Preliminary Communication

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An efficient synthesis of 5-halo-6-trifluoromethylpyridine-3-carbonitriles and carboxylic acids

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Abstract: Trifluoromethyl containing heterocycles are an integral part of many biologically active compounds in the agro and pharmaceutical chemistry. Herein, we report an efficient and concise three-step synthesis of 5-halo-6-trifluoromethylpyridine-3-carbonitriles from a trifluoroacetyl vinylogous enamine starting material. Hydrolysis furnishes the carboxylic acids.

Keywords: cyclisation; enamines; heterocycles; nitriles; pyridines.

The trifluoromethylpyridine structural motif has become a valuable component of research programs seeking molecules with useful biological activity. In the field of crop protection, this approach has met with significant success, with products now introduced as fungicides, herbicides and insecticides. For example, picoxystrobin is a fungicide introduced to the market in 2004 [1]; bicyclopyrone is a herbicide introduced in 2015 [2] and sulfoxaflor is an insecticide introduced to the market in 2013 [3] (Figure 1).

The importance of functionalized trifluoromethylpyridines is further underlined by the continued appearance in the literature of complementary methods to prepare such building blocks [4–11]. To facilitate the identification of new compounds with useful biological activity containing a trifluoromethylpyridine, we believe that a simple access to highly functionalized trifluoromethylpyridine intermediates which can be further elaborated, can be of value. In a previous communication [12], we have reported a simple three-step procedure to prepare 3,5-dicyano-6-trifluoromethylpyridine, together with the selective formation of a mono thioamide. In continuation of this theme, we now report an efficient synthesis of 5-halo-6-trifluoromethylpyridine-3-carbonitriles **1** from readily available starting materials. Hydrolysis of the nitriles then affords the corresponding nicotinic acids **2** (Figure 2).

At the outset of this work, a synthesis of the nicotinic nitriles **1** has not been known and only one of the nicotinic acids, **2b**, has been reported [13] using 3-chloro-2-trifluoromethylpyridine, which has been prepared by the reaction of 3-chloro-2-iodopyridine with a source of nucleophilic

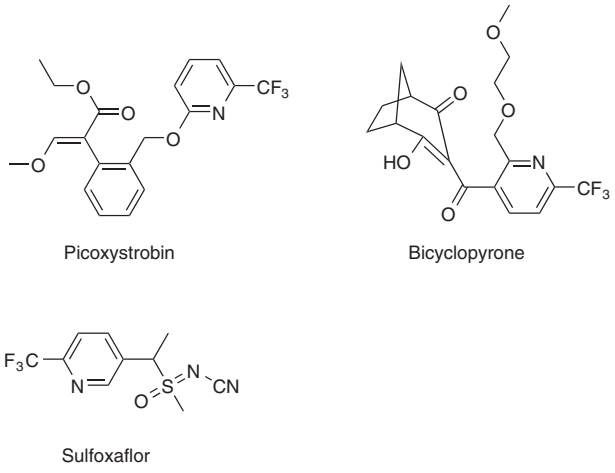

Figure 1 Selected commercial agrochemicals in crop protection.

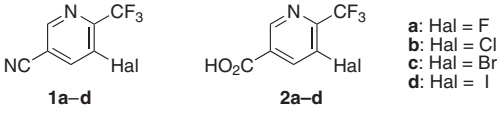

Figure 2 5-Halo-6-trifluoromethyl nicotinic nitriles and acids.

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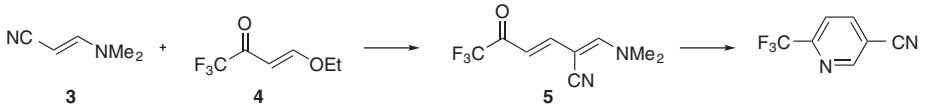


Scheme 1 Synthesis of 2-trifluoromethyl-5-cyanopyridine.

Scheme 2 Attempted synthesis of halogenated enamine **7**.

CF_3 in the presence of copper. In this approach, termed regioexhaustive functionalization, strong bases at low temperatures have been employed followed by treatment with iodine, then with magnesium and quenching with CO_2 to form **2b** in four steps from 3-chloro-2-iodopyridine.

In 1998, Cooke and co-workers [14] reported an efficient synthesis of 2-trifluoromethyl-5-cyanopyridine through the cyclization of the vinylogous enamine **5** with ammonium acetate. Compound **5** was prepared by the reaction of commercially available dimethylaminoacrylonitrile **3** with the vinyl ether **4** (Scheme 1).

