JOC The Journal of Organic Chemistry

Article

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Metal-Free Oxidative Functionalization of a C(sp^3)−H Bond Adjacent to Nitrogen and Intramolecular Aromatic Cyclization for the Preparation of 6-Amidophenanthridines

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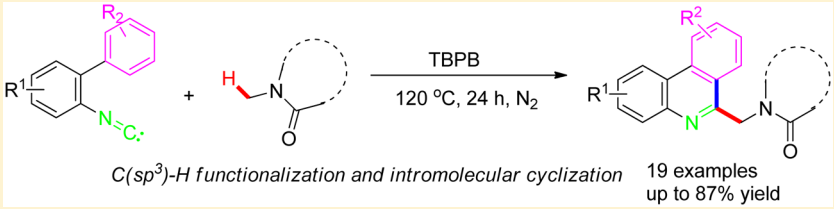
Supporting Information



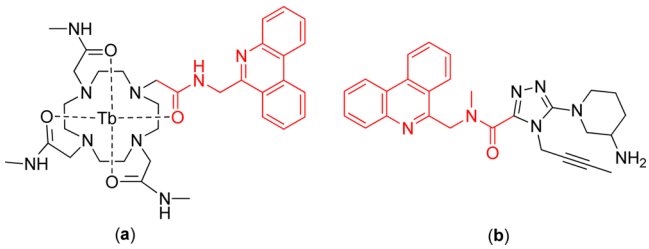
ABSTRACT: A metal-free cyclization reaction of 2-isocyanobiphenyls with amide derivatives by using *tert*-butyl peroxybenzoate (TBPB) as oxidant was developed, which provided an access to pharmacologically interesting 6-amidophenanthridine compounds. The reactions proceeded through a sequence of functionalization of the C(sp^3)−H bond adjacent to the nitrogen atom and intramolecular radical aromatic cyclization with good chemistry yields.

INTRODUCTION

The direct functionalization of a C(sp^3)−H bond to form a new C−C bond provides a potent strategic approach for the synthesis of complex molecules, which is also a great challenge due to their high bond dissociation energy and low polarity.[1] Over the past several years, the groups of Li and others have developed many methodologies on transition-metal-catalyzed cross-dehydrogenative-coupling (CDC) reactions of sp^3 C−H bonds to form C−C bonds.[2] Especially, metal-catalyzed functionalization of C(sp^3)−H bonds adjacent to heteroatoms represents a hot topic and considerable efforts have been devoted to this field.[3] By this strategy diverse functional groups, such as indole, benzofuran, alkyne, alkene, cyano, and enol ether, were introduced to couple with the carbon adjacent to a nitrogen or oxygen atom.[4] Recently, we also reported an iron-catalyzed cross-dehydrogenative coupling for C(sp^2)−C(sp^3) bond formation with ethers as radical precursors.[5] Very recently, the Lee group developed palladium(II)-/copper(II)-catalyzed arylation of an sp^3 C−H bond adjacent to oxygen with phenol and naphthol derivatives.[6] Gaunt and coauthors explored palladium-catalyzed C−H activation of aliphatic amines to give strained nitrogen heterocycles with PhI(OAc)$_2$ as the oxidant.[7] Although considerable advances in this field have been achieved, the efficient and versatile strategies for C(sp^3)−H bond functionalization under metal-free conditions is a more challenging task and is highly desirable.[8] Several groups have reported metal-free C(sp^3)−H bond functionalization by cross-dehydrogenative coupling (CDC) reactions.[9] Very recently, our group also reported a metal-free oxidative C(sp^3)−H bond functionalization of alkanes and alkylation-initiated radical 1,2-aryl migration of α,α-diaryl allylic alcohols using di-*tert*-butyl peroxide (DTBP) as the oxidant.[10] However, examples of direct C−H bond oxidative functionalization adjacent to an amide nitrogen under metal-free conditions are still scarce. Until now, only a few elegant examples were reported by the Li and Patel groups on sp^3 C−H bond functionalization adjacent to a nitrogen atom in an amide and the following reaction with disulfides, alkenes, and alkynes.[11]

Aryl isonitriles, which could directly construct phenanthridine derivatives by a cascade reaction, have attracted much attention in the synthetic community. The resulting phenanthridine derivatives also belong to an important class of biological compounds and widely exist in natural products.[12] Furthermore, the Pierre group recently developed a molecular probe for the luminescent detection of adenosine nucleotides, which bears a 6-amidophenanthridine moiety as the key fragment (Scheme 1).[13]

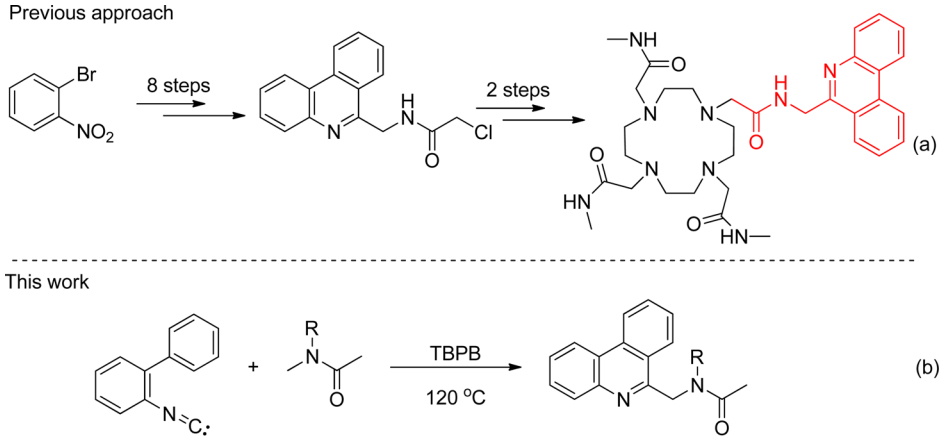
Scheme 1. Molecular Probe for the Luminescent Detection of Adenosine Nucleotides



