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Synthesis of 6-(Arylthio)phenanthridines by Copper-Catalyzed Tandem Reactions of 2-Biaryl Isothiocyanates with Diaryliodonium Salts

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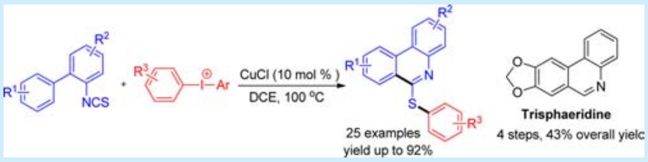
S *Supporting Information*

ABSTRACT: A novel copper-catalyzed tandem C−S/C−C bond-forming reaction of 2-biaryl isothiocyanates with diaryliodonium salts was developed. This is the first general approach to synthesize phenanthridines from 2-biaryl isothiocyanates. This methodology has been successfully applied to the synthesis of trisphaeridine.



The phenanthridine nucleus is a privileged scaffold found in bioactive natural products (Figure 1).[1] Many synthetic phenanthridine-containing molecules show antitumor and antibacterial activities.[2] For example, the monofunctional platinum(II) compound phenanthriplatin displayed significant antitumor properties.[3] In addition, phenanthridine derivatives reveal significant optoelectronic properties.[4] Therefore, diverse methodologies to construct phenanthridines have been developed.[5] Recently, a series of 6-substituted phenanthridines have been successfully constructed from 2-isocyanobiaryl.[6] However, to our knowledge, there is no general method to synthesize phenanthridine derivatives from 2-biaryl isothiocyanates. It is well-known that organosulfur compounds are very important as pharmaceutical agents.[7] In the past decade, various methodologies involving transition-metal-catalyzed cross-coupling reactions[8] and metal-free radical-coupling reactions[9] have been developed to construct C−S bonds.[10] Nevertheless, isothiocyanates are seldom employed to construct C−S bonds.[11]

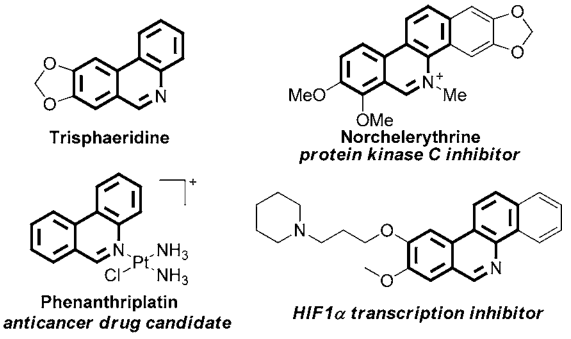


Figure 1. Representative bioactive phenanthridine derivatives.

Diaryliodonium salts are versatile building blocks in organic synthesis due to their high reactivity and low toxicity[12] and have been widely used as electrophilic arylating reagents to obtain aromatic compounds.[13] However, only a few reports have focused on C−S bond formation with diaryliodonium salts.[14] Furthermore, just one example (benzoxathiole) has been reported using phenyl isothiocyanate and a diaryliodonium salt under UV irradiation.[15] Therefore, it is still a challenging task to develop a convenient method by using isothiocyanates and diaryliodonium salts. Based on our previous study on diaryliodonium salts,[16] we report herein a copper-catalyzed tandem arylation−cyclization sequence to construct 6-(arylthio)-phenanthridines from 2-biaryl isothiocyanates and diaryliodonium salts under mild conditions.

Initially, 2-biphenyl isothiocyanate **1a** and diphenyliodonium salts **2a** were chosen as model substrates for reaction condition optimization (Table 1). When a mixture of **1a** and **2a** with a catalytic amount of $Cu(OTf)_2$ was heated to 100 °C in DCE in a sealed tube for 8 h, 6-(phenylthio)phenanthridine **3a** was obtained in 62% yield (entry 1). Then other copper salts were tested (entries 2 and 3). To our delight, 83% yield was achieved with CuCl as catalyst. It is noteworthy that Cu salt was indispensable in the reaction (entry 4). Moreover, anions of the diaryliodonium salts influenced the yields of the reaction dramatically. Triflate (OTf^-) and hexafluorophosphate (PF_6^-) (entry 5) gave good results, but lower yield was obtained when tetrafluoroborate (BF_4^-) (entry 6) was used, and no product was formed with Cl^- (entry 7). Diminished yields were obtained when the reactions were performed in solvents other than DCE or at elevated or decreased temperature (entries 8−11). The yield of **3a** was lowered to 36% when the catalyst loading was reduced to 5 mol % (entry 12). When the reaction was performed under air, a slightly lower yield of 68% was obtained (entry 13).

