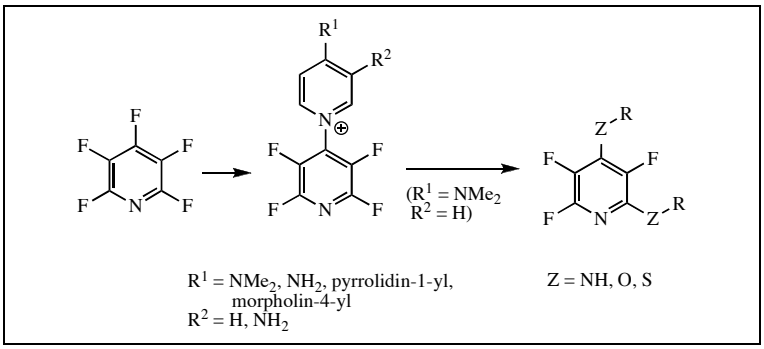
Hetarenium Salts from Pentafluoropyridine. Syntheses, Spectroscopic Properties, and Applications

Andreas Schmidt,* Thorsten Mordhorst, Jan Christoph Namyslo, and Werner Telle

Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld, Germany

Received October 9, 2006



Reaction of pentafluoropyridine with nucleophilic heteroaromatics such as 4-(dimethylamino)pyridine, 4-(pyrrolidin-1-yl)pyridine, 4-(morpholin-4-yl)pyridine, 4-aminopyridine, and 3,4-diaminopyridine resulted in the formation of 4-hetarenium substituted tetrafluoropyridines. The 4-(dimethylamino)-pyridinium derivative underwent substitution reactions with isopropanolate, isopropanethiolate, and benzylthiolate to F^2,F^3,O^4,F^5,F^6- and O^2,F^3,O^4,F^5,F^6-pentasubstituted pyridines as well as their sulfur analogs. *N*-Propylamine, isopropylamine, and piperidine formed 4-amino-N^2,F^3,F^5,F^6-pentasubstituted pyridines in the presence of sodium amide as base, whereas morpholine gave the 4-amino-2,6-bis-morpholino-substituted 3,5-difluoropyridine. ^{19}F, ^{15}N, ^{13}C, and ^1H nmr spectrocopy was performed to elucidate the structures of the substitution products.

J. Heterocyclic Chem., **44**, 679 (2007).

INTRODUCTION

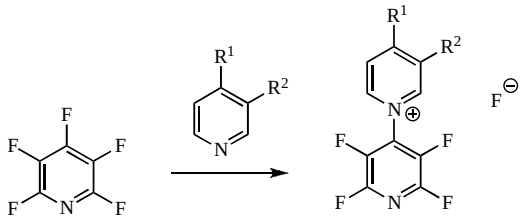
4-(Dimethylamino)pyridine (DMAP) and other nucleophilic heteroaromatics such as 4-(pyrrolidin-1-yl)pyridine and 1-methylimidazole are very versatile reagents in organic chemistry due to catalyzing, stabilizing, and activating properties. Catalysis of acylations [1-4], Baylis-Hillman [5] and Dakin-West reactions [6], silylations [7], and many other syntheses by DMAP is widely applied in organic synthesis. Stabilization of reactive species such as allyl anions [8], allyl radicals [9], uracilates [10,11], pyrimidinium-olates [12-14] as well as -aminides [15,16], pyridinium-olates [17] and heteroaromatics with up to ten positive charges within a common π-electron system by 4-(dimethylamino)-pyridinium and other hetarenium substituents [18] was reported. The activation of perhalogenated heteroaromatics by hetarenium substituents can be applied for the preparation of otherwise unavailable functionalized heteroaromatics. We reported that activation of pentachloropyridine by 4-(dimethylamino)pyridinium substituents enables the synthesis of Cl^2,Cl^3,O^4,Cl^5,Cl^6- and O^2,Cl^3,O^4,Cl^5,Cl^6-pentasubstituted pyridines [19] as well as their sulfur analogs [20]. Similarly, first examples of O^2,Cl^3,O^4,Cl^5,O^6- [17] and N^2,Cl^3,S^4,Cl^5,N^6- [21] substitution patterns, biologically interesting S^2,Cl^3,S^4,Cl^5,S^6- [20], and a variety of O^2,Cl^3,S^4,Cl^5,O^6-pentasubstituted pyridines can be prepared starting from 4-(dimethylaminopyridinium)-activated chloropyridines. In view of the current interest in pentafluoropyridine as valuable building block in sequential controlled substitution reactions [22,23], we report here our results on syntheses of pyridinium salts prepared from pentafluoropyridine, and some reactions of the 4-(4-dimethylamino)pyridinio substituted tetrafluoropyridine.

RESULTS AND DISCUSSION

Reaction of pentafluoropyridine with 4-(dimethylamino)pyridine, 4-(pyrrolidin-1-yl)pyridine, 4-(morpholin-4-yl)pyridine, 4-aminopyridine, and 3,4-diaminopyridine gave the 2',3',5',6'-tetrafluoro-[1,4]bipyridinyl-1-ylium fluorides **2a-e** (Scheme 1). Best yields were obtained when ethyl acetate was used as the solvent, and when reaction times of approximately 6 hours at room temperature were allowed. Heating in 1,2-dichlorobenzene and excessive heteroarene did not improve the yields, but caused the formation of by-products which were difficult to separate.

