A Novel Dehydrofluorination of 2-(Trifluoromethyl)dihydro-3,5-pyridinedicarboxylates to 2-(Difluoromethyl)-3,5-pyridinedicarboxylates

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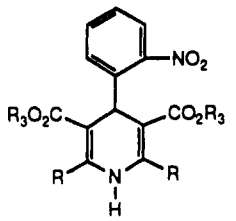
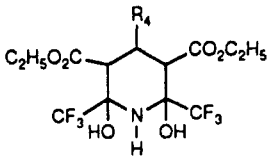
A series of 2-(trifluoromethyl)-1,4- and -3,4-dihydro-3,5-pyridinedicarboxylates **5a-y** and **6a-y** undergo an unprecedented dehydrofluorination upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), trialkylamines, or 2,6-lutidine to give the corresponding 2-(difluoromethyl)-3,5-pyridinedicarboxylates **8a-y**. This novel reaction is believed to involve isomerization of **5a-y** and **6a-y** to the tautomeric anions **13a-y** and **14a-y** or the 1,2-dihydropyridines **16t** followed by elimination of fluoride from **13a-y** or **14a-y** or dehydrofluorination of **16t**.

Introduction

1,4-Dihydro-3,5-pyridinedicarboxylates have been known since Hantzsch developed his dihydropyridine synthesis more than one hundred years ago.[1] This chemistry found little interest until the discovery of vasodilating and antihypertensive properties of 4-aryl-1,4-dihydro-3,5-pyridinedicarboxylates such as nifedipine (**1a**).[2,3] Since then, this area of chemistry has received much attention,[4] and a number of related compounds has been found to possess useful pharmacological properties.[5] Most of these reported compounds are 2,6-dialkyl-1,4-dihydropyridines. We were the first to report the syntheses and herbicidal properties of 2,6-bis(trifluoromethyl)-1,4-dihydro-3,5-pyridinedicarboxylates and the corresponding pyridine analogues.[6,7] An earlier reported synthesis[8] of a series of 2,6-bis(trifluoromethyl)-1,4-dihydro-3,5-pyridinedicarboxylates was found to be incorrect by Singh and Lesher[9] and later retracted by the original workers.[10] They found that the products were 2,6-bis(trifluoromethyl)2,6-dihydroxy-3,5-piperidinedicarboxylates **2** instead of the expected 1,4-dihydropyridines. Singh and Lesher were unable to dehydrate the 2,6-dihydroxy-3,5-piperidinedicarboxylate **2a** to the diethyl ester analogue of nifedipine **1b**. In contrast, we were successful in the synthesis of various 6-(trifluoromethyl)-1,4- and 3,4-dihydropyridines **5a-y** and **6a-y** by dehydration of 2,6-dihydroxypiperidines **3a-t,y** or 2-hydroxy-1,2,3,4-tetrahydropyridines **4u-x** using various dehydration agents (Scheme I; for definition of R_2, R_3 and R_4 see Table I).[6] Later Kim also successfully prepared **1b** by dehydration of **2a** with phosphorus oxychloride-pyridine.[12] Recently other workers also reported a synthesis of diethyl 2,6-bis(trifluoromethyl)-4-[3-chloro-6-fluoro-2-(trifluoro-



1a R, R_3 = CH_3
b R = CF_3, R_3 = C_2H_5



2 R_4 = H, alkyl, aryl
2a R_4 = 2-NO_2Ph

Table I. Effect of Structure and Reaction Conditions on Dehydrofluorination of 5a-y and 6a-y to 8a-y

structure of 8 and its precursors and intermediates, 5 and 6 and 12-17				reaction conditions and yield of 8	
compd	R_2	R_3	R_4	base/solvent	yield,[a] %
a	CF_3	Et	Me	DBU/THF	62
b	CF_3	Et	Et	DBU/THF	79
c	CF_3	Et	*n*-Pr	DBU/THF	63
d	CF_3	Et	*i*-Pr	DBU/THF	38
e	CF_3	Et	*c*-Pr	DBU/THF	76
f	CF_3	Et	CH_2-*c*-Pr	DBU/THF	80
g	CF_3	Et	*n*-Bu	DBU/THF	89
h	CF_3	Et	*i*-Bu	DBU/THF	49
h	CF_3	Et	*i*-Bu	NBu_3/toluene	96
i	CF_3	Et	2-Bu	DBU/THF	74
j	CF_3	Et	*c*-Bu	DBU/THF	53
k	CF_3	Et	neoPen	DBU/THF	30
l	CF_3	Et	*c*-Hex	DBU/THF	49
m	CF_3	Et	Ph	DBU/THF	67
n	CF_3	Et	4-pyridyl	DBU/THF	25
o	CF_3	Et	CH_2OCH_3	DBU/THF	52
p	CF_3	Et	CH_2OCH_2Ph	DBU/THF	50
q	CF_3	Et	$C_2H_5SCH_3$	DBU/THF	60
r	CF_3	Et	CH_2SCH_3	DBU/THF	35 (70[b])
r	CF_3	Et	CH_2SCH_3	2,6-lutidine/ethylene glycol	67[b]
s	CF_3	Et	2-thienyl	2,6-lutidine/ethylene glycol	60
t	CF_3	Me	*i*-Bu	DBU/THF	29 (52[c])
t	CF_3	Me	*i*-Bu	$N(i\text{-}Pr)_2Et$	95
t	CF_3	Me	*i*-Bu	NBu_3	90
t	CF_3	Me	*i*-Bu	NEt_3	66
u	Et	Me	*n*-Pr	DBU/diglyme	10[d]
v	Me	Me	*i*-Bu	DBU/diglyme	25[d]
w	Et	Me	*i*-Bu	DBU/diglyme	5[d]
x	Me	Et	Me	DBU/diglyme	19
y	CF_3	Et	CF_3	DBU/diglyme	12

[a] All yields are unoptimized isolated yields except **8h** and **8t**. [b] GC yield. [c] Including yield from alkylation of **9** and **10** with methyl iodide. [d] Yield after alkylation of the crude reaction products with methyl iodide.

(1) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
(2) Bossert, F.; Vater, W. *Naturwissenschaften* **1971**, *58*, 578.
(3) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macho, E. *J. Med. Chem.* **1974**, *17*, 956.
(4) For a recent review, see: Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269.
(5) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem., Int. Ed. Engl.* **1981**, 762.
(6) (a) Lee, L. F. Eur. Pat. Appl. EP 135,491 (1985); *Chem. Abstr.* **1985**, *103*, 178173. (b) Manuscripts in preparation.
(7) Lee, L. F. Eur. Pat. Appl. EP 133,612 (1985); *Chem. Abstr.* **1986**, *104*, 19514.
(8) Balicki, R.; Nantka-Namirski, P. *Acta Pol. Pharm.* **1974**, *31*, 261.
(9) Singh, B.; Lesher, G. Y. *J. Heterocycl. Chem.* **1980**, *17*, 1109.
(10) Balicki, R.; Nantka-Namirski, P. *Pol. J. Chem.* **1981**, *55*, 2439.
(11) Lee, L. F. Brit. U.K. Pat. Appl. GB 2,145,628 (1986); *Chem. Abstr.* **1986**, *103*, 196005.
(12) Kim, D. H. *J. Heterocycl. Chem.* **1986**, *23*, 1523.

