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Access to 4,6-Diarylpicolinates via a Domino Reaction of Cyclic Sulfamidate Imines with Morita–Baylis–Hillman Acetates of Nitroolefins/Nitrodienes

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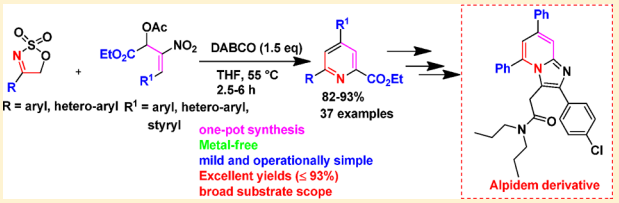
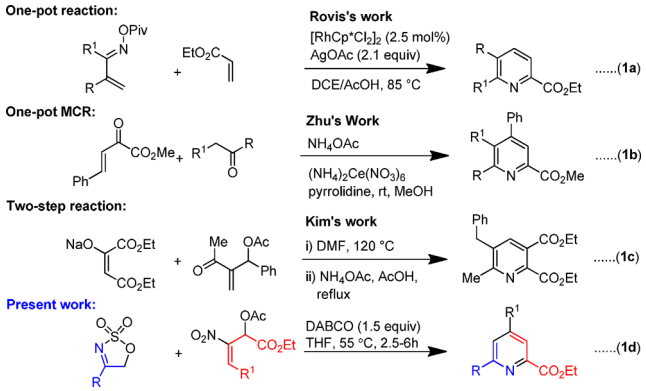
Supporting Information

ABSTRACT: An interesting domino reaction of 5-membered cyclic sulfamidate imines with a variety of Morita–Baylis–Hillman acetates of nitroolefins/nitrodienes in the presence of DABCO as an organic base at 55 °C is reported for the first time. This new synthetic strategy provides a series of pharmacologically interesting 4,6-diarylpicolinates in high to excellent yields and allows several compatible functionalities on aryl rings. Moreover, the biologically interesting imidazo[1,2-*a*]pyridine (alpidem derivative) has been prepared in high chemical yield through a unique procedure.



Design and development of an innovative approach toward the rapid access to important functionalized pyridine frameworks through one-pot operation is one of the most active research areas in synthetic and medicinal chemistry because this popular heterocyclic core has been largely found in a variety of biologically active natural molecules.[1] Moreover, substituted pyridines have shown versatile applications in almost all branches of chemical science such as active pharmaceutical research,[1,2] functional materials,[3] agrochemicals,[4] polymer,[5] coordination chemistry,[6] catalysis,[7] etc. Owing to their broad spectrum of applications, huge efforts have been devoted toward the syntheses of a wide range of functionalized pyridine scaffolds by adopting several classical and modern techniques such as condensation reactions of ketones with amines, multicomponent reactions, cycloaddition reactions, transition-metal salt catalyzed C–H bond functionalization, etc.[8] Despite the rich history of pyridine syntheses, access to functionalized picolinic acid derivatives (carboxylic acid at C-2 position on pyridine ring) has seen little attention (Scheme 1) despite their proven biological and pharmaceutical importance.[9,1d,e] For example, Rovis et al.[9b] has synthesized a novel picolinate derivative through a regioselective coupling reaction between α,β-unsaturated *O*-pivaloyl oxime and ethyl acrylate at 85 °C using Rh salt/AgOAc as the combined catalytic system (Scheme 1a). In 2015, CAN/pyrrolidine-mediated tandem three-component annulation reaction for the access to functionalized picolinates involving β,γ-unsaturated α-ketoester, ketones, and ammonium acetate has been nicely described by Zhu and co-workers (Scheme 1b).[9c] Furthermore, Morita–Baylis–Hillman (MBH) acetates of methyl vinyl ketone as bielectrophiles has been utilized in the two-step reaction with sodium diethyl oxaloacetate and ammonium acetate for the construction of pyridine derivatives as reported by Kim et al.[9d] (Scheme 1c). However, most of the above techniques suffer from one or more practical difficulties such as use of expensive metal salts, limited substrate scope, poor chemical yields with multiple side products, harsh reaction conditions, etc.

Scheme 1. Various Approaches for the Syntheses of Picolinate Derivatives



Therefore, the development of a simple and efficient new synthetic tactic for the rapid construction of multifunctionalized picolinate frameworks under metal-free conditions is always a challenging task in the context of both academic and industrial standpoints of view.

Recently, we found that 5-membered cyclic sulfamidate imines could act as potential nucleophiles while reacting with several aryl aldehydes/α,β-unsaturated aldehydes.[10] On the other hand, MBH acetates of nitroolefins have been extensively used as suitable 1,3-bielectrophiles in the S_N2' addition–elimination sequence reaction with several nucleophiles, constructing a variety of 5/6-membered heterocycles.[11] With this understanding, we thought that cyclic sulfamidate imines

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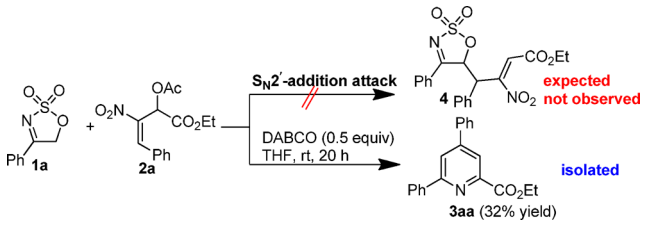
may also attack MBH acetates of nitroolefins in an S_N2'-addition manner using a base (Scheme 2). To verify this

Scheme 2. DABCO-Mediated Domino Reaction between 1a and 2a



synthetic plan, we began the model reaction involving 4-phenyl-5*H*-1,2,3-oxathiazole-2,2-doxide (**1a**) and MBH acetate **2a** in THF at room temperature using 50 mol % of 1,4-diazabicyclo[2.2.2]octane (DABCO) as an organobase. After 20 h, surprisingly, we isolated ethyl 4,6-diphenylpicolinate (**3aa**) in 32% yield instead of addition adduct **4**. The product **3aa** was carefully characterized by its spectroscopic data.

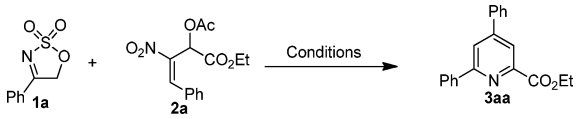
The above fascinating result as well as our continued interest in the development of a new synthetic method for the synthesis of N-heterocycles including pyridine derivatives under metal-free conditions;[12] herein we report a unique and general synthetic strategy for the rapid access to previously unknown functionalized 4,6-diaryl-substituted picolinates in high to excellent yields via a domino reaction of a series of 4-aryl-substituted cyclic sulfamidate imines with MBH acetates of nitroalkenes/nitrodienes as 1,3-bielectrophiles in the presence of DABCO as an inexpensive base under mild conditions (Scheme 1d).

In view of the above interesting results, we further examined this domino reaction in order to improve the chemical yield of **3aa**. Thus, on increasing the amount of DABCO from 0.5 to 1.5 equiv, the yield of **3aa** was dramatically improved from 32% to 84% (entries 2 and 3, Table 1) after 10−12 h. Interestingly, excellent yields (87−92%, entries 4 and 5) of **3aa** were obtained within short time spans (3−6 h) when the reaction was performed under heating conditions (45−55 °C). For this catalyst, screening of organic solvents revealed that nonpolar solvents like toluene, CH_2Cl_2, MeCN, and EtOAc produced better yields (79−86%, entries 6−9) as compared to polar ones (DMSO, DMF, and EtOH, 40−58% yields, entries 10−12) under identical conditions. Considering the yield of **3aa** (92%, entry 5), THF was chosen as the best solvent for this reaction. Next, we investigated the influence of several common organic bases, namely DBU, DMAP, DIPEA, pyridine, triethylamine, and quinine, on this domino reaction at 55 °C for 6 h. Surprisingly, all of these bases produced inferior results (11−50% yields of **3aa**, entries 13−18) as compared to DABCO (92%, 3 h, entry 5).