Whereas the structure elucidation of **2a-c** is unambiguous, alternative structures for **2d** and **2e** had to be taken into consideration. 4-Aminopyridine and 3,4-diaminopyridine are N,N-bis- and N,N,N-tris-

Scheme 1



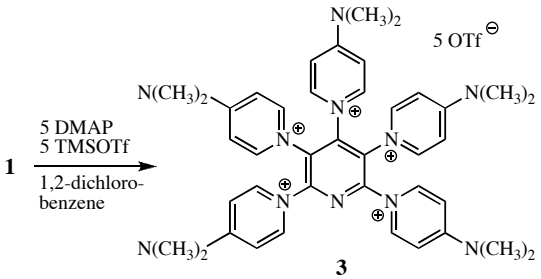
1 **2a - 2e**

Compound	R^1	R^2	Mp (°C)	Yield %	Molecular Formula	HR-ESI-MS Calcd/Found
2a	$N(CH_3)_2$	H	158	93	$C_{12}H_{10}N_3F_5$	272.0811 ($C_{12}H_{10}N_3F_4^+$) / 272.0811
2b	pyrrolidin-1-yl	H	126	79	$C_{14}H_{12}N_3F_5$	298.0967 ($C_{14}H_{12}N_3F_4^+$) / 298.0976
2c	morpholin-1-yl	H	62	99	$C_{14}H_{12}N_3OF_5$	314.0917 ($C_{14}H_{12}N_3OF_4^+$) / 314.0918
2d	NH_2	H	216	75	$C_{10}H_6N_3F_5$	244.0491 ($C_{10}H_6N_3F_4^+$) / 244.0498
2e	NH_2	NH_2	102 (dec.)	88	$C_{10}H_7N_4F_5$	259.0610 ($C_{10}H_7N_4F_4^+$) / 259.0607

nucleophiles, respectively, and amines are known to react smoothly with pentafluoropyridine in the 4-position. The pyridinium salts **2a-e**, however, behave very similar under electrospray ionization mass spectrometry (ESIMS) conditions, which is the method of choice to detect cationic molecules. Thus, the base peaks in the high-resolution ESI mass spectra of all compounds **2a-e** are the molecular peaks. Sodium adducts, which are often observed on measurement of uncharged compounds, are not detected. The formation of pyridinium salts was moreover confirmed by an HMBC spectrum of **2e** which unambiguously displayed the CH-coupling of C-4 to *H*-2' and *H*-6' of the 3,4-diaminopyridinium ring.

Reaction of pentafluoropyridine with five equivalents of 4-(dimethylamino)pyridine and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in 1,2-dichlorobenzene resulted in the formation of the pentacationic species **3** in 90% yield (Scheme 2) which is also available starting from pentachloropyridine applying analogous reaction conditions [18].

Scheme 2

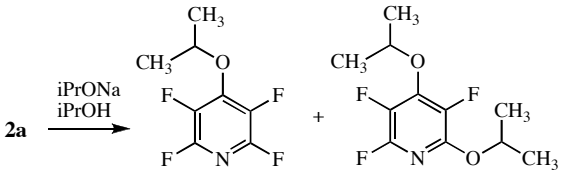


3

We then tested some nucleophilic substitutions on the 4-(dimethylamino)pyridinio substituted 2,3,5,6-tetrafluoropyridine **2a**. This salt is stable toward water over a period of 10 hours at reflux temperature. Whereas pentafluoropyridine reacts with sodium hydroxide to 4-hydroxytetrafluoropyridin [24], the pyridinium salt **2a** gives 3,5,6-trifluoro-2,4-dihydroxypyridine. No reaction was observable on treatment of **2a** with 2-propanolate at room temperature. At reflux temperature, however, a mixture of compounds was obtained after a reaction time of 2 hours. Performing the reaction at 45°C over a period of six hours resulted in the formation of 2,3,5-trifluoro-4,6-di-(2-propoxy)pyridine **5** which was isolated in 45% yield after chromatographic work-up (Scheme 3). 2,3,5,6-Tetrafluoro-4-(2-propoxy)pyridine **4** was found as by-product in 12% yield. This compound is the major product of the reaction of pentafluoropyridine with 2-propanol in dimethylformamide in the presence of triethylamine at room temperature [25]. According to a GCMS analysis of the crude reaction mixture, an additional by-product of this reaction is tris-(2-propoxy)-substituted difluoropyridine, as peaks at *m/z* 289 (M, 51), and characteristic fragmentation patterns at *m/z* 247, 203, and 160 are detectable. In ^{19}F nmr spectroscopy in deuteriochloroform, signals of the monopropoxy derivative **4** were detected at δ -158.8 ppm and δ -91.4 ppm, which were assigned to 3/5-F and 2/6-F, respectively. The value of the *FF* coupling constants through five, three, and four bonds were measured as ≈ –34.3, –17.5 Hz, and –4.6 Hz, respectively. As expected, the bispropoxy derivative **5** gave three distinct ^{19}F nmr resonance frequencies

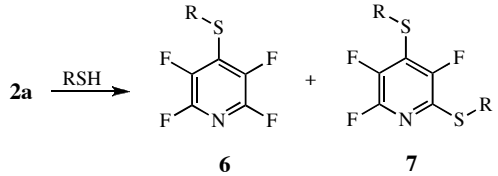
which were detected at δ -167.1, -159.1, and -94.4 ppm. The measurement yielded characteristic coupling constants (see Experimental). This reaction is similar to the preparation of 2,4-di-*tert*-butoxy-3,5,6-trifluoropyridine from pentafluoropyridine and the potassium salt of *tert*-butyl alcohol which is quite temperature-sensitive [26].

