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$FeCl_3$-Catalyzed Four-Component Nucleophilic Addition/Intermolecular Cyclization Yielding Polysubstituted Pyridine Derivatives

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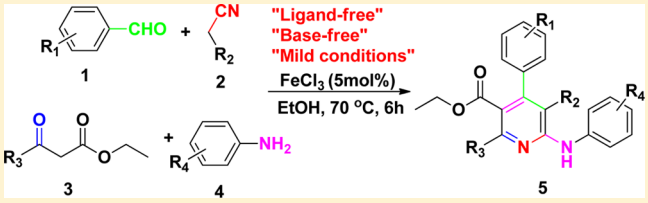
Supporting Information

ABSTRACT: We report an efficient route to pyridine derivatives via an $FeCl_3$-catalyzed four-component nucleophilic addition/intermolecular cyclization. This simple fragment assembly strategy uses mild conditions and affords a broad range of polysubstituted pyridines in moderate to good yield from simple and readily available starting materials. A plausible mechanism for this process is proposed.

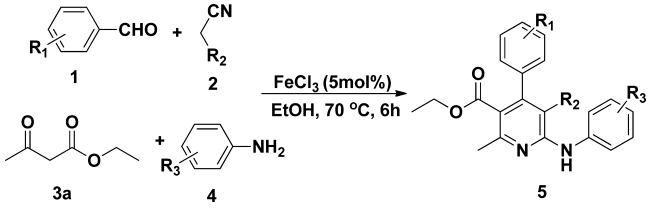


Pyridine derivatives are among the most important classes of nitrogen-containing heterocycles; they are found in many natural products, pharmaceutical agents, and functionalized materials.[1−3] These derivatives possess activity against a wide variety of pathogens and illnesses, such as prions,[4] hepatitis B virus,[5] bacteria,[6] and cancer.[7] Recently, pyridine derivatives have been proposed as potential therapies for Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer, and Creutzfeldt-Jakob disease.[8−10] During recent decades, facile methods, such as the Chichibabin,[11] Kröhnke,[12] Boger,[13] and Hantzsch reactions,[14] have been developed for constructing the pyridine framework. In consideration of efficiency, novel synthetic methods under mild conditions are not only of fundamental interest but are also needed for practical applications.[15] To date, typical methods include reductive cyclizations, such as transition metal catalyzed [2 + 2+2] cycloadditions,[16] copper-catalyzed C−N bond cleavage in aromatic methylamines,[17] synergistic copper/iminium-catalyzed [3 + 3] condensations,[18] and ZnO nanoparticle catalyzed multicomponent reactions.[19]

Multicomponent reactions (MCRs) have gained tremendous attention from medicinal and organic chemists because they offer highly convergent routes to complex molecules. These methods offer rapid and convergent construction of complex molecules without isolation and purification of intermediates, minimizing waste, effort, time, and cost.[20] Thus, they can satisfy the need for high-throughput screening of new bioactive molecules with diverse scaffolds.[21] Owing to their abundance, affordability, and environmental friendliness, Fe[22]-based catalytic MCRs have achieved popularity in promoting a broad range of organic transformations. We previously reported an efficient synthesis of functionalized coumarin derivatives via an $FeCl_3$-catalyzed cascade reaction between salicylaldehydes and activated methylene compounds.[23] We expected this type of MCR to be an effective route to pyridine derivatives; more work should be conducted to test this possibility.

During our ongoing studies on transition metal-mediated synthesis of heterocyclic compounds, we found that pyridines could be efficiently prepared using an iron catalyst under mild reaction conditions. Herein, we report an efficient synthetic pathway to polysubstituted pyridines involving nucleophilic addition/intermolecular cyclization catalyzed by $FeCl_3$ under mild conditions in moderate to good yields (Scheme 1).

Scheme 1. Synthesis of Polysubstituted Pyridines via an $FeCl_3$-Catalyzed Four-Component Reaction



Initially, 4-nitrobenzaldehyde (**1b**), malononitrile (**2a**), ethyl acetoacetate (**3a**), and aniline (**4a**) served as model substrates for optimization of the four-component reaction conditions; results are given in Table 1. Transition metal catalysts, such as $FeCl_3$, $NiCl_2·6H_2O$, $CuSO_4$, $CuBr_2$, and $AgNO_3$, were examined first (Table 1, entries 2−6). Of these, $FeCl_3$ (15 mol %) was found to be the best catalyst, giving **5b** in 80% yield (Table 1, entry 2). In the absence of catalyst, only 35% yield was obtained, even after 24 h (Table 1, entry 1). Further screening of solvents showed that ethanol gave the best result in comparison to DMF, toluene, acetonitrile, H_2O, DMSO, THF, and methanol (Table 1, entries 7−14). Here, the yield could not be improved by increasing the amount of catalyst (Table 1, entries 16, 17). While decreasing the amount of

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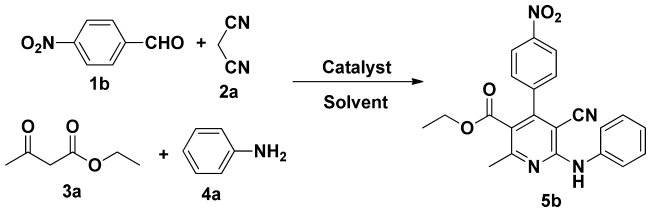
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	solvent	temp./°C	time/h	yield/%[b]
1	—	EtOH	70	24	35
2	$FeCl_3$ (15)	EtOH	70	8	80
3	$NiCl_2{\cdot}6H_2O$ (15)	EtOH	70	8	62
4	$CuSO_4$ (15)	EtOH	70	8	15
5	$CuBr_2$ (15)	EtOH	70	8	50
6	$AgNO_3$ (15)	EtOH	70	8	45
7	$FeCl_3$ (10)	DMF	70	10	trace
8	$FeCl_3$ (10)	Toluene	70	10	50
9	$FeCl_3$ (10)	CH_3CN	70	10	10
10	$FeCl_3$ (10)	H_2O	70	10	60
11	$FeCl_3$ (10)	DMSO	70	10	trace
12	$FeCl_3$ (10)	THF	70	10	40
13	$FeCl_3$ (10)	CH_3OH	70	10	80
14	$FeCl_3$ (10)	EtOH	70	10	81
15	$FeCl_3$ (5)	EtOH	70	6	82
16	$FeCl_3$ (20)	EtOH	70	6	79
17	$FeCl_3$ (30)	EtOH	70	6	79
18	$FeCl_3$ (5)	EtOH	rt	18	25
19	$FeCl_3$ (5)	EtOH	50	10	72
20	$FeCl_3$ (5)	EtOH	100	8	81
21	$FeCl_3$ (5)	EtOH	70	2	41
22	$FeCl_3$ (5)	EtOH	70	5	80
23	$FeCl_3$ (5)	EtOH	70	10	83
24	$FeCl_3$ (2)	EtOH	70	18	57

