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4-Functionally Substituted 3-Heterylpyrazoles: VIII.* 3-Aryl(heteryl)-4-hydroxyl(chloro)methylpyrazoles

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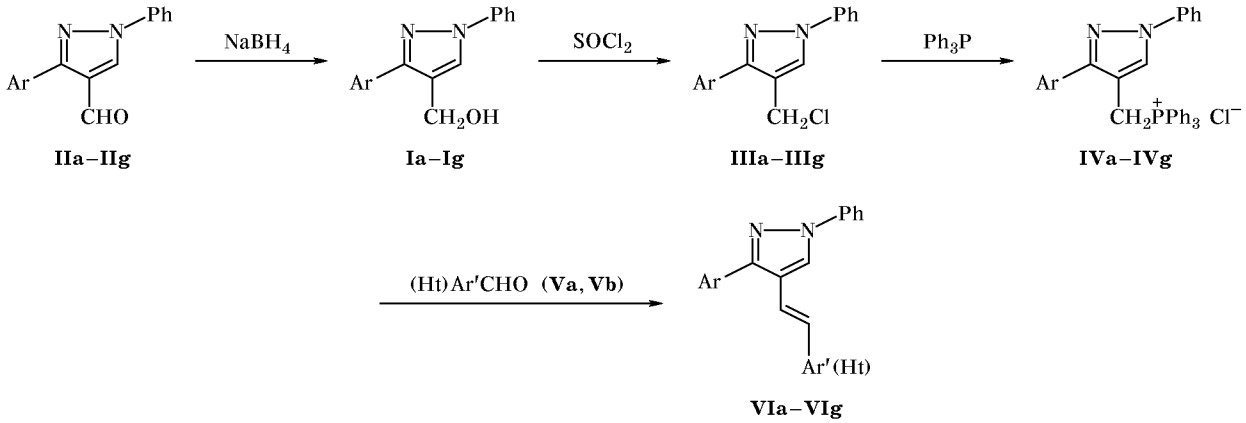
Abstract—3-Aryl(heteryl)pyrazole-4-carbaldehydes were reduced with sodium tetrahydridoborate under mild conditions to give 3-aryl(heteryl)-4-hydroxymethylpyrazoles which were converted into the corresponding 4-chloromethyl derivatives by treatment with thionyl chloride. The subsequent reaction with triphenylphosphine led to formation of triphenyl(4-pyrazolylmethyl)phosphonium chlorides, and Wittig reaction of the latter with aromatic or heteroaromatic aldehydes yielded 4-[2-aryl(heteryl)ethenyl]pyrazoles.

The hydroxy group in hydroxymethylpyrazoles is a very convenient functional substituent ensuring purposeful synthetic transformations. In particular, 1-hydroxymethylpyrazole was used as starting compound to prepare the natural amino acid pyrazolylalanine [2] and 1,3,5-substituted 4-hydroxymethylpyrazoles which are intermediate products in the synthesis of bioactive esters [3]. However, no sysmatic studies on the chemical properties of 4-hydroxymethylpyrazoles have been reported, primarily because of experimental difficulties in the synthesis of these compounds. For example, direct hydroxymethylation of 1,3,5-trisubstituted pyrazoles is often accompanied by formation of dipyrazolylmethanes as by-products [4].

In the present communication we propose a convenient procedure for preparation of 3-aryl(heteryl)-4-hydroxymethyl-1-phenylpyrazoles **Ia**–**Ig** by mild reduction of readily accessible [5] 4-pyrazolecarbaldehydes **IIa**–**IIg** (Scheme 1). The procedure is simple

Scheme 1.