Scheme 3



2-Propanethiole and benzylthiole were chosen as *S*-nucleophiles. The former mentioned thiole replaced the 4-(dimethylamino)pyridinium ring of **2a** in a mixture of acetone and methanol within 18 hours at room temperature to give the 4-(2-propanesulfanyl)-tetrafluoropyridine **6a** which is a known compound [27] (Scheme 4). Benzylthiole reacted to a mixture of 4-mono- and 4,6-bis-sulfanyls **6b** and **7b**, which was separated chromatographically, in 68% yield. According to the Beilstein CrossFire database, **7b** is the first representative of a S^2,F^3,S^4,F^5,F^6-pentasubstituted pyridine.

Scheme 4



6a,7a: R = *i*Pr
6b,7b: R = CH_2Ph

1-Propylamine, 2-propylamine, and piperidine afforded the 2-NR_2-substituted 4-amino-3,5,6-trifluoropyridines **8a-c** on reaction with **2a** (Scheme 5), when the reaction is conducted in the presence of sodium amide as base. The ^{13}C nmr spectra clearly indicated non-symmetric structures in agreement with an α, γ-disubstitution pattern of the former pentafluoropyridine ring. Ten protons in **8a** and **8b** were detected by ^1H nmr spectroscopy, and the mass spectra confirmed one amino group plus one

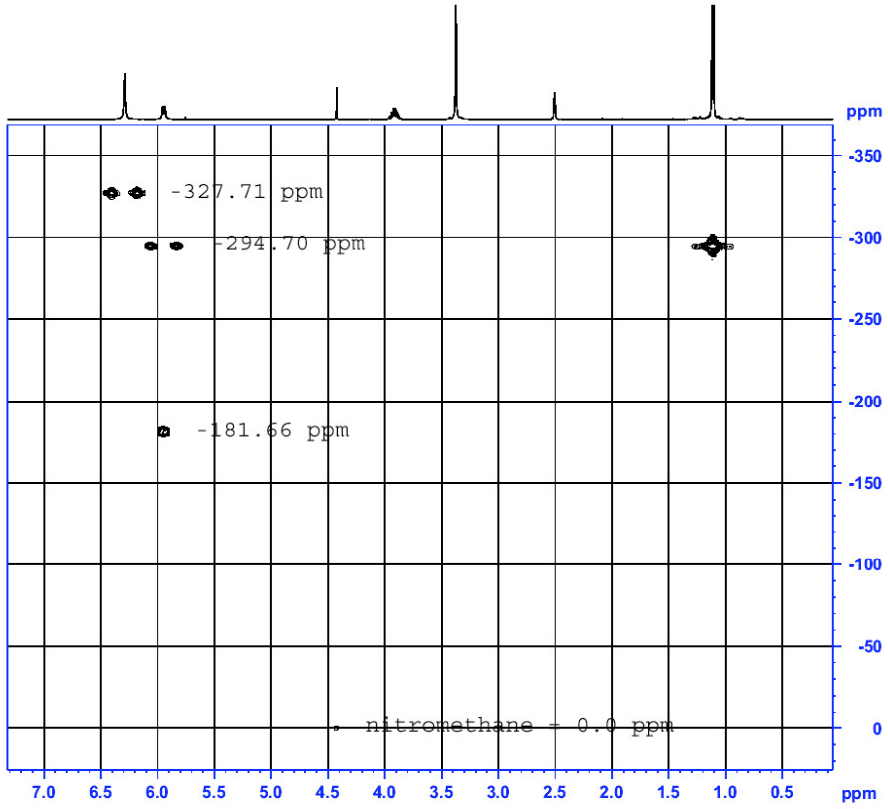
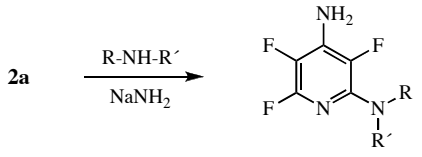
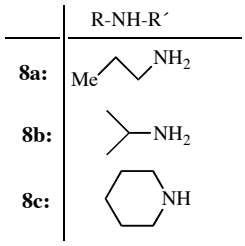


Figure 1. ^1H-^{15}N-HMBC spectrum of **8b** in [D_6]-DMSO.

Scheme 5



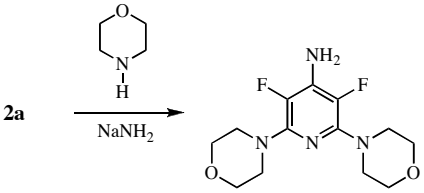
8a-c



propylamino group attached to the trifluoropyridine ring, respectively. In the ^{13}C nmr spectrum taken in deuteriochloroform the resonance frequency of C3 of **8b** is diagnostically important, as it shows the splitting expected for a N^2,F^3,N^4,F^5,F^6-substitution pattern, and the characteristic magnitudes of the coupling constants (dd, $^1J_{CF}$ = 236.6 Hz; $^3J_{CF}$ = 4.4 Hz). Halogen dance reactions were therefore excluded from consideration. The ^{15}N nmr spectrum taken in [D_6]-DMSO displayed three signals at δ -327.7 (NH$_2$), -294.7 (NH), and -181.7 ppm (N_{pyr}). In contrast to the ^1H nmr spectrum taken in deuteriochloroform, separated resonance frequencies of the secondary amine proton at δ 5.9 ppm and the methine proton at δ 3.9 ppm were measured in deuteriodimethylsulfoxide, and after some variation of the concentration of the solution of **8b** we were able to measure an ^1H-^{15}N-HMBC spectrum which is shown in Figure 1. The $^3J_{NH}$-coupling between the nitrogen atom of the pyridine ring and the secondary N*H* proton proves that the isopropylamino group is attached to C2 of the pyridine ring. In accordance with the assigned structure, three ^{19}F nmr resonance frequencies appear at δ –177.1, -164.4, and 97.0 ppm, respectively.

