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Copper-Catalyzed N−O Cleavage of *α,β*-Unsaturated Ketoxime Acetates toward Structurally Diverse Pyridines

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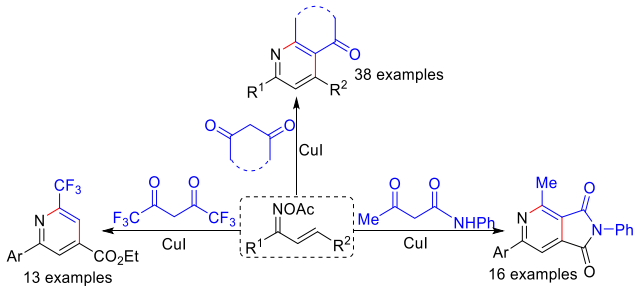
ABSTRACT: The copper-catalyzed [4+2] annulation of *α,β*-unsaturated ketoxime acetates with 1,3-dicarbonyl compounds for the synthesis of three classes of structurally diverse pyridines has been developed. This method employs 1,3-dicarbonyl compounds as C2 synthons and enables the synthesis of multi-functionalized pyridines with diverse electron-withdrawing groups in moderate to good yields. The mechanistic investigation suggests that the reactions proceed through an ionic pathway.



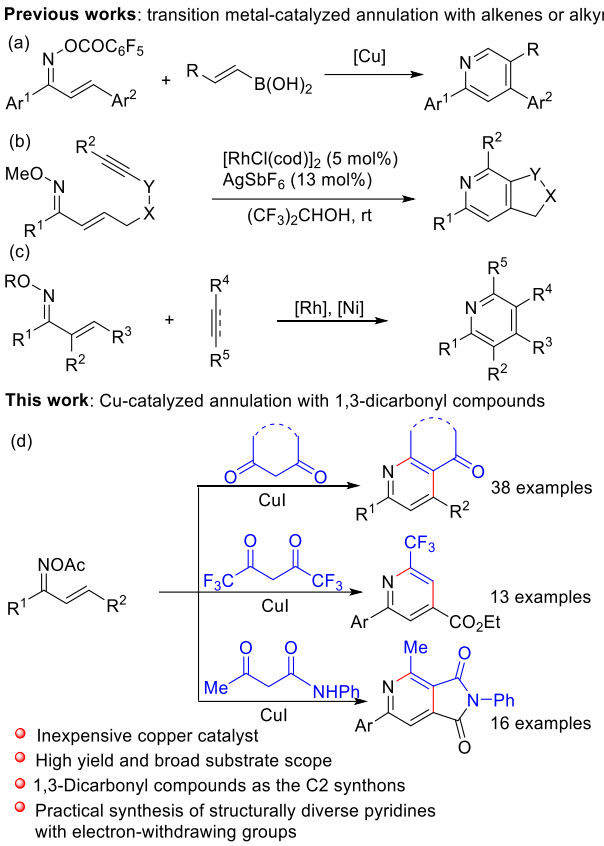
KEYWORDS: Annulation, Copper, Ketoxime Acetates, 1,3-Dicarbonyl compounds, Pyridines

INTRODUCTION

Functionalized pyridines are the most abundant azaheteroaromatic structures that are embedded in many natural products, functional materials, agrochemicals and pharmaceutical drugs.[1] In particular, they play pivotal roles in organic synthesis as building blocks and find use in catalysis and coordination chemistry.[2] Consequently, various synthetic methods, including transition-metal-catalyzed reactions[3] and the metal-free reactions,[4] have been successfully established to access these valuable substituted pyridines. Although some remarkable achievements have been made, versatile and efficient methods for the direct construction of pyridines that are compatible with various functional groups remain highly desirable. On the other hand, ketoximes and derivatives[5] were used as meritorious building blocks for the synthesis and derivatization of pyridines[6] as well as many other nitrogen-containing heterocycles.[7] Among them, transition metal-catalyzed coupling reactions using *α,β*-unsaturated ketoximes as C3N1 synthons in structurally diverse pyridine synthesis have gained increased attention. For example, Liebeskind and co-workers developed Cu-catalyzed cross-coupling of vinyl ketoxime *O*-pentafluorobenzoates with alkenylboronic acids in the modular construction of substituted pyridines (Scheme 1a).[8] Hanzawa et al. investigated the first Rh(I)-catalyzed intramolecular hetero-[4+2] cycloaddition of *ω*-alkynyl-vinyl oximes for the synthesis of bicyclic pyridine compounds (Scheme 1b).[9] Recent advancements in transition metal-catalyzed annulation of *α,β*-unsaturated ketoximes with alkynes or alkenes provided new routes for pyridine synthesis owing to the ability of the ketoxime functionality to serve as a directing group for C−H activation, as has been reported by Cheng,[10] Chiba,[11] Ellman,[12] Rovis,[13] and others (Scheme 1c).[14] Despite these advances, access to pyridines with diverse electron-withdrawing groups have been rather limited. Nonetheless, the

transformation of *α,β*-unsaturated ketoximes with other C2 reaction partners for the construction of pyridines have never been documented.

Scheme 1. The Annulation of *α,β*-Unsaturated Ketoximes for Pyridines Synthesis



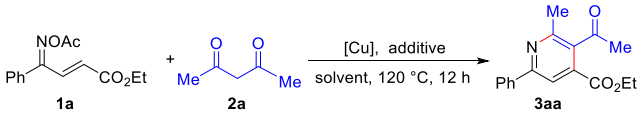
Inspired by the previous works,[15] we envision that the nucleophilic iminylcopper(II) can be generated through reduction of the *α,β*-unsaturated ketoxime acetate by copper, which adds to the carbonyl group, followed by elimination and the subsequent processes to generate the substituted pyridine. Herein, we disclose the copper-catalyzed coupling reactions of *α,β*-unsaturated ketoxime acetates with various 1,3-dicarbonyl compounds, delivering three classes of structurally diverse pyridines that are difficult to assemble through traditional condensation approaches (Scheme 1d).

RESULTS AND DISCUSSION

Initially, we employed ketoxime-enoate **1a** and acetylacetone **2a** as benchmark substrates to explore the optimal reaction conditions. To our delight, the desired product **3aa** was isolated in

83% yield by using CuI as the catalyst in DCE at 120 ℃ for 12 h under N_2 atmosphere (Table 1, entry 1). A brief survey of various solvents demonstrated that THF was the most ideal, affording the product **3aa** in 93% yield (entry 4), as the reaction became sluggish in other solvents such as MeCN and toluene (entry 2−3). In addition, other copper catalysts also effectively produced the desired product in reasonable yields (entry 5−9). No further improvement of the yield was obtained by screening of various additives (entry 10−12). Finally, either increasing or decreasing the reaction temperature resulted in lower yields of **3aa** (entries 13−14). To demonstrate the possibility of large-scale operation, scale up experiments were conducted at the 10 mmol scale to synthesize **3aa** in 88% yield (entry 15).

