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Synthesis of 6-Trichloromethylphenanthridines by Transition Metal-Free Radical Cyclization of 2-Isocyanobiphenyls

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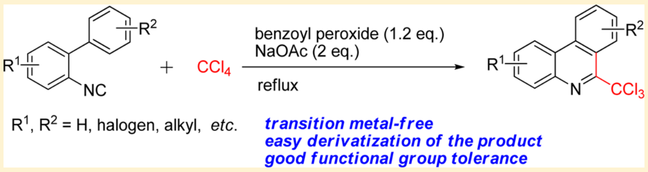
Supporting Information

ABSTRACT: An efficient method for the synthesis of 6-trichloromethylphenanthridines by benzoyl peroxide promoted cyclization reaction of 2-isocyanobiphenyls with carbon tetrachloride is developed. A radical pathway is proposed and evidenced for the reaction mechanism. This reaction tolerates a wide range of functional groups and the resulting 6-trichloromethylphenanthridines can be utilized as a useful synthetic precursor for corresponding 6-substituted phenanthridines.



transition metal-free
easy derivatization of the product
good functional group tolerance

■ INTRODUCTION

Phenanthridines are an important class of compounds in the fields of organic and pharmaceutical chemistry. These heterocycles occur in nature[1] and are used as potential pharmaceuticals with remarkable biological and medicinal activities,[2] such as antitumor, antileukemic, antiviral, and antifungal properties.[3] Also, many substituted phenanthridines have excellent optical and electronic properties in the field of functional materials.[4] Derivatization at 6-position of phenanthridine is a successful strategy to improve its performance. Thus, many C6 diversified, especially 6-alkyl or aryl substituted, phenanthridines with good biological activities have been documented.[5]

Recently, an efficient synthetic approach to C6 functionalized phenanthridines has been developed based on the strategy of radical addition and subsequent cyclization of 2-isocyanobiphenyl species. In this context, many radical precursors have been reported, such as boronic acids,[6] trifluoromethylating reagents,[7] difluoromethyl sources,[8] fluorinated sulfones,[9] fluorinated alkyl iodides,[10] aldehydes,[11] acyl or alkyl peroxides,[12] simple alkanes,[13] halides,[14] diarylphosphine oxides,[15] aryl sulfonyl chlorides,[16] α-oxocarboxylic acids,[17] hydrazines,[18] disulfides,[19] thiols,[20] ethers,[21] amines,[22] unsaturated ketoximes,[23] and *N*-alkyl amides.[24] Among them, the transition-metal-free procedure is more favorable owing to the strict restriction on the residual amount of heavy metals in pharmaceutical industry. Trichloromethyl group is an attractive motif which is widely utilized as a useful synthetic precursor to diverse functional groups, such as methyl, gem-dichloromethyl, trifluoromethyl, carboxyl, ester group, oxazoles, etc.[25] Therefore, it is of interest to prepare 6-trichloromethylphenanthridines. However, to the best of our knowledge, there is no report on the synthesis of 6-trichloromethylphenanthridines. Herein, we present the first example for the synthesis of 6-trichloromethylphenanthridines via a radical addition-cyclization protocol of 2-isocyanobiphenyls with inexpensive carbon tetrachloride under mild and transition-metal-free conditions.

■ RESULTS AND DISCUSSION

The preparation of 6-trichloromethylphenanthridines via the dual C−C bond formation was initiated with 2-isocyano-4′-methoxybiphenyl (**1a**) as a model substrate in CCl_4 (Table 1). At the outset, several radical initiators were examined. Interestingly, the generation of 6-trichloromethylphenanthridines (**2a**) was confirmed in 60% yield by ^1H NMR spectroscopy when azobis(isobutyronitrile) (AIBN) was added (Table 1, entry 1). The low conversion and yield indicated that *t*-BuOOH is not an efficient initiator for this reaction (Table 1, entry 2). Replacing AIBN with dicumyl peroxide resulted in an obvious decrease in both conversion and yield (Table 1, entry 3), and poorer selectivity was witnessed at higher temperature (Table 1, entry 4). Di-*tert*-butyl peroxide was also less efficient, with only 40% conversion and 32% yield being achieved even at 110 °C (Table 1, entry 5). To our delight, benzoyl peroxide-promoted the reaction in 69% yield (Table 1, entry 6). Therefore, benzoyl peroxide was chosen for further study.

It has been reported that the addition of bases has a positive impact on the cyclization of 2-isocyanobiphenyls.[7a,10,14a,17b,18a,20,22] Consequently, the effect of base was investigated. A slight decrease of the yield was observed in the absence of a base (Table 1, entry 7) as well as the use of NaOH and $NaHCO_3$ (Table 1, entries 8 and 9). The organic base NEt_3 was found to be unfavorable (Table 1, entry 13), while K_2CO_3, NaOMe, and NaOAc all promoted the reaction to give the yields of 70, 67, and 71%, respectively (Table 1, entries 10−12). In view of stability and tolerability of functional groups, NaOAc was finally chosen. The amount of benzoyl peroxide can be reduced to 1.2 equiv without compromising the result (Table 1, entry 14). Notably, in the absence of the radical initiator there was no reaction at all (Table 1, entry 15).

