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FLUORINATED HETEROCYCLIC COMPOUNDS: SELECTIVE CHLORINE/FLUORINE EXCHANGE REACTIONS ON PYRIMIDINES*

E. KLAUKE, L. OEHLMANN and B. BAASNER

Central Research and Development Department, Bayer AG, D-5090 Leverkusen (F. R. G.)

SUMMARY

Selective chlorine/fluorine exchange reactions on tetrachloropyrimidine, 6-methyl-, 6-chloromethyl-, 6-dichloromethyl-, and 6-trichloromethyl-2,4,5-trichloropyrimidine are described. Sodium fluoride, potassium fluoride, hydrogen fluoride, and antimony trifluoride were used as the fluorinating agents. It was found that NaF and KF fluorinate only in the heterocyclic nucleus, HF in the nucleus and in the chlorinated methyl group, and SbF_3 only in the chlorinated methyl group. In the first stage of fluorination with NaF only chlorine bound in position 4 of the pyrimidine ring is exchanged. The HF reaction is an equilibrium reaction in which the substitution of the fluorine for the first chlorine atom occurs preferentially in position 2. The behaviour of partly fluorinated pyrimidines in nucleophilic exchange reactions is also discussed.

INTRODUCTION

In past years a number of biologically active substances and dyestuffs based on six-membered heterocyclic nitrogen compounds containing fluorine has been developed [1]. As a rule the fluorine is introduced by

* In memory of Professor Dr. Otto Bayer

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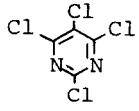
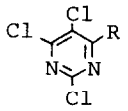
subjecting the already synthesized chlorine-containing heterocyclic systems to chlorine/fluorine exchange reactions [2], for which purpose several fluorinating agents are suitable [2,3]. The fluorination of tetrachloropyrimidine (1) to tetrafluoro- and 2,4,6-trifluoro-5-chloropyrimidine has been investigated intensively by various working groups. As fluorinating agents, sodium fluoride [4] and potassium fluoride [5,6,7,8], and also anhydrous hydrofluoric acid with which fluorination can be performed both in the liquid phase [9] and in the gas phase [10], have given particularly good results.

But the synthesis of partly fluorinated pyrimidine derivatives is likewise interesting in view of the expected modifications of the chemical and physical properties. In this connection the selective fluorination reactions obtained when tetrachloropyrimidine (1) and the pyrimidines substituted in position 6 (2) to (5) are treated with NaF, KF, HF, and SbF_3 as the fluorinating agents were investigated in our laboratory.



(1)



R = CH_3 (2)
CH_2Cl (3)
$CHCl_2$ (4)
CCl_3 (5)

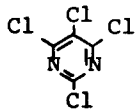
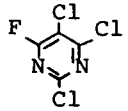
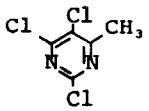
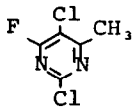
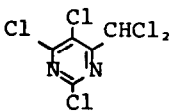
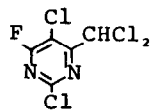
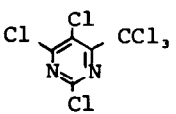
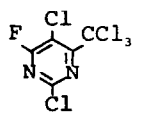
RESULTS AND DISCUSSION

When sodium fluoride was used as the fluorinating agent the first chlorine atom of all the investigated pyrimidine derivatives was replaced by fluorine exclusively in position 4 of the heterocyclic ring system. The experimental conditions are compiled in Table 1.

The specific two-fold fluorination (Table 2) results consistently in the 2,4-difluoropyrimidine derivatives.

