JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 01 Jun 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

NH_4I-Triggered [4 + 2] Annulation of α,β-Unsaturated Ketoxime Acetates with N-Acetyl Enamides for the Synthesis of Pyridines

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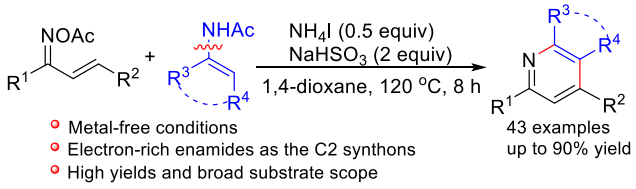
ABSTRACT: The NH_4I-triggered formal [4 + 2] annulation of α,β-unsaturated ketoxime acetates with N-acetyl enamides has been developed. The current protocol employs electron-rich enamides as C2 synthons and enables the efficient and straightforward construction of polysubstituted pyridines in moderate to good yields based on metal-free systems. The reaction tolerates a wide range of functional groups and represents an alternate route towards the synthesis of pyridine derivatives.

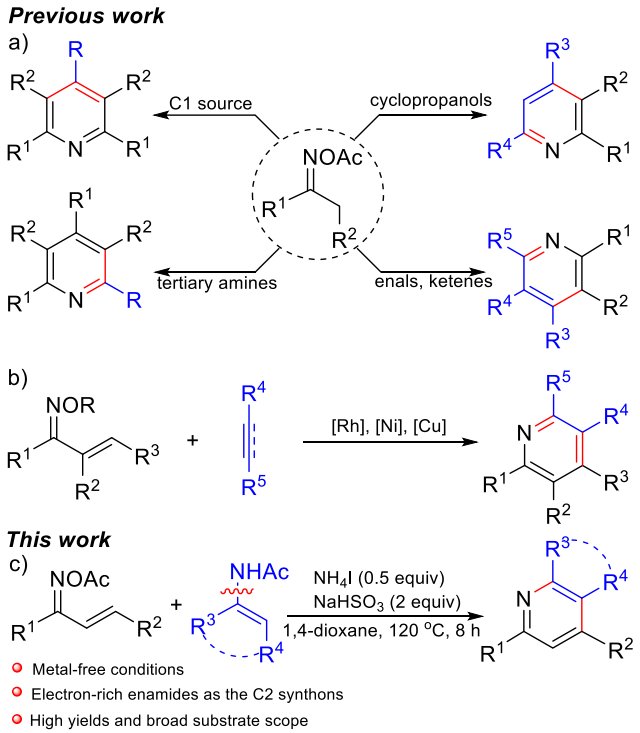


KEYWORDS: Annulation, Metal-free, Ketoxime Acetates, Enamides, Pyridines

Substituted pyridines are privileged scaffolds in medicinal chemistry and versatile building blocks for the construction of natural products, functional materials, agrochemicals and pharmaceutical drugs.[1] Therefore, enormous efforts have been devoted to developing new transformations for constructing various pyridine derivatives.[2] In particularly, the strategy of using oxime derivatives[3] in structurally diverse pyridine construction has gained increased attention in synthetic chemistry. Several representative examples are shown in Scheme 1. For example, oxime acetates bearing *α*-protons have emerged as readily accessible and versatile starting materials for pyridine synthesis. Recent advancements in transition metal-catalyzed or metal-free mediated condensation of two molecules of oxime acetates with a C1 source such as aldehydes, dimethylformamide (DMF), toluenes, N-aryl glycine esters or tertiary amines to give symmetrical pyridines or 2,4-diarylpyridines have been widely investigated by Guan,[4] Chen[5] and Gao groups.[6] Very recently, Han reported pyridine formation through 4-HO-TEMPO-catalyzed cyclization of oxime acetates with cyclopropanols.[7] Furthermore, the Cu-catalyzed or metal-free mediated [3 + 3] annulation of oxime esters with electron-deficient alkenes such as acroleins, *α,β*-unsaturated ketimines/nitriles/ketones in situ generated through Knoevenagel condensation were successively developed by Yoshikai,[8] Cui,[9] Jiang,[10] Deng,[11] and Li groups,[12] providing efficient access to functionalized pyridine derivatives (Scheme 1a). Additionally, transition metal-catalyzed [4 + 2] cycloaddition of *α,β*-unsaturated ketoximes with alkynes[13] or electron-deficient alkenes[14] has also been proved to be a practical strategy for constructing highly substituted pyridines (Scheme 1b). However, most of the reactions require noble transition metal catalysts or various environmentally unfriendly additives. Therefor, the development of environmentally-benign and cost-effective synthetic procedures remain highly desirable. Moreover, the transformation of oxime esters with electron-rich olefins for the construction of pyridines are relatively underdeveloped.[15]

On the other hand, enamides have been thoroughly investigated as C2N1 or C3N1 units for the synthesis of functionalized nitrogen-containing heterocycles via transition-metal-catalyzed coupling reactions,[16] while the strategy using enamides as C2 synthons was less explored.[17] Inspired by the previous works,[18] herein we report an NH_4I-triggered [4 + 2] annulation of *α,β*-unsaturated ketoxime acetates with electron-rich enamides, resulting in the formation of valuable polysubstituted pyridines in moderate to good yields (Scheme 1c).

