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Dedicated to the memory of
Professor Mircea D. Banciu (1941–2005)

SYNTHESIS OF NEW CF_3-CONTAINING PYRIDAZINONE AND LACTAM DERIVATIVES

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The paper presents the convertion of the bifunctional intermediate γ-keto-thioester (**6**), into new of pyridazin-3-ones (**8**) and lactam (**9**), by reaction with hydrazine derivatives. The structures of all new compounds were ascribed using 1D (^{19}F, ^{1}H, ^{13}C) NMR data that confirmed their structure.
The possible reaction mechanisms for the synthesis of pyridazinones (**8**) and lactam (**9**) are presented.

INTRODUCTION

Because fluorine is the most electronegative element and the van der Waals radius of fluorine is close to that of hydrogen, the introduction of a fluorine-containing group into an organic molecule brings about some remarkable changes in its physical and chemical properties.[1] Many new fluorinated materials that take advantage of these useful changes, *e.g.*, drugs and agrochemicals, have been designed [2] and synthesized.[3]

Continuing our efforts directed toward synthesis of new fluorine-containing organic compounds[4-6], in the present paper we report the conversion of the γ-keto-thioester (**6**) into pyridazinones (**8**) and lactam (**9**).

RESULTS AND DISCUSSION

1,1-Bis(ethylsulfanyl)perfluorobut-1-ene **4** was prepared in a two-step procedure from ethyl heptafluorobutyrate according with literature data[7]. In the first experiment, perfluoroester **1** reacts with lithium aluminium hydride yielding heptafluorobutanal hydrate **2** or -hemiacetal that in the second step reacts with ethanethiol in the presence of a Lewis acid (BF_3:OEt_2 or $TiCl_4$) yielding perfluorinated dithioacetal **3**; elimination of HF in basic conditions yields perfluoroketene dithioacetal **4** (Scheme 1).

Perfluoroketene dithioacetal **4** is an excellent building block for the synthesis of heterocycles;[8, 9] its dual reactivity along with the easy nucleophilic displacement of the vinylic fluorine are the keys to the chemistry of compound **4** that is easily converted in two high yielding steps into the bifunctionalized intermediate **6**. The bifunctional intermediates **6** was shown to be an excellent precursor for the preparation of trifluoromethyl γ-lactones and γ-lactams[8, 10, 11] (Scheme 1).

So, the treatment of perfluoroketene dithioacetal **4** with the potassium enolate of acetone led to the ketene dithioacetal **5**, which was hydrolyzed under acidic conditions to give the expected γ-keto-α-pentafluoroethyl thioester **6**. This methodology allowed us to introduce structural diversity at the initial step as well as at the vinylic substitution step (both aliphatic and aromatic enolates are working well).

