# A Simple, Diversity Oriented Synthesis of Highly Substituted Pyridines



Katarzyna Kaczanowska,[a,b] Holger Eickhoff,[a] Klaus Albert,[b] Karl-Heinz Wiesmüller,[a,b] and Arnaud-Pierre Schaffner[a]*

[a]EMC microcollections GmbH, Sindelfinger St. 3, Tübingen D-72070, Germany
[b]Institut für Organische Chemie, Fakultät für Chemie und Pharmazie, Eberhard Karls Universität Tübingen
*E-mail: schaffner@microcollections.de

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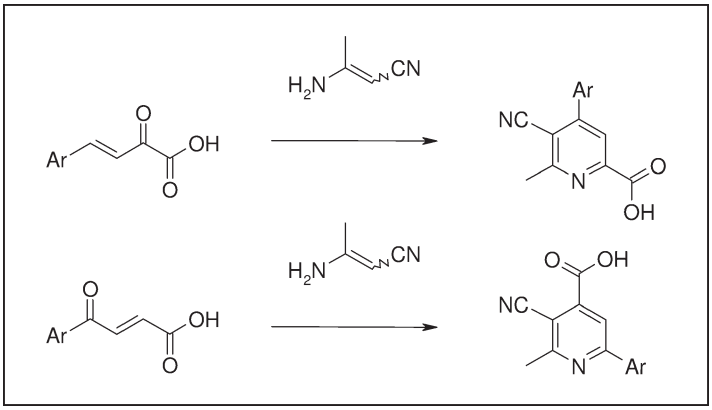


A particularly straightforward and efficient protocol for the synthesis of highly substituted pyridines, based on a condensation reaction of β-aminocrotonitrile and easily accessible (*E*)-2-oxo-4-aryl-but-3-enoic acids and (*E*)-4-oxo-4-aryl-but-2-enoic acids is described.

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## INTRODUCTION

The pyridine motif is among the most common heterocyclic compounds found in various pharmaceuticals, agrochemicals, and natural products [1]. Pyridines exhibit antifungal activity against *Candida albicans* [2,3], a major fungal pathogen, anti-HIV [4] as well as antibacterial activity [3] and target a wide variety of biological receptors [1,5].

In the search for novel bioactive compounds exists a continued strong demand for versatile syntheses of pyridine derivatives. Although numerous approaches leading to the pyridine moiety have been reported over the last decades, the preparation of non-symmetrical, substituted pyridine rings remains a significant challenge [1,6]. A few elegant methods for the synthesis of highly substituted pyridines appeared in the recent literature [6]. Some of these approaches involve multicomponent reactions [6a–c], rhodium-catalyzed activation of alkenyl C—H bond [6f–g], isoxazole ring expansion [6h], or routes based on aza-Diels-Alder reaction [6i]. The described methods are often low-yielding and limited in applicability due to restricted functionalities at certain positions. In this context, our aim was to develop an efficient method that gives a high flexibility considering substituent pattern in the pyridine ring.

We report a particularly straightforward protocol for the synthesis of pyridine regioisomers based on condensation reactions of β-aminocrotonitrile **2** and commercially available or easily accessible (*E*)-2-oxo-4-aryl-but-3-enoic acids **1a–h** [7] and (*E*)-4-oxo-4-aryl-but-2-enoic acids **4a–h** [8]. Although the addition of β-aminocrotonitrile **2** to chalcones is well documented [1,9], the synthesis of pyridines using dicarbonyl systems described herein has not yet been studied.

## RESULTS AND DISCUSSION

Treatment of (*E*)-2-oxo-4-aryl-but-3-enoic acids **1a–h** with potassium *t*-butoxide in acetonitrile at ambient temperature afforded pyridines **3a–h** in good yields (Scheme 1, Table 1). The formation of the product proceeds by condensation of **1** with β-aminocrotonitrile **2** generated *in situ*. When the reaction was performed in dichloromethane or in tetrahydrofuran with commercially available β-aminocrotonitrile, no improvement of the yield or the reaction time was observed. Depending on the substitution pattern of the aromatic ring, full conversion required 3–16 h. The increase of the amount of *t*-butoxide did not significantly influence the reaction time.

The use of (*E*)-4-oxo-4-aryl-but-2-enoic acids **4a–h** under the same reaction conditions makes possible the

**Scheme 1**

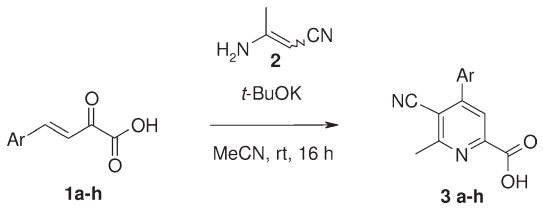



**Table 1**

Synthesis of pyridines **3a–h** *via* scheme 1[a].

| Compound number | Ar | Yield (%) |
|---|---|---|
| **3a** | 2-Fluoro-phenyl | 61/51[b] |
| **3b** | 4-Fluoro-phenyl | 66 |
| **3c** | 3-Chloro-phenyl | 60 |
| **3d** | 4-Chloro-phenyl | 73 |
| **3e** | 2,6-Dichloro-phenyl | 81 |
| **3f** | 4-Methoxy-phenyl | 71/50[b] |
| **3g** | Benzo[1,3]dioxol-5-yl | 62 |
| **3h** | Thiophen-2-yl | 62 |

[a] Unless otherwise mentioned, all reactions were carried out using (*E*)-2-oxo-4-aryl-but-3-enoic acid **1** (1.0 mmol), *t*-BuOK (3.0 mmol), and acetonitrile (5 mL) at room temperature for 16 h.
[b] Product (starting from 20 mmol of substrate) isolated by crystallization from acetonitrile.

substituent flexibility at the 2- and 4-positions of the target molecules (Schemes 1 and 2). Compounds **4a–h** reacted with β-aminocrotonitrile to give the regioisomers **5a–h** in good to excellent yields (Table 2). Similarly as for **3**, some differences in the reactivity depending on the substitution of the aromatic ring were observed. Nevertheless 16 h were sufficient for the full conversion of the substrate to the desired product. Two equivalents of potassium *t*-butoxide were used, because an increase of the amount of base lead to the formation of byproducts. As for the synthesis of the regioisomer **3**, reaction in dichloromethane or tetrahydrofuran with commercially available β-aminocrotonitrile did not improve reaction times and yields of the pyridine **5**. It was observed that the cyano group of the regioisomer **5** is particularly sensitive and undergoes hydrolysis during aqueous acidic workup. Therefore, water free 4*M* HCl/dioxane was used.

