Chemistry of 3-Hydroxypyridine Part 3: Synthesis of Substituted 3-[Fluoro(chloro)alkoxy]pyridines from Halo- or Amino-3-hydroxypyridines

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Dedicated to Prof. Hilger on the occasion of his 60th birthday

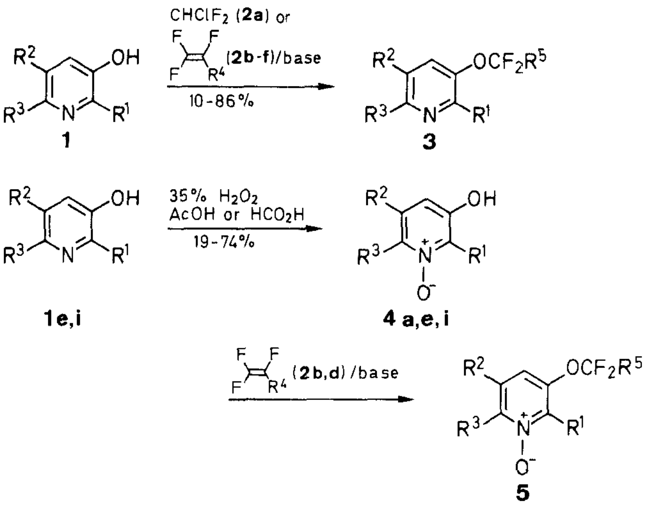
The preparation of new substituted 3-[fluoro(chloro)alkoxy]-pyridines from halo- and amino-3-hydropxypyridines via difluorocarbene insertion or by addition of fluoroolefins is described.

For the preparation of new and highly active herbicides[1] and insecticides,[2] we required substituted 3-[fluoro(chloro)alkoxy]pyridines as precursors. Although [fluoro(chloro)alkoxy]benzenes[3] are well-known, only a limited number of 3-[fluoro(chloro)alkoxy]pyridines have been described in the literature; no 3-[fluoro(chloro)alkoxy]pyridines with amino, halogen or hydroxy groups in the pyridine ring have been described.

Starting from substituted 3-hydroxypyridines **1** or 3-hydroxypyridine *N*-oxides **4**, the latter were prepared from **1** by oxidation with hydrogen peroxide. The 3-[fluoro(chloro)pyridines **3** or **5** were obtained from **1** and **4** by difluorocarbene insertion into the hydroxyl group by **2a** or by base-catalysed addition of the hydroxyl group to an appropriate fluoroalkene **2b–f** (Scheme A).[4]

When hexafluoropropene is used as the fluoroalkene, nucleophilic attack occurs regioselectively at the most electrophilic carbon. However, the reaction between 3-hydroxypyridine (**1a**) and hexafluoropropene (**2d**) gave **3ad**, *E*-**7**, *Z*-**7** and **8** as the main products, (Scheme **B**), together with a further range of unidentified products which amounted to 10% of the total products. The structures of **3ad**, *E*-**7**, *Z*-**7** and **8** were elucidated by ^{19}F-NMR and GC/MS. The product ratios were determined by ^{19}F-NMR and can be altered by varying the cation of the base, temperature and solvent (Table 5). Mechanistically these products can be explained as arising from the intermediate carbanion **6**, which can either be protonated to give the saturated product **3ad** or can eliminate a fluoride ion to give the fluoroalkenes *E*-**7** and *Z*-**7**; further reaction of *E*- or *Z*-**7** with another molecule of **1a** at the vinylic fluorine of $OC\underline{F}=CFCF_3$ yields ketene acetal **8**. Similar byproducts were also observed when substituted 3-hydroxypyridines **1** or 3-hydroxypyridine *N*-oxides **3** were used. The amount of byproducts varied greatly with substitution pattern, base, temperature and solvent.