Under analogous reaction conditions, morpholine gave the 2,6-bis-morpholino-substituted 4-amino-3,5-difluoropyridine **9** (Scheme 6). In accordance to the assigned structure, only one ^{19}F nmr resonance frequency is detectable at δ = -160.0 ppm as a singlet.

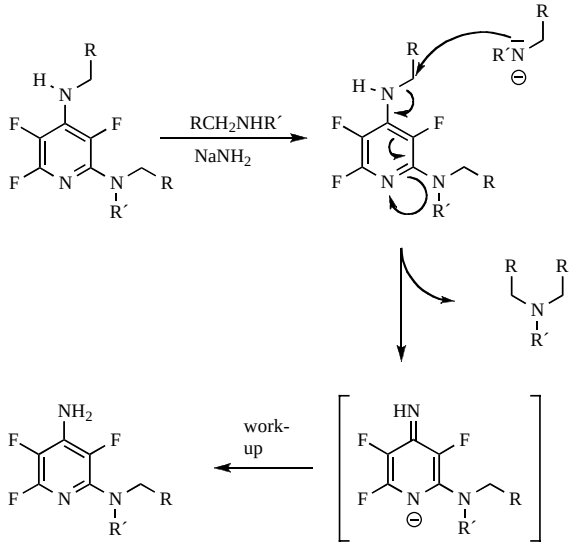
Scheme 6



9

A priori, two mechanisms for the formation of **8a-c** and **9** have to be considered. Thus, substitution of the 4-(dimethylamino)pyridinium ring by amide yielded the observed products. In a control experiment, however, the pyridinium salt **2a** did neither react with sodium amide (DMF, reflux, 6 h), nor with ammonia (dioxane/water, 30 h at rt or 4 h at 90°C) to 4-amino-tetrafluoropyridine. Therefore, we assume a dealkylation mechanism (Scheme 7), which we proved in a reaction of the tetrachloro derivative of **2a** in an analogous series of reactions before [28].

Scheme 7



In summary, we present new (tetrafluoro-4-yl)pyridinium salts which can serve as starting materials for the synthesis of highly functionalized pyridines.

EXPERIMENTAL

The nmr spectra were recorded on a Bruker Avance 400 at 400 MHz (^1H nmr), 100 MHz (^{13}C nmr), 376 MHz (^{19}F nmr) and 40 MHz (^{15}N nmr), respectively. The chemical shifts of the ^1H and ^{13}C nmr spectra are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm). The exact reference for the ^{19}F nmr spectra was trichlorofluoromethane (Cl_3CF) in deuteriochloroform (δ = 0.0 ppm), and for the ^{15}N nmr measurements nitromethane (CH_3NO_2) in deuteriochlorofom (δ = 0.0 ppm). FT-IR spectra were obtained on a Bruker Vector 22 in the range of 400 to 4000 cm^{-1} (2.5 % pellets in KBr). The GC-MS spectra were recorded on a GC Hewlett-Packard 5980, Serie II in combination with a MS Hewlett-Packard 5989 B, and on a Varian GC3900 with SAT2100T mass spectrometer. Melting points are uncorrected. The fluorine contents prevented us from performing CHN analyses.

General procedure for the synthesis of the 2',3',5',6'-tetrafluoro-[1,4]bipyridinyl-1-ylium fluorides (2a-e). Pentafluoropyridine (1.69 g, 10 mmol) and the heteroarene [4-(dimethylamino)pyridine (1.22 g, 10 mmol), 4-(pyrrolidin-1-

yl)pyridine (1.48 g, 10 mmol), 4-(morpholin-4-yl)-pyridine (1.64 g, 10 mmol), 4-aminopyridine (0.94 g, 10 mmol), 3,4-diaminopyridine (1.09 g, 10 mmol), respectively] were suspended in 100 mL of ethyl acetate. The suspensions were stirred for 6 h, respectively. The precipitates were filtered off and dried *in vacuo*.

4-(Dimethylamino)-2',3',5',6'-tetrafluoro-[1,4]bipyridinyl-1-ylium fluoride (2a). This salt was isolated as a yellow solid, mp 155 – 158°C. ^{1}H nmr ([D$_6$]-DMSO): δ 8.45 (d, ^{3}J = 7.8 Hz, 2H; H-2'), 7.36 (d, ^{3}J = 7.8 Hz, 2H; H-3'), 3.35 (s, 6H; C*H*$_3$) ppm; ^{1}H nmr (CD$_3$OD): δ 8.24 (d, ^{3}J = 8.0 Hz, 2H, H-2'), 7.19 (d, ^{3}J = 8.0 Hz, 2H, H-3'), 3.31 (s, 6H, N(C*H*$_3$)$_2$); ^{13}C nmr (CD$_3$OD): δ 39.8 (*C*H$_3$), 108.2 (C-3'), 130.9 (m, C-4), 137.9 (d, ^{1}J = 256.2 Hz, C-2), 141.4 (C-2'), 143.6 (ddd, ^{1}J = 244.7 Hz, ^{2}J = 14.3 Hz, ^{4}J = 4.4 Hz, C-2) 157.2 (C-4'); ir (potassium bromide): 3442, 3033, 2360, 1651, 1585, 1492, 1233, 1164, 970, 847 cm^{-1}.