Table 1. Optimization of Reaction Conditions[a]



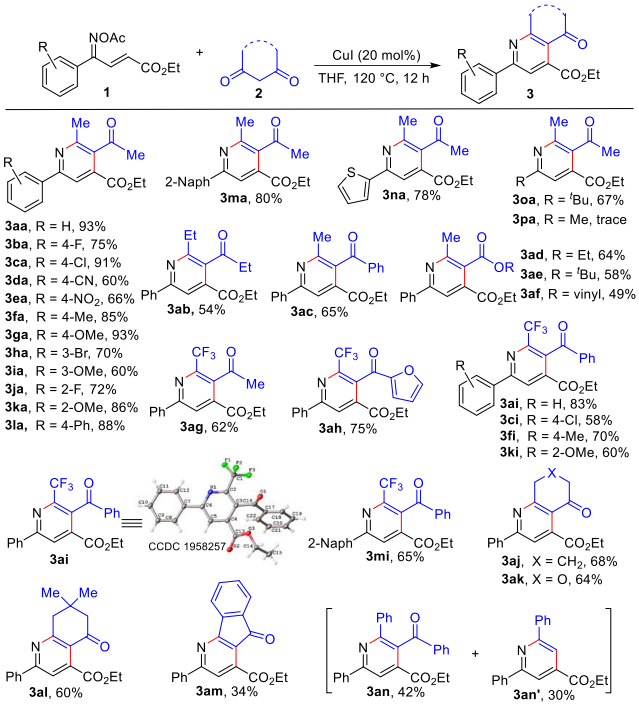
entry	[Cu]	solvent	additive	yield (%)
1	CuI	DCE	None	83
2	CuI	MeCN	None	81
3	CuI	toluene	None	69
4	**CuI**	**THF**	**None**	**93**
5	CuCl	THF	None	75
6	CuBr	THF	None	72
7	CuCN	THF	None	86
8	$CuCl_2$	THF	None	83
9	$Cu(OAc)_2$	THF	None	79
10	CuI	THF	KOAc	72
11	CuI	THF	Li_2CO_3	87
12	CuI	THF	$NaHSO_3$	70
13[b]	CuI	THF	None	90
14[c]	CuI	THF	None	89
15[d]	CuI	THF	None	88

[a]Reaction conditions: oxime **1a** (0.4 mmol), acetylacetone **2a** (0.2 mmol), copper salt (20 mol%), and additive (2 equiv) in solvent (2 mL) at 120 °C for 12 h under N_2. Isolated yields. [b]110°C. [c]130°C. [d]10 mmol scale.

With the optimal reaction conditions established, we then investigated the versatility and limitations of the current copper-catalyzed synthesis of multi-functionalized pyridines, and the representative examples were summarized in Scheme 2. First, various substituted ketoxime-enoates **1,** regardless of the electronic properties, steric hindrances, and substitution positions on the aromatic ring, were broadly tolerated and reacted smoothly with acetylacetone **2a** to generate the corresponding products **3aa**–**3ka** in moderate to good yields (60–93%). Other ketoxime-enoates **1** with aromatic rings such as biphenyl, *β*-naphthyl and thiophenyl were also tested in this transformation, and they all demonstrated good reaction efficiency (**3la**–**3na**). Also tert-butyl substituted ketoxime-enoate readily participated in this reaction, giving rise to **3oa** in 67% yield. However, the methyl-substituted counterparts failed to generate the desired product. Subsequently, we tested the protocol with a set of 1,3-dicarbonyl compounds. *β*-Diketones such as 3,5-heptanedione and benzoylacetone could also be employed to deliver the desired pyridine derivatives **3ab** and **3ac** in 54% and 65% yields, respectively. Ethyl, ^{t}butyl, and allyl acetoacetates were also suitable substrates, providing the desired products in moderate to good yields. Notably, CF_3-substituted *β*-diketones and ketoxime-enoates showed similar reactivity under the standard conditions, furnishing the targeted products in good yields (**3ag**–3**mi**). The structure of **3ai** was unambiguously confirmed by single-crystal X-ray analysis. Therefore, this protocol provides viable access to a diverse range of 2-CF_3 substituted pyridines. Moreover, cyclic *β*-diketones were all efficient for the present transformation and the corresponding bicyclic products **3aj**–**3am** were afforded without any difficulties. When dibenzoylmethane was employed, the desired product **3an** was isolated in 42% yield along with the unexpected product **3an'** in 30% yield, which might be attributed to the debenzoylation of **3an** assisted by Cu(I) salt in the prensence of water. However,

no desired products were obtained when the unactivated aryl/alkyl ketones such as phenylpropone and 2-pentanone were used as substrates in the current protocol.

Scheme 2. Reactions of Various Ketoxime-enoates with 1,3-Dicarbonyl Compounds[a]

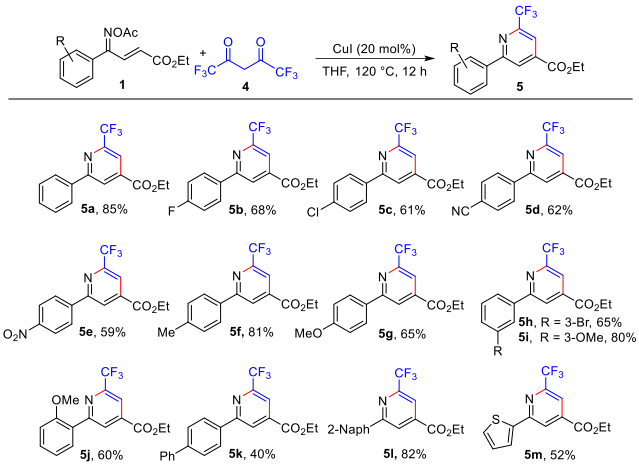


[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol) and CuI (20 mol%) in THF (2 mL) at 120 ℃ for 12 h under N_2. Isolated yields.

The above satisfying results prompted us to further investigate the scope of the transformation. However, when we utilized hexafluoroacetylacetone **4** as the coupling partner, the 2,4,6-trisubstituted pyridine **5a** was obtained in 85% yield. To evaluate the generality of this process, various ketoxime-enoates **1** were subjected to the reaction with hexafluoroacetylacetone **4**. As shown in Scheme 3, various substituents bearing electron-donating groups (Me, MeO) or electron-withdrawing groups (F, Cl, Br, CN, NO_2) on the aromatic ring of the ketoxime-enoate were well-tolerated, leading to the formation of desired pyridines **5b**–**j** in moderate to good yields. The results indicated that no significant electronic effects or steric hindrances were observed. Biphenyl, *β*-

naphthyl and thiophenyl-substituted ketoxime-enoate also proceeded smoothly as well to give the corresponding products (**5k**−**m**).

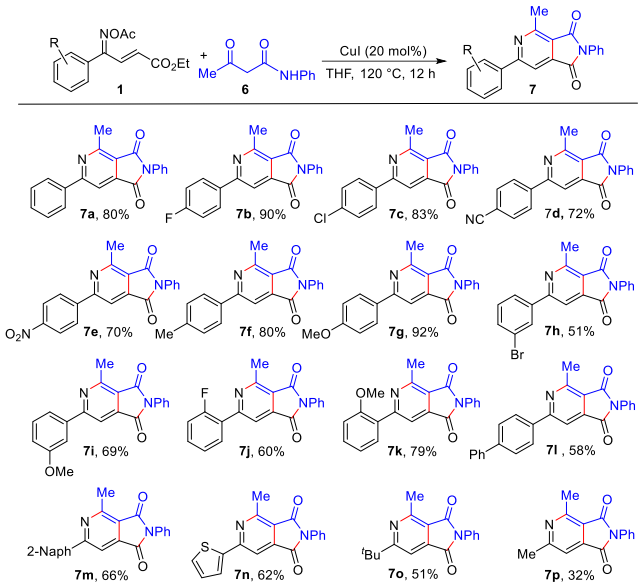
Scheme 3. Reactions of Various Ketoxime-enoates with Hexafluoroacetylacetone[a]



[a]Reaction conditions: **1** (0.4 mmol), **4** (0.2 mmol) and CuI (20 mol%) in THF (2 mL) at 120 ℃ for 12 h under N_2. Isolated yields.

When ketoxime-enoates **1** and acetoacetanilide **6** were conducted under the stand conditions, the bicyclic fused pyridines were synthesized instead of the previous products. Various ketoxime-enoates **1** exhibited good functional-group tolerance, irrespective of the position and electronic property of substituents on the phenyl moiety, and all performed well for the transformation to deliver the desired bicyclic products in high to excellent yield (Scheme 4). In addition, biphenyl, *β*-naphthyl, thiophenyl and alkyl (^{t}Bu, Me) substituted ketoxime-enoates were also applicable in this transformation, providing access to functionalized pyridines **7l**−**p** in 32−66% yields, respectively.

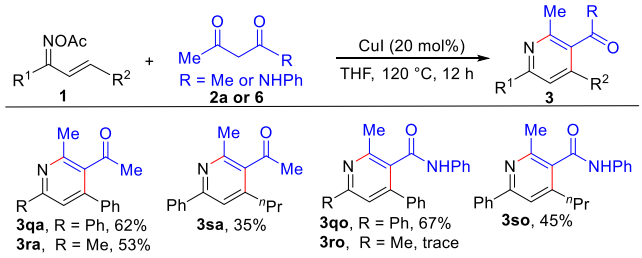
Scheme 4. Reactions of Various Ketoxime-enoates with Acetoacetanilide[a]



[a]Reaction conditions: **1** (0.4 mmol), **6** (0.2 mmol) and CuI (20 mol%) in THF (2 mL) at 120 ℃ for 12 h under N_2. Isolated yields.

