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Cyanoethylation of Pyrazoles under Conditions of Phase-Transfer Catalysis and Hydrogenation of the Cyanoethylation Products

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Abstract — Cyanoethylation of pyrazoles with acrylonitrile was studied under conditions of phase-transfer catalysis. The ease of the process depends on the acidity of pyrazoles. Cyanoethylpyrazoles can be converted into the corresponding aminopropylpyrazoles via reduction of the cyano group. The reduction with lithium tetrahydridoaluminate is accompanied by β-elimination of the cyanoethyl group.
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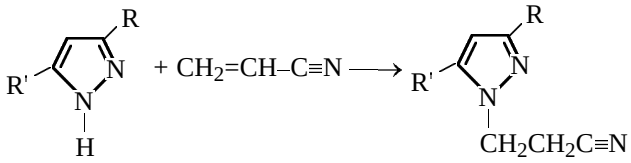
Cyanoethylation of pyrazoles is performed in the absence of a catalyst under pressure at 140–160°C [1]. It is also known that pyrazoles smoothly take up acrylonitrile at 70–120°C in the presence of acid and alkaline catalysts [2]. We succeeded in effecting cyanoethylation of pyrazoles **I**–**III** at room temperature 20–30°C under conditions of phase-transfer catalysis and obtained the corresponding 1-(2-cyanoethyl)pyrazoles **IV**–**VI**. The reaction can be carried out in a liquid–liquid system (water–NaOH) using benzyltriethylammonium chloride as phase-transfer catalyst. The yields of cyanoethylpyrazoles **IV**–**VI** ranged from 80 to 90%.



I–**III** **IV**–**VI**

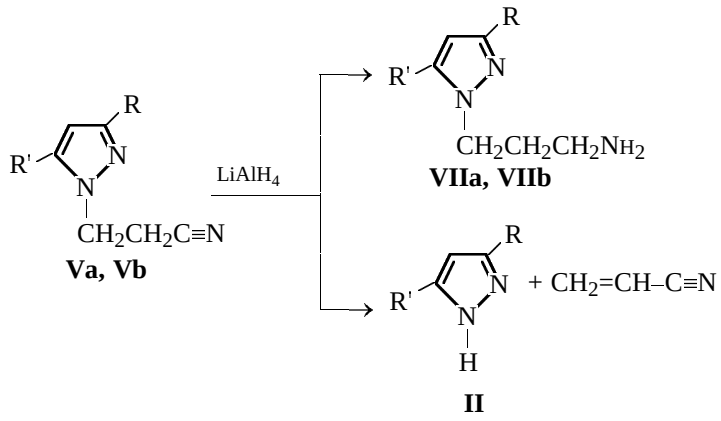
I, IV, R = R' = H, **III, VI**, R = R' = CH_3; **II, V**, R = CH_3, R' = H (**a**), R = H, R' = CH_3 (**b**).

The reaction time strongly depends on the substrate acidity. The reaction with unsubstituted pyrazole (**I**, pK_a 20.4) was complete in 1.5 h, whereas cyanoethylation of 3,5-dimethylpyrazole (**III**, pK_a 22.0) required 5 h, 3(5)-methylpyrazole (pK_a 21.0) occupies an intermediate place in this series. Obviously, introduction of electron-donor methyl groups into the pyrazole ring hampers generation of pyrazolate ion, and the cyanoethylation process slows down.

As might be expected, the reaction with 3(5)-methylpyrazole (**II**) gave a mixture of isomeric 3- and 5-methyl1-cyanomelthylpyrazoles **Va** and **Vb** in an overall yield of 90% [3, 4]. According to the ^{1}H NMR data, the isomer ratio was 3:2. We succeeded in separating and identifying isomers **Va** and **Vb**. Their structure was determined on the basis of chemical shifts of protons in the ring and methyl groups in the spectra recorded from solutions in DMSO-d_6 and benzene [5]. The signal of the 3-H proton in the ^{1}H NMR spectrum of isomer **Vb** in DMSO-d_6 was located in a stronger field (δ 7.28 ppm, d, 1H), while the signal from the methyl group appeared in a weaker field (δ 2.35 ppm, s, 3H, 5-CH_3); in going to benzene, the CH_3 signal was displaced upfield (δ 1.93 ppm, s, 3H, 5-CH_3). By contrast, no analogous shift of the CH_3 proton signal in going from DMSO-d_6 to benzene was observed for isomer **Va**.

