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$FeCl_3$-Promoted Carboxamidation and Cyclization of Aryl Isonitriles with Formamides toward Phenanthridine-6-carboxamides

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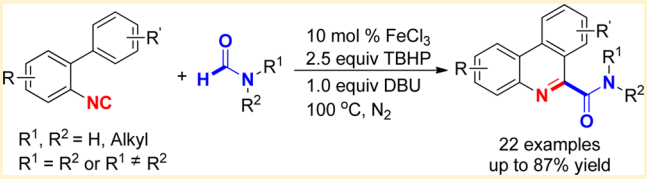
Supporting Information

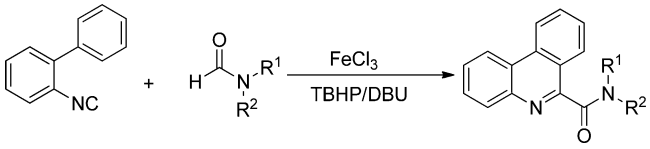
ABSTRACT: An iron-promoted tandem carboxamidation and cyclization between aryl isonitriles and formamides has been developed. The one-pot strategy can be applied to a wide range of 2-isocyanobiphenyls and formamides with excellent functional group tolerance for the synthesis of phenanthridine-6-carboxamides in moderate to excellent yields.



Phenanthridines are essential structural motifs in numerous naturally occurring alkaloids and potential pharmaceuticals with remarkable biological and medicinal activities,[1] including antitumor, antifungal, antileukemic, and antiviral properties.[2] Moreover, many substituted phenanthridines have a wide range of applications in materials science because of their significant optical and electronic properties.[3] As a consequence, extensive efforts have been devoted to the development of methods for the preparation of phenanthridines and their derivatives.[4,5] Recently, the cascade radical addition and subsequent intramolecular homolytic aromatic substitution of 2-isocyanobiphenyls with radical precursors have been established for the efficient construction of various 6-substituted phenanthridines.[5] For example, Studer and co-workers reported an efficient synthesis of 6-aroylated phenanthridines through base-promoted homolytic aromatic substitution of 2-isocyanobiphenyls with aromatic aldehydes using $FeCl_3$ as an initiator.[5a] Meanwhile, aryl carboxamides are known as one of the most important functional groups and precursors for the synthesis of natural products, pharmaceuticals, agrochemicals, and bioactive polymers.[6] However, traditional carboxamidation between carboxylic acids and amines usually requires drastic conditions that are not compatible with some functional groups.[7] Therefore, the development of new and versatile strategies for direct carboxamidation, especially from readily available amino sources, for the synthesis of aryl carboxamides is highly desired.[8] Considering the widespread applications of both phenanthridines and aryl carboxamides, we wish to develop some C−H functionalization and cyclization reactions for the preparation of phenanthridinecarboxamides.[4a] Herein we report a convenient and efficient method for the direct carboxamidation of aryl isonitriles with formamides for the one-pot synthesis of phenanthridine-6-carboxamides (Scheme 1). This procedure is realized through a cascade radical addition and aromatization process with high atom economy and represents the first example of direct carboxamidation using formamides as radical precursors in isocyanide insertion.[9]

We began the study by examining the reaction between 2-isocyanobiphenyl (**1a**)[10] and *N*,*N*-dimethylformamide (DMF, **2a**) to optimize the reaction conditions, and the results are summarized in Table 1. The initial exploration disclosed that the reaction could proceed at 100 °C in the presence of 2.5 equiv of *tert*-butyl hydroperoxide (TBHP) to afford the desired product **3** in 28% yield (entry 1). We subsequently investigated some bases with the aim of increasing the reaction yield. As expected, NaOAc, KOAc, and K_2CO_3 could facilitate the reaction to provide product in moderate yields (41−48%; entries 2−4). To our delight, the reaction yield increased dramatically to 77% in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (entry 5).[11] Further optimization was carried out by testing various catalysts, but the results showed that the reaction was suppressed by $PdCl_2$, CuCl, and $Cu(OAc)_2$ (entries 6−8). Fortunately, we found that iron catalysts could promote the reaction (entries 9 and 10), and an 87% yield of product **3** was isolated when $FeCl_3$ was used as the catalyst. Other organic or inorganic peroxides, such as di-*tert*-butyl peroxide (DTBP), benzoyl peroxide (BPO), and $K_2S_2O_8$, were found to be less effective than TBHP (entries 11−13). However, the reaction did not work in the absence of initiator (entry 14). Lower yields were observed when the reaction was carried out at 120 or 80 °C (entries 15 and 16).