The procedure was easily scaled up to 20 mmol, and the products were isolated in good yields by crystallization from acetonitrile (Table 1, **3a** and **3f**; Table 2, **5d** and **5f**).

**Scheme 2**

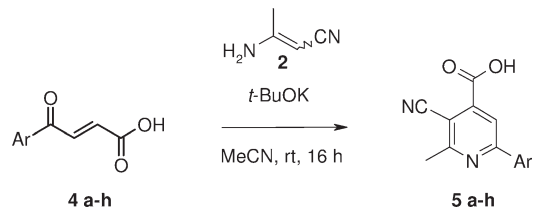



**Table 2**

Synthesis of pyridines **5a-h** *via* scheme 2[a].

| Compound number | Ar | Yield (%) |
|---|---|---|
| **5a** | 4-Fluoro-phenyl | 74 |
| **5b** | 3-Chloro-phenyl | 67 |
| **5c** | 4-Chloro-phenyl | 86 |
| **5d** | 2,4-Dichloro-phenyl | 81/65[b] |
| **5e** | 3,4-Dichloro-phenyl | 54 |
| **5f** | 4-Methoxy-phenyl | 86/55[b] |
| **5g** | Furan-2-yl | 63 |
| **5h** | Thiophen-2-yl | 61 |

[a] Unless otherwise mentioned, all reactions were carried out using (*E*)-4-oxo-4-aryl-but-2-enoic acid **1** (1.0 mmol), *t*-BuOK (2.0 mmol), and acetonitrile (5 mL) at room temperature for 16 h.
[b] Product (starting from 20 mmol of substrate) isolated by crystallization from acetonitrile.

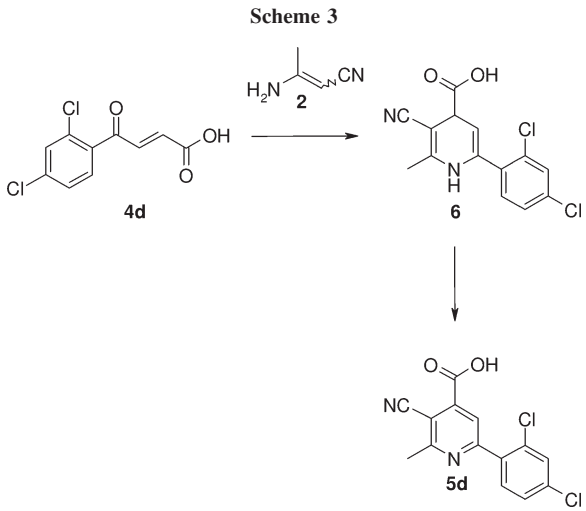
The formation of products **3** and **5** can be described as cyclocondensation reaction of the corresponding substrates **1** and **4** with β-aminocrotonitrile **2**. The enamine **2** is formed *in situ* by dimerization of acetonitrile catalyzed by potassium *t*-butoxide. Within the first hour **4d** gave the intermediate/dihydropyridine **6**, which slowly aromatized to the pyridine **5d** (Scheme 3).

Several modifications of the functional groups of pyridines **3** and **5** were performed to generate compound diversity.

The pyridines were readily converted to the corresponding *N*-oxides **7** and **12** as outlined on Schemes 4 and 5 [10]. 2-Aryl pyridine **5d** reacted only at higher temperature. At 100°C, *N*-oxide formation of **5d** was observed as well as hydrolysis of the cyano group to the corresponding pyridine dicarboxylic acid **12**. Both derivatives, **7** and **12**, were isolated in very good yields.

To form *N*-hydroxyamidines, pyridine carboxylic acids **3** and **5** were first amidated using (benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as coupling reagent to give amides **8** and **13**

**Scheme 3**



(Schemes 4 and 5). Both regioisomers were isolated in excellent yields. Amides **8a** and **13a** were treated with hydroxylamine and potassium *t*-butoxide in dimethyl sulfoxide at 100°C [5a]. 2-Aryl pyridine **13a** formed the expected product **14** within 2 h. The regioisomer **8a** appeared to be more sensitive and at the same conditions hydrolyzed to give the diamide **9**. Any other combination of bases and solvents did not lead to the formation of the hydroxyamidine from **8a**. Additionally, we observed that 4-aryl pyridines **3** with free carboxy group stayed unaffected under the described conditions, but its regioisomer 2-aryl pyridine **5** with carboxy group in position 4 decomposed.

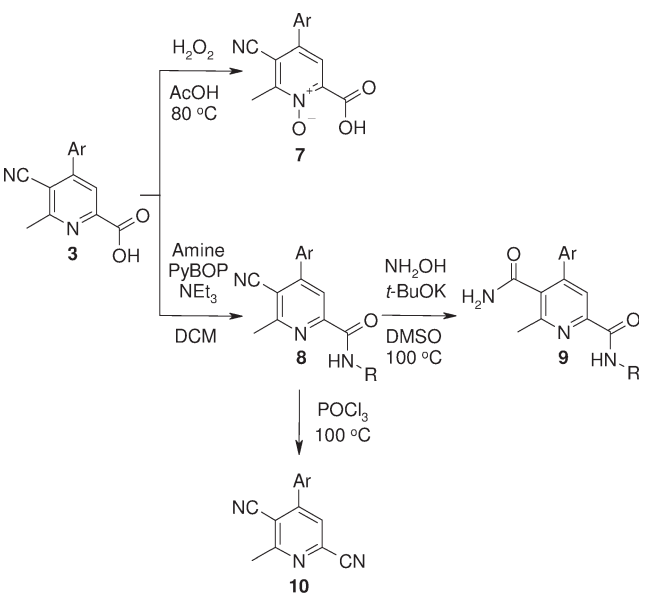
The dicyano-pyridines **10** and **15** were synthesized in high yields by dehydration of the primary amides **8b** and **13b**, respectively, with phosphorus oxychloride (Schemes 4 and 5) [11].

Attempts to transform **3d** into its hydrazide failed. The acid was unreactive in aqueous hydrazine (50%) at 100°C and was unstable at higher temperatures. However, the acid **5c** reacted with hydrazine to give the hydrazide **11** in an excellent yield (Scheme 5) [12].

