Quinoline Synthesis

DOI: 10.1002/anie.201300586

Copper(II)-Catalyzed Three-Component Cascade Annulation of Diaryliodoniums, Nitriles, and Alkynes: A Regioselective Synthesis of Multiply Substituted Quinolines**

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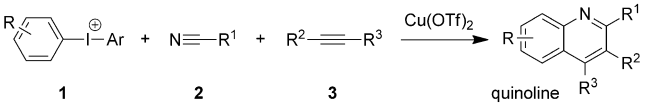
Quinolines are privileged scaffolds in various bioactive natural products and many synthetic therapeutic agents.[1] Also, they are crucial ligands for the preparation of OLED materials[2] and asymmetric catalysts.[3] The demand of synthetic chemists, medicinal chemists, and materials chemists for a wide variety of substituted quinolines has increased exponentially. Numerous named reactions (e.g. Combes synthesis, Conrad–Limpach–Knorr synthesis, and Friedländer synthesis) are known for the synthesis of quinolines, and most of them use anilines or 2-acyl anilines as a starting material.[4] From the point of sustainability and green chemistry, the development of new approaches to quinolines from common building blocks other than anilines is attractive. It is more challenging to synthesize quinolines with diverse substituents, often a requirement by medicinal and material chemists. Although a lot of progress has been made with regard to the modification of quinolines,[5] a more general and elegant way to synthesize multiply substituted quinolines would be to construct the ring from small molecules having functional groups.[6] Herein, we would like to report an efficient method to synthesize multiply substituted quinolines from three components, that is, diaryliodoniums **1**, alkynes **2**, and nitriles **3**. This regioselective [2+2+2] cyclization is catalyzed by $Cu(OTf)_2$ and the aryl group of the diaryliodoniums serves as a C_2 building block (Scheme 1). This cascade annulation method is regioselective, step economic, flexible with regard to functional groups, and is potentially applicable to complex molecules.

Diaryliodonium salts, as environmentally benign regeants with low toxicity, are often used in the synthesis of arylated compounds or macrocyclic supramolecular compounds.[7–9] Our goal is to efficiently synthesize nitrogen-containing heteroarenes from diaryl iodonium salts.[10] When a mixture



Scheme 1. Three-component approach to multiply substituted quinolines. Tf = trifluoromethanesulfonyl.

of diphenyliodonium **1a** (0.5 mmol), phenyl acetylene **2a** (1.0 mmol), and benzonitrile **3a** (1.0 mmol) with $Cu(OTf)_2$ (0.05 mmol) as catalyst was heated at 120 °C in 1,2-dichloroethane (DCE) for 12 h, 2,4-diphenylquinoline **4a** was obtained in 88% yield (determined by GC with *n*-dodecane as internal standard; 73% yield upon isolation). The temperature, solvent, and stoichiometry of the reagents were screened to optimize the reaction conditions (Table 1; see Supporting Information for more details). When the ratio of the three components was adjusted to 1:1.2:1.2, product **4a** was obtained in nearly the same yield (86%, 72% upon isolation). The use of diphenyliodonium salts with non-coordinating anions (PF_6 and OTf) gave good results but a low was obtained when Ph_2ICl was used (entry 15). A

Table 1: Optimization of the reaction conditions for the formation of 2,4-diphenylquinoline (**4a**).

