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Synthesis of 3-Substituted Arylpyrazole-4-carboxylic Acids

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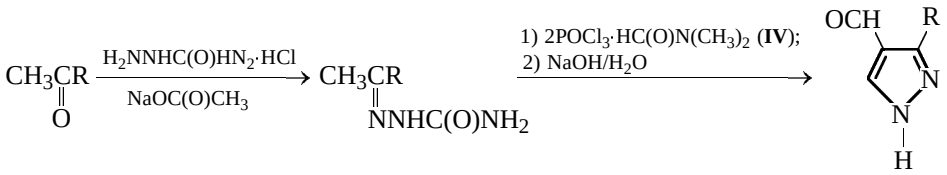
Abstract — A method was suggested for preparing previously unknown 3-aryl-substituted pyrazole-4-carboxylic acids, involving Vilsmeier formylation of semicarbazones of 26 available mono- and disubstituted acetophenones and 2-acetylthiophene followed by oxidation of the resulting 3-aryl-substituted pyrazole-4-carboxaldehydes under the action of potassium permanganate. The mechanism of the formylation reaction is discussed. The method successfully works even with acetophenones containing alkyl substituents. In the latter case, an additional stage that involves isolation of pyrazole-4-carboxylic acids as their silyl esters is used.

It is known [1] that semicarbazones of certain methyl aryl ketones react with phosphoryl chloride in DMF to form 3-arylpyrazole-4-carboxaldehydes. Taking into account that the pyrazole ring is a constituent of natural amino acids [2–4], as well as that pyrazolecarboxylic acids are attractive as intermediates in the synthesis of new medicinals and their precursors, we have studied the conversion of a wide range of available methyl aryl ketones **I** into previously unknown 3-arylpyrazole-4-carboxylic acids **VI** via the intermediate Vismeier formylation of semicarbazones **II** to pyrazolecarboxaldehydes **III**, and oxidation of the latter with potassium permanganate.

It was found that available semicarbazones **II**, as would be expected, are formylated under the action of 2 mol of $POCl_3$–DMF complex **IV** to form the corresponding 3-arylpyrazole-4-carboxaldehydes **III**.



Ia–**Iaa** **IIa**–**IIaa** **IIIa**–**IIIaa**

R = C_6H_5 (**a**), 4-ClC_6H_4 (**b**), 4-HOC_6H_4 (**c**), 4-FC_6H_4 (**d**), 4-$CH_3C_6H_4$ (**e**), 4-$O_2NC_6H_4$ (**f**), 4-$C_2H_5C_6H_4$ (**g**), 4-$(CH_3)_2CHC_6H_4$ (**h**), 4-$CH_3OC_6H_4$ (**i**), 4-BrC_6H_4 (**j**), 4-$C_2H_5OC_6H_4$ (**k**), 4-$CH_3(CH_2)_3OC_6H_4$ (**l**), 3-FC_6H_4 (**m**), 3-BrC_6H_4 (**n**), 3-$O_2NC_6H_4$ (**o**), 3-$CH_3OC_6H_4$ (**p**), 3-HOC_6H_4 (**q**), 3-$CH_3C_6H_4$ (**r**), 2-FC_6H_4 (**s**), 2-$CH_3OC_6H_4$ (**t**), 2,4-$(CH_3)_2C_6H_3$ (**u**), 3,4-$(CH_3)_2C_6H_3$ (**v**), 2,5-$(CH_3)_2C_6H_3$ (**w**), 3,4-$(CH_3O)_2C_6H_3$ (**x**), 2,5-$(CH_3O)_2C_6H_3$ (**y**), 3-Cl-4-$C_2H_5OC_6H_3$ (**z**), 2-thienyl (**aa**).

The yields of pure pyrazolecarboxaldehydes **III** vary from 31 to 87% based on semicarbazones **II** which, in their turn, were isolated in 78–95% yields. The purity of the aldehydes after their recrystallization from water was 96–99%. With other solvents, worse results were obtained in terms of both yields and purity.

The reaction evidently proceeds via intermediate formylation of the methyl group in semicarbazones **II** followed by ring closure to give pyrazoles **V**, and formylation of the latter with a further molecule of complex **IV** into the 4-position of the pyrazole ring.

Evidence for the suggested scheme that involves two successful attacks of complex **IV** on molecules **II** and **V** comes from the detection of pyrazoles **Vb**, **Vf**, **Vg**, and **Vo** by ^1H NMR spectroscopy and GC–MS.