2',3',5',6'-Tetrafluoro-4-(pyrrolidin-1-yl)-[1,4]bipyridinyl-1-ylium fluoride (2b). This compound was isolated as a yellow solid. ^{1}H nmr (DMSO-d$_6$): δ 8.46 (d, ^{3}J = 7.9 Hz, 2H; H-2'), 7.22 (d, ^{3}J = 7.9 Hz, 2H; H-3'), 3.51 – 3.75 (m, 4H; N-C*H*$_2$-), 1.95 – 2.15 (m, 4H; -C*H*$_2$-) ppm; ^{13}C nmr (DMSO-d$_6$): δ 153.5 (C-4'), 143.7 (dtd, ^{1}J$_{CF}$ = 245.0 Hz, ^{2}J$_{CF}$ = 14.7 Hz, ^{3}J$_{CF}$ = 4.4 Hz, 2C, C-2), 141.2 (C-2'), 137.1 (ddd, ^{1}J$_{CF}$ = 262.6 Hz, ^{2}J$_{CF}$ = 29.7 Hz, ^{3}J$_{CF}$ = 5.8 Hz, 2C, C-3), 130.9 (m, 1C, C-4), 109.2 (C-3'), 49.2 (N-*C*H$_2$-), 24.5 (-*C*H$_2$-) ppm; ir (potassium bromide): 3088, 3030, 2880, 1648, 1574, 1508, 1477, 1227, 1164, 972, 848 cm^{-1}.

2',3',5',6'-Tetrafluoro-4-(morpholin-4-yl)-[1,4]bipyridinyl-1-ylium fluoride (2c). This salt was obtained as a yellow solid. ^{1}H nmr (D$_2$O): δ 8.11 (d, ^{3}J = 7.2 Hz, 2H; H-2'), 7.18 (d, ^{3}J = 7.2 Hz, 2H; H-3'), 3.60 – 3.90 (m, 8H; -C*H*$_2$-) ppm; ^{13}C nmr (D$_2$O): δ 156.6 (C-4'), 143.6 (dtd, ^{1}J$_{CF}$ = 243.6 Hz, ^{2}J$_{CF}$ = 15.4 Hz, ^{3}J$_{CF}$ = 2.9 Hz, 2C, C-2), 141.8 (C-2'), 137.6 (ddd, ^{1}J$_{CF}$ = 261.2 Hz, ^{2}J$_{CF}$ = 32.2 Hz, ^{3}J$_{CF}$ = 4.4 Hz, 2C, C-3), 130.9 (m, 1C, C-4), 108.3 (C-3'), 65.7 (-O*C*H$_2$-), 46.9 (N*C*H$_2$-) ppm; ir (potassium bromide): 3443, 1645, 1565, 1490, 1233, 1163, 1114, 972, 932 cm^{-1}.

4-Amino-2',3',5',6'-tetrafluoro-[1,4]bipyridinyl-1-ylium fluoride (2d). This salt was isolated as a yellow solid. ^{1}H nmr ([D$_6$]-DMSO): δ 9.62 (s, br, N*H*$_2$), 8.31 (d, ^{3}J = 7.6 Hz, 2H; H-2'), 7.08 (d, ^{3}J = 7.6 Hz, 2H; H-3') ppm; ^{13}C nmr ([D$_6$]-DMSO): δ 160.2 (C-4'), 142.3 (C-2'), 110.0 (C-3') ppm; the C-atoms of the fluoropyridine moiety gave very small signals; ir (potassium bromide): 3063, 1638, 1475, 1158, 972, 867, 835, 747 cm^{-1}.

3,4-Diamino-2',3',5',6'-tetrafluoro-[1,4]bipyridinyl-1-ylium fluoride (2e). This salt was isolated as a yellow solid. ^{1}H nmr (D$_2$O): δ 7.69 (dd, ^{3}J = 6.5 Hz, ^{4}J = 1.1 Hz, 1H; H-6'), 7.64 (d, ^{4}J = 1.1 Hz, 1H; H-2'), 6.81 (dd, ^{3}J = 6.5 Hz, ^{4}J = 1.1 Hz, 1H; H-5') ppm; ^{13}C nmr (D$_2$O): δ 151.4 (C-4'), 143.7 (ddd, ^{1}J$_{CF}$ = 245.5 Hz, ^{2}J$_{CF}$ = 14.7 Hz, ^{4}J$_{CF}$ = 3.4 Hz, 2C, C-2), 137.7 (ddd, ^{1}J$_{CF}$ = 265.2 Hz, ^{2}J$_{CF}$ = 37.8 Hz, ^{4}J$_{CF}$ = 2.5 Hz, 2C, C-3), 136.3 (C-3'), 132.5 (C-6'), 131.5 (t, ^{2}J$_{CF}$ = 12.1 Hz, 1C, C-4), 122.8 (C-2'), 107.6 (C-5') ppm; ir (potassium bromide): 1618, 1581, 1476, 1333, 1147, 972, 850 cm^{-1}.

1,1',1'',1''',1''''-Pentakis[4-(dimethylamino)-(pyridine-2,3,4,5,6-pentayl)pyridinium]pentakis(trifluoromethanesulfonate) (3). Pentafluoropyridine (1.68 g, 10 mmol), 4-(dimethylamino)-pyridine (6.1 g, 50 mmol) and trimethylsilyl trifluoromethansulfate (12.22 g, 55 mmol) were dissolved under nitrogen in 200 mL of 1,2-dichlorobenzene and heated at 180°C. After one hour, the solution was cooled to room temperature, and the crude reaction product was filtered off, washed several times with petrol and dried *in vacuo*. Analytical and spectroscopic data are in total agreement with those reported earlier [18].