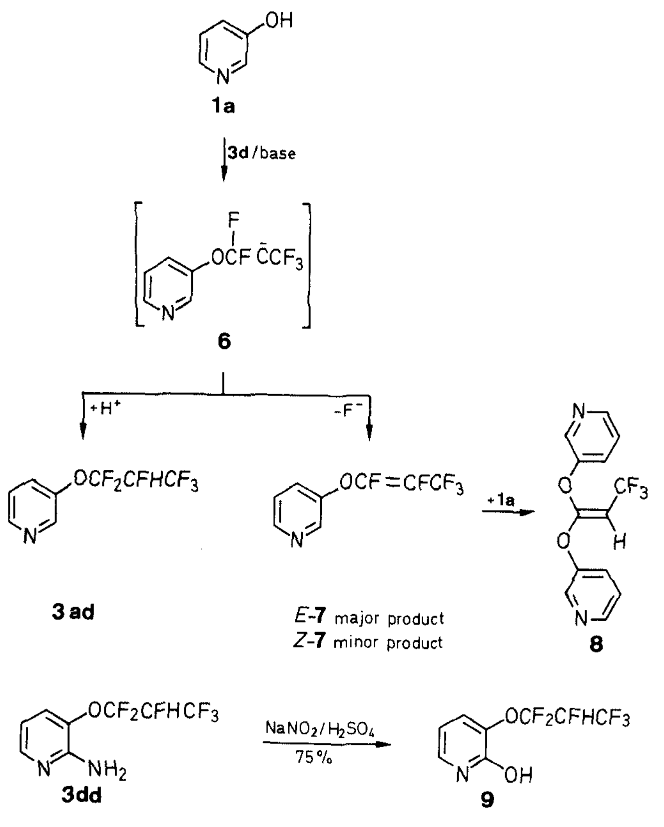
3-(1,1,2,3,3,3-Hexafluoropropanoxy)-2-hydroxypyridine **9** was prepared by diazotation of corresponding amino compound **3dd**. 2,3-Dichloro-5-difluoromethylpyridine (**3ia**) was photochlorinated to yield a mixture of the product **10** and **11** (Scheme C), this mixture can be separated by distillation. Then either **10** or the mixture **10/11** was fluorinated by antimony trifluoride/antimony pentafluoride[4] to give **12** or a mixture of **12** and **13** respectively.



1, 4	R^1	R^2	R^3	2	R^4
a	H	H	H	b	Cl
b	Br	H	H	c	F
c	I	H	H	d	CF_3
d	NH_2	H	H	e	$OCF_2CF_2CHF_2$
e	H	Cl	H	f	$OCF_2CF_2CF_3$
f	Br	H	Br		
g	Br	Cl	H		
h	H	Br	Cl		
i	H	Cl	Cl		
j	Br	Cl	Br		
k	H	H	Cl		

3, 5	R^1	R^2	R^3	R^5
3ad	H	H	H	$CHFCF_3$
3bb	Br	H	H	CHClF
3cb	I	H	H	CHClF
3dd	NH_2	H	H	$CHFCF_3$
3ea	H	Cl	H	H
3ed	H	Cl	H	$CHFCF_3$
3fb	Br	H	Br	CHClF
3ga	Br	Cl	H	H
3gb	Br	Cl	H	CHClF
3ha	H	Br	Cl	H
3ia	H	Cl	Cl	H
3ib	H	Cl	Cl	CHClF
3ic	H	Cl	Cl	CHF_2
3id	H	Cl	Cl	$CHCF_3$
3ie	H	Cl	Cl	$CHFOCF_2CF_2CHF_2$
3if	H	Cl	Cl	$CHFOCF_2CF_2CF_3$
3jb	Br	Cl	Br	CHClF
3kd	H	H	Cl	$CHFCF_3$
5ad	H	H	H	$CHFCF_3$
5eb	H	Cl	H	CHClF
5ib	H	Cl	Cl	CHClF

Scheme A

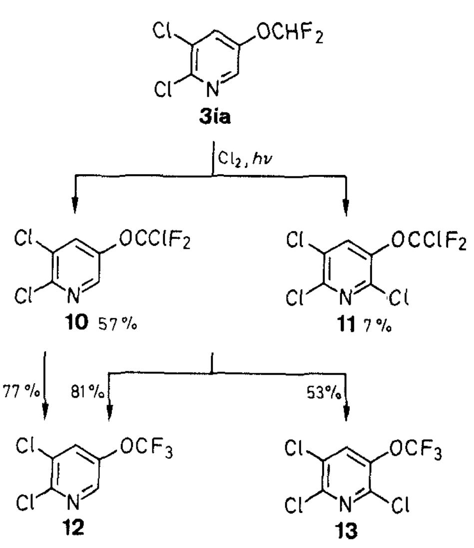


Scheme B

The mixture of **12** and **13** is more easily separated than the mixture of **10** and **11**. We have also attempted to prepare **12** directly from 3-hydroxypyridine **1i** and fluoro phosgen/sulfur tetrafluoride[5] but this reaction failed.

