The Synthesis and Chemistry of 2-Hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylates

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The facile two step, one pot synthesis of heretofore unknown 2-hydroxy-4,6-bis(trifluoromethyl)-pyridine-5-carboxylates by condensation of 3-amino-4,4,4-trifluoro-2-butenoate with 4,4,4-trifluoroacetoacetyl chloride and subsequent intramolecular cyclization of the resultant enamineamide is described. Methodology for the introduction of electrophiles at the 3-position and elaboration of substituents at the 2- and 5-positions is also discussed.

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Introduction.

The preparation and chemistry of 2-hydroxy-4,6-bis(trifluoromethyl)pyridines have been seldom reported. The first reported preparation of 2-hydroxy-4,6-bis(trifluoromethyl)pyridine utilized hydroxide substitution for chloride in 2-chloro-4,6-bis(trifluoromethyl)pyridine [1]. More recently, Balicki and Nantka-Namirski [2] have prepared 2-hydroxy-4,6-bis(trifluoromethyl)pyridine in three steps and 61% overall yield *via* hydrolytic decarboxylation of 2-amino-4,6-bis(trifluoromethyl)nicotinamide (Figure 1). Eichler and coworkers [3] and Hoffman and coworkers [4] have reported the preparation of ethyl 2-amino-4,6-bis(trifluoromethyl)nicotinates in low to moderate yield by the cyclo-condensation of 1,1,1,5,5,5-hexafluoroacetylacetone with 3-iminopropriolates (Figure 2). Presumably, upon appropriate manipulation, ethyl 2-amino-4,6-bis(trifluoromethyl)nicotinate could also be converted to 2-hydroxy-4,6-bis(trifluoromethyl)pyridine utilizing the methodology of Balicki and Nantka-Namirski [2], thereby providing an alternative route for its preparation. The only other report of the preparation of a 2-hydroxy-4,6-bis(trifluoromethyl)-pyridine is that of Portnoy [5] who prepared 3-cyano-2-hydroxy-4,6-bis(trifluoromethyl)pyridine in low yield *via* cyclo-condensation of 1,1,1,5,5,5-hexafluoroacetylacetone with cyanoacetamide.

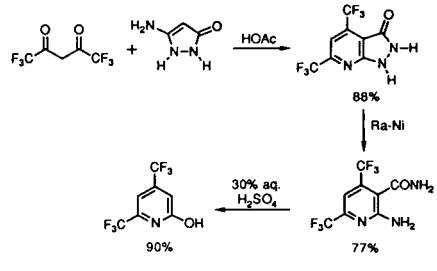


Figure 1

A significant disadvantage of all of these methods is their failure to incorporate substituents other than hydrogen at the 5-position of the pyridine ring. Indeed, with the exception of perfluoroalkylpyridine **1** [6] and 2,4,6-fluoro-

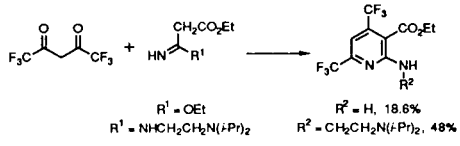


Figure 2

alkylpyridine-3,5-dicarboxylates **2** and **3** [7] (Figure 3) no examples of 4,6-bis(trifluoromethyl)pyridines are known with a substituent other than hydrogen at the 5-carbon.

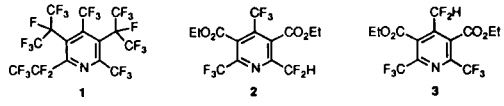


Figure 3

As part of an investigation into the utility of 4,4,4-trifluoroacetoacetyl chloride [8] as a synthon for the preparation of novel fluorinated molecules [9], [10] a facile, three step, one pot synthesis of alkyl 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylates was discovered. The details of the synthesis and chemistry of these heretofore unknown compounds are described herein.

Results and Discussion.

Addition of ketene to trifluoroacetyl chloride, utilizing literature methodology [8], followed by the addition of ethyl 3-amino-4,4,4-trifluoro-2-butenoate [11] to the resultant ethereal solution of 4,4,4-trifluoroacetoacetyl chloride and subsequent warming to ambient temperature affords enamineamide **4** in 67% yield as determined by ^{19}F-nmr using trifluoromethylbenzene as an internal calibration standard (Figure 4). Attempted purification of **4** by chromatography on silica gel or neutral alumina or distillation under reduced pressure resulted in decomposition. Although pure **4** could not be obtained, material of sufficient purity for unambiguous identification by ^{13}C-, ^{1}H- and ^{19}F-nmr spectral analysis was obtained by concentration of the crude reaction mixture. The presence of singlet resonances integrating for one proton each at δ = 5.49 and 5.71 ppm in the ^{1}H-nmr spectrum and singlet resonances at δ = 167.1 and 166.8 ppm and quartet resonances at δ

= 160.6 (J = 37.1 Hz) and 138.7 (J = 36.3 Hz) ppm in the proton decoupled ^{13}C-nmr spectrum clearly established the assigned structure.

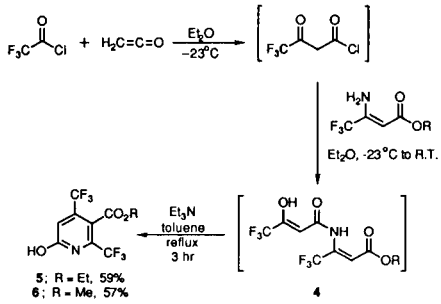


Figure 4

Following removal of the ether solvent, treatment of **4** with 1.2 equivalents of triethylamine in refluxing toluene for three hours afforded ethyl 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**5**) in 86% isolated yield. In a similar manner, methyl 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**6**) was prepared from the reaction of methyl 3-amino-4,4,4-trifluoro-2-butenoate and 4,4,4-trifluoroacetoacetyl chloride. Utilizing this methodology, **5** and **6** could be routinely prepared in 30-40 gram quantities in 57-59% overall yield based on starting alkyl 3-amino-4,4,4-trifluorobutenoate (Figure 4).

Using chlorodifluoroacetyl chloride in place of trifluoroacetyl chloride, under otherwise identical reaction conditions, methyl 2-hydroxy-4-(chlorodifluoromethyl)-6-(trifluoromethyl)pyridine-5-carboxylate (**7**) was obtained in a 50% overall yield (Figure 5). However, attempted preparation of longer chain 4-(perfluoroalkyl)pyridine-5-carboxylates by using pentafluoropropionyl chloride or heptafluorobutyryl chloride as starting materials failed to afford the requisite analogues of **4** or any isolable products either before or after reaction with triethylamine in refluxing toluene.

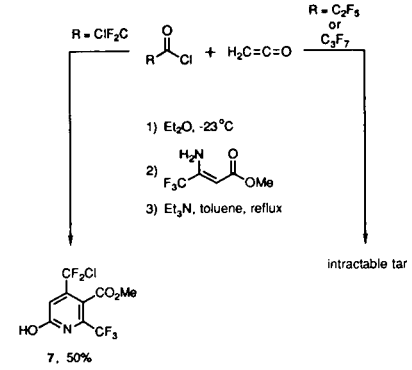
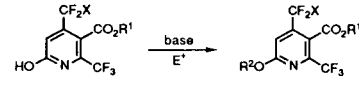


Figure 5

2-Hydroxypyridines exist as tautomeric mixtures with the corresponding 2-pyridones [12]. Nonpolar solvents, electron withdrawing groups at the 6-position, and the vapor state favor the 2-hydroxypyridine tautomer [12]. Consistent with literature precedent, in the vapor phase (gc-ftir) **5** exists exclusively as the 2-hydroxypyridine tautomer as demonstrated by the presence of a sharp absorbance of moderate intensity at 3591.9 cm^{-1} (O-H vibrations) and the absence of absorbances in the 3400 to 3500 cm^{-1} (N-H vibrations) and 1650 to 1690 cm^{-1} (amide C=O vibrations) regions of the spectrum. In the solid phase, the ir spectrum of **5** (Nujol mull) reveals an absorbance at 1685 cm^{-1} which is approximately 50% less intense than the absorbance at 1750 cm^{-1} (ester carbonyl C=O vibrations). As a dilute solution in carbon tetrachloride the ir spectrum of **5** reveals a weak absorbance at 1675 cm^{-1} which is approximately 75% less intense than the absorbance at 1745 cm^{-1}. The carbonyl moiety of 2-pyridones absorbs strongly in the region 1650 to 1690 cm^{-1} [5], [13]. Thus, the presence of moderate and weak absorbances at 1685 and 1675 cm^{-1} in the solid phase and solution ir spectra, respectively, of **5** demonstrates that **5** exists as an equilibrium mixture of 2-hydroxypyridine and 2-pyridone tautomers. Although no attempt was made to quantitate the relative ratio of tautomers, that the 2-pyridone carbonyl absorbance is significantly less intense than the ester carbonyl absorbance indicates that the 2-hydroxypyridine tautomer predominates in both the solid phase and solution.

