Derivation of Fluorine-Containing Pyridinedicarboxylates. III Regio-selective Anion Chemistry at the 2- and 4-Position [1]

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In contrast of Part II of the series, 4-alkyl-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylates, **1**, were reacted with various strength bases to effect regio-selective reaction of electrophiles at either the benzylic carbanion of the 4-position, or at the 2-(difluoromethyl)carbanion. Weaker bases up to and including potassium butoxide or lithium bis(trimethylsilylamide) effected reaction of **1** at the 4-position to produce **2** and **3** by Stobbe-type condensations of aldehydes and ketones. In similar manner carbon disulfide, carbon dioxide, alkyl halides, silyl halides, and hexachloroethane produced the highly functionalized derivatives **4-10**. In contrast, use of lithium diisopropylamide and like bases selectively effected carbanion formation at the 2-position to form, with the cited electrophiles and others, substitution products **11**. The latter were further derived to the highly functional materials, **12-19**.

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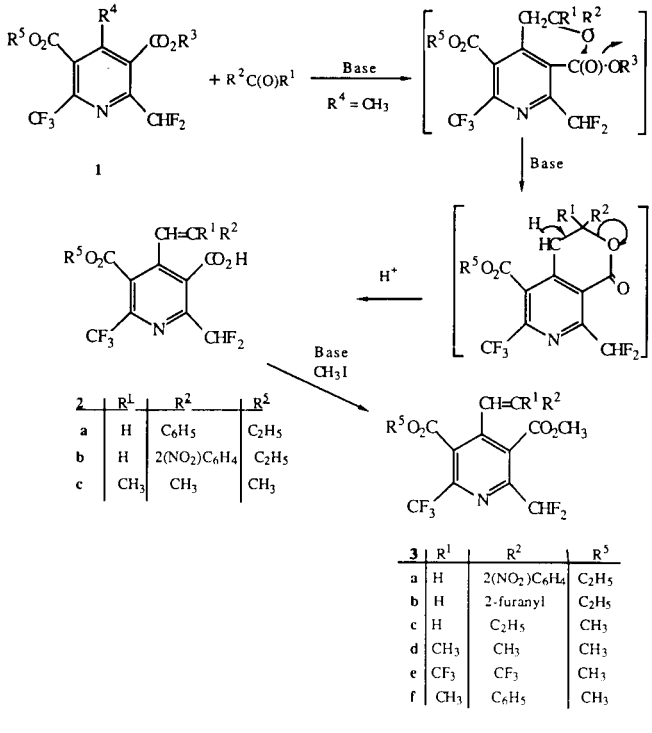
In Part II [1], elaboration of certain fluorine-containing pyridine-3,5-dicarboxylates were described. In this part we wish to report studies wherein derivation takes place *via* intermediary anion generation. Action of weaker bases such as sodium carbonate, potassium *t*-butoxide or even lithium bis(trimethylsilyl)amide in tetrahydrofuran generally caused deprotonation at the 4-alkyl group, and these carbanions in turn reacted at that position with a number of electrophiles. Scheme 1 summarizes the results of aldehyde and ketone interaction with pyridine carboxylates **1**. The reactions went quite well, although attended in every case by saponification to form **2**. This is due to anchimeric assistance from the more labile 3-(rather than 5-) carboxyl group [1,2], as shown in Scheme 1. It is also quite reminescent of the Stobbe condensation of aldehydes with succinates, wherein the alkylidene half-acid esters are formed [3]. Alkylation restores the material to the diesters **3**. Scheme 2 reveals additional electrophiles in reaction at the 4-position of **1**. An improved yield of acid **5a** over that reported in Part II [1] is obtained by simple carboxylation. This is effective for higher 4-alkyl homologs as well, as exemplified by formation of **5b-d**. This material in turn was converted to various acid derivatives **6** and **7**. It would be expected that these acids would be susceptible to decarboxylation, due to the high electron deficient pyridine ring system under study here; in fact **5b** was found to spontaneously decarboxylate in acetone solutions on aging.

Scheme 1



2	R^1	R^2	R^5
a	H	C_6H_5	C_2H_5
b	H	$2(NO_2)C_6H_4$	C_2H_5
c	CH_3	CH_3	CH_3

3	R^1	R^2	R^5
a	H	$2(NO_2)C_6H_4$	C_2H_5
b	H	2-furanyl	C_2H_5
c	H	C_2H_5	CH_3
d	CH_3	CH_3	CH_3
e	CF_3	CF_3	CH_3
f	CH_3	C_6H_5	CH_3

Structure proofs of these new compounds, as compiled in Table 1, were easily garnered by an examination of their spectral properties and micro-analyses. In certain instances the differences between starting material and product could be quite illuminating. Thus comparing the acid **5b** and methylation product **8c** with starting **1**, the prochiral groups [$(CH_3)_2CH$ and CHF_2], can each show as *pairs* of doublets in the products because of the asymmetric center introduced into these materials at the 4-position, in contrast with **1c** (R′ = isopropyl), where no such asymmetry exists. However, such prochirality is also dependent to a degree on steric crowding, since materials such as **5d**, **7d**, **7f** while having pairs of doublets for the R′ = isopropyl group, retains only a single doublet for the potentially prochiral difluoromethyl group.

Literature references [4] would indicate that the difluoromethyl group should be somewhat susceptible to base attack, deprotonation, and carbanion formation. However, because of fluorine's dual nature in both stabilizing and destabilizing geminal carbanions by induc-