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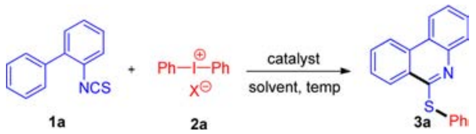
Table 1. Optimization of the Reaction Conditions[a]



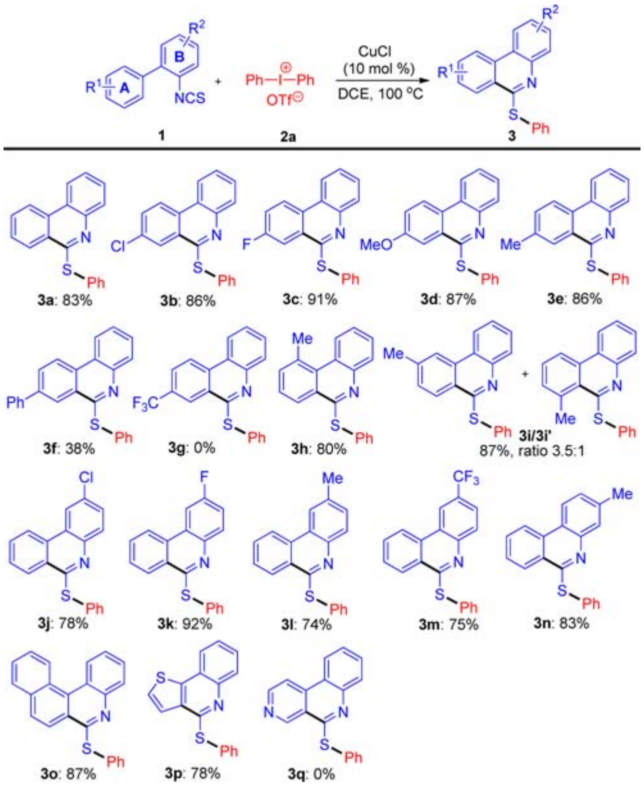
entry	catalyst (mol %)	X	solvent	T (°C)	yield[b] (%)
1	Cu(OTf)$_2$ (10)	OTf	DCE	100	62
2	**CuCl (10)**	**OTf**	**DCE**	**100**	**83**
3	CuBr (10)	OTf	DCE	100	54
4	none	OTf	DCE	100	0
5	CuCl (10)	PF$_6$	DCE	100	76
6	CuCl (10)	BF$_4$	DCE	100	40
7	CuCl (10)	Cl	DCE	100	0
8	CuCl (10)	OTf	THF	100	44
9	CuCl (10)	OTf	toluene	100	75
10	CuCl (10)	OTf	DCE	80	60
11	CuCl (10)	OTf	DCE	120	72
12	CuCl (5)	OTf	DCE	100	36
13[c]	CuCl (10)	OTf	DCE	100	68

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), solvent (1 mL), 8 h, N$_2$. [b]Isolated yield based on **1a**. [c]Under an air atmosphere.

After optimization, the best conditions were established as follows: **1a** (0.2 mmol), **2a** (0.3 mmol), CuCl (0.02 mmol), DCE (1 mL), at 100 °C for 8 h, N$_2$ (entry 2).

