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**LETTERS TO THE EDITOR**

# Esterification of 3,5-Dimethyl-1-phenylpyrazol-4-ylacetic Acid

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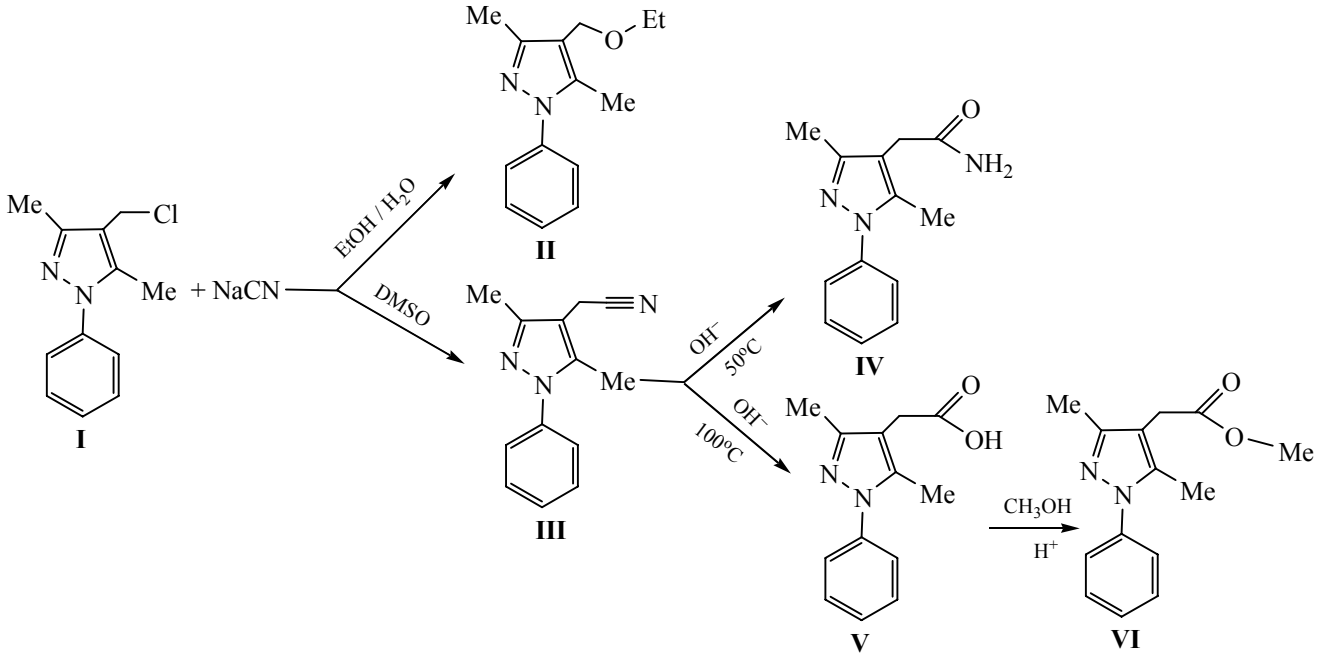
The *ortho*-disubstituted phenylacetic acids in whose structure the carboxy group is not directly connected to the benzene ring are easier subjected to esterification in comparison with the *ortho*-disubstituted benzoic acids. Previously [1] we studied the esterification with methanol of *ortho*-disubstituted pyrazole-4-ylcarboxylic acid. This acid as an analog of *ortho*-disubstituted benzoic acid was shown to be not esterified.

In order to identify the spatial character of the effect of the pyrazole ring on the esterification process, in this work we studied the esterification of 3,5-dimethyl-1-phenylpyrazol-4-ylacetic acid **V** with methanol. The synthesis of 3,5-dimethyl-1-phenylpyrazol-4-ylacetic acid **V** was performed (Scheme 1).

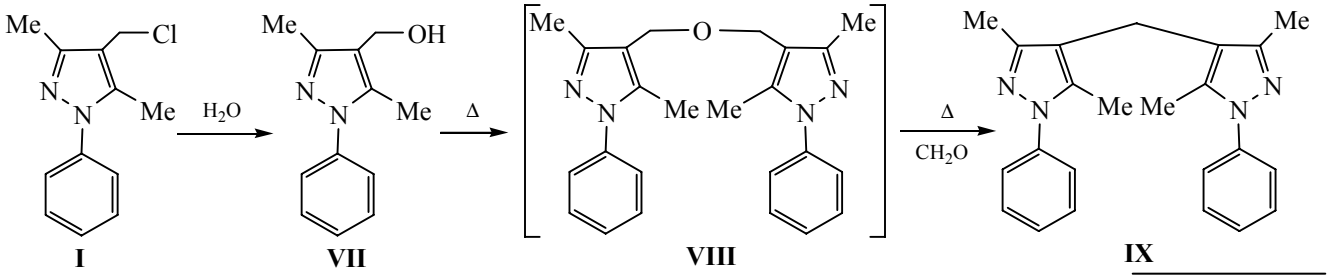
The synthesis of nitrile **III** by the Kolbe method in a water–alcohol mixture failed. 3,5-Dimethyl-1-phenyl-4-chloromethylpyrazole **I**, as an analog of the substituted benzyl halides (which are prone to react by must be deleted $S_N1$ mechanism), leads mainly to the pyrazole ether **II**.