Table 1

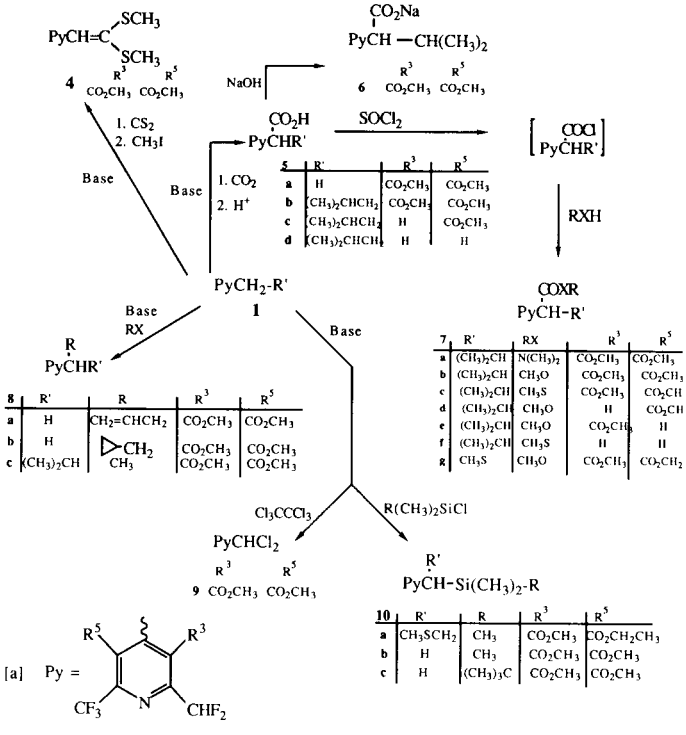
Elaboration of **1** at the 4-Position

Material [a]	Physical Constants mp°, [bp° (mm)] [d], {$n^{25}D$}	Yield [b] %	Pertinent Spectral Data [c] δ^1H (multiplicity, No. H, type H)	$\delta^{19}F$ (multiplicity, type)
2 a	184-187	63	6.9 (m, 2H, =CH), 10.6 (broad s, 1H, OH)	(s, CF_3), (d, CHF_2)
b	155-157	67	8.2 (AB q, 2H, =CH), 9.5 (broad s, 1H, OH)	(s, CF_3), (d, CHF_2)
c	100-101	38	1.6, 1.98 (2 broad s, remotely coupled to H, 6H, $=CCH_3$), 6.2 (m, 1H, =CH)	–65 (s, CF_3), –115 (broad, CHF_2, J = 56 Hz, CHF_2)
3 a	139-140	98	3.8 (s, 3H, OCH_3)	(s, CF_3), (d, CHF_2)
b	91-92	98	3.8 (s, 3H, OCH_3)	
c	[120-130 (1.0)], {1.4606}	25	1.1 (t, 3H, CH_2CH_3), 6.3 (m, 2H, =CH)	–65 (s, CF_3), –115 (d, J = 56 Hz, CHF_2)
d [e]	38-40, [130-140 (1.2)] {1.4514}	85	1.5, 1.9 (2bs, 6H, $=CCH_3$), 6.0 (m, 1H, =CH)	–65 (s, CF_3), –116 (d, J = 56 Hz, CHF_2)
e	[105-115 (1.4)], {1.4088}	14	3.85 (s, 6H, OCH_3), 7.6 (m, 1H, =CH)	–60 (q, J = 7 Hz, CF_3CCF_3), –65 (q, J = 7 Hz, CF_3CCF_3)
f	[155-165 (1.0)], {1.5093}	54	1.90 (s, 3H, $=CCH_3$), 6.6 (m, 1H, =CH)	–65 (s, CF_3), –116 (d, CHF_2)
4 [e]	[160-175 (1.5)], {1.5139}	46	2.2,2.3 (2s, 6H, SCH_3), 6.3 (s, =CH)	–67 (s, CF_3), –118 (d, CHF_2)
5 a	156-157	65	3.8 (s, 2H, CH_2CO)	(s, CF_3), (d, CHF_2)
b	88-89	88	0.7, 1.0 (2d, 6H, prochiral $(CH_3)_2CH$), 3.5 (1H, CHCO), 9.8 (bs, 1H, OH)	(s, CF_3), (2d, prochiral CHF_2)
c	122-124	31	0.65, 1.1 (2d, 6H, prochiral $(CH_3)_2CH$), 3.25 (d, 1H, CH_2CO), 10 (s, 1H, OH)	(s, CF_3), (2d, CHF_2)
d	83-85	13	0.65, 1.05 (2d, 6H, prochiral $(CH_3)_2CH$), 3.25 (d, 1H, CH_2CO), 8.6 (s, 1H, OH)	(s, CF_3), (d, CHF_2)
6	147-149	85	*ca* 0.5, 1.0 (2d, 6H, $(CH_3)_2CH$)	(s, CF_3), (2d, prochiral CHF_2)
7 a	[125-175 (1.5)]	38	0.6, 1.1 (2d, 6H, prochiral $(CH_3)_2CH$), 2.8 (d, 6H, $N(CH_3)_2$)	(s, CF_3), (2d, prochiral CHF_2)
b	[120-150 (1.5)]	62	0.6, 1.1 (2d, 6H, prochiral $(CH_3)_2CH$), 3.6 (s, 3H, OCH_3)	(s, CF_3), (2d, prochiral CHF_2)
c	[140-175 (1.5)] {1.4812}	28	0.6, 1.0 (2d, 6H, prochiral $(CH_3)_2CH$), 2.2 (s, 3H, SCH_3)	(s, CF_3), (2d, prochiral CHF_2)
d	62-66, [120-130 (1.2)]	88	0.7, 1.0 (2d, 6H, prochiral $(CH_3)_2CH$), 3.3 (d, 1H, CHCO)	(s, CF_3), (d, CHF_2)
e	[115-125 (1.5)], {1.4454}	28	0.7, 1.0 (2d, 6H, prochiral $(CH_3)_2CH$), 3.4 (d, 1H, CHCO)	(s, CF_3), (d, CHF_2)
f [e]	39.5-42, [120-140 (1.8)]	85	0.75, 1.1 (2d, 6H, prochiral $(CH_3)_2CH$), 2.2 (s, 3H, SCH_3)	(s, CF_3), (d, CHF_2)
g	79.5-81, [160-170 (1)] {1.4829}	21	3.6 (s, 3H, OCH_3), 4.85 (s, 1H, SCHCO)	–64.1 (s, CF_3), –116 (s, CHF_2)
8 a	42-43	33	2.1-3.0 (m's, 4H, CH_2CH_2C=), 4.7-5.4 (m, 3H, =CH)	(s, CF_3), (d, CHF_2)
b	[120-170 (1)]	13	0.5, 1.5, 2.8 (3m's, 9H, *cyclohexylethyl*)	(s, CF_3), (d, CHF_2)
c	40-43		0.6, 0.9, 1.2 (3d, 9H, prochiral $(CH_3)_2CH$, achiral (CH_3)	(s, CF_3), (bd, prochiral CHF_2)
9 [e]	40-41	19	7.0 (s, 1H, $CHCl_2$)	(s, CF_3), (d, CHF_2)
10 a	[155-165 (1.6)] {1.4763}	7	0.05 (s, 9H, $Si(CH_3)_3$), and many ^1H and ^{19}F non-equivalent peaks due to restricted rotation	
b	[115-125 (1.2)] {1.4586}	65	–0.01 (s, 9H, $Si(CH_3)_3$), 2.33 (s, 2H, CH_2Si)	(s, CF_3), (d, CHF_2)
c	102-103, [145-155 (1.2)]	10	0.02 (s, 6H, $Si(CH_3)_2$), 1.0 (s, 9H, $C(CH_3)_2$), 2.8 (s, 2H, $SiCH_2$)	(s, CF_3), (d, CHF_2)

[a] See schemes 1 and 2 for definition. [b] Isolated, purified product based on immediate precursor. [c] Nmr in deuteriochloroform; generally, δ reported of those nuclei most affected by product formation. [d] Temperatures of kugelrohr oven. [e] Molecular weight confirmed by ms (m/e).

tive and resonance effects respectively, its relative reactivity versus alkyl substituents is largely, *a priori*, unpredictable. Presumably the weaker bases employed in Scheme 1 and 2 are not strong enough to deprotonate the 2-substituent, favoring instead the 4-alkyl substituent. In line with this reasoning, perhaps a stronger base system such as butyl lithium or lithium diisopropyl amid might deprotonate the 2-substituent, and if the latter were less stable (and consequently more reactive) than the 4-alkyl derived anion, react preferentially with electrophiles.

