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FIRST EXAMPLE OF THE SYNTHESIS OF DI(FLUOROALKYL)-SUBSTITUTED PYRIMIDINES

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4,5-Bis(hydroxy)-4-trifluoromethyl-6-(fluoroalkyl)hexahydropyrimidin-2-ones (thiones) have been obtained for the first time by the reaction of ureas (thioureas) with di(fluoroalkyl)-substituted 1,3-diketones and tetraols, the dehydration of which gave 2-hydroxy(mercapto)-4-trifluoromethyl-6-(fluoroalkyl)pyrimidines.

Keywords: pyrimidines with fluoroalkyl substituents.

Interest in the chemistry of pyrimidine derivatives is explained by the observation that some of them have biological activity. The basic method for the synthesis of pyrimidines is the reaction of 1,3-dicarbonyl compounds with urea derivatives [1, 2]. Monofluoroalkyl-substituted pyrimidines have been synthesized from fluorinated 3-oxo esters [3], 1,3-diketones with one fluorine containing substituent [4, 5], and their lithium salts [6].

In the present work we have obtained for the first time pyrimidines with two fluoroalkyl substituents by the reaction of di(fluoroalkyl)-substituted 1,3-diketones **1a,b** with urea and thiourea. Previously the possibility of the reaction between hexafluoroacetylacetone and urea had been denied [7]. The authors [7] concluded, on the basis of a kinetic study, that the first stage of the reaction of 1,3-diketones with urea was nucleophilic substitution at the vinyl carbon atom, followed by cyclization to a pyrimidine. The reaction occurred only in the presence of a small amount of hydrochloric acid which catalyzed the elimination of water. The absence of a reaction between hexafluoroacetylacetone and urea was explained by the difficulty of eliminating water because of the two electron withdrawing groups.

Hexafluoroacetylacetone **1a** and its unsymmetrical analog **1b** react with urea and thiourea in boiling ethanol with and without acid catalysis. In our view, the mechanism of the reaction of the 1,3-diketones **1a,b** containing two fluoroalkyl substituents differs from the reactions of nonfluorinated diketones and those containing a single fluoroalkyl substituent. This is indicated by the fact that the products in the former cases are bis(hydroxy)hexahydropyrimidines **3a-d**, and not the unsubstituted pyrimidines **4** obtained from the reactions of 1,3-diketones with one fluorine-containing substituent [4, 5].

The fluoro-substituted 1,3-diketones add water or ethanol extremely readily to the carbonyl group with the fluoroalkyl radical [8]. Apparently the first step in the reaction of the difluoroalkyl-1,3-diketones **1a,b** in aqueous-alcoholic medium is the formation of the intermediate bis-semiketals or tetraols by addition of water or ethanol, and these then react with urea or thiourea to give the heterocycles **3a-d**.

The possibility of forming hexahydropyrimidines from tetraols was shown by the reactions of the tetraols **2a,b** with urea and thiourea which gave the products **3a-d**.

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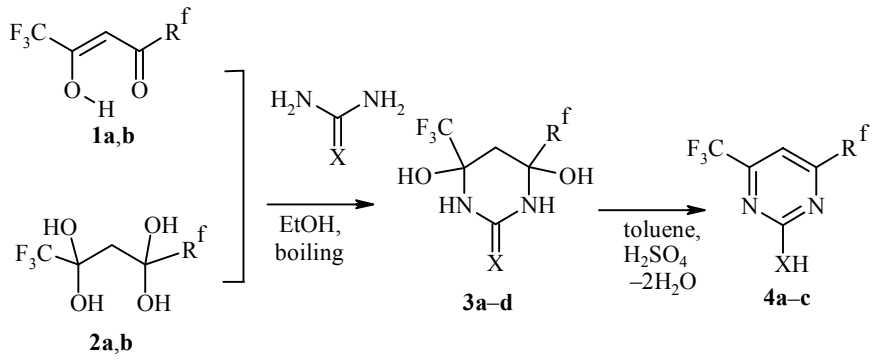


