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Selective fluorination by halogen exchange of chlorodiazines and chloropyridines promoted by the 'proton sponge'—triethylamine tris(hydrogen fluoride) system

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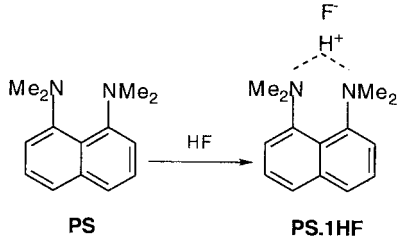
Abstract—The 'proton sponge'—triethylamine tris(hydrogen fluoride) mixtures provide a mild and efficient fluorinating reagent to introduce selectively fluorine atoms by halogen exchange into chlorodiazines and chloronitropyridine series.

1. Introduction

The combinations of hydrogen fluoride with organic bases (the so called 'onium hydrogen fluorides') as classical fluorinating agents were recently reviewed.[1] In this context, special interest has recently focused on triethylamine tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$)[2] for its mild and efficient reactivity. On the other hand, the strain effects on basicity of 'proton sponge' [PS, 1,8-bis(dimethylamino)naphthalene] have been exhaustively documented as well.[3] Nevertheless, relatively little has been reported to describe in detail the ability of PS to bind the proton from hydrogen fluoride (to form the 'PS' hydrogen fluoride, PS·1HF but in a different way to a simple 'onium' structure) and to release fluoride ion (Scheme 1).[4,5]

Our ongoing research in the chemistry of diazines[6,7] prompted us to look for a mild fluorinating reagent, capable of both selective halogen exchange and complete substitution of chlorine atoms in (poly)chloro(benzo)diazines and pyridines. Thus, the mixtures of $Et_3N{\cdot}3HF$ with PS appeared to us appropriate for this purpose and our initial results have been described in a preliminary communication.[8]



Scheme 1.

We now report the extension of these investigations defining more fully the following topics: (a) the combinations of 'PS' with hydrogen fluoride as fluorinating reagents; (b) the ability of mixtures of $Et_3N{\cdot}3HF$ with PS as effective fluorinating reagents; (c) the quantitative and qualitative results of the fluorinations performed by using these systems. To our knowledge, this basic synthetic approach has not been considered so far.

2. Results and discussion

2.1. The fluorinating reagents and test experiments

2.1.1. The combinations of 'PS' with hydrogen fluoride. Our first objective was to compare different ratios of PS and HF to identify the best formulation to achieve the fluorination of the title compounds. In order to access PS·1HF (equimolar ratio PS:HF, Scheme 1) without the need to handle hazardous hydrogen fluoride[4,5] we reacted commercially available $Et_3N{\cdot}3HF$ with PS (1:3 molar ratio) and completely removed the triethylamine under vacuum at 100°C; the reaction was monitored by NMR (Eq. (1)):

$$3PS + Et_3N{\cdot}3HF \rightarrow 3(PS{\cdot}1HF) + Et_3N \quad (1)$$

The resulting solid residue was obtained in almost quantitative yield and its NMR spectrum exhibited signals at chemical shifts close to those previously reported for

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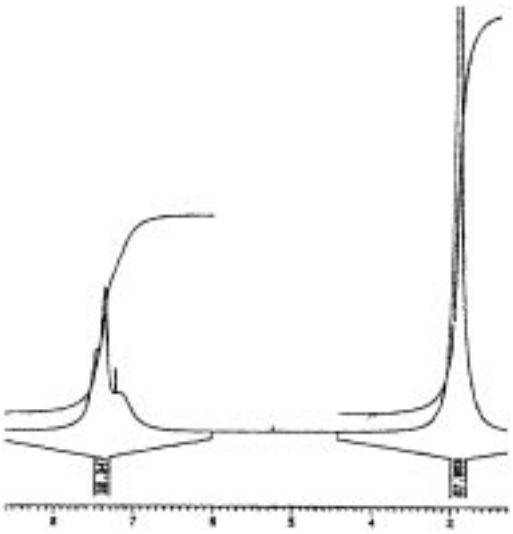


Figure 1. ^{1}H NMR spectra of PS·1HF.

PS·1HF by Chambers and co-workers[4,5] and gave satisfactory elemental analysis. On this basis we assigned this compound as PS·1HF. When this solid was heated, it was converted into a mixture of PS and PS·3HF as shown by the similarity between the temperature (48(9)°C) at which this change occurs and the literature melting point of 49–50°C quoted for commercially available PS itself. This temperature differs from the literature value[4] (117–8°C) given for PS·1HF. Moreover, the work up at room temperature of our product with ether or pentane, afforded a new crystalline solid corresponding to the PS·3HF stoichiometry and the mother liquor yielded the theoretical amount of starting free base PS (Eq. (2)). This product PS·3HF melts at 125–6°C. This behaviour is not altogether unexpected since, as promoted by temperature and/or solvents (Eqs. (2) and (3)), it is similar to some other classical 'onium' salts of hydrogen fluoride such as melamine, pyridine, etc.[1]

$$3(\text{PS}\cdot 1\text{HF}) \xrightarrow{\text{(Ether or Pentane)}} 2\text{PS (as ethereal or pentane solution)} + \text{PS}\cdot 3\text{HF}\downarrow \quad (2)$$

$$3(\text{PS}\cdot 1\text{HF}) \xrightarrow{(50^\circ\text{C}<t<123^\circ\text{C})} 2\text{PS(melted mass)} + \text{PS}\cdot 3\text{HF(solid)} \quad (3)$$

Indeed, supplementary evidence provided by spectral data is in agreement with the existence of two distinct compounds, of different stoichiometry, PS·1HF and PS·3HF at least in the solid state. In the IR spectra (KBr), the previously reported characteristic bands[4,5,9,10] were completely and identically displayed by the two compounds, with the exception of the large peak located at 1800 cm^{-1}, which is assigned as combined band of R_3NH^+ units, strong in PS·3HF but very weak in PS·1HF.[10] PS·1HF and PS·3HF exhibited the strong ν_{NH} stretch band (located at 3500 cm^{-1}) which is completely absent in the PS spectrum.

The NMR spectra showed rather interesting differences between the two types of salts: only PS·3HF displayed all the expected sharp splitting in the aromatic region (see Experimental) (Figs. 1 and 2).

This peculiar behaviour of PS·1HF (Eqs. (2) and (3)) led us to assume that the structure should be, from thermodynamic point of view, less stable than PS·3HF, and that only PS·3HF exhibits enough stability to develop crystals for X-ray analysis.[8] The solid state structure gives the formulation

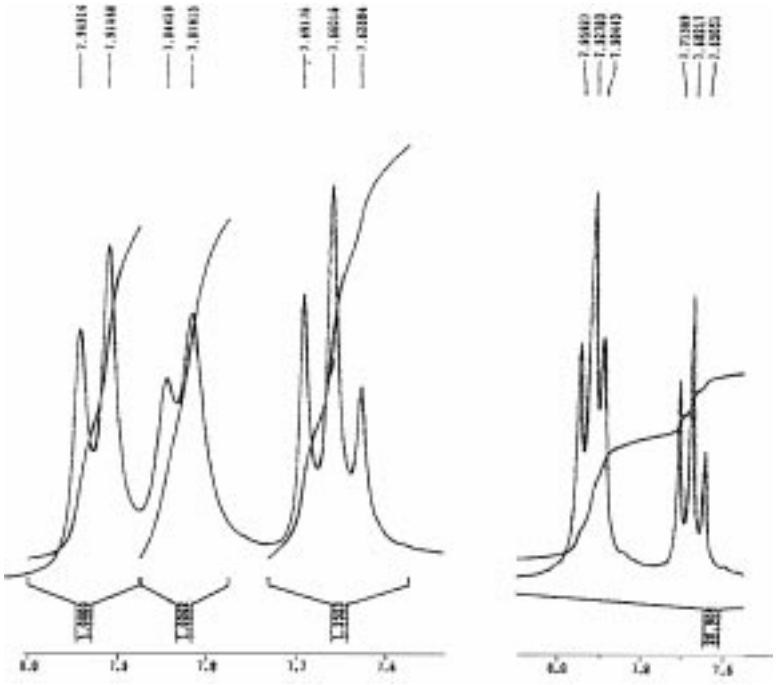


Figure 2. Relevant NMR spectra of PS·3HF; (a) ^{1}H spectrum in the aromatic region (≈0.070 g/mL), from downfield to upfield (δ, ppm): 7.93 (H-*para*, d), 7.83 (d, H-*ortho*), 7.66 (dd as t, H-*meta*); (b) ^{1}H spectrum in the aromatic region (≈0.140 g/mL) from downfield to upfield (δ ppm): 7.94 (H-*para*, d), 7.92 (d, H-*ortho*),7.68 (dd as t, H-*meta*).

