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Functionally Substituted 3-Heterylpyrazoles: XI.* 3-[3-Aryl(heteryl)pyrazol-4-yl]propenoic and Propanoic acids

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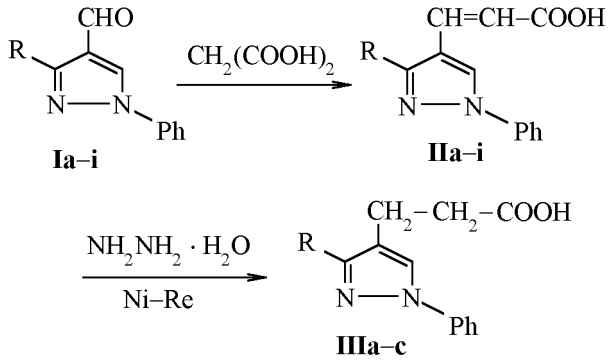
Abstract—3-Aryl(heteryl)-4-formylpyrazoles by condensation with malonic acid furnish 3-[3-aryl(heteryl)-pyrazol-4-yl]propenoic acids that in the presence of Raney nickel are reduced by hydrazine hydrate to 3-[3-aryl(heteryl)pyrazol-4-yl]propanoic acids. The successive conversion of both type acids into the corresponding acyl chlorides, esters, and amides was performed.

3-Aryl(heteryl)-4-formylpyrazoles that we used [2] in the synthesis of the corresponding (pyrazol-4-yl)carboxylic acids proved to be convenient substrates for preparation of 3-(pyrazol-4-yl)propenoic acids. We turned our attention to this type compounds for recently the 3-heterylpropenoic acids were growing in importance because substances with pronounced pharmacological activity were found among them [3–5].

We found that 3-aryl(heteryl)-4-formylpyrazoles **Ia–i** with malonic acid under conditions of Knoevenagel reaction furnish 3-(pyrazol-4-yl)propenoic acids **IIa–i** in high yield (Table 1). In the IR spectra of solid samples appear the absorption bands belonging to bonds C=C (1635–1645), C=O (1710–1720), and also OH (2550–3000 cm^{-1}) thus revealing their dimeric structure [6]. The acids of **II** type are *trans*-isomers that is confirmed by appearance in their ^{1}H NMR spectra of a doublet at 6.36–6.53 ppm with a coupling constant of 17–18 Hz from the α-proton at the double bond. Therewith the doublet from the β-CH= is overlapped by the signals from the aromatic substituents attached to the pyrazole ring (7.11–7.93 ppm).

Taking into consideration that 3-heterylpropanoic acids [7] and their derivatives [8, 9] also are subject to the tests for biological activity we have studied the ways of converting some of unsaturated acids into their hydrogenated analogs **III**. It was established that pyrazolepropenoic acids containing in position *3* of the heterocycle aromatic substituents (**IIa, c, e, f**) and also heterocyclic 3-pyridyl and 3-coumaryl substituents (**IIh, i**) in the presence of catalytic amounts of Raney nickel are reduced with hydrazine hydrate to afford in high yield 3-[3-aryl(heteryl)pyrazol-4-yl]-propanoic acids (**IIIa–f**). At the same time the double bond of acid **IIg** with a thienyl substituent in the pyrazole ring under the same conditions is not hydrogenated apparently due to poisoning of the catalyst by the sulfur-containing moiety of the substrate.

Acids **IIIa–f** (Table 2) are colorless crystalline compounds with the structure consistent with their IR and ^{1}H NMR spectra. Thus in their ^{1}H NMR spectra alongside the signals from substituents R at the pyrazole ring appear broadened singlets from the protons of carboxy groups (12.07–12.24 ppm), and also triplets from the α-methylene protons (2.78–2.90 ppm) and from β-methylene protons (2.56–2.62 ppm) of the hydrocarbon chain.