Pyrazoles **V** are difficult to separate from pyrazole-

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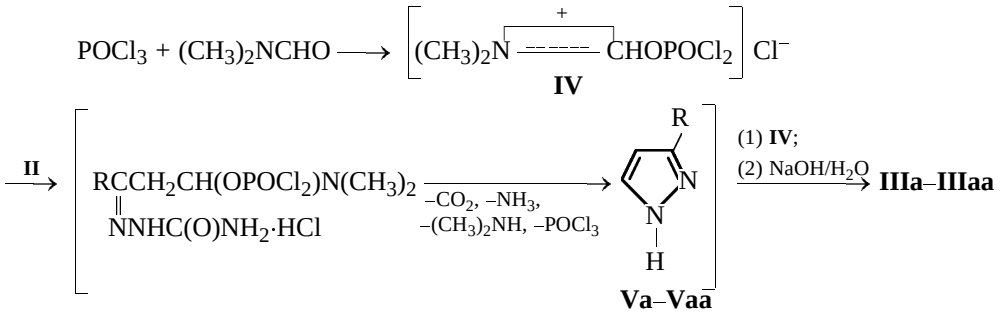
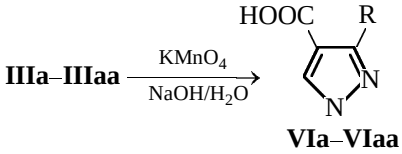


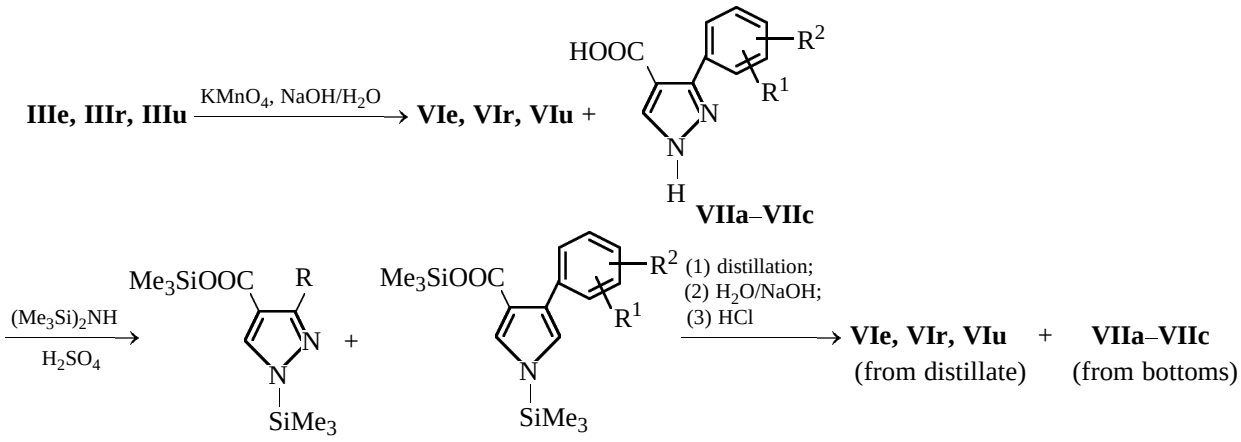
ecarboxaldehydes **III**, and, therefore, semicarbazones **II** should be formylated with at least 2.25 mol of $POCl_3$ to exclude presence of pyrazoles **Va**–**Vaa** in the reaction mixture.

Pyrazolecarboxaldehydes **III** are solid substances (except for **IIIw** which is a viscous oil). Their ^1H NMR spectra reveal a characteristic tautomerism of 3- and 5-substituted pyrazoles (two resonance signals of the CH group at the heteroring nitrogen), associated with intermolecular NH–N hydrogen bonding [5].

Pyrazolecarboxaldehydes **III** are readily soluble in aqueous alkalis. For this reason, we chose potassium permanganate to oxidize compounds **III** into 3-arylpyrazole-4-carboxylic acids **VI**. The reaction occurs in high yield (86–95%) and, therefore, it could be performed with crude aldehydes **III** just after formylation of semicarbazones **II**. This allows the yields of compounds **VIa**–**VIaa** to be much improved (by 5–15% based on starting acetophenones **I**), since compounds **III** are difficult to isolate pure without considerable losses.



