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LETTERS TO THE EDITOR

Aza-Michael Addition of Pyrazoles to Crotonic Acid

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Abstract—Aza-Michael addition of pyrazoles to crotonic acid afforded a series of 3-(1*H*-pyrazol-1-yl)butanoic acids.

Keywords: aza-Michael reaction, pyrazoles, crotonic acid, autocatalysis

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Pyrazoles easily add to acrylic [1] and methacrylic [2] acids, despite the fact that the presence of a methyl group at the double bond of α,β-unsaturated carbonyl compounds complicates significantly this reaction [3]. Similar reactions involving acrylic and methacrylic acids esters occur faster in the case of acrylates [2, 4, 5]. The addition of pyrazoles to acrolein and crotonaldehyde proceeds much easier [6, 7].

Here we report on aza-Michael addition of pyrazoles **1**–**3** to crotonic acid (Scheme 1). The reactions occurred at 85–90°C in 3 h to form pyrazolebutanoic acids **4**–**6**.

3(5)-Methylpyrazole **2** reacted with crotonic acid to give a mixture of two isomers **5a** and **5b** (9 : 1) in a yield of 73%. Isomer **5a** was isolated by fractional crystallization from water.

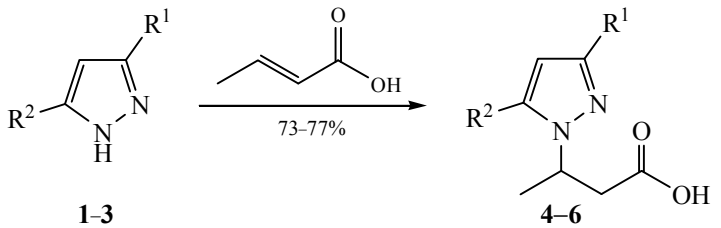
It is presumable on literature grounds [8] that in the case of the pyrazoles addition to the acids the autocatalysis process takes place. This assumption was partly confirmed by the reaction of pyrazoles with crotonic acid esters. In particular, the aza-Michael addition of pyrazole **3** to crotonic acid ethyl ester proceeded much more slowly, forming the corresponding adduct **7** in a yield of ~11% (Scheme 2).

Chromato-mass spectral study of the aza-Michael reaction of crotonic acid with pyrazole **1** in the presence of 3-(1*H*-pyrazol-1-yl)butanoic acid **2** (5 mol % with respect to the starting pyrazole) showed that in the first half hour the catalyzed reaction is 2 times faster than in the absence of a catalyst. Later the rates of both reactions get equal, which indicates the autocatalysis phenomenon.

Structure and composition of the compounds obtained were confirmed by IR and NMR spectra and elemental analysis data.

3-(1*H*-Pyrazol-1-yl)butanoic acid (4). A mixture of 3.4 g (0.05 mol) of pyrazole **4** and 4.7 g (0.055 mol) of crotonic acid was heated for 3 h on a water bath at a

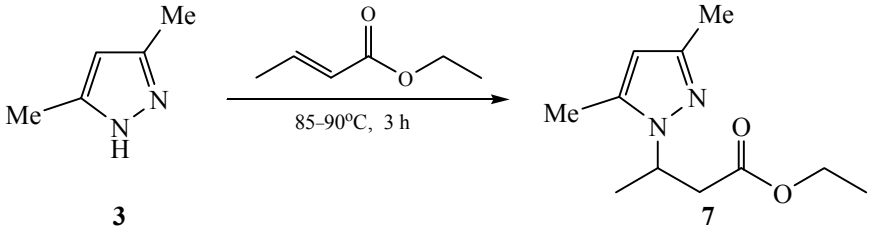
Scheme 1.



1–**3** **4**–**6**

$R^1 = R^2 = H$ (**1**, **4**); R^1 = Me (H), R^2 = H (Me) (**2**, **5**); $R^1 = R^2$ = Me (**3**, **6**).

Scheme 2.



3 **7**

temperature of 85–90°C. After cooling, the reaction mixture was distilled at a reduced pressure. Yield 5.7 g (74%), bp 156–157°C (1 mmHg), mp 59–60°C. IR spectrum, ν, cm^{-1}: 1530 (ring), 1690 (C=O), 3200–3400 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.50 d (3H, C$\underline{CH_3}$, J = 6.8 Hz), 2.64 d.d (1H, CH$\underline{CH_2}$, J = 16.1, 6.7 Hz), 2.84 d.d (1H, CH$\underline{CH_2}$, J = 16.1, 7.2 Hz), 4.66–4.78 m (1H, $\underline{CH}CH_3$), 6.11 d.d (1H, CH^4, J = 2.3, 1.7 Hz), 7.33 d.d (1H, CH^3, J = 1.7, 0.7 Hz), 7.51 d.d (1H, CH^5, J = 2.3, 0.7 Hz), 11.44 br.s (1H, COOH). Found, %: C 54.76; H 6.22; N 18.31. $C_7H_{10}N_2O_2$. Calculated, %: C 54.54; H 6.54; N 18.17.

