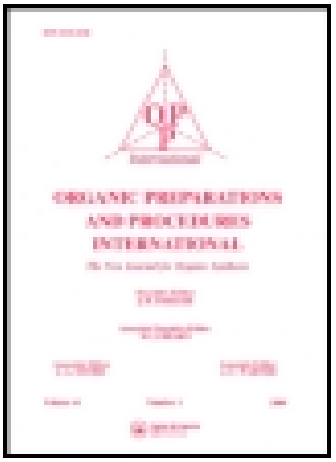

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AN IMPROVED PROCEDURE FOR THE PREPARATION OF 1-ARYL-4-HYDROXY-1H-PYRAZOLES

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AN IMPROVED PROCEDURE FOR THE PREPARATION OF 1-ARYL-4-HYDROXY-1*H*-PYRAZOLES

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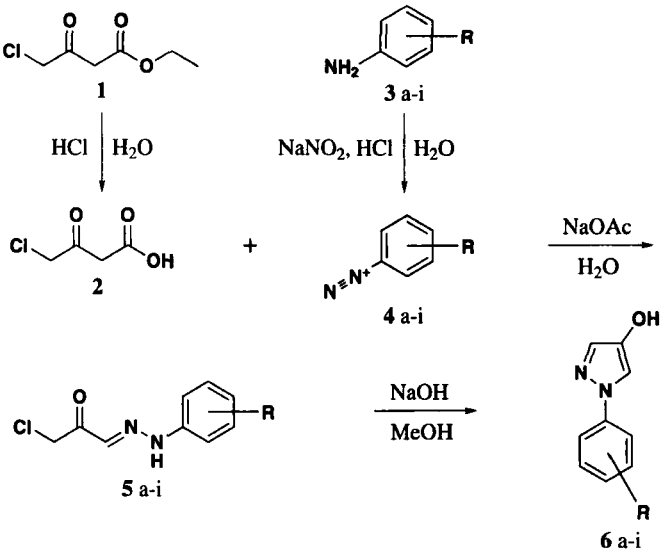
Oxysubstituted 1-arylpyrazole derivatives constitute a heterocyclic class of compounds with remarkable physiological potential.[1] Although approaches to 1-aryl-3-hydroxypyrazoles[2] and 1-aryl-5-hydroxypyrazoles[3] are now well established, only a limited number of 1-aryl-4-hydroxypyrazoles has been prepared. The main reason for this is that 4-oxygenated pyrazoles are in general synthetically less accessible and hence received much less attention than their 3- and 5-hydroxy substituted counterparts. Surprisingly, almost all of the reported 1-aryl-4-hydroxypyrazoles bear further substituents in the 3- or 5-position of the pyrazole moiety.[4] The methods used to obtain these substituted 1-aryl-4-hydroxypyrazoles are diverse: the acid catalyzed condensation of aldehyde hydrazones with glyoxals,[4a] the basic cyclization of 3-halo substituted 1-arylhydrazono-1-phenylsulfonyl-2-propanones[4b] and of 4-halo[4c] or 4-tosylated[4d] 2-arylhydrazono-3-oxobutyrates, the reaction of phenylhydrazine with 2-oxysubstituted 1,3-dione derivatives,[4e] the acetic anhydride/pyridine induced cyclization of 2-(2-alkylidenehydrazino)acetic acids,[4f] the Dieckmann condensation of 2-carbethoxymethylhydrazones of glyoxylic acid esters,[4g] the transformation of furan derivatives with phenylhydrazine[4h] and the Hock degradation of 4-carbethoxypyrazoles.[4i] All these methods are limited to systems which possess 3- and/or 5-substituents. Only one example in the patent literature describes an appropriate approach to unsubstituted 1-aryl-4-hydroxypyrazoles.[5] Unfortunately, the application of this method was limited because many products are formed in low yield. We now present an improved method for the synthesis of such 1-aryl-substituted pyrazol-4-ols with hydrogen atoms in the pyrazole positions 3 and 5.

