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AN EFFCIENT SYNTHESIS OF 1,4-DIHYDRO-6-TRIFLUOROMETHYLPYRIDINES: A FACILE AND USEFUL METHOD FOR DEHYDRATION OF α-TRIFLUOROMETHYL ALCOHOLS BY USE OF PHOSPHOROUS OXYCHLORIDE / PYRIDINE ADSORBED ON SILICA GEL

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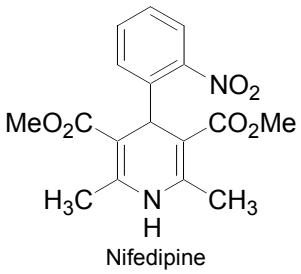
Abstract – The treatment of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones (**1**) with β-aminocrotonates (**2**) affords 2-hydroxy-6-methyl-2-trifluoromethyl-1,2,3,4-tetrahydropyridines (**3**), which undergo facile dehydration by use of phosphorus oxychloride / pyridine adsorbed on silica gel, giving good to high yields of 1,4-dihydro-2-methyl-6-trifluoromethylpyridines (**4**).

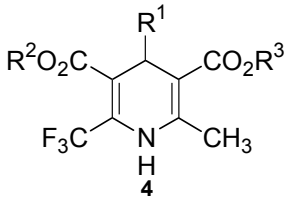
INTRODUCTION

Since the discovery of nifedipine®, which is a clinically important antihypertensive and antiangina drug, much interest has been led to the synthesis of substituted 1,4-dihydropyridines and their ability as therapeutic agents for cardiovascular ailments.[1] This class of compounds is known to indicate its biological effects by the inhibition of calcium ion influx across the cell membrane through slow calcium channels.[2] On the other hand, the introduction of a trifluoromethyl group into a biomolecule has sometimes resulted in an improvement in its biological activity.[3] Therefore, trifluoromethyl-substituted 1,4-dihydropyridines have been worthy of remark for their potential biological properties.
Furthermore, they can be utilized as intermediates for the synthesis of trifluoromethyl-substituted pyridines.[4]



Nifedipine

This paper describes an efficient synthesis of trifluoromethyl-substituted derivatives (**4**) for 1,4-dihydropyridine-3,5-dicarboxylates of the nifedipine® type.



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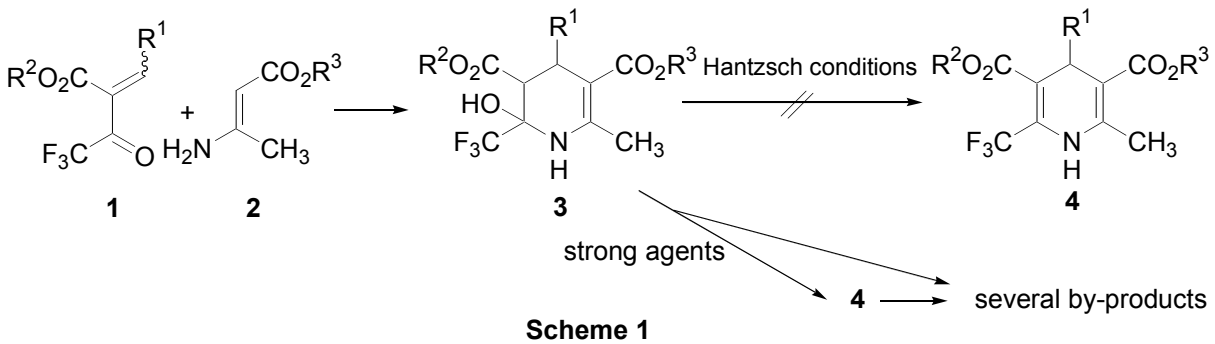
RESULTS AND DISCUSSION

No efficient methods have been reported for the synthesis of unsymmetrical fluorine-containing dihydropyridines such as **4**. The previous methods such as Hantzsch conditions have the following three disadvantages: (i) unsymmetrical dihydropyridines are often more difficult to prepare than their symmetrical counterparts due to the formation of all the possible isomeric Hantzsch condensation products.[5] (ii) the intermediate hydroxytetrahydropyridines (**3**) seem to be very stable,[6] and accordingly difficult to dehydrate under the standard Hantzsch conditions.[7] (iii) the intermediates (**3**) and desired products (**4**) appear to be unstable for strong agents due to the presence of esters. (Scheme 1). In order to improve the disadvantage (i), α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones (**1**) were chosen as a starting material for the synthesis of **4**: the ketones **1** were prepared by the reaction of aldehydes with 4,4,4-trifluoroacetoacetates or by that of the Schiff bases for the aldehydes with the acetoacetates.[8]



