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Reaction of 3-[(alkylsulfanyl)methyl]pentane-2,4-diones with nicotinic hydrazide

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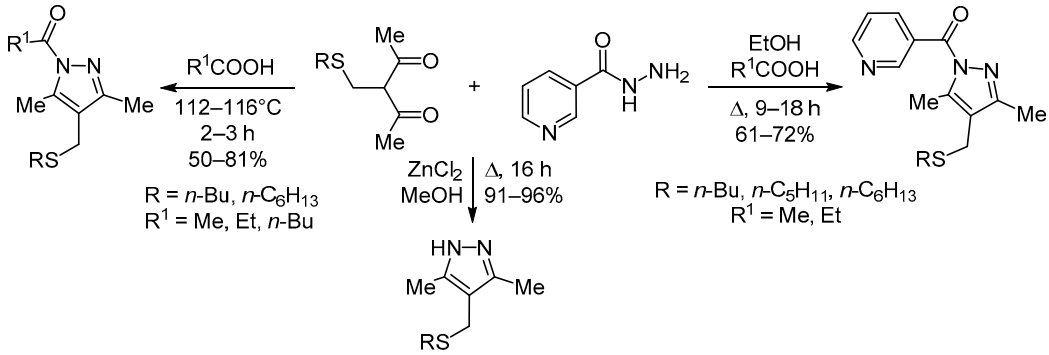


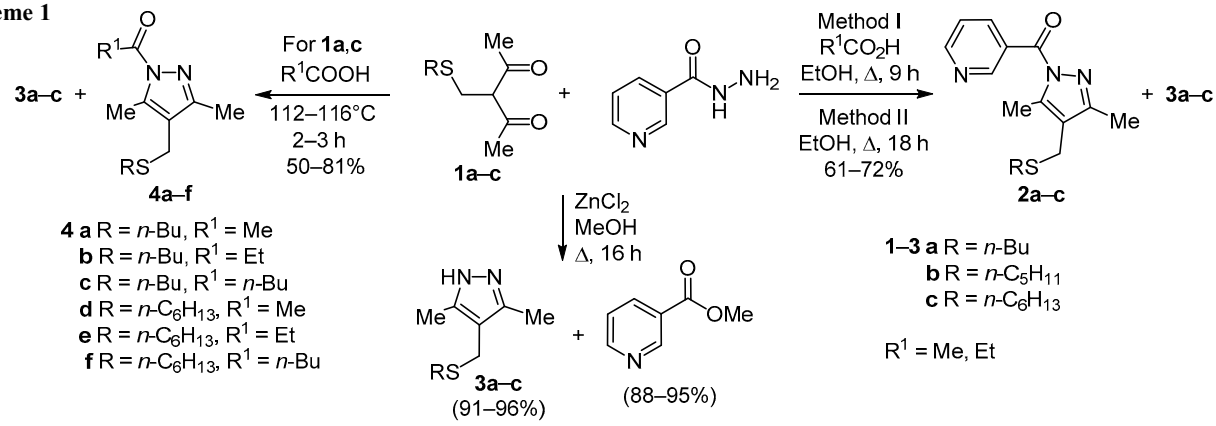
The reaction of 3-[(alkylsulfanyl)methyl]pentane-2,4-diones with nicotinic hydrazide in ethanol as solvent produces 4-[(alkylsulfanyl)-methyl]-substituted 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles, whereas 1-acyl-1*H*-pyrazoles are formed in acetic, propanoic, or pentanoic acid solution. The reaction in methanol in the presence of $ZnCl_2$ is accompanied by elimination of nicotinic acid and the formation of (alkylsulfanyl)methyl-substituted 1*H*-pyrazoles.

Keywords: 1-acyl-1*H*-pyrazole, 3-[(alkylsulfanyl)methyl]pentane-2,4-dione, nicotinic hydrazide, 1-(pyridin-3-yl)carbonyl-1*H*-pyrazole, heterocyclization.

Derivatives of (pyridin-3(4)-yl)carbonyl-1*H*-pyrazoles[1] and acyl-1*H*-pyrazoles,[1a,b,2] together with their hydrogenated analogs pyrazolines, exhibit a wide spectrum of biological activity, including antitumor,[1a–c,2a–d] anti-inflammatory,[2d,e] antimalarial,[1d] antibacterial,[1e,2d,f,g] analgesic,[1f,2d] and neuropsychotropic.[1g–i,2h–j] Among 4(2)-[alkyl(aryl)-sulfanyl(sulfonyl)methyl]-1*H*-pyrazoles, compounds possessing fungicidal[3] activity, properties of progesterone receptor antagonists,[4] N-myristoyltransferase inhibitors,[5] and also selective extractants and ligands in the preparation of sulfur-containing Pt(II) and Pd(II) complexes[6] were found. The variety of useful properties of 1*H*-pyrazoles with alkyl-(aryl)sulfanyl(sulfonyl)methyl, (pyridin-3(4)-yl)carbonyl, or acyl moieties maintains the interest in developing convenient methods for the preparation of new molecules combining such structural units.