2,3,5,6-Tetrafluoro-4-isopropoxypyridine (4). This compound was isolated as a by-product in the synthesis of **5** and was isolated as colorless oil (R$_f$ 0.44, petrol), yield 231 mg (12%). ^{1}H nmr (deuteriochlorofom): 1.48 (d, ^{3}J = 6.1 Hz, 6H; C*H*$_3$), 5.06 (sept, ^{3}J = 6.1 Hz, 1H; C*H*); ^{19}F nmr (trichlorofluoromethane): δ -91.4 (ddd, badly resolved; 2/6-*F*), -158.0 (ddd, ^{5}J$_{3,6}$ = ^{5}J$_{5,2}$ = -34.3 Hz, ^{3}J$_{3,2}$ = ^{3}J$_{5,6}$ = -17.5 Hz, ^{4}J$_{3,5}$ = ^{4}J$_{5,3}$ = -4.6 Hz; 3/5-*F*); ^{13}C nmr (deuteriochlorofom) δ 22.6 (*C*H$_3$), 78.4 (*C*H), 135.7 (d, ^{1}J$_{CF}$ = 255.2 H, C-3/5), 144.3 (d, ^{1}J$_{CF}$ = 239.9 Hz, C-2/6), 146.6 (C-4); ir (sodium chloride): 2932, 2361, 1719, 1643, 1503, 1472, 1389, 1258, 1092, 977, 904, 739, 589, cm^{-1}; ms: *m/z* = 210 ([M+H]$^+$, 100).

2,3,5-Trifluoro-4,6-di-(2-propoxy)-pyridine (5). Sodium 2-propanolate (0.82 g, 10 mmol) and 4-(dimethylamino)-2',3',5',6'-tetrafluoro-[1,4]bipyridinyl-1-ylium fluoride **2a** (2.91 g, 10 mmol) in 50 mL of 2-propanol were heated at 45°C over a period of 5 h. After cooling, the alcohol was distilled off *in vacuo*. The residue was chromatographed on silica gel with ethyl acetate/petrol = 1:8. The pyridine 5 was obtained as colorless solid in 45% yield (1.05 g); R$_f$ = 0.42 (petrol/ethyl acetate = 8:1). ^{1}H nmr (deuteriochloroform): δ 5.20 (sept, ^{3}J = 6.2 Hz, 1H; C*H*), 4.87 (sept, ^{3}J = 6.2 Hz, 1H; C*H*), 1.40 (d, ^{3}J = 6.2 Hz, 6H; C*H*$_3$), 1.37 (d, ^{3}J = 6.2 Hz, 6H; C*H*$_3$) ppm; ^{19}F nmr (trichlorofluoromethane): δ -94.4 (dd, ^{3}J$_{FF}$ = 25.2 Hz; ^{5}J$_{FF}$ = 22.9 Hz; 6-*F*), -159.1 (d, ^{3}J$_{FF}$ = 25.2 Hz; 5-*F*), -167.1 (d, ^{5}J$_{FF}$ = 22.9 Hz; 3-*F*); ^{13}C nmr (deuteriochloroform): δ 21.9 (*C*H$_3$), 22.6 (*C*H$_3$), 70.4 (*C*H), 77.5 (*C*H), 132.5 (dd, ^{1}J$_{CF}$ = 251.3 Hz, ^{2}J$_{CF}$ = 30.4 Hz; C-5), 137.2 (dd, ^{1}J$_{CF}$ = 252.7 Hz, ^{3}J$_{CF}$ = 7.0 Hz; C-3), 144.6 (ddd, ^{1}J$_{CF}$ = 233.3 Hz, ^{2}J$_{CF}$ = 13.6 Hz, ^{4}J$_{CF}$ = 3.3 Hz; C-6), 144.8 (m, C-2), 145.7 (m, C-4); ir (potassium bromide): 1568, 1531, 1436, 1398, 1319, 1299, 1165, 1132, 1095 cm^{-1}; ms: *m/z* = 249 (M$^+$, 56); 189 (M - C$_3$H$_7$O, 100).

2,3,5,6-Tetrafluoro-4-(2-propylsulfanyl)-pyridine (6a). A sample of the pyridinium fluoride 2a (2.91 g, 10 mmol) was dissolved in 100 mL of methanol and acetone (1:10), before 2-propanethiol (0.76 g, 10 mmol) was added. Then, the mixture was stirred at room temperature for 18 h. The solvent mixture was then distilled off *in vacuo*, and the residue was chromatographed (silica gel, ethyl acetate/petrol = 1:1) to give a yellow oil in 40% yield (0.90 g); R$_f$ = 0.86 (ethyl acetate/petrol = 1:1). ^{1}H nmr (deuteriochloroform): δ 3.95 (h, ^{3}J = 6.7 Hz, 1H; C*H*), 1.37 (d, ^{3}J = 6.7 Hz, 6H; C*H*$_3$) ppm. ^{13}C nmr (deuteriochloroform): δ 145.8 (ddd, J = 229.4 Hz, J = 14.0 Hz, J = 2.9 Hz, C-3), 141.0 (ddd, J = 231.4 Hz, J = 14.0 Hz, J = 2.9 Hz, C-2), 130.9 (tt, J = 18.1 Hz, J = 2.9 Hz, C-4), 38.3 (*C*H), 23.3 (*C*H$_3$) ppm; ms: *m/z* = 226 (MH$^+$, 100), 181 (M - C$_3$H$_7$, 18).