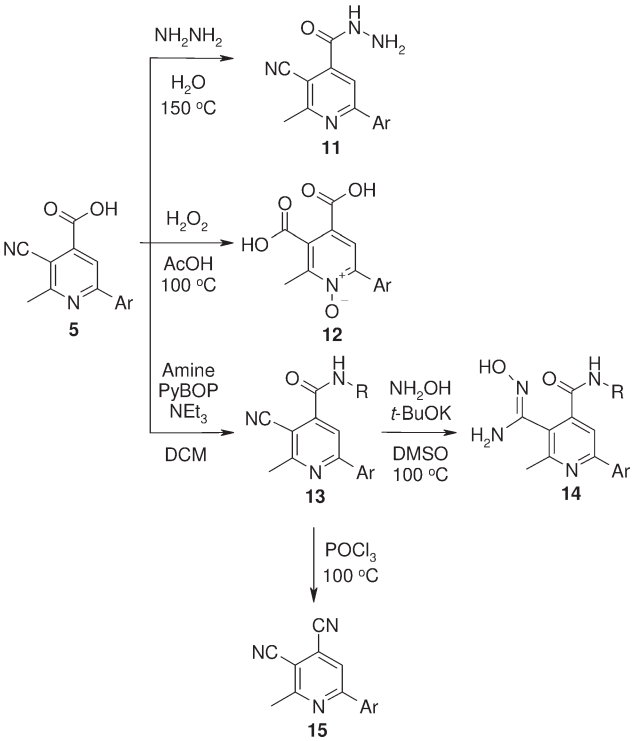
## CONCLUSIONS

In conclusion, we have developed a facile and efficient synthesis of highly substituted pyridines based on the reaction of easily accessible (*E*)-2-oxo-4-aryl-but-3-enoic acids and (*E*)-4-oxo-4-aryl-but-2-enoic acids with β-aminocrotonitrile. The method provides an opportunity for the introduction of a variety of functional groups. Further extension of the reactions and the application of the protocols in the synthesis of biologically active compounds are in progress.

**Scheme 4**




**Scheme 5**




## EXPERIMENTAL

Starting materials (*E*)-2-oxo-4-aryl-but-3-enoic acids **1** and (*E*)-4-oxo-4-aryl-but-2-enoic acids **4** were synthesized according to the literature procedures [7,8] or were obtained commercially and used as received. All chemicals were used as purchased from commercial suppliers. Analytical TLC were performed with ALUGRAM silica gel 60 F254 plate. Flash chromatography was done on Combi Flash 5q 16x. Visualization was accomplished using UV light. Column chromatography was carried out using MN silica gel 60 (70–230 mesh ASTM). The mass spectra were measured on a Waters LC/MS system (Alliance 2795 HPLC, SQD mass detector, PDA 996 detector; Grom-Sil 80 ODS-7 PH 4 μm, 2.0 × 40 mm; ionizing voltage 10 eV). For FT-ICR-MS measurements, the APEX II Bruker Daltonics (4.7 Tesla) spectrometer was used. NMR analyses were performed on a Bruker 400 Ultra Shield instrument. Melting points were measured on Büchi Melting Point B-540. IR spectra were obtained on Bruker-Vector 22.

**General procedure for the synthesis of (*E*)-2-oxo-4-aryl-but-3-enoic acids (1).** A solution of potassium hydroxide (2.52 g, 45 mmol) in methanol (7.5 mL) was added dropwise to a solution of pyruvic acid (2.11 mL, 30 mmol) and benzaldehyde (30 mmol) in methanol (15 mL) at 0°C. The reaction temperature was kept at 25°C for 1 h and at 0°C for 16 h. The yellow solid was filtered off and washed twice with cold methanol and once with diethyl ether. The crude residue was taken up in water, acidified with 1*M* HCl and extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulphate and concentrated to afford the product as a solid that was used without further purification.

**General procedure for the synthesis of (*E*)-4-oxo-4-aryl-but-2-enoic acids (4).** Glyoxylic acid monohydrate (3.68 g, 40 mmol) was added to a solution of acetophenone (40 mmol) in acetic acid (50 mL) and concentrated hydrochloric acid (5 mL). The mixture was refluxed for 16 h. After evaporation of the solvent, the yellow residue was taken up in ethyl acetate, filtered and air dried to afford the desired product as a yellow solid that was used in the next step without further purification.

**General procedure for the synthesis of 4-aryl pyridines (3).** Potassium *t*-butoxide (0.337 g, 3 mmol) was added portionwise to a solution of (*E*)-2-oxo-4-(aryl)-but-3-enoic acid **1** (1 mmol) in acetonitrile (5 mL) at room temperature. After 16 h (the reaction monitored by LC/MS), the solvent was removed under reduced pressure. The crude product was taken up in water, acidified with 1*M* HCl and extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulphate and concentrated. The solid product **3** was isolated by column chromatography with silica gel using a gradient of petroleum ether-ethyl acetate (from 4:1 to 1:1).

***5-Cyano-4-(2-fluoro-phenyl)-6-methyl-pyridine-2-carboxylic acid (3a).*** 61% yield, brown solid, mp 188°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3085, 2882, 2792, 2230, 1945, 1705, 1614, 1581, 1546, 1493, 1452, 1386, 1255, 1220, 919, 869, 796, 756; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.81 (s, 3 H), 7.43 (m, 2 H), 7.63 (m, 2 H), 7.98 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.7 ($CH_3$), 111.0 (C), 115.8 (C), 116.2 (d, $^2J_{C-F}$ = 21.22 Hz, CH), 122.7 (CH), 123.1 (d, $^2J_{C-F}$ = 14.63 Hz, C), 125.2 (d, $^3J_{C-F}$ = 3.66 Hz, CH), 131.2 (d, $^4J_{C-F}$ = 2.19 Hz, CH), 132.7 (d, $^3J_{C-F}$ = 8.05 Hz, CH), 148.4 (C), 150.4 (C), 158.5 (d, $^1J_{C-F}$ = 248.10, C), 161.9 (C), 165.1 (C); FT-ICR-MS: calculated for $C_{14}H_9FN_2O_2H^+$: 257.0721, found: 257.0721.

