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A FACILE SYNTHESIS OF 2-DIFLUOROMETHYL-6-METHYLPYRIDINE-3,5-DICARBOXYLATES

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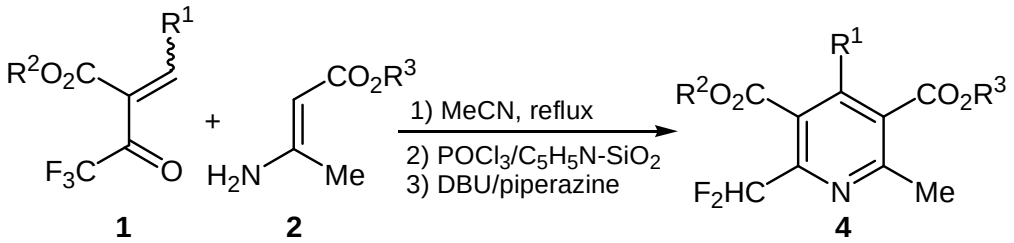
Abstract – α,β-Unsaturated trifluoromethyl ketones **1** react with primary enamines **2** in the presence of phosphorus oxychloride/pyridine adsorbed on silica gel, providing 1,4-dihydro-2-methyl-6-trifluoromethylpyridines **3**, which undergo dehydrofluorination by use of DBU/piperazine, giving moderate to high yields of 2-difluoromethyl-6-methylpyridine-3,5-dicarboxylates **4**.

INTRODUCTION

Some of fluorine-containing heterocycles have proved to be more bioactive than their non-fluorine analogs.[1] Thus, they are becoming increasingly important for the development of excellent biologically active compounds.[2] As an example as fluorine-containing heterocycles, we previously synthesized various trifluoromethyl-substituted pyridines.[3] It is presumed that the variation of kinds of the fluorine-containing substituent in an organic molecule would induce a marked difference in its biological activity. We therefore decided to prepare difluoromethyl-substituted pyridines for the purpose of comparing their biological activites with those of the trifluoromethyl-substituted derivatives.



1 **2** **4**

Scheme 1

This paper closely describes a facile synthesis of 2-difluoromethyl-6-methylpyridine-3,5-dicarboxylates **4** starting from α,β-unsaturated trifluoromethyl ketones **1** (Scheme 1).[4]

RESULTS AND DISCUSSION

Numerous papers have been published for the synthesis of trifluoromethyl-substituted heterocycles.[5] In contrast, only a few papers have been reported for the synthesis of difluoromethyl-substituted heterocycles[6] because they are often more difficult to prepare than trifluoromethyl-substituted derivatives. In practice, no efficient methods have been reported for the synthesis of 2-alkyl-6-difluoromethylpyridines such as **4**.[7]

A possible approach to difluoromethyl-substituted compounds includes direct conversion of aldehydes into difluorides using fluorinating reagents such as DAST,[8] Deoxofluor,[TM 9] DFI,[10] and DFMBA.[11] In fact, the difluomethylation of simple aromatic aldehydes has been achieved using DFMBA/Et_3N-3HF.[12] However, it is presumed that such reagents are hard to react with electron-rich and/or sterically-hindered derivatives in view of nucleophilic fluorinating mechanism.[11] Also CHF_2-compounds are probably difficult to prepare by partial reduction of the corresponding CF_3-derivatives. In particular, CF_3 groups attached to (hetero) aromatic rings are significantly stable. Thus, the reduction of these CF_3 groups usually requires strong reagents. Such conditions, however, luck the chemical selectivity; they must be difficult to achieve both selective reduction of a CF_3 group to a CHF_2 group and that of a CF_3 group in the presence of sensitive functional groups.[13]

An alternative route to the CHF_2-pyridines **4** involves the dehydrofluorination of 2-methyl-6-trifluoromethyl-1,4-dihydropyridines **3**, which are readily prepared by the reaction of **1** with enamines **2** according to the method described in our previous papers.[14] Several methods are known for the dehydrofluorination of trifluoromethyl-substituted compounds.[15]

