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Direct di- and triamination of polyfluoropyridines in anhydrous ammonia

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ABSTRACT

Aminodefluorination of polyfluoropyridines (pentafluoro-, 3,5-dichlorotrifluoro-, 3- and 4-chlorotetrafluoro-, 2,3,5,6- and 2,3,4,6-tetrafluoro-, 3-chloro-2,4,6-trifluoro-, and 2,4,6-trifluoropyridine) in anhydrous ammonia has been investigated. Temperatures of the second and third amino group introduction into pyridine ring were shown to increase significantly thus ensuring conditions for selective preparation of mono-, di- and, in the case of perhalopyridines as starting compounds, triaminoderivatives with high yield and purity.

1. Introduction

Aminodefluorination of electrophilic polyfluoroarenes including polyfluoropyridines efficiently occurs in anhydrous ammonia applied as a reagent and a solvent simultaneously [1,2]. The advantages of this method are: (i) selectivity of synthesis of arenes containing one and (or) two amino groups due to a significant differences in the reaction conditions; (ii) a high purity of products owing to the absence of hydrodefluorination realized in aqueous-ammonia medium [2]; (iii) rationality and universality of this processes as a route to practically important compounds.

The purpose of this study is the development of aminodefluorination of polychlorofluoropyridines in anhydrous ammonia as a selective method for preparation of novel halogenated pyridines containing two and (or) three amino groups, which are bioactive substance precursors [3,4] and building blocks in synthesis of condensation type polymers, in particular, hyperbranched polyimide membranes for gas separation applications [5] and anion-exchange nanofiltration membranes [6].

Perhalogenated pyridines – pentafluoropyridine (**1a**), 3,5-dichlorotrifluoropyridine (**2a**), 3-chlorotetrafluoropyridine (**3a**), 4-chlorotetrafluoropyridine (**4a**), as well as tetra- or tri-halogenated ones – 2,3,5,6-tetrafluoropyridine (**5a**), 2,3,4,6-tetrafluoropyridine (**6a**), 3-chloro-2,4,6-trifluoropyridine (**7a**), 2,4,6-trifluoropyridine (**8a**) have been used as substrates under investigation.

Monoamination of pyridines **1a**–**3a** at the γ-position, and pyridines **4a** and **5a** at the α-position is known to proceed selectively in aqueous NH_3 or in its mixtures with organic solvents (dioxane, THF) (**1a** [7], **2a** [8], **3a** [4], **4a** [9], **5a** [9,10]). Monoamination of pyridines **6a** and **8a** results in a mixture of isomers containing α- or γ-amino group [11,12]; there are no data about ammonolysis of pyridine **7a**. However, the γ-amino derivatives of pyridines **6a**–**8a** can be prepared selectively by one-pot aminodefluorination/hydrodechlorination of **3a** and **2a** by the action of Zn powder in aqueous ammonia [13]. As to the multireplacement of fluorine atoms in pyridine framework with amino groups, bis-aminodefluorination of pyridine **1a** in aqueous NH_3 was an only known example [14] until the work [1], which has demonstrated ability of anhydrous ammonia in carrying out of selective mono- and bisaminodefluorination of pyridines **1a**, **2a**, **4a**, **5a**. Preparation of diaminoderivatives of pyridines **3a**, **6a**–**8a** and triaminohalopyridines has not been reported.

2. Results and discussion

To develop the investigation of activity of ammonia as a nucleophile and a medium for aromatic nucleophilic substitution, we established that bis-aminodefluorination of the all set of substrates (pyridines **1a**–**8a**) proceeds successfully in anhydrous NH_3 (Schemes 1–5). In the reactions of pyridines **1a**–**3a** containing fluorine atoms at the γ- and both α-positions, their triaminoderivatives are formed (Schemes 1 and 2). The processes were carried