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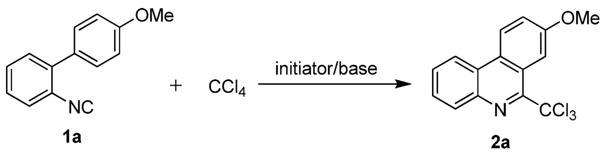
Table 1. Optimization of Initiators and Bases for the Reaction[a]



entry	initiator	base	temp. (°C)	conv.[b] (%)	yield[b] (%)
1	AIBN	*t*-BuOK	reflux	100	60
2	*t*-BuOOH	*t*-BuOK	reflux	13	4
3	dicumyl peroxide	*t*-BuOK	reflux	26	13
4[c]	dicumyl peroxide	*t*-BuOK	110	100	45
5[c]	di-*tert*-butyl peroxide	*t*-BuOK	110	40	32
6	benzoyl peroxide	*t*-BuOK	reflux	100	69
7	benzoyl peroxide		reflux	100	64
8	benzoyl peroxide	NaOH	reflux	100	63
9	benzoyl peroxide	$NaHCO_3$	reflux	100	53
10	benzoyl peroxide	K_2CO_3	reflux	100	70
11	benzoyl peroxide	NaOMe	reflux	100	67
12	benzoyl peroxide	NaOAc	reflux	100	71
13	benzoyl peroxide	NEt_3	reflux	100	N.D.[d]
14	benzoyl peroxide[e]	NaOAc	reflux	100	72
15		NaOAc	reflux	N.R.[f]	

[a] Reaction conditions: **1a** (0.2 mmol), initiator (2 equiv), base (2 equiv), CCl_4 (2 mL) for 16 h under nitrogen. [b] Conversion and yield were determined by ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c] In the sealed tube. [d] Not detected. [e] 1.2 equiv of benzoyl peroxide. [f] No reaction.

Considering the toxicity and danger to the environment of CCl_4, the reaction was carried out with 5 equiv of CCl_4 in various solvents, such as DMF, 1,2-dichloroethane, acetonitrile, and toluene. Unfortunately, no desired product was detected in toluene while poor selectivity was observed in other solvents. ^1H NMR analysis of the crude product showed that 8-methoxy-6-(trichloromethyl)phenanthridine, 8-methoxy-6-phenylphenanthridine, and 8-methoxyphenanthridine were generated in a ratio of 10:11:9, 3:5:4, and 4:11:6, respectively, when DMF, 1,2-dichloroethane, and acetonitrile were used as solvent.

Having established the optimized reaction conditions, we tested a variety of 2-isocyanobiphenyls to define the scope of this transformation (Table 2). It is not surprising that nonsubstituted 2-isocyanobiphenyl was favorable in this system to afford the corresponding product **2b** in 78% yield. Other substituents, either electron-withdrawing or electron-donating groups, such as ester, chlorine, acetyl, *t*-butyl, fluorine, and cyano, were all tolerated well, and the desired products **2c**−**2h** were obtained in 63, 58, 54, 85, 73, and 61% yields, respectively. The isocyanide having a naphthalene ring instead of a benzene ring was also cyclized in this reaction and the desired product (**2i**) was isolated in 30% yields. Subsequently, a series of functional groups on the isocyano-bearing phenyl ring were also evaluated, and good results were obtained. For example, chlorine, cyano, methyl, and trifluoromethyl groups provided yields of 58−78% (products **2k**, **2n**, **2o**, and **2q**). In addition, substrates with functional groups on both phenyl rings also proceeded smoothly, which furnished the desired products **2l**, **2m**, **2p**, **2r**, and **2s** in good yields. To investigate the regioselectivity of the cyclization, 2-isocyanobiphenyl bearing a *m*-methoxy was investigated, which resulted in a mixture of two regioisomers (**2j** and **2j′**) in a ratio of 5:3. And 3-(2-isocyanophenyl)pyridine gave the corresponding product in 39% yield and 1:3 regioselectivity (**2t** and **2t′**).

To probe the mechanism, the control experiment with the radical scavenger was carried out (Scheme 1). When the radical scavenger, (2,2,6,6-tetramethyl−piperidin−1-yl)oxyl (TEMPO), was added to the reaction mixture, no desired product was detected. These results provide evidence for the free radical mechanism. And the reaction did not proceed in the absence of benzoyl peroxide (Table 1, entry 15), which indicated that benzoyl peroxide plays the role of reaction initiator. When the reaction mixture was detected by GC-MS, PhCl and $CHCl_3$ were observed. PhCOOH was also detected by GC-MS and ^1H NMR in the crude product for some substrates.