The existing synthesis methods of 4(2)-[alkyl(aryl)-sulfanyl(sulfonyl)methyl]-1*H*-pyrazoles are based on the substitution of the halogen atom in the corresponding halogen derivatives of 1*H*-pyrazoles with an alkyl(aryl)-sulfanyl group.[4–6c] Cyclization of alkenyl ketones with the corresponding hydrazides[1d,e,2e] or hydrazine hydrate in the presence of AcOH[2b,c,f,h,i] is used for the synthesis of hydrogenated derivatives of 1-(pyridin-3(4)-yl)carbonyl-1*H*-pyrazoles and 1 acyl-1*H*-pyrazoles. 1-(Pyridin-3(4)-yl)-carbonyl-1*H*-pyrazoles and 1-acyl-1*H*-pyrazoles are prepared *via* the reaction of 1,3-dicarbonyl compounds with hydrazides;[1a,f] reactions of 1*H*-pyrazoles with acyl-(nicotinoyl) chlorides[2a,g,7a–c] as well as acids in the presence of $SOCl_2$[7a,d] are most often used, however. An example of multistep synthesis of 4-phenylsulfanyl-1-(pyridin-3-yl)-carbonyl-1*H*-pyrazoles, agonists of G-protein-coupled GPR109A receptors, *via* the reaction of nicotinoyl chlorides with 4-phenylsulfanyl-1*H*-pyrazoles, which, in turn, are obtained in the reaction of 3-chloropentane-2,4-diones with thiophenols and subsequent heterocyclization of the resulting 3-(phenylsulfanyl)pentane-2,4-diones with hydrazine hydrate is known.[8]

Scheme 1



In this work, an alternative approach to access new 4-(alkylsulfanyl)methyl-substituted 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles and 1-acyl-1*H*-pyrazoles is explored that avoids the use of halogen derivatives. The proposed method is based on the cyclization of 3-[(alkylsulfanyl)-methyl]pentane-2,4-diones with nicotinic hydrazide. The starting (sulfanyl)methyl-substituted 2,4-diones are easily formed as a result of the three-component condensation of acetylacetone with aldehydes and thiols, which meets the requirements of green chemistry.[3,9]

3-[(Alkylsulfanyl)methyl]pentane-2,4-diones **1a**–**c** are reacted with an equimolar amount of nicotinic hydrazide in EtOH in the presence of AcOH ($EtCO_2H$) or without acid to form the corresponding 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles **2a**–**c** in up to 72% yields (Scheme 1). When carrying out the reaction in MeCN medium (Table 1), the selectivity of the reaction decreases due to the formation of more than five byproducts.

The main byproducts are 4-[(alkylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazoles **3a**–**c**, the yields of which in EtOH reach 14% (Table 1). In the reaction of pentane-2,4-diones **1a**–**c** with nicotinic hydrazide in MeOH in the presence of $ZnCl_2$, the formation of 1*H*-pyrazoles **3a**–**c** is predominant (91–96% yields). In this case, nicotinic acid methyl ester is formed as a byproduct, the IR spectra, as well as the ^1H and ^{13}C NMR spectra of which are identical to those published.[10]

The $ZnCl_2$-catalyzed reaction of pentane-2,4-dione **1a**–**c** with nicotinic hydrazide in MeOH apparently proceeds according to the mechanism described in the literature,[3] with the difference that heterocyclization is accompanied by elimination of nicotinic acid and the formation of its methyl ester. The obtained results are consistent with the data of studies describing the possible thermolysis of 1-acyl-1*H*-pyrazoles in the presence of catalytic amounts of H_2SO_4[11] and their alcoholysis by the action of benzyl alcohol, accelerated in the presence of NaH or $BF_3 \cdot OEt_2$.[7a]

Heterocyclization of pentane-2,4-diones **1a**,**c** with nicotinic hydrazide in acetic, propanoic, or pentanoic acids is accompanied by reacylation and the formation of 1-acyl-3-[(alkylsulfanyl)methyl]-1*H*-pyrazoles **4a**–**f** in 50–81% yields (Scheme 1). The yield of 1-acyl-1*H*-pyrazole **4b** decreases from 77 to 40% with increasing reaction temperature from 116 to 144 °C.

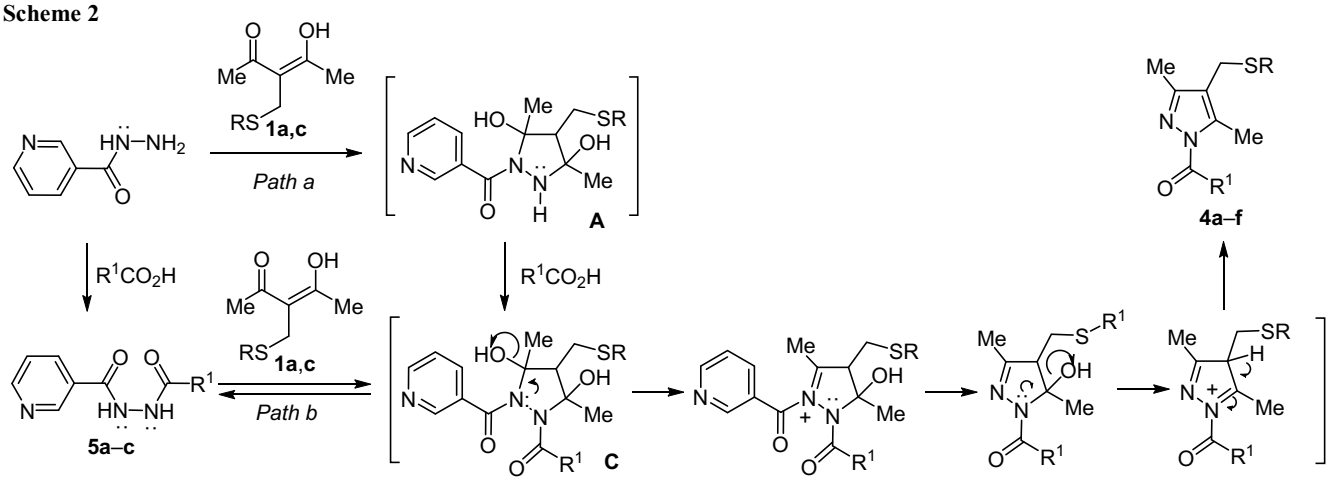
Table 1. Condensation of 3-[(hexylsulfanyl)methyl]pentane-2,4-dione **1c** with nicotinic hydrazide (1:1 molar ratio, reflux)