Scheme 1



With the optimal reaction conditions in hand, we next explored the substrate scope of aryl isonitriles for the tandem carboxamidation and cyclization (Table 2). First, substituents on the phenyl ring bearing the isocyano group were investigated by testing the reaction between various 2-phenyl aryl isonitriles and DMF under the standard conditions. The results displayed that both electron-donating and electron-withdrawing substituents were tolerated well and provided the

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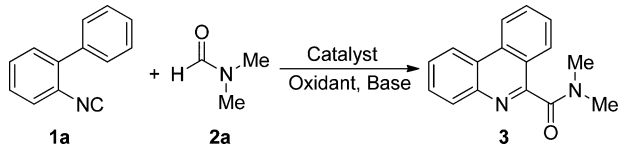
Table 1. Screening of Conditions[a]



1a 2a 3

entry	catalyst	oxidant	base	yield (%)
1	–	TBHP	–	28
2	–	TBHP	NaOAc	45
3	–	TBHP	KOAc	48
4	–	TBHP	K_2CO_3	41
5	–	TBHP	DBU	77
6	$PdCl_2$	TBHP	DBU	trace
7	CuCl	TBHP	DBU	0
8	$Cu(OAc)_2$	TBHP	DBU	0
9	$FeCl_2$	TBHP	DBU	81
10	$FeCl_3$	TBHP	DBU	87
11	$FeCl_3$	DTBP	DBU	58
12	$FeCl_3$	BPO	DBU	37
13	$FeCl_3$	$K_2S_2O_8$	DBU	51
14	$FeCl_3$	–	DBU	0
15[b]	$FeCl_3$	TBHP	DBU	65
16[c]	$FeCl_3$	TBHP	DBU	78

[a]Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol %), initiator (2.5 equiv), and base (1.0 equiv) in DMF (2 mL) under an atmosphere of N_2 at 100 °C for 12 h. TBHP (5.5 M in decane). [b]At 120 °C. [c]At 80 °C.

corresponding products in good yields. For example, methyl and methoxy gave products **4** and **5** in 81% and 75% yield, respectively. The electron-withdrawing fluoro, chloro, and trifluoromethyl groups provided yields of 73−83% (products **6**−**8**). Notably, the reaction of 3-isocyano-2-phenylpyridine also proceeded successfully to afford product **9** in 80% yield. Subsequently, the substituents on the cyclized phenyl ring were evaluated, and similar results were obtained. 4-Methyl and 2-methoxy afforded products **10** and **11** in 67% and 52% yield, respectively. The regioselectivity was observed when 2-isocyano-3′-methoxy-1,1′-biphenyl was used as the coupling partner, and cyclized product **12b** with the MeO group at the *ortho* position was isolated in 42% yield along with product **12a** in 21% yield. The strong electron-withdrawing cyano and acetyl groups provided products **13** and **14** in 80% and 71% yield, respectively.

During the exploration of the substrate scope of formamides, we wished to reduce their loading in order to increase the atom economy of some expensive formamides. After a series of trials, we found that 20 equiv of *N*,*N*-diethylformamide in 2 mL of chlorobenzene under standard conditions provided product **15** in 62% yield, although an 86% yield was obtained when *N*,*N*-diethylformamide used as the solvent (Table 3). A similar yield of **16** (61%) was observed when *N*,*N*-diisopropylformamide was used. The cyclic substrates piperidine-1-carbaldehyde and morpholine-4-carbaldehyde were converted to products **17** and **18** in 53% and 61% yield, respectively. Gratifyingly, non-substituted formamide was also compatible with this oxidative cyclization to afford product **19** in 46% yield. Monosubstituted formamides were suitable substrates, providing the corresponding products in moderate to good yields. For example, methyl, ethyl, *tert*-butyl, and cyclohexyl afforded products **20**−**23** in 62−81% yield. A glycine derivative, ethyl 2-formamidoacetate, underwent the tandem reaction with **1a** smoothly to produce product **24** in 42% yield.

To probe the mechanism of this tandem carboxamidation and cyclization transformation, the reaction of 2-isocyanobiphenyl **1a** with DMF, TBHP, DBU, and $FeCl_3$ was carried out under the standard conditions with the addition of 2.5 equiv of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), a radical scavenger (Scheme 2). As expected, the target product **3** could not be detected and more than 95% of reactant **1a** was recovered, while the TEMPO−DMF adduct **25** was isolated and confirmed by NMR and HRMS analyses. These results revealed that the tandem reaction might involve a free radical pathway.

On the basis of these experimental results and previous reports,[5a] a possible mechanism for this tandem reaction was proposed as outlined in Scheme 3. First, DMF might be transformed into dimethylcarbamic radical **A** through hydrogen abstraction by *tert*-butoxyl radical, which is formed *in situ* from the reaction of TBHP and $FeCl_3$.[12] Subsequently, the addition of **A** to 2-isocyanobiphenyl **1a** produces imidoyl radical intermediate **B**. The intramolecular radical electrophilic attack on the neighboring arene provides cyclohexadienyl radical **C**, which can be deprotonated with DBU to give arene radical anion **D**. Finally, radical anion **D** reduces TBHP by single-electron transfer to afford phenanthridine-6-carboxamide **3** and regenerate *tert*-butoxyl radical.