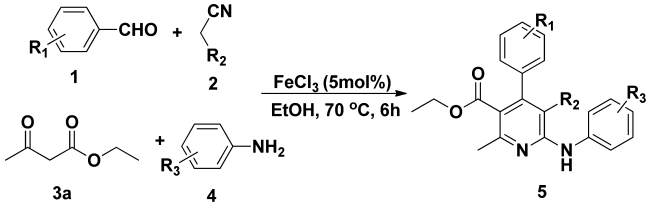
[a]Reaction conditions: 4-nitrobenzaldehyde **1b** (1.0 mmol), malononitrile **2a** (1.0 mmol), ethyl acetoacetate **3a** (1.0 mmol), aniline **4a** (1.0 mmol), catalyst, solvent (3 mL). [b]Isolated yield.

catalyst to 5 mol %, the desired compound was still obtained in 82% comparable yield (Table 1, entry 15). However, the product yield dropped to 57% when further decreasing the catalyst loading to 2 mol % (Table 1, entry 24) after 18 h. Moreover, decreasing or increasing the reaction temperature was detrimental to the yield (Table 1, entries 18–20). Therefore, the optimum reaction conditions giving an 82% yield of the polysubstituted pyridine (**5b**) were 5 mol % of $FeCl_3$, 6 h reaction time, and 70 °C reaction temperature.

After the reaction conditions were optimized, the substrate scope was examined with various aromatic aldehydes **1**, activated methylene compounds **2**, and aromatic amines **4**. The results are summarized in Table 2.

Among various aromatic aldehydes **1** investigated, electron-withdrawing groups (-NO_2, -Cl, -Br) generally gave higher yields (Table 2, entries 2, 4, 5) than electron-donating groups (-OCH_3, -CH_3) (Table 2, entries 6, 7). It should be noted that the positions of these substituents had an obvious effect on the reaction. When aromatic aldehydes bearing *ortho* electron-withdrawing groups (-NO_2, -Br, -OCH_3) were used, lower yields were obtained (Table 2, entries 8–10). When ethyl α-cyanoacetate (**2b**) was used as substrate, the reaction appeared to be quite general with respect to malononitrile (**2a**), and the desired products **5v**, **5w**, **5x**, and **5y** were obtained in 47%, 48%, 39%, and 38% yields, respectively. Among various substituted

Table 2. $FeCl_3$-Catalyzed Four-Component Reaction for the Formation of Polysubstituted Pyridines[a]



entry	R_1	R_2	R_3	product	yield/%[b]
1	H (**1a**)	CN (**2a**)	H (**4a**)	**5a**	75
2	4-NO_2 (**1b**)	**2a**	**4a**	**5b**	82
3	3-NO_2 (**1c**)	**2a**	**4a**	**5c**	83
4	4-Cl (**1d**)	**2a**	**4a**	**5d**	76
5	4-Br (**1e**)	**2a**	**4a**	**5e**	75
6	4-CH_3 (**1f**)	**2a**	**4a**	**5f**	75
7	4-OCH_3 (**1g**)	**2a**	**4a**	**5g**	62
8	2-NO_2 (**1h**)	**2a**	**4a**	**5h**	70
9	2-Br (**1i**)	**2a**	**4a**	**5i**	68
10	2-OCH_3 (**1j**)	**2a**	**4a**	**5j**	60
11	H (**1a**)	CN (**2a**)	4-CH_3 (**4b**)	**5k**	78
12	4-NO_2 (**1b**)	**2a**	**4b**	**5l**	86
13	3-NO_2 (**1c**)	**2a**	**4b**	**5m**	85
14	4-Cl (**1d**)	**2a**	**4b**	**5n**	83
15	4-Br (**1e**)	**2a**	**4b**	**5o**	82
16	4-CH_3 (**1f**)	**2a**	**4b**	**5p**	81
17	2-NO_2 (**1h**)	**2a**	**4b**	**5q**	80
18	2,4-Cl_2 (**1k**)	**2a**	**4b**	**5r**	72
19	3-NO_2 (**1c**)	**2a**	3-NO_2 (**4c**)	**5s**	52
20	4-Cl (**1d**)	**2a**	3-NO_2 (**4c**)	**5t**	46
21	4-Br (**1e**)	**2a**	3-NO_2 (**4c**)	**5u**	45
22	4-NO_2 (**1b**)	COOEt (**2b**)	**4a**	**5v**	47
23	3-NO_2 (**1c**)	**2b**	**4a**	**5w**	48
24	4-Cl (**1d**)	**2b**	**4a**	**5x**	39
25	4-Br (**1e**)	**2b**	**4a**	**5y**	38

[a]Reaction conditions: aromatic aldehyde **1** (1.0 mmol), activated methylene compound **2** (1.0 mmol), ethyl acetoacetate **3a** (1.0 mmol), aromatic amine **4** (1.0 mmol), $FeCl_3$ (5 mol %), ethanol (3 mL), 70 °C, 6 h. [b]Isolated yield.

aromatic amines **4** investigated, electron-donating groups (Table 2, entries 13–15) gave higher yields than electron-withdrawing groups (Table 2, entries 19–21). The chemical structure of compound **5f** was unequivocally confirmed by single-crystal X-ray analysis as shown in Figure 1 in the Supporting Information (SI).