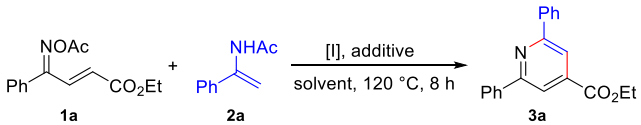
Scheme 1. Utilization of Oxime Derivatives for Diverse Pyridine Construction



At the outset of the investigation, ketoxime-enoate **1a** and N-acetyl enamide **2a** were chosen as model substrates to optimize the reaction conditions. The reaction was first performed in the presence of 50 mol% of NH_4I and 2 equiv of $Na_2S_2O_4$ in THF at 120 °C for 8 h under N_2 atmosphere, and the desired pyridine product **3a** was isolated in 66% yield (Table 1, entry 1). We next examined other iodine reagents including NaI, NIS, TBAI, I_2 and CuI, but none of them gave better results than NH_4I (entries 2−6). Next, the screening of different additives was carried out, with the finding

that $NaHSO_3$ was the optimal choice for the transformation, providing the product **3a** in 75% yield (entry 8). Further investigation of solvents revealed that 1,4-dioxane was more efficient to afford the desired product in 83% yield (entry 11). Notably, either increasing or decreasing the reaction temperature resulted in a slightly lower yield (entries 14 and 15). When the reaction was conducted under an air atmosphere, **3a** could also be afforded in 77% yield (entry 16). To demonstrate the applicability of the method, we scaled up the reaction to 10 mmol and the product **3a** was obtained in 78% yield (entry 17).

Table 1. Optimization of Reaction Conditions[a]



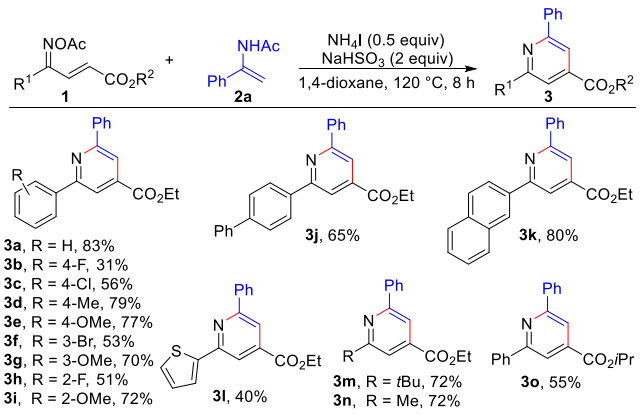
entry	[I]	additive	solvent	yield (%)
1	NH_4I	$Na_2S_2O_4$	THF	66
2	NaI	$Na_2S_2O_4$	THF	20
3	NIS	$Na_2S_2O_4$	THF	14
4	TBAI	$Na_2S_2O_4$	THF	trace
5	I_2	$Na_2S_2O_4$	THF	trace
6	CuI	$Na_2S_2O_4$	THF	trace
7	NH_4I	Pyridine	THF	58
8	NH_4I	$NaHSO_3$	THF	75
9	NH_4I	Et_3N	THF	25
10	NH_4I	$NaHSO_3$	DCE	27
11	NH_4I	$NaHSO_3$	1,4-dioxane	83
12	NH_4I	$NaHSO_3$	MeCN	66
13	NH_4I	$NaHSO_3$	toluene	70
14[b]	NH_4I	$NaHSO_3$	1,4-dioxane	75
15[c]	NH_4I	$NaHSO_3$	1,4-dioxane	77
16[d]	NH_4I	$NaHSO_3$	1,4-dioxane	77
17[e]	NH_4I	$NaHSO_3$	1,4-dioxane	78

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), iodine salt (50 mol%), and additive (2 equiv) in solvent (2 mL) at 120 °C for 8 h under N_2. [b]110 °C. [c]130 °C. [d]under air. [e]10 mmol scale.

The generality of the reaction for various ketoxime-enoates **1** was initially investigated under the optimized reaction conditions. As the results in Scheme 2 revealed, a variety of ketoxime-enoates **1** decorated with functional groups such as halogen (F, Cl, Br), methyl, methoxyl at the

para-, meta-, or ortho-positions on the benzene ring were broadly tolerated and reacted smoothly with N-acetyl enamide **2a** to generate the corresponding products **3a**–**3i** in moderate to good yields. In general, ketoxime-enoates with electron-withdrawing groups showed poor reaction efficiency compared with those with electron-donating groups (**3b** *vs* **3e**, **3f** *vs* **3g**, **3h** *vs* **3i**). Particularly, no desired products were detected when oxime-enoates **1** bearing strong electron-deficient substituents (NO_2, CN) were employed as the coupling substrates. Moreover, other ketoxime-enoates **1** with aromatic rings such as biphenyl, *β*-naphthyl and thienyl also showed good reactivity in this transformation to deliver the desired products without any difficulties (**3j**–**3l**). In addition, alkyl (*t*Bu, Me) substituted ketoxime-enoates also proceeded smoothly to furnish the target products **3m** and **3n** in 72% yield, respectively. However, the steric hindrance arising from the size of ester substituents has critical effects on the reactivity. For example, the substrate with isopropyl ester group slowed down the formation of **3o** in 55% yield.