All reagents were of commercial quality from freshly opened containers. Starting materials were either prepared according to the literature or purchased from Aldrich Chemical Co and used without further purification. The preparation of **1h–j** is described in part 2 of this publication series. Fluoroalkenes **2**[6,7] were all manufactured by Hoechst AG. *Caution*!, tetrafluoroethene must not be pressurized above 10 bar or dangerous self-polymerization takes place.

Melting points were obtained using a Büchi SM 20 melting point apparatus and are uncorrected. Microanalyses were performed in the analytical department of Hoechst AG. ^{1}H-/^{19}F-NMR spectra were recorded on a Bruker AM 100 spectrometer and ^{13}C-NMR on a Bruker AM 360. IR spectra were recored on a Digilab FTS 20C. For high performance distillation a Fischer-Spaltrohr-System 0200/01 was used.



Scheme C

Pyridine *N*-Oxides 4b,c; General Procedure:

3-Hydroxypyridine (**1**, 0.1 mol) is dissolved under reflux in the solvent indicated in Table 1 (60 mL), then cooled to correct temperature and 35% H_2O_2 (9.5 mL, 0.11 mol) is added to the solution over 0.5 h. The mixture is stirred as indicated in Table 1 (monitored by TLC) and then concentrated. To the residue is added ice-water (50 mL) and the resultant solid isolated by vacuum filtration through a glass frit. The product is washed with ice-water (3 × 20 mL) and vacuum dried at 70 °C. Compound **3c** was recrystallized several times from EtOAc to remove unreacted starting material.

3-[Fluoro(chloro)alkoxy]pyridines and -pyridine *N*-Oxides 3 and 5; General Procedure:

Method A (for **3ea, 3ga, 3ha, 3ia**): 3-Hydroxypyridine **1** (0.1 mol) is added to NaOH (20.0 g, 0.5 mol) in dioxan (100 mL) and water (50 mL) and warmed to reaction temperature (Table 2). To this solution is introduced, via a gas frit, a steady stream of chlorodifluoromethane (F22), until no starting material can be detected (TLC monitoring). The mixture is cooled to r.t., Et_2O (400 mL) is added and the organic layer is washed with water (3 × 100 mL). The organic layer is dried ($MgSO_4$), filtered and evaporated. The oily residue is then distilled *in vacuo* (Table 2, 3 and 4).

Method B (**3ad, 3bb, ecb, 3dd, 3ed, 3fb, 3gb, 3ib, 3ic, 3id, 3ie, 3if, 3jb, 3kd, 5ad, 5eb, 5ib**): A steady stream of the appropriate fluoroalkene **2b** or **2d** is introduced at the reaction temperature (Table 2) to the mixture of 3-hydroxypyridine **1** or 3-hydroxypyridine *N*-oxide **4** (0.1 mol) and K_2CO_3 (20 g, 0.14 mol) and the solvent (100 mL) via gas frit until no starting material can be detected (TLC monitoring).

Table 1. Pyridine *N*-Oxides **4**

Substrate	Product	Solvent	Reaction Conditions		Yield (%)	Molecular Formula[a]	IR (KBr) ν(cm^{-1}) $N^+–O^-$	^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz)
			Temp (°C)	Time (h)				
1e	**4e**	AcOH	70	8	74	$C_5H_4ClNO_2$ (145.55)	1170	6.96 (t, 1H, J = 2.3, H-4), 7.80 (t, 1H, J = 2.3, H-2), 8.03 (t, 1H, J = 2.3, H-6), 11.0 (s, br, OH)
1i	**4i**	HCO_2H	100	10	19[b]	$C_5H_3Cl_2NO_2$ (179.99)	1190	7.18 (d, 1H, J = 2.5, H-4), 8.05 (d, 1H, J = 2.5, H-2), 11.06 (s, br, OH)

[a] Satisfactory microanalyses obtained: C +0.25, H +0.13, N +0.28.
[b] Yield not optimized.