To further develop the scope of this reaction, other types of ketoxime acetates were also examined in the [4+2] annulation protocol (Scheme 5). Chalcone, benzalacetone and 1-phenylhex-2-en-1-one derived oxime acetates were all amenable substrates, furnishing the desired pyridines with the coupling of acetylacetone **2a** or acetoacetanilide **6** in moderate yields. However, hexafluoroacetylacetone **4** was inefficient coupling partner under the standard conditions (not shown).

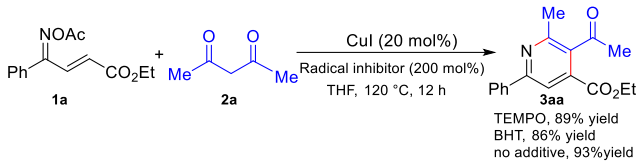
Scheme 5. Reactions of Ketoxime Acetates with 2a or 6[a]



[a]Reaction conditions: **1** (0.4 mmol), **2a** or **6** (0.2 mmol) and CuI (20 mol%) in THF (2 mL) at 120 ℃ for 12 h under N_2. Isolated yields.

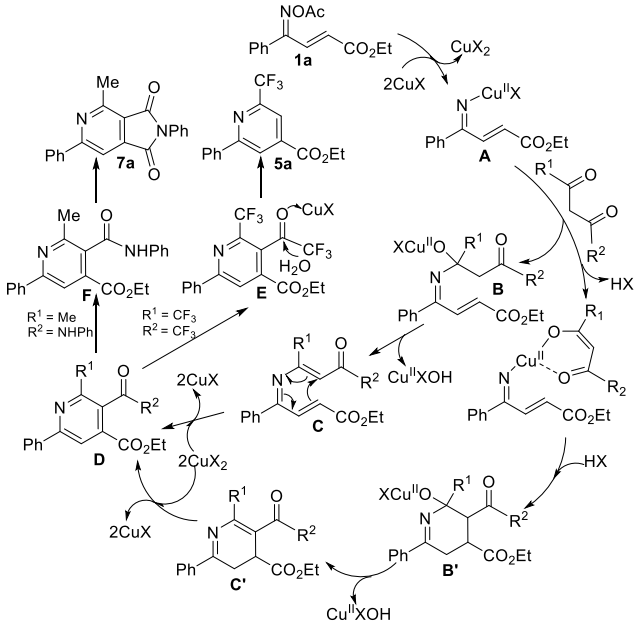
To gain more insight into the reaction mechanism, the radical scavenger TEMPO or BHT was added to the reaction system, while pyridine **3a** was still obtained without obvious inhibition or sluggishness (Scheme 6), and no radical capture intermediate was detected, thus indicating an ionic pathway instead of the radical process.

Scheme 6. Mechanistic Studies



Based on the experimental results and previous studies, the tentative mechanism is postulated in Scheme 7 to account for the construction of diverse pyridines. Oxidation of Cu(I) salt by ketoxime-enoate **1a** through cleavage of the N−O bond generates iminylcopper(II) intermediate **A** together with a Cu(II) species. Subsequently, nucleophilic addition of **A** to the carbonyl of 1,3-diketone gives intermediate **B** followed by *β*-elimination to afford the aza-hexa-1,3,5-triene intermediate **C**. Then the intermediate **C** undergoes thermal 6π-electrocyclization and rapid oxidation by the Cu(II) species[16a] to furnish the pyridine derivatives **D, E** and **F**, while regenerating the copper(I) catalyst for catalytic cycle. Additionally, an alternative approach might still be valid for the pyridines synthesis. The iminylcopper(II) intermediate **A** deprotonates 1,3-diketone to generate *α,β*-unsaturated imine and stabilizes copper enolate of 1,3-diketone. Next, the copper enolate undergoes Michael addition to unsaturated imine, followed by intramolecular N-nucleophilic attack of the carbonyl of 1,3-diketone to generate intermediate **B′**. Subsequent elimination of Cu(II) hydroxide and oxidation by the Cu(II) species would furnish the pyridine derivatives.[6f-h] Finally, deacetylation of the pyridine **E** assisted by Cu(I) salt[17] in the prensence of water formed the 2-CF_3 substituted pyridine **5a** and polycyclic pyridine **7a** was obtained through amidation cyclization of the pyridine **F**.

Scheme 7. Proposed Mechanism of the Copper-Catalyzed Pyridines Synthesis



In summary, we have developed the copper-catalyzed formal [4+2] annulation of *α,β*-unsaturated ketoxime acetates with 1,3-dicarbonyl compounds, providing access to monocyclic and bicyclic fused pyridines with diverse electron-withdrawing groups in generally moderate to good yields. This protocol features operational simplicity, high efficiency and functional group compatibility, representing an alternate route towards the synthesis of pyridine derivatives. Further investigations involving the application of this methodology and novel pyridines design are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all experiments were performed under argon atmosphere. Commercial solvents and reagents were used without further purification. Thin-layer chromatography (TLC) was performed on silica gel plates (60F-254) using UV-light (254 nm). Flash chromatography was conducted on silica gel (200-300 mesh). NMR (400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR) spectra were recorded in $CDCl_3$ with TMS as the internal standard.

Chemical shifts are reported in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quarter; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Ketoxime acetates **1a**,[15] **1q**,[11a] **1b–1p**[16] and **1r–1s**[16] were prepared according to the related literatures (see the Supporting Information for details).

General Procedure for Synthesis of Polysubstituted Pyridine Derivatives. Ketoxime acetates (0.4 mmol, 2.0 equiv), 1,3-dicarbonyl compounds (0.2 mmol, 1.0 equiv) and CuI (7.6 mg, 0.04 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The Schlenk tube was placed under vacuum for 1 min and then N_2 was pumped into it. The solvent THF (2 mL, 0.1 M) was added into the Schlenk tube by syringe. The tube was sealed and magnetically stirred in a preheated 120 ℃ oil bath for 12 h (Caution! The protection shield was needed). Then the reaction tube was allowed to cool to room temperature and the reaction solution was concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel (Petroleum Ether/EtOAc) to give the pyridine derivatives.

Ethyl 3-Acetyl-2-methyl-6-phenylisonicotinate (3aa). White solid; 53 mg, 93% yield; mp 76−78 ℃; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.08 (s, 1H), 8.04 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.53–7.44 (m, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 2.60 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.7, 165.0, 157.7, 154.1, 138.1, 135.5, 135.3, 129.7, 128.9, 127.1, 117.3, 62.4, 31.8, 22.6, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$ 284.1281, found 284.1294.

Ethyl 3-Acetyl-6-(4-fluorophenyl)-2-methylisonicotinate (3ba). Yellow solid; 45 mg, 75% yield; mp 80−83 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.07–7.99 (m, 3H), 7.15 (t, *J* = 8.7 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.5, 165.1 (d, *J* = 250.6 Hz), 164.9, 156.5, 154.2, 135.4, 134.2 (d, *J* = 3.2 Hz), 129.0 (d, *J* = 8.5 Hz), 116.8, 115.9 (d, *J* = 21.8 Hz), 62.5, 31.8, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_3F$ $[M+H]^+$ 302.1187, found 302.1203.

Ethyl 3-Acetyl-6-(4-chlorophenyl)-2-methylisonicotinate (3ca). White solid; 58 mg, 91% yield; mp 73−74 ℃; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.04 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 2.59 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.4, 164.8, 156.3, 154.3, 136.4, 135.9, 135.7, 135.5, 129.1, 128.3, 62.5, 31.8, 22.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_3Cl$ $[M+H]^+$ 318.0891, found 318.0917.