Table 1 indicates the results of the dehydrofluorination of a dihydropyridine **3a** under various conditions. No reaction occurred in the presence of triethylamine (Et_3N), and the starting material was recovered (Entry 1). The dehydrofluorination hardly proceeded even using sodium hydride (NaH), lithium 2,2,6,6-tetramethylpiperidide (LTMP), or potassium *t*-butoxide (*t*-BuOK) (Entries 2-4). The reaction using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) finally afforded the desired difluoromethyl-substituted pyridine **4a** in a 39 % yield together with substantial amounts of trifluoromethyl-substituted pyridine **5a** (Entry 5). Refluxing in acetonitrile instead of in ethanol induced an improvement in the reactivity and the ratio [**4a**]/[**5a**] (Entry 6). The treatment of **3a** with 2.0 equiv of DBU led to a significant increase in the ratio [**4a**]/[**5a**] (Entry 7). The yields of **4a** using both DBU and the other bases were similar to that using 2.0 equiv of DBU. In particular, simultaneous use of DBU and piperazine (Pip) provided the highest yield of **4a** (Entries 8 and 9).

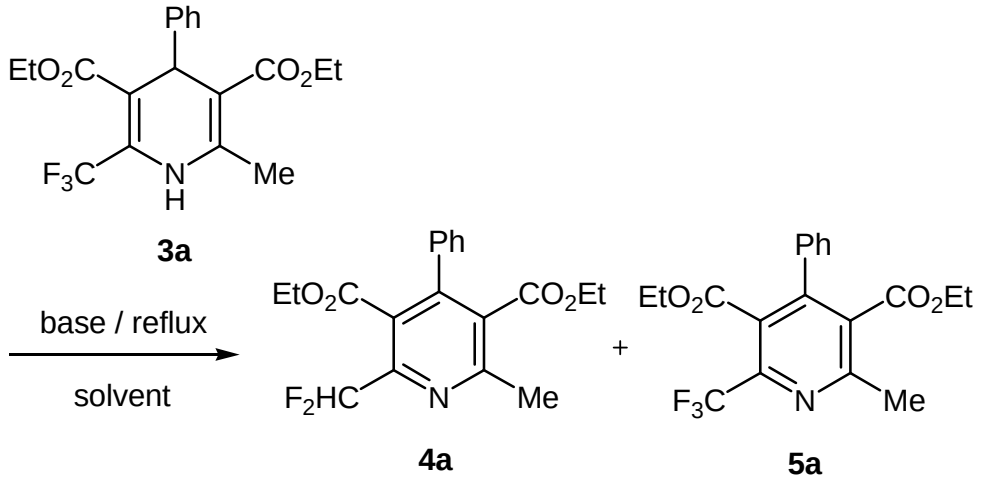


Table 1 Screening of the Reaction Conditions for the Synthesis of **4a** *via* Dehydrofluorination of **3a** under Various Conditions

Entry	Base(equiv.)	Solvent	Time	**3a:4a:5a**[a)]	Yield[b)]/% of **4a**
1	Et_3N(3.0)	MeCN	20 h	no reaction	0
2[c)]	NaH(2.4)	THF	10 h	>98:<1:<1	trace
3[d)]	LTMP(1.2)	THF	18 h	>98:<1:<1	trace
4	*t*-BuOK(2.4)	*t*-BuOH	10 h	>98:<1:<1	trace
5	DBU(1.0)	EtOH	18 h	64:23:13	39
6	DBU(1.0)	MeCN	10 h	1:72:27	62
7	DBU(2.0)	MeCN	10 h	1:96:3	80
8	DBU(1.0)/Et_3N(2.0)	MeCN	8 h	5:87:8	78
9	DBU(1.0)/Pip(1.0)	MeCN	10 h	3:93:4	85

a) Determined by ^{19}F NMR. b) Isolated yields. c) Reacted from 0°C to room temperature. d) Reacted from -78°C to room temperature.