Received: January 10, 2015
Published: March 5, 2015

DOI: 10.1021/acs.joc.5b00058
J. Org. Chem. 2015, 80, 3151−3158

Scheme 2. Methods for the Preparation of 6-Amidophenanthridine Derivatives



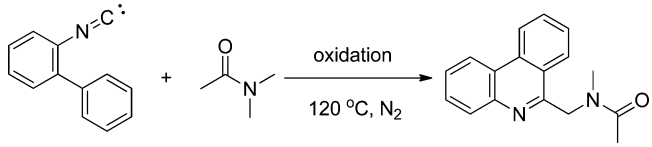
The groups of Studer and others have explored several radical precursors to react with isonitriles for construction of phenanthridine, such as boronic acids, trifluoromethylation reagents, halides, aldehydes, diphenylphosphine oxide, α-oxocarboxylic acids, hydrazines, aryl sulfonyl chlorides, alcohols, ethers, and alkanes.[14] Very recently, our group also developed a metal-free cyclization of isocyanides with disulfides via S−S bond cleavage.[15] Although 2-isocyanobiphenyls are known to react with many radicals, the use of 2-isocycanobiphenyls as an acceptor for the aminomethyl radical to construct 6-amidophenanthridines has never been reported. As mentioned in Scheme 2a, a previous method in preparing 6-amidophenanthridines generally involves several palladium-catalyzed reactions and light-promoted conditions (eight steps). Herein, we report the first example of the cascade functionalization of a C(sp^3)−H bond adjacent to an amide nitrogen atom and intramolecular aromatic cyclization under metal-free conditions (Scheme 2b).

RESULTS AND DISCUSSION

To examine the reactivity of amides, we chose DMAc (*N*,*N*-dimethylacetamide, **2a**) as a model substrate to react with 2-isocyanobiphenyl (**1a**), as shown in Table 1. We conducted the reaction of 2-isocyanobiphenyl (**1a**) with DMAc (2 mL) in the presence of 2.0 equiv of DTBP at 120 °C for 24 h, which gave the expected product of 6-amidophenanthridines (**3a**) in a low yield (31%, Table 1, entry 1). Increasing the amount of oxidant DTBP to 3 equiv resulted in an obviously higher yield (51%, entry 2). Attempts to use transition metals, such as $FeCl_3$, $CuBr_2$, and CuBr, as the catalysts were unsuccessful, resulting in almost no product (entries 3−5). Cu_2O was also tried as a catalyst in the reaction, and no improvement was found (entry 6). Further optimization attempts led us to use other oxidants, including BPO, TBPB, DCP, and TBHP. The reaction could not happen with the use of BPO as oxidant, and almost all of the starting material remained (entry 7). When the reaction was performed in the presence of TBPB, the target product was obtained in a dramatically higher yield of 87% (entry 8). DCP and TBHP could also promote the reaction to give the desired product in moderate yields (34% and 61%, respectively, entries 9 and 10).

After getting the optimized reaction conditions, the next goal of this study was an exploration of the substrate scope of the radical cyclized reactions of the C(sp^3)−H bond adjacent to a nitrogen atom. As shown in Scheme 3, DMAc (**2a**) could react with varieties of 2-isocyanobiphenyl (**1**) to give the expected product in good to excellent chemical yields (63−87%). This reaction could bear several substituents at different positions on the aromatic ring withthe isocyano group, including methoxy (**3b**), methyl (**3k**), chloro (**3f**), and fluoro (**3d**,**l**), giving almost the same level of yields. This brief screening discloses that the electronic properties and steric hindrance have no noticeable effect on the reaction efficiency. A substrate containing two substituted groups (methyl) on the aromatic ring also worked well, giving the corresponding product in 67% yield (**3e**). A further substrate scope study was performed to investigate the effect of substituents on the cyclized aromatic ring. All of the reactions could also proceed smoothly, affording the expected product in good yields, even for a strongly electron donating group (MeO, **3g**) and a strongly electron withdrawing group (F and CF_3, **3h**,**j**). Finally, the more highly sterically hindered naphthyl ring, instead of the phenyl ring, was used as a

Table 1. Optimization of Reaction Conditions[a]



