Novel Synthesis of 1-Substituted 4-Hydroxypyrazoles

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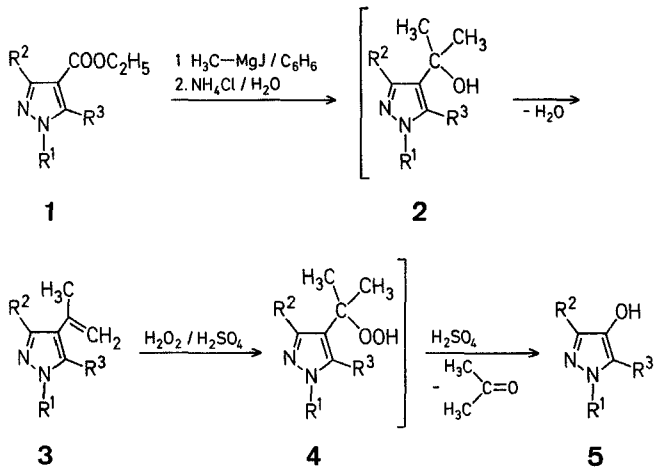
Only a limited number of 4-hydroxypyrazoles **5** have been reported[1-4]. A recently proposed synthesis is based on the reaction of 2-acetoxy-1,3-dione derivatives with hydrazines. However, unsymmetrically substituted β-diketones afford inseparable mixtures of *N*-substituted isomeric pyrazoles[4].

We now report a new method for the preparation of 4-hydroxypyrazoles **5** starting from the readily available 4-ethoxycarbonylpyrazoles **1.** Reaction of methylmagnesium iodide with the starting compounds **1** at room temperature in benzene yields, after aqueous work-up, the tertiary alcohols **2** which are partly dehydrated in the isopropenyl compounds **3.** The mixtures of **2** and **3** are used without purification in the acid-catalyzed addition of hydrogen peroxide to afford intermediate tertiary hydroperoxides **4.** Finally, the 4-hydroxypyrazoles **5** are formed by *in situ* rearrangement of the hydroperoxides **4** (for the mechanism, see Ref.[5]).



1-4	R¹	R²	R³
a	C_6H_5	H	CH_3
b	C_6H_5	H	C_2H_5
c	C_6H_5	H	C_6H_5
d	C_6H_5	CH_3	C_6H_5
e	C_6H_5	CH_3	CH_3
f	CH_3	CH_3	C_6H_5
g	CH_3	CH_3	CH_3

Reaction of Compounds 1 with Methylmagnesium Iodide; General Procedure:

To a solution of methylmagnesium iodide (0.1 mol) in benzene (50 ml) is added dropwise with stirring a solution of the pyrazole **1** (0.03 mol) in benzene (60 ml). The mixture is refluxed for 6 h. After cooling to room temperature, the mixture is poured into saturated aqueous ammonium chloride (300 ml) and extracted with ether (2 × 50 ml). The combined extracts are washed with 10% sodium hydrogen sulfite solution (50 ml), dried with sodium sulfate, and the solvent is removed under reduced pressure. ^{1}H-N.M.R. analysis of the residue indicates that it consists essentially of the tertiary alcohols **2** in the case of **1a–c, e** or of the 4-isopropenyl derivatives **3** in the case of **1d, f, g.** The crude reaction mixture is submitted without further purification to the next step; yield: 80–90%.

4-Hydroxy-pyrazoles 5; General Procedure:

A solution of 30% hydrogen peroxide (5 ml) in concentrated sulfuric acid (6.5 ml) prepared under cooling (< 15°C; exothermic reaction) is added dropwise to a cooled solution of the crude products **2** or **3** (0.022 mol) in dichloromethane (20 ml) at such a rate that the temperature does not rise above 15°C. The solution is then kept at room temperature with stirring for 4 h and aqueous 70% sulfuric acid (7 ml) is added. Vigorous agitation is maintained for 12 h. The organic layer is discarded. The aqueous layer is diluted with ice/water (300 g), neutralized with 5 normal aqueous sodium hydroxide to pH 6–7 and extracted with chloroform (3 × 100 ml). After drying and evaporation of the solvent in vacuo, the residue is recrystallized from ethyl acetate to afford the compounds **5.**