Table 1

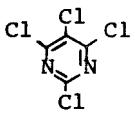
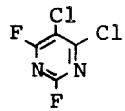
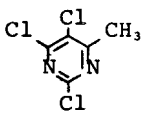
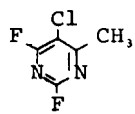
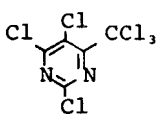
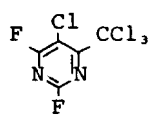
Monofluorination of chloropyrimidines with sodium fluoride

Starting compound *	Quantities		Temp. [°C]	Time [h]	Yield (%)	Product
	NaF [g]	Sulfolane [ml]				
	114	1oo	18o	2	42	
	126	32o	18o	4	5o	
	126	36o	14o	2	38	
	126	36o	16o	3	29	

* A 1-mole batch was used in each case

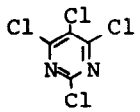
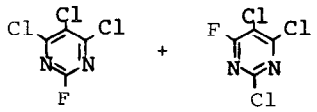
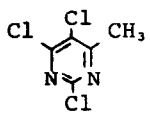
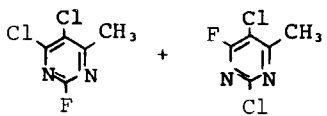
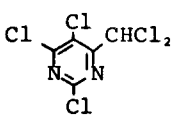
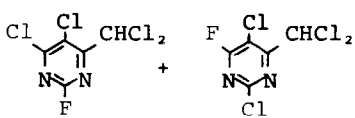
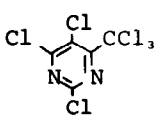
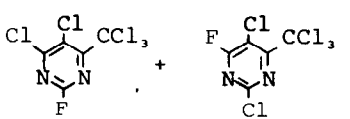
Table 2

Difluorination of chloropyrimidines with sodium fluoride

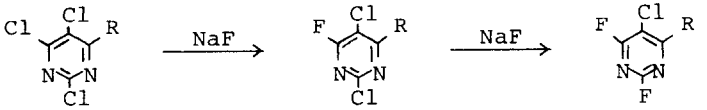
Starting compound *	Quantities		Temp. [°C]	Time [h]	Yield (%)	Product
	NaF [g]	Sulfolane [ml]				
	114	100	180	2	46	
	126	320	200	7	78	
	126	360	200	4	74	

* A 1-mole batch was used in each case

Table 3
Monofluorination of chloropyrimidines with HF

Starting compound *	HF (Mol)	Temp. [°C]	Pressure [bar]	Time [h]	Yield (%)	Products
	2o	8o	15	2	27	 8o : 2o
	3o	1oo	1o	2	44	 85 : 15
	2o	1oo	1o	2	38	 88 : 12
	8	8o	15	2	43	 96 : 4

* A 1-mole batch was used in each case



R =			
Cl	(1)	(6)	(11)
CH_3	(2)	(7)	(12)
CH_2Cl	(3)	(8)	(13)
$CHCl_2$	(4)	(9)	(14)
CCl_3	(5)	(1o)	(15)

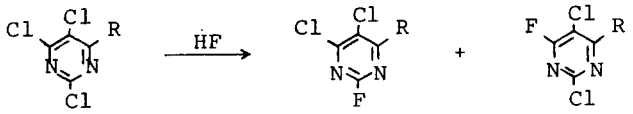
These exchange reactions are performed in solvents, sulfolane generally permitting the highest yields. If a solvent is dispensed with, the thermal sensitivity of these pyrimidines results in their substantial decomposition. Fluorination reactions at the nucleus can also be performed with potassium fluoride, but the proportion of the pyrimidine which is decomposed is then higher than when the reactions are performed with NaF.

The order in which the chlorine atoms of the ring have been found to be nucleophilically replaced by fluorine, i. e. - 4 (- 6) > - 2 >> - 5, agrees with the two-step mechanism and activating effects which have been discussed in connection with nucleophilic aromatic substitutions [7, 8, 11, 12].

A different course of reaction is shown by the chlorine/fluorine exchange reactions with anhydrous hydrogen fluoride, which are carried out in a closed system at elevated temperatures under pressure and in the absence of an additional fluorination catalyst.