We propose a possible mechanism for the formation of **3aa** as shown in Scheme 3. At first, carbanion ion **1a′** is generated from **1a** via abstraction of an active methylene proton by a base which undergoes S_N2' reaction with MBH adduct **2a** to generate intermediate **4**. The latter further may convert into triene intermediate **5** through elimination of SO_3 in the presence of base, which is subsequently cyclized to form cyclic intermediate **6**.[13] Finally, the product **3aa** forms from intermediate **6** through elimination of HNO_2.

After successfully establishing the reaction parameters for the synthesis of 4,6-diphenylpicolinate, the scope and limitation of

Table 1. Optimization Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1[c]	DABCO	THF	rt	20	32
2[d]	DABCO	THF	rt	14	62
3	DABCO	THF	rt	10	84
4	DABCO	THF	45	6	87
5	DABCO	THF	55	3	92
6	DABCO	toluene	55	3	86
7	DABCO	CH_2Cl_2	55	3	80
8	DABCO	MeCN	55	3	79
9	DABCO	EtOAc	55	3	84
10	DABCO	DMSO	55	5	48
11	DABCO	DMF	55	5	40
12	DABCO	EtOH	55	5	58
13	DBU	THF	55	6	12
14	DMAP	THF	55	6	18
15	C_5H_5N	THF	55	6	30
16	DIPEA	THF	55	6	11
17	Et_3N	THF	55	6	42
18	 (quinine)	THF	55	6	50

[a]Unless otherwise noted, all of the reactions were performed with **1a** (0.2 mmol), **2a** (0.22 mmol), and DABCO (0.3 mmol, 1.5 equiv) in specified solvents (0.5 mL) and at specified temperatures. [b]Isolated yield. [c]0.5 equiv of DABCO. [d]1.0 equiv of DABCO.

this reaction were examined by performing the reaction using a series of 4-aryl-substituted cyclic sulfamidate imines **1a−g** with MBH acetates derived from nitroolefins **2a−l** under the present conditions as shown in Table 2. The results showed that electron-donating (Me, OMe, OBn) substituents on aryl rings of MBH acetates **2b−e** are slightly less reactive (3−5 h vs 2.5−3 h) toward **1a** as compared to electron-withdrawing ones (F, Cl, CN, and NO_2). However, all of the reactions led to high to excellent yields (84−93%) of 4,6-diarylpicolinates **3ab−ai**. Moreover, heteroaryl-substituted MBH acetates **2j,k** ran smoothly with **1a** via this procedure, delivering high yields of 85% and 86% of the desired products **3aj** and **3ak**, respectively. Furthermore, incorporation of several substituents (Me, MeO, F, Cl, and Br) on the aryl rings of cyclic sulfamidate imines **1b−g** did not show any difficulty for the annulations with several MBH acetates **2a−l** under standard conditions. Consequently, high to excellent yields (82−91%) of the corresponding picolinate derivatives **3ba−gk** (ORTEP data of **3bd** (CCDC-1456731, Supporting Information) were isolated within short timespans (3−6 h). This metal-free domino procedure is mild enough to sustain several functionalities such as Me, OMe, OBn, F, Cl, NO_2, CN, CO_2Et, furan, thiophene, etc. Therefore,

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Scheme 3. Probable Mechanism of This Domino Reaction

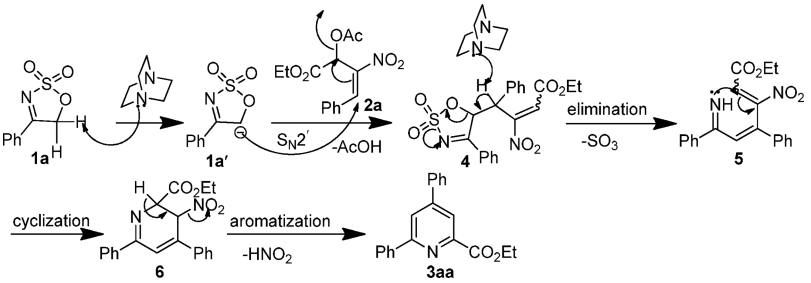
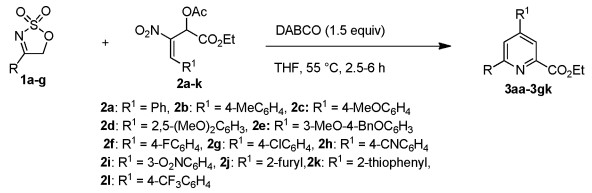
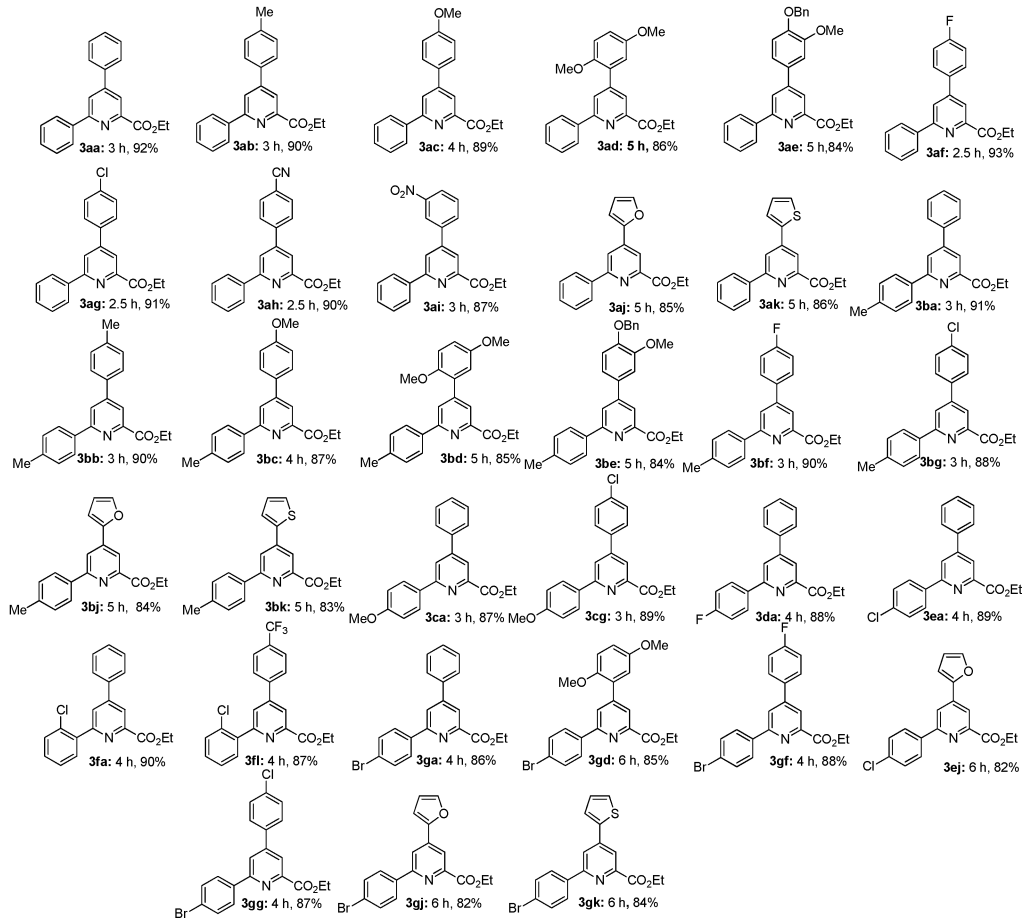


Table 2. Substrate Scope of 4,6-Diarylpicolinate Synthesis



2a: R^1 = Ph, **2b**: R^1 = 4-MeC$_6$H$_4$, **2c**: R^1 = 4-MeOC$_6$H$_4$
2d: R^1 = 2,5-(MeO)$_2$C$_6$H$_3$, **2e**: R^1 = 3-MeO-4-BnOC$_6$H$_3$
2f: R^1 = 4-FC$_6$H$_4$, **2g**: R^1 = 4-ClC$_6$H$_4$, **2h**: R^1 = 4-CNC$_6$H$_4$
2i: R^1 = 3-O$_2$NC$_6$H$_4$, **2j**: R^1 = 2-furyl,**2k**: R^1 = 2-thiophenyl,
2l: R^1 = 4-CF$_3$C$_6$H$_4$



this method provides further opportunity for the synthesis of important therapeutic targets through necessary synthetic modifications of these functional groups.