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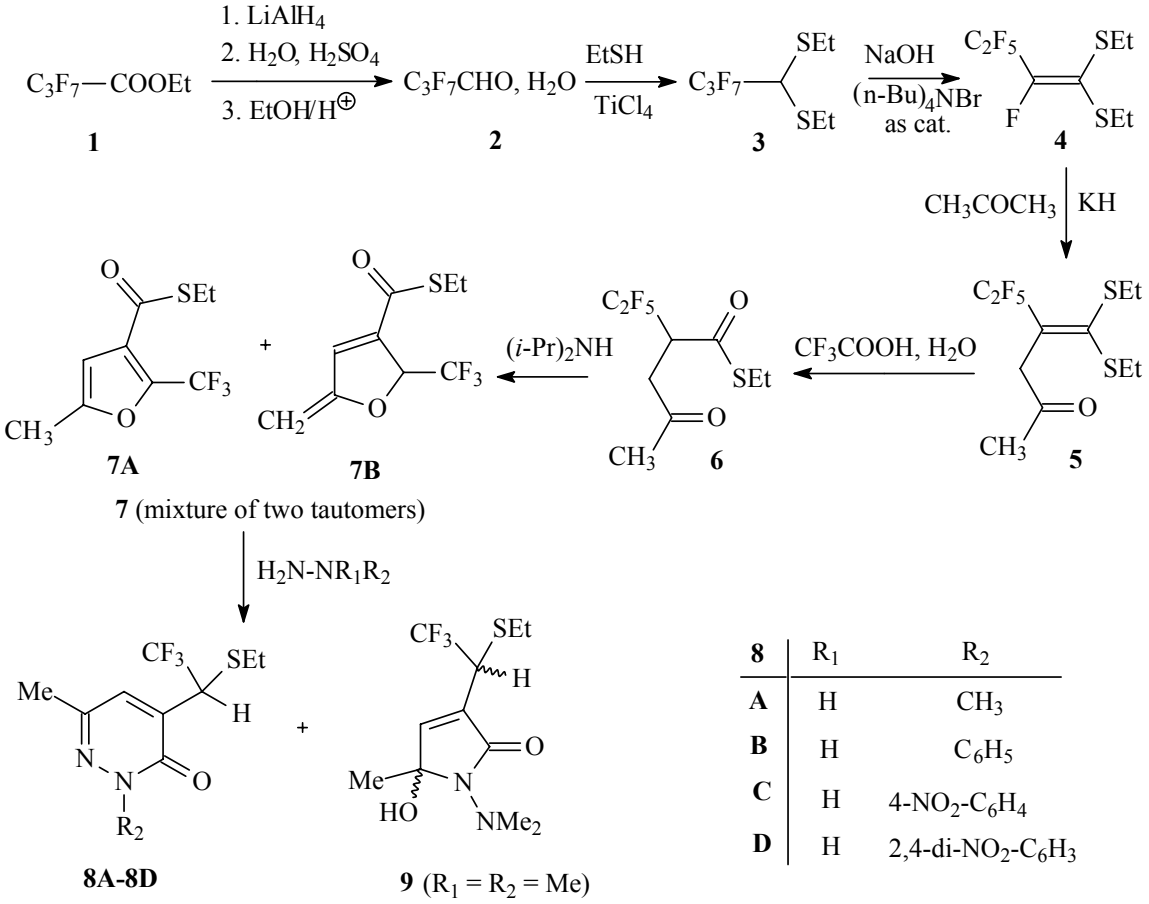
Next, we treated γ-keto-thioester **6** with 2 equivalents of diisopropylamine in diethyl ether at room temperature for 24 hours. The ^{19}F-NMR spectrum of reaction mixture displayed the CF_3-fluorine atoms as a singlet at -59.33 ppm, characteristic for the tautomer **7A** and a doublet, at -68.70 ppm, with a coupling constant J = 8.6 Hz, characteristic for tautomeric methylene form **7B**. After the usual work up, the crude mixture of tautomers **7** was dissolved in ethanol, treated with methylhydrazine and stirred for 24 h at room temperature. After usual work-up (see experimental section), the corresponding pyridazinone **8A** was obtained in 61 % yield (Scheme 1).



8	R_1	R_2
A	H	CH_3
B	H	C_6H_5
C	H	4-NO_2-C_6H_4
D	H	2,4-di-NO_2-C_6H_3

Scheme 1

The furan tautomers **7A** and **7B** are formed by two acid-base reactions followed by an intramolecular addition-elimination (Scheme 2).[12]