Table 2 shows the results of the synthesis of 2-difluoromethyl-6-methylpyridine-3,5-dicarboxylates **4** *via* the dehydrofluorination of the corresponding dihydropyridines **3** starting from **1**. The present method gave moderate to high yields of **4**. In particular, it is worthy to notice that the treatment of the methyl esters **3b**, **d**, **f** with DBU/piperazine gave moderate to good yields of the corresponding **4b**, **d**, **f**. In contrast, it was reported that the reaction of methyl esters with DBU alone afforded poor yields of the desired products together with substantial amounts of by-products, which mainly contain derivatives arising from the demethylation of the methyl ester groups.[7]

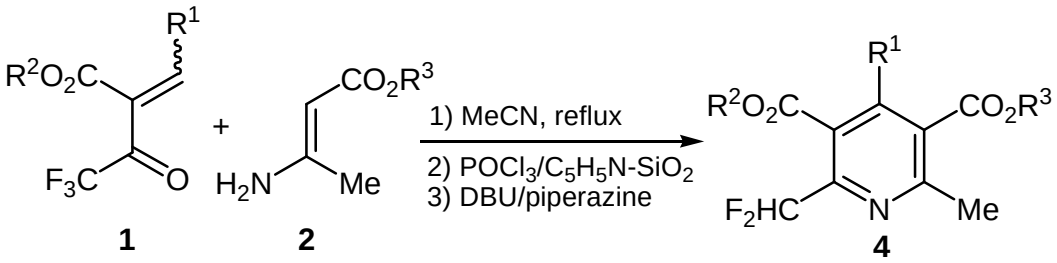
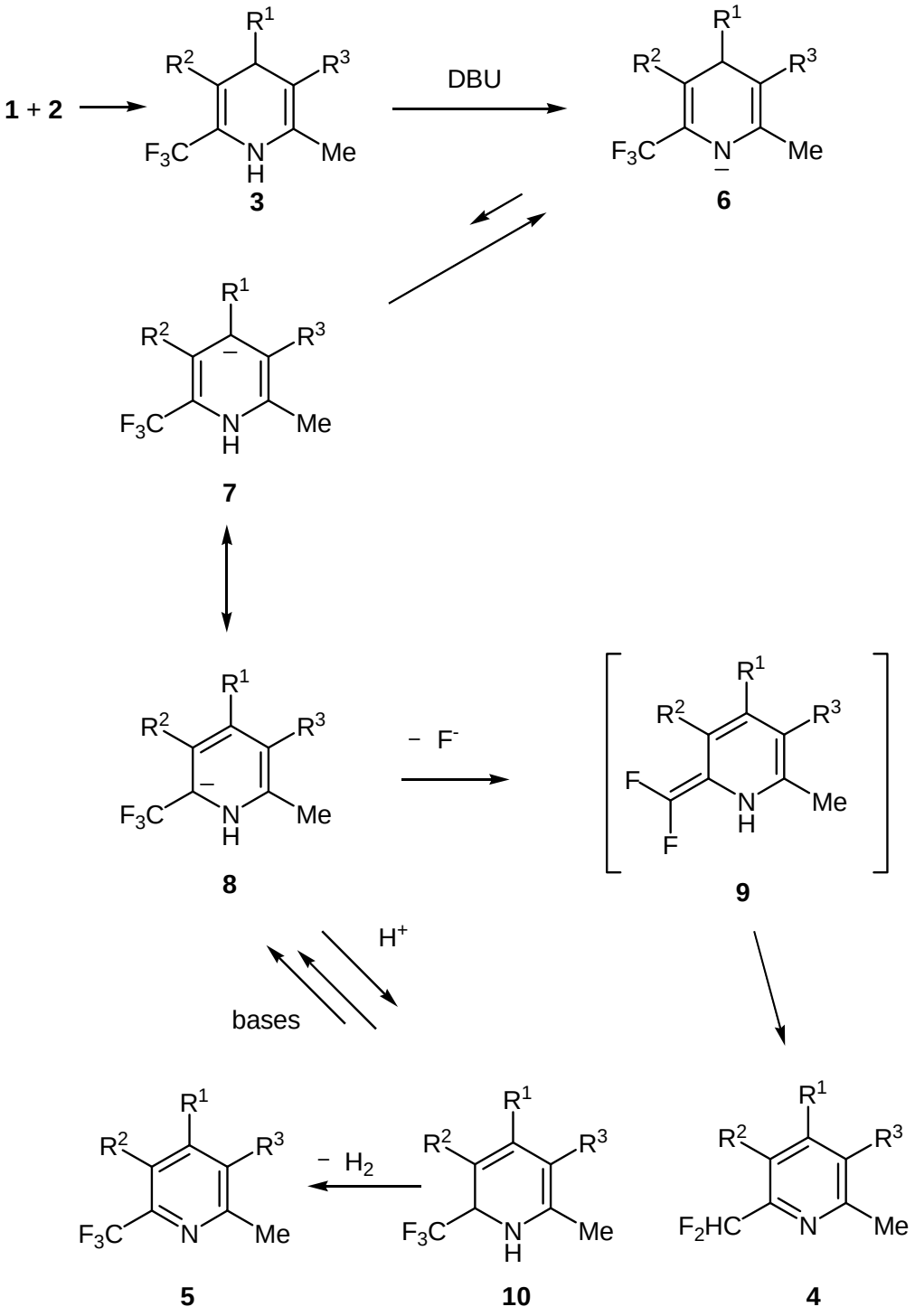


