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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 85th anniversary

Alkylation of 6-Polyfluoroalkyl-2-thiouracils with Haloalkanes

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Abstract—The structure of 6-polyfluoroalkyl-2-thiouracils and reactivity of nucleophilic centers in their molecules were analyzed by quantum chemical calculations. According to the experimental data, methylation of 6-polyfluoroalkyl-2-thiouracils with methyl iodide initially gives 2-methylsulfanyl-substituted pyrimidin-4-one and then *S*,N^3- and *S*,*O*-dimethyl derivatives. The optimal conditions for the selective formation of the *S*,N^3- isomer were heating in *tert*-butyl alcohol in the presence of cesium carbonate as a base. Ethylation of 6-polyfluoroalkyl-2-thiouracils afforded approximately equal amounts of *S*,N^3- and *S*,*O*-dimethyl derivatives. *S*,N^3-Dimethyl-substituted pyrimidines in boiling ethanol in the presence of potassium carbonate were converted into uracil potassium salts as a result of nucleophilic substitution of the methylsulfanyl group by ethoxy and subsequent dealkylation of the latter.

Keywords: 6-polyfluoroalkyl-2-thiouracils, methylation, ethylation, quantum chemical calculations, nucleophilic substitution, dealkylation.

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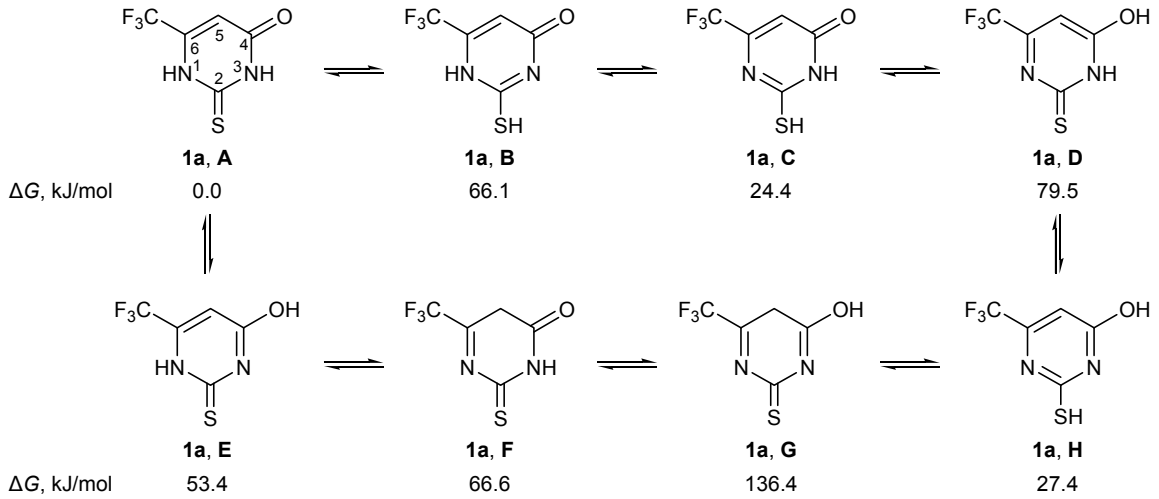
Pyrimidine ring is the key structural unit of many drugs such as barbiturates (phenobarbital, hexobarbital), sulfanylamides (sulfadimethoxine, sulfadiazine), antiviral agents (zidovudine, lamivudine), and metabolic stimulators (6-methyluracil, pentoxifylline). Modern antitumor agents include pyrimidine derivatives acting as nucleic acid exchange antimetabolites (uramustine, 5-fluorouracil) [1, 2]. Introduction of a polyfluoroalkyl group and a thioxo functionality into the pyrimidine ring also gives rise to a broad spectrum of biological activity. For example, 6-trifluoromethyl-2-thiouracil showed a high *in vitro* and *in vivo* antiparasitic activity against *Toxoplasma gondii* [3], and 6-heptafluoropropyl-2-thiouracil was recommended as an antithyroid agent [4]. 2-(4-Methoxybenzylsulfanyl)- and 2-[1-oxo-1-(piperidin-1-yl)ethylsulfanyl]-6-trifluoromethylpyrimidin-4-ones displayed a high inhibitory activity toward fatty acid-binding proteins, which may be efficient in the treatment of type II diabetes [5]. *N*-[4-(1*H*-Benzimidazol-2-yl)phenyl]-2-{[4-(hydroxy)-6-(trifluoromethyl)pyrimidin-2-yl]sulfonyl}-acetamide showed a high antifungal activity against *Candida albicans*, *Candida lunata*, *Aspergillus niger*, and *Aspergillus flavus* [6]. Ethyl 3-[4-hydroxy-6-(trifluoromethyl)pyrimidin-2-yl]sulfanyl}propanoate exhibited anti-inflammatory activity and selectively inhibited cyclooxygenase-1/2 and lipoxygenase *in vitro* [7]. 2-[(Naphthalen-2-ylmethyl)sulfanyl]-6-(trifluoromethyl)pyrimidin-4-amine inhibited HIV-1 reverse transcriptase [8].

The diversity of biological activity of 2-thiouracils and their S-substituted analogs prompted us to study the reactivity of nucleophilic centers in polyfluoroalkyl-substituted 2-thiouracils **1** by quantum chemical calculations, as well as experimentally, by carrying out their alkylation. It is known that organofluorine compounds are of particular interest from the viewpoint of design of new pharmaceuticals and materials due to electronegativity of fluorine atoms that could modify chemical, physical, and biological characteristics of newly formed fluorine-containing molecules [9].

Theoretically, 6-polyfluoroalkyl-2-thiouracils can exist as 8 different tautomers **A**–**H** due to acidity of the

Scheme 1.



two NH protons (Scheme 1). The thermodynamic stability of tautomers **A**–**H** was estimated by quantum chemical calculations using 6-trifluoromethyl-2-thiouracil **1** as model compound. The results showed that structure **A** is the most energetically favorable (the differences in the Gibbs energies calculated in the ideal gas approximation are given in Scheme 1).