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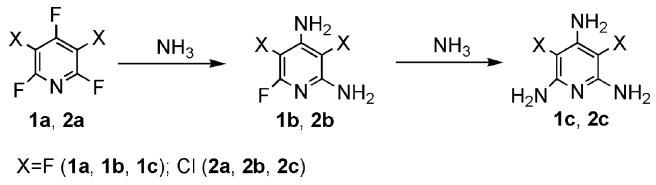
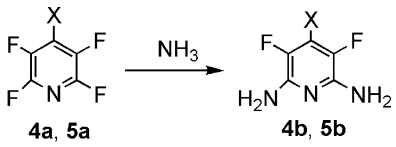
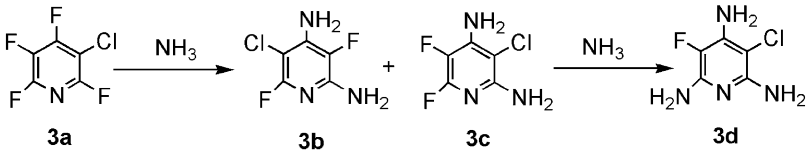


Scheme 1.



Scheme 3.



Scheme 2.

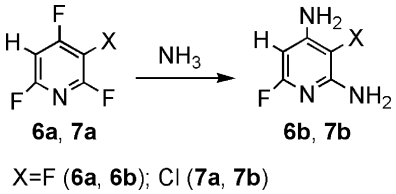
out in a steel autoclave under pressure so that molar volume of the reagents and temperature allowed liquid or liquid-like state of ammonia.[1] Reaction conditions, reactant amounts, and product yields are given in Table 1.

Bis-aminodefluorination of symmetrical pyridines **1a** and **2a** selectively realizes at 60–100 °C and leads to the formation of 2,4-diamino-3,5,6-trifluoropyridine (**1b**) and 2,4-diamino-3,5-dichloro-6-fluoropyridine (**2b**) correspondingly (Entries 1 and 3, Table 1; Scheme 1). Purification of the crude products to more than 99% purity has been easily performed by a single crystallization. Introduction of third amino group into pyridines **1b** and **2b** requires a higher temperature and a longer reaction time (Entries 2 and 4, Table 1; Scheme 1). Crude products contain more impurities, but individual 2,4,6-triamino-3,5-difluoropyridine (**1c**) and 2,4,6-triamino-3,5-dichloropyridine (**2c**) (purity 99%) have been isolated by using simple experimental procedures.

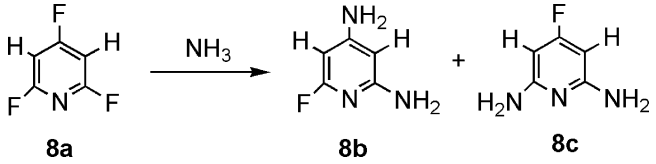
Selective mono-aminodefluorination of pyridine **3a** containing chlorine atom at a β-position, by anhydrous NH_3 occurs at 10 °C and results in known [4] 4-amino-3-chloro-2,5,6-trifluoropyridine according to ^{19}F NMR data of the reaction mixture. Upon bis-aminodefluorination of **3a** the mixture of 2,4-diamino-5-chloro-3,6-difluoropyridine (**3b**) and 2,4-diamino-3-chloro-5,6-difluoropyridine (**3c**) in 3:1 ratio is formed (Entry 5, Table 1; Scheme 2). Diamines **3b** and **3c** have been prepared for the first time and isolated from the mixture by TLC; more convenient technique for isomers separation has not been found. Substituents location in these diamines and in derivatives of pyridines **6a** and **7a** (see below) has been established by ^{19}F NMR data with use of the substituents shielding parameters [16]. Regioselectivity of **3a** bis-aminodefluorination is determined by the known electronic effects of ring halogens [12,17,18]. Replacement of fluorine atom at the position 6 is activated by *ortho*-chlorine effect, but deactivated by *para*-fluorine effect. On the other hand, both *ortho*-fluorine and *para*-chlorine effects promote nucleophilic substitution at the position 2. By these reasons diamine **3b** prevails among the reaction products. Subsequent replacement of the remaining α-fluorine atom in both pyridines **3b** and **3c** results in the formation of 2,4,6-triamino-3-chloro-5-fluoropyridine (**3d**) (Entry 6, Table 1; Scheme 2). Thus, the one-pot tri-aminodefluorination of pyridine **3a** with anhydrous ammonia allows triamine **3d** to be prepared with good yield.