After distillation to remove unreacted starting material and more highly fluorinated products, the specific monofluorination reactions performed with HF under the conditions listed in Table 3 give the pyrimidines which are fluorinated singly in the heterocyclic nucleus. If the trichloromethyl group is in position 6, the proportion of 2-fluoropyrimidine is 96 %. Within

the series of pyrimidines investigated the 2-fluoro-pyrimidine content falls increasingly - to levels of which 80 % is the lowest - in the reaction of the tetrachloropyrimidine with HF. The individual isomeric 4-fluoro-derivative contents increase accordingly:



Ratio*	of 2-F-	to	4-F derivatives
R: CCl_3	96	:	4
$CHCl_2$	88	:	12
CH_3	85	:	15
Cl	80	:	20

If the reaction conditions (Table 4) are so chosen that the compounds whose nuclei are doubly fluorinated become the main products, 2,4-difluoro-5,6-dichloropyrimidine (11) is obtained from tetrachloropyrimidine (1), and 2,4-difluoro-5-chloro-6-methyl pyrimidine (12) is obtained from 2,4,5-trichloro-6-methyl pyrimidine (2).

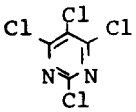
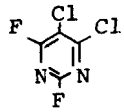
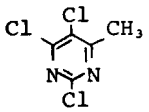
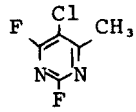
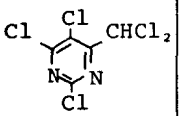
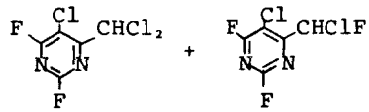
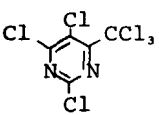
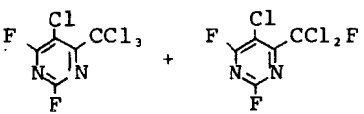
R = Cl (1) (11)

CH_3 (2) (12)

* The values were averaged from those obtained for at least six batches reacted under standardized conditions.

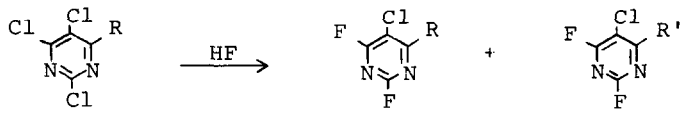
Table 4

Difluorination of chloropyrimidines with HF

Starting compound *	HF (Mol)	Temp. [°C]	Pressure [bar]	Time [h]	Yield (%)	Products
	5	140	21	3	48	
	20	100-140	20	6	88	
	25	120-140	15-20	6	73	 96 : 4
	30	140	25	2	91	 90 : 10

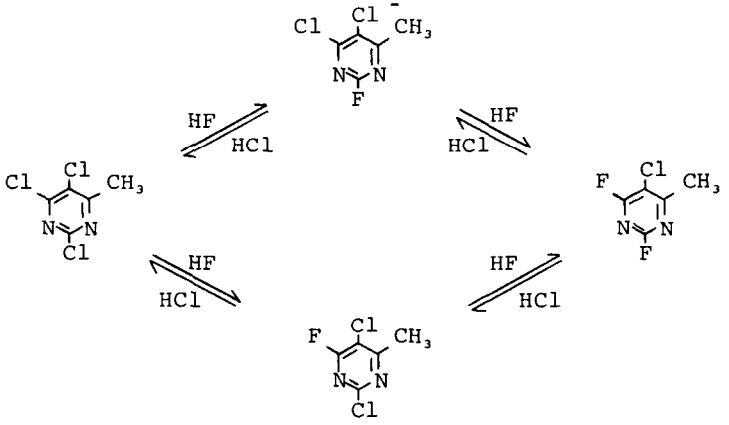
* A 1-mole batch was used in each case

With those pyrimidine derivatives which have chlorinated side chains (4) and (5) a small amount of a compound in which fluorine is substituted for a chlorine atom in the side chain is obtained in addition to the compound which is chlorinated within the nucleus:

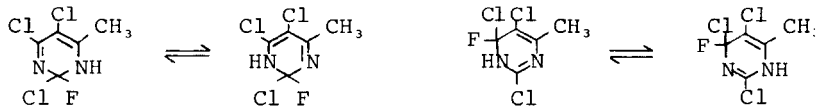


R = $CHCl_2$	(4)		$CHCl_2$	(14)	R' =	CHClF	(16)
		ratio:	96	:		4	
CCl_3	(5)		CCl_3	(15)		CCl_2F	(17)
		ratio:	9o	:		lo	

The reaction of chloropyrimidines with hydrogen fluoride is an equilibrium reaction; in the following formula table it is represented schematically for 2,4,5-trichloro-6-methyl pyrimidine:



Protonation of a nitrogen atom belonging to the ring and nucleophilic attack by the fluoride anion, which may take place at position 2 or 4, give the intermediate stages (I a) and (I b) or (II a) and (II b) respectively, from which, after the elimination of HCl, the monofluorinated products are obtained.