It should be noted that the chosen oxidation method proved insufficiently effective with certain pyrazolecarboxaldehydes methylated in the benzene group, since the methyl group is partially oxidized into carboxyl. Thus formed diacids (8–10%) are inseparable by conventional methods, such as recrystallization, reprecipitation, or chromatography. Therefore, for purification we made use of distillation of silyl pyrazolecarboxylates and their subsequent base hydrolysis. Thus the purity of the target products could be brought to 98–99%. The process was accomplished by the following scheme.



VII, R^1 = H, R^2 = 4-COOH (**a**); R^1 = H, R^2 = 3-COOH (**b**); R^1 = 2(4)-CH_3, R^2 = 4(2)-COOH (**c**). **VIII**, R = 4-$CH_3C_6H_4$ (**a**), 3-$CH_3C_6H_4$ (**b**), 2,4-$(CH_3)_2C_6H_3$ (**c**). **IX**, R^1 = H, R^2 = 4-CO_2SiMe_3 (**a**), R^1 = H, R^2 = 3-CO_2SiMe_3 (**b**), R^1 = 2(4)-CH_3, R^2 = 4(2)-CO_2SiMe_3 (**c**).

According to the ^1H NMR spectra, pyrazolecarboxylic acids **VI**, unlike pyrazolecarboxaldehydes **III**, exhibit no tautomerism of substituent position, which is evidenced by the observation of a single signal of

the CH group on nitrogen and is explained by the fact that hydrogen bonding involving the COOH group is favored over NH···N.

The yields and physicochemical characteristics of pyrazolecarboxaldehydes **III** and pyrazolecarboxylic acids **VI** and their derivatives are listed in the table.

EXPERIMENTAL

The ^{1}H NMR spectra were measured in DMSO-d_6 on a Bruker AM-360 spectrometer, working frequency 360.14 MHz. The mass spectra were obtained on a QP–5000 instrument at an ionizing energy of 70 eV. Gas chromatography–mass spectrometry was performed on the same instrument using an SE-30 capillary column (50 m).

Semicarbazones IIa–IIaa. A thoroughly ground mixture of 100 g of semicarbazide hydrochloride and 100 g of anhydrous sodium acetate was suspended in 1 l of ethanol, and the suspension was refluxed for 45 min and filtered while hot. Methyl aryl ketone **I**, 0.83 mol, was added to the mother liquor under reflux, and the mixture was refluxed for 1 h, cooled to 20°C,

Yields and physicochemical characteristics of synthesized pyrazoles

Comp. no.	Yield, %	mp, °C	$M^{+\cdot}$ (*m*/*z*)	^{1}H NMR spectrum, δ, ppm	Found, %		Formula	Calculated, %	
					C	H		C	H
IIIa	87	145	172	7.10 t (1H, CH), 7.30 t (2H, 2CH), 7.70 d (2H, 2CH), 8.00 and 8.38 d (1H, CHN), 9.88 s (1H, CHO), 13.60 s (1H, NH)	69.59	4.65	$C_{10}H_8N_2O$	69.76	4.68
IIIb	32	142–144	206	7.45 d (2H, 2CH), 7.89 d (2H, 2CH), 8.12 and 8.40 d (1H, CHN), 9.91 s (1H, CHO), 13.60 s (1H, NH)	58.00	3.37	$C_{10}H_7ClN_2O$	58.13	3.41
IIIc	49	202–204	188	6.88 d (2H, 2CH), 7.63 d (2H, 2CH), 8.10 and 8.40 d (1H, CHN), 9.70 s (1H, OH), 9.87 s (1H, CHO), 13.59 s (1H, NH)	63.69	4.24	$C_{10}H_8N_2O_2$	63.82	4.28
IIId	85	172–174	190	7.30 t (2H, 2CH), 7.90 t (2H, 2CH), 8.22 and 8.40 d (1H, CHN), 9.90 s (1H, CHO), 13.60 s (1H, NH)	63.15	3.71	$C_{10}H_7FN_2O$	63.16	3.71
IIIe	54	123–125	186	2.40 s (3H,CH_3), 7.29 d (2H, 2CH), 7.67 d (2H, 2CH), 8.00 and 8.40 d (1H, CHN), 9.87 s (1H, CHO), 13.63 s (1H, NH)	70.86	5.38	$C_{11}H_{10}N_2O$	70.95	5.41
IIIf	76	198–200	217	8.23 d (2H, 2CH), 8.32 d (2H, 2CH), 8.47 s (1H, CHN), 9.97 s (1H, CHO), 13.73 s (1H, NH)	55.36	3.26	$C_{10}H_7N_3O_3$	55.30	3.25
IIIg	49	93–95	200	1.22 t (3H, CH_3), 2.65 q (2H, CH_2), 7.34 d (2H, 2CH), 7.70 d (2H, 2CH), 8.26 d (1H, CHN), 9.89 s (1H, CHO), 13.68 s (1H, NH)	71.91	6.02	$C_{12}H_{12}N_2O$	71.98	6.04
IIIh	55	66–68	214	1.23 d (6H, 2CH_3), 2.95 m (1H, CH), 7.37 d (2H, 2CH), 7.71 d (2H, 2CH), 8.28 s (1H, CHN), 9.88 s (1H, CHO), 13.70 s (1H, NH)	72.80	6.57	$C_{13}H_{14}$ N2O	72.87	6.59
IIIi	63	163–165	202	3.78 s (3H, OCH_3), 7.05 d (2H, 2CH), 7.70 d (2H, 2CH), 8.23 d (1H, CHN), 9.88 s (1H, CHO), 13.65 s (1H, NH)	65.32	4.95	$C_{11}H_{10}N_2O_2$	65.34	4.98
IIIj	55	145–147	251	7.40 d (2H, 2CH), 7.88 d (2H, 2CH), 8.10 and 8.40 d (1H, CHN), 9.90 s (1H, CHO), 13.60 s (1H, NH)	47.83	2.80	$C_{10}H_7BrN_2O$	47.86	2.81