Replacement of fluorine atom at the most reactive γ-position of polyfluoropyridine with chlorine or hydrogen (in going to **4a** and **5a**) leads to the change of the reaction centre from γ- to α-position. α-Monoaminoderivatives (see [1]), and α,α-diamines–2,6-diamino-4-chloro-3,5-difluoropyridine (**4b**) and 2,6-diamino-3,5-difluoropyridine (**5b**) are formed selectively upon the action of anhydrous NH_3 (Entries 7 and 8, Table 1, correspondingly, Scheme 3), and can be obtained with purity 99% by crystallization of the crude products.

Mono-aminodefluorination of tetra- and trihalogenated pyridines **6a**, **7a**, and **8a** with liquid ammonia realizes at 20–50 °C. Comparison of ^{19}F NMR data of the reaction mixtures obtained with spectral characteristics of the known monoaminoderivatives of pyridines **6a**–**8a** [11–13] evidences that mixtures of γ- and α-monoaminoderivatives in 2–4:1 ratio, respectively, are formed in these reactions. Bis-aminodefluorination of pyridines **6a** and **7a** at 120 °C results in the selective formation of α,γ-diamines–2,4-diamino-3,6-difluoropyridine (**6b**) and 2,4-diamino-3-chloro-6-fluoropyridine (**7b**) (Entries 9 and 10, Table 1, correspondingly, Scheme 4). It is necessary to note that ^{19}F NMR data of diamine **7b** do not ensure undoubted ascertainment of its structure by using the substituents shielding parameters [16]. However, taking into account the known effects of F, Cl, and H atoms on the orientation of nucleophilic substitution in polyhalogenated pyridines [12,17,18], replacement of fluorine atoms at C-2 should be realized upon aminodefluorination of both tetrahalogenated pyridines **6a** and **7a**. This regioselectivity is favored by the *ortho*-halogen activating effect and by the absence of *para*-fluorine deactivating effect. The opposite combination of these factors – the presence of *para*-deactivating fluorine and the absence of *ortho*-activating halogen – prevents the replacement of fluorine atom at the position 6. It provides the high selectivity of bis-aminodefluorination of **6a** and **7a**, as compared with reaction of **3a** (see above). The



Scheme 4.



Scheme 5.

[1] Critical parameters for NH_3: ρ_c 0.24 g/cm^3, T_c 132.6 °C, and P_c 112.5 atm [15].

Table 1
Experimental conditions and product yields for reactions of polyfluoropyridines (**1**–**8**) with NH_3.

Entry	Polyfluoropyridines	Reactant amounts[a]		Reaction conditions		Reaction products		
		Substrate (g)	Liquid NH_3 (mL)	Temperature (°C, ±5)	Time (h)	Di(tri)amines	Crude product[b] yields (g)	Isolated product yields (g/%)
1[c]	**1a**	8.0	50	100	15	**1b**	7.1	6.5/81
2	**1a**	3.0	20	150	50	**1c**	2.8	1.8/60
3[c]	**2a**	10	50	60	10	**2b**	9.0	6.5/65
4	**2a**	5.0	40	140	24	**2c**	4.2	3.5/70
5	**3a**	3.0	30	100	7	**3b**,**3c**	2.7[d]	
6	**3a**	3.0	20	160	20	**3d**	2.8	1.9/66
7[c]	**4a**[e]	1.0	25	115	10	**4b**	0.7	0.6/60
8	**5a**	5.0	40	150	67	**5b**	3.8	3.5/70
9	**6a**	3.0	25	120	10	**6b**	2.8	1.5/50
10	**7a**	2.0	30	120	14	**7b**	1.9	1.8/90
11	**8a**	3.0	35	120	35	**8b**,**8c**	2.7[f]	1.1[g]/40

[a] An autoclave volume is 100 mL in Entries 1, 3, 4, 8, and 50 mL in Entries 2, 5, 6, 7, 9–11.
[b] Purity of the crude products in Entries 1, 3, 5, 7–11 is >95%, in Entries 2, 4, 6 is >90% (^{19}F NMR data).
[c] Preparation of compounds **1b**, **2b** and **4b** has been reported in [1].
[d] Composition of the crude product: diamine **3b**:diamine **3c** = 3:1 (^{19}F NMR data).
[e] Replacement of γ-chlorine in diamine **4b** with formation of triamine **1c** (~5%) occurs for 100 h at 180 °C.
[f] Composition of the crude product: diamine **8b**:diamine **8c** = 9:1 (^{19}F NMR data).
[g] Diamine **8b**.

