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REACTION OF POLYFLUORINATED β-DIIMINES WITH KETONES. A NOVEL METHOD FOR THE SYNTHESIS OF FLUORINATED PYRIDINES

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Reaction of polyfluorinated β-diimines with ketones gave polyfluorinated pyridines.

Keywords: ketones, polyfluorinated dihydropyrimidines, polyfluorinated β-diimines, polyfluorinated pyridines, condensation.

The six-membered azaheterocycles pyridine and pyrimidine occupy a special place amongst heterocyclic compounds. Medicinal compounds based on azaheterocyclic structures are found in almost all areas of pharmacology. Fluorinated pyridines and pyrimidines [1-4] are of interest since the introduction of a fluorine into a molecule generally increases the physiological activity of the compound [5] and also increases the stability of the medicinal compound towards oxidation by the oxygen in the air [6]. 1,3-Bifunctional, fluorinated building units are usually used to synthesize fluorinated pyridines. β-Diketones [7-10], β-alkoxyvinyl ketones [10, 11], β-aminovinyl ketones [12], *etc*. can serve as fluorinated 1,3-bifunctional compounds.

We have previously reported the use of 2-amino-4-iminoperfluoroalk-2-enes **1**, which are aza analogs of β-diketones, as convenient starting materials in the synthesis of fluorinated pyrimidines [13, 14].

In this work we propose for the first time the use of the polyfluorinated β-diimines **1** as starting materials for the preparation of fluorinated pyridines. In the literature only one example of the reaction of nonfluorinated β-diimines with ketones has been reported. Moreover, the condensation occurs only in the presence of aluminium chloride and ends with the formation of dihydropyrimidines [15].

We have found that the imino enamines **1** react with methyl alkyl ketones and acetophenone at 90-180°C in the absence of catalysts to give polyfluorinated pyridines.

It was found that the reaction occurs by a scheme which includes the formation of dihydropyrimidines which subsequently eliminate ammonia to give the polyfluorinated pyridines. The course of the reaction was monitored using ^{19}F NMR spectroscopy.

The fluorinated β-diimine **1a** reacts with acetone, evidently, initially to form adduct **A** which cyclizes, in the conditions selected by us, with the loss of water to give the dihydropyrimidines **2** and **3**.

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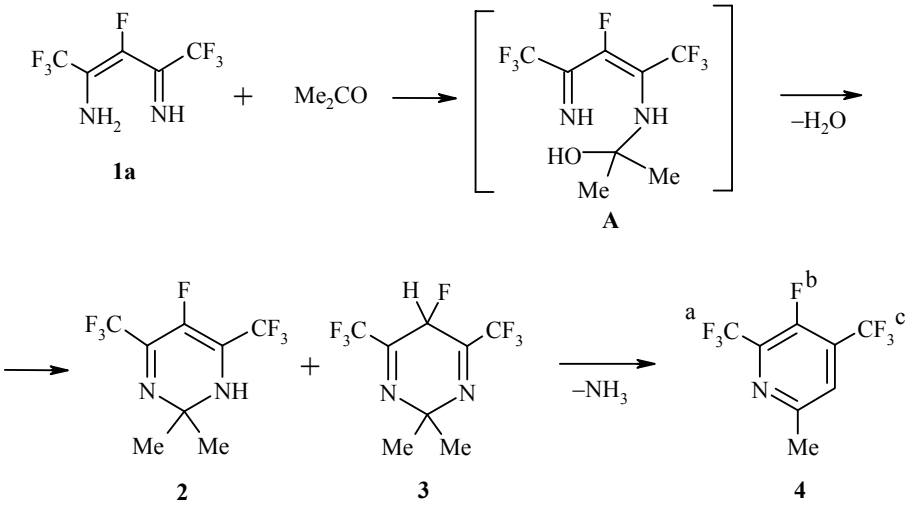
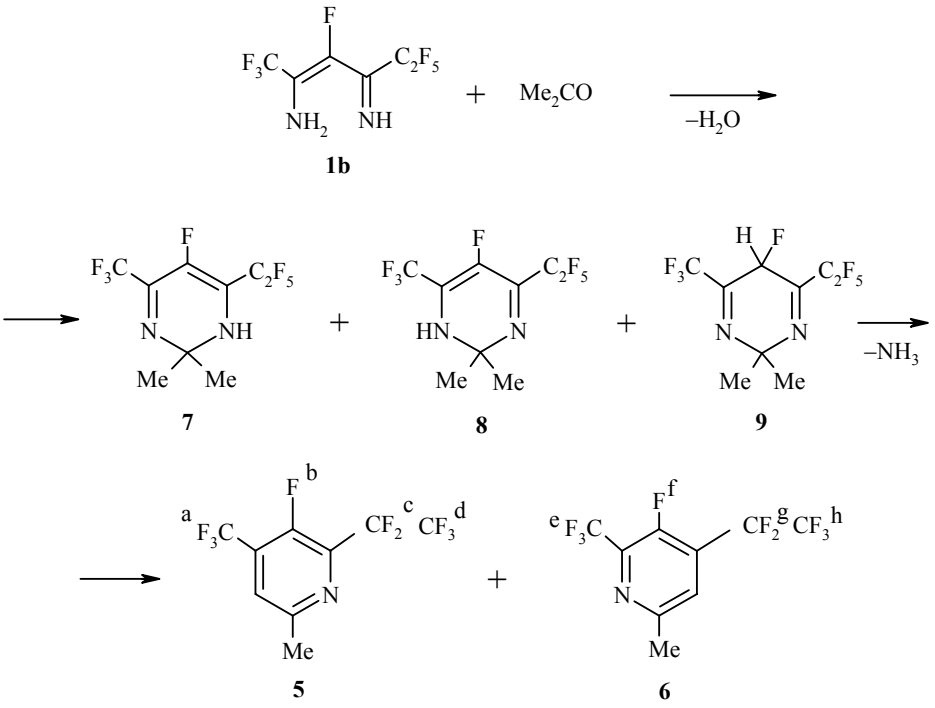


