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Synthesis of phenanthridine derivatives *via* cascade annulation of diaryliodonium salts and nitriles †

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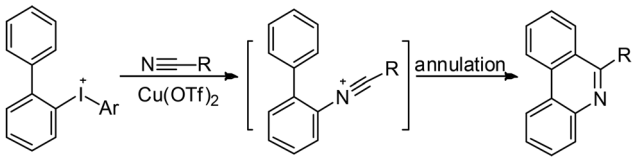
A cascade coupling reaction toward a variety of phenanthridine derivatives has been developed. This cascade transformation proceeds *via* the copper-catalyzed coupling reaction of diaryliodonium salts and nitriles, and undergoes cyclization into the phenanthridine core.

Introduction

The synthesis of substituted phenanthridines is of considerable interest in the fields of organic and pharmaceutical chemistry, since this basic skeleton is an important unit due to its involvement in pharmaceuticals and biologically active natural compounds, such as antiviral, antiprotozoal, antitumor agents, and functional materials.[1] Therefore, substantial efforts have been focused on the synthetic methods of phenanthridines, and a number of well-established methods are now available involving transition-metal-catalyzed, microwave-assisted, benzyne-mediated and hypervalent iodine-promoted reactions.[2] All these approaches have provided powerful methods for the selective assembly of phenanthridine. However, the challenges such as multistep synthetic reactions and limited substrate scope are still present. To meet the high demand of the efficient synthesis of phenanthridines, it is imperative to develop more general and convenient methods with a new strategy.

On the other hand, diaryliodonium salts,[3] as highly electron-deficient and environmentally benign reagents with low toxicity, have emerged as attractive and versatile arylating agents in the synthesis of arylated compounds.[4] In this context, Gaunt has made seminal contributions to the design of new reaction methods in a step-economical fashion that allow for the rapid construction of many complex compounds.[5] In 2008, Gaunt's group developed a site-selective Cu(II)-catalyzed C–H bond functionalization process that can selectively arylate indoles at either the C3 or C2 position with diaryliodonium salts under mild conditions; they proposed the mechanism of the arylation reaction *via* a highly electrophilic aryl-Cu(III) species, which would enable a mild arylation process.[6] Recently, MacMillan's group reported an enantioselective arylation–cyclization cascade using a combination of diaryliodonium salts and chiral copper catalysis. They postulated that the aryl-Cu(III) could form and serve as a platform for pyrroloindoline construction *via* an enantioselective arylation–cyclization cascade process using indole-based nucleophiles.[7] Very recently, Chen and co-workers demonstrated a regioselective [2 + 2 + 2] cyclization approach to the nitrogenous hetero-arenes with diaryliodonium salts and nitriles catalyzed by $Cu(OTf)_2$.[8] The reaction proceeded *via* a series of electrophilic reactions and a key intermediate was the *N*-aryl nitrilium cation generated *in situ* by the reaction of nitrile and iodonium salt in the presence of $Cu(OTf)_2$ *via* the same aryl-Cu(III) process.

Inspired by the aryl-Cu(III) activation mode, combined with our ongoing interest in developing application of diaryliodonium salts *via* transition metal catalysis,[9] we developed an efficient cascade coupling reaction toward a variety of phenanthridine derivatives; this cascade transformation proceeds *via* the copper-catalyzed coupling reaction of diaryliodonium salts and nitriles, and undergoes cyclization into the phenanthridine core. Our design plan is outlined in Scheme 1. We proposed that the key intermediate *N*-aryl nitrilium cation



Scheme 1 Synthesis of phenanthridine derivatives *via* cascade annulation of diaryliodonium salts and nitriles.

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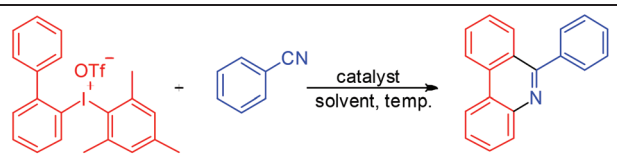
generated *in situ* by the reaction of nitrile and iodonium salt in the presence of $Cu(OTf)_2$.[10] Subsequent intramolecular cyclization would then yield the desired phenanthridine.

