Aminopyrazoles. III (1). Novel "One-Flask" Preparation of 1-Phenylpyrazol-3-amine

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2-Chloroacrylonitrile (**1a**), 2,3-dichloropropanenitrile (**1b**), 2,3-dibromopropanenitrile (**1c**) or 3-chloroacrylonitrile (**1d**) react with phenylhydrazine (**2**) in the presence of potassium *t*-butoxide with the formation of 1-phenylpyrazol-3-amine (**3**) free of the 5-amino isomer.

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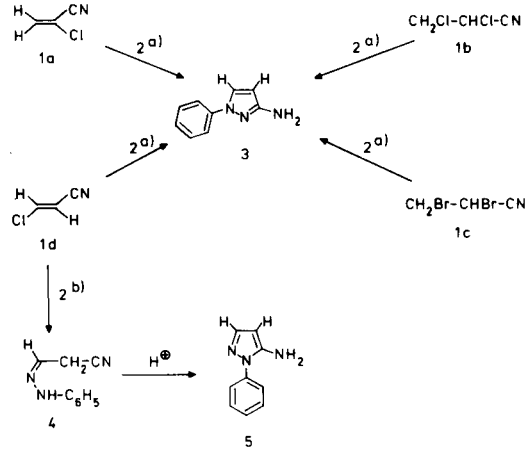
We recently reported a facile synthesis of pyrazol-3-amines using 2-chloroacrylonitrile (**1a**) or 2,3-dihalopropanenitriles (**1b,c**) in alkaline medium together with hydrazine or alkylhydrazines, respectively (1,2).

In this communication we describe the application of this "one-flask" multi-step reaction to phenylhydrazine (**2**), under conditions where 1-phenylpyrazol-3-amine (**3**) free of the 5-amino isomer is formed. Hitherto all known syntheses of **3** involve a multi-step reaction path comprising the protection of the amino group of an aminopyrazoline, a dehydrogenation step to the corresponding pyrazole and the removal of the protecting group (3-5).

It has been reported that the reaction of phenylhydrazine with 2-chloroacrylonitrile (6) or with 2,3-dihalopropanenitriles (7) yield the 1-phenylpyrazol-5-amine (**5**). Since in the addition of phenylhydrazine to acrylonitrile the relative nucleophilicity of the nitrogens can be influenced by acids or bases (8-10), we tried to obtain the 1-phenylpyrazol-3-amine (**3**) instead of the 5-amino isomer by means of a strong base. Thus, phenylhydrazine was treated with potassium *t*-butoxide in *t*-butyl alcohol with the presumed formation of the N(1)-anion that adds to the β-carbon of either 2-chloroacrylonitrile (**1a**) or of 2,3-dihalopropanenitrile (**1b,c**) after elimination of the hydrogen halide to the corresponding 2-haloacrylonitrile. In either case 1-phenylpyrazol-3-amine (**3**) is formed free of the 5-amino isomer. The yields of **3** with these halonitriles are poor (10%, 19%, 19%) because of the formation of many tarry products. However, an excellent yield of **3** (94%) could be obtained with phenylhydrazine (**2**) and 3-chloroacrylonitrile (**1d**) in the presence of potassium *t*-butoxide.

The cyanovinylation of phenylhydrazine (**2**) with 3-chloroacrylonitrile (**1d**) in benzene without any base has formerly been performed, but no structure was established for the reaction product (11). Repetition of this experiment led to the formation of cyanoacetaldehyde phenylhydrazone (**4**) whose structure follows from ^{1}H nmr. Compound **4** could by cyclized to 1-phenylpyrazol-5-amine (**5**) with acid in 85% yield.

Scheme 1



2 = phenylhydrazine
a) in *t*-butylalcohol with potassium *t*-butoxide
b) in benzene without any base

EXPERIMENTAL

Melting points were determined on a Bock-Monoscope and are uncorrected. The ^{1}H nmr spectra were obtained on a 60 MHz Varian EM 360 spectrometer. Chemical shifts are reported in δ-values relative to tetramethylsilane as an internal standard. The ir spectra were recorded on a Beckman IR 4240 spectrometer.

"One-Flask" Preparation of 1-Phenylpyrazol-3-amine (**3**).

Twenty g (0.5 mole) of potassium was dissolved in 500 ml of *t*-butyl alcohol under reflux, then 21.6 g (0.2 mole) of phenylhydrazine (**2**) was added to the hot solution, and after cooling to 5° 24.8 g (0.2 mole) of 2,3-dichloropropanenitrile (**1b**) (12), 42.6 g (0.2 mole) of 2,3-dibromopropanenitrile (**1c**) (13), 17.5 g (0.2 mole) of 2-chloroacrylonitrile (**1a**) (14) or 17.5 g (0.2 mole) of (*E*)-3-chloroacrylonitrile (**1d**) (15) in 50-100 ml of *t*-butyl alcohol was added dropwise (in the case of **1a** 13 g (0.33 mole) of potassium were used). The reaction mixture immediately became dark. Thereafter it was boiled under reflux for 3 hours; after cooling to room temperature the solvent was removed under reduced pressure and the resulting tarry product was diluted with a small amount of water to dissolve inorganic salts and extracted continuously with ether in a rotary perforator for several hours. The ether was distilled off in vacuum and the resulting reddish oil was extracted several times with light petroleum (bp 60-70°). On cooling the product separated as a yellow powder which was recrystallized from water (with a small amount of char-

coal to remove coloured impurities) to give **3** as colourless analytically pure needles, mp 91-92°, reported (3) 88-89°; ^{1}H nmr (deuteriochloroform): δ 3 = 7.67 (d, 1H, 5-H, J = 2.55 Hz), 7.0-7.7 (m, 5H, phenyl), 5.82 (d, 1H, 4-H, J = 2.55 Hz), 3.75 (s, broad, 2H, NH_2, exchangeable). The yields are given in the Table.

Table

Yield of **3**

from	g	%
1a	3.2	10
1b	6.1	19
1c	6.1	19
1d	29.9	94

Cyanoacetaldehyde Phenylhydrazone (**4**).

This compound was prepared as described (11), mp 79-80°, reported mp (11) 80-85°; ir (potassium bromide): 3295, 2270 (C≡N), 1605, 1500, 1270, 750, 695 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 7.82 (s, broad, 1H, NH, exchangeable), 6.78-7.62 (m, 6H, C_6H_5 and 3-H), 3.36 (d, 2H, $-CH_2-$, J = 4.8 Hz; s, when irradiating the resonance frequency of 3-H at 6.82 ppm).

1-Phenylpyrazol-5-amine (**5**).

A mixture of 1 g (6.3 mmoles) of **4** in 20 ml of methanol and 0.5 ml of hydrochloric acid was refluxed for 1 hour. After evaporation to dryness the residue was taken up in water, made alkaline with 2*N* sodium hydroxide and extracted twice with 50 ml of dichloromethane yielding 0.85 g (85%) of **5** as the only reaction product; mp 50°, reported (9) mp 50-51°; ^{1}H nmr (deuteriochloroform): δ = 7.17-7.73 (m, 6H, 3-H and phenyl), 5.56 (d, 1H, 4-H, J = 1.8 Hz), 3.82 (s, broad, 2H, NH_2, exchangeable); compound **5**, prepared as described above, was identical in the ir with a sample prepared by literature methods (9).

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