In summary, we have developed a general and practical tandem carboxamidation and cyclization for the synthesis of phenanthridine-6-carboxamides. In the presence of $FeCl_3$, TBHP, and DBU, a variety of 2-isocyanobiphenyls successfully underwent the radical addition and subsequent intramolecular hemolytic aromatic substitution with various formamides to afford phenanthridine-6-carboxamides in moderate to excellent yields. The tandem reaction exhibits excellent functional group tolerance and is compatible with nonsubstituted, monosubstituted, and disubstituted formamides. The present method provides a new strategy for constructing the phenanthridine ring and also for the synthesis of aryl carboxamides from readily available formamides.

EXPERIMENTAL SECTION

General Information. Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts (δ) are given in parts per million relative to TMS, and coupling constants (J) are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. All of the reactions performed under a nitrogen atmosphere were conducted using standard Schlenk techniques. Melting points were measured on an X4 melting point apparatus and are uncorrected. Column chromatography was performed using EM Silica gel 60 (300−400 mesh).

General Procedure A for the Synthesis of Phenanthridine-6-carboxamides. A flame-dried Schlenk tube with a magnetic stirring bar was charged with **1** (0.2 mmol), $FeCl_3$ (3.2 mg, 0.02 mmol), TBHP (0.5 mmol, 0.09 mL, 5.5 M in decane), and DBU (30.4 mg, 0.2 mmol) in DMF **2a** (2 mL) under an atmosphere of N_2. The reaction mixture was stirred at 100 °C until complete consumption of the starting material as detected by TLC or GC−MS analysis. After the reaction was finished, the mixture was poured into ethyl acetate, which was washed with brine (3 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue

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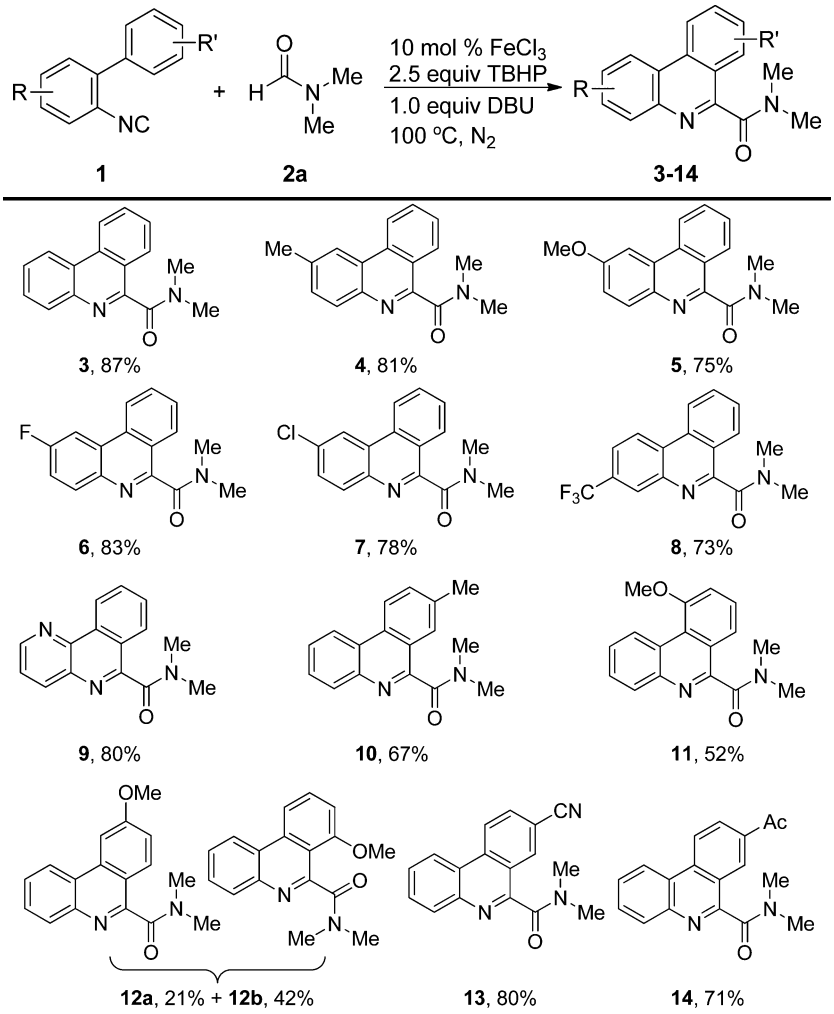
Table 2. Tandem Carboxamidation and Cyclization of Aryl Isonitriles with DMF[a]



[a]Reaction conditions: **1** (0.2 mmol), DMF (2 mL), $FeCl_3$ (10 mol %), TBHP (2.5 equiv), and DBU (1.0 equiv) under an atmosphere of N_2 at 100 °C for 12 h.

was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product **3**–**14**.