Solvent	Time, h	Yield of compound, %	
		2c	**3c**
MeCN	5	43	11
MeCN	13	15	27
EtOH (method II)	18	56	14
EtOH, EtCOOH (1.5 equiv) (method I)	9	72	12
EtOH, AcOH (1.5 equiv) (method I)	9	68	12
EtOH, AcOH (1 equiv) (method I)	9	66	10

The mechanism of the formation of 1-acyl-1*H*-pyrazoles **4a**–**f** under the studied reaction conditions probably involves nucleophilic addition of the amino group of nicotinic hydrazide to the enol form of pentane-2,4-dione **1a**,**c**, similar to that described in the literature,[12] and subsequent acylation of the amino group of intermediate pyrazolidine-3,5-diols **A** with carboxylic acids (Scheme 2, path *a*). The initial acylation of nicotinic hydrazide with carboxylic acids is also possible with the formation of 1,2-diacyl hydrazines **5a**–**c**, which then participate in the reaction with pentane-2,4-diones **1a**,**c** (Scheme 2, path *b*). Aromatization of pyrazolidine-3,5-diols **C** is accompanied by elimination of hydroxyl and (pyridin-3-yl)carbonyl groups followed by the loss of proton leading to target compounds **4a**–**f**. In this case, the eliminated nicotinic acid has weaker basic properties. The physicochemical properties of the isolated nicotinic acid are consistent with published data.[13]

When heating 1*H*-pyrazoles **3a**,**c** with an excess of AcOH under reflux, the formation of 1-acyl-1*H*-pyrazoles **4a**,**d** is not observed. At the same time, nicotinic hydrazide under these conditions forms *N*'-acetylnicotinic hydrazide (**5a**) in a 43% yield. We also obtained 1,2-diacyl hydrazine **5a** following a published method.[14] The possibility of using 1,2-disubstituted hydrazines in the synthesis of 1*H*-pyrazole derivatives is shown in the literature.[15] It was found that the reaction of acetylnicotinic hydrazide **5a** with pentane-2,4-diones **1a**,**c** in AcOH leads to 1-acyl-1*H*-pyrazoles **4a**,**d** in less than 10% yields. The obtained results suggest that the formation of 1-acyl-1*H*-pyrazoles can proceed *via* both path *a* and path *b* (Scheme 2).

Scheme 2



The structure of 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles **2a**–**c** was characterized by spectroscopic techniques. Their IR spectra contain intense absorption bands of stretching vibrations of the carbonyl group at 1699 cm^{-1}, C=C and C=N bonds of the pyrazole and pyridine rings in the 1583–1586 cm^{-1} range.

The ^{1}H NMR spectra of compounds **2a**–**c** exhibit the characteristic signals of protons of the pyridine ring, methylsulfanylalkyl fragment, and two methyl substituents 3-CH_3 (2.27–2.30 ppm) and 5-CH_3 (2.62–2.64 ppm) of the pyrazole ring. In the ^{13}C NMR spectrum of compounds **2a**–**c**, the signals in the 152.9–153.0, 141.7–141.9, and 119.3–120.1 ppm regions correspond to the C-3, C-5, and C-4 carbon atoms of the 1*H*-pyrazole ring, and signals at 166.4 ppm can be assigned to the carbon atom of the carbonyl group.

The IR spectra of 1-acyl-1*H*-pyrazoles **4a**–**f** contain intense absorption bands of stretching vibrations of the carbonyl group in the region of 1726–1729 cm^{-1} and of the C=C and C=N bonds of the pyrazole ring at 1601 cm^{-1}.

In contrast to the spectra of 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles **2a**–**c**, the proton signals of the pyridine fragment are absent in the ^{1}H NMR spectra of 1-acyl-1*H*-pyrazoles **4a**–**f**. In the ^{1}H NMR spectra of 1-acetyl-1*H*-pyrazoles **4a**,**d**, an additional singlet signal of the methyl protons of the acetyl group is detected at 2.60 ppm, and in the spectra of 1-propionyl- and 1-pentanoyl-1*H*-pyrazoles **4b**,**c**,**e**,**f**, signals of the protons of methyl (0.92–1.22 ppm) and methylene groups (1.39–1.70, 3.06–3.10 ppm) of the acyl fragments can be observed.