I, II$(24), R = Ph (**a**), 4-$FC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-$CH_3C_6H_4$ (**e**), 4-$CH_3OC_6H_4$ (**f**), 2-thienyl (**g**), 3-pyridyl (**h**), 3-coumaryl (**i**); **III**, R = Ph (**a**), 4-ClC_6H_4(b), 4-$CH_3C_6H_4$ (**c**), 4-$CH_3OC_6H_4$ (**d**), 3-pyridyl (**e**), 3-coumaryl (**f**).

* For communication X see [1].

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Table 1. Yields, melting points, IR and ^{1}H NMR spectra and elemental analyses of 3-(pyrazol-4-yl)propenoic acids **IIa**–**i**

Compd. no.	Yield %	mp, °C	^{1}H NMR spectra, δ, ppm	IR spectra, KBr, cm^{-1}			Found			Formula	Calcd.		
				ν(C=C)	ν(C=O)	ν(OH)	C	H	N		C	H	N
IIa	78	203–205	6.45 e (1H, CH=), 7.38–7.92 m (11H, H arom, CH=), 9.24 s (1H, C^5H), 12.15 br.s (1H, COOH)	1640	1715	2600–3000	74.68	5.07	9.61	$C_{18}H_{14}N_2O_2$	74.47	4.86	9.65
IIb	80	218–219	6.43 e (1H, CH=), 7.27–7.89 m (10H, H arom, CH=), 9.24 s (1H, C^5H), 12.16 br.s (1H, COOH)	1645	1720	2550–2980	70.51	4.20	9.18	$C_{18}H_{13}FN_{202}$	70.12	4.25	9.09
IIc	83	217–218	6.45 e (1H, CH=), 7.39–7.95 m (10H, H arom, CH=), 9.23 s (1H, C^5H), 12.18 br.s (1H, COOH)	1640	1715	2580–3000	66.22	3.76	8.78	$C_{18}H_{13}C_1N_2O_2$	66.57	4.03	8.63
IId	77	223–225	6.40 e (1H, CH=), 7.29–7.74 m (10H, H arom, CH=), 8.95 s (1H, C^5H), 12.11 br.s (1H, COOH)	1635	1720	2600–2950	58.43	3.57	7.42	$C_{18}H_{13}BrN_2O_2$	58.56	3.55	7.59
IIe	71	215–216	2.34 s (3H, CH_3), 6.39 e (1H, CH=), 7.25–7.89 m (10H, H arom, CH=), 9.22 s (1H, C^5H), 12.40 br.s (1H, COOH)	1635	1720	2500–2950	74.64	5.11	9.41	$C_{19}H_{16}N_2O_2$	74.98	5.30	9.20
IIf	69	232–233	3.18 s (3H, CH3O), 6.46 e (1H, CH=), 7.11 e (2H, H arom), 7.39 t (1H, H arom), 7.51–7.59 m (^{5}H, H arom, 2950 CH=), 7.93 e (H arom), 9.20 s (1H, C^5H), 12.37 br.s (1H, COOH)	1640	1710	2600–	69.88	5.27	8.70	$C_{19}Hi_6N_2O_3$	71.24	5.03	8.74
IIg	67	222–224	6.53 e (1H, CH=), 7.25–7.90 m (9H, H arom, CH=), 9.24 s (1H, C^5H), 12.24 br.s (1H, COOH)	1635	1715	2550–2980	65.03	3.93	9.34	$C_{16}H_{12}N_2O_2S$	64.85	4.08	9.45
IIh	75	223–225	6.49 e (1H, CH=), 7.41–8.88 m (9H, H arom, CH=), 9.28 s (1H, C^5H), 12.35 br.s (1H, COOH)	1640	1715	2590–2990	70.37	4.57	14.26	$C_{17}H_{13}N_3O_2$	70.09	4.50	14.42
IIi	66	259–260	6.36 e (1H, CH=), 7.43–7.91 m (10H, H arom, CH=), 8.40 s (1H, CH=), 9.23 (1H, C^5H), 12.28 br.s (1H, COOH)	1645	1710, 1740[a]	2600–2950	70.12	4.11	7.63	$C_{21}H_{14}N_{204}$	70.39	3.94	7.82

[a] Absorption band of C=O group from coumarin ring.

