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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02796 • Publication Date (Web): 02 Feb 2016

One-pot Synthesis of Highly Substituted Nicotinic Acid Derivatives Based on a Formylation Strategy of Enamino Keto Esters

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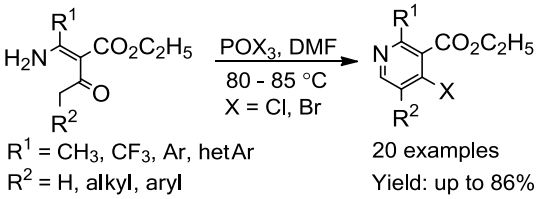


ABSTRACT: A facile one-pot synthesis of 4-chloro or 4-bromonicotinic acid esters with optional 2- and 2,5-disubstitution on the pyridine ring has been developed from easily accessible enamino keto esters by a formylation followed by *in situ* intramolecular cyclization strategy under optimized Vilsmeier reaction conditions. The effect of the substituents on the β-carbon and the nature of the keto functionality were explored in detail to understand the mechanism of pyridine ring formation under the described conditions.

1. INTRODUCTION

While nicotinic acid (niacin) is used as a drug to treat dyslipidemia, its derivatives, especially the ester derivatives are used as therapeutic agents for diverse indications.[1] Hexopal, etofibrate, tazarotene, nicergoline, nicomorphine, morniflumate, nikethamide and nicardipine are some of the marketed drugs that contain the nicotinic acid core. Apart from these nicotinic acid based drugs, several substituted pyridines, especially 2-aryl pyridines are prevalent in many natural products, pharmaceuticals and agrochemicals.[2] 2-Substituted pyridines are generally prepared from the corresponding 2-halopyridines through displacement reactions or transition metal-assisted coupling reactions.[3] However, direct halogenation of functionalized pyridine or functionalization of halogenated pyridine is often difficult to accomplish due to poor reactivity of the pyridine ring under electrophilic reaction conditions.[4]

We required 2-phenyl-4-(3-(trifluoromethyl)-phenyl)-1*H*-pyrazolo[4,3-c]pyridin-3(2H)-one and its derivatives for screening in one of our ongoing medicinal chemistry projects. As outlined in Figure 1, this class of compounds is best prepared from

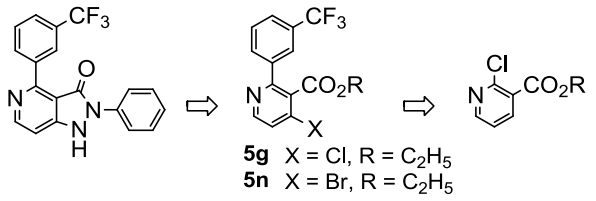


Figure 1. Synthesis of pyrazolopyridin-3(2*H*)-one derivatives.

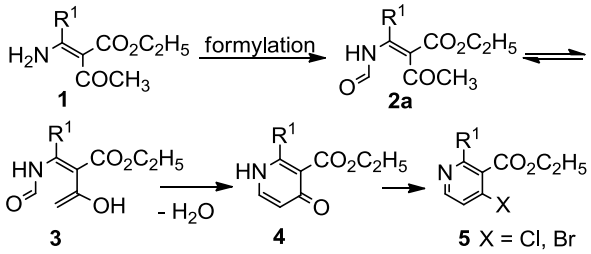
4-halonicotinic acid esters (e.g. **5g** or **5n**). The reported procedure for the synthesis of 2-substituted 4-halonicotinic acid esters comprises of 4 steps from 2-chloronicotinic acid esters. The steps involved are (i) Suzuki coupling (ii) ester hydrolysis (iii) directed metallation/bromination and (iv) re-esterification with (trimethylsilyl)diazomethane to give the corresponding methyl ester.[3] The overall approach is cumbersome and involves expensive chemicals and reagents.

In this study we report a novel one-pot methodology for the synthesis of various 2- and 2,5-disubstituted nicotinic acid esters starting from easily accessible enamino keto esters.

2. RESULTS AND DISSCUSSION

We envisioned that the bifunctional substrate, ethyl 2-(aminomethylene)-3-oxobutanoate **1**, bearing an appropriately positioned amino group and an enolizable ketone could be used as starting material for a mechanistically viable approach for the synthesis of 4-halonicotinic acid esters as shown in Scheme 1. We reasoned that enamino keto ester **1** could be formylated to give the *N*-formyl derivative **2**, which on *in situ* intramolecular condensation via its enol tautomer **3** would give pyridone **4**.[5] The 4-pyridone derivatives are well known to yield the corresponding 4-halopyridines upon treatment with phosphorus halides or phosphorus oxyhalides.[6]

Scheme 1. Proposed Synthetic Approach for Pyridine 5

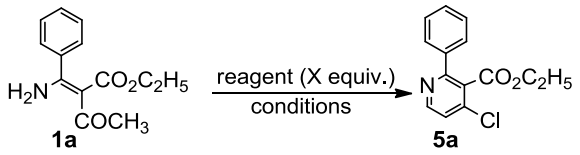


We chose ethyl 2-(amino(phenyl)methylene)-3-oxobutanoate **1a** (R^1 = Ph) as a test substrate for feasibility studies. Initial formylation attempts using acetic formic anhydride[7] and formic acid in the presence of zinc oxide[8] failed to give the desired *N*-formyl derivative **2a**. We also attempted the introduction of a dimethylamino methylene group (formyl equivalent) either on the amino group or on the active methylene carbon using *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) at elevated temperature, but without success.[9,6b] In yet another attempt, we explored the possibility of formylation **1a** under Vilsmeier reaction conditions.[10] The reaction of **1a** with Vilsmeier reagent (DMF-$POCl_3$) in dichloromethane at ambient temperature overnight resulted in

the formation of small amounts of a nonpolar product that was characterized as the chloropyridine **5a** based on spectral and analytical data.

With evidence of a direct formation of chloropyridine **5a** in hand, we sought to optimize the reaction conditions for improved synthesis of **5a**. The details of the conditions screened are given in Table 1. The reaction of **1a** with 1.5 equiv. of Vilsmeier reagent in dichloromethane for 24 h afforded the pyridine **5a** in 9% isolated yield (entry 1). Part of the enamino keto ester **1a** remained unchanged under this condition. The yield of **5a** was increased to 21% with excess of Vilsmeier reagent (3 equiv.) in dichloromethane (entry 2). The reaction of **1a** with 3.0 equiv. of Vilsmeier reagent in ethylene dichloride (EDC) at 80 °C for 12 h showed significant improvement in the yield (43%). The use of DMF as a cosolvent in the reaction at room temperature resulted in incomplete conversion and pyridine **5a** was isolated in 32% yield. A reaction carried out with excess reagent (3 equiv.) at 80 °C in DMF for a shorter reaction time of 1 h yielded 69% of **5a**. A similar yield (65%) was obtained when the reaction was performed at 90 °C in DMF as a solvent (not shown in Table 1). However, the reactions conducted above 90 °C showed significant reduction in the yield due to polymerization (entry 6). The reaction of **1a** with Vilsmeier reagent prepared from DMF and oxalyl chloride resulted in poor yield (27%) due to polymerization (entry 7).[10,11] A reaction using thionyl chloride under identical conditions gave **5a** in poor 38% isolated yield (entry 8).[10,12]

Table 1. Optimization of Reaction Conditions



entry	reagent	X	solvent/conditions	yield[a] (%)
1	DMF-$POCl_3$	1.5	CH_2Cl_2, r.t., 24h	9[b]
2	DMF-$POCl_3$	3.0	CH_2Cl_2, r.t., 24h	21[b]
3	DMF-$POCl_3$	3.0	EDC, 80 °C, 12h	43
4	DMF-$POCl_3$	3.0	DMF, r.t., 24h	32[b]
5	DMF-$POCl_3$	3.0	DMF, 80 °C, 1h	69
6	DMF-$POCl_3$	3.0	DMF, 110 °C, 1h	58
7	DMF-$(COCl)_2$	3.0	DMF, 80 °C, 1h	27[c]
8	DMF-$SOCl_2$	3.0	DMF, 80 °C, 1h	38[c]

[a]Yields are of pure isolated products. [b]Incomplete reaction and starting material recovered. [c]Significant polymerization observed.

The optimization studies discussed above clearly suggested that DMF was the solvent of choice over halogenated solvents. The reaction was very sensitive to temperature and 80–85 °C gave the optimum results. The addition of enamino keto ester to the pre-heated reagent and reducing the reaction time had beneficial effects in improving the yield. The best yield was obtained when **1a** was treated with 3 equiv. of Vilsmeier reagent in DMF for 1 h at 80–85 °C.

