ISSN 1070-3632, Russian Journal of General Chemistry, 2007, Vol. 77, No. 2, pp. 297–300. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © O.S. Attaryan, A.O. Baltayan, S.G. Matsoyan, 2007, published in Zhurnal Obshchei Khimii, 2007, Vol. 77, No. 2, pp. 325–328.

Synthesis of α-Methyl-β-(3-methylpyrazol-1-yl)- and α-Methyl-β-(5-Methylpyrazol-1-yl)propionic Acids and Their Esterification with Vinyl Acetate

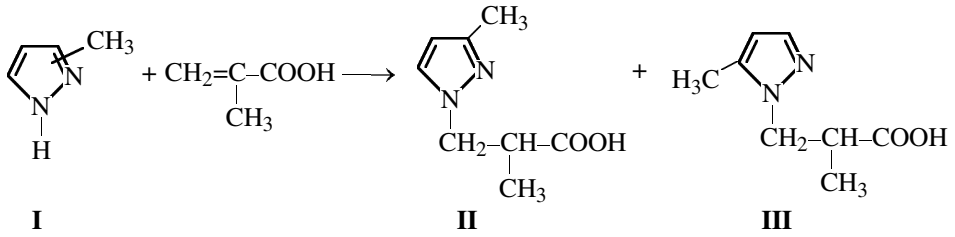
O. S. Attaryan, A. O. Baltayan, and S. G. Matsoyan

Institute of Organic Chemistry, National Academy of Science of Armenia,
ul. Zakariya Sarkavaga 167a, Erevan, 375091 Armeniya
e-mail: angelabaltayan@mail.ru

Received August 3, 2006

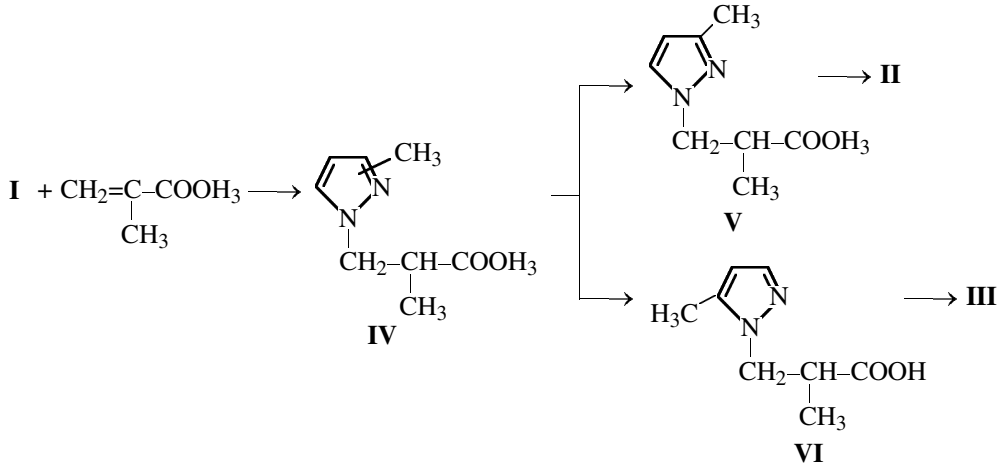
Abstract — α-Methyl-β-(3-methylpyrazol-1-yl)- and α-methyl-β-(5-methylpyrazol-1-yl)propionic acids were synthesized by reaction of 3(5)-methylpyrazole with methyl methacrylate, followed by separation of the resulting isomeric esters and their hydrolysis. Esterification of the title acids was performed via vinyl exchange reaction with vinyl acetate in the catalytic system mercury acetate–trifluoroacetic acid.
DOI: 10.1134/S107036320702017X

It is known that 3(5)-methylpyrazole (**I**) readily adds to acrylic acid at 80–90°C with formation of 1-carboxyethyl-3(5)-methylpyrazole [1]. We have found that 3(5)-methylpyrazole reacts with methacrylic acid in a similar way to give a mixture of isomeric acids **II** and **III** which are difficult to separate.