Results and discussion

At the outset of our studies, [1,1′-biphenyl]-2-yl(mesityl)iodonium (**1a**) derived from 2-iodo-1,1′-biphenyl[11] and benzonitrile (**2a**) were selected as model substrates to commence this project. The blank experiments (in the absence of a catalyst) of **1a** and **2a** were investigated in DCE at 80 °C and 130 °C for 20 h, respectively, no desired compound was detected (Table 1, entries 1 and 2). Interestingly, the reaction produced the 6-phenylphenanthridine **3a** in 31% yield in the presence of 10 mol% of $Cu(OTf)_2$ (Table 1, entry 3). To optimize reaction conditions, different copper based catalysts were examined, the screening results indicated that $Cu(OTf)_2$ was the most effective catalyst for this transformation (Table 1, entries 4–8). To further improve the efficiency of the reaction, several frequently used aprotic polar solvents were also examined. However, the reaction did not work well (Table 1, entries 9–12). Further study was thus carried out about the temperature, to our delight, significant improvement was achieved at 150 °C and 80% yield was obtained (Table 1, entry 13). The thermal stability test of **1a** (1.0 mol) in DCE (2.0 mL) proceeded at 150 °C; 14% of **1a** was decomposed after 20 h. Moreover, under microwave irradiation the reaction occurred to afford **3a** in 43% yield in 2 hours at 150 °C (Table 1, entry 14).

With the optimized reaction conditions in hand, we probed the scope of different aryl nitriles (Table 2). A variety of

Table 1 Optimization of reaction conditions for the preparation of **3a**[a]

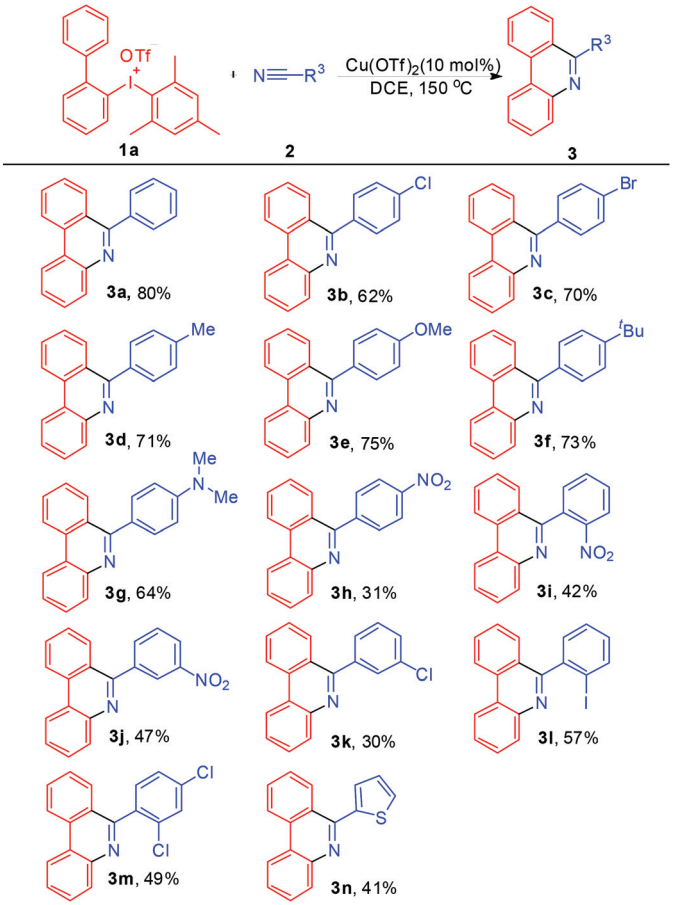


1a **2a** **3a**

Entry	Catalyst	T (°C)	Solvent	Yield (%)[b] **3a**
1	—	80	DCE	—
2	—	130	DCE	—
3	$Cu(OTf)_2$	130	DCE	31
4	CuI	130	DCE	13
5	CuBr	130	DCE	9
6	CuCl	130	DCE	11
7	$CuBr_2$	130	DCE	Trace
8	$CuCl_2$	130	DCE	—
9	$Cu(OTf)_2$	130	DMSO	Trace
10	$Cu(OTf)_2$	130	DMF	—
11	$Cu(OTf)_2$	130	Toluene	15
12	$Cu(OTf)_2$	130	PhCl	7
13	$Cu(OTf)_2$	150	DCE	80
14[c]	$Cu(OTf)_2$	150	DCE	43

[a] Standard reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), catalyst (10 mol%), solvent (2.0 mL) were heated in a sealed tube, 20 h. [b] Isolated yield. [c] Heated with microwave, 2 h.

