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POLYFUNCTIONAL PYRAZOLES.
4*. SYNTHESIS OF 3-[3-ARYL-1-(2-ETHOXYCARBONYL)-4-PYRAZOLYL]ACRYLIC AND -PROPIONIC ACIDS

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3-(3-Aryl-4-formyl-1-pyrazolyl)propionic acids are converted by Knoevenagel condensation under conditions of microwave activation into 3-[3-aryl-1-(2-ethoxycarbonyl)-4-pyrazolyl]acrylic acids. Reduction of the latter with hydrazine hydrate in the presence of Raney nickel gives 3-[3-aryl-1-(2-ethoxycarbonyl)-4-pyrazolyl]propionic acids.

Keywords: 3-(4-formyl-1-pyrazolyl)propionic acids, 3-(4-pyrazolyl)acrylic acids, 3-(4-pyrazolyl)-propionic acids, microwave activation, reduction.

In continuation of investigations started previously [1,2] on the design of polyfunctional pyrazoles, we have attempted to synthesize systems containing two carboxyl groups in the side chains. Convenient subjects for solving this problem are the 3-(4-formyl-1-pyrazolyl)propionic acids, described in [1], the aldehyde group of which may readily be converted sequentially into vinyl- and ethylcarboxyl functions. Derivatives of 3-pyrazolylacrylic and 3-pyrazolylpropionic acids attract the steady attention of investigators since substances with high pharmacological activity are found among them [3-5].

For this reason we carried out the Knoevenagel reaction of 3-(3-aryl-4-formyl-1-pyrazolyl)propionic acids **1a-i** with malonic acid under microwave activation conditions, which for some time past has been widely applied in the synthesis and conversions of heterocyclic compounds [6]. However, the microwave variant of the Knoevenagel reaction is limited by the use of chalcones and cinnamic acids in the synthesis [7]. We have found that the condensation of compounds **1a-i** with malonic acid in pyridine in the presence of catalytic amounts of piperidine on microwave irradiation for 5 min leads to the formation of 3-[3-aryl-1-(2-ethoxycarbonyl)-4-pyrazolyl]acrylic acids **2a-i** in 79-94% yield. It was shown, using aldehyde **1d** as an example, that under the conditions of the classical Knoevenagel condensation (5 h boiling in pyridine), the yield of the desired product **2d** was reduced by 6%.

The compositions of acids **2a-i** were in agreement with the results of elemental analysis (Table 1) and the structures with data of IR and ^{1}H NMR spectra (Table 2).

There were triplets in the ^{1}H NMR spectra for the protons of the α-methylene (2.85-2.90 ppm) and β-methylene (4.35-4.41 ppm) groups, and doublets for the α-proton of the ethylenic bond at 6.13-6.22 ppm with coupling constant 15.9 Hz, which shows the *trans* structure of these acids. For compounds **2f,h,i** it was possible

* For Part 3 see [1].

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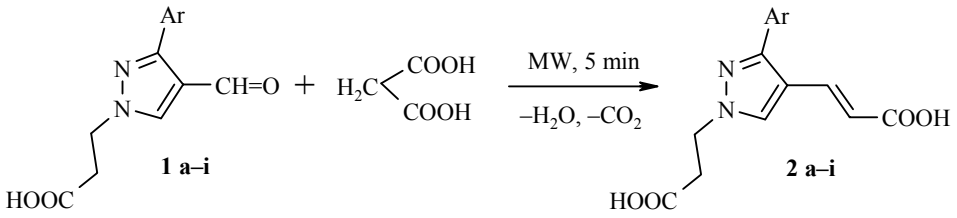


1, 2, **a** Ar = C_6H_5, **b** Ar = 4-ClC_6H_4, **c** Ar = 3-BrC_6H_4, **d** Ar = 4-BrC_6H_4, **e** Ar = 4-MeC_6H_4, **f** Ar = 4-$MeOC_6H_4$, **g** Ar = 3-$O_2NC_6H_4$, **h** Ar = 3,4-$(MeO)_2C_6H_3$, **i** Ar = 3-NO_2-4-$MeOC_6H_3$

to identify the doublet of the β-proton of the double bond in the range 7.48-7.49 ppm. For the remaining compounds of this series they were superimposed on the signals of the protons of the aromatic substituents in position 3. The H-5 proton of the pyrazole nucleus was recorded as a singlet at 8.25-8.41 ppm, and the hydroxyl protons of the carboxylic acid groups by a broadening of the signal at 12.15-12.34 ppm.