entry	**1a**/**2a**/**3a**[a]	Solvent	$Cu(OTf)_2$ (equiv)	Base (1 equiv)	*T* [°C]	Yield [%][b]
1	1:2:2	DCE	0	–	120	0
2	1:2:2	DCE	0.1	–	75	6
3	1:2:2	DCE	1.0	–	75	55
4	1:2:2	DCE	0.1	–	120	88
5	1:1.2:1.2	DCE	0.1	–	120	86[c]
6	1:1.2:1.2	DCE	0.1	–	130	86
7	1:1:1	DCE	0.1	–	120	67
8	1:2:2	DCE	0.1	K_2CO_3	120	0
9	1:2:2	DCE	0.1	DIPEA	120	0
10	1:2:2	DCE	0.1	DMAC	120	58
11	1:2:2	THF	0.1	–	120	1
12	1:2:2	$PhCF_3$	0.1	–	120	13
13	1:2:2	CH_3CN	0.1	–	120	0
14[d]	1:1.2:1.2	DCE	0.1	–	120	83
15[e]	1:1.2:1.2	DCE	0.1	–	120	5
16[f]	1:1.2:1.2	DCE	0.1	–	120	48[c]

[a] The reaction was performed with 0.5 mmol of Ph_2IPF_6. [b] Determined by GC with *n*-dodecane as internal standard. [c] **4a** was isolated in 73% yield. [d] 0.5 mmol of Ph_2IOTf was used instead of Ph_2IPF_6. [e] 0.5 mmol of Ph_2ICl was used instead of Ph_2IPF_6. [f] 0.1 equiv of $CuCl_2$ was used instead of $Cu(OTf)_2$. DIPEA = diisopropylethylamine, DMAC = dimethylacetamide.

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[**] This work was supported by National Natural Science Foundation of China (21102080) and Tsinghua University Initiative Scientific Research Program (2011Z02150).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300586.

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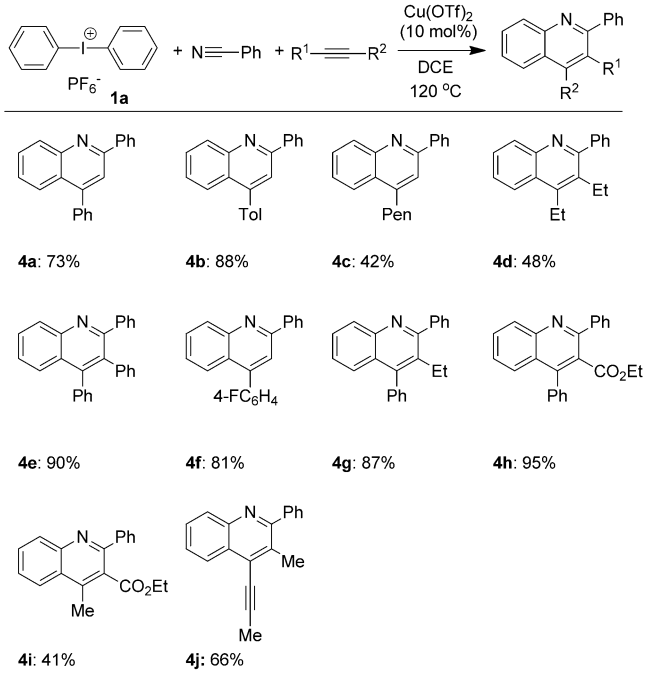
similar anion effect was observed for the copper salts; the use of $Cu(OTf)_2$ gave better results than $CuCl_2$ or $Cu(OAc)_2$ (see the Supporting Information). Based on the material economy and ease of purification, the reaction conditions shown in entry 5 were chosen as the optimal conditions. The reaction was monitored by GC–MS and none of the isomer 2,3-diphenylquinoline was observed. The structure of **4a** was further confirmed by single-crystal X-ray diffraction (see the Supporting Information).[11]

With optimized conditions established, the scope of our method was examined. Initially, a range of alkynes were treated with diphenyliodonium salt **1a** and benzonitrile (**2a**) to synthesize quinolines with a variety of substituents at the 3- and 4-positions. As shown in Scheme 2, reactions of terminal



Scheme 2. Synthesis of 3- and 4-substituted quinolines from various alkynes. The yields are of the isolated products.

