Synthesis of fluorinated pyrimidines by the reaction of perfluoro-2-methylpent-2-ene with amidines

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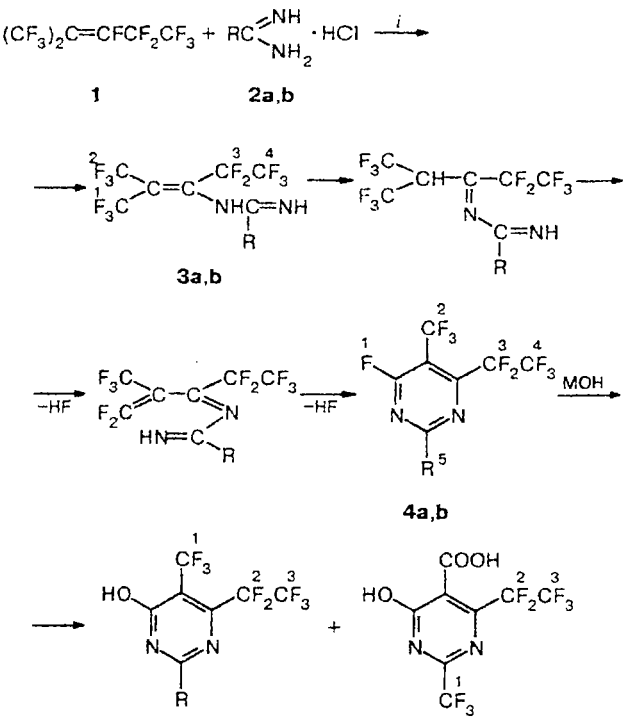
4-Fluoro-6-pentafluoroethyl-5-trifluoromethylpyrimidines have been synthesized by the reaction of perfluoro-2-methylpent-2-ene with aceto- and trifluoroacetoamidines. The high activity of the fluorine atom at position 4 of these compounds in reactions with nucleophilic reagents was found.

Key words: fluoroolefins, condensation with amidines; synthesis and nucleophilic reactions of 4-fluoropyrimidines.

One of the methods for the synthesis of fluorinated pyrimidines is known to be based on the reaction of fluorine-containing unsaturated compounds with amidines. Dinitriles $CF_3CCl=C(CN)_2$,[1] 2-chloroperfluorocycloalkene-1-carbonitriles,[2] $C_2F_5CF=CR[PO(OEt)_2]$,[3] and $(CF_3)_2C=CFOMe$ [4] have been involved in this reaction. The reaction was carried out with amidine free bases using an excess of the amidine to bind the hydrogen halide that was liberated in the course of the reaction.[1,2] On the contrary, equimolar amounts of the reagents were used by others,[3,4] thus the more available amidine hydrochlorides were involved in the reaction in the presence of alkaline reagents of the NaOH, KOH, or NaH type generating an amidine free base that directly enters the reaction. In an especially convenient modification, the reaction of unsaturated fluorinated compounds with amidine hydrochlorides is carried out in an organic solvent that is immiscible with water in the presence of an aqueous alkaline solution and a phase transfer catalyst.[4]

We studied the reaction of perfluoro-2-methyl-2-pent-2-ene (**1**) with aceto- and trifluoroacetoamidines (**2**)* using the two latter experimental versions. We used either diethyl ether or Freon-113 (F-113) (in which fluoroolefin **1** is very soluble) as a medium for the reaction and NaOH or KOH aqueous solutions and benzyltriethylammonium chloride (BTEA) as a base and a catalyst, respectively.

We showed that the reaction occurs according to the scheme involving the formation of the product of substitution of the vinylic fluorine atom (**3**), which further undergoes prototropic isomerization,** dehydrofluorination, and cyclization. The fluoropyrimidines **4** that formed in this case can be defluorinated with an aqueous alkali to give hydroxypyrimidines **5** and, in the case of amidine **2b**, hydroxy acid **6**.



† Deceased.