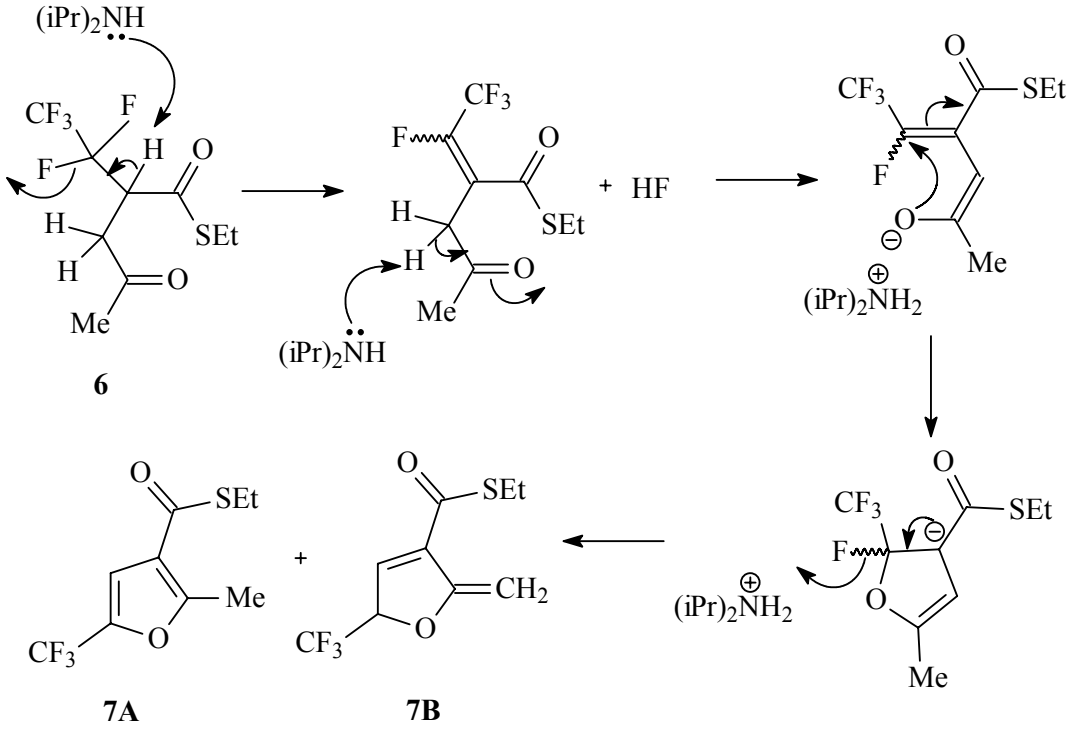
Next, we turned our atention to the reaction of γ-keto-tioesters **6** with arylhydrazines (phenyl, 4-nitrophenyl and 2,4-dinitrophenylhydrazine).

It was found that phenylhydrazines required stronger conditions. After 48 hours of stirring at room temperature, only the furan tautomer **7B** reacted with phenylhydrazine ; ^{19}F NMR spectrum of reaction mixture displayed CF_3-fluorine atoms as a singlet at -59.33 ppm, characteristic for the unreacted furan tautomer **7A** and a doublet at -68.0, characteristic for pyridazinone structure. Same spectrum was obtained after other 24 hours stirring at room temperature. The singlet characteristic to CF_3 group from furan **7A** disappeared by heating the reaction mixture at boiling point of ethanol, for 24 hours.

4-Nitrophenylhydrazine reacts with γ-keto-thioester **6** at room temperature for 24 hours, yielding the corresponding pyridazone **8C**, yield : 31 %.

In reaction with γ-keto-thioester **6**, 2,4-dinitrophenylhydrazine required stronger conditions; after 24 hours. at room temperature, ^{19}F NMR spectrum of reaction mixture displayed a singlet at -59.33 ppm characterictic to the unreacted furan tautomer **7A**, and a doublet characteristic to pyridazinone structure.

After heating the reaction mixture at the boiling point of ethanol, for 24 hours, the singlet characteristic to furan dissapeared. Unfortunately, owing to the difficult separation of this compound, it was not further investigated.



Scheme 2

We assume that the formation of pyridazinones **8** in reaction of γ-keto-thioester **6** first with a primary amine (diisopropylamine) and then with hydrazine derivatives, can be explained by a possible reaction mechanism shown in Scheme 3 in which the nucleophilic hydrazines attack the electrophilic carbon atom from carbonyl group as a secondary amine (path a). Owing to the enhanced nucleophilicity of amine group from hydrazines, the first step could be a substitution reaction of ethylsulfanyl group leading to the corresponding furan **A**.