On the basis of these experimental results, a plausible mechanism is proposed in Scheme 2. First, the homolytic cleavage of benzoyl peroxide produces a benzoate radical, which releases CO_2 producing a phenyl radical. Then, the phenyl radical abstracts a chlorine atom from CCl_4 to generate trichloromethyl radical[26] and PhCl. The addition of the trichloromethyl radical to 2-isocyanobiphenyl produces another radical intermediate (**A**). Subsequently, the intermediate **A** cyclizes to generate the cyclohexadienyl radical (**B**). Further reaction of the radical **B** has two plausible directions. One is further oxidation by the benzoate radical to give the intermediate **C**, then the desired phenanthridine **D** is delivered after deprotonation by a base. The other is that the trichloromethyl radical abstracts H atom from the intermediate **B**, resulting in the product (**D**).

One of the most important merits of introducing trichloromethyl group into phenanthridines is its diverse derivatizations. Thus, several representative transformations of 6-trichloromethyl phenanthridines were explored (Scheme 3). Treatment of **2b** with concentrated sulfuric acid at 150 °C gave the expected phenanthridine-6-carboxylic acid (**3**) in excellent yield. And 6-(1*H*-benzo[*d*]imidazol-2-yl) phenanthridine (**4**) can be obtained via the condensation of **2b** with *o*-phenylenediamine. In addition, hydrodechlorination of **2a** catalyzed by Pd/C at room temperature can easily lead to 6-methyl phenanthridine (**5**) in good yield.

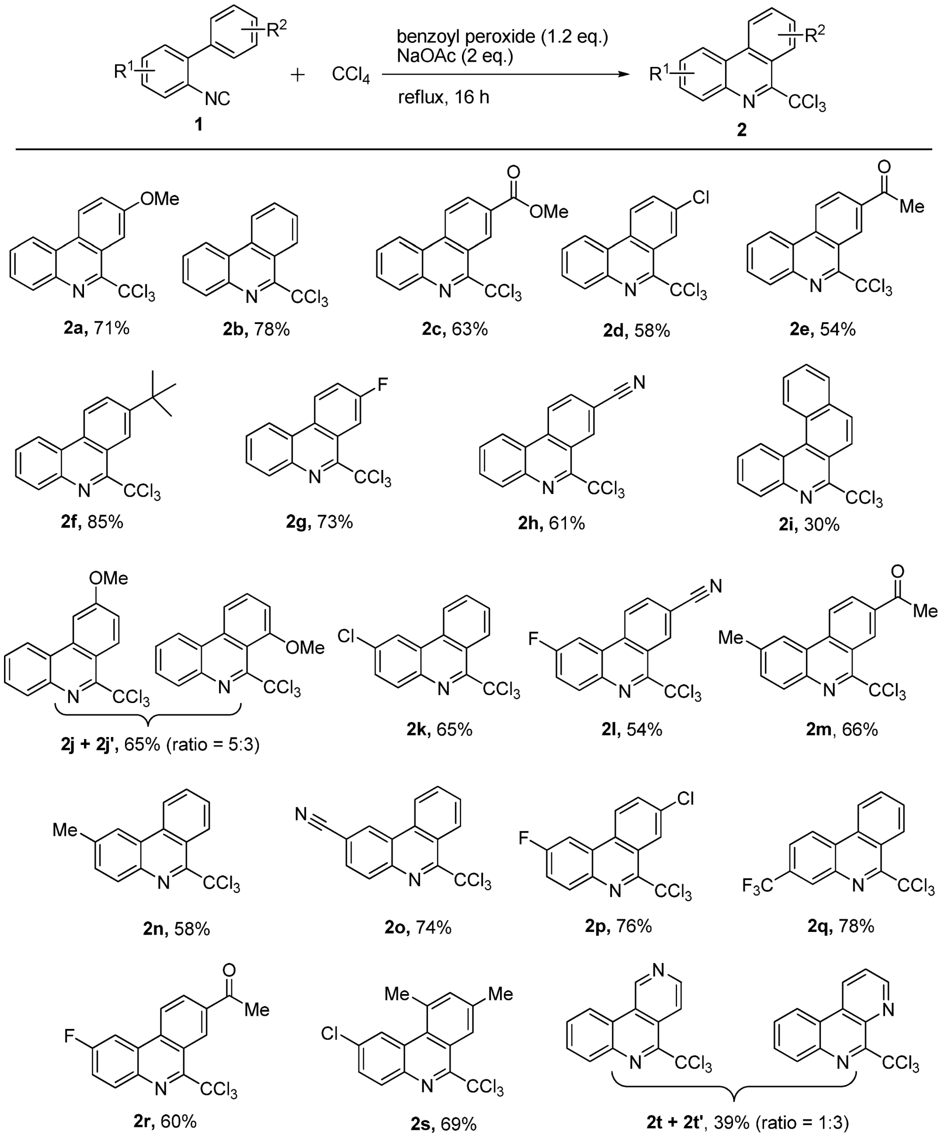
■ CONCLUSION

In conclusion, we have developed a transition-metal-free approach to 6-trichloromethylphenanthridines via the addition-cyclization of 2-isocyanobiphenyls with inexpensive carbon tetrachloride. A radical pathway was proposed and evidenced for the reaction mechanism. The functional groups, such as ester, cyano, alkyl, methoxy, fluorine, and chlorine were tolerated well, and the desired products were obtained in good yields. The nature of easy derivatization of trichloromethyl group makes it a useful synthetic precursor for corresponding C6 substituted phenanthridines. This represents a practical approach to access 6-trichloromethylphenanthridines and related derivatives.