I **II** **III**

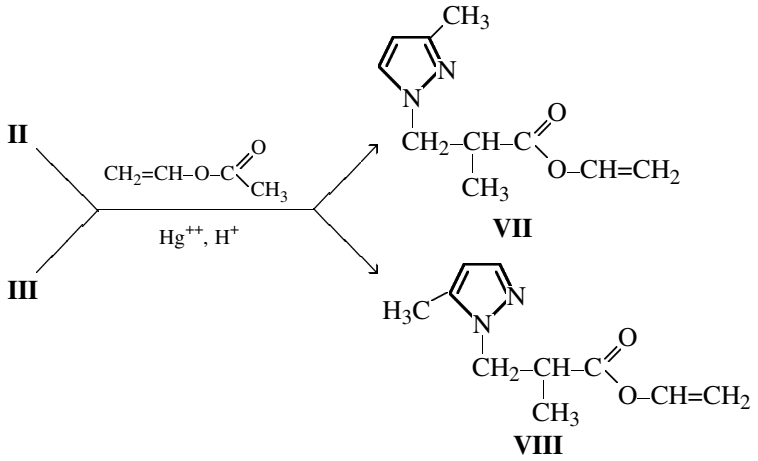
With a view to obtain individual isomers **II** and **III**, i.e., α-methyl-β-(3-methylpyrazol-1-yl)- and α-methyl-β-(5-methylpyrazol-1-yl)propionic acids, we propose the following scheme which includes separation of intermediate esters **V** and **VI**.



IV **V** **VI**

According to published data [2], methyl methacrylate reacts with 3,5-dimethylpyrazole at 200°C under pressure. We succeeded in obtaining addition product **IV** by heating the reactants in an open vessel for 20 h at 160–170°C. The yield of methyl α-methyl-β-[3(5)-methylpyrazol-1-yl]propionate (**IV**) was 80%. Hydrolysis of esters **V** and **VI** in the presence of sodium hydroxide gave the corresponding sodium salts, and acidification of the latter afforded target acids **II** and **III**.

The IR spectra of carboxypropylpyrazoles **II** and **III** contained a strong absorption band at 1730 cm^{-1} due to stretching vibrations of the acid carbonyl group; absorption bands at 1510–1520 and 3300–3500 cm^{-1} were assigned to vibrations of the pyrazole ring and hydroxy group, respectively. According to the ^1H NMR data, the ring proton in isomer **III** resonates in a stronger field, at δ 7.19 ppm (d, 1H, 3-H), and the methyl proton signal is located in a weaker field, at δ 2.29 ppm (s, 3H, 5-CH_3), as compared to the corresponding signals of isomer **II**. The positions of the 4-H signals in the ^1H NMR spectra of isomeric acids **II** and **III** are almost similar (δ 5.86– 5.87 ppm).



We also examined vinylation of acids **II** and **III** with vinyl acetate in the presence of mercury(II) acetate and various acids with a view to obtain new vinyl monomers of the pyrazole series (vinyl esters **VII** and **VIII**). The use of mercury(II) acetate alone [3] was unsuccessful; in this case, the yield of the target products was very poor. We succeeded in raising the yield to 25% using the system $Hg(OAc)_2$–H_2SO_4 [4]. The catalytic system mercury(II) acetate–$BF_3 \cdot Et_2O$ [5] was also ineffective. Only the system mercury(II) acetate–trifluoroacetic acid [6] enabled us to synthesize vinyl pyrazolylpropionates **VII** and **VIII** in 45–50% yield.

Vinyl esters **VII** and **VIII** characteristically showed in the IR spectra an absorption band at 1620–1630 cm^{-1}, which corresponds to stretching vibrations of the vinyl group. In the ^1H NMR spectra of these compounds, protons in the vinyl group gave rise to an *ABX* pattern (CH_AH_B=CH_X) with the following chemical shifts, δ, ppm: **VII**: 4.85 (H_A), 4.86 (H_B), 7.21 (H_X); **VIII**: 4.57 (H_A), 4.85 (H_B), 7.19 (H_X); J_{AX} 14.0, J_{BX} 6.3, J_{AB} 1.6 Hz.

