Alternative approaches to the synthesis of polyfluoroalkyl-containing 1-methyl-4-nitrosopyrazoles

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We studied different approaches to the synthesis of polyfluoroalkyl-containing 1-methyl-4-nitrosopyrazoles, which are based on the cyclization of 4,4,4-trifluoro-3,3-dihydroxy-2-hydroxyimino-1-R-butan-1-ones or 2-hydroxyimino-1,3-diketones with methylhydrazine and on a one-pot sequential treatment of 1,3-diketones with sodium nitrite and methylhydrazine. It was found that the regioselectivity of the formation of 1-methyl-4-nitrosopyrazoles is affected by the steric factors of 1,3-dicarbonyl reagents. The study of the mycostatic effect of 4-nitrosopyrazoles showed that the introduction of a bulky polyfluoroalkyl or *tert*-butyl substituent leads to a decrease in their activity.

Key words: 4,4,4-trifluoro-3,3-dihydroxy-2-(hydroxyimino)butan-1-ones, polyfluoroalkyl-2-hydroxyimino-1,3-diketones, 1-methyl-4-nitrosopyrazoles, mycostatic activity.

The pyrazole framework provides rich opportunities for the design of physiologically active molecules, since its functionalization allows one to obtain multifunctional compounds capable of binding to biological targets, which leads to different pharmacological activities.[1—5] Fluorine-containing pyrazoles are of particular interest for the preparation of biologically active molecules[6—8] due to the presence of electron-withdrawing fluorine atoms, which affect the properties of compounds containing this element, changing their physicochemical and biological parameters.[9—12]

Recently, among trifluoromethyl-containing 1-methyl-4-nitrosopyrazoles we found compounds with high antimycotic activity in combination with moderate acute toxicity.[13] We suggest that the nitroso group makes a significant contribution to the antifungal effect, since these compounds may act as antimicrobial agents of the nitrofuran group, the exact mechanism of action of which is unknown.[14] Apparently, nitrofurazone and nitroimidazoles (for example, metronidazole, ornidazole, *etc.*) are metabolized by reduction of the nitro group with the formation of reactive forms, which can covalently bind to bacterial enzymes, disrupting the DNA of microbial cells.[15]

To synthesize trifluoromethyl-containing 4-nitrosopyrazoles, we used the cyclization of 2-hydroxyimino-1,3-diketones **2** with hydrazines (method ***A***)[16] or a one-pot sequential treatment of 1,3-diketones **1** with sodium nitrite and hydrazines (method ***B***).[17,18] However, we have earlier found that the synthesis of trifluoromethyl-containing 2-hydroxyimino-1,3-diketones **2** by nitrosation of 1,3-diketones **1** with sodium nitrite in aqueous solutions of organic acids is complicated by their isolation as hydrates **3** at the trifluoroacetyl fragment.[19]

In this connection, in the present work we studied the possibility of synthesizing 1-methyl-4-nitrosopyrazoles **4** by the reaction of 4,4,4-trifluoro-3,3-dihydroxy-2-(hydroxyimino)butan-1-ones **3** with methylhydrazine and compared the outcome with the results of the synthesis of the target compounds by a one-pot three-component cyclization of 1,3-diketones **1** and cyclocondensation of polyfluoroalkyl-2-hydroxyimino-1,3-diketones **2**.

