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POLYFUNCTIONAL PYRAZOLES.

1. SYNTHESIS OF 3-ARYL-1-(2-CYANOETHYL)-4-FORMYLPYRAZOLES AND THEIR 3-(5-METHYLFUR-2-YL)-SUBSTITUTED ANALOG

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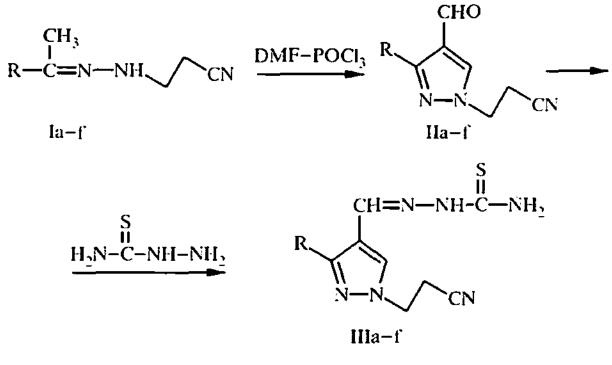
Previously unknown substituted pyrazoles were obtained by the reaction of the 2-cyanoethylhydrazones of aryl methyl ketones and 5-methylfur-2-yl methyl ketone with the Vilsmeier–Haack reagent.

Heterocyclic compounds of the pyrazole series with several functional substituents in the ring are of great interest for synthetic investigations [1-3]. Of particular value in our opinion are the pyrazoles containing electrophilic groups (e.g., formyl or nitrile). The former, in particular, can be used successfully in various forms of the pyrazole ring annellation [4], while the latter can be used to create an assembly of rings with an azole unit, especially if they are attached to the heterocycle by means of a methylene chain [5, 6]. For this reason an attempt was made in the present work to synthesize new polyfunctional pyrazoles containing a 2-cyanoethyl substituent at position 1 and a formyl substituent at position 4 of the heterocycle. The simplest and preparatively most acceptable method for the production of such derivatives was the approach based on the cyclization of the respective 2-cyanoethylhydrazones of aryl methyl ketones (Ia-e) and 5-methylfur-2-yl methyl ketone (If) by the action of the DMF–$POCl_3$ system, which was successfully used earlier in the synthesis of 1-aryl-4-formylpyrazoles [7-9]. In spite of the low stability the hydrazones of type (I) are converted with high yields under the conditions of the Vilsmeier–Haack reaction into 3-aryl-1-(2-cyanoethyl)-4-formylpyrazoles (IIa-e) and 1-(2-cyanoethyl)-4-formyl-3-(5-methylfur-2-yl)pyrazole (IIf) respectively.



I-III a R = C_6H_5; b R = 4-BrC_6H_4; c R = 4-ClC_6H_4; d R = 4-FC_6H_4;
e R = 4-$C_6H_5C_6H_4$; f R = 5-methylfur-2-yl

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TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, % C	H	N	mp, °C (ethanol)	Yield, %
IIa	$C_{13}H_{11}N_3O$	68.83 69.33	4.90 4.88	18.32 18.67	68-70	67
IIb	$C_{13}H_{10}BrN_3O$	50.90 51.31	3.07 3.28	13.62 13.82	116-117	78
IIc	$C_{13}H_{10}ClN_3O$	59.74 60.11	3.63 3.85	15.93 16.18	104-105	76
IId	$C_{13}H_{10}FN_3O$	63.93 64.19	4.01 4.11	16.91 17.24	88-90	73
IIe	$C_{19}H_{15}N_3O$	76.03 75.74	6.45 6.31	13.68 13.95	107-108	65
IIf	$C_{12}H_{11}N_3O_2$	62.52 62.88	4.98 4.80	18.10 18.34	80-90	74
IIIa	$C_{14}H_{14}N_6S$	56.04 56.37	4.51 4.69	27.88 28.18	190-191	85
IIIb	$C_{14}H_{13}BrN_6S$	44.29 44.56	3.32 3.44	22.18 22.28	125-126	91
IIIc	$C_{14}H_{13}ClN_6S$	52.79 50.52	3.71 3.90	25.03 25.26	122-123	93
IIId	$C_{14}H_{13}FN_6S$	52.81 53.16	4.29 4.11	26.26 26.58	177-178	87
IIIe	$C_{20}H_{18}N_6S$	63.83 64.17	4.60 4.80	22.61 22.75	182-183	81
IIIf	$C_{13}H_{14}N_6OS$	51.79 51.65	4.78 4.63	27.44 27.81	184-186	84