Toward the further possible substrate scope, the chemically challenging MBH acetates of nitrodienes **2m−n** have been employed as acceptors in the domino reaction with a variety of 4-aryl-substituted cyclic sulfamidate imines **1a−g** under the present conditions. Interestingly, the cyclic imines **1a**,**b**,**g** attacked nitrodienes **2m**,**n** and have been employed as acceptors in the domino reaction with a variety of 4-aryl-substituted cyclic sulfamidate imines **1a−g** under the present conditions. Interestingly, the cyclic imines **1a**,**b**,**g** attacked nitrodienes **2m**,**n** exclusively at the *β*-position by this current procedure. As a consequence, high yields (79−85%) of the corresponding 6-aryl-(*E*)-4-styryl-substituted picolinates **3am−gm** were obtained in Scheme 4. It is worth mentioning that this is the first successful synthetic protocol for access to (*E*)-4-styrylpicolinates in a one-pot manner including transition-metal salt mediated reactions.

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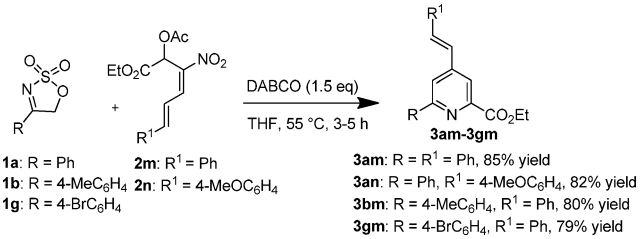
Scheme 4. One-Pot Synthesis of (*E*)-6-Aryl-4-styryl-Substituted Picolinates 3am−gm



In order to show the potential utility of the synthesized compounds, picolinate **3aa** was further transformed into a synthetically as well as pharmaceutically useful 2-aminopyridine **7** in 78% combined yield (two-step) via a hydrolysis of ester group of **3aa** by using a LiOH in $MeCN/H_2O$ at room temperature, followed by in situ azidonation/Curtius rearrangement/hydrolysis of resultant picolinic acid using $(PhO)_2P(O)N_3/Et_3N$ in toluene under heating conditions. Furthermore, 2-amino-4,6-diphenylpyridine (**7**) was subjected to reaction with MBH acetate **2g** in MeOH, providing a biologically attractive imidazo[1,2-*a*]pyridine derivative **8**[14] in 81% yield. Finally, anxiolytic drug alpidem derivative **9**[15] was synthesized in high yield (82%, two-step) via a hydrolysis of ester group of **9**, followed by amidation reaction of the resultant acid with dipropylamine using EDCI/DMAP as an efficient amide bond coupling reagent in Scheme 5.

CONCLUSION

In this work, we have developed the first, simple, convenient, metal-free, and general new domino synthetic technique for the rapid access to an important class of 4,6-diarylpicolinates from several 4-aryl-5*H*-1,2,3-oxathiazole-2,2-dioxides and MBH acetates of nitroalkenes/nitrodienes in the presence DABCO as a cheap organobase under heating conditions. Moreover, this metal-free domino technique delivers high to excellent yields of above title compounds and excels for a wide range of sensitive functional groups. Furthermore, high yield of anxiolytic drug alpidem derivative has been successfully obtained through our synthetic methodology. Therefore, we believe this new domino method will gain great importance in synthetic organic and medicinal chemistry as a powerful tactic for the access to functionalized picolinates.

EXPERIMENTAL SECTION

General Information. All of the 4-aryl-5*H*-1,2,3-oxathiazole-2,2-doxides **1a**−**g**[16a] and MBH acetates of nitroolefins/nitrodienes **2a**−**l**[16b] were synthesized by known literature procedures. All of the catalysts were purchased from commercial sources. All of the reactions were carried out either under inert atmosphere or air and monitored by TLC using Merck 60 F_{254} precoated silica gel plates, and the products were visualized by UV detection. Flash chromatography was carried out using silica gel (200−300 mesh). FT-IR spectra were recorded on a KBr plate or neat. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Data for ^1H NMR are reported as chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant J (Hz), integration, and assignment; data for ^{13}C are reported as chemical shift. High-resolution mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. Melting points were recorded on an Electro thermal melting points apparatus and are uncorrected.

Representative Procedure for the Synthesis of Ethyl 4,6-Diphenylpicolinate (3aa). To a stirred solution of compounds **1a** (39.4 mg, 0.2 mmol) and **2a** (67.39 mg, 0.22 mmol) in THF (0.5 mL) was added DABCO (33.6 mg, 0.3 mmol) at room temperature. The reaction mixture was then heated at 55 °C for 3 h (monitored by TLC). Upon completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), washed with water and brine, respectively, and dried over Na_2SO_4. The combined organic phases were evaporated under reduced pressure to afford the crude product. Finally, the product was obtained in pure form (55.7 mg, 92%) through column chromatography over silica gel using a mixture of EtOAc/hexane (1:4, v/v) as the eluent. The product was fully characterized by its spectroscopic data (IR, ^1HNMR, ^{13}C NMR, and HRMS).

All of the products (**3ab**−**gk**) in Table 2 and Scheme 4 (**3am**−**gm**) were synthesized following the above procedure. All of the products were characterized by their corresponding spectroscopic data (IR, ^1H NMR, ^{13}C NMR, and HRMS).

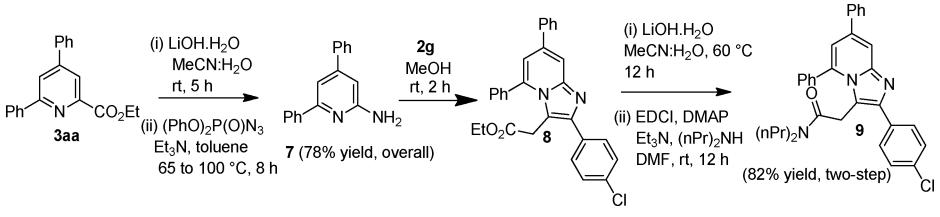
*Ethyl 4,6-diphenylpicolinate (**3aa**):* white solid (55.6 mg, 92%); mp 65−67 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2984, 2932, 2902, 1714, 1600, 1546, 1425, 1372, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.09−8.13 (m, 3H), 7.73−7.75 (m, 2H), 7.43−7.55 (m, 6H), 4.52 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 158.6, 150.7, 149.3, 139.0, 138.1, 129.8, 129.6, 129.1, 127.6, 127.4, 121.8, 121.8 (2C), 62.2, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{17}NO_2$ $[M + H]^+$ 304.1332, found 304.1334.