absence in pyridine **8a** of the both β-halogen atoms (fluorine or chlorine) activating the nucleophilic substitution in polyfluoropyridines leads to the reaction deceleration and closing in the rates of α- and γ-fluorine replacement, so that complete bis-aminodefluorination of this substrate takes a three times greater process duration and results in the mixture of 2,4-diamino-6-fluoropyridine (**8b**) and 2,6-diamino-4-fluoropyridine (**8c**) in 9:1 ratio (Entry 11, Table 1; Scheme 5). Considerably predominant α,γ-diamine **8b** has been isolated in a preparative scale with purity >99% using the technique based on the different capacity of diamines to form complexes with 18-crown-6 [1,2]. Replacement of the remaining fluorine atom by amino group in diamines **6b**–**8b** is not realized up to 160 °C that can be caused by reduced electrophilicity of these partially halogenated compounds in comparison with diaminotrihalopyridines **1b**, **2b**, **3b**, and **3c**.

3. Conclusion

Thus, the polyhalogenated pyridines undergo aminodefluorination by the action of anhydrous ammonia at −33 to 160 °C with formation of mono- (see also [1]), di- and even triaminopyridines (the last ones have been obtained from perhalopyridines). The revealed relative reactivity of polyfluoropyridines and their aminoderivatives, as well orientation of fluorine replacement are in agreement with the known set of total electronic effects of substituents. Considerable temperature differences provide high selectivity of the first, second and third amino group introduction into pyridine framework independently of starting compound (one-pot synthesis); isolated product yields (purity 99%) are 50–80%. These results together with data of [1,2] characterize the direct amination of electrophilic arenes with anhydrous ammonia as universal route to aromatic compounds containing one, two, and three amino groups, which are demanded for modern materials and fine organic synthesis.

4. Experimental

4.1. Materials

The following commercial products were used: 18-crown-6, *tert*-butyl methyl ether (*t*-BuMeO), acetone, liquid NH_3, plates Kieselgel 60 F_{254} (Merck), silica gel 60 0.063–0.100 mm (Merck).

Pentafluoropyridine (**1a**), 3,5-dichlorotrifluoropyridine (**2a**), 4-chlorotetrafluoropyridine (**4a**), and 2,3,5,6-tetrafluoropyridine (**5a**) were prepared by published procedures [1]; 3-chlorotetrafluoropyridine (**3a**), 2,3,4,6-tetrafluoropyridine (**6a**), 3-chloro-2,4,6-trifluoropyridine (**7a**), and 2,4,6-trifluoropyridine (**8a**) were prepared with use of original methods, their physical parameters were identical to those reported in the literature ((**3a**) and (**6a**) [19], (**7a**) [20], (**8a**) [10]).

4.2. General

^{1}H and ^{19}F NMR spectra were recorded on NMR spectrometers Bruker AV-300 (300.13 and 282.36 MHz for ^{1}H and ^{19}F correspondingly) using residual proton signals of the deuterated solvent and C_6F_6 (δ = −163.0 ppm from CCl_3F) as internal standards; δ are given in ppm relative to TMS and CCl_3F, *J* are given in Hz. IR spectra were recorded on Bruker Vector-22 instrument. UV spectra were recorded on Fourier spectrometer HP 8453. The precise molecular weights of ions were determined by high resolution mass spectrometry on Thermo Scientific DFS instrument, ionizing energy 70 eV. GC–MS identification of mixture components was performed using Hewlett Packard G1081A equipment comprising an HP 5890 Series II gas chromatograph and an HP5971 mass selective detector; electron ionization energy of 70 eV; HP5 column (5% of biphenyl and 95% of dimethylsiloxane), 30 m × 0.25 mm × 0.25 μm; with helium as carrier gas, flow rate 1 mL min^{-1}; column temperature programming from 50 °C (2 min) at an increment of 10 °C min^{-1} to 280 °C (5 min); injector temperature 280 °C; ion source temperature 173 °C; data acquisition rate 1.2 scan s^{-1} in the mass range 30–650 amu. Analyses of product mixtures and purity of products were performed on HP 5890 Series II gas chromatograph (thermo conductivity detector); HP5 column (5% of biphenyl and 95% of dimethylsiloxane), 30 m × 0.22 mm × 2.6 μm; with helium as carrier gas, flow rate 1 mL min^{-1}; column temperature programming from 90 °C (2 min) at an increment of 10 °C min^{-1} to 330 °C (5 min); injector temperature 300 °C; detector temperature 320 °C.