The IR and NMR spectra of **1a** and **1b** and X-ray diffraction data for **1a** [10] also indicated that they exist in solution and in crystal as 2-thioxo-2,3-dihydropyrimidin-4(1*H*)-ones (structure **A** in Scheme 1). The IR spectra of both crystalline samples of **1a** and **1b** and their solutions in acetonitrile contained lactam carbonyl band at 1683–1689 and 1717–1719 cm^{-1}, respectively. The ^1H NMR spectra of **1a** and **1b** in DMSO-d_6 displayed a signal of 5-H at δ 6.37–6.41 ppm and downfield singlets typical of NH groups at δ 12.76–12.85 and 13.40–13.48 ppm. In the ^{13}C NMR spectrum of **1a** (DMSO-d_6), the C=S carbon atom resonated at δ_C 176.8 ppm, and the carbonyl carbon signal appeared at δ_C 159.9 ppm.

2-Thiouracils **1** possess five nucleophilic centers (N^1, N^3, S, O, C^5); therefore, their alkylation could lead to the formation of four regioisomeric monoalkyl derivatives and six dialkyl-substituted isomers. In order to evaluate the reactivity of these centers in the molecule of 6-trifluoromethyl-2-thiouracil (**1a**), we calculated their local reactivity indices for tautomer **A** in the ideal gas approximation (Table 1). It was found that the most nucleophilic in structure **A** is the sulfur atom, N^1 and N^3 atoms are less nucleophilic, and O and C^5 are weakly electrophilic.

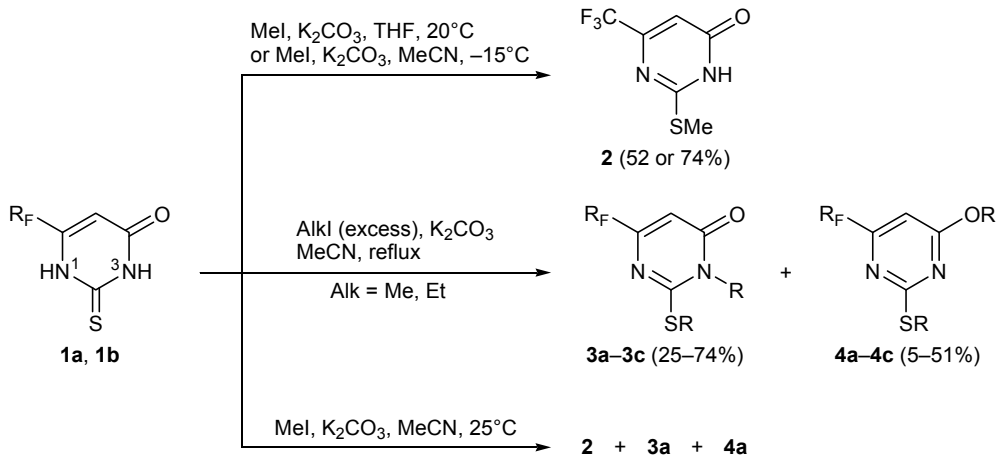
The reactivity of nucleophilic centers of 2-thiouracils **1** was studied experimentally by analyzing products of their alkylation with methyl iodide and ethyl iodide. According to published data, methylation of 6-trifluoromethyl-2-thiouracil (**1a**) with methyl iodide in THF in the presence of a base [11] and with dimethyl sulfate under alkaline conditions (NaOH, H_2O) [12] involves the sulfur atom to give 2-methylsulfanyl derivative **2**. In our experiments, thiouracil **1a** was alkylated with excess methyl iodide (3 equiv) in

Table 1. Fukui indices of the reaction centers of thiouracil **1a** (tautomer **A**)

Atom	q_{N+1}	q_N	q_{N-1}	f_{i+}	f_{i-}	Δf
C^5	–0.412	–0.305	–0.258	0.107	0.047	0.060
S	–0.382	–0.133	0.458	0.249	0.591	–0.342
O	–0.702	–0.563	–0.446	0.139	0.117	0.022
N^1	–0.576	–0.584	–0.543	–0.008	0.041	–0.049
N^3	–0.648	–0.618	–0.583	0.030	0.035	–0.005

[a] q_N, q_{N-1}, and q_{N+1} are the charges on an atom in the neutral molecule, radical cation, and radical anion, respectively; f_{i+} and f_{i-} are the Fukui indices for nucleophilic and electrophilic attack respectively; Δf are the Fukui dual descriptors: if $\Delta f > 0$, nucleophilic attack is preferred, and if $\Delta f < 0$, electrophilic attack is preferred.

Scheme 2.



1, $R_F = CF_3$ (**a**), C_3F_7 (**b**); **3**, **4**, R = Me (**a**, **b**), Et (**c**); $R_F = CF_3$ (**a**, **c**), C_3F_7 (**b**).

the presence of K_2CO_3 in THF at 20°C or in acetonitrile at –10 to –15°C to produce the same compound (Scheme 2). 2-Methylsulfanylpyrimidine **2** was also synthesized by us previously [13] by condensation of ethyl 4,4,4-trifluoro-3-oxobutanoate with *S*-methylisothiourea hydrogen sulfate in a potassium carbonate solution, and spectral characteristics of samples of **2** obtained by different methods were identical.

When the reaction of thiouracils **1a** and **1b** with 3 equiv of methyl iodide was carried out in acetonitrile in the presence of potassium carbonate, the products were mixtures of isomeric dimethyl derivatives **3a**, **3b** (68–74%) and **4a**, **4b** (5–9%) (Scheme 2). With the goal of finding conditions for the selective formation of one of the isomers, different solvents and bases were tried. The product mixtures were analyzed by GC/MS. The best results with the highest overall yields are summarized in Table 2.

The highest substrate conversion (99%) was achieved in the reactions of **1a** and **1b** with methyl iodide in acetone or acetonitrile in the presence of K_2CO_3 or Cs_2CO_3, and in all cases isomers **3** were the major products. The ratio **3**:**4** changed insignificantly, from 3.6:1 to 4.6:1 for compounds **3a** and **4a** and from 5.4:1 to 5.8:1 for **3b** and **4b**. In the presence of Na_2CO_3 as a base, the conversion and reaction rate were lower, but the ratio **3a**:**4a** increased (6.2:1 to 6.8:1). The reactions in alcohols were more selective; however, the overall yield decreased and depended on the alcohol nature. In the reactions in ethanol, the overall yield almost did not depend on the metal carbonate (40–46%), whereas in *tert*-butyl alcohol the overall yield considerably increased (from 3 to 85%) as the metal cation radius increased. The best result was obtained in the system *t*-BuOH/Cs_2CO_3 which ensured a **3a**:**4a** ratio of 40.5:1 and an overall yield of 85% (Table 2). These conditions can be regarded as optimal for the selective formation of isomer **3a**.