or internal alkynes with alkyl, aryl, or ester groups all proceeded smoothly under standard conditions and gave the expected quinolines in moderate to excellent yields upon isolation. This synthetic method gives quinolines with high regioselectivity when asymmetric alkynes are used: for terminal alkynes with either alkyl or aryl groups, these substituents are located in the 4-position in the products (**4a**–**4c**, **4f**); for the internal alkyne 1-phenyl-1-butyne, the phenyl group is located in the 4-position and ethyl group to 3-position in the product (**4g**); for internal alkynes, such as 1-phenyl-1-propiolate and 2-butynoate, with electron-withdrawing groups, the ester group is located in the 3-position in the product (**4h** and **4i**). Interestingly, 1,3-hexadiyne was also applicable to this reaction and the corresponding 4-propynyl quinoline (**4j**) was isolated exclusively. The structure of **4j** was unequivocally confirmed by single-crystal X-ray diffraction analysis (Figure 1).[12] The high regioselectivity for

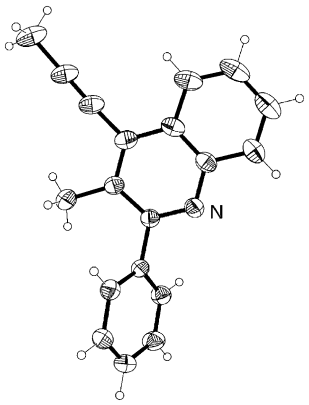
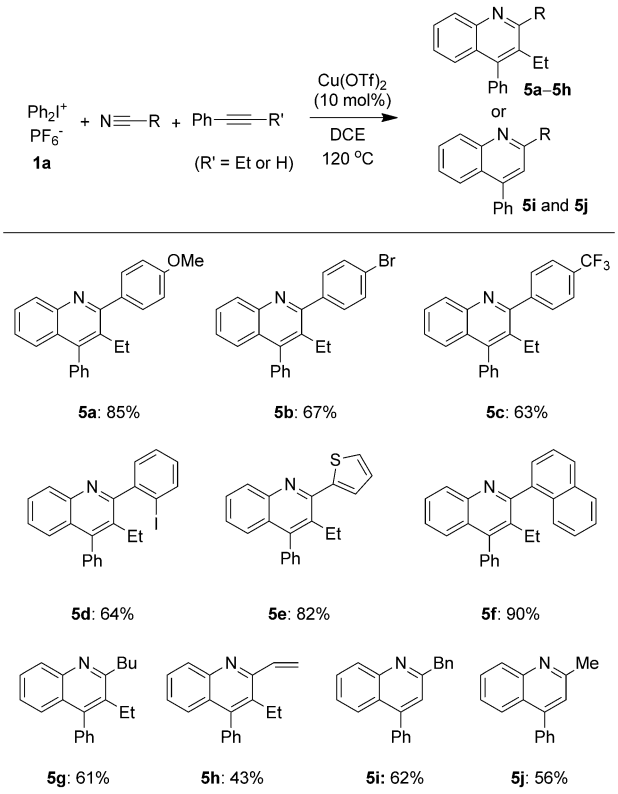


Figure 1. Single-crystal X-ray diffraction structure of **4j**. The thermal ellipsoids are set at 35% probability.

unsymmetric alkynes may be attributed to the highly electrophilic process of this annulation (see below).

Next, a variety of nitriles were evaluated in the reaction with diphenyliodonium and asymmetric alkynes, phenyl acetylene (**3a**) or 1-phenyl-1-butyne (**3b**), to synthesize quinolines with various substituents at the 2-positon. Aryl nitriles bearing functional groups, such as 4-methoxy, 4-bromo, 4-trifluromethyl and 2-iodo groups, were compatible under the reaction conditions (Scheme 3). The reactions of 2-cyano thiophene and 1-cyano naphthalene successfully produced 2-thienyl quinoline **5e** and 1-naphthyl quinoline **5f** in excellent yields. Alkyl nitriles, such as acetonitrile, valeroni-



Scheme 3. Synthesis of 2-substituted quinolines from various nitriles. The yields are of the isolated products.