Table. (Contd.)

Comp. no.	Yield, %	mp, °C	$M^{+\cdot}$ (*m*/*z*)	^{1}H NMR spectrum, δ, ppm	Found, %		Formula	Calculated, %	
					C	H		C	H
IIIk	59	170–173	216	1.24 t (3H, CH_3), 4.06 q (2H, OCH_2), 7.04 d (2H, 2CH), 7.72 d (2H, 2CH), 8.10 and 8.40 d (1H, CHN), 9.87 s (1H, CHO), 13.63 s (1H, NH)	66.61	5.57	$C_{12}H_{12}N_2O_2$	66.65	5.59
IIIl	50	179–181	244	0.97 t (3H, CH_3), 1.43 m (2H, CH_2), 1.71 m (2H, CH_2), 4.03 t (2H, OCH_2), 7.03 d (2H, 2CH), 7.72 d (2H, 2CH), 8.25 d (1H, CHN), 9.87 s (1H, CHO), 13.63 s (1H, NH)	68.73	6.62	$C_{14}H_{16}N_2O_2$	68.83	6.60
IIIm	81	137–138	190	7.29 t (1H, CH), 7.52 q (1H, CH), 7.73 m (2H, 2CH), 8.48 s (1H, CHN), 9.91 s (1H, CHO), 13.80 s (1H, NH)	63.16	3.70	$C_{10}H_7FN_2O$	63.16	3.71
IIIn	53	149–151	251	7.25 d (1H, CH), 7.56 t (1H, CH), 7.70 m (2H, 2CH), 8.44 s (1H, CHN), 9.90 s (1H, CHO), 13.82 s (1H, NH)	47.84	2.81	$C_{10}H_7BrN_2O$	47.86	2.81
IIIo	51	156–158	217	7.70 t (1H, CH), 8.27 d (1H, CH), 8.38 d (1H, CH), 8.70 d (1H, CHN), 8.81 s (1H, CH), 9.95 s (1H, CHO), 13.90 s (1H, NH)	55.27	3.22	$C_{10}H_7N_3O_3$	55.30	3.25
IIIp	44	158–161	202	3.77 s (3H, OCH_3), 7.10 d (1H, CH), 7.42 m (2H, 2CH), 7.55 t (1H, CH), 8.34 d (1H, CHN), 9.90 s (1H, CHO), 13.81 s (1H, NH)	65.31	4.96	$C_{11}H_{10}N_2O_2$	65.34	4.98
IIIq	31	204–205	188	6.87 d (1H, CH), 7.18 d (2H, 2CH), 7.29 t (1H, CH), 8.27 d (1H, CHN), 9.60 s (1H, OH), 9.88 s (1H, CHO), 13.82 s (1H, NH)	63.72	4.25	$C_{10}H_8N_2O_2$	63.82	4.28
IIIr	75	98–102	186	2.25 s (3H, CH_3), 7.20 d (1H, CH), 7.32 t (1H, CH), 7.50 m (2H, 2CH), 8.30 d (1H, CHN), 9.88 s (1H, CHO), 13.60 s (1H, NH)	70.88	5.39	$C_{11}H_{10}N_2O$	70.95	5.41
IIIs	61	146–148	190	7.30 m (2H, 2CH), 7.54 m (2H, 2CH), 8.28 d (1H, CHN), 9.88 s (1H, CHO), 13.62 s (1H, NH)	63.15	3.71	$C_{10}H_7FN_2O$	63.16	3.71
IIIt	50	153–154	202	3.76 s (3H, OCH_3), 7.10 m (2H, 2CH), 7.46 m (2H, 2CH), 8.00 and 8.40 d (1H, CHN), 9.68 s (1H, CHO), 13.58 s (1H, NH)	65.34	4.98	$C_{11}H_{10}N_2O_2$	65.34	4.98
IIIu	46	73–75	200	2.16 s (3H, CH_3), 2.32 s (3H, CH_3), 7.09 d (1H, CH), 7.16 s (1H, CH), 7.21 d (1H, CH), 8.20 s (1H, CHN), 9.60 s (1H, CHO), 13.60 s (1H, NH)	71.85	6.06	$C_{12}H_{12}N_2O$	71.98	6.04
IIIv	52	103–105	200	2.18 s (3H, CH_3), 2.34 s (3H, CH_3), 7.15 m (3H, 3CH), 8.22 s (1H, CHN), 9.70 s (1H, CHO), 13.50 s (1H, NH)	71.95	6.02	$C_{12}H_{12}N_2O$	71.98	6.04