Alkylation of 2-hydroxypyridines generally affords mixtures of *O*-alkylated and *N*-alkylated products [14]. Polar aprotic solvents, alkali metal salts, and electron withdrawin substituents at the 5-position are known to significantly favor *N*-alkylation [15], [16]. In contrast, alkylation of the potassium salts of **5-7** afforded, exclusively, the products of *O*-alkylation (Figure 6) [17]. In a similar manner, silylation and sulfonylation of **5** and **6** gave only the corresponding silyl ethers and sulfonate esters, respectively (Figure 6). Although exclusive formation of silyl ethers **8** and **9** was expected due to the greater affinity of silicon for oxygen compared to nitrogen, exclusive *O*-alkylation and *O*-sulfonylation were not predicted based on literature precedent. Although a detailed study of steric effects upon the ratio of *O*-alkylation and *N*-alkylation of 2-pyridones has not been reported, an increase in the steric bulk of the alkylating agent [15], [16] and the presence of substituents at

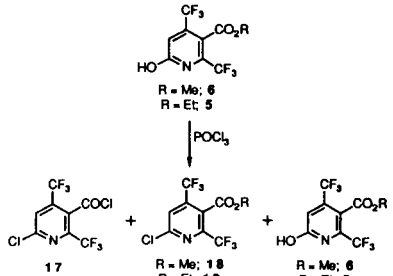


Compound	X	R^1	R^2	% yield
8	F	Me	$SiMe_3$	86
9	F	Et	$SiMe_3$	70
10	F	Me	Me	56
11	F	Et	Me	79
12	Cl	Me	Me	89
13	F	Me	CH_2Ph	80
14	F	Me	$MeCHCO_2Et$	84
15	F	Et	SO_2CF_3	61
16	F	Me	SO_2(4-MePh)	42

Figure 6

the 6-position [18], [19] are report to increase the ratio of *O*-alkylation to *N*-alkylation. Thus, the exclusive *O*-alkylation and *O*-sulfonylation found in the present study are most reasonably attributed to a steric effect due to the 6-trifluoromethyl group which prevents reaction at nitrogen.

Preparation of the corresponding 2-chloropyridine of **6** was less straightforward than expected [20]. Treatment of **6** with phosphorus oxychloride at reflux for 24 hours failed to afford any isolable products. In contrast, upon reaction with 2 equivalents of 2,6-lutidine in refluxing phosphorus oxychloride **6** was consumed over 112 hours and afforded a 55:44 mixture of 2-chloropyridine-5-acid chloride **17** and methyl 2-chloro-4,6-bis(trifluoromethyl)pyridine-5-carboxylate **18** as determined by gcms analysis (Figure 7). Alternatively, treatment of **6** with 1.1 equivalents of dimethylformamide in refluxing phosphorus oxychloride for 72 hours afforded a 10:50:39 mixture of **17:18:6** (Figure 7). When **6** was treated with 3 equivalents of the more nucleophilic base, pyridine, in refluxing phosphorus oxychloride, a 7:1 mixture of **17** and **18** was obtained after 24 hours (Figure 7). These results suggested that formation of **17** occurred by S_N2 attack of the amine base on the methyl group of the ester with displacement of the 4,6-bis(trifluoromethyl)pyridine-5-carboxylate anion, which undergoes subsequent chlorination with excess phosphorus oxychloride. In keeping with this postulate was the finding that reaction of ethyl ester **5** with 1.1 equivalent of lutidine in refluxing phosphorus oxychloride for 72 hours afforded a 6:87:6 mixture of **17:19:5**, from which **19** was isolated by distillation in 67% yield.



Conditions			
2 eq. lutidine, reflux 112 hr, R = Me	55	44	0
1.1 eq. DMF, reflux 72 hr, R = Me	10	50	39
3 eq. pyridine, reflux 24 hr, R = Me	70	10	0
1.1 eq. lutidine, reflux 72 hr, R = Et	6	87 (67% isolated)	6

Figure 7

Reaction of **19** with cyclopropylamine [21] or potassium ethylthiolate [22] gave ethyl 2-cyclopropylamino-4,6-bis(trifluoromethyl)pyridine-5-carboxylate **20** and ethyl 2-ethylthio-4,6-bis(trifluoromethyl)pyridine-5-carboxylate **21** in 73% and 82% yields, respectively (Figure 8).

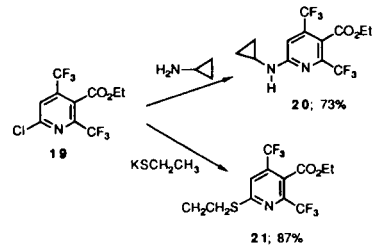
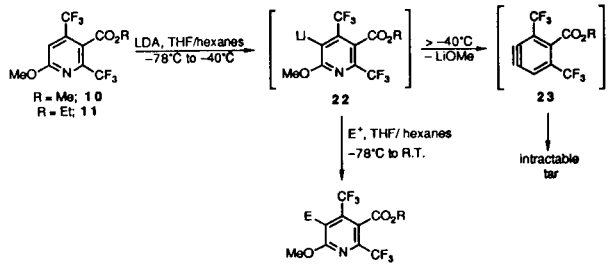


Figure 8

Introduction of substituents at the 3-position of **10** and **11** was readily effected *via* metallation with lithium diisopropylamide and subsequent trapping of pyridyl anion **22** with electrophiles (Figure 9). Utilizing **10** and deuterium oxide quenching, exploratory studies revealed that little metallation occurred at −78° (>20% deuterium incorporation), and that warming the reaction to approximately −40° was necessary for efficient anion formation (70% deuterium incorporation). However, warming the reaction above −40° resulted in decomposition, presumably *via* the intermediacy of pyridyne **23** (Figure 9). These early studies also revealed that the solvent system employed was critical for achieving high yields of anion trapping. Thus, reaction of the anion of **10** with ethyl chloroformate in 4:1 tetrahydrofuran:hexanes afforded pyridine-3,5-dicarboxylate **24** in only 5% isolated yield. In contrast, using 1:1 tetrahydrofuran:hexanes as the solvent, under otherwise identical conditions, **24** was obtained in 69% isolated yield. Further increases in the hexanes to tetrahydrofuran ratio failed to afford increased yields of anion trapping. Addition of 2.4 equivalents of 1,3-dimethyl-2-oxo-hexahydropyrimidine [23] as an anion complexing agent resulted in the formation of an intractable tar, presumably due to anion decomposition. Utilizing the optimized metallation and subsequent electrophilic quenching conditions, the 3-substituted 2-alkoxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylates shown in Figure 9 were readily prepared.



compound	R	E	% yield[1]
24	Me	CO_2Et	69
25	Me	CO_2Me	55
26	Me	SMe	65
27	Me	SEt	64
28	Et	SPh	46
29	Et	CO_2Me	65
30[2]	Me	CO_2H	15
31[2]	Me	I	29

[1]Isolated yields.
[2]4:1 THF:hexanes employed as solvent.

Figure 9

With the successful demonstration of methodology for the introduction of substituents at position 3 and the manipulation of functionality at position 2, attention was directed toward manipulation of the 5-carboxylate functionality. Although the two trifluoromethyl groups were expected to activate the 5-carboxylate moiety due to inductive electron withdrawal, *a priori*, saponification was expected to be sluggish due to the steric bulk of the two adjacent trifluoromethyl groups which would significantly hinder hydroxide attack. Indeed, standard base promoted hydrolysis of **6** required very vigorous conditions and afforded the corresponding acid, 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylic acid **32**, in only modest yields (Figure 10). Moreover, attempts to prepare the isopropyl ester of **32** by reaction with refluxing thionyl chloride followed by quenching with 2-propanol failed to give the desired ester, and instead afforded only an intractable tar. This disappointing result suggested that protection of the 2-hydroxyl group would be necessary to cleanly prepare and derivatize the 5-acyl chloride analogue of **32**.

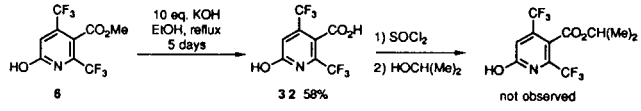


Figure 10

Initially it was hoped that benzyl ether **13** would be a suitably protected substrate for saponification, since following chlorination and derivatization of the 5-carboxylate group, reductive cleavage of the benzyl group would liberate the 2-hydroxyl moiety. However, base promoted saponification of **13** resulted in rapid benzyloxy displacement by ethoxide to afford benzyl alcohol and methyl 2-ethoxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate **33** as the major products in addition to minor amounts of unreacted **13** and 2-hydroxypyridine **6** (Figure 11). Attempted formation of the acid analogue of **13** by nucleophilic attack at methyl with displacement of 2-benzyloxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate by reaction with sodium iodide in refluxing dimethylformamide [24] or 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in refluxing xylene [25] also failed. In the case of the sodium iodide reaction, numerous unidentified products where formed. In the case of the DBU reaction, 2-benzyloxy-4,6-bis(trifluoromethyl)pyridine **34**, presumably formed by decarboxylation of 2-benzyloxy-4,6-bis(trifluoromethyl)-pyridine-5-carboxylate, was obtained in low yield as the only major volatile product (Figure 11).