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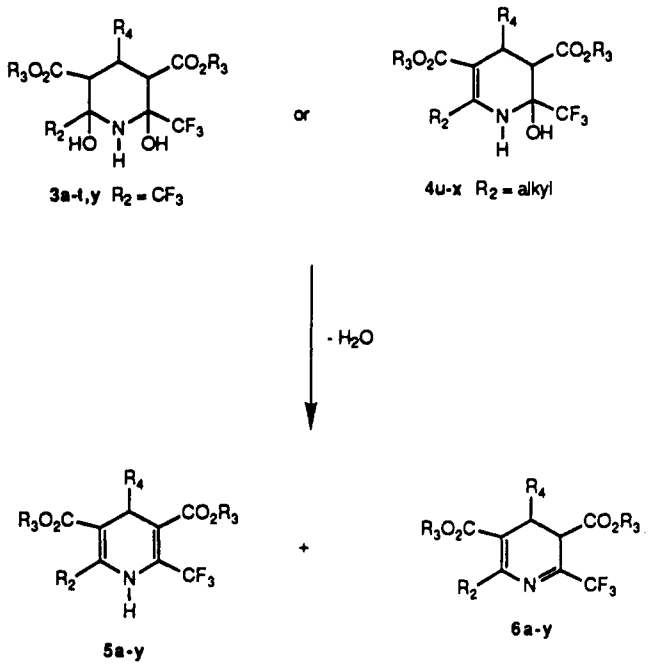
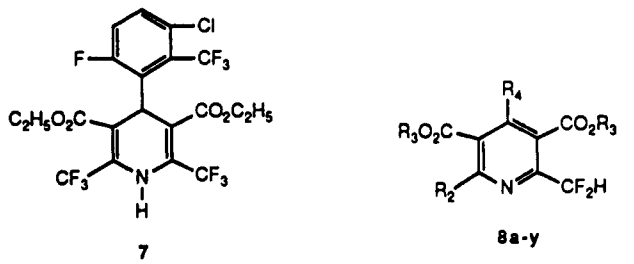
Scheme I

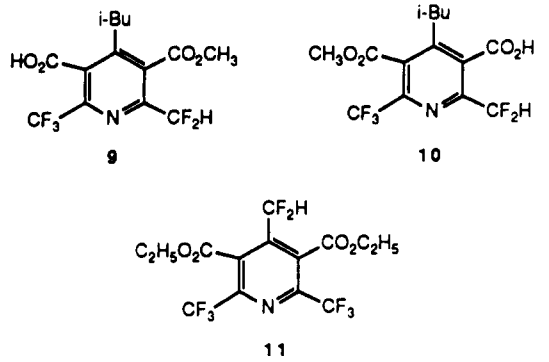


methyl)phenyl]-1,4-dihydro-3,5-pyridinedicarboxylate (**7**) by dehydration of the corresponding 2,6-dihydroxy-3,5-piperidinedicarboxylate with sulfuric acid.[13] During the course of our studies, we discovered an unprecedented dehydrofluorination of **5a–y** and **6a–y** to 2-(difluoromethyl)-3,5-pyridinedicarboxylates **8a–y**. We would like to communicate here the results of this novel reaction.



Results and Discussion

Reaction of diethyl esters **5a–r** and **6a–r** with 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing THF gave moderate to good yields of **8a–r** (Table I). The weaker bases such as trialkylamines and 2,6-lutidine also worked well but required higher reaction temperature and longer reaction time. It was more advantageous to use 2,6-lutidine to dehydrofluorinate **5s** and **6s** since fewer byproducts were formed in this case. When the dimethyl esters **5t–w** and **6t–w** were reacted with DBU, subtantial amounts of byproducts were formed. The major bypyroducts were found to derive from demethylation of the methyl ester groups of the products **8t–w** by DBU.[14] For instance, reaction of **5t** with DBU gave a mixture of monoacids, **9** and **10**, along with **8t** (29% yield). Further alkylation of this mixture of acids with methyl iodide gave an additional 23% yield of **8t**. In contrast, reaction of **5t** with a trialkylamine such as *N,N*-diisopropylethylamine, tri-*n*-butylamine, or triethylamine gave good to excellent yields (66–95%) of **8t** with the most sterically hindered base, *N,N*-diisopropylethylamine, providing the best yields of **8t**. Reactions of the 2-alkyl-6-(trifluoromethyl) analogues **5u–x** and **6u–x** with DBU were sluggish and required higher reaction temperature (110–150 °C) to provide **8u–x** in poor yields. Reaction of the 4-(trifluoromethyl) analogues **5y** and **6y** with DBU gave the 4-(difluoromethyl)-2,6-bis(trifluoromethyl)pyridine **11** as the major product (46%) and **8y** as the minor product (12%).



We believe **5a–y** and **6a–y** react with the organic base to form the N-1 anion **12a–y** first which isomerizes to the C-2 anion **14a–y** via the C-4 anion **13a–y**. Either the C-4 anion **13a-y** or the C-2 anion **14a–y** can eliminate fluoride to give the unstable 2-(difluoromethylene)-1,2-dihydropyridine intermediate **15a–y**, which rearranges to **8a–y** (see Scheme II). We were able to isolate the 1,2-dihydropyridine **16t** in 64% yield by heating **5t** in pyridine at 105 °C for 1–2 h (see Scheme III). Since pyridine is a weaker base than DBU, only a small amount of **16t** was converted to **8t** in a short reaction period. However, prolonged reaction of **5t** in pyridine did give **8t** as the major product. Conversion of **5a–y** and **6a–y** to **8a–y** occurs significantly only in the presence of an amine base. For instance, heating **5t** in toluene alone under nitrogen resulted only in isomerization of **5t** to **6t**.

We found that if **5t** is treated with DBU at room temperature in benzene-d_6, it forms a DBU salt **12t**. This event can be shown by the instant color change from yellow to orange and by the changes in the **13C** NMR spectra. The first proton being removed by DBU is the NH proton; this can be shown by the little change of the ^1H NMR spectra except a slight downfield shift of the H-4 signal from δ 4.1 to δ 4.25. On the other hand, the ^{13}C signal of C-3 shifts significantly upfield from δ 110.2 to δ 97.4, indicating the formation of an N-1 anion **12t**, which tautomerizes to the C-3 anion **17t** (see Scheme II) causing the upfield shift of the C-3 signal. If **5t** is treated with the weaker base, triethylamine, at room temperature, there is no color change or change in both ^1H and ^{13}C NMR spectra, indicating no anion formation at room temperature. The N-1 anion **12t** may be in equilibrium with the C-4 anion **13t** upon heating, although the equilibrium is expected to favor **12t**. Tautomerization of **13t** to the C-2 anion **14t** under heating followed by protonation may give **16t**, which has a H-2 signal at δ 5.53 as a quartet of doublets due to couplings from both the NH proton and the three CF_3 fluorines. In the presence of a strong base such as DBU, either **13t** or **14t** may lose fluoride directly to give **8t**, or the 1,2-dihydropyridine **16t** may be dehydrofluorinated to **8t**. The latter was indeed demonstrated. A 0.3 M solution of **16t** in toluene was reacted readily with one equivalent of DBU at *room temperature* to give **8t** (see Scheme III). The reaction was 95% complete in 4 h. A similar reaction using tributylamine as the base was only 8% complete in 4 h. The even weaker base, pyridine, did not react with **16t** at room temperature. This facile dehydrofluorination of **16t** by DBU is in contrast to the fact