Scheme 2. Substrate Scope of Ketoxime-enoates[a]

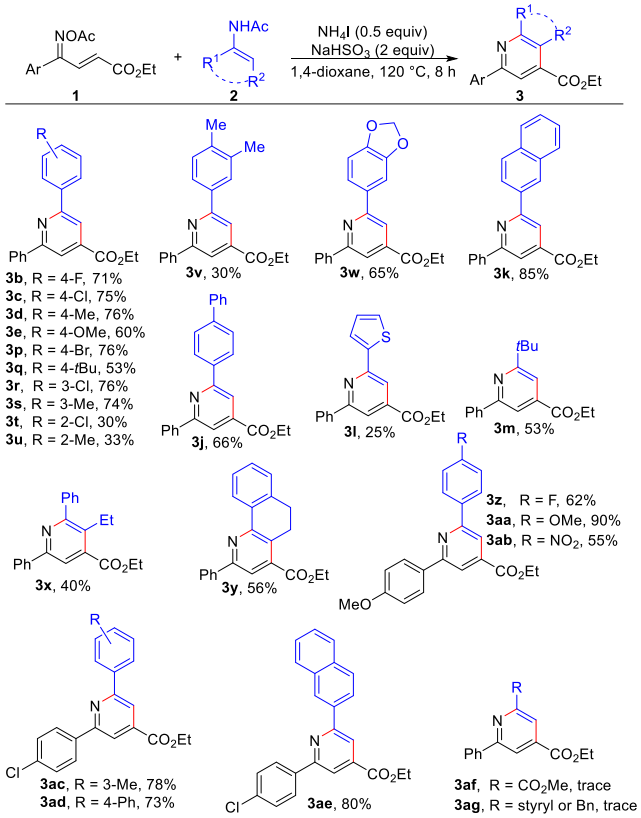


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), NH_4I (50 mol%), and $NaHSO_3$ (2 equiv) in 1,4-dioxane (2 mL) at 120 °C for 8 h under N_2.

Subsequently, we tested the NH_4I-based annulation protocol with respect to the scope of enamides and the results are summarized in Scheme 3. Various aryl enamides **2** bearing a wide

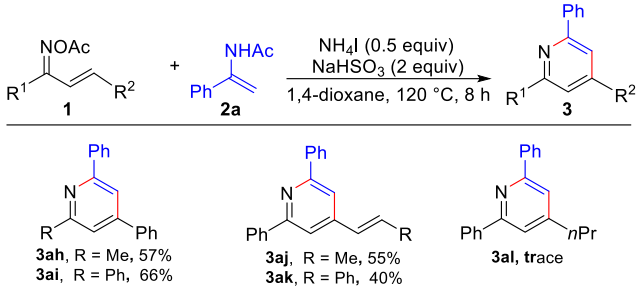
range of functional groups with different substitution patterns on the benzene ring were well tolerated, conferring the corresponding products in moderate to good yields (**3b**−**3u**, **3ac**). It should be noted that increasing steric hindrance posed by the ortho-position led to a significant decrease in reactivity (**3t** and **3u**). Moreover, disubstituted aryl enamides also engaged in this reaction smoothly, affording the desired products (**3v** and **3w**), albeit in lower yields. The current protocol could be further applied to enamides with *β*-naphthyl, biphenyl, thiophenyl and *tert*-butyl substituents (**3k**−**3m**, **3ad**, **3ae**). Importantly, enamides derived from butyrophenone and tetralone were also readily accommodated under the standard reaction conditions, leading to the formation of desired products **3x** and **3y** in 40% and 56% yields, respectively. Notably, the enamide bearing a para-methoxy group gave generally higher yield than those with electron-withdrawing groups such as fluoro and nitro substituents (**3aa** *vs* **3z** and **3ab)**, showing that electronic effect of the substrates had a strong impact on the catalytic reactivity. To our disappointment, no desired products were detected when methyl 2-acetamidoacrylate, styryl and benzyl enamides were employed as the coupling substrates.

Scheme 3. Substrate Scope of N-Acetyl Enamides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), NH_4I (50 mol%), and $NaHSO_3$ (2 equiv) in 1,4-dioxane (2 mL) at 120 °C for 8 h under N_2.

Scheme 4. Further Scope of Ketoxime Acetates[a]

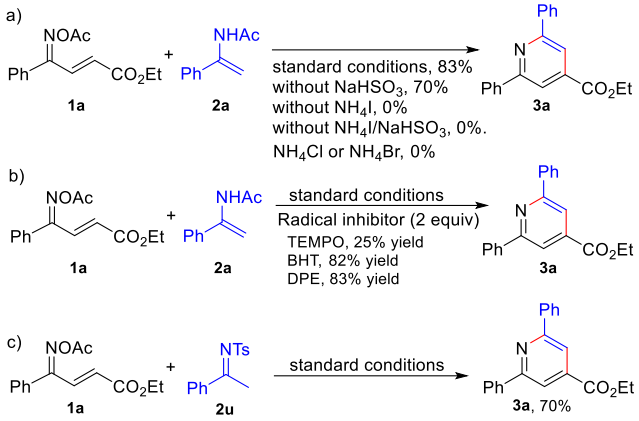


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), NH_4I (50 mol%), and $NaHSO_3$ (2 equiv) in 1,4-dioxane (2 mL) at 120 °C for 8 h under N_2.

To further demonstrate the potential practicality and efficiency of this protocol, benzalacetone- and chalcone-derived oxime acetates were subjected to the above standard conditions, affording the target products **3ah** and **3ai** in 57 and 66% yields, respectively. In addition, the reaction

conditions were also compatible for oxime acetates prepared from conjugated unsaturated ketones, providing the corresponding products **3aj** and **3ak** in acceptable yields, which significantly expanded the utility of this method. Unfortunately, 1-phenylhex-2-en-1-one-derived oxime acetate failed to assemble the desired product (Scheme 4).

