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LETTERS TO THE EDITOR

Vilsmeier–Haack Formylation of 2-(1*H*-Pyrazol-1-yl)ethanol and Its Methyl Derivatives

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It is known that 2-(3,5-dimethyl-1*H*-pyrazol-1-yl) ethanol does not undergo the Vilsmeier–Haack formylation [1]; the reaction results was the replacement of the hydroxyl group with the chlorine atom. Apparently, this is caused by the decreased nucleophilicity of the pyrazole ring due to the quaternization of the pyridine nitrogen atom. This assumption is supported by the fact that the direct Vilsmeier–Haack formylation of 1-(2-chloroethyl)-3,5-dimethylpyrazole affords the target product in 70% yield [2], and the reaction does not occur in the presence of hydrochloric acid.

In this work we found that 2-(1*H*-pyrazol-1-yl)-ethanol **I**, 2-(3-methyl-1*H*-pyrazol-1-yl)ethanol **II**, and 2-(5-methyl-1*H*-pyrazol-1-yl)ethanol **III** underwent no formylation under the Vilsmeier–Haack reaction conditions, but were transformed into 1-(2-chloroethyl)pyrazoles **IV**–**VI** (Scheme 1).

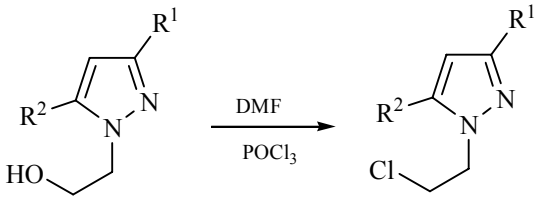
The Vilsmeier–Haack formylation of compounds **I**–**III** and **VII** [4, 5] required their protection. In particular, prior acetylation of the hydroxyl group allowed formylation of the pyrazole ring at position 4 [1, 4]. Acylation of compounds **I**–**III** and **VII** with vinyl acetate in the presence of a catalytic amount of copper acetate afforded 2-(1*H*-pyrazol-1-yl)ethyl acetate **VIII** and its methyl derivatives **IX**–**XI**, which in turn were easily subject to formylation via the Vilsmeier–Haack reaction to form 2-(4-formyl-1*H*-pyrazol-1-yl)-ethyl acetate **XII** and its methyl derivatives **XIII**–**XV**. Hydrolysis of the latter yielded the corresponding aldehydes **XVI**–**XIX** (Scheme 2).

In addition, 1-(2-chloroethyl)pyrazole-4-carbaldehydes **XX**–**XXIII** were isolated from the reaction mixture with yields of 7–10% (Scheme 3).

The starting compounds **I**–**III**, **VII**–**XI** were obtained as described elsewhere [4, 5].

1-(2-Chloroethyl)pyrazole (IV). 30 g (0.2 mol) of phosphorus oxychloride was added to a mixture of 11.2 g of (0.1 mol) of 2-(1*H*-pyrazol-1-yl)ethanol **I** and 95.0 g (0.6 mol) of DMF upon stirring at 90°C (maintaining the temperature below 120°C). The reac-

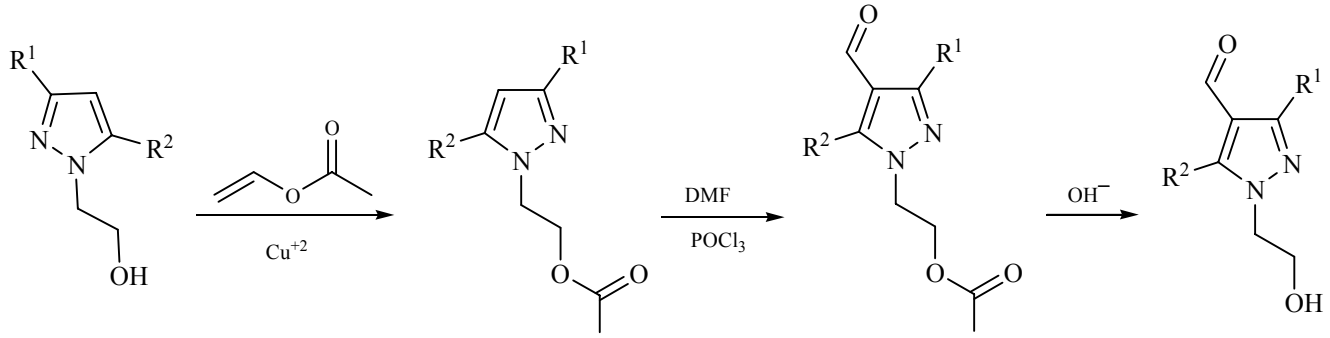
Scheme 1.



