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Vilsmeier–Haak Formylation of 3,5-Dimethylpyrazoles

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Abstract — Formylation of *N*-alkyl-3,5-dimethyl-1*H*-pyrazoles according to Vilsmeier–Haak led to the formation of the corresponding 4-formyl derivatives. 3,5-Dimethyl-1*H*-pyrazole having no substituent on the nitrogen atom failed to undergo formylation at the 4 position under analogous conditions. 3,5-Dimethyl-1*H*-pyrazole-4-carbaldehyde was synthesized by alkaline hydrolysis of methyl β-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionate and subsequent heating of the acid thus formed.

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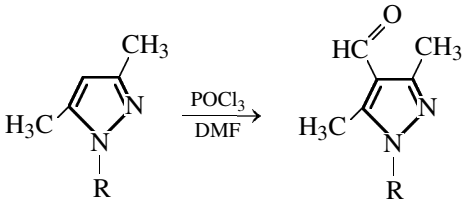
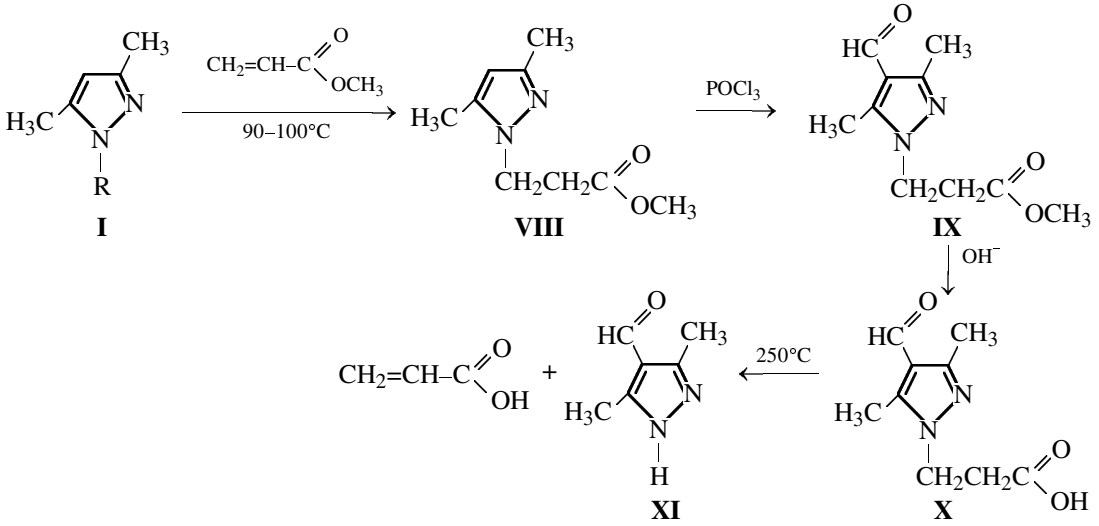
Like 1,3-diazoles, electrophilic substitution in pyrazole molecules occurs either at the ring carbon atom or at the pyridine-type nitrogen atom [1–7]. The regioselectivity of electrophilic substitution strongly depends on the reaction conditions; however, the formylation of NH-pyrazole **I** and 1-alkyl-3,5-dimethyl-1*H*-pyrazoles **II**–**IV** takes different pathways despite similar reaction conditions. By formylation of compounds **II**–**IV** according to Vilsmeier–Haak (i.e., with phosphoryl chloride in DMF at 90–120°C) we obtained 60–80% of the corresponding pyrazole-4-carbaldehydes **V**–**VII**, while the results of formylation of 3,5-dimethyl-1*H*-pyrazole (**I**) were unsatisfactory.



I–**IV** **V**–**VII**

I, R = H; **II**, **V**, R = CH_3; **III, VI**, R = C_2H_5; **IV, VII**, R = C_3H_7.

It is presumed that electrophilic substitution in molecule **I** occurs at the nitrogen atom to give ammonium ion [8–9], which hampers formylation at the 4 position. The formyl group in 3,5-dimethyl-1*H*-pyrazole-1-carbaldehyde is extremely labile and is readily eliminated by the action of basic reagents (NaOH). We succeeded in synthesizing 3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde (**XI**) according to the following scheme.



I **VIII** **IX** **X** **XI**

Methyl β-(3,5-dimethyl-1*H*-pyrazol-1-yl)propionate (**VIII**) was obtained in 88% yield by addition of methyl acrylate to compound **I** on heating to 90–100°C. Formylation of **VIII** with $POCl_3$–DMF gave methyl β-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)-propionate (**IX**) which was subjected to alkaline hydrolysis. By subsequent acidification we isolated acid **X**, and heating of the latter at 250°C (3 mm Hg) gave 4-formylpyrazole **XI** in 65% yield.

The IR spectrum of **XI** contained absorption bands at 1600 cm^{-1} due to stretching vibrations of the aldehyde carbonyl and 1520 cm^{-1} due to vibrations of the pyrazole ring. Absorption bands at 3200–3300 cm^{-1} were asigned to stretching vibrations of the NH group. In the ^1H NMR spectrum of **XI**, the NH signal appeared in a weak field (δ 12.50 ppm), and the aldehyde proton gave a signal at δ 9.15 ppm.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Mercury-300 instrument (300 MHz). The IR spectra were obtained on a Specord 75-IR spectrometer from samples prepared as thin films. GLC analysis was performed on an LKhM-8MD chromatograph equipped with a 1.5-m × 3-mm column packed with 10% of Carbowax-20 M on Inerton AW-HMDS (0.20–0.25 mm); carrier gas helium, flow rate 50 ml min^{-1}.

