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Synthesis of 2-benzyl-2*H*-pyrazole-3,4-diamine dihydrochloride

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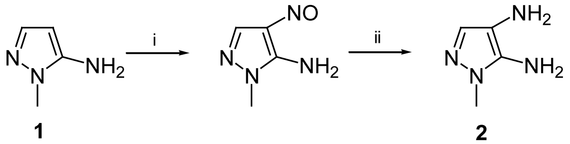
Abstract—This report describes a straightforward, high yield synthesis of a previously inaccessible *N*-protected diaminopyrazole in five steps starting from acrylonitrile, hydrazine and benzaldehyde. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The title compound, 2-benzyl-2*H*-pyrazole-3,4-diamine dihydrochloride, **6**, is a versatile building block for the synthesis of 1*H*-pyrazolo[3,4-*b*]pyrazines,[1] in which the benzyl group represents a suitable protective group for pyrazole N-1. Up to now the literature[1] describes the synthesis of only one homologue, 2-methyl-2*H*-pyrazole-3,4-diamine dihydrochloride **2**, prepared by the electrophilic nitrosation of 2-methyl-2*H*-pyrazol-3-ylamine **1** followed by reduction of the nitroso group (Scheme 1).



Scheme 1. Synthesis of diamine **2** via a nitrosation–reduction sequence.[1] *Reagents*: (i) C_5H_9ONO, HCl; (ii) $SnCl_2$.

Compound **3**, the benzyl homologue of **1**, has been obtained by the same group[2] in a three-step synthesis by condensation of benzylhydrazine with ethoxymethylene cyanoacetic acid ethyl ester, followed by saponification and thermal decarboxylation in an overall yield of 90% (Scheme 2).

One of our ongoing projects required larger amounts of **6** and, since benzylhydrazine is very expensive, we devised a simple procedure for the preparation of intermediate **3**, using readily available and cheap reagents. Based on a general method for the synthesis of 3-aminopyrazoles,[3] hydrazine hydrate was condensed with acrylonitrile and the resulting 3-hydrazinopropionitrile was reacted with benzaldehyde to give hydrazone **4**. Base-catalyzed cyclization of **4** yielded 2-benzyl-2*H*-pyrazol-3-ylamine, **3**. Carrying out this synthetic sequence as a one-pot procedure without the isolation of hydrazone **4** gave the amine in a yield of 85%. Amine **3** was converted to its hydrochloride salt, **3a**, using HCl gas in diethyl ether. Nitrosation of **3** using 3-methylbutyl nitrite and subsequent reduction of the resulting unstable 2-benzyl-4-nitroso-2*H*-pyrazol-3-ylamine hydrochloride, **5**, with $SnCl_2$ in aqueous HCl completed the synthesis of **6** (Scheme 3).

This strategy can be applied to the synthesis of a variety of differently 2-substituted 2*H*-pyrazole-3,4-diamine salts, which are versatile building blocks in heterocyclic chemistry.

2. Experimental

Melting points were measured on an Electrothermal™ apparatus and are uncorrected. The Zentralabteilung für chemische Analysen at the Forschungszentrum Jülich performed elemental analyses, which agreed with calculated composition within ±0.4%. Thin-layer chromatography (TLC) employed precoated sheets of silica (SIL G-25/UV_{254}) or aluminium oxide (ALOX N/UV_{254}) (Polygram™, Macherey-Nagel, Düren, Germany). ^1H and ^{13}C NMR spectra were obtained at 200.13 and 50.32 MHz, respectively, in a Bruker DPX-200 spectrometer (Avance 200) in ca. 5% solution at 25°C. Chemical shifts are reported as δ ppm based on the proton signals of the deuterated solvents ($\delta_{H(CDCl3)}=7.30$, $\delta_{H(DMSO\text{-}d_6)}=2.52$, $\delta_{C(CDCl_3)}=77.48$,

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Keywords: diaminopyrazole; condensation; nitrosation; reduction.

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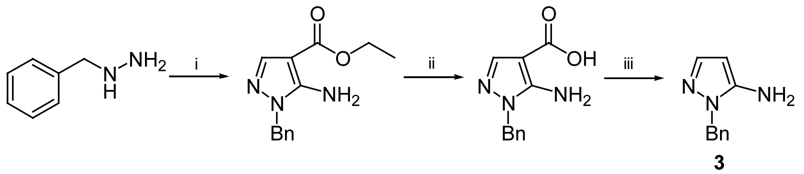


Scheme 2. Synthesis of **3** starting from benzylhydrazine.[2] *Reagents and conditions*: (i) ethoxymethylene cyano acetic acid ethylester; (ii) (a) NaOH, (b) HCl; (iii) heat.