Ethyl 3-Acetyl-6-(4-cyanophenyl)-2-methylisonicotinate (3da). White solid; 37 mg, 60% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 124−125 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (d, *J* = 8.4 Hz, 2H), 8.11 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 2.59 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.0, 164.5, 155.2, 154.8, 142.0, 136.7, 135.6, 132.7, 127.6, 118.6, 117.7, 113.1, 62.7, 31.7, 22.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{17}N_2O_3$ $[M+H]^+$ 309.1234, found 309.1249.

Ethyl 3-Acetyl-2-methyl-6-(4-nitrophenyl)isonicotinate (3ea). Light yellow solid; 43 mg, 66% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 127−128 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.34 (d, *J* = 8.9 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 8.15 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 2.60 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz,

Chloroform-*d*): δ 203.9, 164.5, 154.9, 154.8, 148.6, 143.7, 136.9, 135.7, 127.9, 124.1, 117.9, 62.7, 31.7, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}N_2O_5$ $[M+H]^+$ 329.1132, found 329.1151.

Ethyl 3-Acetyl-2-methyl-6-(p-tolyl)isonicotinate (3fa). Light yellow solid; 51 mg, 85% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 66–67 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.04 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 2.58 (s, 3H), 2.41 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.7, 165.1, 157.6, 154.0, 139.8, 135.3, 135.1, 129.6, 126.9, 116.9, 62.4, 31.8, 22.6, 21.4, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$ 298.1438, found 298.1452.

Ethyl 3-Acetyl-6-(4-methoxyphenyl)-2-methylisonicotinate (3ga). Light yellow solid; 58 mg, 93% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 8:1); mp 93–95 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.03–7.98 (m, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.57 (s, 6H), 1.40 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.8, 165.1, 161.0, 157.2, 153.9, 135.3, 134.7, 130.6, 128.4, 116.4, 114.2, 62.3, 55.4, 31.8, 22.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1387, found 314.1409.

Ethyl 3-Acetyl-6-(3-bromophenyl)-2-methylisonicotinate (3ha). Yellow oil; 51 mg, 70% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.14 (s, 1H), 7.96 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.52–7.46 (m, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 2.51 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.3, 164.7, 155.9, 154.4, 140.0, 136.1, 135.5, 132.5, 130.4, 130.1, 125.6, 123.2, 117.2, 62.5, 31.7, 22.5, 14.1 ppm; HRMS (ESI, ESI-TOF): m/z calcd for $C_{17}H_{17}NO_3Br$ $[M+H]^+$ 362.0386, found 362.0403.

Ethyl 3-Acetyl-6-(3-methoxyphenyl)-2-methylisonicotinate (3ia). White solid; 38 mg, 60% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 106–107 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.06 (s, 1H), 7.63–7.56 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 2.60 (s, 3H), 2.59 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.6, 165.0, 160.1, 157.4, 154.1, 139.5, 135.6, 135.3, 129.9, 119.5, 117.4, 115.4, 112.5, 62.4, 55.4, 31.8, 22.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1387, found 314.1408.

Ethyl 3-Acetyl-6-(2-fluorophenyl)-2-methylisonicotinate (3ja). White solid; 43 mg, 72% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 89–90 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.15 (s, 1H), 7.99 (td, *J* = 7.8, 1.6 Hz, 1H), 7.42 (ddd, *J* = 13.3, 6.2, 1.6 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.22–7.16 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 2.61 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.4, 164.9, 161.8 (d, *J* = 251.4 Hz), 154.1, 153.6 (d, *J* = 2.1 Hz), 135.9, 135.0, 131.2 (d, *J* = 8.6 Hz), 131.0 (d, *J* = 2.5 Hz), 126.3 (d, *J* = 11.4 Hz), 124.7 (d, *J* = 3.6 Hz), 121.3 (d, *J* = 9.8 Hz), 116.4 (d, *J* = 22. 8 Hz), 62.4, 31.8, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NO_3F$ $[M+H]^+$ 302.1187, found 302.1203.

Ethyl 3-Acetyl-6-(2-methoxyphenyl)-2-methylisonicotinate (3ka). White solid; 54 mg, 86% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 100–102 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 (s, 1H), 7.77 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.38 (td, *J* = 8.3, 1.8 Hz, 1H), 7.12–6.94 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.58 (s, 3H), 2.58 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.8, 165.2, 157.1, 156.4, 153.5, 135.0, 134.3, 131.1, 130.6, 127.8, 122.0, 121.2, 111.5, 62.2, 55.7, 31.8, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1387, found 314.1407.

Ethyl 6-([1,1'-Biphenyl]-4-yl)-3-acetyl-2-methylisonicotinate (3la). White solid; 63 mg, 88% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 115–116 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.15 (s, 1H), 8.13 (s, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 2.61 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.6, 165.0, 157.1, 154.2, 142.4, 140.4, 136.9, 135.5, 135.4, 128.9, 127.7, 127.6, 127.5, 127.1, 117.1, 62.4, 31.8, 22.6, 14.1 ppm; HRMS (ESI, ESI-TOF): m/zcalcd for $C_{23}H_{22}NO_3$ $[M+H]^+$ 360.1594, found 360.1583.

Ethyl 3-Acetyl-2-methyl-6-(naphthalen-2-yl)isonicotinate (3ma). White solid; 53 mg, 80% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 130–132 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.53 (s, 1H), 8.23–8.14 (m, 2H), 7.96 (t, *J* = 8.4 Hz, 2H), 7.87 (dd, *J* = 5.9, 3.3 Hz, 1H), 7.52 (dd, *J* = 6.2, 3.2 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.63 (d, *J* = 15.3 Hz, 6H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 204.5, 165.0, 157.4, 154.2, 135.5, 135.4, 135.3, 134.0, 133.4, 128.8, 128.6, 127.7, 126.9, 126.8, 126.5, 124.4, 117.4, 62.5, 31.8, 22.6, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.1438, found 334.1462.

Ethyl 3-Acetyl-2-methyl-6-(thiophen-2-yl)isonicotinate (3na). Yellow solid; 45 mg, 78% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 83–84 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.94 (s, 1H), 7.66 (d, *J* = 3.7 Hz, 1H), 7.43 (d, *J* = 5.0 Hz, 1H), 7.14–7.09 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 2.53 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 204.3, 164.8, 154.2, 152.8, 143.5, 135.3, 135.1, 128.7, 128.2, 125.7, 115.6, 62.5, 31.8, 22.4, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{16}NO_3S$ $[M+H]^+$ 290.0845, found 290.0848.

Ethyl 3-Acetyl-6-(tert-butyl)-2-methylisonicotinate (3oa). Yellow oil; 35 mg, 67% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.63 (s, 1H), 4.35

(q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 2.48 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 9H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 205.2, 169.9, 165.4, 152.7, 134.6, 134.3, 115.6, 62.2, 37.6, 31.7, 29.9, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$ 264.1594, found 264.1595.

Ethyl 2-Ethyl-6-phenyl-3-propionylisonicotinate (3ab). Yellow oil; 34 mg, 54% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.15–8.03 (m, 3H), 7.47 (dt, *J* = 13.9, 7.0 Hz, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.86–2.73 (m, 4H), 1.38 (td, *J* = 7.3, 6.2 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 207.4, 165.0, 159.1, 157.5, 138.2, 135.5, 134.9, 129.6, 128.8, 127.0, 117.1, 62.3, 38.1, 29.0, 14.1, 13.8, 7.8 ppm; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1594, found 312.1599.

Ethyl 3-Benzoyl-2-methyl-6-phenylisonicotinate (3ac). White solid; 45 mg, 65% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 113–114 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.19 (s, 1H), 8.11 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.63–7.57 (m, 1H), 7.55–7.44 (m, 5H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 196.7, 164.8, 157.9, 156.1, 138.1, 137.2, 137.0, 133.6, 132.7, 129.7, 129.0, 128.9, 128.9, 127.1, 117.4, 62.2, 23.1, 13.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{20}NO_3$ $[M+H]^+$ 346.1438, found 346.1456.