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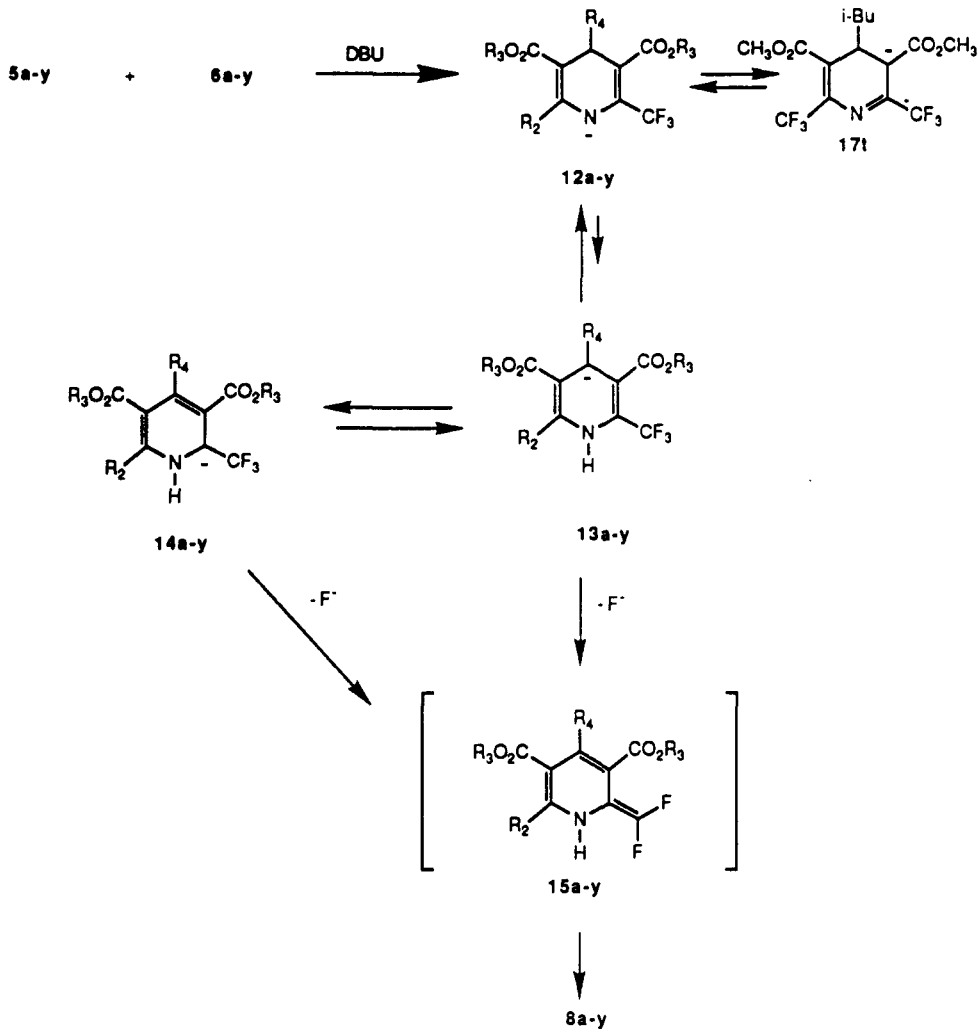
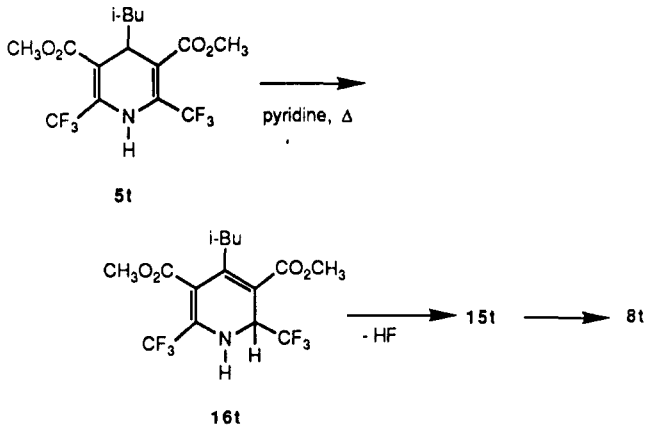
(14) Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1973**, *28*, 1223.

Scheme II



Scheme III



that no dehydrofluorination of **5t** by DBU at room temperature was observed.

The remarkable aromatization of dihydropyridines **5a–y** and **6a–y** to pyridines **8a–y** by a dehydrofluorination is unprecedented in dihydropyridine chemistry. Generally dihydropyridines are converted to pyridines by oxidation or thermal dehydrogenation.[15] After we had completed our work,[6] formations of 2,6-bis(trifluoromethyl)-1,2-dihydropyridines from isomerization of **1b** and **7** were reported recently,[12,13] but no dehydrofluorination of these compounds was mentioned. The above described dehydrofluorination reaction for the 2,6-bis(trifluoromethyl)-1,4- and -3,4-dihydro-3,5-pyridinedicarboxylates is general and gives moderate to excellent yields. It is applicable to a variety of 4-substituted analogues (see Table I) except **7**, which was recently reported[13] to give the corresponding 1,2-dihydropyridine isomer and the 4-unsubstituted pyridine as the major product upon heating with DBU in DMF and THF, respectively. The 2-(difluoromethyl)-pyridines prepared by the above method possess herbicidal activity.[7] These compounds are difficult to prepare by other methods.

Experimental Section

Melting points were determined with a Laboratory Devices Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Varian T-60 (60 MHz), a Varian EM-360 (60 MHz), a Varian XL 300 (300 MHz), a Bruker AM 360 (360 MHz), or a Varian XL 400 (400 MHz) spectrometer. ^{13}C NMR spectra were measured either at 25.05 MHz with a JEOL FX-100, at 75.4 MHz with a Varian XL 300, at 90 MHz with a Bruker AM 360, or at 100 MHz with a Varian XL 400 spectrometer. ^{19}F NMR spectra were obtained with a Varian EM-390 (90 MHz) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted and are expressed in parts per million (ppm) downfield from Me_4Si; the coupling constants are expressed as ^nJ where n is the number of bonds between carbon and fluorine or carbon and hydrogen; coupling constants are in hertz. ^{19}F NMR spectra were recorded in $CDCl_3$ using benzotrifluoride (δ –63.73) in a sealed capillary as an external standard and are expressed

(15) For a recent review, see: Sausins, A.; Duburs, G. *Heterocycles* 1988, 27, 291.

in ppm relative to CCl_3F, with upfield shifts taken as negative. Mass spectra were determined with a Varian Mat 311 A instrument operating on either electron-impact (EI) or field-ionization (FI) mode. GC mass spectra (GC–MS) were carried out on a Finnigan 4500 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 7727 B spectrometer. Gas chromatography (GC) was performed on a Perkin-Elmer gas chromatograph using a 2 ft × 0.25 in. column packed with 10% OV 17 on 80/100 Chromosorb W. Column chromatography (CC) was performed with 60–200-mm silica gel 60 (EM Reagents). Preparative medium-pressure liquid chromatography (MPLC) was done on a EM LOBAR size C silica gel column. Preparative high-performance liquid chromatography (HPLC) was carried out with a Waters PrepLC System 500A on PrepPak silica gel columns. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Unless otherwise noted, the organic layers were dried over $MgSO_4$ and concentrated in vacuo with a Büchi rotary evaporator. The flash distillations were performed using a Kugelrohr distillation apparatus, and the recorded temperature for a specific fraction was the tempertature of the Kugelrohr oven.