During the optimization studies, we observed that chloropyridine **5a** was formed as the only major isolable product under Vilsmeier reaction conditions, whereas pyridone **4** (R^1 = Ph) was not observed. The absence of pyridone in the reaction mixture suggested that Vilsmeier reagent preferentially reacts with the acyl group rather than the amino group to form the intermediate chlorovinyl iminium salt **2b**,[10] which then undergoes intramolecular cyclization to give chloropyridine **5a** (Figure 2). The intermediate iminium salt **2c** (enol form is shown) required for the formation of pyridone was not formed in the reaction.

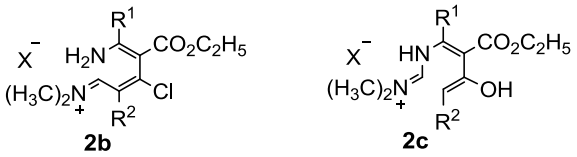


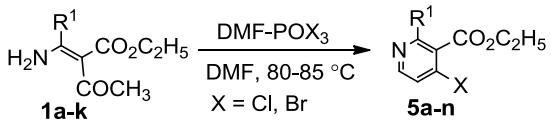
Figure 2. Suggested Vilsmeier intermediates **2b** and **2c**.

Having established the best conditions, various enamino keto esters were subjected to the optimized reaction conditions to evaluate the scope and generality of this transformation. The required enamino keto esters **1a**, **1e**–**k** were prepared by $SnCl_4$ assisted addition of ethyl acetoacetate to aryl- or heteroaryl nitriles according to a known procedure.[13] The methyl derivative **1b** and the *tert*-butyl derivative **1d** were prepared from the reaction of corresponding nitriles with ethyl bromoacetate under Blaise reaction conditions followed by *in situ* acylation of the enamine ester.[14] The trifluoromethyl derivative **1c** was prepared by potassium *tert*-butoxide-assisted addition of ethyl acetoacetate to trifluoroacetonitrile, generated *in situ* from 2,2,2-trifluoroacetamide.[15] It may be noted that the enamino keto esters **1a**–**k** are capable of existing as two geometrical isomers.[16] Careful examination of proton NMR spectra of these enamino keto esters revealed that they exist as *E*-isomers as the two amino protons showed separate signals approximately at 5.5 and 11 ppm. In the *E*-geometry, one of the amino protons forms an intramolecular hydrogen bond (N–H···O bond) with the acyl oxygen and thus appears downfield at around 11 ppm.

The optimized Vilsmeier reaction conditions for **1a** were then applied to substrates **1b**–**k** and the results are shown in Table 2. The reaction of **1b** with the methyl group on the β-carbon gave disappointing results and the pyridine **5b** was isolated in poor 26% yield. Several attempts to improve the yield of **5b** under varying conditions failed because of incomplete conversion and formation of polar side products. It is noteworthy that the corresponding fluorinated analogue **1c** gave an excellent yield (71%) of pyridine **5c**. Even the substrate **1d**, bearing a bulky *tert*-butyl group at the β-position of the enamino keto ester was smoothly transformed into the corresponding pyridine **5d** (entry 4). The probable reason for the poor yield of **5b** could be attributed to the presence of acidic methyl protons on the substrate **1b**. The substrates bearing neutral or electron withdrawing aryl substituents at the β-position of the

enamino keto esters were smoothly transformed into the corresponding pyridines in good yields (entries 5–8). The substrate bearing an electron donating aryl group (**1i**) or a basic electron donating aryl group (**1j**) both resulted in slightly lower yields (entries 9 and 10). The substrate **1k** with a 2-thienyl group on the β-carbon resulted in the formation of **5k** in good yields (70%). We next explored the scope of this approach for the synthesis of 4-bromonicotinic acid esters using phosphorous oxybromide ($POBr_3$) instead of $POCl_3$ in the Vilsmeier reaction. The bromopyridines **5l**–**n** were isolated in relatively better yields compared to the corresponding chloro compounds **5a**, **5f** and **5g** (entries12–14). We were pleased to note that the methodology worked quite well across a variety of substituents on the β-carbon of the enamino keto ester and also was useful for the synthesis of both 4-chloro- and 4-bromonicotinic acid esters.

Table 2. Synthesis of Pyridine Esters 5a–n

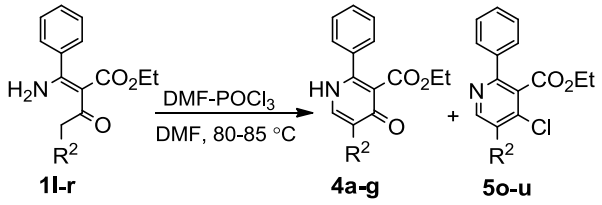


entry	SM	R^1	pyridine	X	yield[a] (%)
1	**1a**	C_6H_5	**5a**	Cl	69
2	**1b**	CH_3	**5b**	Cl	26
3	**1c**	CF_3	**5c**	Cl	71
4	**1d**	$C(CH_3)_3$	**5d**	Cl	59
5	**1e**	2-FC_6H_4	**5e**	Cl	61
6	**1f**	4-FC_6H_4	**5f**	Cl	63
7	**1g**	3-$CF_3C_6H_4$	**5g**	Cl	67
8	**1h**	4-$NO_2C_6H_4$	**5h**	Cl	86
9	**1i**	4-$MeOC_6H_4$	**5i**	Cl	56
10	**1j**	4-$(CH_3)_2NC_6H_4$	**5j**	Cl	52
11	**1k**	2-thienyl	**5k**	Cl	70
12	**1a**	C_6H_5	**5l**	Br	80
13	**1f**	4-FC_6H_4	**5m**	Br	76
14	**1g**	3-$CF_3C_6H_4$	**5n**	Br	73

[a]Yields are of pure isolated products.

We next sought to explore the scope of the reaction for the synthesis of 2,5-disubstituted nicotinic acid esters as shown in Table 3. The desired enamino keto esters **1l**–**r** bearing homologues keto functionality on the α-carbon were prepared from benzonitrile and appropriate β-keto esters as described in the case of **1a**.[13] Enamino keto esters **1l**–**r** also existed as the *E*-isomers.[16] The treatment of 3-oxopentanoate ester **1l** with Vilsmeier reagent under optimized reaction conditions resulted in the formation of two distinct products (TLC). The LC-MS/MS analysis of the reaction mixture after aqueous work-up showed molecular ion peaks at 258 (RT = 11.4 min) and 276 (RT = 12.3 min). The mass spectrum of the polar compound was devoid of a chloro pattern, whereas the nonpolar compound clearly showed the presence of a chlorine atom in the molecule as in the case of **5a**–**k**. The nonpolar compound was characterized as the pyridine **5o** (38%) and the polar product formed was characterized as the pyridone **4a** (22%). The 3-oxohexanoate derivative **1m** also gave a mixture of pyridone **4b** (26%) and pyridine **5p** (32%) under the same reaction conditions. The branched chain 5-methyl-3-oxohexanoate derivative **1n** under the described reaction conditions afforded a single product in 63% yield, which was characterized as the pyridone **4c**. The 5,5-dimethyl-3-oxohexanoate derivative **1o** also yielded pyridone **4d** in 45% yield as a single product. The 6-methyl-3-oxoheptanoate derivative **1p** gave pyridone **4e** as the major product (50%) and pyridine **5s** (12%) as the minor product. The 3-oxo-4-phenylbutanoate ester **1q** also gave a mixture of pyridone **4f** (23%) and pyridine **5t** (41%). A similar trend was observed in the case of 4-(4-methoxyphenyl)-3-oxobutanoate **1r** and resulted in the formation of a mixture of products **4g** (26%) and **5u** (43%).