We first attempted to introduce halogen (chloro and bromo) at an early stage in the synthesis; conversion of the vinyl ether **4** into the halo derivatives **6** by halogenation and dehydrohalogenation has been reported [15]. However, all attempts to couple these vinyl ethers **6** with dimethylaminoacrylonitrile **3** were unsuccessful, with only complex mixtures resulting (Scheme 2).

We believe the lack of success of this approach may be due to reduced electrophilicity of the haloenones **6** compared to **4**. Indeed, a steric hindrance between the halogen and the trifluoromethyl group in **6** has been postulated [15]; such an interaction could well reduce the conjugation between the double bond and the trifluoroacetyl group. To investigate this further, we compared ^{13}C nuclear magnetic resonance (NMR) spectra of enone **4** and **6** (Hal = Br). Chemical shifts for C(3) and C(4) carbon are shown for compounds **4** and **6** (Hal = Br) in Figure 3. The chemical shift for C(4) in **6** (Hal = Br) is upfield compared to that for C(4) in **4**, indicating a higher electron density at this position in **6** (Hal = Br). We believe this could explain the lack of success for the attempted reaction shown in Scheme 2. We then investigated the introduction of a halogen at a later stage in the synthesis and were pleased to find out that this approach was successful. We decided to first replace the dimethylamino leaving group by pyrrolidine and undertook some limited process studies to optimize the formation of the vinylogous system. Reaction of equimolar amounts of *trans*-3-pyrrolidine acrylonitrile [16] **8** and vinyl ether **4** in toluene at 100°C for 3 h gave the desired product **9** in only 34% yield. Significant amounts of two by-products were obtained, as shown in Scheme 3.

By-product **10** is formed by the self-condensation [17] of **8** and by-product **11** is presumably formed by the reaction of vinyl ether **4** with pyrrolidine liberated upon formation of **10**. By increasing the amount of vinyl ether **4** to seven equivalents, product **9** was obtained in 85% yield; lower molar equivalents of **4** resulted in lower yields of **9**. For the synthesis of halo-vinylogous enamines **12b–d**, it was found that chlorination, bromination or iodination was best carried out at low temperatures, –50°C to 20°C in dichloromethane, using a 1.2–1.4 molar excess of sulfuryl chloride, bromine or *N*-iodosuccinimide, followed by the addition of 1.2 molar equivalents of triethylamine at –50°C. Compounds **12b–d** were isolated after normal workup in good yields, and could be used without further purification. The stereochemistry around the diene system was not investigated; however, ^{19}F NMR indicates the presence of only one isomer. Cyclisation of the vinylogous enamines **12b–d** gave the pyridine derivatives **1b–d** in good yields (Scheme 4).

Rather than attempting the reaction of compound **9** with an electrophilic source of fluorine, we anticipated that a Halex type of reaction on pyridine **1b** using potassium fluoride would lead to the formation of **1a**, and were pleased to see this was the case, with **1a** being formed in 58% yield after purification. Care should be taken when isolating **1a**, as excessive drying under low pressure can

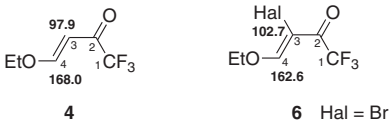
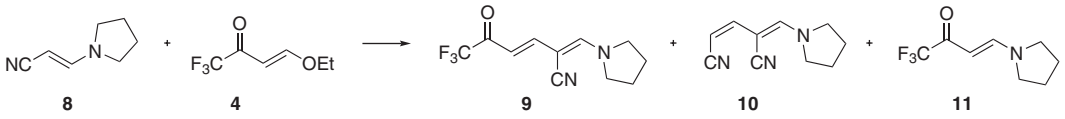
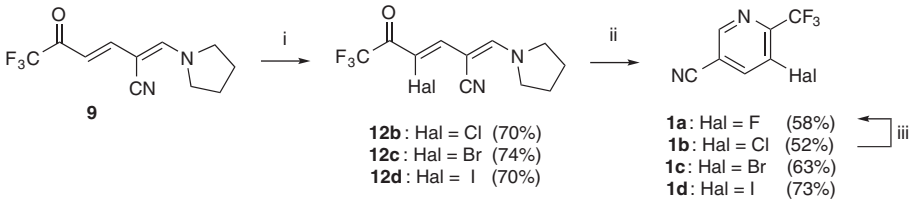


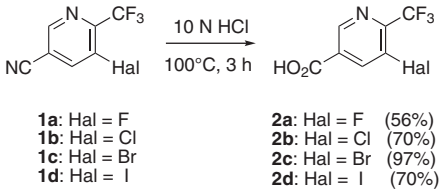
Figure 3 ^{13}C chemical shifts of C(3) and C(4) in **4** and **6**.