To test the versatility of this reaction, the optimized conditions were applied to other nucleophiles, such as ethanol (Scheme 2) and ammonium chloride (Scheme 3). In comparison with aromatic amines, when ethanol was used (Scheme 2), the desired products **7a**, **7b**, and **7c** were obtained in 75%, 73%, and 68% yield, respectively.

Initial mechanistic studies indicated that an intermediate formed after 3 h and gradually transformed to the polysubstituted pyridine product. We isolated this intermediate and found it to be 1,4-dihydropyridine **6** (Scheme 4). The structure of intermediate **6a** was confirmed by X-ray analysis as shown in Figure 2 in the SI. Treatment of **6a** with 5 mol % $FeCl_3$ in ethanol afforded a polysubstituted pyridine in 85% yield. However, ammonium chloride as substrate did not give the desired product under these conditions (Scheme 2). In

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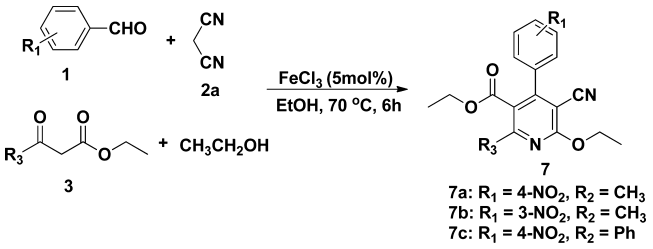
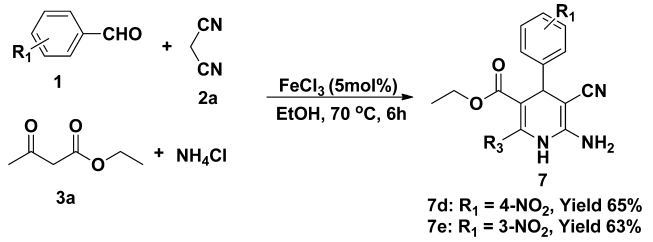
Scheme 2. Synthesis of 2-Alkoxy Pyridines via an $FeCl_3$-Catalyzed Four-Component Reaction between Aromatic Aldehydes, Malononitrile, β-Ketoesters, And Ethanol



Scheme 3. Synthesis of 2-Amino-1,4-dihydropyridines via an $FeCl_3$-Catalyzed Four-Component Reaction between Aromatic Aldehydes, Malononitrile, β-Ketoesters, And Ammonium Chloride



contrast, the reaction stopped at the 1,4-dihydropyridines, giving **7d** and **7e** in 65% and 63% yield, respectively, illustrating that the conjugation effect of the aromatic ring bearing amino group can promote the aromatization of 1,4-dihydropyridines based on the planar structure of the compound **5f**.

On the basis of previous studies[24] and our experimental results, a possible reaction mechanism is proposed in Scheme 4. First, the intermediate **A** is produced by the Knoevenagel condensation between aromatic aldehydes **1** and malononitrile **2a**. Then, intermediate **B** is produced from Michael addition of ethyl acetoacetate **3** on intermediate **A**. Subsequently, aromatic amine **4** attacks **B** to form **C**, which isomerizes to **D**. Then, intermediate **6** results from intermolecular cycloaddition with loss of H_2O from intermediate **E**, which is derived in turn from **D**. Finally, $FeCl_3$-oxidized aromatization of intermediate **6** furnishes the final product **5**.

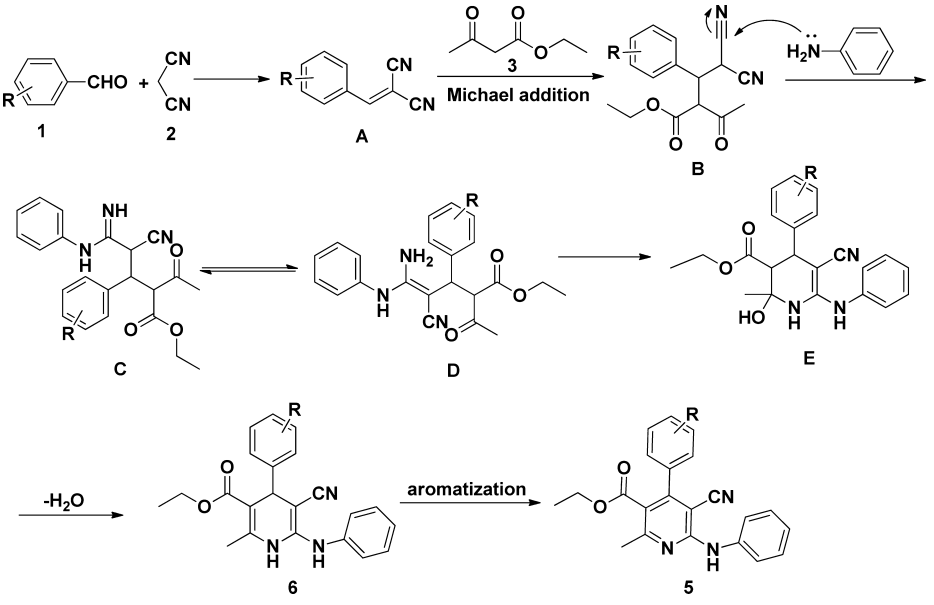
In summary, we have developed a simple one-pot, four-component nucleophilic addition/intermolecular cyclization reaction using iron(III) chloride catalyst to give polysubstituted pyridine derivatives. The advantages of this method include mild conditions, environmentally friendly catalyst, and readily available starting materials. No base or ligand is required, and the reaction proceeds under air. This mild annulation strategy may offer a protocol for synthesizing other *N*-heterocyclic compounds of interest to medicinal chemists.

EXPERIMENTAL SECTION

General Comments. Solvents were purified and dried by standard procedures unless otherwise stated. Unless otherwise specified, all reagents and starting materials were purchased from commercial sources and used as received. Chromatography solvents were technical grade, distilled prior to use. Flash chromatography was performed using 200−300 mesh silica gel with the indicated solvent system using standard techniques. ^1H and ^{13}C NMR spectra were recorded at 300 and 400 MHz unless otherwise specified. Chemical shifts (δ) in parts per million are reported relative to the residual signals of chloroform (7.26 ppm for ^1H and 76.1 ppm for ^{13}C). Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet); coupling constants (J) are reported in Hz. HRMS analysis was performed using a quadrupole time-of-flight mass spectrometer; mass/charge (m/z) ratios are given in atomic mass units. IR spectra were measured using dry films on KBr disks, and the peaks are reported in wavenumber (cm^{-1}).