The IR spectrua of cyanoethylpyrazoles **IV**–**VI** contained a strong absorption band at 2250 cm^{-1} due to stretching vibrations of the cyano group, and absorption bands in the region 1510–1530 cm^{-1} were assigned to vibrations of the pyrazole ring.

The cyano group in pyrazoles **Va** and **Vb** was reduced to amino by treatment with lithium tetrahydridoaluminate; however, the yields of the corresponding aminopropylpyrazoles **VIIa** and **VIIb** were 30 and 36%, respectively, owing to concurrent β-elimination of the cyanoethyl group [6–9].



EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films or KBr pellets. The ^1H NMR spectra were measured on a Varian Mercury-300 instrument in $(CD_3)_2SO$ using HMDS as internal reference. GLC analysis was performed on an LKhM-8MD chromatograph equipped with a 1-m column packed with 10% of Carbowax-20M on Inerton AW-HMDS; carrier gas helium, flow rate 40 ml min^{-1}; detector temperature 220°C.

3-(1*H*-Pyrazol-1-yl)propanenitrile (IV). Acrylonitrile, 8 g, was added dropwise to a mixture of 6.8 g of pyrazole **I**, 1.36 g of sodium hydroxide, 50 ml of water, and 1 g of benzyltriethylammonium chloride under stirring at room temperature. The mixture was stirred for 1.5 h and extracted with chloroform. The extract was dried over $MgSO_4$, the solvent and excess acrylonitrile were distilled off, and the residue was distilled under reduced pressure. Yield 10.4 g (86%), bp 105–110°C (1 mm), n_D^{20} 1.4920, d_4^{20} 1.0800. IR spectrum, ν, cm^{-1}: 1520 (ring), 2250 (CN). ^1H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 2.97 t (2H, CH_2CH_2, *J* 6.6), 4.40 t (2H, CH_2CH_2, *J* 6.6), 6.19 d.d (1H, 4-H, *J* 2.3, 1.9), 7.41 d (1H, 3-H, *J* 1.9), 7.66 d (1H, 5-H, *J* 2.3). Found, %: C 59.38; H 5.48; N 34.34. $C_6H_7N_3$. Calculated, %: C 59.50; H 5.79; N 34.71.

3-[3(5)-Methyl-1*H*-pyrazol-1-yl]propanenitrile (V) was synthesized in a similar way from 8.2 g of 3(5)-methylpyrazole (I). Yield 12.6 g (94%), bp 105–125°C (2 mm), n_D^{20} 1.4910, d_4^{20} 1.0847. Found, %: C 62.09; H 6.31; N 31.30. $C_7H_9N_3$. Calculated, %: C 62.22; H 6.67; N 31.11. The isomers were separated by rectification through a 30 × 4-cm column charged with a metal packing (column head temperature 110–120°C, still temperature 180°C, pressure 3 mm, reflux number *R* 10). Separation of 100 g of a 3 : 2 isomer mixture gave 40 g of **3-(3-methyl-1*H*-pyrazol-1-yl)-propanenitrile (Va)** and 20 g of **3-(5-methyl-1*H*-pyrazol-1-yl)propanenitrile (Vb).**

Isomer Va. bp 108°C (2 mm), n_D^{20} 1.4890, d_4^{20} 1.0830. IR spectrum, ν, cm^{-1}: 1520 (ring), 2250 (CN); ^1H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 2.20 s (3H, 3-CH_3), 2.92 t (2H, CH_2CN, *J* 6.6), 4.29 t (2H, CH_2N, *J* 6.6), 5.93 d (1H, 4-N, *J* 2.2), 7.49 d (1H, 5-H, *J* 2.2).