***5-Cyano-4-(4-fluoro-phenyl)-6-methyl-pyridine-2-carboxylic acid (3b).*** 66% yield, colorless solid, mp 201°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3292, 3115, 3078, 2229, 1757, 1602, 1550, 1506, 1417, 1388, 1344, 1314, 1226, 1159, 1108, 849, 717; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.79 (s, 3 H), 7.43 (m, 2 H), 7.77 (m, 2 H), 7.96 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 109.7 (C), 116.0 (C), 116.3 (d, $^2J_{C-F}$ = 21.96, CH), 121.9 (CH), 131.1 (d, $^3J_{C-F}$ = 8.78, CH), 131.8 (d, $^4J_{C-F}$ = 2.93, C), 150.1 (C), 152.6 (C), 162.2 (C), 163.3 (d, $^1J_{C-F}$ = 248.83, C), 165.2 (C); FT-ICR-MS: calculated for $C_{14}H_9FN_2O_2H^+$: 257.0721, found: 257.0719.

***5-Cyano-4-(3-chloro-phenyl)-6-methyl-pyridine-2-carboxylic acid (3c).*** 60% yield, colorless solid, mp 206°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3078, 3048, 2886, 2775, 2672, 2605, 2222, 1705, 1565, 1543, 1447, 1381, 1329, 1270, 1233, 1144, 1108, 908, 879, 798; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.80 (s, 3 H), 7.64 (m, 3 H), 7.79 (m, 1 H), 7.98 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 109.8 (C), 116.3 (C), 121.9 (CH), 127.4 (CH), 128.4 (CH), 130.1 (CH), 130.9 (CH), 133.7 (C), 137.4 (C), 150.3 (C), 152.1 (C), 162.2 (C), 165.1 (C); FT-ICR-MS: calculated for $C_{14}H_9ClN_2O_2H^+$: 273.0425, found: 273.0426.

***5-Cyano-4-(4-chloro-phenyl)-6-methyl-pyridine-2-carboxylic acid (3d).*** 73% yield, colorless solid, mp 208°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3085, 2982, 2937, 2864, 2229, 1742, 1713, 1602, 1580, 1543, 1506, 1417, 1226, 1181, 1144, 1085, 1049, 967, 857; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.79 (s, 3 H), 7.66 (m, 2 H), 7.73 (m, 2 H), 7.97 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 109.7 (C), 116.3 (C), 121.8 (CH), 129.1 (CH), 130.5 (CH), 134.2 (C), 135.3 (C), 150.2 (C), 152.4 (C), 162.2 (C), 165.1 (C); FT-ICR-MS: calculated for $C_{14}H_9ClN_2O_2H^+$: 273.0425, found: 273.0425.

***5-Cyano-4-(2,4-dichloro-phenyl)-6-methyl-pyridine-2-carboxylic acid (3e).*** 71% yield, colorless solid, mp 226–227°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3144, 2974, 2937, 2878, 2827, 2229, 1683, 1587, 1558, 1477, 1432, 1388, 1226, 1181, 1056, 1004; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.78 (s, 3 H), 7.59 (m, 1 H), 7.70 (m, 2 H), 7.81 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.5 ($CH_3$), 109.1 (C), 115.4 (C), 121.8 (CH), 128.7 (CH), 132.3 (C), 132.9 (CH), 133.6 (C), 149.0 (C), 156.4 (C), 161.5 (C), 166.0 (C); FT-ICR-MS: calculated for $C_{14}H_8Cl_2N_2O_2H^+$: 307.0036, found: 307.0036.

***5-Cyano-4-(4-methoxy-phenyl)-6-methyl-pyridine-2-carboxylic acid (3f).*** 71% yield, colorless solid, mp 196°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3284, 3174, 2974, 2937, 2871, 2229, 1727, 1602, 1536, 1499, 1425, 1388, 1336, 1233, 1174, 1130, 1063, 1026, 916, 835; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.77 (s, 3 H), 3.84 (s, 3 H), 7.13 (m, 2 H), 7.67 (m, 2 H), 7.92 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 55.5 ($CH_3$), 109.2 (C), 114.6 (CH), 116.8 (C), 121.6 (CH), 127.4 (C), 130.2 (CH), 150.0 (C), 153.3 (C), 161.0 (C), 162.3 (C), 165.3 (C); FT-ICR-MS: calculated for $C_{15}H_{12}N_2O_3H^+$: 269.0921, found: 269.0919.

***4-Benzo[1,3]dioxol-5-yl-5-cyano-6-methyl-pyridine-2-carboxylic acid (3g).*** 62% yield, colorless solid, mp 211°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3306, 3174, 3078, 2974, 2945, 2871, 2229, 1764, 1727, 1587, 1536, 1499, 1447, 1388, 1336, 1233, 1196, 1152, 1034, 916; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.77 (s, 3 H), 6.14 (s, 2 H), 7.11 (m, 1 H), 7.19 (m, 1 H), 7.29 (m, 1 H), 7.91 (m, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 101.9 ($CH_2$), 108.7 (CH), 108.8 (CH), 109.4 (C), 116.6 (C), 121.7 (CH), 123.2 (CH), 129.0 (C), 147.9 (C), 149.1 (C), 150.0 (C), 153.2 (C), 162.2 (C), 165.2 (C); FT-ICR-MS: calculated for $C_{15}H_{10}N_2O_4H^+$: 283.0713, found: 283.0712.

***5-Cyano-6-methyl-4-thiophen-2-yl-pyridine-2-carboxylic acid (3h).*** 62% yield, yellow solid, mp 200°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3336, 3100, 2893, 2849, 2222, 1919, 1764, 1713, 1580, 1536, 1417, 1388, 1299, 1218, 1144, 849, 798, 702; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.77 (s, 3 H), 7.33 (m, 1 H), 7.97 (m, 2 H), 8.04 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.9 ($CH_3$), 106.8 (C), 116.9 (C), 120.3 (CH), 129.1 (CH), 130.5 (CH), 131.5 (CH), 136.2 (C), 145.3 (C), 150.3 (C), 163.1 (C), 165.1 (C); FT-ICR-MS: calculated for $C_{12}H_8N_2O_2SH^+$: 245.0379, found: 245.0378.

**General procedure for the synthesis of 2-aryl pyridines (5).** Potassium *t*-butoxide (0.224 g, 2 mmol) was added portionwise to a solution of (*E*)-4-oxo-4-(aryl)-but-2-enoic acid **4** (1 mmol) in acetonitrile (5 mL) at room temperature. After 16 h (reaction monitored by LC/MS), the solvent was removed under reduced pressure. The mixture was suspended in dioxane and acidified with water free 4*M* HCl in dioxane. After evaporation of the solvent, the residue was taken up in water and extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulphate and concentrated. The solid product **5** was isolated by flash chromatography using dichloromethane-methanol gradient (from 99:1 to 95:5).

