

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

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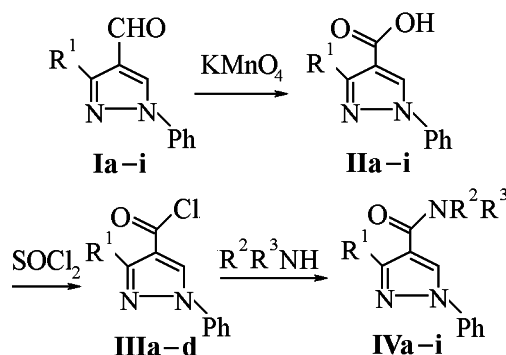
Abstract—3-Aryl(heteryl)-4-formylpyrazoles were cleanly oxidized by potassium permanganate in water-pyridine medium to afford in high yield 3-aryl(heteryl)pyrazole-4-carboxylic acids, that were further converted into the corresponding chlorides and amides.

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).

Acids **II** (Table 1) are high-melting colorless or light yellow substances. Their structure was confirmed by ¹H 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

Scheme.



I, II, $\text{R}^1 = \text{Ph}$ (**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**, $\text{R}^1 = \text{Ph}$ (**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**, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = 3\text{-Et}_2\text{NSO}_2\text{C}_6\text{H}_4$ (**a**); $\text{R}^2, \text{R}^3 = 1\text{-CH}_2\text{-2-C}_2\text{H}_4\text{C}_6\text{H}_4$ (**b**); $\text{R}^1 = 4\text{-FC}_6\text{H}_4$, $\text{R}^2 = \text{H}$, $\text{R}^3 = 3,5\text{-Cl}_2\text{C}_6\text{H}_3$ (**c**); $\text{R}^2, \text{R}^3 = 2,2'\text{-C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{C}_6\text{H}_4$ (**d**); $\text{R}^1 = 4\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{H}$, $\text{R}^3 = 2\text{-tetrahydrofurylmethyl}$ (**g**); $\text{R}^2, \text{R}^3 = (\text{CH}_2\text{CH}_2)_2\text{NPh}$ (**f**); $\text{R}^1 = 2\text{-thienyl}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = 3\text{-morpholinosulfonylphenyl}$ (**g**); $\text{R}^2, \text{R}^3 = 2,2'\text{-C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{C}_6\text{H}_4$ (**h**).

evidences the dimeric character of the acids synthesized [15]. In the ¹H 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].

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

Compd. no.	Yield, %	mp, °C	IR spectrum, cm^{-1}		^1H NMR spectrum, δ , ppm ^a
			$\nu(\text{C}=\text{O})$	$\nu(\text{OH})$	
IIa	94	204–205 ^b	1710	2550–3050	7.21–7.65 m (10H, H arom), 8.87 s (1H, C ⁵ H)
IIb	89	229–230	1705	2600–3000	7.40–8.03 m (9H, H arom), 8.96 s (1H, C ⁵ H)
IIc	86	240–242	1710	2600–3100	7.30–7.71 m (9H, H arom), 9.03 s (1H, C ⁵ H)
IId	90	249–250	1705	2600–3000	7.34–7.78 m (9H, H arom), 8.85 s (1H, C ⁵ H)
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 ⁵ H)
IIff	74	198–199	1710	2550–3050	7.28–7.84 m (14H, H arom), 8.88 s (1H, C ⁵ H)
IIgg	84	236–238	1710	2600–3000	7.39–8.35 m (9H, H arom), 8.93 s (1H, C ⁵ H)
IIhh	71	180–171	1700	2600–3050	7.17–8.12 m (8H, H arom), 9.08 s (1H, C ⁵ H)

Compd. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
IIa	73.09	4.80	10.50	$\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2$	72.71	4.55	10.61
IIb	67.65	4.07	9.30	$\text{C}_{16}\text{H}_{11}\text{FN}_2\text{O}_2$	68.09	3.90	9.43
IIc	64.61	3.89	9.63	$\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}_2$	64.32	3.69	9.40
IId	56.33	3.03	8.42	$\text{C}_{16}\text{H}_{11}\text{BrN}_2\text{O}_2$	55.98	3.21	8.16
IIe	73.54	5.67	10.00	$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$	73.95	5.51	9.58
IIff	77.42	4.97	8.07	$\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_2$	77.63	4.74	8.23
IIgg	67.66	4.49	15.67	$\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_2$	67.93	4.18	15.84
IIhh	62.52	3.99	10.19	$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$	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. ^1H 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 [$\nu(\text{C}=\text{O})$]. ^1H NMR spectrum (CDCl_3), δ , ppm: 1.13 t (3H, CH₃), 3.12 q (2H, CH₂), 7.25–7.74 m (9H, H arom), 8.56 s (1H, C⁵H), 10.05 s (1H, HC=O). Found, %: C 77.93; H 5.63; N 10.03. $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$. 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 ₂ O	12.56	9.91
IIIb	90	140–141	11.96	9.04	C ₁₆ H ₁₀ ClFN ₂ O	11.79	9.32
IIIc	88	124–125	22.51	8.88	C ₁₆ H ₁₀ Cl ₂ N ₂ O	22.36	8.83
IIId	91	126–127	32.14 ^a	8.03	C ₁₆ H ₁₁ BrClN ₂ O	31.90 ^a	7.75
IIIe	81	184–188 ^b	11.09	9.36	C ₁₈ H ₁₅ ClN ₂ O	11.41	9.02
IIIf	85	162–164	12.68	10.49	C ₁₄ H ₉ ClN ₂ OS	13.00	10.27

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

Table 3. Yields, melting points, ¹H 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 ⁵ H), 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 ⁵ H)				
IVc	80	183–184	7.27–7.92 m (12H, H arom), 9.13 s (1H, C ⁵ H), 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 ⁵ H)				
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 ⁵ H)				
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 ⁵ H)				
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 ⁵ H), 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 ⁵ H), 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 ₄ O ₃ S	65.82	5.49	11.81
IVb	80.01	5.50	10.80	C ₂₅ H ₂₁ N ₃ O	79.15	5.54	11.08
IVc	62.20	3.49	9.64	C ₂₂ H ₁₄ Cl ₂ FN ₃ O	61.97	3.29	9.86
IVd	78.60	5.05	8.90	C ₃₀ H ₂₂ FN ₃ O	78.43	4.79	9.15
IVe	66.30	4.73	10.50	C ₂₁ H ₂₀ ClN ₃ O ₂	66.05	5.28	11.00
IVf	70.80	5.35	12.78	C ₂₆ H ₂₃ ClN ₄ O	70.51	5.20	12.66
IVg	58.55	4.70	11.50	C ₂₄ H ₂₂ N ₄ O ₄ S ₂	58.30	4.45	11.34
IVh	75.50	5.15	9.11	C ₂₈ H ₂₁ N ₃ OS	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-4-carbonyl 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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