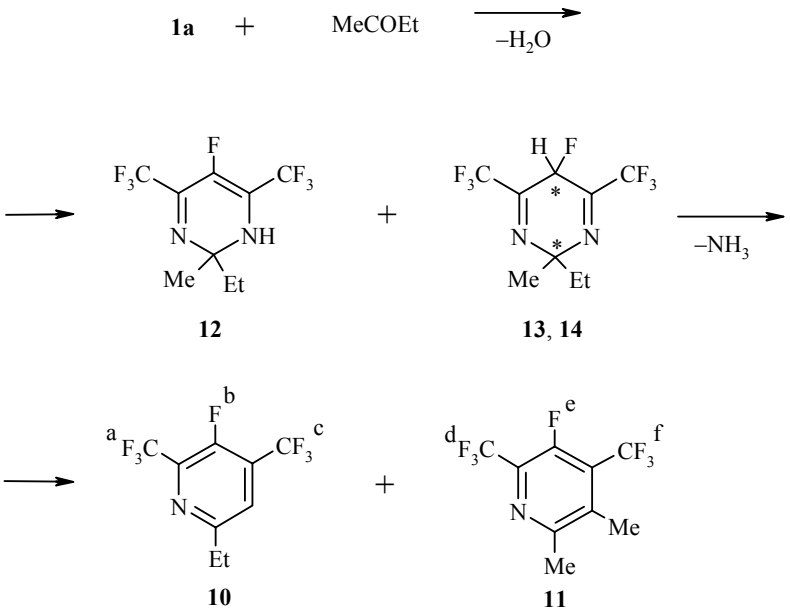
The presence and the reactions of the 1,2- and 2,5-dihydropyrimidines **2** and **3** were established using ^{19}F NMR spectroscopy. In the course of the reaction, the heptet signal at δ = 94.0 ppm (J = 15 Hz) for the vinyl fluorine atom of the dihydropyrimidine **2** and the double heptet at 106.0 ppm (J = 46 and 8 Hz) for the CFH group of the dihydropyrimidine **3** are slowly transformed to a multiplet at 57.0 ppm for the pyridine **4**. The formation of the dihydropyrimidines **2** and **3** was also confirmed by mass spectroscopic data. After preliminary separation on a capillary chromatographic column the mass spectra of the reaction mixture showed the M^+ molecular ions for compounds **2** and **3**.