General Procedure for the Synthesis of Polysubstituted Pyridines 5. To a stirred solution of 4-nitrobenzaldehyde **1b** (0.151 g, 1 mmol), malononitrile **2a** (0.066 g, 1 mmol), ethyl acetoacetate **3a** (0.130 g, 1 mmol), and aniline **4a** (0.093 g, 1 mmol) in ethanol (3 mL) was added anhydrous $FeCl_3$ (0.080 g, 0.05 mmol). The mixture was heated in an oil bath at 70 °C for 6 h and cooled to room temperature. Solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (200−300 mesh) with ethyl acetate and petroleum ether (1:10, v/v) as eluent to afford the product **5b** (0.329 g, 0.82 mmol) in 82% yield.

Scheme 4. Proposed Mechanism for the Formation of Pyridines via $FeCl_3$-Catalyzed Four-Component Reactions



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*Ethyl 5-Cyano-2-methyl-4-phenyl-6-(phenylamino)nicotinate (**5a**).* Petroleum ether/ethyl acetate 10:1, 75% yield (267 mg), white solid; mp 205−206 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 6.6 Hz, 3H), 7.31−7.36 (m, 4H), 7.08−7.17 (m, 1H), 3.91 (q, J = 6.9 Hz, 2H), 2.55 (s, 3H), 0.82 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 160.3, 155.4, 154.0, 138.4, 135.9, 129.5, 128.9, 128.6, 128.4, 127.9, 126.4, 124.1, 120.7, 120.5, 115.8, 90.8, 61.3, 23.8, 13.4 ppm; IR (KBr) ν: 3344, 2222, 1707, 1552, 1498, 1442, 1365, 1271, 1180, 1070, 748, 707 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}N_3O_2$ ([M + H]$^+$) 358.1555, found 358.1553.

*Ethyl 5-Cyano-2-methyl-4-(4-nitrophenyl)-6-(phenylamino)-nicotinate (**5b**).* Petroleum ether/ethyl acetate 10:1, 82% yield (329 mg), pale yellow solid; mp 220−221 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.12−7.19 (m, 1H), 3.95 (q, J = 6.9 Hz, 2H), 2.58 (s, 3H), 0.89 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 161.5, 155.3, 151.8, 148.4, 142.4, 137.9, 129.2, 129.0, 124.5, 123.8, 121.0, 119.6, 115.2, 90.3, 61.5, 24.2, 13.6 ppm; IR (KBr) ν: 3327, 2222, 1712, 1606, 1556, 1514, 1496, 1444, 1350, 1278, 1184, 1008, 852, 748 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}N_4O_4$ ([M + H]$^+$) 403.1406, found 403.1406.

*Ethyl 5-Cyano-2-methyl-4-(3-nitrophenyl)-6-(phenylamino)-nicotinate (**5c**).* Petroleum ether/ethyl acetate 8:1, 83% yield (332 mg), yellow solid; mp 198−200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 7.64−7.73 (m, 4H), 7.39 (t, J = 7.8 Hz, 2H), 7.14−7.23 (m, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.62 (s, 3H), 0.95 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 162.7, 155.4, 151.4, 148.2, 137.9, 134.1, 129.8, 124.5, 124.2, 123.2, 121.1, 119.9, 115.2, 90.5, 61.6, 24.2, 13.6 ppm; IR (KBr) ν: 3361, 2218, 1714, 1624, 1531, 1442, 1348, 1271, 1186, 898 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}N_4O_4$ ([M + H]$^+$) 403.1406, found 403.1404.

*Ethyl 4-(4-Chlorophenyl)-5-cyano-2-methyl-6-(phenylamino)-nicotinate (**5d**).* Petroleum ether/ethyl acetate 10:1, 76% yield (297 mg), yellow solid; mp 192−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 7.14 (t, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 160.6, 155.4, 152.7, 138.2, 135.8, 134.3, 129.4, 129.0, 128.9, 124.2, 120.8, 120.3, 115.9, 90.6, 61.4, 23.9, 13.6 ppm; IR (KBr) ν: 3331, 2216, 1714, 1598, 1556, 1442, 1365, 1278, 1180, 1089, 1016, 827 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}ClN_3O_2$ ([M + H]$^+$) 392.1165, found 392.1165.

*Ethyl 4-(4-Bromophenyl)-5-cyano-2-methyl-6-(phenylamino)-1,4-dihydropyridine-3-carboxylate (**5e**).* Petroleum ether/ethyl acetate 10:1, 75% yield (326 mg), pale yellow solid; mp 176−178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.25 (t, J = 5.4 Hz, 2H), 7.07−7.18 (m, 3H), 4.75 (s, 1H), 4.00 (q, J = 6.9 Hz, 2H), 2.33 (s, 3H), 1.00 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 155.3, 137.0, 136.8, 135.2, 134.7, 132.4, 131.7, 131.5, 130.1, 129.8, 126.6, 123.5, 122.9, 114.6, 113.3, 89.8, 60.0, 47.7, 43.6, 39.5, 30.9, 21.0, 14.0 ppm; IR (KBr) ν: 3329, 2216, 1714, 1651, 1593, 1490, 1440, 1180, 1072, 1047, 1010, 906, 825, 732, 698 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{21}BrN_3O_2$ ([M + H]$^+$) 438.0817, found 438.0812.

*Ethyl 5-Cyano-2-methyl-6-(phenylamino)-4-(p-tolyl)nicotinate (**5f**).* Petroleum ether/ethyl acetate 10:1, 75% yield (278 mg), white solid; mp 211−212 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.17−7.23 (m, 4H), 7.07−7.12 (m, 1H), 3.97 (q, J = 7.2 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 160.0, 159.7, 155.4, 154.1, 146.3, 139.6, 138.4, 132.9, 130.9, 130.3, 129.3, 128.9, 128.5, 127.9, 124.0, 120.7, 116.0, 90.9, 23.8, 21.3, 13.5 ppm; IR (KBr) ν: 3342, 2222, 1707, 1664, 1620, 1498, 1442, 1365, 1246, 1188, 815, 752 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}N_3O_2$ ([M + H]$^+$) 372.1712, found 372.1709.