In the ^{13}C NMR spectra of compounds **4a**–**f**, the characteristic signals of the carbon atom of the carbonyl group (171.4–174.8 ppm) predictably appear downfield relative to the signals of a similar carbon atom in the spectra of 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles **2a**–**c** (166.4 ppm).

The structure of 1*H*-pyrazoles **3a**,**c** was confirmed by comparing the spectral characteristics with published data.[16] A characteristic feature of the ^{1}H NMR spectrum of 1*H*-pyrazole **3b** is the presence of the singlet signal of the equivalent 3-CH_3, 5-CH_3 groups at 2.26 ppm and the broadened singlet signal of the amino group proton at 10.6 ppm. The signal of the C-4 carbon atom of the pyrazole ring in the ^{13}C NMR spectrum of compound **3b** is located upfield (111.9 ppm) compared to the corresponding signals in the spectra of 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles **2a**–**c** (119.3–120.1 ppm).

To conclude, either 4-(alkylsulfanyl)methyl-substituted 1-(pyridin-3-yl)carbonyl-1*H*-pyrazoles or 1-acyl-1*H*-pyrazoles, promising in the synthesis of biologically active compounds, depending on the conditions, can be obtained by reacting 4-[(alkylsulfanyl)methyl]pentane-2,4-diones with nicotinic hydrazide.

Experimental

IR spectra were registered on a Shimadzu IR Prestige-21 spectrometer using a thin film of the sample in petroleum jelly. ^{1}H, ^{13}C, and ^{15}N NMR spectra were acquired on a Bruker Avance III 500 MHz spectrometer (500, 125, and 50 MHz, respectively) in DMSO-d_6 (compound **5a**) or $CDCl_3$ (remaining compounds), using residual solvent signals as internal standard ($CDCl_3$: 7.27 ppm for ^{1}H nuclei, 77.1 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei). COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC spectra for compound **2b** were acquired on a Bruker Avance III 500 MHz spectrometer. Mass spectra were recorded on a Shimadzu LCMS-2010 EV system with one quadrupole in positive ion registration mode at a capillary potential of 4.5 kV, electrospray ionization, eluent MeCN–H_2O, 95:5. Elemental analysis was performed on a HEKAtech Euro EA 3000 CHNS-analyzer. Melting points were determined on a Boetius heating bench. GC analysis of the obtained compounds and monitoring of the reaction progress were done on a Khromos 1000 chromatograph, 1 m × 3 mm column, SE-30 (5%) stationary phase, on chromaton N-AW-DMCS (0.16–0.20 mm), at 50–300°C, flame ionization detector, helium carrier gas. Chromatographic separation of compounds was carried out on MN Kieselgel 60 (0.063–0.2 μm) silica gel.

Compounds **1a**–**c**[9a] and *N*-acetylnicotinohydrazide[14] were synthesized by published methods.

Synthesis of {4-[(alkylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}(pyridin-3-yl)methanones 2a–c (General procedure). Method I. Nicotinic hydrazide (0.28 g, 2 mmol)

in EtOH (5 ml) and AcOH (or $EtCO_2H$) (3 mmol) were added with stirring to a solution of compound **1a**–**c** (2 mmol) in EtOH (5 ml). The reaction mixture was heated under reflux for 9 h; it was then diluted with H_2O (in 1:4 ratio), and the resulting mixture as extracted with $CHCl_3$. The extracts were successively washed with 4% aqueous $NaHCO_3$, H_2O, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel, eluent EtOAc–hexane, 1:4 to 1:2 gradient.

Method II. Nicotinic hydrazide (0.28 g, 2 mmol) in EtOH (5 ml) was added with stirring to a solution of compound **1a**–**c** (2 mmol) in EtOH (5 ml). The reaction mixture was heated under reflux for 18 h; it was then diluted with H_2O (in 1:4 ratio), and the resulting mixture was extracted with $CHCl_3$. The extracts were washed with H_2O and dried over $MgSO_4$. They were then processed as in method I.

{4-[(Butylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}(pyridin-3-yl)methanone (2a). Yield 0.37 g (61%, method I), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1699 (C=O), 1583 (C=C, C=N), 1455, 1417, 1378, 1347, 1292, 1245, 1193, 994, 936. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, t, ^3J = 7.4, 6'-CH_3); 1.41 (2H, sext, ^3J = 7.4, 5'-CH_2); 1.60 (2H, quint, ^3J = 7.4, 4'-CH_2); 2.30 (3H, s, 3-CH_3); 2.49 (2H, t, ^3J = 7.4, 3'-CH_2); 2.64 (3H, s, 5-CH_3); 3.53 (2H, s, 1'-CH_2); 7.34–7.44 (1H, m, H-5"); 8.29 (1H, d, ^3J = 7.9, H-4"); 8.75 (1H, br. s, H-6"); 9.18 (1H, s, H-2"). ^{13}C NMR spectrum, δ, ppm: 12.4 (3-CH_3); 12.7 (5-CH_3); 13.7 (C-6'); 22.0 (C-5'); 24.0 (C-1'); 31.4 (C-3'(C-4')); 31.7 (C-4'(C-3')); 120.1 (C-4); 123.0 (C-5"); 129.8 (C-3"); 139.0 (C-4"); 141.9 (C-5); 151.8 (C-2"); 152.1 (C-6"); 152.9 (C-3); 166.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 304 $[M+H]^+$ (65), 345 $[M+H+MeCN]^+$ (100). Found, %: C 63.49; H 7.01; N 13.90; S 10.62. $C_{16}H_{21}N_3OS$. Calculated, %: C 63.33; H 6.98; N 13.85; S 10.57.