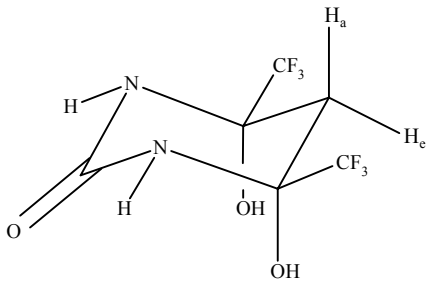
1a, **2a** $R^f = CF_3$, **3a**, **4a** X = O, **3b**, **4b** X = S; **1b**, **2b** $R^f = H(CF_2)_2$, **3c**, **4c** X = O, **3d** X = S

The absence of the desired heterocyclic products when the 1,3-diketone **1a** was boiled with urea in the absence of water and ethanol, in particular in absolute benzene and tetrahydrofuran, is in complete agreement with the proposed mechanism.

Use of tetraols as synthetic equivalents of 1,3-diketones for the synthesis of heterocycles has potential, since fluorine containing 1,3-diketones are unstable and readily add water to form stable hydrates when stored in air [8].

The hexahydropyrimidines **3** contain two asymmetric carbon atoms. The ^1H and ^{19}F NMR spectra of heterocycle **3a** contain groups of signals which correspond to only one of the two possible stereoisomers. The signals of the nonequivalent diastereotopic methylene protons in the form of an AB system in the ^1H NMR spectrum (Table 2) show that the heterocycle exits exclusively as the *cis* isomer. The positions of the trifluoromethyl and hydroxyl substituents can be judged by comparing the conformational energies taking into account that the substituent with the higher energy takes the equatorial position [9]. Consequently the trifluoromethyl group (ΔG = 8.8 kJ/mol) is in the equatorial position, while the hydroxyl group (ΔG = 2.2 kJ/mol) is in the axial position (Fig. 1).

In contrast to the carbonyl analog **3a**, two sets of signals are present in the ^1H and ^{19}F NMR spectra of the hexahydropyrimidin-2-thione **3b** (Table 1). In the ^1H NMR spectrum the singlet signal for the proton of the *trans* isomer (because the same substituents are in positions 4 and 6 of heterocycle the *trans* isomer reflects into itself and the methylene protons are equivalent) appear along with those of the *cis* isomer. Thus the heterocycle **3b** exists as a mixture of the *cis* and *trans* isomers in a ratio of 3:1 (Fig. 2). We were unable to separate the isomers either by crystallization or column chromatography.



cis 100%

Fig. 1. Conformational structure of 4,6-bis(hydroxy)-4-trifluoromethyl-6-fluoroalkylhexahydropyrimidin-2-ones(thiones) **3a,c,d**.

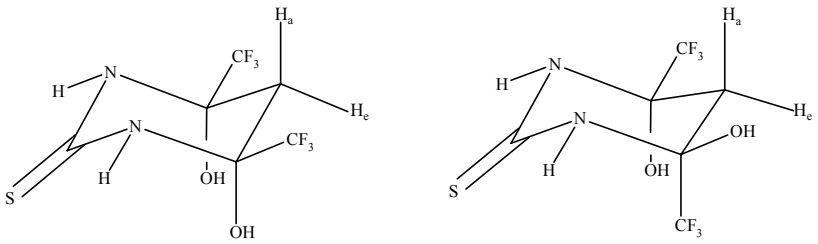


Fig. 2. Conformational structures of 4,6-bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidin-2-thione **3b**.

The ^{1}H NMR spectra of hexahydropyrimidines **3c,d** contain a single set of signals (Table 2) which indicates the presence of a single stereoisomer in each case. In our view it is not possible to judge the conformational structure of these compounds from the ^{1}H NMR spectra because the signals of the methylene group in both the *cis* and *trans* isomers will have the form of an AB system because of the different fluoroalkyl substituents in the heterocycles. Taking into account that the equatorial position is more suitable for the fluoroalkyl groups, it can be suggested that compounds **3c,d** exist as the *cis* isomers (Fig. 1).

Pyrimidines **4a-c** were obtained by boiling the hexahydropyrimidines **3a-c** in toluene in the presence of *p*-toluenesulfonic acid for azeotropic removal of the water formed. Since for compounds **4a,c** amide-imine, and for **4b** thione-thiol, tautomers are possible, it may be anticipated that these heterocycles would exist as 2-hydroxy(mercapto) pyrimidines **A**, 1,2-dihydropyrimidin-2-ones(thiones) **B**, or a mixture of the tautomers.