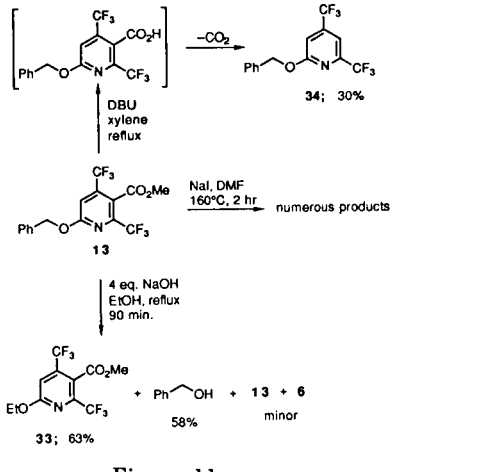


Figure 11

In contrast, reaction of **13** with sodium methanethiolate in dimethylformamide at ambient temperature [26] followed by acidic workup afforded the desired carboxylic acid **35** in moderate yield (Figure 12). In a similar fashion, 2-methoxypyridine **10** was converted to the corresponding carboxylic acid **36**. Carboxylic acids **35** and **36** proved difficult to purify, contributing in part to their moderate isolated yields. For subsequent preparative purposes, it was advantageous to convert the crude reaction mixture of **35** directly to acid chloride **37**, which was obtained analytically pure in 49% overall yield (Figure 12).

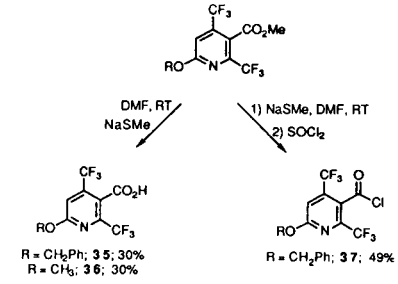


Figure 12

Despite the steric hindrance due to the adjacent trifluoromethyl groups, upon reaction with cyclopropylamine and ethanolamine, **37** was converted to the corresponding amides **38** and **39**, respectively, in excellent yields. Amide **39** was further transformed to the corresponding thiazoline analogue **40** in 81% overall yield by reaction with phosphorus pentachloride to give imidoyl chloride **41**, which, without purification was cyclized with lithium sulfide (Figure 13). In a similar fashion, pyrazole amide **42** was conveniently prepared in 33% overall yield from **10** without purification of intermediate carboxylic acid **36** or acid chloride **43** (Figure 14).

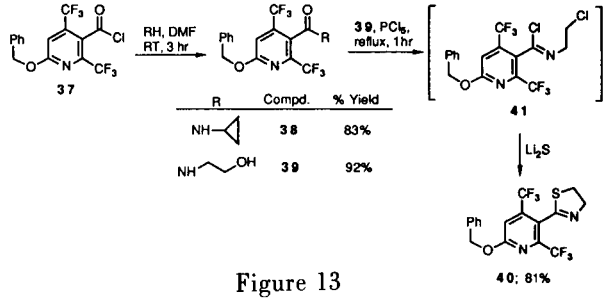


Figure 13

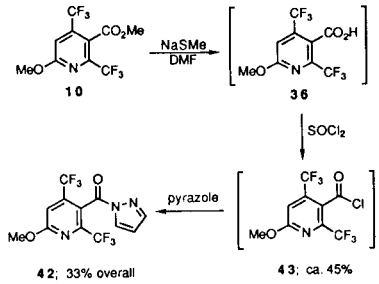


Figure 14

In conclusion, novel methodology for the facile perparation of heretofore unknown 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylates has been demonstrated. In addition, methodology for derivatization of the 2-hydroxyl and 5-carboxylate groups and introduction of electrophiles at the 3-position has been demonstrated. In general, the chemistry of 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylates has been shown to be analogous to that of more conventional 2-hydroxypyridines.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Varian EM360L (60 MHz, proton only), Varian XL-400 (400 MHz), Varian XL-300 (300 MHz) or Bruker AM-360 (360 MHz) spectrometer and are reported on the δ scale relative to tetramethylsilane. The ^{19}F-nmr spectra were recorded on an IBM AF-300 (300 MHz) spectrometer, and chemical shifts are reported on the δ scale relative to fluorotrichloromethane. Chromatographic separations were performed on a Waters Prep 500A HPLC or a Harrison Research Chromatotron Radial TLC. Trifluoroacetyl chloride was purchased from PCR® Inc., and was used without further purification. Trifluoroacetyl chloride purchased from other venders was found to contain varying amounts of hydrogen chloride which significantly reduced the yield of 4,4,4-trifluoroacetoacetyl chloride.

Methyl 3-Amino-4,4,4-trifluoro-2-butenoate.

Anhydrous ammonia (52 g, 3.06 moles) was added subsurface over 1.5 hours to 431.98 g (2.54 moles) of methyl 4,4,4-trifluoroacetoacetate heated to 75-80°. The addition of ammonia resulted in a gradual exotherm to 100-110°. When the addition of ammonia was complete, the reaction was heated at 100° for 3 hours, cooled to ambient temperature, dissolved in an equal volume of diethyl ether, dried (magnesium sulfate), concentrated, and Kugelrohr distilled (81°, 55 Torr) to afford 252.8 g (1.5 moles, 59% yield) of methyl 3-amino-4,4,4-trifluoro-2-butenoate, mp 65-69°; ^{19}F-nmr (60 MHz, chloroform-d_1): δ = −72.43; ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 3.65 (s, 3H), 5.08 (s, 1H), 6.3 (broad s, 2H); ^{13}C-nmr (360 MHz, chloroform-d_1): δ = 169.407, 147.368 (q, J = 33.14 Hz), 120.277 (q, J = 274.95 Hz), 85.39 (q, J = 3.88 Hz), 50.64.

Anal. Calcd. for $C_5H_6F_3NO_2$: C, 35.51; H, 3.58; N, 8.28. Found: C, 35.57; H, 3.58; N, 8.24.

Ethyl 3,7-Bis(trifluoromethyl)-7-hydroxy-5-oxo-4-azahepta-2,6-dienoate (**4**).

Purified ketene was prepared following the general procedure of Andreades and Carlson [27]. Thus, 10.73 g (0.13 mole) of diketene was added dropwise at the rate of approximately 0.1 ml/minute to a vertical 1 ft. x 1 inch quartz tube packed with quartz chips enclosed in a tube furnace thermostated at 560-570°. The volatiles were swept through the furnance with dry nitrogen at a flow rate of 3.8 to 4.2 ml/minute and were condensed in a cold trap cooled to −78°. When the pyrolysis was complete, ketene was distilled by heating to −23° into a solution of 15.43 g (0.12 mole) of trifluoroacetyl chloride dissolved in 50 ml of dry diethyl ether cooled to −23°. During the addition of ketene, the reaction exothermed to *ca.* −15°. When the addition was complete, the reaction was allowed slowly warm to −5°. After cooling to −23°, the reaction was quenched by the rapid addition of 15.45 g (0.084 mole) of ethyl 3-amino-4,4,4-trifluoro-2-butenoate [11]. Analysis of the crude reaction mixture by ^{19}F-nmr, after warming to ambient temperature, revealed major signals at δ = −68.1 and −75.3 (1:1 ratio), and unreacted ethyl 3-amino-4,4,4-trifluoro-2-butenoate (δ = −72.2), in addition to minor signals at δ = −73.7, −76.0, and −82.2. The principal product of the reaction, which by ^{19}F-nmr using trifluoromethylbenzene as an internal calibration standard was formed in 67% yield, was identified as **4** on the basis of its spectral data following *in vacuo* removal of the volatiles; ^{19}F-nmr (chloroform-d_1): δ = −68.1 (s, CF_3), −75.3 (s, CF_3); ^{1}H-nmr (chloroform-d_1): δ = 1.2 (t, J = 6.6 Hz, 3H), 4.1 (q, J = 6.6 Hz, 2H), 5.49 (s, 1H), 5.71 (s, 1H), 10.55 (br s, 1H), 12.75 (br s, 1H); ^{13}C-nmr (chloroform-d_1): δ = 167.05, 166.81, 160.59 (q, J = 37.1 Hz), 138.71 (q, J = 36.30 Hz), 119.26 (q, J = 274.77 Hz), 118.14 (q, J = 274.79 Hz), 105.12, 93.05, 61.71, 13.42.

Ethyl 2-Hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**5**).