Scheme 2[a]



Initial results were not encouraging. Material **1** (R′ = isopropyl) with butyl lithium gave no evidence of promoting alkylation. Moreover, **1** (R′ = H) gave low yields of 4-ethyl product and much tar when contacted with lithium diisopropyl amid and methyl iodide. However when this base was used with **1** wherein R′ is alkyl, facile reaction occurred for the most part, nearly exclusively at the 2-substituent. These results are illustrated in Scheme 3. Yield figures (Table 2) are calculated from pure isolated product, and are not necessarily representative of yield if the latter would have been based on product assay from the crude reaction mixture. Workup generally involved treating the reaction mixture with dilute acid, either before or after vacuum treatment, to remove solvent. Methylene chloride was the usual extractive solvent, although ether was occasionally used. The crude was generally distilled *via* Kugelrohr prior to recrystallization of hplc treatment. Tar formation was variable, generally being lower with reactive nucleophiles such as methyl iodide, iodine, and carbon dioxide, and somewhat more with chloroformate and methyl disulfide.

Structure proof was fairly easy with but several exceptions. Thus, the elimination of the characteristic difluoromethyl triplet and doublet in the ^1H and ^{19}F nmr respectively, was proof of reaction at that moiety. For instance, with formation of **11a-c** the absorptions at the 2-position were typlified by a triplet and quartet, in the ^1H and ^{19}F nmr respectively. Substitution on the difluoromethyl group does not give rise to an asymmetric center and hence prochiral multiplets as is the case with 4-isobutyl derivation, except where the latter group was concommitantly modified as in bromination and chlorination to give **11g** and **11i** as minor products.

During preparation of the sulfide, **11i**, a second component was isolated, **12**. This latter material, by spectral analysis, did not seem to be present in the crude reaction mixture, but rather was apparently generated in small amounts by Kugelrohr distillation of the crude. Prolonged heating at 165-170° or distillation of **11j** did not produce **12**. Ir is revealing, showing three distinct carbonyl peaks consistent for COF, CO_2Me, and COSMe respectively. The ^{19}F nmr reveals the trifluoromethyl at *ca* δ -68 ppm and carbonyl fluoride at δ +55 ppm. A high field study of ^{13}C

Scheme 3[a]

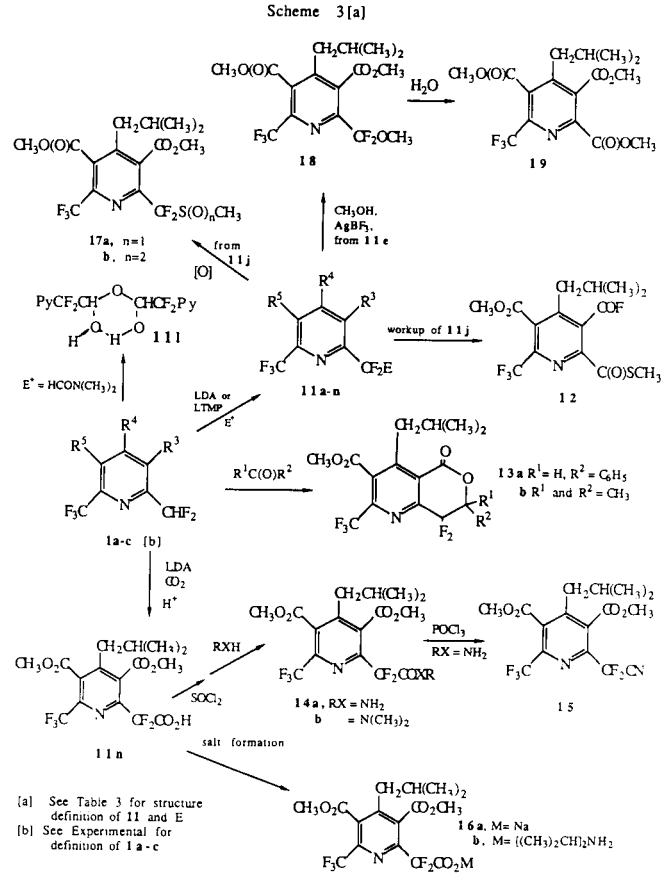


Table 2

Elaboration of **1** at the 2-Position

No.	Material [a] R^4	E	Physical Constants mp°, [bp(mm)] [d], {$n^{25}D$}	Yield [b] %	Reactant E with 1	ms as m/e (ir, cm^{-1})	Pertinent Specral Data [c] δ ^1H and/or ^{19}F (multiplicity, No. nuclei, type nuclei)
11a	C_2H_5 [e]	CH_3	[130-160 (2)], [1.4412]	26	CH_3I		2.0 (t, J = 19 Hz, 3H, CF_2CH_3), -89 (q, J = 19 Hz, CH_3CF_2)
11b	$(CH_3)_2CH$	CH_3	[100-120 (1.5)], {1.4465}	23	CH_3I		1.9 (t, J = 19 Hz, 3H, CF_2CH_3), -89 (q, J = 19 Hz, CH_3CF_2)
11c	$(CH_3)_2CHCH_2$	CH_3	67-68	68	CH_3I	384	2.0 (t, J = 19 Hz, 3H, CF_2CH_3), -89 (q, J = 19 Hz, CH_3CF_2)
11d	$(CH_3)_2CHCH_2$	CH_3OCH_2	[140-160 (1.5)], {1.4476}	30	CH_3OCH_2Br		4.07 (t, J = 19 Hz, 2H, CF_2CH_2O), -104 (t, J = 19 Hz, OCH_2CF_2)
11e	$(CH_3)_2CHCH_2$	I	73-74	40	I_2		-46 (s, CF_2I)
11f	$(CH_3)_2CHCH_2$	Br	75-76	22	BrCN	447	-50 (s, CF_2Br)
11g	$(CH_3)_2CHCHBr$	Br	-	5	BrCN	527	4.45 (d, 1H, CHBrCH$(CH_3)_2$), -50 (bs, prochiral CF_2Br)
11h	$(CH_3)_2CHCH_2$	Cl	81-81.5	6	N-chlorosuccinimide	403	-51 (s, CF_2Cl)
11i	$(CH_3)2CHCHCl$	Cl	[140-160 (1)]	30	CCl_3CCl_3	437	4.35 (d, 1H, CHClCH$(CH_3)_2$), -54 (d, prochiral CF_2Cl)
11j	$(CH_3)_2CHCH_2$	SCH_3	52-53	37	CH_3SSCH_3		2.38 (s, 3H, SCH_3), -75 (s, CF_2SCH_3)
11k	$(CH_3)_2CHCH_2$	CF_3CO	74-79.5	23	$CF_3CO_2C_2H_5$		-65 (s, 6-CF_3), -81 (t, J = 13 Hz, CF_3CO), -108 (q, J = 13 Hz, CF_2CO)
11l	$(CH_3)_2CHCH_2$	CHO	[140-180 (1.5)]	10	$(CH_3)_2NCHO$	397 (3240, OH) [f]	-65 (m's, CF_3), -80 to -120 (m's, CF_2CHO)
11m	$(CH_3)_2CHCH_2$	CO_2H	62-66	80	CO_2		10.4 (broad s, 1H, OH), -103 (s, CF_2CO_2H)
11n	$(CH_3)_2CHCH_2$	$(CH_3)_3Si$	[120-150 (1.5)], {1.4516}	63	$(CH_3)_3SiCl$	441	0.3 (s, 9H, $Si(CH_3)_3$), -110 (s, CF_2Si)
12			91-92.5	17		(1830, CO)	2.4 (s, 3H, SCH_3)
13a			175-176	19		443	5.45-5.75 (m, 1H, OC$H$$CF_2$), -114 and -116 (2d, prochiral CHF_2)
13b			120-124	46			1.55 (s 6H, $C(CH_3)_2$), -108 (s, $CF_2C(CH_3)_2$)
14a			124-128	19			6.95 (bs, 2H, NH_2), -103 (s, CF_2CO)
14b			[160-170 (1 mm)]	55			3.05 (s, 6H, $N(CH_3)_2$), -100 (bs, CF_2CO)
15			44-45, [130-160 (1)}]	48		(2270, CN)	-86 (s, CF_2CN)
16a			decompose	quant.			
16b			108-113 dec	41		(1730, CO)	0.7 (d, 6H (CH_3)$_2$CHCH$_2$), 1.2 (d 12H, CH(CH_3)$_2$), -101 (s, CF_2CO)
17a			62-63.5				2.8 (bs, 3H, CH_3SOCF_2), -104 (bd, prochiral CF_2SO)
17b			97-98				3.2 (J = 7 Hz, 3H,CH_3SOCF$_2$), -103 (q , J = 1 Hz, CF_2SOCH_3)
18			[120-140 (1.5)]	44		399	3.7 (s, 3H, CF2OCH_3), -74 (s, CF_2OCH_3)
19			120 (1)	27		377	4.0 (2 closely spaced s, 9H, CO_2CH_3); -65 (s, CF_3)