***3-Cyano-6-(4-fluoro-phenyl)-2-methyl-isonicotinic acid (5a).*** 74% yield, colorless solid, mp 286–287°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3240, 3085, 2229, 1794, 1727, 1602, 1580, 1558, 1513, 1454, 1403, 1358, 1307, 1226, 1159, 1137, 842, 657; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.78 (s, 3 H),

7.33 (m, 2 H), 8.22 (m, 3 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.9 ($CH_3$), 104.9 (C), 116.0 (d, $^2J_{C-F}$ = 21.23 Hz, CH), 116.0 (C), 117.1 (CH), 129.8 (d, $^3J_{C-F}$ = 9.52 Hz, CH),132.8 (d, $^4J_{C-F}$ = 2.93 Hz, C), 142.8 (C), 157.4 (C), 162.8 (C), 163.8 (d, $^1J_{C-F}$ = 248.83 Hz, C), 164.5 (C); FT-ICR-MS: calculated for $C_{14}H_9FN_2O_2Na^+$: 279.0540, found: 279.0541.

***3-Cyano-6-(3-chloro-phenyl)-2-methyl-isonicotinic acid (5b).*** 67% yield, colorless solid, mp 194°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3011, 2819, 2635, 2524, 2214, 1713, 1624, 1572, 1513, 1425, 1381, 1373, 1322, 1263, 1233, 1144, 1093, 938, 879; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.80 (s, 3 H), 7.57 (m, 2 H), 8.13 (m, 1 H), 8.21 (m, 1 H), 8.30 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.9 ($CH_3$), 105.7 (C), 115.9 (C), 117.6 (CH), 126.0 (CH), 127.0 (CH), 130.5 (CH), 131.0 (CH), 134.0 (C), 138.4 (C), 143.2 (C), 156.9 (C), 162.9 (C), 164.5 (C); FT-ICR-MS: calculated for $C_{14}H_9ClN_2O_2H^+$: 273.0425, found: 273.0425.

***3-Cyano-6-(4-chloro-phenyl)-2-methyl-isonicotinic acid (5c).*** 86% yield, brown solid, mp 295–297°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3454, 2805, 2635, 2236, 1720, 1601, 1575, 1551, 1494, 1431, 1386, 1337, 1248, 1091, 1015, 903, 829, 746, 667; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.80 (s, 3 H), 7.58 (m, 2 H), 8.20 (m, 2 H), 8.27 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.9 ($CH_3$), 105.3 (C), 116.0 (C), 117.3 (CH), 129.1 (CH), 129.2 (CH), 135.1 (C), 135.7 (C), 143.0 (C), 157.2 (C), 162.9 (C), 164.5 (C); FT-ICR-MS: calculated for $C_{14}H_9ClN_2O_2H^+$: 273.0425, found: 273.0426.

***3-Cyano-6-(2,4-dichloro-phenyl)-2-methyl-isonicotinic acid (5d).*** 65% yield, red solid, mp 180°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3100, 3070, 2882, 2852, 2230, 1750, 1584, 1554, 1404, 1329, 1224, 1142, 1097, 1037, 872, 819, 789, 722, 609; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.80 (s, 3 H), 7.58 (dd, $J$ = 8.34, 2.02 Hz, 1 H), 7.67 (d, $J$ = 8.33 Hz, 1 H), 7.79 (d, $J$ = 2.02 Hz, 1 H), 8.05 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.7 ($CH_3$), 105.9 (C), 115.8 (C), 121.8 (CH), 127.9 (CH), 129.7 (CH), 132.2 (C) , 133.1 (CH), 135.1 (C), 135.8 (C), 142.6 (C), 157.6 (C), 162.9 (C), 164.3 (C); FT-ICR-MS: calculated for $C_{14}H_8Cl_2N_2O_2H^+$: 307.0036, found: 307.0037.

***3-Cyano-6-(3,4-dichloro-phenyl)-2-methyl-isonicotinic acid (5e).*** 54% yield, colorless solid, mp 165°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3100, 2897, 2860, 2230, 1705, 1569, 1427, 1329, 1269, 1247, 1149, 1029, 887, 834, 677; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.79 (s, 3 H), 7.75 (d, $J$ = 8.65 Hz, 1 H), 8.14 (dd, $J$ = 8.39, 2.03 Hz, 1 H), 8.31 (s, 1 H), 8.37 (d, $J$ = 2.03 Hz, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 105.8 (C), 115.8(C), 117.6 (CH), 127.4 (CH), 129.0 (CH), 131.2 (CH), 132.0 (C), 133.5 (C), 136.7 (C), 143.1 (C), 155.8 (C), 162.9 (C), 164.4 (C); FT-ICR-MS: calculated for $C_{14}H_8Cl_2N_2O_2H^+$: 307.0036, found: 307.0038.

***3-Cyano-6-(4-methoxy-phenyl)-2-methyl-isonicotinic acid (5f).*** 86% yield, yellow solid, mp 186°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3011, 2974, 2871, 2842, 2237, 1742, 1602, 1565, 1513, 1454, 1388, 1322, 1292, 1263, 1226, 1174, 1144, 1026, 820, 672; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.76 (s, 3 H), 3.83 (s, 3 H), 7.06 (m, 2 H), 8.14 (m, 2 H), 8.17 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.9 ($CH_3$), 55.4 ($CH_3$), 103.8 (C), 114.4 (CH), 116.2 (C), 116.3 (CH), 128.7 (C), 129.0 (CH), 142.5 (C), 158.2 (C), 161.6 (C), 162.7 (C), 164.7 (C); FT-ICR-MS: calculated for $C_{15}H_{12}N_2O_3H^+$: 269.0921, found: 269.0921.

***3-Cyano-6-furan-2-yl-2-methyl-isonicotinic acid (5g).*** 63% yield, yellow solid, mp 170°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3182, 3092, 2897, 2222, 1720, 1577, 1532, 1442, 1352, 1322, 1269, 1239, 1202, 1089, 1037, 917, 707, 662; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.74 (s, 3 H), 6.74 (m, 1 H), 7.39 (m, 1 H), 7.99 (m, 1 H), 8.00 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.7 ($CH_3$), 104.1 (C), 115.8 (CH), 116.1 (C), 129.0 (CH), 129.2 (CH), 131.8 (CH), 142.2 (C), 142.6 (C), 154.3 (C), 163.0 (C), 164.5 (C); FT-ICR-MS: calculated for $C_{12}H_8N_2O_3H^+$: 229.0608, found: 229.0610.