{3,5-Dimethyl-4-[(pentylsulfanyl)methyl]-1*H*-pyrazol-1-yl}(pyridin-3-yl)methanone (2b). Yield 0.41 g (64%, method I), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1699 (C=O), 1586 (C=C, C=N), 1456, 1418, 1377, 1348, 1292, 1242, 1193, 995, 935. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (3H, t, ^3J = 7.3, 7'-CH_3); 1.28–1.40 (4H, m, 6',5'-CH_2); 1.61 (2H, quint, ^3J = 7.3, 4'-CH_2); 2.29 (3H, s, 3-CH_3); 2.48 (2H, t, ^3J = 7.3, 3'-CH_3); 2.63 (3H, s, 5-CH_3); 3.54 (2H, s, 1'-CH_2); 7.44 (1H, dd, ^3J = 7.8, ^3J = 4.8, H-5"); 8.32 (1H, d, ^3J = 7.8, H-4"); 8.77 (1H, d, ^3J = 4.8, H-6"); 9.21 (1H, br. s, H-2"). ^{13}C NMR spectrum, δ, ppm: 12.4 3-CH_3); 12.7 (5-CH_3); 14.0 (C-7'); 22.3 (C-6'); 24.2 (C-1'); 29.2 (C-4'); 31.2 (C-5'); 32.0 (C-3'); 119.3 (C-4); 122.9 (C-5"); 129.8 (C-3"); 139.0 (C-4"); 141.8 (C-5); 151.8 (C-2"); 152.1 (C-6"); 153.0 (C-3); 166.4 (C=O). ^{15}N NMR spectrum, δ, ppm: 227.2; 299.6. Mass spectrum, *m*/*z* (I_{rel}, %): 318 $[M+H]^+$ (63), 359 $[M+H+MeCN]^+$ (100). Found, %: C 64.36; H 7.35; N 13.31; S 10.18. $C_{17}H_{23}N_3OS$. Calculated, %: C 64.32; H 7.30; N 13.24; S 10.10.

{4-[(Hexylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}(pyridin-3-yl)methanone (2c). Yield 0.45 g (68%, method I), 0.37 g (56%, method II), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1699 (C=O), 1586 (C=C, C=N), 1455, 1417, 1378, 1347, 1292, 1243, 1193, 994, 936. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, ^3J = 7.1, 8'-CH_3); 1.22–1.32 (4H, m, 7',6'-CH_2); 1.32–1.41 (2H, m, 5'-CH_2); 1.58 (2H, quint, ^3J = 7.4, 4'-CH_2); 2.27 (3H, s, 3-CH_3); 2.46 (2H, t, ^3J = 7.4, 3'-CH_2); 2.62 (3H, s, 5-CH_3); 3.52 (2H, s, 1'-CH_2); 7.40 (1H, dd, ^3J = 7.9, ^3J = 4.8, H-5"); 8.29 (1H, dt, ^3J = 7.9, ^4J = 1.6, H-4"); 8.74 (1H, dd, ^3J = 4.8, ^4J = 1.6, H-6"); 9.18 (1H, s, H-2"). ^{13}C NMR spectrum, δ, ppm: 12.3 (3-CH_3); 12.7 (5-CH_3); 14.0 (C-8'); 22.5 (C-7'); 24.1 (C-1'); 28.6 (C-4'); 29.4 (C-5'); 31.4 (C-3'(C-6')); 32.0 (C-6'(C-3')); 119.3 (C-4); 122.7 (C-5"); 129.6 (C-3"); 138.7 (C-4"); 141.7 (C-5); 151.9 (C-2"); 152.3 (C-6"); 152.9 (C-3); 166.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 332 $[M+H]^+$ (68), 373 $[M+H+MeCN]^+$ (100). Found, %: C 65.29; H 7.67; N 12.76; S 9.72. $C_{18}H_{25}N_3OS$. Calculated, %: C 65.22; H 7.60; N 12.68; S 9.67.

Synthesis of 4-[(alkylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazoles 3a–c (General method). Nicotinic hydrazide (0.28 g, 2 mmol) in MeOH (5 ml) and $ZnCl_2$ (0.11 g, 0.8 mmol) were added with stirring to a solution of compound **1a**–**c** (2 mmol) in MeOH (5 ml). The reaction mixture was heated under reflux for 16 h; it was then diluted with H_2O (in 1:4 ratio), and the resulting mixture was extracted with $CHCl_3$. The extracts were washed with H_2O and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford a mixture of compounds **3a**–**c** with methyl nicotinate in a 1:0.7 ratio (0.66, 0.70, 0.73 g, respectively). The mixture was purified by column chromatography on silica gel, eluent EtOAc–hexane, 1:4 to 1:2 gradient to give analytical samples of methyl nicotinate and compounds **3a**–**c**.