The synthetic route starts from 4-chloroacetoacetic acid (**2**).[6] Immediately after its preparation, **2** is decarboxylated in the presence of a freshly prepared aryldiazonium salt **4** under the conditions of the Japp-Klingemann reaction.[7,8] The resulting 3-chloropyruvic aldehyde hydrazone **5** can easily be cyclized under basic conditions to the desired 1-aryl-4-hydroxypyrazole **6**. A special feature of this concise approach is that the key step consists of the coupling of two unstable intermediates **2** and **4**, which both have to be prepared *in situ* from stable precursors. For the preparation of the sensitive 4-chloroacetoacetic acid (**2**),[6] we worked out a new and safe procedure based on the saponification of commercially available ethyl 4-chloroacetoacetate (**1**). The different aryldiazonium salts **4** are obtained by standard diazotization of the corresponding anilines **3**. A closer look at the mechanism of the key step (**2** + **4** --> **5**) elucidates the previous problems with this synthesis. Careful pH-control is crucial for the success of the reaction. If the pH value gets lower than 4, then the decomposition of the

diazonium salt **4** yields a phenol as main product. pH Values of 4 or 5, attainable by simply buffering the hydrochloric acid with sodium acetate, result in the successful and high-yielding preparation of **5**.



In summary, we presented an improved method for the preparation of 1-aryl-4-hydroxypyrazols from 4-chloroacetoacetic acid and aryldiazonium salts, which should complement known methodologies of pyrazole synthesis.

EXPERIMENTAL SECTION

All new compounds were characterized by standard spectroscopical and microanalytical methods. ^{1}H-NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 Mhz, using $CDCl_3$ or $(CD_3)_2SO$ as solvents and TMS as internal standard. Chemical shifts are reported in ppm downfield from the standard ($\delta = 0.00$). Elemental analyses were performed on a Heraeus CHN-Rapid Analyser. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected.

4-Chloroacetoacetic Acid (2).- A mixture of ethyl 4-chloroacetoacetate (**1**, 30 g, 0.18 mol) and 200 ml of conc. hydrochloric acid (37 %) was stirred for 16 h at room temperature. The reaction mixture was then poured on ice and extracted twice with ethyl acetate. The combined organic layer was dried over magnesium sulfate and evaporated in vacuo at 25° bath temperature to yield 17.5 g (72 %) of a colorless liquid. ^{1}H-NMR: δ 3.71 (s, 2H), 4.20 (s, 2H). **CAUTION:** 4-Chloroacetoacetic acid (**2**) may **decompose spontanously** when heated without solvent! Therefore the organic phase should be evaporated without any external heating! With this precaution, no incident occurred during more than 40 experiments in our laboratory.

3-Chloropyruvaldehyde 1-(3-Trifluoromethyl)phenylhydrazone (5g).- To a solution of 3-aminobenzotrifluoride (**3g**, 18 g, 0.11 mol) in a mixture of 80 ml water and 40 ml conc. hydrochloric acid (37 %), cooled in an ice bath, was added dropwise a solution of sodium nitrite (7.5 g, 0.11 mol) in 20 ml water over a period of 30 min while the temperature was maintained at 0°. Subsequently, a solution of 4-chloroacetoacetic acid (**2**, 15 g, 0.11 mol) in 30 ml water was added dropwise also at 0°. Finally,

a solution of sodium acetate (18 g, 0.22 mol) in 50 ml water was added dropwise over a period of 30 min. The reaction was stirred for 1 h at room temperature, during which time the product precipitated. The crystalline product was collected, washed with water and dried *in vacuo*. The product **5g** (22 g, 78 %) is usually used in the next step without further purification. However, it may be purified by recrystallization from toluene/ethyl acetate. The following compounds have been synthesized by application of this procedure:

Table 1. Yields, mps, ^{1}H-NMR Spectroscopic and Microanalytical Data for 3-Chloropyruvaldehyde Hydrazones