Scheme 5. Mechanistic Studies

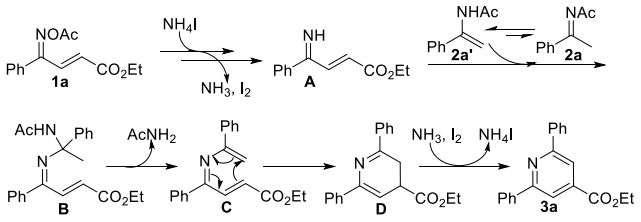


In order to achieve insights into the mechanism of this transformation, we conducted a series of control experiments. With the omission of additive, the product **3a** was still obtained in 70% yield. However, no product **3a** or intermediates were detected without NH_4I or in the presence of other types of halogen ammonium salts (NH_4Cl, NH_4Br), illustrating that the protocol was first triggered by iodine salt (Scheme 5a). Furthermore, this conversion was partially inhibited when the oxidative radical scavenger TEMPO was added to the reaction system. The addition of a non-oxidizing radical catcher tertbutylhydroxytoluene (BHT) or 1,1-diphenylethene (DPE) obtained the product **3a** without any inhibition or sluggishness (Scheme 5b), indicating that a radical pathway might not be involved in this transformation. Subsequently, the annulation of ketoxime-enoate **1a** with N-sulfonyl ketimine **2u** afforded the product **3a** in 70% yield (Scheme 5c).

On the basis of the experimental results and previous reports,[11] a plausible mechanism was postulated for this reaction as shown in Scheme 6. Initially, NH_4I-mediated reduction of the N–O bond of ketoxime-enoate **1a** generated ketimine **A**, which subsequently underwent condensation

with acetyl imine **2a′** in situ-formed through tautomerization of enamide **2a** to afford the intermediate **B**.[19] Elimination of intermediate **B** by the release of $AcNH_2$ resulted in the formation of an aza-hexa-1,3,5-triene intermediate **C**. Finally, thermal 6π-electrocyclization and rapid I_2-mediated oxidative aromatization furnished the pyridine product **3a**. Nevertheless, the effect of $NaHSO_3$ was not very clear currently. The possible explanation to address this involved that $NaHSO_3$ could inhibit the hydrolysis of ketoxime-enoates[4e] and effectively promote the reduction process as the reducing agent.[11b]

Scheme 6. Plausible Reaction Mechanism



In summary, we have successfully developed the NH_4I-triggered formal [4 + 2] annulation of *α,β*-unsaturated ketoxime acetates with N-acetyl enamides, providing efficient access to valuable highly substituted pyridines in moderate to good yields. The present strategy marks the first use of oxime derivatives with electron-rich enamides for the straightforward construction of pyridines based on metal-free systems and features broad substrate scope, good functional group tolerance and simple operation. Further investigations involving the elucidation of the detailed mechanism and application of this methodology are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an N_2 atmosphere unless otherwise noted. 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 ^1H NMR,

100 MHz for ^{13}C NMR) spectra were recorded in $CDCl_3$ with TMS as the internal standard. High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points were measured with a melting point instrument without correction. All the enamides,[17] ketoxime acetates (**1a**−**1n**),[18b] and N-sulfonyl ketimine[20] were all known compounds and synthesized according to previously reported literature procedures, while the ketoxime acetates **1o**−**1q** were prepared for the first time whose characterization data were presented.

Isopropyl (2E)-4-(acetoxyimino)-4-phenylbut-2-enoate (1o). Yellow oil; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 16.2 Hz, 1H), 7.55−7.51 (m, 2H), 7.48−7.44 (m, 3H), 6.14 (d, *J* = 16.2 Hz, 1H), 5.15−5.09 (m, 1H), 2.27 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.8, 164.7, 160.7, 131.7, 130.5, 129.7, 129.1, 128.5, 68.8, 21.6, 19.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1332, found 292.1340.

(2E,4E)-1-Phenylhexa-2,4-dien-1-one O-acetyl oxime (***1p***). Yellow oil; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 3H), 6.87 (d, *J* = 15.6 Hz, 1H), 6.43 (dd, *J* = 15.6, 10.7 Hz, 1H), 6.31−6.23 (m, 1H), 5.95−5.87 (m, 1H), 2.35 (s, 3H), 1.78 (dd, *J* = 20.1, 7.0 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.8, 162.3, 143.7, 138.4, 134.8, 131.0, 130.5, 129.6, 128.5, 128.3, 126.9, 118.3, 19.7, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{14}H_{16}NO_2$ $[M+H]^+$ 230.1176, found 230.1174.

(1Z,2E,4E)-1,5-Diphenylpenta-2,4-dien-1-one O-acetyl oxime (***1q***). Red solid; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 65–67 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56−7.52 (m, 2H), 7.49−7.41 (m, 5H), 7.36−7.26 (m, 3H), 7.11 (d, *J* = 15.6 Hz, 1H), 6.99 (dd, *J* = 15.4, 10.9 Hz, 1H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.65 (dd, *J* = 15.5, 10.7 Hz, 1H), 2.30 (s, 3H) ppm; $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$): δ 168.9, 163.4, 143.4, 139.7, 136.1, 133.2, 130.1, 129.7, 129.0, 128.9, 128.5, 127.6, 127.1, 120.6, 19.9 ppm; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1332, found 292.1340.