Table 3. Synthesis of Pyridones 4a–g and Pyridines 5o–u



1l-r **4a-g** **5o-u**

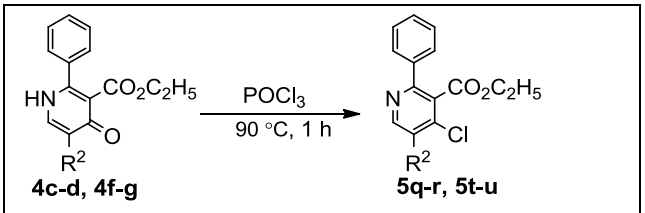
entry	SM	R^2	**4** (%)[a]	**5** (%)[a]
1	**1l**	CH_3	**4a** (22)	**5o** (38)
2	**1m**	CH_2CH_3	**4b** (26)	**5p** (32)
3	**1n**	$CH(CH_3)_2$	**4c** (63)	**5q** (-)[b]
4	**1o**	$C(CH_3)_3$	**4d** (45)	**5r** (-)[b]
5	**1p**	$CH_2CH(CH_3)_2$	**4e** (50)	**5s** (12)
6	**1q**	C_6H_5	**4f** (23)	**5t** (41)
7	**1r**	4-$MeOC_6H_4$	**4g** (26)	**5u** (43)

[a]Parenthetic values are the isolated yield of the products. [b]Pyridines **5q** and **5r** were not formed in the reaction.

The mechanistic aspects of the reaction discussed previously suggest that pyridone **4** and pyridine **5** are formed independently in the reaction mixture (Figure 2). To further confirm this hypothesis, we carried out a Vilsmeier reaction of **1l** with 6.0 equiv. of $POCl_3$ and 3.0 equiv. of DMF using EDC as a cosolvent at 80 °C. The reaction resulted in the formation of a mixture of **4a** and **5o** (TLC) as in the previous reaction. The free $POCl_3$ present in the reaction mixture failed to convert **4a** to the corresponding chloropyridine **5o** through dehydrohalogenation even after extending the reaction for another 3 h. The formation of pyridones **4c** and **4d** as lone products in the case of substrates **1n** and **1o** respectively, can be rationalized on the basis of the reactivity of the keto functionality toward Vilsmeier reagent. The branched alkyl group adjacent to the active methylene carbon impedes the formation of chlorovinyl iminium intermediate **2b**. Therefore, formylation preferentially occurs at the amino end to give the intermediate **2c** which leads to the exclusive formation of pyridones **4c** and **4d**.

The formation of pyridones as unexpected product in case of **1l**–**r** can be viewed as a limitation to the stated objective of this methodology for the synthesis of 2,5-disubstituted nicotinic acid esters. Therefore, we attempted conversion of selected 4-pyridones to the corresponding 4-chloropyridines and the results are shown in Table 4. Appropriately substituted 4-pyridones are reported to yield the corresponding 4-halopyridines upon treatment with a variety of phosphorus- halides or oxyhalides such as PCl_5, PBr_3, $POCl_3$ or $POBr_3$.[6] The treatment of pyridone **4c** with excess $POCl_3$ at 100 °C for 1 h indeed afforded the desired chloropyridine **5q** in 69% yield. However, the pyridone **4d** under identical conditions failed to give the expected pyridine **5r**. Forcing the reaction at elevated temperature (120 °C) resulted in a complex mixture of products. The failure of this reaction may be attributed to the steric hindrance offered by the bulky *tert*-butyl group, which precludes the approach of the reagent to the adjacent carbonyl group. The diaryl pyridones **4f** and **4g** were also transformed smoothly into the corresponding pyridines **5t** and **5u** in 72 and 76% yield respectively.

Table 4. Conversion of Pyridones to Pyridines



4c-d, 4f-g **5q-r, 5t-u**

entry	**4**	R^2	**5** (%)[a]
1	**4c**	$CH(CH_3)_2$	**5q** (69)
2	**4d**	$C(CH_3)_3$	**5r** (-)[b]
3	**4f**	C_6H_5	**5t** (72)
4	**4g**	4-$MeOC_6H_4$	**5u** (76)

[a]Parenthetic values are isolated yields of the products. [b]Pyridone **4d** failed to give pyridine **5r**.

3. CONCLUSION

In conclusion, we have developed a simple, one-pot formylation/cyclization strategy for the synthesis of 2-substituted and 2,5-disubstituted 4-halonicotinic acid esters starting from easily accessible enamino keto esters bearing appropriate substituents at the α and/or β carbon atoms. The methodology developed has an advantage of introducing up to four substituents onto a pyridine ring in a single step and does not use any expensive intermediates or reagents. Furthermore, the chlorine or bromine substituent at 4-position of the pyridine ring can be gainfully exploited for the introduction of additional substituents or functional groups for further synthetic transformations. To the best of our knowledge, direct synthesis of 2- and 2,5-disubstituted 4-halonicotinic acid esters from enamino keto esters has not been reported previously.

4. EXPERIMENTAL SECTION

General Information. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR Spectrometer. ^{1}H NMR spectra were recorded on a 300 MHz FT NMR spectrometer in either $CDCl_3$ or DMSO-d_6 as specified using tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on either a 300 MHz FT NMR spectrometer or a 400 MHz spectrometer at 75 and 100 MHz respectively. Chemical shifts are quoted in ppm (δ) relative to TMS (^{1}H) using residual protonated solvent as internal standard. Routine mass spectra (MS) were recorded by direct infusion method using ESI or APCI source at positive or negative polarity mode. High-resolution mass spectra (HRMS) of compounds were measured on a LTQ Orbitrap Discovery MS system coupled with LQT Tune Plus software - operating in a positive electron spray ionization (ESI) mode.

Preparation of Enamino Keto Esters 1a–r

Typical Procedure for the Preparation of *(E)-Ethyl 2-[amino(phenyl)methylidene]-3-oxobutanoate (1a)*[13,14] (Method A). To a stirred solution of benzonitrile (10 mL, 0.097 mmol) in toluene (150 mL) was added ethyl acetoacetate (12.4 mL, 0.097 mmol) followed by stannic chloride (11.74 mL, 0.097 mmol) at room temperature and the resultant mixture was refluxed for 3 h. The mixture was cooled to ambient temperature and quenched carefully with saturated aqueous sodium bicarbonate solution (400 mL). The mixture was extracted with ethyl acetate (3 x 200 mL). The combined extracts were washed with water (2 x 250 mL) and dried over anhydrous sodium sulfate (Na_2SO_4). The residue obtained after evaporation of solvent was purified by flash silica gel column chromatography using 20% ethyl acetate (EtOAc) in petroleum ether to yield 14.02 g (62%) of product as a white solid. Mp 66 – 68 °C; R_f = 0.5 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1}: 3381, 3112, 1679, 1599, 1295, 1132; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (t, *J* = 6.9 Hz, 3H), 2.35 (s, 3H), 3.73 (q, *J* = 6.9 Hz, 2H), 5.61 (br s, 1H), 7.34–7.47 (m, 5H), 10.94 (br s, 1H); ESI-MS (*m/z*) 234 $(M+H)^+$. [CAS RN: 21486-57-7]

Typical Procedure for the Preparation of *(E)-Ethyl 2-acetyl-3-aminobut-2-enoate (1b)*[14] (Method B). To a stirred suspension of zinc dust (6.51 g, 99.571 mmol) in dry THF (40 mL) was added catalytic amount of methane sulfonic acid (16 µL, 0.249 mmol) and the mixture was refluxed for 10 min. To the refluxing mixture was added acetonitrile (2.5 mL, 48.721 mmol) followed by ethyl bromoacetate (8 mL, 80.00 mmol) over 1.0 h. The reaction mixture was gradually cooled to 0 °C and *n*-butyllithium in

hexane (1.6 M, 30.2 mL, 49.890 mmol) was added followed by acetic anhydride (6.0 mL, 63.591 mmol). The reaction mixture was then stirred at room temperature for 3.0 h. The mixture was quenched with saturated aqueous ammonium chloride solution (150 mL), and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. The residue obtained after evaporation of solvent was purified by flash silica gel column chromatography using 20% EtOAc in petroleum ether to yield 6.75 g (81%) of product as pale yellow oil. R_f = 0.4 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3259, 2986, 1703, 1601, 1469, 1285, 1133, 1058, 709; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 2.30 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 5.70 (br s, 1H), 11.05 (br s, 1H); ESI-MS (*m/z*) 172 $(M+H)^+$. [CAS RN: 26682-94-0]