A solution of 50 ml of toluene, 0.0613 mole of **4** (determined by calibrated ^{19}F-nmr using trifluoromethylbenzene as an internal calibration standard), and 15 ml (10.89 g, 0.108 mole) of triethylamine were refluxed for 3 hours. After cooling to ambient temperature, analysis by calibrated ^{19}F-nmr revealed the presence of 0.0607 mole (99% yield) of **5**. The crude reaction mixture was concentrated *in vacuo*, diluted with 200 ml of diethyl ether, washed thrice with dilute aqueous hydrochloric acid, dried (magnesium sulfate), concentrated, and recyrstallized from carbon tetrachloride/hexanes to afford 16 g (0.0528 mole, 86% yield) of **5**, mp 71-74°; ^{19}F-nmr (chloroform-d_1): δ = −63.2 (s, CF_3), −65 (s, CF_3); ^{1}H-nmr (chloroform-d_1): δ = 1.39 (t, J = 7.5 Hz, 3H), 4.42 (q, J = 7.5 Hz, 2H), 7.3 (s, 1H), 10.42 (br s, 1H); ^{13}C-nmr (chloroform-d_1): δ = 163.35, 162.98, 141.33 (q, J = 35.9 Hz), 141.12 (q, J = 34.4 Hz), 124.09 (q, J = 275.8 Hz), 119.75 (q, J = 276.2 Hz), 117.31, 114.81, 63.19, 13.35; gc-ftir: 3591.9, 1762.95, 1620.20, 1398.7, 1273.5, and 1208.6 cm^{-1}; ir (Nujol): 1750, 1685, 1630, and 1581 cm^{-1}; ir (dilute carbon tetrachloride): 3520, broad absorbance centered at 3000, 1745, 1675, 1620, and 1570 cm^{-1}.

Anal. Calcd. for $C_{10}H_7F_6O_3N$: C, 39.60; H, 2.31; N, 4.62. Found: C, 39.73; H, 2.37; N, 4.62.

Methyl 2-Hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**6**).

Ketene, generated by the pyrolysis of acetone in an Ace® ketene generator (Catolog #7470) [28], was passed successively at a rate of approximately 3.2 mmoles/minute through two cold traps cooled to −23°, and was condensed at −78° and added

dropwise to a solution of trifluoroacetyl chloride (41.75 g, 0.32 mole) in 75 ml of chloroform cooled to −23°. When the consumption of trifluoroacetyl chloride was complete, as determined by ^{19}F-nmr, the addition of ketene was stopped and the reaction was allowed to warm to 0°. The reaction was then cooled to −23°, and was quenched by the rapid addition of 40 g (0.24 mole) of methyl 3-amino-4,4,4-trifluoro-2-butenoate dissolved in 50 ml of anhydrous diethyl ether. The resulting reaction was warmed to ambient temperature, concentrated *in vacuo*, and dissolved in 400 ml of toluene. The resulting solution was treated with 50 ml of triethylamine and heated at 90° for 2 hours. Following cooling to ambient temperature, the reaction was diluted with 200 ml of diethyl ether, washed twice with 10% hydrochloric acid, dried (magnesium sulfate), concentrated, and crystallized from toluene to afford 41.0 g (0.14 mole, 59% yield) of **6**, mp 137-140°; ^{1}H-nmr (360 MHz, acetone-d_6): δ = 3.9 (s, 3H), 7.3 (s, 1H), 10.8 (broad s, 1H); ^{13}C-nmr (360 MHz, acetone-d_6): δ = 165.11, 165.01, 144.50 (q, J = 34.58 Hz), 140.74 (q, J = 33.69 Hz), 122.65 (q, J = 274.54 Hz), 121.50 (q, J = 274.91 Hz), 118.66, 112.23, 55.74; ir (Nujol): 1740, 1685, 1625, and 1575 cm^{-1}.

Anal. Calcd. for $C_9H_5F_6NO_3$: C, 37.39; H, 1.74; N, 4.84. Found: C, 37.41; H, 1.76; N, 4.82.

Repetition of the aforementioned reaction typically afforded **6** in 57% isolated yield on a 30-40 gram scale. Utilizing the same reaction conditions and ethyl 3-amino-4,4,4-trifluoro-2-butenoate, **5** was typically prepared in 59% isolated yield on a 30-40 gram scale.

Methyl 4-(Chlorodifluoromethyl)-2-hydroxy-6-(trifluoromethyl)-pyridine-5-carboxylate (**7**).

Reaction of 42.55 g (0.28 mole) of chlorodifluoroacetyl chloride, ketene, and 42.95 g (0.25 mole) of methyl 3-amino-4,4,4-trifluoro-2-butenoate utilizing the general procedure used for the preparation of **5** and **6** afforded 42.35 g of crude crystalline material. Recrystallization from hexanes/toluene afforded 38.99 g (0.13 mole, 50% yield) of **7**, mp 103.5-106°; ^{1}H-nmr (chloroform-d_1): δ = 7.26 (s, 1H), 3.95 (s, 3H); ^{13}C-nmr (chloroform-d_1): δ = 163.70, 146.47 (t, J = 28.4 Hz), 141.64 (q, J = 35.4 Hz), 122.77 (t, J = 291.95 Hz), 119.87 (q, J = 275.3 Hz), 116.25 (q, J = 2.6 Hz), 113.51 (t, J = 6 Hz), 53.62.

Anal. Calcd. for $C_9H_5ClF_5NO_3$: C, 35.37; H, 1.65; N, 4.58. Found: C, 35.60; H, 1.70; N, 4.55.

Methyl 2-(Trimethylsiloxy)-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**8**) and Ethyl 2-(Trimethylsiloxy)-4,6-bis(trifluoromethyl)-pyridine-5-carboxylate (**9**).

To a stirred solution of 21.36 g (0.074 mole) of **6** and 7.62 g (0.075 mole) of anhydrous triethylamine in 75 ml of carbon tetrachloride was added, dropwise, 8.05 g (0.074 mole) of freshly distilled chlorotrimethylsilane. The resulting slurry was stirred at ambient temperature for 16 hours, filtered through celite, concentrated, and Kugelrohr distilled (55°, 0.03 Torr) to afford 23.05 g (0.064 mole, 86% yield) of **8** as a clear colorless oil. ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 0.48 (s, 9H), 4.00 (s, 3H), 7.27 (s, 1H).

Anal. Calcd. for $C_{12}H_{13}F_6NO_3Si$: C, 39.89; H, 3.63; N, 3.88. Found: C, 40.27; H, 3.72; N, 4.18.

Silyl ether **9** was prepared in a manner analogous to that for **8**, and was purified by Kugelrohr distillation (58°, 0.2 Torr), 70% yield; ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 0.50 (s, 9H), 1.41 (t, J = 7.6 Hz, 3H), 4.45 (q, J = 7.6 Hz, 2H), 7.19 (s, 1H); ^{13}C-nmr (360 MHz, chloroform-d_1): δ = 163.76, 162.37, 143.90 (q, J = 34.90 Hz), 140.27 (q, J = 33.59 Hz), 121.432 (q, J = 274.86 Hz), 120.322 (q, J = 275.37 Hz), 118.655, 113.361 (q, J = 4.32 Hz), 62.68, 13.68, 9.57.

Anal. Calcd. for $C_{13}H_{15}F_6NO_3Si$: C, 41.60; H, 4.03; N, 3.73. Found: C, 42.07; H, 3.90; N, 3.74.

Methyl 2-Methoxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**10**).

A suspension of 30.1 g (0.104 mole) of **6**, 34.2 g (0.241 mole) of methyl iodide, and 20 g (0.145 mole) of potassium carbonate in 250 ml of dimethylformamide was stirred at ambient temperature for 24 hours. The resulting slurry was diluted with an equal volume of diethyl ether, washed twice with 10% hydrochloric acid, dried (magnesium sulfate), concentrated, and Kugelrohr distilled (58°, 0.2 Torr) to afford 17.68 g (0.058 mole, 56% yield) of **10**, mp 47-50°; ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 4.00 (s, 3H), 4.11 (s, 3H), 7.35 (s, 1H); ^{13}C-nmr (360 MHz, chloroform-d_1): δ = 164.06, 163.81, 144.03 (q, J = 35.76 Hz), 139.72 (q, J = 33.76 Hz), 121.30 (q, J = 274.91 Hz), 120.28 (q, J = 275.73 Hz), 118.36, 111.82 (q, J = 4.41 Hz), 54.46, 53.01; ir (Nujol): 1757, 1622, and 1570 cm^{-1}.

Anal. Calcd. for $C_{10}H_7F_65NO_3$: C, 39.62; H, 2.33; N, 4.62. Found: C, 39.89; H, 2.35; N, 4.59.

Ethyl 2-Methoxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**11**).

Reaction of **5** and methyl iodide following the general procedure described for the preparation of **10** afforded a 79% yield of **11** after Kugelrohr distillation (40°, 0.12 Torr) and crystallization from cold hexanes; mp = 29-31.5°; ^{1}H-nmr (400 MHz, chloroform-d_1): δ = 1.36 (t, J = 7.4 Hz, 3H), 4.04 (s, 3H), 4.40 (q, J = 7.4 Hz, 2H), 7.21 (s, 1H); ^{13}C-nmr (400 MHz, chloroform-d_1): δ = 163.82, 163.77, 144.09 (q, J = 34.3 Hz), 139.81 (q, J = 34.20 Hz), 121.50 (q, J = 276.10 Hz), 120.48 (q, J = 275.90 Hz), 118.91, 111.92 (q, J = 4.3 Hz), 62.90, 54.77, 13.55; ir (Nujol): 1743, 1610, and 1557 cm^{-1}.