General Procedure for the Synthesis of Polysubstituted Pyridine Derivatives. Ketoxime-enoates (0.2 mmol, 1.0 equiv), enamides (0.4 mmol, 2.0 equiv), NH_4I (15 mg, 0.1 mmol) and $NaHSO_3$ (42 mg, 0.4 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 1,4-dioxane (2 mL, 0.1 M) was added into the Schlenk tube by syringe. The reaction mixture was stirred at 120 ºC (oil bath) for 8 h. Upon completion of the reaction, the mixture was then allowed to cool down to room temperature and flushed through a short column of silica gel with ethyl acetate (3 mL). After rotary evaporation, the residue was purified by column chromatography on silica gel (Petroleum Ether/EtOAc) to afford the pyridine derivatives **3**.

Ethyl 2,6-diphenylisonicotinate (3a). White solid; 50 mg, 83% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 94−96 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 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{^{1}H} NMR (100 MHz, $CDCl_3$): 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 304.1366.

Ethyl 2-(4-fluorophenyl)-6-phenylisonicotinate (3b). White solid; 20 mg, 31% yield; 46 mg, 71% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); Mp 124−126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 1.0 Hz, 1H), 8.20 (t, *J* = 7.1 Hz, 5H), 7.50 (dt, *J* = 23.9, 7.1 Hz, 3H), 7.20 (t, *J* = 8.7 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 165.1 (d, *J* = 250.1 Hz), 157.8, 156.7, 139.5, 138.6, 134.8 (d, *J* = 3.1 Hz), 129.5, 128.9 (d, *J* = 8.4 Hz), 128.8, 127.1, 117.7, 117.4, 115.8 (d, *J* = 21.7 Hz), 61.9, 14.3 ppm; HRMS (ESI-TOF):

m/z calcd for $C_{20}H_{17}NO_2F$ $[M+H]^+$ 322.1238, found 322.1230.

Ethyl 2-(4-chlorophenyl)-6-phenylisonicotinate (3c). White solid; 38 mg, 56% yield; 51 mg, 75% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); Mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 1.1 Hz, 1H), 8.22−8.12 (m, 5H), 7.55−7.45 (m, 5H), 4.48 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 157.9, 156.5, 139.6, 138.5, 137.1, 135.6, 129.6, 129.0, 128.8, 128.4, 127.1, 118.1, 117.5, 62.0, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{17}NO_2Cl$ $[M+H]^+$ 338.0942, found 338.0926.

Ethyl 2-phenyl-6-(p-tolyl)isonicotinate (3d). White solid; 50 mg, 79% yield; 48 mg, 76% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.4 Hz, 4H), 8.12 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 7.3 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.6, 157.8, 157.7, 139.5, 139.4, 138.8, 136.0, 129.5, 129.4, 128.8, 127.1, 127.0, 117.5, 61.8, 21.4, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489, found 318.1470.

Ethyl 2-(4-methoxyphenyl)-6-phenylisonicotinate (3e). White solid; 51 mg, 77% yield; 40 mg, 60% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 97−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.15 (m, 6H), 7.52 (t, J = 7.3 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 8.9 Hz, 2H), 4.48 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.6, 160.9, 157.6, 157.4, 139.4, 138.9, 131.4, 129.4, 128.8, 128.4, 127.1, 117.0, 114.2, 61.8, 55.4, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.1438, found 334.1433.

Ethyl 2-(3-bromophenyl)-6-phenylisonicotinate (3f). Yellow oil; 40 mg, 53% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (t, J = 1.8 Hz, 1H),

8.27 (d, *J* = 1.1 Hz, 1H), 8.22−8.17 (m, 3H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 158.0, 156.2, 140.7, 139.7, 138.4, 132.4, 130.3, 130.2, 129.7, 128.9, 127.1, 125.6, 123.1, 118.5, 117.9, 62.1, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{17}NO_2Br$ $[M+H]^+$ 382.0437, found 382.0430.

Ethyl 2-(3-methoxyphenyl)-6-phenylisonicotinate (3g). Yellow oil; 47 mg, 70% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25−8.20 (m, 4H), 7.83−7.80 (m, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.49−7.41 (m, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.5, 160.1, 157.7, 157.5, 140.2, 139.5, 138.7, 129.8, 129.5, 128.8, 127.1, 119.5, 117.9, 115.0, 112.7, 61.9, 55.4, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.1438, found 334.1434.

Ethyl 2-(2-fluorophenyl)-6-phenylisonicotinate (3h). White solid; 33 mg, 51% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); Mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 12.1 Hz, 2H), 8.19 (d, *J* = 7.1 Hz, 3H), 7.54−7.51 (m, 2H), 7.48−7.40 (m, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.26–7.18 (m, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 162.1 (d, *J* = 251.5 Hz), 157.9, 153.9 (d, *J* = 2.3 Hz), 139.2, 138.6, 131.3 (d, *J* = 2.7 Hz), 130.9 (d, *J* = 8.6 Hz), 129.5, 128.9, 127.1, 127.0 (d, *J* = 11.2 Hz), 124.6 (d, *J* = 3.6 Hz), 122.0 (d, *J* = 10.3 Hz), 118.3, 116.4 (d, *J* = 23.1 Hz), 61.9, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{17}NO_2F$ $[M+H]^+$ 322.1238, found 322.1233.

Ethyl 2-(2-methoxyphenyl)-6-phenylisonicotinate (3i). White solid; 48 mg, 72% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 20:1); Mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 1.3 Hz, 1H), 8.25 (d, *J* = 1.3 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.05 (dd, *J* = 7.6, 1.8 Hz, 1H),

7.52 (t, *J* = 7.3 Hz, 2H), 7.48–7.39 (m, 2H), 7.14 (td, *J* = 7.5, 1.0 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.8, 157.6, 157.4, 156.6, 139.0, 138.4, 131.5, 130.4, 129.2, 128.8, 128.5, 127.1, 122.8, 121.1, 117.4, 111.5, 61.7, 55.7, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.1438, found 334.1438.

