ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 4, pp. 796–798. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © V.I. Rstakyan, A.E. Akopyan, G.B. Zakaryan, H.S. Attaryan, G.V. Asratyan, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 4, pp. 700–702.

LETTERS TO THE EDITOR

Oxidation of 1-(2-Hydroxyethyl)-3,5-dimethylpyrazole-4-carbaldehyde under Phase-Transfer Catalysis

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Received January 16, 2014

Keywords: pyrazole, oxidation, phase transfer catalysis, chemoselectivity

DOI: 10.1134/S1070363214040343

We have previously synthesized N-substituted pyrazole-4-carboxylic acids from the corresponding aldehydes under phase-transfer catalysis (PTC) [1, 2]. The chemoselective oxidation of the formyl group occurred in these cases when the substituent at the pyrazole nitrogen atom contained no hydroxy groups.

The oxidation of 1-(2-hydroxyethyl)-3,5-dimethylpyrazole-4-carbaldehyde **I** under phase-transfer catalysis (water–benzene–$KMnO_4$–triethylbenzylammonium chloride) in the temperature range of 0–30°C resulted in a mixture of two acids **II, III** in a ratio of 4 : 1 (according to ^{1}H NMR spectroscopy) (Scheme 1).

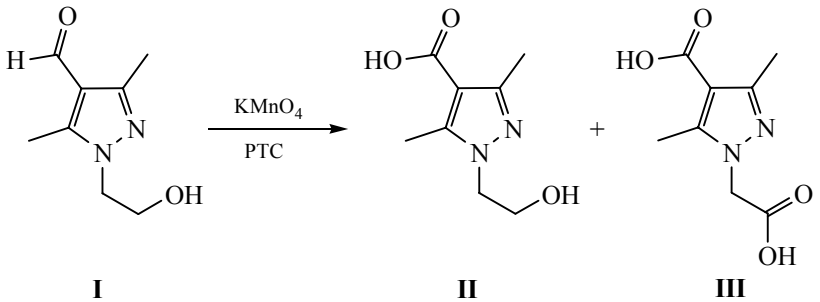
3,5-Dimethyl-1-carboxymethylpyrazole-4-carboxylic acid **III** was obtained in a 40% yield when the reaction was performed at higher temperature (60°C) in the presence of an excess of $KMnO_4$.

For chemoselective oxidation of formyl group in the molecule of 1-(2-hydroxyethyl)-3,5-dimethylpyrazole-4-carbaldehyde **I** without affecting hydroxymethyl moiety we introduced such protecting groups into the organic molecule [3] which would prevent the possibility of interaction of protecting groups with other reactive centers of the molecule and with reagents. When selecting protective groups, a proper attention was paid to their convenient introduction into the molecule, their stability in various reactions, and ease of their removal.

First experiments have shown that acetyl group meets the above requirements.

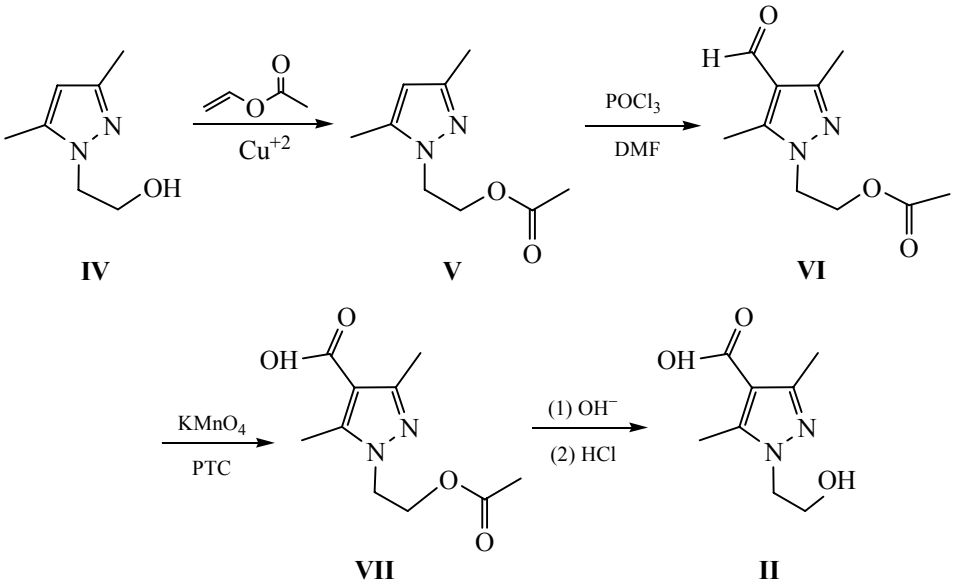
Acylation of 1-(2-hydroxyethyl)-3,5-dimethylpyrazole **IV** with vinyl acetate in the presence of a catalytic amount of copper acetate afforded compound **V**. The latter was readily subjected to Vilsmeier–Haack formylation to give 2-(3,5-dimethyl-4-formylpyrazol-1-yl)ethyl acetate **VI**. Then, compound **VI** was oxidized with potassium permanganate under phase-transfer catalysis. The resulting 1-(2-acetoxyethyl)-3,5-dimethylpyrazole-4-carboxylic acid **VII** was hydrolyzed with aqueous NaOH to afford the desired

Scheme 1.



I **II** **III**

Scheme 2.



1-(2-hydroxyethyl)-3,5-dimethylpyrazole-4-carboxylic acid **II** (Scheme 2).