Diethyl 2-Methyl-6-phenylpyridine-3,4-dicarboxylate (3ad). White solid; 40 mg, 64% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 66–68 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.96 (dd, *J* = 9.0, 2.3 Hz, 3H), 7.44–7.34 (m, 3H), 4.40–4.29 (m, 4H), 2.61 (s, 3H), 1.32 (td, *J* = 7.2, 3.5 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 168.3, 165.1, 158.1, 156.3, 138.1, 137.2, 129.7, 128.9, 127.2, 126.7, 117.0, 62.2, 61.9, 22.9, 14.1, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1387, found 314.1383.

3-(Tert-butyl) 4-Ethyl 2-methyl-6-phenylpyridine-3,4-dicarboxylate (3ae). White solid; 40 mg, 58% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 93–95 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.02 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.98 (s, 1H), 7.51–7.41 (m, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.72 (s, 3H), 1.64 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.1, 165.2, 157.6, 156.2, 138.2, 137.0, 129.6, 128.8, 127.8, 127.1, 117.0, 82.9, 62.1, 28.0, 22.9, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$ 342.1700, found 342.1703.

3-Allyl 4-Ethyl 2-methyl-6-phenylpyridine-3,4-dicarboxylate (3af). Yellow oil; 32 mg, 49% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.10–7.98 (m, 3H), 7.48 (d, *J* = 7.4 Hz, 3H), 6.05 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.44 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.93–4.84 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.9, 165.0, 158.2, 156.4, 138.0, 137.4, 131.6, 129.8, 128.9, 127.2, 126.3, 119.3, 117.0, 66.6, 62.3, 22.9, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{20}NO_4$ $[M+H]^+$ 326.1387, found 326.1392.

Ethyl 3-Acetyl-6-phenyl-2-(trifluoromethyl)isonicotinate (3ag). White solid; 42 mg, 62% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 15:1); mp 94–96 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.44 (s, 1H), 8.12 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.56–7.51 (m, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.67 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 187.4 (q, *J* = 37.8 Hz), 164.8, 159.9, 156.2, 138.0, 137.4, 130.3, 129.0, 127.3, 127.1, 116.7, 115.7 (q, *J* = 292.3 Hz), 63.3, 22.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{15}NO_3F_3$ $[M+H]^+$ 338.0999, found 338.1008.

Ethyl 3-(Furan-2-carbonyl)-6-phenyl-2-(trifluoromethyl)isonicotinate (3ah). Yellow solid; 58 mg, 75% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 144–146 °C; ^{1}H NMR (400

MHz, Chloroform-*d*): δ 8.52 (s, 1H), 8.17 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.59 (s, 1H), 7.57–7.52 (m, 3H), 7.14 (s, 1H), 6.59 (dd, *J* = 3.6, 1.6 Hz, 1H), 4.27 (qd, *J* = 7.1, 1.9 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 180.2, 163.7, 158.6, 153.0, 147.1, 145.8 (q, *J* = 34.9 Hz), 140.0, 136.1, 130.9, 130.5, 129.2, 127.3, 122.6, 121.1 (q, *J* = 277.4 Hz), 118.3, 112.8, 62.9, 13.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{15}NO_4F_3$ $[M+H]^+$ 390.0948, found 390.0969.

Ethyl 3-Benzoyl-6-phenyl-2-(trifluoromethyl)isonicotinate (3ai). White solid; 66 mg, 83% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 119–120 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.55 (s, 1H), 8.18 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.62–7.53 (m, 4H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 192.7, 163.6, 158.4, 145.8(q, *J* = 34.8 Hz), 137.2, 136.2, 133.7, 131.8, 130.8, 129.2, 128.9, 128.7, 127.3, 122.7, 121.1 (q, *J* = 277.5 Hz), 76.8, 62.9, 13.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{17}NO_3F_3$ $[M+H]^+$ 400.1155, found 400.1174.

Ethyl 3-Benzoyl-6-(4-chlorophenyl)-2-(trifluoromethyl)isonicotinate (3ci). White solid; 50 mg, 58% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 8:1); mp 131–132 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.51 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 192.4, 163.5, 157.1, 146.0 (q, *J* = 34.9 Hz), 139.9, 137.2, 137.1, 134.6, 133.8, 132.1, 129.4, 128.9, 128.7, 128.6, 122.4, 121.0 (q, *J* = 277.4 Hz), 62.9, 13.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{16}NO_3F_3Cl$ $[M+H]^+$ 434.0765, found 434.0738.

Ethyl 3-Benzoyl-6-(p-tolyl)-2-(trifluoromethyl)isonicotinate (3fi). White solid; 58 mg, 70% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 8:1); mp 124–126 °C; ^1H NMR (400 MHz, Chloroform-

d): δ 8.51 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 192.8, 163.7, 158.4, 145.8 (q, *J* = 34.4 Hz), 141.3, 139.6, 137.2, 133.7, 133.5, 131.4, 129.9, 128.9, 128.7, 127.2, 121.1 (q, *J* = 277.5 Hz), 122.3, 62.8, 21.5, 13.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{19}NO_3F_3$ $[M+H]^+$ 414.1312, found 414.1324.

Ethyl 3-Benzoyl-6-(2-methoxyphenyl)-2-(trifluoromethyl)isonicotinate (3ki). White solid; 52 mg, 60% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 8:1); mp 122–124 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.79 (s, 1H), 8.05 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 3H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 192.9, 163.9, 157.6, 157.2, 145.3 (q, *J* = 34.6 Hz), 138.5, 137.3, 133.6, 131.8, 131.5, 131.3, 128.9, 128.7, 127.8, 125.8, 121.4, 121.2 (q, *J* = 277.4 Hz), 111.6, 62.6, 55.7, 13.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{19}NO_4F_3$ $[M+H]^+$ 430.1261, found 430.1288.

Ethyl 3-Benzoyl-6-(naphthalen-2-yl)-2-(trifluoromethyl)isonicotinate (3mi). Yellow solid; 58 mg, 65% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 129–131 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.66 (d, *J* = 7.3 Hz, 2H), 8.28 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.92–7.87 (m, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.62–7.54 (m, 3H), 7.48 (t, *J* = 7.8 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 192.7, 163.7, 158.3, 145.9 (q, *J* = 34.7 Hz), 139.7, 137.2, 134.5, 133.7, 133.5, 133.3, 131.7, 129.1, 129.1, 128.9, 128.8, 127.8, 127.6, 127.5, 126.8, 124.0, 122.9, 121.2 (q, *J* = 277.5 Hz), 62.9, 13.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{19}NO_3F_3$ $[M+H]^+$ 450.1312, found 450.1326.

Ethyl 5-Oxo-2-phenyl-5,6,7,8-tetrahydroquinoline-4-carboxylate (3aj). White solid; 40 mg, 68% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 114–115 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.08 – 8.02 (m, 2H), 7.60 (s, 1H), 7.49 (dd, *J* = 5.2, 2.0 Hz, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.24 (t, *J* = 6.2 Hz, 2H), 2.76–2.70 (m, 2H), 2.26–2.20 (m, 2H), 1.41 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.5, 168.8, 164.6, 160.7, 142.9, 137.6, 130.5, 129.0, 127.5, 122.8, 116.9, 62.3, 38.6, 33.2, 21.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281, found 296.1288.

Ethyl 5-Oxo-2-phenyl-5,8-dihydro-6H-pyrano[3,4-b]pyridine-4-carboxylate (3ak). White solid; 38 mg, 64% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 134–135 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.06 (d, *J* = 3.4 Hz, 2H), 7.73 (s, 1H), 7.55–7.48 (m, 3H), 5.02 (s, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.42 (s, 2H), 1.42 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 192.1, 167.6, 161.7, 161.5, 142.0, 137.1, 131.0, 127.6, 120.3, 117.8, 73.0, 62.6, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}NO_4$ $[M+H]^+$ 298.1074, found 298.1088.

Ethyl 7,7-Dimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinoline-4-carboxylate (3al). White solid; 39 mg, 60% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 100–102 °C; ^{1}H NMR (400 MHz, Chloroform-d): δ 8.05 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.60 (s, 1H), 7.49 (dd, *J* = 5.3, 1.9 Hz, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.14 (s, 2H), 2.60 (s, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 6H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d): δ 196.7, 168.8, 163.2, 161.1, 137.6, 130.5, 129.0, 127.5, 121.9, 116.8, 62.3, 52.2, 47.0, 33.0, 28.3, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$ 324.1594, found 324.1602.