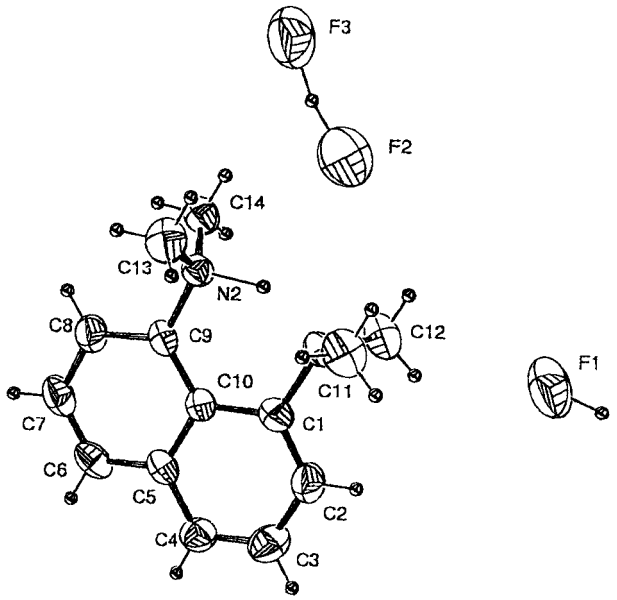


Figure 3. The ORTEP diagram of PS·3HF.

(PSH^+) (HF_2^-) (HF) (Fig. 3) whereas PS·1HF revealed slow decomposition as hygroscopicity and oxidation.

A comparative test of reactivity of these two reagents (PS·1HF and PS·3HF) against 2,4,6-trichloropyrimidine and 2-chloro-3,5-dinitropyridine was straightforward and supported this assumption (Scheme 2).

As shown by the conversions, PS·1HF exhibited a higher reactivity than PS·3HF. We note however that, in the case of 2,4,6-trichloropyrimidine, in contrast to the results previously reported by Chambers and co-workers,[4,5] no reaction occurred at room temperature with any of the above reagents; no side product ('PS' hydrochloride PS·1HCl) precipitated from the reaction mixture with acetonitrile solution. It is also worth mentioning that, although the presence of trifluoropyrimidine was unambiguously revealed by ^{19}F NMR spectroscopy (e.g. two signals located at −40.6 and −52.3 ppm in 1:2 intensity ratio, respectively), its effective isolation in the conditions depicted in Scheme 2 was irrelevant due to its high volatility. Therefore, the conversion was calculated based on the effective amounts of the isolated PS·1HCl and a supplementary test, provided by 2-chloro-3,5-dinitropyridine, was considered.

Surprisingly, the NMR monitoring of the reactions (Scheme 2) unambiguously revealed the presence of unreacted PS·3HF in both cases **I**, **II** for both compounds (Fig. 4).

In our opinion these facts support the below preliminary conclusions:

(a) the real fluorinating reagent, in both cases, is PS·3HF; consequently, a structure having the PS·1HF stoichiometry is valid in solid state only. In solution one has rather to consider an equilibrium involving the generation of another stoichiometry assigned as $(PS)_2(PS{\cdot}3HF)$ in which the two 'free' PS units are designed to bind the resulting HCl (Eq. (4)):

$$3(PS{\cdot}1HF) \rightleftarrows (PS)_2(PS{\cdot}3HF) \quad (4)$$

(b) the lower reactivity of PS·3HF alone (Eqs. (5) and (6)), compared with that of PS·1HF (Eq. (7)) (in identical conditions, Scheme 2) can be explained by simple acid-base considerations:

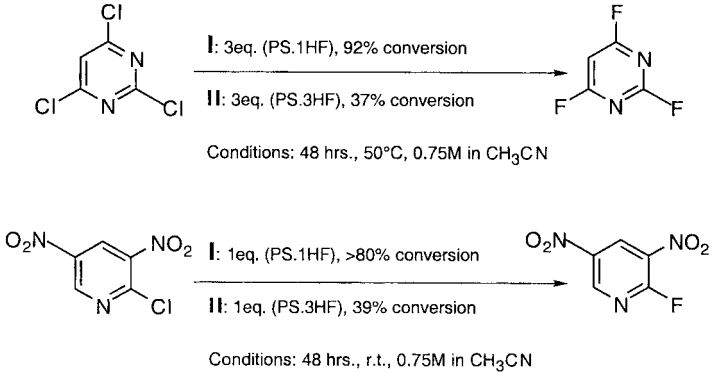
$$R{-}Cl + PS{\cdot}3HF \rightarrow R{-}F + PS{\cdot}2HF + HCl \quad (5)$$

$$PS{\cdot}2HF + HCl \rightarrow PS{\cdot}HCl\downarrow + 2HF \quad (6)$$

$$R{-}Cl + PS{\cdot}1HF \rightarrow R{-}F + PS{\cdot}1HCl\downarrow \quad (7)$$

In the case of PS·3HF, there is no free base to neutralise the resulting HCl. Next, one should take into account the normal higher stability of PS·1HCl vs. all the analogous PS·*x*HF (e.g. $x=2$, Eq. (6)); that is, in conditions depicted in Scheme 2, just one of the three HF units in PS·3HF is 'active'.

2.1.2. The 'PS'—triethylamine tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$) system. The idea to test the above mixtures as fluorinating reagents was evidently inspired by the possibility to generate in situ the PS hydrogen fluorides in connection with the presence of another base, triethylamine, assigned a priori as HCl acceptor.



Scheme 2.

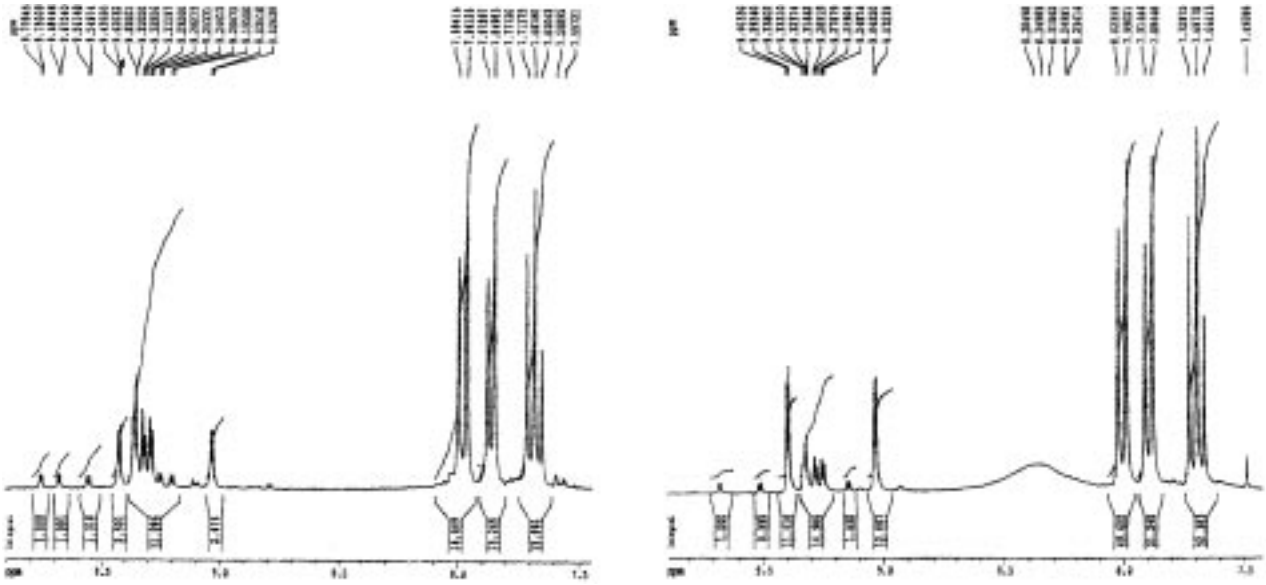


Figure 4. ^{1}H NMR spectra of the crude reaction mixtures of 2-chloro-3,5-dinitropyridine with 'PS' hydrogen fluorides, after 24 h (details); (a) Route **I** (Scheme 2, fluorinating reagent PS·1HF, 69% conversion), from downfield to upfield (δ ppm, J Hz): 9.43 (1H, d, 2.5, chloro derivative); 9.36 (1H, dd, 3.2, 2.5, fluoro derivative); 9.31 (1H, dd, 7.5, 2.5, fluoro derivative); 9.03 (1H, d, 2.5, chloro derivative); 8.00–7.50, PS·3HF (aromatic protons); (b) Route **II** (Scheme 2, fluorinating reagent PS·3HF, conversion38%).