The structure and composition of compounds **II, III** were confirmed by ^{1}H NMR, IR spectroscopy and elemental analysis.

3,5-Dimethyl-1-carboxymethylpyrazole-4-carboxylic acid (III). To a mixture of 16.8 g (0.1 mol) of 1-(2-hydroxyethyl)-3,5-dimethylpyrazole-4-carbaldehyde **I**, 50 mL of water, 50 mL of benzene, and 1 g of Et_3BnNCl was added by portions 79 g (0.5 mol) of potassium permanganate with stirring at 60°C, so that the temperature of the reaction mixture did not exceed 60°C. After addition of potassium permanganate, the mixture was stirred for 2 h at 60°C. After cooling, MnO_2 was filtered off and washed with water. Aqueous layer was extracted with diethyl ether. After distilling off 2/3 of the amount of water, aqueous solution of the potassium salt of the acid **III** was acidified with hydrochloric acid. The precipitated crystals were filtered off and dried. Yield 8 g (40.5%), mp 210°C. IR spectrum, ν, cm^{-1}: 1530 (ring), 1730 (C=O), 3200–3400 (COOH). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 2.42 s (3H, CH_3), 4.72 s (2H, CH_2), 11.82 br.s (2H, COOH). Found, %: C 48.21; H 5.38; N 14.38. $C_8H_{10}N_2O_4$. Calculated, %: C 48.48; H 5.05; N 14.14.

1-(2-Acetoxyethyl)-3,5-dimethylpyrazole-4-carboxylic acid (VII). To a mixture of 15.6 g (0.1 mol) of 2-(3,5-dimethyl-4-formylpyrazol-1-yl)ethyl acetate **VI**, 50 mL of water, 50 mL of benzene and 1 g Et_3BnNCl was added by portions 23.7 g of (0.15 mol) of potassium permanganate with stirring, so that the temperature of the reaction mixture did not exceed 30°C. After addition of potassium permanganate, the mixture was stirred for 12 h at room temperature. After cooling, MnO_2 was filtered off and washed with water. Aqueous layer was extracted with diethyl ether. After distilling off 2/3 of water, aqueous solution of pyrazolecarboxylic acid potassium salt was acidified with hydrochloric acid. The precipitated crystals were filtered off and dried. Yield 10.6 g (55%), mp 200°C. IR spectrum, ν, cm^{-1}: 1530 (ring), 1730 (C=O), 3200–3400 (COOH). ^{1}H NMR spectrum, δ, ppm: 2.00 s (3H, OCH_3), 2.30 s (3H, CH_3), 2.48 s (3H, CH_3), 4.17–4.22 m (2H, CH_2), 4.29–4.34 m (2H, CH_2), 17.72 br.s (1H, COOH). Found, %: C 53.4; H 6.44; N 12.09. $C_{10}H_{14}N_2O_4$. Calculated, %: C 53.09; H 6.19; N 12.38.

1-(2-Hydroxymethyl)-3,5-dimethylpyrazole-4-carboxylic acid (II). A mixture of 18.4 g (0.1 mol) of the acid **VII**, 8.0 g of sodium hydroxide and 50 mL of water was stirred for 3 h at room temperature. Organic compounds were removed from the reaction mixture with chloroform. After distilling off 2/3 of water, aqueous solution of pyrazolecarboxylic acid potassium salt was acidified with hydrochloric acid. The precipitated crystals were filtered off and dried. Yield 11.9 g (65%), mp 185°C. IR spectrum, ν, cm^{-1}: 1530 (ring), 1570 (C=O), 3200–3400 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 s (3H, CH_3), 2.53 s (3H,

CH_3), 3.72 t (2H, NCH_2, *J* 5.6), 4.05 t (2H, CH_2OH, J 5.6), 4.68 br.s (1H, OH), 11.83 br.s (1H, COOH). Found, %: C 58.46; H 6.82; N 15.51. $C_8H_{12}N_2O_3$. Calculated, %: C 58.17; H 6.52; N 15.21.

IR spectra were obtained on a Specord 75 IR spectrophotometer from KCl pellets. ^1H NMR spectra were recorded on a Varian Mercury-300 (300 MHz) in DMSO-d_6. The starting pyrazoles **IV–VI** were synthesized by known methods [4–6].

REFERENCES

1. Badalyan, K.S., Akopyan, A.E., Sahakyan, A.A., Attaryan, H.S., and Asratyan, G.V., *Khim. Zh. Armenii*, 2012, vol. 65, no. 3, p. 394.
2. Baltayan, A.H., Sahakyan, A.A., Attaryan, H.S., and Asratyan, G.V., *Russ. J. Gen. Chem*., 2010, vol. 80, no. 5, p. 1004. DOI: 10.1134/S1070363210050257.
3. McOmie, J.F.W., *Protective Groups Inorganic Chemistry*, London; New York: Plenium Press, 1973, p. 391.
4. Attaryan, H.S., Antanosyan, S.K., and Asratyan, G.V., *Russ. J. Gen. Chem*., 2008, vol. 78, no. 3, p. 508. DOI: 10.1134/S1070363208030298.
5. Baltayan, A.H., Rstakyan, V.I., Antanosyan, S.K., Kikoyan, F.S., Attaryan, H.S., and Asratyan, G.V., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 4, p. 2417. DOI: 10.1134/S107036320911022X.
6. Attaryan, H.S., Grigoryan, A.D., Matsoyan, M.S., Kinoyan, F.S., and Matsoyan, S.G., *Khim. Zh. Armenii*, 2000, vol. 53, nos. 1–2, p. 92.