1 **2** **3** **4**

Scheme 1

The reaction of the trifluoromethyl ketone (**1a**) with β-aminocrotonate (**2a**) gave a quantitative yield of the intermediate hydroxytetrahydropyridine (**3a**), which did not undergo dehydration in the absence of catalysts in boiling alcohol (standard Hantzsch conditions) (Table 1, Entry 1). Here, it was confirmed that a dehydration reagent is essential[9] for the synthesis of **4**. The dehydration of **3a** using several agents was then attempted for the synthesis of **4a**. The use of usual catalysts[10] resulted in both a moderate consumption of **3a** and formation of **4a** in a low yield (Table 1, Entries 2-4). The reaction using other reagents[11] led to the satisfactory consumption of **3a**. These conditions, however, gave only a low to moderate yield of **4a** (Table 1, Entries 5-6). In addition, most of the above methods require hazardous reagents and aqueous workup procedure that are detrimental to the environment. Therefore, another procedure was investigated for this reaction.

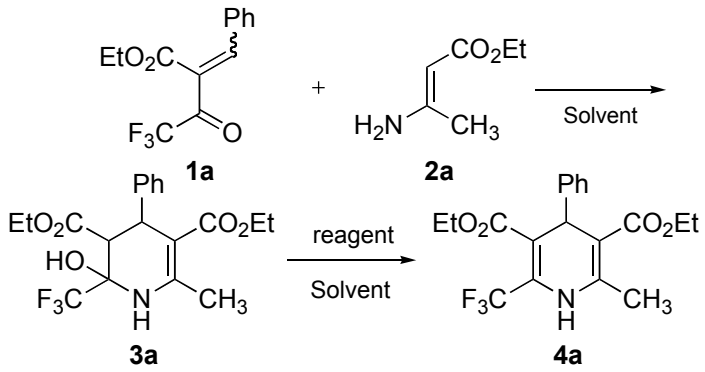


Table 1 Synthesis of CF_3-Dihydropyridine under Various Conditions

Entry	Reagent	Solvent	Temperature	Time[a] /h	Yield[b]/ %	
					3a	**4a**
1	——	EtOH	reflux	6	98	trace
2	conc.HCl	MeOH	reflux	2	50	14
3	H_3PO_4	EtOH	reflux	3	50	8
4	conc.H_2SO_4	CH_2Cl_2	5-10°C	1	54	14
5	*p*-TsOH	EtOH	reflux	3	trace	31
6	$(CF_3CO)_2O$	$(CH_2Cl)_2$	rt	3	trace	57
7	$POCl_3/C_5H_5N$	$(CH_2Cl)_2$	reflux	3	trace	39
8	$POCl_3/C_5H_5N$-SiO_2	$(CH_2Cl)_2$	reflux	3	trace	91

[a] Dehydration time. [b] Isolated yields referred to **1a**.

Phosphorus oxychloride or thionyl chloride/ pyridine is known to be a good dehydration system and therefore is often used for the dehydration of alcohols.[12] However, this system usually require large excess amount of phosphorus oxychloride or thionyl chloride and pyridine; this is inconvenient to manipulate and may cause severe bodily harm because of quite strong corrosion. Thus, the dehydration

of **3a** using small excess amount of the reagents was attempted for the synthesis of **4a**. However, at rt no reaction proceeded while at higher temperature **4a** was obtained only in a low yield (Table 1, Entry 7). During the further studies, phosphorus oxychloride / pyridine adsorbed on silica gel ($POCl_3/C_5H_5N$-SiO_2) has been found to be an efficient reagent for the synthesis of **4a** *via* the dehydration of **3a** (Table 1, Entry 8). The high yield was due to both a satisfactory consumption of **3a** and a decrease in the amount of by-products. Moreover, it was found that this reagent does not have severe stimulating smell in contrast to $POCl_3/C_5H_5N$; this is convenient to manipulate.

