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Copper-Catalyzed Annulation: A Method for the Systematic Synthesis of Phenanthridinium Bromide

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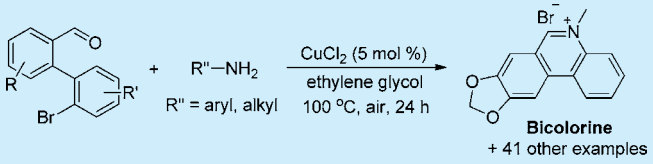
Supporting Information

ABSTRACT: A novel procedure for the Cu-catalyzed systematic synthesis of phenanthridinium bromide is reported. This transformation was achieved with direct construction of central pyridinium core by using an in situ formed biaryl imine as a substrate. Tolerance of a very wide variety of *N*-substituents is indicated; this has never previously been disclosed by other reports. Application of this method to synthesis of the natural alkaloid bicolorine, and its derivatives, was also carried out in only three synthetic steps from commercially available compounds.



Phenanthridinium is an important structural motif with many natural alkaloids containing this building block[1] (Figure 1). As such, molecules of this genre are widely explored in antitumor research and are of potential value to anticancer chemotherapy. They exhibit cytotoxicity toward tumor cells by inhibiting diverse targets such as DNA topoisomerase I/II,[2] protein kinase C,[3] and others.[4] Some derivatives have antibacterial[5] and antimalaria[6] functions as well. Recent research has demonstrated that phenanthridiniums could be a new class of human DOPA decarboxylase inhibitors, which might provide a new route to cure Parkinson's disease.[7] Apart from their medicinal properties, 5-arylphenanthridiniums that have a high ability to engage in DNA intercalation are commonly applied as DNA probes.[8] Moreover, due to their UV behavior, their applications as DNA fluorescent dyes[9] and switchable materials[10] are feasible.

Despite these fascinating applications having received significant attention, their preparation is still limited to specific structures. Past reported methods have approached these compounds mainly through a substitution from phenanthridines, thus restricting their formation to *N*-primary and less hindered *N*-secondary alkylphenanthridiniums.[11] Transformations from phenanthridinones[12] and dihydrophenanthridines[13] have also been reported; however, a multistep synthetic route was required for annulation of the central heterocycle. No tertiary alkyl and aryl groups could be attached to the quaternary nitrogen atom of phenanthridinium by these protocols. Construction of such heterocyclic compounds via an intramolecular coupling reaction of an imine might be able to address this issue. This concept has caused methods to emerge for direct construction of pyridinium,[14] quinolinium, and isoquinolinium[15] structures with versatile *N*-substituents by late transition-metal catalysis. A similar idea was also utilized to furnish a phenanthridinium through a microwave-assisted intramolecular S_NAr coupling reaction of a biaryl imine.[16] However, limitations on the synthesis of *N*-primary alkylphenanthridiniums still exist. An effective method for the synthesis of phenanthridinium derivatives with various substituents on nitrogen is desired to support pharmaceutical and materials research. Our experience in Cu-catalyzed cyclizations involving C−N bond formation[17] encouraged us to explore the possibility of constructing phenanthridiniums with versatile substituents by Cu-mediated catalysis. Herein, we report the first systematic synthesis of phenanthridiniums through a Cu-catalytic cycle.

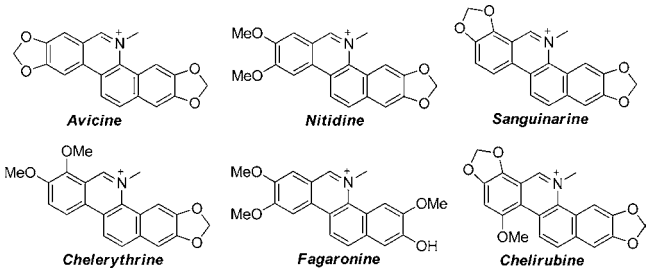


Figure 1. Selected phenanthridinium alkaloids.

At the outset of our studies, the reaction conditions were surveyed by using 2′-bromo-[1,1′-biphenyl]-2-carbaldehyde (**1a**) as a model substrate (Table 1). Initially, **1a** (0.1 mmol) was treated with 1.2 equiv of 2-methylpropan-1-amine (**2a**) and 5 mol % of CuI in 1 mL of THF at 100 °C for 24 h; the desired product 5-isobutylphenanthridin-5-ium bromide (**3aa**) was obtained in only 6% NMR yield (entry 1). Product **3aa** was confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and X-ray analysis. After the reactions were worked up, only substrates, product, and corresponding imine were observed in the crude NMR spectra.