■ EXPERIMENTAL SECTION

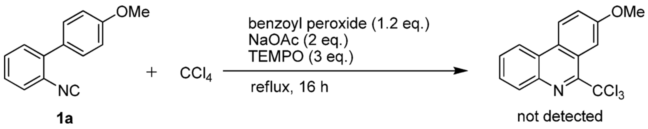
General Information. Melting points were measured on a melting point instrument. All ^1H NMR (400 MHz) and $^{13}C\{H\}$ NMR (125 Hz) or $^{13}C\{H\}$ NMR (100 Hz) spectra were measured in $CDCl_3$ and recorded on a spectrometer with chemical shifts reported as ppm (with TMS as an internal

Table 2. Preparation of 6-Trichloromethylphenanthridine Derivatives[a]



[a]Reaction conditions: **1** (0.5 mmol), benzoyl peroxide (1.2 equiv), NaOAc (2 equiv), CCl_4 (2 mL), reflux for about 16 h under nitrogen.

Scheme 1. Control Experiment for Mechanism



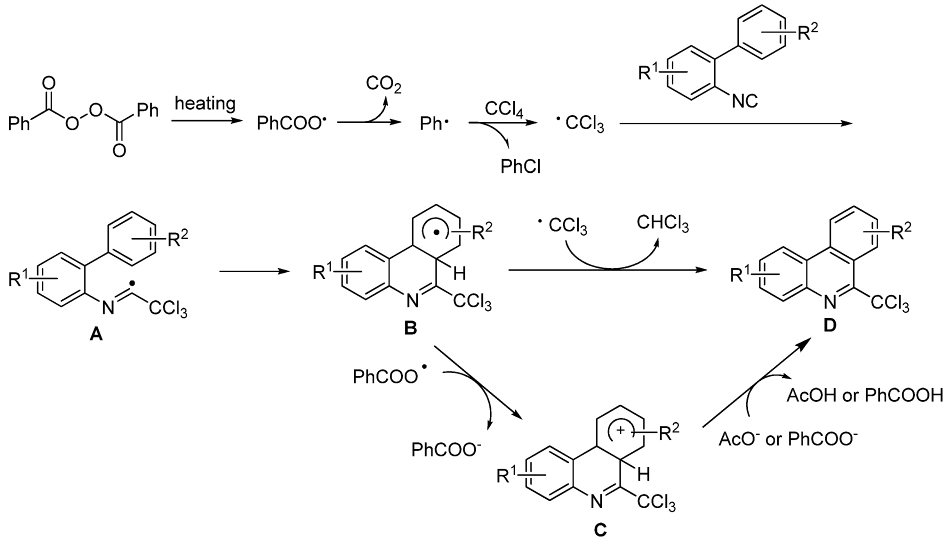
standard). For chromatography, silica gel (200−300 mesh) was employed. HRMS were conducted on a GC-TOF mass spectrometer (EI) or a Orbitrap mass spectrometer in positive electrospray ionization (ESI+) mode. 2-Isocyanobiphenyls **1** were synthesized via a three-step route according to the previous paper.[7c,20]

General Procedure for Radical Addition-Cyclization of 2-Isocyanobiphenyls. A flame-dried Schlenk tube with a magnetic stirring bar were charged with 2-isocyanobiphenyls **1** (0.5 mmol), benzoyl peroxide (145.2 mg, 0.6 mmol), and NaOAc (82.0 mg, 1.0 mmol) in CCl_4 (2 mL) under an atmosphere of N_2. The reaction mixture was stirred under reflux until complete consumption of the starting material as detected by TLC analysis (about 16 h). The solution of the crude product was concentrated in vacuum, brine (20 mL) was added, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (15 mL × 3) then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by flash chromatography using the appropriate gradient of petroleum ether and EtOAc to afford the product 6-trichloromethylphenanthridine **2**.