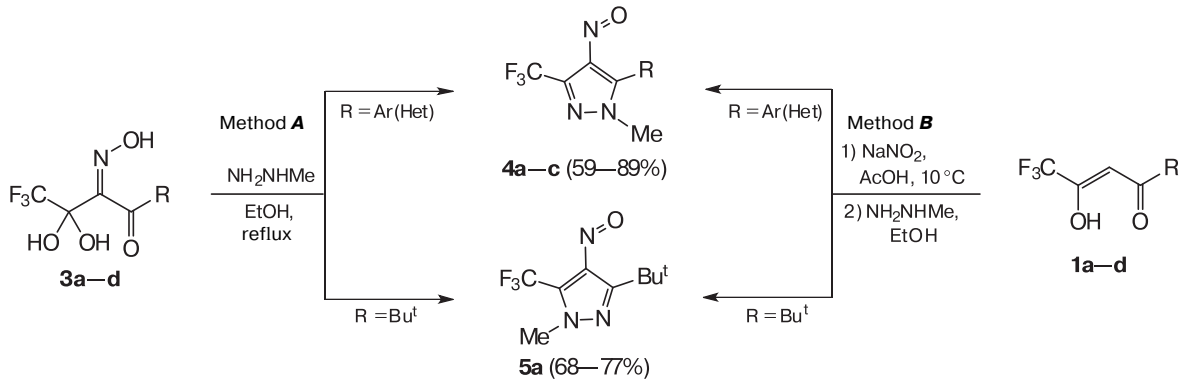
It was found that hydrates **3a—c** having (het)aryl substituents undergo cyclization with methylhydrazine to form 3-trifluoromethyl-substituted 4-nitrosopyrazoles **4a—c** (Scheme 1, method ***A***), similar to those obtained earlier from the corresponding 1,3-diketones **1a—c** or their lithium salts using a one-pot approach (method ***B***).[13]

However, compound **3d** containing a *tert*-butyl substituent reacts with methylhydrazine to give 5-trifluoromethyl-substituted 4-nitrosopyrazole **5a** (see Scheme 1, method ***A***). The direction of cyclization was not changed when the one-pot approach, *i.e.*, the sequential nitrosation of 1,3-diketone **1d** and condensation with methylhydrazine (method ***B***) was used.

* Dedicated to Academician of the Russian Academy of Sciences V. N. Charushin on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1135—1140, June, 2021.
1066-5285/21/7006-1135

Scheme 1

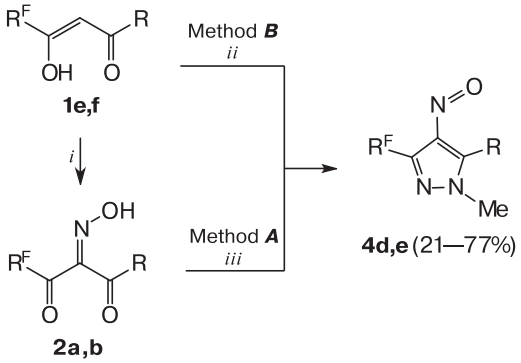


1, 3, 4: R = Ph (**a**), thiophen-2-yl (**b**), furan-2-yl (**c**), Bu^t (**d**)

Note that we previously observed the formation of 1,3-dimethyl-4-nitroso-5-trifluoromethylpyrazole (**5b**) in small amounts only in the one-pot reaction of lithium trifluoropentenoate with methylhydrazine. Compound **5b** was formed in a mixture with the predominant 3-trifluoromethyl-substituted isomer in a ratio of ~1 : 2.[13]

In contrast to trifluoromethyl-substituted diketones **1a—d**,[19] their polyfluoroalkyl-containing analogs **1e,f** do not form hydrates upon nitrosation with sodium nitrite in acetic acid, rather giving 2-hydroxyimino-1,3-diketones **2a,b** (Scheme 2). The ^{13}C NMR spectrum of compound **2a**, which exists in solution in $CDCl_3$ as a single isomer, exhibits a triplet at δ 178.58 corresponding to the carbonyl carbon atom of the $\underline{C}(O)CF_2$ fragment. The stability of the carbonyl group at the polyfluoroalkyl substituent may be due to its lower electron-withdrawing ability as compared to a trifluoromethyl residue.

Scheme 2



$R^F = C_2F_5$, R = Ph (**1e, 2a, 4d**), $R^F = C_4F_9$, R = Me (**1f, 2b, 4e**)

Reagents and conditions: *i.* $NaNO_2$, AcOH, H_2O, 0 °C, 15 min, then 20 °C, 1—2 h; *ii* (method ***B***). 1) $NaNO_2$, AcOH, 10 °C, 2) NH_2NHMe, EtOH; *iii* (method ***A***). NH_2NHMe, EtOH, reflux.