Scheme 3 Synthesis of trifluoroacetyl vinylogous enamine **9**.



Scheme 4 Synthesis of 5-halo-6-trifluoromethyl nicotinic nitriles **1a–d**.
Reagents and conditions: (i) **12b**: SO_2Cl_2, DCM, –50°C, 0.5 h, then TEA, –50°C, 1 h; **12c**: Br_2, DCM, –50°C, 0.5 h, then TEA, –50°C, 1 h; **12d**: NIS, DCM, 25°C, 2 h; (ii) NH_4OAc, DMF, rt, 16 h; (iii) KF, sulfolane, 180°C, 4 h.



Scheme 5 Synthesis of 5-halo-6-trifluoromethyl nicotinic acids **2a–d**.

lead to significant losses. Hydrolysis of the nitrile group under acidic or basic conditions then yielded the nicotinic acids **2a–d** in good yields, isolated by column chromatography (Scheme 5).

In summary, the nucleophilic character of the readily prepared trifluoroacetyl vinylogous enamine system **9** was used to introduce halogen. Treatment of the resultant products **12b–d** with ammonium acetate leads to 5-halo-6-trifluoromethyl nicotinic nitriles **1b–d** in good yields. Such pyridine derivatives can be further developed, for example by Halex exchange to give the fluoro derivative **1a**, or by hydrolysis to the corresponding nicotinic acids **2**. All additional information and supporting data for all compounds reported is available in the online Appendix.

Experimental

All reagents were purchased and used as received. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (377 MHz) spectra were obtained using a Bruker Avance II-400 spectrometer in $CDCl_3$ or DMSO-d_6 solution. The HRMS analyses were performed on an Agilent QTOF 6520 mass spectrometer and LCMS analyses were conducted on a Thermo MSQ Plus mass spectrometer. IR spectra were recorded in KBr pellets on a Shimadzu DRS Prestige 21 instrument. Column chromatographic purifications were performed on a CombiFlashRf instrument (Teledyne Isco) using silica gel and mobile phases indicated below. Melting points were determined with a Mel-Temp-Electrothermal digital melting point apparatus and are uncorrected.

6,6,6-Trifluoro-5-oxo-2-(pyrrolidin-1-ylmethylene) hex-3-enenitrile (9)

The starting vinylogous enamine **9** was prepared adapting the literature procedure [14]. A solution of 3-pyrrolidin-1-ylprop-2-enenitrile (20.0 g, 164 mmol) and 4-ethoxy-1,1,1-trifluoro-3-butene-2-one (105 mL, 1.15 mol) in toluene (50 mL) was heated at 100°C for 3 h. The mixture was cooled to room temperature and diluted with cyclohexane (400 mL). The resulting precipitate was collected by filtration, washed with cyclohexane (120 mL) and dried to afford enamine **9** in 85% yield as pale yellow solid; mp 138–140°C; ^{1}H NMR ($CDCl_3$): δ 7.68 (d, 1H, J = 14.5 Hz), 7.42 (s, 1H), 6.36 (d, 1H, J = 14.5 Hz), 3.96 (br t, 2H, J = 7 Hz), 3.69 (br t, 2H, J = 7 Hz), 2.12 (quin, 2H, J = 7 Hz), 1.99 (quin, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 178.8 (q, J = 34 Hz), 155.0, 151.6, 121.3 (q, J = 291 Hz), 107.1, 80.0, 55.4, 48.6, 25.7, 24.2; ^{19}F NMR ($CDCl_3$): δ –77.4 (s, 3F); IR: 3083, 2996, 2209, 1638, 1532, 1226, 1079, 825 cm^{-1}. HRMS (ESI). Calcd for $C_{11}H_{11}F_3N_2O$: m/z 244.0823. Found: m/z 244.0820.