*Ethyl 6-phenyl-4-(4-methylphenyl)picolinate (**3ab**):* white solid (57.1 mg, 90%); mp 68−71 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2994, 2952, 2925, 2901, 2854, 1715, 1601, 1544, 1516, 1451, 1430, 1370, 1345, 1279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.11−8.13 (m, 2H), 8.07 (s, 1H), 7.64−7.65 (m, 2H), 7.48−7.52 (m, 2H), 7.42−7.46 (m, 1H), 7.32−7.34 (m, 2H), 4.52 (q, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 158.5, 150.5, 149.2, 139.9, 139.0, 135.0, 130.2, 129.6, 129.0, 127.6, 127.2, 121.5, 121.4, 62.1, 21.5, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{19}NO_2$ $[M + H]^+$318.1489, found 318.1492.

*Ethyl 4-(4-methoxyphenyl)-6-phenylpicolinate (**3ac**):* orange solid (59.3 mg, 89%); mp 79−81 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2963, 2926, 2853, 1715, 1606, 1544, 1516, 1458, 1433, 1371, 1349, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.06−8.08 (m, 2H), 8.00 (s, 1H), 7.65−7.67 (m, 2H), 7.38−7.48 (m, 3H), 6.98−7.00 (m, 2H), 4.48 (q, J = 7.0 Hz, 2H), 3.83 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 161.1, 158.5, 150.0, 149.1, 139.1, 130.1, 129.6, 129.0, 128.6, 127.5, 121.1, 121.0, 114.9, 62.1, 55.8, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{19}NO_3$ $[M + H]^+$ 334.1438, found 334.1439.

*Ethyl 4-(2,5-dimethoxyphenyl)-6-phenylpicolinate (**3ad**):* yellow solid (62.4 mg, 86%); mp 80−82 °C; R_f = 0.50 (EtOAc/hexane = 1:4);

Scheme 5. Synthesis of 2-Amino-4,6-diphenylpyridine (7) and Alpidem Derivative 9



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IR (KBr) ν 2961, 2928, 2837, 1719, 1596, 1543, 1503, 1466, 1427, 1368, 1303 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.07−8.09 (m, 3H), 7.42−7.51 (m, 3H), 6.97−6.98 (m, 3H), 4.50 (q, J = 7.0 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.9, 154.2, 151.1, 148.5, 148.4, 139.2, 129.5, 129.0, 128.4, 127.7, 124.6, 124.3, 116.5, 115.3, 113.2, 62.1, 56.6, 56.2, 14.6; HRMS (ESI) m/z calcd for $C_{22}H_{21}NO_4$ $[M + H]^+$ 364.1543, found 364.1548.

*Ethyl 4-(4-(benzyloxy)-3-methoxyphenyl)-6-phenylpicolinate (**3ae**):* light greenish solid (73.7 mg, 84%); mp 83−85 °C; R_f = 0.43 (EtOAc/hexane = 1:4); IR (KBr) ν 2982, 2936, 2871, 1715, 1593, 1453, 1516, 1468, 1453, 1430, 1384, 1368, 1348, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.10−8.12 (m, 2H), 8.03 (s, 1H), 7.47−7.51 (m, 5H), 7.38−7.41 (m, 2H), 7.33−7.35 (m,1H), 7.26 (s, 2H), 7.01−7.03 (m, 2H), 5.24 (s, 2H), 4.53 (q, J = 6.8 Hz, 2H), 4.01 (s, 3H), 1.49 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 158.5, 150.5, 150.4, 149.8, 149.2, 139.2, 137.0, 131.1, 129.7, 129.1, 128.9, 128.3, 127.8, 127.5, 121.4, 121.3, 120.1, 114.4, 110.9, 71.3, 62.2, 56.6, 14.8; HRMS (ESI) m/z calcd for $C_{28}H_{25}NO_4$ $[M + H]^+$ 440.1856, found 440.1857.

*Ethyl 4-(4-fluorophenyl)-6-phenylpicolinate (**3af**):* white solid (59.9 mg, 93%); mp 90−92 °C; R_f = 0.80 (EtOAc/hexane = 1:4); IR (KBr) ν 2994, 2952, 2902, 1714, 1605, 1550, 1512, 1435, 1371, 1345, 1283, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 1.5 Hz, 1H), 8.09−8.12 (m, 2H), 8.02 (d, J = 1.5 Hz, 1H), 7.70−7.73 (m, 2H), 7.45−7.52 (m, 3H), 7.19−7.23 (m, 2H), 4.51 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 164.0 (J_{C-F} = 248.0 Hz), 158.7, 149.6, 149.3, 138.8, 134.1, 134.1, 129.8, 129.3, 129.2, 129.1, 127.6, 121.6, 121.5, 116.7, 116.5, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{16}FNO_2$ $[M + H]^+$ 322.1238, found 322.1241.

*Ethyl 4-(4-chlorophenyl)-6-phenylpicolinate (**3ag**):* light greenish solid (61.4 mg, 91%); mp 91−93 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2994, 2950, 2898, 1713, 1602, 1543, 1491, 1432, 1372, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.09−8.11 (m, 2H), 8.02 (s, 1H), 7.66−7.67 (m, 2H), 7.44−7.51 (m, 5H), 4.51 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.7, 149.4 (2C), 138.7, 136.4, 136.0, 129.8, 129.7, 129.1, 128.7, 127.6, 121.5, 121.4, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{16}ClNO_2$ $[M + H]^+$ 338.0942, found 338.0938.

*Ethyl 4-(4-cyanophenyl)-6-phenylpicolinate (**3ah**):* white solid (59.1 mg, 90%); mp 105−107 °C; R_f = 0.46 (EtOAc/hexane = 1:4); IR (KBr) ν 2993, 2951, 2900, 2225, 1716, 1599, 1543, 1506, 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.24 (s, 1H), 8.10−8.12 (m, 2H), 8.05 (s, 1H), 7.83 (s, 4H), 7.46−7.52 (m, 3H), 4.52 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.0, 149.6, 148.7, 142.5, 138.4, 133.3, 130.1, 129.2, 128.2, 127.6, 121.6 (2C), 118.5, 113.5, 62.4, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{16}N_2O_2$ $[M + Na]^+$ 351.1104, found 351.1106.

*Ethyl 4-(3-nitrophenyl)-6-phenylpicolinate (**3ai**):* white solid (60.6 mg, 87%); mp 110−112 °C; R_f = 0.43 (EtOAc/hexane = 1:4); IR (KBr) ν 2984, 2929, 2871, 1723, 1599, 1531, 1443, 1423, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.34−8.37 (m, 1H), 8.29 (s, 1H), 8.11−8.15 (m, 3H), 8.06−8.08 (m, 1H), 7.72−7.76 (m, 1H), 7.46−7.55 (m, 3H), 4.54 (q, J = 7.2 Hz, 2H), 1.50 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.2, 149.8, 149.3, 148.2, 139.9, 138.5, 133.4, 130.7, 130.2, 129.3, 127.7, 124.4, 122.5, 121.6 (2C), 62.5, 14.7; HRMS (ESI) m/z calcd for $C_{20}H_{16}N_2O_4$ $[M + Na]^+$ 371.1002, found 371.1027.

*Ethyl 4-(2-furyl)-6-phenylpicolinate (**3aj**):* white solid; yield 85% (49.8 mg); mp 69−71 °C; R_f = 0.66 (EtOAc/hexane = 1:4); IR (KBr) ν 2973, 2926, 2905, 2858, 1735, 1612, 1568, 1551, 1489, 1451, 1428, 1368, 1341, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23−8.24 (m, 1H), 8.09−8.11 (m, 3H), 7.57−7.58 (m, 1H), 7.42−7.51 (m, 3H), 7.00 (d, J = 3.5 Hz, 1H), 6.55−6.56 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.6, 151.1, 149.2, 144.4, 139.5, 138.8, 129.7, 129.0, 127.5, 117.9, 117.4, 112.6, 109.8, 62.2, 14.6; HRMS (ESI) m/z calcd for $C_{18}H_{15}NO_3$ $[M + H]^+$ 294.1125, found 294.1128.