Table 2. Yields, melting points, IR and ^{1}H NMR spectra, and elemental analyses of 3-(pyrazol-4-yl)propanoic acids **IIIa–f**

Compd. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm	IR spectrum, KBr, cm^{-1}		Found, %			Formula	Calculated, %		
				ν(C=O)	ν(OH)	C	H	N		C	H	N
IIIa	64	141–142	2.59 t (2H, CH_2), 2.87 t (2H, CH_2), 7.29–7.89 m (10H, H arom), 8.49 s (1H, C^5H), 12.07 br.s (1H, COOH)	1720	2570–2980	74.31	5.36	9.64	$C_{18}H_{16}N_2O_2$	73.96	5.52	9.58
IIIb	58	121–122	2.62 t (2H, CH_2), 2.91 t (2H, CH_2), 7.36–7.93 m (9H, H arom), 8.43 s (1H, C^5H), 12.19 br.s (1H, COOH)	1725	2600–2950	66.49	4.48	8.77	$C_{18}H_{15}ClN_2O_2$	66.16	4.63	8.57
IIIc	72	103–104	2.29 s (3H, CH_3), 2.60 t (2H, CH_2), 2.84 t (2H, CH_2), 7.21–7.75 m (9H, H arom), 8.44 s (1H, C^5H), 12.24 br.s (1H, COOH)	1720	2580–2960	74.21	6.02	9.01	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.14
IIId	59	140–141	2.62 t (2H, CH_2), 2.90 t (2H, CH_2), 3.81 s (3H, CH_3O), 7.04–7.87 m (9H, H arom), 8.39 s (1H, C^5H), 12.31 br.s (1H, COOH)	1720	2600–3000	80.05	5.59	8.74	$C_{19}H_{18}N_2O_3$	70.79	5.63	8.69
IIIe	61	194–195	2.52 t (2H, CH_2), 2.94 t (2H, CH_2), 7.33–8.86 m (9H, H arom), 9.27 s (1H, C^5H), 12.31 br.s (1H, COOH)	1720	2600–2980	69.39	5.13	14.47	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
IIIf	49	159–160	2.56 t (2H, CH_2), 2.78 t (2H, CH_2), 7.32–7.87 m (9H, H arom), 8.39 s (1H, CH=), 8.44 s (1H, C^5H), 12.13 br.s (1H, COOH)	1720, 1745[a]	2570–2950	69.69	4.51	7.80	$C_{21}H_{16}N_2O_4$	69.99	4.48	7.77

[a] Absorption band of C=O group from coumarin ring.

Acids **IIa–c, f, g** and **IIIa–d** treated with thionyl chloride provide the corresponding acyl chlorides **IVa–e** and **Va–d** in high yield (Table 3). The latter react with alcohols, phenols, and amines to furnish esters **VIa–d** and amides **VIe–j** of 3-(pyrazol-4-yl)-propenoic acids (Table 4), and also esters **VIIa–c** and amides **VIId–f** of 3-(pyrazol-4-yl)propanoic acids (Table 5).

By treating acyl chlorides **IVa, b, d** with sodium thiocyanate in acetone substituted 3-(pyrazol-4-yl)-propenoyl isothiocyanates **VIIIa–c** were obtained in high yield.