I–**III** **IV**–**VI**

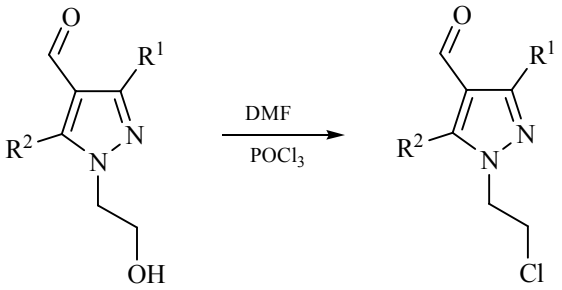
$R^1 = R^2 = H$ (**I, IV**); R^1 = Me, $R^2 = H$ (**II, V**); $R^1 = H$, R^2 = Me (**III, VI**).

Scheme 2.



$R^1 = R^2 = H$ (**I**, **VIII**, **XII**, **XVI**); R^1 = Me, $R^2 = H$ (**II**, **IX**, **XIII**, **XVII**); $R^1 = H$, R^2 = Me (**III**, **X**, **XIV**, **XVIII**); $R^1 = R^2$ = Me (**VII**, **XI**, **XV**, **XIX**).

Scheme 3.



tion mixture was stirred during 1 hour at 100°C, cooled, and neutralized with aqueous Na_2CO_3. The reaction product was extracted with chloroform and dried over magnesium sulfate. After removing the solvent, the residue was distilled in vacuum. Yield 9.7 g (75%), bp 47–48°C (1 mmHg), n_D^{20} 1.5020, d_4^{20} 1.1190 g/mL. IR spectrum, ν, cm^{-1}: 1520 (ring). ^1H NMR data coincided with that in [6].

1-(2-Chloroethyl)-3-methylpyrazole (V) was prepared similarly from 12.6 g of 2-(3-methyl-1*H*-pyrazol-1-yl)ethanol **II**. Yield 11.6 g (80%), bp 55–60°C (1 mmHg), n_D^{20} 1.5000. IR spectrum, ν, cm^{-1}: 1530 (ring). ^1H NMR data coincided with that in [6].

1-(2-Chloroethyl)-5-methylpyrazole (VI) was prepared similarly from 12.6 g of 2-(5-methyl-1*H*-pyrazol-1-yl)ethanol **III**. Yield 10.3 g (71.5%), bp 63–65°C (1 mmHg), n_D^{20} 1.5050. IR spectrum, ν, cm^{-1}: 1540 (ring). ^1H NMR data coincided with that in [6].

1-(2-Hydroxyethyl)-1*H*-pyrazol-4-carbaldehyde (XVI). 30 g (0.2 mol) of phosphorus oxychloride was added to a mixture of 15.4 g (0.1 mol) of 2-(1*H*-pyrazol-1-yl)ethyl acetate **VIII** and 95 g (0.6 mol) of DMF upon stirring at 90°C (maintaining the temperature below 120°C). The reaction mixture was stirred during 1 hour at 100°C, cooled, and neutralized with aqueous Na_2CO_3. The reaction products were extracted with chloroform, the extract was dried over magnesium sulfate. After removing the solvent, the residue was distilled under vacuum collecting the fraction with bp 150–155°C (1 mmHg). According to ^1H NMR data, it contained 2-(4-formyl-1*H*-pyrazol-1-yl)ethyl acetate **XII** and 1-(2-chloroethyl)-1*H*-pyrazole-4-carbaldehyde **XX**. The resulting mixture was hydrolyzed with a solution of 8 g (0.2 mol) NaOH in 50 mL of water at stirring during 3 h at room temperature. The reaction product was extracted with diethyl ether and then with chloroform. After removing chloroform, the residue was distilled in vacuum. Yield 9.7 g (69%), bp 160–170°C (1 mmHg), n_D^{20} 1.5370. IR spectrum, ν, cm^{-1}: 1520 (ring), 1680 (CHO), 3200–3400 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.82 q (2H, CH_2OH, *J* 5.13), 4.22 t (2H, NCH_2, *J* 5.3), 4.56 t (1H, OH, *J* 5.5), 7.32 s (1H, H^3), 7.53 s (1H, H^5), 9.80 s (CHO). Found, %: C 51.87; H

5.83; N 20.95. $C_6H_8N_2O_2$. Calculated, %: C 51.42; H 5.72; N 20.00.

From the ethereal extract 1.3 g (8%) of **1-(2-chloroethyl)-1*H*-pyrazole-4-carbaldehyde XX** was isolated, bp 151°C (1 mmHg), n_D^{20} 1.5395. IR spectrum, ν, cm^{-1}: 1520 (ring), 1680 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.46 t (2H, CH_2Cl, *J* 6.1), 3.93 t (2H, NCH_2, *J* 6.1), 7.73 s (1H, H^3), 8.14 s (1H, H^5), 9.80 s (1H, CHO). Found, %: C 45.73; H 4.68; N 18.05; Cl 22.73. $C_6H_7N_2Cl$. Calculated, %: C 45.43; H 4.42; N 17.67; Cl 22.74.