2-Hydroxyimino-1,3-diketones **2a,b**, regardless of the length of the polyfluoroalkyl substituent and the nature of the non-fluorinated residue, give 3-polyfluoroalkyl-1-methyl-4-nitrosopyrazoles **4d,e**. One-pot transformations of 1,3-diketones **1e,f** lead to the same pyrazoles **4d,e** (see Scheme 2).

Note that 4-nitrosopyrazoles cannot be synthesized by nitrosation of preliminary obtained 3-polyfluoroalkylpyrazoles, whereas the most efficient method for the synthesis of 4-hydroxyimino-5-polyfluoroalkylpyrazol-3-ones is the nitrosation of 3-polyfluoroalkylpyrazol-5-ols.[20]

The regioisomeric structure of 3-trifluoromethyl-substituted 4-nitrosopyrazoles **4a—c** has been established by us earlier[13] based on the ^1H, ^{13}C, and ^{19}F NMR spectroscopy data.

In the determination of the regioisomeric structure of 5-trifluoromethyl-substituted pyrazole **5a**, its ^1H and ^{19}F NMR spectra, which differed from the spectra of 3-trifluoromethylpyrazoles **4a—c** in the signal splitting patterns of the CF_3 and N(1)Me groups, were the most informative. Thus, the signals for the CF_3 and N(1)Me groups of compound **5a** were observed as quartets with spin-spin coupling constants of 1.7 Hz due to the coupling between the fluorine atoms and the protons of the neighboring Me substituent (see Experimental), while the signals for these groups in the spectra of pyrazoles **4a—c** were observed as singlets.[13]

In the ^1H NMR spectra of 3-polyfluoroalkyl-4-nitrosopyrazoles **4d,e**, the protons of the N(1)Me group resonate as singlets, which indicates their remoteness from perfluoroalkyl substituents.

The regioisomeric structure of 3-pentafluoroethyl-substituted pyrazole **4d** was additionally confirmed by X-ray diffraction analysis (Fig. 1).

From the data obtained, it can be concluded that the method for the synthesis of 4-nitrosopyrazoles **4a—d** and **5a** does not affect their regioisomeric structure. It is obvious that the regioselectivity of cyclization is determined

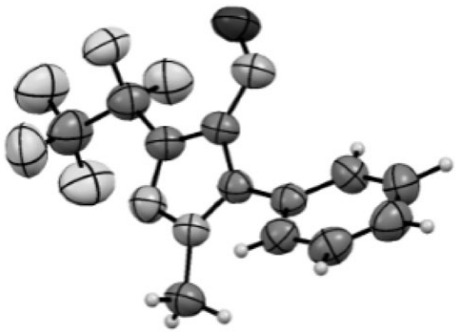


Fig. 1. General view of the molecule of 4-nitrosopyrazole **4d** according to X-ray diffraction analysis. Thermal ellipsoids are shown with a 50% probability.

by the structure of the substituents at the 1,3-dicarbonyl fragment of the starting reagents **1—3**. In most cases, the more nucleophilic MeNH group of methylhydrazine reacts with the carbonyl group at the non-fluorinated substituent of the 1,3-dicarbonyl agent as the most electrophilic position.[8] A dramatic change in the direction of the reaction we observed only in the case of compounds **1d** and **3d** having a bulky *tert*-butyl substituent, which hinders the attack by a MeNH group on the neighboring carbonyl function.

Comparing the efficiency of the methods used, we can note the expectedly higher yields of the target 4-nitrosopyrazoles **4** and **5** in the synthesis from hydroxyimines **2** or **3** by method ***A*** (Table 1), but this advantage can be neutralized by the stage of their isolation and purification.

As mentioned above, 3-trifluoromethyl-substituted 4-nitrosopyrazoles **4a—c** possess a pronounced ability to inhibit the growth of pathogenic dermatophyte fungi, while 5-trifluoromethyl-substituted 4-nitrosopyrazole **5b** is less efficient (Table 2).