According to ^{19}F NMR spectroscopic data the condensation of the unsymmetrical β-diimine **1b** with acetone occurs over a longer time and gives a mixture of the isomeric pyridines **5** and **6** in the ratio 75: 25. As in the preceding case, the pyridines **5** and **6** are formed from the corresponding dihydropyrimidines **7-9**. This is

confirmed by the presence in the ^{19}F NMR spectrum of the reaction mixture of signals for the fluorine α-atoms of compounds **7, 8** as multiplets at 92.0 and 93.5 ppm and also the appearance of a double multiplet at δ = 104.0 ppm (*J* = 47 Hz) for the CFH group of the dihydropyrimidine **9**. Subsequently, the fluorine α-atom signals of all the dihydropyrimidines are transformed to a multiplet at δ = 54.1 ppm corresponding to the pyridine **5** and a multiplet at δ = 53.8 ppm for the corresponding pyridine **6**. The synthesized pyridines **5** and **6** were obtained as a mixture and we were unable to separate the individual compounds.

We have studied the reaction of the imino enamine **1a** with methyl ethyl ketone, in which the reaction can occur both at the methyl and at a methylene group and it was found that both routes are realized.



The reaction of **1a** with methyl ethyl ketone gives a mixture of the 6-ethyl- and 2,3-dimethylpyridines **10** and **11**. In the initial cyclization of compound **1a** with the ketone the 1,2-dihydropyrimidine (**12**) and the two diastereomers of the 2,5-dihydropyrimidine **13** and **14** are formed. The ^{19}F NMR spectrum shows pyrimidine signals as a heptet at δ = 96.0 ppm (*J* = 15z) for **12** and two doublets of heptets for **13** and **14** at δ = 103 and 104 ppm (with repeated spin-spin couplings of 46 and 7 Hz). Further reaction of the pyrimidines **12-14** to the pyridines **10, 11** occurs via the elimination of ammonia. The structure of the pyridines obtained was confirmed by the NMR and mass spectroscopic data. Hence the ^{19}F NMR spectrum shows signals for the CF group fluorine of the pyridine **10** as a quartet of quartets of doublets at 53.6 ppm and a quartet of quartets at 52.2 ppm in **11**. The ^{1}H NMR spectrum shows signals for the methyl groups as singlets in the pyridine **11** and two signals assigned to the ethyl group of compound **10** as a triplet and quartet. In addition, after preliminary chromatographic separation on a capillary column the mass spectrum shows the molecular ions for the synthesized pyridines.

The pyridines **10** and **11** were obtained as a mixture and separation into the individual components was not achieved.

The reaction of the β-diimine **1a** with acetophenone under analogous conditions gave the pyridine **15**, the occurrence of which also infers the formation of the corresponding dihydropyrimidines **16-18**. The CF group fluorine atom signals for the latter are seen in the ^{19}F NMR spectrum of the reaction mixture as a multiplet at δ = 91.0 ppm for the compound **16** and two doublets of multiplets at δ = 106.0 and 108.0 ppm (*J* = 46 Hz in each case) for **17** and **18**. The unsymmetrical imino enamine **1b** reacts with acetophenone to give a mixture of the isomeric pyridines **19** and **20**. However the intermediate dihydropyrimidines **21-24** could not be identified by the ^{19}F NMR method. The structure of the obtained pyridines was proved from NMR and mass spectroscopic data.