N,N-Dimethylphenanthridine-6-carboxamide (***3***). White solid (43.5 mg, 87% yield), mp 51–53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 8.0 Hz, 1H), 8.59 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.90–7.87 (m, 1H), 7.78–7.69 (m, 3H), 3.31 (s, 3H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.1, 156.2, 143.1, 133.2, 131.3, 130.2, 129.0, 127.8, 127.7, 127.0, 124.0, 123.1, 122.3, 122.1, 38.2, 34.8; LRMS (EI, 70 eV) m/z (%) 250 (M^+, 14), 193 (15), 179 (100), 178 (22), 151 (23); HRMS (ESI) calcd for $C_{16}H_{15}N_2O^+$ ([M + H]$^+$) 251.1179, found 251.1184.

N,N-2-Trimethylphenanthridine-6-carboxamide (***4***). Pale-yellow solid (42.8 mg, 81% yield), mp 30–32 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 8.0 Hz, 1H), 8.36 (s, 1H), 8.08–8.04 (m, 2H), 7.86–7.83 (m, 1H), 7.69–7.66 (m, 1H), 7.57 (d, J = 8.0 Hz, 1H), 3.30 (s, 3H), 2.92 (s, 3H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.3, 155.3, 141.4, 137.7, 131.0, 130.7, 130.0, 127.7, 127.0, 123.9, 123.3, 122.2, 121.7, 38.3, 34.8, 22.0; LRMS (EI, 70 eV) m/z (%) 264 (M^+, 15), 207 (19), 193 (100); HRMS (ESI) calcd for $C_{17}H_{17}N_2O^+$ ([M + H]$^+$) 265.1335, found 265.1345.

2-Methoxy-N,N-dimethylphenanthridine-6-carboxamide (***5***). Pale-yellow solid (42.0 mg, 75% yield), mp 137–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.85–7.82 (m, 1H), 7.69–7.66 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H), 3.30 (s, 3H), 2.92 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.4, 159.1, 153.7, 138.3, 132.6, 131.6, 130.8, 127.9, 127.0, 125.3, 123.3, 122.3, 118.9, 103.0, 55.7, 38.3, 34.9; LRMS (EI, 70 eV) m/z (%) 280 (M^+, 28), 209 (100), 193 (32); HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2^+$ ([M + H]$^+$) 281.1285, found 281.1283.

2-Fluoro-N,N-dimethylphenanthridine-6-carboxamide (***6***). White solid (44.5 mg, 83% yield), mp 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 8.5 Hz, 1H), 8.20–8.16 (m, 2H), 8.08 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.55–7.45 (m, 1H), 3.31 (s, 3H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.0, 161.8 (d, J_{CF} = 246.9 Hz), 155.5, 139.9, 132.4, 132.1, 131.3, 128.5, 127.2, 125.5, 123.2, 122.4, 117.9 (d, J_{CF} = 24.2 Hz), 107.1, 38.2, 34.8; LRMS (EI, 70 eV) m/z (%) 268 (M^+, 16), 211 (15), 197 (100); HRMS (ESI) calcd for $C_{16}H_{14}FN_2O^+$ ([M + H]$^+$) 269.1085, found 269.1093.

2-Chloro-N,N-dimethylphenanthridine-6-carboxamide (***7***). Brown solid (44.3 mg, 78% yield), mp 185–187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 8.5 Hz, 1H), 8.53 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.91–7.88 (m, 1H), 7.75–7.72 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 3.31 (s, 3H), 2.92 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.9, 156.5, 141.5, 133.7, 132.2, 131.7, 131.6, 129.6, 128.5, 127.2, 125.2, 123.3, 122.3, 121.8, 38.2, 34.8; LRMS (EI, 70 eV) m/z (%) 284 (M^+, 15), 215 (32), 213 (100), 177 (49); HRMS (ESI) calcd for $C_{16}H_{14}ClN_2O^+$ ([M + H]$^+$) 285.0789, found 285.0803.