Typical Procedure for the Preparation of *(E)-Ethyl 2-acetyl-3-amino-4,4,4-trifluorobut-2-enoate (1c)*[15] (Method C). A stirred solution of 2,2,2-trifluoroacetamide (1.30 g, 11.526 mmol) in dry pyridine (10 mL) was added trifluoroacetic anhydride (1.63 mL, 11.526 mmol) at room temperature. The trifluoroacetonitrile gas thus formed was directly bubbled into a stirred solution containing ethyl acetoacetate (0.98 mL, 7.684 mmol) and potassium *tert*-butoxide (26 mg, 0.231 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature. The reaction mixture was stirred overnight. The mixture was concentrated and the residue obtained was dissolved in ethyl acetate (200 mL). The solution was washed with water (2 x 50 mL) and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to result a viscous yellow residue. The residue was purified by flash silica gel column chromatography using 10% EtOAc in petroleum ether to yield 1.20 g (69%) of product as white solid. Mp 61–63 °C; R_f = 0.5 (EtOAc/petroleum ether, 2:8); ^1H NMR (300 MHz, DMSO-d_6) δ 1.21 (t, *J* = 6.9 Hz, 3H), 2.17 (s, 3H), 4.15 (q, *J* = 6.9 Hz, 2H), 8.99 (br s, 1H), 10.13 (br s, 1H); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_8H_{10}F_3NO_3$, 226.0679, found 226.0685. [CAS RN: 22070-95-7]

*(E)-Ethyl 2-acetyl-3-amino-4,4-dimethylpent-2-enoate (**1d**).* The coupling reaction of *tert*-butyl nitrile (7.0 mL, 63.322 mmol) with ethyl bromoacetate (10.5 mL, 94.983 mmol) in the presence of zinc dust (8.28 mg, 126.644 mmol) and catalytic amount of methanesulfonic acid followed by acetylation of the resultant enamine ester with acetic anhydride (9.0 mL, 95.386 mmol) in the presence of *n*-butyllithium in hexane (1.6 M, 47.5 mL, 75.986 mmol) as per the procedure described in the case of **1b** (Method B) gave 7.02 g (52%) of the titled compound **1d** as a colorless oil. R_f = 0.3 (EtOAc/petroleum ether, 2:8); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.36 (t, *J* = 7.5 Hz, 3H), 2.14 (s, 3H), 4.21 (q, *J* = 7.5 Hz, 2H), 5.64 (br s, 1H), 11.76 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 28.3, 28.5 (3C), 37.7, 60.9, 103.3, 172.0, 173.2, 194.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{19}NO_3$ 214.1433, found 214.1437.

*(E)-Ethyl 2-[amino(2-fluorophenyl)methylidene]-3-oxobutanoate (**1e**).*[13] Reaction of 2-fluorobenzonitrile (4.0 g, 33.027 mmol) with ethyl acetoacetate (4.3 mL, 33.702 mmol) in the presence of stannic chloride (3.9 mL, 33.236 mmol) as described in Method A yielded 4.98 g (60%) of the product as off-white solid. Mp 68–71 °C; R_f = 0.6 (EtOAc/petroleum ether, 3:7); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J* = 6.9 Hz, 3H), 2.39 (s, 3H), 3.84 (q, *J* = 6.9 Hz, 2H), 5.58 (br s, 1H), 7.02–7.24 (m, 2H), 7.25–7.35 (m, 1H), 7.36–7.47 (m, 1H), 11.11 (br s, 1H); ESI-MS (*m/z*) 252 $(M+H)^+$. [CAS RN: 1172590-40-7]

(E)-Ethyl 2-[amino(4-fluorophenyl)methylidene]-3-oxobutanoate ***(1f)***.[14] Reaction of 4-fluorobenzonitrile (8.0 g, 66.055 mmol) with ethyl acetoacetate (8.4 mL, 65.936 mmol) in the presence of stannic chloride (7.8 mL, 66.472 mmol) as described in Method A yielded 10.45 g (63%) of the product as white solid. Mp 60–62 °C; R_f = 0.6 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3342, 3136, 1673, 1606, 1471, 1295, 1057, 851; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, *J* = 6.9 Hz, 3H), 2.36 (s, 3H), 3.81 (q, *J* = 6.9 Hz, 2H), 5.47 (br s, 1H), 7.06–7.15 (m, 2H), 7.30–7.39 (m, 2H), 10.93 (br s, 1H); ESI-MS (*m/z*) 252 $(M+H)^+$. [CAS RN: 1092970-67-6]

(E)-Ethyl 2-{amino[3-(trifluoromethyl)phenyl] methylidene}-3-oxobutanoate ***(1g)***. Reaction of 3-(trifluoromethyl)benzonitrile (8.0 g, 46.750 mmol) with ethyl acetoacetate (6.0 mL, 47.026 mmol) in the presence of stannic chloride (6.0 mL, 47.026 mmol) as described in Method A yielded 8.16 g (58%) of the product as a colorless oil. R_f = 0.7 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3312, 2984, 1671, 1603, 1327, 1120, 807, 702; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, *J* = 6.9 Hz, 3H), 2.39 (s, 3H), 3.78 (q, *J* = 6.9 Hz, 2H), 5.48 (br s, 1H), 7.56 (d, *J* = 3.9 Hz, 2H), 7.64 (s, 1H), 7.68–7.75 (m, 1H), 10.98 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.2, 29.7, 60.1, 104.4, 123.7 (q, *J* = 274.0 Hz), 123.8, 125.4, 126.4, 126.6, 130.5 (q, *J* = 32.6 Hz), 139.1, 164.9, 169.0, 197.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}F_3NO_3$ 302.0998, found 302.0991.

Ethyl 2-(amino(4-nitrophenyl)methylene)-3-oxobutanoate ***(1h)***.[17] Reaction of 4-nitrobenzonitrile (3.0 g, 20.253 mmol) with ethyl acetoacetate (2.6 mL, 20.253 mmol) in the presence of stannic chloride (2.4 mL, 20.253 mmol) as described in Method A yielded 3.7 g (66%) of the product as pale yellow solid. Mp 91–93 °C; R_f = 0.3 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3290, 2991, 1703, 1590, 1463, 1346, 1127, 874, 670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J* = 6.9 Hz, 3H), 2.40 (s, 3H), 3.81 (q, *J* = 6.9 Hz, 2H), 5.47 (br s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 8.29 (d, *J* = 8.4 Hz, 2H), 11.05 (br s, 1H); APCI-MS (*m/z*) 279 $(M+H)^+$. [CAS RN: 1636141-15-5]

(E)-Ethyl 2-[amino(4-methoxyphenyl)methylidene]-3-oxobutanoate ***(1i)***.[18] Reaction of 4-methoxybenzonitrile (6.0 g, 45.055 mmol) with ethyl acetoacetate (5.8 mL, 45.458 mmol) in the presence of stannic chloride (5.3 mL, 45.166 mmol) as described in Method A yielded 7.47 g (63%) of the product as a yellow oil. R_f = 0.4 (EtOAc/petroleum ether, 3:7); IR (neat) cm^{-1} 3333, 2901, 1696, 1607, 1461, 1219, 1252, 772; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.2 Hz, 3H), 2.34 (s, 3H), 3.84 (s, 3H), 3.86 (q, *J* = 7.2 Hz, 2H), 5.49 (br s, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 10.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.5, 29.3, 55.4, 60.1, 104.0, 114.0 (2C), 128.2 (2C), 130.5, 161.1, 166.5, 170.2, 196.6; ESI-MS (*m/z*) 264 $(M+H)^+$.

(E)-Ethyl 2-{amino[4-(dimethylamino)phenyl] methylidene}-3-oxobutanoate ***(1j)***. Reaction of 4-(dimethylamino)benzonitrile (4.0 g, 27.361 mmol) with ethyl acetoacetate (3.5 mL, 27.431 mmol) in the presence of stannic chloride (4.8 mL, 41.041 mmol) as described in Method A yielded 5.59 g (74%) of the product as a yellow crystalline solid. Mp 120–123 °C; R_f = 0.3 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3410, 3301, 2981, 1699, 1687, 1604, 1439, 1360, 1291, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3H), 2.34 (s, 3H), 3.00 (s, 6H), 3.87 (q, *J* = 6.9 Hz, 2H), 5.46 (br s, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 7.27

(d, *J* = 8.4 Hz, 2H), 10.95 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 29.4, 40.3 (2C), 60.2, 103.6, 111.7 (2C), 125.3, 128.2 (2C), 152.0, 167.2, 170.9, 196.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}N_2O_3$ 277.1546, found 277.1544.