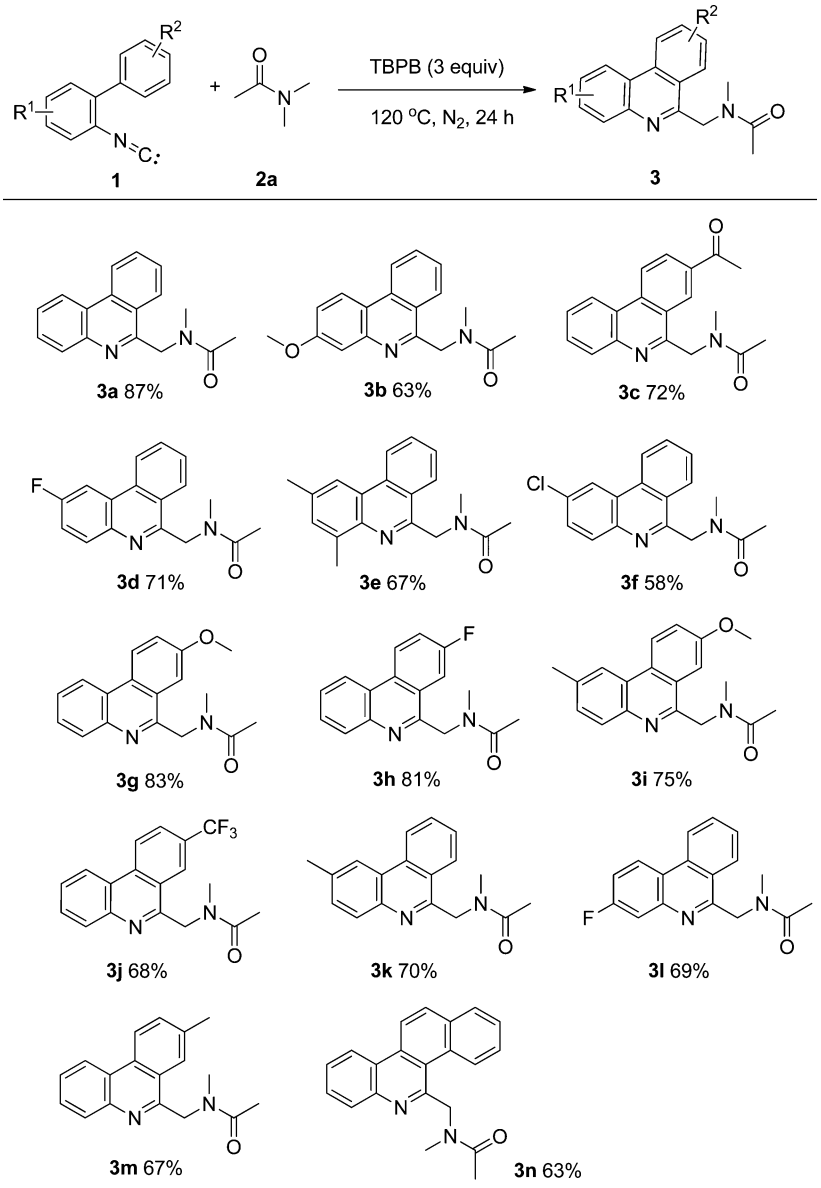
1a 2a 3a

entry	catalyst	oxidant (amt (equiv))[d]	yield (%)[b]
1		DTBP (2.0)	31
2		DTBP (3.0)	53
3	$FeCl_3$[c]	DTBP (3.0)	trace
4	$CuBr_2$[c]	DTBP (3.0)	trace
5	CuBr[c]	DTBP (3.0)	trace
6	Cu_2O[c]	DTBP (3.0)	46
7		BPO (3.0)	trace
8		TBPB (3.0)	87
9		DCP (3.0)	34
10		TBHP (3.0)	61

[a]Reaction conditions: **1a** (0.3 mmol), DMAc (**2a**) 2 mL, 120 °C for 24 h under nitrogen. [b]Isolated yields based on **1a**. [c]10 mol % of catalyst was used. [d]Abbreviations: DTBP, di-*tert*-butyl peroxide; BPO, benzoyl peroxide; TBPB, *tert*-butyl peroxybenzoate; DCP, dicumyl peroxide; TBHP, *tert*-butyl hydroperoxide.

DOI: 10.1021/acs.joc.5b00058
J. Org. Chem. 2015, 80, 3151−3158

Scheme 3. Reaction of DMAc with Various Isocyanides[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (2 mL), TBPB (0.9 mmol, 3.0 equiv), 120 °C for 24 h under nitrogen. Isolated yields are based on **1**.

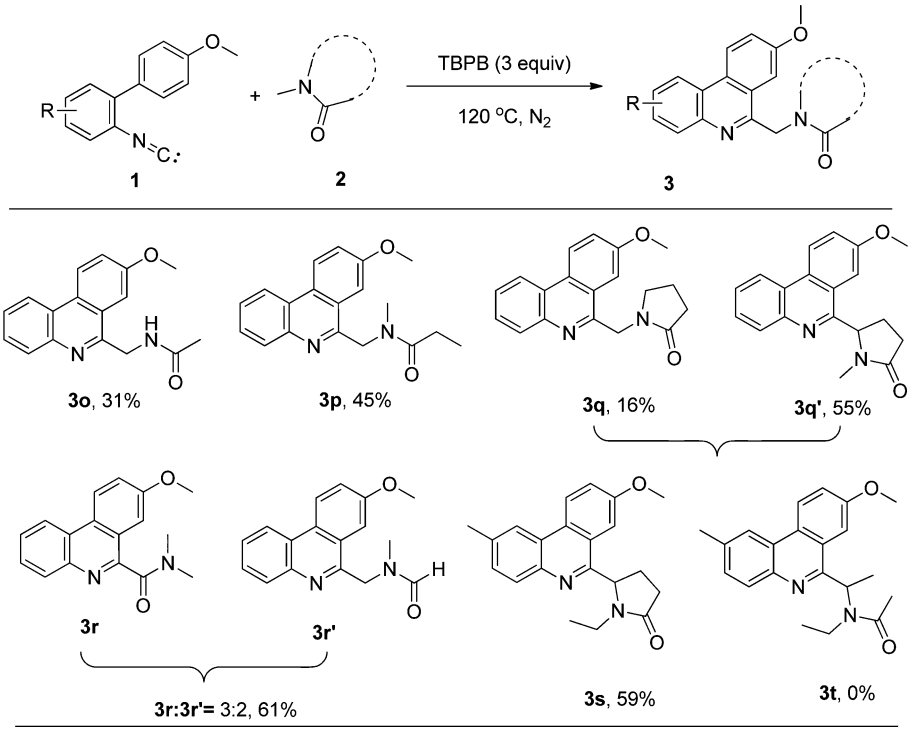
substrate in the reaction, which also could react with *N*,*N*-dimethylacetamide to afford the product in 63% yield (**3n**).

As a continuation of this study on the radical cyclization reaction, we focused on exploring the generality of these reactions bearing the variation in the amide substrates (Scheme 4). First, we used monomethyl-substituted acetamide as a substrate to check the reaction efficiency. The reaction did happen and gave the desired product in 31% yield (**3o**) with excellent chemoselectivity. This result showed that the key fragment of the molecular probe (Scheme 1, (**a**) and (**b**)) could be directly synthesized in one step from simple starting materials, although the yield was not satisfied. It is noteworthy that *N*,*N*-dimethylpropionamide also worked in this reaction with a slightly higher yield (45%, **3p**). In order to investigate the regioselectivity of this radical reaction, the lactam 1-methylpyrrolidin-2-one was tried in the reaction, and the corresponding products were obtained in 71% yield with a ratio of 2:7 (**3q**:**3q**′). Interestingly, these two isomers could be isolated with a regular column. *N*,*N*-Dimethylformamide (DMF) was examined in this reaction, which contains two potential reaction sites. The reaction could proceed through both C(sp^3)−H and C(sp^2)−H cleavage to give the corresponding products in a total 61% yield with a ratio of 3:2 (**3r**:**3r**′ = 3:2). The compound **3r** from C(sp^2)−H cleavage has also been reported from the iron-promtoted carboxamidation and cyclization of aryl isonitriles with formamides.[16] Finally, 1-ethylpyrrolidin-2-one was tried as a substrate in the reaction, which afforded the desired product **3s** in 59% chemical yield with excellent regioselectivity. Unfortunately, the reaction with *N*,*N*-diethylacetamide failed to give the corresponding product (**3t**).