Table 2 Synthesis of 2-Difluromethyl-6-methylpyridine-3,5-dicarboxylates **4**

R^1	R^2	R^3	Precursor	Product	Yield[a] /%
Ph	Et	Et	**3a**	**4a**	83
Ph	Et	Me	**3b**	**4b**	72
4-MeC_6H_4	Et	Et	**3c**	**4c**	85
4-MeC_6H_4	Me	Et	**3d**	**4d**	62
4-$MeOC_6H_4$	Et	Et	**3e**	**4e**	85
4-$MeOC_6H_4$	Et	Me	**3f**	**4f**	75
4-ClC_6H_4	Et	Et	**3g**	**4g**	89
2-Furyl	Et	Et	**3h**	**4h**	76
2-Thienyl	Et	Et	**3i**	**4i**	89

a) Isolated yields referred to **1**.

Scheme 2 illustrates a plausible mechanism for the formation of the desired difluoromethylpyridines **4** and the undesired trifluoromethylpyridines **5**. The first step involves the formation of the N-1 anions **6** from **3**; this event can be shown by the instant color change from yellow to orange according to the literature.[7] The anions **6** may be in equilibrium with the C-4 anions **7** upon heating although the equilibrium is expected to favor **6**. On the other hand, the anions **7** should have favorable resonance structures, the C-6 anions **8** stabilized by the CF_3 group. The anions **8** can eliminate fluoride, giving the unstable 2-(difluoromethylene)-1,2-dihydropyridine intermediates **9**, which rearrange to the desired **4**. On the other hand, the protonation of **8** can afford the 1,6-dihydropyridines **10**, which undergo dehydrogenation to give the undesired **5** or deprotonation by bases to give **8** again. This mechanism can explain the facts that EtOH increases the ratio [**5a**]/[**4a**] (Scheme 1, Entries 5-6) and that excess bases increase the ratio [**4a**]/[**5a**] (Scheme 1, Entries 6-9); protic solvents can accelerate the formation of **10** by the protonation of **8** and excess bases can accelerate the formation of **9** by the trapping of HF *via* the deprotonation from **10** and the elimination of fluoride from **8**.



Scheme 2

In conclusion, a facile method was found for the synthesis of 2-difluoromethyl-6-methylpyridine-3,5-dicarboxylates by use of DBU/piperazine under mild conditions. It is also applicable to the treatment of compounds having methyl ester groups that are susceptible to demethylation. This method is, therefore, expected to be a useful approach to poly-substituted CHF_2-pyridines bearing sensitive functional groups.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP-S2 micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Perkin Elmer FT-IR 1640 spectrometer. ^{1}H NMR spectra were recorded with a JEOL α-400 spectrometer using tetramethylsilane (TMS) as an internal standard. ^{19}F NMR spectra were obtained on the same apparatus using trifluoroacetic acid (TFA) as an external standard. Mass (MS) spectra (EI, 70 eV) were obtained on a Shimadzu QP-1000 spectrometer. All the commercially available reagents were used without further purification. Starting materials **1** were prepared according to the method described in our previous papers.[16]