*(E)-Ethyl 2-[amino(thiophen-2-yl)methylidene]-3-oxobutanoate (**1k**).* Reaction of thiophene-2-carbonitrile (4.0 g, 36.646 mmol) with ethyl acetoacetate (4.7 mL, 36.837 mmol) in the presence of stannic chloride (4.3 mL, 36.646 mmol) as described in Method A yielded 6.08 g (69%) of the product as a yellow oil. R_f = 0.5 (EtOAc/petroleum ether, 3:7); IR (neat) cm^{-1} 3275, 3126, 2975, 1698, 1594, 1284, 712; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 6.9 Hz, 3H), 2.33 (s, 3H), 3.94 (q, *J* = 6.9 Hz, 2H), 5.47 (br s, 1H), 7.06 (t, *J* = 5.4 Hz, 1H), 7.25 (d, *J* = 6.6 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 10.75 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.7, 29.4, 60.7, 105.1, 127.7, 128.3 (2C), 138.5, 158.0, 169.9, 196.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}NO_3S$ 240.0688, found 240.0689.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-3-oxopentanoate (**1l**).* Reaction of benzonitrile (3.0 g, 29.092 mmol) with ethyl 3-oxopentanoate (4.2 mL, 29.481 mmol) using stannic chloride (3.5 mL, 29.827 mmol) as described in Method A afforded 4.68 g (65%) of the product as a white solid. Mp 72–75 °C; R_f = 0.6 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3390, 3166, 2973, 1680, 1468, 1289, 1113, 1034, 705; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 2.72 (q, *J* = 7.2 Hz, 2H), 3.76 (q, *J* = 7.2 Hz, 2H), 5.44 (br s, 1H), 7.35–7.48 (m, 5H), 10.92 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 9.3, 13.5, 34.2, 60.2, 104.1, 126.8 (2C), 128.8 (2C), 130.1, 138.6, 166.3, 169.9, 200.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}NO_3$ 248.1281, found 248.1274.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-3-oxohexanoate (**1m**).* Reaction of benzonitrile (5.0 g, 48.487 mmol) with ethyl 3-oxohexanoate (7.9 mL, 49.087 mmol) using stannic chloride (5.7 mL, 48.575 mmol) as described in Method A afforded 6.96 g (55%) of the product as a white solid. Mp 87–90 °C; R_f = 0.6 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3338, 2985, 1671, 1573, 1459, 1445, 1291, 1143, 1030, 998, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 9.0 Hz, 3H), 1.60–1.72 (m, 2H), 2.65 (t, *J* = 6.9 Hz, 2H), 3.77 (q, *J* = 6.9 Hz, 2H), 5.45 (br s, 1H), 7.35–7.48 (m, 5H), 10.91 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.3, 13.9, 18.5, 42.8, 60.0, 104.1, 126.6 (2C), 128.6 (2C), 129.9, 138.4, 166.1, 169.7, 199.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{19}NO_3$ 262.1437, found 262.1430.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-5-methyl-3-oxohexanoate (**1n**).* Reaction of benzonitrile (1.5 g, 14.546 mmol) with ethyl 5-methyl-3-oxohexanoate (2.5 g, 14.516 mmol) as described in Method A afforded 2.28 g (57%) of the product as a white solid. Mp 79–81 °C; R_f = 0.6 (EtOAc/petroleum ether, 2:8); IR (KBr) cm^{-1} 3437, 2958, 1685, 1594, 1466, 1284, 1100, 779; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 6H), 2.10–2.21 (m, 1H), 2.56 (d, *J* = 6.3 Hz, 2H), 3.80 (q, *J* = 6.9 Hz, 2H), 5.32 (br s, 1H), 7.35–7.43 (m, 5H), 10.98 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.5, 22.9, 25.8, 49.7, 60.2, 104.8, 126.8 (2C), 128.8 (2C), 130.1, 138.6, 166.3, 170.0, 199.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}NO_3$ 276.1588, found 276.1594.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-5,5-dimethyl-3-oxohexanoate (**1o**)*. Reaction of benzonitrile (1.0 g, 9.697 mmol) with ethyl 5,5-dimethyl-3-oxohexanoate (1.8 g, 9.670 mmol) using stannic chloride (1.2 mL, 10.226 mmol) as described in Method A afforded 1.48 g (53%) of the product as a white solid. Mp 105–109 °C; R_f = 0.6 (EtOAc/petroleum ether, 2:8); IR (KBr) cm^{-1} 3398, 3147, 2954, 2866, 1681, 1589, 1569, 1469, 1361, 1285, 1106, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 2.66 (s, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 5.41 (br s, 1H), 7.35–7.46 (m, 5H), 11.13 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.5, 30.2 (3C), 32.0, 51.7, 60.2, 106.1, 126.9 (2C), 128.8 (2C), 130.1, 138.7, 166.1, 170.3, 199.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}NO_3$ 290.1750, found 290.1745.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-5-methyl-3-oxohexanoate (**1p**)*. Reaction of benzonitrile (1.0 g, 9.697 mmol) with ethyl 6-methyl-3-oxoheptanoate (1.8 g, 9.670 mmol) using stannic chloride (1.2 mL, 10.226 mmol) as described in Method A afforded 1.79 g (64%) of the product as a colorless oil. R_f = 0.6 (EtOAc/petroleum ether, 2:8); IR (KBr) cm^{-1} 3354, 2955, 2869, 1700, 1597, 1466, 1282, 1131, 772; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (t, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 5.7 Hz, 6H), 1.49–1.70 (m, 3H), 2.69 (t, *J* = 5.7 Hz, 2H), 3.76 (q, *J* = 6.9 Hz, 2H), 5.42 (br s, 1H), 7.34–7.49 (m, 5H), 10.96 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.6, 22.7 (2C), 28.1, 34.4, 39.1, 60.3, 104.3, 126.9 (2C), 128.8 (2C), 130.2, 138.5, 166.4, 169.9, 200.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}NO_3$ 290.1750, found 290.1742.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-3-oxo-4-phenylbutanoate (**1q**)*. Reaction of benzonitrile (1.0 g, 9.697 mmol) with ethyl 3-oxo-4-phenylbutanoate (2.0 g, 9.697 mmol) using stannic chloride (1.2 mL, 10.226 mmol) as described in Method A afforded 2.1 g (70%) of the product as a white solid. Mp 67–68 °C; R_f = 0.6 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3444, 2983, 2927, 1731, 1434, 1231, 703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (t, *J* = 6.9 Hz, 3H), 3.74 (q, *J* = 6.9 Hz, 2H), 4.06 (s, 2H), 5.50 (br s, 1H), 7.22–7.48 (m, 10H), 10.89 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.4, 47.2, 60.2, 103.9, 126.5, 126.8, 128.3 (2C), 128.7 (2C), 129.9 (3C), 130.1, 136.4, 138.4, 167.3, 169.8, 196.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}NO_3$ 310.1437, found 310.1431.

*(E)-Ethyl 2-[amino(phenyl)methylidene]-4-(4-methoxyphenyl)-3-oxobutanoate (**1r**)*. Reaction of benzonitrile (1.5 g, 14.546 mmol) with ethyl 4-(4-methoxyphenyl)-3-oxobutanoate (3.4 g, 14.546 mmol) using stannic chloride (1.8 mL, 15.339 mmol) as described in Method A afforded 2.66 g (54%) of the product as a white solid. Mp 132–136 °C; R_f = 0.6 (EtOAc/petroleum ether, 3:7); IR (KBr) cm^{-1} 3417, 3172, 1687, 1592, 1462, 1280, 1103, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, *J* = 7.2 Hz, 3H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.97 (s, 2H), 5.55 (br s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 7.30–7.46 (m, 5H), 10.87 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.3, 46.2, 55.1, 60.1, 103.7, 113.7 (2C), 126.6, 128.2, 128.6 (2C), 130.0, 130.7 (3C), 138.3, 158.2, 166.9, 169.6, 197.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}NO_4$ 340.1543, found 340.1535.

Preparation of 2-Substituted Nicotinic Acid Esters 5a–n

Typical Procedure for the Preparation of *Ethyl 4-chloro-2-phenylpyridine-3-carboxylate (5a)*. Phosphorus oxychloride (0.6 mL, 6.437 mmol) was added to dry *N*,*N*-dimethylformamide (DMF) (0.55 mL, 7.133 mmol) at 0 °C under nitrogen atmosphere and the mixture was then stirred at room temperature for 1 h. A solution of enamino keto ester **1a** (500 mg, 2.143 mmol) in dry DMF (5.0 mL) was added slowly (3 min) to the reagent (exothermic reaction) and the mixture was further stirred at 80–85 °C (oil bath temperature) for 1 h to result a reddish brown solution. The mixture was cooled to 0 °C and carefully quenched with saturated aqueous solution of sodium bicarbonate (150 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with water (3 x 50 mL). The solution was dried over anhydrous Na_2SO_4 and concentrated under *vacuum* to afford a brown residue. The crude product was purified by flash silica gel column chromatography using 5% acetone in petroleum ether to yield 387 mg (69%) of **5a** as a colorless oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2982, 1735, 1561, 1545, 1255, 1124, 1056, 760. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, *J* = 6.9 Hz, 3H), 4.22 (q, *J* = 6.9 Hz, 2H), 7.36 (d, *J* = 5.4 Hz, 1H), 7.39–7.45 (m, 3H), 7.48–7.63 (m, 2H), 8.61(d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 62.3, 122.9, 128.4 (2C), 128.6 (2C), 129.2, 129.5, 138.7, 142.0, 150.4, 158.0, 166.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}ClNO_2$ 262.0629, found 262.0623.