The double bond in isomer **VII** (3-CH_3) is less polarized than that in isomer **VIII** (5-CH_3) [7]. Nevertheless, this difference did not affect their radical homopolymerization: unlike isomeric *N*-vinylpyrazoles [8, 9], vinyl esters **VII** and **VIII** exhibited almost similar reactivities in the polymerization process. It should also be noted that, in contrast to *N*-vinylazoles [10], compounds **VII** and **VIII** readily undergo copolymerization with vinyl acetate.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument from samples prepared as thin films or KBr pellets. The ^1H NMR spectra were measured on a Varian Mercury-300 spectrometer (300 MHz) from solutions in DMSO-d_6. GLC analysis was performed on an LKhM-8MD chromatograph equipped with a 1-m column packed with 10% of Carbowax-20M on Inerton AW-HMDS; carrier gas helium, flow rate 40 ml min^{-1}; detector temperature 220°C.

2-Methyl-3-[3(5)-methylpyrazol-1-yl]propionic acid (II/III) (mixture of isomers). A mixture of 8.2 g

of 3(5)-methylpyrazole (**I**), 10 ml of methacrylic acid, and 0.1 g of hydroquinone was heated for 8 h at 90–100°C under reflux. Excess methacrylic acid was removed, and the residue was distilled under reduced pressure. Yield 12.5 g (75%), bp 155°C (1 mm Hg), white crystals, mp 73°C (from water). IR spectrum, ν, cm^{-1}: 1510 (ring), 1700 (CO), 3300–3500 (OH). Isomer ratio 3 : 2.

Methyl 2-methyl-3-[3(5)-methylpyrazol-1-yl]-propionate (IV) (mixture of isomers). Methyl methacrylate, 6.5 ml, was added dropwise to 4.1 g of 3(5)-methylpyrazole (**I**) heated to 160–170°C. The mixture was heated for 20 h at the boiling point, excess methyl methacrylate was distilled off, and the residue was distilled under reduced pressure. Yield 7.3 g (80%), bp 81–86°C (1 mm Hg), n_D^{20} 1.4778, d_4^{20} 1.0633. IR spectrum, ν, cm^{-1}: 1520 (ring), 1720 (CO).

Isomeric esters **V** and **VI** were separated by fractional distillation through a 30 × 4-cm column packed with a metal filling. The upper part of the column was heated at 110–120°C; still temperature 180°C; reflux number *R* 10; pressure 5 mm. Fractionation of 100 g of isomer mixture **IV** (isomer ratio 3 : 2) gave 40 g of **V** and 20 g of **VI**.

Methyl 2-methyl-3-(3-methylpyrazol-1-yl)propionate (V). bp 85°C (1 mm Hg), n_D^{20} 1.4778, d_4^{20} 1.0640. IR spectrum, ν, cm^{-1}: 1510 (ring), 1720 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 d (3H, CHCH_3, *J* 7.1), 2.18 s (3H, 3-CH_3), 3.00 sextet (1H, CHCH_3, *J* 7.1), 3.64 s (3H, OCH_3), 4.02 d.d (1H, CH_2, *J* 13.6, 6.9), 4.26 d.d (1H, CH_2, *J* 13.6, 7.1), 5.87 d (1H, 4-H, *J* 2.2), 7.29 d (1H, 5-H, *J* 2.2). Found, %: C 59.57; H 7.83; N 15.21. $C_9H_{14}N_2O_2$. Calculated, %: C 59.34; H 7.69; N 15.39.