IIa–IIg **Ia–Ig** **IIIa–IIIg** **IVa–IVg** **VIa–VIg**

I–**IV**, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 3-BrC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-PhC_6H_4 (**f**), 2-thienyl (**g**); **V**, Ar′ = 4-$O_2NC_6H_4$ (**a**), 5-nitro-2-furyl (**b**); **VI**, Ar = 4-FC_6H_4, Ar′ = 4-$O_2NC_6H_4$ (**a**), 5-nitro-2-furyl (**b**); Ar = 4-ClC_6H_4, Ar′ = 4-$O_2NC_6H_4$ (**c**); Ar = 4-BrC_6H_4, Ar′ = 4-$O_2NC_6H_4$ (**d**), 5-nitro-2-furyl (**e**); Ar = 2-thienyl, Ar′ = 4-$O_2NC_6H_4$ (**f**), 5-nitro-2-furyl (**g**).

* For communication VII, see [1].

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Table 1. Yields, melting points, spectral parameters, and elemental analyses of 3-aryl(heteryl)-4-hydroxymethyl-1-phenylpyrazoles **Ia**–**Ig**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν(OH), cm^{-1}	^1H NMR spectrum, δ, ppm
Ia	91	71–73	3320	4.59 d (2H, CH_2), 5.30 t (1H, OH), 7.32–7.64 m (10H, H_{arom}), 8.54 s (1H, =CH)
Ib	96	94–96	3350	4.70 d (2H, CH_2), 5.26 t (1H, OH), 7.42–7.94 m (9H, H_{arom}), 8.59 s (1H, =CH)
Ic	84	126–127	3345	4.56 d (2H, CH_2), 5.37 t (1H, OH), 7.34–7.83 m (9H, H_{arom}), 8.62 s (1H, =CH)
Id	87	103–104	3370	4.72 d (2H, CH_2), 5.31 t (1H, OH), 7.39–7.87 m (9H, H_{arom}), 8.50 s (1H, =CH)
Ie	94	132–133	3345	4.61 d (2H, CH_2), 5.30 t (1H, OH), 7.41–7.92 m (9H, H_{arom}), 8.49 s (1H, =CH)
If	81	114–115	3360	4.53 d (2H, CH_2), 5.33 t (1H, OH), 7.29–7.31 m (14H, H_{arom}), 8.60 s (1H, =CH)
Ig	87	93–95	3340	4.59 d (2H, CH_2), 5.37 t (1H, OH), 7.19–8.01 m (8H, H_{arom}), 8.55 s (1H, =CH)

Comp. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
Ia	76.60	5.31	11.04	$C_{16}H_{14}N_2O$	76.80	5.60	11.20
Ib	71.34	4.61	10.26	$C_{16}H_{13}FN_2O$	71.64	4.85	10.44
Ic	67.21	4.33	9.71	$C_{16}H_{13}ClN_2O$	67.48	4.56	9.84
Id	58.02	3.70	8.32	$C_{16}H_{13}BrN_2O$	58.35	3.95	8.51
Ie	58.15	4.12	8.40	$C_{16}H_{13}BrN_2O$	58.35	3.95	8.51
If	81.30	5.34	8.31	$C_{22}H_{18}N_2O$	80.90	5.52	8.58
Ig	65.43	4.39	11.04	$C_{14}H_{12}N_2OS$	65.02	4.58	10.93

from the preparative viewpoint: the reactions are carried out in ethanol at room temperature, and the yields of the reduction products attain 81–96%. The structure of compounds **Ia**–**Ig** (Table 1) was proved by the IR spectra which contained absorption bands in the region 3320–3370 cm^{-1}, characteristic of hydroxy groups, and by the ^1H NMR spectra. The latter contained multiplet signals from aromatic protons of the substituents in positions *1* and *3* of the pyrazole ring, a singlet at δ 8.49–8.62 ppm from the 5-H proton, a triplet at δ 5.26–5.37 ppm from the hydroxy proton, and a doublet at 4.56–4.72 ppm from protons of the CH_2 group in position *4*.

Grandberg *et al.* [4] previously found that 1,3,5-trisubstituted 4-hydroxymethylpyrazoles react with thionyl chloride in a nonselective fashion. 5-Chloro-4-hydroxymethyl-3-methyl-1-phenylpyrazole and 4-hydroxymethyl-1,3,5-triphenylpyrazole were the only compounds which were converted into the corresponding chloromethyl derivatives without side formation of dipyrazolylmethanes. We have shown that treatment of 4-hydroxymethylpyrazoles **Ia**–**Ig** with thionyl chloride gives 4-chloromethylpyrazoles **IIIa**–**IIIg** in 75–78% yield (Table 2). No dipyrazolylmethanes were formed, which may be explained in terms of stabilizing effect of aromatic and heteroaromatic substituents in positions *1* and *3*.