Table. (Contd.)

Comp. no.	Yield, %	mp, °C	$M^{+\cdot}$ (*m*/*z*)	^{1}H NMR spectrum, δ, ppm	Found, %		Formula	Calculated, %	
					C	H		C	H
IIIw	50	–	200	2.14 s (3H, CH_3), 2.30 s (3H, CH_3), 7.14 s (1H, CH), 7.20 q (2H, 2CH), 8.25 s (1H, CHN), 9.80 s (1H, CHO), 13.40 s (1H, NH)	71.88	6.01	$C_{12}H_{12}N_2O$	71.98	6.04
IIIx	40	150–152	232	3.81 s (6H, $2OCH_3$), 7.08 d (1H, CH), 7.39 d (1H, CH), 7.45 s (1H, CH), 8.22 d (1H, CHN), 9.89 s (1H, CHO), 13.62 s (1H, NH)	62.05	5.20	$C_{12}H_{12}N_2O_3$	62.06	5.21
IIIy	62	156–158	232	3.77 s (3H, OCH_3), 3.80 s (3H, OCH_3), 7.15 d (1H, CH), 7.22 d (1H, CH), 7.44 s (1H, CH), 8.20 d (1H, CHN), 9.90 s (1H, CHO), 13.60 s (1H, NH)	62.03	5.18	$C_{12}H_{12}N_2O_3$	62.06	5.21
IIIz	71	191–193	250	1.38 t (3H, CH_3), 4.18 q (2H, OCH_2), 7.22 d (1H, CH), 7.81 d (1H, CH), 8.00 s (1H, CH), 8.57 s (1H, CHN), 9.87 s (1H, CHO), 13.72 s (1H, NH)	57.50	4.42	$C_{12}H_{11}ClN_2O_2$	57.50	4.42
IIIaa	45	69–71	178	7.17 t (1H, CH), 7.62 d (1H, CH), 8.03 d (1H, CHS), 8.54 s (1H, CHN), 9.97 s (1H, CHO), 13.68 c (1H, NH)	53.78	3.34	$C_8H_6N_2OS$	53.92	3.39
Vb	8[a]	–	178	6.62 d (1H, CH), 7.38 d (2H, 2CH), 7.62 d (1H, CHN), 7.78 d (2H, 2CH), 12.85 s (1H, NH)	–	–	$C_9H_7ClN_2$	–	–
Vf	4[a]	–	189	6.72 d (1H, CH), 7.62 d (1H, CHN), 8.02 d (2H, 2CH), 8.21 d (2H, 2CH), 13.00 s (1H, NH)	–	–	$C_9H_7N_3O_2$	–	–
Vg	3[a]	–	172	1.21 t (3H, CH_3), 2.66 q (2H, CH_2), 6.47 d (1H, CH), 7.17 d (2H, 2CH), 7.48 d (1H, CHN), 7.53 d (2H, 2CH), 13.40 s (1H, NH)	–	–	$C_{11}H_{12}N_2$	–	–
Vo	3[a]	–	189	6.70 d (1H, CH), 7.60 m (2H, 2CH), 8.08 d (1H, CH), 8.31 d (1H, CH), 8.60 s (1H, CH), 12.95 s (1H, NH)	–	–	$C_9H_7N_3O_2$	–	–
VIa	98	>270	188	7.07 t (1H, CH), 7.25 t (2H, 2CH), 7.63 d (2H, 2CH), 8.06 s (1H, CHN), 12.80 br (2H, NH + COOH)	63.69	4.24	$C_{10}H_8N_2O_2$	63.82	4.28
VIb	95	>270	222	7.38 d (2H, 2CH), 7.81 d (2H, 2CH), 8.20 s (1H, CHN), 13.00 br (2H, NH + COOH)	53.89	3.14	$C_{10}H_7ClN_2O_2$	53.95	3.17
VId	98	>270	206	7.23 t (2H, 2CH), 7.82 t (2H, 2CH), 8.20 s (1H, CHN), 13.05 s (2H, NH + COOH)	58.24	3.41	$C_{10}H_7FN_2O_2$	58.26	3.42
VIe	88	>270	202	2.34 s (3H, CH_3), 7.23 d (2H, 2CH), 7.61 d (2H, 2CH), 8.07 s (1H, CHN), 12.70 br (2H, NH + COOH)	65.29	4.96	$C_{11}H_{10}N_2O_2$	65.34	4.98
VIf	93	>270	233	8.06 d (2H, 2CH), 8.26 d (2H, 2CH), 8.30 s (1H, CHN), 13.50 br (2H, NH + COOH)	51.46	3.01	$C_{10}H_7N_3O_4$	51.51	3.03