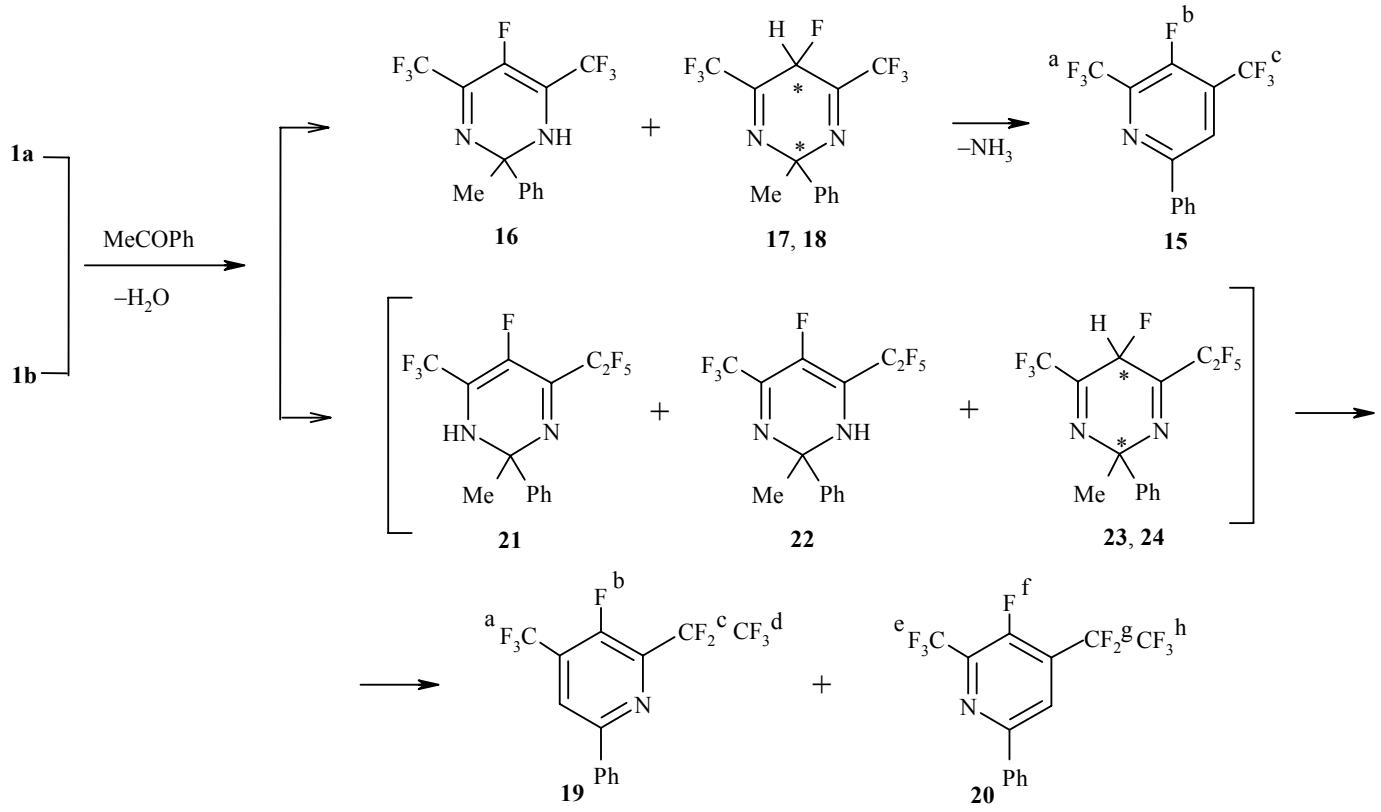

1a
1b
MeCOPh
–H2O
16
17, 18
–NH3
15
21
22
23, 24
19
20

TABLE 1. Characteristics of Compounds **4-6, 10, 11, 15, 19, 20**

Compound	Empirical formula	Found, % / Calculated, %				Bp, °C (mm Hg)	Reaction time, h	Yield, %
		C	H	F	N			
4	$C_8H_4F_7N$	38.69 / 38.87	1.85 / 1.62	53.64 / 53.85	—	46-48 (13)	48	47.6
5, **6**	$C_9H_4F_9N$	36.23 / 36.36	1.52 / 1.35	57.05 / 57.58	—	48-50 (15)	60	64.0
10, **11**	$C_9H_6F_7N$	41.62 / 41.38	2.43 / 2.30	50.56 / 50.96	—	60-63 (14)	25	70.0
15	$C_{13}H_6F_7N$	50.56 / 50.48	1.84 / 1.94	—	4.47 / 4.53	—*	22	62.8
19, **20**	$C_{14}H_6F_9N$	47.11 / 46.80	2.06 / 1.67	—	3.92 / 3.90	125-127 (14)	31	61.0

* Mp 65-67°C, sublimation 140-142°C (23 mm Hg).