(I a) (I b) (II a) (II b)

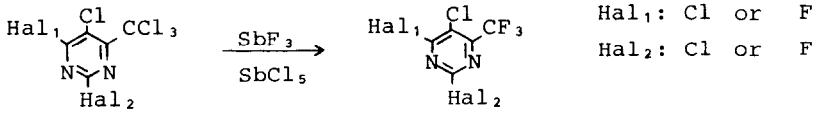
Renewed HF addition, followed by elimination of HCl, gives the difluorinated pyrimidine derivative.

As these chlorine/fluorine exchange reactions with HF are equilibrium reactions, the product distribution can be influenced by varying the pressure, time, temperature, and molar ratio of the reaction partners. In order, for example, to achieve complete exchange of the activated chlorine atoms, the HCl formed in the reaction must, if possible, be removed quantitatively.

In an extreme case, this complete exchange is achieved by working at the hydrogen fluoride boiling point for the respective pressure.

In the case of compounds chlorinated at the methyl group bound in position 6, the fluorination of the side chains competes with the chlorine/fluorine exchange reaction in the nucleus. The position can be summarized by saying that, where reactions of this type are concerned, anhydrous hydrogen fluoride serves as a reaction medium, a fluoride ion donor, and as an electrophilic catalyst.

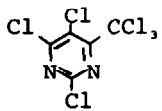
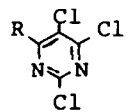
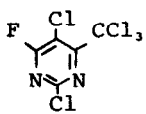
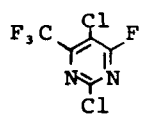
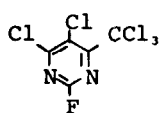
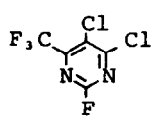
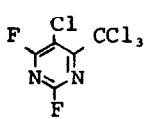
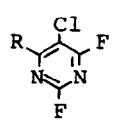
When antimony trifluoride is used as the fluorinating agent it is possible to fluorinate the trichloromethyl group selectively in position 6 independently of the halogen substituents in position 2, 4, and 5 of the heterocyclic nucleus. Antimony pentachloride is used as catalyst (Table 5).



Hal_1: Cl or F
Hal_2: Cl or F

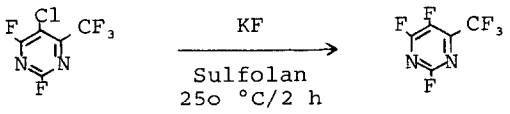
Table 5

Side chain fluorination of pyrimidines with SbF_3

Starting compound	Quantities			Temp.	Time	Yield	Products	
	Starting compound [g]	SbF_3 [g]	$SbCl_5$ [ml]	[°C]	[h]	(%)		
	15o	3o	2	15o	o,5	14	R = $CFCl_2$	
	15o	45	3	18o	o.5	4o	CF_2Cl	
	25o	156	24	175	1.o	52	CF_3	
	8o	8o	1o	165	1	38		
	8o	8o	1o	15o	3	42		
	123	3o	4.3	135	1	4o	R = CF_2Cl	
	92.6	44.2	6.3	135	1.5	65	CF_3	

The individual intermediate compounds produced by monofluorination and difluorination of the side chain can all be isolated.

With potassium fluoride as the fluorinating agent, even the last chlorine atom, which is bound in position 5 of the nucleus, can be replaced by fluorine. This gives the perfluorinated 2,4,5-trifluoro-6-trifluoromethyl pyrimidine, which has been detected so far only as a pyrolysis product of the tetrafluoropyrimidine in mixtures consisting of itself and of its isomers [8].