4-[(Butylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazole (3a). Yield 0.38 g (96%). IR, ^1H, and ^{13}C NMR spectra of compound **3a** match those published earlier.[16]

3,5-Dimethyl-4-[(pentylsulfanyl)methyl]-1*H*-pyrazole (3b). Yield 0.40 g (95%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 3201 (N–H), 3144 (N–H), 3091 (N–H), 1590 (C=N), 1514 (C=C), 1465, 1437, 1420, 1378, 1303, 1248, 1203, 1152 (N–H), 1033, 1001. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, ^3J = 7.1, 7'-CH_3); 1.24–1.36 (4H, m, 6',5'-CH_2); 1.57 (2H, quint, ^3J = 7.1, 4'-CH_2); 2.26 (6H, s, 3,5-CH_3); 2.42 (2H, t, ^3J = 7.4, 3'-CH_3); 3.53 (2H, s, 1'-CH_2); 10.60 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 10.8 (3,5-CH_3); 14.0 (C-7'); 22.3 (C-6'); 24.7 (C-1'); 29.2 (C-5'); 31.5 (C-3'(C-4')); 31.7 (C-4'(C-3')); 111.9 (C-4); 142.8 (C-3,5). Found, %: C 62.28; H 9.53; N 13.24; S 15.16. $C_{11}H_{20}N_2S$. Calculated, %: C 62.22; H 9.49; 13.19; S 15.10.

4-[(Hexylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazole (3c). Yield 0.41 g (91%). IR, ^1H, and ^{13}C NMR spectra of compound **3c** match those published earlier.[16]

Methyl nicotinate. Yield 0.24–0.26 g (88–95%), mp 38–39°C (EtOAc–hexane, 1:4) (mp 38–39°C[10a]). IR, ^1H, and ^{13}C NMR spectra of methyl nicotinate match those published earlier.[10]

Synthesis of 1-{4-[(alkylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}alkanones 4a–f (General method). Nicotinic hydrazide (0.28 g, 2 mmol) in carboxylic acid (acetic, propanoic, pentanoic) (3 ml) was added with

stirring to a solution of compound **1a**,**c** (2 mmol) in carboxylic acid (3 ml). The reaction mixture was stirred at 112–116°C for 2–3 h. After the completion of the reaction, the formed precipitate of nicotinic acid was separated by filtration. The filtrate was diluted with H_2O (in 1:8 ratio), and the resulting mixture was extracted with $CHCl_3$ (3×15 ml). The extracts were successively washed with 4% aqueous $NaHCO_3$ (3×15 ml), H_2O (2×15 ml), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel, eluent EtOAc–hexane, 1:7.

1-{4-[(Butylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanone (4a). Yield 0.39 g (81%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1726 (C=O), 1601 (C=C, C=N), 1457, 1429, 1377, 1368, 1334, 1291, 1241. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, t, ^3J = 7.3, 6'-CH_3); 1.38 (2H, sex, ^3J = 7.3, 5'-CH_2); 1.55 (2H, quint, ^3J = 7.3, 4'-CH_2); 2.27 (3H, s, 3-CH_3); 2.42 (2H, t, ^3J = 7.3, 3'-CH_2); 2.50 (3H, s, 5-CH_3); 2.64 (3H, s, CH_3CO); 3.46 (2H, s, 1'-CH_2). ^{13}C NMR spectrum, δ, ppm: 12.3 (3-CH_3); 12.8 (5-CH_3); 13.7 (C-6'); 22.1 (C-5'); 23.6 (CH_3CO); 24.1 (C-1'); 31.4 (C-3'(C-4')), 31.5 (C-4'(C-3')); 118.6 (C-4); 140.6 (C-5); 151.9 (C-3); 171.4 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 241 $[M+H]^+$ (100), 282 $[M+H+MeCN]^+$ (8). Found, %: C 60.07; H 8.34; N 11.61; S 13.45. $C_{12}H_{20}N_2OS$. Calculated, %: C 59.96; H 8.39; N 11.65; S 13.34.

1-{4-[(Butylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}propan-1-one (4b). Yield 0.39 g (77%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1729 (C=O), 1601 (C=C, C=N), 1459, 1429, 1377, 1363, 1317, 1277, 1237. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 (3H, t, ^3J = 7.3, 6'-CH_3); 1.22 (3H, t, ^3J = 7.4, C$\underline{H}_3CH_2CO$); 1.40 (2H, sex, ^3J = 7.3, 5'-CH_2); 1.55 (2H, quint, ^3J = 7.3, 4'-CH_2); 2.27 (3H, s, 3-CH_3); 2.43 (2H, t, ^3J = 7.3, 3'-CH_2); 2.51 (3H, s, 5-CH_3); 3.10 (2H, q, ^3J = 7.4, $CH_3C\underline{H}_2CO$); 3.47 (2H, s, 1'-CH_2). ^{13}C NMR spectrum, δ, ppm: 8.4 ($\underline{C}H_3CH_2CO$); 12.3 (3-CH_3); 12.8 (5-CH_3); 13.7 (C-6'); 22.1 (C-5'); 24.1 (C-1'); 28.7 ($CH_3\underline{C}H_2CO$); 31.4 (C-3'(C-4')); 31.5 (C-4'(C-3')); 118.2 (C-4); 140.6 (C-5); 151.6 (C-3); 174.8 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 255 $[M+H]^+$ (100), 296 $[M+H+MeCN]^+$ (8). Found, %: C 61.49; H 8.84; N 11.08; S 12.68. $C_{13}H_{22}N_2OS$. Calculated, %: C 61.38; H 8.72; N 11.01; S 12.60.