To gain insight into this reaction, a control reaction of **1k** and **2a** under the standard conditions with the addition of the radical-trapping reagents 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was carried out (Scheme 5). As expected, the reaction gave almost no expected product **3k**, and only a

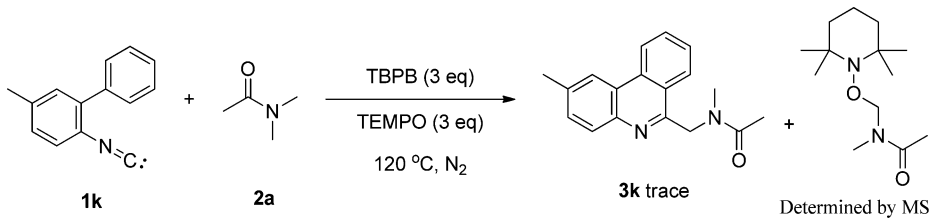
DOI: 10.1021/acs.joc.5b00058
J. Org. Chem. 2015, 80, 3151−3158

Scheme 4. Reaction of Isocyanides with Various Amides[a]

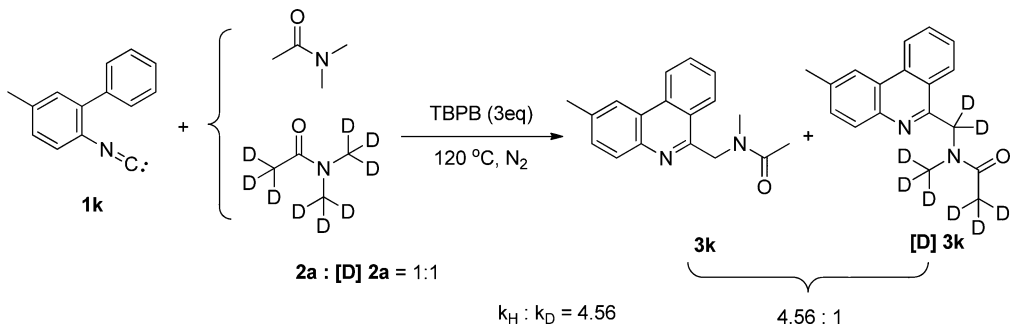


[a]Reaction conditions: **1** (0.3 mmol), **2** (2 mL), TBPB (0.9 mmol), 120 °C for 24 h under nitrogen. Isolated yields based on **1**.

Scheme 5. Investigation of the Reaction Mechanism



Scheme 6. KIE Studies



TEMPO–DMAc adduct was detected (determined by ESI-MS analysis). The result clearly discloses that the current reaction is a radical course.

To further investigate the mechanism, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out (Scheme 6). As a result, a significant KIE was observed with k_H/k_D = 4.56 (the KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of **3k** and [**D**]**3k**). The result indicates that C(sp^3)–H bond cleavage may be one of the rate-determining steps of this procedure.

Taking into account the above results and literature reports,[14,15] we can propose a plausible mechanism for this functionalization of the C(sp^3)–H bond and intramolecular radical aromatic cyclization reaction (Scheme 7). In the initial step, the cleavage of TBPB gives the *tert*-butoxy radical intermediate **A** on heating, which reacts with DMAc (**2a**) to give radical **B** through C(sp^3)–H bond cleavage. Then, the addition of intermediate **B** to isonitrile (**1a**) affords the intermediate **C**. Subsequently, the intramolecular radical cyclization of intermediate **C** generates the intermediate

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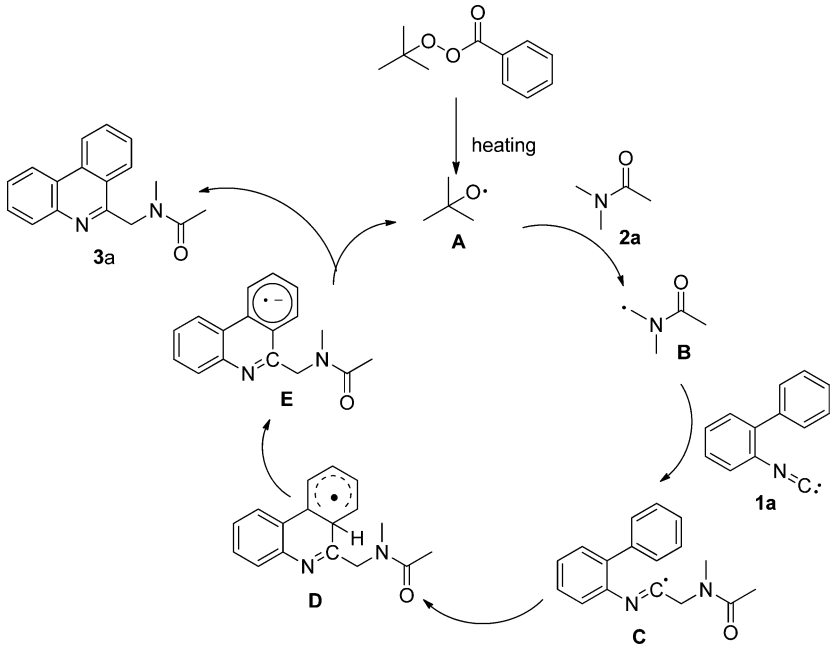
Scheme 7. Possible Mechanism



cyclohexadienyl radical **D**, which undergoes deprotonation to give the radical anion **E**. Finally, radical anion **E** reacts with TBPB via a single electron transfer process, giving the product **3a** and the *tert*-butoxy radical **A** for the next cycle.