Thus, we have shown that the alkylation of thiouracil **1a** with excess methyl iodide in acetonitrile in the presence of K_2CO_3 at –10 to –15°C gives 2-methylsulfanyl derivative **2** and that in boiling acetonitrile, a mixture of dimethyl-substituted pyrimidines **3a** and **4a** is formed (Scheme 2). The methylation of **1a** was also carried out in MeCN/K_2CO_3 at 25°C. After 3 h, the reaction mixture contained compounds **2**, **3a**, and **4a** at a ratio of 24:65:11 (according to the GLC data). The results obtained at room temperature provide an experimental proof of the following reaction mechanism: initially formed thiouracil potassium salt **I** is methylated first at the most nucleophilic sulfur atom, and further methylation involves the N^3 and 4-O competitive centers with predominant formation of N^3-methyl isomer **3a** (Scheme 3).

We have found no published data on ethylation of 6-trifluoromethyl-2-thiouracil (**1a**), though it was proposed previously to synthesize 2-ethylsulfanyl-6-trifluoromethylpyrimidin-4-one by cyclization of ethyl 4,4,4-trifluoro-3-oxobutanoate with *S*-ethylisothiourea [14]. The ethylation of thiouracil **1a** with ethyl iodide was carried out under different conditions, and the reaction mixtures were analyzed by GC/MS. The results with the maximum overall yield are given in Table 3. The alkylation of **1a** with ethyl iodide led to the formation of comparable amounts of isomers **3c** and **4c**. In the reactions in acetone and acetonitrile in the presence of Na_2CO_3 isomer **3c** slightly prevailed, and the ratio **3c**/**4c** was 1.1:1 to 1.4:1, whereas in the

Table 2. Methylation of thiouracils **1a** and **1b** with methyl iodide (GLC data)

Thiouracil no.	Solvent/base	Temperature,[a] °C	Reaction time, h	Product ratio **3**/**4**	Overall yield (**3**+**4**), %
1a	Me_2CO/Na_2CO_3	56	4	6.8:1	88
1a	Me_2CO/K_2CO_3	56	2	4.6:1	99
1a	Me_2CO/Cs_2CO_3	56	4	3.7:1	99
1a	$MeCN/Na_2CO_3$	82	6	6.2:1	78
1a	$MeCN/K_2CO_3$	82	1	4.1:1	99
1a	$MeCN/Cs_2CO_3$	82	2	3.6:1	99
1a	THF/K_2CO_3	66	6	17:1	86
1a	$EtOH/Na_2CO_3$	78	5	16.5:1	40
1a	$EtOH/K_2CO_3$	78	5	12.5:1	43
1a	$EtOH/Cs_2CO_3$	78	5	14.9:1	46
1a	*t*-$BuOH/Na_2CO_3$	83	3	1:0	3
1a	*t*-$BuOH/K_2CO_3$	83	5	49.7:1	38
1a	***t*-BuOH/Cs_2CO_3**	**83**	**7**	**40.5**:**1**	**85**
1a	*t*-BuOH/NaOH	83	5	3.2:1	5
1a	1,4-Dioxane/K_2CO_3	101	1	No reaction	
1b	Me_2CO/K_2CO_3	56	1	5.8:1	99
1b	$MeCN/K_2CO_3$	82	1	5.4:1	99
1b	$EtOH/K_2CO_3$	78	2	15.4:1	40

[a] Boiling point of the solvent is given.

presence of K_2CO_3 and Cs_2CO_3 the isomer ratio changed to the opposite, **3c**/**4c** 1:1.3 to 1:1.9. The overall yield **3c** and **4c** in alcohols decreased to 35–41%, though the reaction was more selective in favor of isomer **3c** (**3c**/**4c** 4.2:1 to 21.4:1; Table 3).

It was convenient to determine the structure of regioisomeric dialkyl derivatives **3a**–**3c** and **4a**–**4c** by IR spectroscopy since the IR spectra of *S*,*O*-dimethyl isomers **4a**–**4c** lacked lactam carbonyl band which appeared in the spectra of *S*,*N*-dimethyl derivatives **3a**–**3c** at 1696–1699 cm^{-1}. In the ^1H NMR spectra of **3a**, **3b**, **4a**, and **4b** in $CDCl_3$, protons of the methylsulfanyl group resonated at δ 2.56–2.63 ppm, whereas the MeN signal of **3a** and **3b** was located at δ 3.54–3.55 ppm, and the MeO signal of **4a** and **4b**, at δ 4.03 ppm.

The ^1H NMR spectra of *S*,*N*- and *S*,*O*-diethyl derivatives **3c** and **4c** in $CDCl_3$ displayed an insignificant difference in the chemical shifts of the methylene protons of the EtS substituent (δ 3.15 and 3.23 ppm), as well as of the EtN and EtO groups (δ 4.11 and 4.47 ppm, respectively). The SCH_2 and NCH_2 carbons resonated in the ^{13}C NMR spectrum of **3c** at δ_C 26.91 and 40.12 ppm, respectively, and the SCH_2 and OCH_2

Scheme 3.