N,N-Dimethyl-3-(trifluoromethyl)phenanthridine-6-carboxamide (***8***). Pale-yellow solid (46.4 mg, 73% yield), mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69–8.66 (m, 2H), 8.47 (s, 1H), 8.12 (d, J =

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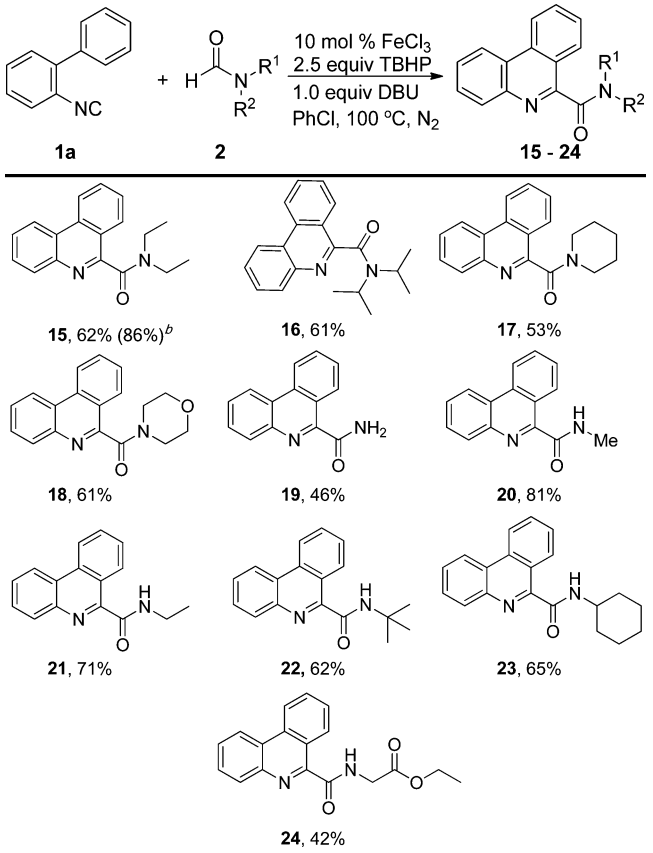
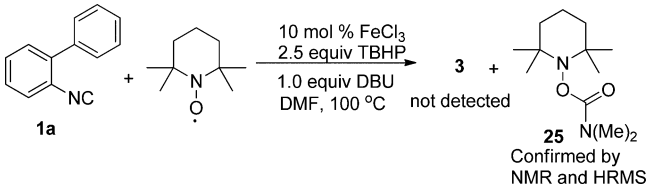
Table 3. Tandem Carboxamidation and Cyclization of 2-Isocyanobiphenyls with Formamides[a]

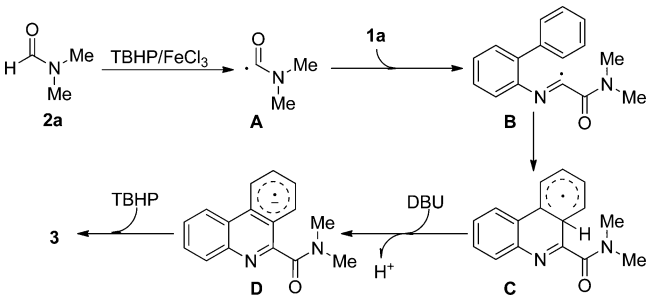


[a]Reaction conditions: **1** (0.2 mmol), formamide (20 equiv), $FeCl_3$ (10 mol %), TBHP (2.5 equiv), and DBU (1.0 equiv) in PhCl (2 mL) under an atmosphere of N_2 at 100 °C for 12 h. [b]*N,N*-Diethylformamide (2 mL) was used as the solvent.

Scheme 2. Control Experiment



Scheme 3. Possible Mechanism



8.0 Hz, 1H), 7.95–7.89 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 3.33 (s, 3H), 2.94 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.6, 157.7, 142.4, 132.4 131.9, 130.8 (q, J_{CF} = 32.6 Hz), 129.0, 127.7, 127.4, 126.3, 125.0 (q, J_{CF} = 270.6 Hz), 123.8, 123.5, 123.2, 122.6, 38.2, 34.8; LRMS (EI, 70 eV) m/z (%) 318 (M^+, 20), 261 (20), 247 (100); HRMS (ESI) calcd for $C_{17}H_{14}F_3N_2O^+$ ([M + H]$^+$) 319.1053, found 319.1052.

N,N-Dimethylbenzo[c][1,5]naphthyridine-6-carboxamide (**9**). Pale-yellow solid (40.7 mg, 80% yield), mp 134–136 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, J = 8.0 Hz, 1H), 9.05 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.00–7.97 (m, 1H), 7.84–7.81 (m, 1H), 7.72–7.70 (m, 1H), 3.32 (s, 3H), 2.93 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.8, 157.2, 150.1, 141.0, 138.1, 137.3, 134.2, 131.8, 129.5, 126.4, 125.2, 124.1, 123.9, 38.2, 34.9; LRMS (EI, 70 eV) m/z (%) 251 (M^+, 20), 197 (33), 180 (100), 179 (34); HRMS (ESI) calcd for $C_{15}H_{14}N_3O^+$ ([M + H]$^+$) 252.1131, found 252.1141.