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When olefin **1 reacts with ammonia or aniline in ether, the reaction does not stop at the stage of the vinylic substitution. Instead, it affords the products of enamine-imine isomerization.[6]

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When olefin **1** interacts with amidine **2a**, vinylamidine **3a**, fluoropyrimidine **4a**, or hydroxypyrimidine **5a** can be isolated. The type of reaction product depends on the nature of the solvent, the presence of the catalyst, and the duration of the process. Thus, we found that in relatively polar diethyl ether, the first stage, which gives vinylamidine **3a**, occurs more rapidly than the subsequent cyclization and defluorination, making possible isolation and characterization of this compound. At the same time, transformations **3a** → **4a** and **4a** → **5a** proceed at comparable rates (^{19}F NMR data). This fact hampers the use of the reaction carried out in ether for the synthesis of fluoropyrimidine **4a**. However, hydroxypyrimidine **5a** can be obtained under these conditions in 60% yield.

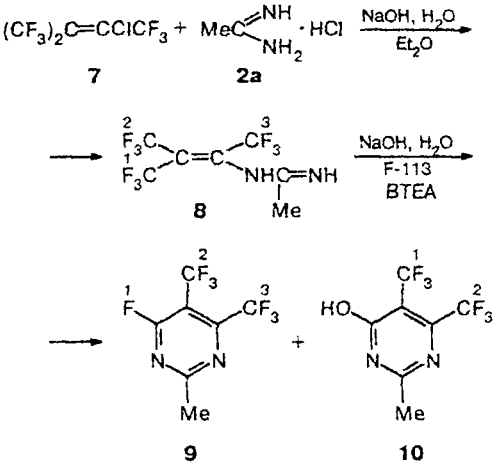
A similar result was obtained when the reaction of olefin **1** with amidine **2a** was carried out in non-polar Freon-113. The only difference consists in slowing down the first stage, the vinylic substitution. Therefore, both vinyl amidine **3a** and fluoropyrimidine **4a** are involved in further transformations as they are formed. For this reason, the reaction in Freon can also be used only for the synthesis of hydroxypyrimidine **5a**.

However, it turned out that in the presence of BTEA, the ratio between the rates of the stages of the overall process sharply changes, and in this case fluoropyrimidine **4a** can be isolated in 50% yield.

Somewhat different results were obtained in the studies of the reaction of olefin **1** with amidine **2b**. As it turned out, olefin **1** does not react with amidine **2b** in a solution of Freon-113, obviously due to the lower basicity of amidine **2b** compared to that of non-fluorinated analog. At the same time, olefin **1** readily reacts with amidine **2b** in a water—diethyl ether system to give vinylamidine **3b** in satisfactory yield (*ca.* 50%) under controlled conditions. Vinylamidine **3b** gives pyrimidine **4b** when it reacts with an aqueous alkali in Freon-113 in the presence of BTEA. However, the yield of pyrimidine **4b** does not exceed 10%, and the major reaction product is hydroxy acid **6**.

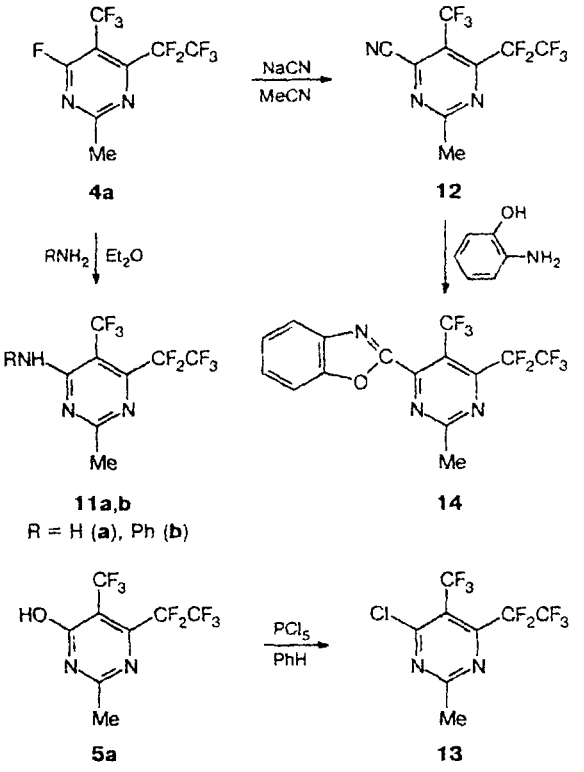
Attempts to carry out cyclization of vinyl amidine **3b** to fluoropyrimidine **4b** in an anhydrous medium failed. Thus, we found that the reaction does not occur in ether in the presence of Li_2CO_3, and in a KF—MeCN or a powdered KOH—ether system, a mixture of products is formed that does not contain fluoropyrimidine **4b**. At the same time, when vinylamidine **3b** is heated with Me_3N, Et_3N, or $Et_3N \cdot BF_3$ complex in ether, DMF, or without solvent, a mixture of products is formed that contains ~10% 4-hydroxypyrimidine **5b**. The same compound (but not fluoropyrimidine **4b**) was synthesized in high yield in the reaction of compound **3b** with 1,4-diazabicyclo[2.2.2]octane.