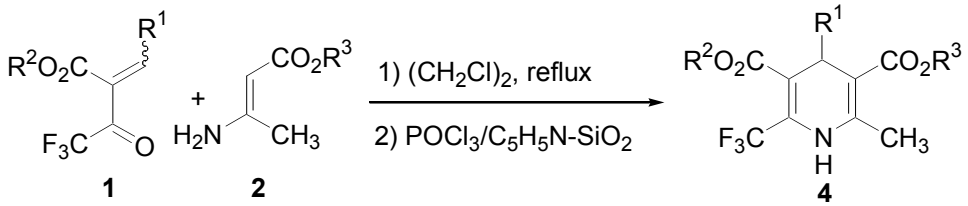


Table 2 One-pot Synthesis of 1,4-Dihydro-2-methyl-6-trifluoromethylpyridines (**4**)

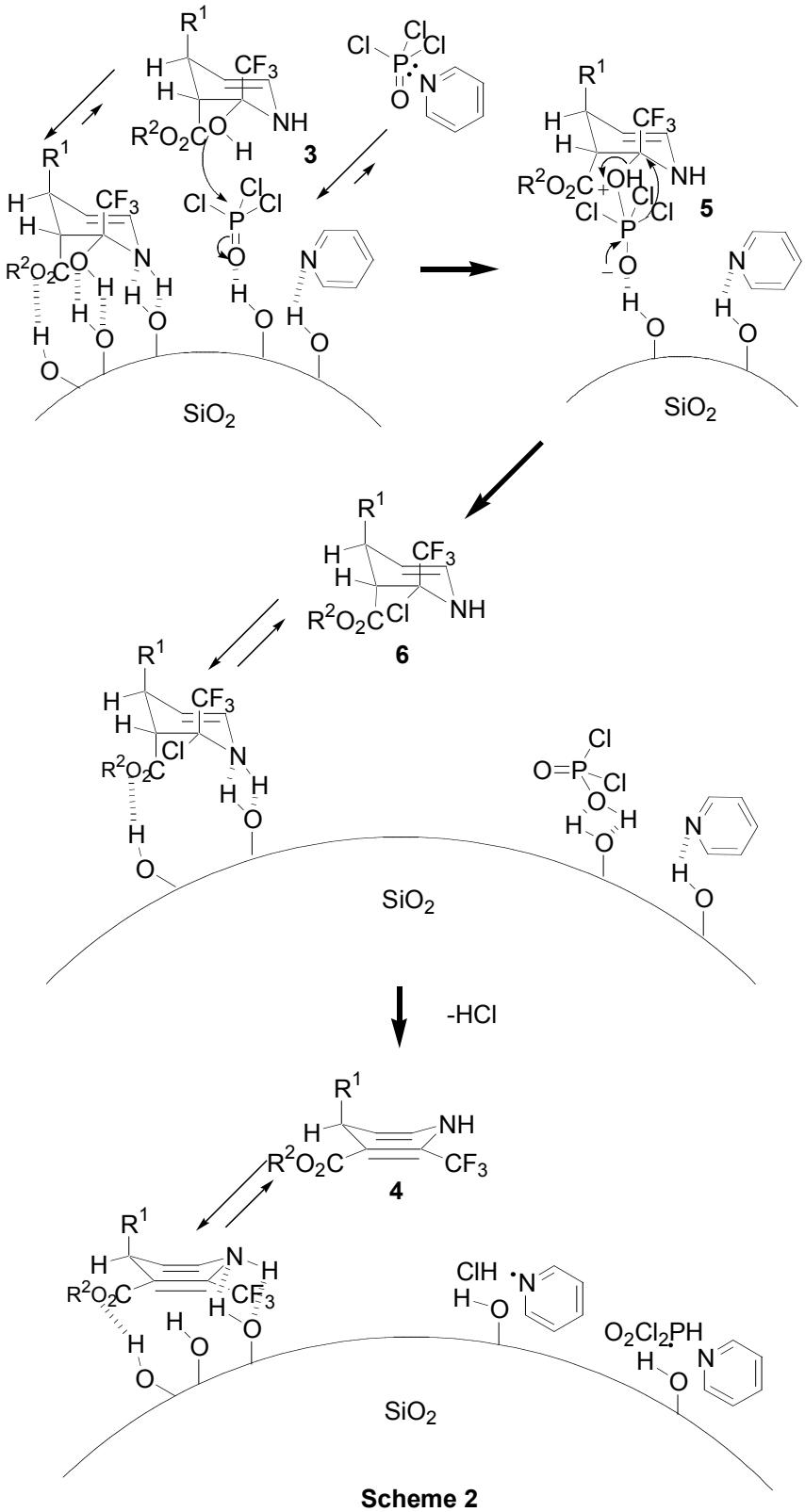
R^1	R^2	R^3	Time[a]/ h	Product /%	Yield[b]
Ph	Et	Et	3	**4a**	91
2-ClC_6H_4	Et	Et	5	**4b**	77
2-ClC_6H_4	Me	Et	5	**4c**	76
2-$CF_3C_6H_4$	Et	Et	6	**4d**	73
2-$NO_2C_6H_4$	Et	Et	3	**4e**	77
2-$NO_2C_6H_4$	Et	Me	5	**4f**	80
3-$NO_2C_6H_4$	Et	Et	6	**4j**	78
3-$NO_2C_6H_4$	Et	Me	6	**4h**	91
2-Furyl	Et	Et	4	**4i**	80
2-Thienyl	Et	Et	6	**4j**	88