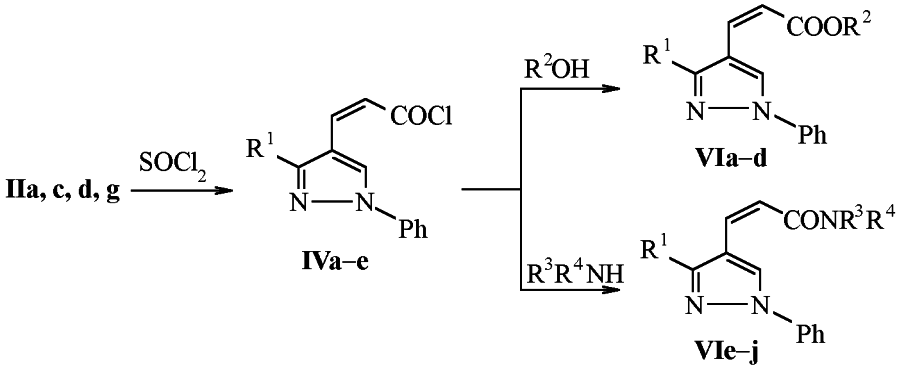
EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from KBr pellets. ^{1}H NMR spectra were registered on spectrometer Varian Gemini (300 MHz) in $(CD_3)_2SO$, internal reference TMS.

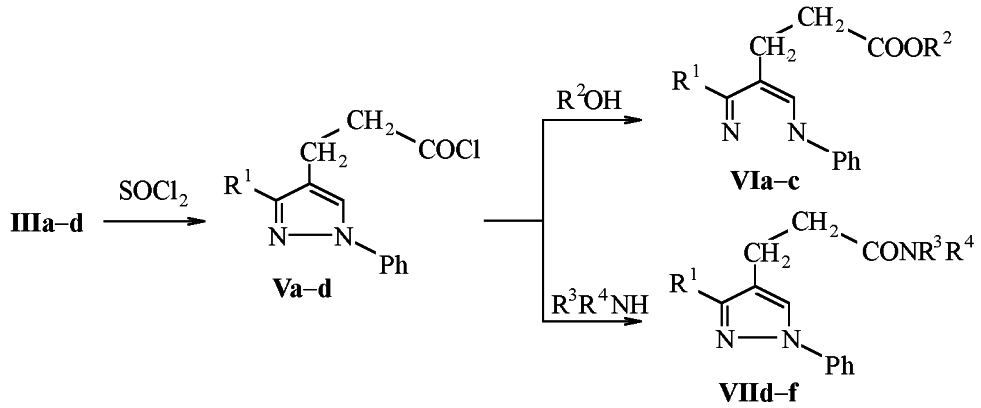
3-[3-Aryl(heteryl)pyrazol-4-yl]propenoic acids IIa–i. To a solution of 0.04 mol of aldehyde **Ia–i** in 60 ml of anhydrous pyridine was added 8.74 g (0.084 mol) of malonic acid, 1 ml of piperidine, and the mixture was heated on a sand bath first to 100°C for 0.5 h, and then 4 h at reflux till the end of carbon

Table 3. Yields, melting points, and elemental analyses of 3-(pyrazol-4-yl)propenoyl and propanoyl chlorides **IVa–e, Va–d**

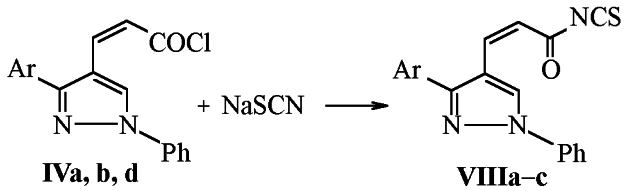
Compd. no.	Yield, %	mp, °C	Found Cl, %	Formula	Calculated Cl, %
IVa	84	121–122	11.13	$C_{18}H_{13}ClN_2O$	11.48
IVb	81	176–177	11.09	$C_{18}H_{12}FClN_2O$	10.85
IVc	92	155–157	20.87	$C_{18}H_{12}Cl_2N_2O$	20.66
IVd	84	150–152	10.04	$C_{19}H_{15}ClN_2O_2$	10.46
IVe	68	221–223	11.67	$C_{16}H_{11}ClN_2OS$	11.26
Va	81	92–93	11.13	$C_{18}H_{15}ClN_2O$	11.41
Vb	78	80–81	20.89	$C_{18}H_{14}Cl_2N_2O$	20.54
Vc	74	106–107	11.13	$C_{19}H_{17}ClN_2O$	10.91
Vd	64	107–108	9.98	$C_{19}H_{17}ClN_2O_2$	10.40