[a] See scheme 3 for added definition; R^3 and R^5 = CO_2CH_3 unless otherwise indicated. [b] Isolated, purified product based on immediate precursor. [c] Nmr in deuteriochloroform except metallic salts (in deuterium oxide); δ reported generally of those nuclei most affected by product formation. [d] Temperatures of kugelrohr oven. [e] R^3 and R^5 = $CO_2C_2H_5$. [f] see Discussion for more details.

Table 3

Micro-Analysis of Materials **2-19**

Material	Formula	Calcd./Found C	H	N	(X)
2a	$C_{19}H_{14}F_5NO_4$	54.95 54.69	3.40 3.43	3.37 3.33	
2b	$C_{19}H_{13}F_5N_2O_6$	49.58 49.40	2.85 2.83	6.09 5.99	
2c	$C_{14}H_{12}F_5NO_4$	50.38 50.00	2.98 3.16	3.46 3.35	
3a	$C_{20}H_{15}F_5N_2O_6$	50.64 50.89	3.19 3.10	5.91 5.98	
3b	$C_{18}H_{14}F_5NO_5$	51.56 51.46	3.37 3.32	3.34 3.30	
3c	$C_{15}H_{14}F_5NO_4$	49.05 49.08	3.84 3.85	3.81 3.79	
3d	$C_{15}H_{14}F_5NO_4$	49.05 49.15	3.84 3.91	3.81 3.76	
3e	$C_{15}H_8F_{11}NO_4$	37.91 38.31	1.70 1.71	2.95 3.01	
3f	$C_{20}H_{16}F_5NO_4$	55.95 56.09	3.76 3.83	3.26 3.27	
4	$C_{15}H_{14}F_5NO_4S_2$	41.76 42.14	3.27 3.36	3.25 3.23	(S) 14.86 14.56
5a	$C_{13}H_{10}F_5NO_6$	42.06 41.97	2.72 2.49	3.77 3.75	
5b	$C_{17}H_{18}F_5NO_4$	51.65 51.89	4.59 4.64	3.54 3.55	
5c	$C_{14}H_{14}F_5NO_4$	47.33 47.28	3.97 3.98	3.94 3.89	
5d	$C_{12}H_{12}F_5NO_2$	48.49 48.38	4.07 4.08	4.68 4.68	
6	$C_{16}H_{15}F_5NO_6$ (and 0.5 H_2O)	43.25 43.16	3.62 3.51	3.15 3.20	
7a	$C_{18}H_{21}F_5N_2O_5$	49.10 49.19	4.81 4.83	6.36 6.34	
7b	$C_{17}H_{18}F_5NO_6$	47.78 47.76	4.25 4.26	3.28 3.25	
7c	$C_{17}H_{18}F_5NO_5S$	46.06 46.20	4.09 4.10	3.16 3.13	
7d	$C_{15}H_{16}F_5NO_4$	48.79 48.61	4.37 4.32	3.79 3.77	
7e	$C_{15}H_{16}F_5NO_4$	48.79 48.86	4.37 4.36	3.79 3.80	
7f	$C_{13}H_{14}F_5NOS$	47.70 47.78	4.31 4.32	4.28 4.28	(S) 9.80 9.82
7g	$C_{16}H_{13}F_5NO_6S$	43.15 43.18	3.62 3.66	3.15 3.13	
8a	$C_{15}H_{14}F_5NO_4$	49.05 48.81	3.84 3.78	3.81 3.75	
8b	$C_{16}H_{16}F_5NO_4$	50.40 50.61	4.23 4.27	3.67 3.61	
8c	$C_{16}H_{18}F_5NO_4$	50.14 50.27	4.73 4.76	3.65 3.61	
9	$C_{12}H_8Cl_2F_5NO_4$	36.39 36.54	2.04 2.04	3.54 3.51	(Cl) 17.90 17.79
10a	$C_{17}H_{22}F_5NO_4SSi$	44.44 44.44	4.83 4.82	3.05 3.00	
10b	$C_{15}H_{18}F_5NO_4Si$	45.11 45.19	4.54 4.56	3.51 3.49	
10c	$C_{18}H_{24}F_5NO_4Si$	48.97 49.20	5.48 5.45	3.17 3.13	
11a	$C_{16}H_{18}F_5NO_4$	50.14 50.15	4.73 4.75	3.65 3.62	
11b	$C_{15}H_{16}F_5NO_4$	48.79 48.75	4.37 4.37	3.78 3.78	
11c	$C_{16}H_{18}F_5NO_4$	50.14 50.14	4.73 4.75	3.65 3.63	
11d	$C_{17}H_{20}F_5NO_5$	49.40 49.40	4.88 4.89	3.39 3.35	
11e	$C_{15}H_{15}F_5INO_4$	36.38 36.80	3.05 3.12	2.83 2.85	
11f	$C_{15}H_{15}BrF_5NO_4$	40.20 40.60	3.37 3.34	3.13 3.09	(Br) 17.83 17.73
11g	$C_{15}H_{14}Br_2F_5NO_4$	34.18 34.62	2.68 2.91	2.66 2.52	
11h	$C_{15}H_{15}ClF_5NO_4$	44.62 45.02	3.75 3.72	3.47 3.49	(Cl) 8.78 8.62
11i	$C_{15}H_{14}Cl_2F_2NO_4$	41.12 41.45	3.22 3.28	3.20 3.13	(Cl) 16.18 15.99
11j	$C_{16}H_{18}F_5NO_4S$	46.27 45.88	4.37 4.54	3.37 3.13	(S) 7.72 7.27
11k	$C_{17}H_{15}F_8NO_5$ (and 0.5 H_2O)	42.34 42.50	3.34 3.47	2.90 2.87	
11l	$C_{16}H_{16}F_5NO_5$ (and 0.5 H_2O)	47.30 47.42	4.22 4.25	3.45 3.54	
11m	$C_{16}H_{16}F_5NO_6$	46.50 46.71	3.90 4.04	3.39 3.34	
11n	$C_{18}H_{24}F_5NO_4$	48.98 49.02	5.48 5.48	3.17 3.15	