With the optimal conditions in hand, the scope of the reaction was examined using a broad range of substituted 2-biaryl isothiocyanates **1** and diphenyliodonium salt **2a** (Scheme 1). The *ortho* and *para* substituents on phenyl ring A did not have significant influence on the yield of the reaction (80−91% yields for **3b**−**h**), except for *p*-phenyl- **1f** (38% yield) and *p*-CF$_3$-substituted **1g** (0% yield). While *m*-methyl-substituted **1i** gave two unseparated isomers in a 3.5:1 ratio and 87% overall yield (**3i**/**3i′**). Additionally, electron-donating or electron-withdrawing groups on phenyl ring B (**1j**−**n**) did not influence the transformation, and the desired phenanthridines **3j**−**n** were isolated in good to excellent yields (74−92%). Moreover, benzo[*k*]phenanthridine **3o** was obtained in 87% yield regioselectively. A heterocycle such as thiophene was also tolerated in the reaction, and product **3p** was isolated in 78% yield. Unfortunately, no product **3q** was detected with pyridine instead of the phenyl ring A.

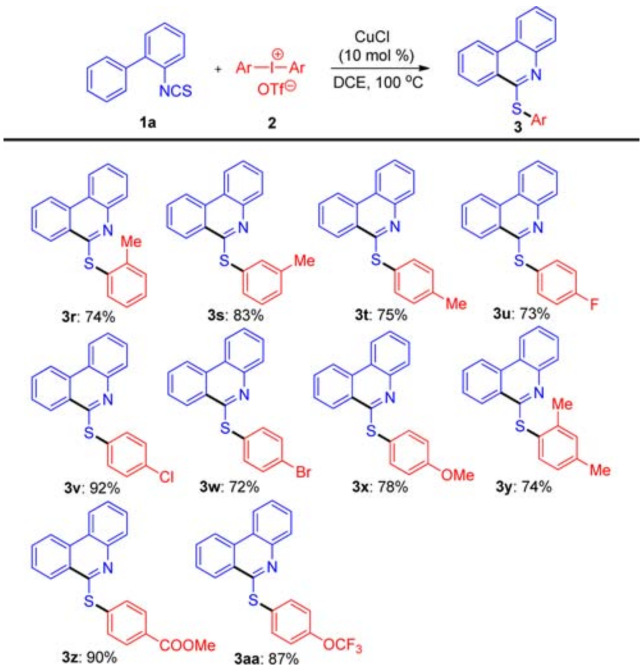
Scheme 1. Synthesis of Substituted Phenanthridines 3a−q from Various 2-Biaryl Isothiocyanates 1[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), DCE (2.5 mL); yields of isolated products.

The scope of diaryliodonium salts **2** was also examined with 2-biphenyl isothiocyanate **1a** under the optimal conditions (Scheme 2). The desired 6-(arylthio)phenanthridines (**3r**−**t**) were obtained in good yields regardless of the position of methyl on the phenyl ring. Diaryliodonium salts bearing 4-fluoro, 4-chloro, 4-bromo, 4-methoxy, and 2,4-dimethyl groups also afforded the desired products (**3u**−**y**) in good yields. Furthermore, excellent yields were obtained when substrates with COOMe and OCF$_3$ groups were investigated, exhibiting the generality of the method.

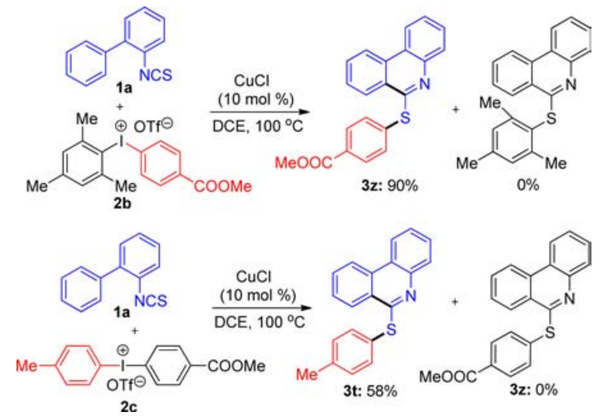
Scheme 2. Synthesis of Substituted Phenanthridines 3r−aa from Various Diaryliodonium Salts 2[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), DCE (2.5 mL); yields of isolated products.