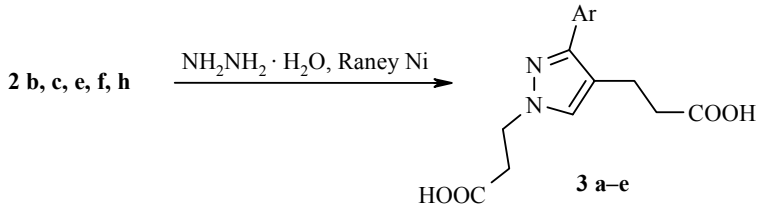
Hydrogenation of the alkenyl fragment of acids **2** makes it possible to obtain new 1,3-bifunctional derivatives of pyrazole, in which both carboxyl groups are linked with the heterocycle by ethylenic bridges. We have established that 3-(4-pyrazolyl)acrylic acids **2b,c,e,f,h** are reduced by the action of hydrazine hydrate in the presence of Raney nickel in 61-78% yield to 3-[3-aryl-1-(2-ethoxycarbonyl)-4-pyrazolyl]propionic acids **3a-e** (Tables 1, 2), the structures of which were also reliably confirmed by IR and ^{1}H NMR spectroscopy. It is appropriate to note that in the ^{1}H NMR spectra a high field displacement of 0.8 ppm was observed for the H-5 proton of the pyrazole ring, which, in our opinion, is caused by the shielding effect of the 4-ethoxycarbonyl group.

TABLE 1. Characteristics of the Synthesized Compounds **2a-i**, **3a-e**

Compound	Empirical formula	Found, % / Calculated, %			mp,°C	Yield, %
		C	H	N		
2a	$C_{15}H_{14}N_2O_4$	62.73 / 62.94	4.70 / 4.89	9.61 / 9.79	187-189	84
2b	$C_{15}H_{13}ClN_2O_4$	55.84 / 56.16	3.91 / 4.05	8.57 / 8.74	211-212	89
2c	$C_{15}H_{13}BrN_2O_4$	49.09 / 49.31	3.60 / 3.56	7.44 / 7.67	185-187	79
2d	$C_{15}H_{13}BrN_2O_4$	49.65 / 49.31	3.38 / 3.56	7.50 / 7.67	206-207	92
2e	$C_{16}H_{16}N_2O_4$	63.71 / 64.00	5.07 / 5.33	9.09 / 9.33	211-212	93
2f	$C_{16}H_{16}N_2O_5$	60.70 / 60.76	4.98 / 5.06	8.68 / 8.86	206-207	88
2g	$C_{15}H_{13}N_3O_6$	54.11 / 54.38	3.91 / 3.93	12.80 / 12.69	201-202	94
2h	$C_{17}H_{18}N_2O_6$	58.58 / 58.96	5.25 / 5.20	7.90 / 8.09	204-205	87
2i	$C_{16}H_{15}N_3O_7$	53.92 / 53.18	3.98 / 4.15	11.75 / 11.63	195-196	83
3a	$C_{15}H_{15}ClN_2O_4$	55.57 / 55.81	4.54 / 4.65	8.43 / 8.68	153-154	64
3b	$C_{15}H_{15}BrN_2O_4$	48.90 / 49.04	3.93 / 4.08	7.41 / 7.63	121-122	61
3c	$C_{16}H_{17}N_2O_4$	63.91 / 63.78	5.49 / 5.64	9.46 / 9.30	125-126	74
3d	$C_{16}H_{17}N_2O_5$	60.40 / 60.56	5.48 / 5.36	8.61 / 8.83	128-129	78
3e	$C_{17}H_{19}N_2O_6$	59.12 / 58.79	5.37 / 5.47	8.13 / 8.07	134-135	68