IV, R^1 = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-$CH_3OC_6H_4$ (**d**), 2-thyonyl (**e**); VI, R^1 = 4-$CH_3OC_6H_4$, R^2 = Et (**a**); R^2 = $PhCH_2$: R^1 = 4-ClC_6H_4 (**b**), 4-$CH_3OC_6H_4$ (**c**); R^1 = Ph, R^2 = 2-CH_3O-4-(CH=O)C_6H_3 (**d**); R^1 = 4-ClC_6H_4, R^3 = R^4 = H (**e**); R^1 = 4-FC_6H_4, R^3 = H, R^4 = $PhCH_2$ (**f**); R^1 = Ph, R^3 = H, R^4 = 4-$CH_3OC_6H_4$ (**g**); R^1 = 4-FC_6H_4, R^3 = H, R^4 = 2,5-$Cl_2C_6H_3$ (**h**); R^1 = Ph, R^3 = R^4 = Et (i); R^1 = 4-$CH_3OC_6H_4$, R^3 = R^4 = $(CH_2)_2O(CH_2)_2$ (**j**).



VII, R^2 = Et, R^1 = Ph (**a**), R^1 = 4-ClC_6H_4 (**b**), R^1 = 4-$CH_3OC_6H_4$ (**c**); R^1 = 4-ClC_6H_4, R^3 = H, R^4 = 4-FC_6H_4 (**d**); R^3 = H, R^4 = 1-naphthyl, R^1 = Ph (**e**), 4-$CH_3C_6H_4$ (**f**).



VIII, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-$CH_3OC_6H_4$ (**c**).

Table 4. Yields, melting points, IR and ^{1}H NMR spectra, and elemental analyses of esters **VIa**–**d** and amides **VIe**–**j** of 3-(pyrazol-4-yl)propenoic acids

Compd. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm	IR spectrum, KBr, cm^{-1}		Found, %			Formula	Calculated, %		
				ν(C=O)	ν(OH)	C	H	N		C	H	N
VIa	71	132–133	1.18 t (3H, CH_3), 4.07 s (2H, CH_2), 3.84 s (3H, CH_3O), 6.58 d (1H, CH=), 7.09–7.84 m (10H, H arom, CH=), 9.34 s (1H, C^5H)	1630	1720	72.71	5.69	7.83	$C_{21}H_{20}N_2O_3$	72.40	5.79	8.04
VIb	68	208–209	5.19 s (2H, CH_2), 6.55 d (1H, CH=), 7.35–7.91 m (15H, H arom, CH=), 9.34 s (1H, C^5H)	1635	1715	72.08	4.80	6.84	$C_{25}H_{19}ClN_2O_2$	72.37	4.62	6.72
VIc	68	140–141	3.84 s (3H, CH_3O), 5.21 s (2H, CH_2O), 6.55 d (1H, CH=), 7.12–7.89 m (15H, H arom, CH=), 9.21 s (1H, C^5H)	1625	1715	75.62	5.69	7.03	$C_{26}H_{22}N_2O_3$	76.08	5.40	6.82
VId	78	164–165	3.87 s (3H, CH_3O), 6.77 d (1H, CH=), 7.41–7.97 m (14H, H arom, CH=), 9.38 s (1H, C^5H), 9.99 s (1H, CH=O)	1630	1720 1690	73.23	4.85	6.63	$C_{26}H_{20}N_2O_4$	73.57	4.75	6.60
VIe	69	179–180	6.45 d (1H, CH=), 7.11–7.92 m (12H, H arom, CH=, NH_2), 9.15 s (1H, C^5H)	1640	1700	67.10	4.09	12.73	$C_{18}H_{14}ClN_3O$	66.77	4.36	12.98
VIf	83	213–214	4.38 s (2H, CH_2), 6.51 d (1H, CH=), 7.23–7.95 m (15H, H arom, CH=), 8.62 t (1H, NH), 8.99 s (1H, C^5H)	1640	1670	75.81	5.20	10.69	$C_{25}H_{20}FN_3O$	75.55	5.07	10.57
VIg	76	199–200	3.73 s (3H, CH_3O), 6.63 d (1H, CH=), 6.91–7.94 m (15H, H arom, CH=), 9.00 s (1H, C^5H), 10.06 s (1H, NH)	1630	1660	76.14	5.21	10.52	$C_{25}H_{21}N_3O_2$	75.93	5.35	10.63
VIh	65	220–221	6.48 d (1H, CH=), 7.14–7.89 m (13H, H arom, CH=), 8.94 s (1H, C^5H), 10.09 s (1H, NH)	1635	1670	63.99	3.36	9.44	$C_{24}H_{16}Cl_2FN_3O$	63.75	3.57	9.29
VIi	81	146–147	1.08 t (3H, CH_3), 1.18 t (3H, CH_3), 3.34 q (2H, CH_2), 3.44 q (2H, CH_2), 6.93 d (1H, CH=), 7.34–7.92 m (11H, H arom, CH=), 9.19 s (1H, C^5H)	1630	1675	76.30	6.87	12.32	$C_{22}H_{23}N_3O$	76.49	6.71	12.16
VIj	74	184–185	3.44–3.70 m (8H, CH_2), 3.83 s (3H, CH_3O), 7.11–7.91 m (14H, H arom, CH=), 9.15 s (1H, C^5H)	1635	1660	71.24	6.08	10.71	$C_{23}H_{23}N_3O_3$	70.93	5.95	10.79

