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Synthesis of 1-Vinyl-4-pyrazolecarboxylic Acids

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Abstract—A convenient oxidation method of 1-(2-chloroethyl)-4-formylpyrazoles followed by dehydrochlorination was developed for preparation of 1-vinyl-4-pyrazolecarboxylic acids. Dehydrochlorination rate was established to decrease with the growing number of electron-donor substituents.

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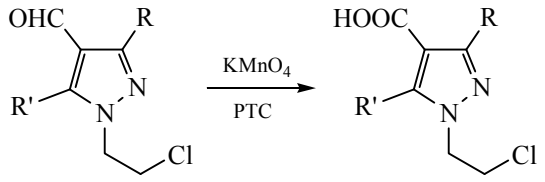
The oxidation in organic synthesis is among the most common processes. It is of great practical importance for the synthesis of various oxygen-containing compounds. The great significance of this reaction for industrial processes impelled us to investigate usability of phase-transfer catalysts in the oxidation reaction where organic substrate is insoluble in aqueous media and oxidizer is in turn insoluble or poorly soluble in organic solvents.

The principal possibility to use phase-transfer catalysts in aprotic solvent for oxidation of water-insoluble substrates was shown as early as in 1965 [1]. A tertiary arsonium salt, methylphenylarsonium chloride, was used as catalyst. In potassium permanganate aqueous solution the exchange of chloride anion was replaced by permanganate-anion and its transport into the chloroform solution of substrate occurred, where the oxidation proceeded. Further extractability of permanganate ions from aqueous solution into benzene was examined. It was shown that when the aqueous solution contained 1 mmol of MnO_4^- and 3.2 mmol of TBAB (tetrabutylammonium bromide) was used, 0.97 mmol of MnO_4^- passed into benzene. They might be consumed in the oxidation process [2]. Similar results were obtained in the case, when benzyltriethylammonium chloride (TEBAC) was used [3].

Further crimson benzene solution of permanganate was widely used in oxidation processes [4, 5].

We suggested a convenient oxidation method of 1-(2-chloroethyl)-4-formylpyrazoles **I–IV** in liquid-liquid system (water–benzene–TEBAC–substrate) at room temperature over 12 h to form acids in 70–75% yields.



I–IV **V–VIII**

I, V, R = R' = H; **II, VI**, R = CH_3, R' = H; **III, VII**, R = H, R' = CH_3; **IV, VIII**, R = R' = CH_3.

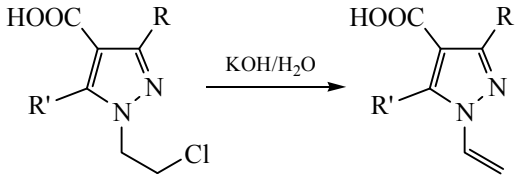
In the absence of catalyst or benzene the oxidation reaction of compounds **I–IV** does not proceed. From this follows that formylpyrazole **I–IV** oxidation occurs in crimson benzene solution of potassium permanganate.

It was established that formylpyrazoles **I–IV** oxidation proceeds smoothly leaving intact thet chloroethyl moiety.

In the ^1H NMR spectra of **V–VIII** the signal of aldehyde hydrogen atom at 9.15–9.25 ppm, disappeared and new signal appears at 11.25–11.88 ppm belonging to the carboxy hydrogen atom. Chemical shifts of chloroethyl group protons in compounds **V–VIII** (3.93–4.46 ppm) and **I–IV** are practically the same.

The IR spectra of **V–VIII** contain characteristic absorption bands at 1670–1700 (carbonyl group) and 1520–1550 cm^{-1} (pyrazole ring). There are also absorption bands at 3100–3500 cm^{-1} originating from stretching vibrations of –COOH groups.

Vinylpyrazoles **IX–XII** were obtained by dehydrochlorination of 1-(2-chloroethyl)-4-pyrazolecarboxylic acids **V–VIII** in potassium hydroxide aqueous solution at ~100°C.



V–VIII **IX–XII**

V, IX, R = R' = H; **VI, X**, R = CH_3, R' = H; **VII, XI**, R = H, R' = CH_3; **VIII, XII**, R = R' = CH_3.

In these conditions dehydrochlorination processes of compounds **V–VIII** proceeds smoothly. Dehydrochlorination rate was found to decrease as follows: **V** > **VI** > **VII** > **VIII**. This difference may be explained by the difficulty in the proton abstraction by the action of electron–donor substituents. Indeed, comparison of the ^{1}H NMR spectra of compounds **V–VIII** indicates that electron density on N–CH_2 group protons is decreased in going from **V** to **VIII**, and the deshielding amounts to ~0.11–0.21 ppm.

