Condensation of polyfluorinated β-diimines with aromatic aldehydes

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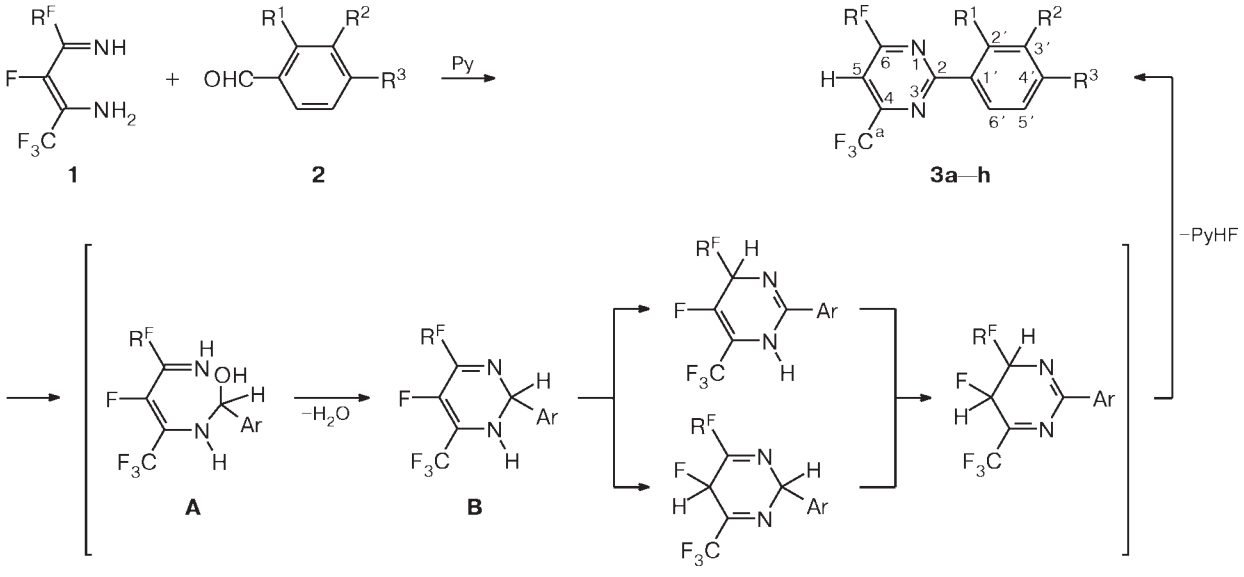
Polyfluorinated 2-arylpyrimidines were synthesized by the reaction of polyfluorinated β-diimines with aromatic aldehydes.

Key words: polyfluorinated β-diimines, aromatic aldehydes, condensation, dehydrofluorination; polyfluorinated pyrimidines.

Fluorinated pyrimidines exhibit a wide spectrum of biological activity.[1—4] One of the general methods for syntheses of pyrimidines is the reaction of compounds containing the N—C—C—C—N fragments with acylating agents. A classical example for this type of cyclization is the reaction of malonodiamide with ethyl formate in the presence of sodium ethoxide.[5] We have previously shown[6,7] that 2-amino-4-iminoperfluoroalk-2-enes (**1**) are convenient precursors of polyfluorinated pyrimidines. In this work, we established that iminoenamines (β-diimines) **1** smoothly reacted with aromatic aldehydes **2** on heating in the presence of pyridine to form pyrimidines with polyfluorinated substituents (**3**) (Scheme 1).

It is most likely that adduct **A** is primarily formed and then eliminates water to give dihydropyrimidine **B**. The latter gives fluorine-containing pyrimidines **3** due to prototropic tautomeric transformations and dehydrofluorination. The nature of substituents in aldehydes **2**, an increase in the length of the fluoroalkyl group of iminoenamines **1**, and the absence of pyridine (in this case, the glass of the flask plays the role of the hydrogen fluoride acceptor) have no substantial effect on the yield

Scheme 1



R^F = CF_3 (**a**—**d**), C_2F_5 (**e**—**g**), C_4F_9 (**h**).