***3-Cyano-6-thiophen-2-yl-2-methyl-isonicotinic acid (5h).*** 61% yield, yellow solid, mp 207–208°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3152, 3130, 2920, 2852, 2215, 1692, 1592, 1547, 1479, 1404, 1232, 1172, 1074, 1037, 954, 887, 767, 714; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.72 (s, 3 H), 7.22 (dd, $J$ = 4.83, 3.81 Hz, 1 H), 7.83 (m, 1 H), 8.08 (m, 1 H), 8.21 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 104.2 (C), 113.2 (CH), 113.2 (CH), 115.3 (CH), 116.1 (C), 142.6 (C), 146.5 (CH), 150.3 (C), 151.3 (C), 163.3 (C), 164.3 (C); FT-ICR-MS: calculated for $C_{12}H_8N_2O_2SH^+$: 245.0379, found: 245.0380.

**3-Cyano-6-(2,4-dichloro-phenyl)-2-methyl-1,4-dihydro-pyridine-4-carboxylic acid (6).** Brown crystals, mp 179–181°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3262, 3233, 3115, 3004, 2849, 2620, 2207, 1698, 1668, 1624, 1580, 1513, 1469, 1417, 1381, 1307, 1248, 1122, 1085, 916; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 2.01 (s, 3 H), 4.02 (d, $J$ = 4.83 Hz, 1 H), 4.71 (m, 1 H), 7.37 (d, $J$ = 8.14 Hz, 1 H), 7.46 (dd, $J$ = 8.19, 2.03 Hz, 1 H), 7.69 (d, $J$ = 2.03 Hz, 1 H), 8.84 (s, 1 H), 12.61 (s, 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ ppm 17.9 ($CH_3$), 41.0 (CH), 73.1 (C), 99.2 (CH), 120.9 (C), 127.5 (CH), 129.2 (CH), 132.3 (CH), 133.4 (C), 133.6 (C), 134.1 (C), 134.2 (C), 149.7 (C), 173.0 (C); FT-ICR-MS: calculated for $C_{14}H_{10}Cl_2N_2O_2H^+$: 309.0192, found: 309.0192.

**5-Cyano-4-(4-fluoro-phenyl)-6-methyl-1-oxy-pyridine-2-carboxylic acid (7).** 5-Cyano-6-methyl-4-(4-fluoro-phenyl)-pyridine-2-carboxylic acid **3b** (0.064 g, 0.25 mmol) was dissolved in acetic acid (2 mL) and 30% hydrogen peroxide was added (2 mL). The mixture was stirred for 2 h at 80°C and then kept at room temperature for 16 h. The resulting yellow crystals were filtered, washed with acetic acid and water, and air dried to give 0.041 g (60%) of the product **7**. Mp 160–162°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3347, 3071, 2991, 2926, 2867, 2809, 2221, 1735, 1655, 1510, 1401, 1365, 1292, 1241, 1161, 1060, 1002, 907, 828, 777; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 2.95 (s, 3 H), 7.29 (m, 2 H), 7.66 (m, 2 H), 8.45 (s, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ ppm 17.2 ($CH_3$), 113.6 (C), 113.6 (C), 116.9 (d, $^2J_{C-F}$ = 21.95 Hz, CH), 127.3 (CH), 129.6 (d, $^4J_{C-F}$ = 3.66 Hz, C), 130.7 (d, $^3J_{C-F}$ = 8.78, CH), 138.6 (C), 144.7 (C), 153.8 (C), 160.1 (C), 164.5 (d, $^1J_{C-F}$ = 253.95, C); FT-ICR-MS: calculated for $C_{14}H_9FN_2O_3Na^+$: 295.0489, found: 295.0490.

**5-Cyano-4-(4-methoxy-phenyl)-6-methyl-pyridine-2-carboxylic acid 3,4-dichloro-benzylamide (8a).** 5-Cyano-6-methyl-4-(4-methoxy-phenyl)-pyridine-2-carboxylic acid **3f** (0.040 g, 0.15 mmol) was dissolved in 5 mL dichloromethane. PyBOP (0.088 g, 0.17 mmol) and triethylamine (0.042 mL, 0.30 mmol) were successively added followed by addition of 3,4-dichloro-benzylamine (0.031 mL, 0.23 mmol). After 3-h stirring at room temperature (the reaction monitored by TLC), the solvent was removed, and the product as a colorless solid (0.063 g, 99%) was isolated by filtration on silica gel using

petroleum ether–ethyl acetate (2:1) as eluent. Mp 152°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3415, 3385, 2927, 2357, 2222, 1735, 1682, 1517, 1457, 1352, 1269, 1232, 1179, 1142, 1059, 999, 887, 797; $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 2.83 (s, 3 H), 3.87 (s, 3 H), 4.63 (d, $J = 6.36$ Hz, 2 H), 7.04 (m, 2 H), 7.20 (m, 1 H), 7.40 (m, 1 H), 7.44 (m, 1 H), 7.62 (m, 2 H), 8.17 (s, 1 H), 8.44 (t, $J = 5.98$ Hz, 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ ppm 24.0 ($CH_3$), 42.5 ($CH_2$), 55.4 ($CH_3$), 109.5 (C), 114.6 (CH), 116.8 (C), 119.6 (CH), 127.1 (CH), 127.6 (C), 129.7 (CH), 130.1 (CH), 130.7 (CH), 131.7 (C), 132.8 (C), 138.2 (C), 150.3 (C), 154.6 (C), 161.5 (C), 161.9 (C), 163.2 (C); FT-ICR-MS: calculated for $C_{22}H_{17}Cl_2N_3O_2Na^+$: 448.0590, found: 448.0591.

**4-(4-Chloro-phenyl)-5-cyano-6-methyl-pyridine-2-carboxylic acid amide (8b).** 5-Cyano-6-methyl-4-(4-chloro-phenyl)-pyridine-2-carboxylic acid **3d** (0.041 g, 0.15 mmol) was dissolved in 5 mL dichloromethane. PyBOP (0.088 g, 0.17 mmol) and triethylamine (0.042 mL, 0.30 mmol) were successively added followed by addition of 1-hydroxybenzotriazol ammonium salt (0.035 mg, 0.23 mmol). After 3 h stirring at room temperature (the reaction monitored by TLC), the solvent was removed and the product **8b** as a colorless solid (0.030 g, 73%) was isolated by filtration on silica gel using petroleum ether–ethyl acetate (2:1) as eluent. Mp 214–216°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3449, 3360, 3277, 3155, 3041, 2218, 1707, 1643, 1580, 1535, 1490, 1420, 1382, 1356, 1318, 1241, 1152, 1095, 1018, 910, 852, 827, 699; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ ppm 2.81 (s, 3 H), 7.69 (m, 4 H), 7.96 (s, 2 H), 8.28 (s, 1 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ ppm 23.7 ($CH_3$), 109.2 (C), 116.5 (C), 119.2 (CH), 129.1 (CH), 130.5 (CH), 134.4 (C), 135.2 (C), 151.8 (C), 152.6 (C), 161.6 (C), 164.6 (C); FT-ICR-MS: calculated for $C_{14}H_{10}ClN_3ONa^+$: 294.0405, found: 294.0404.