When **1** is reacted with tetrafluoroethene **2c** the reaction is performed under pressure (< 10 bar!!) in a stainless steel autoclave.

The fluoroalkenes **2e** and **2f** (0.11 mol) are added dropwise.

The solid is filtered off at r. t., the resulting solution is evaporated and the residue distilled under reduced pressure (Table 2, 3 and 4).

Method C (for **3ad**): Hexafluoropropene (**2d**) is introduced via a gas burette into the mixture of 3-hydroxypyridine (**1a**) (9.51 g, 0.1 mol) and base in the solvent (100 mL) (see Table 5). When no more hexafluoropropene is consumed, the mixture is filtered and the solvent evaporated *in vacuo*. From this crude mixture the ^{19}F-NMR was recorded and the products **3ad**, *E*-**7**, *Z*-**7** and **8** identified by GC/MS (Table 5).

Table 2. Compound **3** and **5** Prepared

Product	Method	Solvent	Reaction Conditions		Yield (%)	GC Purity (%)	mp (°C) or bp (°C)/mbar	Molecular Formula[a]
			Temp (°C)	Time (h)				
3ad	C	see Table 5					70/10	$C_8H_5F_6NO$ (245.14)
3bb	B	MeCN	20	1.5	73	92.9	95/0.08	$C_7H_4BrClF_3NO$ (290.47)
3cb	B	MeCN	55	8	79	99.9	70/0.001	$C_7H_4ClF_3INO$ (337.47)
3dd	B	MeCN	25	4	86	97.4	65/0.1	$C_8H_6F_6N_2O$ (260.14)
3ea	A	dioxan	50	8	72	98.8	32/0.01	$C_6H_4ClF_2NO$ (179.55)
3ed	B	MeCN	25	9	42	99.1	37/0.04	$C_8H_4ClF_6NO$ (279.57)
3fb	B	MeCN	55	4	63	91.3	105/0.08	$C_7H_3Br_2ClF_3NO$ (369.37)
3ga	A	dioxan	55	4	65	95.2	48/0.01	$C_6H_3BrClF_2NO$ (258.46)
3gb	B	MeCN	40	8	59	94.8	64/0.001	$C_7H_3BrCl_2F_3NO$ (324.92)
3ha	A	dioxan	50	3	69	98.5	100/0.1	$C_6H_3BrClF_2NO$ (258.46)
3ia	A	dioxan	50	1	79	99.6	56/0.1	$C_6H_3Cl_2F_2NO$ (214.00)
3ib	B	MeCN	35	4	83	96.5	90/0.03	$C_7H_3Cl_3F_3NO$ (280.46)
3ic	B	MeCN	77	19	86	99.9	60/0.005	$C_7H_3Cl_2F_4NO$ (264.01)
3id	B	MeCN	0	5	10	95.1	152.6/100	$C_8H_3Cl_2F_6NO$ (314.02)
3ie	B	DMF	27	0.3	75	–	76/0.2	$C_{10}H_4Cl_2F_9NO_2$ (412.06)
3if	B	DMF	25	1	82	–	70/0.1	$C_{10}H_3Cl_2F_{10}NO_2$ (430.05)
3jb	B	MeCN	50	14	65	95.0	97/0.001	$C_7H_2Br_2Cl_2F_3NO$ (403.82)
3kd	B	MeCN	25	0.7	56	98.2	45/10	$C_8H_4ClF_6NO$ (279.57)
5ad	B	MeCN	25	3	74	91.1	42–44	$C_8H_5F_6NO_2$ (261.12)
5eb	B	MeCN	40	5	59	94.8	105/0.02	$C_7H_4Cl_2F_3NO_2$ (262.02)
5ib	B	MeCN	35	2	57	91.6	83/0.0001	$C_7H_3Cl_3F_3NO_2$ (296.46)

[a] Satisfactory microanalyses were obtained: C ± 0.26, H ± 0.15, F ± 0.30, N ± 0.29.