Preparations of pure 1,4-dihydropyridines **5a–y** or the mixture of **5a–y** and their 3,4-dihydropyridine isomers **6a–y** have been reporated previously[6] as has an authentic sample of compound **10**.[7] The monoacid **9** was prepared by hydrolysis of methyl 2-(difluoromethyl)-5-chlorocarbonyl-4-isobutyl-6-(trifluoromethyl)-3-pyridinecarboxylate[16] with aqueous potassium carbonate.[17]

General Procedure for Dehydrofluorination of 5a–q and 6a–q with DBU in Refluxing THF. A solution of **5a–q** (0.05 mol) or a mixture of **5a–q** and **6a–q** and 0.05 mol of 1,8-diazabicyclo[5.4.0]undece-7-ene (DBU) in 200 mL of THF was held at reflux for 18 h, cooled, and poured into 500 mL of ice water. The mixture was extracted with ether, and the ether extract was washed with dilute hydrochloric acid, dried, and concentrated. The residue was Kugelrohl distilled at 1 Torr to give the pure product (see Table I for specific reaction conditions).

Diethyl 2-(difluoromethyl)-4-methyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8a) was obtained from reaction of **5a** with DBU: n^{25}_D 1.4410; ^{1}H NMR δ 6.7 (t, J = 54, 1 H), 4.47 (q, J = 7, 4 H), 2.43 (s, 3 H), 1.40 (t, J = 7, 6 H). Anal. Calcd for $C_{14}H_{14}F_5NO_4$: C, 47.33; H, 3.97; N, 3.94. Found: C, 47.25; H, 4.02; N, 3.87.

Diethyl 2-(difluoromethyl)-4-ethyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8b) was obtained from reaction of **5b** with DBU: bp 110 °C (2 Torr); ^{1}H NMR δ 6.75 (t, J = 54, 1 H), 4.50 (q, J = 7, 4 H), 2.76 (q, J = 7, 2 H), 1.41 and 1.26 (2 overlapped t, total 9 H); ^{19}F NMR δ –65.59 (s, 3 F), –116.66 (d, J = 54, 5 F). Anal. Calcd for $C_{15}H_{16}F_5NO_4$: C, 48.78; H, 4.37; N, 3.79. Found: C, 48.75; H, 4.29; N, 3.72.

Diethyl 2-(difluoromethyl)-4-propyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8c) was obtained from reaction of **5c** with DBU: n^{25}_D 1.4436; ^{1}H NMR δ 6.76 (t, J = 54, 1 H), 4.50 (q, J = 7, 4 H), 2.6–3.0 (m, 2 H), 1.3–2.2 (m overlapped with a t at δ 1.40, total 8 H), 1.00 (t, J = 7, 3 H). Anal. Calcd for $C_{16}H_{18}F_5NO_4$: C, 50.13; H, 4.73; N, 3.65. Found: C, 49.92; H, 4.71; N, 3.58.

Diethyl 2-(difluoromethyl)-4-isopropyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8d) was obtained from reaction of **5d** with DBU: n^{25}_D 1.4465; ^{1}H NMR δ 6.70 (t, J = 54, 1 H), 4.46 (q, J = 7, 4 H), 3.20 (h, J = 7, 1 H), 1.2–1.7 (m, 12 H). Anal. Calcd for $C_{16}H_{18}F_5NO_4$: C, 50.13; H, 4.73; N, 3.65. Found: C, 50.16; H, 4.76; N, 3.65.

Diethyl 2-(difluoromethyl)-4-cyclopropyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8e) was obtained from reaction of **5e** with DBU: mp 30–32 °C; ^{1}H NMR δ 6.73 (t, J = 54, 1 H), 4.40 (q, J = 7, 4 H), 1.9–2.1 (m, 1 H), 1.40 (t, J = 7, 6 H), 0.5–1.1 (m, 4 H). Anal. Calcd for $C_{16}H_{16}F_5NO_4$: C, 50.40; H, 4.23; N, 3.67. Found: C, 50.48; H, 4.32; N, 3.78.

Diethyl 2-(difluoromethyl)-4-(cyclopropylmethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8f) was obtained from reaction of **5f** with DBU: bp 100 °C (0.5 Torr); ^{1}H NMR δ 6.67 (t, J = 54, 1 H), 4.43 (q, J = 7, 4 H), 2.68 (d, J = 6, 2 H), 1.38 (t, J = 7, 6 H), 0.15–0.6 (m, 5 H). Anal. Calcd for $C_{17}H_{18}F_5NO_4$: C, 51.65; H, 4.59; N, 3.54. Found: C, 51.73; H, 4.62; N, 3.51.

Diethyl 2-(difluoromethyl)-4-butyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8g) was obtained from reaction of **5g** with DBU: n^{25}_D 1.4443; ^{1}H NMR δ 6.76 (t, J = 54, 1 H), 4.50 (q, J = 7, 4 H), 2.6–3.0 (m, 2 H), 0.8–2.0 (m, 13 H); ^{19}F NMR δ –65.83 (s, 3 F), –116.63 (d, J = 54, 2 F). Anal. Calcd for $C_{17}H_{20}F_5NO_4$: C, 51.39; H, 5.07; N, 3.53. Found: C, 51.43; H, 5.17; N, 3.48.

Diethyl 2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8h) was obtained from reaction of **5h** with either DBU in refluxing THF or tributylamine in refluxing toluene (see Table I): n^{25}_D 1.4436; ^{1}H NMR δ 6.73 (t, J = 54, 1 H), 4.46 (q, J = 7, 4 H), 2.76 (d, J = 7, 2 H), 1.93 (h, J = 7, 1 H), 1.40 (t, J = 7, 6 H), 0.95 (d, J = 7, 6 H); ^{19}F NMR δ –65.70 (s, 3 F), –116.83 (d, J = 54, 2 F). Anal. Calcd for $C_{17}H_{20}F_5NO_4$: C, 51.39; H, 5.07; N, 3.53. Found: C, 51.35; H, 5.08; N, 3.51.

Diethyl 2-(difluoromethyl)-4-(2-butyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8i) was obtained from reaction of **5i** and **6i** with DBU: n^{25}_D 1.4471; ^{1}H NMR δ 6.67 (t, J = 54. 1 H), 4.43 (q, J = 7, 4 H), 2.6–3.2 (m, 1 H), 1.2–2.0 (m, 11 H), 0.93 (t, J = 7, 3 H). Anal. Calcd for $C_{17}H_{20}F_5NO_4$: C, 51.39; H, 5.07; N, 3.53. Found: C, 51.32; H, 5.08; N, 3.50.