TABLE 2. Spectral Characteristics of Compounds **2a-i**, **3a-e**

Com-pound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	C=C	C=O	O–H	
2a	1625	1705	2560-2940	2.88 (2H, t, *J* = 7.5, α-CH_2); 4.36 (2H, t, *J* = 7.5, β-CH_2); 6.15 (1H, d, *J* = 15.9, α-CH=); 7.38-7.52 (6H, m, H_{Ar} + + β-CH=); 8.29 (1H, s, H-5); 12.15 (2H, br. s, COOH)
2b	1625	1720	2580-3000	2.86 (2H, t, *J* = 7.5, α-CH_2); 4.37 (2H, t, *J* = 7.5, β-CH_2); 6.16 (1H, d, *J* = 15.9, α-CH=); 7.41-7.54 (5H, m, H_{Ar} + + β-CH=); 8.30 (1H, s, H-5); 12.04 (2H, br. s, COOH)
2c	1630	1725	2550-2970	2.86 (2H, t, *J* = 7.5, α-CH_2); 4.37 (2H, t, *J* = 7.5, β-CH_2); 6.17 (1H, d, *J* = 15.9, α-CH=); 7.46-7.68 (5H, m, H_{Ar} + + β-CH=); 8.32 (1H, s, H-5); 12.20 (2H, br. s, COOH)
2d	1625	1720	2600-3000	2.87 (2H, t, *J* = 7.5, α-CH_2); 4.36 (2H, t, *J* = 7.5, β-CH_2); 6.18 (1H, d, *J* = 15.9, α-CH=); 7.44-7.62 (5H, m, H_{Ar} + + β-CH=); 8.33 (1H, s, H-5); 12.27 (2H, br. s, COOH)
2e	1620	1700	2560-2970	2.26 (3H, s, CH_3); 2.87 (2H, t, *J* = 7.5, α-CH_2); 4.35 (2H, t, β-CH_2); 6.18 (1H, d, *J* = 15.9, α-CH=); 7.30-7.48 (5H, m, H_{Ar} + β-CH=); 8.36 (1H, s, H-5); 12.23 (2H, br. s, COOH)
2f	1630	1700	2550-2970	2.85 (2H, t, *J* = 7.5, α-CH_2); 3.82 (3H, s, CH_3O); 4.35 (2H, t, *J* = 7.5, β-CH_2); 6.13 (1H, d, *J* = 15.9, α-CH=); 7.30-7.48 (5H, m, H_{Ar} + β-CH=); 8.36 (1H, s, H-5); 12.23 (2H, br. s, COOH)
2g	1625	1695	2520-2960	2.89 (2H, t, *J* = 7.5, α-CH_2); 4.41 (2H, t, *J* = 7.5, β-CH_2); 6.22 (1H, d, *J* = 15.9, α-CH=); 7.48 (1H, d, *J* = 15.9, β-CH=); 7.77 (1H, t, *J* = 8.5, H_{Ar}-5); 7.94 (1H, d, *J* = 8.6, H_{Ar}-6); 8.24 (1H, d, *J* = 8.5, 4-H_{Ar}); 8.35 (1H, s, H_{Ar}-2); 8.37 (1H, s, H-5); 12.34 (2H, br. s, COOH)
2h	1630	1705	2530-2940	2.87 (2H, t, *J* = 7.5, α-CH_2); 3.78 (3H, s, CH_3O); 3.80 (3H, s, CH_3O); 4.35 (2H, t, *J* = 7.5, β-CH_2); 6.17 (1H, d, *J* = 15.9, α-CH=); 6.98-7.12 (3H, m, H_{Ar}); 7.48 (1H, d, *J* = 15.9, β-CH=); 8.39 (1H, s, H-5); 12.34 (2H, br. s, COOH)
2i	1620	1700	2570-2980	2.88 (2H, t, *J* = 7.5, α-CH_2); 3.98 (3H, s, CH_3O); 4.36 (2H, t, *J* = 7.5, β-CH_2); 6.21 (1H, d, *J* = 15.9, α-CH=); 7.48 (1H, d, *J* = 15.9, β-CH=); 7.51 (1H, d, *J* = 8.7, 6-H_{Ar}); 7.76 (1H, d, *J* = 8.7, H_{Ar}-5); 7.98 (1H, s, H_{Ar}-2); 8.41 (1H, s, H-5); 12.14 (2H, br. s, COOH)
3a		1720	2550-2940	2.46 [2H, t, *J* = 7.7, 4-(β-CH_2)], 2.76-2.82 [4H, m, 1-(α-CH_2) + 4-(α-CH_2)], 4.29 [2H, t, *J* = 7.5, 1-(β-CH_2)]; 7.28-7.62 (6H, m, H_{Ar} + H-5); 12.19 (2H, br. s, COOH)
3b		1725	2560-2980	2.48 [2H, t, *J* = 7.7, 4-(β-CH_2)], 2.75-2.81 [4H, m, 1-(α-CH_2) + 4-(α-CH_2)], 4.29 [2H, t, *J* = 7.5, 1-(β-CH_2)]; 7.40 (2H, d, *J* = 8.5, H_{Ar}-3,5); 7.58 (1H, s, H-5); 7.61 (2H, d, *J* = 8.5, H_{Ar}-2,6); 12.17 (2H, br. s, COOH)
3c		1720	2600-2950	2.39 (3H, s, CH_3); 2.47 [2H, t, *J* = 7.7, 4-(β-CH_2)]; 2.78-2.83 [4H, m, 1-(α-CH_2) + 4-(α-CH_2)], 4.31 [2H, t, *J* = 7. 5, 1-(β-CH_2)], 7.25 (2H, d, *J* = 8.3, H_{Ar}-3,5); 7.47 (2H, d, *J* = 8.3, H_{Ar}-2,6); 7.53 (1H, s, H-5); 12.16 (2H, br. s, COOH)
3d		1720	2580-2950	2.45 [2H, t, *J* = 7.7, 4-(β-CH_2)], 2.75-2.79 [4H, m, 1-(α-CH_2) + 4-(α-CH_2)], 4.27 [2H, t, *J* = 7.5, 1-(β-CH_2)]; 6.96 (2H, d, *J* = 8.8, H_{Ar}-3,5); 7.51 (2H, d, *J* = 8.8, H_{Ar}-2,6); 7.56 (1H, s, H-5); 12.29 (2H, br. s, COOH)
3e		1725	2530-2960	2.48 [2H, t, *J* = 7.7, 4-(β-CH_2)], 2.75-2.79 [4H, m, 1-(α-CH_2) + 4-(α-CH_2)], 4.26 [2H, t, *J* = 7.5, 1-(β-CH_2)]; 7.04-7.16 (3H, m, H_{Ar}); 7.56 (1H, s, H-5); 12.07 (2H, br. s, COOH)