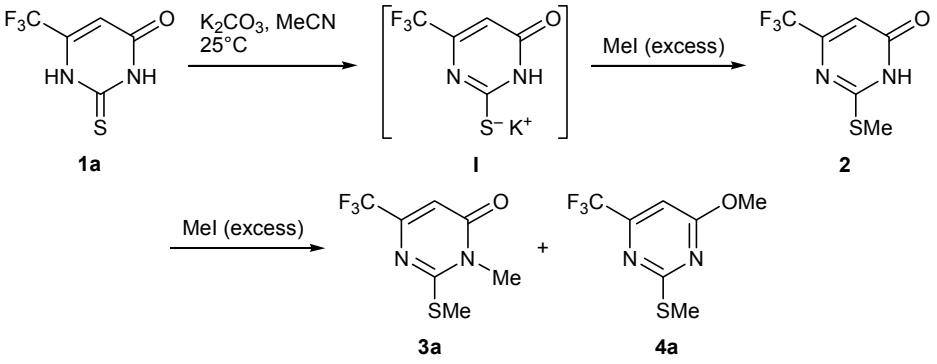


Table 3. Ethylation of thiouracil **1a** with ethyl iodide (GLC data)

Solvent/base	Temperature,[a] °C	Reaction time, h	Product ratio **3c**:**4c**	Overall yield (**3c**+**4c**), %
Me_2CO/Na_2CO_3	56	5	1.4:1	68
Me_2CO/K_2CO_3	56	4	1:1.3	82
Me_2CO/Cs_2CO_3	56	3	1:1.6	94
$MeCN/Na_2CO_3$	82	6	1.1:1	40
$MeCN/K_2CO_3$	82	3	1:1.9	91
$MeCN/Cs_2CO_3$	82	1	1:1.3	92
$EtOH/Na_2CO_3$	78	1	17.9:1	40
$EtOH/K_2CO_3$	78	3	21.4:1	41
$EtOH/Cs_2CO_3$	78	3	4.2:1	35
t-$BuOH/Cs_2CO_3$	83	3	5:1	36

[a] Boiling point of the solvent is given.

signals of **4c** were observed at δ_C 25.42 and 63.42 ppm, respectively; i.e., in the regions typical of the corresponding fragments.

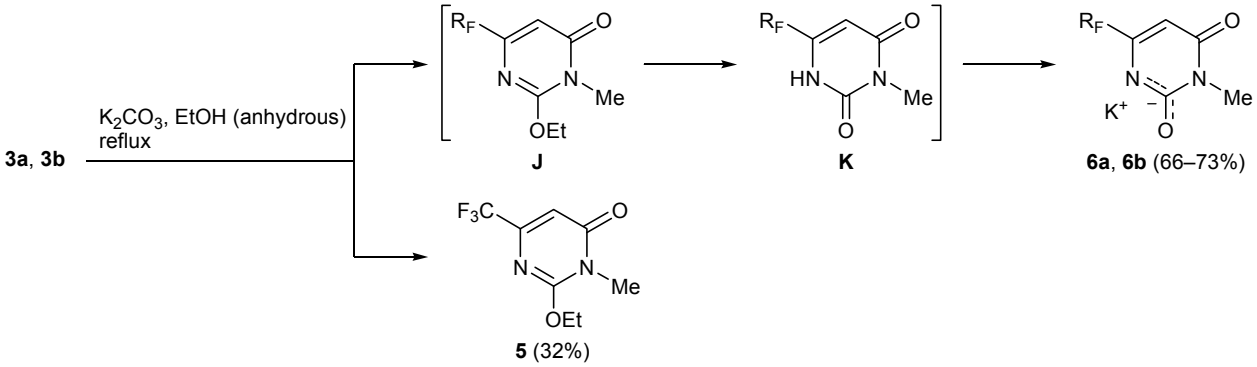
In the ^{19}F NMR spectra of **3a** and **3c** we observed neither splitting of the CF_3 signal nor its shift (δ_F 89.91, 89.80 ppm; $CDCl_3$) relative to the corresponding signal of 2-(methylsulfanyl)-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (δ_F 89.88 ppm; $CDCl_3$) [13], which would be expected if the CF_3 group were located closely to alkyl substituent on N^1. This means that the alkyl group is attached to N^3.

It should be noted that *S*,*O*-dimethylpyrimidine **4a** was synthesized previously [15] by a different method from 4-chloro-2-(methylsulfanyl)-6-(trifluoromethyl)-pyrimidine, but the product was characterized only by elemental analysis and melting point. According to Bhabak and Mugesh [16], methylation of 6-methyl-2-thiouracil with methyl iodide in acetone in the presence of potassium hydroxide gave two isomeric *S*,N^1- and *S*,N^3-dimethyl derivatives, though Erkin and Krutikov [17] earlier reported the formation of only one *S*,N^3-dimethyl isomer in this reaction. The *S*,*O*-dimethyl isomer was synthesized by Senda and Suzui [18] by methoxylation of 4-chloro-6-methyl-2-(methylsulfanyl)pyrimidine.

We have found that the low overall yield of compounds **3b** and **4b** (40%, Table 1) in the alkylation of thiouracil **1b** with methyl iodide in ethanol in the presence of K_2CO_3 is related to further transformations of *S*,N^3-isomer **3b**. After 2 h, GC/MS analysis of the reaction mixture revealed a ion peak with *m*/*z* 322 corresponding to the molecular ion $[M]^+$ of 2-ethoxypyrimidinone **J** ($R_F = C_3F_7$), and 6-(heptafluoropropyl)-3-methyluracil **K** ($R_F = C_3F_7$, *m*/*z* 294 $[M]^+$) was detected in the reaction mixture after 4 h (Scheme 4).

By specially heating compounds **3a** and **3b** in anhydrous ethanol in the presence of potassium carbonate we obtained uracil potassium salts **6a** and **6b**, and in the reaction with **3a** we succeeded in isolating intermediate product, 2-ethoxy-3-methyl-6-(trifluoromethyl)-

Scheme 4.



3, **6**, $R_F = CF_3$ (**a**), C_3F_7 (**b**).

pyrimidin-4-one (**5**) (Scheme 4). The ^{1}H NMR spectrum of **5** showed a singlet at δ 3.44 ppm due to the NMe group and a triplet and a quartet at δ 1.45 and 4.54 ppm, respectively, typical of ethoxy group.