Diethyl 2-(difluoromethyl)-4-cyclobutyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8j) was obtained from reaction of **5j** and **6j** with DBU: n^{25}_D 1.4628; ^{1}H NMR δ 6.8 (t, J = 54, 1 H), 4.43 (q, J = 7, 4 H), 4.03 (m, J = 7, 1 H), 1.6–2.6 (m, 6 H), 1.38 (t, J = 7, 6 H). Anal. Calcd for $C_{17}H_{18}F_5NO_4$: C, 51.65; H, 4.59; N, 3.54. Found: C, 51.67; H, 4.65; N, 3.54.

Diethyl 2-(difluoromethyl)-4-neopentyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8k) was obtained from reaction of **5k** and **6k** with DBU: n^{25}_D 1.4522; ^{1}H NMR δ 6.73 (t, J = 54, 1 H), 4.37 (q, J = 7, 4 H), 3.0 (s, 2 H), 1.37 (t, J = 7, 6 H), 0.90 (s, 9 H). Anal. Calcd for $C_{18}H_{22}F_5NO_4$: C, 52.55; H, 5.39; N, 3.40. Found: C, 52.54; H, 5.42; N, 3.40.

Diethyl 2-(difluoromethyl)-4-cyclohexyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8l) was obtained from reaction **5l** and **6l** with DBU: n^{25}_D 1.4614; ^{1}H NMR δ 6.67 (t, J = 54, 1 H), 4.46 (q, J = 7, 4 H), 2.4–3.0 (br, 1 H), 1.0–2.0 (br overlapped with a t at δ 1.40 total 16 H). Anal. Calcd for $C_{19}H_{22}F_5NO_4$: C, 53.90; H, 5.24; N, 3.31. Found: C, 54.19; H, 5.33; N, 3.51.

Diethyl 2-(difluoromethyl)-4-phenyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8m) was obtained from reaction of **5m** with DBU: n^{25}_D 1.4859; ^{1}H NMR (400 MHz) δ 7.25–7.50 (m, 5 H), 6.82 (t, J = 54, 1 H), 4.08 (q, J = 7, 4 H), 0.9–1.1 (two overlapped t, J = 7, 6 H). Anal. Calcd for $C_{19}H_{16}F_5NO_4$: C, 54.68; H, 3.86; N, 3.36. Found: C, 54.72; H, 3.88; N, 3.33.

Diethyl 2-(difluoromethyl)-4-(4-pyridyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (8n) was obtained from reaction of **5n** with DBU: mp 43–45 °C; ^{1}H NMR δ 8.72 and 8.68 (two overlapped d, J = 6, 2 H), 7.27 and 7.23 (two overlapped d, J = 6, 2 H), 6.83 (t, J = 54, 1 H), 4.08 (q, J = 7, 4 H), 1.06 and 1.03 (two overlapped t, J = 7, 6 H). Anal. Calcd for $C_{18}H_{15}F_5N_2O_4$: C, 51.68; H, 3.61; N, 6.70. Found: C, 51.51; N, 3.63; N, 6.66.

Diethyl 2-(difluoromethyl)-4-(methoxymethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8o) was obtained from reaction of **5o** and **6o** with DBU: n^{25}_D 1.4448; ^{1}H NMR δ 6.83 (t, J = 54, 1 H), 4.60 (s, 2 H), 4.47 (q, J = 7, 4 H), 3.30 (s, 3 H), 2.7 (t, J = 7, 6 H); ^{19}F NMR δ –64.53 (s, 3 F), –115.13 (d, J = 54, 2 F). Anal. Calcd for $C_{15}H_{16}F_5NO_5$: C, 46.73; H, 4.19; N, 3.64. Found: C, 46.83; H, 4.21; N, 3.88.

Diethyl 2-(difluoromethyl)-4-((benzyloxy)methyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8p) was obtained from reaction of **5p** with DBU: mp 48–51.5 °C; ^{1}H NMR δ 7.28 (s, 5 H), 6.76 (t, J = 54, 1 H), 4.70 (s, 2 H), 4.46 (s, 2 H), 4.1–4.5 (2 overlapped q, total 4 H), 1.28 (t, J = 7, 6 H); ^{19}F NMR δ –65.63 (s, 3 F), –116.66 (d, J = 54, 2 F). Anal. Calcd for $C_{21}H_{20}F_5NO_5$: C, 54.67; H, 4.37; N, 3.04. Found: C, 54.43; H, 4.17; N, 3.01.

Diethyl 2-(difluoromethyl)-4-(2-(methylthio)ethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8q) was obtained from reaction of **5q** and **6q** with DBU: n^{25}_D 1.4709; ^{1}H NMR δ 6.90 (t, J = 54, 1 H), 4.48 (q, J = 7, 4 H), 2.4–3.4 (m, 4 H), 2.15 (s, 3 H), 1.43 (t, J = 7, 6 H); ^{19}F NMR δ –65.98 (s, 3 F), –118.07

(16) Lee, L. F.; Sing, Y. L. Eur. Pat. Appl. EP 278,944 (1988); *Chem. Abstr.* **1989**, *109*, 230818.

(17) Manuscripts in preparation.

(d, J = 54, 2 F). Anal. Calcd for $C_{16}H_{18}F_5NO_4S$: C, 46.26; H, 4.37; N, 3.37. Found: C, 46.40; H, 4.41; N, 3.42.

Diethyl 2-(Difluoromethyl)-4-((methylthio)methyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8r). (a) Dehydrofluorination with DBU. To a solution of 245 g (0.547 mol) of a 94% pure mixture of **5r** and **6r** in 700 mL of THF was added 88.5 g (0.56 mol) of DBU. The reaction mixture was held at reflux for 24 h. An additional 13.3 g (0.084 mol) of DBU was added to the reaction mixture, and the refluxing was continued for 24 h. The reaction mixture was worked up as described in the general procedure to give a residue which was analyzed to be 70% pure **8r** by GC. This residue was Kugelrohr distilled first at 1.6 Torr (130–160 °C) to remove 51.7 g of a first fraction and then at 0.6 Torr to give 52.6 g of a second fraction (145–165 °C), 42.5 g of a third fraction (166–190 °C), and 10.4 g of a fourth fraction (191–200 °C). The third fraction was 95% pure **8r** (18% yield). A portion (15 g) of the second fraction was purified by HPLC (EtOAc–cyclohexane, 1:9) to give 10.5 g (17% yield from **5r** and **6r**) of pure **8f**: n^{25}_D 1.4748; ^{1}H NMR δ 6.80 (t, J = 54, 1 H), 4.48 (q, J = 7, 4 H), 3.9 (s, 2 H), 2.03 (s, 3 H), 1.43 (t, J = 7, 6 H). Anal. Calcd for $C_{15}H_{16}F_5NO_4S$: C, 44.89; H, 4.02; N, 3.49. Found: C, 45.04; H, 4.07; N, 3.35.

(b) Dehydrofluorination with 2,6-Lutidine. To a crude mixture of 842 g (2.0 mol) of **5r** and **6r** was added 200 mL of ethanol, 2 L of ethylene glycol, and 214 g (2.0 mol) of 2,6-lutidine. The reaction mixture was heated and held at 120 °C for 24 h, cooled, poured into 6 L of water, and extracted with CH_2Cl_2 (1 × 1 L, then 3 × 250 mL). The combined CH_2Cl_2 extracts were washed successively with 1% HCl and 2% NaCl solution, dried, and concentrated. GC analysis of the residue (800 g) indicated a 67% pure **8r**.