Table 5. Yields, melting points, IR and ^{1}H NMR spectra, and elemental analyses of esters **VIIa**–**c** and amides **VIId**–**f** of 3-(pyrazol-4-yl)propanoic acids

Compd. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm	IR spectrum, KBr, cm^{-1}	Found, %			Formula	Calculated, %		
				ν(C=O)	C	H	N		C	H	N
VIIa	66	82–84	1.14 t (3H, CH_3), 2.66 t (2H, CH_2), 2.93 t (2H, CH_2), 4.05 q (2H, CH_2), 7.29–7.87 m (10H, H arom), 8.39 s (1H, C^5H)	1730	75.35	6.17	8.76	$C_{20}H_{20}N_2O_2$	74.98	6.29	8.74
VIIb	79	177–178	1.15 t (3H, CH_3), 2.68 t (2H, CH_2), 2.93 t (2H, CH_2), 4.04 q (2H, CH_2), 7.29–7.87 m (9H, H arom), 8.42 s (1H, C^5H)	1725	67.95	5.27	8.06	$C_{20}H_{19}ClN_2O_2$	67.70	5.40	7.89
VIIc	77	49–50	1.15 t (3H, CH_3), 2.67 t (2H, CH_2), 2.89 t (2H, CH_2), 3.81 s (3H, CH_3O), 4.06 q (2H, CH_2O), 7.03–7.86 m (9H, H arom), 8.40 s (1H, C^5H)	1735	71.72	6.27	8.12	$C_{21}H_{22}N_2O_3$	71.98	6.33	7.99
VIId	74	143–144	2.69 t (2H, CH_2), 2.92 t (2H, CH_2), 7.25–7.84 m (13H, H arom), 8.47 s (1H, C^5H), 9.84 s (1H, NH)	1665	68.88	4.50	10.17	$C_{24}H_{19}ClFN_3O$	68.65	4.56	10.01
VIIe	70	151–152	2.89 t (2H, CH_2), 3.09 t (2H, CH_2), 7.31–7.90 m (17H, H arom), 8.52 s (1H, C^5H), 9.56 s (1H, NH)	1660	80.14	5.39	10.19	$C_{28}H_{23}N_3O$	80.55	5.55	10.06
VIIf	71	172–173	2.83 t (2H, CH_2), 2.99 t (2H, CH_2), 3.80 s (3H, CH_3O), 7.11–7.84 m (16H, H arom), 8.50 s (1H, C^5H), 9.59 s (1H, NH)	1660	81.04	5.73	9.87	$C_{29}H_{25}N_3O$	80.72	5.84	9.74

dioxide evolution. The reaction mixture was cooled and poured into a mixture of 300 g of ice and 40 m of concn. hydrochloric acid. The precipitate was filtered off, dried, and crystallized from glacial acetic acid.