CONCLUSION

To conclude, we showed that amide easily undergoes an oxidative radical reaction with 2-isocyanobiphenyl derivatives in the presence of TBPB. It involves new $C(sp^2)-C(sp^2)$ and $C(sp^3)-C(sp^2)$ bond formation in one step via $C(sp^3)-H$ bond functionalization and an intramolecular cyclization process. The reactions show wide generality and good chemical yields, providing an easy way to prepare 6-amidophenanthridine derivatives.

EXPERIMENTAL SECTION

General Procedure for the Reaction of Amide with Isocyanide. In a Schlenk tube were placed 2-isocyanobiphenyls (**1**; 0.30 mmol), DMAc (2 mL), and TBPB (0.9 mmol, 3.0 equiv), then the tube was and charged with nitrogen, and the contents were stirred at 120 °C for 24 h. After the reaction was finished, the reaction mixture was diluted with 20 mL of ethyl acetate, washed with saturated brine (15 mL × 3), dried with anhydrous sodium sulfate, and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (elute: PE/EtOAc = 1:1) to afford the product **3**.

*N-Methyl-N-(phenanthridin-6-ylmethyl)acetamide (**3a**).* Yield: 69 mg, 87%; pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 and 8.61 (2 × d, J = 8.3 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8.3 Hz, 1H), 8.14 and 8.07 (2 × d, J = 8.0 Hz, 1H), 7.83 (t, J = 8.3 Hz, 1H), 7.76–7.60 (m, 3H), 5.30 and 5.17 (2 × s, 2H), 3.10 and 2.99 (2 × s, 3H), 2.19 and 2.14 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 and 170.7, 156.6 and 153.8, 143.5 and 143.3, 133.0 and 132.9, 130.7 and 130.7, 130.5 and 130.0, 128.8 and 128.6, 127.8 and 127.5, 127.1 and 127.0, 126.3 and 124.0, 124.7 and 123.7, 124.2 and 124.2, 122.8 and 122.3, 122.0 and 121.8, 54.0 and 51.0, 35.4 and 34.9, 21.9, and 21.5. IR (cm^{-1}): 2925, 1647, 1486, 1405, 755, 726. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{17}N_2O$ 265.1341, found 265.1338.

*N-((3-Methoxyphenanthridin-6-yl)methyl)-N-methylacetamide (**3b**).* Yield: 56 mg, 63%; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 and 8.51 (2 × d, J = 8.3 Hz, 1H), 8.43 and 8.41 (2 × d, J = 9.0 Hz, 1H), 8.38 and 8.04 (2 × d, J = 8.1 Hz, 1H), 7.80 (m, 1H), 7.65–7.58 (m, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.29 (dd, J = 9.0, 2.7 Hz, 1H), 5.29 and 5.17 (2 × s, 2H), 3.99 and 3.98 (2 × s, 3H), 3.11 and 2.98 (2 × s, 3H), 2.19 and 2.15 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 160.0, 157.2, 144.9, 133.2, 130.8, 126.7, 126.4, 123.8, 123.2, 121.8, 118.2, 118.1, 109.8, 55.7 and 55.6, 54.0 and 51.1, 35.3 and 35.0, 21.9, and 21.5. IR (cm^{-1}): 2929, 1650, 1616, 1487, 1215, 1038, 758. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1445.

*N-((8-Acetylphenanthridin-6-yl)methyl)-N-methylacetamide (**3c**).* Yield: 66 mg, 72%; white solid, mp 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (d, J = 1.6 Hz, 1H), 8.65 (d, J = 8.7 Hz, 1H), 8.59–8.52 (m, 1H), 8.41 (dd, J = 8.7, 1.7 Hz, 1H), 8.16 (dd, J = 8.1, 1.0 Hz, 1H), 7.83–7.76 (m, 1H), 7.73–7.64 (m, 1H), 5.33 and 5.26 (2 × s, 2H), 3.11 and 3.01 (2 × s, 3H), 2.79 and 2.77 (2 × s, 3H), 2.18 and 2.15 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1 and 197.0, 170.5, 157.4, 144.2, 136.1, 135.8, 130.1, 129.9, 128.9, 128.7, 127.5, 124.1, 123.6, 122.8, 122.6, 54.0 and 51.2, 35.3 and 35.0, 26.96 and 26.8, 21.9, and 21.5. IR (cm^{-1}): 2929, 1681, 1642, 1615, 1574, 1261, 992, 846, 773. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found: 307.1441.

*N-((2-Fluorophenanthridin-6-yl)methyl)-N-methylacetamide (**3d**).* Yield: 60 mg, 71%; white solid, mp 49–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 and 8.48 (2 × d, J = 8.2 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 8.16–8.06 (m, 2H), 7.84 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.72 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 7.44 (ddd, J = 8.8, 8.1, 2.8 Hz, 1H), 5.28 and 5.17 (2 × s, 2H), 3.10 and 3.01 (s, 3H), 2.20 and 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 and 170.8, 161.3 (d, J = 247.1 Hz), 155.8 and 153.0 (2 × d, J = 2.7 Hz), 140.3 and 140.1, 132.7, and 132.1 (2 × d, J = 9.2 Hz), 132.4 (d, J = 4.3 Hz), 130.8 and 130.7, 128.4 and 128.2, 126.4 and 124.1, 125.5 (d, J = 9.2 Hz), 124.7 and 124.2, 123.0 and 122.4, 117.4 (d, J = 24.2 Hz), 106.9 and 106.8 (2 × d, J = 23.4 Hz), 53.8 and 50.9, 35.5 and 35.0, 21.9, and 21.5. IR (cm^{-1}): 2924, 1644, 1404, 1177, 828, 754. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{16}FN_2O$ 283.1247, found 283.1245.