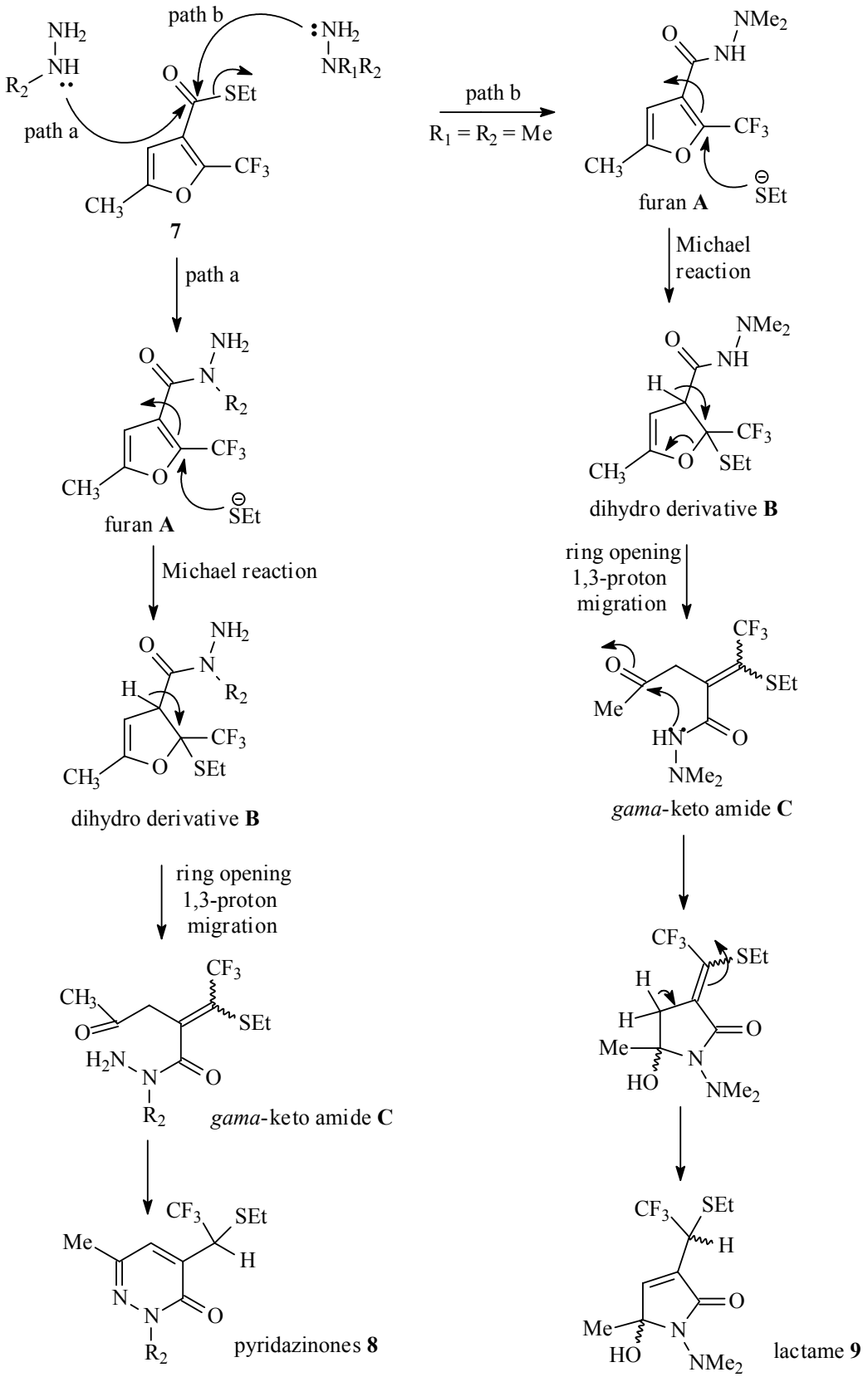
This compound exhibits an interesting conjugated system that is activated by both the trifluoromethyl substituent and the amide function, and could react as a Michael acceptor with thiol released in the reaction medium, to give the corresponding dihydro derivative **B**. Such an intermediatae might undergo ring opening followed by a 1,3-proton migration to afford the γ-keto amide **C**.

Finally, the desired pyridazinones **8** are obtained by cyclization of γ-keto amide **C**.

In order to prove this reaction mechanism, the reaction was also applied to *N*,*N*-dimethylhydrazine leading exclusively to lactam **9** as a mixture of diastereomers in the ratio 54/46.