Material	Formula	Calcd./Found C	H	N	(X)
12	$C_{15}H_{15}F_4NO_4S$	47.24 47.27	3.96 4.02	3.67 3.48	(S) 8.44 8.14
13a	$C_{21}H_{18}F_5NO_4$	56.89 56.96	4.09 4.16	3.16 3.16	
13b	$C_{17}H_{18}F_5NO_4$	51.65 51.89	4.49 4.64	3.54 3.55	
14a	$C_{16}H_{17}F_5N_2O_5$	46.61 46.66	4.16 4.37		
14b	$C_{18}H_{21}F_5N_2O_5$	49.10 49.19	4.81 4.85	6.36 6.35	
15	$C_{16}H_{15}F_5N_2O_4$	48.74 48.75	3.83 3.86	7.10 7.10	
16a	$C_{16}H_{15}F_5NO_6$ (and 0.4 H2O)	43.43 43.63	3.60 3.67	3.17 3.19	
16b	$C_{22}H_{31}F_5N_2O_6$	51.36 51.65	6.07 6.11	5.44 5.46	
17a	$C_{16}H_{18}F_5NO_5S$	44.55 44.45	4.21 4.21	3.25 3.25	(S) 7.43 7.52
17b	$C_{16}H_{18}F_5NO_6S$	42.96 43.04	4.06 4.08	3.13 3.11	(S) 7.17 7.22
18	$C_{16}H_{18}F_5NO_5$	48.13 48.30	4.54 4.55	3.51 3.48	
19	$C_{16}H_{18}F_3NO_6$	50.93 51.02	4.81 4.84	3.71 3.58	

coupling with ^{19}F and ^{1}H reveals that the ring sp^2 carbon connected to the carbonyl fluoride group, coupled as a doublet to fluorine, is in turn coupled through three bonds to the isobutyl*methyl* protons to form a pair of triplets. On this basis the acid fluoride moiety is assigned with attachment to C-3, rather than C-2 pyridine carbon.

Dimethylformamide was used in its well known capacity to introduce a formyl moiety by electrophilic reaction with carbanions. The kugelrohr distilled material gave a consistent analysis for monomeric aldehyde by glc/ms and glc/ir, but at room temperature the ^{1}H nmr was not consistent for monomeric aldehyde, showing only a tiny triplet for CF_2CHO at δ 9.81, with other multiplets at 5.1, 5.5 and 5.92. The methoxy and isobutyl absorptions were also complex. Moreover there was an obvious O-H stretching frequency in the room temperature ir including water at 3500 cm^{-1} and 1650 cm^{-1} but no high frequency aldehyde carbonyl. Micro-analysis of **11l** contained 0.5 water. The above data are consistent for a dimer-hemihydrate at room temperature (see Scheme 3).

EXPERIMENTAL

All melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The ^{1}H and ^{19}F nmr spectra were recorded on a Varian EM-360-L(60 MHz), XL300 (300 MHz), or XL400(400 MHz) with instruments referenced to tetramethylsilane and fluorotrichloromethane respectively. Exact ^{19}F chemical shifts were not always recorded, although they were usually in the regions found for CF_3 (-65 ppm) and CHF_2 (-115 ppm). Emphasis rather was given to number and type of multiplicity to confirm sample identity and purity. Mass spectra were measured by a Varian CH7 mass spectrometer with *ei* or isobutane chemical ionization (*ci*) expressed as molecular weight (m/e). Liquid chromatography purification was achieved on a Waters Prep LC, model 500A, with refractive index detector (hplc), or by Chromatotron (rotary tlc). Prior to use of one of these two methods, the reaction mixtures were developed on silica tlc plates. The solvent concentration of ethyl acetate in cyclohexane necessary to give Rf values between 0.05-0.2 (usually 0.5-10%) would then be used to effect macro-separation. Unless otherwise noted, bp's are recorded as oven temperatures during bulb-to-bulb (Kugelrohr) distillations. All microanalyses were preformed by Atlantic Microlab Inc., Atlanta, Georgia 30366.

The preparation of materials **1a-c** by Hantzsch sequences from the corresponding trifluoroacetoacetic esters and aldehyde are detailed in reference [2]. Their structures are defined in preparations for **2b**, **2c**, and **5b** respectively.

Since the chemistry, yield, physical constants, pertinent spectra and micro-analysis are reported elsewhere in this paper for each of the materials **2-19**, the following procedures describing certain preparations will serve as typical, or as required in certain cases, atypical examples.

5-(Carboethoxy)-2-(difluoromethyl)-6-(trifluoromethyl)-4-[2-(2-nitrophenyl)vinyl]-3-pyridinecarboxylic Acid (**2b**).

Material **1a** [defined as diethyl 2-(difluoromethyl)-6-(trifluoromethyl)-4-methyl-3,5-pyridinedicarboxylate], 3 g (8.6 mmoles) was dissolved in 30 ml methanol containing 1.5 g potassium carbonate and 0.9 g (6.0 mmoles) *o*-nitrobenzaldehyde. The mixture was stirred for 24 hours at room temperature, then poured into water to give a cloudy suspension. This mixture in turn was extracted with ether twice, then the aqueous layer acidified with hydrochloric acid to give solid, which was filtered off, washed on the filter with water, then air dried. Recrystallization from isopropanol gave 2.7 g.

5-(Carbomethoxy)-2-(difluoromethyl)-4-(2-methyl-1-propenyl)-6-(trifluoromethyl)-3-pyridinecarboxylic acid (**2c**).

Material **1b** [defined as dimethyl 2-(difluoromethyl)-4-methyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate], (4.0 g, 0.012 mole), was dissolved in 80 ml of anhydrous tetrahydrofuran in a dry flask under nitrogen, cooled to -30°, and 1.68 g (0.015 mole) of potassium t-butoxide added. The mixture was held at -20° for 30 minutes, and then 2 ml (0.03 mole) of acetone added. The reaction mixture was allowed to warm slowly to room temperature, acidified with 3 ml of acetic acid, followed by vacuum removal of volatiles. The residue was taken up in a mixture of 200 ml of 2% sodium bicarbonate solution and 150 ml of ether. The ether phase was extracted again with a second portion of sodium bicarbonate solution. The combined bicarbonate extracts were acidified with excess concentrated hydrochloric acid, then extracted several times with 100 ml portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered and evaporated. Half of the residue was recrystallized from methylene chloride/methylcyclohexane to give 0.81 g of white solid.

5-Ethyl 3-Methyl 2-(Difluoromethyl)-4-[2-(2-nitrophenyl)ethenyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**3b**).