*Ethyl 5-Cyano-4-(4-methoxyphenyl)-2-methyl-6-(phenylamino)-nicotinate (**5g**).* Petroleum ether/ethyl acetate 10:1, 62% yield (239 mg), white solid; mp 179−180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 7.5 Hz, 2H), 7.30−7.39 (m, 4H), 7.10−7.19 (m, 1H), 6.99 (d, J = 8.1 Hz, 2H), 4.03 (q, J = 7.5 Hz, 2H), 3.85 (s, 3H), 2.56 (s, 3H), 0.95 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 160.6, 159.9, 155.4, 153.6, 138.3, 129.4, 128.9, 127.9, 123.9, 120.7, 120.6, 116.2, 114.0, 90.7, 61.4, 55.3, 23.8, 13.6 ppm; IR (KBr) ν: 3317, 2220, 1712, 1598, 1554, 1521, 1442, 1363, 1276, 1253, 1176, 1083, 1028, 829 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}N_3O_3$ ([M + H]$^+$) 388.1661, found 388.1661.

*Ethyl 5-Cyano-2-methyl-4-(2-nitrophenyl)-6-(phenylamino)-nicotinate (**5h**).* Petroleum ether/ethyl acetate 10:1, 70% yield (281 mg), brown solid; mp 187−189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, J = 7.8 Hz, 1H), 7.71−7.81 (m, 4H), 7.44 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 1H), 7.19−7.23 (m, 1H), 4.00 (q, J = 7.2 Hz, 2H), 2.72 (s, 3H), 0.93 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 162.7, 155.0, 152.9, 147.3, 138.0, 133.7, 132.1, 130.3, 129.0, 124.9, 124.4, 121.0, 117.7, 115.0, 91.0, 61.2, 25.0, 13.5 ppm; IR (KBr) ν: 3361, 2216, 1708, 1610, 1558, 1521, 1496, 1444, 1377, 1348, 1276, 1176, 1068, 1018, 794 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}N_4O_4$ ([M + H]$^+$) 403.1406, found 403.1402.

*Ethyl 4-(2-Bromophenyl)-5-cyano-2-methyl-6-(phenylamino)-nicotinate (**5i**).* Petroleum ether/ethyl acetate 10:1, 68% yield (295 mg), white solid; mp 125−127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 7.5 Hz, 2H), 7.34−7.42 (m, 5H), 7.12−7.24 (m, 4H), 3.97 (q, J = 6.9 Hz, 2H), 2.66 (s, 3H), 0.86 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 162.0, 155.0, 153.6, 138.1, 137.4, 132.8, 130.5, 129.4, 129.0, 127.4, 126.3, 124.2, 121.9, 120.7, 115.1, 91.8, 61.1, 24.6, 13.4 ppm; IR (KBr) ν: 3334, 2223, 1714, 1658, 1602, 1496, 1444, 1363, 1244, 1182, 1056, 1024, 752 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}BrN_3O_2$ ([M + H]$^+$) 436.0660, found 436.0650.

*Ethyl 5-Cyano-4-(2-methoxyphenyl)-2-methyl-6-(phenylamino)-nicotinate (**5j**).* Petroleum ether/ethyl acetate 10:1, 60% yield (232 mg), white solid; mp 151−153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8.1 Hz, 2H), 7.34−7.45 (m, 3H), 7.10−7.18 (m, 2H), 6.98−7.05 (m, 2H), 3.96 (q, J = 6.9 Hz, 2H), 3.82 (s, 3H), 2.62 (s, 3H), 0.86 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 160.8, 156.0, 155.2, 151.8, 138.4, 130.9, 129.3, 128.9, 125.1, 123.8, 120.7, 120.6, 120.5, 115.9, 111.1, 92.2, 61.0, 55.6, 24.2, 13.4 ppm; IR (KBr) ν: 3340, 2222, 1726, 1606, 1558, 1494, 1442, 1377, 1267, 1242, 1163, 1066, 1022, 759 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{21}N_3O_3$ ([M + H]$^+$) 388.1661, found 388.1662.

*Ethyl 5-Cyano-2-methyl-4-phenyl-6-(p-tolylamino)nicotinate (**5k**).* Petroleum ether/ethyl acetate 12:1, 78% yield (289 mg), white solid; mp 141−142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 9.0 Hz, 2H), 7.45−7.47 (m, 3H), 7.35 (d, J = 9.6 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 3.96 (q, J = 7.5 Hz, 2H), 2.57 (s, 3H), 2.35 (s, 3H), 0.85 (t, J = 7.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 160.4, 155.5, 153.9, 136.0, 135.6, 133.8, 129.9, 129.5, 129.4, 128.6, 127.9, 126.1, 121.0, 120.1, 116.0, 90.4, 61.3, 23.9, 20.9, 13.4 ppm; IR (KBr) ν: 3331, 2220, 1712, 1604, 1556, 1516, 1452, 1365, 1278, 1180, 1082, 813 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{21}N_3O_2$ ([M + H]$^+$) 372.1712, found 372.1709.

*Ethyl 5-Cyano-2-methyl-4-(4-nitrophenyl)-6-(p-tolylamino)-nicotinate (**5l**).* Petroleum ether/ethyl acetate 16:1, 86% yield (357 mg), brown solid; mp 163−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H,), 7.21 (d, J = 8.4 Hz, 2H), 4.01 (q, J = 6.9 Hz, 2H), 2.61 (s, 3H), 2.36 (s, 3H), 0.93 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 153.1, 147.0, 146.7, 144.0, 136.1, 133.7, 130.7, 127.9, 123.9, 123.5, 120.1, 102.5, 60.2, 20.8, 19.6, 14.1 ppm; IR (KBr) ν: 3273, 2181, 1654, 1608, 1508, 1479, 1344, 1267, 1186, 1109, 1068, 1006, 848, 827 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}NaN_4O_4$ ([M + Na]$^+$) 439.1388, found 439.1382.