*Ethyl 6-phenyl-4-(2-thiophene-yl)picolinate (**3ak**):* yellow powder (53.2 mg, 86%); mp 75−77 °C; R_f = 0.66 (EtOAc/hexane = 1:4); IR (KBr) ν 2975, 2924, 2901, 1737, 1597, 1552, 1477, 1432, 1367, 1321, 1235, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23−8.24 (m, 1H), 8.08−8.10 (m, 2H), 8.02−8.03 (m, 1H), 7.63−7.64 (m, 1H), 7.45−7.52 (m, 4H), 7.16−7.18 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.8, 149.4, 143.6, 140.9, 138.7, 129.8, 129.1, 128.8, 128.0, 127.5, 126.3, 119.9, 119.7, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{18}H_{15}NO_2S$ $[M + H]^+$ 310.0896, found 310.0904.

*Ethyl 4-phenyl-6-(4-methylphenyl)picolinate (**3ba**):* light yellowish solid (57.7 mg, 91%); mp 63−65 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2976, 2923, 2855, 1732, 1600, 1543, 1367, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.89−7.92 (m, 3H), 7.58−7.60 (m, 2H), 7.33−7.40 (m, 3H), 7.16−7.18 (m, 2H), 4.39 (q, J = 7.0 Hz, 2H), 2.28 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 158.5, 150.5, 149.1, 139.7, 138.0, 136.1, 129.8, 129.6, 129.4, 127.4 (2C),121.4, 121.3, 62.1, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{19}NO_2$ $[M + H]^+$ 318.1489, found 318.1492.

*Ethyl 4,6-bis(4-methylphenyl)picolinate (**3bb**):* pale yellow solid; yield 90% (59.6 mg); mp 65−67 °C; R_f = 0.73 (EtOAc/hexane = 1:4); IR (neat): ν 1713, 1600, 1544, 1514, 1435, 1368, 1344, 1257, 1239 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 1.7 Hz, 1H), 8.03−8.04 (m, 2H), 8.01 (s, 1H), 7.63−7.65 (m, 2H), 7.29−7.33 (m, 4H), 4.52 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.42 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.5, 150.3, 149.0, 139.8, 139.7, 136.2, 135.1, 130.1, 129.7, 127.4, 127.2, 121.2, 121.1, 62.1, 21.5, 21.5, 14.6; HRMS (ESI) m/z calcd for $C_{22}H_{21}NO_2$ $[M + H]^+$ 332.1651, found 332.1655.

*Ethyl 4-(4-methoxyphenyl)-6-(4-methylphenyl)picolinate (**3bc**):* light yellowish solid (60.4 mg, 87%); mp 78−80 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2980, 2903, 1716, 1602, 1543, 1512, 1462, 1434, 1402, 1372, 1348, 1290 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.02 (s, 3H), 7.68−7.70 (m, 2H), 7.29−7.30 (m, 2H), 7.02−7.04 (m, 2H), 4.51 (q, J = 6.8 Hz, 2H), 3.87 (s, 3H), 2.41 (s, 3H), 1.48 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 160.1, 157.5, 148.9, 148.1, 138.7, 135.3, 129.3, 128.8, 127.6, 126.4, 119.9, 119.7, 113.9, 61.1, 54.7, 20.6, 13.6; HRMS (ESI) m/z calcd for $C_{22}H_{21}NO_3$ $[M + H]^+$ 348.1594, found 348.1595.

*Ethyl 4-(2,5-dimethoxyphenyl)-6-(4-methylphenyl)picolinate (**3bd**):* light yellowish solid (64.1 mg, 85%); mp 80−82 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2987, 2961, 2940, 2906, 2836, 1717, 1638, 1596, 1541, 1468, 1426, 1302, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.04 (s, 1H), 7.98−8.00 (m, 2H), 7.28−7.30 (m, 2H), 6.95−6.98 (m, 3H), 4.49 (q, J = 6.5 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.41 (s, 3H), 1.46 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 157.8, 154.2, 151.1, 148.4, 148.2, 139.6, 136.4, 129.7, 128.4, 127.5, 124.2, 124.0, 116.5, 115.2, 113.1, 62.0, 56.6, 56.2, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{23}H_{23}NO_4$ $[M + H]^+$ 378.1700, found 378.1697.

*Ethyl 4-(4-(benzyloxy)-3-methoxyphenyl)-6-(4-methylphenyl)-picolinate (**3be**):* light yellowish solid (76.1 mg, 84%); mp 96−98 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2855, 1715, 1593, 1540, 1516, 1463, 1433, 1409, 1380, 1348, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.94 (s, 1H), 7.91 (s, 2H), 7.38−7.39 (m, 2H), 7.29−7.32 (m, 2H), 7.21−7.23 (m, 3H), 7.16−7.17 (m, 2H), 6.91−6.93 (m, 1H), 5.14 (s, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.91 (s, 3H), 2.33 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.5, 150.4, 150.2, 149.7, 149.0, 139.7, 136.9, 136.2, 131.1, 129.7, 128.9, 128.2, 127.5, 127.4, 121.1, 121.0, 120.1, 114.4, 110.8, 71.2, 62.1, 56.5, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{29}H_{27}NO_4$ $[M + H]^+$ 454.2013, found 454.2020.

*Ethyl 4-(4-fluorophenyl)-6-(4-methylphenyl)picolinate (**3bf**):* white solid (60.5 mg, 90%); mp 88−90 °C; R_f = 0.80 (EtOAc/hexane = 1:4); IR (KBr) ν 2989, 2923, 2860, 1712, 1603, 1548, 1510, 1437,

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1372, 1345, 1241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.99−8.01 (m, 3H), 7.67−7.70 (m, 2H), 7.27−7.29 (m, 2H), 7.17−7.21 (m, 2H), 4.50 (q, J = 7.0 Hz, 2H), 2.40 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 163.9 (J_{C-F} = 248.0 Hz) 158.6, 149.4, 149.2, 139.9, 135.9, 134.2, 134.1, 129.8, 129.2 (2C), 127.4, 121.2, 121.0, 116.6, 116.4, 62.2, 21.5, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{18}FNO_2$ $[M + H]^+$ 336.1394, found 336.1392.

*Ethyl 4-(4-chlorophenyl)-6-(4-methylphenyl)picolinate (**3bg**):* light yellowish solid (61.9 mg, 88%); mp 90−92 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2976, 2925, 2858, 1724, 1600, 1542, 1491, 1441, 1366, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.01 (s, 1H), 7.99 (s, 2H), 7.64−7.66 (m, 2H), 7.47−7.49 (m, 2H), 7.28−7.30 (m, 2H), 4.51 (q, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.7, 149.2 (2C), 139.9, 136.5, 135.9, 135.9, 129.8, 129.7, 128.6, 127.4, 121.1, 121.0, 62.2, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{18}ClNO_2$ $[M + H]^+$ 352.1099, found 352.1100.

*Ethyl 4-(2-furyl)-6-(4-methylphenyl)picolinate (**3bj**):* gummy liquid (51.6 mg, 84%); R_f = 0.66 (EtOAc/hexane = 1:4); IR (KBr) ν 2922, 2853, 1719, 1609, 1548, 1486, 1431, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 1.5 Hz, 1H), 8.09 (d, J = 1.3 Hz, 1H), 8.00−8.02 (m, 2H), 7.57−7.58 (m, 1H), 7.28−7.30 (m, 2H), 7.00−7.01 (m, 1H), 6.55−6.57 (m 1H), 4.50 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.6, 151.3, 149.1, 144.4, 139.9, 139.5, 136.0, 129.8, 127.4, 117.7, 117.1, 112.6, 109.8, 62.2, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_3[M + H]^+$ 308.1281, found 308.1286.