Since the dipolar aprotic solvents (acetone, DMF, DMSO, etc.) favor the $S_N2$ reaction mechanism, the synthesis of nitrile **III** was carried out in a dimethylsulfoxide environment. 2-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)acetonitrile **III** was obtained in 52% yield. In addition, the solvolysis product **VII** of the reactive chloride **I** was isolated and identified. Compound **VII** undergoes the cross-coupling to form

**Scheme 1.**



**Scheme 2.**




the corresponding symmetrical ether **VIII**. When distilling, the latter splits off a formaldehyde molecule to give compound **IX**. The formation route of bis(3,5-dimethyl-1-phenylpyrazol-4-yl)methane **IX** have been studied in detail in [2, 3] (Scheme 2).

Due to the low carbonyl-type activity of the nitrile group (especially in aromatic nitriles), the hydrolysis of 2-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)acetonitrile **III** was carried out in 50% solutions of sodium hydroxide.

At 50–60°C the hydrolysis of compound **III** proceeds slowly with the low yield and stops at the stage of the amide **IV** formation. The hydrolysis rate increases at 95–100°C to give carboxylic acid **V**.

Even the initial experiments showed that 3,5-dimethyl-1-phenylpyrazol-4-ylacetic acid **V** is easily esterified with methanol in the presence of hydrochloric acid, i. e., it behaves like the *ortho*-disubstituted phenylacetic acid. These results and the results of [1] give reason to believe that when the carboxy group is directly linked to the pyrazole ring, the latter creates steric hindrances to the attack of the alcohol molecule on the carboxyl carbon, and vice versa.

Due to the fact that the carbonyl group has a trigonal planar form (owing to the $sp^2$-hybridized carbon atom), the reagent can attack it with any of the two sides with equal probability. Therefore the pyrazole ring should not cause steric hindrances to the esterification. On the other hand, in pyrazol-4-ylcarboxylic acids the bulky pyrazole substituent is directly bonded with the carbon atom of the carboxyl group, and in the pyrazol-4-ylacetic acid molecule this bonding is performed via the methylene bridge.

It is also known that the rate of carboxylic acids esterification decreases, if the reagent species occupies a large volume or the carbonyl group is surrounded with bulky groups. As expected, a similar dependence of the carbonyl group reactivity on the size of the neighboring substituents is also observed in pyrazol-4-ylcarboxylic and pyrazol-4-ylacetic acids.

**4-(Ethoxymethyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (II).** To a solution of 1.9 g of sodium cyanide in 10 ml of water was added dropwise a solution of 8.4 g of compound **I** in 15 ml of ethanol while stirring at 75–80°C. The stirring was continued for 11 h at room temperature. Then the mixture was extracted with 50 ml of chloroform, the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. Yield 4.0 g (51%), mp 140°C (1 mm Hg), $n_D^{20}$ 1.5526. IR spectrum, ν, $cm^{-1}$: 1360 (pyrazole), 1580 ($C_6H_5$), 1070–1080 (C–O–C). $^1H$ NMR spectrum, ($CDCl_3$), $\delta_H$, ppm, (*J*, Hz): 1.25 t (3H, $CH_2\underline{CH_3}$, *J* 7.0), 2.31 s (3H, 3-$CH_3$), 2.33 s (3H, 5-$CH_3$), 3.53 q (2H, $\underline{CH_2}CH_3$, *J* 7.0), 4.35 s (2H, $CH_2$), 7.30–7.51 m (5H, Ph). Found, %: C 73.31; H 8.12; N 12.45. $C_{13}H_{14}O_2$. Calculated, %: C 73.04; H 7.82; N 12.17.

**2-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)acetamide (IV).** A mixture of 2.1 g of compound **III** and 0.4 g of potassium hydroxide was dissolved in 3 ml of water and stirred for 4 h at 60°C. After cooling, the reaction mixture was decanted, and the aqueous layer was extracted with 30 ml of chloroform. After the removal of the solvent the resulting crystals were recrystallized from hexane. Yield 0.08 g (10%). IR spectrum, ν, $cm^{-1}$: 1560 (pyrazole), 1580 ($C_6H_5$), 1680 (C=O), 3200–3400 ($NH_2$). $^1H$ NMR spectrum, (DMSO-$d_6$), $\delta_H$, ppm, (*J*, Hz): 2.18 s (3H, 3-$CH_3$), 2.28 s (3H, 5-$CH_3$), 3.16 s (2H, $CH_2$), 6.58 br. s (1H, $NH_2$), 6.89 m (1H, $NH_2$), 7.31 m (1H, Ph), 7.41–7.44 m (4H, Ph). Found, %: C 68.44; H 6.89; N 18.10. $C_{13}H_{15}N_3O$. Calculated, %: C 68.12; H 6.55; N 18.34.