Since the above mixtures are, clearly, acid-base equilibria-systems and based on the difference between pKa values of the two bases (12.10 PS and 10.75 Et_3N),[3] in a preliminary experiment we attempted to prepare PS·3HF in a similar pathway as PS·1HF (equimolar ratio PS:Et_3N·3HF, Eq. (8)).

$$PS + Et_3N{\cdot}3HF \rightleftarrows PS{\cdot}3HF + Et_3N \quad (8)$$

This experiment failed, indicating that the difference between pK_a values it is too small for complete 'transfer' of all three HF units (but one, Eq. (9)) to the stronger base from the weaker one even by attempting to remove the latter (to be compared with Eq. (1)).

$$PS + Et_3N{\cdot}3HF \leftrightarrows PS{\cdot}1HF + Et_3N{\cdot}2HF \quad (9)$$

On the other hand, as we recently reported,[8] the behaviour of these mixtures against (poly)chloro(benzo)diazines was like authentic fluorinating reagents on a large scale of molar ratio between PS and Et_3N·3HF and very different than Et_3N·3HF alone. Therefore, we investigated from the NMR point of view several mixtures defined as xPS+y(Et_3N·3HF) by varying the molar ratio between components x:y from 4:1 to 1:4[†] The appearance of these spectra revealed unambiguously the presence of PS·1HF and PS·3HF environments, depending on x:y ratio.

Obviously, the intimate nature of all possible terms involved in the above equilibria is quite impossible to elucidate averaged δ values by means of NMR. Nevertheless, in our opinion, only two successive equilibria are rather relevant to support the spectral data (Eqs. (9) and (10)).

$$PS{\cdot}1HF + 2(Et_3N{\cdot}3HF) \rightleftarrows PS{\cdot}3HF + 2(Et_3N{\cdot}2HF) \quad (10)$$

Thus, we attempted at estimating the compositions but restricted to the same type of species: derived from triethylamine (Et_3N·3HF and Et_3N·2HF, Eqs. (9) and (10)) and derived from PS (in Eq. (9): PS and PS·1HF; in Eq. (10): PS·1HF and PS·3HF). We selected as relevant signals the most separated and influenced ones belonging to the same basic unit: ^{13}C δ value of methyl groups in PS, PS·1HF, PS·3HF and ^{1}H δ value of methylene groups in Et_3N·3HF and Et_3N·2HF. The estimated compositions, according to the selected equilibria 9 and 10, are collected in Table 1.

Data summarised in Table 1 prompted us the following remarks:

(a) the option to restrict the acid-base process to the equilibria 9 and 10 only as dominant seems to be satisfactory since the observed averaged δ values of the mixtures xPS+y(Et_3N·3HF) ranged strictly between chemical shifts of the pure involved species (e.g. no free Et_3N is present since the δ values of methylene group ranged only between 2.91–3.00 ppm).

(b) in the domain of excess of PS vs. Et_3N·3HF (x:y from 4:1 to 1:1, respectively) the reagents can be described by the Eq. (9): the content of PS·1HF species increases rapidly with increasing the ratio of Et_3N·3HF. In turn, the variation of the δ values for F^- suggests rather the Et_3N·2HF environment. Anyhow, its ability to halogen exchange should increase from left to right. It was expected that this type of reagent should be useful for compounds possessing themselves a good reactivity (see Scheme 2).

[†] This domain of variation of x:y molar ratio was currently used in our syntheses; see later.

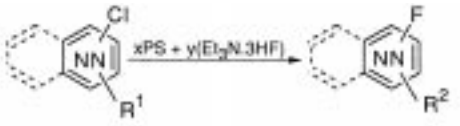
Table 1. Relevant NMR data for the equilibria (9) and (10) (solvent $CDCl_3$)

δ[a] (ppm) in pure compound	Reagent (Eq. (9))			Reagent (Eq. (10))			δ (ppm) in pure compound
	x:*y* in *x*PS+*y*(Et_3N·3HF)			*x*:*y* in *x*PS+*y*(Et_3N·3HF)			
	4:1		1:1	1:2		1:4	
44.8 (δ ^{13}C CH_3) 100% PS	44.9[b]		45.1[c]	46.0		46.1	**46.6** (δ ^{13}C CH_3) 100% PS·3HF
	80%[d]	PS	50%				
	20%	PS·1HF	50%	50%	PS·1HF	38%	
				50%	PS·3HF	62%	
2.85[c] (δ ^{1}H CH_2) 100% Et_3N·2HF	2.91		2.96	2.96		3.00	**3.13** (δ ^{1}H CH_2) 100% Et_3N·3HF
	80%	Et_3N·2HF	60%				
	20%	Et_3N·3HF	40%	40%	Et_3N·3HF	54%	
				60%	Et_3N·2HF	46%	
−**154.4** (δ ^{19}F) 100% Et_3N·2HF	−158.0		−158.7	−159.5		−160.5	−**167.6** (δ ^{19}F) 100% PS·3HF

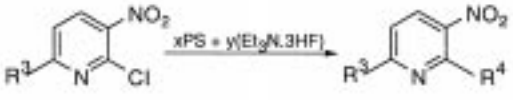
[a] δ All signals were measured against the solvent peak, throughout located at 78.0 ppm (^{13}C NMR) and 7.27 ppm (^{1}H NMR).
[b] δ Minimal value in the successive mixtures, by varying *x*:*y*.
[c] δ Maximal value in the successive mixtures, by varying *x*:*y*; δ value for CH_3 group in isolated PS·1HF is 45.4 ppm
[d] All percentages were calculated starting from the averaged δ values applied to Eqs. (9) and (10) by using the known relationship $\delta=\delta_1x_1+\delta_2x_2$ where $x_{1,2}$ are the molar fractions of the considered environments: PS/PS·1HF (Eq. (9)) PS·1HF/PS·3HF (Eq. (10)) and Et_3N·2HF/Et_3N·3HF (Eqs. (9) and (10)).

(c) in the domain of excess of Et_3N·3HF vs. PS (*x*:*y* from 1:1 to 4:1, respectively) the reagents should obey to Eq. (10): one can see only a slight increasing of PS·3HF species. Indeed, the HF acceptor in these mixtures is now PS·1HF and not the free base PS (to compare with Eq. (9)). Nevertheless, the appearance of PS·3HF environment was clearly displayed in the mixture *x*=1, *y*=4.

Based on the test experiments, we assumed that these reagents should be appropriate for less reactive substrates.