Diethyl 2-(Difluoromethyl)-4-(2-thienyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8s). A mixture of 39.9 g (0.09 mol) of a crude mixture of **5s** and **6s**, 10.0 g (0.093 mol) of 2,6-lutidine, 50 mL of ethanol, and 200 mL of ethylene glycol was held at reflux (110 °C) for 24 h, cooled, and poured into a mixture containing 10 mL of concentrated hydrochloric acid and 2 L of water. The mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 extract was dried and concentrated. The residue was purified by HPLC (4% EtOAc in cyclohexane). The first fraction was Kugelrohr distilled at 0.5 Torr (140–150 °C) to give 23 g (60%) of a light yellow solid: mp 38–40 °C; ^{1}H NMR δ 7.56 (d of d, J = 4 and 2, 1 H), 7.0–7.3 (m, 2 H), 6.76 (t, J = 54, 1 H), 4.23 (q, J = 7, 4 H), 1.01 (t, J = 7, 6 H); ^{19}F NMR δ −64.46 (s, 3 F), −115.22 (d, J = 54, 2 F). Anal. Calcd for $C_{17}H_{14}F_5NO_4S$: C, 48.23; H, 3.33; N, 3.31. Found: C, 48.45; H, 3.39; N, 3.29.

Dimethyl 2-(Difluoromethyl)-6-(trifluoromethyl)-4-isobutyl-3,5-pyridinedicarboxylate (8t). (a) Dehydrofluorination of 5t with DBU. A mixture of 23.0 g (0.0591 mol) of **5t**, 12.2 g (0.077 mol) of DBU, and 100 mL of THF was held at reflux for 3 days and poured into 250 mL of 3 N HCl. The oil precipitate was extracted into ether (2 × 100 mL). The ether extracts were dried and concentrated to give 14.4 g of an oil which, according to ^{1}H NMR, contained the desired product and the acidic products. This oil was dissolved in ether and extracted with 100 mL of saturated sodium bicarbonate. The ether layer was dried and concentrated to give 8.9 g of an oil which was 71% pure **8t** (by ^{19}F NMR).

The sodium bicarbonate extract was acidified with concentrated HCl to give an oil, which was extracted into ether. The ether layer was dried and concentrated to give 4.8 g of a residue which contained **9** and **10** (1:9). This residue was treated with 32.0 g (0.0217 mol) of potassium carbonate, 20 mL of methyl iodide, and 50 mL of acetone. The mixture was held at reflux for 42 h and concentrated. The residue was treated with water and extracted with ether (2 × 100 mL). The ether layer was dried and concentrated. The residue was Kugelrohr distilled at 1 Torr (pot temperature of 130 °C) to give 5.1 g (23% from **5t**) of the desired product as an oil, n^{25}_D 1.4478. This product crystallized after standing: mp 36–37 °C; ^{1}H NMR δ 6.73 (t, J = 54, 1 H), 4.0 (s, 6 H), 2.73 (d, J = 7, 2 H), 1.62–2.2 (m, 1 H), 0.90 (d, J = 7, 6 H); ^{19}F NMR δ −66.16 (s, 3 F), −117.3 (d, J = 53, 2 F). Anal. Calcd for $C_{15}H_{16}F_5NO_4$: C, 48.79; H, 4.37; N, 3.79. Found: C, 48.75; H, 4.39, N, 3.77.

The 71% pure desired product described previously was chromatographed by HPLC using 3% ethyl acetate in cyclohexane as eluent to give an earlier fraction (0.79 g) which was dicarded. The second fraction was an additional 6.4 % (29%) of pure **8t**.

(b) Dehydrofluorination of 5t with *N,N*-Diisopropylethylamine. A mixture of 20.9 g (0.0532 mol) of 99.2% (GC wt % assay) pure **5t**, 7.08 g (0.0536 mol) of *N,N*-diisopropylethylamine, and 30 mL of toluene was held at reflux for 2 h and diluted with 200 mL of toluene. The toluene solution was washed twice with 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 20.2 g of a residue which was Kugelrohr distilled at 1 Torr (130 °C) to give 19.47 g (95.3% yield) of 96.2% (GC wt % assay) pure **8t**.

(c) Dehydrofluorination of 5t with Tributylamine. A mixture of 11.7 g (0.0299 mol) of 99.5% pure (GC area %) **5t**, 5.93 g (0.0320 mol) of tributylamine, and 25 mL of toluene was held at reflux for 3 h, cooled, and diluted with 50 mL of toluene. The toluene solution was washed twice with 50 mL of water and concentrated in vacuo. The residue (12.7 g) was distilled at 1 Torr to give 0.83 g of tributylamine in the first fraction (50–80 °C) and 10.38 g (90%) of 96% (GC area %) pure **8t** in the second fraction.

(d) Reaction of 5t and 6t with Triethylamine. A mixture of 11.8 g (0.0252 mol) of 83% pure (by calibrated ^{19}F NMR) mixture of **5t** and **6t** and 3.34 g (0.033 mol) of triethylamine was heated at 120 °C for 15 min. ^{19}F NMR indicated that the reaction was complete. The reaction mixture was cooled and diluted with toluene. The toluene solution was washed successively with 30 mL of water, 30 mL of 3 N HCl, 30 mL of brine, and 30 mL of saturated $NaHCO_3$, dried, and concentrated to give 8.14 g (66%) of 75.8% pure (GC area %) **8t**.

Reaction of 5t with DBU at Room Temperature. A mixture of 0.36 g (10 mmol) of **5t**, 0.15 g (10 mmol) of DBU, and 3 mL of toluene was stirred for 20 h. ^{19}F NMR showed no reaction.

Comparison of the Rates of Reaction of 5t with DBU and with Tributylamine in Refluxing Benzene-d_6. The reaction was carried out by refluxing a mixture of 10 mmol of **5t**, 10 mmol of the base, and 6 g of benzene-d_6, and monitored by ^{19}F and ^{1}H NMR spectroscopy.

(a) Reaction of 5t with DBU. The reaction was found to be 57% and 70% complete in 30 and 50 min, respectively, giving **8t** as the major product. After 2 h and 50 min, the reaction was 88% complete, and the product consisted of 7% of **9**, 11% of **10**, and 82% of **8t**. After 29 h the reaction was 100% complete, giving 13% of **9**, 26% of **10**, and 61% of **8t**. The ^{19}F NMR signals for **9** and **10** were identified by spiking with authentic samples with **9** absorbing at δ −64.33 (s) and −115.20 (d), **10** absorbing at δ −64.46 (s) and −116.67 (d), and **8t** absorbing at δ −65.20 (s), and −116.20 (d).

(b) Reaction of 5t with Tributylamine. The reaction was only 13% complete in 1 h. After 24 h the reaction was 100% complete giving 7% of **9**, 12% of **10**, and 80% of **8t**.

Reaction of 5t with 1 Equiv of Pyridine in Refluxing Toluene. A mixture of 3.890 g (0.01 mol) of **5t**, 0.8 g (0.01 mol) of pyridine, and 10 mL of toluene was held at reflux for 40 min. ^{19}F NMR showed a 17% reaction with **16t** as the only detectable product. After 4 h and 20 min, the reaction was 73% complete with **16t**, accounting for 94% of the product. After 19 h, the reaction was 83% complete, giving a 1:1 mixture of **16t** and **8t** as the products.