To optimize the reaction conditions, the effect of solvents, ligands, copper salts, and reaction temperatures was investigated, and the results are summarized in Table 1 (see the Supporting Information for the effect of solvents and ligands in detail). We first evaluated the effect of solvent on this reaction (entries 1−6) and found that only *t*-BuOH effectively improved the yield of **3aa**. Other solvents such as aromatic solvents, polar solvents, ethers,

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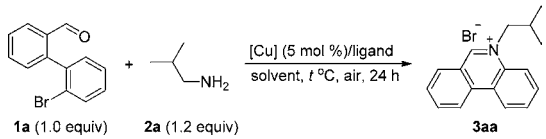
Table 1. Optimization of Reaction Conditions[a]



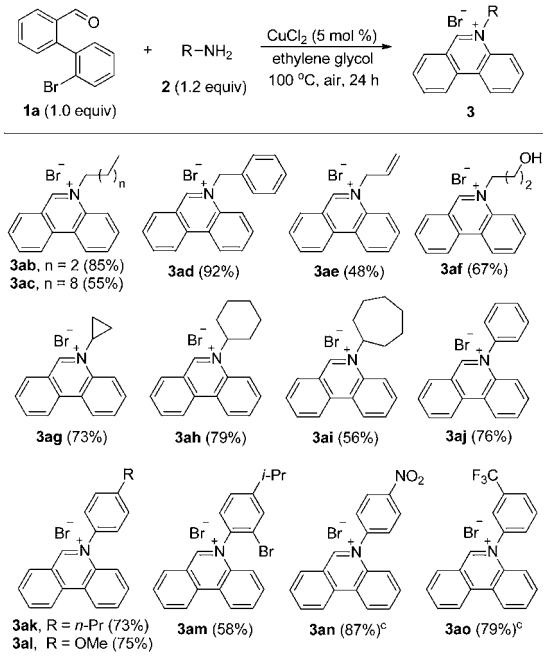
entry	[Cu]	ligand	solvent	temp (°C)	yield[b] (%)
1	CuI		THF	100	6
2	CuI		aromatic solvents[c]	100	3−14
3	CuI		polar solvents[d]	100	18−23
4	CuI		ethers[e]	100	0−12
5	CuI		ROH[f]	100	4−27
6	CuI		*t*-BuOH	100	31
7[g]	CuI	ethylene glycol	*t*-BuOH	100	53
8[g]	CuI	2,3-butanediol	*t*-BuOH	100	51
9[g]	CuI	catechol	*t*-BuOH	100	49
10	CuI		ethylene glycol	100	79
11	CuBr		ethylene glycol	100	89
12	CuCl		ethylene glycol	100	88
13	$Cu(OAc)_2$		ethylene glycol	100	71
14	$CuCl_2$		ethylene glycol	100	96 (91)[h]
15	$CuCl_2$		ethylene glycol	120	97
16	$CuCl_2$		ethylene glycol	90	83
17[i]	$CuCl_2$		ethylene glycol	100	93
18[j]	$CuCl_2$		ethylene glycol	100	68
19[k]	$CuCl_2$		ethylene glycol	100	99
20			ethylene glycol	100	7

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), [Cu] (5 mol %), solvent (1.0 mL), indicated temperature, under air, 24 h. [b]^{1}H NMR yield based on internal standard mesitylene. [c]Benzene, toluene, *o*-xylene, mesitylene, chlorobenzene, and *o*-dichlorobenzene were used. [d]DMSO, DMF and NMP were used. [e]Et_2O, 1,4-dioxane, and DME were used. [f]EtOH, cyclohexanol, and *i*-PrOH were used. [g]20 mol % of ligand. [h]Isolated yield in 0.5 mmol scale. [i]40 h. [j]16 h. [k]Under N_2.

and alcohols are not effective for this reaction. We then employed ligands to facilitate this Cu-catalyzed process. This demonstrated that only diol ligands are efficient, improving the reaction yields up to 53% (entries 7−9). This result suggests that a five-membered cyclic copper complex might be the active catalyst. The *t*-BuOH was then replaced with ethylene glycol, and the yield of **3aa** was significantly improved to 79% (entry 10). The copper source was also influential in this reaction (entries 10−14). Among the copper salts that we examined, $CuCl_2$ showed the best catalytic efficacy and improved the yield of **3aa** to 96%. The reaction proceeded smoothly at 90−120 °C (entries 15 and 16). Higher reaction temperature or longer reaction time did not further improve the reaction yield (entries 15 and 17), and the reaction needed at least 24 h to complete when it was conducted at less than or at 100 °C (entry 16, 18). Furthermore, the reaction proceeded smoothly under a nitrogen atmosphere (entry 19) but gave only a trace amount of **3aa** without the copper catalyst (entry 20).