NN disposal	Substrate	R^1	Products	R^2
1,3	2,4-Dichloropyrimidine **1**	Cl	**1a**	Cl (C-2)
			1b	F
			1c	Cl (C-4)
1,3	4-Chloro-2-methylsulfanylpyrimidine **2**	SMe	**2a**	SMe
1,2	3,6-Dichloropyridazine **3**	Cl	**3a**	Cl
			3b	F
1,2	3-Chloro-6-phenylpyridazine **4**	Ph	**4a**	Ph
1,4	2,3-Dichloroquinoxaline **5**	Cl	**5a**	Cl
			5b	F
2,3	1,4-Dichlorophthalazine **6**	Cl	**6a**	Cl
			6b	F

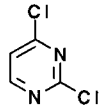
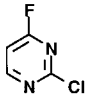
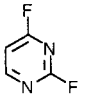
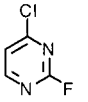
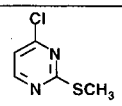
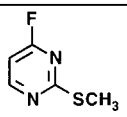
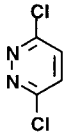
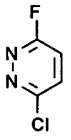
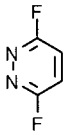
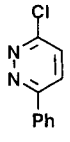
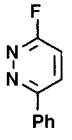


7 R^3 = H
8 R^3 = Cl

7a R^3 = H, R^4 = F
8a R^3 = R^4 = F
8b R^3 = Cl, R^4 = F
8c R^3 = F, R^4 = Cl

Scheme 3.

Table 2. Relevant results of the fluorination of the diazines **1–4**

No.	Starting material	Reagent and molar ratio *vs.* 1 mole substrate	Solvent	Temp (°C); total time (hrs)	Products (main product in **bold**) and molar ratios			Total conversion[a]; yield[b] (%)
1.	 **1**	1 (PS.1HF) portionwise (24hrs)[c]	none	65; 48	 **1a** **4.6**[d]	 **1b** 1.0	 **1c** 1.3	69; 40 (**1a**)
		1 (PS.1HF) portionwise (24hrs)	CH_3CN	65; 72	**4.3**	1.5	1.0	74; 28(**1a**)
		1PS+1/3(Et_3N.3HF)	none	60; 24	**4.6**	1.0	1.0	70; -
2.	 **2**	3PS+3(Et_3N.3HF)[e]	none	120; 24	 **2a**			100; 70 (**2a**)
3.	 **3**	2PS+4(Et_3N.3HF)[f] portionwise (66hrs)	none	80; 96[g]	 **3a** **24.0**	 **3b** 1.0		82; 53 (**3a**)
4.	 **4**	4PS+6(Et_3N.3HF)[e]	none	100; 144	 **4a**			82; 63 (**4a**)

[a] Total conversion (% molar) of the starting materials **1–4** towards all products **1a–c**, **2a**, **3a**, **b** and **4**, respectively.
[b] Yields are calculated as isolated materials; the amount of the recyclable starting material was not taken into account.
[c] See Experimental for this result as Method **A**.
[d] Relative molar ratios between reaction products in the crude reaction mixture as issued from ^1H correlated with ^{19}F NMR spectra.
[e] See Experimental for this result as Method **B**.
[f] See Experimental for this result as Method **C**.
[g] For the compounds **3a**, **b** Fukuhara, T. and Yoneda, N. reported a 92% yield (as 56% difluro- **3b** vs. 44% mono fluoroderivative **3a**) by using anhydrous HF in autoclave (2 h at 100°C); no structural assignment accompanied these data.[11] However, if the complete substitution of chlorine is desired, much stronger conditions are required, in two step synthesis.[13,17]

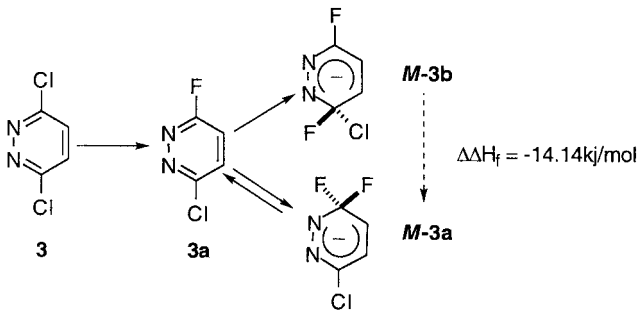
Indeed, the greater stability of PS·3HF allows its use at higher temperatures and hard conditions. However, a base should be present to bind the resulting HCl and this can be readily accomplished (Eq. (6)) by the excess of $Et_3N{\cdot}x$HF (x=2, 3) to yield the more thermodynamically stable triethylamine hydrochloride. The free hydrogen fluoride could either activate the substrate towards nucleophilic substitution, in agreement with the recent Yoneda and co-workers assignments.[11]

2.2. Selective fluorinations by using the PS–$Et_3N{\cdot}3HF$ system

In this section, attention is dedicated to the selective nucleophilic replacement of chlorine atoms in some π-deficient heteroaromatic compounds[4,5,11–13] according to Scheme 3.

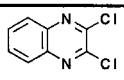
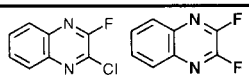
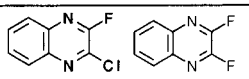
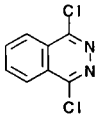
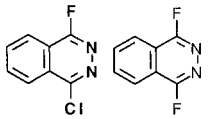
2.2.1. Fluorination of the chlorodiazines 1–4 (Table 2, Scheme 4). Chloropyrimidines were suitable substrates to undergo either selective or complete substitution of the chlorine atoms.

As usually observed,[14–16] 2,4-dichloropyrimidine **1** (Table 2, entry 1) exhibited higher reactivity at C-4 than at C-2 position and regioselectivity was not found to be dependent on the use of a solvent or type of reagent, if global equimolar ratio (dichloroderivative:F^-) was used. If the reaction was carried out in acetonitrile, a lower yield was observed as the consequence of the loss of the product during the work-up (promoted by its high volatility), in order to remove the



Scheme 4.

Table 3. Relevant results of the fluorination of the dichlorobenzodiazines **5** and **6**

No.	Starting material	Reagent and molar ratio *vs.* 1 mole substrate	Solvent	Temp (°C); total time (hrs)	Products (main product in **bold**) and molar ratios	Total conversion[a]; yield[b] (%)
1.	 **5**	*x*PS + *y*(Et_3N.3HF) x=4, y=4/3[c]	none	90; 75	 **5a** 1.0[d] **5b** **7.0**	90; 50 (**5b**)
		x=1, y=1/3 portionwise (96hrs)[e]	CH_3CN	80; 105	 **5a** **2.5** **5b** 1.0	57; 35 (**5a**)
2.	 **6**	1PS +1/3(Et_3N.3HF) portionwise (48hrs)[e]	CH_3CN	85; 96	 **6a** **24.0** **6b** 1.0	86; 37 (**6a**)

[a] Total conversion (% molar) of the starting material **5**, **6** towards all products **5a**, **b** and **6a**, **b**, respectively.
[b] Yields are calculated as isolated materials; the amount of the recyclable starting materials was not taken into account.
[c] See Experimental for this result as Method **B**.
[d] Relative molar ratios between reaction products in the crude reaction mixture as issued from ^1H correlated with ^{19}F NMR spectra.
[e] See Experimental for this result as Method **D**.

solvent. Apparently, the use of the mixture 1PS+1/3(Et_3N·3HF) without solvent had been more convenient but the isolated product was strongly contaminated with triethylamine during the isolation by vacuum distillation. Consequently, the use of PS·1HF alone was the best pathway to access **1a**.

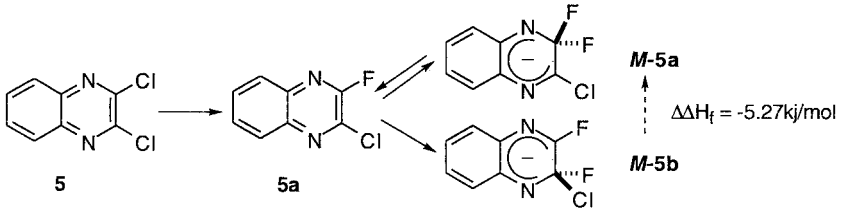
Complete fluorination to access **1b** (seen as trivial case) was not attempted.[6]

4-Chloro-2-methylsulfanylpyrimidine **2** (Table 2, entry 2) required stronger conditions, presumably because of the electron-donating substituent attached at C-2. Previous 'classical' fluorination of this compound by us[6] (150°C, KF, 6 h in tetraglyme) afforded **2a** in 67% yield. With the present reagent (3PS+3Et_3N·3HF) quantitative conversion was observed; due to losses of product during the work-up to remove triethylamine, the isolated yield was reduced to 70%. In turn, step by step ^1H NMR monitoring of the same fluorination but promoted by single PS·1HF or PS·3HF showed a faster decomposition of the reaction mixture than a satisfactory conversion of **2** into **2a**.