**4-(4-Methoxy-phenyl)-6-methyl-pyridine-2,5-dicarboxylic acid 5-amide 2-(3,4-dichlorobenzylamide) (9).** Hydroxylamine hydrochloride (0.021 g, 0.30 mmol) and potassium *t*-butoxide (0.045 g, 0.40 mmol) were successively added to the suspension of 5-cyano-4-(4-methoxy-phenyl)-6-methyl-pyridine-2-carboxylic acid 3,4-dichloro-benzylamide **8a** (0.043 g, 0.10 mmol) in dimethyl sulfoxide (1 mL). The mixture was stirred for 16 h at 100°C, cooled to room temperature and diluted with water. After acidification with 1*M* HCl, the mixture was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulphate, concentrated, and the residue was purified by column chromatography with on silica gel using dichloromethane-methanol (40:1) as eluent to afford product **9** as a colorless solid (0.037 g, 84%). Mp 151°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3705, 3668, 3351, 3107, 2974, 2864, 1735, 1661, 1506, 1358, 1285, 1240, 1137, 1056, 1026, 820, 650; $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 2.62 (s, 3 H), 3.82 (s, 3 H), 4.58 (d, $J = 6.36$ Hz, 1 H), 5.74 (s, 1 H), 5.81 (s, 1 H), 6.92 (m, 2 H), 7.18 (dd, $J = 8.39$, 2.03 Hz, 1 H), 7.39 (d, $J = 8.39$ Hz, 2 H), 7.45 (m, 3 H), 7.97 (s, 1 H), 8.48 (t, $J = 6.36$ Hz, 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ ppm 22.5 ($CH_3$), 42.3 ($CH_2$), 55.3 ($CH_3$), 114.3 (CH), 120.3 (CH), 127.1 (CH), 129.2 (C), 129.6 (CH), 129.7 (CH), 130.6 (CH), 131.5 (C), 132.7 (C), 132.7 (C), 138.5 (C), 147.8 (C), 148.4 (C), 154.9 (C), 160.5 (C), 164.0 (C), 170.3 (C); FT-ICR-MS: calculated for $C_{22}H_{19}Cl_2N_3O_3Na^+$: 466.0696, found: 466.0696.

**4-(4-Chloro-phenyl)-6-methyl-pyridine-2,5-dicarbonitrile (10).** 5-Cyano-6-methyl-4-(4-chloro-phenyl)-pyridine-2-carboxylic acid amide **8b** (0.054 g, 0.20 mmol) was dissolved in phosphorus oxychloride (2 mL), and the mixture was heated at 100°C for 2 h. The excess of the reagent was removed *in vacuo*, and the product as a colorless solid (0.044 g, 86%) was isolated by column chromatography (petroleum ether–ethyl acetate, 10:1). Mp 174–176°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3449, 3363, 3267, 3155, 3089, 2948, 2229, 1807, 1703, 1637, 1585, 1533, 1481, 1422, 1362, 1318, 1229, 1088, 1007, 822; $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 2.91 (s, 3 H), 7.55 (m, 4 H), 7.66 (s, 1 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ ppm 24.2 ($CH_3$), 110.8 (C), 115.2 (C), 116.0 (C), 125.5 (CH), 129.7 (CH), 129.8 (CH), 132.5 (C), 135.4 (C), 137.6 (C), 153.4 (C), 164.6 (C); FT-ICR-MS: calculated for $C_{14}H_8ClN_3H^+$: 254.0480, found: 254.0478.

**6-(4-Chloro-phenyl)-3-cyano-2-methyl-isonicotinic acid hydrazide (11).** A suspension of **5c** (0.082 g, 0.3 mmol) in 50% hydrazine/water (2mL) in a sealed tube was heated at 150°C for 24 h. The precipitate was filtered, washed with water, and air-dried to afford the product **11** (0.080 g, 94%) as a yellow solid. Mp 336–339°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3295, 3202, 2992, 2906, 2826, 1659, 1609, 1541, 1474, 1412, 1381, 1350, 1165, 1103, 1035, 998, 825, 782, 733; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ ppm 3.08 (s, 3 H), 5.56 (s, 2 H), 7.57 (d, $J = 8.39$ Hz, 2 H), 8.22 (d, $J = 8.65$ Hz, 2 H), 8.37 (s, 1 H), 12.00 (s, 1 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ ppm 26.7 ($CH_3$), 112.4 (CH), 118.6 (C), 128.7 (CH), 129.1 (CH), 134.9 (C), 136.0 (C), 136.5 (C), 146.1 (C), 154.0 (C), 157.3 (C), 157.7 (C); FT-ICR-MS: calculated for $C_{14}H_{11}ClN_4OH^+$: 287.0694, found: 287.0694.

**6-(2,4-Dichloro-phenyl)-2-methyl-1-oxy-pyridine-3,4-dicarboxylic acid (12).** 3-Cyano-2-methyl-6-(2,4-dichloro-phenyl)-isonicotinic acid **5d** (0.077 g, 0.25 mmol) was dissolved in acetic acid (2 mL), and then 30% hydrogen peroxide was added (2 mL). After stirring for 5 h at 100°C, the mixture was poured on ice/water and extracted with chloroform (3 × 10 mL). The aqueous phase was then concentrated *in vacuo* and dried by lyophilization to afford the product **12** (0.075 g, 87%) as a brown solid. Mp 172–173°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3520, 3415, 3175, 3032, 2882, 2785, 1705, 1577, 1412, 1374, 1322, 1262, 1202, 1142, 1092, 1052, 977, 902, 857, 812, 774, 677; $^1H$ NMR (400 MHz, $D_2O$) δ ppm 2.49 (s, 3 H), 7.36 (d, $J = 8.39$ Hz, 1 H), 7.47 (d, $J = 8.14$ Hz, 1 H), 7.64 (s, 1 H), 7.85 (s, 1 H); $^{13}C$ NMR (100 MHz, $D_2O$/DMSO-$d_6$) δ ppm 16.7 ($CH_3$), 128.0 (CH), 129.2 (C), 129.4 (CH), 131.0 (CH), 131.7 (C), 133.3 (CH), 135.7 (C), 137.8 (C), 140.2 (C), 147.8 (C), 148.4 (C), 168.7 (C), 173.8 (C); FT-ICR-MS: calculated for $C_{14}H_9Cl_2NO_5H^+$: 341.9931, found: 341.9929.