Methyl 2-methyl-3-(5-methylpyrazol-1-yl)propionate (VI). bp 99–100°C (1 mm Hg), n_D^{20} 1.4713, d_4^{20} 1.0567. IR spectrum, ν, cm^{-1}: 1530 (ring), 1720 (CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 d (3H, CHCH_3, *J* 7.1), 2.28 s (3H, 5-CH_3), 3.08 sextet (1H, CHCH_3, *J* 7.1), 3.62 s (3H, OCH_3), 3.96 d.d (1H, CH_2, *J* 13.7, 6.9), 4.24 d.d (1H, CH_2, *J* 13.7, 7.4), 5.87 br.d (1H, 4-H), 7.19 d (1H, 3-H, *J* 1.9). Found, %: C 59.59; H 7.78; N 15.18. $C_9H_{14}N_2O_2$. Calculated, %: C 59.34; H 7.69; N 15.39.

2-Methyl-3-(3-methylpyrazol-1-yl)propionic acid (II). A mixture of 18.2 g of methyl 2-methyl-3-(3-methylpyrazol-1-yl)propionate (**V**), 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 neautralized with hydrochloric acid, and the precipitate was filtered off. Yield 13.8 g (82%), white crystals, mp 103–104°C (from water). IR spectrum, ν, cm^{-1}: 1510 (ring), 1710 (CO), 3300–3500 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 d (3H, CHCH_3, *J* 7.1), 2.17 s (3H, 3-CH_3), 2.89 sextet (1H, CHCH_3, *J* 7.1), 3.95 d d (1H, CH_2, *J* 13.5, 7.1), 4.27 d.d (1H, CH_2, *J* 13.5, 6.7), 5.86 d (1H, 4-H, *J* 2.2), 7.30 d (1H, 5-H, *J* 2.2), 12.01 br.s (1H, COOH). Found, %: C 57.48; H 7.34; N 16.31. $C_8H_{12}N_2O_2$. Calculated, %: C 57.14; H 7.14; N 16.67.

2-Methyl-3-(5-methylpyrazol-1-yl)propionic acid (III) was synthesized in a similar way from ester **VI**. Yield 12.6 g (75%), white crystals, mp 101–102°C (from water). IR spectrum, ν, cm^{-1}: 1520 (ring), 1720 (CO), 3300–3500 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 d (3H, CHCH_3, *J* 7.1), 2.29 s (3H, 5-CH_3), 2.98 sextet (1H, CHCH_3, *J* 7.1), 3.90 d.d (1H, CH_2, *J* 13.6, 7.4), 4.25 d.d (1H, CH_2, *J* 13.6, 6.9), 5.87 br.d (1H, 4-H, *J* 1.8), 7.19 d (1H, 3-H, *J* 1.8), 11.95 br.s (1H, COOH). Found, %: C 57.37; H 7.42; N 16.21. $C_8H_{12}N_2O_2$. Calculated, %: C 57.14; H 7.14; N 16.67.

General procedure for vinylation of 2-methyl-3-(3-methylpyrazol-1-yl)- and 2-methyl-3-(5-methylpyrazol-1-yl)propionic acids II and III. A mixture of 0.1 mol of acid **II** or **III**, 50 ml of vinyl acetate, 4.0 g of mercury(II) acetate, 2 ml of trifluoroacetic acid, and 0.1 g of hydroquinone was heated for 20 h at 70– 80°C. Sodium acetate, 8.0 g, was then added to decompose mercury catalyst. After 2 h, the precipitate was filtered off, and the filtrate was neautralized with a 2 N solution of sodium carbonate and extracted with diethyl ether. The extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure.

Vinyl 2-methyl-3-(3-methylpyrazol-1-yl)propionate (VII). Yield 47%, bp 88–89°C (1 mm Hg), n_D^{20} 1.4790, d_4^{20} 1.0545. IR spectrum, ν, cm^{-1}: 1510 (ring), 1730 (CO), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 d (3H, CHCH_3, *J* 7.2), 2.17 s (3H, 3-CH_3), 3.10 sextet (1H, CHCH_3, *J* 7.0), 4.08 d.d (1H, NCH_2, J_1 13.6, J_2 6.8), 4.30 d.d (1H, NCH_2, J_1 = 13.6, J_2 6.9), 4.58 d.d (1H, C$H_A H_B$, J_1 6.3, J_2 1.6), 4.86 d.d (1H, CH_AH$_B$, J_1 14.0, J_2 1.6), 5.87 d (1H, 4-H, *J* 2.2), 7.21 d.d (1H, CH=CH_2, J_1 14.0, J_2 6.3), 7.32 d (1H, 5-H, *J* 2.2). Found, %: C 61.38; H 7.60; N 14.11. $C_{10}H_{14}\cdot N_2O_2$. Calculated, %: C 61.86; H 7.22; N 14.43.