Table. (Contd.)

Comp. no.	Yield, %	mp, °C	$M^{+\cdot}$ (*m*/*z*)	^{1}H NMR spectrum, δ, ppm	Found, %		Formula	Calculated, %	
					C	H		C	H
VIi	99	>270	218	3.78 s (3H, OCH_3), 7.00 d (2H, 2CH), 7.63 d (2H, 2CH), 8.20 s (1H, CHN), 12.90 br (2H, NH + COOH)	60.55	4.60	$C_{11}H_{10}N_2O_3$	60.55	4.62
VIj	96	>270	267	7.30 d (2H, 2CH), 7.77 d (2H, 2CH), 8.12 s (1H, CHN), 13.10 s (2H, NH + COOH)	44.93	2.67	$C_{10}H_7BrN_2O_2$	44.99	2.64
VIk	97	>270	232	1.26 t (3H, CH_3), 4.03 q (2H, OCH_2), 7.02 d (2H, 2CH), 7.67 d (2H, 2CH), 8.15 s (1H, CHN), 13.00 br (2H, NH + COOH)	62.02	5.18	$C_{12}H_{12}N_2O_3$	62.06	5.21
VIl	98	>270	260	0.93 t (3H, CH_3), 1.44 m (2H, CH_2), 1.71 m (2H, CH_2), 4.01 t (2H, OCH_2), 6.97 d (2H, 2CH), 7.66 d (2H, 2CH), 8.05 s (1H, CHN), 12.7 br (2H, NH + COOH)	64.55	6.16	$C_{14}H_{16}N_2O_3$	64.60	6.20
VIm	99	>270	206	7.22 t (1H, CH), 7.45 q (1H, CH), 7.62 d (2H, 2CH), 8.20 s (1H, CHN), 13.00 br (2H, NH + COOH)	58.25	3.42	$C_{10}H_7FN_2O_2$	58.26	3.42
VIn	98	>270	267	7.18 d (1H, CH), 7.49 t (1H, CH), 7.64 m (2H, 2CH), 8.14 s (1H, CHN), 13.28 br (2H, NH + COOH)	44.97	2.63	$C_{10}H_7BrN_2O_2$	44.99	2.64
VIo	92	>270	233	7.73 t (1H, CH), 8.24 m (2H, 2CH), 8.32 s (1H, CHN), 8.68 s (1H, CH), 13.60 br (2H, NH + COOH)	51.62	3.07	$C_{10}H_7N_3O_4$	51.51	3.03
VIp	98	>270	218	3.78 s (3H, OCH_3), 6.96 m (1H, CH), 7.33 m (3H, 3CH), 8.10 s (1H, CHN), 12.60 br (2H, NH + COOH)	60.51	4.59	$C_{11}H_{10}N_2O_3$	60.55	4.62
VIr	86	>270	202	2.34 s (3H, CH_3), 7.21 d (1H, CH), 7.29 t (1H, CH), 7.50 d (2H, 2CH), 8.07 s (1H, CHN), 12.80 br (2H, NH + COOH)	65.24	4.92	$C_{11}H_{10}N_2O_2$	65.34	4.98
VIs	98	>270	206	7.26 m (2H, 2CH), 7.47 m (2H, 2CH), 8.14 s (1H, CHN), 12.60 br (2H, NH + COOH)	58.25	3.40	$C_{10}H_7FN_2O_2$	58.26	3.42
VIt	96	>270	218	3.78 s (3H, OCH_3), 7.03 m (2H, 2CH), 7.38 m (2H, 2CH), 8.03 s (1H, CHN), 13.00 br (2H, NH + COOH)	60.51	4.60	$C_{11}H_{10}N_2O_3$	60.55	4.62
VIu	93	>270	216	2.08 s (3H, CH_3), 2.31 s (3H, CH_3), 7.03 d (1H, CH), 7.10 d (2H, 2CH), 8.01 s (1H, CHN), 12.60 br (2H, NH + COOH)	66.62	5.57	$C_{12}H_{12}N_2O_2$	66.65	5.59
VIv	95	>270	216	2.10 s (3H, CH_3), 2.33 s (3H, CH_3), 7.07 m (3H, 3CH), 8.08 s (1H, CHN), 12.70 br (2H, NH + COOH)	66.60	5.61	$C_{12}H_{12}N_2O_2$	66.65	5.59
VIx	97	>270	248	3.79 s (6H, $2OCH_3$), 7.02 d (1H, CH), 7.32 d (1H, CH), 7.37 s (1H, CH), 8.11 s (1H, CHN), 12.70 br (2H, NH + COOH)	58.01	4.83	$C_{12}H_{12}N_2O_4$	58.06	4.87