After the reaction conditions were optimized, the capacity of this Cu-catalyzed cyclization to work with different amines and anilines was then investigated (Scheme 1). The reaction tolerates a wide range of amines and anilines, while the yields depend on the structures of the amine and aniline. Primary alkylamines were smoothly converted to the desired products, with the yields of products depending on the chain length (**3ab**−**ad**). Functional alkyl groups provided slightly lower yields of the desired products (**3ae**,**af**) accompanied by unidentified compounds. Reactions with the cycloalkylamines proceeded smoothly, providing the desired products **3ag**−**ai** in moderate to good yields. Apart from **3aa**, the structure of compound **3ag** (Figure 2) was also verified by single-crystal X-ray diffraction. *N*-Aryl compounds containing both electron-donating (**3ak**−**am**) and electron-withdrawing

Scheme 1. Scope of Amines and Anilines[a,b]



[a]Reactions were carried out using 0.5 mmol (1.0 equiv) of **1a** with 1.2 equiv of RNH_2 (**2**) and 5 mol % of $CuCl_2$ in 5.0 mL of ethylene glycol at 100 °C for 24 h. [b]Isolated yield. [c]130 °C.

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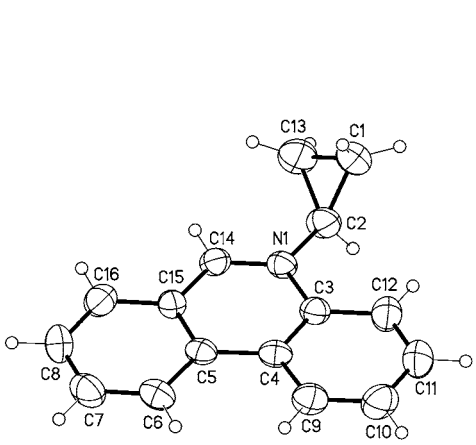


Figure 2. X-ray structure of compound **3ag**.

groups (**3an**,**ao**) were obtainable by this method in good yield. However, products **3an** and **3ao** could be generated only at 130 °C because of the low electron density on nitrogen. Their corresponding imines (**1an** and **1ao**) were not detected under 100 °C. It is worth remarking that the *N*-arylphenanthridinium compounds are not able to be synthesized by other process. Our methodology can give versatile *N*-arylphenanthridiniums, including bromide (**3am**), and derivatives with strong electron-donating (**3al**) and strong electron-withdrawing groups (**3an** and **3ao**) attached to the aryl ring.

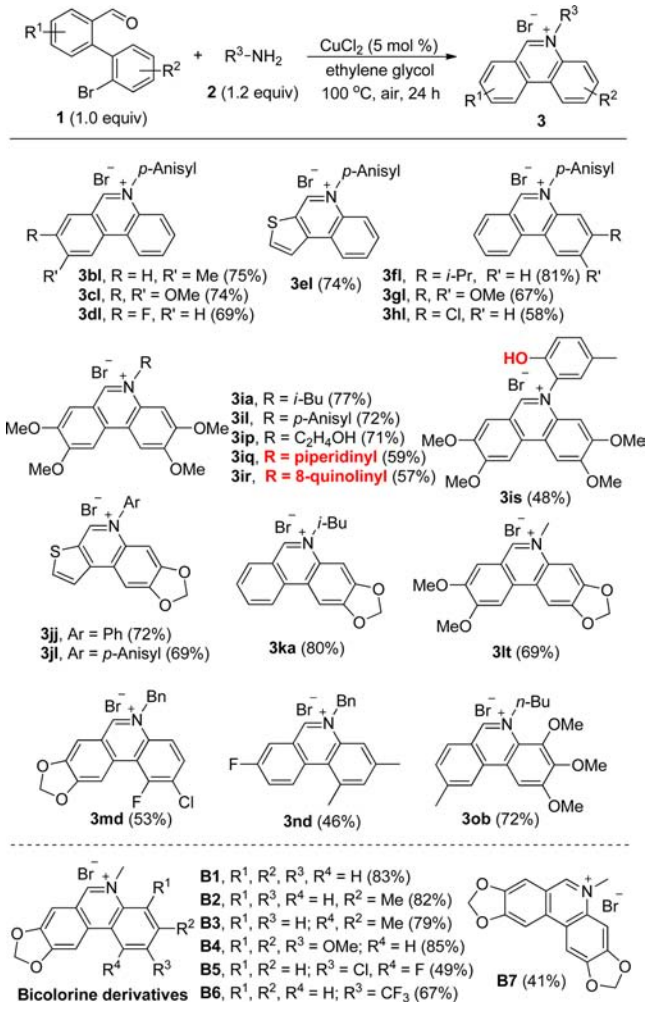
Further investigation of the scope of our phenanthridinium synthesis was also undertaken, and the results are shown in Scheme 2. As indicated, substrates with electron-donating and electron-deficient groups on the moieties of the benzaldehyde and the aryl bromide engaged in this transformation (**3bl**−**il**); higher electron density on the aromatic rings generally led to a higher yield of the desired product (**3bl**, **3cl** vs **3dl** and **3fl**, **3gl** vs **3hl**). Synthesis of heterocyclic compounds was also possible, with the products **3el**, **3jj**, and **3jl** being afforded in 74%, 72%, and 69% yields, respectively.