Table. 4-Hydroxypyrazoles **5a–g** prepared

Product	Yield [%][a]	m.p. [°C][b]	Molecular formula[c] or Lit. m.p. [°C]	I.R. (CH_3Cl) OH	ν [cm^{-1}] C=N	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5a	53	139°	$C_{10}H_{10}N_2O$ (174.2)	3600	1605	2.18 (s, 3H); 7.28 (s, 1H); 7.3 (br. s, 1H, exchangeable with D_2O); 7.4 (m, 5H)
5b	51	131°	$C_{11}H_{12}N_2O$ (188.2)	3600	1600	1.03 (t, 3H, J=7 Hz); 2.60 (q, 2H, J=7 Hz); 7.20 (s, 1H); 7.3 (br. s, 1H, exchangeable with D_2O); 7.4 (m, 5H)
5c	52	179°	$C_{15}H_{12}N_2O$ (236.3)	3600	1610	5.8 (br. s, 1H, exchangeable with D_2O); 7.3 (m, 10H); 7.38 (s, 1H)
5d	53	175°	175°[6]	3600	1605	2.25 (s, 3H); 6.9 (br. s, 1H, exchangeable with D_2O); 7.2–7.3 (m, 10H)
5e	75	139°	138–140°[4]	3600	1605	2.00 (s, 3H); 2.08 (s, 3H); 7.2 (br. s, 1H, exchangeable with D_2O); 7.3 (m, 5H)
5f	51	160°	$C_{11}H_{12}N_2O$[d] (188.2)	3600	1605	2.11 (s, 3H); 3.57 (s, 3H); 6.8 (br. s, 1H, exchangeable with D_2O); 7.35 (m, 5H)
5g	35	186°	187–189°[4]	3600	1610	2.13 (s, 6H); 3.5 (br. s, 1H, exchangeable with D_2O); 3.65 (s, 3H)

[a] Yield of recrystallized product based on starting material **1.**

[b] Recrystallized from ethyl acetate.

[c] Satisfactory microanalyses obtained: C ±0.28, H ±0.08, N ±0.33.

[d] In Lit.[4], a mixture of 4-hydroxy-1,3-dimethyl-5-phenylpyrazole **(5f)** and 4-hydroxy-1,5-dimethyl-3-phenylpyrazole in a 7:3 ratio is described; m.p. 126–140°C.

The 4-ethoxycarbonylpyrazoles **1a**[7], **1c**[8], **1d**[9], **1e**[10], **1f**[11], and **1g**[12] are prepared according to known methods.

Ethyl 5-Ethyl-1-phenylpyrazole-4-carboxylate (1b):

A solution of dimethylformamide dimethylacetal (9.5 g, 0.08 mol) in benzene (50 ml) is added dropwise at room temperature to a stirred solution of ethyl 3-oxopentanoate (7.2 g, 0.05 mol) in benzene (100 ml). The mixture is refluxed for 30 min. After evaporation of the solvent and excess reagent, the crude ethyl 2-dimethylaminomethylene-3-oxopentanoate is dissolved in ethanol (100 ml), phenylhydrazine (5.4 g, 0.05 mol) in ethanol (50 ml) is added and the mixture is refluxed for 6 h. The solvent is then evaporated and the residue is distilled in vacuo to give **1b;** yield: 10.9 g (89%); b.p. 170–172°C/1.5 torr.

$C_{14}H_{16}N_2O_2$	calc.	C 68.83	H 6.60	N 11.47
(244.3)	found	68.36	6.68	11.30

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.16 (t, 3H, J=7 Hz); 1.38 (t, 3H, J=7 Hz); 2.95 (q, 2H, J=7 Hz); 4.33 (q, 2H, J=7 Hz); 7.45 (s, 5H); 8.05 (s, 1H).

Received: June 6, 1983

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1 F. Sachs, A. Röhmer, *Ber. Dtsch. Chem. Ges.* **35,** 3307 (1902).

2 I. L. Finar, T. Foster, *J. Chem. Soc.* [C] **1967,** 1494.

3 J. P. Freeman, J. J. Gannon, D. L. Surbey, *J. Org. Chem.* **34,** 187 (1969).

4 P. J. Fagan, E. E. Neidert, M. J. Nye, M. J. O'Hare, Wah-Piu Tang, *Can. J. Chem.* **57,** 904 (1979).

5 E. G. E. Hawkins, *Organic Peroxides,* E. and F. F. Spon Ltd., London, 1961, p. 90.

6 H. Böhme, H. Schneider, *Chem. Ber.* **91,** 1100 (1958).

7 B. Dains, E. W. Brown, *J. Am. Chem. Soc.* **31,** 1148 (1909).

8 G. Scherowsky, H. Franke, *Tetrahedron Lett.* **1974,** 1673.

9 L. Knorr, A. Blank, *Ber. Dtsch. Chem. Ges.* **18,** 313 (1885).

10 L. Knorr, *Ber. Dtsch. Chem. Ges.* **20,** 1101 (1887).

11 F. S. Al-Saleh, I. A. Khawaja, J. A. Joule, *J. Chem. Soc. Perkin Trans. 1* **1981,** 642.

12 C. A. Rojahn, H. E. Kühling, *Arch. Pharm.* **264,** 337 (1926).