4-Chloro-6,6,6-trifluoro-5-oxo-2-(pyrrolidin-1-ylmethylene)hex-3-enenitrile (12b) Sulfuryl chloride (2.3 mL, 29 mmol) in dichloromethane (5 mL) was added dropwise to a solution of 6,6,6-trifluoro-5-oxo-2-(pyrrolidin-1-ylmethylene)hex-3-enenitrile (**9**) (6.1 g, 25 mmol) in dichloromethane (55 mL) at –50°C. The reaction mixture was stirred for 30 min till the complete consumption of starting material (^{1}H NMR monitoring doublets of the alkene protons). Triethylamine (4.1 mL, 29 mmol) was added dropwise over a period of 5 min at –50°C. After 60 min, the mixture was diluted with dichloromethane (5 mL) and washed with aqueous 10% $NaHCO_3$ (5 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated. Crude product was subjected to CombiFlash chromatography on silica gel with dichloromethane as mobile phase to afford enamine **12b** in 70% yield as a pale yellow solid; mp 138–140°C; ^{1}H NMR (DMSO-d_6): δ 8.34 (s, 1H), 7.58 (s, 1H), 3.92 (t, 2H, J = 7 Hz), 3.75 (t, 2H, J = 7 Hz), 2.01 (quin, 2H, J = 7 Hz), 1.85 (quin, 2H, J = 7 Hz); ^{13}C NMR (DMSO-d_6): δ 171.6 (q, J = 33 Hz), 160.6, 146.9, 121.6 (q, J = 291 Hz), 117.4, 110.8, 76.9, 56.1, 48.7, 25.2, 23.4; ^{19}F NMR (DMSO-d_6): δ –67.2 (s, 3F); IR: 2996, 2948, 2928,

2206, 1675, 1623, 1539, 1444, 1261, 1124, 861 cm^{-1}. HRMS (ESI). Calcd for $C_{11}H_{10}ClF_3N_2O$: *m/z* 278.0434. Found: *m/z* 278.0434.

4-Bromo-6,6,6-trifluoro-5-oxo-2-(pyrrolidin-1-ylmethylene)hex-3-enenitrile (12c) Bromine (0.6 mL, 12.0 mmol) in dichloromethane (3.0 mL) was added dropwise to a solution of 6,6,6-trifluoro-5-oxo-2-(pyrrolidin-1-ylmethylene)hex-3-enenitrile (**9**, 2.5 g, 10 mmol) in dichloromethane (12 mL) at −50°C. The mixture was stirred for 30 min till the complete consumption of starting material (^{1}H NMR monitoring doublets of the alkene protons). Triethylamine (1.7 mL, 12 mmol) was added dropwise over a period of 5 min at −50°C. After 60 min, the mixture was diluted with dichloromethane (20 mL) and washed with aqueous 10% $NaHCO_3$ (5 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated. Crude product was subjected to CombiFlash chromatography on silica gel with dichloromethane–MeOH, 9.8:0.2 as mobile phase to afford enamine **12c** in 74% yield as a pale yellow solid; mp 93°C; ^{1}H NMR (DMSO-d_6): δ 8.36 (s, 1H), 7.71 (s, 1H), 3.92 (br t, 2H, *J* = 7 Hz), 3.75 (t, 2H, *J* = 7 Hz), 2.01 (quin, 2H, *J* = 7 Hz), 1.85 (quin, 2H, *J* = 7 Hz); ^{13}C NMR (DMSO-d_6): δ 172.0 (q, *J* = 33 Hz), 161.3, 149.6, 121.1 (q, *J* = 292 Hz), 117.4, 101.7, 78.6, 56.4, 49.1, 25.4, 23.6; ^{19}F NMR (DMSO-d_6): δ −66.5 (s, 3F); IR: 2998, 2880, 2204, 1683, 1623, 1559, 1117, 862 cm^{-1}. HRMS (ESI). Calcd for $C_{11}H_{10}BrF_3N_2O$: *m/z* 321.9929. Found: *m/z* 321.9939.

6,6,6-Trifluoro-4-iodo-5-oxo-2-(pyrrolidin-1-ylmethylene)hex-3-enenitrile (12d) *N*-Iodosuccinimide (2.7 g, 12 mmol) was added to a solution of 6,6,6-trifluoro-5-oxo-2-(pyrrolidin-1-ylmethylene)hex-3-enenitrile (**9**, 2.5 g, 10 mmol) in dichloromethane (20 mL) at room temperature. The mixture was stirred for 2 h, diluted with dichloromethane (20 mL) and washed with aqueous 10% $Na_2S_2O_3$ (10 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated. Crude product was subjected to CombiFlash chromatography on silica gel eluting with cyclohexane-EtOAc, 6:4, as mobile phase to afford enamine **12d** in 70% yield as a yellow solid; mp 124–126°C; ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1H), 7.47–7.33 (m, 1H), 4.02 (br t, 2H, *J* = 7 Hz), 3.75 (t, 2H, *J* = 7 Hz), 2.12 (quin, 2H, *J* = 7 Hz), 1.99 (quin, 2H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 174.9 (q, *J* = 33 Hz), 158.3, 152.1, 116.8, 115.9 (q, *J* = 293 Hz), 82.5, 81.4, 56.4, 49.4, 25.8, 24.01; ^{19}F NMR ($CDCl_3$): δ −66.6 (s, 3F); IR: 3000, 2925, 2202, 1621, 1545, 1226.78, 1108, 862 cm^{-1}. HRMS (ESI). Calcd for $C_{11}H_{10}F_3IN_2O$: *m/z* 369.9790. Found: *m/z* 369.9788.