In the reaction mechanism shown in Scheme 3 (path b), the *N*,*N*-dimethylhydrazine acts as a primary amine in nucleophilic attack on carbonyl group (path b)[11]. It can be observed from Scheme 1 that depending on the nucleophilic center of hydrazine, two reaction pathways can operate. If N-1 nitrogen behaves as a secondary amine, it can attack the electrophilic thioester affording furan derivative by path a, and finally the corresponding pyridazin-3-ones were obtained. If N-2 nitrogen may act as a primary amine (*N*,*N*-dimethylhydrazine), (path b), the corresponding furan regioisomer was obtained and finally the lactam **9** is obtained (Scheme 3).

The new lactam and pyridazinones were characterized by spectral analyses that confirmed their structure. ^{19}F NMR spectra of pyridazinones **8A-8D** displayed CF_3-fluorine atoms as doublet, at -68.11 (d, $^3J_{F,H}$ = 8.6 Hz, 3F). The identification of S-Et, C-CF_3, C-C=N and C-N groups, the presence of carbonyl group at 157-159 ppm in the ^{13}C NMR spectra, allowed us to identify the structure of pyridazinones and lactam.


path b
path a
7
path a
furan A
Michael reaction
dihydro derivative B
ring opening
1,3-proton
migration
gama-keto amide C
pyridazinones 8
path b
R1 = R2 = Me
furan A
Michael
reaction
dihydro derivative B
ring opening
1,3-proton
migration
gama-keto amide C
lactame 9

Scheme 3

^{19}F NMR spectrum of lactam **9** showed the presence of two doublets at -68.8, and -69 ppm, with coupling constants $^3J_{F,H}$ = 8.6 Hz that correspond to CF_3 groups from lactams structures.[10]

CONCLUSION

This study extends the field of synthetic applications of perfluoroketene dithioacetals; γ -keto thioesters prepared in moderate to good yields from perfluoroketene dithioacetals, are good building block for the synthesis of a variety of heterocycles. We synthesized new CF_3-containing lactam and pyridazin-3-ones in two steps. Two possible reaction mechanisms are discussed.

EXPERIMENTAL PART

IR spectra were registered on a FT-IR Perkin Elmer PARAGON 500. ^1H, ^{19}F and ^{13}C NMR spectra were recorded, in $CDCl_3$ as solvent, on a Brucker Advance DMX Instrument (400 MHz) spectometer. $CHCl_3$ (δ = 7.27 ppm) was used for internal standard for ^1H, $CDCl_3$ (δ = 77.23 ppm) for ^{13}C NMR spectra, and $CFCl_3$ (δ = 0.00 ppm) for ^{19}F NMR spectra. The abbreviations for the multiplicity of the proton signals are as follows: s for singlet, d for doublet, t fir triplet, q for quartet, qv for quintet, m for multiplet. Column chromatography was conducted with silicagel (63-200 mesh, Normasil Prolabo, Fontenay-sous-bois, France). GC analyses were performed using a Navigator (Finigan) instrument (flame ionization detector, FID) with an owen temperature program of 5°C/min, from to 150°C after 5 min at 40°C.

General procedure for the preparation of pyridazin-3-ones **8A-8D** *and lactam* **9**.

i-Pr_2NH (7.2 mmol, 2.0 equiv.) was added to a solution of γ-keto thioester **5** (3.6 mmol, 1.0 equiv.) in Et_2O (20 mL). The mixture was stirred for 24 hours at room temperature, then diluted with Et_2O (10 mL) and washed with brine (20 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude tautomers, checked by ^{19}F NMR spectroscopy, were using as starting material for the synthesis of pyridazinones **8** and lactam **9** without purification. So, the residue **7** was dissolved in Et_2O (10 mL), and the desired hydrazine (4.3 mmol, 1.2 equiv.) was added to the resulting solution. The reaction mixture was refluxed 24 h, then, after cooling, EtOH was evaporated in vacuo. The crude was chromatographed on silica gel to give pyridazinones **8A-8D** and lactam **9**.