3 a Ar = 4-ClC_6H_4, **b** Ar = 3-BrC_6H_4, **c** Ar = 4-MeC_6H_4, **d** Ar = 4-$MeOC_6H_4$, **e** 3,4-$(MeO)_2C_6H_3$

EXPERIMENTAL

The IR spectra were recorded on a UR 20 instrument in KBr disks. The ^{1}H NMR spectra were obtained on a Varian Gemini (300 MHz) instrument in DMSO-d_6 solution, internal standard was TMS.

3-(3-Aryl-4-formyl-1-pyrazolyl)propionic Acids 1a-i were obtained by the method of [2].

Compound 1c. Yield 82%; mp 125-126°C (AcOH–H_2O, 1:5). IR spectrum, ν, cm^{-1}: 1650, 1710 (C=O), 2950-3150 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.86 (2H, t, *J* = 7.5. α-CH_2); 4.41 (2H, t, *J* = 7.5, β-CH_2); 7.53-7.84 (4H, m, H_{Ar}); 8.49 (1H, s, H-5); 9.83 (1H, s, CH=O); 12.36 (1H, br. s, COOH). Found, %: C 48.01; H 3.19; N 8.42. $C_{13}H_{11}BrN_2O_3$. Calculated, %: C 48.32; H 3.43; N 8.67.

Compound 1e. Yield 79%; mp 123-125°C (AcOH–H_2O, 1:5). IR spectrum, ν, cm^{-1}: 1645, 1715 (C=O), 2970-3180 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24 (3H, CH_3); 2.87 (1H, t, *J* = 7.5, α-CH_2); 4.42 (2H, t, *J* = 7.5, β-CH_2); 7.29 (2H, d, *J* = 8.5, H_{Ar}); 7.48 (2H, d, *J* = 8.5, H_{Ar}); 8.50 (1H, s, H-5); 9.86 (1H, s, CH=O); 12.43 (1H, br. s, COOH). Found, %: C 64.90; H 5.26; N 10.71. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.11; H 5.46; N 10.85.