Table 3. ^1H-NMR Data for Compound **3** and **5**

Product	^1H-NMR (solvent/TMS) δ, J(Hz)
3bb	DMSO-d_6: 7.44 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 7.55–7.66 (m, 1H, H-5), 7.89 (m, 1H, H-4), 8.44 (dd, 1H, $^3J = 5.0$, $^4J = 2.0$, H-6), 7.89–7.94 (m, 1H, H-4)
3cb	DMSO-d_6: 7.45 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 7.49–7.89 (m, 2H, H-4, H-5), 8.41 (dd, 1H, $^3J = 5.0$, $^4J = 2.3$, H-6)
3dd	$CDCl_3$: 4.84 (s, br, 2H, NH_2), 5.06 (dsext, 1H, $^2J = 41.3$, $^3J = 6.3$, $OF_2C\underline{H}FCF_3$), 6.65 (dd, 1H, $J = 5.0$, $J = 7.5$, H-5), 7.31–7.46 (m, 1H, H-4), 8.00 (dd, 1H, $J = 1.5$, $J = 5.0$, H-6)
3ea	$CDCl_3$: 6.60 (t, 1H, $OC\underline{H}F_2$, $J = 72.5$), 7.51–7.55 (m, 1H, H-4), 8.36–8.41 (m, 1H, H-2), 8.46 (d, 1H, $J = 2.2$, H-6)
3ed	DMSO-d_6: 6.50 (dsext, 1H, $^2J = 41.3$, $^3J = 6.3$, $OF_2C\underline{H}FCF_3$), 7.98–8.05 (m, 1H, H-4), 8.55–8.60 (m, 1H, H-2), 8.63–8.73 (m, 1H, H-6)
3fb	DMSO-d_6: 7.44 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 7.76–7.90 (m, 2H, H-4, H-5)
3ga	$CDCl_3$: 6.64 (t, 1H, $J = 72.5$, $OC\underline{H}F_2$), 7.55–7.60 (m, 1H, H-4), 8.23 (d, 1H, $J = 2.3$, H-6)
3gb	DMSO-d_6: 7.46 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 8.13–8.19 (m, 1H, H-4), 7.56 (d, 1H, $J = 2.3$, H-6)
3ha	$CDCl_3$: 6.58 (t, 1H, $J = 72.5$, $OC\underline{H}F_2$), 7.78–7.83 (m, 1H, H-4), 8.21–8.28 (m, 1H, H-2)
3ia	$CDCl_3$: 6.60 (t, 1H, $J = 72.5$, $OC\underline{H}F_2$), 7.61–7.68 (m, 1H, H-4), 8.15–8.19 (m, 1H, H-2)
3ib	DMSO-d_6: 7.40 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 8.26–8.30 (m, 1H, H-4), 8.45–8.53 (m, 1H, H-2)
3ic	$CDCl_3$: 5.98 (tt, 1H, $^2J = 52.5$, $^3J = 2.8$, $OF_2C\underline{H}F_2$), 7.65–7.76 (m, 1H, H-4), 8.20–8.35 (m, 1H, H-6)
3id	$CDCl_3$: 5.05 (dsext, 1H, $^2J = 41.3$, $^3J = 6.3$, $OF_2C\underline{H}FCF_3$), 7.70–7.75 (m, 1H, H-4), 8.21–8.29 (m, 1H, H-2)
3ie	$CDCl_3$: 6.05 (tt, 1H, $^2J = 52.5$, $^3J = 5.0$, $C\underline{H}F_2$), 6.14 (dt, 1H, $^2J = 53.0$, $^3J = 2.75$, $C\underline{H}FO$), 7.62–7.79 (m, 1H, H-4), 8.14–8.37 (m, 1H, H-6)
3if	$CDCl_3$: 6.11 (dt, 1H, $^2J = 53.0$, $^3J = 2.3$, $C\underline{H}FO$), 7.63–7.78 (m, 1H, H-4), 8.13–8.36 (m, 1H, H-6)
3jb	DMSO-d_6: 7.48 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 8.35 (t, 1H, $^5J = 1.3$, H-4)
3kd	$CDCl_3$: 5.05 (dsext, 1H, $^2J = 43.8$, $^3J = 5.5$, $OF_2C\underline{H}FCF_3$), 7.30–7.46 (m, 1H, H-3), 7.46–7.63 (m, 1H, H-4), 8.22–8.45 (m, 1H, H-6)
5ad	DMSO-d_6: 6.48 (dsext, 1H, $^2J = 41.3$, $^3J = 6.3$, $OF_2C\underline{H}FCF_3$), 7.31–7.65 (m, 2H, H-4, H-5), 8.28–8.40 (m, 2H, H-2, H-6)
5eb	$CDCl_3$: 6.38 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 7.19–7.28 (m, 1H, H-4), 8.11–8.20 (m, 2H, H-2, H-6)
5ib	$CDCl_3$: 6.34 (dt, 1H, $^2J = 47.5$, $^3J = 3.8$, $OF_2C\underline{H}ClF$), 7.69–7.75 (m, 1H, H-4), 8.24–8.30 (m, 1H, H-2)