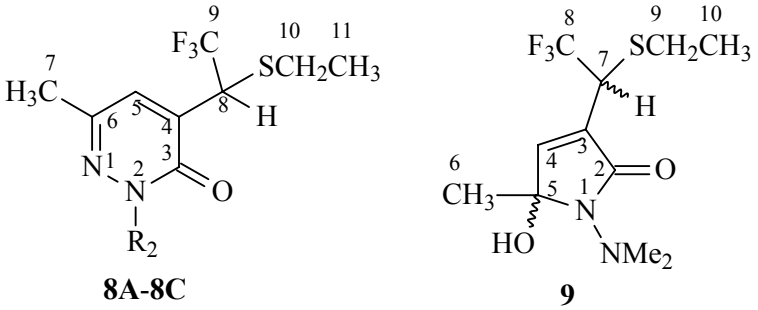


Fig. 1 – Numbering of hydrogens and carbons for pyridazin-3-ones **8A-8D** and lactam **9**.

4-(1-Ethylthio-2,2,2-trifluoroethyl)-2,6-dimethylpyridazin-3(2H)-one (**8A**): was purified by chromatography on silica gel, eluting with 3:1 mixture of petroleum ether and ethyl acetate to give a yellow solid, mp 67 °C, yield: 61%.

^1H-NMR ($CDCl_3$, δ ppm): 1.25 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, H-11); 2.27 (s, 3H, H-7); 2.7-2.8 (m, 2H, H-10); 3.72 (s, 3H, NMe); 4.87 (q, $^3J_{H,F}$ = 8.7 Hz, 1H, H-8); 7.20 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$, δ ppm): -68.11 (d, $^3J_{F,H}$ = 8.6 Hz, 3F). ^{13}C NMR ($CDCl_3$, δ ppm): 14.2 (s, C-11); 20.9 (s, C-7); 28.2 (s, C-10); 40.6 (s, NMe); 42.7 (q, $^2J_{C,F}$ = 31.0 Hz, C-8); 125.8 (q, $^1J_{C,F}$ = 279.4 Hz, C-9); 129.6 (s, C-5); 134.8 (s, C-4); 143.9 (s, C-6); 158.5 (s, C-3). IR (film, cm^{-1}): 3392, 1652, 1609, 1382, 1250; GC-MS: m/z = 266 [M^+], 246, 217, 206. Formula: $C_{10}H_{13}F_3N_2OS$: calcd. C 45.1, H 4.9, N 10.5, S 12.0; found C 45.6, H 4.5, N 10.1, S 12.1. HRMS: Calc. 267.0779, Found 267.0778.

4-(1-Ethylthio-2,2,2-trifluoroethyl)-6-methyl 2-phenylpyridazin-3(2H)-one (**8B**) was purified by chromatography on silica gel, eluting with 3:1 mixture of petroleum ether and ethyl acetate to give yellow solid, mp. 74 °C, yield: 39%.

^1H-NMR ($CDCl_3$, δ ppm): 1.34 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, H-11); 2.41 (s, 3H, H-7); 2.81-2.86 (m, 2H, H-10); 4.96 (q, $^3J_{H,F}$ = 8.8 Hz, 1H, H-8); 7.42-7.66 (m, 6H, H-5, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): -68.00 (d, $^3J_{F,H}$ = 8.6 Hz, 3F). ^{13}C NMR ($CDCl_3$, δ ppm): 14.3 (s, C-11); 21.2 (s, C-7); 28.4 (s, C-10); 42.9 (q, $^2J_{C,F}$ = 31.0 Hz, C-8); 124.5 (s, 2 x CH Ph); 124.6 (s, C-5); 124.8 (q, $^1J_{C,F}$ = 280.5 Hz, C-9); 127.4 (s, CH Ph); 127.8 (s, 2 x CH Ph); 129.2 (q, $^4J_{C,F}$ = 1.1 Hz, C-5); 135.9

(s, C-4); 140.6 (s, C_q, Ph); 143.8 (s, C-6); 157.1 (s, C-3). IR (film, cm^{-1}): 2933, 1778, 1660, 1616, 1494, 1254; HRMS: Calcd. for $C_{15}H_{16}F_3N_2OS$ m/z 329.0935, found 329.0932.