3	a	b	c	d	e	f	g	h
R^1	H	H	H	H	OH	H	H	H
R^2	H	H	OMe	H	H	OMe	H	H
R^3	H	OMe	OMe	NMe_2	H	OMe	NMe_2	OMe

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Table 1. Characterization of compounds **3a—h**

Compound	τ/h	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
				C	H	F	
3a	9	79	64—65	49.24 49.31	2.31 2.05	39.11 39.04	$C_{12}H_6F_6N_2$
3b	3	82	88—90	48.04 47.80	2.64 2.52	35.71 35.85	$C_{13}H_8F_6N_2O$
3c	3	96.5	159—161	46.08 46.15	2.35 2.37	33.85 33.73	$C_{13}H_8F_6N_2O_2$
3d	2	84.5	199—201	50.12 50.15	3.34 3.28	34.02 34.03	$C_{14}H_{11}F_6N_3$
3e	2	73	53—54	43.21 43.57	1.58 1.68	42.94 42.46	$C_{13}H_6F_8N_2O$
3f	4.5	80	100—102	44.58 44.78	2.64 2.49	37.65 37.81	$C_{15}H_{10}F_8N_2O_2$
3g	2	92.5	145—147	47.04 46.75	2.90 2.86	39.32 39.48	$C_{15}H_{11}F_8N_3$
3h	2.5	75	49—51	40.37 40.68	1.63 1.69	48.26 48.30	$C_{16}H_8F_{12}N_2O$

Note. τ is the duration of boiling.

Table 2. Spectral parameters of compounds **3a—h**

Compound, R^F	Mass spectrum, m/z (I_{rel} (%))	NMR spectrum, δ (J/Hz)	
		^{19}F	^1H
3a, CF_3	292 $[M]^+$ (100), 273 $[C_{12}H_7F_5N_2]$ (12), 223 $[C_{11}H_7F_3N_2]$ (89), 103 $[C_7H_5N_1]$ (13), 77 $[C_6H_5]$ (27), 69 $[CF_3]$ (12)	−3.0 (s, 6 F, 2 CF_3)	7.1 (m, 3 H, H(3′), H(4′), H(5′)); 7.5 (s, 1 H, H(5)); 8.0 (m, 2 H, H(2′), H(6′))
3b, CF_3	322 $[M]^+$ (100), 303 $[C_{12}H_8F_5N_2O]$ (8), 279 $[C_{11}H_5F_6N_2]$ (20), 253 $[C_{12}H_8F_3N_2O]$ (27)	−7.0 (s, 6 F, 2 CF_3)	3.95 (s, 3 H, OMe); 7.0 (m, 2 H, H(3′); H(5′)), 7.7 (s, 1 H, H(5)); 8.5 (m, 2 H, H(2′), H(6′))
3s, CF_3	338 $[M]^+$ (100), 323 $[C_{12}H_5F_6N_2O_2]$ (23), 319 $[C_{13}H_8F_5N_2O_2]$ (15), 295 $[C_{11}H_5F_6N_2O]$ (43)	−7.0 (s, 6 F, 2 CF_3)	4.3 (s, 3 H, OMe); 7.05 (s, 1 H, H(5)); 7.3 (d, 1 H, H(5′), J = 8.8); 8.25 (s, 1 H, OH); 8.35—8.50 (m, 2 H, H(2′), H(6′))
3d, CF_3	335 $[M]^+$ (100), 334 $[C_{14}H_{10}F_6N_3]$ (81), 316 $[C_{14}H_{11}F_5N_3]$ (5), 291 $[C_{12}H_5F_6N_2]$ (8)	−7.0 (s, 6 F, 2 CF_3)	3.0 (s, 6 H, NMe_2); 6.7 (d, 2 H, H(3′); H(5′), J = 9.4); 7.5 (s, 1 H, H(5)); 8.3 (d, 2 H, H(2′), H(6′), J = 9.4)
3e, $CF_2^bCF_3^c$	358 $[M]^+$ (100), 339 $[C_{13}H_6F_7N_2O_1]$ (13), 330 $[C_{12}H_6F_8N_2]$ (10), 289 $[C_{12}H_6F_5N_2O_1]$ (14), 239 $[C_{11}H_6F_3N_2O_1]$ (18)	−4.5 (s, 3 F_a); 8.8 (s, 3 F_c); 45.0 (s, 2 F_b)	6.35 (d, 1 H, H (3′), J = 8.8); 6.55, 7.05 (both d.d, 1 H each, H(4′), H(5′), J = 8.8, J = 7.7); 7.7 (s, 1 H, H(5)); 7.95 (d, 1 H, H(6′), J = 7.7); 10.65 (s, 1 H, OH)
3f, $CF_2^bCF_3^c$	402 $[M]^+$ (100), 383 $[C_{15}H_{10}F_7N_2O_2]$ (12), 359 $[C_{13}H_7F_7N_2O_1]$ (31)	−3.0 (s, 3 F_a); 9.0 (s, 3 F_c); 44.0 (s, 2 F_b)	3.6 (s, 3 H, *m*-OMe); 3.7 (s, 3 H, *p*-OMe); 6.6 (d, 1 H, H(5′), J = 8.8); 7.1 (s, 1 H, H(5)); 7.5—7.7 (m, 2 H, H(2′), H(6′))
3g, $CF_2^bCF_3^c$	385 $[M]^+$ (100), 384 $[C_{15}H_{10}F_8N_3]$ (81), 157 $[C_4F_5N]$ (11), 142 $[C_{3F5}N]$ (7), 69 $[CF_3]$ (7)	−7.0 (s, 3 F_a); 5.0 (s, 3 F_c); 41.5 (s, 2 F_b)	2.9 (s, 6 H, NMe_2); 6.3 (d, 2 H, H(3′); H(5′), J = 9.3); 7.4 (s, 1 H, H(5)); 7.3 (d, 2 H, H(2′), H(6′))
3h $CF_2^bCF_2^cCF_2^dCF_3^e$	472 $[M]^+$ (100), 453 $[C_{16}H_8F_{11}N_2O_2]$ (50), 429 $[C_{14}H_5F_{12}N_2O_2]$ (30), 403 $[C_{15}H_8F_9N_2O_2]$ (30), 253 $[C_{12}H_8F_3N_2O_2]$ (87), 69 $[CF_3]$ (20)	−3.2 (s, 3 F_a); 7.0 (t, 3 F_e, J = 10.0); 41.2 (t, 2 F_b, J = 13.0); 47.8 (m, 2 F_c); 51.0 (t, 2 F_d)	3.7 (s, 3 H, OMe); 6.55 (d, 2 H, H(3′), H(5′), J = 8.8); 7.55 (s, 1 H, H(5)), 8.0 (d, 2 H, H(2′), H(6′))