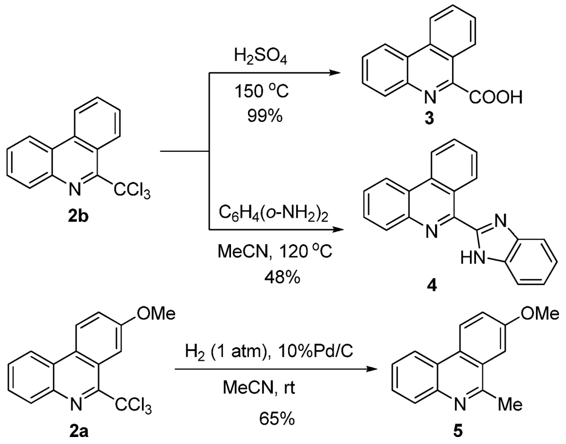
8-Methoxy-6-(trichloromethyl)phenanthridine ***(2a)***. Yellow solid (115.4 mg, 71% yield), mp 142−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 9.2 Hz, 1H), 8.49−8.46 (m, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.25−8.23 (m, 1H), 7.73−7.70 (m, 2H), 7.50 (dd, J = 9.2, 2.4 Hz, 1H), 4.01(s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.7, 151.8, 140.0, 131.2, 129.3, 129.1, 128.2, 125.1, 124.3, 122.0, 121.5, 121.4, 109.0, 98.7, 55.6. HRMS (ESI) m/z: calcd for $C_{15}H_{11}Cl_3NO^+$ ($[M + H]^+$) 325.9906, found 325.9904.

6-(Trichloromethyl)phenanthridine ***(2b)***. White solid (115.0 mg, 78% yield), mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 8.4 Hz, 1H), 8.65 (d, J = 8.4 Hz,

Scheme 2. Proposed Mechanism



Scheme 3. Derivatizations of 6-Trichloromethylphenanthridines



1H), 8.52 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 7.84 (m, 1H), 7.77−7.69 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.8, 140.8, 134.9, 131.2, 130.7, 129.2, 129.0, 128.4, 126.7, 125.0, 122.8, 121.8, 120.7, 98.5. HRMS (ESI) m/z: calcd for $C_{14}H_9Cl_3N^+$ ([M+H]$^+$) 295.9801, found 295.9801.

Methyl 6-(Trichloromethyl)phenanthridine-8-carboxylate ***(2c)***. White solid (111.2 mg, 63% yield), mp 171−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.73 (d, J = 8.8 Hz, 1H), 8.58 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.84−8.78 (m, 2H), 4.05(s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 153.2, 141.4, 137.7, 131.3, 130.5,130.4, 130.3, 129.4, 128.1, 124.2, 123.1, 122.4, 120.2, 98.0, 52.7. HRMS (ESI) m/z: calcd for $C_{16}H_{11}Cl_3NO_2^+$ ([M+H]$^+$) 353.9855, found 353.9855.

8-Chloro-6-(trichloromethyl)phenanthridine ***(2d)***. White solid (95.4 mg, 58% yield), mp 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 2.0 Hz, 1H), 8.58 (d, J = 8.8 Hz, 1H), 8.47 (m, 1H), 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 8.81−8.74 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.7, 140.6, 133.2, 132.9, 131.4, 131.3, 129.6, 129.5, 127.6, 124.4, 124.3, 121.7, 121.5, 98.0. HRMS (ESI) m/z: calcd for $C_{14}H_8Cl_4N^+$ ([M+H]$^+$) 329.9411, found 329.9409.

1-(6-(Trichloromethyl)phenanthridin-8-yl)ethanone ***(2e)***. White solid (91.0 mg, 54% yield), mp 194−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J = 1.6 Hz, 1H), 8.79 (d, J = 8.8 Hz, 1H), 8.63 (d, J = 8.0 Hz, 1H), 8.46 (dd, J = 8.8, 1.6 Hz, 1H), 8.33−8.30 (m, 1H), 7.88−7.83 (m, 2H), 2.80 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 197.0, 153.3, 141.63, 137.9, 134.6, 131.4, 130.5, 129.7, 129.6, 128.9, 124.3, 123.4, 122.5, 120.3, 98.1, 26.7. HRMS (ESI) m/z: calcd for $C_{16}H_{11}Cl_3NO^+$ ([M+H]$^+$) 337.9906, found 337.9903.

8-(Tert-butyl)-6-(trichloromethyl)phenanthridine ***(2f)***. Orange solid (149.1 mg, 85% yield), mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 8.8 Hz, 1H), 8.51−8.49 (m, 1H), 8.25−8.22 (m, 1H), 7.93 (dd, J = 8.8, 2.0 Hz, 1H), 7.74−7.70 (m, 2H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.9, 149.7, 140.6, 132.7, 131.2, 129.0, 128.9, 128.8, 125.0, 124.5, 122.5, 121.7, 120.6, 98.8, 35.4, 31.3. HRMS (ESI) m/z: calcd for $C_{18}H_{17}Cl_3N^+$ ([M+H]$^+$) 352.0427, found 352.0425.