Structure of compounds **IX–XII** was confirmed by IR and ^{1}H NMR spectroscopy. In the IR spectra absorption bands at 1670–1690 (carbonyl group) and 1630–1650 cm^{-1} (vinyl group) were registered. There are also vibrations at 1530–1560 cm^{-1} characteristic of the pyrazole ring.

By the ^{1}H NMR spectral data, chemical shifts values for ring protons of vinylpyrazoles **IX–XII** are registered downfield (7.75–8.39), and those of the signals belonging to the methyl groups at the heteroring methyl protons appear in a stronger field (2.18–2.50). In the ^{1}H NMR spectrum signals of vinyl protons appear as spin system of ABX type (CH_AH_B=CH_X) with chemical shifts 4.82–4.94 (H_A), 5.61–5.75 (H_B) and 7.00–7.18 ppm (H_X), and constants J_{AX} 15.2–15.8; J_{BX} 8.8–8.9; J_{AB} 1.6 Hz.

EXPERIMENTAL

The IR spectra were taken on a Specord 75-UR instrument (thin layer). The ^{1}H NMR spectra were registered on a Varian Mercury instrument (300 MHz) in DMSO-d_6.

Starting 1-(2-chloroethyl)-4-formylpyrazoles **I–IV** were synthesized by the known procedure. 1-(2-Chloroethyl)-4-formylpyrazol **I,** bp 125–130°C (2 mm Hg); 1-(2-chloroethyl)-3-methyl-4-formylpyrazole **II**, bp 130–132°C (1 mm Hg); 1-(2-chloroethyl)-5-methyl-4-formylpyrazole **III**, mp 42°C; 1-(2-chloroethyl)-3,5-dimethyl-4-formylpyrazole **IV**, mp 50°C [6].

1-(2-Chloroethyl)-4-pyrazolecarboxylic acid (V). To a mixture of 15.85 g of compound **I**, 50 ml of water, 50 ml of benzene, and 1 g of TEBAC was added by portions 15.9 g of potassium permanganate under stirring and at 30°C so that the reaction mixture temperature would not exceed 35°C. After completing potassium permanganate addition, the reaction mixture was stirred for 12 h at room temperature, then cooled and filtered. The precipitate was washed with hot water. When 2/3 of water was distilled off, the solution was neutralized with hydrochloric acid. The formed white crystals were filtered off and dried. Yield 12.15 g (70%), mp 128–131°C. IR spectrum, ν, cm^{-1}: 1550 (ring), 1680 (COOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.93 t (2H, CH_2–Cl, J 6.0 Hz), 4.46 t (2H, N–CH_2, J 6.0 Hz), 7.73 s (1H, 3-H), 8.14 s (1H, 5-H), 11.86 br (1H, COOH). Found, %: C 41.44; H 4.38; N 16.28; Cl 20.56. $C_6H_7N_2O_2Cl$. Calculated, %: C 41.26; H 4.01; N 16.05; Cl 20.34.

1-(2-Chloroethyl)-3-methyl-4-pyrazolecarboxylic acid (VI) was prepared similarly from 17.25 g of **II**, 50 ml of water, 50 ml of benzene, 1 g of TEBAC and 15.9 g of potassium permanganate. Yield 14.14 g (75%), mp 131–133°C. IR spectrum, ν, cm^{-1}: 1520 (ring), 1670 (COOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.35 s (3H, CH_3), 3.90 t (2H, CH_2–Cl, J 6.0 Hz), 4.35 t (2H, N–CH_2, J 6.0 Hz), 8.01 s (1H, 5-H), 11.77 br (1H, COOH). Found, %: C 44.32; H 4.85; N 14.69; Cl 18.43. $C_7H_9N_2O_2Cl$. Calculated, %: C 44.56; H 4.78; N 14.85; Cl 18.83.

1-(2-Chloroethyl)-5-methyl-4-pyrazolecarboxylic acid (VII) was prepared similarly from 17.25 g of **III**, 50 ml of water, 50 ml of benzene, 1 g of TEBAC and 15.9 g of potassium permanganate. Yield 13.57 g (72%), mp 148–150°C. IR spectrum, ν, cm^{-1}: 1530 (ring), 1690 (COOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.56 s (3H, 5-CH_3), 3.93 t (2H, CH_2–Cl, J 6.0 Hz), 4.36 t (2H, N–CH_2, J 6.0 Hz), 7.69 s (1H, 3H), 11.88 br (1H, COOH). Found, %: C 44.82; H 4.98; N 14.58; Cl 18.54. $C_7H_9N_2O_2Cl$. Calculated, %: C 44.56; H 4.78; N 14.85; Cl 18.83.