*Ethyl 4-chloro-2-methylpyridine-3-carboxylate (**5b**).*[19] Reaction of **1b** (1.0 g, 5.841 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.6 mL, 17.165 mmol) and DMF (1.5 mL, 19.455 mmol) as described in the typical procedure afforded 303 mg (26%) of **5b** as a colorless oil. R_f = 0.5 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2982, 1734, 1570, 1556, 1274, 1113, 1075, 854; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.2 Hz, 3H), 2.58 (s, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 5.4 Hz, 1H) 8.42 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.3, 22.8, 62.4, 122.2, 129.7, 141.5, 149.9, 156.9, 166.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{10}ClNO_2$ 200.0472, found 200.0475. [CAS RN: 164390-30-1]

*Ethyl 4-chloro-2-(trifluoromethyl)pyridine-3-carboxylate (**5c**).* Reaction of **1c** (850 mg, 3.774 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.1 mL, 11.801 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure afforded 680 mg (71%) of **5c** as a colorless oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2987, 1746, 1574, 1321, 1321, 1273, 1147, 1063, 838. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 5.4 Hz, 1H), 8.66 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 63.3, 120.8 (q, *J* = 273.6 Hz), 127.4, 129.1, 143.3, 145.8 (q, *J* = 35.4 Hz), 150.5, 163.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_7ClF_3NO_2$ 254.0190, found 254.0182.

*Ethyl 2-tert-butyl-4-chloropyridine-3-carboxylate (**5d**).* Reaction of **1d** (1.0 g, 4.688 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.3 mL, 13.947 mmol) and DMF (1.2 mL, 15.564 mmol) as described in the typical procedure afforded 669 mg (59%) of **5d** as a colorless oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2964, 1732, 1546, 1260, 1064, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (br s, 12H), 4.42 (q, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 5.4 Hz, 1H) 8.47 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 30.1 (3C), 39.9, 62.0, 121.6, 128.4, 141.8, 148.9, 165.9, 167.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}ClNO_2$ 242.0937, found 242.0942.

*Ethyl 4-chloro-2-(2-fluorophenyl)pyridine-3-carboxylate (**5e**).* Reaction of **1e** (1.0 g, 3.980 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.1 mL, 11.801 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure afforded 679 mg (61%) of **5e** as a colorless oil; R_f = 0.6 (acetone/petroleum ether, 1:9); IR (neat) cm^{-1} 2983, 1733, 1547, 1256, 1128, 759; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, *J* = 6.9 Hz, 3H), 4.20 (q, *J* = 6.9 Hz, 2H), 7.10–7.28 (m, 2H), 7.37–7.52 (m, 3H), 8.63 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 62.2, 115.9 (d, *J* = 21.7 Hz), 124.2 (d, *J* = 25.2 Hz), 124.4, 126.8, 130.2, 131.2 (d, *J* = 8.0 Hz), 131.4 (d, *J* = 8.0 Hz), 142.5, 150.5, 154.1, 159.8 (d, *J* = 247.3 Hz), 165.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}ClFNO_2$ 280.0535, found 280.0538.

*Ethyl 4-chloro-2-(4-fluorophenyl)pyridine-3-carboxylate (**5f**).* Reaction of **1f** (1.0 g, 3.980 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.1 mL, 11.801 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure afforded 701 mg (63%) of **5f** as a colorless oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2983, 1734, 1561, 1253, 1124, 844, 756; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.2 Hz, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 7.13 (t, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 5.4 Hz, 1H), 7.62 (t, *J* = 6.0 Hz, 2H), 8.61 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 62.4, 115.7 (d, *J* = 21.7 Hz, 2C), 123.0, 123.1, 129.2, 130.5 (d, *J* = 7.8 Hz, 2C), 142.1, 150.5 (2C), 162.2 (d, *J* = 248.5 Hz, 1C), 166.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}ClFNO_2$ 280.0535, found 280.0528.

*Ethyl 4-chloro-2-[3-(trifluoromethyl)phenyl]pyridine-3-carboxylate (**5g**).* Reaction of **1g** (1.5 g, 4.979 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.4 mL, 15.019 mmol) and DMF (1.2 mL, 15.564 mmol) as described in the typical procedure afforded 1.10 g (67%) of **5g** as a colorless oil. R_f = 0.7 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2987, 1732, 1551, 1334, 1133, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.5 Hz, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 5.1 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.92 (s, 1H), 8.64 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 62.6, 123.6, 124.5 (q, *J* = 274.8 Hz), 126.2, 126.3, 129.3, 129.5, 131.2 (q, *J* = 32.9 Hz), 132.0, 139.4, 142.4, 150.7, 156.4, 165.8; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{11}ClF_3NO_2$ 330.0503, found 330.0508.

*Ethyl 4-chloro-2-(4-nitrophenyl)pyridine-3-carboxylate (**5h**).* Reaction of **1h** (500 mg, 1.797 mmol) with Vilsmeier reagent prepared from $POCl_3$ (0.50 mL, 5.392 mmol) and DMF (0.46 mL, 5.929 mmol) as described in the typical procedure afforded 474 mg (86%) of **5h** as a yellow solid. Mp 97–99 °C; R_f = 0.25 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2988, 1733, 1523, 1351, 1260, 1109, 871; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 5.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 8.31 (d, *J* = 8.1 Hz, 2H), 8.66 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.7, 62.5, 123.6 (2C), 123.9, 129.4, 129.5 (2C), 142.3, 144.6, 148.3, 150.6, 155.4, 165.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}ClN_2O_4$ 307.0480, found 307.0470.

*Ethyl 4-chloro-2-(4-methoxyphenyl)pyridine-3-carboxylate (**5i**).* Reaction of **1i** (1.0 g, 3.798 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.1 mL, 11.394 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure afforded 620 mg (56%) of **5i** as a white solid. Mp 55–58 °C; R_f = 0.5 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2925, 1729, 1609, 1257,

1119, 1053, 844; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 6.9 Hz, 3H), 3.85 (s, 3H), 4.27 (q, *J* = 6.9 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 5.4 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 8.58 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 55.3, 62.1, 113.9 (2C), 122.1, 128.6, 129.8 (2C), 131.1, 141.7, 150.2, 157.4, 160.6, 166.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}ClNO_3$ 292.0735, found 292.0729.

*Ethyl 4-chloro-2-[4-(dimethylamino)phenyl]pyridine-3-carboxylate (**5j**).* Reaction of **1j** (1.5 g, 5.428 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.5 mL, 16.104 mmol) and DMF (1.4 mL, 18.158 mmol) as described in the typical procedure afforded 860 mg (52%) of **5j** as a yellow viscous liquid. R_f = 0.4 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2981, 2897, 1731, 1609, 1557, 1363, 1252, 1121, 820; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3H), 3.02 (s, 6H), 4.31 (q, *J* = 7.2 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 5.4 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 2H), 8.55 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 40.4 (2C), 62.1, 112.1 (2C), 121.4, 126.4, 128.0, 129.5 (2C), 141.7, 150.1, 151.1, 157.8, 166.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}ClN_2O_2$ 305.1051, found 305.1044.

*Ethyl 4-chloro-2-(thiophen-2-yl)pyridine-3-carboxylate (**5k**).* Reaction of **1k** (1.0 g, 4.179 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.2 mL, 12.874 mmol) and DMF (1.1 mL, 14.267 mmol) as described in the typical procedure afforded 783 mg (70%) of **5k** as a colorless oil. R_f = 0.7 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3019, 1731, 1215, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.2 Hz, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 7.08 (br s, 1H), 7.26 (br s, 1H), 7.37 (br s, 1H), 7.48 (d, *J* = 5.4 Hz, 1H), 8.51 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0, 62.7, 122.3, 126.9, 127. 4, 128.2 (2C), 129.6, 141.8, 142.1, 150.3, 166.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{10}ClNO_2S$ 268.0193, found 268.0195.

