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4-Functionally Substituted 3-Heterylpyrazoles: III.* 3-Aryl(heteryl)pyrazole-4-carboxylic Acids and Their Derivatives

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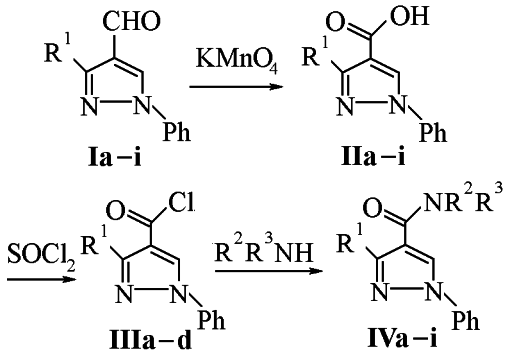
Abstract—3-Aryl(heteryl)-4-formylpyrazoles were cleanly oxidized by potassium permanganate in water-pyridine medium to afford in high yield 3-aryl(heteryl)pyrazole-4-carboxylic acids, that were further converted into the corresponding chlorides and amides.

In the series of functionally substituted pyrazoles are important 4-pyrazolecarboxylic acids. On their capability to decarboxylate at elevated temperature is based an extensively used preparation method for pyrazoles unsubstituted in 4 position [2–4]. Besides some derivatives of 4-pyrazolecarboxylic acids, e.g. amides, possess pronounced farmaceutical activity [5, 6]. The main described method of preparation for 4-pyrazolecarboxylic acids is the alkaline hydrolysis of the corresponding esters [4, 7, 8] or acid hydrolysis of their amides [2]. The oxidation of 4-pyrazolecarbaldehydes apart from singular examples [3, 9] up till now have not found application in the synthesis of the pyrazole-substituted carboxylic acids. Yet for preparation of 1,3-disubstituted 4-pyrazolecarboxylic acids oxidation of the corresponding aldehydes can be a promising approach taking into account the preparative accessibility of the latter [10–14]. The oxidation with potassium permanganate was studied by an example of 3-aryl(heteryl)-1-phenyl-4-formylpyrazoles **Ia–h**.

We found that aldehydes **Ia–h** treated with potassium permanganate in 50% aqueous pyridine at 18–20°C afford 4-pyrazolecarboxylic acids in high yield (71–94%) (see the Scheme).

Scheme.



I, II, R^1 = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-EtC_6H_4 (**e**), 4-PhC_6H_4 (**f**), 3-pyridyl (**g**), 2-thienyl (**h**); **III**, R^1 = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-EtC_6H_4 (**e**), 2-thienyl (**f**); IV, R^1 = Ph, R^2 = H, R^3 = 3-$Et_2NSO_2C_6H_4$ (**a**); R^2,R^3 = 1-CH_2-2-$C_2H_4C_6H_4$ (**b**); R^1 = 4-FC_6H_4, R^2 = H, R^3 = 3,5-$Cl_2C_6H_3$ (**c**); R^2,R^3 = 2,2'-$C_6H_4CH_2CH_2C_6H_4$ (**d**); R^1 = 4-ClC_6H_4, R^2 = H, R^3 = 2-tetrahydrofurylmethyl (**g**); R^2,R^3 = $(CH_2CH_2)_2NPh$ (**f**); R^1 = 2-thienyl, R^2 = H, R^3 = 3-morpholinosulfonylphenyl (**g**); R^2,R^3 = 2,2'-$C_6H_4CH_2CH_2C_6H_4$ (**h**).

Acids **II** (Table 1) are high-melting colorless or light yellow substances. Their structure was confirmed by ^{1}H NMR and IR spectra. In particular, the presence in their IR spectra recorded from solid samples of characteristic wide absorption bands in the 2500–3100 cm^{-1} region corresponds to OH groups participating in hydrogen bonds, together with the absorption bands of the stretching vibrations of C=O groups in 1700–1710 cm^{-1} region evidences the dimeric character of the acids synthesized [15]. In the ^{1}H NMR spectra the protons of aromatic and heteroaromatic substituents in positions 1 and 3 of the pyrazole ring are clearly seen as sets of multiplet signals in the region 7.17–8.35 ppm, and the singlet of the proton in position 5 (8.85–9.08 ppm) is shifted downfield by about 0.5 ppm compared to the corresponding singlet in the spectra of 4-formylpyrazoles [14].