4.3. Synthetic procedures

4.3.1. Typical procedure for the reaction of polyhalopyridines with liquid NH_3

Polyhalopyridine was placed into a steel autoclave, the required amount of liquid NH_3 was added through a measuring funnel with back pressure and the autoclave was sealed. The reaction mixture was heated up to the given temperature upon stirring by rotation

of the autoclave and kept under these conditions for the necessary time. On completion, the autoclave was cooled, NH_3 was slowly vented through a pressure release valve, and products were extracted with acetone (3 × 40 mL). Solvent was evaporated to give crude product, which was then purified. Reactant amounts, reaction conditions, and product yields are listed in Table 1. Methods of isolation of compounds obtained for the first time and their characteristics are given below.

*4.3.2. 2,4-Diamino-3,5,6-trifluoropyridine (**1b**)*

The crude product (Entry 1, Table 1) was purified by crystallization from a benzene–hexane mixture (1:1, v/v), purity 99%, mp 114–116 °C [1].

*4.3.3. 2,4,6-Triamino-3,5-difluoropyridine (**1c**)*

The crude product (Entry 2, Table 1) was sublimed, dissolved in *t*-BuMeO, and filtered through a SiO_2 layer (50 g). Fraction with R_f 0.3 (by TLC, eluent $CHCl_3$:CH_3OH, 5:6, v/v) was collected, solvent was evaporated and the product obtained was crystallized from $CHCl_3$ to give triamine **1c**, purity 99%, mp 210–210.5 °C. UV (EtOH): λ_{max} (log ε) 209 (2.5), 293 (0.6) nm. IR (KBr): ν 3465, 3436, 3360, 3190 (NH_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 4.64 (br.s, 4H, C(2)NH_2, C(6)NH_2), 5.03 (br.s, 2H, C(4)NH_2). ^{19}F NMR (acetone-d_6): δ −172.1 (s, 2F, F-3, F-5). EIMS, *m*/*z* (rel. int): 160 $[M]^+$ (100), 133 $[M-HCN]^+$ (11), 132 $[M-CNH_2]^+$ (12). HRMS calcd. for $C_5H_6F_2N_4$: 160.0555, found: 160.0541.

*4.3.4. 2,4-Diamino-3,5-dichloro-6-fluoropyridine (**2b**)*

The crude product (Entry 3, Table 1) was purified by crystallization from CH_2Cl_2, purity 99%, mp 137–139 °C, for spectral characteristics see [1].

*4.3.5. 2,4,6-Triamino-3,5-dichloropyridine (**2c**)*

The crude product (Entry 4, Table 1) was purified by crystallization from $CHCl_3$, purity 99%, mp 193–194 °C. UV (EtOH): λ_{max} (log ε) 221 (1.8), 294 (0.3) nm. IR (KBr): ν 3451, 3432, 3349, 3299, 3164 (NH_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 5.15 (br.s, 4H, C(2)NH_2, C(6)NH_2), 5.32 (br.s, 2H, C(4)NH_2). EIMS, *m*/*z* (rel. int): 196 $[M]^+$ (10), 194 $[M]^+$ (65), 192 $[M]^+$ (100), 165 $[M-HCN]^+$ (15), 156 $[M-HCl]^+$ (14), 130 $[M-HCN-Cl]^+$ (14). HRMS calcd. for $C_5H_6Cl_2N_4$: 191.9969, found: 191.9970.

