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**LETTERS TO THE EDITOR**

# Vilsmeier–Haack Formylation of 1*H*-Pyrazoles

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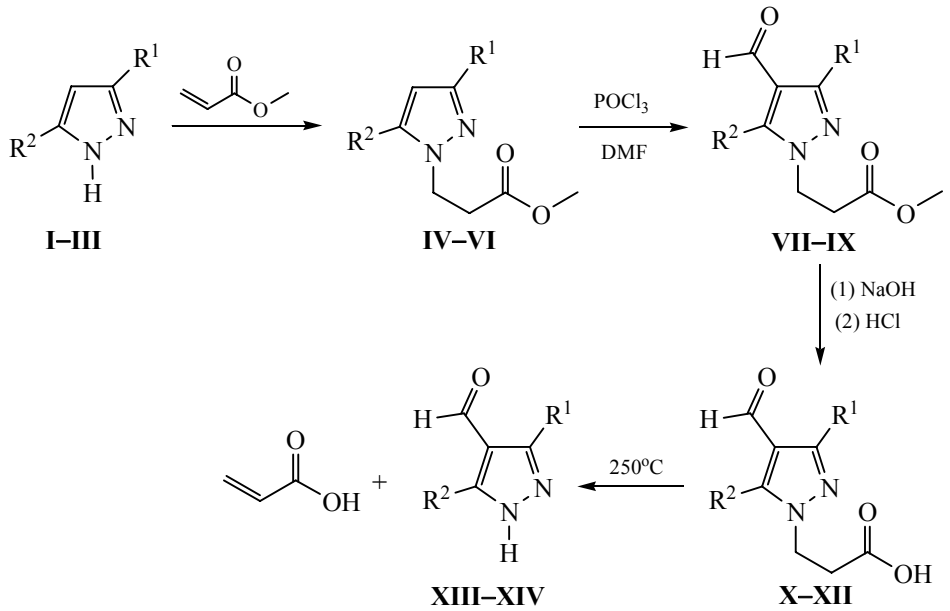
Vilsmeier–Haack Formylation of alkylpyrazoles with phosphorus oxychloride in DMF at 90–120°C resulted to the corresponding products in yields of 33–86% [1–3], while formylation of 1*H*-pyrazoles **I–III** under these conditions did not occur.

Previously, synthesis of 3,5-dimethyl-1*H*-pyrazol-4-carbaldehyde **XIV** has been performed via initial 1-alkoxycarbonylethylation followed by hydrolysis and thermal β-cleavage of the acid obtained [3]. In the present work we carried out Vilsmeier–Haack formylation of pyrazole **I** and its methyl derivatives **II, III** (Scheme 1).

Adducts **IV–Va, Vb** were obtained in yields of 80–96% by heating methyl acrylate with pyrazoles **I–III** at 80–90°C. Then they were formylated to give compounds **VII–IX**, whose alkaline hydrolysis afforded derivatives **X–XII**.

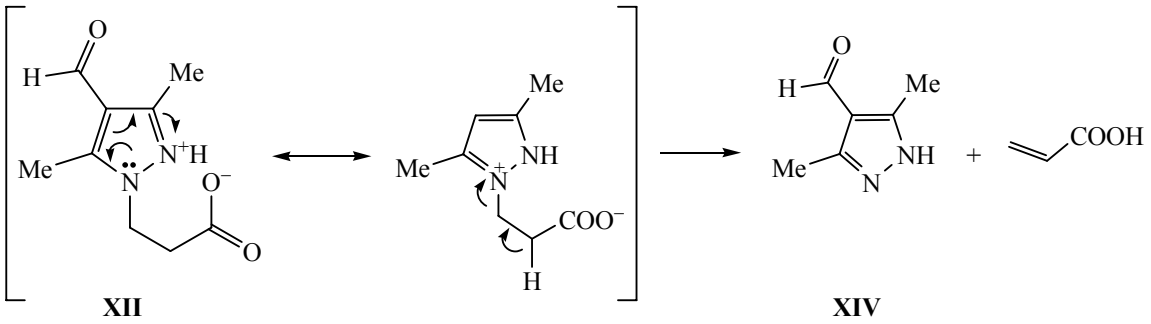
As expected, reaction of 3(5)-methylpyrazole **II** and methyl acrylate gave rise to mixture of isomeric pyrazoles **VIIIa** and **VIIb** in a ratio of 3 : 2 (according

**Scheme 1.**




$R^1 = R^2 = H$ (**I, IV, VII, X**); $R^1 = CH_3$, $R^2 = H$ (**a**), $R^1 = H$, $R^2 = CH_3$ (**b**) (**II, V, VIII, XI, XIII**); $R^1 = R^2 = CH_3$ (**III, VI, IX, XII, XIV**).