Table. (Contd.)

Comp. no.	Yield, %	mp, °C	$M^{+\cdot}$ (*m*/*z*)	^{1}H NMR spectrum, δ, ppm	Found, %		Formula	Calculated, %	
					C	H		C	H
VIy	96	>270	248	3.76 s (3H, OCH_3), 3.80 s (3H, OCH_3), 7.09 d (1H, CH), 7.15 d (1H, CH), 7.35 s (1H, CH), 8.08 s (1H, CHN), 12.72 br (2H, NH + COOH)	58.03	4.85	$C_{12}H_{12}N_2O_4$	58.06	4.87
VIx	95	>270	266	1.40 t (3H, CH_3), 4.18 q (2H, OCH_2), 7.18 d (1H, CH), 7.72 d (1H, CH), 7.86 s (1H, CH), 8.10 s (1H, CHN), 12.70 br (2H, NH + COOH)	54.02	4.16	$C_{12}H_{11}ClN_2O_3$	54.05	4.16
VIaa	90	>270	194	7.03 t (1H, CH), 7.30 d (1H, CH), 8.03 t (2H, CHS + CHN), 12.52 br (2H, NH + COOH)	49.38	3.06	$C_8H_6N_2O_2S$	49.48	3.11
VIIa	8	–	232	7.82 d (2H, 2CH), 8.00 d (2H, 2CH), 8.17 s (1H, CHN), 12.70 br (3H, NH + 2COOH)	–	–	$C_{11}H_8N_2O_4$	–	–
VIIb	10	–	232	7.52 d (1H, CH), 7.97 m (2H, 2CH), 8.18 s (1H, CHN), 8.30 s (1H, CH), 12.75 br (3H, NH + 2COOH)	–	–	$C_{11}H_8N_2O_4$	–	–
VIIc	6	–	246	2.25 s (3H, CH_3), 7.30 d (1H, CH), 7.75 d (1H, CH), 7.82 s (1H, CH), 8.10 s (1H, CHN), 12.60 br (3H, NH + 2COOH)	–	–	$C_{12}H_{10}N_2O_4$	–	–
VIIIa	96	–	346	–	–	–	$C_{17}H_{26}N_2O_2Si_2$	–	–
VIIIb	96	–	346	0.02 s (9H, $3CH_3$), 0.06 s (9H, $3CH_3$), 2.35 s (3H, CH_3), 7.21 d (1H, CH), 7.31 t (1H, CH), 7.53 d (2H, 2CH), 8.06 s (1H, CHN)	58.72	7.49	$C_{17}H_{26}N_2O_2Si_2$	58.92	7.56