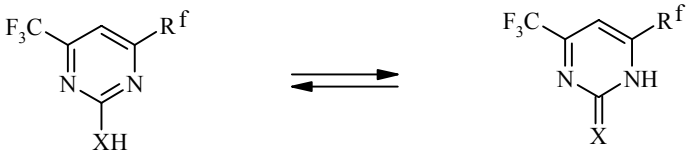


TABLE 1. Characteristics of Compounds **2b**, **3a-d**, and **4a-c**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	Yield, % (method)
		C	H	F	N	S		
2b	$C_6H_7F_7O_4$	26.10 / 25.99	2.53 / 2.56	48.00 / 48.17			125-126	89
3a	$C_6H_6F_6N_2O_3$	26.98 / 26.88	2.31 / 2.26	42.62 / 42.51	10.45 / 10.45		211-212	72 (A) 36 (B)
3b	$C_6H_6F_6N_2O_2S$	25.28 / 25.36	2.05 / 2.13	40.16 / 40.11	10.17 / 9.86	11.28 / 11.28	164-165	56
3c	$C_7H_7F_7N_2O_3$	27.90 / 28.01	2.31 / 2.35	44.26 / 44.31	9.34 / 9.33		178-180	65(A) 36(B)
3d	$C_7H_7F_7N_2O_2S$	26.67 / 26.59	2.35 / 2.23	42.10 / 42.06	8.77 / 8.86	10.15 / 10.14	161-162	37
4a	$C_6H_2F_6N_2O$	31.05 / 31.05	0.83 / 0.87	49.32 / 49.11	11.90 / 12.07		133-135	68
4b	$C_6H_2F_6N_2S$	29.21 / 29.04	1.09 / 0.81	45.91 / 45.94	11.36 / 11.29	12.92 / 12.92	50-51	62
4c	$C_7H_3F_7N_2O$	31.85 / 31.83	1.14 / 1.15	50.21 / 50.35	10.87 / 10.61		108-109	57

TABLE 2. Spectroscopic Characteristics of the Compounds Synthesized, **2b**, **3a-d**, **4a-c**