1-(2-Chloroethyl)-3,5-dimethyl-4-pyrazolecarboxylic acid (VIII) was prepared similarly from 18.65 g of **IV**, 50 ml of water, 50 ml of benzene, 1 g of

TEBAC and 15.9 g of potassium permanganate. Yield 13.77 g (68%), mp 139–141°C. IR spectrum, ν, cm^{-1}: 1520 (ring), 1690–1700 (COOH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.31 s (1H, 3-CH_3), 2.50 s (1H, 5-CH_3), 3.95 t (2H, CH_2–Cl, *J* 6.7 Hz), 4.25 t (2H, N–CH_2, *J* 6.7 Hz), 11.25 br (1H, COOH). Found, %: C 47.81; H 5.00; N 13.68; Cl 17.28. $C_8H_{11}N_2O_2Cl$. Calculated, %: C 47.41; H 5.43; N 13.83; Cl 17.53.

1-Vinyl-4-pyrazolecarboxylic acid (IX). A mixture of 17.45 g of compound **V**, 18 g of KOH, 100 ml of water, and 0.01 g of hydroquinone was refluxed for 2 h at about 100°C. After cooling the solution was neutralized with hydrochloric acid. The formed crystals were filtered off and dried. Yield 12.42 g (90%), mp 207–209°C (isopropanol:water = 8:2). IR spectrum, ν, cm^{-1}: 1550 (ring), 1650 (C=C), 1670 (COOH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 4.93 d (1H, =CH_2, *J* 8.8 Hz), 5.72 d (1H, =CH_2, *J* 15.8 Hz), 7.18 d. d (1H, =CH, *J* 15.8 and 8.8 Hz), 7.80 s (1H, 3-H), 8.39 s (1H, 5-H), 11.5 br (1H, COOH). Found, %: C 52.38; H 4.58; N 20.49. $C_6H_6N_2O_2$. Calculated, %: C 52.17; H 4.35; N 20.29.

1-Vinyl-3-methyl-4-pyrazolecarboxylic acid (X) was prepared similarly from 18.8 g of **VI**, 18.0 g of KOH, 100 ml of water and 0.01 g of hydroquinone for 3.0 h. Yield 10.64 g (70%), mp 168–170°C (isopropanol:water = 8:2). IR spectrum, ν, cm^{-1}: 1530 (ring), 1630 (HC=CH_2), 1690 (COOH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.39 s (3H, 3-CH_3), 4.82 d (1H, =CH_2, *J* 8.9 Hz), 5.61 d (1H, =CH_2, *J* 15.6 Hz), 7.03 d. d (1H, =CH, *J* 15.6 and 8.9 Hz), 8.20 s (1H, 5-H), 11.91 br (1H, COOH). Found, %: C 55.48; H 5.48; N 18.72. $C_7H_8N_2O_2$. Calculated, %: C 55.26; H 5.26; N 18.42.

1-Vinyl-5-methyl-4-pyrazolecarboxylic acid (XI) was prepared similarly from 18.8 g of **VII**, 18.0 g of KOH, 100 ml of water and 0.01 g of hydroquinone for 3.0 h. Yield 9.93 g (75%), mp 158–160°C (isopropanol:water = 8:2). IR spectrum, ν, cm^{-1}: 1560 (ring), 1650 (HC=CH_2), 1690 (COOH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.59 s (3H, 5-CH_3), 4.94 d (1H, =CH_2, *J* 8.8 Hz), 5.75 d (1H, =CH_2, *J* 15.2 Hz), 7.10 d. d (1H, =CH, *J* 15.2 and 8.8 Hz), 7.75 s (1H, 3-H), 11.97 br (1H, COOH). Found, %: C 55.49; H 5.00; N 18.69. $C_7H_8N_2O_2$. Calculated, %: C 55.26; H 5.26; N 18.42.

1-Vinyl-3,5-dimethyl-4-pyrazolecarboxylic acid (XII) was prepared similarly from 20.2 g of **VIII**, 18.0 g of KOH, 100 ml of water and 0.01 g of hydroquinone for 3.0 h. Yield 13.5 g (66%), mp 161–163°C (isopropanol:water = 8:2). IR spectrum, ν, cm^{-1}: 1550 (ring), 1640 (HC=CH_2), 1680 (COOH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.38 s (3H, 3-CH_3), 2.48 s (3H, 5-CH_3), 4.82 d (1H, =CH_2, *J* 15.6 Hz), 5.68 d (1H, =CH_2, *J* 8.8 Hz), 7.00 d. d (1H, =CH, *J* 15.6 and 8.8 Hz), 11.92 br (1H, COOH). Found, %: C 58.11; H 6.38; N 16.48. $C_8H_{10}N_2O_2$. Calculated, %: 57.83; H 6.02; N 16.87.

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