*4.3.6. 2,4-Diamino-5-chloro-3,6-difluoropyridine (**3b**) and 2,4-diamino-3-chloro-5,6-difluoropyridine (**3c**)*

The crude product (Entry 5, Table 1) being the mixture of diamines **3b** and **3c** (3:1, ^{19}F NMR data) was separated by thin-layer chromatography, eluent $CHCl_3$:CH_3OH (10:1, v/v). 2,4-Diamino-5-chloro-3,6-difluoropyridine (**3b**) (R_f 0.3), mp 127–129 °C. UV (EtOH): λ_{max} (log ε) 212 (2.7), 278 (0.4) nm. IR (KBr): ν 3491, 3437, 3387, 3303, 3190 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.2 (br.s, 4H, C(2)NH_2, C(4)NH_2). ^{19}F NMR (DMSO-d_6): δ −165.2 (d, 1F, $J_{F,F}$ = 25, F-3), −80.0 (d, 1F, $J_{F,F}$ = 25, F-6). EIMS, *m*/*z* (rel. int): 181 $[M]^+$ (32), 179 $[M]^+$ (100), 159 $[M-HF]^+$ (15), 152 $[M-HCN]^+$ (22), 151 $[M-CNH_2]^+$ (13). HRMS calcd. for $C_5H_4ClF_2N_3$: 179.0062, found: 179.0063.

2,4-Diamino-3-chloro-5,6-difluoropyridine (**3c**) (R_f 0.5), mp 105–106 °C. UV (EtOH): λ_{max} (log ε) 211 (2.4), 281 (0.3) nm. IR (KBr): ν 3473, 3447, 3361, 3312, 3193 (NH_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 5.48 (br.s, 2H, C(2)NH_2), 5.94 (br.s, 2H, C(4)NH_2). ^{19}F NMR (acetone-d_6): δ −176.6 (d, 1F, $J_{F,F}$ = 26, F-5), −95.6 (d, 1F, $J_{F,F}$ = 26, F-6). EIMS, *m*/*z* (rel. int): 181 $[M]^+$ (31), 179 $[M]^+$ (100), 159 $[M-HF]^+$ (17), 152 $[M-HCN]^+$ (13), 151 $[M-CNH_2]^+$ (10). HRMS calcd. for $C_5H_4ClF_2N_3$: 179.0062, found: 179.0060.

*4.3.7. 2,4,6-Triamino-3-chloro-5-fluoropyridine (**3d**)*

The crude product (Entry 6, Table 1) was sublimed, dissolved in *t*-BuMeO, and filtered through a SiO_2 layer (50 g). Fraction with R_f 0.4 (by TLC, eluent $CHCl_3$:CH_3OH, 5:6, v/v) was collected, solvent was evaporated and the product obtained was crystallized from $CHCl_3$ to give triamine **3d**, purity 99%, mp 202–203 °C. UV (EtOH): λ_{max} (log ε) 213 (2.2), 294 (0.5) nm. IR (KBr): ν 3437, 3324, 3188 (NH_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 4.89 (br.s, 4H, C(2)NH_2, C(6)NH_2), 5.17 (br.s, 2H, C(4)NH_2). ^{19}F NMR (acetone-d_6): δ −173.7 (s, 1F, F-5). EIMS, *m*/*z* (rel. int): 178 $[M]^+$ (30), 176 $[M]^+$ (100), 149 $[M-HCN]^+$ (12), 114 $[M-HCN-Cl]^+$ (12). HRMS calcd. for $C_5H_6ClFN_4$: 176.0259, found: 176.0256.

*4.3.8. 2,6-Diamino-4-chloro-3,5-difluoropyridine (**4b**) (Entry 7, Table 1)*

The crude product was purified by crystallization from CCl_4, purity 99%, mp 145–146 °C, for spectral characteristics see [1].

*4.3.9. 2,6-Diamino-3,5-difluoropyridine (**5b**) (Entry 8, Table 1)*

The crude product was purified by sublimation, purity 99%, mp 156.5–158 °C, for spectral characteristics see [1].