Heating 5t in Refluxing Xylene. A mixture of 0.87 g of **5t** and 3.28 g of xylene was held at reflux under nitrogen for 24 h and concentrated. GC–MS and ^{1}H NMR analyses showed that the product was a mixture of **5t** and **6t**.

Dimethyl 2-(Difluoromethyl)-6-ethyl-4-propyl-3,5-pyridinedicarboxylate (8u). A mixture of 6.7 g (0.019 mol) of **5u** and **6u**, 3.0 g (0.019 mol) of DBU, and 35 mL of diglyme was heated and held at 130 °C for 5 h. To the cool reaction mixture was added 5.6 g (0.04 mol) of methyl iodide and 3.3 g (0.04 mol) of Na_2CO_3, and the mixture was stirred for 18 h at ambient temperature. The reaction mixture was poured into 300 mL of 3% hydrochloric acid, and the product was extracted with ether (4 × 50 mL). The combined extracts were washed with 100 mL of 1% sodium chloride, dried, and concentrated. The residue was dissolved in 5 mL of methanol, and 15 mL of 20% sodium methoxide was added. The reaction mixture was stirred for 48 h at room temperature and poured into 250 mL of 2% hydrochloric acid, and the product was extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were washed with 100 mL of 2%

sodium chloride, dried, and concentrated. Kugelrohr distillation afforded 0.60 g (10%) of a water-white liquid: bp 135–145 °C (0.2 Torr); n^{25}_D 1.4772; ^{1}H NMR δ 6.70 (t, J = 54, 1 H), 3.97 (s, 6 H), 2.5–3.0 (m, 4 H), 1.3–1.8 (m, 5 H), 0.9 (t, J = 7, 3 H); ^{19}F NMR δ −115.18 (d, J = 54). Anal. Calcd for $C_{15}H_{19}F_2NO_4$: C, 57.14; H, 6.07; N, 4.44. Found: C, 57.48; H, 6.21; N, 4.46.

Dimethyl 2-(Difluoromethyl)-6-methyl-4-isobutyl-3,5-pyridinedicarboxylate (8v). A stirred mixture of 27 g (0.06 mol) of crude **5v** and **6v**, 18 g (0.12 mol) of DBU, and 120 mL of diglyme was heated to 120 °C for 3 h and then at 150 °C for 6 h. After cooling to room temperature, 17.0 g (0.12 mol) of methyl iodide was added. The mixture was stirred for 2 h and poured into 1 L of 2% hydrochloric acid/1% sodium chloride, and the product was extracted with ether (250 mL, then 100 mL twice). The combined extracts were washed with 400 mL of 1% hydrochloric acid/1% sodium chloride, dried, and concentrated. Purification by silica gel HPLC (4% ethyl acetate in cyclohexane) followed by Kugelrohr distilolation afforded 4.94 g (25%) of a light yellow liquid: bp 105–115 °C (0.15 Torr); n^{25}_D 1.4795; ^{1}H NMR δ 6.67 (t, J = 54, 1 H), 3.96 (s, 6 H), 2.63 and 2.55 (a d overlapped with a s, total 5 H), 2.63 (m, 1 H), 0.87 (d, J = 7, 6 H); ^{19}F NMR: δ −116.03 (d, J = 54, CF_2H). Anal. Calcd for $C_{15}H_{19}F_2NO_4$: C, 57.14; H, 6.07; N, 4.44. Found: C, 56.98; H, 6.05; N, 4.44.

Dimethyl 2-(Difluoromethyl)-6-ethyl-4-isobutyl-3,5-pyridinedicarboxylate (8w). A mixture of 22.6 g (0.062 mol) of crude **5w** and **6w**, 9.5 g (0.062 mol) of DBU, and 50 mL of diglyme was heated to and held at 130–140 °C for 8 h. The cooled reaction mixture was poured into 1 L of 0.5% sodium bicarbonate and extracted with CH_2Cl_2 (1 × 200 mL, 2 × 100 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether (3 × 150 mL). The combined ether extracts were dried and concentrated. The residue was dissolved in 35 mL of DMF, and 2.7 g (0.02 mol) of K_2CO_3 and 4.2 g (9.93 mol) of methyl iodide were added. The reaction mixture was stirred for 3 days at room temperature and then poured into 300 mL of 3% hydrochloric acid. The product was extracted with CH_2Cl_2 (1 × 100 mL, 2 × 50 mL). The combined extracts were washed with 200 mL of 0.5% hydrochloric acid/1% sodium chloride, dried, and concentrated. To the residue was added 15 mL of 25% sodium methoxide in methanol, and the resulting solution was stirred for 5 days at room temperature. The solution was poured into 250 mL of 4% hydrochloric acid, and the product was extracted with CH_2Cl_2 (1 × 100 mL, 2 × 50 mL). The combined extracts were washed with 150 mL o f 1% sodium chloride, dried, and concentrated. Purification by silica gel HPLC and Kugelrohr distillation yielded 1.02 g (5%) of a light yellow liquid: bp 150–160 °C (0.5 Torr); n^{25}_D 1.4772; ^{1}H NMR δ 6.67 (t, J = 54, 1 H), 4.17 (s, 6 H), 2.7–3.4 (m, 4 H), 1.6–2.2 (m, 1 H), 1.37 (t, J = 7, 3 H), 0.9 (d, J = 7, 6 H); ^{19}F NMR δ −115.56 (d, J = 54). Anal. Calcd for $C_{16}H_{21}F_2NO_4$: C, 58.35; H, 6.43; N, 4.25. Found: C, 58.51; H, 6.47; N, 4.24.

Diethyl 2-(Difluoromethyl)-4,6-dimethyl-3,5-pyridinedicarboxylate (8x). A mixture of 4.85 g (0.015 mol) of **5x** and **6x**, 2.3 g (0.015 mol) of DBU, and 34 mL of diglyme was heated at 110–120 °C for 18 h. The cooled reaction mixture was poured into 400 mL of 1% hydrochloric acid, and the product was extracted with ether (4 × 100 mL). The combined ether extracts were washed with 200 mL of 1% hydrochloric acid, dried, and concentrated. Purification by silica gel HPLC using 5% ethyl acetate in cyclohexane as the eluent, and then by radially accelerated silica gel chromatography using 2% 2-propanol in cyclohexane as the eluent followed by Kugelrohr distillation, afforded 0.88 g (19%) of a light yellow oil: bp 120–130 °C (0.015 Torr); n^{25}_D 1.4752; ^{1}H NMR δ 6.70 (t, J = 54, 1 H), 4.43 (q, J = 7, 4 H), 2.53 (s, 3 H), 2.33 (s, 3 H), 1.40 (t, J = 7, 6 H); ^{19}F NMR δ −115.39 (d, J = 54 Hz, CF_2H). Anal. Calcd for $C_{14}H_{17}F_2NO_4$: C, 55.81; H, 5.69; N, 4.65. Found: C, 55.42; H, 5.64; N, 4.62.