4-(1-Ethylthio-2,2,2-trifluoroethyl)-6-methyl-2-(4-nitrophenyl)pyridazin-3(2H)-one (**8C**) was purified by chromatography on silica gel, eluting with 3:1 mixture of petroleum ether and ethyl acetate to give yellow solid, mp. 68 °C, yield: 31%.

^{1}H-NMR ($CDCl_3$, δ ppm): 1.31 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, H-11); 2.43 (s, 3H, H-7); 2.8-2.9 (m, 2H, H-10); 4.94 (q, $^3J_{H,F}$ = 8.6 Hz, 1H, H-8); 7.25 (s, 1H, H-5); 7.92 (d, $^3J_{H,H}$ = 9.2 Hz, 2H, CH, Ar); 8.32 (d, $^3J_{H,H}$ = 9.2 Hz, 2H, CH Ar). ^{19}F NMR ($CDCl_3$, δ ppm): -68.00 (d, $^3J_{F,H}$ = 8.6 Hz, 3F). ^{13}C NMR ($CDCl_3$, δ ppm): 14.4 (s, C-11); 21.4. (s, C-7); 28.6 (s, C-10); 43.0 (q, $^2J_{C,F}$ = 31.6 Hz, C-8); 124.19 (s, C_4); 124.2 (s, 2 x CH Ar); 126.0 (s, 2 x CH Ar); 126.1 (q, $^1J_{C,F}$ = 279.6 Hz, C-9); 130.6 (s, C-5); 137.6 (s, C-4); 145.9 (s, C_q); 146.5 (s, C_q); 146.7 (s, C_q); 158.1 (s, C-3). IR (film, cm^{-1}): 2967, 1770, 1669, 1526, 1258; HRMS: Calcd. for $C_{15}H_{15}F_3N_3O_3S$ m/z 374.0786, found 374.0793.

1-(N,N-dimethylamino)-3-(1-ethylthio-2,2,2-trifluoroethyl)-5-hydroxy-5-methyl-1,5-dihydro-2H-pyrrol-2-one (**9**). It was purified by chromatography on silica gel, eluting with a mixture (25:75) of ethyl acetate and petroleum ether. Mixture (54/46) of diastereomers. Oil, yield: 50 %.

^{1}H-NMR ($CDCl_3$, δ ppm): 1.26 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, H-10); 1.30 (t, $^3J_{H,H}$ = 7.4 Hz, 3H, H-10); 1.57 (s, 3H, H-6); 1.58 (s, 3H, H-6); 2.05 (brs, 1H, OH); 2.6-2.8 (m, 2H, H-9); 2.93 (s, 6H, NMe_2); 4.0-4.2 (m, 1H, H-7); 6.77 (m, 1H, H-4). ^{19}F NMR ($CDCl_3$, δ ppm): -68.8 (d, $^3J_{F,H}$ = 8.6 Hz); -69.0 (d, $^3J_{F,H}$ = 8.6 Hz).

^{13}C NMR ($CDCl_3$, δ ppm): 14.2 (s, C-10); 22.8 (s, C-6); 22.9 (s, C-6) ; 27.7 (s, C-9); 29.8 (s, C-9); 41.01 (q, $^2J_{C,F}$ = 31.6 Hz, C-7); 41.06 (q, $^2J_{C,F}$ = 31.6 Hz, C-7); 45.33 (s, NMe_2); 45.34 (s, NMe_2); 87.7 (s, C-5); 87.9 (s, C-5); 124.75 (q, $^1J_{C,F}$ = 278.5 Hz, C-8); 124.81 (q, $^1J_{C,F}$ = 278.5 Hz, C-8); 130.4 (s, C-3); 130.5 (s, C-3); 142.9 (s, C-4); 143.1 (s, C-4); 164.95 (s, C-2); 164.98 (s, C-2). IR (film, cm^{-1}): 3402, 2931, 1694, 1526, 1645, 1350, 1255; GC-MS: m/z = 298 [M^+], 279, 177, 69, 59, 43. HRMS: Calcd. for $C_{11}H_{18}F_3N_2O_2S$ m/z 299.1041, found 299.1043.

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