8-Fluoro-6-(trichloromethyl)phenanthridine ***(2g)***. Yellow solid (114.2 mg, 73% yield), mp 195−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J = 9.2, 5.6 Hz, 1H), 8.59 (dd, J = 10.8, 2.8 Hz, 1H), 8.49−8.47 (m, 1H), 8.26−8.24 (m, 1H), 7.77−7.74 (m, 2H), 7.65−7.60 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3 (d, J = 247.1 Hz), 152.0 (d, J = 4.2 Hz), 140.4, 131.6 (d, J = 1.7 Hz), 131.4, 129.5, 129.2, 125.3 (d, J = 8.7 Hz), 124.6, 121.9 (d, J = 8.7 Hz), 121.6, 120.2 (d, J = 23.8 Hz), 113.5 (d, J = 23.9 Hz), 98.1. HRMS (ESI) m/z: calcd for $C_{14}H_8Cl_3FN^+$ ([M+H]$^+$) 313.9706, found 313.9709.

6-(Trichloromethyl)phenanthridine-8-carbonitrile ***(2h)***. Orange solid (97.5 mg, 61% yield), mp 216−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.77 (d, J = 8.8 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.90−7.81 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.1, 141.5, 137.3, 133.5, 131.8, 131.6, 131.0, 129.9, 124.1, 123.7, 122.4, 120.2, 118.3, 110.5, 97.5. HRMS (ESI) m/z: calcd for $C_{15}H_8Cl_3N_2^+$ ([M+H]$^+$) 320.9753, found 320.9754.

6-(Trichloromethyl)benzo[k]phenanthridine ***(2i)***. Yellow oil (51.5 mg, 30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 8.8 Hz, 1H), 8.97 (d, J = 8.0 Hz, 1H), 8.86 (d, J = 9.2 Hz, 1H), 8.38 (dd, J = 8.4, 1.6 Hz, 1H), 8.07−8.05 (m, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.83−7.73 (m, 4H); ^{13}C{^{1}H} NMR (100

MHz, $CDCl_3$) δ 152.3, 142.5, 134.8, 134.2, 130.9, 129.0, 128.9, 128.7, 128.5, 128.4, 127.2, 127.1, 126.9, 125.1, 123.7, 120.1, 98.8. HRMS (ESI) *m/z*: calcd for $C_{18}H_{11}Cl_3N^+$ ($[M+H]^+$) 345.9957, found 345.9954.

*9-Methoxy-6-(trichloromethyl)phenanthridine (**2j**) and 7-Methoxy-6-(trichloromethyl) Phenanthridine (**2j′**) (5:3 Mixture of **2j** and **2j′**).* White solid (105.9 mg, 65% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 9.6 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1.6H), 8.23−8.18 (m, 2.2H), 7.96 (s, 1H), 7.79−7.68 (m, 3.8H), 7.32 (d, *J* = 9.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 0.6H), 4.06 (s, 3H), 4.03 (s, 1.8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 156.5, 152.7, 152.6, 141.2, 140.6, 137.4, 137.1, 131.6, 131.2, 130.6, 130.2, 129.3, 128.8, 128.5, 124.8, 124.4, 122.3, 121.9, 116.9, 115.4, 114.7, 113.8, 109.6, 103.5, 98.6, 55.6, 54.9. HRMS (ESI) *m/z*: calcd for $C_{15}H_{10}Cl_3NO^+$ ($[M+H]^+$) 325.9906, found 325.9906.

*2-Chloro-6-(trichloromethyl)phenanthridine (**2k**).* White solid (106.9 mg, 65% yield), mp 178−179 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.84−7.80 (m, 1H), 7.74−7.70 (m, 1H), 7.65 (dd, *J* = 8.8, 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.0, 139.1, 135.2, 133.8, 132.6, 130.9, 129.8, 128.4, 127.4, 126.0, 122.7, 121.6, 120.8, 98.2. HRMS (ESI) *m/z*: calcd for $C_{14}H_8Cl_4N^+$ ($[M+H]^+$) 329.9411, found 329.9412.

*2-Fluoro-6-(trichloromethyl)phenanthridine-8-carbonitrile (**2l**).* White solid (91.2 mg, 54% yield), mp 210−211 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.66 (d, *J* = 8.8 Hz, 1H), 8.31 (dd, *J* = 9.2, 5.6 Hz, 1H), 8.17 (dd, *J* = 9.6, 2.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.65−7.60 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 251.0 Hz), 151.6 (d, *J* = 3.1 Hz), 138.4 (d, *J* = 1.5 Hz), 136.7 (d, *J* = 4.3 Hz), 134.1 (d, *J* = 9.4 Hz), 133.5, 132.0, 125.4 (d, *J* = 9.5 Hz), 124.3, 120.4, 120.2 (d, *J* = 24.3 Hz), 118.1, 111.3, 107.8 (d, *J* = 23.9 Hz), 97.3. HRMS (ESI) *m/z*: calcd for $C_{15}H_7Cl_3FN_2^+$ ($[M+H]^+$) 338.9659, found 338.9657.