Diethyl 2-(Difluoromethyl)-4,6-bis(trifluoromethyl)-3,5-pyridinecarboxylate (8y) and Diethyl 4-(Difluoromethyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylate (11). A stirred mixture of 15.0 g (0.035 mol) of **5y**, 4.1 g (0.038 mol) of 2,6-lutidine, 1.0 g (0.0065 mol) of DBU, and 75 mL of diglyme was heated to 110–120 °C for 45 min. The cooled mixture was poured into 500 mL of 1% hydrochloric acid, and the product was extracted with ether (150 mL and then 75 mL three times). The combined extracts were washed with 200 mL of 0.5% hydrochloric acid, dried, and concentrated. Separation of the two products was accomplished by silica gel HPLC (using 2% ethyl acetate in cyclohexane as eluent). The first component to elute was Kugelrohr distilled to give 1.82 g (12%) of **8y** as a water white oil: bp 95–105 °C (0.15 Torr); n^{25}_D 1.4191; ^{1}H NMR δ 6.83 (t, J = 54, 1 H), 4.46 (q, J = 7, 4 H), 1.36 (t, J = 7, 6 H); ^{19}F NMR δ −57.36 (s, 3 F), −64.14 (s, 3 F), −115.34 (d, J = 54, 2 F). Anal. Calcd for $C_{14}H_{11}F_8NO_4$: C, 41.09; H, 2.71; N, 3.42. Found: C, 41.08; H, 2.74; N, 3.42.

The second component to elute crystallized on evaporation of solvent to give 9.4 g of **11** as a white solid. Recrystallization of 3.0 g of this solid afforded 2.14 g (46%) of a white solid: mp 50.5–52.5 °C; ^{1}H NMR δ 6.93 (t, J = 54, 1 H), 4.50 (q, J = 7, 4 H), 1.4 (t, J = 7, 6 H); ^{19}F NMR δ −64.23 (s, 6 F), −113.30 (d, J = 54, 2 F). Anal. Calcd for $C_{14}H_{11}F_8NO_4$: C, 41.09; H, 2.71; N, 3.42. Found: C, 41.08; H, 2.74; N, 3.42.

Dimethyl 2,6-Bis(trifluoromethyl)-1,2-dihydro-4-isobutyl-3,5-pyridinedicarboxylate (16t). A mixture of 77.8 g (0.2 mol) of **5t** and 115 g of pyridine was held at reflux for 40 min, cooled, diluted with 400 mL of toluene, and poured into 1 L of ice water containing 150 mL of concentrated hydrochloric acid. The toluene layer was separated. The aqueous layer was extracted with 400 mL of toluene. The combined toluene extracts were washed with 500 mL of brine, dried, and concentrated in vacuo to give 80 g of a residue. The residue was purified by HPLC (ethyl acetate) to give 70 g of a syrup, which was further purified by HPLC (cyclohexane–ethyl acetate, 11:1) to give 13.4 g of a first fraction and 40.3 g of a second fraction. The column was eluted with ethyl acetate to give 8.1 g of a third fraction. The second fraction was crystallized from petroleum ether to give 31.6 g (40.6%) of **16t**, mp 75–77.5 °C. The mother liquor was concentrated, and the residue was further purified by HPLC (cyclohexane–ethyl acetate, 10:1) to give 6.2 g of fraction A and 0.9 g of fraction B. Fraction A was crystallized from petroleum ether to give an additionalo 3.5 g (8%) of **16t**; ^{1}H NMR (360 MHz) δ 5.59 (d, exchangeable with D_2O, 1 H, NH), 5.53 (dq, J = 8, J_{HF} = 8, 1 H, CF_3CH), 3.36 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 2.96 and 2.82 (d AB q, J = 8, J_{AB} = 29, 2 H, CH_2), 1.81 (m, 1 H, CH), 0.90 (d, J = 7, 3 H, CH_3), 0.82 (d, J = 7, 3 H, CH_3); ^{19}F NMR δ −66.79 (s, 3 F), −80.03 (d, J = 8, 3 F); ^{13}C NMR (90 MHz) δ 166.40, 166.10, 150.30, 136.39 (q, $^2J_{CF}$ = 34.4), 124.37 (q, $^1J_{CF}$ = 288), 120.26 (q, $^1J_{CF}$ = 275.7), 109.29, 106.48, 52.59, (q, $^2J_{CF}$ = 32), 52.49, 51.97, 36.67, 29.81, 22.09, 22.02. Anal. Calcd for $C_{15}H_{17}F_6NO_4$: C, 46.28; H, 4.40: N, 3.60. Found: C, 46.25; H, 4.41; N, 3.60.

Comparison of the Rates of Reaction of 16t with DBU and with Tributylamine. The reaction was carried out by stirring a mixture of 1 mmol of **16t**, 1 mmol of the base, and 3 mL of toluene for a period of 24 h, and monitoring by ^{19}F NMR spectroscopy.

(a) Reaction with DBU. ^{19}F NMR indicated that the reaction was 90% and 95% complete in 2 and 4 h, respectively.

(b) Reaction with Tributylamine. ^{19}F NMR indicated that the reaction was 8% and 40% complete in 4 and 24 h, respectively.

Reaction of 16t with Pyridine at Room Temperature. A solution of 0.77 g (2 mmol) of **16t** and 0.18 g (2.2 mmol) of pyridine in 6 mL of toluene was stirred for 64 h. GC–MS of an aliquot showed only **16t**.

Registry No. **5a**, 54770-47-7; **5b**, 54770-48-8; **5c**, 54770-49-9; **5d**, 97898-75-4; **5e**, 97898-25-4; **5f**, 125541-43-7; **5g**, 97898-76-5; **5h**, 97898-77-6; **5i**, 97898-19-6; **5j**, 125541-44-8; **5k**, 97898-21-0; **5l**, 125541-45-9; **5m**, 54770-50-2; **5n**, 54770-53-5; **5o**, 97898-80-1; **5p**, 97918-88-2; **5q**, 97898-14-1; **5r**, 97898-12-9; **5s**, 97898-73-2; **5t**, 97898-70-9; **5u**, 125541-46-0; **5v**, 98849-25-3; **5w**, 125541-47-1; **5x**, 98849-26-4; **5y**, 98849-24-2; **6i**, 125541-48-2; **6j**, 125541-49-3; **6k**, 97898-22-1; **6l**, 97898-79-8; **6o**, 97898-09-4; **6p**, 98836-09-0; **6q**, 97898-15-2; **6r**, 97898-13-0; **6s**, 125541-50-6; **6t**, 97898-71-0; **6u**, 125541-51-7; **6v**, 125567-53-5; **6w**, 125541-52-8; **6x**, 125541-53-9; **8a**, 97887-81-5; **8b**, 97887-75-7; **8c**, 97887-76-8; **8d**, 97887-78-0; **8e**, 97887-80-4; **8f**, 97897-76-2; **8g**, 97887-83-7; **8h**, 97887-79-1; **8i**, 97887-89-3; **8j**, 125541-54-0; **8k**, 97898-83-4; **8l**, 97887-84-8; **8m**, 125541-55-1; **8n**, 97886-25-4; **8o**, 97887-87-1; **8p**, 97887-82-6; **8q**, 97887-86-0; **8r**, 97887-88-2; **8s**, 97918-85-9; **8t**, 97887-77-9; **8u**, 125541-56-2; **8v**, 97887-36-0; **8w**, 125541-57-3; **8x**, 97887-13-3; **8y**, 97887-37-1; **9**, 125541-58-4; **10**, 97887-92-8; **11**, 97897-62-6; **16t**, 98849-17-3.