3-[3-Aryl(heteryl)pyrazol-4-yl]propanoic acids IIIa–f. To a suspension of acid **IIa, c, e, f, h, i** in 20 ml of ethanol was added 5 ml of 5 M solution of sodium hydroxide, 2.4 g of 85% hydrazine hydrate, and 0.06 g of Renay nickel. The reaction mixture was heated to moderate boiling till the end of nitrogen liberation (for around 3–4 h), then it was cooled, diluted with 100 ml of water, and filtered. The transparent filtrate was acidified with concn. hydrochloric acid, the precipitate was dried and crystallized from benzene.

3-[3-Aryl(heteryl)pyrazol-4-yl]propenoyl and 3-[3-aryl(heteryl)pyrazol-4-yl]propanoyl chlorides IVa–e, Va–d. To a suspension of 0.1 mol of acid **IIa–c, f, g**, **IIIa–d** in 10 ml of anhydrous benzene was added 1.75 g (0.015 mol) of thionyl chloride, and the mixture was heated to reflux for 1 h. Then excess thionyl chloride and benzene were distilled off, the residue was washed with hexane, dried, and crystallized from a mixture hexane–benzene, 1:1.

Esters and amides of 3-[3-aryl(heteryl)pyrazol-4-yl]propenoic and propanoic acids **VIa–j, VIIa–f**. To a solution of 0.002 mol of acyl chloride **IVa–e**, **Va–d** in 10 ml of anhydrous acetonitrile was added 0.0021 mol of an appropriate alcohol or amine, 0.2 ml of triethylamine, and the mixture was boiled

for 2 h. The solvent was evaporated, the residue was washed with water, dried, and crystallized from a mixture dioxane–water, 4:1.

3-[3-Arylpyrazol-4-yl]propenoyl isothiocyanates VIIIa–c. To a solution of 0.005 mol of acyl chloride **IVa, b, d** in 30 ml of anhydrous acetone was added 0.012 mol of sodium thiocyanate, and the mixture was stirred for 4 h at room temperature. The precipitate of sodium chloride was filtered off, the filtrate was evaporated, the residue was purified by crystallization.

3-(3-Phenylpyrazol-4-yl)propenoyl isothiocyanate (VIIIa). Yield 73%, mp 164–165°C. IR spectrum, ν, cm^{-1}: 1720 (C=O), 2050 (N=C=S). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.43 d (1H, CH=), 7.30–7.84 m (11H arom, CH=), 9.21 s (1H, C^5H). Found, %: N 12.92; S 9.54. $C_{19}H_{13}N_3OS$. Calculated, %: N 12.68; S 9.68.

3-[3-(4-Fluorophenyl)pyrazol-4-yl]propenoyl isothiocyanate (VIIIb). Yield 71%, mp 176–177°C. IR spectrum, ν, cm^{-1}: 1715 (C=O), 2060 (N=C=S). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.47 d (1H, CH=), 7.38–7.93 m (10H arom, CH=), 9.23 s (1H, C^5H). Found, %: N 12.23; S 9.01. $C_{19}H_{12}FN_3OS$. Calculated, %: N 12.03; S 9.18.

3-[3-(4-Methoxyphenyl)pyrazol-4-yl]propenoyl isothiocyanate (VIIIc). Yield 65%, mp 209–210°C. IR spectrum, ν, cm^{-1}: 1720 (C=O), 2050 (N=C=S). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.43 s (3H, CH_3O), 6.53 d (1H, CH=), 7.19 d (2H arom), 7.63 m (5H arom, CH=), 7.89 d (2H arom), 9.27 s (1H, C^5H). Found, %: N 11.50; S 8.94. $C_{20}H_{15}N_3O_2S$. Calculated, %: N 11.63; S 8.87.

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