3ad:

^{19}F-NMR ($CDCl_3/CFCl_3$): $\delta = -75.8-(-76.3)$(m, 3 F, $OC\underline{F}_3$), $-78.3-(-80.3)$($ABMNX_3$, 2 F, $^2J = 145.9$ Hz, $OC\underline{F}_2CHFCF_3$), -213.8 (dsext, 1 F, $^2J = 43.3$ Hz, $^3J = 10.4$ Hz, $OCF_2CH\underline{F}CF_3$).

***E*-7:**

^{19}F-NMR ($CDCl_3/CFCl_3$): $\delta = -68.0$ (dd, 3 F, $^3J = 21.5$ Hz, $^4J = 12.8$ Hz, $OCF{=}CFC\underline{F}_3$), -107.9 (dd, 1 F, $^3J = 122$ Hz, $^4J = 12.8$ Hz, $OC\underline{F}{=}CFCF_3$), -184.2 (dq, 1 F, $^3J = 122$ Hz, $^3J = 21.5$ Hz, $OCF{=}C\underline{F}CF_3$).

***Z*-7:**

^{19}F-NMR ($CDCl_3/CFCl_3$): $\delta = -67.8$ (dd, 3 F, $^3J = 12.4$ Hz, $^4J = 9.4$ Hz, $OCF{=}CFC\underline{F}_3$), -91.9 (dd, 1 F, $^3J = 20.8$ Hz, $^4J = 9.4$ Hz, $OC\underline{F}{=}CFCF_3$), -177.5 (dq, 1 F, $^3J = 20.8$ Hz, $^3J = 12.4$ Hz, $OCF{=}C\underline{F}CF_3$).

8:

^{19}F-NMR ($CDCl_3/CFCl_3$): $\delta = -67.6$ (d, 3 F, $^3J = 11.8$ Hz, CF_3), -171.5 (q, 1 F, $^3J = 11.8$ Hz, CF).

5-Chlorodifluoromethoxy-2,3-dichloropyridine (10) and 5-Chlorodifluoromethoxy-2,3,6-trichloropyridine (11):

To 2,3-Dichloro-5-difluoromethoxypyridine **(3ia)** (85.6 g, 0.4 mol) is introduced at 100 °C a steady stream of chlorine via a glass frit. The mixture is illuminated by UV light from an external source (UV lamp, Osram Ultravitalux 300 W). After 10 h most of the starting material is consumed. The mixture is cooled to r.t. and excess chlorine is removed by a stream of Ar gas. The liquid is then distilled with a Fischer-Spaltrohr-System device with a reflux ratio 1:20 to obtain **10** and **11**. Besides unreacted starting material, 2,3,5,6-tetrachloropyridine was identified as a byproduct by GC/MS.

10:

Yield: 56.6 g (57 %); bp 91 °C/17 mbar.

		C	H	Cl	F	N
$C_6H_2Cl_3F_2NO$ (248.5)	calc.	29.01	0.81	42.81	15.29	5.64
	found	28.92	0.74	42.61	15.41	5.80

^{1}H-NMR ($CDCl_3$): $\delta = 7.70-7.75$ (m, 1 H, H-4), 8.26–8.30 (m, 1 H, H-2).

^{13}C-NMR (DMSO-d_6/TMS): $\delta = 124.55$ (t, 1 C, $J = 291$ Hz, $O\underline{C}ClF_2$), 129.93 (s, 1 C, C-5), 132.59 (s, 1 C, C-4), 140.77 (s, 1 C, C-2), 145.12 (s, 1 C, C-3), 146.27 (s, 1 C, C-6).