Recent progress in copper-catalyzed diaryliodonium salt participated reactions suggests that both aryl carbocation[13,16] and aryl radical[17] mechanisms would be possible. Thus, control experiments were carried out to gain additional mechanistic insights (Scheme 3). A competition reaction of isothiocyanate **1a** with unsymmetrical diaryliodonium salt **2b** was performed under standard conditions. The less bulky product **3z** was generated exclusively. Another competition reaction of isothiocyanate **1a** with unsymmetrical diaryliodonium salt **2c** was also conducted,

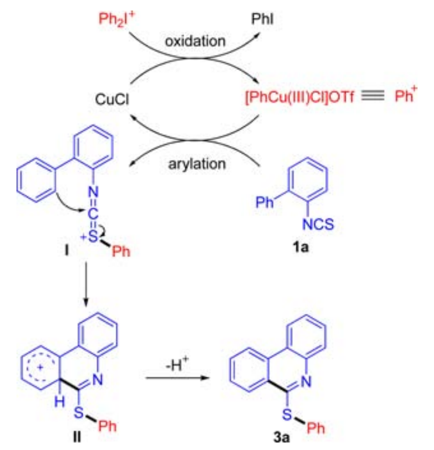
Scheme 3. Control Experiments



in which **3t** was obtained in 58% yield and no product **3z** was observed. These results indicate that aryl carbocation rather than aryl radical would be involved in our reaction.[17,18] It is consistent with the early research that the decomposition of diphenyliodonium salts with electron-donating substituent favors to yield aryl carbocation.[16a] Additionally, when ring A of **1** was electron deficient, no desired products (**3g** and **3q**) were obtained, which indicates that the cyclization would involve an ionic Friedel−Crafts-type mechanism rather than homolytic aromatic substitution.

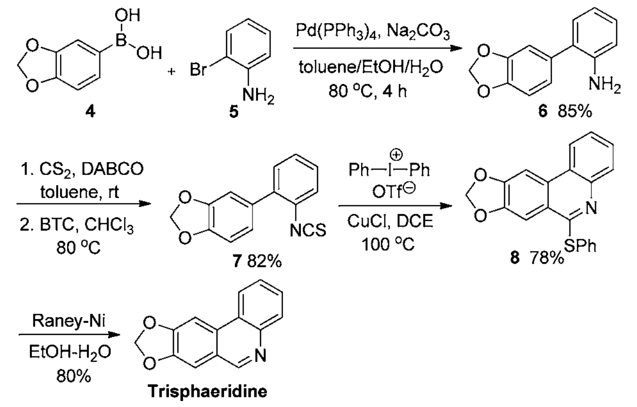
On the basis of the above experimental results, a plausible mechanism is depicted in Scheme 4. Oxidative addition to the Cu(I) salt by diphenyliodonium salt **2a** would generate a Ph-Cu(III) species,[16] which transfers the phenyl group to the isothiocyanate **1a** to give sulfonium intermediate **I**.[19] Subsequently, the intermediate **I** would undergo intramolecular Friedel−Crafts-type cyclization to afford intermediate **II**, which deprotonates to provide the final product **3a**.

Scheme 4. Proposed Reaction Mechanism



To exhibit the application value of this transformation, we synthesized the Amaryllidaceae alkaloid trisphaeridine (Scheme 5).[20] Our synthetic route started from the commercially available boronic acid **4** and 2-bromoaniline **5**. Suzuki coupling followed by isothiocyanate formation obtained the precursor **7**. Under the above standard cyclization conditions, the 6-(phenylthio)-phenanthridine **8** was generated in 78% yield. Finally, desulfurization by Raney Ni afforded the natural alkaloid trisphaeridine.

Scheme 5. Application in the Synthesis of Trisphaeridine



In conclusion, we have developed a copper-catalyzed tandem reaction of 2-biaryl isothiocyanates with diaryliodonium salts, which provides an effficient approach to construct 6-(arylthio)-phenanthridines and analogues. In addition, this method was successfully applied to the short synthesis of alkaloid trisphaeridine in good overall yields. Further efforts to explore novel synthetic methods using 2-biaryl isothiocyanates are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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