This method will contribute to pharmaceutical research toward development of structure−activity relationships in the antitumor field. Previous research[2] has shown that the basic requirement for inhibitors of topoisomerase is at least two oxygenated groups on the left ring. Additional groups, which can offer more hydrogen bonding, also have a favorable effect on the antitumor activities. Therefore, a series of structures can be constructed by reacting substrate **1i** with various amines and anilines (**3ia**−**is**). Notably, some interesting compounds with *N*-heterocyclic (**3iq** and **3ir**) and *N*-phenol groups (**3is**) were provided as well. No other methods could be utilized for the synthesis of similar structures. Moreover, the combination of different subunits established diverse structures (**3ka**−**ob**) in moderate to good yields.

The present methodology was applied in the synthesis of the Amaryllideceae alkaloid bicolorine (**B1**)[20] and its derivatives (**B2**−**B7**). To the best of our knowledge, this is the shortest synthetic route to bicolorine from a commercial source (three steps, 58% overall yield). Bicolorine and its analogues have attracted considerable attention for a long time because of their multibioactivities, particularly their anticancer effects.[1−4,7] This strategy represents an efficient pathway to these bioactive compounds and will bring high convenience to this area of medicinal research.

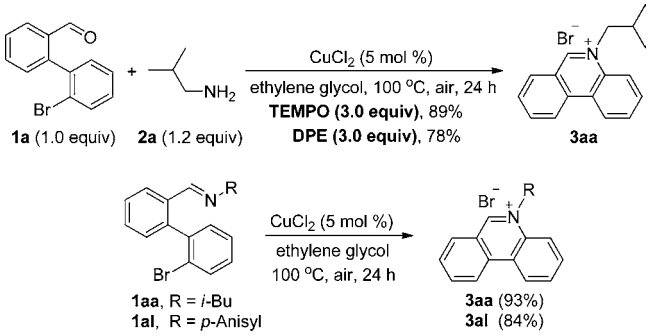
To study the reaction mechanism, some control experiments were conducted to clarify the reaction pathway (Scheme 3).

Scheme 2. Scope of Phenanthridinium Salts[a,b]



[a]Reactions were carried out using 0.5 mmol (1.0 equiv) of **1** with 1.2 equiv of RNH_2 (**2**) and 5 mol % of $CuCl_2$ in 5.0 mL of ethylene glycol at 100 °C for 24 h. [b]Isolated yield.

Scheme 3. Control Experiments



These experiments delivered two pieces of information. First, this reaction does not involve a radical pathway (reactions were not prevented by introducing two radical scavengers TEMPO and DPE). Second, the reaction passes through an in situ formed biaryl imine (reactions proceeded smoothly and provided slightly higher yields via the supposed intermediate biaryl imines).

On the basis of previous reports[17−19] and the above results, a tentative reaction pathway can be proposed as shown below (Scheme 4). The reaction is likely to be initiated by the

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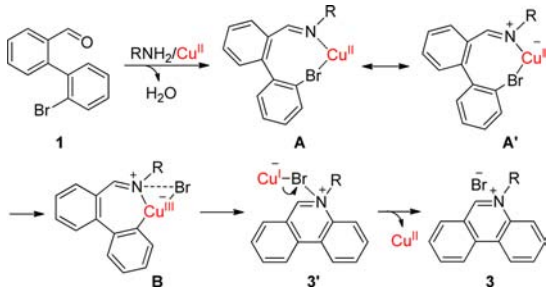
Scheme 4. Proposed Reaction Pathway



condensation of compound **1** with amine **2** to form the corresponding biaryl imine. The biaryl imine then chelates to the Cu(II) complex (**A**) with an electron transfer reducing Cu(II) to Cu(I) (**A′**). A subsequent oxidative addition of the Cu(I) affords a Cu(III) complex (**B**). Reductive elimination of the Cu(III) complex provides desired product **3** and regenerates Cu(II) via the intermediate **3′**.

In conclusion, we have developed a novel method for the Cu-catalyzed annulative synthesis of a wide range of phenanthridinium bromides in moderate to excellent yields. In addition, this methodology was applied in the synthesis of the natural alkaloid bicolorine and its derivatives in a short synthetic route. Further studies to explore other applications are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00269.

X-ray data for **3aa** (CIF)
X-ray data for **3ag** (CIF)
Experimental procedures, characterization, spectral data, X-ray structure, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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