of the products. The reaction cessation was detected by the disappearance (due to dehydrofluorination) of the signal from the vinylic fluorine atom of the initial β-diimine **1** (+98.0 ppm) in the ^{19}F NMR spectrum.

The synthesized pyrimidines **3**, being crystalline compounds, are soluble in acetone, ether, dioxane, and benzene and are insoluble in water. They were characterized using NMR spectroscopy, mass spectrometry, and elemental analysis (Tables 1 and 2).

Thus, polyfluorinated β-diimines are convenient compounds for the synthesis of fluorine-containing pyrimidines.

Experimental

^1H and ^{19}F NMR spectra of hexafluorobenzene solutions of compounds **3a—h** were recorded on a Bruker AC-200F spectrometer (200 and 188.3 MHz, respectively) relatively to Me_4Si and CF_3COOH (external standards). Mass spectra (EI) were obtained using a VG-7070 E spectrometer (ionizing voltage 70 V). The yields and parameters of the obtained compounds are presented in Tables 1 and 2.

2-Phenyl-4,6-bis(trifluoromethyl)pyrimidine (3a). A mixture of iminoenamine **1a** (1.4 g, 6.3 mmol), benzaldehyde (0.8 g, 7.5 mmol), and pyridine (0.6 g, 7.6 mmol) was boiled for 9 h (detecting the end of the reaction by the disappearance of the signal from the vinylic fluorine atom in the ^{19}F NMR spectrum). The reaction mixture was dissolved in ethanol (50 mL) and poured into water, and a precipitate was filtered off, washed with a 70% ethanolic solution (2×30 mL), and dried in air. Pyrimidine **3a** was obtained in 79.0% yield (1.5 g), m.p. 64—65 °C.

Compounds **3b—h** were obtained similarly (see Tables 1 and 2).

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