General procedure for the synthesis of 2-difluoromethyl-6-methylpyridine-3,5-dicarboxylates 4: A solution of *α,β*-unsaturated trifluoromethyl ketones **1** (1 mmol) and primary enamines **2** (1 mmol) in MeCN (4 mL) was refluxed for 1-2 h. To the mixture was added phosphorus oxychloride/pyridine adsorbed on silica gel (0.9 g) and further refluxed while being stirred for 3-4 h. After the reaction mixture was filtered through a pad of silica gel with the aid of *n*-hexane/AcOEt (3/1), the filtrate was concentrated. To an MeCN (4 mL) solution of the residue were added DBU (1.0 equiv) and piperazine (1.0 equiv), and the mixture was refluxed while being stirred for 10-13 h. After removal of the solvent, the residue was chromatographed on silica gel using CH_2ClCH_2Cl/AcOEt (20/1) as an eluent. Spectral data of **4** are shown bellow.

Diethyl 2-(difluoromethyl)-6-methyl-4-phenylpyridine-3,5-dicarboxylate (4a): mp 41-42 °C (EtOH-H_2O); IR (Nujol) ν 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.1 Hz, 6H), 2.67 (s, 3H), 4.04 (q, *J* = 7.1 Hz, 4H), 6.79 (t, *J* = 54.7 Hz, 1H), 7.26-7.40 (m, 5H); ^{19}F NMR ($CDCl_3$) δ -37.84 (d, *J* = 54.7 Hz, 2F); MS m/z (rel intensity) 363 (M^+, 100), 318 (74), 272 (93), 195 (52), 168 (41), 140 (59), 84 (80). Anal. Calcd for $C_{19}H_{19}F_2NO_4$: C, 62.80, H, 5.27, N, 3.85. Found: C, 62.57, H, 5.19, N, 3.78.

3-Ethyl 5-methyl 2-(difluoromethyl)-6-methyl-4-phenylpyridine-3,5-dicarboxylate (4b): mp 70-71 °C (EtOH-H_2O); IR (Nujol) ν 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3H), 2.66 (s, 3H), 3.56 (s, 3H), 4.04 (q, *J* = 7.2 Hz, 2H), 6.79 (t, *J* = 54.6 Hz, 1H), 7.24-7.41 (m, 5H); ^{19}F NMR ($CDCl_3$) δ -37.90 (d, *J* = 54.6 Hz, 2F); MS m/z (rel intensity) 349 (M^+, 63), 304 (43), 272 (100). Anal. Calcd for $C_{19}H_{17}F_2NO_4$: C, 61.89, H, 4.91, N, 4.01. Found: C, 61.73, H, 4.77, N, 3.94.

Diethyl 2-(difluoromethyl)-6-methyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (4c): mp 57-58 °C (EtOH-H_2O); IR (Nujol) ν 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 6.8 Hz, 3H), 2.37 (s, 3H), 2.65 (s, 3H), 4.07 (q, *J* = 6.8 Hz, 4H), 6.77 (t, *J* = 54.7 Hz, 1H), 7.15 and 7.19 (ABq, *J* = 8.0 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ -37.79 (d, *J* = 54.7 Hz, 2F); MS m/z (rel intensity) 377 (M^+, 100), 332 (32), 304 (29), 286 (62), 236 (27). Anal. Calcd for $C_{20}H_{21}F_2NO_4$: C, 63.65, H, 5.61, N, 3.71. Found: C, 63.63, H, 5.51, N, 3.63.

5-Ethyl 3-methyl 2-(difluoromethyl)-6-methyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (4d): mp 88-89 °C (EtOH-H_2O); IR (Nujol) ν 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, *J* = 7.2 Hz, 3H), 2.37 (s, 3H), 2.65 (s, 3H), 3.59 (s, 3H), 4.07 (q, *J* = 7.2 Hz, 4H), 6.75 (t, *J* = 54.6 Hz, 1H), 7.14 and 7.19 (ABq, *J* = 8.1 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ -38.01 (d, *J* = 54.6 Hz, 2F); MS m/z (rel intensity) 363 (M^+, 100), 298 (40), 286 (39). Anal. Calcd for $C_{19}H_{19}F_2NO_4$: C, 62.80, H, 5.27, N, 3.85. Found: C, 62.72, H, 5.16, N, 3.78.