TABLE 2. Spectroscopic Characteristics of Compounds **4-6, 10, 11, 15, 19, 20**

Compound	Mass spectrum, *m/z* (I_{rel}, %)	NMR spectrum, δ, ppm (*J*, Hz)	
		^{19}F	^{1}H
4	247 $[M]^+$ (100), 228 $[C_8H_4F_6N]$ (60), 227 $[C_8H_3F_6N]$ (83), 178 $[C_7H_4F_4N]$ (19), 177 $[C_7H_3F_4N]$ (53), 158 $[C_7H_3F_3N]$ (46), 69 $[CF_3]$ (12)	-12 (3F, d, J = 12.5, CF_3^c), -10 (3F, d, J = 16.5, CF_3^a), 57.0 (1F, m, F^b)	2.6 (3H, s, CH_3), 7.6 (1H, d, $J_{(F-H)}$ = 4.4)
5	297 $[M]^+$ (68), 278 $[C_9H_4F_8N]$ (22), 277 $[C_9H_3F_8N]$ (18), 228 $[C_8H_4F_6N]$(100), 208 $[C_8H_3F_5N]$ (15), 69 $[CF_3]$ (20)	-13.0 (3F, d, J = 12.0, CF_3^a), 7.0 (3F, d, J = 6.0, CF_3^d), 38.8 (2F, d, J = 23.0,CF_2^c), 53.8 (1F, m, F^b)	2.8 (3H, s, CH_3), 7.85 (1H, d, $J_{(F-H)}$ = 4.4)
6		-10.5 (3F, d, J = 16.0, CF_3^e), 9.0 (3F, d, J = 11.0, CF_3^h), 38.3 (2F, d, J = 20.0, CF_2^g), 54.1 (1F, m, F^f)	2.8 (3H, s, CH_3), 7.8 (1H, d, $J_{(F-H)}$ = 4.4)
10	261 $[M]^+$ (100), 260 $[C_9H_5F_7N]$ (100), 242 $[C_9H_6F_6N]$ (30), 240 $[C_9H_4F_6N]$ (78), 213 $[C_7H_1F_6N]$ (23), 69 $[CF_3]$ (22)	-14.8 (3F, d, J = 13.5, CF_3^c), -12.0 (3F, d, J = 15.5, CF_3^a), 53.6 (1F, qqd, J = 4.4, F^b)	1.55 (3H, t, J = 7.0, $CH_2\underline{CH_3}$), 3.1 (2H, q, $\underline{CH_2}CH_3$), 7.75 (1H, d, $J_{(F-H)}$ = 4.4)
11	261 $[M]^+$ (100), 242 $[C_9H_6F_6N]$ (37), 241 $[C_9H_5F_6N]$ (90), 69 $[CF_3]$ (18)	-21.0 (3F, d, J = 30.0, CF_3^f), -12.0 (3F, d, J = 15.5, CF_3^d), 52.2 (1F, qq, F^e)	2.65 and 2.75 (6H, both s, $2CH_3$)
15	309 $[M]^+$ (100), 290 $[C_{13}H_6F_6N]$ (27), 240 $[C_{12}H_6F_4N]$ (18), 77 $[C_6H_5]$ (3), 69 $[CF_3]^+$ (6)	-15.0 (3F, d, J = 13.5, CF_3^c), -12.0 (3F, d, J = 16.0, CF_3^a), 52.0 (1F, m, F^b)	7.2-7.95 (5H, m, Ar), 8.0 (1H, d, $J_{(F-H)}$ = 4.4)
19	359 $[M]^+$ (100), 340 $[C_{14}H_8F_8N]$ (25), 290 $[C_{13}H_8F_6N]$ (92), 220 $[C_{12}H_7F_3N]$ (15), 77 $[C_6H_5]$ (8)	-13.0 (3F, d, J = 13.0, CF_2^a), 6.5 (3F, d, J = 4.0, CF_3^d), 38.0 (2F, d, J = 22.0, CF_2^c), 53.0 (1F, m, F^b)	6.1-7.65 (12H, m, H(3) and Ar)
20	359 $[M]^+$ (100), 340 $[C_{14}H_8F_8N]$ (9), 290 $[C_{13}H_8F_6N]$ (24), 220 $[C_{12}H_7F_3N]$ (8), 77 $[C_6H_5]$ (4)	-11.0 (3F, d, J = 15.5, CF_3^e), 8.5 (3F, d, J = 11.5, CF_3^h), 38.5 (2F, d, J = 20.0, CF_2^g), 52.0 (1F, m, F^f)	

By varying the conditions of the reaction and the ratio of starting reagents we found that the optimum yields of the pyridines **4, 5, 10, 11** could be achieved with the use of a two fold excess of the ketone and the pyridines **15, 19, 20** by carrying out the reaction with the use of dioxane or diglyme solvent.