Ethyl 2-([1,1'-biphenyl]-4-yl)-6-phenylisonicotinate (3j). White solid; 49 mg, 65% yield; 50 mg, 66% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 20:1); Mp 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.30 (d, *J* = 2.7 Hz, 2H), 8.28−8.22 (m, 3H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 3H), 7.39 (t, *J* = 7.4 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 157.9, 157.4, 142.2, 140.6, 139.5, 138.7, 137.6, 129.5, 128.9, 128.8, 127.6, 127.5, 127.1, 127.1, 117.8, 117.7, 61.9, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{21}NO_2$ $[M+H]^+$ 380.1670, found 380.1645.

Ethyl 2-(naphthalen-2-yl)-6-phenylisonicotinate (3k). White solid; 56mg, 80% yield; 60 mg, 85% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69–8.64 (m, 1H), 8.38 (dd, *J* = 9.7, 1.4 Hz, 2H), 8.26 (d, *J* = 7.3 Hz, 3H), 8.03−7.96 (m, 2H), 7.94–7.86 (m, 1H), 7.59−7.47 (m, 5H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 157.9, 157.7, 139.5, 138.8, 136.0, 133.9, 133.5, 129.5, 128.9, 128.8, 128.5, 127.7, 127.2, 126.8, 126.7, 126.4, 124.6, 118.1, 117.9, 61.9, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$ 354.1489, found 354.1483.

Ethyl 2-phenyl-6-(thiophen-2-yl)isonicotinate (3l). Yellow solid; 25 mg, 40 % yield; 15 mg, 25% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 5.6 Hz, 3H), 8.14 (s, 1H), 7.60 (s, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.2 Hz,

1H), 7.29−7.26 (m, 1H), 6.59 (dd, J = 3.3, 1.7 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 157.9, 153.5, 150.1, 143.7, 139.4, 138.5, 129.5, 128.8, 127.1, 117.7, 116.0, 112.2, 109.6, 61.9, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{16}NO_2S$ $[M+H]^+$ 310.0896, found 310.0885.

Ethyl 2-(tert-butyl)-6-phenylisonicotinate (3m). Yellow oil; 41 mg, 72% yield; 30 mg, 53% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.20−8.11 (m, 3H), 7.83 (s, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.47 (s, 9H), 1.44 (d, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 166.0, 156.4, 139.1, 138.8, 129.1, 128.7, 127.0, 116.7, 116.3, 61.7, 38.0, 30.2, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.1645, found 284.1645.

Ethyl 2-methyl-6-phenylisonicotinate (3n). Pink solid; 35 mg, 72% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 73−74 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 8.04 (d, J = 7.3 Hz, 2H), 7.65 (s, 1H), 7.48 (t, J = 7.3 Hz, 2H), 7.45−7.39 (m, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.69 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 159.4, 157.9, 138.9, 138.7, 129.2, 128.8, 127.1, 120.8, 116.9, 61.8, 24.8, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1181, found 242.1195.

Isopropyl 2,6-diphenylisonicotinate (3o). White solid; 35 mg, 55% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); Mp 96−98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 2H), 8.24−8.19 (m, 4H), 7.53 (t, J = 7.3 Hz, 4H), 7.50−7.44 (m, 2H), 5.39−5.33 (m, 1H), 1.45 (d, J = 6.3 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 157.8, 139.9, 138.8, 129.4, 128.8, 127.1, 117.9, 69.6, 21.9 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489, found 318.1476.

Ethyl 2-(4-bromophenyl)-6-phenylisonicotinate (3p). White solid; 58 mg, 76% yield; Mp 127−127 °C; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.25

(d, J = 1.1 Hz, 1H), 8.18 (dd, J = 8.4, 1.4 Hz, 3H), 8.07 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.53 (t, J = 7.2 Hz, 2H), 7.49−7.45 (m, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 157.9, 156.6, 139.6, 138.5, 137.6, 131.9, 129.6, 128.8, 128.6, 127.1, 124.0, 118.1, 117.5, 62.0, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{17}NO_2Br$ $[M+H]^+$ 382.0437, found 382.0423.

Ethyl 2-(4-(tert-butyl)phenyl)-6-phenylisonicotinate (3q). Yellow oil; 38 mg, 53% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.29−8.21 (m, 4H), 8.17 (d, J = 8.4 Hz, 2H), 7.56 (dd, J = 17.0, 8.1 Hz, 4H), 7.48 (t, J = 7.2 Hz, 1H), 4.50 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.42 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 157.9, 157.7, 152.7, 139.4, 136.1, 129.4, 128.8, 127.1, 126.9, 125.8, 117.7, 117.5, 61.8, 34.8, 31.4, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{26}NO_2$ $[M+H]^+$ 360.1958, found 360.1954.

Ethyl 2-(3-chlorophenyl)-6-phenylisonicotinate (3r). White solid; 52 mg, 76% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 61−62 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.22 (s, 2H), 8.19 (d, J = 7.2 Hz, 2H), 8.07 (d, J = 6.5 Hz, 1H), 7.54 (t, J = 7.4 Hz, 2H), 7.49−7.44 (m, 3H), 4.49 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 158.0, 156.3, 140.5, 139.7, 138.4, 134.9, 130.1, 129.7, 129.4, 128.9, 127.3, 127.1, 125.2, 118.5, 117.9, 62.0, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{17}NO_2Cl$ $[M+H]^+$ 338.0942, found 338.0932.