Material **2b** (2.5 g, 7.0 mmoles) was mixed with 2 g of potassium carbonate in 20 ml of dimethylformamide and 3 g of methyl iodide. This mixture was stirred overnight, then poured into water to give a white solid which was filtered, washed on the filter with water, then air dried to give 2.5 g. Recrystallization could be effected from 2-propanol.

Dimethyl 2-(Difluoromethyl)-4-(2-phenyl-1-propenyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (*E*/*Z* stereochemistry indeterminate) (**3f**).

To a solution of 6.0 g (0.018 mole) of **1b** in 75 ml of anhydrous tetrahydrofuran in a dry flask under nitrogen at -20° was added 2.5 g (0.022 mole) of potassium *t*-butoxide. The reaction mixture was held at -20° for 0.5 hour, then 5.2 g (0.043 mole) acetophenone was added, therafter allowing the reaction mixture to warm to ambient temperature. The mixture was acidified with 4 ml of acetic acid, then the mixture vacuum treated to remove solvent. The residue was taken up in ether and extracted 2x with dilute sodium bicarbonate. The combined aqueous extracts were washed with ether, then acidified with concentrated hydrochloric acid, followed by ether extraction. After drying over magnesium sulfate, the ether solvent was removed and the residue dissolved in 100 ml dimethylformamide with 5.6 g (0.04 mole) methyl iodide and 3.3 g (0.04 mole) sodium bicarbonate added. The mixture was stirred for 18 hours then poured into dilute hydrochloric acid. The product was extracted with methylene chloride, and after solvent removal, purified by hplc (3% ethyl acetate in cyclohexane). Kugelrohr distillation of the product fractions afforded 4.2 g water white oil.

Dimethyl 2-(Difluoromethyl)-4-[2,2-bis(methylthio)ethenyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**4**).

Material **1b**, (3.27 g, 0.01 mole) was dissolved in 50 ml of tetrahydrofuran and 2.0 g of carbon disulfide added. The whole was cooled to -30° and 20 ml of 1*M* lithium bis(trimethylsilyl)amide in tetrahydrofuran was added dropwise. The temperature was then permitted to reach -20° when 0.025 mole methyl iodide was added, then allowed to warm to ambient temperature followed by 0.5 hour at reflux. After cooling and standing overnight, the solvent was vacuum evaporated, and the residue was taken up in ether, washed twice with water, then dried over magnesium sulfate. After solvent removal, 2.6 g residue remained; this was kugelrohr distilled at 160-174° (1.5 mm Hg) to give 2.0 g yellow oil.

Dimethyl 4-(Carboxylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**5a**).

Material **1b** (3.27 g, 0.01 mole) was dissolved in dry tetrahydrofuran, cooled to *ca* -35° and 0.01 mole of potassium *t*-butoxide dissolved in tetrahydrofuran was added at that temperature. The solution became dark. Dryice (3.0 g) was added, and the mixture allowed to stir at that temperature. The color lightened, and precipitate formed. The material was then allowed to warm to ambient temperature, then poured into an ice and water mixture. Solid was filtered off (0.4 g, unchanged starting material), and the filtrate acidified with hydrochloric acid. The resulting insoluble product was filtered, washed on the filter, then air dried to give 2.4 g of pure product.

Dimethyl 4-(1-Carboxy-2-methylpropyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**5b**).

Dry tetrahydrofuran (100 ml) and 25 g (0.068 mole) of **1c** (defined as dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate] was added to a 500 ml 4 neck flask, that had been flamed and was blanketed with nitrogen. The temperature was reduced to -30° and 10.5 g of potassium *t*-butoxide dissolved in 25 ml of tetrahydrofuran was added with care taken to keep the dark red-purple mixture at -30°. Then excess solid carbon dioxide was added with exotherm to -20°. After addition and 10 minutes at -20 to -30°, the mixture was allowed to slowly warm to room temperature, then poured into cold 5% hydrochloric acid and extracted with methylene chloride. The organic solution was washed again with water then solvent vacuum removed. The ^{19}F and ^{1}H nmr of the 29.9 g crude showed mostly product. This could be further purified by hplc, with elution by 82% cyclohexane, 17% ethyl acetate, and 1% acetic acid.

Dimethyl 4-(1-Carboxy-2-methylpropyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate, Sodium Salt (**6**).

Material **5b** (1.5 g, 3.8 mmoles) was added portionwise to a solution of 0.8 g sodium bicarbonate. A yellow solution resulted which still showed basic to *p*H paper. More **5b** was added until the free acid would not dissolve and *p*H *ca* 7 achieved. The solution was evaporated to give solid which, when dissolved in deuterium oxide, showed impurities in ^{1}H nmr, with unsatisfactory microanalysis. The material, 1.7 g, was split in half and chromatographed in two parts using 55% water, 45% methanol on a C_{18} reverse phase Waters hplc column. Near baseline separation was achieved, and after methanol, then water evaporation (the latter by freeze-drying), 1.35 g white solid remained, which was pure by ^{1}H nmr (deuterium oxide) but had 0.5 H_2O by microanalysis.

Dimethyl 2-(Difluoromethyl)-4-[1-(dimethylamino)carbonyl-2-methylpropyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**7a**).

The acid chloride was prepared from acid **5b**. The latter (5.0 g) was contacted in a one neck r.b. flask with 40 ml of thionyl chloride, refluxed 1 hour, then let stand overnight. The ^{1}H nmr showed mostly product plus *ca.* 10% **1c**. Thionyl chloride was taken off under vacuum using portions of methylene chloride to help vaporize vestiges of hydrogen chloride and thionyl chloride. the residue was used directly in the reaction with dimethylamine. In 500 ml r.b. 4-necked flask the whole of the preceding acid chloride in ether was stirred with addition of 2.2 equivalents of dimethylamine in ether. The contents was stirred for 2 hours at room temperature, after which time glc was satisfactory for product formation. The contents of the flask was then washed with 3% hydrochloric acid solution (methylene chloride added), and washed once again with water. After vacuum removal of organic solvent, the 4.5 g crude residue was directly eluted by hplc using 15% ethyl acetate in cyclohexance to give 0.85 g fraction 5 with 85% assay and fractions 6-8 (1.3 g) with 96% assay. The latter was distilled at 125-175° (1.5-0.8 mm Hg) *via* Kugelrohr (no decomposition) to give a very viscous oil.

Dimethyl 4-(3-Butenyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**8a**).

Material **1b**, (6.6 g, 0.02 mole) was dissolved in 25 ml tetrahydrofuran and 6.0 g (0.02 mole) 1,3-diiodopropane added. The mixture was cooled to -30° and 0.4 mole of potassium *t*-butoxide (5.0 g dissolved in 25 ml of tetrahydrofuran) was added

dropwise. The mixture was kept at -30° for 20 minutes, then gradually allowed to warm to room temperature. The reaction solution was washed with dilute acid, then vacuum treated to remove solvent, giving 7.3 g of residue. This was Kugelrohr distilled to give 6.4 g plus 0.7 g of residue. Hplc was then performed using 2% ethyl acetate in cyclohexane, with fractions 3 and 4 collected as 2.6 g product. Kugelrohr distillation of this material gave 2.4 g distillate which solidified and was recrystallized from heptane.