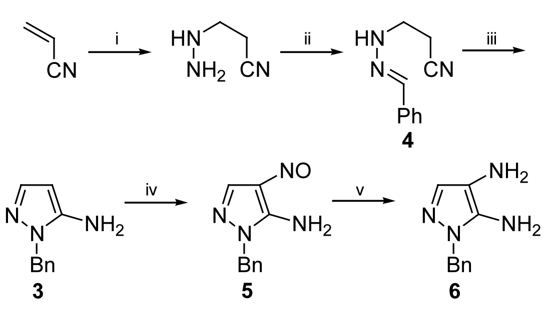
$\delta_{C(DMSO\text{-}d_6)}=40.38$). The multiplicity symbols s, d, t and m refer to singlet, doublet, triplet and multiplet, respectively. Solvents and reagents were used as supplied by the vendors.

2.1. 3-(*N*′-Benzylidenehydrazino)propionitrile 4

Hydrazine hydrate (19.4 mL, 0.4 mol) was added over 10 min to a vigorously stirred, cooled (< 20°C, water bath) solution of acrylonitrile (27 mL, 0.41 mol) in dry ethanol (200 mL). After stirring for 24 h at room temperature the flask was cooled in an ice/water bath and benzaldehyde (40.15 mL, 0.395 mol) was added at a rate keeping the reaction temperature below 20°C. The mixture was stirred in the ice bath for another 10 min and then at room temperature for 5 h, when TLC (ethyl acetate/hexane: 50/50 v/v) showed the absence of benzaldehyde (R_f 0.89) and the formation of product (R_f 0.70). Evaporation of ethanol and high vacuum distillation gave **4** as a viscous yellow oil that was pure by TLC. Yield 61.7 g (89%), bp$_{0.04\ \mathrm{mbar}}$ 135–138°C (lit.[3] bp$_{0.3\ \mathrm{torr}}$ 143–146°C). ^{1}H NMR ($CDCl_3$): δ 2.72 (t, 2H, CH_2CN); 3.52 (t, 2H, NHCH_2); 5.2–5.9 (s$_{br}$, 1H, NH); 7.33–7.40 (m, 3H, 3,4,5-C_6H_5); 7.57–7.61 (m, 2H, 2,6-C_6H_5); 7.72 (s, 1H, CH=N). ^{13}C NMR ($CDCl_3$): δ 18.83 (CH_2CN); 46.18 (NHCH_2); 118.99 (CN); 126.44, 129.09, 129.46 (C_6H_5-2,3,4); 135.43 (C_6H_5-1); 141.09 (CH=N).

2.2. 2-Benzyl-2*H*-pyrazol-3-ylamine 3

Solid NaOH (200 mg, 5 mmol) was added to a solution of **4** (43.5 g, 0.2 mol) in 1-propanol and the orange mixture was stirred at 120°C for 5 h, during which the solution became deep red. TLC (Al_2O_3, ethyl acetate/hexane: 25/75 v/v) indicated the absence of **4**, R_f 0.43, and formation of product **3**, R_f 0.15. Evaporation of the solvent and high vacuum distillation (bp$_{0.04\ \mathrm{mbar}}$ 115–120°C) gave **3** as a pale yellow oil that solidified on standing. Yield 35 g (98%), mp 71–73°C (lit.[2] 70–72°C, di-*n*-butyl ether). ^{1}H NMR ($CDCl_3$): δ 3.59 (s$_{br}$, 2H, NH_2); 5.17 (s, 2H, $C_6H_5CH_2$); 5.5 (d, 1H, pyrazole H-4, J=1.8 Hz); 7.12–7.16 (m, 2H, phenyl H-2 and H-6); 7.28–7.37 (m, 4H, C_6H_5-2,3,4 and pyrazole H-5). ^{13}C NMR ($CDCl_3$): δ 51.82 ($C_6H_5CH_2$); 91.99 (pyrazole C-4); 127.24, 128.16, 129.08 (C_6H_5-2,3,4); 137.17 (C_6H_5-1); 139.14 (pyrazole C-5); 145.27 (pyrazole C-3).



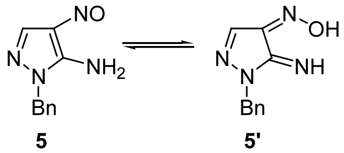
Scheme 3. Synthesis of **3** starting from acrylonitrile and transformation into **6**. *Reagents and conditions*: (i) $N_2H_4{\cdot}H_2O$; (ii) C_6H_5CHO; (iii) NaOH, heat; (iv) C_5H_9ONO, HCl; (v) $SnCl_2$.