*Ethyl 4-bromo-2-phenylpyridine-3-carboxylate (**5l**).* Reaction of **1a** (500 mg, 2.143 mmol) with Vilsmeier reagent prepared from $POBr_3$ (1.84 g, 6.418 mmol) and DMF (0.55 mL, 7.133 mmol) as described in the typical procedure afforded 525 mg (80%) of **5l** as a colorless oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2981, 1732, 1538, 1253, 1125, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 6.9 Hz, 3H), 4.22 (q, *J* = 6.9 Hz, 2H), 7.37–7.45 (m, 3H), 7.54 (d, *J* = 5.4 Hz, 1H), 7.56–7.65 (m, 2H), 8.51 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 62.4, 126.3, 128.6 (2C), 128.7 (2C), 129.6, 131.6, 131.7, 138.4, 149.9, 157.7, 166.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}BrNO_2$ 306.0124, found 306.0118.

*Ethyl 4-bromo-2-(4-fluorophenyl)pyridine-3-carboxylate (**5m**).* Reaction of **1f** (1.0 g, 3.980 mmol) with Vilsmeier reagent prepared from $POBr_3$ (3.42 g, 11.929 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure afforded 981 mg (76%) of **5m** as a colorless oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3019, 1730, 1215, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 7.13 (t, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 5.4 Hz, 1H), 7.56–7.63 (m, 2H), 8.50 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 62.4, 115.6 (d, *J* = 29.0 Hz, 2C), 126.2, 130.4 (d, *J* = 11.4 Hz, 2C), 130.7, 131.6, 134.1, 149.6, 156.2, 163.6 (d, *J* = 331.2 Hz), 166.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}BrFNO_2$ 324.0030, found 324.0023.

*Ethyl 4-bromo-2-[3-(trifluoromethyl)phenyl]pyridine-3-carboxylate (**5n**).* Reaction of **1g** (1.0 g, 3.319 mmol) with Vilsmeier reagent prepared from $POBr_3$ (2.85 g, 9.958 mmol) and DMF (0.85 mL, 11.024 mmol) as described in the typical procedure afforded 907 mg (73%) of **5n** as a yellow oil. R_f = 0.7 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3021, 2987, 1732, 1543, 1333, 1133, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 3H), 4.25 (q, *J* = 7.5 Hz, 2H), 7.55–7.65 (m, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.91 (s, 1H), 8.54 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.6, 62.4, 123.6 (q, *J* = 274.3 Hz), 125.2, 125.3, 126.6 (2C), 129.0 (2C), 130.7 (q, *J* = 32.8 Hz), 131.2, 139.3, 150.2, 156.0, 166.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{11}BrF_3NO_2$ 373.9994, found 373.9998.

Synthesis of 2,5-Disubstituted Pyridones 4a–g and Pyridines 5o–p and 5s–u

The 2,5-disubtituted pyridine esters **5o–p** and **5s–u** were prepared by Vilsmeier reaction of the corresponding enamino keto esters by following the typical procedure for the synthesis of pyridine ester **5a**. In all these cases, the corresponding pyridone esters were also formed as co-product.

*Ethyl 4-chloro-5-methyl-2-phenylpyridine-3-carboxylate (**5o**) and Ethyl 5-methyl-4-oxo-2-phenyl-1,4-dihydropyridine-3-carboxylate (**4a**).* Reaction of **1l** (1.0 g, 4.043 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.2 mL, 12.874 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure for **5a** followed by chromatographic purification (eluent, 1.5% acetone in petroleum ether) afforded 424 mg (38%) of **5o** as a white solid. Mp 80–83 °C; R_f = 0.7 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2975, 1723, 1532, 1435, 1228, 1137, 1025, 834; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3H), 2.44 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.38–7.45 (m, 3H), 7.56–7.63 (m, 2H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.8, 17.0, 62.2, 128.4 (2C), 128.6 (2C), 129.1, 129.3, 130.8, 138.6, 141.9, 150.9, 155.4, 166.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}ClNO_2$ 276.0785, found 276.0788. Further elution of the column with same solvent system gave 229 mg of **4a** (22%) as a colorless oil. R_f = 0.5 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3019, 2918, 1701, 1678, 1276, 1185, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 1.73 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 7.40–7.49 (m, 5H), 8.15 (d, *J* = 10.2 Hz, 1H), 11.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 4.5, 14.4, 61.8, 73.7, 90.1, 128.8 (2C), 129.2 (2C), 130.2 (2C), 132.6, 155.8, 162.6, 168.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}NO_3$ 258.1119, found 258.1124.

*Ethyl 4-chloro-5-ethyl-2-phenylpyridine-3-carboxylate (**5p**) and Ethyl 5-ethyl-4-oxo-2-phenyl-1,4-dihydropyridine-3-carboxylate (**4b**).* Reaction of **1m** (1.0 g, 3.826 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.1 mL, 11.801 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure yielded a mixture of **5p** and **4b**. Flash silica gel chromatography (eluent, 1.5% acetone in petroleum ether) afforded 365 mg (32%) of **5p** as a white solid. Mp 37–40 °C; R_f = 0.7 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2975, 1734, 1530, 1436, 1227, 1125, 1019; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.5 Hz, 3H), 2.85 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.5 Hz, 2H), 7.38–7.45 (m, 3H), 7.55–7.65 (m, 2H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 24.3, 29.9, 62.3, 128.5 (2C), 128.6 (2C), 129.3, 129.4, 136.0, 138.6, 141.4, 150.2, 155.3,

166.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{16}ClNO_2$ 290.0942, found 290.0945. Further elution of column with same solvent system gave 270 mg (26%) of **4b** as a pale yellow semi-solid. R_f = 0.5 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3227, 2975, 1696, 1673, 1590, 1372, 1188, 789, 728; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.8 Hz, 3H), 1.36 (t, *J* = 6.9 Hz, 3H), 2.10 (q, *J* = 7.8 Hz, 2H), 4.30 (q, *J* = 6.9 Hz, 2H), 7.38–7.48 (m, 5H), 8.16 (d, *J* = 10.2 Hz, 1H), 11.45 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.3, 13.5, 14.3, 61.7, 74.2, 96.0, 128.9 (2C), 129.2 (2C), 130.1 (2C), 132.7, 155.8, 162.5, 167.9; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}NO_3$ 272.1281, found 272.1276.

*Ethyl 4-oxo-2-phenyl-5-(propan-2-yl)-1,4-dihydropyridine-3-carboxylate (**4c**).* Reaction of **1n** (1.0 g, 3.631 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.1 mL, 11.801 mmol) and DMF (1.0 mL, 12.970 mmol) as described in the typical procedure followed by flash silica gel chromatography (eluent, 5% EtOAc in petroleum ether) afforded 653 mg (63%) of **4c** as a pale yellow solid. Mp 60–61 °C; R_f = 0.6 (acetone/petroleum ether, 2:8); IR (KBr) cm^{-1} 3019, 2972, 1701, 1677, 1589, 1215, 1022, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.9 Hz, 6H), 1.36 (t, *J* = 7.2 Hz, 3H), 2.38–2.49 (m, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 7.38–7.48 (m, 5H), 8.18 (d, *J* = 9.9 Hz, 1H), 11.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0, 21.1, 22.4 (2C), 61.4, 73.9, 99.9, 128.6 (2C), 129.0 (2C), 129.8 (2C), 132.6, 155.5, 162.3, 167.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}NO_3$ 286.1431, found 286.1437.

*Ethyl 5-tert-butyl-4-oxo-2-phenyl-1,4-dihydropyridine-3-carboxylate (**4d**).* Reaction of **1o** (1.0 g, 3.455 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.0, 3.455 mmol) and DMF (0.9 mL, 11.636 mmol) as described in the typical procedure followed by flash silica gel chromatography (5% EtOAc in petroleum ether) afforded 465 mg (45%) of **4d** as an off-white solid. Mp 52–53 °C; R_f = 0.7 (acetone/petroleum ether, 2:8); IR (neat) cm^{-1} 3223, 2968, 1708, 1677, 1365, 1287, 1022; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.35 (t, *J* = 7.2 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.35–7.49 (m, 5H), 8.18 (d, *J* = 10.2 Hz, 1H), 11.43 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0, 27.8, 30.4 (3C), 61.3, 73.3, 102.6, 128.6 (2C), 129.0 (2C), 129.5, 129.8, 132.6, 155.3, 162.3, 167.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}NO_3$ 300.1594, found 300.1587.