Fluoroolefin **7** was also involved in the reaction with amidine **2a**.[7] In this case fluoropyrimidine **9** was obtained in addition to hydroxypyrimidine **10** by a two-step process with preliminary isolation of vinylamidine **8**.



7 **2a** **8** **9** **10**

The structures of the compounds synthesized were confirmed by the NMR spectral data and several chemical transformations. Thus, fluoropyrimidine **4a** was converted to hydroxy-, amino- (**11a**), phenylamino- (**11b**), and cyano (**12**) derivatives. In turn, hydroxypyrimidine **5a** gave the corresponding chloropyrimidine **13** by reacting with PCl_5, and the reaction of the nitrile **12** with *o*-aminophenol afforded benzoxazolylpyrimidine **14**.



4a **12** **11a,b** **14**

R = H (**a**), Ph (**b**)

5a **13**

Comparison of the results obtained with the data on the nucleophilic substitution of the fluorine in

Table 1. Characteristics of the compounds synthesized

Compound	Yield (%)	B.p./°C (*p*/Torr) [M.p./°C]	Found / Calculated (%) C	H	F	Molecular formula
3a	68	60—63 (2) [49—51]	27.72 / 28.38	1.61 / 1.48	61.63 / 61.85	$C_8H_5F_{11}N_2$
3b	53.7	85—86 (40)	24.31 / 24.49	0.76 / 0.51	67.97 / 67.86	$C_8H_2F_{14}N_2$
4a	47	53—55 (22)	31.80 / 32.21	1.00 / 0.92	56.98 / 57.38	$C_8H_3F_9N_2$
4b	7	55—56 (38)	27.19 / 27.27	—	65.06 / 64.77	$C_8F_{12}N_2$
5a	58	[162—164]	32.32 / 32.43	1.32 / 1.35	50.87 / 51.35	$C_8H_4F_8ON_2$
5b	78	[72—74]	27.27 / 27.24	0.23 / 0.29	59.73 / 59.75	$C_8HF_{11}ON_2$
6	34	[228—230]	29.18 / 29.45	0.67 / 0.61	47.33 / 46.63	$C_8H_2F_8O_3N_2$
8	60	73—74 (3) [40—43]	29.70 / 29.17	1.87 / 1.74	60.52 / 59.38	$C_7H_5F_9N_2$
9	21	55—56 (40)	33.53 / 33.87	1.21 / 1.21	53.51 / 53.63	$C_7H_3F_7N_2$
10	34	[162—163]	34.12 / 34.15	1.59 / 1.63	46.45 / 46.34	$C_7H_4F_6N_2O$
11a	73	[98—100]	32.79 / 32.54	1.71 / 1.69	51.37 / 51.52	$C_8H_5F_8N_3$
11b	84	[45—47]	44.92 / 54.28	2.56 / 2.42	41.34 / 40.97	$C_{14}H_9F_8N_3$
12	45	65—67 (2)	35.33 / 35.41	1.01 / 0.98	49.54 / 49.83	$C_9H_3F_8N_3$
13	56	78—80 (20)	30.63 / 30.52	1.06 / 0.95	—	$C_8H_3ClF_8N_2$
14	57	[72—74]	27.27 / 27.24	1.60 / 0.29	59.73 / 59.75	$C_8HF_{11}ON_2$

4-fluoro-6-methoxy-2-methyl-5-trifluoromethylpyrimidine[4] indicates that accumulation of perfluoroalkyl groups in a 4-fluoropyrimidine makes the fluorine atom especially sensitive to nucleophilic attack. In the case of fluoropyrimidine **4b**, a susceptibility of the fluorine atoms of the trifluoromethyl group to hydrolysis appears additionally.