The chlorine atom in 4-chloromethylpyrazoles **III** is fairly labile, and we succeeded in reacting compounds **III** with triphenylphosphine to obtain hitherto unknown triphenyl(4-pyrazolylmethyl)phosphonium salts **IVa**–**IVg** (Table 3). Using phosphonium salts **IVb**, **IVc**, and **IVe** as examples, we brought them into the Wittig reaction with *p*-nitrobenzaldehyde (**Va**) and 5-nitro-2-furaldehyde (**Vb**). As a result, 4-(2-arylethenyl)pyrazoles **VIa**–**VIg** were obtained (Table 4).

Table 2. Yields, melting points, ^{1}H NMR spectra, and elemental analyses of 3-aryl(heteryl)-4-chloromethyl-1-phenylpyrazoles **IIIa**–**IIIg**

Comp. no.	Yield, %	mp, °C	^{1}H NMR spectrum, δ, ppm	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIIa	87	84–85	4.92 s (2H, CH_2), 7.34–7.88 m (10H, H_{arom}), 8.77 s (1H, =CH)	71.21	5.06	10.23	$C_{16}H_{13}ClN_2$	71.50	4.84	10.42
IIIb	81	92–93	4.90 s (2H, CH_2), 7.40–7.92 m (9H, H_{arom}), 8.83 s (1H, =CH)	66.88	3.96	9.69	$C_{16}H_{12}ClFN_2$	67.01	4.18	9.47
IIIc	79	74–75	4.98 s (2H, CH_2), 7.30–7.64 m (9H, H_{arom}), 8.72 s (1H, =CH)	63.03	3.71	9.54	$C_{16}H_{12}Cl_2N_2$	63.36	3.96	9.24
IIId	85	84–85	4.93 s (2H, CH_2), 7.36–7.82 m (9H, H_{arom}), 8.76 s (1H, =CH)	55.42	3.18	7.83	$C_{16}H_{12}BrClN_2$	55.25	3.45	8.05
IIIe	83	103–104	4.93 s (2H, CH_2), 7.24–7.63 m (9H, H_{arom}), 8.80 s (1H, =CH)	55.03	3.27	7.91	$C_{16}H_{12}BrClN_2$	55.25	3.45	7.91
IIIf	75	140–141	4.91 s (2H, CH_2), 7.30–7.87 m (14H, H_{arom}), 8.74 s (1H, =CH)	76.97	4.71	7.98	$C_{22}H_{17}ClN_2$	76.63	4.93	8.12
IIIg	76	79–81	4.97 s (2H, CH_2), 7.04–7.79 m (8H, H_{arom}), 8.77 s (1H, =CH)	60.90	3.83	10.43	$C_{14}H_{11}ClN_2S$	61.20	4.00	10.20

Compounds **VI** are mono- and dihetero analogs of stilbene, and they can be regarded as promising synthons for prepatration of dyes, complexing agents, and medicinals [6].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in KBr. The ^{1}H NMR spectra were measured on a Varian Gemini instrument (300 MHz) using DMSO-d_6 as solvent and TMS as internal reference.

3-Aryl(heteryl)-4-hydroxymethyl-1-phenylpyrazoles Ia–**Ig** (Table 1). A solution of 0.76 g (0.02 mol) of sodium tetrahydridoborate in 100 ml of ethanol was added with stirring to a solution of 0.02 mol of 4-pyrazolecarbaldehyde **IIa**–**IIg** in 60 ml of ethanol. The mixture was stirred for 1 h, 200 ml of water was added, and the mixture was left to stand for 12 h at 0°C. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

3-Aryl(heteryl)-4-chloromethyl-1-phenylpyrazoles IIIa–**IIIg** (Table 2). Thionyl chloride, 2.4 g (0.02 mol), was added to a suspension of 0.01 mol of 4-hydroxymethylpyrazole **Ia**–**IIg** in 10 ml of benzene. The mixture was refluxed for 2 h and evaporated to 1/4 of the initial volume. After cooling, the precipitate was filtered off, washed with hexane, and recrystallized from benzene–hexane (3:1).