Anal. Calcd. for $C_{11}H_9F_6N_1O_3$: C, 41.65; H, 2.86; N, 4.42. Found: C, 41.50; H, 2.87; N, 4.35.

Methyl 2-Methoxy-4-(chlorodifluoromethyl)-6-(trifluoromethyl)-pyridine-5-carboxylate (**12**).

Reaction of **7** and methyl iodide following the general procedure described for the preparation of **10** afforded a 89% yield of **12** following chromatography on silica gel with 1% ethyl acetate/hexanes elution and Kugelrohr distillation (60-61°, 0.3 Torr); ^{1}H-nmr (chloroform-d_1): δ = 7.17 (s, 1H), 4.03 (s, 3H), 3.93 (s, 3H); ^{13}C-nmr (chloroform-d_1): δ = 164.35, 164.91, 145.11 (t, J = 27.9 Hz), 144.12 (q, J = 35.8 Hz), 121.84 (t, J = 291.6 Hz), 120.46 (q, J = 275.8 Hz), 117.48, 110.89, 54.70, 53.20; ir (neat): 1745, 1605, and 1550 cm^{-1}.

Anal. Calcd. for $C_{10}H_7F_5ClNO_3$: C, 37.58; H, 2.21; N, 4.38. Found: C, 37.68; H, 2.26; N, 4.33.

Methyl 2-Benzyloxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**13**).

Reaction of **6**, benzyl chloride, and catalytic sodium iodide following the general procedure described for the preparation of **10** afforded an 80% yield of **13** after Kugelrohr distillation (96-100°, 0.05 Torr); ^{1}H-nmr (400 MHz, chloroform-d_1): δ = 3.96 (s, 3H), 5.50 (s, 2H), 7.27 (s, 1H), 7.38 to 7.41 (m, 3H), 7.46 to 7.5 (m, 2H); ^{13}C-nmr (400 MHz, chloroform-d_1): δ = 164.28, 163.28, 144.01 (q,

J = 35.70 Hz), 140.03 (q, J = 34.10 Hz), 135.27, 128.75, 128.56, 121.45 (q, J = 275.90 Hz), 120.48 (q, 274.30 Hz), 118.69, 112.39 (q, J = 5.6 Hz), 69.52, 53.45; ir (neat): 1740, 1609, and 1555 cm^{-1}.

Anal. Calcd. for $C_{16}H_{11}F_6N_1O_3$: C, 50.67; H, 2.92; N, 3.69. Found: C, 50.63; H, 2.95; N, 3.64.

Methyl 2-(2-Ethoxy-1-methyl-2-oxoethoxy)-4,5-bis(trifluoromethyl)pyridine-5-carboxylate (**14**).

Reaction of **6** and ethyl 2-bromoproprionate following the general procedure described for the preparation of **10** afforded an 84% yield of **14** after Kugelrohr distillation (60°, 0.05 Torr); ^{1}H-nmr (chloroform-d_1): δ = 7.24 (s, 1H), 5.25 (q, J = 7 Hz, 2H), 4.10 (m, 2H), 3.82 (s, 3H), 1.55 (d, J = 7 Hz, 3H), 1.16 (t, J = 7 Hz, 3H); ^{13}C-nmr (chloroform-d_1): δ = 170.71, 164.07, 162.33, 143.72 (q, J = 35.4 Hz), 140.31 (q, J = 34 Hz), 121.34 (q, J = 275.70 Hz), 120.23 (q, J = 275.00), 119.17, 112.17 (q, J = 3.1 Hz).

Anal. Calcd. for $C_{14}H_{13}F_6NO_5$: C, 43.20; H, 3.37; N, 3.60. Found: C, 43.14; H, 3.41; N, 3.58.

Ethyl 2-Trifluoromethylsulfonyloxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**15**).

To a stirred solution of 6.02 g (0.0199 mole) of **5** and 2.8 ml (0.0201 mole) of triethylamine in 100 ml of toluene under an atmosphere of dry nitrogen was added 2.2 ml (0.01 mole) of trifluoromethylsulfonyl chloride. The resulting solution, which slowly deposited a precipitate, was stirred at ambient temperature for 16 hours, filtered through celite, washed twice with 10% hydrochloric acid, once with water, dried (magnesium sulfate), and concentrated to afford 7.76 g of crude product. Chromatography on silica gel with 10% ethyl acetate/hexanes elution followed by Kugelrohr distillation (80°, 0.5 Torr) afforded 5.31 g (0.012 mole, 61% yield) of crystalline **15**, mp 65-67.5°; ^{1}H-nmr (chloroform-d_1): δ = 7.70 (s, 1H), 4.49 (q, J = 7 Hz, 2H), 1.41 (t, J = 7 Hz, 3H); ^{13}C-nmr (chloroform-d_1): δ = 161.7, 154.87, 145.70 (q, J = 38.1 Hz), 142.82 (q, J = 34.6 Hz), 126.60, 120.62 (q, J = 276.60 Hz), 119.51 (q, J = 275.0 Hz), 118.50 (q, J = 321.0 Hz), 115.96 (q, J = 3.2 Hz), 63.93, 13.49.

Anal. Calcd. for $C_{11}H_6F_9NSO_5$: C, 30.36; H, 1.39; N, 3.22. Found: C, 30.60; H, 1.41; N, 3.21.

Methyl 2-(4-Methylphenyl)sulfonyloxy-4,6-bis(trifluoromethyl)-pyridine-5-carboxylate (**16**).

To a solution of 5.70 g (0.0197 mole) of triethylamine in 50 ml of diethyl ether was added 3.77 g (0.0198 mole) of 4-methylphenylsulfonyl chloride. The reaction was stirred at ambient temperature for 24 hours after which an additional 3.42 g (0.043 mole) of triethylamine was added. The reaction was then stirred for 72 hours at ambient temperature. An additional 2 g (0.01 mole) of 4-methylphenylsulfonyl chloride was then added, and stirring was continued for 18 hours. The reaction was filtered through celite, diluted with 100 ml of diethyl ether, washed thrice with 10% hydrochloric acid, dried (magnesium sulfate), concentrated, and crystallized from 10% ethyl acetate/cyclohexane to afford 3.68 g (0.008 mole, 42% yield) of **16**, mp 122-124°; ^{1}H-nmr (360 MHz, acetone-d_6): δ = 1.49 (s, 3H), 4.01 (s, 3H), 7.53 (d, 2H), 8.03 (m, 3H); ^{13}C-nmr (360 MHz, acetone-d_6): δ = 163.81, 158.29, 147.6, 144.67 (q, J = 36.57 Hz), 142.09 (q, J = 34.60 Hz), 133.71, 130.84 120.025, 124.74, 122.14 (q, J = 274.81 Hz), 121.04 (q, J = 275.15 Hz), 117.82, 54.35, 21.61.

Anal. Calcd. for $C_{16}H_{11}F_6NO_5S$: C, 43.35; H, 2.50; N, 3.16. Found: C, 43.42; H, 2.51; N, 3.14.

Ethyl 2-Chloro-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**19**).

To a solution of 30.94 g (0.10 mole) of **5** in 200 ml of phosphorus oxychloride was added 15 g (0.92 mole) of 2,6-lutidine. The resulting suspension was heated at reflux for 72 hours to afford a black solution which was concentrated, diluted with 250 ml of anhydrous ethanol and refluxed for 24 hours. The resulting solution was diluted with 500 ml of diethyl ether, washed thrice with 10% hydrochloric acid, dried (magnesium sulfate), concentrated, and distilled (70-71°, 1.2 Torr) to afford 21.5 g (0.067 mole, 67% yield) of **19**; ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 1.42 (t, J = 7 Hz, 3H), 4.55 (q, J = 7 Hz, 2H), 8.05 (s, 1H); ^{13}C-nmr (360 MHz, chloroform-d_1): δ = 162.14, 152.67, 146.04 (q, J = 36.81 Hz), 139.72 (q, J = 35.06 Hz), 124.66, 124.27, 120.81 (q, J = 275.92 Hz), 119.75 (q, J = 275.21 Hz), 63.28, 13.13; ir (neat): 1741 and 1583 cm^{-1}.

Anal. Calcd. for $C_{10}H_6ClF_6NO_2$: C, 37.35; H, 1.88; N, 4.36. Found: C, 37.55; H, 1.90; N, 4.34.

Ethyl 2-Cycloproplylamino-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**20**).