^{19}F-NMR ($CDCl_3/CFCl_3$): $\delta = -27.60$ (m, 2 F, $OCClF_2$).

11:

Yield 7.9 g (7 %), bp 108 °C/17 mbar.

		C	H	Cl	F	N
$C_6HCl_4F_2NO$ (282.9)	calc.	25.47	0.36	50.13	13.43	4.95
	found	25.68	0.33	49.99	13.24	5.18

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 7.86$ (t, 1 H, $^5J = 1.2$ Hz, H-4).

^{19}F-NMR ($CDCl_3/CFCl_3$): $\delta = -27.33$ (d, 2 F, $^2J = 1.2$ Hz, $OCClF_2$).

Table 4. ^{13}C- and ^{19}F-NMR Data of Selected Compounds

Product	^{13}C-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{19}F-NMR ($CDCl_3/CFCl_3$) δ, J(Hz)
3ha	114.40 (t, 1 C, $O\underline{C}HF_2$, $J = 265.6$), 119.40 (s, 1 C, C-5), 133.34 (s, 1 C, C-4), 139.34 (s, 1 C, C-2), 145.22 (s, 1 C, C-3), 146.66 (s, 1 C, C-6)	-82.59 (d, 2 F, $J = 72.5$)
3ib		-84.45 (-84.62) (m, 2 F, $OC\underline{F}_2CHClF$), -154.35 (dt, 1 F, $^2J = 47.5$, $^3J = 11.8$, $OCF_2CHCl\underline{F}$)
3ic		-88.5 (t, 2 F, $OC\underline{F}_2CHF_2$), -137.25 (dt, 1 F, $^2J = 52.5$, $^3J = 2$, $OCF_2CH\underline{F}_2$)
3id	84.60 (dsext, 1 C, $^1J = 201.2$, $^2J = 38.2$, $OCF_2\underline{C}HFCF_3$), 117.80 (dt, 1 C, $^1J = 279.7$, $^2J = 24.1$, $O\underline{C}F_2CHFCF_3$), 119.80 (dq, 1 C, $^1J = 279.7$, $^2J = 24.1$, $OCF_2CHF\underline{C}F_3$), 130.96 (s, 1 C, C-4), 132.13 (s, 1 C, C-5), 140.69 (s, 1 C, C-2), 144.30 (s, 1 C, C-3), 147.15 (s, 1 C, C-6)	-74.88 (-75.48) (m, 3 F, $OCF_2CHFC\underline{F}_3$), -78.50 (-79.40) (m, 2 F, $OC\underline{F}_2CHFCF_3$), $-211.20-(-212.28)$ (m, 1 F, $OCF_2CH\underline{F}CF_3$)
5ib		$-82.92-(-83.08)$ (m, 2 F, $OC\underline{F}_2CHClF$), -154.63 (dt, 1 F, $^2J = 47.5$, $^3J = 11.8$, $OCF_2CHCl\underline{F}$)

Table 5. Reaction of 3-Hydroxypyridine **(1a)** with Hexafluoropropene **(3d)**

Base	Solvent	Temperature (°C)	Product Ratio (mole %)				
			3ad : *E*-**7** : *Z*-**7** : **8**				**3ad** : *E*-**7** + *Z* − **7** + **8**
Li_2CO_3	DMF	20–25	86	7	7	–	86 : 14
Na_2CO_3	DMF	20–25	76	13	11	–	76 : 24
K_2CO_3	DMF	20–25	72	4	9	15	72 : 28
Cs_2CO_3	DMF	20–25	56	–	–	44	56 : 44
K_2CO_3	DMF	−20	80	9	11	–	80 : 20
K_2CO_3	DMF	20–25	72	4	9	15	72 : 28
K_2CO_3	DMF	50	68	8	8	16	68 : 32
K_2CO_3	MeCN	20–25	87	7	6	–	87 : 13
K_2CO_3	acetone	20–25	80	11	8	–	80 : 20
K_2CO_3	THF	20–25	78	12	10	–	78 : 22
K_2CO_3	sulfolane	20–25	66	11	11	12	66 : 34
40% aq KOH	MeCN	20–25	92	6	2	–	92 : 4
KOH	MeCN	20–25	88	7	5	–	88 : 12
KF	MeCN	20–25	86	8	6	–	86 : 14
Et_3N	MeCN	20–25	85	10	5	–	85 : 15