*Ethyl 5-Cyano-2-methyl-4-(3-nitrophenyl)-6-(p-tolylamino)-nicotinate (**5m**).* Petroleum ether/ethyl acetate 16:1, 85% yield (353 mg), white solid; mp 181−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32−8.36 (m, 1H), 8.25 (s, 1H), 7.49−7.72 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 4.02 (q, J = 6.9 Hz, 2H), 2.60 (s, 3H), 2.35 (s, 3H), 0.95 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 161.5, 155.5, 151.4, 148.1, 137.6, 135.2, 134.3, 134.1, 129.8, 129.5, 124.2, 123.2, 121.3, 119.6, 115.3, 90.2, 61.5, 24.3, 20.9, 13.6 ppm; IR (KBr) ν: 3332, 2214, 1714, 1560, 1535, 1348, 1273,

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1022, 813, 713 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}N_4O_4$ ([M + H]$^+$) 417.1563, found 417.1561.

*Ethyl 4-(4-Chlorophenyl)-5-cyano-2-methyl-6-(p-tolylamino)-nicotinate (**5n**).* Petroleum ether/ethyl acetate 16:1, 83% yield (336 mg), pale yellow solid; mp 198−200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 6.6 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 4.01 (q, J = 6.9 Hz, 2H), 2.56 (s, 3H), 2.35 (s, 3H), 0.94 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 160.7, 155.5, 152.7, 135.7, 135.5, 134.3, 134.0, 129.5, 129.3, 128.9, 121.1, 119.9, 115.7, 90.2, 61.4, 23.9, 20.8, 13.5 ppm; IR (KBr) ν: 3325, 2222, 1710, 1610, 1573, 1552, 1514, 1452, 1373, 1280, 1182, 1082, 1018, 835, 815 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}ClN_3O_2$ ([M + H]$^+$) 406.1322, found 406.1322.

*Ethyl 4-(4-Bromophenyl)-5-cyano-2-methyl-6-(p-tolylamino)-nicotinate (**5o**).* Petroleum ether/ethyl acetate 16:1, 82% yield (368 mg), pale yellow solid; mp 166−168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.15−7.24 (m, 5H), 4.01 (q, J = 7.2 Hz, 2H), 2.56 (s, 3H), 2.35 (s, 3H), 0.94 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 160.7, 155.5, 152.7, 135.4, 134.8, 134.0, 132.4, 132.0, 131.8, 131.3, 129.9, 129.6, 129.5, 123.9, 121.1, 119.8, 115.8, 90.1, 61.4, 24.0, 20.9, 13.5 ppm; IR (KBr) ν: 3323, 2222, 1708, 1662, 1610, 1552, 1512, 1490, 1454, 1367, 1282, 1219, 1182, 1012, 817 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}BrN_3O_2$ ([M + H]$^+$) 450.0817, found 450.0819.

*Ethyl 5-Cyano-2-methyl-4-(p-tolyl)-6-(p-tolylamino)nicotinate (**5p**).* Petroleum ether/ethyl acetate 16:1, 81% yield (311 mg), pale yellow solid; mp 163−165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 6.6 Hz, 2H), 4.00 (q, J = 6.9 Hz, 2H), 2.55 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 160.1, 155.6, 154.0, 139.5, 135.7, 133.7, 133.0, 129.4, 129.2, 127.8, 126.0, 121.0, 120.3, 119.7, 116.1, 90.5, 61.2, 23.8, 21.3, 20.8, 13.5 ppm; IR (KBr) ν: 3327, 2222, 1718, 1614, 1556, 1512, 1456, 1413, 1375, 1271, 1176, 1072, 815 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}N_3O_2$ ([M + H]$^+$) 386.1868, found 386.1869.

*Ethyl 5-Cyano-2-methyl-4-(2-nitrophenyl)-6-(p-tolylamino)-nicotinate (**5q**).* Petroleum ether/ethyl acetate 16:1, 80% yield (333 mg), brown solid; mp 162−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27−8.30 (m, 1H), 7.63−7.76 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.28−7.31 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H), 3.94 (q, J = 7.2 Hz, 2H), 2.65 (s, 3H), 2.36 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 162.8, 155.1, 153.0, 147.4, 135.3, 134.2, 133.7, 132.2, 130.2, 129.5, 124.8, 121.3, 117.7, 115.0, 90.6, 61.2, 25.1, 20.9, 13.4 ppm; IR (KBr) ν: 3406, 2216, 1710, 1606, 1556, 1512, 1450, 1342, 1278, 1261, 1178, 817, 796 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}N_4O_4$ ([M + H]$^+$) 417.1563, found 417.1559.

*Ethyl 5-Cyano-4-(2,4-dichlorophenyl)-2-methyl-6-(p-tolylamino)-nicotinate (**5r**).* Petroleum ether/ethyl acetate 16:1, 72% yield (316 mg), pale yellow solid; mp 135−137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.54 (m, 2H), 7.33−7.37 (m, 1H), 7.15−7.20 (m, 4H), 4.02 (q, J = 7.2 Hz, 2H), 2.64 (s, 3H), 2.36 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 162.3, 155.3, 151.2, 135.8, 135.3, 134.1, 134.0, 133.3, 130.3, 130.1, 129.6, 129.5, 127.2, 121.2, 115.0, 91.3, 61.2, 24.7, 20.9, 13.5 ppm; IR (KBr) ν: 3329, 2225, 1720, 1618, 1562, 1510, 1454, 1363, 1273, 1176, 1083, 1055, 812 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}Cl_2N_3O_2$ ([M + H]$^+$) 440.0932, found 440.0930.

*Ethyl 5-Cyano-2-methyl-4-(3-nitrophenyl)-6-((3-nitrophenyl)-amino)nicotinate (**5s**).* Petroleum ether/ethyl acetate 8:1, 52% yield (243 mg), yellow solid; mp 191−193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.36 (s, 1H), 8.26 (s, 1H), 7.99−8.02 (m, 1H), 7.83−7.85 (m, 1H), 7.70−7.72 (m, 1H), 7.47−7.56 (m, 2H), 4.06 (q, J = 6.9 Hz, 2H), 2.67 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 161.3, 154.7, 151.5, 148.7, 148.1, 139.2, 137.0, 134.0, 129.9, 129.6, 126.0, 124.4, 123.2, 121.5, 118.7, 115.6, 114.8, 91.3, 61.8, 24.1, 13.6 ppm; IR (KBr) ν: 3350, 2233, 1732, 1612, 1556, 1525, 1479, 1438, 1348, 1273, 1184, 815, 738 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}N_5O_6$ ([M + Na]$^+$) 470.1076, found 470.1074.