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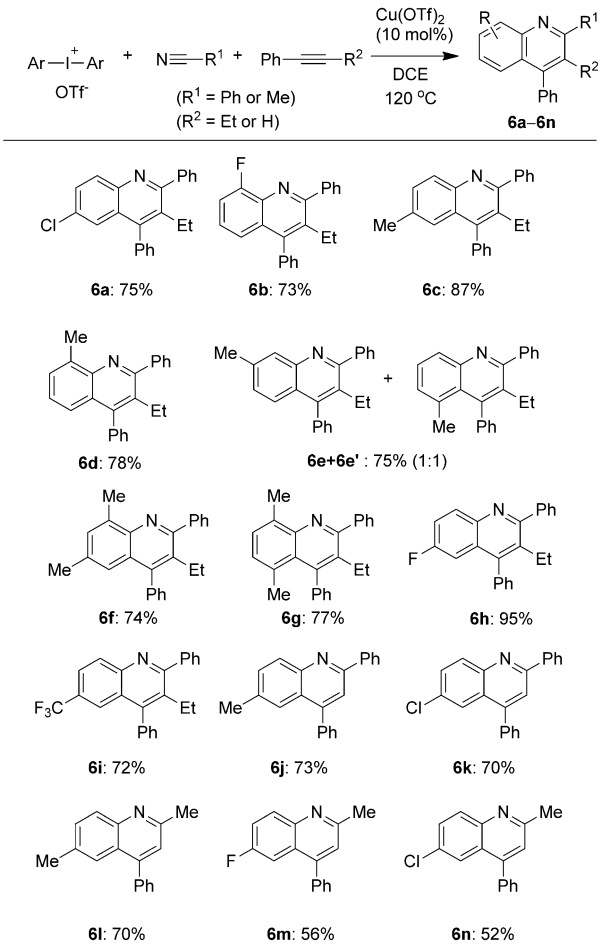
trile and phenylacetonitrile, underwent the cascade annulation to afford desired products, albeit in relatively lower yields. When 3-methoxy propionitrile was used, 2-vinyl quinoline **5h** was isolated instead of 2-(2-methoxyethyl)quinoline. However, ethyl cyanoformate ($NCCO_2Et$) and diethyl cyanphosphate ($NCPO(OEt)_2$) didn't undergo the quinoline annulation presumably because of their electron deficiency. Gratifyingly, all the reactions gave the same regioselectivity at 3- and 4-positions.

The results above have shown the facile construction of quinolines that are highly functionalized on the pyridine ring. Finally, we attempted to prepare quinolines with functional groups on the phenyl ring from various diaryliodoniums. Functionalized diaryliodonium triflates were used as they are easily prepared according to known methods.[13] Reactions of diaryliodoniums having a range of substituents, including 2-methyl, 4-methyl, 2-fluoro, 4-fluoro, 4-chloro, and 4-trifluoromethyl groups, all gave the desired products (Scheme 4). The



Scheme 4. Synthesis of phenyl-substituted quinolines from various diaryliodoniums. The yields are of the isolated products.

reaction of di(*m*-tolyl)iodonium produced two regioisomers in a ratio of 1:1 (**6e** and **6e′**). As well as characterization by NMR spectroscopy, the structure of **6a** was unambiguously confirmed by single-crystal X-ray diffraction (Figure 2).[14] In the crystal structure it is clearly shown that the ipso position of iodonium salt is substituted by nitrogen atom. This method provides a convenient access to quinolines with diverse subsituents on the phenyl ring.