N,N,8-Trimethylphenanthridine-6-carboxamide (**10**). Pale-yellow solid (35.4 mg, 67% yield), mp 135–137 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 9.0 Hz, 2H), 8.17 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.75–7.68 (m, 3H), 3.32 (s, 3H), 2.93 (s, 3H), 2.58 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.4, 156.0, 142.8, 138.1, 133.2, 131.2, 130.2, 128.5, 127.6, 126.3, 124.2, 123.4, 122.2, 121.9, 38.3, 34.9, 21.6; LRMS (EI, 70 eV) m/z (%) 264 (M^+, 15), 207 (20), 193 (100); HRMS (ESI) calcd for $C_{17}H_{17}N_2O^+$ ([M + H]$^+$) 265.1335, found 265.1338.

10-Methoxy-N,N-dimethylphenanthridine-6-carboxamide (**11**). Brown solid (29.1 mg, 52% yield), mp 127–129 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, J = 8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H), 7.76–7.73 (m, 1H), 7.71–7.65 (m, 3H), 7.37–7.26 (m, 1H), 4.16 (s, 3H), 3.30 (s, 3H), 2.90 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.6, 158.3, 156.2, 143.8, 130.0, 128.3, 128.1, 128.0, 127.5, 125.2, 123.9, 123.6, 119.2, 112.2, 55.9, 38.2, 34.8; LRMS (EI, 70 eV) m/z (%) 280 (M^+, 25), 209 (100), 193 (30); HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2^+$ ([M + H]$^+$) 281.1285, found 281.1296.

9-Methoxy-N,N-dimethylphenanthridine-6-carboxamide (**12a**). Yellow solid (11.8 mg, 21% yield), mp 155–157 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 8.0 Hz, 1H), 8.37 (s, 1H), 8.08–8.04 (m, 2H), 7.85 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 3.30 (s, 3H), 2.92 (s, 3H), 2.64 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.3, 155.3, 141.4, 137.7, 132.9, 131.0, 130.7, 129.9, 127.7, 127.0, 123.9, 123.2, 122.2, 121.7, 38.3, 34.8, 22.0; LRMS (EI, 70 eV) m/z (%) 280 (M^+, 14), 223 (12), 210 (15), 209 (100); HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2^+$ ([M + H]$^+$) 281.1285, found 281.1293.

7-Methoxy-N,N-dimethylphenanthridine-6-carboxamide (**12b**). Pale-yellow solid (23.5 mg, 42% yield), mp 176–178 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.77–7.74 (m, 1H), 7.70–7.67 (m, 1H), 7.30–7.26 (m, 2H), 4.06 (s, 3H), 3.29 (s, 3H), 2.92 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.4, 162.0, 155.7, 143.5, 135.5, 130.2, 129.1, 129.0, 127.2, 123.9, 122.1, 118.21, 118.19, 103.0, 55.6, 38.3, 34.8; LRMS (EI, 70 eV) m/z (%) 280 (M^+, 13), 223 (12), 210 (16), 209 (100); HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2^+$ ([M + H]$^+$) 281.1285, found 281.1283.

8-Cyano-N,N-dimethylphenanthridine-6-carboxamide (**13**). Pale-yellow solid (44.0 mg, 80% yield), mp 222–224 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 8.0 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.01–7.98 (m, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 3.34 (s, 3H), 2.99 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.0, 155.0, 143.7, 135.6, 132.6, 132.3, 130.8, 130.5, 128.6, 123.6, 122.73, 122.71, 122.6, 118.0, 111.4, 38.4, 35.0; LRMS (EI, 70 eV) m/z (%) 275 (M^+, 25), 218 (24), 204 (100), 176 (34); HRMS (ESI) calcd for $C_{17}H_{14}N_3O^+$ ([M + H]$^+$) 276.1131, found 276.1134.

8-Acetyl-N,N-dimethylphenanthridine-6-carboxamide (**14**). White solid (41.5 mg, 71% yield), mp 187–189 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 8.5 Hz, 1H), 8.66 (d, J = 8.5 Hz, 1H), 8.62 (d, J = 8.5 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.85–7.82 (m, 1H), 7.78–7.75 (m, 1H), 3.35 (s, 3H), 2.99 (s, 3H), 2.75 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 197.0, 167.6, 162.4, 156.4, 143.8, 136.2, 136.1, 130.4, 130.2, 129.7, 128.3, 128.2, 123.4, 122.9, 122.7, 38.5, 35.1, 26.7; LRMS (EI, 70 eV) m/z (%) 292 (M^+, 36), 221 (100), 206 (36), 178 (33), 151 (25); HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2^+$ ([M + H]$^+$) 293.1285, found 293.1297.