**2-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)acetonitrile (III).** A mixture of 1.4 g of sodium cyanide at 60°C was dissolved in 15 ml of DMSO and cooled to 30°C. Then to the mixture was added dropwise a solution of 6.1 g of compound **I** in 5 ml of DMSO at 45°C. The stirring was continued for 1 h at 60°C. After cooling, 10 ml of water was added to dissolve the salt. The solution was extracted with chloroform; the

extract was dried over magnesium sulfate. The solvent was distilled off, and the residue was distilled in a vacuum. Yield 3 g (52%), mp 178–180°C (1 mm Hg), $n_D^{20}$ 1.5720. IR spectrum, ν, $cm^{-1}$: 1550 (pyrazole), 1580 ($C_6H_5$), 2230 (C=N). $^1H$ NMR spectrum, ($CDCl_3$), $\delta_H$, ppm, (*J*, Hz): 2.32 s (3H, 3-$CH_3$), 2.34 s (3H, 5-$CH_3$), 4.37 s (2H, $CH_2$), 7.33–7.50 m (5H, Ph). Found, %: C 73.61; H 6.48; N 20.01. $C_{13}H_{13}N_3$. Calculated, %: C 73.93; H 6.16; N 19.90.

**1,2-Bis(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-methane (IX).** Yield 1.2 g (24.5%), mp 258–262°C (1 mm Hg), mp 117–118°C (water–acetone). IR spectrum, ν, $cm^{-1}$: 1550 (pyrazole), 1580 ($C_6H_5$). $^1H$ NMR spectrum, (DMSO-$d_6$), $\delta_H$, ppm, (*J*, Hz): 2.1 s (6H, 3-$CH_3$), 2.23 s (6H, 5-$CH_3$), 3.52 s (2H, $CH_2$), 7.27–7.46 m (10H, Ph). Found, %: C 77.30; H 6.89; N 15.34. $C_{23}H_{24}N_4$. Calculated, %: C 77.52; H 6.74; N 15.73.

**1-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-hydroxyethanone (V).** A mixture of 1.1 g of compound **III** and 0.57 g of potassium hydroxide was dissolved in 2.5 ml of water and heated to reflux for 18 h until the release of ammonia ceased. The solution was extracted with chloroform. The aqueous residue was neutralized with hydrochloric acid and extracted with chloroform. The extract was dried with magnesium sulfate. After the solvent removal, the resulting crystals were recrystallized from water. Yield 0.8 g (70%), mp 122–129°C. IR spectrum, ν, $cm^{-1}$: 1550 (pyrazole), 1580 ($C_6H_5$), 1700 (C=O), 3200–3400 (OH). $^1H$ NMR spectrum, (DMSO-$d_6$), $\delta_H$, ppm, (*J*, Hz): 2.19 s (3H, 3-$CH_3$), 2.28 s (3H, 5-$CH_3$), 3.28 s (2H, $CH_2$), 7.31 m (1H, Ph), 7.40–7.47 (4H, Ph). Found, %: C 67.58; H 6.31; N 12.35. $C_{13}H_{14}N_2O_2$. Calculated, %: C 67.82; H 6.08; N 12.17.

**1-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methoxymethanone (VI).** To a mixture of 0.8 g of **V** in 20 ml of methanol was added a catalytic amount of conc. hydrochloric acid. The mixture was refluxed for 12 h. After cooling the solvent was removed without heating. The residue was neutralized with $Na_2CO_3$ solution and extracted with chloroform. The extract was dried over magnesium sulfate. After the solvent removal the resulting crystals were recrystallized from water. Yield 0.7 g (80%), mp 61–62°C. IR spectrum, ν, $cm^{-1}$: 1550 (pyrazole), 1580 ($C_6H_5$), 1690 (C=O). $^1H$ NMR spectrum, (DMSO-$d_6$–$CCl_4$, 1:3), $\delta_H$, ppm, (*J*, Hz): 2.18 s (3H, 3-$CH_3$), 2.28 s (3H, 5-$CH_3$), 3.37 s (2H, $CH_2$), 7.31 m (1H, Ph), 7.39–7.47 m (4H, Ph). Found, %: C 68.31; H 6.22; N 11.31. $C_{14}H_{16}N_2O_2$. Calculated, %: C 68.85; H 6.55; N 11.47.

The $^1H$ NMR spectra were recorded on a Varian Mercury spectrometer (300 MHz) using DMSO-$d_6$–$CCl_4$ mixture (1:3) as a solvent. The IR spectra were obtained on a Specord 75-IR instrument (thin film).

## REFERENCES

1. Sahakyan, A.A., *Zh. Obshch. Khim.,* 2011, vol. 81, no. 8, p. 1403.
2. Attaryan, O.S., Gevorkyan, A.A., Antanosyan, S.K., Martirosyan, S.S., Panosyan, G.A., and Matsoyan, S.G., *Zh. Obshch. Khim.,* 2005, vol. 75, no. 9, p. 1575.
3. Attaryan, O.S., Gevorkyan, A.A., Antanosyan, S.K., Martirosyan, S.S., and Matsoyan, S.G., *Zh. Obshch. Khim.,* 2007. vol. 77, no. 6, p. 1053.