We investigated the antimycotic and antibacterial activity of pyrazoles **4d** and **5a** against eight test strains of pathogenic dermatophytes and yeast-like fungi *Candida albicans*. A reference drug was the known antifungal agent fluconazole. It turned out that the replacement of the trifluoromethyl substituent in compound **4a** with a pentafluoroethyl group led to a decrease in the antimycotic effect of pyrazole **4d**, which exhibited a moderate activity (MIC 25 μg mL^{-1}) against fungi of the strain *T. interdigitale*, a weak inhibitory effect (MIC 50 μg mL^{-1}) against *T. rubrum, T. violaceum, E. floccosum*, and had no effect (MIC 100 μg mL^{-1}) against *T. tonsurans, T. schonleinii, M. canis*.

A comparison of the antifungal effect of 5-trifluoromethyl-containing pyrazoles **5a** and **5b** showed that the

Table 1. Yields of compounds **2—5**

Hydroxyimine **2**, **3**	Yield of **2**, **3** (%)	4-Nitrosopyrazole	Yield of compounds **4**, **5** (%)		
			from hydroxyimines **2**, **3** (method ***A***)	total yield on two steps[a]	from 1,3-diketone **1** (method ***B***)
3a[19]	55[b], 84[c]	**4a**	76	42[b] 64[c]	68
3b[19]	52[b], 87[c]	**4b**	68	35[b], 59[c]	59
3c[19]	71[b], 78[c]	**4c**	89	63[b], 69[c]	84
2a	72	**4d**	77	55	44
2b	77	**4e**	38	29	21
3d[19]	49[b], 78[c]	**5a**	77	37[b], 60[c]	68

[a] Calculated on the corresponding starting 1,3-diketone **1**.
[b] For synthesis of hydroxyimines **3** in aqueous AcOH.
[c] For synthesis of hydroxyimines **3** in aqueous citric acid.

Table 2. Fungistatic activity of 4-nitrosopyrazoles **4** and **5**

Compound	MIC (mg mL^{-1}) for inhibition of fungal strains								
	T. rubrum	*T. gypseum*	*T. tonsurans*	*T. violaceum*	*T. interdigitale*	*T. schonleinii*	*E. floccosum*	*M. canis*	*C. albicans*
4a	12.5	25	3.12	6.25	12.5	—*	0.38	100	—*
4b	12.5	50	50	—*	25	—*	50	25	25
4c	12.5	50	12.5	6.25	25	—*	12.5	12.5	н/а
4d	50	>200	100	50	25	100	50	100	>200
5a	>200	>200	>200	200	>200	200	200	>200	>200
5b	12.5	25	25	100	100	—*	100	100	>200
Fluconazole	3.12	6.25	6.25	1.95	0.78	1.56	1.56	3.12	1.56

* Not tested.

replacement of the methyl group at position C(3) with a bulky *tert*-butyl substituent leads to a complete loss of the antimycotic effect.

In conclusion, we showed the possibility of using 4,4,4-trifluoro-3,3-dihydroxy-2-hydroxyimino-1-R-butan-1-ones formed by nitrosation of trifluoromethyl-1,3-diketones in aqueous solutions of organic acids[19] for the synthesis of 4-nitrosopyrazoles. In contrast to trifluoromethyl analogs, the nitrosation of polyfluoroalkyl-1,3-diketones yielded 2-hydroxyimino-1,3-diketones, which were also converted to 4-nitrosopyrazoles. It was found that the regioselectivity of the formation of 4-nitrosopyrazoles is affected by the structure of the 1,3-dicarbonyl agent, and not by the method of its preparation. The study of the antifungal effect of 4-nitrosopyrazoles showed that the introduction of a bulky polyfluoroalkyl or *tert*-butyl substituent leads to a decrease in their inhibitory activity.

Experimental

Melting points were determined in open capillaries on a Stuart SMP30 apparatus. IR spectra in the 4000—400 cm^{-1} range were recorded on a Spectrum Two infrared Fourier-transform spectrometer equipped with a diamond attenuated total reflectance (ATR) attachment (Perkin Elmer, USA). ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on Bruker DRX-400 and Bruker Avance 500 spectrometers in DMSO-d_6 or $CDCl_3$, using Me_4Si (^1H) and C_6F_6 (^{19}F) as internal standards. Elemental analysis (C, H, N) was performed on a PerkinElmer PE 2400 series II CHN-O EA 1108 or Carlo Erba CHNS-O EA 1108 elemental analyzers. Column chromatography was performed on Macherey-Nagel silica gel 60 (0.063—0.2 mm). The reaction progress was monitored by TLC on ALUGRAM® Xtra SIL G/UV_{254} plates.