*1-(2-Methyl-6-(trichloromethyl)phenanthridin-8-yl)ethanone (**2m**).* Yellow solid (116.1 mg, 66% yield), mp 167−168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.61−8.56 (m, 1H), 8.32−8.21 (m, 2H), 8.10−8.06 (m, 1H), 7.59−7.57 (m, 1H), 2.76 (s, 3H), 2.6 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 152.2, 139.8, 139.7, 137.4, 134.4, 132.1, 130.9, 129.5, 128.5, 124.0, 123.2, 122.0, 120.2, 98.2, 26.6, 22.1. HRMS (ESI) *m/z*: calcd for $C_{17}H_{13}Cl_3NO^+$ ($[M+H]^+$) 352.0063, found 352.0065.

*2-Methyl-6-(trichloromethyl)phenanthridine (**2n**).* Yellow solid (89.6 mg, 58% yield), mp 165−166 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 8.4 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.78−7.74 (m, 1H), 7.67−7.63 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.9, 139.3, 139.0, 134.5, 130.9, 130.8, 130.4, 128.2, 126.5, 124.8, 122.7, 121.4, 120.7, 98.7, 22.2. HRMS (ESI) *m/z*: calcd for $C_{15}H_{11}Cl_3N^+$ ($[M+H]^+$) 309.9957, found 309.9963.

*6-(Trichloromethyl)phenanthridine-2-carbonitrile (**2o**).* Orange solid (118.4 mg, 74% yield), mp 173−174 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 8.4 Hz, 1H), 8.83 (s, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.96−7.89 (m, 2H), 7.84−7.79 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.5, 142.3, 133.8, 132.3, 131.8, 130.7, 128.7, 128.1, 127.5, 125.0, 122.7, 120.9, 118.5, 112.4, 97.7. HRMS (ESI) *m/z*: calcd for $C_{15}H_8Cl_3N_2^+$ ($[M+H]^+$) 320.9753, found 320.9752.

*8-Chloro-2-fluoro-6-(trichloromethyl)phenanthridine (**2p**).* White solid (131.5 mg, 76% yield), mp 167−168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.24−8.21 (m, 1H), 8.06−8.03 (m, 1H), 7.80 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.53−7.48 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.8 (d, *J* = 249.7 Hz), 151.2 (d, *J* = 3.1 Hz), 137.4, 133.8 (d, *J* = 9.5 Hz), 133.7, 132.6 (d, *J* = 4.4 Hz), 131.5, 127.8, 126.0 (d, *J* = 9.6 Hz), 124.5, 121.6, 118.9 (d, *J* = 24.3 Hz), 107.0 (d, *J* = 23.8 Hz), 97.7. HRMS (ESI) *m/z*: calcd for $C_{14}H_7Cl_4FN^+$ ($[M+H]^+$) 347.9317, found 347.9317.

*6-(Trichloromethyl)-3-(trifluoromethyl)phenanthridine (**2q**).* Orange solid (134.3 mg, 74% yield), mp 159−160 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 8.8 Hz, 1H), 8.64 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.53 (s, 1H), 7.91−7.88 (m, 2H), 7.81−7.77 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.2, 140.1, 134.1, 131.3, 131.1 (q, *J* = 33.0 Hz), 128.7 (q, *J* = 4.1 Hz), 128.6, 127.9, 127.2, 124.8 (q, *J* = 3.3 Hz), 123.9 (q, *J* = 270.8 Hz), 123.2, 123.0, 121.3, 97.9. HRMS (ESI) *m/z*: calcd for $C_{15}H_8Cl_3F_3N^+$ ($[M+H]^+$) 363.9674, found 363.9677.

*1-(2-Fluoro-6-(trichloromethyl)phenanthridin-8-yl)ethanone (**2r**).* Yellow solid (106.5 mg, 60% yield), mp 171−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.57 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.27 (dd, *J* = 9.2, 5.6 Hz, 1H), 8.14 (d, *J* = 10.0 Hz, 1H), 7.59−7.54 (m, 1H), 2.79 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.8, 162.8 (d, *J* = 249.9 Hz), 152.6 (d, *J* = 2.9 Hz), 138.3, 137.1 (d, *J* = 4.4 Hz), 135.1, 133.8 (d, *J* = 9.4 Hz), 129.6, 129.0, 125.9 (d, *J* = 9.5 Hz), 123.5, 120.4, 119.5 (d, *J* = 24.2 Hz), 107.7 (d, *J* = 23.8 Hz), 97.8, 26.7. HRMS (ESI) *m/z*: calcd for $C_{16}H_{10}Cl_3FNO^+$ ($[M+H]^+$) 355.9812, found 355.9812.

*2-Chloro-8,10-dimethyl-6-(trichloromethyl)phenanthridine (**2s**).* White solid (130.3 mg, 73% yield), mp 189−190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.69 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.70−7.68 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.57 (s, 1H), 3.07 (s, 3H), 2.60 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 139.9, 137.0, 136.6, 135.6, 134.0, 132.7, 131.4, 128.5, 127.2, 126.5, 125.7, 122.3, 98.7, 26.8, 21.8. HRMS (ESI) *m/z*: calcd for $C_{16}H_{12}Cl_4N^+$ ($[M+H]^+$) 357.9724, found 357.9727.