Compound	IR spectra, ν, cm^{-1}	^1H NMR spectra (DMSO-d_6), δ, ppm, *J*, Hz	
		^1H	^{19}F
2b	3330 (OH), 3020 (C–H stretching vibrations), 1200-1100 (C–F)	3.19 (2H, s, CH_2); 5.16 (4H, s, 4OH); 6.54 (1H, tt, $H(CF_2)_2$, $^2J_{HF}$ = 52.4, $^3J_{HF}$ = 6.0)	
3a	3290, 3130, 1500 (NH, OH), 1660 (CONH); 1200-1140 (C–F)	2.15 (2H, m, 5-H_a,5-H_e, AB-system, Δν = 18.28, *J* = 13.7); 6.94, 7.97 (4H, 2s, 2NH, 2OH)	78.60 (6F, s, $2CF_3$)
3b	3290, 3180, 1505 (NH, OH), 3080 (C–H stretching vibrations), 1555 (C=S), 1230-1150 (C–F)	*cis/trans* = 3/1 *cis*: 2.21 (2H, m, 5-H_a,5-H_e, AB-system, Δν = 24.00, *J* = 13.9); 7.32, 9.50 (4H, 2s, 2NH, 2OH); *trans*: 2.38 (2H, s, 5-H_a,5-H_e); 7.38, 9.24 (4H, 2s, 2NH, 2OH)	*cis/trans* = 3/1 *cis*: 79.56 (6F, s, $2CF_3$); *trans*: 80.52 (6F, s, $2CF_3$)
3c	3460, 3290, 3120, 1500 (NH, OH), 1650 (CONH); 1240-1090 (C–F)	2.15 (2H, m, 5-H_a,5-H_e, AB-system, Δν = 14.40, *J* = 14.0); 6.61 (1H, tt, $H(CF_2)_2$, $^2J_{HF1,2}$ = 51.7, $^3J_{HF3,4}$ = 6.4); 6.82, 6.89, 7.41, 7.93 (4H, 4s, 2NH, 2OH)	26.53 (2F, m, $H\underline{CF_2}CF_2$, AB-system, Δν = 295.53, $^2J_{F1F2}$ = 301.8, $^2J_{F1,2H}$ = 51.3, $^3J_{F1F3,4}$ = 6.8, $^3J_{F2F3,4}$ = 8.8); 31.54 (2F, m, $HCF_2\underline{CF_2}$); 78.63 (3F, s, CF_3)
3d	3450, 3260, 1500 (NH, OH), 1550 (C=S), 1200-1100 (C–F)	2.19 (2H, m, 5-H_a,5-H_e, AB-system, Δν = 21.60, $^2J_{H5aH5e}$ = 14.3); 6.71 (1H, tt, $H(CF_2)_2$, $^2J_{HF1,2}$ = 51.7, $^3J_{HF3,4}$ = 6.9); 7.27, 7.35 (2H, 2s, 2OH), 8.80, 9.60 (2H, 2s, 2NH)	26.60 (2F, m, $H\underline{CF_2}CF_2$, AB-system, Δν = 285.3, $^2J_{F1F2}$ = 302.7, $^2J_{F1,2H}$ = 51.7, $^3J_{F1F3,4}$ = 6.8, $^3J_{F2F3,4}$ = 8.8); 32.29 (2F, m, $HCF_2\underline{CF_2}$, $^3J_{F3,4H}$ = 6.9, $^3J_{F3,4F1}$ = 6.8, $^3J_{F3,4F2}$ = 8.8); 79.58 (3F, s, CF_3)
4a	3290, 3210, 3120, 2660, 1585 (NH), 1665 (CONH); 1580 (C=S, C=N), 1290-1150 (C–F)	7.91 (1H, s, 5-H); 13.74 (1H, br. s, OH)	93.65 (6F, s, $2F_3$)
4b	3090 (C–H stretching vibrations), 1580 (NH), 1555 (C=N, C=C), 1300-1100 (C–F)	7.21 (1H, br. s, SH); 8.48 (1H, br. s, 5-H)	93.72 (6F, s, $2F_3$)
4c	3320, 2640, 1600 (NH); 1670 (CONH); 1580 (C=S, C=N); 1260-1100 (C–F)	6.88 (1H, tt, $H(CF_2)_2$, $^2J_{HF}$ = 51.3, $^3J_{HF}$ = 5.3); 7.78 (1H, s, 5-H); 12.95 (1H, s, OH)	24.86 (2F, dt, $H\underline{CF_2}CF_2$, $^2J_{FH}$ = 51.3, $^3J_{FF}$ = 7.3); 42.69 (2F, m, $HCF_2\underline{CF_2}$, $^3J_{FH}$ = 5.3, $^3J_{FF}$ = 7.3); 93.64 (3F, s, CF_3)

Analysis of the ^{1}H NMR spectra of products **4a-c** shows that only one of the tautomers exists in solution. The presence of a low-field signal in the 12.95-13.74 ppm region of the ^{1}H NMR spectra of compounds **4a,c** corresponds in our view and by comparison with published data [10] with the resonance of a hydroxyl proton at the C=N bond of structure **A**, and not with the amide proton of tautomer **B**. However there are intense absorptions in the IR spectra of compounds **4a,c** which correspond to amide vibrations (3320-3120 and 1670-1665 cm^{-1}) which shows the presence of tautomer **B** in crystals of these compounds.

The categorical denial of the existence of form **A** is impossible in our view since the observed bands may correspond to a mixture of tautomers.

It was not possible to confirm the structure of heterocycle **4b** by IR and ^{1}H NMR spectroscopy. To obtain additional information we recorded the UV spectrum of compound **4b** in methanol. Bands of $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions in the conjugated chromophores of the pyrimidine ring were observed (λ_{max}, nm (ε): 244 (12000), 299 sh (2300)) which overlapped the $n\rightarrow\sigma^*$ band of the C–SH auxochromic group at 230 nm [10]. The low intensity $n\rightarrow\pi^*$ band of the isolated C=S chromophore (λ_{max}, nm (ε): 490-510 (~10) [10] was absent. All these indicate that compound **4b** has the 2-mercaptopyrimidine structure **A**.