[a] Dehydration time. [b] Isolated yields referred to **1**.

Table 2 summarizes the results of the one-pot synthesis of 1,4-dihydro-2-methyl-6-trifluoromethylpyridines (**4**) *via* the dehydration of the intermediate (**3**) by use of $POCl_3/C_5H_5N$-SiO_2 starting from **1**. In every case, the desired dihydropyridines (**4**) were obtained in good to high yields. It is worthy to notice that reactive functional groups such as esters are found to be stable under the reaction conditions.

Scheme 2 shows a possible mechanism for the synthesis of 1,4-dihydro-2-methyl-6-trifluoromethylpyridines (**4**) *via* the dehydration of **3** by use of $POCl_3/C_5H_5N$-SiO_2. In the present conditions, most of **3** and $POCl_3/C_5H_5N$ are presumably adsorbed on the silica surface although the latter would present as the coordinated pyridine complex in a solution. The first step involves the condensation of **3** in the liquid phase with $POCl_3$ activated by the silanol group. The resulting

intermediates (**5**) undergo the addition of the chlororide and the elimination of the phosphoric moiety, yielding the chlorination derivatives (**6**) along with HPO_2Cl_2. The dehydrochlorination of **6** provides the dihydropyridines (**4**). The adsorption of $POCl_3$ and HPO_2Cl_2 on SiO_2 can prevent the formation of by-products arising from the addition of these phosphoric compounds to **3**, **4**, **5**, or **6**.



Scheme 2

In conclusion, 1,4-dihydro-6-trifluoromethylpyridines have successfully been synthesized by use of phosphorus oxychloride / pyridine adsorbed on silica gel ($POCl_3/C_5H_5N$-SiO_2), which has been developed as an efficient reagent for the dehydration of α-trifluoromethyl alcohols. The significant advantages offered by this method are: (i) the reagent can be readily handled, (ii) the procedure does not require aqueous workup and large excess amount of dehydration reagent, (iii) it is compatible with a sensitive functional group. Thus, this method is expected to provide wide application in particular when the dehydration of α-trifluoromethyl alcohols is required in complex molecules containing sensitive functional groups.

EXPERIMENTAL

All the commercially available reagents were used without further purification. 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. Starting materials (**1**) were prepared by using the method described in our previous papers.[8] Phosphorus oxychloride / pyridine adsorbed on silica gel ($POCl_3/C_5H_5N$-SiO_2) was prepared by the following our procedure.[13]

General Procedure for the Preparation of $POCl_3/C_5H_5N$-SiO_2: To a solution of phosphorus oxychloride (3 mL) and pyridine (6 mL) in CH_2Cl_2 (50 mL) was slowly added silica gel (Merck Art. 7734, 20 g) while being cooled. The mixture was stirred for 1 h at rt. After removal of the solvent, the residue was dried in a rotary evaporator over a period of several hours.