**3-Cyano-*N*-(3,4-dichloro-benzyl)-6-(4-methoxy-phenyl)-2-methyl-isonicotinamide (13a).** This compound was obtained according to the procedure for **8a**, using compound **5f** as a starting material. Eluent dichloromethane–methanol (40:1), yield: 0.063 g (99%), colorless solid, mp 242°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3454, 3100, 2893, 2834, 2347, 1764, 1698, 1595, 1513, 1425, 1381, 1336, 1248, 1167, 1130, 1093, 1019.019.8, 835, 753; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ ppm 2.76 (s, 3 H), 3.83 (s, 3 H), 4.52 (d, $J = 5.85$ Hz, 2 H), 7.10 (m, 2 H), 7.39 (dd, $J = 8.39$, 2.03 Hz, 1 H), 7.62 (d, $J = 8.39$ Hz, 1 H), 7.66 (d, $J = 2.03$ Hz, 1 H), 8.11 (s, 1 H), 8.20 (m, 2 H), 9.50 (t, $J = 5.85$ Hz, 1 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ ppm 23.9 ($CH_3$), 41.8 ($CH_2$), 55.4 ($CH_3$), 103.5 (C), 114.4 (CH), 114.7 (CH), 116.8 (C), 127.8 (CH), 129.0 (C), 129.1 (CH), 129.5 (CH), 129.6 (C), 130.6 (CH), 131.0 (C), 139.8 (C), 146.8 (C), 158.1 (C), 161.6 (C), 162.2 (C), 164.2 (C); FT-ICR-MS: calculated for $C_{22}H_{17}Cl_2N_3O_2H^+$: 426.0771, found: 426.0772.

**6-(4-Chloro-phenyl)-3-cyano-2-methyl-isonicotinamide (13b).** This compound was obtained according to the procedure for **8b**, using compound **5c** as a starting material. Eluent dichloromethane–methanol (40:1), yield: 0.040 g (99%), colorless solid, mp 203–205°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3467, 3348, 3178, 2948, 2859, 2222, 1666, 1570, 1540, 1414, 1311, 1244, 1199, 1073, 1007, 836, 733, 651; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ ppm 2.77 (s, 3 H), 7.60 (m, 2 H), 8.04 (s, 1 H), 8.17 (s, 1 H), 8.21 (m, 2 H), 8.41 (s, 1 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ ppm 23.8 ($CH_3$), 104.6 (C), 115.7 (CH), 116.1 (C), 129.1 (CH), 129.2 (CH), 135.4 (C), 135.7 (C), 147.5 (C), 156.9 (C), 162.4 (C), 165.5 (C); FT-ICR-MS: calculated for $C_{14}H_{10}ClN_3ONa^+$: 294.0405, found: 294.0404.

**5-(*N*-Hydroxycarbamimidoyl)-4-(4-methoxy-phenyl)-6-methyl-pyridine-2-carboxylic acid 3,4-dichlorobenzylamide (14).** Hydroxylamine hydrochloride (0.021 g, 0.30 mmol) and potassium *t*-butoxide (0.034 g, 0.30 mmol) were successively added to the suspension of 3-cyano-*N*-(3,4-dichloro-benzyl)-6-(4-methoxy-phenyl)-2-methyl isonicotinamide **13a** (0.043 g, 0.10 mmol) in dimethyl sulfoxide (1 mL). The mixture was stirred for 2 h at 100°C, cooled to room temperature, and diluted with water. The yellow precipitate was filtered, washed with water, and air dried to give the product **14** as a yellow solid (0.043 g, 94%). Mp 270°C (dec.); IR (neat, $cm^{-1}$) $\lambda_{max}$: 3484, 3329, 3210, 2886, 2834, 2783, 1735, 1639, 1558, 1513, 1462, 1417, 1358, 1285, 1255, 1181, 1122, 1026, 938, 827, 606; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ ppm 2.57 (s, 3 H), 3.81 (s, 3 H), 4.44 (d, $J = 5.85$ Hz, 2 H), 5.88 (s, 2 H), 7.05 (m, 1 H), 7.40 (m, 1 H), 7.61 (m, 1 H), 7.73 (s, 1 H), 8.08 (m, 2 H), 8.75 (t, $J = 5.85$ Hz, 1 H), 9.45 (s, 1 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ ppm 22.6 ($CH_3$), 41.5 ($CH_2$), 55.3 ($CH_3$), 114.2 (CH), 114.5 (CH), 124.2 (C), 127.5 (CH), 128.1 (CH), 129.0 (CH), 129.2 (C), 130.3 (C), 130.6 (CH), 130.7 (C), 140.2 (C), 145.5 (C), 149.8 (C), 155.1 (C), 157.7 (C), 160.5 (C), 166.9 (C); FT-ICR-MS: calculated for $C_{22}H_{20}Cl_2N_4O_3H^+$: 459.0985, found: 459.0986.

**6-(4-Chloro-phenyl)-2-methyl-pyridine-3,4-dicarbonitrile (15).** This compound was obtained according to the procedure for **10**, using compound **13b** as a starting material. Yield: 0.043 g (84%), colorless solid, mp 193°C; IR (neat, $cm^{-1}$) $\lambda_{max}$: 3378, 3252, 3155, 3096, 2963, 2926, 2229, 1644, 1577, 1540, 1451, 1407, 1370, 1325, 1236, 1088, 999, 881, 844, 747, 644; $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 2.90 (s, 3 H), 7.50 (m, 2 H), 7.89 (s, 1 H), 8.01 (m, 2 H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ ppm 24.3 ($CH_3$), 108.0 (C), 114.0 (C), 114.1 (C), 119.5 (CH), 124.8 (C), 128.8 (CH), 129.6 (CH), 134.1 (C), 138.2 (C), 159.2 (C), 163.4 (C); FT-ICR-MS: calculated for $C_{14}H_8ClN_3Na^+$: 276.0299, found: 276.0299.

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