Ethyl 2-phenyl-6-(m-tolyl)isonicotinate (3s). White solid; 47 mg, 74% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 93−95 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28−8.17 (m, 4H), 8.03 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.3 Hz, 2H), 7.46 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.6, 158.0, 157.8, 139.4, 138.8, 138.7, 138.4, 130.2,

129.4, 128.8, 128.7, 127.8, 124.3, 117.9, 117.8, 61.9, 21.6, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489, found 318.1486.

Ethyl 2-(2-chlorophenyl)-6-phenylisonicotinate (3t). White solid; 20 mg, 30% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 56−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.14 (d, *J* = 6.9 Hz, 3H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 8.9 Hz, 3H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.42−7.35 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.4, 158.0, 157.6, 138.8, 138.7, 138.5, 132.4, 131.8, 130.3, 129.9, 129.5, 128.9, 127.2, 127.1, 122.3, 118.3, 62.0, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{17}NO_2Cl$ $[M+H]^+$ 338.0942, found 338.0937.

Ethyl 2-phenyl-6-(o-tolyl)isonicotinate (3u). Yellow oil; 21 mg, 33% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.16 (d, *J* = 7.2 Hz, 2H), 7.94 (s, 1H), 7.55−7.48 (m, 3H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.34 (s, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 160.9, 157.5, 139.9, 139.0, 138.7, 136.3, 131.0, 129.8, 129.4, 128.8, 128.7, 127.1, 126.0, 121.5, 117.4, 61.9, 20.7, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489, found 318.1487.

Ethyl 2-(3,4-dimethylphenyl)-6-phenylisonicotinate (3v). White solid; 20 mg, 30% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 20:1); Mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 3.1 Hz, 3H), 8.19 (t, *J* = 1.3 Hz, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 158.0, 157.7, 139.3, 138.9, 138.3, 137.0, 136.3, 130.1, 129.4, 128.8, 128.2, 127.1, 124.5, 117.6, 117.5, 61.9, 20.0, 19.8, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{22}NO_2$ $[M+H]^+$ 332.1645, found 332.1641.

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-6-phenylisonicotinate (3w). White solid; 45 mg, 65% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 6.8 Hz, 3H), 8.14 (d, *J* = 1.0 Hz, 1H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.70 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.6, 157.6, 157.2, 148.9, 148.4, 139.4, 138.7, 133.2, 129.4, 128.8, 127.1, 121.2, 117.3, 117.2, 108.5, 107.5, 101.4, 61.9, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{18}NO_4$ $[M+H]^+$ 348.1230, found 348.1223.

Ethyl 3-ethyl-2,6-diphenylisonicotinate (3x). Yellow oil; 26 mg, 40 % yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.99 (s, 1H), 7.54 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.47 (q, *J* = 7.8, 7.2 Hz, 5H), 7.43−7.38 (m, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.95 (q, *J* = 7.4 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.5, 160.7, 154.5, 140.9, 140.0, 138.6, 134.4, 129.0, 128.9, 128.7, 128.1, 128.0, 126.9, 118.8, 61.8, 22.7, 15.7, 14.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{22}NO_2$ $[M+H]^+$ 332.1645, found 332.1644.

Ethyl 2-phenyl-5,6-dihydrobenzo[h]quinoline-4-carboxylate (3y). White solid; 37 mg, 56% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 7.2 Hz, 2H), 8.01 (s, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.41−7.37 (m, 1H), 7.36−7.33 (m, 1H), 7.25 (d, *J* = 6.1 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.33−3.29 (m, 2H), 2.96–2.92 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.9, 154.9, 153.7, 138.8, 138.3, 138.0, 134.5, 130.0, 129.5, 129.1, 128.8, 127.6, 127.1, 126.8, 125.8, 118.4, 61.7, 27.6, 24.9, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{20}NO_2$ $[M+H]^+$ 330.1489, found 330.1482.

Ethyl 2-(4-fluorophenyl)-6-(4-methoxyphenyl)isonicotinate (3z). White solid; 43 mg, 62% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19−8.13 (m, 4H), 8.11 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.5, 165.0 (d, *J* = 249.8 Hz), 160.9, 157.5, 156.5, 139.4, 135.0 (d, *J* = 3.1 Hz), 131.2, 128.9 (d, *J* = 8.4 Hz), 128.4, 117.0, 116.6, 115.8 (d, *J* = 21.7 Hz), 114.2, 61.9, 55.4, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{19}NO_3F$ $[M+H]^+$ 352.1343, found 352.1341.

Ethyl 2,6-bis(4-methoxyphenyl)isonicotinate (3aa). White solid; 65 mg, 90 % yield; R_f = 0.2 (petroleum ether/ethyl acetate = 20:1); Mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 4H), 8.10 (s, 2H), 7.02 (d, *J* = 8.8 Hz, 4H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 6H), 1.46 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 160.8, 157.2, 139.2, 131.5, 128.4, 116.2, 114.1, 61.8, 55.4, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{22}NO_4$ $[M+H]^+$ 364.1543, found 364.1534.

Ethyl 2-(4-methoxyphenyl)-6-(4-nitrophenyl)isonicotinate (3ab). White solid; 40 mg, 55% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 4H), 8.24 (d, *J* = 16.4 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.2, 161.2, 158.0, 155.0, 148.3, 144.6, 139.8, 130.7, 128.5, 127.8, 124.0, 118.5, 117.7, 114.3, 62.1, 55.4, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{19}N_2O_5$ $[M+H]^+$ 379.1294, found 379.1314.