Table 2 The synthesis of phenanthridine **3** from various nitriles **2**[a,b,c]

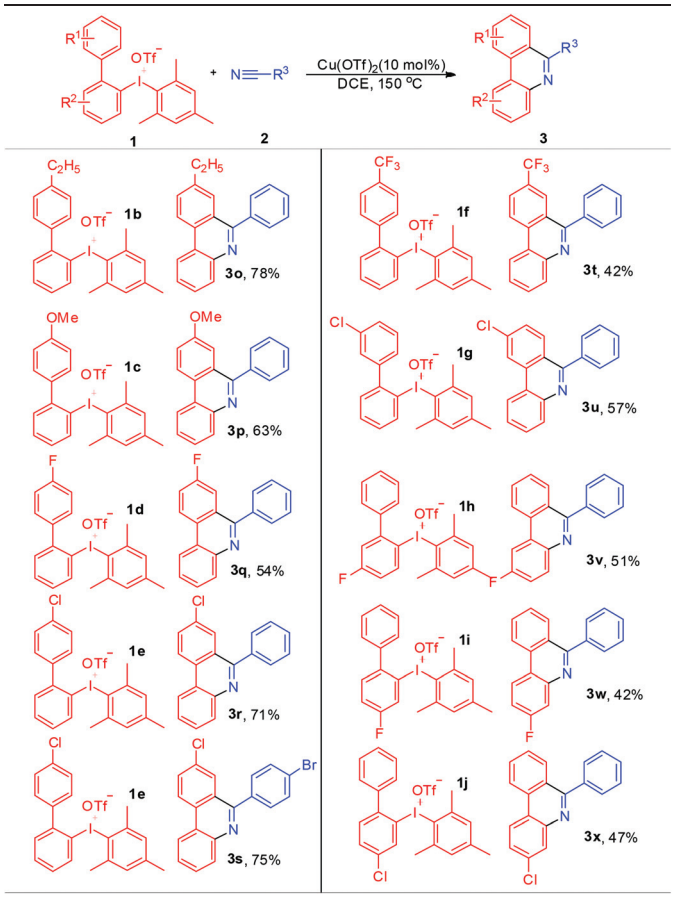


[a] Standard reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), $Cu(OTf)_2$ (10 mol%), DCE (2.0 mL) were heated in a sealed tube, 20 h. [b] Be cautious of potentially hazardous high temperature. [c] Isolated yield.

different groups at the aromatic moiety of benzonitrile, such as halogen, nitro, methyl and aniline, were well tolerated in this transformation. The nitrile substrates bearing an electron-donating group were found suitable than an electron-withdrawing group to afford the final products (Table 2, **3d–3h**). Moreover, a range of *meta*- and *ortho*-substituted aryl nitriles with steric and electronic properties can be readily exploited (Table 2, **3i–3m**). Further exploration of the substrate scope involved heterocyclic nitrile derivatives. It was found that the reaction successfully provided 6-(thiophen-2-yl)phenanthridine **3n** in 41% yield.

Next we turned our attention to the scope of the diaryliodonium salt coupling partner. As revealed in Table 3, the current catalytic system exhibited good reactivity for various substituted diaryliodonium salts. A range of unsymmetrical [Ar-I-Mes]OTf salts were tested and we were pleased to find that the salts were all readily converted to the corresponding substituted phenanthridines in moderate to good yields *via* this reaction (42–78% yields). The diaryliodonium salts bearing an electron-donating group on the 1′-benzene ring (Table 3, **1b**, **1c**) resulted in better yields than that bearing an electron-withdrawing

Table 3 The synthesis of phenanthridine **3** from various diaryliodonium triflates **1** [a,b,c]



[a] Standard reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $Cu(OTf)_2$ (10 mol%), DCE (2.0 mL) were heated in a sealed tube, 20 h. [b] Be cautious of potentially hazardous high temperature. [c] Isolated yield.

group (Table 3, **1f**). The structure of compound **1f** was unequivocally confirmed by single-crystal X-ray diffraction analysis (Fig. 1).[12]

The catalytic system tolerated valuable electrophilic functional groups, such as fluoro and chloro substituents (Table 3, **1d**, **1e** and **1g**). Moreover, 1-benzene substituted diaryliodonium salts **1h**, **1i** and **1j** were also suitable substrates for the cyclization, and led to the corresponding products in 42%–51% yields.