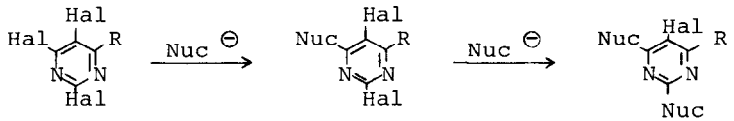


All the compounds prepared by means of the various fluorination reactions have been isolated by distillation or crystallization. The characterizations were performed by elementary analysis, mass spectroscopy, and ^{19}F NMR spectroscopy. The isomer ratios in mixtures were determined by gas chromatography. The isomer assignments were obtained by ^{19}F NMR. The physical data of the compounds produced are compiled in Table 6. The reaction conditions are not in all cases such as to give the optimum yields and conversions.

The ^{19}F NMR measurements were carried out with a Bruker WP 80 FT nuclear resonance spectrometer with a $^{1}H,^{19}F$ dual sample holder at a measurement frequency of 75.39 MHz. The stated shifts refer to trifluoroacetic acid (δ_{CF_3COOH} = 0 ppm) as an external standard. $CDCl_3$ is used as solvent in all cases.

The ^{19}F resonance signal for the fluorine atoms in position 2 and in position 4 or 6 is greatly broadened in consequence of the quadrupole coupling with the two neighbouring nitrogen atoms. Half widths between 6 Hz and 20 Hz are observed.

The pyrimidine derivatives obtained in the experiments described above were also subjeceted to nucleophilic exchange reactions. It was found that, in accordance with the rules for nucleophilic aromatic substitutions, position 4 is more strongly activated against a nucleophilic attack than postion 2 - regardless of the substitution pattern of the heterocyclic compound - and that no further exchange reactions take place in position 5 under the mild conditions under which such reactions are normally performed.



Hal: Cl, F R: CH_3, $CHCl_2$, CCl_3

For example, these reactions were carried out with methanol in a slightly basic medium, and also with primary and secondary amines and with ammonia, at temperatures of 0 °C to + 30 °C. Under these conditions only the products substituted in position 4 were found. If, however, the reactions are carried out with sodium methanolate, a mixture of the products monosubstituted in position 2 or 4 is obtained. More severe reaction conditions, finally, bring about two-fold substitution in position 2 and in position 4. Further details will be found in the experimental section.

EXPERIMENTAL

Reactions with sodium fluoride

A reaction vessel is charged with sodium fluoride, sulfolane, and a pyrimidine derivative, nitrogen at 5 bar is introduced, and the contents of the vessel are heated to the reaction temperature under stirring. After a suitable reaction time the temperature is reduced to about 150 °C and a fractional distillation is performed. This procedure gives the compounds listed in Tables 1 and 2.

Table 6

Physical data of the pyrimidines

Substitution				b.p./m.p. (°C)	n_D^{20}	^{19}F δ (ppm)			
2-	4-	5-	6-			2-	4-	5-	6-
F	Cl	Cl	Cl	b.p.: 195	1.5392	- 34.00			
Cl	F	Cl	Cl	b.p.: 77/15 mbar	1.5428		- 22.00		
F	F	Cl	Cl	b.p.: 156/15 mbar	1.4908	- 33.90	- 22.50		
F	F	Cl	F	b.p.: 115	1.4390	- 34.00	- 21.05		- 21.05
F	F	F	F	b.p.: 83	1.3868	- 33.36	- 6.84	+ 94.98	- 6.84 a)
F	Cl	Cl	CH_3	b.p.: 88/20 mbar	1.5182	- 34.38			
Cl	F	Cl	CH_3	b.p.: 86/20 mbar m.p.: 7	1.5178		- 16.90		
F	F	Cl	CH_3	b.p.: 158. m.p.: 3	1.4685	- 32.14	- 18.65		
F	F	Cl	CH_2Cl	b.p.: 86/19 mbar	1.5025	- 33.70	- 21.40		
F	Cl	Cl	$CHCl_2$	b.p.: 117/17 mbar m.p.: 12	1.5553	- 34.85			
Cl	F	Cl	$CHCl_2$	b.p.: 119-20/12 mbar m.p.: 45	1.5562		- 22.28		
F	F	Cl	$CHCl_2$	b.p.: 96/20 mbar	1.5145	- 35.33	- 23.98		