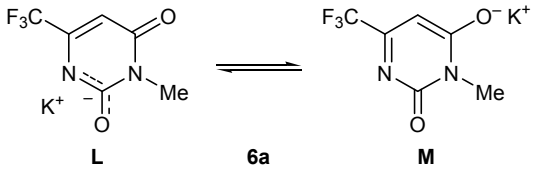
Acid-catalyzed hydrolysis of methylsulfanylpyrimidines is widely used to obtain uracils [19, 20]. However, we believe that in the above reactions uracils **6a** and **6b** are formed along a different path. Presumably, the first stage is nucleophilic substitution of the MeS group by the solvent to give intermediate 2-ethoxypyrimidinone **J** (compound **5** was isolated in the reaction with **3a**; Scheme 4). Nucleofugality of methylsulfanyl group is well known. For example, we previously showed [13] the possibility of substitution of the 2-MeS group in 6-(polyfluoroalkyl)pyrimidin-4-ones by a hydrazine or morpholine fragment. Replacement of the 2-MeS group in pyrido[3,4-*d*]pyrimidin-4-one by ethoxy on heating in ethanolic sodium ethoxide under microwave irradiation was described in [21].

The next stage is likely to be dealkylation of the ethoxy group in intermediate **J** by the action of ethanol as nucleophile on the α- or β-carbon atom of the ethyl group according to the S_N2 or E2 mechanism to form intermediate uracil **K** which we failed to isolate because of its rapid transformation to potassium salt **6** (Scheme 4). The possibility of dealkylation according to the proposed scheme was described previously by Dean and Papadopoulos [22] for 3-benzyl-2-ethoxyquinazolin-4-one on heating with benzylamine to 150°C or with morpholine to 100°C. The authors believed that the attack of nucleophiles, benzylamine and morpholine, is directed at the α- or β-carbon atom of the ethyl group rather than at C^2 to give 3-benzylquinazoline-2,4-dione due to steric hindrances in 3-benzyl-2-ethoxyquinazolin-4-one.

Salts **6a** and **6b** were characterized by IR and NMR spectra and elemental analyses. Their IR spectra contained a lactam carbonyl band at 1654–1668 cm^{-1}, which is shifted to lower frequencies relative to the C=O band of **3a** and **3b**. In the ^{1}H NMR spectra of **6a** and **6b** in DMSO-d_6 we observed a singlet of the NMe group at δ 3.06 ppm and a singlet of 5-H at δ 5.47 ppm. The ^{13}C NMR spectrum of **6b** showed a signal at δ_C 26.54 ppm, which is typical of NMe carbon atom.

Potassium salts **6a** and **6b** could have different structures, depending on localization of the negative charge. It was disfficult to unambiguously determine their structure on the basis of spectral data. According to quantum chemical calculations, the negative charge in the anion of **6a** is strongly delocalized (Fig. 1). Analysis of the electron density distribution suggests two most probable positions of potassium ion: between the O^2 and N^3 atoms (structure **L**) or at the O^6 atom (structure **M**). Structure **L** is more thermodynamically stable (Scheme 5).

Scheme 5.



L **6a** **M**

Δ*G*, kJ/mol 0.0 23.2

Thus, the results of quantum chemical calculations and experimental data showed that 6-polyfluoroalkyl-2-thiouracils exist as 6-(polyfluoroalkyl)-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one tautomers. Our results and published data [6–8, 11, 12] indicated that polyfluoroalkyl-substituted thiouracils are alkylated first at the most nucleophilic sulfur atom. However, we found that in basic medium (especially on heating) further alkylation of the *S*-alkyl derivatives involves the N^3 and O atoms and that methylation gives preferentially *S*,N^3-dimethyl isomers, whereas ethylation leads to the formation of approximately equal amounts of *S*,N^3- and *S*,*O*-diethyl derivatives. The observed difference in the alkylation directions may be related to steric hindrances created by bulkier ethyl group on the sulfur atom to attack of the alkylating agent on the neighboring nitrogen atom. Furthermore, the methylsulfanyl group in *S*,N^3-dimethylpyrimidines is substituted by ethoxy on heating in ethanol under basic conditions, followed by dealkylation of the ethoxy fragment to afford uracil potassium salts.

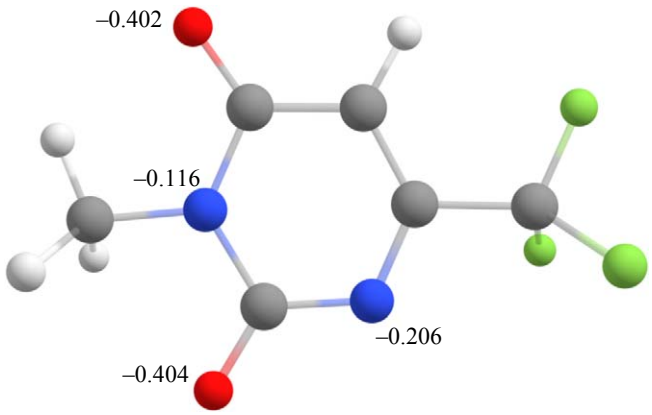


Fig. 1. Negative charge distribution in the anion of uracil potassium salt **6a**.

EXPERIMENTAL

The NMR spectra were recorded on Bruker DRX-400 (400 MHz for ^{1}H and 376 MHz for ^{19}F) and Bruker Avance 500 spectrometers (500 MHz for ^{1}H, 470 MHz for ^{19}F, and 126 MHz for ^{13}C); the chemical shifts were measured relative to tetramethylsilane (^{1}H), hexafluorobenzene (^{19}F) or the solvent signal (^{13}C; $CDCl_3$, DMSO-d_6). The IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer in the range 4000–400 cm^{-1} using a diffuse reflectance accessory, as well as on a Thermo Electron Corporation Nicolet 6700 spectrometer with Fourier transform equipped with an ATR accessory. The elemental analyses (C, H, N) were obtained with a Perkin Elmer 2400 Series II analyzer. The melting points were measured in open capillaries on a Stuart SMP30 melting point apparatus. Silicagel 60 (0.063–0.02 mm, Merck) was used for column chromatography.

The reaction mixtures were analyzed by GLC on a Shimadzu GC 2010Plus gas chromatograph equipped with a flame ionization detector and a ZB-5 capillary column (30 m×0.25 mm, film thickness 0.25 μm); oven temperature programming from 40°C (3 min) to 280°C at a rate of 10 deg/min, followed by 30 min at the final temperature; injector temperature 250°C, detector temperature 300°C; carrier gas nitrogen, split ratio 1:30, flow rate 1.0 mL/min. The mass spectra were recorded with a Trace GC Ultra DSQ II gas chromatograph coupled with a quadrupole MS detector (Thermo TR-5MS capillary column, 30 m×0.25 mm, film thickness 0.25 μm; oven temperature programming from 40°C (3 min) to 280°C at a rate of 10 deg×min^{-1}, followed by 40 min at the final temperature; injector temperature 250°C, interface temperature 230°C, ion source temperature 200°C; carrier gas helium, split ratio 1:50, flow rate 1.0 mL/min; electron impact, 70 eV, a.m.u. range 20–1000).