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Table 1. Yields, melting points, IR and ^{1}H NMR spectra, and elemental analyses of 4-pyrazolecarboxylic acids **IIa–h**

Compd. no.	Yield, %	mp, °C	IR spectrum, cm^{-1}		^{1}H NMR spectrum, δ, ppm[a]
			ν(C=O)	ν(OH)	
IIa	94	204–205[b]	1710	2550–3050	7.21–7.65 m (10H, H arom), 8.87 s (1H, C^5H)
IIb	89	229–230	1705	2600–3000	7.40–8.03 m (9H, H arom), 8.96 s (1H, C^5H)
IIc	86	240–242	1710	2600–3100	7.30–7.71 m (9H, H arom), 9.03 s (1H, C^5H)
IId	90	249–250	1705	2600–3000	7.34–7.78 m (9H, H arom), 8.85 s (1H, C^5H)
IIe	82	200–202	1700	2500–3100	1.30 t (3H, CH_3), 2.55 q (2H, CH_2), 7.18–7.59 m (9H, H arom), 8.94 s (1H, C^5H)
IIf	74	198–199	1710	2550–3050	7.28–7.84 m (14H, H arom), 8.88 s (1H, C^5H)
IIg	84	236–238	1710	2600–3000	7.39–8.35 m (9H, H arom), 8.93 s (1H, C^5H)
IIh	71	180–171	1700	2600–3050	7.17–8.12 m (8H, H arom), 9.08 s (1H, C^5H)

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
IIa	73.09	4.80	10.50	$C_{16}H_{12}N_2O_2$	72.71	4.55	10.61
IIb	67.65	4.07	9.30	$C_{16}H_{11}FN_2O_2$	68.09	3.90	9.43
IIc	64.61	3.89	9.63	$C_{16}H_{11}ClN_2O_2$	64.32	3.69	9.40
IId	56.33	3.03	8.42	$C_{16}H_{11}BrN_2O_2$	55.98	3.21	8.16
IIe	73.54	5.67	10.00	$C_{18}H_{16}N_2O_2$	73.95	5.51	9.58
IIf	77.42	4.97	8.07	$C_{22}H_{16}N_2O_2$	77.63	4.74	8.23
IIg	67.66	4.49	15.67	$C_{15}H_{11}N_3O_2$	67.93	4.18	15.84
IIh	62.52	3.99	10.19	$C_{14}H_{10}N_2O_2S$	62.21	3.73	10.36

[a] The protons of COOH group and of water present in the solvent due to fast exchange appear as a broad signal in the region 3.30–3.50 ppm.

[b] mp 206°C [2].

In order to obtain new derivatives of 4-pyrazolecarboxylic acids, in particular, those possessing biological activity, we converted compounds **IIa–e, h** by treating with thionyl chloride into 4-pyrazolecarbonyl chlorides **IIIa–f** in close to quantitative yield. The constants of compounds **IIIa–f** are listed in Table 2.

We established that 4-pyrazolecarbonyl chlorides **IIIa–c, f** were less reactive than typical aroyl chlorides, and they acylate primary and secondary aliphatic and aromatic amines by heating in toluene for 3 h affording amides **IVa–h** (Table 3).

EXPERIMENTAL

IR spectra were recorded on spectrometer UR-20 from KBr pellets. ^{1}H NMR spectra were registered in DMSO-d_6 solutions on spectrometer Varian-Gemini (300 MHz), internal reference TMS.

Aldehydes used in the study were synthesized by the following methods: **Ia, b, d–f** [13], **Ic** [12], **Ig** [16]. **Ih** [14].

1-Phenyl-3-(4-ethylphenyl)-4-pyrazolecarbaldehyde Ie was obtained by a procedure from [13]. Yield 78%, mp 113–115°C (from ethanol). IR spectrum, ν, cm^{-1}: 1700 [ν(C=O)]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 t (3H, CH_3), 3.12 q (2H, CH_2), 7.25–7.74 m (9H, H arom), 8.56 s (1H, C^5H), 10.05 s (1H, HC=O). Found, %: C 77.93; H 5.63; N 10.03. $C_{18}H_{16}N_2O$. Calculated, %: C 78.26; H 5.79; N 10.14.