*N-((2,4-Dimethylphenanthridin-6-yl)methyl)-N-methylacetamide (**3e**).* Yield: 63 mg, 67%; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 and 8.58 (2 × d, J = 8.3 Hz, 1H), 8.30 and 8.03 (2 × d, J = 8.2 Hz, 1H), 8.16 (s, 1H), 7.82–7.75 (m, 1H), 7.69–7.62 (m, 1H), 7.42 and 7.40 (2 × s, 1H), 5.28 and 5.14 (2 × s, 2H), 3.12 and 3.10 (2 × s, 3H), 2.81 and 2.77 (2 × s, 3H), 2.57 and 2.56 (2 × s, 3H), 2.22 and 2.11 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7 and 171.0, 153.0 and 150.8, 140.3 and 140.3, 138.0 and 137.2, 136.5 and 136.1,

DOI: 10.1021/acs.joc.5b00058
J. Org. Chem. 2015, 80, 3151–3158

133.1 and 133.0, 131.3 and 131.0, 130.2 and 130.1, 127.2 and 127.2, 125.6 and 124.4, 124.0 and 123.8, 123.7 and 123.4, 123.1 and 122.5, 119.4 and 119.2, 53.9 and 51.0, 36.2 and 35.3, 21.9 and 21.4, 18.2, and 14.1. IR (cm^{-1}): 2922, 1648, 1405, 853, 758. HRMS (TOF MS ESI): $[M + Na]^+$ calcd for $C_{19}H_{20}N_2ONa$ 315.1473, found 315.1470.

N-((2-Chlorophenanthridin-6-yl)methyl)-N-methylacetamide (**3f**). Yield: 52 mg, 58%; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.51−8.46 (m, 2H), 8.40 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.66−7.59 (m, 1H), 5.27 and 5.16 (2 × s, 2H), 3.09 and 3.01 (2 × s, 3H), 2.19 and 2.12 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2 and 170.7, 156.9 and 154.2, 141.9 and 141.7, 133.0 and 132.9, 131.9, 131.5, 131.0, 129.3 and 129.0, 128.4 and 128.2, 126.3 and 124.0, 125.2 and 124.3, 124.8 and 124.8, 122.9 and 122.3, 121.6 and 121.5, 53.9 and 50.9, 35.6 and 35.0, 21.8, and 21.5. IR (cm^{-1}): 2923, 1650, 1587, 1410, 1292, 821, 752, 576. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{16}ClN_2O$ 299.0951, found 299.0952.

N-((8-Methoxyphenanthridin-6-yl)methyl)-N-methylacetamide (**3g**). Yield: 73 mg, 83%; yellow solid, mp 127−128 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 9.1 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.17−8.06 (m, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.71−7.61 (m, 2H), 7.46 (dd, J = 9.0, 2.5 Hz, 1H), 5.29 and 5.14 (2 × s, 2H), 4.00 and (2 × s, 3H), 3.11 and 2.96 (2 × s, 3H), 2.18 and 2.17 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 159.1, 156.1, 142.5, 129.9, 127.6, 127.3, 127.1, 126.1, 124.4, 123.8, 122.2, 121.5, 106.1, 55.9, 51.4, 35.0, 21.8. IR (cm^{-1}): 2939, 1638, 1573, 1227, 1027, 990, 840, 768. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1444.

N-((8-Fluorophenanthridin-6-yl)methyl)-N-methylacetamide (**3h**). Yield: 68 mg, 81%; white oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 and 8.58 (2 × dd, J = 9.1, 5.3 Hz, 1H), 8.48−8.43 (m, 1H), 8.14−8.05 (m, 2H), 7.73−7.67 (m, 1H), 7.67−7.62 (m, 1H), 7.55 (ddd, J = 9.1, 8.0, 2.6 Hz, 1H), 5.21 and 5.09 (2 × s, 2H), 3.10 and 3.01 (2 × s, 3H), 2.19 and 2.12 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2 and 170.8, 161.4 (d, J = 249.0 Hz), 155.8 (d, J = 4.0 Hz), 143.0 (d, J = 1.1 Hz), 130.6 and 130.1, 129.6 (d, J = 1.9 Hz), 128.7 and 128.4, 127.5 and 127.4, 125.9, and 124.8 (2 × d, J = 8.5 Hz), 123.7 (d, J = 0.5 Hz), 121.7 and 121.6, 119.9, and 119.8 (2 × d, J = 24.0 Hz), 111.0 and 108.8 (2 × d, J = 22.0 Hz), 53.9 and 51.0, 35.6 and 35.0, 21.9, and 21.5. IR (cm^{-1}): 2920, 2850, 1647, 1485, 1408, 1207, 831, 768. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{16}FN_2O$ 283.1247, found 283.1242.

N-((8-Methoxy-2-methylphenanthridin-6-yl)methyl)-N-methylacetamide (**3i**). Yield: 69 mg, 75%; pale yellow solid, mp 139−140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 9.1 Hz, 1H), 8.23 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.90 (s, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.43−7.41 (m, 1H), 5.25 and 5.09 (2 × s, 2H), 3.97 and 3.96 (2 × s, 3H), 3.08 and 2.93 (2 × s, 3H), 2.60 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 and 170.5, 158.9 and 158.6, 155.1 and 151.8, 141.0 and 140.7, 137.1 and 137.1, 130.1 and 129.5, 129.9 and 129.3, 128.2 and 127.0, 126.1 and 125.5, 124.5 and 123.8, 124.2 and 123.7, 122.0 and 120.9, 121.1 and 120.6, 106.0 and 104.4, 55.9 and 55.5, 54.2 and 51.3, 35.0 and 34.8, 22.0 and 21.5, 21.8, and 21.5. IR (cm^{-1}): 2922, 1645, 1618, 1573, 1398, 1262, 1231, 1037, 831. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1609.