Quantum chemical calculations. The calculations (geometry optimization and solution of vibrational problem) were carried out using GAUSSIAN 09 software package [23] with the TPSS functional [24] and 6-311+G(*d*,*p*) basis set [25]. The thermodynamic parameters of different tautomers of **1a** were determined, and NBO analysis of the reaction centers therein was performed, for the isolated molecule. Potassium salts **6a** and **6b** were calculated with account taken of solvent effects (according to the PCM model [26]; temperature 298.15 K; pressure 1 atm; solvent ethanol).

The Fukui function [26] for a reaction center can be represented as $f_A^+ = q_N^A + q_{N+1}^A$ for nucleophilic attack and $f_A^- = q_{N-1}^A - q_N^A$ for electrophilic attack, where q_N^A, q_{N+1}^A, and q_{N-1}^A are the charges on an atom in the neutral molecule, radical anion, and radical cation, respectively.

The Fukui dual descriptor is calculated as follows:

$$\Delta f_A = f_A^+ - f_A^- = (q_N^A - q_{N+1}^A) - (q_{N-1}^A - q_N^A) = 2q_N^A - q_{N+1}^A - q_{N-1}^A.$$

2-Sulfanylidene-6-(trifluoromethyl)-2,3-dihydropyrimidin-4(1*H*)-one (1a) was synthesized as described in [10]. Neither IR nor NMR spectra of **1a** were given in previous publications [10, 27]. IR spectrum (DR), ν, cm^{-1}: 3128, 3064, 2968, 2895 (NH, CH), 1689 (C=O), 1655, 1582 (C=N, C=C, δNH), 1090–1210 (C–F). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.41 d (1H, 5-H, J = 1.4 Hz), 12.85 s (1H, NH), 13.48 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 105.17 q (C^5, J = 3.8 Hz), 118.85 q (CF_3, J = 275 Hz), 140.57 q (C^6, J = 36 Hz), 159.86 (C^4), 176.85 (C^2). ^{19}F NMR spectrum (DMSO-d_6): δ_F 94.47 ppm (CF_3). Mass spectrum, m/z (I_{rel}, %): 196 (83) $[M]^{+\cdot}$, 177 (3) $[M - F]^+$, 163 (4) $[M - HS]^+$, 149 (4) $[M - CH_2SH]^+$, 138 (29) $[M - NCS]^+$, 69 (13) $[CF_3]^+$, 68 (100) $[C_2H_2NCO]^+$, 45 (3) $[CHS]^+$.

6-(Heptafluoropropyl)-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one (1b). A mixture of ethyl 4,4,5,5,6,6,6-heptafluoro-3-oxohexanoate (4.262 g, 15 mmol), thiourea (1.52 g, 20 mmol), and 2 M ethanolic sodium ethoxide (15 mL) was refluxed for 20 h. The solvent was removed under reduced pressure, the residue was dissolved in distilled water, and the solution was acidified with glacial acetic acid and left overnight. The precipitate was filtered off, washed with water, and recrystallized from acetic acid. Yield 2.088 g (47%), white powder, mp 229–231°C. IR spectrum (ATR), ν, cm^{-1}: 3128, 3072, 2952, 2883 (NH, CH), 1683 (C=O), 1122–1233 (C–F). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.37 s (1H, 5-H), 12.76 s (1H, NH), 13.40 br.s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 37.15 m (2F, CF_2), 46.92 m (2F, CF_2), 82.97 t (3F, CF_3, J = 9.3 Hz). Mass spectrum, m/z (I_{rel}, %): 296 (41) $[M]^{+\cdot}$, 263 (2) $[M - HS]^+$ (2), 249 (2) $[M - CH_2SH]^+$, 238 (22) $[M - NCS]^+$, 69 (16) $[CF_3]^+$, 68 (100) $[C_2H_2NCO]^+$, 45 (4) $[CHS]^+$. Found, %: C 28.56; H 1.12; N 9.39. $C_7H_3F_7N_2OS$. Calculated, %: C 28.39; H 1.02; N 9.46.

Alkylation of thiouracils 1a and 1b (*general procedures*). *a*. A mixture of thiouracil **1a** (200 mg,

1 mmol), methyl iodide (426 mg, 3 mmol), and potassium carbonate (276 mg, 2 mmol) in THF (15 mL) was stirred for 40 min at 20°C. The precipitate was filtered off, excess methyl iodide and the solvent were distilled off from the filtrate under reduced pressure, and the product (compound **2**) was isolated from the residue by column chromatography using chloroform–ethyl acetate (1 : 1) as eluent.

b. A mixture of thiouracil **1a** (200 mg, 1 mmol), methyl iodide (426 mg, 3 mmol), and potassium carbonate (276 mg, 2 mmol) in acetonitrile (15 mL) was stirred for 3 h at –10 to –15°C. The precipitate was filtered off, excess methyl iodide and the solvent were distilled off from the filtrate under reduced pressure, and the product (compound **2**) was isolated from the residue by column chromatography using chloroform–ethyl acetate (1 : 1) as eluent.

c. A mixture of thiouracil **1a** or **1b** (1 mmol), methyl or ethyl iodide (3 mmol), and potassium carbonate (276 mg, 2 mmol) in acetonitrile (15 mL) was refluxed for 1–3 h. The precipitate was filtered off, and the filtrate was concentrated. The products were isolated by column chromatography using hexane–ethyl acetate at a ratio of 4 : 1 as eluent for compounds **3a**, **3c**, **4a**, and **4c** or at a ratio of 6 : 1 for **3b** and **4b**.