General procedure for formylation of pyrazoles I–IV and VIII. A mixture of 0.1 mol of compound **I–IV** or **VIII** and 0.6 mol of dimethylformamide was heated to 90°C under stirring, and 0.2 mol of phosphoryl chloride was added over a period of 1 h under stirring, maintaining the temperature below 120°C. The mixture was then cooled with ice water, neutralized with an aqueous solution of sodium hydroxide, and extracted with chloroform, the extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure.

1,3,5-Trimethyl-1*H*-pyrazol-4-carbaldehyde (V). Yield 10 g (59%), bp 130°C (5 mm Hg), mp 80–83°C (from CCl_4). IR spectrum, ν, cm^{-1}: 1510 (ring). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm : 2.33 s (3H, CH_3), 2.49 s (3H, CH_3), 3.70 s (3H, NCH_3), 9.80 s (1H, CHO). Found, %: C 60.62; H 7.02; N 20.02. $C_7H_{10}N_2O$. Calculated, %: C 60.87; H 7.25; N 20.29.

1-Ethyl-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde (VI). Yield 11.8 g (65%), bp 122°C (5 mm Hg), n_D^{20} = 1.5176, d_4^{20} = 1.0670. IR spectrum, ν, cm^{-1}: 1510 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.38 t (3H, CH_3, *J* = 7.2), 2.34 s (3H, CH_3), 2.49 s (3H, CH_3), 4.03 q (2H, CH_2, *J* = 7.2), 9.81 s (1H, CHO). Found, %: C 63.16; H 7.89; N 18.42. $C_8H_{12}N_2O$. Calculated, %: C 62.91; H 7.64; N 18.17.

3,5-Dimethyl-1-propyl-1*H*-pyrazole-4-carbaldehyde (VII). Yield 28.6 g (86%), bp 125°C (5 mm Hg), n_D^{20} = 1.5124, d_4^{20} = 1.0656. IR spectrum, ν, cm^{-1}: 1510 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 0.92 t (3H, CH_3, *J* = 7.4), 1.81 m (2H, CH_2, *J* = 7.3), 2.33 s (3H, CH_3), 2.48 s (3H, CH_3), 3.93 t (2H, NCH_2, *J* = 7.1), 9.81 s (1H, CHO). Found, %: C 62.94; H 7.64; N 18.17. $C_8H_{12}N_2O$. Calculated, %: C 63.16; H 7.89; N 18.42.

Methyl β-(3,5-dimethyl-1*H*-pyrazol-1-yl)propionate (VIII). A mixture of 9.6 g (0.1 mol) of 3,5-dimethyl-1*H*-pyrazole (**I**), 10 ml of methyl acrylate, and 0.1 g of hydroquinone was heated for 8 h at 90°C under reflux. Excess methyl acrylate was removed, and the residue was distilled under reduced pressure. Yield 16 g (87.9%), bp 98–101°C (1 mm Hg), n_D^{20} = 1.4802, d_4^{20} = 1.0674. IR spectrum, ν, cm^{-1}: 1510 (ring), 1700 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 2.33 s (3H, CH_3), 2.55 s (3H, CH_3), 2.88 t (2H, CH_2, *J* = 6.6), 3.64 s (3H, OCH_3), 4.20 t (2H, NCH_2, *J* = 6.6). Found, %: C 59.12; H 7.44; N 15.16. $C_9H_{14}N_2O_2$. Calculated, %: C 59.34; H 7.69; N 15.38.

Methyl β-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionate (IX). Yield 21.4 g (68%), bp 168°C (1 mm Hg), n_D^{20} = 1.5164, d_4^{20} = 1.2374. IR spectrum, ν, cm^{-1}: 1510 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.33 s (3H, CH_3) 2.55 s (3H, CH_3), 2.88 t (2H, CH_2, *J* = 6.6), 3.64 s (3H, OCH_3), 4.20 t (2H, NCH_2, *J* = 6.6), 9.81 s (1H, CHO). Found, %: C 56.89; H 6.42; N 13.11. $C_{10}H_{14}N_2O_3$. Calculated, %: C 57.14; H 6.67; N 13.33.

β-(4-Formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionic acid (X). A mixture of 21.4 g of methyl β-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionate (**IX**), 8 g of sodium hydroxide, and 50 ml of water was stirred for 3 h at room temperature. It was then extracted with diethyl ether, the aqueous phase was neutralized with hydrochloric acid, and the precipitate was filtered off. Yield 16.4 g (82%), white crystals (from water), mp 119–121°C. IR spectrum, ν, cm^{-1}: 1510 (ring), 1710 (C=O), 3300–3500 (O–H). ^1H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 2.34 s (3H, CH_3) 2.54 s (3H, CH_3), 2.78 t (2H, CH_2, *J* = 6.7), 4.16 t (2H, NCH_2, *J* = 6.7), 9.81 s (1H, CHO), 12.15 br.s (1H, COOH). Found, %: C 54.88; H 5.90; N 14.03. $C_9H_{12}N_2O_3$. Calculated, %: C 55.10; H 6.12; N 14.28.

3,5-Dimethyl-1*H*-pyrazole-4-carbaldehyde (XI). β-(4-Formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionic acid (**X**), 6.2 g, was placed in a vacuum distillation

setup and was distilled at a bath temperature of 250°C (3 mm Hg). The distillate was neutralized with potassium carbonate and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated, and the residue crystallized. Yield 62%, mp 112°C (from benzene). IR spectrum, ν, cm^{-1}: 1550 (ring), 1670 (CHO). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.40 s (6H, CH_3), 9.83 s (1H, CHO), 12.50 br.s (1H, NH). Found, %: C 57.84; H 6.23; N 22.36. $C_6H_8N_2O$. Calculated, %: C 58.06; H 6.45; N 22.58.

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