[a] Detected only at **II**/**IV** = 1:2.

allowed to stand for 10 h, and the precipitate that formed was filtered off, washed with a little ethanol cooled to –5°C, and dried to isolate semicarbazones **II**. The mother liquor was reduced to 150–200 ml and poured into 1 l of water. The precipitate that formed was filtered off, heated for 1 h in 70–100 ml of ethanol under reflux, and cooled to 5°C. The precipitate was filtered off and washed with a little ethanol cooled to –5°C to obtain an additional crop of semicarbazone **II**. In the case of acetophenones **Ic** and **IIq**, the alcohol was removed immediately after the synthesis had been complete. The yields of semicarbazones were 90–95%, except for compounds **IIc** and **IIq** (78 and 82%, respectively).

3-Arylpyrazole-4-carboxaldehydes IIIa–IIIaa. Freshly distilled $POCl_3$, 353 g, was added dropwise at 0°C to 440 ml of dry DMF. The mixture was allowed to stand for 20 min at 20°C and cooled to 0°C, after which 1 mol of semicarbazone **II** was added so as the temperature of the reaction mixture did not rise over 40–50°C and uniform gas evolution was observed. After all semicarbazone had been added, the mixture was stirred for 1.5 h at 80°C and quickly poured onto 1.5 kg of ice. Most ice melted. The mixture was treated with 30% aqueous NaOH to pH 8–9, allowed to stand for 30 min, and treated with conc. HCl until heterogenization (pH 5–7). After 18 h, the solid material was separated (pH ≤7), washed with water, recrystallized from water (0.5–5.0 g of compound per 1 l of water), and dried at 50°C to obtain pyrazole **III**. Pyrazole **IIIw** was extracted with chloroform after recrystallization. For direct oxidation of crude pyrazoles **III**, they were extracted from the heterogeneous mixture with chloroform and used without recrystallization. After the syntheses with 2 mol of $POCl_3$ and recrystallization, from semicarbazones **IIb**, **IIf**, **IIg**, and **IIo** we obtained compounds

IIIb, **IIIf**, **IIIg**, and **IIIo** mixed with compounds **Vb**, **Vf**, **Vg**, and **Vo** which were identified with ^{1}H NMR and GC–MS.

3-Arylpyrazole-4-carboxylic acids VIa–VIaa. Aldehyde **III**, 0.17 mol, was dissolved with stirring in a solution of 33 g of NaOH in 650 ml of water. The solution was cooled to 15°C, and a solution of 22.5 g of $KMnO_4$ in 650 ml of water was quickly added. The mixture was stirred for 1 h at 20°C, heated to 96–98°C, allowed to decolorize, and cooled. The MnO_2 precipitate was filtered off and washed with 200 ml of water. The combined mother liquor was acidified with conc. HCl to pH 3. The precipitate was filtered off, washed with water, and dried at 110–120°C. The dry residue was thoroughly ground and suspended in 800 ml of water. The suspension was stirred at 10 min and filtered. The filtrate was washed with water to neutral and evaporated at 100°C to obtain acids **VI** as white fine powders.

Crude aldehydes were oxidized in a similar way. In this case, aldehydes **III** were dissolved in the alkali, and the undissolved material was filtered off or extracted with chloroform, after which the solution of $KMnO_4$ was added dropwise. To purify acids **VId**, **VIr**, and **VIu**, which contained 8–12% of diacids **VII**, they were treated with 60 ml of hexamethyldisilazane, 2–4 drops of conc. H_2SO_4 was added, and the mixture was refluxed for 2 h, cooled, and distilled in a vacuum, collecting as the first high-boiling fraction silyl esters **VIII**. The latter were treated with 400 ml of 5% aqueous NaOH, the mixture was stirred for 1 h at 100°C, cooled, and extracted with ether (2×40 ml). The aqueous layer was acidified with HCl to pH 3. Pure compounds **VId**, **VIr**, and **VIu** precipitated and were treated as described above. The bottoms were subjected to base hydrolysis and acidified to obtain compounds **VII** mixed with 15–20% of compounds **VId**, **VIr**, and **VIu**. Given are comp. no. and bp, °C (*p*, mm Hg): **VIIIa**, 173–175 (2.5); **VIIIb**, 190–192 (4); and **VIIIc**, 196–198 (3).

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