*Ethyl 4-chloro-5-(2-methylpropyl)-2-phenylpyridine-3-carboxylate (**5s**) and Ethyl 5-(2-methylpropyl)-4-oxo-2-phenyl-1,4-dihydropyridine-3-carboxylate (**4e**).* Reaction of **1p** (1.0 g, 3.455 mmol) with Vilsmeier reagent prepared from $POCl_3$ (1.0, 3.455 mmol) and DMF (0.9 mL, 11.636 mmol) as described in the typical procedure afforded a mixture of **5s** and **4e**. Flash silica gel chromatography (3% acetone in petroleum ether) afforded 132 mg (12%) of **5s** as a yellow oil. R_f = 0.6 (acetone/petroleum ether, 1:9); IR (neat) cm^{-1} 2958, 2869, 1734, 1528, 1438, 1226, 1123, 697; ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.3 Hz, 6H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.99–2.18 (m, 1H), 2.68 (d, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 7.40–7.56 (m, 3H), 7.59–7.63 (m, 2H), 8.48 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 13.9, 22.5 (2C), 28.5, 38.9, 62.4, 128.4 (2C), 128.9 (2C), 129.7, 130.4, 133.6, 137.7, 138.5, 152.5, 154.6, 166.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}ClNO_2$ 318.1255, found 318.1248. Further elution of the column with same solvent system gave 517 mg (50%) of **4e** as a colorless oil. R_f = 0.5 (ace-

tone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3019, 1701, 1677, 1215, 759; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.9 Hz, 6H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.49–1.62 (m, 1H), 2.00 (d, *J* = 6.9 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 7.37–7.50 (m, 5H), 8.13 (d, *J* = 10.2 Hz, 1H), 11.43 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.3, 21.9 (2C), 28.1, 28.8, 61.7, 75.5, 93.8, 129.0 (2C), 129.3 (2C), 130.1(2C), 132.8, 155.5, 162.6, 168.0; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}NO_3$ 300.1594, found 300.1589.

*Ethyl 4-chloro-2,5-diphenylpyridine-3-carboxylate (**5t**) and Ethyl 4-oxo-2,5-diphenyl-1,4-dihydropyridine-3-carboxylate (**4f**).* Reaction of **1q** (500 mg, 1.616 mmol) with Vilsmeier reagent prepared from $POCl_3$ (0.5 mL, 5.364 mmol) and DMF (0.4 mL, 5.188 mmol) a as described in the typical procedure yielded a mixture of **5t** and **4f**. Flash silica gel column chromatography (eluent, 8% acetone in petroleum ether) afforded 224 mg (41%) of **5t** as a white solid. Mp 120–122 °C; R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2990, 2940, 1727, 1519, 1434, 1234, 1142, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 7.43–7.51 (m, 8H), 7.65–7.72 (m, 2H), 8.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 62.4, 128.5 (2C), 128.7 (2C), 128.8 (2C), 128.9 (2C), 129.5, 129.7 (2C), 135.0, 135.1, 138.7, 140.0, 151.1, 156.4, 166.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{16}ClNO_2$ 338.0942, found 338.0945. Further elution of the column with same solvent system afforded 119 mg (23%) of **4f** as a pale yellow viscous liquid. R_f = 0.5 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3019, 2926, 1702, 1679, 1585, 1571, 1374, 1296, 1196, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 6.9 Hz, 3H), 4.35 (q, *J* = 6.9 Hz, 2H), 7.00–7.10 (m, 2H), 7.15–7.25 (m, 3H), 7.45–7.56 (m, 5H), 8.25 (d, *J* = 10.2 Hz, 1H), 11.51 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.3, 61.8, 84.5, 93.7, 123.5, 128.0, 128.3, 128.9 (3C), 129.4 (3C), 130.5, 130.9 (2C), 132.4, 156.5, 162.4, 167.5; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}NO_3$ 320.1281, found 320.1275.

*Ethyl 4-chloro-5-(4-methoxyphenyl)-2-phenylpyridine-3-carboxylate (**5u**) and Ethyl 5-(4-methoxyphenyl)-4-oxo-2-phenyl-1,4-dihydropyridine-3-carboxylate (**4g**).* Reaction of **1r** (1.0 g, 2.948 mmol) with Vilsmeier reagent prepared from $POCl_3$ (0.8 mL, 8.582 mmol) and DMF (0.8 mL, 10.376 mmol) as described in the typical procedure yielded a mixture of **5u** and **4g**. Flash silica gel column chromatography (acetone/petroleum ether, 1:9) of the mixture afforded 466 mg (43%) of **5u** as a white crystalline solid. Mp 128–130 °C; R_f = 0.7 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3010, 2972, 1724, 1519, 1435, 1238, 833; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, *J* = 6.9 Hz, 3H), 3.88 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.38–7.51 (m, 5H), 7.62–7.70 (m, 2H), 8.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.6, 55.3, 62.2, 114.0 (2C), 126.9, 128.3, 128.5 (2C), 129.3 (2C), 129.5, 130.8 (2C), 134.5, 138.2, 140.0, 150.7, 155.6, 160.0, 166.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}ClNO_3$ 368.1048, found 368.1051. Further elution of the column with same solvent system gave 268 mg (26%) of **4g** as a yellow solid. Mp 115–118 °C; R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 3185, 1697, 1668, 1508, 1286, 1212, 1025, 737; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 6.9 Hz, 3H), 3.76 (s, 3H), 4.34 (q, *J* = 6.9 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.50–7.55 (m, 5H), 8.25 (d, *J* = 10.2 Hz, 1H), 11.51 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.3, 55.4, 61.8, 83.1, 93.7, 114.0 (2C), 115.7, 128.9 (2C), 129.5 (2C), 130.3, 132.4 (3C), 132.6, 155.7, 159.5, 162.5, 167.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}NO_4$ 350.1386, found 350.1391.

Conversion of Pyridone Esters to Pyridine Esters

Typical Procedure for the Preparation of *Ethyl 4-chloro-5-isopropyl-2-phenylnicotinate (5q)*. Excess phosphorus oxychloride (1 mL) was added in one portion to pyridone ester **4c** (150 mg, 0.493 mmol) and the mixture was heated at 100 °C for 1 h. The resultant light brown solution was added drop-wise to a vigorously stirred ice-cold solution of sodium bicarbonate. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with water (2 x 100 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated in vacuum. The residue obtained was purified by flash silica gel column chromatography using 5% acetone in petroleum ether to yield to yield 65 mg (69%) of **5q** as an off-white solid. Mp 58–59 °C; R_f = 0.6 (acetone/petroleum ether, 1:9); IR (KBr) cm^{-1} 2976, 2963, 1724, 1530, 1438, 1235, 1119, 701; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.2 Hz, 3H), 1.36 (d, *J* = 7.2 Hz, 6H), 3.40– 3.49 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.40–7.44 (m, 3H), 7.57–7.61 (m, 2H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.6, 22.2 (2C), 28.8, 62.1, 128.3 (2C), 128.4 (2C), 129.1 (2C), 138.4, 139.4 140.7, 148.2, 154.8, 166.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}ClNO_2$ 304.1095, found 304.1098.

*Ethyl 4-chloro-2,5-diphenylpyridine-3-carboxylate (**5t**)*. Reaction of pyridone **4f** (50 mg, 0.156 mmol) with excess $POCl_3$ (0.5 mL) as described in the case of **5q** gave 38 mg (72%) of pyridine **5t** as a white solid. The ^1H NMR spectrum of 5s prepared by this method was in complete agreement with the spectrum of **5t** prepared directly from enamino keto esters **1q**.

*Ethyl 4-chloro-5-(4-methoxyphenyl)-2-phenylpyridine-3-carboxylate (**5u**)*. Reaction of pyridone **4g** (50 mg, 0.143 mmol) with excess $POCl_3$ (0.5 mL) as described in the case of **5q** gave 40 mg (76%) of pyridine **5u** as a white solid. The ^1H NMR spectrum of **5u** prepared by this method was in complete agreement with the spectrum of **5u** prepared directly from enamino keto esters **1r**.

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C nmr spectra for all new compounds are included in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Professor S. H. Mashraqui for his valuable inputs and insightful suggestions. We are also grateful to Mr. Rambabu Pattem for the HRMS analysis of the samples.

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