Experimental

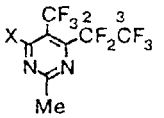
The NMR spectra were recorded on a Bruker-200 SY spectrometer (200 and 188. 3 MHz for ^1H and ^{19}F, respectively) in either CCl_4 or diethyl ether. Me_4Si and CF_3COOH were used as the external standards (^1H and ^{19}F, respectively). The IR spectra were recorded on an UR-20 spectrophotometer. The yields and the characteristics of the compounds synthesized are presented in Table 1. The ^{19}F NMR spectra of vinyl amidines **3a,b** and **8** and pyrimidines **5a**, **11—14** are given in Tables 2 and 3, respectively.

***N*-(Perfluoro-2-methylpent-2-en-3-yl)acetamidine (3a), *N*-(perfluoro-2-methylpent-2-en-3-yl)trifluoroacetamidine (3b), and *N*-(perfluoro-3-methylbut-2-en-2-yl)acetamidine (8).** A solution of KOH (2 g) in water (14 mL) was added dropwise to a mixture of amidine **2a** (2 g), olefin **1** (8.4 g), diethyl ether (25 mL), and water (7 mL) with stirring and on cooling to 0—5 °C and the reaction mixture was warmed to 20 °C for 1 h. The ether layer was separated and dried over $MgSO_4$. Product **3a** was isolated by distillation. IR, ν/cm^{-1}: 1610, 1675 cm^{-1}. ^1H NMR, δ: 2.5 (s, Me); 5.2—7.1 (br. s, NH). Vinyl amidines **3b** and **8** were obtained similarly.

Table 2. ^{19}F NMP spectra of vinylamidines **3a,b**, and **8**

Compound	δ F-1 (m)	F-2 (q)	F-3 (q)	F-4 (q)	F-5 (s)	*J*/Hz 1—2	1—3	2—3	2—4
3a	−22.9	−18.3	34.6	3.5		10		22	6.5
3b	−26.0	−21.0	31.1	0.2	−7.9	10		22	6.5
8	−21.8 (q)	−25.1 (qq)	−17.0			9.5	1.5	15	

Table 3. ^{19}F NMR spectra of pyrimidin



Compound	X	δ F-1 (t)	F-2 (q)	F-3 (s)	J_{1-2}/Hz
5a	HO	−19.0	32.7	2.2	22
11	H_2N	−21.8	32.1	1.7	22
12	NC	−21.9	33.0	2.5	20
13	Cl	−20.5	31.2	2.0	22
14	Benzoxazol-2-yl	−22.6	33.0	2.8	20

4-Fluoro-2-methyl-6-pentafluoroethyl-5-trifluoromethylpyrimidine (4a). A solution of NaOH (3.5 g) in water (15 mL) was added dropwise to a mixture of olefin **1** (7.1 g), amidine **2a** (1.8 g), F-113 (20 mL), BTEA (0.1 g), and water (7 mL) with stirring at temperature not exceeding 10 °C; the reaction mixture was warmed to 20 °C during 40 min. After 30 min the reaction mixture was acidified with HCl (1 : 5), the organic layer was dried over $MgSO_4$ and distilled to give compound **4a**, n_D^{20} 1.3625. ^1H NMR, δ: 2.43 (s, Me). ^{19}F NMR, δ: −23.7 (q, F-1); −20.1 (q, F-2); 4.2 (s, F-4); 33.6 (q, F-3); $J_{1-2} = J_{2-3} = 22$ Hz.

4-Fluoro-6-pentafluoroethyl-2,5-bis(trifluoromethyl)pyrimidine (4b) and 4-hydroxy-6-pentafluoroethyl-2-trifluoromethylpyrimidine-5-carboxylic acid (6). The crude vinylamidine **3b** obtained from olefin **1** (6 g) and amidine **2b** (2.3 g) as described above was dissolved in F-113 (20 mL) and TBEA (0.1 g) was added. A solution of NaOH (2.8 g) in water (15 mL) was added to the resulting mixture with stirring and on cooling to 5 °C. The reaction mixture was stirred for 2.5 h. The organic layer that formed was dried over $MgSO_4$ and distilled to give compound **4b**, n_D^{20} 1.3350. ^{19}F NMR, δ: −34.3 (q, F-1); −24.9 (q, F-2); −10.0 (s, F-5); −1.1 (s, F-4); 28.3 (q, F-3); $J_{1-2} = 22$ Hz. The aqueous layer was acidified, the crystals that precipitated were dried and sublimed *in vacuo* to give compound **6**. ^{19}F NMR (Et_2O), δ: −6.9 (s, F-1); 3.9 (s, F-3); 37.1 (s, F-2).