General Procedure for the Synthesis of 1,4-Dihydro-6-trifluoromethyl-pyridines (4): A solution of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones (**1**) (1 mmol) and β-aminocrotonates (**2**) (1 mmol) in dichloroethane (4 mL) was refluxed for 2-3 h. Phosphorus oxychloride / pyridine adsorbed on silica gel (0.9 g; ca.1mmol based on $POCl_3/C_5H_5N$) was then added, and the mixture was further refluxed while being stirred until **3** was consumed as monitored by GLC analysis. After removal of the solvent, the residue was chromatographed on silica gel using CH_2Cl_2 /CH_3CO_2Et (20 /1) as an eluent. Spectral data of **4** are shown bellow.

Diethyl 1,4-Dihydro-2-methyl-4-phenyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4a): mp 111-112 °C (hexane/Et_2O); IR (Nujol)ν 3356, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 6H), 2.39 (s, 3H), 4.12 (m, 4H), 5.05 (s, 1H), 6.05 (br s, 1H), 7.18-7.26 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 14.25 (s,

3F); MS m/z (%) 383 (M^+, 5), 306 (100), 278 (15), 183 (18). Anal. Calcd for $C_{19}H_{20}NO_4F_3$: C, 59.53; H, 5.26; N, 3.65. Found: C, 59.28; H, 5.17; N, 3.70.

Diethyl 4-(2-Chlorophenyl)-1,4-dihydro-2-methyl-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (4b): mp 119-120 °C (hexane/Et_2O); IR (Nujol)ν 3311, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 4.04 (m, 2H), 4.13 (m, 2H), 5.05 (s, 1H), 5.89 (br s, 1H), 7.12 (td, J = 7.7, 1.6 Hz, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H), 7.28 (dd, J = 7.7, 1.6 Hz, 1H), 7.35 (dd, J = 7.7, 1.6 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 13.28 (s, 3F); MS m/z (%) 417 (M^+, 3), 306 (100), 278 (16), 182 (19). Anal. Calcd for $C_{19}H_{19}NO_4ClF_3$: C, 54.62; H, 4.58; N, 3.35. Found: C, 54.37; H, 4.51; N, 3.40.

3-Ethyl 5-Methyl 4-(2-Chlorophenyl)-1,4-dihydro-2-methyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4c): mp 116-117 °C (hexane/Et_2O); IR (Nujol)ν 3381, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 3.67 (s, 3H), 4.05 (m, 2H), 5.49 (s, 1H), 5.91 (br s, 1H), 7.12 (td, J = 7.7, 1.6 Hz, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H), 7.29 (dd, J = 7.7, 1.6 Hz, 1H), 7.34 (dd, J = 7.7, 1.6 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 13.28 (s, 3F); MS m/z (%) 403 (M^+, 7), 374 (23), 292 (100), 244 (22). Anal. Calcd for $C_{18}H_{17}NO_4ClF_3$: C, 53.54; H, 4.24; N, 3.47. Found: C, 53.39; H, 4.14; N, 3.60.

Diethyl 1,4-Dihydro-2-methyl-6-(trifluoromethyl)-4-[(2-trifluoromethyl)-phenyl]pyridine-3,5-dicarboxylate (4d): mp 95-96 °C (hexane/Et_2O); IR (Nujol)ν 3315, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 3.96-4.13 (m, 4H), 5.41 (s, 1H), 5.78 (br s, 1H), 7.32-7.57 (m, 4H); ^{19}F NMR ($CDCl_3$) δ 12.73 (s, 3F), 21.11 (s, 3F); MS m/z (%) 451 (M^+, 9), 306 (100), 278 (20). Anal. Calcd for $C_{20}H_{19}NO_4F_6$: C, 53.22; H, 4.24; N, 3.10. Found: C, 52.85; H, 4.14; N, 3.15.

Diethyl 1,4-Dihydro-2-methyl-4-(2-nitrophenyl)-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (4e): mp 113-115 °C (hexane/Et_2O); IR (Nujol)ν 3359, 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 3.92-4.20 (m, 4H), 5.75 (s, 1H), 5.92 (br s, 1H), 7.32-7.78 (m, 4H); ^{19}F NMR ($CDCl_3$) δ 12.87 (s, 3F); MS m/z (%) 428 (M^+, 6), 411 (100), 352 (35), 338 (70), 322 (28). Anal. Calcd for $C_{19}H_{19}N_2O_6F_3$: C, 53.27; H, 4.47; N, 6.54. Found: C, 53.18; H, 4.37; N, 6.56.