Dimethyl 4-(Dichloromethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**9**).

The starting material **16** (6.6 g, 0.02 mole) was dissolved in 30 ml of tetrahydrofuran contained in a 3 neck, 100 ml flask. To the contents was added 0.08 mole (1.9 g) of hexachloroethane in 10 ml of tetrahydrofuran. The contents were then cooled to 0° and 0.07 mole potassium *t*-butoxide (8 g) dissolved in 25 ml of tetrahydrofuran was added dropwise at -10°. After addition the contents was permitted to warm to room temperature. The contents was worked up by treatment with cold 5% hydrochloric acid with extraction by methylene chloride. The separated organic phase was vacuum treated to 95° (to remove residual hexachloroethane). This residue on Kugelrohr distillation gave 8.0 g at 120-165° (1-2 mm Hg). Hplc with 3% ethyl acetate in cyclohexane gave 1.6 g recovery of product, with material eventually solidifying.

Dimethyl 2-(Difluoromethyl)-6-(trifluoromethyl)-4-(trimethylsilylmethyl)-3,5-pyridinedicarboxylate (**10b**).

To a solution of 3.4 g (0.011 mole) of **1b** in 35 ml of anhydrous tetrahydrofuran in a dry flask under nitrogen was added 12.5 g (0.012 mole) 1.0 *M* sodium bis(trimethylsilyl)amide in tetrahydrofuran controlling the temperature at -30 to -40°. After stirring 10 minutes at -30°, 4 ml (0.015 mole) of triethylsilyl trifluoromethane sulfonate was slowly added and the mixture allowed to warm to room temperature. The reaction mixture was worked up with aqueous hydrochloric acid and ether. Purification by hplc (1.5% ethyl acetate in cyclohexane) and Kugelrohr distillation afforded 2.87 g water white liquid.

Dimethyl 2-(1,1-Difluoroethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**11c**).

A lithium diisopropylamide solution was made up by adding 2.21 g (0.02 mole) of diisopropylamine to 100 ml 3-necked r.b., magnetically stirred flamed flask with 20 ml of dry tetrahydrofuran under nitrogen. To the contents at -60° was added 8.4 ml (*ca.* 0.02 mole) of *n*-butyllithium in pentane, with temperature allowed to reach -10°. The contents were then cooled to -75° with dryice/acetone, and 7.4 g (0.02 mole) **1c** in 25 ml dry of tetrahydrofuran added dropwise, with the temperature kept below -70°. A 2-fold excess of methyl iodide was added with some exotherm and the color lightened from characteristic dark red. After stirring at -65° or below for 15 minutes, the contents were allowed to warm to ambient temperature. After vacuum removal of most of the tetrahydrofuran, the mixture was poured into 3% hydrochloric acid and the contents extracted with methylene chloride. The material was washed again with water. The organic phase was then vacuum treated to remove solvent, leaving 7.7 g of dark brown oil. Kugelrohr distillation at 140-175° (1.0 mm Hg) gave 6.0 g, which solidified overnight. Hplc using 1.35% ethyl acetate in cyclohexane gave fractions of product with number 5 most pure. Recrystallization was from methylcyclohexane.

Dimethyl 2-(Difluoroiodomethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**11e**).

Material **1c** was added in 20 ml of tetrahydrofuran to 0.021 mole of lithium diisopropyl amide at 70° in 25 ml of tetrahydrofuran. Aftr a 15 minute hold period, 5.2 g of iodine dissolved in 10 ml of tetrahydrofuran was added dropwise, whereupon there was a strong exotherm initially, followed by a lesser exotherm with the bulk of electrophile addition. A further 15 minutes at -65 to -75° was allowed, followed by a slow rise to room temperature. An aliquot at this time, added to dilute acid gave by glc an 85% assay for product and 15% starting material; this result was confirmed by ^{19}F nmr of the crude reaction mixture. The reaction mixture was washed with 200 ml of 10% hydrochloric acid while extracting with methylene chloride. Sodium thiosulfate wash removed iodine color. Vacuum removal of solvent from the organic phase gave 10.2 g of residue. Kugelrohr to 105° (vacuum) gave 0.5 g of black colored solid. The next fraction taken between 110-165° (1 mm Hg) gave 6.0 g containing elemental iodine. This material was subjected to hplc with 25% methylene chloride in cyclohexane and fractions 4-8 gave 4 g of pure material which was recrystallized from cold heptane to give 3.8 g white solid. This material was stable (*i.e.* remained white) when contained in a bottle in the dark, but decomposed with iodine color generation in deuteriochloroform.

Dimethyl 2-(Carboxydifluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridindicarboxylate (**11m**).

Material **1c** (18.5 g, 0.05 mole) was dissolved in 30 ml dry tetrahydrofuran and added dropwise to a 500 ml stirred flask containing 150 ml of a 10% molar excess of lithium diisopropylamide in the same solvent. During addition the reaction flask contents was kept at -70°. Twenty minutes after addition excess solid carbon dioxide was added and the contents of the flask allowed to warm to room temperature (0.5 hour). The material was then poured into a 300 ml volume of an ice/water mixture containing 32 g of sulfuric acid. The resulting water insoluble product was extracted with ether, and dried over magnesium sulfate. Upon ether evaporation 21.1 g of crude brown syrup was isolated as product. This material was adequate for further transformations, but could be further purified by dissolving in dilute caustic, and reacidifying.

Methyl 5-(Fluorocarbonyl)-4-(2-methylpropyl)-6-[(methylthio)carbonyl]-2-(trifluoromethyl)-3-pyridinecarboxylate (**12**).

Material **1c** was treated with slightly more than a molar equivalent of lithium diisopropylamide in tetrahydrofuran by adding the pyridine in tetrahydrofuran dropwise at -70° to the lithio base solution. Then 4 g of dimethyl disulfide was added at -71° to -68°. This caused an immediate loss of dark red color, and the solution became dark green over 2 hours, warming to room temperature. Excellent glc displayed a main peak at *ca*, 4.80 [this was later determined to represent the retention times for both **12** and **11j** (see below)]. After dilute hydrochloric acid wash and methylene chloride extraction, the solvent was removed to give 18.0 g crude red oil. It was determined by tlc and ir that the title compound was not present; nor could it be generated by heat treatment of pure **11j**. Instead 8.4 g of the crude oil was Kugelrohr distilled at 140-200° (1-2 mm Hg), with **12** evident in the 6 g of dark distillate. This material was subjected to hplc

chromatography with 1% ethyl acetate in cyclohexane to give **12** in fractions 2,3 and **11j** in fractions 6-9.

Dimethyl 2-[Difluoro(methylthio)methyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**11j**).

Chromatography (1% ethyl acetate in cyclohexane) of either the crude or the distilled crude from **12** (see above) gave fractions 6-9 containing **11j**. Heating this pure compound at 160-170° for 0.5 hour or distilling the materal at 160-200° did *not* give evidence of **12**. From 8.44 g crude, 2.8 g pure **11j** was obtained.