4,4,4-Trifluoro-3,3-dihydroxy-2-hydroxyimino-1-R-butan-1-ones **3a—d** were obtained by the procedure described in the work.[19]

Synthesis of 2-hydroxyimino-1,3-diketones (2a,b) (general procedure). A solution of sodium nitrite (0.41 mg, 6 mmol) in water (5 mL) was added dropwise over 10—15 min to a cooled to 0 °C solution of 1,3-diketone **1e,f** (5 mmol) in acetic acid (3—5 mL) with stirring. Then the reaction mixture was stirred at room temperature for 1—2 h, neutralized with saturated aqueous sodium bicarbonate, and extracted with diethyl ether (2×15 mL). The organic layers were combined, dried, and concentrated. The target compounds were isolated by a suitable method.

4,4,5,5,5-Pentafluoro-2-hydroxyimino-1-phenylpentane-1,3-dione (2a). The yield was 72% (washed with hexane), colorless crystals, m.p. 119—120 °C. IR (ATR), ν/cm^{-1}: 3242 (O—H), 1721, 1644 (C=O), 1593 (C=N), 1222—1192 (C—F). ^1H NMR ($CDCl_3$), δ: 7.52—7.56, 7.67—7.70, 7.80—7.82 (all m, 5 H, Ph); 9.33 (br.s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 107.75 (tq, CF_2, J = 269.7 Hz, J = 37.5 Hz); 117.67 (qt, CF_3, J = 287.8 Hz, J = 34.1 Hz); 128.90, 129.52, 133.54, 135.44 (Ph); 152.22 (C=O); 178.58 (t, CF_2C=O, J = 26.1 Hz); 189.66 (C=N). ^{19}F NMR ($CDCl_3$), δ: 44.32 (q, 2 F, CF_2, J = 0.9 Hz), 80.70 (s, 3 F, CF_3). Found (%): C, 44.92; H, 1.95; N, 4.84. $C_{11}H_6F_5NO_3$. Calculated (%): C, 44.76; H, 2.05; N, 4.75.

5,5,6,6,7,7,8,8,8-Nonafluoro-3-(hydroxyimino)heptane-2,4-dione (2b). The yield was 77% (after column chromatography, eluent $CHCl_3$), colorless crystals, m.p. 49—50 °C. A mixture of *E*- and *Z*-isomers in the ratio of 86 : 14 (^1H NMR spectroscopy data). IR (ATR), ν/cm^{-1}: 3241 (O—H), 1719, 1639 (C=O), 1591 (C=N), 1224—1190 (C—F). ^1H NMR ($CDCl_3$), δ, *E*-isomer: 2.48 (s, 3 H, Me); 10.16 (br.s, 1 H, OH); *Z*-isomer: 2.49 (s, 3 H, Me); 11.39 (br.s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ, *E*-isomer: 36.0, 39.2, 42.1 (all m, 2 F each, CF_2); 80.9 (tt, 3 F, CF_3, J = 9.7 Hz, J = 2.4 Hz); *Z*-isomer: 36.1, 40.4, 42.1 (all m, 2 F each, CF_2), 81.0 (tt, 3 F, CF_3, J = 9.7 Hz, J = 2.4 Hz). Found (%): C, 28.72; H, 1.34; N, 4.31. $C_8H_4F_9NO_3$. Calculated (%): C, 28.85; H, 1.21; N, 4.20.

Synthesis of 4-nitrosopyrazoles 4a—e and 5a (general procedure). Method *A*. Methylhydrazine (0.46 mg, 10 mmol) was added to a solution of hydrate **3a—d** or 2-hydroxyimino-1,3-diketone **2a,b** (10 mmol) in ethanol (20 mL) and the mixture was refluxed for 3—4 h. After cooling to room temperature, the solvent was evaporated, the residue was extracted with diethyl ether (2×20 mL), the organic layer was washed with saturated aqueous sodium bicarbonate until the washings were neutral, dried with sodium sulfate, and concentrated *in vacuo*. The residue was washed with water (10 mL), hexane (10 mL) and dried.