2-(Methylsulfanyl)-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (2). Yield 109 mg (52%) (*a*), 155 mg (74%) (*b*); white powder, mp 178–180°C [13]. Mass spectrum, *m*/*z* (I_{rel}, %): 210 (100) $[M]^{+\cdot}$, 190 (16) $[M - HF]^+$, 177 (2) $[M - HS]^+$, 163 (40) $[M - CH_3S]^+$, 138 (14) $[M - NCS,CH_2]^+$, 69 (9) $[CF_3]^+$, 68 (16) $[C_2H_2NCO]^+$, 46 (9) $[CH_2S]^+$.

3-Methyl-2-(methylsulfanyl)-6-(trifluoromethyl)-pyrimidine-4(3*H*)-one (3a). Yield 152 mg (68%) (*c*), white powder, mp 83–85°C. IR spectrum (DR), ν, cm^{-1}: 3065, 2937 (CH), 1696 (C=O), 1519 (C=N, C=C), 1136–1173 (C–F). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.63 s (3H, SCH_3), 3.54 s (3H, NCH_3), 6.55 s (1H, 5-H). ^{19}F NMR spectrum ($CDCl_3$): δ_F 89.91 ppm, s (CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 224 (40) $[M]^{+\cdot}$, 209 (6) $[M - CH_3]^+$, 205 (7) $[M - F]^+$, 196 (1) $[M - CO]^+$, 191 (3) $[M - HS]^+$, 179 (100) $[M - CHS]^+$, 138 (3) $[M - NCS - C_2H_4]^+$, 69 (12) $[CF_3]^+$, 68 (4) $[C_2H_2NCO]^+$, 45 (11) $[CHS]^+$. Found, %: C 37.66; H 3.13; N 12.35. $C_7H_7F_3N_2OS$. Calculated, %: C 37.50; H 3.15; N 12.49.

6-(Heptafluoropropyl)-3-methyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one (3b). Yield 240 mg (74%) (*c*), white powder, mp 29–30°C. IR spectrum (ATR), ν, cm^{-1}: 3085, 2939 (CH), 1699 (S=O), 1516 (C=N, C=C), 1100–1227 (C–F). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.60 s (3H, SCH_3), 3.55 s (3H, NCH_3), 6.59 s (1H, 5-H). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 35.50 m (2F, CF_2), 43.92 m (2F, CF_2), 81.42 t (3F, CF_3, J = 9.2 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 324 (30) $[M]^{+\cdot}$, 309 (4) $[M - CH_3]^+$, 305 (<1) $[M - F]^+$, 295 (1) $[M - HCO]^+$, 291 (2) $[M - HS]^+$, 279 (100) $[M - CHS]^+$, 238 (5) $[M - NCS - C_2H_4]^+$, 69 (29) $[CF_3]^+$, 68 (15) $[C_2H_2NCO]^+$, 45 (17) $[CHS]^+$. Found, %: C 33.61; H 2.19; N 8.45. $C_9H_7F_7N_2OS$. Calculated, %: C 33.34; H 2.18; N 8.64.

3-Ethyl-2-(ethylsulfanyl)-6-(trifluoromethyl)-pyrimidin-4(3*H*)-one (3c). Yield 63 mg (25%) (*c*), colorless oil, mp 21–22°C. IR spectrum (neat), ν, cm^{-1}: 2981, 2937 (CH), 1698 (C=O), 1505 (C=N, C=C), 1070–1183 (C–F). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (3H, $SCH_2C\mathbf{H}_3$, J = 7.3 Hz), 1.41 t (3H, $NCH_2C\mathbf{H}_3$, J = 7.3 Hz), 3.23 q (2H, SCH_2, J = 7.3 Hz), 4.11 q (2H, NCH_2, J = 7.3 Hz), 6.52 s (1H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.13 (CH_3), 13.60 (CH_3), 26.91 (SCH_2), 40.12 (NCH_2), 107.31 q (C^5, J = 3.5 Hz), 120.34 q (CF_3, J = 274.7 Hz), 150.44 q (C^6, J = 35.5 Hz), 161.13 (C^4), 164.70 (C^2). ^{19}F NMR spectrum ($CDCl_3$): δ_F 89.80 ppm, s (CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 252 (23) $[M]^{+\cdot}$, 233 (8) $[M - F]^+$, 224 (25) $[M - CO]^+$, 223 (79) $[M - C_2H_5]^+$, 219 (15) $[M - HS]^+$, 191 (40) $[M - C_2H_5S]^+$, 163 (100) $[C_5H_2F_3N_2O]^+$, 138 (21) $[M - NCS - C_4H_8]^+$, 69 (17) $[CF_3]^+$, 68 (31) $[C_2H_2NCO]^+$, 45 (12) $[CHS]^+$. Found, %: C 43.06; H 4.33; N 11.17. $C_9H_{11}F_3N_2OS$. Calculated, %: C 42.85; H 4.40; N 11.11.

4-Methoxy-2-(methylsulfanyl)-6-(trifluoromethyl)pyrimidine (4a). Yield 20 mg (9%) (*c*), colorless oil; published data [15]: mp 36–37°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.58 s (3H, SCH_3), 4.03 s (3H, OCH_3), 6.69 s (1H, 5-H). ^{19}F NMR spectrum ($CDCl_3$): δ_F 91.17 ppm, s (CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 224 (100) $[M]^{+\cdot}$, 209 (59) $[M - CH_3]^+$, 205 (9) $[M - F]^+$, 191 (<1) $[M - HS]^+$, 178 (32) $[M - CH_2S]^+$, 138 (11) $[M - NCS - C_2H_4]^+$, 109 (18) $[M - CH_3O - CH_3 - CF_3]^+$, 69 (12) $[CF_3]^+$, 68 (9) $[C_2H_2NCO]^+$, 45 (11) $[CHS]^+$.