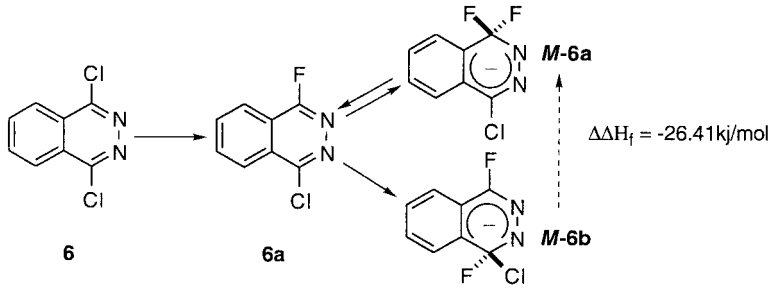
Preliminary attempts performed on 3,6-dichloropyridazine **3** at 80°C with Et_3N·3HF alone shown that it required more than 20 equiv. of F^- for the detection of **3a** in small traces only. Hence **3** exhibited lower reactivity than the chloropyrimidines **1**, **2** and we selected stronger reagents (Table 1, *x*=2, *y*=4). Thus (Table 2, entry 3), we found convenient conditions for a chemoselective process, as a compromise between conversion and selectivity. This option was then supported by the results obtained when the reaction was attempted with single PS·1HF (too weak: **3a** was detected in traces after 111 h/80°C, 3:1 molar ratio reagent:**3**) or PS·3HF/Et_3N (best selectivity as 30:1 **3a**:**3b** but only 23% yield).

In the case of 3,6-dichloropyridazine, the high selectivity generally observed could be correlated with the difference between the PM3 calculated stability of the corresponding *Meisenheimer* complex: **M-3a** was found more stable than **M-3b** as precursor of **3b** (Scheme 4).

It is of interest to note that the presence of phenyl substituent at C-4 (compound **4**) significantly decreased the reactivity (entry 4) since it acts like a releasing group; accordingly, no reaction occurred with 4-methoxy derivative.



Scheme 5.



Scheme 6.

2.2.2. Fluorination of the dichlorobenzodiazines 5 and 6 (Table 3, Schemes 5 and 6). As the type of fluorinating reagents used indicate, the dichlorobenzodiazines **5** and **6** were found with middle reactivity between the corresponding pyrimidines and pyridazines.

For 2,3-dichloroquinoxaline **5**, preliminary examination of the results of PM3 calculations led us to anticipate that selectivity should be poorer since the $\Delta\Delta H_f$ value between the two *Meisenheimer* complex **M-5a** vs. **M-5b** (Scheme 5) was found much smaller as compared to 3,6-dichloropyridazine (Scheme 4).

Accordingly, we successfully performed either monochloro (**5a**) or dichloro (**5b**) substitution by changing molar ratio of the reagents to the substrate (entry 1). We outline that complete separation of the reaction products was easily achieved by classical protocols (see Experimental). No peculiar susceptibility of difluoro derivative **5b** towards hydrolysis, during the work-up, was observed.[18]

Unexpected problems were encountered concerning the fluorination of 1,4-dichlorophthalazine **6** (entry 2) since the target product, the monofluoro derivative **6a**, exhibited instability in aqueous media. It seemed to us the behaviour of these 1,4-dihalophthalazines as similar to that of their perchloro- and perfluoro-analogues which were also reported as very sensitive to nucleophilic replacement of halogen atoms.[19] The selectivity was very high, in mild conditions, with reasonable time reaction and supported by the greater stability of the *Meisenheimer* complex **M-6a** against **M-6b** (precursor of difluoro derivative **6b**, Scheme 6).

2.2.3. Fluorination of the chloronitropyridines 7 and 8 (Table 4). The test experiments revealed as appropriate substrates to be fluorinated by the present reagents only chloronitropyridines among chloropyridines: no reaction occurred with 2,3-dichloropyridine.

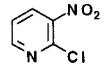
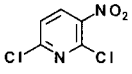
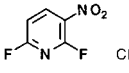
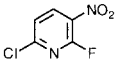
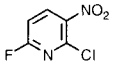
We have already seen the high reactivity of 2-chloro-3,5-dinitro-pyridine (Scheme 3). 2-Chloro-3-nitropyridine **7** yielded **7a** comparably with already reported results if potassium fluoride had been used (150°C, DMF, 6 h, 76% yield).[20]

Attempts at regioselective monofluorination of 2,6-dichloro-3-nitropyridine **8** failed. The regioisomers **8b**, **c** were detected in almost equal proportion (^{19}F NMR monitoring) on a large scale of molar ratio (*x* vs. *y*), to afford the difluoro derivative **8a** (entry 2) as the major product. Thus, total substitution was found to be the dominant process. Despite excellent conversions, yields were poor due to the high volatility of **8a** (vacuum distillation or flash column chromatography).

3. Conclusion

'PS' hydrogen fluorides or reagents generated in situ from

Table 4. Relevant results of the fluorination of the chloronitropyridines **7** and **8**

No.	Starting material	Reagent and molar ratio *vs.* 1 mole substrate	Temp (°C); time (hrs)	Products (main product in **bold**) and molar ratio	Total conversion[a]; yield[b] (%)
1.	 **7**	*x*PS + *y*($Et_3N.3HF$) x=2, y=6[c]	80 36	 **7a**	89; 58 (**7a**)
2.	 **8**	x=2.5, y=2.5/3[d]	80 72	 **8a** **2.0**[e]  **8b** 1.0  **8c** 1.0	95; 20 (**8a**)

[a] Total conversion (% molar) of the starting materials **7**, **8** towards all products **7a**, **8a–c**.
[b] Yields are calculated as isolated materials; the amount of the recyclable starting materials was not taken into account.
[c] See Experimental for this result as Method **B**.
[d] See Experimental for this result as Method **E**.
[e] Relative molar ratios between reaction products in the crude reaction mixture as issued from ^{1}H correlated with ^{19}F NMR spectra.

mixtures of triethylamine tris(hydrogen fluoride) and PS provide versatile and efficient fluorinating reagents. Their use is compatible with wide ranges of temperature and concentration. For the first time, complete or selective fluorinations of certain dichloro(benzo)diazines can be conveniently carried out using this type of reagent with satisfactory yields. In some cases, the selectivity can be explained based on the difference between thermodynamic stability of the *Meisenheimer* complexes.

4. Experimental

4.1. General

All reagents were purchased from Aldrich® and used without supplementary purification. All syntheses were carried out under dry nitrogen. Melting points were determined on a Reichert Austria instrument and are not corrected. NMR spectra were recorded on Brucker 250 instrument operating at 250, 62.5 and 235 MHz for ^{1}H, ^{13}C and ^{19}F nuclei, respectively. No $SiMe_4$ was added; chemical shifts (ppm) were measured against the solvent peak (throughout $CDCl_3$) except δ values for ^{19}F nuclei ($CFCl_3$ as external standard). Samples were directly prepared in NMR tubes by using concentrations ranging between 0.015–0.28 g/mL and measured after 128 scans (for ^{1}H NMR spectra). High resolution mass spectra were performed on JEOL AX500 instrument operating at IE=70 ev. IR spectra were recorded in solid state (KBr) on a Perkin–Elmer 16PC FT-IR instrument. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm) (Merck®).

4.2. Special remarks

Several factors should be outlined as common for the entire series: the difference between essential physical data (volatility, polarity, basicity, etc.) regarding the starting materials and products is minor for complete analytical separation. Thus, the option for a certain fluorinating reagent [PS·1HF, PS·3HF or xPS+y(Et_3N·3HF)] was crucial since it had to consider not only the reactivity of the substrate but also the volatility of the desired products. Accordingly, five different synthetic methods (**A**–**E**) were used. PS·1HF, PS·3HF, 2-fluoro-3,5-dinitropyridine and compounds **2a**, **5a**, **5b**, **8a** were isolated as pure analytical samples and exhibited satisfactory elemental analysis and/or HR-MS results; for the rest of the series, the desired compounds (**1a**, **3a**, **4a**, **6a**, **7a**) were isolated as inseparable mixtures. Their identity was fully confirmed by NMR spectra and HR-MS.