3-Aryl(heteryl)-1-phenylpyrazole-4-carboxylic acids IIa–h. To a suspension of 0.05 mol of aldehyde **Ia–h** in 50 ml of 50% aqueous pyridine at stirring and cooling with tap water was added within 1 h by small portions 7.9 g (0.05 mol) of potassium permanganate maintaining the temperature of the reaction mixture at 20–22°C. The mixture was stirred till the violet color disappeared, the manganese dioxide precipitate was filtered off, washed with 5% water solution of sodium hydroxide, and to the filtrate was added diluted hydrochloric acid. The separated pre-

Table 2. Yields, melting points, and elemental analyses of 4-pyrazolecarbonyl chlorides **IIIa**–**f**

Compd. no.	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
			Cl	N		Cl	N
IIIa	95	99–100	12.74	10.20	$C_{16}H_{11}ClN_2O$	12.56	9.91
IIIb	90	140–141	11.96	9.04	$C_{16}H_{10}ClFN_2O$	11.79	9.32
IIIc	88	124–125	22.51	8.88	$C_{16}H_{10}Cl_2N_2O$	22.36	8.83
IIId	91	126–127	32.14[a]	8.03	$C_{16}H_{11}BrClN_2O$	31.90[a]	7.75
IIIe	81	184–188[b]	11.09	9.36	$C_{18}H_{15}ClN_2O$	11.41	9.02
IIIf	85	162–164	12.68	10.49	$C_{14}H_9ClN_2OS$	13.00	10.27

[a] Overall content of Cl and Br. [b] bp at 0.02 mm Hg.

Table 3. Yields, melting points, ^{1}H NMR spectra, and elemental analyses of 4-pyrazolecarboxamides **IVa**–**h**

Compd. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm
IVa	69	200	1.06 t (6H, CH_3), 3.17 q (4H, CH_2), 7.42–8.18 m (14H, H arom), 9.14 s (1H, C^5H), 0.47 s (1H, NH)
IVb	68	121	2.61–2.87 m (2H, CH_2), 3.54–3.95 m (2H, CH_2), 4.62–4.81 m (2H, CH_2), 7.16–7.97 m (14H, H arom), 8.84 s (1H, C^5H)
IVc	80	183–184	7.27–7.92 m (12H, H arom), 9.13 s (1H, C^5H), 9.71 s (1H, NH)
IVd	75	234	2.90 m (2H, CH_2), 3.33 m (2H, CH_2), 7.25–7.86 m (17H, H arom), 8.27 s (1H, C^5H)
IVe	71	139	1.57–1.82 m (6H, CH_2), 3.65–3.96 m (3H, CH, CH_2), 7.36–7.89 m (9H, H arom), 8.23 s (1H, NH), 8.93 s (1H, C^5H)
IVf	68	159–160	2.95–3.97 m (8H, CH_2), 6.80–7.96 m (14H, H arom), 8.85 s (1H, C^5H)
IVg	82	188	2.92 m (4H, CH_2), 3.65 m (4H, CH_2), 7.14–8.15 m (12H, H arom), 9.17 s (1H, C^5H), 10.52 s (1H, NH)
IVh	78	204–205	2.83 m (2H, CH_2), 3.64 m (2H, CH_2), 8.21 s (1H, C^5H), 7.21–7.77 m (16H, H arom)

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
IVa	66.02	5.59	11.63	$C_{26}H_{26}N_4O_3S$	65.82	5.49	11.81
IVb	80.01	5.50	10.80	$C_{25}H_{21}N_3O$	79.15	5.54	11.08
IVc	62.20	3.49	9.64	$C_{22}H_{14}Cl_2FN_3O$	61.97	3.29	9.86
IVd	78.60	5.05	8.90	$C_{30}H_{22}FN_3O$	78.43	4.79	9.15
IVe	66.30	4.73	10.50	$C_{21}H_{20}ClN_3O_2$	66.05	5.28	11.00
IVf	70.80	5.35	12.78	$C_{26}H_{23}ClN_4O$	70.51	5.20	12.66
IVg	58.55	4.70	11.50	$C_{24}H_{22}N_4O_4S_2$	58.30	4.45	11.34
IVh	75.50	5.15	9.11	$C_{28}H_{21}N_3OS$	75.17	4.70	9.39

cipitate of the 4-pyrazolecarboxylic acid was filtered off, dried, and recrystallized from glacial acetic acid.

3-Aryl(heteryl)-1-phenylpyrazole-4carbonyl chlorides IIIa–f. To a suspension of 0.002 mol of acid **IIa–e**, h in 15 ml of anhydrous toluene was added 0.05 mol of thionyl chloride, 3–4 drops of dimethylformamide, and the mixture was boiled for 2 h. Then the excess thionyl chloride and solvent were distilled off, the residue was washed with hexane and crystallized from a mixture benzene–hexane, 3 : 1.

3-Aryl(heteryl)-1-phenylpyrazole-4-carboxamides IVa–h. To a solution of 0.0025 mol of chloride **IIIa–c, f** in 10 ml of toluene was added at stirring 0.0025 mol of amine and 0.4 ml of triethylamine. The mixture was heated to boiling for 3 h and

left standing at room temperature for 12 h. The solvent was evaporated, the residue was treated with water, filtered, dried, and crystallized from an appropriate solvent.

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