F	Cl	Cl	CCl_3	b.p. : 13o/1o mbar	1.5618	- 34.59		
Cl	F	Cl	CCl_3	b.p. : 128/11 mbar	1.5615		- 23.17	
F	F	Cl	CCl_3	b.p. : 1o2/12 mbar	1.552o	- 35.95	- 25.11	
F	Cl	Cl	CF_3	b.p. : 161	1.4537	- 34.28		- 1o.35
Cl	F	Cl	CF_3	b.p. : 157-8	1.4535		- 23.73	- 11.o2
F	F	Cl	CF_3	b.p. : 126-8	1.411o	- 35.49	- 25.81	- 1o.49
Cl	Cl	Cl	CF_3	b.p. : 81/18 mbar	1.4925			- 1o.74
F	F	F	CF_3	b.p. : 96	1.3675	- 33.65	- 1o.o3	+ 75.36 - 11.o3 [b]
Cl	Cl	Cl	$CFCl_2$	b.p. : 131/12 mbar	1.5628			- 19.96
Cl	Cl	Cl	CF_2Cl	b.p. : 1o3/12 mbar	1.5292			- 21.46
F	F	Cl	CF_2Cl	b.p. : 158	1.4492	- 35.83	- 25.92	- 21.28
F	F	Cl	$CFCl_2$	b.p. : 78/17 mbar	1.4875	- 35.97	- 25.8o	- 19.44
F	F	Cl	CHClF	b.p. : 1oo/1oo mbar	1.4618	- 38.49	- 28.59	- 14.17 [c]

[a] 2-F: δ = - 33.36, d; J_{FF} = 26 Hz (strongly broadened); 4-F a. 6-F: - 6.84, d; J_{FF} = 18 Hz (broadened); 5-F: + 94.98, d, t;

[b] 2-F: - 33.65, d; J_{FF} = 3o Hz; 4-F: - 1o.o3, d; J_{FF} = 21 Hz (broadened); 5-F: + 75.36 d, d, q; $J_{5\text{-}F,\ CF_3}$ = 16 Hz; 6-CF_3: - 11.o3, d;

[c] 2-F: - 38.49 (broadened) ; 4-F: - 28.59; 6-CF: - 14.17, d, d, d,; $^1J_{FF}$ = 2 Hz, $^2J_{FF}$ = 1 Hz; J_{HF} = 2 Hz

Reactions with hydrogen fluoride

A stainless steel autoclave having an agitator, a brine-cooled reflux condenser, and a pressure relaxation valve is charged with the anhydrous hydrofluoric acid, the temperature of the acid is adjusted to - 5 °C to + 5 °C, and the pyrimidine derivative is added from a metering device. Then the autoclave is closed, nitrogen at 10 bar is introduced, and the contents of the autoclave are heated to the reaction temperature in the course of about an hour. Hydrogen chloride is formed and it is continuously vented to keep the pressure at 10 to 15 bar. In some cases the reaction temperature is increased by 20 °C. After the HCl has escaped, the batch is stirred for a further 60 minutes and is then cooled to 15 °C. The HF is distilled off at normal pressure through a column with a reflux divider, after which the residue is fractionated up a column under reduced pressure. This procedure gives the compounds listed in Tables 3 and 4.

Reactions with antimony trifluoride

A pyrimidine derivative, antimony trifluoride, and antimony pentachloride are heated to the reaction temperature and are left to react for up to three hours, after which the contents of the vessel are distilled. The distillate is washed with dilute hydrochloric acid and water, dried, and subjected to fractional distillation. This procedure gives the compounds listed in Table 5.