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General Procedure B for the Synthesis of Phenanthridine-6-carboxamides. A flame-dried Schlenk tube with a magnetic stirring bar was charged with **1a** (0.2 mmol), formamide **2** (20 equiv), $FeCl_3$ (3.2 mg, 0.02 mmol), TBHP (0.5 mmol, 0.09 mL, 5.5 M in decane), and DBU (30.4 mg, 0.2 mmol) in PhCl (2 mL) under an atmosphere of N_2. The reaction mixture was stirred at 100 °C until complete consumption of the starting material as detected by TLC or GC−MS analysis. After the reaction was finished, the mixture was poured into ethyl acetate, which was washed with saturated $NaHSO_4$ (2 × 10 mL) and then brine (1 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product **15**−**24**.

N,N-Diethylphenanthridine-6-carboxamide (***15***). Brown solid (34.5 mg, 62% yield), mp 28−30 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.76−7.72 (m, 1H), 7.65−7.62 (m, 1H), 7.59−7.56 (m, 2H), 3.64 (q, J = 7.5 Hz, 2H), 3.09 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.7, 156.3, 143.0, 133.0, 131.1, 130.2, 128.8, 127.7, 127.4, 126.9, 123.9, 123.2, 122.1, 122.0, 43.0, 39.4, 14.0, 13.0; LRMS (EI, 70 eV) m/z (%) 278 (M^+, 15), 207 (38), 179 (99), 178 (48), 151 (35), 72 (100); HRMS (ESI) calcd for $C_{18}H_{19}N_2O^+$ ([M + H]$^+$) 279.1492, found 279.1489.

N,N-Diisopropylphenanthridine-6-carboxamide (***16***). Pale-yellow solid (37.3 mg, 61% yield), mp 198−199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 8.0 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.87−7.84 (m, 1H), 7.75−7.72 (m, 1H), 7.70−7.67 (m, 2H), 3.71−3.61 (m, 2H), 1.75 (d, J = 7.0 Hz, 6H), 1.14 (d, J = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.8, 157.2, 143.4, 133.2, 131.1, 130.4, 128.8, 127.7, 127.3, 127.0, 124.0, 123.3, 122.2, 122.0, 50.9, 46.3, 20.6; LRMS (EI, 70 eV) m/z (%) 306 (M^+, 13), 264 (15), 207 (20), 179 (100), 178 (41), 151 (28); HRMS (ESI) calcd for $C_{20}H_{23}N_2O^+$ ([M + H]$^+$) 307.1805, found 307.1816.

Phenanthridin-6-yl(piperidin-1-yl)methanone (***17***). Yellow solid (30.7 mg, 53% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 8.0 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.87−7.83 (m, 1H), 7.75−7.72 (m, 1H), 7.70−7.66 (m, 2H), 3.92 (t, J = 5.5 Hz, 2H), 3.22 (t, J = 5.5 Hz, 2H), 1.81−1.77 (m, 2H), 1.71−1.66 (m, 2H), 1.49−1.44 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.5, 156.4, 143.1, 133.0, 131.2, 130.2, 128.8, 127.7, 127.5, 127.0, 123.9, 123.3, 122.2, 122.0, 47.8, 42.6, 26.3, 25.6, 24.4; LRMS (EI, 70 eV) m/z (%) 290 (M^+, 20), 179 (60), 178 (35), 151 (25), 84 (100); HRMS (ESI) calcd for $C_{19}H_{19}N_2O^+$ ([M + H]$^+$) 291.1492, found 291.1498.

Morpholino(phenanthridin-6-yl)methanone (***18***). White solid (35.6 mg, 61% yield), mp 180−182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.90−7.87 (m, 1H), 7.78−7.70 (m, 3H), 4.01 (t, J = 5.0 Hz, 2H), 3.90 (t, J = 5.0 Hz, 2H), 3.61 (t, J = 5.0 Hz, 2H), 3.33 (t, J = 5.0 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.6, 155.2, 142.9, 133.1, 131.4, 130.2, 129.0, 127.9, 127.8, 126.8, 124.0, 123.2, 122.3, 122.0, 66.8, 47.1, 42.1; LRMS (EI, 70 eV) m/z (%) 292 (M^+, 10), 179 (100), 178 (36), 151 (24); HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2^+$ ([M + H]$^+$) 293.1285, found 293.1289.

Phenanthridine-6-carboxamide (***19***). Pale-yellow solid (20.4 mg, 46% yield), mp 191−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, J = 8.5 Hz, 1H), 8.67 (d, J = 8.5 Hz, 1H), 8.62 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.06 (br, 1H), 7.91−7.88 (m, 1H), 7.78−7.75 (m, 3H), 5.82 (br, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.6, 148.7, 141.9, 133.8, 131.0, 130.6, 129.0, 128.9, 128.7, 128.0, 125.7, 124.3, 122.1, 121.8; LRMS (EI, 70 eV) m/z (%) 222 (M^+, 64), 204 (40), 179 (100), 151 (46); HRMS (ESI) calcd for $C_{14}H_{11}N_2O^+$ ([M + H]$^+$) 223.0866, found 223.0870.