5-Ethyl 3-Methyl 1,4-Dihydro-2-methyl-4-(2-nitrophenyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4f): mp 127-128 °C (hexane/*i*-Pr_2O); IR (Nujol)ν 3312, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 3.53 (s, 3H), 3.53 (s, 3H), 4.10-4.22 (m, 2H), 5.68 (s, 1H), 5.90 (br s, 1H), 7.32-7.74 (m, 4H); ^{19}F NMR ($CDCl_3$) δ 13.03 (s, 3F); MS m/z (%) 414 (M^+, 5), 397 (100), 352 (28), 338 (70), 324 (33), 322 (23). Anal. Calcd for $C_{18}H_{17}N_2O_6F_3$: C, 52.18; H, 4.14; N, 6.76. Found: C, 51.89; H, 4.03; N, 6.71.

Diethyl 1,4-Dihydro-2-methyl-4-(3-nitrophenyl)-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (4g): mp 103-104 °C (hexane/Et_2O); IR (Nujol)ν 3341, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 6H), 2.44 (s, 3H), 4.07-4.20 (m, 4H), 5.17 (s, 1H), 6.23 (br s, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.06-8.13 (m, 2H); ^{19}F NMR ($CDCl_3$) δ 14.30 (s, 3F); MS m/z (%) 428 (M^+, 4), 306 (100), 278 (21). Anal. Calcd for $C_{19}H_{19}N_2O_6F_3$: C, 53.27; H, 4.47; N, 6.54. Found: C, 53.07; H, 4.36; N, 6.54.

5-Ethyl 3-Methyl 1,4-Dihydro-2-methyl-4-(3-nitrophenyl)-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (4h): mp 105-107 °C (hexane/Et_2O); IR (Nujol)ν 3365, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 2.45 (s, 3H), 3.67 (s, 3H), 4.13-4.22 (m, 2H), 5.17 (s, 1H), 6.23 (br s, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.06-8.12 (m, 2H); ^{19}F NMR ($CDCl_3$) δ 14.35 (s, 3F); MS m/z (%) 414 (M^+, 4), 292 (100), 264 (17), 196 (19). Anal. Calcd for $C_{18}H_{17}N_2O_6F_3$: C, 52.18; H, 4.14; N, 6.76. Found: C, 51.92; H, 4.01; N, 6.80.

Diethyl 1,4-Dihydro-2-methyl-4-(2-furyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4i): mp 68-70 °C (hexane/Et_2O); IR (Nujol)ν 3339, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 4.12-4.25 (m, 4H), 5.23 (s, 1H), 6.03 (d, J = 2.8 Hz, 1H), 6.25 (br s, 1H), 6.25 (s, 1H), 7.26 (d, J = 2.8 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 14.34 (s, 3F); MS m/z (%) 373 (M^+, 21), 344 (20), 328 (22), 300 (100), 272 (20). Anal. Calcd for $C_{17}H_{18}NO_5F_3$: C, 54.69; H, 4.86; N, 3.75. Found: C, 54.44; H, 4.83; N, 3.76.

Diethyl 1,4-Dihydro-2-methyl-4-(2-thienyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4j): mp 81-82 °C (hexane/Et_2O); IR (Nujol)ν 3344, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 4.14-4.26 (m, 4H), 5.38 (s, 1H), 6.27 (br s, 1H), 6.83-6.84 (m, 1H), 6.88 (dd, J = 5.1, 3.7 Hz, 1H), 7.12 (dd, J = 5.1, 1.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 14.38 (s, 3F); MS m/z (%) 389 (M^+, 21), 360 (60), 343 (31), 320 (30), 316 (100), 306 (34), 288 (30), 204 (51), 111 (35). Anal. Calcd for $C_{17}H_{18}NO_4F_3S$: C, 52.44; H, 4.66; N, 3.60. Found: C, 52.29; H, 4.61; N, 3.66.

ACKNOWLEDGEMENTS

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