Methyl 8,8-Difluoro-7,8-dihydro-4-(2-methylpropyl)-5-oxo-7-phenyl-2-(trifluoromethyl)-5*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (**13a**).

The starting material, **1c** (7.4 g, 0.02 mole) was converted to anion with 0.022 mole of lithium diisopropylamide at -75°, then excess (0.022 mole) of benzaldehyde added in the same solvent. After 15 minutes the mixture was warmed to room temperature, and after 1 hour poured into a mixture of dilute hydrochloric acid and methylene chloride. Workup gave 8.0 g of crude product as a solid, which gave 1.7 g of product from the first fraction upon recrystallization from methylcyclohexane and ethyl acetate.

Dimethyl 2-(2-Amino-1,1-difluoro-2-oxoethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**14a**).

The acid chloride, described in **14b** (see below) (5.6 g, 14.3 mmoles) was dissolved in methylene chloride and added dropwise to a 20% aqueous ammonium hydroxide solution with stirring at 20-25°. A white colloidal suspension immediately formed. After standing for 24 hours, the clear lower organic layer was evaporated to give 5.4 g. The ^{19}F nmr indicated several components. The white solid was triturated with water. A solid, weighing 1 g, was filtered off to give the title compound which was recrystallized from toluene/ethyl acetate.

Dimethyl 2-[1,1-Difluoro-2-(dimethylamino)-2-oxoethyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**14b**).

Crude **11m**, 15 g, containing traces of tetrahydrofuran, but otherwise fairly pure was mixed with 50 ml of thionyl chloride and heated to reflux in a one-neck flask. After reflux for 1 hour, the material was cooled, and let stand overnight. Thionyl chloride was then distilled off, using a final oil pump vacuum at 80° on a rotary evaporator. The residue, 14.5 g, was distilled by Kugelrohr at 130-160° (0.2 mm Hg) to give 5.1 g of residue and 9.3 g of distillate that solidified. A portion was recrystallized from very cold heptane to give white crystals, mp 41-46°. This acid chloride (3.0 g) dissolved in methylene chloride, was treated with 4 g of anhydrous dimethylamine (18% dimethylamine in ether) at room temperature overnight. Workup included a 3% hydrochloric acid wash and vacuum treatment to remove solvent. Hplc with 12.5% ethyl acetate in cyclohexane gave, after Kugelrohr distillation at 160-170° (0.1 mm Hg), 1.7 g of yellow oil.

Dimethyl 2-(Cyanodifluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**15**).

Material **14a** (3.34 g, 8.1 mmoles) was placed in 20 ml of phosphorus oxychloride and refluxed for 6 hours. The cooled reaction mixture was then filtered through a sintered glass funnel, vacuum treated to remove phosphorus oxychloride, and the residue (still containing small amounts of phosphorus oxychloride), treated once with water and extracted by methylene chloride; the latter phase was then washed with dilute sodium bicarbonate solution. The organic solvent was removed by vacuum evaporation and the residue Kugelrohr distilled to give 1.6 g of oil at 130-160° (1 mm Hg), which solidified on standing; recrystallization of a portion from methanol gave the analytical sample.

Dimethyl 2-(Carboxydifluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate, Salt with Diisopropylamine (**16b**).

Lithium diisopropyl amide solution was made by adding 1.11 g (0.01 mole) of diisopropylamine to a 100 ml 3 neck r.b., magnetically stirred flamed flask with 20 ml of dry tetrahydrofuran under nitrogen. To the contents at -60° was added 8.4 ml (*ca.* 0.02 mole) butyl lithium in pentane, with the temperature allowed to reach -10°. The contents was then cooled to -75° with dryice/acetone, and 3.7 g (0.01 mole) **1c** in 25 ml of dry tetrahydrofuran added dropwise, with the temperature kept below -70°. Then a 10-fold excess of dryice was added causing some exotherm, with color fading from characteristc dark red. After stirring at -65° or below for 15 minutes, the contents was allowed to reach ambient temperature, then poured into water (green to *p*H paper). Ether was used to extract considerable insolubles. A second ether extraction was combined with the first. The organic solvent was evaporated to give 3.9 g solid which was further purified by trituration with methylcyclohexane containing a small amount of ether, to give 2.1 g light tan solid. Recrystallization could be accomplished from ethyl acetate.

Dimethyl 2-[Difluoro(methylsulfonyl)methyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**17b**).

The starting material, **11j** (1.0 g, 2.4 mmoles) was dissolved in 25 ml of methylene chloride and 2.3 g of *m*-chloroperbenzoic acid was added. Reaction was complete overnight. The flask contents was washed with sodium bicarbonate, then sodium sulfate. Final purification by hplc using 1% ethyl acetate in cyclohexane gave 0.4 g, with recrystallization from hexane.

Dimethyl 2-[Difluoro(methylsulfinyl)methyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarboxylate (**17a**).

The starting material, **11j** (1.8 g, 4.3 mmoles) was dissolved in 20 ml of methylene chloride and 0.8 g of 40% peracetic acid was added thereto. The reaction was monitored by tlc, and it was found necessary to add more increments of oxidizing agent to effect complete disappearance of sulfide **11j**. Some sulfone was also formed during the oxidation. Chromatotron separation with 25% ethyl acetate in cyclohexane gave good separation (sulfoxide Rf > sulfone Rf). The sulfoxide was recovered as a viscous oil which after two weeks solified, with recrystallization from hexane/ethyl acetate.

Dimethyl 2-(Methoxydifluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**18**).

The starting material, **11e** (1 g, 2.0 mmoles) was dissolved in 20 ml of methanol and 3.0 mmoles of silver tetrafluoroborate was added. After refluxing 1 hour the material was permitted to stand at room temperature overnight. The reaction mixture was then decanted, and the clear solution vacuum treated to remove most of the methanol. The residue was treated with methylene chloride, followed by aqueous sodium chloride and sodium bicarbonate washes. The material was then filtered through a sintered glass filter, and after separating layers and evaporating the

organic phase, the residue weighed 0.65 g; glc showed two main peaks. Chromatotron separation with 2% ethyl acetate in cyclohexane gave fractions 1-3 (0.35 g) as the title product.

Trimethyl 4-(2-Methylpropyl)-6-(trifluoromethyl)-2,3,5-pyridinetricarboxylate (**19**).

From chromatography described above for the preparation of **18**, fractions 5,6 gave **19** (0.2 g).

REFERENCES AND NOTES

[1] Part **II**, J. P. Chupp and J. M. Molyneaux, *J. Heterocyclic Chem.*, **26**, 645 (1989); Presented in Poster Session, Symposium on Carbanion Chemistry, Ottawa, Canada, July 24, 1989.

[2] L. F. Lee, U. S. Patent 4,692,184 (Monsanto).

[3] J. March, "Advanced Organic Chemistry," John Wiley and Sons, NY, 1985, p 835.

[4] For a comparison of p*K*a's and other acidic properties of the R-CHF_2 group see discussion and additional references in "CH-ACIDS", by O. A. Rentov, I. P. Beletskaya, and K. P. Butin, Pergamon Press, Elmsford, NY, 10523, pp 51-57.