All of the polyfluoropyridines are liquids characterised by their smell, light-yellow color, and insolubility in water. An exception is the pyridine **15** which is a solid material.

Hence the proposed, novel method yields polyfluoropyridines from available fluorinated imino enamines [16].

EXPERIMENTAL

^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer (200 and 188 MHz respectively) with TMS and CF_3COOH external standard and mass spectra on a VG-7070E spectrometer (ionizing voltage 70 eV). The yields and characteristics of the compounds obtained are given in Tables 1 and 2.

3-Fluoro-6-methyl-2,4-bis(trifluoromethyl)pyridine (4). A mixture of the β-diimine **1a** (4.0 g, 17.7 mmol) and acetone (2.3 g, 40.3 mmol) was refluxed with a reflux condenser for 48 h. The cooled reaction mixture was poured into CH_2Cl_2 (20 ml), washed with water (2 × 30 ml), and the organic layer was separated, dried over $CaCl_2$, and distilled to give the pyridine **4** (2.1 g)

3-Fluoro-6-methyl-2-pentafluoroethyl-4-trifluoromethylpyridine (5) and 3-Fluoro-6-methyl-4-pentafluoroethyl-2-trifluoromethylpyridine (6). A mixture of the β-diimine **1b** (5.3 g, 19.3 mmol) and acetone (2.8 g, 50.0 mmol) was refluxed with a reflux condenser for 60 h. The cooled reaction mixture was poured into CH_2Cl_2 (30 ml), washed with water (2 × 30 ml), and the organic layer was separated, dried over $CaCl_2$, and distilled to give a mixture (3.7 g) containing 75% of the pyridine **5** and 25% of pyridine **6** from ^{19}F NMR data.

6-Ethyl-3-fluoro-2,4-bis(trifluoromethyl)pyridine (10) and 5-Fluoro-2,3-dimethyl-4,6-bis-(trifluoromethyl)pyridine (11). A mixture of the β-diimine **1a** (3.8 g, 17 mmol) and methyl ethyl ketone (2.4 g, 34.0 mmol) was refluxed with a reflux condenser for 25 h. The cooled reaction mixture was poured into CH_2Cl_2 (30 ml), washed with water (2 × 30 ml), and the organic layer was separated, dried over $CaCl_2$, and distilled to give a mixture (3.1 g) containing 68% of compound **10** and 32% of compound **11** from ^{19}F NMR data.

3-Fluoro-6-phenyl-2,4-bis(trifluoromethyl)pyridine (15). A solution of the β-diimine **1a** (8.2 g, 36.6 mmol) and acetophenone (4.4 g, 36.6 mmol) in diglyme (10 ml) was refluxed with a reflux condenser for 22 h. The cooled reaction product was poured into water and the precipitate formed was filtered off, dried in air, and sublimated to give the pyridine **15** (7.1 g, 62.8%).

3-Fluoro-2-pentafluoroethyl-6-phenyl-4-trifluoromethylpyridine (19) and 3-Fluoro-4-penta-fluoroethyl-6-phenyl-2-trifluoromethylpyridine (20). A solution of the β-diimine **1b** (4.0 g, 14.6 mmol) and acetophenone (1.8 g, 15 mmol) in dioxane (10 ml) was refluxed with a reflux condenser for 31 h. The cooled reaction mixture was poured into CH_2Cl_2 (30 ml), washed with water (2 × 30 ml), dried over $CaCl_2$, and distilled to give a mixture (3.3 g) which contained 73% of the pyridine **19** and 27% of pyridine **20** from ^{19}F NMR data.

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