*Ethyl 4-(2-thiophene-yl)-6-(4-methylphenyl)picolinate (**3bk**):* yellow powder (53.6 mg, 83%); mp 80−82 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2923, 2855, 1736, 1593, 1548, 1420, 1366, 1320, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 1.2 Hz, 1H), 7.98−8.00 (m, 3H), 7.62 (d, J = 3.8 Hz, 1H), 7.44 (d, J = 5.2 Hz, 1H), 7.28−7.31 (m, 2H), 7.14−7.16 (m, 1H), 4.51 (q, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.7, 149.2, 143.5, 141.0, 139.9, 135.9, 129.8, 128.8, 127.8, 127.4, 126.2, 119.6, 119.4, 62.2, 21.6, 14.6; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_2S$ $[M + H]^+$ 324.1053, found 324.1057.

*Ethyl 6-(4-methoxyphenyl)-4-phenylpicolinate (**3ca**):* yellow powder (53.3 mg, 87%); mp 77−79 °C; R_f = 0.50 (EtOAc/hexane =1:4); IR (KBr) ν 2970, 2926, 2852, 1734, 1601, 1543, 1515, 1451, 1415, 1366, 1345, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.99 (s, 1H), 7.68−7.70 (m, 2H), 7.44−7.50 (m, 3H), 6.98 (d, J = 8.7 Hz, 2H), 4.48 (q, J = 7.0 Hz, 2H), 3.83 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 161.1, 158.2, 150.5, 149.0, 138.1, 131.5, 129.6, 129.4, 128.9, 127.4, 121.1, 120.9, 114.4, 62.1, 55.6, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{19}NO_3$ $[M + H]^+$ 334.1438, found 334.1444.

*Ethyl 4-(4-chlorophenyl)-6-(4-methoxyphenyl)picolinate (**3cg**):* yellowish solid (65.5 mg, 89%); mp 92−94 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2988, 2960, 2936, 2901, 1731, 1601, 1543, 1516, 1487, 1462, 1421, 1366, 1347, 1311 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.06−8.08 (m, 2H), 7.96 (s, 1H), 7.64−7.66 (m, 2H), 7.47−7.49 (m, 2H), 7.00−7.02 (m, 2H), 4.50 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 161.2, 158.3, 149.2 (2C), 136.6, 135.9, 131.3, 129.7, 128.9, 128.7, 120.8, 120.6, 114.5, 62.2, 55.6, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{18}ClNO_3$ $[M + Na]^+$ 390.0867, found 390.0882.

*Ethyl 6-(4-fluorophenyl)-4-phenylpicolinate (**3da**):* orange solid; yield 88% (56.5 mg); mp 91−93 °C; R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 2989, 2920, 2856, 1711, 1602, 1547, 1510, 1447, 1419, 1372, 1344, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.10−8.13 (m, 2H), 8.03 (s, 1H), 7.72−7.74 (m, 2H), 7.47−7.55 (m, 3H), 7.16−7.20 (M, 2H), 4.51 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 164.2 (J_{C-F} = 248.0 Hz) 157.6, 150.9, 149.3, 137.9, 135.2, 129.8, 129.6, 129.5, 127.4, 121.8, 121.4, 116.2, 116.0, 62.3, 14.7; HRMS (ESI) m/z calcd for $C_{20}H_{16}FNO_2[M + H]^+$ 322.1238, found 322.1233.

*Ethyl 6-(4-chlorophenyl)-4-phenylpicolinate (**3ea**):* pale yellow solid; yield 89% (60.1 mg); mp 85−87 °C; R_f = 0.83 (EtOAc/hexane = 1:4); IR (KBr) ν 2983, 2959, 2855, 1725, 1598, 1546, 1490, 1444, 1406, 1369, 1345, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.06−8.08 (m, 3H), 7.71−7.73 (m, 2H), 7.45−7.54 (m, 5H), 4.51 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 157.3, 150.9, 149.3, 137.8, 137.3, 135.9, 129.8, 129.5, 129.3, 128.8, 127.4, 122.0, 121.4, 62.2, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{16}ClNO_2$ $[M + H]^+$ 338.0942, found 338.0945.

*Ethyl 6-(4-chlorophenyl)-4-(2-furyl)picolinate (**3ej**):* pale yellow solid; yield 82% (53.7 mg); mp 89−91 °C; R_f = 0.83 (EtOAc/hexane = 1:4); IR (KBr) ν 2980, 2960, 2925, 2853, 1721, 1610, 1547, 1491, 1368, 1342, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.03−8.06 (m, 3H), 7.58−7.59 (m, 1H), 7.44−7.46 (m, 2H), 7.01−7.02 (m, 1H), 6.56−6.57 (m, 1H), 4.50 (q, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 157.3, 151.0, 149.2, 144.6, 139.7, 137.2, 136.0, 129.2, 128.8, 118.2, 117.1, 112.7, 110.1, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{18}H_{14}ClNO_3$ $[M + H]^+$ 328.0735, found 328.0751.

*Ethyl 6-(2-chlorophenyl)-4-phenylpicolinate (**3fa**):* white solid; yield 90% (60.8 mg); mp 90−92 °C; R_f = 0.66 (EtOAc/hexane = 1:4); IR (KBr) ν 2991, 2960, 2942, 2901, 1718, 1640, 1601, 1548, 1499, 1479, 1447, 1425, 1386, 1368, 1343, 1288, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.05 (s, 1H), 7.71−7.74 (m, 3H), 7.48−7.54 (s, 4H), 7.34−7.41 (m, 2H), 4.52 (q, J = 6.5 Hz, 2H), 1.48 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 157.9, 149.6, 149.3, 138.9, 137.7, 132.6, 132.3, 130.4, 130.3, 129.8, 129.5, 127.5, 127.5, 126.2, 122.1, 62.3, 14.7; HRMS (ESI) m/z calcd for $C_{20}H_{16}ClNO_2[M + H]^+$ 338.0942, found 338.0943.

*Ethyl 6-(2-chlorophenyl)-4-(4-trifluoromethylphenyl)picolinate (**3fl**):* pale yellow solid; yield 87% (70.6 mg); mp 99−101 °C; R_f = 0.56 (EtOAc/hexane = 1:4); IR (KBr) ν 2989, 2924, 2854, 1715, 1605, 1546, 1378, 1327, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 1.4 Hz, 1H), 8.06 (d, J = 1.4 Hz, 1H), 7.77−7.85 (m, 4H), 7.71−7.74 (m, 1H), 7.48−7.50 (m, 1H), 7.35−7.42 (m, 2H), 4.52 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 158.1, 149.5, 148.2, 141.2, 141.2, 138.5, 132.5, 132.3,131.6, 130.5, 130.4, 128.0, 127.6, 126.6, 126.5, 126.5, 126.5, 126.5, 125.5, 122.8, 122.1, 62.5, 14.6; HRMS (ESI) m/z calcd for $C_{21}H_{15}ClF_3NO_2$ $[M + H]^+$ 406.0816, found 406.0819.

*Ethyl 6-(4-bromophenyl)-4-phenylpicolinate (**3ga**):* light green solid; yield 86% (65.7 mg); mp 93−95 °C; R_f = 0.83 (EtOAc/hexane = 1:4); IR (KBr)ν 2982, 2926, 2901, 2854, 1727, 1596, 1548, 1488, 1442, 1405, 1369, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.04 (s, 1H), 7.99−8.01 (m, 2H), 7.72−7.73 (m, 2H), 7.61−7.63 (m, 2H), 7.47−7.55 (m, 3H), 4.51 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 157.3, 150.9, 149.3, 137.8, 137.8, 132.2, 129.9, 129.5, 129.1, 127.4, 124.3, 122.1, 121.4, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{16}{}^{79}BrNO_2$ $[M + H]^+$ 382.0437, found 382.0457; HRMS (ESI) m/z calcd for $C_{20}H_{16}{}^{81}BrNO_2$ $[M + H]^+$ 384.0418, found 384.0434.