Ethyl 5-Oxo-2-phenyl-5H-indeno[1,2-b]pyridine-4-carboxylate (3am). Yellow solid; 22 mg, 34% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 5:1); mp 109–110 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.79 (s, 1H), 7.74 (d, *J*

= 7.4 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.1 Hz, 3H), 7.47 (t, *J* = 7.5 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 189.0, 166.0, 165.5, 162.1, 142.8, 138.2, 137.7, 135.4, 135.1, 131.4, 130.6, 129.0, 127.5, 124.1, 123.1, 121.2, 118.3, 62.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{16}NO_3$ $[M+H]^+$ 330.1125, found 330.1126.

Ethyl 3-Benzoyl-2,6-diphenylisonicotinate (3an). White solid; 34 mg, 42% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); mp 97–99 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.20 (s, 1H), 8.10 (d, *J* = 6.9 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.45 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.41 (s, 1H), 7.40–7.34 (m, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.14 (dd, *J* = 4.5, 2.3 Hz, 3H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.00 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 196.4, 165.3, 158.0, 157.3, 139.3, 139.1, 137.8, 137.5, 133.2, 132.3, 130.0, 129.4, 129.0, 129.0, 128.8, 128.5, 128.1, 127.3, 118.1, 62.4, 13.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$ 408.1594, found 408.1600.

Ethyl 2,6-Diphenylisonicotinate (3an'). White solid; 18 mg, 30% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 105–107 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.26 (s, 2H), 8.21 (dd, *J* = 8.3, 1.3 Hz, 4H), 7.56–7.45 (m, 6H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 165.6, 157.8, 139.5, 138.7, 129.5, 128.8, 127.1, 117.8, 61.9, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{18}NO_2$ $[M+H]^+$ 304.1332, found 304.1344.

1-(2-Methyl-4,6-diphenylpyridin-3-yl)ethan-1-one (3qa). White solid; 35 mg, 62% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 94–96 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.06–8.02 (m, 2H), 7.58 (s, 1H), 7.49–7.40 (m, 8H), 2.63 (s, 3H), 2.01 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 206.4, 157.0, 154.1, 147.3, 138.8, 138.4, 134.5, 129.3, 129.0, 129.0, 128.8,

128.5, 127.1, 118.6, 32.1, 23.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{18}NO$ $[M+H]^+$ 288.1383, found 288.1384.

1-(2,6-Dimethyl-4-phenylpyridin-3-yl)ethan-1-one (3ra). Yellow oil; 24 mg, 53% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.44–7.41 (m, 3H), 7.33 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.02 (s, 1H), 2.58 (s, 3H), 2.52 (s, 3H), 1.95 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 206.5, 158.2, 153.4, 146.9, 138.2, 133.5, 129.0, 128.9, 128.4, 121.2, 32.2, 24.4, 22.7 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found 226.1224.

1-(2-Methyl-6-phenyl-4-propylpyridin-3-yl)ethan-1-one (3sa). Yellow oil; 18 mg, 35% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.46 (q, *J* = 7.7, 7.1 Hz, 3H), 7.41 (s, 1H), 2.55 (d, *J* = 2.3 Hz, 6H), 2.53 (d, *J* = 8.7 Hz, 2H), 1.67 (dq, *J* = 15.1, 7.5 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 206.7, 156.9, 152.5, 147.6, 139.1, 135.9, 129.1, 128.8, 127.1, 118.6, 34.9, 32.7, 23.9, 22.9, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{20}NO$ $[M+H]^+$ 254.1539, found 254.1540.

2-Methyl-N,4,6-triphenylnicotinamide (3qo). White solid; 49 mg, 67% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 239–240 ºC; ^{1}H NMR (400 MHz, Chloroform-d): δ 8.03 (d, *J* = 6.9 Hz, 2H), 7.63–7.51 (m, 3H), 7.51–7.36 (m, 6H), 7.24 (d, *J* = 9.3 Hz, 4H), 7.14–7.02 (m, 2H), 2.78 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.0, 157.5, 156.4, 147.7, 138.8, 138.0, 137.1, 129.4, 129.0, 128.9, 128.1, 127.2, 125.0, 120.5, 118.6, 23.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{21}N_2O$ $[M+H]^+$ 365.1648, found 365.1658.

2-Methyl-N,6-diphenyl-4-propylnicotinamide (3so). White solid; 30 mg, 45% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 15:1); mp 205–206 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*): δ

7.96 (d, *J* = 6.9 Hz, 2H), 7.86 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.1 Hz, 2H), 7.45–7.39 (m, 3H), 7.37 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 2.65 (s, 3H), 2.55–2.50 (m, 2H), 1.66 (dq, *J* = 14.9, 7.5 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.2, 157.1, 154.4, 149.3, 139.0, 137.6, 131.2, 129.3, 129.2, 128.8, 127.1, 125.0, 120.0, 118.3, 34.8, 23.6, 22.8, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{23}N_2O$ $[M+H]^+$ 331.1805, found 331.1816.

Ethyl 2-Phenyl-6-(trifluoromethyl)isonicotinate (5a). White solid; 50 mg, 85% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 66–68 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.48 (s, 1H), 8.15–8.11 (m, 3H), 7.51 (t, *J* = 7.3 Hz, 3H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 163.1, 157.9, 148.0 (q, *J* = 35.3 Hz), 139.2, 135.9, 129.3, 128.0, 126.2, 121.2, 120.3 (q, *J* = 275.6 Hz), 116.8 (q, *J* = 2.8 Hz), 61.4, 13.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{13}NO_2F_3$ $[M+H]^+$ 296.0893, found 296.0907.

Ethyl 2-(4-Fluorophenyl)-6-(trifluoromethyl)isonicotinate (5b). Light yellow solid; 43 mg, 68% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 100–101 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 8.06–8.02 (m, 3H), 7.11 (t, *J* = 8.6 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 165.5 (d, *J* = 252 Hz), 164.0, 157.8, 149.1 (q, *J* = 35.4 Hz), 140.4, 133.1 (d, *J* = 3.1 Hz), 129.3 (d, *J* = 8.7 Hz), 121.9, 121.3 (q, *J* = 275.5 Hz), 117.8 (q, *J* = 2.7 Hz), 116.2 (d, *J* = 21.9 Hz), 62.5, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}NO_2F_4$ $[M+H]^+$ 314.0799, found 314.0819.

Ethyl 2-(4-Chlorophenyl)-6-(trifluoromethyl)isonicotinate (5c). White solid; 40 mg, 61% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 96–97 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.43 (s, 1H), 8.13 (s, 1H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 163.9, 157.7,

149.2 (q, *J* = 35.4 Hz), 140.4, 136.6, 135.3, 129.2, 128.5, 121.9, 121.2 (q, *J* = 275.5 Hz), 118.1 (q, *J* = 2.8 Hz), 62.5, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}NO_2F_3Cl$ $[M+H]^+$ 330.0503, found 330.0518.

Ethyl 2-(4-Cyanophenyl)-6-(trifluoromethyl)isonicotinate (5d). White solid; 40 mg, 62% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 118–119 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.52 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 2H), 8.21 (d, *J* = 1.1 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.7, 156.7, 149.5 (q, *J* = 35.6 Hz), 140.9, 132.8, 127.8, 122.7, 121.1 (q, *J* = 275.7 Hz), 119.1 (q, *J* = 2.7 Hz), 118.4, 113.9, 62.7, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{12}N_2O_2F_3$ $[M+H]^+$ 321.0845, found 321.0862.

Ethyl 2-(4-Nitrophenyl)-6-(trifluoromethyl)isonicotinate (5e). White solid; 40 mg, 59% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 123–124 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.55 (s, 1H), 8.38–8.29 (m, 4H), 8.23 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.6, 156.3, 149.6 (q, *J* = 35.7 Hz), 148.9, 142.6, 140.9, 128.2, 124.2, 122.9, 121.1 (q, *J* = 275.7 Hz), 119.3 (q, *J* = 2.7 Hz), 62.7, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}N_2O_4F_3$ $[M+H]^+$ 341.0744, found 341.0768.