The methods **A**–**E** are summarised below; for the reagent xPS+y(Et_3N·3HF), the parameters x and y indicate the number of mole of each component vs. 1 mol of substrate. Vigorous stirring was required in all cases. Although all experiments were carried out at least twice, yields were not optimised.

*Method **A**:* PS·1HF is added portionwise to the substrate heated at the required temperature; no solvent is used.

*Method **B**:* the substrate and the entire amount of reagent xPS+y(Et_3N·3HF) are intimately mixed and then heated at the required temperature; no solvent is used.

*Method **C**:* the reagent xPS+y(Et_3N·3HF) is added portionwise to the substrate heated at the required temperature; no solvent is used.

*Method **D**:* the reagent xPS+y(Et_3N·3HF) is added portionwise to the substrate (the latter as acetonitrile solution) under heating at 80°C.

*Method **E**:* the substrate and the entire amount of reagent xPS+y(Et_3N·3HF) are dissolved in acetonitrile and heated at 80°C.

4.3. Preparation of 1,8-bis(dimethylamino)naphthalene hydrogen fluoride, PS·1HF

'PS' PS, 0.5 g, (2.33 mmol) was dissolved in dry dichloromethane (10 mL) then triethylamine tris(hydrogen fluoride) Et_3N·3HF (0.125 g, 0.126 mL, 0.77 mmol) was added. The resulting solution was evaporated under vacuum at room temperature to give a crystalline solid that was heated for 1.5 h at 90–5°C (under vacuum, 10–15 mmHg) on a steam bath. The crystalline residue was cooled at room temperature, to yield a sticky mass. Yield 98% (0.535 g).

4.3.1. 1,8-Bis(dimethylamino)naphthalene hydrogen fluoride, PS·1HF. Grey crystalline powder; slow thermal dissociation up to 49°C. Careful inspection of the crystals and the behaviour of the solid between 45–50°C did not reveal the presence of two distinct types of crystals, but only one which converted into melted mass and a similar type of crystal; the latter exhibited a higher melting point, at 125–6°C. ^{1}H NMR (δ ppm, J Hz): 2.95 (bs, 12H, $-CH_3$), 7.48, 7.39, 7.23 (2H, 2H, 2H as three broad singlets); ^{13}C NMR (δ ppm): 45.4 (4C, $-CH_3$), 126.3 and 120.5; ^{19}F NMR: −167.2 (s) Anal. calcd for $C_{14}H_{19}FN_2$: C 71.76%, H 8.17%, N 11.95%; found C 72.41%, H 8.50%, N 12.35%. IR (KBr, s-strong, m-medim, w-weak, cm^{-1}): 3450 (s, ν_{NH}), 2000 (w, ν_{NH^+}), 1800 (w, ν_{N^+} comb.), 1500 (s, naphthalene ring[9]), 1600–1400 (s, δ_{NH}), 600 (m, ν_{NH^+N}).

4.4. Preparation of 1,8-bis(dimethylamino)naphthalene tris(hydrogen fluoride), PS·3HF

The PS·1HF (0.535 g, as the solid residue, see above) was taken with dry diethyl ether (or pentane) (10 mL) and stirred at room temperature to give a fine suspension. After filtering, very well washing with diethyl ether (or pentane) and drying at room temperature, PS·3HF (0.200 g, 96% yield) was obtained. Evaporation of the mother liquor afforded 0.310 g (95% recovered) PS as free base. These syntheses allowed a scale up to 10 g of the starting PS, with the same yields.

4.4.1. Bis(dimethylamino)naphthalene tris(hydrogen fluoride). White crystalline powder; mp=125–6°C. ^{1}H NMR (δ ppm, J Hz): 3.25 (s, 12H, $-CH_3$), 7.93 (d, 2H, 7.9), 7.83 (d, 2H, 7.8), 7.66 (dd as t, 2H 7.8); ^{13}C NMR (δ ppm): 46.6 (4C, $-CH_3$), 119.2 (2C), 121.6 (2C), 127.4 (2C), 129.5 (2C), 135.8 (1C), 144.9 (1C); ^{19}F NMR: −167.6 (s).

Anal. calcd for $C_{14}H_{21}F_3N_2$: C 61.29%, H 7.71%, N 10.21%; found C 61.38%, H 7.79%, N 10.23%. IR (KBr, s-strong, m-medium, w-weak, cm^{-1}): 3450 (s, ν_{NH}), 2000 (w, ν_{NH^+}), 1800 (s, ν_{N^+} comb.), 1500 (s, naphthalene ring[9]), 1600–1400 (s, δ_{NH}), 600 (m, ν_{NH^+N}).

4.5. NMR-monitoring of the equilibria (9) and (10)

The mixtures xPS+y($Et_3N{\cdot}3HF$) were prepared directly in the NMR tube and x and y were selected as absolute values to give about 0.28–0.29 g/mL; all tubes were measured consequently by using the same shimming values, at room temperature. Pure compounds PS, PS·1HF, PS·3HF, $Et_3N{\cdot}3HF$ were measured individually as 0.280, 0.150, 0.080 and 0.015 g/mL. $Et_3N{\cdot}2HF$ was prepared from $Et_3N{\cdot}3HF$ and the corresponding amount of triethylamine free base by using the same method, as described in the literature.[2]

4.6. Preparation of 2-chloro-4-fluoropyrimidine, 1a (Method A, Table 2)

2,4-Dichloropyrimidine (1.50 g, 10.00 mmol) and PS·1HF (15% from the equivalent amount required by the 1:1 stoichiometry) were intimately mixed and heated at 65°C with stirring. The rest of the amount of PS·1HF was added portionwise as follows: 20% (after 3 h), 30% (after 10 h) and 35% (after 24 h). After additional 24 h at 65°C, the ^1H and ^{19}F NMR monitoring of the crude reaction mixture indicated the composition (as molar ratios) **1a**:**b**:**c** as depicted in Table 2. The crude reaction mixture was directly distilled under vacuum (125°C, 15 mmHg) in a kugelrohr instrument to afford 1.11 g mixture of **1a**–**c** (about the same composition as the crude). Yield 40%, with respect to the main product **1a**. The solid residue was kept to recycle the PS.

4.6.1. 2-Chloro-4-fluoropyrimidine, 1a. Colourless liquid; ^1H NMR (δ ppm, J Hz): 8.72 (1H, dd, 5.5, 10.9), 7.05 (1H, dd, 2.7, 5.5); ^{13}C NMR (δ ppm, J Hz): 168.2 (1C, d, 258.4), 163.3 (1C, d, 6.9), 161.9 (1C, d, 12.5), 106.5 (1C, d, 28.1); ^{19}F NMR (δ ppm, J Hz): −56.5 (1F, d, 10.9). HR MS for $C_4H_2N_2ClF$ 131.9891 and 133.9861; found 131.9890 and 133.9876.

4.6.2. 2,4-Difluoropyrimidine, 1b. ^1H NMR (δ ppm, J Hz): 8.71 (1H, dd, 5.5, 11.0), 7.05 (1H, dd, 2.7, 5.5); ^{13}C NMR (δ ppm, J Hz): 170.2 (1C, d, 258.8), 170.1 (1C, dd, 14.1, 258.4), 158.7 (1C, dd, 9.7, 24.1), 103.8 (1C, dd, 6.25, 28.1); ^{19}F NMR (δ ppm, J Hz): −56.0 (1F, d, 9.2), −43.6 (1F, s).

4.6.3. 4-Chloro-2-fluoropyrimidine, 1c. ^1H NMR (δ ppm, J Hz): 7.40 (1H, dd, 3.0, 5.2); ^{13}C NMR (δ ppm, J Hz): 170.0 (1C, d, 258.1), 162.7 (1C, d, 6.3), 160.1 (1C, d, 12.5), 118.4(1C, d, 5.0); ^{19}F NMR (δ ppm, J Hz): −43.8 (1F, s). Only distinct signals were listed.