Compound 1g. Yield 86%; mp 122-123°C (AcOH–H_2O, 1:4). IR spectrum, ν, cm^{-1}: 1655, 1720 (C=O), 2960-3130 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.88 (2H, t, *J* = 7.5, α-CH_2); 4.41 (2H, t, *J* = 7.5, β-CH_2); 7.75 (1H, t, *J* = 8.5, H_{Ar}); 7.90 (1H, d, *J* = 8.5, H_{Ar}); 8.20 (1H, d, *J* = 8.5, H_{Ar}); 8.32 (1H, s, *J* = 8.5, H_{Ar}); 8.56 (1H, s, H-5); 9.80 (1H, s, CH=O); 12.30 (1H, br. s, COOH). Found, %: C 53.78; H 3.63; N 14.40. $C_{13}H_{11}N_3O_5$. Calculated, %: C 53.98; H 3.83; N 14.53.

Compound 1h. Yield 77%; mp 143-144°C (AcOH–H_2O, 1:6). IR spectrum, ν, cm^{-1}: 1650, 1710 (C=O), 2950-3200 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.87 (2H, t, *J* = 7.5, α-CH_2); 3.76 (3H, s, CH_3O); 3.79 (3H, s, CH_3O); 4.39 (2H, t, *J* = 7.5, β-CH_2); 7.03-7.18 (3H, m, H_{Ar}); 8.48 (1H, s, H-5); 9.84 (1H, s, CH=O); 12.07 (1H, br. s, COOH). Found, %: C 58.88; H 5.41; N 8.98. $C_{15}H_{16}N_2O_5$. Calculated, %: C 59.21; H 5.30; N 9.21.

Compound 1i. Yield 83%; mp 156-157°C (AcOH–H_2O, 1 : 5). IR spectrum, ν, cm^{-1}: 1650, 1715 (C=O), 2950-3180 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.88 (2H, t, *J* = 7.5, α-CH_2); 3.92 (3H, s, CH_3O); 4.43 (2H, t, *J* = 7.5, β-CH_2); 7.54 (1H, d, *J* = 8.7, H_{Ar}); 7.77 (1H, d, *J* = 8.5, H_{Ar}); 8.00 (1H, s, H_{Ar}); 8.45 (1H, s, H-5); 9.84 (1H, s, CH=O); 12.24 (1H, br. s, COOH). Found, %: C 52.42; H 3.97; N 12.98. $C_{14}H_{13}N_3O_6$. Calculated, %: C 52.67; H 4.07; N 13.16.

3-[3-Aryl-1-(2-ethoxycarbonyl)-4-pyrazolyl]acrylic Acids 2a-i. A one-necked flask of capacity 25 ml containing 3-(3-aryl-4-formyl-1-pyrazolyl)propionic acid **1a-i** (5 mmol), malonic acid (1.04 g, 10 mmol), pyridine (1 ml), and piperidine (3 drops), was placed in a domestic microwave oven (Lunik 600, 800 W, 2450 MHz) fitted with a reflux condenser, and heated for 5 min. After cooling, 6 N HCl (10 ml) was added to the reaction mixture, which was then left at room temperature for 1 h. The resulting solid was filtered off, dried, and crystallized from a mixture of acetic acid–water, 1:5.

3-[3-Aryl-1-(2-ethoxycarbonyl)-4-pyrazolyl]propionic Acids 3a-e. Water (2 ml) and sodium hydroxide (3 g) were added to nickel-aluminum alloy (1 g) containing 50% nickel, and the mixture heated on a water bath for 0.5 h. The solid residue was separated from the solution, washed with distilled water (2 × 10 ml), and then 3-(4-pyrazolyl)acrylic acid **2b,c,e,f,h** (2 mmol) and 60% hydrazine hydrate (2 ml) were added to it. The mixture was heated on a water bath for 2 h. After cooling, the solid residue was separated, and the filtrate acidified with 6 N HCl to pH 2. The resulting precipitate was filtered off, dried, and crystallized from 50% acetic acid.

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