*4.3.10. 2,4-Diamino-3,6-difluoropyridine (**6b**) (Entry 9, Table 1)*

The crude product was purified by crystallization from a benzene–hexane mixture (1:1, v/v), purity 99%, mp 91.5–92.5 °C. UV (EtOH): λ_{max} (log ε) 210 (2.3), 273 (0.4) nm. IR (KBr): ν 3499, 3484, 3304, 3192 (NH_2); 2965 (C_{ap}–H) cm^{-1}. ^1H NMR (acetone-d_6): δ 5.30 (br.s, 2H, C(2)NH_2), 5.52 (br.s, 2H, C(4)NH_2), 5.65 (d, 1H, $J_{H,F}$ = 4, H-5). ^{19}F NMR (acetone-d_6): δ −173.1 (dd, 1F, $J_{H,F}$ = 4, $J_{F,F}$ = 24, F-3), −76.6 (d, 1F, $J_{F,F}$ = 24, F-6). EIMS, *m*/*z* (rel. int): 145 $[M]^+$ (100), 125 $[M-HF]^+$ (19), 118 $[M-HCN]^+$ (17), 117 $[M-CNH_2]^+$ (16). HRMS calcd. for $C_5H_5F_2N_3$: 145.0452, found: 145.0451.

*4.3.11. 2,4-Diamino-3-chloro-6-fluoropyridine (**7b**)*

The crude product (Entry 10, Table 1) was purified by sublimation, purity 99%, mp 104.5–106 °C (from CCl_4). UV (EtOH): λ_{max} (log ε) 217 (2.2), 275 (0.2) nm. IR (KBr): ν 3479, 3457, 3361, 3300 (NH_2); 2920 (C_{ap}–H) cm^{-1}. ^1H NMR (acetone-d_6): δ 5.55 (br.s, 2H, C(2)NH_2), 5.71 (s, 1H, H-5), 5.77 (br.s, 2H, C(4)NH_2). ^{19}F NMR (acetone-d_6): δ −74.7 (s, 1F, F-6). EIMS, *m*/*z* (rel. int): 163 $[M]^+$ (38), 161 $[M]^+$ (100), 143 $[M-HF]^+$ (17), 141 $[M-HF]^+$ (52), 134 $[M-HCN]^+$ (13), 133 $[M-CNH_2]^+$ (11). HRMS calcd. for $C_5H_5ClFN_3$: 161.0156, found: 161.0161.

*4.3.12. 2,4-Diamino-6-fluoropyridine (**8b**) and 2,6-diamino-4-fluoropyridine (**8c**)*

The crude product (Entry 11, Table 1) contains diamines **8b** and **8c** in 9:1 ratio (^{19}F NMR data). 2,6-Diamino-4-fluoropyridine (**8c**) being the minor component has the signal at −106.0 ppm in ^{19}F NMR spectrum of the mixture and M 127 (GC–MS data). The major component diamine **8b** was isolated by the followed procedure. The crude product was solved in *t*-BuMeO (50 mL) under reflux and insoluble admixture was filtered off. To the solution obtained 18-crown-6 (5.3 g, 20 mmol) was added and the mixture was kept for 1 h at ~20 °C upon stirring. The precipitate was filtered off and washed with a small amount of *t*-BuMeO. Complex of diamine **8b** with 18-crown-6 (6.1 g) was obtained. The complex was decomposed with water (50 mL) and diamine **8b** was extracted with *t*-BuMeO (8 mL × 20 mL). The combined extract was dried over $MgSO_4$, and solvent was distilled off to give diamine **8b**.

2,4-Diamino-6-fluoropyridine (**8b**), mp 100.5–101.5 °C. UV (EtOH): λ_{max} (log ε) 218 (2.2), 271 (0.2) nm. IR (KBr): ν 3454, 3367, 3189 (NH_2); 2925 (C_{ap}–H) cm^{-1}. ^1H NMR (acetone-d_6): δ 5.12 (br.s, 2H, C(2)NH_2), 5.39 (br.s, 2H, C(4)NH_2), 5.47 (d, 1H, $J_{H,H}$ = 1.5, H-3), 5.62 (dd, 1H, $J_{H,H}$ = 1.5, $J_{H,F}$ = 2, H-5). ^{19}F NMR (acetone-d_6): δ −76.0 (br.s, 1F, F-6). EIMS, *m*/*z* (rel. int): 127 $[M]^+$ (100), 107 $[M-HF]^+$ (15), 100 $[M-HCN]^+$ (24). HRMS calcd. for $C_5H_6FN_3$: 127.0546, found: 127.0539.

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