Diethyl 2-(difluoromethyl)-4-(4-methoxylphenyl)-6-methylpyridine-3,5-dicarboxylate (4e): mp 56-57 °C (EtOH-H_2O); IR (Nujol) ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 2.65 (s, 3H), 3.83 (s, 3H), 4.09 (q, *J* = 7.1 Hz, 4H), 6.77 (t, *J* = 54.7 Hz, 1H), 6.92 and 7.20 (ABq, *J* = 8.9 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ -37.77 (d, *J* = 54.7 Hz, 2F); MS m/z (rel intensity) 393 (M^+, 100), 300 (24). Anal. Calcd for $C_{20}H_{21}F_2NO_5$: C, 61.06, H, 5.38; N, 3.56. Found: C, 60.80, H, 5.29, N, 3.43.

3-Ethyl 5-methyl 2-(difluoromethyl)-4-(4-methoxyphenyl)-6-methylpyridine-3,5-dicarboxylate (4f): mp 86-87 °C (EtOH-H_2O); IR (Nujol) ν 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.1 Hz, 3H), 2.64 (s, 3H), 3.61 (s, 3H), 3.83 (s, 3H), 4.09 (q, *J* = 7.1 Hz, 2H), 6.76 (t, *J* = 54.7 Hz, 1H), 6.92 and 7.19 (ABq, *J* = 8.5 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ -37.76 (d, *J* = 54.7 Hz, 2F); MS m/z (rel intensity) 379 (M^+, 68), 302 (39), 155 (41), 135 (34), 91 (100). Anal. Calcd for $C_{19}H_{19}F_2NO_5$: C, 60.16, H, 5.05, N, 3.69. Found: C, 60.13, H, 4.94, N, 3.62.

Diethyl 4-(4-chlorophenyl)-2-(difluoromethyl)-6-methylpyridine-3,5-dicarboxylate (4g): mp 40-41 °C (EtOH-H_2O); IR (Nujol) ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H), 2.66 (s, 3H), 4.08 (q, *J* = 7.1 Hz, 4H), 6.77 (t, *J* = 54.7 Hz, 1H), 7.22 and 7.38 (ABq, *J* = 8.4 Hz, 4H); ^{19}F NMR ($CDCl_3$) δ = -37.84 (d, *J* = 54.7 Hz, 2F); MS m/z (rel intensity) 397 (M^+, 100), 352 (68), 324 (39), 306 (65), 256 (26), 139 (27). Anal. Calcd for $C_{19}H_{18}ClF_2NO_4$: C, 57.37, H, 4.56, N, 3.52. Found: C, 57.45, H, 4.41, N, 3.43.

Diethyl 2-(difluoromethyl)-4-(2-furyl)-6-methylpyridine-3,5-dicarboxylate (4h): mp 44-45 °C (EtOH-H_2O); IR (Nujol) ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 6H), 2.64 (s, 3H), 4.32 (q, *J* = 7.1 Hz, 4H), 6.52 (dd, *J* = 3.2, 1.5 Hz, 1H), 6.71 (d, *J* = 3.2 Hz, 1H), 6.75 (t, *J* = 54.7 Hz, 1H), 7.53 (d, *J* = 1.5Hz, 1H); ^{19}F NMR ($CDCl_3$) δ -37.97 (d, *J* = 54.7 Hz, 2F); MS m/z (rel intensity) 353 (M^+, 100), 325 (31), 308 (63), 279 (77), 251 (63), 232 (48). HREIMS: m/z Calcd for $C_{17}H_{17}F_2NO_5$ 353.1075, Found 353.1070 (M^+, 100%).

Diethyl 2-(difluoromethyl)-6-methyl-4-(2-thienyl)pyridine-3,5-dicarboxylate (4i): IR (neat) ν 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 2.65 (s, 3H), 4.16 (q, *J* = 7.1 Hz, 4H), 6.75 (t, *J* = 54.0 Hz, 1H), 7.06-7.09 (m, 2H), 7.45 (d, *J* = 4.6 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ

-37.80 (d, J = 54.0 Hz, 2F); MS m/z (rel intensity) 369 (M^+, 100), 324 (29), 296 (41), 275 (32), 251 (30), 228 (27). HREIMS: m/z Calcd for $C_{17}H_{17}F_2NO_4S$ 369.0846, Found 369.0837 (M^+, 100%).

ACKNOWLEDGEMENTS

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