Reactions of pyrimidine derivatives with ammonia to give 4-aminopyrimidines

At 0 °C to + 5°C 5 ml of concentrated ammonia is added dropwise to 30 mmole of the pyridine derivative in 20 ml of absolute THF. The batch is stirred at the same temperature for a further 60 minutes, the volatile

constituents are removed under reduced pressure, and 100 ml of water is added. The precipitates are filtered by vacuum and dried (with P_2O_5 under a vacuum). This procedure gives:

4-amino-2,5-dichloro-6-dichloromethyl pyrimidine (from 4-fluoro-2,5-dichloro-6-dichloromethyl pyrimidine); yield: 83 %, m. p.: 197 - 9 °C

4-amino-2-fluoro-5-chloro-6-dichloromethyl pyrimidine (a. from 2-fluoro-4,5-dichloro-6-dichloromethyl pyrimidine); yield: 87 %, m. p.: 188 - 9 °C
(b. from 2,4-difluoro-5-chloro-6-dichloromethyl pyrimidine); yield: 92 %, m. p.: 188 - 9 °C; ^{19}F NMR: δ = -31.14 ppm (2-F)

4-amino-2,5-dichloro-6-trifluoromethyl pyrimidine (from 4-fluoro-2,5-dichloro-6-trifluoromethyl pyrimidine); yield: 88 %, m. p.: 132 - 4°C; ^{19}F NMR: δ = -11.72 ppm ($-CF_3$)

4-amino-2-fluoro-5-chloro-6-trifluoromethyl pyrimidine (from 2,4-difluoro-5-chloro-6-trifluoromethyl pyrimidine); yield: 78 %, m. p.: 140 - 1 °C, ^{19}F NMR: δ = -31,64 ppm (2-F) and -11.05 ppm ($-CF_3$)

4-amino-2,5-trifluoro-6-trifluoromethyl pyrimidine (from 2,4,5-trifluoro- 6-trifluoromethyl pyrimidine); yield: 84 %; m. p.: 112 - 3 °C, ^{19}F NMR: δ = - 29.48 ppm (2-F; broadened, half width: 6 Hz), + 77.53 (5-F) and - 11.00 ppm ($-CF_3$); $J_{2,5}$ = 28 Hz; $J_{5\text{-F},\ CF_3}$ = 17 Hz

Synthesis of 2,4-diamino-5-chloro-6-trichloromethyl pyrimidine

At 60 °C 7 ml of concentrated ammonia in 7 ml of dioxane is added dropwise to 5.7 g (20 mmole) of 2-fluoro-4,5-dichloro-6-trichloromethyl pyrimidine in 5 ml

of dioxane in the course of 30 minutes. The batch is stirred for a further 30 minutes at this temperature, after which it is cooled and 20 ml of water is added. The precipitate is removed by filtration and dried under a vaccum.
Yield: 4 g (76 %), m.p.: 80 - 82 °C.

Synthesis of 2-fluoro-4-methoxy-5-chloro-6-trichloromethyl pyrimidine

14.2 g (50 mmole) of 2-fluoro-4,5-dichloro-6-trichloromethyl pyrimidine is stirred for 30 minutes at room temperature with 2.8 g of Na_2CO_3 in 20 ml of methanol The volatile constituents are removed under reduced pressure and the residue is distilled under a vaccum.
Yield: 7.1 g (51 %), b.p.: 150 - 152 °C/18 mbar; n_D^{20}: 1.5703; ^{19}F NMR: δ = -33.92 ppm.

Under analogous conditions 10.5 g (50 mmole) of 2,4-difluoro-5-chloro-6-trifluoromethyl pyrimidine is reacted to 2-fluoro-4-methoxy-5-chloro-6-trifluoromethyl pyrimidine.
Yield: 6.0 g (52 %), b.p.: 128 - 130 °C/18 mbar; ^{19}F NMR: δ = 31.36 (2-F) and - 12.83 ppm ($-CF_3$).

Synthesis of 2,4-dimethoxy-5-chloro-6-trifluoromethyl pyrimidine

At + 5 °C to + 10 °C 2.2 g of sodium methanolate in 2 ml MeOH and 15 ml of absolute THF is added dropwise to 8.8 g of 2,4-difluoro-5-chloro-6-trifluoromethyl pyrimidine in 10 ml of absolute THF. After the batch has been stirred for a further two hours at the same temperature it is concentrated under reduced pressure and the residue is distilled.
Yield: 5 g (51 %); b.p.: 100 - 102 °C/18 mbar; n_D^{20}: 1.4728; ^{19}F NMR: δ = - 10.89 ppm.

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