4-Benzylsulfanyl-2,3,5,6-tetrafluoropyridine (6b) and 4,6-Bisbenzylsulfanyl-2,3,5-trifluoropyridine (7b). A sample of the pyridinium fluoride 2a (2.91 g; 10.0 mmol) and 1.24 g (10.0 mmol) of benzylthiol was dissolved in 100 mL of acetone and methanol (5:1) and stirred at room temperature for 36 h. A small portion of silica gel was added to the reaction mixture, and then the solvent was evaporated *in vacuo*. The residue was then chromatographed (silica gel, petrol).

4-Benzylsulfanyl-2,3,5,6-tetrafluoropyridine (6b). This compound was isolated as yellow oil, R$_f$ = 0.33 (petrol), yield: 936 mg (34%). ^{1}H nmr (deuteriochloroform): δ 4.31 (s, 2H; C*H*$_2$), 7.15 – 7.35 (m, 5H; *H*$_{Ph}$); ^{13}C nmr (deuteriochloroform): δ 43.4, 127.4, 128.3, 128.9, 135.3, 137.4, 141.2 (d, ^{1}J$_{CF}$ = 254.2 Hz, C3/5), 143.4 (d, ^{1}J$_{CF}$ = 244.3 Hz); ir (sodium chloride): 3031, 1629, 1460, 1070, 1027, 949, 892, 765, 698, 580, 565, cm^{-1} ms: *m/z* = 181 (M-CH$_2$C$_6$H$_5$; 20%).

2,4-Bisbenzylsulfanyl-3,5,6-trifluoropyridine (7b). This compound was isolated as yellow oil, R_f 0.08 (petrol), yield: 910 mg (34%). ^{1}H nmr (deuteriochloroform): δ 4.12 (s, 2H; CH_2), 4.23 (d, J = 5.7 Hz, 2H; CH_2), 6.99 – 7.40 (m, 10H; H_{Ph}); ^{13}C nmr (deuteriochloroform): δ 34.0, 38.2, 135.9, 137.0, 127.6 – 129.8 (10 C, overlapped); ir (sodium chloride): 3063, 3030, 1596, 1560, 1495, 1454, 1432, 1385, 1356, 1316, 1265, 1239, 1205, 1155, 1071, 1029, 999, 909, 842, 802, 767, 739, 700, 563 cm^{-1}; ms: *m/z* = 377 (M^+, 100%).

4-Amino-3,5,6-trifluoro-2-propylamino-pyridine (8a). A sample of 0.7 g of pyridinium fluoride **2a** (2.4 mmol) and 0.47 g of sodium amide (12 mmol) in 30 mL of n-propylamine was heated at 35°C for 5 h. A small amount of silica gel was added and the excess amine was evaporated *in vacuo*. The residue was then chromatographed (silica gel, ethyl acetate/petrol = 1:7). The product was isolated as a brown oil (R_f 0.24; ethyl acetate/petrol = 1:7), mp. 137 – 141°C. ^{1}H nmr (deuteriochloroform): δ 0.96 (t, J = 7.3 Hz, 3H; CH_3), 1.60 (m, 2H, $CH_3CH_2CH_2$), 3.32 (m, 2H, $CH_3CH_2CH_2$); ^{13}C nmr (deuteriochloroform): δ 11.4, 23.1, 42.9; the resonance frequencies of the pyridine ring were too small to be assigned; ms: *m/z* = 205 (M^+, 80%), 176 (M^+-C_2H_5, 100%).

4-Amino-3,5,6-trifluoro-2-(2-propylamino)-pyridine (8b). A sample of the pyridinium salt **2a** (0.3 g; 1.37 mmol) and sodium amide (0.27 g; 6.9 mmol) in 15 mL of 2-propylamine was heated at reflux temperature for 5 h. A small amount of silica gel was added and the excess amine was distilled off *in vacuo*. The residue was then chromatographed (petrol/ethyl acetate = 5:1) to give 8b as brown oil (R_f = 0.38; petrol/ethyl acetate = 5:1). ^{1}H nmr (deuteriochloroform): δ 1.23 (d, ^{3}J = 6.3 Hz, 6H; CH_3), 4.10 (s, br, N*H*), 4.12 (sept, ^{3}J = 6.6 Hz, 1H; C*H*), 4.31 (s, br, 2H, NH_2); ^{19}F nmr (trichlorofluoromethane): δ -97.0 (dd, $^3J_{FF}$ = -26.7 Hz, $^5J_{FF}$ = -24.4 Hz; 6-*F*), -164.4 (d, $^5J_{FF}$ = -24.4 Hz; 3-*F*), -177.1 (dd, $^3J_{FF}$ = -26.7 Hz; 5-*F*); ^{13}C nmr (deuteriochloroform): δ 23.2 (*C*H$_3$), 42.5 (*C*H), 126.2 (ddd, $^1J_{CF}$ = 240.0 Hz, $^2J_{CF}$ = 34.0 Hz, $^3J_{CF}$ = 1.2 Hz; C-5), 131.8 (dd, $^1J_{CF}$ = 236.6 Hz, $^3J_{CF}$ = 4.4 Hz; C-3), 133.1 (ddd, $^2J_{CF}$ = 13.3 Hz, $^3J_{CF}$ = 6.6 Hz, $^3J_{CF}$ = 4.5 Hz; C-4), 140.2 (ddd, $^2J_{CF}$ = 18.5 Hz, $^3J_{CF}$ = 11.6 Hz, $^4J_{CF}$ = 1.9 Hz; C-2), 145.7 (ddd, $^1J_{CF}$ = 224.7 Hz, $^2J_{CF}$ = 11.6 Hz, $^4J_{CF}$ = 2.1 Hz; C-6); ms: *m/z* = 205 (M^+, 62%), 190 (M^+ - NH_2, 100%).