5-Fluoro-6-(trifluoromethyl)pyridine-3-carbonitrile (1a) To a solution of 5-chloro-6-(trifluoromethyl) pyridine-3-carbonitrile **(1b)** (1.8 g, 9 mmol) in sulfolane (11 mL) was added anhydrous potassium fluoride (1.3 g, 22 mmol) at room temperature. The mixture was heated to 180°C for 4 h, then cooled to room temperature and directly purified by column chromatography eluting with cyclohexane-EtOAc, 9:1, to afford product **1a** in 58% yield as a yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.79 (s, 1H), 7.94 (dd, 1H, *J* = 9 Hz and 1 Hz); ^{13}C NMR ($CDCl_3$): δ 157.4 (d, *J* = 274 Hz), 147.3 (d, *J* = 6 Hz), 139.6 (dq, *J* = 12 Hz and 37 Hz), 129.1 (d, *J* = 22 Hz), 121.1 (dq, *J* = 5 Hz and 274 Hz), 114.5 (d, *J* = 4 Hz), 113.8; ^{19}F NMR ($CDCl_3$): δ −66.2 (s, 3F), −118.7 (s, 1F); IR: 3080, 3026, 2243, 1609, 1572, 1325, 1210, 1150, 1060, 906 cm^{-1}; GCMS (EI): *m/z* 189.9, [M^+].

General procedure for preparation of 5-halo-6-trifluoromethyl nicotinic nitriles 1b–d

Enamine **12b–d** (2.0 g, 5 mmol) was dissolved in *N*,*N*-dimethylformamide (14 mL), and the solution was treated with ammonium acetate (2.5 g, 23 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. After complete conversion of the starting material the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water (2×5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by CombiFlash chromatography on silica gel eluting with cyclohexane-EtOAc, 9:1, to afford the product **1b–d**.

5-Chloro-6-(trifluoromethyl)pyridine-3-carbonitrile (1b) White solid; yield 52%; mp 43–44°C; ^{1}H NMR ($CDCl_3$): δ 8.87–8.82 (m, 1H), 8.20–8.17 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 148.9, 148.3 (q, *J* = 35 Hz), 142.5, 131.1, 121.5 (q, *J* = 276 Hz), 114.0, 113.7; ^{19}F NMR ($CDCl_3$): δ −66.7 (s, 3F); IR: 3072, 2243, 1872, 1730, 1581, 1537, 1460, 1323, 1388, 1396, 1163, 1043, 925 cm^{-1}. HRMS (ESI). Calcd for $C_7H_2ClF_3N_2$: *m/z* 206.9937. Found: *m/z* 206.9934.

5-Bromo-6-(trifluoromethyl)pyridine-3-carbonitrile (1c) White solid; yield 63%; mp 88–90°C; ^{1}H NMR ($CDCl_3$): δ 8.88 (s, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 148.3, 147.9 (q, *J* = 36 Hz), 144.9, 120.6 (q, *J* = 276 Hz), 117.3, 118.8, 112.9, 112.7; ^{19}F NMR ($CDCl_3$): δ −66.7 (s, 3F); IR: 3070, 2949, 2243, 1892, 1585, 1529, 1454, 1375, 1321, 1209, 1037, 939 cm^{-1}. HRMS (ESI). Calcd for $C_7H_2BrF_3N_2$: *m/z* 250.9425. Found: *m/z* 250.9426.