The structure of compounds IIa-f (Table 1), which are stable colorless or light-yellow crystalline substances, was confirmed by elemental analysis, IR and PMR spectra (Table 2), and chemical transformations. Their IR spectra are characterized by the presence of strong absorption bands for the stretching vibrations of the C=O bond (1660-1665 cm^{-1}) and weak bands for the C≡N bond (2260-2270 cm^{-1}). In the PMR spectra in the downfield region there are singlets for the aldehyde group at 9.93-10.09, for the proton at position 5 of the pyrazole ring at 8.49-8.61 ppm, and also characteristic doublets or multiplets for the protons of the substituent at position 3. The protons of the cyanoethyl group appear in the form of two triplets with a spin–spin coupling constant of 7 Hz in the regions of 4.63-4.70 (α-CH) and 3.22-3.30 ppm (β-CH).

The pyrazoles IIa-f are converted by the action of thiosemicarbazide into the corresponding semicarbazones IIIa-f, the characteristics of which are presented in Table 1.

TABLE 2. The Spectral Characteristics of Compounds IIa-f

Compound	IR spectrum, ν, cm^{-1} C=O	IR spectrum, ν, cm^{-1} C≡N	PMR spectrumt, δ (ppm) CH=O s (1H)	5-CH= s (1H)	Ar	α-CH$_2$ t (2H)	β-CH$_2$ t (2H)
IIa	1660	2265	9.98	8.50	7.39-7.93 (5H, m)	4.64	3.32
IIb	1660	2260	10.07	8.56	7.34 (2H, d); 7.68 (2H, d)	4.70	3.28
IIc	1665	2260	10.07	8.54	7.28 (2H, d); 7.70 (2H, d)	4.68	3.30
IId	1665	2270	9.93	8.49	7.35-7.84 (4H, m)	4.60	3.23
IIe	1665	2265	10.04	8.54	7.28-8.12 (9H, m)	4.67	3.26
IIf*	1660	2260	10.09	8.61	6.20 (2H, d)	4.63	3.30

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* The singlet signal of the CH_3 group is found at 2.34 ppm.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in KBr tablets. The PMR spectra were obtained on a Bruker WP-100SY instrument at 100 MHz for solutions in DMSO-d_6.

2-Cyanoethylhydrazones of Aryl Methyl Ketones (Ia-e) and 5-Methylfur-2-yl Methyl Ketone (If). To a solution of the respective ketone (0.12 mol) in of glacial acetic acid (15 ml) 2-cyanoethylhydrazine (9.5 g, 0.12 mol) was added in one portion. After 3 h the precipitated hydrazone was filtered off, washed with ethanol, and dried for 1 h in a vacuum desiccator over phosphorus pentoxide. The yields of the products Ia-f amounted to 70-80%. On account of their low stability the products were used immediately in further transformations.

3-Aryl- and 3-(5-Methylfur-2-yl)-1-(2-cyanoethyl)-4-formylpyrazoles (IIa-f). Phosphorus oxychloride (38.4 g, 0.25 mol) was added with stirring to 40 ml of dry DMF cooled to 0°C. After 0.5 h a solution of the hydrazone Ia-f (0.1 mol) in 20 ml of DMF was added at the same temperature. After 0.5 h the temperature of the mixture was raised to room temperature, and the mixture was stirred for 0.5 h and then for a further 2 h at 60-65°C. After cooling the reaction mixture was poured into 500 ml of icy water, neutralized to pH 7-8 with sodium bicarbonate solution, and filtered. The precipitate was washed with water, dried, and crystallized from ethanol.

The Thiosemicarbazones of 3-Aryl- and 3-(5-Methylfur-2-yl)-1-(2-cyanoethyl)-4-formylpyrazoles (IIIa-f). A mixture of the aldehyde IIa-f (0.01 mol) and thiosemicarbazide (1 g, 0.011 mol) in 5 ml of ethanol was boiled for 2 h. After cooling the precipitate was filtered off and crystallized from ethanol.

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