A solution of **19** (6.51 g, 0.022 mole), 3.3 g (0.058 mole) of cyclopropylamine, and 50 ml of acetonitrile was stirred at reflux for 3 hours. After cooling to ambient temperature, the reaction was diluted with 100 ml of water and extracted once with diethyl ether. The organic phase was dried (magnesium sulfate), concentrated, and Kugelrohr distilled (80°, 0.07 Torr) to afford 5.18 g of distillate. The distillate was further purified by chromatography on silica gel with 5% ethyl acetate/cyclohexane elution followed by Kugelrohr distillation (84°, 0.075 Torr) to afford 4.58 g (0.014 mole, 73% yield) of **20**; ^{1}H-nmr (400 MHz, chloroform-d_1): δ = 0.59 (m, 2H), 0.89 (m, 2H), 1.34 (t, J = 7 Hz, 3H), 2.59 (m, 1H), 4.35 (q, J = 7 Hz, 2H), 5.83 (s, 1H), 7.11 (s, 1H); ^{13}C-nmr (400 MHz, chloroform-d_1): δ = 164.72, 159.43, 145.11 (q, J = 34.9 Hz), 138.78 (q, J = 33.50 Hz), 12.98 (q, J = 274.7 Hz), 120.66 (q, J = 175.7 Hz), 114.70, 105.13, 62.56, 23.70, 13.53, 7.50.

Anal. Calcd. for $C_{13}H_{12}F_6N_2O_2$: C, 45.62; H, 3.53; N, 8.19. Found: C, 45.55; H, 3.54; N, 8.19.

Ethyl 2-Ethylthio-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**21**).

A mixture of 7.45 g (0.0232 mole) of **19**, 1.68 g (0.0270 mole) of ethanethiol, and 6.73 g (0.049 mole) of potassium carbonate in 100 ml of dimethylformamide was heated with stirring at 50° for 16 hours. The resulting mixture was diluted with an equal volume of diethyl ether and washed once with water. The aqueous wash was extracted once with 100 ml of diethyl ether. The combined organic phases were extracted once with saturated sodium bicarbonate, once with water, dried (magnesium sulfate), concentrated, and Kugelrohr distilled (50°, 0.75 Torr) to afford 7.02 g (0.02 mole, 87% yield) of **19**; ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 1.36 (overlapping pair of t, J = 7.8 Hz, 6H), 3.31 (q, J = 7.8 Hz, 2H), 4.52 (q, J = 7.8 Hz, 2H), 7.80 (s, 1H); ^{13}C-nmr (360 MHz, chloroform-d_1): δ = 163.49, 145.35 (q, J = 35.59 Hz), 136.51 (q, 33.50 Hz), 121.48 (q, J = 275.20 Hz), 121.09, 120.49 (q, J = 275.50 Hz), 120.46, 62.87, 24.76, 13.72, 13.40.

Anal. Calcd. for $C_{12}H_{11}F_6NO_2S$: C, 41.50; H, 3.19; N, 4.03. Found: C, 41.58; H, 3.21; N, 4.02.

General Methodology for the Metallation and Electrophilic Quenching of **10** and **11**.

In a typical reaction 37 ml of 1.6 molar *n*-butyllithium (0.06 mole) in hexane was added dropwise over approximately 10 minutes to a solution of dry diisopropylamine in 25 ml of anhydrous tetrahydrofuran cooled to −78° under an atmosphere of dry nitrogen. When the addition was complete, the reaction was stirred for 15 minutes at −78°. A solution of 0.05 mole of **10** or **11** in 15 ml of anhydrous tetrahydrofuran was then added dropwise over approximately 15 minutes to the lithium diisopropylamide solution cooled to −78°. When this latter addition was complete, the reaction was allowed to warm to −40° over 1-2 hours. After cooling the reaction to −78°, 3-5 molar equivalents of the requisite electrophile was added rapidly. The reaction was then allowed to warm to ambient temperature, and was stirred at ambient temperature for 16 hours. The resulting solution was diluted with 250 ml of diethyl ether, washed twice with 10% hydrochloric acid, twice with water, dried (magnesium sulfate), and concentrated. The product was purified by Kugelrohr distillation, chromatography, or crystallization.

3-Ethyl 5-Methyl 2-Methoxy-4,6-bis(trifluoromethyl)pyridine-3,5-dicarboxylate (**24**).

Reaction of 15.04 g (0.05 mole) of **10** and 22.70 g (0.21 mole) of ethyl chloroformate as described above followed by Kugelrohr distillation (70°, 0.03 Torr) afforded 12.79 g (0.034 mole, 69% yield) of **24**; ^{1}H-nmr (60 MHz, chloroform-d$_1$): δ = 1.20 (t, J = 7.2 Hz, 3H), 3.82 (s, 3H), 4.0 (s, 3H), 4.34 (q, J = 7.2 Hz, 2H); ^{13}C-nmr (360 MHz, chloroform-d$_1$): δ = 163.68, 162.35, 160.49, 143.91 (q, J = 35.92 Hz), 136.08 (q, 34.13 Hz), 121.03 (q, J = 277.02 Hz), 120.00 (q, J = 275.63 Hz), 119.50, 118.72, 62.80, 55.36, 53.35, 13.44.

Anal. Calcd. for $C_{13}H_{11}F_6NO_5$: C, 41.61; H, 2.95; N, 3.73. Found: C, 41.90; H, 3.07; N, 3.76.

Dimethyl 2-Methoxy-4,6-bis(trifluoromethyl)pyridine-3,5-dicarboxylate (**25**).

Reaction of 10.00 g (0.033 mole) of **10** and 12.23 g (0.13 mole) of methyl chloroformate according to the general methodology afforded 6.56 g (0.0182 mole, 55% yield) of **25** following crystallization from cold hexanes, mp 73-75°; ^{1}H-nmr (chloroform-d$_1$): δ = 4.09 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H); ^{13}C-nmr (chloroform-d$_1$): δ = 163.77, 163.06, 160.56, 144.24 (q, J = 36.7 Hz), 136.41 (q, J = 32.9 Hz), 121.06 (q, J = 277.3 Hz), 120.09 (q, J = 276.9 Hz), 119.17, 118.86, 55.61, 53.61, 53.53.

Anal. Calcd. for $C_{12}H_9F_6NO_5$: C, 39.90; H, 2.51; N, 3.88. Found: C, 39.97; H, 2.54; N, 3.87.

Methyl 2-Methoxy-3-methylthio-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**26**).

Reaction of 15.60 g (0.05 mole) of **10** and 20.92 g (0.22 mole) of dimethyl disulfide followed by Kugelrohr distillation (70°, 0.03 Torr) afforded 11.76 g (0.034 mole, 65% yield) of **26**; ^{1}H-nmr (60 MHz, chloroform-d$_1$): δ = 2.51 (s, 3H), 3.99 (s, 3H), 4.20 (s, 3H); ^{13}C-nmr (360 MHz, chloroform-d$_1$): δ = 164.57, 163.39, 141.43 (q, J = 35.81 Hz), 140.23 (q, J = 30.53 Hz), 125.51, 121.58 (q, J = 277.21 Hz), 120.39 (q, J = 275.75 Hz), 119.59, 55.99, 53.31, 17.43.

Anal. Calcd. for $C_{11}H_9F_6NO_3S$: C, 37.83; H, 2.60; N, 4.01. Found: C, 38.28; H, 2.78; N, 3.98.

Methyl 2-Methoxy-3-ethylthio-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**27**).

Reaction of 9.99 g (0.033 mole) of **10** and 14.90 g (0.122 mole) of diethyl disulfide afforded, after Kugelrohr distillation (30-40°, 0.1 Torr), 7.60 g (0.021 mole, 64% yield) of **27**; ^{1}H-nmr (chloroform-d$_1$): δ = 4.12 (s, 3H), 3.91 (s, 3H), 3.02 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ^{13}C-nmr (chloroform-d$_1$): δ = 164.70, 163.55, 141.46 (q, J = 35.80 Hz), 140.78 (q, J = 30.50 Hz), 124.30, 121.66 (q, J = 278.5 Hz), 120.52 (q, J = 275.70 Hz), 119.76, 55.49, 53.39, 28.43, 14.62.

Anal. Calcd. for $C_{12}H_{11}F_6NO_3S$: C, 39.68; H, 3.05; N, 3.86. Found: C, 40.14; H, 3.01; N, 4.00.

Ethyl 2-Methoxy-3-phenylthio-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**28**).

Reaction of 9.99 g (0.032 mole) of **11** and 23.18 g (0.11 mole) of diphenyl disulfide afforded, after chromatography on silica gel with hexanes elution and subsequent Kugelrohr distillation (80°, 0.1 Torr), 6.17 g (0.015 mole, 46% yield) of **28**, ^{1}H-nmr (360 MHz, chloroform-d$_1$): δ = 1.41 (t, J = 7 Hz, 3H), 3.84 (s, 3H), 4.44 (q, J = 7 Hz, 2H), 7.2 (s with broadening at the baseline, 5H); ^{13}C-nmr (360 MHz, chloroform-d$_1$): δ 163.99, 163.05, 142.19 (q, J = 35.73 Hz), 140.55 (q, J = 30.69 Hz), 133.33, 130.25, 128.95, 127.51, 122.96, 121.68 (q, J = 277.45 Hz), 120.42 (q, J = 275.61 Hz), 119.99, 62.92, 55.13, 13.48.