3-[3(5)-Methyl-1*H*-pyrazol-1-yl]butanoic acid (5a, 5b) was prepared similarly. After cooling the reaction product was crystallized from water. Yield of compound **5a** 5.2 g (62%), mp 115°C. IR spectrum, ν, cm^{-1}: 1540 (ring), 1700 (C=O), 3200–3400 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.47 d (3H, CH$\underline{CH_3}$, J = 6.8 Hz), 2.18 s (3H, CH_3), 2.60 d.d (1H, CH$\underline{CH_2}$, J = 16.1, 6.8 Hz), 2.80 d.d (1H, CH$\underline{CH_2}$, J = 16.1, 6.8 Hz), 4.60 sextet (1H, $\underline{CH}CH_2$, J = 6.8 Hz), 5.85 d (1H, CH^4, J = 2.2 Hz), 7.36 d (1H, CH^5, J = 2.2 Гц), 11.92 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 13.2 (CH_3), 20.6 (CH_3), 40.9 (CH_2), 53.2 (CH), 103.5 (CH^4), 128.1 (CH^5), 146.5 (C^3), 171.3 (COOH). Found, %: C 57.41; H 6.85; N 16.81. $C_8H_{12}N_2O_2$. Calculated, %: C 57.13; H 7.19; N 16.66.

After evaporation of the filtrate, 2 g (11%) of a mixture of isomers **5a** and **5b** (1 : 1, NMR) melting at 70–80°C was isolated.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)butanoic acid (6) was prepared similarly. Yield 7.0 g (76.9%), mp 150–151°C. IR spectrum, ν, cm^{-1}: 1540 (ring), 1700 (C=O), 3200–3400 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.37 d (3H, CH$\underline{CH_3}$, J = 6.7 Hz), 2.11 s (3H, CH_3), 2.24 d (3H, CH_3, J = 0.7 Hz), 2.60 d.d (1H, CH$\underline{CH_2}$, J = 16.3, 5.7 Hz), 2.86 d.d (1H, CH$\underline{CH_2}$, J = 16.3, 8.0 Hz), 4.49–4.60 m (1H, $\underline{CH}CH_3$), 5.61 br.s (1H, CH^4), 11.92 br.s (1H, COOH). Found, %: C 59.61; H 7.44; N 15.53. $C_9H_{14}N_2O_2$. Calculated, %: 59.32; H 7.74; N 15.37.

Ethyl 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)butanoate (7). A mixture of 4.8 g (0.05 mol) of 3,5-dimethylpyrazole **3** and 6.3 g (0.055 mol) of crotonic acid ethyl ester was heated for 3 h on a water bath at a temperature of 85–90°C. After cooling, the crystals of unreacted 3,5-dimethylpyrazole were filtered off. The filtrate was distilled in a vacuum. Yield 1.1 g (10.47%), bp 101–102°C (1 mmHg), n_D^{20} 1.4670. IR spectrum, ν, cm^{-1}: 1540 (ring), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, $\underline{CH_3}CH_2$, J = 7.1 Hz), 1.38 d (3H, $\underline{CH_3}CH$, J = 6.7 Hz), 2.11 s (3H, CH_3), 2.23 s (3H, CH_3), 2.68 d.d (1H, CH$\underline{CH_2}$, J = 16.2, 5.6 Hz), 2.96 d.d (1H, CH$\underline{CH_2}$, J = 16.2, 8.5 Hz), 4.02 d.q (2H, $\underline{CH_2}O$, J = 7.1, 1.1 Hz), 4.60–4.63 m (1H, NCH), 5.61 s (1H, H^4). Found, %: C 63.75; H 9.21; N 12.25. $C_{12}H_{21}N_2O_2$. Calculated, %: C 63.97; H 9.39; N 12.43.

IR spectra were recorded on a Thermo Nicolet Nexus spectrometer from mulls in mineral oil. The ^{1}H and ^{13}C NMR spectra of the solutions in DMSO-d_6–CCl_4 (1 : 3) were registered on a Varian Mercury spectrometer (300 and 75 MHz, respectively) at 300 K, internal reference TMS. Elemental analysis was performed on a Eurovector EA 3000 instrument. Chromato-mass spectral analysis was performed on a GC MS Bruker EM 640S instrument. Melting points were determined on a Boetius instrument.

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