**Scheme 2.**




to $^1$H NMR) in 96% yield [4]. Heating the hydrolysis products **X–XII** at 250°C (3 mmHg) led to the formation of 4-formyl-1*H*-pyrazoles **XIII–XIV** in yields of 30–60%.

The lability of carboxyethyl group varies considerably depending on the structure of the starting pyrazole **X–XII**. The deprotection of 3-(4'-formyl-3',5'-dimethylpyrazol-1'-yl)propionic acid **XII** showing basic properties owing to pyrazole core [5] occurred much better (yield 60%) [3] compared with compounds **X** and **XI**. Under the same conditions deprotection of compound **X** containing unsubstituted pyrazole ring did not proceed. More rigid conditions (300°C) led to complete tarring. In contrast, a mixture of 3-(3'-methyl-4-formylpyrazol-1-yl)- and 3-(5'-methyl-4-formylpyrazol-1-yl)propionic acids **XIa** and **XIb** was converted into the corresponding NH-formylpyrazoles **XIIIa** and **XIIIb** with a yield of 30%.

These results can be explained by the fact that in case of more alkylated pyrazole rings more basic nitrogen atom is protonated with carboxyl hydrogen, which largely contributes to the β-cleavage (Scheme 2).

**Methyl 3-(pyrazol-1'-yl)propionate (IV).** A mixture of 6.8 g (0.1 mol) of pyrazole I, 9.5 g (0.11 mol) of methyl acrylate, and 0.1 g of hydroquinone was heated for 8 h at 90°C. After removing an excess of methyl acrylate the residue was distilled in vacuum. Yield 12.3 g (80%), bp 81°C (1 mmHg), $n_D^{20}$ 1.4751. IR spectrum, ν, cm$^{-1}$: 1510 (ring), 1730 (C=O). $^1$H NMR spectrum (DMSO-$d_6$, 300 MHz), δ, ppm (*J*, Hz): 2.84 t (2H, $CH_2\underline{CH_2}$, *J* 6.2), 3.65 s (3H, $OCH_3$), 4.25 t (2H, $NCH_2$, *J* 6.2), 6.13 d. d (1H, 4-H, *J* 2.3, 1.9), 7.32 d (1H, 3-H, *J* 1.9), 7.53 d (1H, 5-H, *J* 2.3). Found, %: C 54.60; H 6.50; N 18.24. $C_7H_{10}N_2O_2$. Calculated, %: C 54.55; H 6.54; N 18.17.

**A mixture of methyl 3-(3'-methylpyrazol-1'-yl)-propionate (Va)** and **3-(5'-methylpyrazol-1'-yl)-propionate (Vb)** was prepared similarly from 3-methylpyrazole (8.2 g, 0.1 mol). Yield 16.2 g (96%), ratio of 3:2, bp 94–97°C (1 mmHg). IR spectrum, ν, cm$^{-1}$: 1520 (ring), 1730 (C=O). Found, %: C 56.98; H 7.21; N 16.71. $C_8H_{12}N_2O_2$. Calculated, %: C 57.13; H 7.19; N 16.66.

**Methyl 3-(4'-formylpyrazol-1'-yl)propionic acid (VII).** A mixture of 14.4 g (0.1 mol) of methyl 3-(pyrazol-1'-yl)propionate and 95 g (0.6 mol) of dimethyl formamide was heated to 90°C with stirring. Then to the mixture 30 g (0.2 mol) of phosphorus oxychloride was carefully added, so that the temperature of the reaction mixture did not exceed 120°C. The phosphorus oxychloride was added over 1 h, then the mixture was stirred at 100°C for 1 h. The mixture was cooled with ice water, neutralized with aqueous $Na_2CO_3$, extracted with chloroform, and dried with magnesium sulfate. After distilling off the solvent, the residue was distilled in vacuum. Yield 12.4 g (68%), bp 162°C (3 mmHg), $n_D^{20}$ 1.5112. IR spectrum, ν, cm$^{-1}$: 1510 (ring), 1700 (CHO). $^1$H NMR spectrum (DMSO-$d_6$, 300 MHz), δ, ppm (*J*, Hz): 2.82 t (2H, $CH_2\underline{CH_2}$, *J* 6.0), 3.60 s (3H, $OCH_3$), 4.25 t (2H, $NCH_2$, *J* 6.0), 7.30 s (1H, 3H), 7.50 s (1H, 5-H), 9.80 s (1H, CHO). Found, %: C 52.70; H 5.57; N 15.43. $C_8H_{10}N_2O_3$. Calculated, %: C 52.74; H 5.53; N 15.38.