1-(2-Hydroxyethyl)-3-methyl-1*H*-pyrazole-4-carbaldehyde (XVII) was prepared similarly from 16.8 g (0.1 mol) of 2-(3-methyl-1*H*-pyrazol-1-yl)ethyl acetate **IX**. Yield 8.9 g (63.0%), bp 168–175°C (1 mmHg), mp 82°C (hexane). IR spectrum, ν, cm^{-1}: 1530 (ring), 1680 (CHO), 3200–3400 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.41 s (3H, 3-CH_3), 3.72 q (2H, $C\underline{H_2}OH$, *J* 5.6), 4.51 t (2H, NH_2, *J* 5.6), 4.62 t (1H, OH, *J* 5.6), 8.35 s (1H, H^5), 9.8 s (1H, CHO). Found, %: C 52.69; H 5.83; N 17.95. $C_7H_{10}N_2O_2$. Calculated, %: C 54.54; H 6.49; N 18.19.

1-(2-Chloroethyl)-3-methyl-1*H*-pyrazole-4-carbaldehyde (XXI). Yield 1.7 g (10%), bp 130–140°C (1 mmHg), mp 37–38°C (CCl_4), n_D^{20} 1.5370. IR spectrum, ν, cm^{-1}: 1530 (ring), 1670 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.40 s (3H, 3-CH_3), 3.93 t (2H, NCH_2, *J* 5.8), 4.41 t (2H, CH_2Cl, *J* 5.9), 8.24 s (1H, H^5), 9.82 s (1H, CHO). Found, %: C 48.69; H 5.72; N 16.73; Cl 20.81. $C_7H_9N_2ClO$. Calculated, %: C 48.86; H 5.21; N 16.23; Cl 20.57.

1-(2-Hydroxyethyl)-5-methyl-1*H*-pyrazole-4-carbaldehyde (XVIII) was obtained similarly from 16.8 g (0.1 mol) of 2-(5-methyl-1*H*-pyrazol-1-yl)ethyl acetate **X**. Yield 8.0 g (56.6%), bp 177°C (1 mmHg), n_D^{20} 1.5325. IR spectrum, ν, cm^{-1}: 1550 (ring), 1670 (CHO), 3200–3400 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.26 s (3H, 5-CH_3), 3.70 q (2H, $C\underline{H_2}OH$, *J* 5.6), 4.62 t (1H, OH, *J* 5.6), 8.12 s (1H, H^3), 9.8 s (1H, CHO).

1-(2-Chloroethyl)-5-methyl-1*H*-pyrazole-4-carbaldehyde (XXII). Yield 1.5 g (8.5%), bp 130–135°C (1 mmHg), n_D^{20} 1.5425. IR spectrum, ν, cm^{-1}: 1530 (ring), 1690 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.45 s (3H, 5-CH_3), 3.95 t (2H, NCH_2, *J* 5.9), 4.42 t (2H, CH_2Cl, *J* 5.9), 7.95 s (1H, H^3), 9.9 s (1H, CHO). Found, %: C 45.84; H 4.58; N 18.23; Cl 22.68. $C_6H_7N_2Cl$. Calculated, %: C 45.43; H 4.42; N 17.67; Cl 22.40.

1-(2-Hydroxyethyl)-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde (XIX) was obtained similarly from 17.0 g (0.1 mol) of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl) ethyl acetate **XI**. Yield 12 g (75%), bp 160–170°C (1 mmHg), mp 64–66°C (CCl_4). IR spectrum, ν, cm^{-1}: 1510 (ring), 1680 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.34 s (3H, 3-CH_3), 2.52 s (3H, 5-CH_3), 2.73 q (2H, $O\underline{CH_2}$, *J* 5.4), 4.02 t (2H, NCH_2, *J* 5.4), 4.68 t (1H, OH, *J* 5.4), 9.81 s (1H, CHO).

1-(2-Chloroethyl)-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde (XXIII). Yield 1.9 g (≈10%), bp 140–145°C (1 mmHg), mp 50°C (CCl_4). IR spectrum, ν, cm^{-1}: 1535 (ring), 1670 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 2.36 s (3H, 3-CH_3), 2.54 s (3H, 5-CH_3), 3.93 t (2H, NCH_2, *J* 5.9), 4.31 t (2H, CH_2Cl, *J* 5.9), 9.84 s (1H, CHO). Found, %: C 51.63; H 6.12; N 15.42; Cl 12.27. $C_6H_7N_2Cl$. Calculated, %: C 51.47; H 5.90; N 15.01; Cl 19.09.

IR spectra were recorded using a Nexus Thermo Nicolet spectrometer. ^1H NMR spectra of the solutions in DMSO-d_6–CCl_4 were registered with a Varian Mercury (300 MHz) instrument.

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