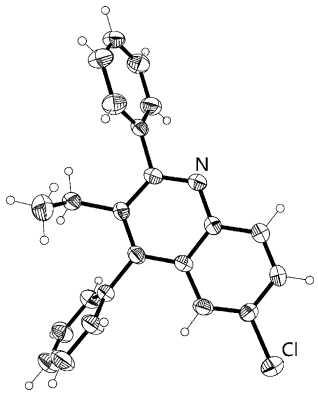
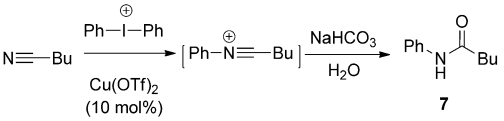


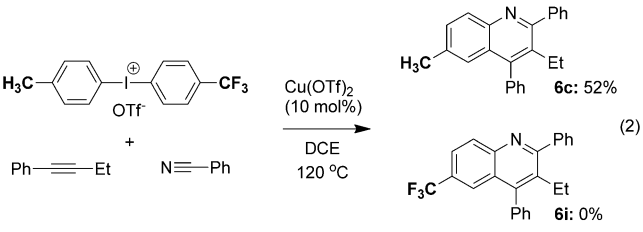
Figure 2. Single-crystal X-ray diffraction structure of **6a**. The thermal ellipsoids are set at 35% probability.

In the preparation of quinoline **5g**, *N*-phenyl pentanamide (**7**; presumably formed by hydrolysis of the *N*-phenyl nitrilium salt[15]) was determined to be in the reaction mixture by GC–MS (around 10% yield). *N*-phenyl pentanamide (**7**) was formed in 85% yield when Ph_2IPF_6 and valeronitrile (1 equiv) were heated with $Cu(OTf)_2$ (0.1 equiv) in the



(1)

absence of alkyne [Eq. (1)]. This result suggests that valeronitrile can be readily phenylated by Ph_2IPF_6 (in the presence of $Cu(OTf)_2$) to give the *N*-phenyl nitrilium salt, which upon hydrolysis forms *N*-phenyl pentanamide. Additionally, in the competition reaction of benzonitrile **2a**, 1-phenyl-1-butyne **3b** with $[(4\text{-}CH_3C_6H_4)(4\text{-}CF_3C_6H_4)I]^+[OTf]^-$ under standard conditions, product **6c** was formed exclusively; **6i** was not



(2)

formed [Eq. (2)]. This result may be attributed to the dominant formation of $[4\text{-}CH_3C_6H_4]^+$ (leading to compound **6c**) rather than $[4\text{-}CF_3C_6H_4]^+$ from $[(4\text{-}CH_3C_6H_4)(4\text{-}CF_3C_6H_4)I]^+[OTf]^-$.

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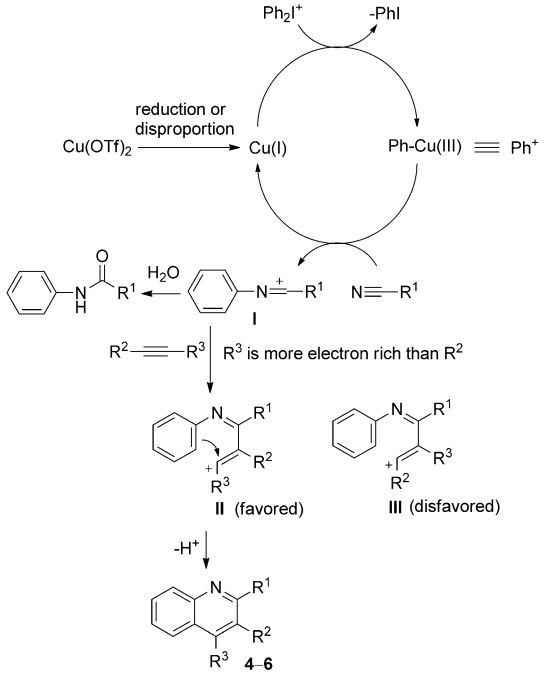
The anion effects of iodonium salts and copper catalysts (non-coordinating, weakly nucleophilic anions are superior) imply that this reaction is an electrophilic process. It has been reported that diaryliodonium salts could undergo reactions with nucleophiles catalyzed by copper salts and proceeding via Ar–Cu^{III} species, which act as carbocation equivalents.[8,16] Based on the above findings, we propose a reaction mechanism involving a Ar–Cu^{III} species (Scheme 5). Initially, $Cu(OTf)_2$ is converted into Cu^{I} by either a reduction or disproportion, as discussed in previous reports (a purple solution was obtained, thus indicating the existence of Cu^{I} species).[8,16] Oxidative addition to the Cu^{I} species by the diaryliodonium salt (as exemplified by Ph_2I^+) gives a Ph–Cu^{III} species, which transfers the phenyl group to the nitrile to give *N*-phenylnitrilium intermediate **I**, which upon hydrolysis gives the anilide. *N*-phenylnitrilium is a highly reactive species and quickly reacts with acetylenes to give intermediate **II** (favored by electronic effects) or **III** (disfavored). Intermediate **II** undergoes an electrophilic annulation to give quinoline product.[17] The series of cationic intermediates in this cascade annulation ensure the high regioselectivity seen for asymmetric alkynes.