Ethyl 2-(p-Tolyl)-6-(trifluoromethyl)isonicotinate (5f). White solid; 50 mg, 81% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 81–83 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.44 (s, 1H), 8.09 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.1, 157.9, 147.9 (q, *J* = 35 Hz), 139.6, 139.1, 133.2, 128.7, 126.0, 120.8, 120.3 (q, *J* = 275.5 Hz), 116.4 (q, *J* = 2.8 Hz), 61.3, 20.3, 13.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_2F_3$ $[M+H]^+$ 310.1049, found 310.1062.

Ethyl 2-(4-Methoxyphenyl)-6-(trifluoromethyl)isonicotinate (5g). White solid; 42 mg, 65% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 81–82 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.40 (s, 1H), 8.08 (d, *J* = 9.0 Hz, 2H), 8.04 (d, *J* = 1.1 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 4.47 (q, 2H), 3.87 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.3, 161.5, 158.6, 148.9 (q, *J* = 35.1 Hz), 140.0, 129.5, 128.7, 121.4, 121.4 (q, *J* = 275.6 Hz), 116.9 (q, *J* = 2.8 Hz), 114.4, 62.3, 55.4, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_3F_3$ $[M+H]^+$326.0999, found 326.1022.

Ethyl 2-(3-Bromophenyl)-6-(trifluoromethyl)isonicotinate (5h). White solid; 48 mg, 65% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 103–105 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.44 (s, 1H), 8.27 (t, *J* = 1.7 Hz, 1H), 8.16 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.9, 157.3, 149.2 (q, *J* = 35.6 Hz), 140.5, 138.9, 133.3, 130.5, 130.3, 125.8, 123.3, 122.3, 121.2 (q, *J* = 275.7 Hz), 118.5 (q, *J* = 2.8 Hz), 62.6, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{12}NO_2F_3Br$ $[M+H]^+$ 373.9998, found 374.0000.

Ethyl 2-(3-Methoxyphenyl)-6-(trifluoromethyl)isonicotinate (5i). White solid; 52 mg, 80% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 154–155 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.46 (s, 1H), 8.13 (s, 1H), 7.74–7.64 (m, 2H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.08–7.00 (m, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.1, 160.2, 158.7, 149.0 (q, *J* = 35.3 Hz), 140.2, 138.4, 130.0, 122.4, 121.3 (q, *J* = 275.5 Hz), 119.6, 118.0 (q, *J* = 2.8 Hz), 116.1, 112.7, 62.4, 55.5, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_3F_3$ [M+H]+ 326.0999, found 326.1013.

Ethyl 2-(2-Methoxyphenyl)-6-(trifluoromethyl)isonicotinate (5j). White solid; 39 mg, 60% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 81–83 °C; ^{1}H NMR (400 MHz, Chloroform-

d): δ 8.66 (s, 1H), 8.11 (s, 1H), 7.93 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.47–7.40 (m, 1H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 164.4, 157.8, 157.3, 148.6 (q, *J* = 35.2 Hz), 139.0, 131.4, 131.3, 127.3, 126.7, 121.4 (q, *J* = 275.4 Hz), 121.3, 117.4 (q, *J* = 2.9 Hz), 111.5, 62.2, 55.6, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{15}NO_3F_3$ $[M+H]^+$ 326.0999, found 326.1014.

Ethyl 2-([1,1'-Biphenyl]-4-yl)-6-(trifluoromethyl)isonicotinate (5k). White solid; 30 mg, 40% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 152–154 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.53 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 2H), 8.14 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 164.2, 158.6, 149.1 (q, *J* = 35.3 Hz), 143.1, 140.3, 140.2, 135.8, 128.9, 127.9, 127.7, 127.7, 127.2, 122.1, 121.3 (q, *J* = 275.6 Hz), 117.8 (q, *J* = 2.8 Hz), 117.8, 62.5, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}NO_2F_3$ $[M+H]^+$ 372.1206, found 372.1195.

Ethyl 2-(Naphthalen-2-yl)-6-(trifluoromethyl)isonicotinate (5l). White solid; 57 mg, 82% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); mp 191–192 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.49 (s, 2H), 8.14 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.03 (d, *J* = 1.1 Hz, 1H), 7.86 (t, *J* = 8.2 Hz, 2H), 7.79–7.75 (m, 1H), 7.46–7.40 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 164.1, 158.8, 149.1 (q, *J* = 35.3 Hz), 140.3, 134.2, 133.3, 129.0, 128.8, 127.7, 127.3, 127.2, 126.6, 124.2, 122.4, 121.4 (q, *J* = 275.6 Hz), 117.8 (q, *J* = 2.8 Hz), 62.4, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{15}NO_2F_3$ $[M+H]^+$ 346.1049, found 346.1065.

Ethyl 2-(Thiophen-2-yl)-6-(trifluoromethyl)isonicotinate (5m). White solid; 31mg, 52% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 80–82 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.32 (s, 1H), 8.01 (d, *J* = 0.9 Hz, 1H), 7.78 (d, *J* = 3.7 Hz, 1H), 7.49 (d, *J* = 5.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.0, 154.3, 148.9(q, *J* = 35.4 Hz), 142.4, 140.1, 129.6, 128.4, 126.9, 121.1 (q, *J* = 275.6 Hz), 120.8, 117.3 (q, *J* = 2.8 Hz), 62.5, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{13}H_{11}NO_2F_3S$ $[M+H]^+$ 302.0457, found 302.0475.

4-Methyl-2,6-Diphenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7a). White solid; 50 mg, 80% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 166–168 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.14 (dd, *J* = 7.3, 2.1 Hz, 2H), 8.09 (s, 1H), 7.56–7.50 (m, 5H), 7.44 (d, *J* = 7.7 Hz, 3H), 3.01 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.2, 166.1, 162.8, 157.5, 141.0, 137.7, 131.4, 130.8, 129.2, 129.1, 128.4, 127.7, 126.6, 120.5, 111.6, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{15}N_2O_2$ $[M+H]^+$ 315.1128, found 315.1140.

6-(4-Fluorophenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7b). Light yellow solid; 60 mg, 90% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 180–182 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.16 (dd, *J* = 8.8, 5.4 Hz, 2H), 8.04 (s, 1H), 7.56–7.48 (m, 2H), 7.43 (dd, *J* = 7.7, 1.7 Hz, 3H), 7.21 (t, *J* = 8.6 Hz, 2H), 2.99 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.1, 166.0, 165.8(d, *J* = 252.8 Hz), 163.3, 161.6, 141.1, 133.9(d, *J* = 3.2 Hz), 131.3, 129.8 (d, *J* = 8.7 Hz) ,129.2, 128.5, 126.6, 120.5, 116.3 (d, *J* = 21.9 Hz), 111.2, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}N_2O_2F$ $[M+H]^+$ 333.1034, found 333.1056.

6-(4-Chlorophenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7c). White solid; 58 mg, 83% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 238–239 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.10 (d, *J* = 8.5 Hz, 2H), 8.06 (s, 1H), 7.51 (t, *J* = 7.9 Hz, 4H), 7.44

(d, J = 7.9 Hz, 3H), 3.00 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.0, 166.0, 161.5, 157.7, 141.2, 137.1, 136.1, 131.3, 129.3, 129.2, 128.9, 128.5, 126.6, 120.8, 111.3, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}N_2O_2Cl$ $[M+H]^+$ 349.0755, found 349.0738.

4-(4-Methyl-1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)benzonitrile (7d). Light yellow solid; 49 mg, 72% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 263–265 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.28 (d, J = 8.5 Hz, 2H), 8.15 (s, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.45 (t, J = 7.4 Hz, 3H), 3.03 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.8, 165.7, 160.4, 158.0, 141.6, 141.4, 132.8, 131.2, 129.3, 128.6, 128.2, 126.5, 121.7, 118.4, 114.2, 112, 21.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{14}N_3O_2$ calcd for $C_{21}H_{14}N_3O_2$ $[M+H]^+$ 340.1081, found 340.1093.