Anal. Calcd. for $C_{17}H_{13}F_6NO_3S$: C, 48.05; H, 3.08; N, 3.29. Found: C, 48.07; H, 3.09; N, 3.28.

3-Methyl 5-Ethyl 2-Methoxy-4,6-bis(trifluoromethyl)pyridine-3,5-dicarboxylate (**29**).

Reaction of 10.44 g (0.033 mole) of **11** and 12.23 g (0.13 mole) of methyl chloroformate afforded, after chromatography on silica gel with 1% ethyl acetate/hexanes elution followed by Kugelrohr distillation (78°, 0.15 Torr), 8.06 g (0.022 mole, 65% yield) of **29**; ^{1}H-nmr (chloroform-d$_1$): δ = 4.39 (q, J = 7.1 Hz, 2H), 4.07 (s, 3H), 3.04 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}H-nmr chloroform-d$_1$): δ = 163.19, 163.10, 160.43, 144.15 (q, J = 35.4 Hz), 136.4 (q, J = 34.3 Hz), 121.13 (q, J = 277.4 Hz), 120.2 (q, J = 275.4 Hz), 119.33, 119.17, 63.12, 55.12, 53.43, 13.46.

Anal. Calcd. for $C_{13}H_{11}F_6NO_5$: C, 41.61; H, 2.96; N, 3.73. Found: C, 41.72; H, 2.95; N, 3.71.

2-Methoxy-4,6-bis(trifluoromethyl)pyridine-3,5-dicarboxylic Acid. 5-Methyl Ester (**30**).

Reaction of 4.82 g (0.016 mole) of **10** and excess solid carbon dioxide afforded, after Kugelrohr distillation (88°, 0.5 Torr) and recrystallization of the resultant pot residue from chloroform/hexanes, 0.80 g (0.0023 mole, 15% yield) of **30**, mp 124.5-126°; ^{1}H-nmr (60 MHz, acetone-d$_6$): δ = 4.01 (s, 3H), 4.20 (s, 3H), 10.5 (broad s, 1H).

Anal. Calcd. for $C_{11}H_7F_6NO_5$: C, 38.06; H, 2.03; N, 4.03. Found: C, 38.09; H, 2.07; N, 4.03.

Methyl 2-Methoxy-3-iodo-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**31**).

Reaction of 5.01 g (0.017 mole) of **10** and 6.5 g (0.26 mole) of iodine afforded, after Kugelrohr distillation (100°, 0.2 Torr), 2.07 g (0.005 mole, 29% yield) of **31**, mp 104-107°; ^{1}H-nmr (60 MHz, chloroform-d$_1$): δ = 4.2 (s, 5H), 4.0 (s, 3H); ^{13}C-nmr (360 MHz, chloroform-d$_1$): δ = 163.84, 162.96, 143.21 (q, J = 35.60 Hz), 142.64 (q, J = 31.83 Hz), 120.77 (q, J = 278.15 Hz), 120.25 (q, J = 275.84 Hz), 120.263, 84.66, 56.36, 53.43.

Anal. Calcd. for $C_{10}H_6F_6INO_3$: C, 27.99; H, 1.41; N, 3.26. Found: C, 28.21; H, 1.61; N, 3.17.

2-Hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylic Acid (**32**).

A solution of 34.11 g (0.118 mole) of **6**, 30 g (0.54 mole) of potassium hydroxide, 60 ml of water, and 250 ml of ethanol was heated at reflux with stirring for 5 days. After cooling to ambient temperature the solution was poured onto 450 ml of ice, diluted with 200 ml of water, acidified by the addition of concentrated hydrochloric acid, and extracted thrice with 200 ml portions of diethyl ether. The organic phases were combined, dried (magnesium sulfate), concentrated, and the residue recrystallized from diethyl ether/hexanes to afford 18.66 g (0.068 mole, 58% yield) of **32**, mp 243-246.5°; ^{1}H-nmr (60 MHz, acetone-d_6): δ = 7.33 (s, 1H), 9.18 (s, 2H); ^{13}C-nmr (360 MHz, acetone-d_6): δ = 165.38, 164.73, 144.10 (q, J = 34.72 Hz), 140.61 (q, J = 34.11 Hz), 122.76 (q, J = 274.34 Hz), 121.63 (q, J = 274.76 Hz), 119.72, 112.12 (q, J = 4.73 Hz).

Anal. Calcd. for $C_8H_3F_6NO_3$: C, 34.93; H, 1.10; N, 5.09. Found: C, 35.10; H, 1.15; N, 5.08.

Methyl 2-Ethoxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (**33**).

A stirred solution of 4.29 g (0.011 mole) of **13** and 2.15 g (0.054 mole) of sodium hydroxide in 125 ml of ethanol was heated at reflux for 45 minutes. After cooling to ambient temperature, the reaction was diluted with an equal volume of diethyl ether, washed twice with 10% hydrochloric acid, washed twice with water, dried (magnesium sulfate), and concentrated to afford 3.73 g of a colorless oil. Chromatography on silica gel afforded 2.26 g (0.007 mole, 63% yield) of **33** (eluted with 10% ethyl acetate/hexanes) and 0.70 g (0.0065 mole, 58% yield) of benzyl alcohol (eluted with 100% ethyl acetate). Pyridine **33** and benzyl alcohol were identified by comparison of their gc retention times and nmr spectra with those of authentic samples. Authentic **33** was prepared in 81% yield following Kugelrohr distillation (65-70°, 0.01 Torr) by the alkylation of **6** with ethyl iodide following the general procedure used for the preparation of **10**; ^{1}H-nmr (300 MHz, chloroform-d_1): δ = 7.10 (s, 1H), 4.40 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C-nmr (300 MHz, chloroform-d_1): δ = 164.73, 163.98, 144.46 (q, J = 35.4 Hz), 140.12 (q, J = 34.0 Hz), 121.82 (q, J = 275.1 Hz), 120.78 (q, J = 275.3 Hz), 118.53, 112.46 (q, J = 4.8 Hz), 64.17, 53.69, 14.30.

Anal. Calcd. for $C_{11}H_9F_6NO_3$: C, 41.65; H, 2.86; N, 4.42. Found: C, 41.74; H, 2.88; N, 4.44.

2-Benzyloxy-4,6-bis(trifluoromethyl)pyridine (**34**).

A stirred solution of 30.60 g (0.081 mole) of **13**, 125.21 g (0.81 mole) of DBU, and 400 ml of xylenes was heated at 100° for *ca* 7 hours. The resulting solution was cooled to ambient temperature, diluted with diethyl ether, washed twice with 10% hydrochloric acid, once with water, dried (magnesium sulfate), concentrated, and Kugelrohr distilled (70°, 0.07 Torr) to afford 13.7 g of an oil containing a solid precipitate. The oil was filtered and the filtrate was diluted with 200 ml of diethyl ether, washed twice with 10% sodium hydroxide, once with water, dried (magnesium sulfate), and concentrated to afford 8.38 g (0.026 mole, 30% yield) of **34**; ^{1}H-nmr (60 MHz, chloroform-d_1): δ = 5.51 (s, 2H), 7.2 to 7.7 (m, 7H); ^{13}C-nmr (360 MHz, chloroform-d_1): δ = 164.00, 147.02 (q, J = 35.96 Hz), 142.14 (q, J = 34.76 Hz), 135.65, 128.78, 128.42, 128.29, 121.91 (q, J = 273.28 Hz), 120.65 (q, 273.94 Hz), 111.64, 109.18, 69.02.

Anal. Calcd. for $C_{14}H_9F_6NO$: C, 52.35; H, 2.82; N, 4.36. Found: C, 52.76; H, 3.14; N, 4.37.

2-Benzyloxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylic Acid (**35**).

To a solution of 5.81 g (0.015 mole) of **13** in 100 ml of dimethylformamide was added 2.08 g (0.03 mole) of sodium methanethiolate. The resulting deep red solution was stirred at ambient temperature for 15 minutes, diluted with an equal volume of diethyl ether, washed twice with 10% hydrochloric acid, once with water, dried (magnesium sulfate), and concentrated to afford 5.28 g of a crystalline solid. Recrystallization from acetone/hexanes afforded 1.69 g (0.0046 mole, 30% yield) of **35**, mp 178-180°; ^{1}H-nmr (400 MHz, acetone-d_6): δ = 5.54 (s, 2H), 7.34 to 7.57 (m, 6H); ^{13}C-nmr (400 MHz, acetone-d_6): δ = 165.03, 164.19, 143.62 (q, J = 35.90 Hz), 140.11 (q, J = 34.10 Hz), 136.65, 129.33, 129.19, 129.06, 122.64 (q, J = 275.1 Hz), 121.65 (q, J = 275.0 Hz), 120.47, 113.88 (q, J = 6.1 Hz), 70.03.

Anal. Calcd. for $C_{15}H_9F_6NO_3$: C, 49.33; H, 2.48; N, 3.84. Found: C, 49.41; H, 2.48; N, 3.83.

2-Methoxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylic Acid (**36**).