*Ethyl 6-(4-bromophenyl)-4-(2,5-dimethoxyphenyl)picolinate (**3gd**):* orange solid; yield 85% (75.2 mg); mp 99−101 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2960, 2933, 2834, 1734, 1639, 1598, 1545, 1495, 1462, 1421, 1400, 1371, 1339, 1301, 1278, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.03 (s, 1H), 7.96−7.98 (m, 2H), 7.59−7.62 (m, 2H), 6.96−6.97 (m, 3H), 4.49 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 156.6, 154.2, 151.0, 148.6, 148.6, 138.0, 132.2, 129.2, 128.1, 124.6, 124.3, 124.1, 116.5, 115.4, 113.1, 62.1, 56.6, 56.2, 14.6; HRMS (ESI) m/z calcd for $C_{22}H_{20}{}^{79}BrNO_4$ $[M + H]^+$ 442.0648, found 442.0656; HRMS (ESI) m/z calcd for $C_{22}H_{20}{}^{81}BrNO_4$ $[M + H]^+$ 444.0629, found 444.0644.

*Ethyl 6-(4-bromophenyl)-4-(4-fluorophenyl)picolinate (**3gf**):* pale yellow solid; yield 88% (70.4 mg); mp 100−102 °C; R_f = 0.83 (EtOAc/hexane = 1:4); IR (KBr) ν 2987, 2925, 2905, 1717, 1640, 1603, 1549, 1512, 1490, 1439, 1397, 1369, 1345, 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.98−8.00 (m 3H), 7.69−7.72 (m,

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2H), 7.60−7.62 (m, 2H), 7.19−7.23 (m, 2H), 4.51 (q, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 164.0 (J_{C-F} = 248.0 Hz), 157.4, 149.8, 149.4, 137.7, 133.9, 132.3, 129.3, 129.1, 124.4, 121.8, 121.1, 116.7, 116.5, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{15}{}^{79}BrFNO_2$ [M + H]$^+$ 400.0343, found 400.0352; HRMS (ESI) m/z calcd for $C_{20}H_{15}{}^{81}BrFNO_2$ [M + H]$^+$ 402.0323, found 402.0337.

*Ethyl 6-(4-bromophenyl)-4-(4-chlorophenyl)picolinate (**3gg**):* pale yellow solid; yield 87% (72.5 mg); mp 105−107 °C; R_f = 0.83 (EtOAc/hexane = 1:4); IR (KBr) ν 2980, 2924, 2855, 1725, 1602, 1543, 1494, 1442, 1368, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.23 (m, 1H), 7.98−8.00 (m, 2H), 7.97 (s, 1H), 7.61−7.67 (m, 4H), 7.49−7.51 (m, 2H), 4.51 (q, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 157.5, 149.6, 149.5, 137.6, 136.2, 136.2, 132.3, 129.8, 129.1, 128.7, 124.5, 121.8, 121.1, 62.4, 14.6; HRMS (ESI) m/z calcd for $C_{20}H_{15}{}^{79}BrClNO_2$ [M + H]$^+$ 416.0047, found 416.0058; HRMS (ESI) m/z calcd for $C_{20}H_{15}{}^{81}BrClNO_2$ [M + H]$^+$ 418.0027, found 418.0037.

*Ethyl 6-(4-bromophenyl)-4-(2-furyl)picolinate (**3gi**):* brown solid; yield 82% (61.0 mg); mp 100−102 °C; R_f = 0.50 (EtOAc/hexane = 1:4); IR (KBr) ν 2974, 2925, 2855, 1730, 1609, 1546, 1487, 1418, 1367, 1338, 1241 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.05 (s, 1H), 7.96−7.98 (m, 2H), 7.59−7.61 (m, 3 H), 7.00−7.01 (m, 1H), 6.56 (s, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 156.3, 149.9, 148.2, 143.5, 138.7, 136.6, 131.1, 128.0, 123.3, 117.1, 116.0, 111.6, 109.1, 61.2, 13.6; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{79}BrNO_3$ [M + H]$^+$ 372.0230, found 372.0245; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{81}BrNO_3$ [M + H]$^+$ 374.0210, found 374.0225.

*Ethyl 6-(4-bromophenyl)-4-(2-thiophene-yl)picolinate (**3gk**):* yellowish solid; yield 84% (65.2 mg); mp 101−103 °C; R_f = 0.73 (EtOAc/hexane = 1:4); IR (KBr) ν 2979, 2925, 2901, 2856, 1731, 1598, 1549, 1485, 1443, 1422, 1368, 1323, 1239, 1211 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.24 (m, 1H), 7.98−7.99 (m, 2H), 7.96 (s, 1H), 7.63−7.64 (m, 2H), 7.61 (s, 1H), 7.47−7.48 (m, 1H), 7.16−7.19 (m, 1H), 4.51 (q, J = 7.0 Hz, 1H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 157.3, 151.0, 149.3, 144.6, 139.7, 137.6, 132.2, 129.0, 124.3, 118.2, 117.0, 112.7, 110.1, 62.3, 14.6; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{79}BrNO_2S$[M + H]$^+$ 388.0001, found 388.0009; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{81}BrNO_2S$ [M + H]$^+$ 389.9981, found 389.9988.

*(E)-Ethyl 6-phenyl-4-styrylpicolinate (**3am**):* light yellow liquid; yield 85% (56.0 mg); R_f = 0.80 (EtOAc/hexane = 1:4); IR (KBr) ν 3059, 2980, 1738, 1714, 1635, 1595, 1546, 1432, 1370, 1252, 1193, 1084, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.09 (d, J = 7.6 Hz, 2H), 7.91 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.39−7.52 (m, 7H), 7.12−7.18 (m, 1H), 4.52 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.3, 148.8, 146.6, 138.7, 135.9, 134.1, 129.4, 129.0, 128.9, 128.8, 127.3, 127.1, 125.5, 120.9, 120.3, 61.9, 14.3; HRMS (ESI) m/z calcd for $C_{22}H_{19}NO_2$[M + H]$^+$ 330.1489, found 330.1478.

*(E)-Ethyl 4-(4-methoxystyryl)-6-phenylpicolinate (**3an**):* light yellow gummy liquid; yield 82% (58.9 mg); R_f = 0.65 (EtOAc/hexane = 1:4); IR (neat): ν 1738, 1714, 1591, 1579, 1545, 1510, 1435, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.01 (d, J = 7.6 Hz, 2H), 7.81 (s, 1H), 7.31−7.46 (m, 6H), 6.85−6.95 (m, 2H), 4.43 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 160.7, 158.5, 149.0, 147.3, 139.1, 134.0, 129.6, 129.0, 129.0, 128.9, 127.5, 123.5, 120.9, 120.4, 114.7, 62.2, 55.7, 14.7; HRMS (ESI) m/z calcd for $C_{23}H_{21}NO_3$ [M + H]$^+$ 360.1594, found 360.1595.

*(E)-Ethyl 4-styryl-6-(4-methylphenyl)picolinate (**3bm**):* light yellow liquid; yield 80% (54.9 mg); R_f = 0.76 (EtOAc/hexane = 1:4); IR (KBr) ν 3029, 2979, 2855, 1738, 1714, 1636,1596, 1546,1447, 1424, 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.92 (d, J = 7.8 Hz, 2H), 7.81 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.17−7.38 (m, 6H), 7.03−7.07 (m, 1H), 4.43 (q, J = 7.0 Hz, 2H), 2.34 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 158.3, 148.8, 146.5, 139.5, 136.0, 135.9, 134.0, 129.5, 129.0, 128.9, 127.2, 127.1, 125.6, 120.6, 120.0, 61.9, 21.3, 14.4; HRMS (ESI) m/z calcd for $C_{23}H_{21}NO_2$ [M + H]$^+$ 344.1645, found 344.1635.