2.3. 2-Benzyl-2*H*-pyrazol-3-ylamine hydrochloride 3a

Bubbling HCl gas through an ice-cooled solution of **3** (35 g, 202 mmol) in dry ethyl ether (300 mL) precipitated **3a** as a gum that solidified on standing. The hydrochloride salt was filtered off, air-dried and triturated with hot acetone (2×50 mL) to remove colored impurities. After drying in air the yield of **3a** was 42.3 g (100%). Recrystallization from 2-propanol gave an analytical sample, mp 166°C. TLC on Al_2O_3 (ethyl acetate/hexane: 50/50 v/v) showed a single spot for **3a**, R_f 0.67, while TLC on silica gel caused decomposition of both the amine **3** and the hydrochloride salt **3a**. ^{1}H NMR (DMSO-d_6): δ 5.77 (s, 2H, $C_6H_5CH_2$); 5.78 (d, 1H, pyrazole H-4, J=3 Hz) 7.28–7.38 (m, 5H, C_6H_5); 8.02 (d, 1H, pyrazole H-5, J=3 Hz); 7.39–8.62 (s$_{br}$, 3H, NH_3^+). ^{13}C NMR (DMSO-d_6): δ 49.74 ($C_6H_5CH_2$); 92.06 (pyrazole C-4); 128.51, 129.04, 129.57 (C_6H_5-2,3,4); 135.26 (C_6H_5-1); 136.26 (pyrazole C-5); 151.43 (pyrazole C-3).

2.4. 2-Benzyl-4-nitroso-2*H*-pyrazol-3-ylamine hydrochloride 5

Under argon a suspension of finely ground **3**·HCl (20.9 g, 100 mmol in dry ethanol (80 mL) and 5N ethanolic HCl (60 mL, 300 mmol) was stirred in a salt–ice bath until the flask temperature was <0°C. The addition of isoamyl nitrite (11.7 g, 13.4 mL, 100 mmol) over 30 min gave a clear yellow solution from which product precipitated. After an additional hour at 0°C the dark yellow product was filtered off and washed with 25 mL acetone. Drying in air gave **5**, 17.2 g, 72%, as a yellow solid. The product decomposed on heating so was immediately used in the next step. The presence of four exchangeable protons in the ^{1}H NMR spectrum of **5** was evidence for the existence of two tautomers, **5** and **5′** (Scheme 4). ^{1}H NMR (DMSO-d_6): δ 5.33+5.41 (2 s, $C_6H_5CH_2$); 7.19–7.55 (m, C_6H_5); 8.18+8.55 (s, pyrazole H-5); 9.64 (s$_{br}$, N-OH); 10.63 (s$_{br}$, NH_3^+).



Scheme 4. Tautomers of **5**.

The ^{13}C NMR spectrum shows 16 resonances instead of the eight expected for compound **5**, additional support for two tautomers, **5** and **5**′.

2.5. 2-Benzyl-2*H*-pyrazole-3,4-diamine dihydrochloride 6

A suspension of **5** (11.9 g, 50 mmol) in ethanol (100 mL) acidified with 32% HCl (25 mL, 250 mmol) was stirred at 60–70°C The addition of a solution of $SnCl_2·2H_2O$ (24.8 g, 110 mmol) in ethanol (25 mL) over 15 min dissolved educt. Stirring continued for 30 min, then the clear solution was cooled to room temperature and diluted with water (100 mL). After evaporation of ethanol and dilution with additional water (250 mL), the solution was saturated with H_2S. Centrifugation (10 min, 2600×*g*) gave a clear supernatant. Evaporation of the supernatant and co-evaporation with acetonitrile (50 mL) gave crude **6** as a colorless glassy residue (11.5 g, 90%). Shaking a solution of **6** (2.6 g, 10 mmol) in 5 mL water with acetonitrile (100 mL) deposited product as white crystals. (**NOTE**: Air and moisture sensitivity necessitated storage under argon.) The diamine salt decomposed upon heating at ±220°C. ^{1}H NMR (DMSO-d_6): δ 5.26 (s, 2H, $C_6H_5CH_2$); 5.40–7.20 (s_{br}, 6H, 2 NH_3^+); 7.19–7.32 (m, 5H, C_6H_5); 7.40 (s, 1H, pyrazole H-5). ^{13}C NMR (DMSO-d_6): δ 51.76 ($C_6H_5CH_2$); 117.87 (pyrazole C-4); 127.31, 128.42, 129.01 (phenyl C_6H_5-2,3,4); 137.33 (C_6H_5-1); 139.87 (pyrazole C-5); 142.01 (pyrazole C-3). Elemental analysis (free base, FW 188.23) calcd: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.97; H, 6.42; N, 39.92.

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