2,3-Dichloro-5-trifluoromethoxypyridine (12); Typical Procedure for *the Fluorination of the Chlorodifluoromethoxy Group:*

5-Chlorodifluoromethoxy-2,3-dichloropyridine **(10)** (12.4 g, 50 mmol) is added dropwise to a molten mixture of SbF_3 (5.96 g, 33 mmol) and $SbCl_5$ (2.99 g, 10 mmol) at 120 °C and stirred for 10 h at this temperature. The mixture is then cooled to 0 °C and dissolved in CH_2Cl_2 (100 mL). The solution is washed with 10% aq KF (300 mL), the aqueous layer is extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers are dried (Na_2SO_4) and the solvent evaporated. The residue is distilled under vacuum to give **12** yield: 8.96 g (77%); bp 66–67 °C/11 mbar.

$C_6H_2Cl_2F_3NO$	calc.	C 31.06	H 0.87	N 6.04
(232.0)	found	30.87	0.72	6.48

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 7.70–7.76$ (m, 1 H, H-4), 8.28–8.32 (m, 1 H, H-6)

^{13}C-NMR (DMSO-d_6/TMS): $\delta = 120.51$ (q, 1 C, $J = 260$ Hz, OCF_3), 131.30 (s, 1 C, C-3), 131.49 (s, 1 C, C-4), 140.26 (s, 1 C, C-6), 144.99 (s, 1 C, C-5), 147.59 (s, 1 C, C-2).

^{19}F-NMR ($CDCl_3$-$CFCl_3$): $\delta = -58.94$ (m, 3 F, OCF_3).

2,3-Dichloro-5-trifluoromethoxypyridine (12) and 2,3,6-Trichloro-*5-trifluoromethoxypyridine* (13):

A mixture consisting of 5-chlorodifluoromethoxy-2,3-dichloropyridine (**10**, 35.9 g, 145 mmol) and 5-chlorodifluoromethoxy-2,3,6-trichloropyridine (**11**, 21.4 g, 76 mmol) is fluorinated by the typical procedure. Distillation of the crude material through a vigreux column (20 cm) gives the following fractions:

bp (°C)/mbar	**12** (g/mole%)	**13** (g/mol%)
75–80/15	17.7/95.5	0.8/ 4.5
81–89/15	6.8/92.6	0.5/ 7.4
90–94/15	2.5/40.6	3.6/59.4
94/15	0.4/ 6.7	5.8/93.3

13:

$C_6HCl_3F_3NO$	calc.	C 27.05	H 0.38	N 5.26
(266.4)	found	26.93	0.39	5.47

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 7.78–7.86$ (m, 1 H, H-4).

^{19}F-NMR ($CDCl_3$/$CFCl_3$): $\delta = -58.50$ (s, 3 F, OCF_3).

3-(1,1,2,3,3,3-Hexafluoropropyloxy)-2-hydroxypyridine 9:

$NaNO_2$ (2.1 g, 30 mmol) in water (15 mL) is added at −15 °C to conc. H_2SO_4 (34 mL). To this mixture is added 2-amino-3-(1,1,2,3,3,3-hexafluoropropyloxy)pyridine (**3dd**, 2.6 g, 10 mmol) in AcOH (20 mL) over 0.5 h. After 2 h water is added (200 mL) and the product is isolated via vacuum filtration through a glass frit. The solid is washed with ice-water and is vacuum dried at 50 °C to give **9**; yield: 1.95 g (75%); mp 89 °C.

$C_8H_5F_6NO_2$	calc.	C 36.80	H 1.93	F 43.65	N 5.36
(261.1)	found	37.17	2.08	43.34	5.21

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 6.15–6.29$ (m, 1 H, H-5), 6.36 (dsext, 1 H, $^2J = 41.3$ Hz, $^3J = 6.3$ Hz, OCF_2CHFCF_3), 7.36–7.55 (m, 2 H, H-2, H-4), 12.20 (s, br, 1 H, OH).

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