EXPERIMENTAL

IR spectra of nujol mulls were recorded over the 400-4000 cm^{-1} range with a Specord IR-75 spectrometer. UV spectra were measured with a Specord UV-vis spectrometer. ^{1}H NMR spectra were recorded with a Tesla BS-567 A machine (80 MHz, internal standard TMS) and ^{19}F NMR spectra with a Tesla BS-587 A machine (^{19}F, 75 MHz, internal standard C_6F_6). Elemental analyses were carried out with a Carlo Erba CHNS-O EA 1108 elemental analyser.

2,2,4,4-Tetrahydroxy-1,1,1,5,5,6,6-heptafluorohexane (2b). A mixture of the 1,3-diketone **1b** (240 mg, 2.0 mmol) and distilled water (144 mg, 8 mmol) was kept at room temperature for 3 days with occasional shaking. The precipitate was filtered off, washed with chloroform and dried to give tetraol **2b** (491 mg) as a colorless powder (Table 1).

4,6-Bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidin-2-one (3a). A. A mixture of 1,3-diketone **1a** (416 mg, 2.0 mmol) and urea (120 mg, 2.0 mmol) was boiled in ethanol (8 ml) containing 2 drops of conc. HCl for 2 h. The ethanol was evaporated and the residue was washed with chloroform and a small amount of water to give compound **3a** (386 mg) as a colorless powder (Table 1).

B. A mixture of tetraol **2a** (488 mg, 2.0 mmol) and urea (120 mg, 2.0 mmol) was boiled in ethanol (8 ml) containing 2 drops of conc. HCl for 5 h. The ethanol was evaporated, the residue was recrystallized from 50% ethanol and dried to give compound **3a** (193 mg) (Table 1).

4,6-Bis(hydroxy)-4,6-bis(trifluoromethyl)hexahydropyrimidine-2-thione (3b). Product **3b** (318 mg) was obtained as a colorless powder (Table 1) by method A from 1,3-diketone **1a** (416 mg, 2.0 mmol) and thiourea (152 mg, 2.0 mmol) after washing with dichloromethane.

4,6-Bis(hydroxy)-4-tetrafluoroethyl-6-trifluoromethylhexahydropyrimidin-2-one (3c). Product **3c** was obtained as a colorless powder (390 mg) (Table 1) by method A from 1,3-diketone **1b** (480 mg, 2.0 mmol) and urea (120 mg, 2.0 mmol) after washing the residue with chloroform and a small amount of water.

Product **3c** (216 mg) was obtained as a colorless powder by method B from tetraol **2b** (552 mg, 2.0 mmol) and urea (120 mg, 2.0 mmol) after washing with dichloromethane.

4,6-Bis(hydroxy)-4-tetrafluoroethyl-6-trifluoromethylhexahydropyrimidine-2-thione (3d). Product **3d** was obtained as a colorless powder (234 mg) (Table 1) by method B from tetraol **2b** (552 mg, 2.0 mmol) and thiourea (152 mg, 2.0 mmol).

2-Hydroxy-4,6-bis(trifluoromethyl)pyrimidine (4a). *p*-Toluenesulfonic acid (344 mg, 2.0 mmol) was added to a solution of hexahydropyrimidine **3a** (536 mg, 2.0 mmol) in toluene (15 ml). The mixture was boiled for 2 h with azeotropic removal of the water formed in the reaction. The toluene was evaporated to give product **4a** as colorless crystals (316 mg) (Table 1).

2-Mercapto-4,6-bis(trifluoromethyl)pyrimidine (4b) was prepared analogously from hexahydropyrimidine **3b** (568 mg, 2.0 mmol) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol): **4b** (308 mg), colorless crystals (Table 1).

2-Hydroxy-4-tetrafluoroethyl-6-trifluoromethylpyrimidine (4c) was prepared analogously from hexahydropyrimidine **3c** (600 mg, 2.0 mmol) and *p*-toluenesulfonic acid (344 mg, 2.0 mmol): **4c** (301 mg), colorless crystals (Table 1).

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