4-Methyl-6-(4-nitrophenyl)-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7e). Yellow solid; 50 mg, 70% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 10:1); mp 195–197 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.36 (q, J = 9.0 Hz, 4H), 8.19 (s, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.45 (t, J = 7.0 Hz, 3H), 3.05 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.8, 165.7, 160.0, 158.1, 149.1, 143.3, 141.4, 131.2, 129.3, 128.6, 128.6, 126.5, 124.2, 121.9, 112.3, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}N_3O_4$ $[M+H]^+$ 360.0979, found 360.0990.

4-Methyl-2-phenyl-6-(p-tolyl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7f). Light yellow solid; 53 mg, 80% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 204–206 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.08–8.02 (m, 3H), 7.55–7.49 (m, 2H), 7.44 (d, J = 8.2 Hz, 3H), 7.32 (d, J = 8.0 Hz, 2H), 2.99 (s, 3H), 2.43 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.2, 166.2, 162.7, 157.4, 141.2, 140.9, 135.0, 131.5, 129.8, 129.2, 128.3, 127.6, 126.6, 120.1, 111.1, 21.6, 21.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}N_2O_2$ $[M+H]^+$ 329.1290, found 329.1304.

6-(4-Methoxyphenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7g). Yellow solid; 63 mg, 92% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 175–177 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.14 (d, *J* = 8.9 Hz, 2H), 8.04 (s, 1H), 7.55–7.50 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 3H), 7.04 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H), 2.98 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.3, 166.3, 162.3, 162.0, 157.4, 140.9, 131.5, 130.3, 129.2, 129.2, 128.3, 126.6, 119.6, 114.5, 110.6, 55.5, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}N_2O_3$ $[M+H]^+$ 345.1234, found 345.1249.

6-(3-Bromophenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7h). White solid; 54 mg, 69% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 15:1); mp 191–193 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.33 (s, 1H), 8.05 (d, *J* = 10.9 Hz, 2H), 7.66–7.61 (m, 1H), 7.56–7.50 (m, 2H), 7.47–7.37 (m, 4H), 3.01 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.0, 161.1, 157.7, 141.2, 139.6, 133.6, 131.3, 130.7, 130.6, 129.2, 128.5, 126.6, 126.1, 123.4, 121.1, 111.6, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}N_2O_2Br$ $[M+H]^+$ 393.0233, found 393.0246.

6-(3-Methoxyphenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7i). White solid; 47 mg, 69% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 206–207 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.07 (s, 1H), 7.75 –7.66 (m, 2H), 7.57–7.49 (m, 2H), 7.49–7.39 (m, 4H), 7.06 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.91 (s, 3H), 3.00 (s, 3H) ppm; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 167.2, 166.1, 162.6, 160.3, 157.5, 141.0, 139.1, 131.4, 130.1, 129.2, 128.4, 126.6, 120.6, 120.0, 116.8, 112.8, 111.7, 55.5, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}N_2O_3$ $[M+H]^+$ 345.1234, found 345.1211.

6-(2-Fluorophenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7j). White solid; 40 mg, 60% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); mp 198–200 °C; ^{1}H NMR

(400 MHz, Chloroform-*d*): δ 8.19 (d, *J* = 1.4 Hz, 1H), 8.13 (td, *J* = 7.9, 1.8 Hz, 1H), 7.56–7.46 (m, 3H), 7.46–7.41 (m, 3H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.22 (ddd, *J* = 11.5, 8.3, 0.9 Hz, 1H), 3.02 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.1, 166.0, 162.3 (d, *J* = 252.9 Hz), 158.8 (d, *J* = 2.2 Hz), 157.4, 140.6, 132.2 (d, *J* = 8.8 Hz), 131.4 (d, *J* = 3.5 Hz), 131.4, 129.2, 128.4, 126.6, 126.1 (d, *J* = 10.8 Hz), 124.8 (d, *J* = 3.6 Hz), 121.0, 116.7 (d, *J* = 22.9 Hz), 115.9 (d, *J* = 11.2 Hz), 21.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}N_2O_2F$ $[M+H]^+$ 333.1039, found 333.1072.

6-(2-Methoxyphenyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7k). Yellow solid; 54 mg, 79% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 173–174 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.28 (s, 1H), 7.94 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.56–7.50 (m, 2H), 7.49–7.40 (m, 4H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H), 3.00 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.4, 166.4, 161.8, 157.6, 157.0, 139.7, 131.7, 131.6, 131.5, 129.2, 128.3, 127.4, 126.7, 121.2, 120.1, 116.7, 111.5, 55.7, 21.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}N_2O_3$ $[M+H]^+$ 345.1234, found 345.1257.

6-([1,1'-Biphenyl]-4-yl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7l). White solid; 45 mg, 58% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 245–247 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25 (d, *J* = 8.4 Hz, 2H), 8.16 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.56–7.40 (m, 8H), 3.03 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.2, 166.2, 162.4, 157.6, 143.5, 141.0, 140.1, 136.5, 131.4, 129.2, 129.0, 128.4, 128.1, 128.0, 127.8, 127.2, 126.6, 120.5, 111.4, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{19}N_2O_2$ $[M+H]^+$ 391.1441, found 391.1410.

4-Methyl-6-(naphthalen-2-yl)-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7m). White solid; 48 mg, 66% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 10:1); mp 245–246 °C; ^{1}H NMR

(400 MHz, Chloroform-*d*): δ 8.67 (s, 1H), 8.32–8.25 (m, 2H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.93–7.88 (m, 1H), 7.60–7.52 (m, 4H), 7.46 (d, *J* = 7.7 Hz, 3H), 3.06 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.2, 166.2, 162.7, 157.6, 141.1, 135.0, 134.5, 133.3, 131.4, 129.2, 129.1, 128.9, 128.4, 128.0, 127.8, 127.6, 126.7, 126.6, 124.4, 120.5, 111.7, 21.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{17}N_2O_2$ $[M+H]^+$ 365.1285, found 365.1306.

4-Methyl-2-phenyl-6-(thiophen-2-yl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7n). Yellow solid; 40 mg, 62% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 10:1); mp 246–248 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (s, 1H), 7.81 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.57–7.50 (m, 3H), 7.46–7.40 (m, 3H), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.95 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.9, 166.0, 157.9, 157.6, 143.6, 140.9, 131.3, 130.8, 129.2, 128.7, 128.4, 127.7, 126.6, 119.8, 109.9, 21.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{13}N_2O_2S$ $[M+H]^+$ 321.0692, found 321.0700.

6-(Tert-butyl)-4-methyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7o). Yellow oil; 30 mg, 51% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 20:1); ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.72 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 3H), 2.92 (s, 3H), 1.43 (s, 9H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 176.6, 167.5, 166.7, 156.4, 131.5, 129.2, 128.3, 126.6, 119.6, 110.7, 38.9, 30.0, 21.5 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1441, found 295.1440.

4,6-Dimethyl-2-phenyl-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (7p). White solid; 16 mg, 32% yield; R_f = 0.4 (petroleum ether/ethyl acetate = 15:1); mp 196–197 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.56–7.49 (m, 3H), 7.42 (t, *J* = 9.0 Hz, 3H), 2.93 (s, 3H), 2.75 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.3, 166.2, 165.5, 157.1, 140.4, 131.3, 129.2, 128.4,

126.6, 119.9, 114.7, 25.6, 21.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0972, found 253.0966.

Scale-up Synthesis of Compound 3aa. Ketoxime-enoate **1a** (5.22 g, 20 mmol), acetylacetone **2a** (1 g, 10 mmol) and CuI (379 mg, 2 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The Schlenk tube was placed under vacuum for 1 min and then Ar was pumped into it. The solvent THF (70 mL) was added into the Schlenk tube by syringe. The reaction mixture was stirred at 120 °C for 12 h. Then the reaction tube was allowed to cool to room temperature and the reaction solution was concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel (Petroleum Ether/EtOAc= 10:1) to give the product **3aa** 2.49 g (88% yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ….

NMR spectra of all new compounds (PDF)

X-ray crystallography data for compound **3ai** (CCDC 1958257) (CIF)

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Notes

The authors declare no competing financial interest.

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