Scheme 5. Proposed mechanism.

In summary, an efficient and regioselective synthesis of multiply substituted quinolines from three components, that is, diaryliodoniums **1**, alkynes **2**, and nitriles **3**, has been presented. This [2+2+2] cyclization is catalyzed by $Cu(OTf)_2$ and the aryl group of the diaryliodoniums serves as a C_2 building block. This strategy marks a significant departure from known approaches based on condensation chemistry (e.g. Combes synthesis, Conrad–Limpach–Knorr synthesis, and Friedländer synthesis) and enables variation in the substitution patterns on the quinolines. The cascade annulation is believed to involve a series of cationic intermediates, thus ensuring an efficient process and high regioselectivity. We believe that this study reveals a new way to prepare nitrogen-containing heterocycles from diaryliodoniums. Further studies are being undertaken in our laboratory and will be reported in due course.

Experimental Section

A sealed tube was charged with diaryliodonium salt **1** (1.0 mmol) and $Cu(OTf)_2$ (0.1 mmol, 36.2 mg). The tube was evacuated and recharged with N_2 three times. Acetylene **2** (1.2 mmol), nitrile **3** (1.2 mmol), and 1,2-dichloroethane (2.0 mL) were added, the tube was sealed and the mixture was stirred at 120 °C for 12 h. After completion, the mixture was cooled to room temperature, then aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with dichloromethane (5 mL × 3). The organic phase was dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification by column chromatography on silica gel (petroleum ether/diethyl ether/triethylamine, 50:5:1 to 500:5:1) provided the corresponding product as a yellow solid.

Received: January 23, 2013
Revised: February 27, 2013
Published online: ■■ ■■, ■■■■

Keywords: alkynes · annulation · diaryliodonium · nitriles · nitrogen heterocycles

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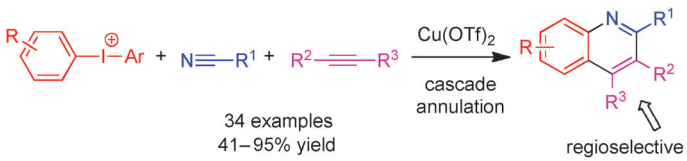
Communications

Quinoline Synthesis

Y. Wang, C. Chen,* J. Peng,
M. Li ——— ■■■■–■■■■

Copper(II)-Catalyzed Three-Component Cascade Annulation of Diaryliodoniums, Nitriles, and Alkynes: A Regioselective Synthesis of Multiply Substituted Quinolines



Three become one: Multiply substituted quinolines were synthesized from diaryliodoniums, alkynes, and nitriles by a Cu^{II}-catalyzed method. This cascade annulation is highly regioselective, step-economic, flexible with regard to the functional groups, and could potentially be applied to the synthesis of complex molecules.

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