1-{[4-(Butylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}pentan-1-one (4c). Yield 0.42 g (74%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1729 (C=O), 1601 (C=C, C=N), 1456, 1429, 1377, 1353, 1321, 1280, 1233. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, t, ^3J = 7.4, 6'-CH_3); 0.92 (3H, t, ^3J = 7.4, 5"-CH_3); 1.31−1.43 (4H, m, 5',4"-CH_2); 1.53 (2H, quint, ^3J = 7.4, 4'-CH_2); 1.68 (2H, quint, ^3J = 7.4, 3"-CH_2); 2.25 (2H, s, 3-CH_3); 2.40 (2H, t, ^3J = 7.4, 3'-CH_2); 2.49 (3H, s, 5-CH_3); 3.06 (2H, t, ^3J = 7.4, 2"-CH_2); 3.45 (2H, s, 1'-CH_2). ^{13}C NMR spectrum, δ, ppm: 12.3 (3-CH_3); 12.8 (5-CH_3); 13.6, 13.9 (C-6',5"); 22.0 (C-5'(C-4")); 22.2 (C-4"(C-5')); 24.0 (C-1'); 26.4 (3"-CH_2); 31.4 (C-3'(C-4')); 31.5 (C-4'(C-3')); 34.8 (2"-CH_2); 118.2 (C-4); 140.6 (C-5); 151.5 (C-3); 174.1 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 283 $[M+H]^+$ (100), 324 $[M+H+MeCN]^+$ (8). Found, %: C 63.89; H 9.34; N 10.01; S 11.45. $C_{15}H_{26}N_2OS$. Calculated, %: C 63.79; H 9.28; N 9.92; S 11.35.

1-{4-[(Hexylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}ethanone (4d). Yield 0.34 g (63%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1727 (C=O), 1601 (C=C, C=N), 1457, 1429, 1377, 1368, 1334, 1291, 1241. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (3H, t, ^3J = 7.1, 8'-CH_3); 1.21–1.31 (4H, m, 7',6'-CH_2); 1.31–1.36 (2H, m, 5'-CH_2); 1.56 (2H, quint, ^3J = 7.4, 4'-CH_2); 2.28 (3H, s, 3-CH_3); 2.42 (2H, t, ^3J = 7.4, 3'-CH_2); 2.51 (3H, s, 5-CH_3); 2.65 (3H, s, CH_3CO); 3.47 (2H, s, 1'-CH_2). ^{13}C NMR spectrum, δ, ppm: 12.3 (3-CH_3); 12.9 (5-CH_3); 14.0 (C-8'); 22.5 (C-7'); 23.6 ($\underline{C}H_3CO$); 24.1 (C-1'); 28.6 (C-4'); 29.4 (C-5'); 31.4 (C-3'(C-6')); 31.8 (C-6'(C-3')); 118.6 (C-4); 140.6 (C-5); 151.9 (C-3); 171.5 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 269 $[M+H]^+$ (100), 310 $[M+H+MeCN]^+$ (7). Found, %: C 62.74; H 9.10; N 10.36; S 12.02. $C_{14}H_{24}N_2OS$. Calculated, %: C 62.64; H 9.01; N 10.44; S 11.95.

1-{4-[(Hexylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}propan-1-one (4e). Yield 0.34 g (60%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1729 (C=O), 1601 (C=C, C=N), 1461, 1428, 1377, 1362, 1317, 1278, 1234. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.86 (3H, t, ^3J = 7.3, 8'-CH_3); 1.21 (3H, t, ^3J = 7.4, C$\underline{H}_3CH_2CO$); 1.21–1.30 (4H, m, 7',6'-CH_2); 1.30–1.42 (2H, m, 5'-CH_2); 1.57 (2H, quint, ^3J = 7.3, 4'-CH_2); 2.26 (3H, s, 3-CH_3); 2.41 (2H, t, ^3J = 7.3, 1'-CH_2); 2.50 (3H, s, 5-CH_3); 3.10 (2H, q, ^3J = 7.4, $CH_3C\underline{H}_2CO$); 3.46 (2H, s, 1'-CH_2). ^{13}C NMR spectrum, δ, ppm: 8.4 ($\underline{C}H_3CH_2CO$); 12.3 (3-CH_3); 12.8 (5-CH_3); 14.0 (C-8'); 22.5 (C-7'); 24.1 (C-1'); 28.6, 28.7 (C-4', $CH_3\underline{C}H_2CO$); 29.4 (C-5'); 31.4 (C-3'(C-6')); 31.7 (C-6'(C-3')); 118.3 (C-4); 140.6 (C-5); 151.6 (C-3); 174.8 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 283 $[M+H]^+$ (100), 324 $[M+H+MeCN]^+$ (5). Found, %: C 63.84; H 9.30; N 9.99; S 11.42. $C_{15}H_{26}N_2OS$. Calculated, %: C 63.79; H 9.28; N 9.92; S 11.35.