Reaction of 3.61 g (0.01191 mole) of **10** and 0.85 g (0.0121 mole) of sodium methanethiolate in 50 ml of anhydrous dimethylformamide following the general procedure described for **35**, with the exception that the reaction was conducted at 0°, afforded 3.76 g of crude product. Purification by silica gel chromatography with elution by 60:40:4 ethyl acetate/cyclohexane/acetic acid followed by crystallization from hexanes afforded 1.03 g (0.0036 mole, 30% yield) of **36**; mp 161.5-164.5°; ^{1}H-nmr (400 MHz, acetone-d_6): δ = 4.08 (s, 3H), 7.50 (s, 1H); ^{13}C-nmr (400 MHz, acetone-d_6): δ = 165.04, 164.82, 143.74 (q, J = 35.9 Hz), 139.92 (q, J = 33.0 Hz), 122.63 (q, J = 274.0 Hz), 121.63 (q, J = 275.3 Hz), 120.29 (q, J = 2.4 Hz), 113.54 (q, J = 5.2 Hz), 55.19.

Anal Calcd. for $C_9H_5F_6NO_3$: C, 37.39; H, 1.74; N, 4.84. Found: C, 37.49; H, 1.82; N, 4.82.

2-Benzyloxy-4,6-bis(trifluoromethyl)pyridine-5-carbonyl Chloride (**37**).

Technical **35** (15.71 g, 0.043 mole) was dissolved in 100 ml of thionyl chloride and the resulting solution was refluxed for 16 hours. Removal of unreacted thionyl chloride *in vacuo* followed by Kugelrohr distillation (80°, 0.2 Torr) and crystallization of the resulting distillate from cold hexanes afforded 10.10 g (0.027 mole, 49% yield based on starting **13**) of **37**, mp 68-59.5°; ^{1}H-nmr (400 MHz, chloroform-d_1): δ = 5.35 (s, 2H), 7.31 to 7.53 (m, 6H); ^{13}C-nmr (400 MHz, chloroform-d_1): δ = 164.20, 163.68, 142.32 (q, J = 35.0 Hz), 138.43 (q, J = 35.10 Hz), 134.82, 128.87, 128.77, 128.65, 122.84, 121.16, (q, J = 275.70 Hz), 120.19 (q, J = 275.30 Hz), 112.75 (q, J = 4.5 Hz), 70.03.

Anal Calcd. for $C_{15}H_8ClF_6NO_2$: C, 46.96; H, 2.10; N, 3.65. Found: C, 47.08; H, 2.12; N, 3.52.

2-Benzyloxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylic Acid. Cyclopropyl Amide (**38**).

A solution of 2.01 g (0.0053 mole) of **37** and 0.824 g (0.0144 mole) of cyclopropylamine in 40 ml of anhydrous dimethylformamide was stirred at ambient temperature for 3 hours. The reaction was diluted with 50 ml of water, and the resulting precipitate was collected by filtration, air dried, and recrystallized from methylene chloride/hexanes to afford 1.76 g (0.0044 mole, 83% yield) of **38**, mp 160.5-161.5°; ^{1}H-nmr (400 MHz, chloroform-d_1): δ = 0.60 (m, 2H), 0.82 (m, 2H), 2.78 (m, 1H), 5.45 (s, 2H), 6.23 (s,

1H), 7.18 to 7.50 (m, 6H); ^{13}C-nmr (400 MHz, chloroform-d$_1$): δ = 163.90, 162.87, 143.86 (q, J = 34.70 Hz), 140.19 (q, J = 33.40), 135.35, 128.70, 128.53, 128.50, 121.89 (q, J = 274.30 Hz), 120.67 (q, J = 275.50 Hz), 112.30, 69.32, 22.99, 6.23.

Anal. Calcd. for $C_{18}H_{14}F_6N_2O_2$: C, 53.47; H, 3.49; N, 6.93. Found: C, 53.55; H, 3.54; N, 6.91.

2-Benzyloxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylic Acid. 2-Hydroxyethyl Amide (**39**).

Reaction of 5.0 g (0.0131 mole) of **37** and 1.822 g (0.03 mole) of ethanolamine following the same procedure used for the preparation of **38** afforded 4.90 g (0.0120 mole, 92% yield) of **39** after air drying, mp 114.5-116°; ^{1}H-nmr (400 MHz, acetone-d$_6$): δ = 3.51 (d of d, J = 5.9 Hz, J = 11.88 Hz, 2H), 3.70 (d of d, J = 5.8 Hz, J = 11.4 Hz, 2H), 3.89 (t, J = 5.23 Hz, 1H), 5.52 (s, 2H), 7.35 to 7.60 (m, 6H), 7.90 (s, 1H); ^{13}C-nmr (400 MHz, acetone-d$_6$): δ = 163.64, 163.37, 143.77 (q, J = 35.30 Hz), 140.66 (q, J = 33.4 Hz), 136.85, 129.35, 129.19, 129.03, 123.93, 122.81 (q, J = 276.2 Hz), 121.85 (q, J = 275.7 Hz), 113.42 (q, J = 4.1 Hz), 69.69, 60.95, 43.24.

Anal. Calcd. for $C_{17}H_{14}F_6N_2O_3$: C, 50.01; H, 3.46; N, 6.86. Found: C, 50.01; H, 3.48; N, 6.84.

2-Benzyloxy-4,6-bis(trifluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-pyridine (**40**).

A suspension of 3.01 g (0.0074 mole) of **39** and 2.05 g (0.015 mole) of phosphorous pentachloride in 75 ml of carbon tetrachloride was stirred for 2 hours at ambient temperature to afford a clear solution. The solution was then heated at reflux for 1 hour, cooled, and concentrated to afford 3.8 g of oil. The oil was dissolved in 60 ml of anhydrous tetrahydrofuran to which was added, with stirring, 0.61 g (0.013 mole) of lithium sulfide. The resulting reaction was refluxed for 16 hours, cooled, quenched with 10 ml of 10% hydrochloric acid, diluted with 100 ml of diethyl ether, washed twice with 10% hydrochloric acid, once with brine, dried (magnesium sulfate), and concentrated to afford 3.32 g of an oil. Purification by Kugelrohr distillation (140°, 0.02 Torr) afforded 2.42 g (0.0060 mole, 81% yield) of **40**; ^{1}H-nmr (360 MHz, chloroform-d$_1$): δ = 3.54 (t, J = 8.4 Hz, 2H), 4.44 (t, J = 8.4 Hz, 2H), 5.49 (s, 3H), 7.30 to 7.51 (m, 6H); ^{13}C-nmr (360 MHz, chloroform-d$_1$: δ = 163.09, 161.18, 144.95 (q, J = 34.53 Hz), 141.22 (q, J = 32.97 Hz), 135.32, 128.69, 128.46, 128.43, 121.57, (q, J = 276.06 Hz), 120.70 (q, J = 276.89 Hz), 119.51, 112.59 (q, J = 4.96 Hz), 69.24, 65.39, 35.81.

Anal. Calcd. for $C_{17}H_{12}F_6N_2OS$: C, 50.25; H, 2.98; N, 6.89. Found: C, 49.93; H, 3.16; N, 6.56.

2-Methoxy-4,6-bis(trifluoromethyl)pyridine-3-carboxylic Acid. Pyrazole Amide (**43**).

Technical **36**, prepared from 16.46 g (0.054 mole) of **10**, by reaction with 200 ml of thionyl chloride following the general procedure described for the preparation of **37**, afforded 7.58 g (*ca.* 45% yield) of technical acid chloride **42**. Without further purification, a solution of 7.58 g of technical **42**, 5.2 g (0.076 mole) of pyrazole, and 100 ml of acetonitrile was stirred at 80° for 24 hours. An additional 3 g (0.044 mole) of pyrazole was added, and heating was continued for 8 hours. After cooling to ambient temperature, the reaction was diluted with an equal volume of 10% hydrochloric acid, and extracted once with 250 ml of diethyl ether. The ether phase was washed once with water, dried (magnesium sulfate), and concentrated to afford 7.58 g of crude product. Purification by Kugelrohr distillation (66°, 0.3 Torr) afforded 6.43 g (0.019 mole, 73% yield based on technical **42**, 33% overall) of **43**; mp = 68-71°; ^{1}H-nmr (400 MHz, chloroform-d$_1$): δ = 8.4 (d, J = 2.4 Hz, 1H), 7.69 (s, 1H), 7.29 (s, 1H), 6.55 (m, 1H), 4.09 (s, 3H); ^{13}C-nmr (400 MHz, chloroform-d$_1$): δ = 164.38, 162.75, 145.11, 144.12 (q, J = 35.8 Hz), 140.00 (q, J = 34.2 Hz), 128.64, 121.48 (q, J = 275.8 Hz), 120.38 (q, J = 275.6 Hz), 118.53, 112.30 (q, J = 4.4 Hz), 110.92, 54.93.

Anal. Calcd. for $C_{12}H_7F_6N_3O_2$: C, 42.49; H, 2.08; N, 12.39. Found: C, 42.53; H, 2.08; N, 12.36.

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