3-Aryl(heteryl)-1-phenyl-4-pyrazolylmethyl(triphenyl)phosphonium chlorides IVa–**IVg.** A solution of 0.01 mol of 4-chloromethylpyrazole **IIIa**–**IIIg** and 2.62 g (0.01 mol) of triphenylphosphine in 20 ml of dry benzene was heated for 3 h under reflux. After cooling, the precipitate was filtered off and washed with 5 ml of benzene, and the filtrate was heated again for 3 h. The precipitate was separated and combined with the first portion, and the product was recrystallized from chloroform–ethyl acetate (4:1).

3-Aryl-4-[2-aryl(heteryl)ethenyl]-1-phenylpyrazoles VIa–**VIg.** A solution of 0.33 g (0.006 mol) of sodium methoxide in 10 ml of methanol was added under stirring to a solution of 0.005 mol of phosphonium salt **IIIa**–**IIIg** and 0.005 mol of aldehyde **Va** or **Vb** in 20 ml of methanol. The mixture was stirred for 3 h, and the precipitate was filtered off, washed with methanol, and recrystallized from toluene.

Table 3. Yields, melting points, and elemental analyses of 3-aryl(heteryl)-1-phenyl-4-pyrazolylmethyl(triphenyl)phosphonium chlorides **IVa**–**IVg**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
IVa	87	273–275	76.49	5.03	6.31	6.05	$C_{34}H_{28}ClN_2P$	76.90	5.27	6.69	5.84
IVb	82	244–246	74.03	4.63	6.20	5.31	$C_{34}H_{27}ClFN_2P$	74.38	4.92	6.47	5.65
IVc	81	261–263	71.84	4.51	6.09	5.15	$C_{34}H_{27}Cl_2N_2P$	72.21	4.77	6.28	5.48
IVd	79	259–260	67.25	4.18	5.61	4.81	$C_{34}H_{27}BrClN_2P$	66.94	4.43	5.82	5.08
IVe	89	263–264	66.71	4.26	5.50	5.34	$C_{34}H_{27}BrClN_2P$	66.94	4.43	5.82	5.08
IVf	71	272–274	78.84	5.44	5.53	4.95	$C_{40}H_{32}ClN_2P$	79.14	5.27	5.85	5.11
IVg	91	255–256	71.32	4.51	6.32	5.60	$C_{32}H_{26}ClN_2PS$	71.57	4.84	6.61	5.77

Table 4. Yields, melting points, IR spectra, and elemental analyses of 3-aryl-4-[2-aryl(heteryl)ethenyl]-1-phenylpyrazoles **VIa**–**VIg**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν(C=C), cm^{-1}	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
VIa	63	161–163	1635	71.40	3.86	10.63	$C_{23}H_{16}FN_3O_2$	71.68	4.15	10.90
VIb	57	159–160	1630	67.43	3.61	11.02	$C_{21}H_{14}FN_3O_3$	67.20	3.73	11.20
VIc	56	183–184	1640	68.99	3.69	10.28	$C_{23}H_{16}ClN_3O_2$	68.74	3.98	10.46
VId	64	158–159	1630	61.81	3.44	9.18	$C_{23}H_{16}BrN_3O_2$	61.88	3.58	9.41
VIe	51	201–202	1630	57.61	3.09	9.41	$C_{23}H_{16}BrN_3O_3$	57.79	3.21	9.63
VIf	50	165–166	1635	67.33	3.88	11.05	$C_{21}H_{15}N_3O_2S$	67.56	4.02	11.26
VIg	43	104–105	1640	63.11	3.43	11.34	$C_{19}H_{13}N_3O_3S$	62.80	3.58	11.57

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