Method *B*. A solution of 1,3-diketone **1a—f** (10 mmol) in acetic acid (10 mL) was cooled to 10 °C, followed by a dropwise addition over 30 min of a solution of sodium nitrite (0.86 g, 12.5 mmol) in water (10 mL) with stirring. Then, a solution of methylhydrazine (0.51 g, 11 mmol) in ethanol was added and the mixture was stirred at room temperature for 3—4 h. The products were isolated as in method *A*.

1-Methyl-4-nitroso-5-phenyl-3-trifluoromethyl-1*H*-pyrazole (4a) was purified by column chromatography (eluent chloroform). The yield was 76% (method *A*), 68% (method *B*), blue crystals, m.p. 97—98 °C (*cf.* Ref. 17: m.p. 97—98 °C). The spectral data agree with those published earlier.[17] ^{13}C NMR ($CDCl_3$), δ: 38.08 (Me), 119.69 (q, CF_3, J = 269.7 Hz); 126.46 (q, $\underline{C}CF_3$, J = 40.6 Hz); 125.73, 129.14, 130.64, 131.22 (Ph), 150.12, 155.12 ($\underline{C}NO$, $\underline{C}Ph$).

1-Methyl-4-nitroso-5-(thiophen-2-yl)-3-trifluoromethyl-1*H*-pyrazole (4b) was purified by column chromatography (eluent chloroform—diethyl ether—hexane, 2 : 2 : 1). The yield was 68% (method *A*), 59% (method *B*), green crystals, m.p. 102—103 °C (*cf.* Ref. 13: m.p. 102—103 °C). The IR, ^1H and ^{19}F NMR spectral data agree with those published earlier.[13]

5-(Furan-2-yl)-1-methyl-4-nitroso-3-trifluoromethyl-1*H*-pyrazole (4c). The yield was 89% (method *A*), 84% (method *B*), a light green powder, m.p. 95 °C (*cf.* Ref. 13: m.p. 95 °C). The IR, ^1H and ^{19}F NMR spectral data agree with those published earlier.[13]

3-*tert*-Butyl-1-methyl-4-nitroso-5-trifluoromethyl-1*H*-pyrazole (5a) was purified by column chromatography (eluent chloroform). The yield was 77% (method *A*), 68% (method *B*), a blue oil. IR, ν/cm^{-1}: 1523, 1487, 1451, 1431 (C=N, C=C, N=O); 1149—1090 (C—F). ^1H NMR ($CDCl_3$), δ: 1.42 (s, 9 H, Bu^t); 4.04 (q, 3 H, $N\underline{Me}$, J = 1.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 29.16 (Bu^t), 33.95 ($\underline{C}Me_3$), 39.92 (q, $N\underline{Me}$, J = 3.0 Hz); 119.20 (q, CF_3, J = 271.9 Hz); 126.18 (q, $\underline{C}CF_3$, J = 41.1 Hz); 153.31, 157.09 ($\underline{C}NO$, $\underline{C}—Bu^t$). ^{19}F NMR ($CDCl_3$), δ: 103.62 (q, CF_3, J = 1.7 Hz). Found (%): C, 46.48; H, 5.36; N, 18.65. $C_9H_{12}F_3N_3O$. Calculated (%): C, 45.96; H, 5.14; N, 17.87.

1-Methyl-4-nitroso-3-pentafluoroethyl-5-phenyl-1*H*-pyrazole (4d). The yield was 77% (method ***A***), 44% (method ***B***), light blue crystals, m.p 107—109 °C. IR, ν/cm^{-1}: 1602, 1519, 1478, 1454 (C=N, C=C, N=O); 1125—1109 (C—F). ^{1}H NMR ($CDCl_3$), δ: 3.96 (s, 3 H, Me); 7.62 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 38.04 (Me), 110.20 (tq, CF_2, J = 253.2 Hz, J = 39.5 Hz); 118.69 (qt, CF_3, J = 286.8 Hz, J = 36.5 Hz); 125.78, 129.08, 130.43, 131.10 (Ph), 146.31, 156.04 (signals for the CNO, CPh, CCF_2 carbons overlap with signals for carbon atoms of Ph group). ^{19}F NMR ($CDCl_3$), δ: 49.0 (q, CF_2, J = 2.2 Hz), 78.9 (t, CF_3, J = 2.2 Hz). Found (%): C, 47.33; H, 2.72; N, 27.39. $C_{12}H_8F_5N_3O$. Calculated (%): C, 47.22; H, 2.64; N, 13.77.

