unknown product observed in the case of the Ms substrate (**4a**) was identified as quinolin-4-ylmethanesulfonamide **6a** by X-ray analysis.[24] Surprisingly, the yield of **6a** increased to 91% with LiHMDS in THF with no formation of **5a**. The reaction proceeded via deprotonation of the Ms group and [1,3] N-to-C rearrangement through unusual 4-membered ring formation owing to the electron-deficient quinoline ring.[27] The reaction has a wide scope as shown in

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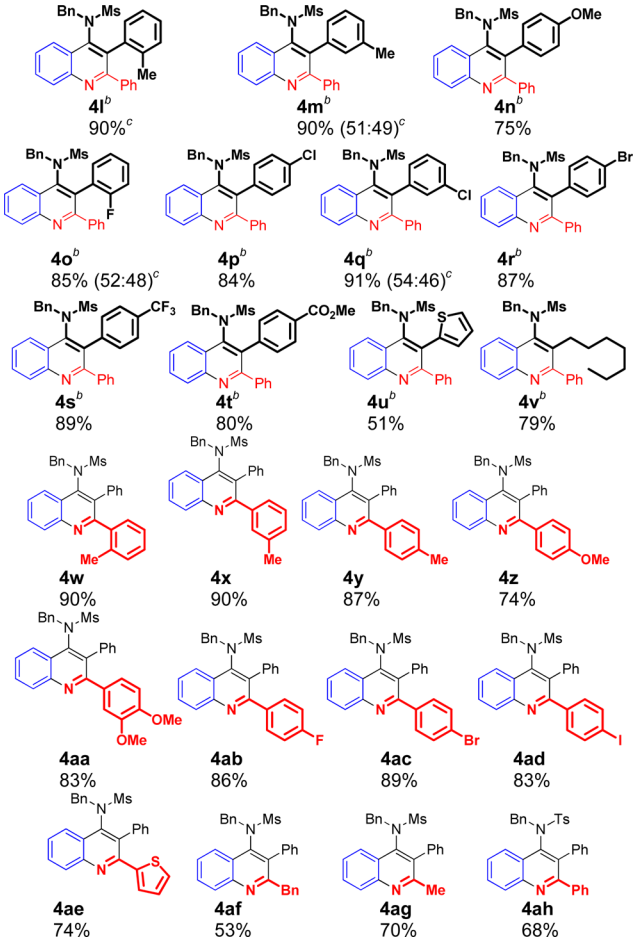
Scheme 3. Substrate Scope of Ynamides and Nitriles[a]

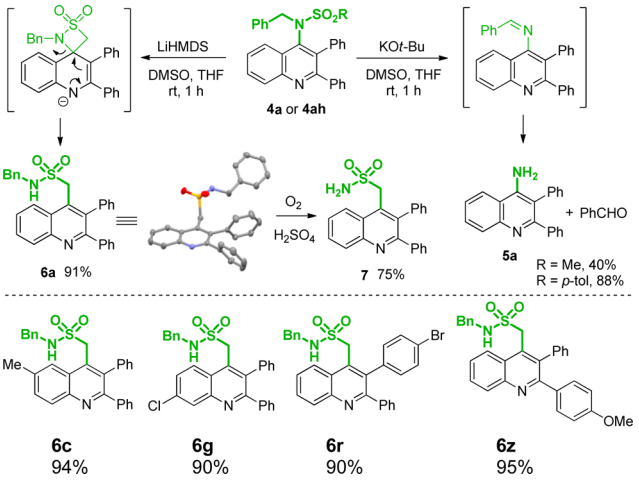


[a]Standard reaction conditions. [b]Reaction time was 2 h. [c]Atropdiastereomeric ratio determined by ^{1}H NMR.

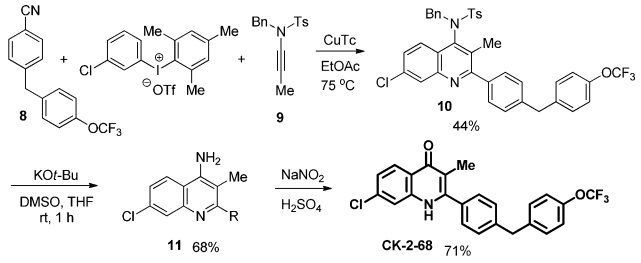
Scheme 4. Subsequent debenzylation to **7** was accomplished with H_2SO_4 under O_2 in 75% yield.

To demonstrate the utility of this synthetic method, we prepared the active antimalarial compound CK-2-68,[28] as shown in Scheme 5. Three-component condensation of *m*-

Scheme 4. Simultaneous Deprotection of Benzyl and Sulfonamide Group and [1,3] Rearrangement



Scheme 5. Synthesis of CK-2-68



chlorophenyliodonium salt, nitrile **8**, and ynamide **9** gave **10** in 44% yield with inseparable oxidized ynamide. Finally, simultaneous deprotection to **11** with KO*t*-Bu, followed by diazonium salt formation and hydration, afforded CK-2-68 in 68% and 71% yields, respectively.

In summary, we developed a Cu-catalyzed regiocontrolled [2 + 2 + 2] three-component tandem reaction that provides highly functionalized 4-aminoquinolines. *m*-Substituted aryliodonium salts gave C7-substituted isomers regioselectively. To show the utility of the transformation, we discovered [1,3] rearrangement of the methanesulfonamide group to quinolin-4-ylmethanesulfonamides and simultaneous deprotection of the benzyl and sulfonamide group and successfully prepared the active antimalarial compound CK-2-68. We expect our synthetic approach to provide a convenient tool for the syntheses of valuable compounds toward useful applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01701.

Experimental procedures, full characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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