N-Methyl-N-((8-(trifluoromethyl)phenanthridin-6-yl)methyl)-acetamide (**3j**). Yield: 68 mg, 68%; white solid, mp 160−161 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 and 8.69 (2 × d, J = 8.7 Hz, 1H), 8.74 and 8.35 (2 × s, 1H), 8.52 (d, J = 7.5 Hz, 1H), 8.18 and 8.14 (2 × dd, J = 8.1, 0.9 Hz, 1H), 8.05 and 8.00 (2 × dd, J = 8.7, 1.5 Hz, 1H), 7.81−7.74 (m, 1H), 7.72−7.65 (m, 1H), 5.30 and 5.22 (2 × s, 2H), 3.12 and 3.06 (2 × s, 3H), 2.21 and 2.14 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2 and 170.8, 156.4 and 153.7, 144.1 and 144.0, 135.2 and 135.1, 130.7 and 130.3, 130.0, 129.5, 129.7 and 129.2, 127.7 and 127.5, 126.5 (q, J = 3.03 Hz), 123.9 (q, J = 272.7 Hz), 123.9 (q, J = 5.05 Hz), 123.3 and 123.1, 122.3 and 122.2, 53.8 and 51.0, 35.9 and 35.1, 21.7, and 21.4. IR (cm^{-1}): 2920, 1641, 1590, 1488, 1408, 1330, 1277, 1113, 1081, 839, 780. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{18}H_{16}F_3N_2O$ 333.1215, found 333.1210.

N-Methyl-N-((2-methylphenanthridin-6-yl)methyl)acetamide (**3k**). Yield: 58 mg, 70% ; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 and 8.59 (d, J = 8.2 Hz, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.31 (s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 5.28 and 5.14 (2 × s, 2H), 3.08 and 2.96 (2 × s, 3H), 2.61 (s, 3H), 2.18 and 2.14 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 and 170.6, 155.7 and 152.8, 141.8 and 141.6, 137.0 and 137.0, 132.7 and 132.7, 130.5 and 130.5, 130.4 and 130.3, 130.2 and 129.7, 127.6 and 127.4, 126.3 and 123.9, 124.7 and 124.3, 124.0 and 123.6, 122.8 and 122.2, 121.6 and 121.5, 54.0 and 51.0, 35.3 and 34.9, 21.9, and 21.5. IR (cm^{-1}): 2942, 1648, 1585, 1497, 1404, 1295, 1259, 827, 756. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{18}H_{19}N_2O$ 279.1497, found 279.1499.

N-((3-Fluorophenanthridin-6-yl)methyl)-N-methylacetamide (**3l**). Yield: 59 mg, 69%; pale yellow solid, mp 123−124 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 9.1 Hz, 1H), 8.52−8.48 (m, 1H), 8.40 and 8.09 (2 × d, J = 8.0 Hz, 1H), 7.86−7.82 (m, 1H), 7.77 (dd, J = 9.8, 2.7 Hz, 1H), 7.71−7.63 (m, 1H), 7.40 (ddd, J = 9.0, 8.2, 2.7 Hz, 1H), 5.28 and 5.18 (2 × s, 2H), 3.10 and 3.03 (2 × s, 3H), 2.20 and 2.13 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2 and 170.8, 162.5 (d, J = 247.9 Hz), 158.0 and 155.3, 144.6 (d, J = 11.8 Hz), 132.7 and 131.1, 127.6 and 127.4, 126.4 and 124.1, 124.2 (d, J = 0.8 Hz), 123.9, 123.8, 122.7 and 122.1, 120.8 (d, J = 2.1 Hz), 116.1 and 116.0 (2 × d, J = 23.7 Hz), 115.0 and 114.5 (2 × d, J = 20.4 Hz), 53.9 and 51.0, 35.7 and 35.0, 21.9, and 21.5. IR (cm^{-1}): 2921, 1642, 1584, 1487, 1408, 1296, 1207, 1153, 998, 825, 750. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{16}FN_2O$ 283.1247, found 283.1242.

N-Methyl-N-((8-methylphenanthridin-6-yl)methyl)acetamide (**3m**). Yield: 56 mg, 67%; pale yellow solid, mp 104−105 °C.^1H NMR (400 MHz, $CDCl_3$): δ 8.54 and 8.49 (2 × d, J = 8.4 Hz, 2H), 8.18 and 7.84 (2 × s, 1H), 8.12 (d, J = 6.9 Hz, 1H), 7.72−7.59 (m, 3H), 5.28 and 5.15 (2 × s, 2H), 3.11 and 3.01 (2 × s, 3H), 2.61 and 2.58 (2 × s, 3H), 2.20 and 2.14 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 and 170.7, 156.3 and 153.4, 143.2 and 143.0, 137.7 and 137.5, 132.5 and 132.4, 130.8 and 130.8, 130.4 and 129.9, 128.3 and 128.1, 127.0 and 126.9, 125.7 and123.5, 124.8 and 124.4, 124.2 and 123.8, 122.7 and 122.1, 121.8 and 121.7, 54.0 and 51.0, 35.6 and 35.0, 21.9 and 21.9, 21.8, and 21.5. IR (cm^{-1}): 2921, 2851, 1641, 1630, 1574, 1483, 1259, 835, 763. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{18}H_{19}N_2O$ 279.1497, found 279.1498.

N-(Benzo[i]phenanthridin-5-ylmethyl)-N-methylacetamide (**3n**). Yield: 59 mg, 63%; pale yellow solid, mp 141−142 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.63−8.45 (m, 3H), 8.18−7.99 (m, 3H), 7.85−7.56 (m, 4H), 5.63 and 5.45 (2 × s, 2H), 2.95 and 2.93 (2 × s, 3H), 2.27 and 2.18 (2 × s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8 and 171.9, 154.1 and 153.4, 143.9 and 143.8, 134.1 and 133.9, 133.3 and 133.1, 132.0 and 131.9, 130.1 and 129.8, 129.7 and 129.5, 129.4 and 129.0, 128.7, 127.4 and 127.4, 127.1 and 127.0, 127.0 and 126.6, 126.7 and 126.7, 123.4 and 123.3, 122.7 and 122.4, 122.4 and 122.4, 120.5 and 120.3, 58.8 and 55.8, 37.0 and 35.0, 21.8, and 21.6. IR (cm^{-1}): 2920, 1640, 1565, 829, 760. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{21}H_{19}N_2O$ 315.1497, found: 315.1494.