N-Methylphenanthridine-6-carboxamide (***20***). White solid (38.2 mg, 81% yield), mp 156−157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, J = 8.5 Hz, 1H), 8.63 (d, J = 8.5 Hz, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.16−8.12 (m, 2H), 7.88−7.85 (m, 1H), 7.77−7.71 (m, 3H), 3.13 (d, J = 5.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.8, 149.7, 141.9, 133.8, 131.0, 130.3, 129.1, 128.8, 128.4, 128.0, 125.5, 124.3, 122.1, 121.8, 26.4; LRMS (EI, 70 eV) m/z (%) 236 (M^+, 13), 207 (21), 179 (100), 178 (28), 151 (23); HRMS (ESI) calcd for $C_{15}H_{13}N_2O^+$ ([M + H]$^+$) 237.1022, found 237.1022.

N-Ethylphenanthridine-6-carboxamide (***21***). White solid (35.5 mg, 71% yield), mp 144−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, J = 8.0 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.0 Hz, 1H), 8.15 (br, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.79−7.75 (m, 1H), 7.68−7.63 (m, 3H), 3.62−3.56 (m, 2H), 1.34 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.9, 149.7, 141.7, 133.5, 130.7, 130.2, 128.9, 128.6, 128.2, 127.7, 125.2, 124.1, 121.9, 121.6, 34.4, 14.7; LRMS (EI, 70 eV) m/z (%) 250 (M^+, 11), 207 (19), 179 (100), 178 (32), 151 (24); HRMS (ESI) calcd for $C_{16}H_{15}N_2O^+$ ([M + H]$^+$) 251.1179, found 251.1178.

N-(tert-Butyl)phenanthridine-6-carboxamide (***22***). Pale-yellow solid (34.5 mg, 62% yield), mp 112−113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (d, J = 8.5 Hz, 1H), 8.54 (d, J = 8.5 Hz, 1H), 8.49 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 8.05 (br, 1H), 7.81−7.78 (m, 1H), 7.72−7.64 (m, 3H), 1.59 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.5, 150.3, 141.7, 133.7, 130.7, 130.3, 129.1, 128.6, 128.1, 127.7, 125.3, 124.2, 122.0, 121.6, 51.2, 28.7; LRMS (EI, 70 eV) m/z (%) 278 (M^+, 24), 263 (34), 235 (25), 193 (30), 179 (45), 178 (100), 151 (28); HRMS (ESI) calcd for $C_{18}H_{19}N_2O^+$ ([M + H]$^+$) 279.1492, found 279.1502.

N-Cyclohexylphenanthridine-6-carboxamide (***23***). Pale-yellow solid (39.5 mg, 65% yield), mp 148−149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, J = 8.0 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.07 (br, 1H), 7.83−7.80 (m, 1H), 7.73−7.66 (m, 3H), 4.10−4.03 (m, 1H), 2.14−2.11 (m, 2H), 1.84−1.80 (m, 2H), 1.70−1.66 (m, 1H), 1.51−1.40 (m, 4H), 1.28−1.25 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.2, 149.8, 141.8, 133.6, 130.8, 130.3, 129.0, 128.6, 128.2, 127.7, 125.3, 124.3, 122.0, 121.6, 48.4, 33.0, 25.6, 24.9; LRMS (EI, 70 eV) m/z (%) 304 (M^+, 30), 247 (22), 207 (28), 178 (96), 179 (100), 151 (30), 98 (67); HRMS (ESI) calcd for $C_{20}H_{21}N_2O^+$ ([M + H]$^+$) 305.1648, found 305.1653.

Ethyl 2-(Phenanthridine-6-carboxamido)acetate (***24***). Brown solid (25.9 mg, 42% yield), mp 91−93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (d, J = 8.5 Hz, 1H), 8.68 (br, 1H), 8.60 (d, J = 8.5 Hz, 1H), 8.55 (d, J = 7.5 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.86−7.82 (m, 1H), 7.74−7.70 (m, 3H), 4.35 (d, J = 6.0 Hz, 2H), 4.30 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.8, 166.2, 148.6, 141.8, 133.7, 130.9, 130.5, 129.1, 128.8, 128.5, 127.9, 125.5, 124.2, 122.0, 121.7, 61.5, 41.6, 14.2; LRMS (EI, 70 eV) m/z (%) 308 (M^+, 15), 235 (52), 179 (76), 178 (100), 151 (22); HRMS (ESI) calcd for $C_{18}H_{17}N_2O_3^+$ ([M + H]$^+$) 309.1234, found 309.1219.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of the products. 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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