4-Hydroxy-2-methyl-6-pentafluoroethyl-5-trifluoromethylpyrimidine (5a). A solution of NaOH (3.5 g) in water (15 mL) was added dropwise to a mixture of olefin **1**, diethyl ether (20 mL) amidine **2a** (1.5 g), and water (7 mL) at temperature not exceeding 20 °C with stirring. The reaction mixture was stirred

for 3 h; and NaOH was added. The organic layer was separated, the aqueous layer was acidified, and the precipitate that formed was extracted with ether and dried over $MgSO_4$. The ether was removed to afford compound **5a**. ^1H NMR (freon-113), δ: 3.1 (s, Me); 7.7 (s, OH).

4-Hydroxy-6-pentafluoroethyl-2,5-bis(trifluoromethyl)pyrimidine (5b). A mixture of vinylamidine **3b** (1 g), 1,4-diazobicyclo[2.2.2]octane (0.9 g), and ether (10 mL) was refluxed for 25 h and washed with dilute HCl. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Compound **5b** was isolated from the residue by sublimation. ^{19}F NMR (Et_2O), δ: −18.0 (t, F-1); −5.0 (s, 2-CF_3); 2.8 (s, F-3); 32.0 (q, F-2); J_{1-2} = 20 Hz.

4-Fluoro-2-methyl-5,6-bis(trifluoromethyl)pyrimidine (9) and 4-hydroxy-2-methyl-5,6-bis(trifluoromethyl)pyrimidine (10). A solution of NaOH (1.4 g) in water (14 mL) was added dropwise to a mixture of vinylamidine **8** (1.7 g), F-113 (9 mL), and TBEA (0.1 g) with stirring and on cooling to 0 °C. After 1.5 h the organic layer was separated, dried, and distilled to give product **9**. ^{19}F NMR, δ: −27.6 (q, F-1); −24.1 (dq, F-2); −15.7 (q, F-3); J_{1-2} = 22, J_{2-3} = 26 Hz. The aqueous layer was acidified with HCl (1 : 5), the crystals that formed were extracted with ether, and dried. After removal of the solvent compound **10** was isolated by sublimation *in vacuo*. ^{19}F NMR, δ: −17.7 (q, F-1); −12.3 (q, F-2); J = 14 Hz.

4-Amino-2-methyl-6-pentafluoroethyl-5-trifluoromethylpyrimidine (11a) and 2-methyl-4-pentafluoroethyl-6-phenylamino-5-trifluoromethylpyrimidine (11b). A solution of fluoropyrimidine **4a** (3 g) in anhydrous diethyl ether was saturated with ammonia and concentrated by evaporation. The solid residue that formed was crystallized from CCl_4. ^1H NMR (CCl_4), δ: 3.3 (s, Me); 6.5 (s, H_2N). Derivative **11b** was obtained similarly.

2-Methyl-6-pentafluoroethyl-5-trifluoromethylpyrimidine-4-carbonitrile (12). Sodium cyanide (0.5 g) was added to a solution of fluoropyrimidine **4a** (2.6 g) in dry MeCN (8 mL) at temperature not exceeding 20 °C. The resulting mixture was stirred for 2 h until the initial material **4a** was completely transformed (GLC monitoring) and poured into water, the oil that formed was extracted with ether. Distillation gave product **12**, n_D^{20} 1.3965. IR, ν 2255 cm^{-1}.

4-Chloro-2-methyl-6-pentafluoroethyl-5-trifluoromethylpyrimidine (13). A mixture of hydroxypyrimidine **5a** (4.7 g), PCl_5 (5 g), and benzene (15 mL) was refluxed for 2.5 h and quenched with water. The organic layer that formed was dried and distilled to afford compound **13**, n_D^{20} 1.3997.

4-(Benzoxazol-2-yl)-2-methyl-6-(pentafluoroethyl)-5-trifluoromethylpyrimidine (14). A mixture of nitrile **12** (1.6 g), and *o*-aminophenol (0.6 g) was heated under argon at 175 °C for 2 h. The reaction mixture was dissolved in ether, washed with HCl (1 : 5), dried over $MgSO_4$, and distilled *in vacuo* (2 Torr). The product **14** crystallized during storage.

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