Cmpd	R	Yield (%)	mp. (°C)	δH (ppm)	Elemental Analysis Found (Calcd) C	H	N
5a	H	90	112–113	4.31 (s, 2H), 6.91–7.12 (m, 6H)	55.06 (54.97)	4.49 (4.61)	14.34 (14.25)
5b	2-Cl	92	105–107	4.75 (s, 2H), 6.98–7.60 (m, 5H)	46.73 (46.78)	3.48 (3.49)	12.01 (12.12)
5c	3-Cl	91	161–162	4.70 (s, 2H), 7.05–7.56 (m, 5H)	46.58 (46.78)	3.55 (3.49)	12.08 (12.12)
5d	4-Cl	96	189-190	4.89 (s, 2H), 7.21–7.42 (m, 5H)	46.89 (46.78)	3.40 (3.49)	12.25 (12.12)
5e	4-F	89	187–188	4.90 (s, 2H), 7.18–7.63 (m, 5H)	50.61 (50.36)	3.39 (3.76)	13.14 (13.05)
5f	2-CH_3	81	115-117	2.28 (s, 3H), 4.20 (s, 2H), 6.76–7.04 (m, 5H)	57.27 (57.01)	5.00 (5.26)	13.41 (13.29)
5g	3-CF_3	78	142–143	4.73 (s, 2H), 7.28–7.49 (m, 5H)	45.11 (45.39)	3.28 (3.05)	10.59 (10.58)
5h	2,4-Cl_2	90	136–137	4.68 (s, 2H), 7.10–7.56 (m, 4H)	40.76 (40.71)	2.62 (2.66)	10.67 (10.55)
5i	3,4-Cl_2	83	170-172	4.71 (s, 2H), 7.12–7.67 (m, 4H)	40.93 (40.71)	2.70 (2.66)	10.48 (10.55)

4-Hydroxy-1-(3-trifluoromethyl)phenylpyrazole (6g).- To a solution of sodium hydroxide (7.6 g, 0.19 mol) in 100 ml methanol, was added **5g** (20 g, 76 mmol) at room temperature in portions, causing the temperature to rise to 40°. After stirring the mixture 1 h at room temperature, the solvent

was removed *in vacuo* and the residue was taken up in water. Insoluble material were filtered off and the filtrate was neutralized with conc. hydrochloric acid. The desired product which precipitated was collected, washed with water and dried. After recrystallization from toluene, **6g** was obtained as colorless crystals. (12 g, 69 %). The following compounds were prepared in an analogous manner.

Table 2. Yields, mps, ^{1}H-NMR Spectroscopic and Microanalytical Data for 1-Aryl-4-hydroxy-1*H*-pyrazoles **6**

Cmpd	R	Yield (%)	mp. (*lit.*)[5] (°C)	δH (ppm)	Elemental Analysis Found (Calcd) C	H	N
6a	H	69	117–119 (118–120)	6.90–7.48 (m, 7H)	67.47 (67.49)	5.10 (5.03)	17.77 (17.49)
6b	2-Cl	65	106–107 (105–106)	7.11–7.53 (m, 6H)	55.67 (55.54)	3.59 (3.62)	14.37 (14.39)
6c	3-Cl	65	98–100 (98–99)	7.17–7.61 (m, 6H)	55.65 (55.54)	3.70 (3.62)	14.21 (14.39)
6d	4-Cl	74	126–127 (127–128)	7.38–7.96 (m, 6H)	55.38 (55.54)	3.88 (3.62)	14.55 (14.39)
6e	4-F	71	156–158 (155–157)	6.91–7.58 (m, 6H)	60.98 (60.67)	3.76 (3.96)	15.70 (15.72)
6f	2-CH_3	67	128–130 (128–130)	2.30, (s, 3H) 7.01–7.53 (m, 6H)	69.11 (68.95)	5.57 (5.78)	15.90 (16.08)
6g	3-CF_3	69	95–96 (96–97)	7.43–8.18 (m, 6H)	52.39 (52.64)	3.30 (3.09)	12.52 (12.28)
6h	2,4-Cl_2	66	148–149 (148–149)	7.51–7.82 (m, 5H)	47.22 (47.19)	2.53 (2.64)	12.22 (12.22)
6i	3,4-Cl_2	65	151–153 (152–154)	7.42–7.79 (m, 5H)	46.95 (47.19)	2.81 (2.64)	12.10 (12.22)

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