1-{4-[(Hexylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazol-1-yl}pentan-1-one (4f). Yield 0.31 g (50%), colorless oil. IR spectrum (thin film), ν, cm^{-1}: 1728 (C=O), 1601 (C=C, C=N), 1456, 1428, 1378, 1353, 1321, 1281, 1231. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.86 (3H, t, ^3J = 7.1, 8'-CH_3); 0.94 (3H, t, ^3J = 7.4, 5"-CH_3); 1.20–1.32 (4H, m, 7',6'-CH_2); 1.30–1.36 (2H, m, 5'-CH_2); 1.39 (2H, sex, ^3J = 7.4, 4"-CH_2); 1.55 (2H, quint, ^3J = 7.4, 4'-CH_2); 1.70 (2H, quint, ^3J = 7.4, 3"-CH_2); 2.27 (3H, s, 3-CH_3); 2.41 (2H, t, ^3J = 7.4, 3'-CH_2); 2.50 (3H, s, 5-CH_3); 3.07 (2H, t, ^3J = 7.4, 2"-CH_2); 3.46 (2H, s, 1'-CH_2). ^{13}C NMR spectrum, δ, ppm: 12.3 (3-CH_3); 12.8 (5-CH_3); 13.9, 14.0 (C-5", C-8'); 22.2 (C-7'(C-4")); 22.5 (C-4"(C-7')); 24.1 (C-1'); 26.4 (C-3"); 28.6 (C-4'); 29.5 (C-5'); 31.4, 31.7 (C-6', C-3'); 34.9 (C-2"); 118.3 (C-4); 140.6 (C-5); 151.6 (C-3); 174.1 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 311 $[M+H]^+$ (100), 352 $[M+H+MeCN]^+$ (5). Found, %: C 65.84; H 9.80; N 9.16; S 10.46. $C_{17}H_{30}N_2OS$. Calculated, %: C 65.76; H 9.74; N 9.02; S 10.33.

Nicotinic acid. Yield 0.24–0.25 g (98–99%), mp 236–237°C (EtOH) (mp 237.7–239.1°C (EtOAc–EtOH, 4:1)[13a]). IR, ^{1}H, and ^{13}C NMR spectra of nicotinic acid match those published earlier.[13]

***N*'-Acetylpyridine-3-carbohydrazide (5a)**. Method I.[14] Ac_2O (0.4 ml, 4 mmol) was added to a solution of nicotinic hydrazide (0.41 g, 3 mmol) in H_2O (4.5 ml). The reaction mixture was stirred at room temperature for 30 min. Then the solvent was evaporated under reduced pressure, and the residue was recrystallized from PhH. Yield 0.51 g (95%), mp 139–140°C (PhH). IR spectrum (petroleum jelly), ν, cm^{-1}: 3282 (NH), 3206 (NH), 1651 (C=O), 1645 (C=O), 1509, 1486, 1420, 1358 (C–N), 1336, 1275 (C–N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.92 (3H, s, CH_3CO); 7.50–7.53 (1H, m, H-5'); 8.18 (1H, d, ^3J = 8.0, H-4'); 8.71 (1H, dd, ^3J = 4.7, ^4J = 1.5, H-6'); 8.98 (1H, br. s, H-2'); 9.99 (1H, br. s, NHCO); 10.52 (1H, br. s, N<u>H</u>COCH$_3$) ^{13}C NMR spectrum, δ, ppm: 20.9 (<u>C</u>H$_3$CO); 124.1 (C-5'); 128.6 (C-3'); 135.7 (C-4'); 148.7 (C-2'); 152.8 (C-6'); 164.7 (CO); 169.3 (<u>C</u>OCH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 178 $[M–H]^+$ (100). Found, %: C 53.71; H 5.15; N 23.52. $C_8H_9N_3O_2$. Calculated, %: C 53.63; H 5.06; N 23.45.

Method II. A solution of nicotinic hydrazide (0.28 g, 2 mmol) in AcOH (6 ml) was stirred at 112−116°C for 2.5 h. AcOH was then evaporated under reduced pressure, the residue was washed with $CHCl_3$ and dried. A mixture (0.32 g) was obtained, which contains the starting compound and *N*'-acetylpyridine-3-carbohydrazide (**5a**) in a 1:1 ratio according to ^{1}H NMR.

Reaction of 3-[(butylsulfanyl)methyl]pentane-2,4-dione (1a) with *N*'-acetylpyridine-3-carbohydrazide (5a). A mixture of compound **1a** (0.20 g, 1 mmol) and *N*'-acetylpyridine-3-carbohydrazide (**5a**) (0.18 g, 1 mmol) in AcOH (3 ml) was stirred at 112−116°C for 2.5 h. AcOH was then evaporated, and the residue was mixed with H_2O in 1:8 ratio. The resulting mixture was extracted with $CHCl_3$ (3×10 ml). The extracts were successively washed with 4% aqueous $NaHCO_3$ (3×10 ml), H_2O (2×10 ml) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure; the residue (0.23 g) was subjected to chromatography on silica gel, eluent EtOAc–hexane, 1:7.

Starting compound **1a** (0.16 g, 80%) and 1-{4-[(hexylsulfanyl)methyl]-3,5-dimethylpyrazol-1-yl]ethanone (**4d**) (0.021 g, 8%) were obtained from *N*'-acetylpyridine-3-carbohydrazide (**5a**) (0.18 g, 1 mmol) and compound **1c** (0.23 g, 1 mmol).

The study was carried out on the subject of state assignment (No. AAAA-A19-119011790021-4).

Spectral and analytical results were obtained using the equipment of the Center for Collective Use "Chemistry" of Ufa Institute of Chemistry of the Ufa Federal Research Center of the Russian Academy of Sciences.

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