5-Iodo-6-(trifluoromethyl)pyridine-3-carbonitrile (1d) White solid; yield 73%; mp 126–128°C; ^{1}H NMR ($CDCl_3$): δ 8.90 (d, 1H, *J* = 1.6 Hz), 8.62 (d, 1H, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$): δ 152.5, 151.8 (q, *J* = 35 Hz), 149.7, 124.5 (q, *J* = 277 Hz), 113.7, 113.2, 88.1; ^{19}F NMR ($CDCl_3$): δ −66.5 (s, 3F); IR: 3060, 3011, 2942, 2245, 1891, 1577, 1324, 1207, 1396, 1164, 1033, 938 cm^{-1}. HRMS (ESI). Calcd for $C_7H_2F_3IN_2$: *m/z* 297.9215. Found: *m/z* 297.9220.

General procedure for prepration of 5-halo-6-trifluoromethyl nicotinic acids 2a–d

A suspension of pyridine **1a–d** (0.4 g, 2 mmol) in 10 N HCl (1.2 mL) was heated at 100°C for 3 h. The reaction mixture was cooled to room temperature and pH of mixture was increased to 4–5 using aqueous 10% sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate (3×8 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by CombiFlash chromatography on silica gel eluting with cyclohexane-EtOAc, 7:3, to afford the desired product **2a–d**.

5-Fluoro-6-(trifluoromethyl)pyridine-3-carboxylic acid (2a) White solid; yield 56%; mp 102–104°C; ^{1}H NMR (DMSO-d_6): δ 9.00 (s, 1H), 8.41 (d, 1H, *J* = 11 Hz); ^{13}C NMR (DMSO-d_6): δ 164.2, 157.8 (d, *J* = 267 Hz), 145.8 (d, *J* = 5 Hz), 136.8 (dd, *J* = 12 Hz and 35 Hz), 132.8 (d, *J* = 4 Hz), 127.3 (d, *J* = 20 Hz), 121.9 (dq, *J* = 5 Hz and 274 Hz); ^{19}F NMR (DMSO-d_6): δ −64.7 (s, 3F), −123.0 (q, *J* = 15 Hz, 1F); IR: 3514, 3254, 2505, 1913, 1712, 1485, 1425, 1329, 1315, 1227, 1159, 1060, 923 cm^{-1}. HRMS (ESI). Calcd for $C_7H_3F_4NO_2$: *m/z* 209.0100. Found: *m/z* 209.0100.

5-Chloro-6-(trifluoromethyl)pyridine-3-carboxylic acid (2b) White solid; yield 70%; mp 108–110°C; ^{1}H NMR ($CDCl_3$): δ 11.00 (br s, 1H), 9.25 (s, 1H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 167.9, 148.6 (q, *J* = 35 Hz), 147.9, 141.2, 130.9, 128.8, 121.8 (q, *J* = 276 Hz); ^{19}F NMR ($CDCl_3$): δ −66.5 (s, 3F); IR (KBr): 3215, 2522, 1866, 1737, 1693, 1467, 1392, 1317,

1165, 1120, 1047, 889 cm^{-1}. HRMS (ESI). Calcd for $C_7H_3ClF_3NO_2$: *m*/*z* 224.9804. Found: *m*/*z* 224.9807.

5-Bromo-6-(trifluoromethyl)pyridine-3-carboxylic acid (2c) White solid; yield 97%; mp 196–198°C; ^1H NMR ($CDCl_3$): δ 11.78 (br s, 1H), 9.29 (s, 1H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 167.9, 150.0 (q, *J* = 34.0 Hz), 148.4, 144.7, 128.6, 122.0 (q, *J* = 276 Hz), 118.3; ^{19}F NMR ($CDCl_3$): δ −66.4 (s, 3F). IR: 3215, 3080, 2873, 2522, 1737, 1686, 1693, 1392, 1317, 1170, 1045, 702 cm^{-1}. HRMS (ESI). Calcd for $C_7H_3BrF_3NO_2$: *m*/*z* 268.9299. Found: *m*/*z* 268.9301.

5-Iodo-6-(trifluoromethyl)pyridine-3-carboxylic acid (2d) White solid; yield 70%; mp 148–150°C; ^1H NMR ($CDCl_3$): δ 10.35 (br s, 1H), 9.33–9.28 (m, 1H), 9.01 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 167.8, 153.1 (q, *J* = 34 Hz), 151.8, 149.1, 128.5, 122.4 (q, *J* = 277 Hz), 88.4; ^{19}F NMR ($CDCl_3$): δ −66.2 (s, 3F); IR: 3200, 3067, 2511, 2359, 2342, 1740, 1686, 1396, 1317, 1165, 1031, 756 cm^{-1}. HRMS (ESI). Calcd for $C_7H_3F_3INO_2$: *m*/*z* 316.9273. Found: *m*/*z* 316.9237.

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