2,3,5-Trifluoro-6-(*N*-piperidino)-4-amino-pyridine (8c). A solution of pyridinium fluoride 2a (2.91 g, 10 mmol) and sodium amide (0.59 g, 15 mmol) in 100 mL of piperidine was heated at reflux temperature for 4 h. The piperidine was then distilled off and the residue was chromatographed (silica gel, ethyl acetate/petrol = 1:1) to give a grey solid, mp 59 °C, in 66% yield (R_f = 0.81; ethyl acetate / petrol = 1:1). ^{1}H nmr (deuteriochloroform): δ 4.53 (s, 2H; CH_2), 3.25 – 3.30 (m, 4H; CH_2), 1.55 – 1.73 (m, 6H; CH_2) ppm; ^{13}C nmr (deuteriochloroform): δ 48.8, 25.7, 24.5 ppm; the signals of the pyridine are too small; ir (potassium bromide): 3512, 3395, 2933, 2850, 1639, 1487, 1464, 1450, 1249, 1118, 1091, 932 cm^{-1}; ms: *m/z* = 232 (MH^+, 100).

4-Amino-3,5-difluoro-2,6-dimorpholino-pyridine (9). A sample of pyridinium salt **2a** (0.73 g; 2.5 mmol) and sodium amide (0.49 g; 12.5 mmol) in 25 mL of morpholine was heated at reflux temperature for 5 h. A small amount of silica gel was added to the solution and then the excess amine was distilled off *in vacuo*. The residue was then chromatographed (silica gel; petrol / ethyl acetate = 2/1). The product (R_f = 0.20; petrol/ethyl acetate = 2:1) was finally recrystallized from hexane/dichloromethane (5:1) to give 8b in 32% yield. ^{1}H NMR (deuteriochloroform): δ 3.36 (m, 8H; -N(CH_2)$_2$-), 3.84 (m, 8H; O(CH_2)$_2$-), 4.17 (s, 1H; NH_2); 4.19 (s, 1H; NH_2); ^{19}F nmr (trichlorofluoromethane) δ -160.0 (s); ^{13}C nmr (deuteriochloroform): δ 48.3 (-N(*C*H$_2$)$_2$), 66.9 (O(*C*H$_2$)$_2$-), 133.0 (C-4), 134.1 (d, J = 221 Hz; C-3/5), 141.9 (C-2/6); ir (potassium bromide) = 3218, 2964, 2857, 1639, 1603, 1476, 1446, 1371, 1350, 1289, 1263, 1160, 1114, 1068, 939; ms: *m/z* = 300 (M+, 100%).

Acknowledgement. The Deutsche Forschungsgemeinschaft is gratefully acknowleged for the financial support. We thank Dr. Gerald Dräger, University of Hannover, for measuring the HR-ESI-MS spectra.

REFERENCES

[1] Steglich, W; Höfle, G. *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

[2] Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem.* **1978**, 90, 602; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

[3] Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

[4] Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4040.

[5] Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965.

[6] Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 19.

[7] Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21.

[8] Waterman, K. C.; Streitwieser, Jr., A. *J. Am. Chem. Soc.* **1984**, *106*, 3874.

[9] DiMagno, S. G.; Waterman, K. C.; Speer, D. V.; Streitwieser, A. *J. Am. Chem. Soc.* **1991**, *113*, 4679.

[10] Schmidt, A.; Kindermann, M. K.; Vainiotalo, P.; Nieger, M. *J. Org. Chem.* **1999**, *64*, 9499.

[11] Schmidt, A.; Kindermann, M. K. *J. Org. Chem.* **1997**, *62*, 3910.

[12] Schmidt, A.; Kindermann, M. K. *J. Org. Chem.* **1998**, *63*, 4636.

[13] Schmidt, A.; Nieger, M. *Heterocycles* **2001**, *55*, 827.

[14] Schmidt, A.; Nieger, M. *Heterocycles* **1999**, *51*, 2119.

[15] Schmidt, A.; Nieger, M. *J. Chem. Soc., Perkin Trans 1* **1999**, 1325.

[16] Schmidt, A. *J. Heterocycl. Chem.* **2002**, *39*, 949.

[17] Schmidt, A.; Mordhorst, T.; Habeck, T. *Org. Lett.* **2002**, *4*, 1375.

[18] Schmidt, A.; Mordhorst, T.; Nieger, M. *Org. Biomol. Chem.*, **2005**, *3*, 3788.

[19] Schmidt, A.; Mordhorst, T. *Synthesis* **2005**, 781.

[20] Schmidt, A.; Mordhorst, T. *Z. Naturforsch.* **2005**, *60b*, 683.

[21] Schmidt, A.; Mordhorst, T. *Tetrahedron* **2006**, *62*, 1667.

[22] Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, *1*, 2137.

[23] Chambers, R. D.; Hoskin, P. R.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2788.

[24] Admason, A. J.; Jondi, W. J.; Tipping, A. E. *J. Fluorine Chem.* **1996**, *76*, 67.

[25] Litvak, V. V.; Mainagashev, I. Ya.; Bukhanets, O. G. *Russ. J. Bioorg. Chem. (Engl. Transl.)* **2004**, *30*, 47; *Bioorg. Khim.* **2004**, 30, 61.

[26] Cheong, C. C.; Wakefield, B. J. *J. Chem. Soc. Perkin Trans. 1* **1988**, 3301.

[27] Wielgat, J.; Wozniacki, R.; Domagla, Z. *Pol. J. Chem.* **1978**, *52*, 869.

[28] Schmidt, A.; Namyslo, J. C.; Mordhorst, T. *Tetrahedron* **2006**, *62*, 6893.