A plausible mechanism for the reaction between diaryliodonium salts and aryl nitriles is illustrated in Scheme 2. First, Cu(I) was formed from $Cu(OTf)_2$ by either a reduction or disproportionation.[7b,8] Next, oxidative insertion of $Cu(OTf)_2$ into a suitable diaryliodonium salt **1** would result in a highly electrophilic Ar-Cu(III) species **4**,[7] which acts as carbocation equivalents; subsequent addition of the aryl nitrile **2** would produce the key intermediate *N*-aryl nitrilium cation **6** [8,10] while reconstituting the catalyst. The resonance occurs between *N*-phenylnitrilium **6** and intermediate **7**, which undergoes an electrophilic annulation to afford phenanthridine **3**.

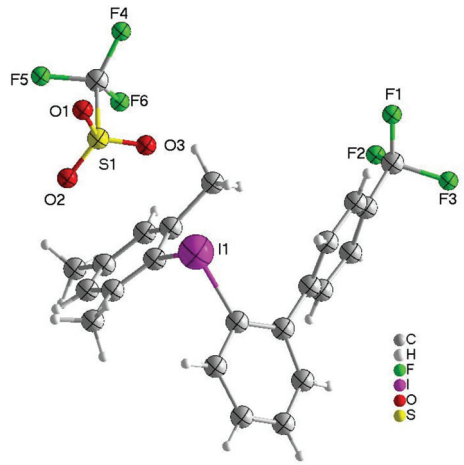
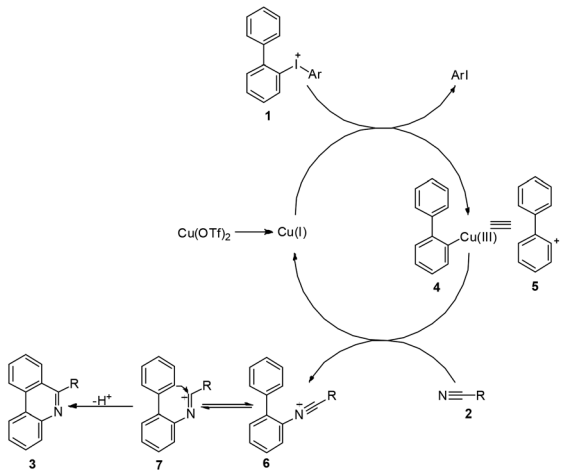
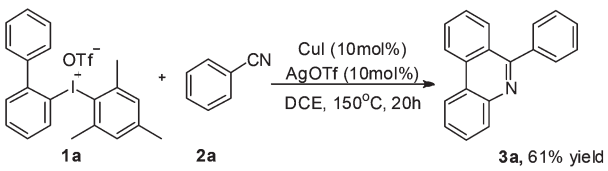


Fig. 1 The X-ray diffraction pattern of compound **1f**.



Scheme 2 Plausible mechanism for the reaction.



Scheme 3 Mechanism experiment catalyzed by Cu(I) *in situ*.

In order to prove the reaction process *via* Cu(I) catalysis, AgOTf and CuI were utilized as catalysts for this transformation (Scheme 3). It was found that 61% of the desired phenanthridine **3a** was formed smoothly in the presence of AgOTf and CuI, which could produce Cu(I) species *in situ*.

Conclusions

In conclusion, we have demonstrated a cascade coupling reaction toward a variety of phenanthridine derivatives. This

cascade transformation proceeds *via* the copper-catalyzed coupling reaction of diaryliodonium salts and nitriles, undergoes cyclization into the phenanthridine core. The reaction outcomes provide a new strategy for synthetically and medicinally phenanthridine derivatives. Further studies to extend the scope and synthetic utility for the synthesis of substituted phenanthridines are in progress in our laboratory.

Experimental section

General experimental methods

All experiments were conducted under an air atmosphere. Flasks were flame dried and cooled under nitrogen before use. All solvents were dried appropriately. For column chromatography, 200–300 mesh silica gel was employed. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz, 400 MHz or 500 MHz spectrometer in $CDCl_3$ solution and the chemical shifts were reported in parts per million (δ) relative to the internal standard TMS (0 ppm). For HRMS measurements, the mass analyzer is GC-TOFMS. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for cascade annulation of diaryliodonium salts and nitriles. A solution of diaryliodonium salts **1** (1 mmol), nitriles **2** (2.0 mmol) and $Cu(OTf)_2$ (36 mg, 0.1 mmol) in DCE (2 mL) was stirred at 150 °C for 20 h. After completion of the reaction (observed on TLC), the solvent was evaporated under reduced pressure to obtain the crude mixture. The residues were purified by silica-gel column chromatography (ethyl acetate–petroleum ether = 1/10–1/4) to afford the pure product **3**. The obtained product was analyzed by ^{1}H NMR, ^{13}C NMR and HRMS.

Acknowledgements

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