4-(Heptafluoropropyl)-6-methoxy-2-(methylsulfanyl)pyrimidine (4b). Yield 16 mg (5%) (*c*), colorless oil. IR spectrum (ATR), ν, cm^{-1}: 1586, 1558 (C=N, C=C), 1123–1227 (C–F). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.56 s (3H, SCH_3), 4.03 s (3H, OCH_3), 6.72 s (1H, 5-H). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 36.22 m (2F, CF_2), 45.51 m (2F, CF_2), 82.35 t

(3F, CF_3, J = 9.3 Hz). Mass spectrum, m/z (I_{rel}, %): 324 (100) $[M]^{+\cdot}$, 309 (54) $[M - CH_3]^+$, 305 (11) $[M - F]^+$, 291 (<1) $[M - HS]^+$, 278 (33) $[M - CH_2S]^+$, 238 (18) $[M - NCS - C_2H_4]^+$, 69 (33) $[CF_3]^+$, 68 (24) $[C_2H_2NCO]^+$, 45 (17) [CHS]. Found, %: C 33.49; H 2.09; N 8.60. $C_9H_7F_7N_2OS$. Calculated, %: C 33.34; H 2.18; N 8.64.

4-Ethoxy-2-(ethylsulfanyl)-6-(trifluoromethyl)-pyrimidine (4c). Yield 129 mg (51%) (*c*), colorless oil. IR spectrum (ATR), ν, cm^{-1}: 2985, 2934 (CH), 1590, 1558 (C=N, C=C), 1101–1185 (C–F). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.41 t (6H, CH_2CH_3, J = 7.2 Hz), 3.15 q (2H, SCH_2, J = 7.2 Hz), 4.47 q (2H, OCH_2, J = 7.2 Hz), 6.66 s (1H, 5-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.04 (CH_3), 14.23 (CH_3), 25.42 (SCH_2), 63.42 (OCH_2), 100.41 q (C^5, J = 3.1 Hz), 120.33 q (CF_3, J = 274.7 Hz), 155.91 q (C^6, J = 35.5 Hz), 169.47 (C^4), 173.56 (C^2). ^{19}F NMR spectrum ($CDCl_3$): δ_F 91.15 ppm, s (CF_3). Mass spectrum, m/z (I_{rel}, %): 252 (98) $[M]^{+\cdot}$, 233 (10) $[M - F]^+$, 223 (68) $[M - C_2H_5]^+$, 219 (23) $[M - HS]^+$, 191 (100) $[M - C_2H_5S]^+$, 138 (83) $[M - NCS - C_4H_8]^+$, 109 (21) $[M - C_2H_5O - C_2H_5 - CF_3]^+$, 69 (16) $[CF_3]^+$, 68 (40) $[C_2H_2NCO]^+$, 45 (16) $[CHS]^+$. Found, %: C 42.62; H 4.49; N 11.01. $C_9H_{11}F_3N_2OS$. Calculated, %: C 42.85; H 4.40; N 11.11.

2-Ethoxy-3-methyl-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (5). A mixture of compound **3a** (1 mmol) and potassium carbonate (414 mg, 3 mmol) in anhydrous ethanol (15 mL) was refluxed for 3 h. The precipitate was filtered off, the filtrate was concentrated, and the product was isolated by column chromatography using hexane–ethyl acetate (4:1) as eluent. Yield 71 mg (32%), colorless oil. IR spectrum (DR), ν, cm^{-1}: 3068, 2996 (CH), 1697 (C=O), 1556, 1507 (C=N, C=C), 1071–1163 (C–F). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 t (3H, CH_2CH_3, J = 7.1 Hz), 3.44 s (3H, NCH_3), 4.54 q (2H, OCH_2, J = 7.1 Hz), 6.48 s (1H, 5-H). ^{19}F NMR spectrum ($CDCl_3$): δ_F 89.72 ppm, s (CF_3). Mass spectrum, m/z (I_{rel}, %): 222 (30) $[M]^{+\cdot}$, 207 (10 $[M - CH_3]^+$, 203 (8) $[M - F]^+$, 194 (100) $[M - C_2H_4]^{+\cdot}$, 178 (23) $[M - OC_2H_4]^+$, 166 (19) $[M - COC_2H_4]^+$, 137 (59) $[M - COC_2H_4 - NCH_3]^+$, 108 (13) $[M - OC_2H_5 - CF_3,]^+$, 69 (9) $[CF_3]^+$, 68 (41) $[C_2H_2NCO]^+$. Found, %: C 42.97; H 4.03; N 12.44. $C_8H_9F_3N_2O_2$. Calculated, %: C 43.25; H 4.08; N 12.61.

Uracil potassium salts 6a and 6b (*general procedure*). A mixture of compound **3a** or **3b** (1 mmol) and potassium carbonate (414 mg, 3 mmol) in ethanol (15 mL) was refluxed for 3 h. The precipitate was filtered off, the filtrate was concentrated, and the residue was recrystallized from acetonitrile (**6a**) or ethanol–chloroform (1:2, **6b**).

Potassium 1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-2-olate (6a). Yield 153 mg (66%), white powder, mp 364–365°C (decomp.). IR spectrum (DR), ν, cm^{-1}: 3152, 3097 (CH), 1668 (C=O), 1643, 1624, 1600, 1568 (C=N, C=C), 1107–1207 (C–F). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.06 s (3H, NCH_3), 5.47 s (1H, 5-H). ^{19}F NMR spectrum (DMSO-d_6): δ_F 92.37 ppm, s (CF_3). Found, %: C 30.89; H 1.75; N 12.01. $C_6H_4F_3KN_2O_2$. Calculated, %: C 31.04; H 1.74; N 12.06.

Potassium 4-(heptafluoropropyl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-olate (6b). Yield 242 mg (73%), white powder, mp 372–374°C (decomp.). IR spectrum (DR), ν, cm^{-1}: 3089, 2952 (CH), 1654 (C=O), 1590, 1567 (C=N, C=C), 1116–1232 (C–F). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.06 s (3H, NCH_3), 5.47 s (1H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 26.54 (NCH_3), 92.94 t (C^5, J = 4.6 Hz), 108.67 t.sext (CF_2, J = 266, 37 Hz), 112.56 t.t (CF_2, J = 255.1, 28.9 Hz), 117.62 (CF_3, J = 287.5, 34.3 Hz), 153.08 t (C^4, J = 23.5 Hz), 158.88 (C^2), 165.30 (C^6). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 36.77 m (2F, CF_2), 46.02 m (2F, CF_2), 82.64 t (3F, CF_3, J = 9 Hz). Found, %: C 28.72; H 1.43; N 8.22. $C_8H_4F_7KN_2O_2$. Calculated, %: C 28.92; H 1.21; N 8.43.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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