*(E)-Ethyl 6-(4-bromophenyl)-4-styrylpicolinate (**3gm**):* light yellow gummy liquid; yield 79% (67.7 mg); R_f = 0.73 (EtOAc/hexane = 1:4); IR (KBr) ν 3058, 2979, 2923, 1737, 1716, 1635, 1597, 1545, 1491, 1446, 1251 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.88 (s, 1H), 7.57−7.63 (m, 4H), 7.35−7.47 (m, 4H), 7.11−7.16 (m, 1H), 4.51 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 157.0, 148.9, 146.8, 137.5, 135.8, 134.4, 131.9, 129.1, 128.9, 128.8, 127.2, 125.2, 124.0, 120.5, 62.0, 14.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}{}^{79}BrNO_2$ [M + H]$^+$ 408.0594, found 408.0614; HRMS (ESI) m/z calcd for $C_{22}H_{18}{}^{81}BrNO_2$ [M + H]$^+$ 410.0574, found 410.0607.

Synthesis of 2-Amino-4,6-diphenylpyridine (9). $LiOH{\cdot}H_2O$ (210 mg, 5.0 mmol) was added to a stirred solution of ethyl 4,6-diphenylpicolinate (**3aa**, 303.3 mg, 1.0 mmol) in $MeCN/H_2O$ (5.0 mL, 4:1) at room temperature. Then the reaction mixture was allowed to stir for 5 h (monitored by TLC). After completion of the reaction, organic solvent was removed by rotary evaporator and acidified with 1 M acetic acid. The water layer was extracted with ethyl acetate (5 × 10 mL), washed with brine solution, and dried over Na_2SO_4. Evaporation of the solvent left the crude 4,6-diphenylpicolinic acid, which was reasonable pure and directly used for the next step without further purification.

A mixture of the resultant 4,6-diphenylpicolinic acid, DPPA (385.0 mg, 1.4 mmol), and triethylamine (405.0 mg, 4.0 mmol) in toluene (2.0 mL) was heated at 65 °C for 2 h and then 100 °C for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3 × 10 mL) before being quenched with water. The combined organic layer was washed with brine solution and dried over Na_2SO_4. Afterward, the organic phase was concentrated under reduced pressure to furnish the crude product. It was purified by flash chromatography over silica gel using EtOAc/hexane (2:3 v/v) as the eluent to give **2**-amino-4,6-diphenylpyridine (**7**) in 78% yield (191.9 mg, overall).

*2-Amino-4,6-diphenylpyridine (**7**):*.[17] pale yellow solid; R_f = 0.50 (EtOAc/hexane = 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 7.4 Hz, 2H), 7.39−7.49 (m, 6H), 7.31 (s, 1H), 6.67 (s, 1H), 4.66 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.5, 151.2, 139.5, 139.0, 128.8, 128.7, 128.7, 128.5, 126.9 (2C), 110.0, 105.1; HRMS (ESI) m/z calcd for $C_{17}H_{14}N_2$ [M + H]$^+$ 247.1230, found 247.1228.

Typical Procedure for the Synthesis of Ethyl 2-(2-(4-Chlorophenyl)-5,7-diphenylimidazo[1,2-*a*]pyridin-3-yl)acetate (8).[11a] 2-Amino-4,6-diphenylpyridine (7, 123.0 mg, 0.5 mmol) and MBH acetate (**2g**, 180.23 mg, 0.55 mmol) were stirred in MeOH (4.0 mL) for 2 h (monitored by TLC). Upon completion of the reaction, the reaction mixture was extracted by ethyl acetate (3 × 10 mL) before removal of MeOH. The combined organic layer was washed with brine solution and dried over sodium sulfate. The organic phase was removed by rotary evaporator to furnish the crude product which was purified by flash chromatography over silica gel (EtOAc/hexane = 2:3 as an eluent) to give ethyl 2-(2-(4-chlorophenyl)-5,7-diphenylimidazo-[1,2-*a*]pyridin-3-yl)acetate (**8**, 81% yield) as a yellow solid product.

*Ethyl 2-(2-(4-chlorophenyl)-5,7-diphenylimidazo[1,2-a]pyridin-3-yl)acetate (**8**):* yellow solid; R_f = 0.45 (EtOAc/hexane = 2:3); yield 81% (189.0 mg); IR (neat) ν 1731, 1597, 1545, 1487, 1473, 1367, 1254, 1186 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.39−7.54 (m, 10H), 6.96 (s, 1H), 3.89 (q, 7.2 Hz, 2H), 3.54 (s, 2H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 146.9, 146.2, 138.6, 138.3, 137.1, 134.4, 134.0, 132.9, 130.1, 129.9, 129.5, 129.0, 128.7, 128.3, 128.2, 126.7, 115.2, 114.8, 113.5, 61.0, 32.3, 13.9; HRMS (ESI) m/z calcd for $C_{29}H_{23}ClN_2O_2$ [M + H]$^+$ 467.1521, found 467.1509.

Experimental Procedure for the Synthesis of 2-(2-(4-Chlorophenyl)-5,7-diphenylimidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-Dipropylacetamide (9). $LiOH{\cdot}H_2O$ (126.0 mg, 3.0 mmol) was added at room temperature to a stirred solution of ethyl 2-(2-(4-

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chlorophenyl)-5,7-diphenylimidazo[1,2-*a*]pyridin-3-yl)acetate (**8**, 140.0 mg, 0.3 mmol) in MeCN/H_2O (4.0 mL, 3:1). Afterward, the reaction mixture was heated at 60 °C for 12 h. After completion of the reaction (monitored by TLC), solvent was removed by rotary evaporator to provide the crude mass which was acidified with 1 M acetic acid solution. The water layer was extracted with ethyl acetate (5 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Next, the organic phase was evaporated under reduced pressure to obtain the crude imidazopyridine carboxylic acid as a white solid which was sufficiently pure to carry out the next step.

A mixture of imidazopyridine carboxylic acid, EDCI·HCl (0.45 mmol), Et_3N (1.0 mmol), DMAP (0.06 mmol), and *N*,*N*-dipropylamine (0.6 mmol) in DMF (1.0 mL) was stirred at room temperature under argon atmosphere for 12 h (monitored by TLC). Then the reaction mixture was extracted with ethyl acetate (3 × 10 mL) before being quenched with saturated NH_4Cl solution. The combined rganic layers were washed with brine and dried over Na_2SO_4. Next, evaporation of the organic slovent left the crude material, which was purified by column chromatography over silica gel (EtOAc/hexane 1:4 as a mixture of solvent) to furnish the pure product (**9**, 128.4 mg, 82% yield, two steps).

*2-(2-(4-Chlorophenyl)-5,7-diphenylimidazo[1,2-a]pyridin-3-yl)-N,N-dipropylacetamide (**9**):* yellow solid; yield 82%; R_f = 0.40 (EtOAc/hexane = 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.36−7.58 (m, 12H), 6.89 (s, 1H), 3.49 (s, 2H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 8.0 Hz, 2H), 1.45−1.51 (m, 2H), 1.19−1.24 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 146.9, 145.6, 138.5, 138.4, 136.7, 135.2, 133.6, 133.4, 130.1, 130.0, 129.1, 129.0, 128.5, 128.1, 128.0, 126.7, 116.6, 115.1, 113.6, 49.6, 48.4, 31.5, 21.8, 20.9, 11.5, 11.2; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{32}ClN_3O$ $[M + H]^+$ 522.2307, found 522.2313.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00472.

IR and ^{1}H and ^{13}C NMR spectra for the products (PDF)
X-ray crystal data for compound **3bd** (CIF)

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Notes

The authors declare no competing financial interest.

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