Isomer Vb. bp 115°C (2 mm), n_D^{20} 1.4960, d_4^{20} 1.0865. IR spectrum, ν, cm^{-1}: 1520 (ring), 2250 (CN); ^1H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 2.35 s (3H, 5-CH_3), 2.94 t (2H, CH_2CN, *J* 6.5), 4.28 t (2H, CH_2N, *J* 6.5), 5.95 d (1H, 4-H, *J* 1.9), 7.28 d (1H, 3-H, *J* 1.9).

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)propanenitrile (VI) was synthesized as described above for compound **IV** from 9.6 g of 3,5-dimethyl-1*H*-pyrazole (**III**). Yield 12.5 g (84%), bp 123–125°C (1 mm), n_D^{20}

1.4880, mp 45–47°C. IR spectrum, ν, cm^{-1}: 1520 (ring), 2250 (CN). ^1H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 2.15 s (3H, 3-CH_3), 2.30 s (3H, 5-CH_3), 2.98 t (2H, CH_2CN, *J* 6.6), 4.20 t (2H, CH_2N, *J* 6.6), 5.72 s (1H, 4-H). Found, %: C 64.64; H 7.13; N 28.36. $C_8H_{11}N_3$. Calculated, %: C 64.43; H 7.38; N 28.19.

3-(3-Methyl-1*H*-pyrazol-1-yl)propan-1-amine (VIIa). A solution of 10 g of cyanoethylpyrazole **Va** in 150 ml of anhydrous diethyl ether was added dropwise under stirring to a mixture of 7 g of lithium tetrahydridoaluminate and 100 ml of anhydrous diethyl ether at such a rate that the mixture evenly boiled. The mixture was heated for 3 h under reflux and cooled to room temperature, 25 ml of water was carefully added in a dropwise fashion, and 30 ml of a 30% solution of sodium hydroxide was added. The organic phase was separated, the residue was washed with diethyl ether (3 × 50 ml), the extract was dried, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 3.4 g (30%), bp 78–83°C (1 mm), n_D^{20} 1.5000, d_4^{20} 1.0319. IR spectrum, ν, cm^{-1}: 1520 (ring), 3350–3400 (NH_2). ^1H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 1.85 q (2H, CH_2, *J* 7.4, 7.0), 2.20 s (3H, 3-CH_3), 2.58 t (2H, CH_2NH_2, *J* 7.4), 4.08 t (2H, CH_2N, *J* 7.0), 4.08 br (2H, NH_2), 5.88 d (1H, 4-H, *J* 2.2), 7.31 d (1H, 5-H, *J* 2.2). Found, %: C 60.25; H 9.57; N 30.08. $C_7H_{13}N_3$. Calculated, %: C 60.43; H 9.35; N 30.22.

3-(5-Methyl-1*H*-pyrazol-1-yl)propan-1-amine (VIIb) was obtained in a similar way from 10 g of pyrazole **Vb**. Yield 4 g (36%), bp 100–105°C (5 mm), n_D^{20} 1.5065, d_4^{20} 1.0424. IR spectrum, ν, cm^{-1}: 1520 (ring), 3350–3400 (NH_2). ^1H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 1.85 q (2H, CH_2, *J* 7.4, 7.0), 1.85 br.s (2H, NH_2), 2.60 t (2H, CH_2NH_2, *J* 7.4), 4.15 t (2H, CH_2N, *J* 7.0), 5.95 d (1H, 4-H, *J* 1.9), 7.28 d (1H, 3-H, *J* 1.9). Found, %: C 60.18; H 9.09; N 30.46. $C_7H_{13}N_3$. Calculated, %: C 60.43; H 9.35; N 30.22.

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