**A mixture of methyl 3-(4'-formyl-3'-methyl-pyrazol-1'-yl)propionate (VIIIa)** and **3-(4'-formyl-5'-methylpyrazol-1'-yl)propionate (VIIIb)** was obtained similarly from a mixture of Va, Vb (16.8 g, 0.1 mol). Yield 14 g (72 %), ratio of 3:2, bp 138–141°C (1 mmHg). IR spectrum, ν, cm$^{-1}$: 1530 (ring), 1650 (CHO). Found, %: C 55.28; H 6.21; N 14.31. $C_9H_{12}N_2O_3$. Calculated, %: C 55.09; H 6.16; N 14.28.

**3-(4'-Formylpyrazol-1'-yl)propionic acid (X).** A mixture of 16.8 g (0.1 mol) of methyl 3-(4'-formylpyrazol-1'-yl)propionate, 8 g (0.2 mol) NaOH

and 50 g of water was stirred for 3 h at room temperature. The reaction product was extracted with ether, the aqueous extract was neutralized with hydrochloric acid, and the formed crystals were filtered off. Yield 10.4 g (62%), mp 98°C (water). IR spectrum, ν, $cm^{-1}$: 1510 (ring), 1680 (CHO), 1720 (C=O), 3200–3330 (OH). $^1$H NMR spectrum (DMSO-$d_6$, 300 MHz), δ, ppm (*J*, Hz): 2.82 t (2H, $CH_2\underline{CH_2}$, *J* 6.1), 4.25 t (2H, $NCH_2$, *J* 6.1), 7.31 s (1H, 3-H), 7.52 s (1H, 5-H), 9.80 s (1H, CHO), 12.0 s (1H,OH). Found, %: C 49.90; H 4.83; N 16.69. $C_7H_8N_2O_3$. Calculated, %: C 50.00; H 4.80; N 16.66.

**A mixture of methyl 3-(4'-formyl-3'-methylpyrazol-1'-yl)propionic acid (XIa)** and **3-(4'-formyl-5'-methylpyrazol-1'-yl)propionic acid (XIb)** was prepared similarly from a mixture of methyl esters **VIIIa, VIIIb** (19.6 g, 0.1 mol). Yield 12g (65%), ratio of 3 : 2, mp 120–125°C (water). IR spectrum, ν, $cm^{-1}$: 1530 (ring), 1680 (CHO), 1700 (C=O), 3200–3330 (OH). Found, %: C 52.85; H 5.58; N 15.42. $C_8H_{10}N_2O_3$. Calculated, %: C 52.74; H 5.53; N 15.38.

**3(5)-Methyl-4-formylpyrazole (XIII).** A mixture of 5.5 g (0.05 mol) of acids **XIa, XIb** was distilled at 250°C (3 mmHg). The condensate was neutralized with potassium carbonate, treated with chloroform and dried over magnesium sulfate. After distilling off the solvent, the residue was recrystallized. Yield 3.3 g (30%), mp 108–110°C. IR spectrum, ν, $cm^{-1}$: 1520 (ring), 1680 (CHO). $^1$H NMR spectrum (DMSO-$d_6$, 300 MHz), δ, ppm (*J*, Hz): 2.42 s [3H, 3(5)-$CH_3$], 7.82 s [1H, 3(5)-H], 9.81 s (1H, $CH_2O$), 14 br (1H, NH). Found, %: C 53.69; H 5.47; N 25.48. $C_5H_6N_2O$. Calculated, %: C 54.54; H 5.49; N 25.44.

IR spectra were recorded on a Specord 75-IR spectrometer (from thin film). $^1$H NMR spectra were registered on a Varian Mercury spectrometer in DMSO-$d_6$ operating at 300 MHz. Elemental analysis was performed on a Korshun–Klimova instrument.

Synthesis and physicochemical constants of compounds **VI, IX, XII, XIV** have been reported in [3].

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