4.7. Preparation of 4-fluoro-2-methylsulfanyl-pyrimidine, 2a (Method B, Table 2)

4-Chloro-2-thiomethylpyrimidine (1.00 g, 6.10 mmol), and the required amount of the reagent 3PS+3($Et_3N{\cdot}3HF$) were mixed together and heated with stirring, at 120°C for 24 h. After cooling at room temperature, diethyl ether (3×25 mL) was used to extract the crude product from the reaction mixture (the unsoluble solids were kept to recycle the PS). The ethereal solution was washed with water (3×25 mL), dried over $MgSO_4$, then evaporated in vacuo without heating to yield 0.870 g crude product. After distillation of the latter in a kugelrohr instrument (100°C, 15 mmHg), 0.610 g (70% yield) **2a** was obtained as yellow liquid.

4.7.1. 4-Fluoro-2-methylsulfanylpyrimidine, 2a. Yellow liquid, bp=100°C/15 mmHg. Elemental analysis and NMR data were listed elswhere.[6] HR MS for $C_5H_5FN_2S$ 144.0157; found 144.0157.

4.8. Preparation of 6-chloro-3-fluoropyridazine, 3a (Method C, Table 2)

3,6-Dichloropyridazine (7.22 g, 46.9 mmol) and 50% from the required amount of the reagent 2PS+4($Et_3N{\cdot}3HF$) were mixed together and heated with stirring at 80°C. The rest of the reagent was added as follows: 33% (after 30 h) and 17% (after 36 h). After additional 30 h, the reaction mixture was cooled at room temperature, dissolved in dichloromethane (200 mL) and the organic solution was washed with water (200 mL). The aqueous layer was kept to recycle the PS. The dichloromethane layer was washed with water (3×50 mL), dried over $MgSO_4$ then concentrated under vacuum to yield 6.15 g crude product (see composition in Table 2). The distillation in a kugelrorh instrument (150°C, 0.5 mmHg) gave 4.25 g mixture (**3**, **3a**, **b**) isolated as colourless liquid (about the same composition as the crude, 53% yield with respect to the main product, **3a**).

4.8.1. 6-Chloro-3-fluoropyridazine, 3a. Yellowish liquid; ^1H NMR (δ ppm, J Hz): 7.91(1H, dd, 6.4, 9.1), 7.54 (1H, dd, 2.1, 9.1); ^{13}C NMR (δ ppm, J Hz): 166.4 (1C, d, 244.4), 155.3 (1C, d, 2.5), 134.2 (1C, d, 7.5), 119.2(1C, d, 35.0); ^{19}F NMR (δ ppm, J Hz): −81.6 (1F, d, 5.7). HR MS for $C_4H_2ClFN_2$ 131.9891 and 133.9861; found 131.9903 and 133.9872.

4.8.2. 3,6-Difluoropyridazine, 3b. Yellowish liquid; ^1H NMR (δ ppm, J Hz): 7.67(2H, dd as t, 1.5); ^{13}C NMR (δ ppm, J Hz): 165.5 (2C, d, 244.6), 122.2(2C, t, 22.5); ^{19}F NMR (δ ppm, J Hz): −82.7 (2F, s). Only distinct peaks were listed.

4.9. Preparation of 3-fluoro-6-phenylpyridazine, 4a (Table 2)

Method **B** was used, starting from 0.750 g (3.93 mmol) 3-chloro-6-phenylpyridazine and the corresponding amount of the reagent 4PS+6($Et_3N{\cdot}3HF$); in the work up, diethyl ether was replaced by the corresponding amount dichloromethane. The crude product (0.950 g) was purified by column chromatography (15 g silica gel, eluent Et_2O/Pentane 3:1 v/v, typical fraction 8 mL) to give 0.527 g product as mixture 84% **4a**+16% **4** in a single fraction (63% yield with respect to **4a**).

4.9.1. 3-Fluoro-6-phenylpyridazine, 4a. White crystalline powder, mp=123–4°C (pentane). ^1H NMR (δ ppm, J Hz):

8.02–7.96 (3H, m), 7.54–7.50 (3H, m), 7.29 (1H, dd, 6.6, 7.2);^{13}C NMR (δ ppm, J Hz): 166.5 (1C, d, 243.8), 159.7 (1C, s), 135.5 (1C, s), 130.9(1C, s), 130.0 (1C, d, 7.5), 129.5 (2C, s), 127.5 (2C, s), 116.5 (1C, d, 33.1); ^{19}F NMR (δ ppm, J Hz): −82.6 (1F, d, 6.6). HR MS for $C_{10}H_7FN_2$ 174.0593; found 174.0587.

4.10. Preparation of 2,3-difluoroquinoxaline, 5b (Table 3)

Method **B** was used, starting from 1.00 g (5.02 mmol) 2,3-dichloroquinoxaline and the corresponding amount of reagent 4PS+4/3(Et_3N·3HF). In the work up, diethyl ether was replaced by the corresponding amount dichloromethane. The crude product (0.770 g) was purified by column chromatography (45 g silica gel, eluent chloroform/pentane 1:5 v/v, typical fraction 8 mL) to give 0.420 g difluoroderivative **5b** and 0.070 g monofluoro derivative **5a** as two distinct fractions. Yield 50% with respect to the desired product **5b**.

4.10.1. 3-Chloro-2-fluoroquinoxaline, 5a. (White crystalline powder, mp=88–9°C); ^{1}H NMR (δ ppm, J Hz): 8.11–8.05 (1H, m), 8.03–7.92 (1H, m), 7.86–7.53 (2H, m); ^{13}C NMR (δ ppm, J Hz): 152.1(1C, d, 256.3), 141.2 (1C, d, 2.5), 139.0(1C, d, 8.8), 137.1 (1C, d, 40.6), 131.7 (1C, s), 130.6 (1C, d, 3.1), 128.6 (1C, s), 128.2 (1C, d, 1.9); ^{19}F NMR (δ ppm, J Hz): −82.7 (1F, s). HR MS for $C_8H_4ClFN_2$ 182.0047 and 184.0019, found 182.0052 and 184.0007. Anal. calcd for $C_8H_4ClFN_2$: C 52.63%, H 2.20%, N 15.33%; found C 52.96%, H 2.29%, N 15.06%.

4.10.2. 2,3-Difluoroquinoxaline, 5b. (Yellowish crystalline powder, mp=92–3°C); ^{1}H NMR (δ ppm, J Hz): 7.88 (2H, dd, 6.3, 3.5), 7.69 (2H, dd, 6.3, 3.5); ^{13}C NMR (δ ppm, J Hz): 146.5 (2C, dd, 261.3, 39.4), 138.8 (2C, dd as t, 5.6), 130.7(2C, s), 128.2(2C, s); ^{19}F NMR (δ ppm, J Hz): −82.7 (1F, s). HR MSfor $C_8H_4N_2F_2$ 166.0342; found 166.0347. Anal. calcd for $C_8H_4F_2N_2$: C 57.83%, H 2.42%, N 16.86%; found C 57.93%, H 2.54%, N 16.61%.

4.11. Preparation of 3-chloro-2-fluoroquinoxaline, 5a (Method D, Table 3)

2,3-Dichloroquinoxaline (1.00 g, 5.02 mmol) was dissolved in acetonitrile (5 mL); to this solution, heated at 80°C, PS (1.08 g, 5.02 mmol) and Et_3N·3HF (0.300 mL, 1.80 mmol) were added during 96 h, as three equal portions (each 48 h). After an additional 24 h the reaction mixture was cooled at room temperature, taken up with 15 mL dichloromethane and the organic layer was washed several times with water (15 mL). After drying and removing the solvent, flash column chromatography (silica gel, eluent pentane/chloroform 5:1 v/v) was performed to yield 0.100 g **5b** 0.250 g **5a** (35% yield) and 0.260 g unreacted **5**.

4.12. Preparation of 4-chloro-1-fluorophthalazine, 6a (Table 3)

Method **D** was used, starting from 1,4-dichlorophthalazine (0.500 g, 2.51 mmol) in acetonitrile (3 mL). The total amount of the reagent 1PS+1/3(Et_3N·3HF) was added portionwise (50, 30 and 20%, respectively, each 24 h) at 85°C. After additional 48 h the crude reaction mixture was directly submitted to column chromatography (eluent dichloromethane/ethyl acetate 30:1 v/v) to afford: 0.016 g (as the first fraction: **6b** 24% and PS·3HF 76%) and 0.275 g (as the second fraction: **6a** 62%, **6** 38%, 37% yield with respect to **6a**).