Vinyl 2-methyl-3-(5-methylpyrazol-1-yl)propionate (VIII). Yield 40%, bp 102–105°C (1 mm Hg), n_D^{20} 1.4846, d_4^{20} 1.0548. IR spectrum, ν, cm^{-1}: 1530 (ring), 1750 (CO), 1630 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 d (3H, CHCH_3, *J* 7.1),

2.28 s (3H, 5-CH_3), 3.19 sextet (1H, C*H*CH_3, *J* 7.1), 4.03 d.d (1H, NCH_2, J_1 13.8, J_2 6.7), 4.28 d.d (1H, NCH_2, J_1 13.8, J_2 7.4), 4.57 d.d (1H, CH_AH_B, J_1 6.3, J_2 1.6), 4.85 d.d (1H, CH_AH_B, J_1 14.0, J_2 1.6), 5.88 d (1H, 4-H, *J* 1.8), 7.19 d.d (1H, C*H*=CH2, J_1 14.0, J_2 6.3), 7.20 d (1H, 3-H, *J* 1.8). Found, %: C 61.35; H 7.81; N 14.85. $C_{10}H_{14}\cdot N_2O_2$. Calculated, %: C 61.86; H 7.22; N 14.43.

REFERENCES

1. Darbinyan, E.G., Matsoyan, M.S., Oganesyan, K.G., Mitardzhyan, Yu.B., Saakyan, A.A., and Matsoyan, S.G., USSR Inventor's Certificate no. 688 499, 1978; *Byull. Izobret.,* 1979, no. 36.
2. Grandberg, I.I. and Kost, A.N., *Zh. Obshch. Khim.,* 1959, vol. 29, no. 4, p. 1099.
3. Attaryan, O.S., Eliazyan, G.A., Asratyan, G.V., and Darbinyan, E.G., *Arm. Khim. Zh.,* 1983, vol. 36, no. 6, p. 415.
4. Grandberg, I.I. and Sharova, G.I., *Khim. Geterotsikl. Soedin.,* 1968, no. 6, p. 1097.
5. Vereshchagin, L.I., Buzilova, S.R., Mityukova, T.K., Proidakov, A.G., Kizhnyaev, V.N., Il'ina, V.V., Sukhanov, G.T., Gareev, G.A., and Bagers, A.K., *Zh. Org. Khim.,* 1986, vol. 22, no. 9, p. 1979.
6. Kizhnyaev, V.N., Pokatilov, F.A., Tsypina, N.A., Ratovskii, G.V., Vereshchagin, L.I., and Smirnov, A.M., *Russ. J. Org. Chem.,* 2002, vol. 38, no. 7, p. 1056.
7. Trofimov, B.A., Sigalov, M.V., Bzhezovskii, V.M., Kalabin, G.A., Mikhaleva, A.I., and Vasil'ev, A.N., *Khim. Geterotsikl. Soedin.,* 1978, no. 3, p. 350.
8. Gzyryan, A.G., Egoyan, R.V., Attaryan, O.S., Danielyan, V.A., and Darbinyan, E.G., *Arm. Khim. Zh.,* 1986, vol. 39, no. 6, p. 369.
9. Attaryan, O.S., Gavalyan, V.B., Eliazyan, G.A., Asratyan, G.V., and Darbinyan, E.G., *Arm. Khim. Zh.,* 1988, vol. 41, no. 8, p. 496.
10. Attaryan, O.S., Eliazyan, G.A., Ovakimyan, E.V., Asratyan, G.V., Darbinyan, E.G., and Matsoyan, S.G., *Khim. Zh. Arm.,* 1996, vol. 49, nos. 1–3, p. 167.