N-((8-Methoxyphenanthridin-6-yl)methyl)acetamide (**3o**). Yield: 26 mg, 31%; white solid, mp 175−176 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 9.1 Hz, 1H), 8.50−8.44 (m, 1H), 8.12 (dd, J = 7.9, 1.2 Hz, 1H), 7.81 (s, 1H), 7.72−7.61 (m, 2H), 7.49 (dd, J = 9.0, 2.5 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 5.05 (d, J = 3.9 Hz, 2H), 3.99 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 159.1, 153.2, 141.7, 129.3, 127.8, 127.1, 125.3, 124.2, 124.1, 122.1, 121.6, 104.1, 55.8, 42.6, 23.4. IR (cm^{-1}): 3281, 2953, 1751, 1647, 1619, 1462, 1373, 1224, 1036, 758. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1290, found 281.1285.

N-((8-Methoxyphenanthridin-6-yl)methyl)-N-methylpropionamide (**3p**). Yield: 42 mg, 45%; pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J = 9.1 Hz, 1H), 8.49−8.45 (m, 1H), 8.18−8.05 (m, 1H), 7.94 (d, J = 2.6 Hz, 1H), 7.69−7.61 (m, 2H), 7.45 (dd, J = 9.0, 2.6 Hz, 1H), 5.30 (s, 2H), 3.98 (s, 3H), 2.92 (s, 3H), 2.41 (q, J = 7.4 Hz, 2H), 1.20 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 159.0, 156.4, 142.5, 129.8, 127.6, 127.3, 127.1, 126.1, 124.4, 123.8, 122.3, 121.5, 106.1, 77.3, 77.0, 76.7, 55.9, 51.6, 34.1, 26.9, 9.48. IR (cm^{-1}): 2922, 1637, 1574, 1463, 1378, 1226, 837, 763. HRMS

DOI: 10.1021/acs.joc.5b00058
J. Org. Chem. 2015, 80, 3151−3158

(TOF MS ESI): $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1601.

*1-((8-Methoxyphenanthridin-6-yl)methyl)pyrrolidin-2-one (**3q**).* Yield: 14 mg, 16%; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 9.1 Hz, 1H), 8.52−8.45 (m, 1H), 8.17−8.08 (m, 1H), 7.94 (d, J = 2.6 Hz, 1H), 7.71−7.63 (m, 2H), 7.48 (dd, J = 9.0, 2.6 Hz, 1H), 5.13 (s, 2H), 4.01 (s, 3H), 3.35−3.30 (t, J = 8.1 Hz, 2H), 2.46 (t, J = 8.1 Hz, 2H), 1.94 (dt, J = 15.4, 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 159.1, 155.3, 129.8, 127.6, 127.3, 127.3, 125.9, 124.5, 123.9, 122.4, 121.5, 105.8, 56.1, 48.3, 46.9, 30.9, 17.6. IR (cm^{-1}): 2925, 1683, 1463, 1228, 1036, 763. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1445.

*5-(8-Methoxyphenanthridin-6-yl)-1-methylpyrrolidin-2-one (**3q′**).* Yield: 50 mg, 55%; white solid, mp 112−113 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 9.1 Hz, 1H), 8.50−8.40 (m, 1H), 8.16−8.03 (m, 1H), 7.69−7.59 (m, 2H), 7.50 (dd, J = 9.0, 2.6 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 5.48 (dd, J = 8.5, 3.6 Hz, 1H), 3.99 (s, 3H), 2.91 (s, 3H), 2.71−2.59 (m, 2H), 2.55−2.47 (m, 1H), 2.22−2.11 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0, 158.7, 156.6, 142.4, 130.4, 127.8, 127.8, 127.2, 125.1, 124.7, 123.9, 121.3, 120.6, 105.0, 55.6, 29.9, 29.2, 25.4. IR (cm^{-1}): 2922, 1682, 1616, 1575, 1461, 1392, 1224, 1038, 757. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1444.

*8-Methoxy-N,N-dimethylphenanthridine-6-carboxamide (**3r**).* ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 9.1 Hz, 1H), 8.50−8.44 (m, 1H), 8.15−8.11 (m, 1H), 7.74−7.60 (m, 2H), 7.50−7.44 (m, 1H), 7.39 (d, J = 2.6 Hz, 1H), 3.94 (s, 3H), 3.30 (s, 3H), 2.93 (s, 3H).

*N-((8-Methoxyphenanthridin-6-yl)methyl)-N-methylformamide (**3r′**).* ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 9.1 Hz, 1H), 8.50−8.44 (m, 1H), 8.17 (s, 1H), 8.15−8.11 (m, 1H), 7.74−7.60 (m, 2H), 7.50−7.44 (m, 1H), 7.39 (d, J = 2.6 Hz, 1H), 3.98 (s, 3H), 3.30 (s, 3H), 2.88 (s, 2H). HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$ 281.1285, found 281.1290.

*1-Ethyl-5-(8-methoxy-2-methylphenanthridin-6-yl)pyrrolidin-2-one (**3s**).* Yield: 59 mg, 59%; pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.63−8.54 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.53−7.41 (m, 3H), 5.58 (dd, J = 7.8, 3.4 Hz, 1H), 3.98 (s, 3H), 3.88 (td, J = 14.5, 7.3 Hz, 1H), 3.01−2.87 (m, 1H), 2.72−2.45 (m, 6H), 2.26−2.10 (m, 1H), 1.06 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.63, 158.56, 155.89, 140.76, 137.12, 130.09, 129.53, 127.54, 125.13, 124.60, 123.69, 120.90, 120.37, 104.92, 55.54, 36.39, 30.31, 21.94, 12.52. IR (cm^{-1}): 2928, 1683, 1573, 1498, 1241, 1119, 1040, 827. HRMS (TOF MS ESI): $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_2$ 335.1754, found 335.1760.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving experimental procedures, full spectroscopic data for compounds **3**, and ^1H and ^{13}C NMR spectra. 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Nos. 21102071 and 21472082). The Jiangsu 333 program (for Y.P.) and Changzhou Jin-Feng-Huang program (for J.H.) are also acknowledged.

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