4.12.1. 4-Chloro-1-fluorophthalazine, 6a. ^{1}H NMR (δ ppm, J Hz): 8.24–8.13 (4H, m); ^{13}C NMR (δ ppm, J Hz): 161.3 (1C, d, 251.9), 159.3 (1C, d, 6.9), 135.0 (1C, d, 21.3), 135.0 (1C, s), 134.8 (1C, d, 10.6), 134.9 (1C, s), 123.0 (2C, s); ^{19}F NMR (δ ppm, J Hz): −87.5 (1F, s). HR MS for $C_8H_4ClFN_2$ 182.0047 and 184.0019, found 184.0040 and 182.0057.

4.12.2. 1,4-Difluorophthalazine, 6b. ^{1}H NMR (δ ppm, J Hz): 7.64 (2H, dd, 5.7, 3.3), 7.46 (2H, dd, 5.7, 3.3); ^{19}F NMR (δ ppm, J Hz): −84.2 (2F, s); only distinct peaks were listed.

4.13. Preparation of 2-fluoro-3-nitropyridine, 7a (Table 4)

Method **B** was used starting from 2-nitropyridine (0.635 g, 4 mmol) and the corresponding amount of the reagent 2PS+6(Et_3N·3HF). Diethyl ether was replaced by dichloromethane in the work-up. The crude product (0.578 g 60% **7a**, 40% **7** according to ^{1}H NMR spectrum) was distilled in a kugelrohr instrument (bp=75°C/0.6 mmHg) to give 0.426 g as a single fraction (89% **7a**, 58% yield and 11% **7**).

4.13.1. 2-Fluoro-3-nitropyridine, 7a. Bright yellow oil; ^{1}H NMR (δ ppm, J Hz): 8. 63–8.55 (2H, m), 7.54(1H, ddd, 7.9, 4.9, 0.7); ^{13}C NMR (δ ppm, J Hz): 155.5 (1C, d, 248.1), 153.3 (1C, d, 24.8), 153.0 (1C, d, 15.0), 137.3 (1C, s), 122.8 (1C, d, 5.6); ^{19}F NMR (δ ppm, J Hz): −68.4 (1F, d, 7.5). HR MS for $C_5H_3FN_2O_2$ 142.0179; found 142.0167.

4.14. Preparation of 2,6-difluoro-3-nitropyridine, 8a (Method E, Table 4)

2,6-Dichloro-3-nitropyridine (1.11 g, 5.18 mmol), and the required amount of the reagent 2.5PS+2.5/3(Et_3N·3HF) in acetonitrile (3 mL) were heated at 80°C for 72 h. After cooling at room temperature, the dark red reaction mixture was diluted with dichloromethane (15 mL) then very well washed with water (15 mL) to colourless aqueous layer. The aqueous layers were kept for recycling the PS. After drying over $MgSO_4$, the dichloromethane solution was evaporated under vacuum to afford 1.17 g crude reaction mixture as a red oil that was purified by column chromatography on 40 g silica gel (eluent pentane/diethyl ether 3:1 v/v). Yield 20% (0.155 g **8a**) as a red liquid.

4.14.1. 2,6-Difluoro-3-nitropyridine, 8a. Red liquid. ^{1}H NMR (δ ppm, J Hz): 8.69 (1H, ddd, 8.7, 8.7, 6.5), 7.06(1H, dd, 8.6, 3.2); ^{13}C NMR (δ ppm, J Hz): 163.1 (1C, dd, 255.6, 13.5), 154.9 (1C, dd, 258.1, 16.6), 142.4 (1C, d, 10.0), 108.3 (2C, dd, 36.3, 6.3); ^{19}F NMR (δ ppm, J Hz): −56.4 (1F, s), −65.2 (1F, s). HR MS for $C_5H_2F_2N_2O_2$ 160.0798; found 160.0775.

4.14.2. 6-Chloro-2-fluoro-3-nitropyridine, 8b. ^{1}H NMR

(δ ppm, *J* Hz): 8.44 (1H, dd, 8.9, 6.5), 7.30(1H, dd, 8.1, 2.2); ^{19}F NMR (δ ppm, *J* Hz): −66.6 (1F, s).

4.14.3. 2-Chloro-6-fluoro-3-nitropyridine, 8c. ^{1}H NMR (δ ppm, *J* Hz): 8.54 (1H, dd, 9.3, 8.4), 7.64 (1H, dd, 8.4, 1.0); ^{19}F NMR (δ ppm, *J* Hz): −59.2 (1F, d, 9.4). Only the distinct peaks were given, as revealed by the crude NMR spectra.

4.15. Preparation of 2-fluoro-3,5-dinitropyridine (Scheme 2)

2-Chloro-3,5-dinitropyridine (0.300 g, 1.47 mmol) was dissolved in acetonitrile (2 mL) and PS·1HF (0.344 g, 1.47 mmol) was added. The reaction mixture was stirred at room temperature for 48 h. ^{1}H NMR monitoring of the crude reaction mixture indicated the presence of the starting material as about 20%. The reaction mixture was diluted with acetonitrile (2 mL), cooled at −20°C for 12 h then the solid PS·1HCl was filtered off. The organic solution was evaporated in vacuo without heating to afford 0.250 g crude product. This was purified by column chromatography on silica gel (20 g, eluent pentane/acetone 4:1 v/v) to give the desired product as a red liquid (0.137 g, 50% yield).

4.15.1. 2-Fluoro-3,5-dinitropyridine. Red liquid. ^{1}H NMR (δ ppm, *J* Hz): 9.36 (1H, dd, 3.2, 2.5), 9.31(1H, dd, 7.5, 2.5); ^{13}C NMR (δ ppm, *J* Hz): 155.5 (1C, d, 258.1), 148.6 (1C, d, 16.9), 147.5 (1C, s), 133.3 (1C, s), 130.1 (1C, s); ^{19}F NMR (δ ppm, *J* Hz): −57.4 (1F, s). HR MS for $C_5H_2FN_3O_4$ 187.0869; found 187.0899.

4.15.2. 2,4,6-Trifluoropyrimidine. Colourless liquid. ^{1}H NMR (δ ppm, *J* Hz): 6.61 (1H, m); ^{13}C NMR (δ ppm, *J* Hz): 174.2 (2C, dd, 261.2, 17.2), 174.4 (1C, dd, 243.1, 17.2); 90.9 (1C, ddd, 34.4, 34.4, 7.5) ^{19}F NMR (δ ppm, *J* Hz): −40.6 (1F, s); −52.3 (2F, s). HR MS for $C_4HF_3N_2$ 134.0605; found 134.0622.

4.16. Recycling of 1,8-bis(dimethylamino)naphthalene, 'PS'

According to Method **A**, the solid residue after distillation was dissolved in water (about 10% solid as aqueous solution). According to Methods **B**–**D**, the first aqueous layer was used; according to Method **E**, the recovered PS·1HCl was dissolved in water as about 10% aqueous solution. All the above aqueous solutions were made alkaline (pH up to 8) with solid Na_2CO_3 and the deposited solid (crude PS) was let to stand at room temperature for several hours. After filtering, washing with cold water to neutrality and drying at room temperature, the recovered PS was distilled in vacuo (150°C/0.5 mmHg) in a kugelrorh instrument.Yield 60–90%, white crystalline solid; mp=50–1°C (49–50°C Aldrich® product). ^{1}H NMR (δ ppm, *J* Hz): 2.93 (s, 12H, $-CH_3$), 7.41 (dd, 2H, 8.8, 1.4), 7.29 (dd, 2H, 8.8, 7.5), 6.98 (dd, 2H, 7.5, 1.4); ^{13}C NMR (δ ppm): 44.8 (4C, $-CH_3$), 113.2 (2C), 121.0 (1C), 122.2 (2C), 125.9 (2C), 138.3 (1C), 151.2 (2 C).

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