1,5-Dimethyl-4-nitroso-3-nonafluorobutyl-1*H*-pyrazole (4e). The yield was 38% (method ***A***), 21% (method ***B***), a green oil. IR, ν/cm^{-1}: 1694, 1563, 1479, 1455 (C=N, C=C, N=O). ^{1}H NMR ($CDCl_3$), δ: 2.54 (s, 3 H, Me); 3.91 (s, 3 H, NMe). ^{19}F NMR ($CDCl_3$), δ: 36.1 (m, 2 F, γ-CF_2), 39.7 (m, 2 F, β-CF_2); 53.1 (m, 2 F, α-CF_2); 80.8 (tt, 3 F, CF_3, J = 9.7 Hz, J = 2.7 Hz). Found (%): C, 31.44; H, 1.73; N, 12.33. $C_9H_6F_9N_3O$. Calculated (%): C, 31.50; H, 1.76; N, 12.25.

X-ray diffraction analysis of compound 4d. Single crystals of compound **4d** were obtained by crystallization from diethyl ether, $C_{12}H_8F_5N_3O$, M = 305.21, single crystals are monoclinic, space group $P2_1/n$, a = 13.3053(16) Å; b = 7.7036(7) Å; c = 13.5295(19) Å; α = 90.000°, β = 112.029°, γ = 90.000°, V = 1285.5(3) Å^3, Z = 4, d_{calc} = 1.577 g cm^{-3}, μ(MoKα) = 0.153 cm^{-1}, F(000) = 616. A 9003 total number of reflections was measured on a Xcalibur 3 diffractometer at 295(2) K (MoKα radiation, graphite monochromator, CCD detector, ω/2θ scan technique), the number of independent reflections was 3517 (R_{int} = 0.0423), the number of reflections with $I \geqslant 2\sigma(I)$ was 1563. The crystal structure was solved by direct methods and refined using the SHELXL-97 program[21] by the least squares method in the anisotropic full-matrix approximation for all nonhydrogen atoms to R_1 = 0.0522, wR_2 = 0.1346 and GOOF = 1.006 (for reflections with $I \geqslant 2\sigma(I)$).

A complete set of crystallographic data was deposited with the Cambridge Crystallographic Data Center (CCDC 2063016) and is available at http://www.ccdc.cam.ac.uk/conts/retrieving.html (12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Microbiological study of compounds 4d and 5a. The microbiological study was carried out at the Ural Research Institute of Dermatovenerology and Immunopathology. The following test strains of dermatophyte fungi were used in the study: *Trichophyton rubrum* (RKPG (Russian collection of pathogenic fungi) F 1408), *Trichophyton mentagrophytes var. gypseum* (RKPG F 1425), *Trichophyton tonsurans* (RKPG F 1396/228), *Trichophiton violaceum* (RKPG F 1211), *Trichophyton mentagrophytes var. interdigitale* (RKPG F 1459/11044), *Trichophyton schoenleinii* (RKPG F 235/25), *Epidermophyton floccosum* (RKPG F 1659/17), *Microsporum canis* (RKPG F 1643/1585) and yeast-like fungi *Candida albicans* (RKPG Y 401/NCTC 885/653). Antimicrobial properties were assessed using the serial dilution method recommended by the Clinical and Laboratory Standards Institute (CLSI, 2014) according to the procedure described in the work.[13]

The work was carried out in the framework of the Russian state assignment AAAA-A19-119011790134-1, using the equipment of the Centre for Joint Use "Spectroscopy and Analysis of Organic Compounds" (CJU "SAOC").

This work does not involve human participants and animal subjects.

The authors declare no competing interest.

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Received February 16, 2021;
in revised form March 23, 2021;
accepted March 24, 2021