Ethyl 2-(4-chlorophenyl)-6-(m-tolyl)isonicotinate (3ac). White solid; 55 mg, 78% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 18.0, 1.1 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 8.01–7.94 (m, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.41 (t,

J = 7.6 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 158.1, 156.5, 139.5, 138.5, 137.2, 135.6, 130.4, 129.0, 128.7, 128.4, 127.7, 124.3, 118.2, 117.5, 62.0, 21.6, 14.3 ppm; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{19}NO_2Cl$ $[M+H]^+$ 352.1099, found 352.1089.

Ethyl 2-([1,1'-biphenyl]-4-yl)-6-(4-chlorophenyl)isonicotinate (3ad). White solid; 60 mg, 73% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 117−118 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30–8.26 (m, 2H), 8.25 (s, 1H), 8.19 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.49 (d, J = 8.6 Hz, 4H), 7.40 (t, J = 7.3 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ 165.4, 157.5, 156.5, 142.3, 140.5, 139.6, 137.4, 137.1, 135.6, 129.0, 128.9, 128.4, 127.7, 127.5, 127.5, 127.1, 118.0, 117.5, 62.0, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{21}NO_2Cl$ $[M+H]^+$ 414.1255, found 414.1245.

Ethyl 2-(4-chlorophenyl)-6-(naphthalen-2-yl)isonicotinate (3ae). White solid; 63 mg, 80% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 20:1); Mp 160−161 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.36 (s, 1H), 8.32 (dd, J = 8.6, 1.7 Hz, 1H), 8.18 (d, J = 5.1 Hz, 2H), 8.15 (s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.89 (d, J = 9.4 Hz, 1H), 7.54 (dd, J = 6.2, 3.2 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 4.50 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 157.7, 156.6, 139.6, 137.1, 135.8, 135.6, 134.0, 133.4, 129.0, 128.9, 128.5, 128.4, 127.7, 126.8, 126.7, 126.4, 124.5, 118.3, 117.5, 62.0, 14.4 ppm; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{19}NO_2Cl$ $[M+H]^+$ 388.1099, found 388.1083.

2-Methyl-4,6-diphenylpyridine (3ah). Yellow solid; 28 mg, 57% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 60−61 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 7.3 Hz, 2H), 7.71 (s, 1H), 7.67 (d, J = 7.0 Hz, 2H), 7.50 (d, J = 6.8 Hz, 2H), 7.48−7.46 (m, 2H), 7.44 (d, J = 7.2

Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.33−7.29 (m, 1H), 2.69 (s, 3H) ppm; $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ 158.9, 157.7, 149.5, 139.9, 138.8, 129.1, 128.9, 128.8, 128.8, 127.2, 127.1, 119.9, 116.2, 24.9 ppm; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{16}N$ $[M+H]^+$ 246.1277, found 246.1276.

2,4,6-Triphenylpyridine (3ai). White solid; 41 mg, 66% yield; R_f = 0.2 (petroleum ether/ethyl acetate = 30:1); Mp 137−138 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.1 Hz, 4H), 7.92 (s, 2H), 7.77 (d, *J* = 7.0 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 6H), 7.52–7.45 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.5, 150.2, 139.6, 139.1, 129.2, 129.1, 129.0, 128.8, 127.2, 127.2, 117.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{18}N$ $[M+H]^+$ 308.1434, found 308.1434.

(E)-2,6-diphenyl-4-(prop-1-en-1-yl)pyridine (3aj). Yellow oil; 30 mg, 55% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.3, 1.3 Hz, 4H), 7.47 (s, 2H), 7.39−7.36 (m, 4H), 7.32−7.28 (m, 2H), 6.50−6.42 (m, 1H), 6.38−6.31 (m, 1H), 1.83 (dd, *J* = 6.5, 1.5 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.1, 145.6, 138.6, 129.6, 128.6, 127.8, 127.5, 126.0, 114.7, 17.6 ppm; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{18}N$ $[M+H]^+$ 272.1434, found 272.1417.

(E)-2,6-Diphenyl-4-styrylpyridine (3ak). Yellow oil; 26 mg, 40% yield; R_f = 0.3 (petroleum ether/ethyl acetate = 30:1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.25−8.17 (m, 4H), 7.78 (s, 2H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 4H), 7.50−7.41 (m, 5H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 16.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 157.5, 146.2, 139.6, 136.4, 132.9, 129.0, 128.9, 128.7, 127.1, 127.1, 126.7, 118.7, 116.2 ppm; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{20}N$ $[M+H]^+$ 334.1590, found 334.1588.

Scale-up Synthesis of Compound 3aa. Ketoxime-enoate **1a** (2.61 g, 10 mmol), N-acetyl enamide **2a** (3.22 g, 20 mmol), NH_4I (0.72 g, 5 mmol) and $NaHSO_3$ (2.08 g, 20 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 1,4-dioxane (80 mL) was added into the Schlenk tube by syringe. The reaction mixture was stirred at 120 ºC for 8 h. Upon completion of the reaction, the mixture was then allowed to cool down to room temperature and flushed through a short column of silica gel with ethyl acetate (15 mL). After rotary evaporation, the residue was purified by column chromatography on silica gel (Petroleum Ether/EtOAc= 20:1) to give the product **3aa** 2.36 g (78% 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)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support for this study from the Jiangsu Synergetic Innovation Center for Advanced Bio-Manufacture (NO. XTE1826) and the Natural Science Research Projects of Jiangsu Higher Education (19KJB150027) is gratefully acknowledged.

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