*Ethyl 4-(4-Chlorophenyl)-5-cyano-2-methyl-6-((3-nitrophenyl)-amino)nicotinate (**5t**).* Petroleum ether/ethyl acetate 8:1, 46% yield (200 mg), yellow solid; mp 145−146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.96−7.99 (m, 1H), 7.81−7.84 (m, 1H), 7.43−7.54 (m, 3H), 7.33 (d, J = 8.7 Hz, 2H), 4.05 (q, J = 7.5 Hz, 2H), 2.63 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 160.5, 154.7, 152.8, 148.7, 139.5, 136.1, 133.8, 129.6, 129.5, 129.3, 129.0, 125.8, 121.6, 118.4, 115.3, 115.2, 91.4, 61.6, 23.8, 13.5 ppm; IR (KBr) ν: 3346, 2220, 1716, 1612, 1552, 1523, 1483, 1348, 1282, 1182, 1095, 879, 819 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}ClN_4O_4$ ([M + H]$^+$) 437.1016, found 437.1017.

*Ethyl 4-(4-Bromophenyl)-5-cyano-2-methyl-6-((3-nitrophenyl)-amino)nicotinate (**5u**).* Petroleum ether/ethyl acetate 8:1, 45% yield (216 mg), yellow solid; mp 188−190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H), 7.96−8.00 (m, 1H), 7.80−7.84 (m, 1H), 7.61−7.64 (m, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.05 (q, J = 7.2 Hz, 2H), 2.64 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 160.6, 154.8, 152.9, 148.7, 139.5, 134.3, 132.5, 132.0, 131.8, 131.4, 131.3, 129.6, 125.8, 124.3, 121.6, 118.5, 115.4, 91.4, 61.7, 23.8, 13.6 ppm; IR (KBr) ν: 3344, 2220, 1716, 1612, 1550, 1523, 1483, 1350, 1282, 1182, 1074, 1014, 879, 819 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}BrN_4O_4$ ([M + H]$^+$) 481.0511, found 481.0510.

*Diethyl 2-Methyl-4-(4-nitrophenyl)-6-(phenylamino)pyridine-3,5-dicarboxylate (**5v**).* Petroleum ether/ethyl acetate 10:1, 47% yield (211 mg), white solid; mp 165−166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 9.0 Hz, 2H), 7.43−7.47 (m, 3H), 7.12 (d, J = 6.6 Hz, 2H), 4.14 (q, J = 7.2 Hz, 4H), 2.05 (s, 3H), 1.23 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 154.5, 148.1, 146.6, 140.0, 130.0, 129.6, 129.0, 128.9, 128.3, 124.4, 123.4, 115.2, 104.7, 85.9, 60.2, 18.8, 14.2, 14.0 ppm; IR (KBr) ν: 2981, 1702, 1648, 1583, 1556, 1348, 1282, 1182, 1153, 1078, 1044, 845 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}N_3O_6$ ([M + H]$^+$) 450.1665, found 450.1667.

*Diethyl 2-Methyl-4-(3-nitrophenyl)-6-(phenylamino)pyridine-3,5-dicarboxylate (**5w**).* Petroleum ether/ethyl acetate 10:1, 48% yield (215 mg), white solid; mp 161−162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.43−7.51 (m, 5H), 7.23 (d, J = 6.6 Hz, 2H), 5.17 (s, 1H), 4.13 (q, J = 7.2 Hz, 4H), 2.07 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 149.5, 148.2, 140.0, 134.0, 130.1, 129.7, 129.4, 129.1, 128.9, 128.6, 124.2, 122.7, 121.4, 117.8, 105.0, 60.2, 39.1, 18.8, 14.2 ppm; IR (KBr) ν: 2976, 1693, 1637, 1573, 1521, 1346, 1278, 1201, 1143, 1083, 1024, 810 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}N_3O_6$ ([M + H]$^+$) 450.1665, found 450.1665.

*Diethyl 4-(4-Chlorophenyl)-2-cyano-6-(phenylamino)pyridine-3,5-dicarboxylate (**5x**).* Petroleum ether/ethyl acetate 10:1, 39% yield (175 mg), white solid; mp 189−190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J = 8.1 Hz, 2H), 7.18−7.22 (m, 2H), 7.18−7.32 (m, 5H), 7.13 (d, J = 8.4 Hz, 2H), 4.27 (q, J = 8.1 Hz, 2H), 3.96 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 166.3, 156.6, 138.8, 138.5, 135.7, 134.2, 133.6, 131.0, 130.5, 129.3, 128.7, 128.3, 126.4, 126.1, 117.4, 91.1, 62.9, 59.6, 13.9 ppm; IR (KBr) ν: 2928, 1746, 1662, 1608, 1593, 1562, 1493, 1444, 1241, 1128, 10626, 1014, 842 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}ClN_3O_4$ ([M + H]$^+$) 450.1220, found 450.1218.

*Diethyl 4-(4-Bromophenyl)-2-methyl-6-(phenylamino)pyridine-3,5-dicarboxylate (**5y**).* Petroleum ether/ethyl acetate 10:1, 38% yield (183 mg), white solid; mp 246−247 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 6.6 Hz, 2H), 7.18−7.32 (m, 3H), 7.07 (d, J = 8.4 Hz, 2H), 4.62 (s, 1H, NH), 4.29 (q, J = 7.5 Hz, 2H), 3.97 (q, J = 6.9 Hz, 2H), 2.16 (s, 3H), 1.28 (t, J = 6.6 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 166.2, 156.6, 139.3, 138.5, 136.2, 131.6, 131.4, 131.2, 130.9, 129.3, 126.4, 126.1, 122.4, 121.9, 117.4, 91.0, 62.9, 59.6, 30.5, 13.9 ppm; IR (KBr) ν: 2924, 1745, 1651, 1606, 1593, 1579, 1492, 1433, 1240, 1122, 1056, 1010, 840 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}BrN_2O_4$ ([M + H]$^+$) 483.0919, found 483.0922.