*5-(Trichloromethyl)benzo[c][2,6]naphthyridine (**2t**).* Yellow solid (14.8 mg, 10% yield), mp 178−179 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.93 (d, *J* = 6.0 Hz, 1H), 8.73−8.70 (m, 1H), 8.66 (d, *J* = 6.0 Hz, 1H), 8.33−8.31 (m, 1H), 7.87−7.85 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 151.9, 147.6, 145.4, 141.2, 131.6, 130.4, 130.2, 128.4, 124.3, 123.2, 121.2, 119.9, 97.3. HRMS (ESI) *m/z*: calcd for $C_{13}H_8Cl_3N_2^+$ ($[M+H]^+$) 296.9753, found 296.9754.

*5-(Trichloromethyl)benzo[f][1,7]naphthyridine (**2t′**).* Yellow solid (42.9 mg, 29% yield), mp 180−181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 4.4 Hz, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 8.34−8.32 (m, 1H), 7.85−7.78 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.6, 149.0, 140.8, 138.0, 131.4, 130.5, 130.1, 130.0, 129.3, 125.2, 124.8, 121.8, 97.2. HRMS (ESI) *m/z*: calcd for $C_{13}H_8Cl_3N_2^+$ ($[M+H]^+$) 296.9753, found 296.9754.

Procedure for Derivatizations of 6-Trichloromethylphenanthridines. *Synthesis of Phenanthridine-6-carboxylic Acid (**3**).*[27] A stirred mixture of **2b** (59.0 mg, 0.2 mmol) in H_2SO_4 (98%, 2 mL) was heated to 130 °C for 5 h. After cooling, H_2O (0.5 mL) was slowly added with rapid stirring. Then, the resulting mixture was heated to 150 °C in a sealed tube overnight. After cooling the reaction mixture, H_2O (15 mL) was added and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with H_2O (10 mL × 3), dried over anhydrous Na_2SO_4 and evaporated in vacuum to give the product **3**. White solid (44.0 mg, 99% yield); mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (br, 1H), 9.72 (d, *J* = 8.4 Hz, 1H), 8.75−8.55 (m, 2H), 8.20 (m, 1H), 7.95 (t, *J* = 7.6 Hz, 1H), 7.82 (m, 3H). ^{13}C{1H} NMR (125 MHz, CDCl3) δ 162.9, 143.3, 139.4, 133.2, 130.9, 129.0, 128.8, 128.5, 127.9, 127.8, 125.6, 123.0, 121.4, 1210. HRMS (EI): $[M\text{-}CO_2]^{+\cdot}$ *m/z*: calcd for $C_{13}H_9N^{+\cdot}$ $(M\text{-}CO_2)^{+\cdot}$ 179.0735, found 179.0738.

*Synthesis of 6-(1H-Benzo[d]imidazol-2-yl)phenanthridine (**4**).* The mixture of 6-(trichloromethyl)phenanthridine **2b** (59.0 mg, 0.2 mmol), benzene-1,2-diamine (43.0 mg, 0.4 mmol) and K_2CO_3 (55.2 mg, 0.4 mmol) in MeCN (2 mL) was heated at 120 °C overnight in a sealed tube. After cooling the reaction mixture, brine (15 mL) was added to the solution and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by flash chromatography using a mixture of petroleum ether and EtOAc (10:1) to afford the product **4**. Yellow solid (28.0 mg, 48% yield); mp 187−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 9.74 (d, *J* = 8.4 Hz, 1H), 8.69 (d, *J* = 8.3 Hz, 1H), 8.63 (dd, *J* = 6.6, 2.9 Hz, 1H), 8.23 (dd, *J* = 6.6, 2.9 Hz, 1H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.85−7.69 (m, 3H), 7.61−7.52 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.92 (dd, *J* = 7.3, 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 164.1, 148.4, 141.6, 140.7, 133.9, 131.0, 130.6, 129.0, 128.9, 128.8, 128.1, 127.0, 125.7, 125.1, 124.5, 124.3, 122.1, 121.9, 119.6, 117.8. HRMS (ESI) *m/z*: calcd for $C_{20}H_{14}N_3^+$ ($[M+H]^+$) 296.1182, found 296.1183.

*Synthesis of 8-Methoxy-6-methylphenanthridine (**5**).* A solution of **2a** (65.0 mg, 0.2 mmol) in MeCN (30 mL) containing 10% Pd/C (28.0 mg) was hydrogenated under an atmosphere press at room temperature for 5 h. After the reaction completed (detected by TLC analysis), the solution was filtered. Then brine (20 mL) was added and the aqueous layer was extracted with EtOAc (15 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by flash chromatography using a mixture of petroleum ether and EtOAc (10:1) to afford the product **5**. White solid (29.0 mg, 65% yield); mp 56−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 9.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.08 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.72−7.52 (m, 2H), 7.51−7.41 (m, 2H), 3.99 (s, 3H), 3.00 (s, 3H). The spectroscopic data correspond to previously reported date.[12b]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00885.

NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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