*Ethyl 5-Cyano-2-methyl-4-(4-nitrophenyl)-6-(phenylamino)-1,4-dihydropyridine-3-carboxylate (**6a**).* Petroleum ether/ethyl acetate

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10:1, 85% yield (343 mg), pale yellow solid; mp 198−200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 8.7 Hz, 2H), 7.38−7.44 (m, 4H), 7.07 (d, J = 7.8 Hz, 2H), 6.33−6.36 (m, 1H), 6.01 (s, 1H), 4.81 (s, 1H), 4.06 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 152.0, 145.9, 145.5, 143.1, 135.9, 129.3, 127.0, 124.9, 123.1, 121.8, 118.9, 101.7, 64.0, 59.4, 39.7, 18.7, 13.2 ppm; IR (KBr) ν: 3284, 3220, 2185, 1651, 1598, 1475, 1346, 1271, 1238, 1105, 1064, 825 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{20}N_4O_4$ ([M + H]$^+$) 405.1563, found 405.1562.

*Ethyl 5-Cyano-2-methyl-6-(phenylamino)-4-(p-tolyl)-1,4-dihydropyridine-3-carboxylate (**6b**).* Petroleum ether/ethyl acetate 16:1, 78% yield (290 mg), white solid; mp 167−168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.34 (m, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.17 (d, J = 7.5 Hz, 2H), 7.05−7.13 (m, 3H), 4.73 (s, 1H), 3.96 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 154.1, 138.2, 137.4, 134.0, 132.2, 128.9, 128.8, 128.5, 128.2, 127.1, 125.5, 125.4, 114.4, 112.9, 90.2, 58.9, 47.1, 38.5, 30.3, 20.3, 13.0 ppm; HRMS (ESI) calcd for $C_{23}H_{23}N_3O_2$ ([M + H]$^+$) 374.1868, found 374.1867.

*Ethyl 5-Cyano-6-ethoxy-2-methyl-4-(4-nitrophenyl)nicotinate (**7a**).* Petroleum ether/ethyl acetate 10:1, 75% yield (266 mg), yellow solid; mp 150−152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 4.06 (q, J = 7.5 Hz, 2H), 2.64 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 163.5, 160.3, 152.7, 148.3, 141.6, 129.3, 128.6, 123.8, 123.6, 122.1, 113.8, 93.7, 64.1, 61.8, 23.7, 14.3, 13.6 ppm; IR (KBr) ν: 2216, 1716, 1656, 1564, 1456, 1298, 1269, 1043, 1004, 702 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}N_3O_5$ ([M + H]$^+$) 356.1246, found 356.1244.

*Ethyl 5-Cyano-6-ethoxy-2-methyl-4-(3-nitrophenyl)nicotinate (**7b**).* Petroleum ether/ethyl acetate 10:1, 73% yield (259 mg), white solid; mp 78−80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31−8.35 (m, 1H), 8.23 (s, 1H), 7.64−7.72 (m, 2H), 4.59 (q, J = 7.2 Hz, 2H), 4.04 (q, J = 7.2 Hz, 2H), 2.60 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 163.5, 160.2, 152.3, 148.1, 136.7, 134.2, 129.8, 124.3, 123.2, 122.4, 113.8, 94.1, 64.0, 61.8, 23.7, 14.3, 13.6 ppm; IR (KBr) ν: 2233, 1720, 1556, 1512, 1444, 1350, 1273, 1157, 1095, 1022, 825, 740, 702 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}N_3O_5$ ([M + H]$^+$) 356.1246, found 356.1244.

*Ethyl 5-Cyano-6-ethoxy-4-(4-nitrophenyl)-2-phenylnicotinate (**7c**).* Petroleum ether/ethyl acetate 10:1, 68% yield (283 mg), pale yellow solid; mp 162−163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, J = 8.1 Hz, 2H), 7.62−7.64 (m, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.45−7.47 (m, 3H), 4.66 (q, J = 6.9 Hz, 2H), 3.88 (q, J = 7.2 Hz, 2H$_2$), 1.49 (t, J = 6.9 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 163.4, 158.9, 153.4, 148.5, 141.0, 138.0, 130.5, 130.2, 129.5, 129.0, 128.7, 128.5, 128.4, 123.8, 122.2, 113.7, 94.9, 64.3, 61.9, 14.3, 13.3 ppm; IR (KBr) ν: 2229, 1720, 1550, 1519, 1350, 1247, 1141, 1014, 862, 690 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_3O_5$ ([M + H]$^+$) 418.1403, found 418.1402.

*Ethyl 6-Amino-5-cyano-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**7d**).* Petroleum ether/ethyl acetate 10:1, 65% yield (213 mg), yellow solid; mp 151−153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 4.63 (s, 2H), 4.55 (s, 1H), 4.04 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 1.09 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 158.0, 157.6, 151.0, 147.0, 128.4, 124.0, 118.3, 106.7, 61.0, 38.7, 18.6, 13.9 ppm; IR (KBr) ν: 3402, 3328, 2198, 1689, 1649, 1608, 1517, 1346, 1211, 1174, 1060, 858, 738 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}N_4O_4$ ([M + H]$^+$) 329.1249, found 329.1250.

*Ethyl 6-Amino-5-cyano-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**7e**).* Petroleum ether/ethyl acetate 10:1, 63% yield (206 mg), yellow solid; mp 158−159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 9.3 Hz, 1H), 8.04 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 4.63 (s, 2H), 4.57 (s, 1H), 4.05 (q, J = 6.9 Hz, 2H), 2.40 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 157.9, 157.7, 148.5, 146.0, 134.0, 133.9, 129.5, 122.5, 122.4, 106.9, 60.9, 38.7, 18.6, 13.9 ppm; IR (KBr) ν: 3404, 3325, 2250, 1707, 1625, 1471, 1433, 1155, 1049, 1024, 842, 761 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}N_4O_4$ ([M + H]$^+$) 329.1249, found 329.1251.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all compounds and crystallographic data of compound **5f** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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