

LETTERS TO THE EDITOR

Aza-Michael Addition of Pyrazoles to Maleic Acid

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We have previously investigated the reactivity of pyrazoles **I–III** in addition reactions to the carbon–carbon double bond conjugated with electron-withdrawing groups [1, 2]. In order to verify the possibility of attaching azoles to conjugated systems under mild conditions, we performed reactions of pyrazoles **I–III** with maleic acid; in the latter molecule the double bond is not polarized due to a mismatched action of two electron-withdrawing groups [3].

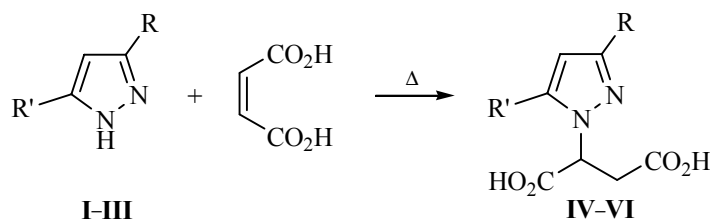
The experiments showed that pyrazoles **I–III** react with maleic acid similarly to the cases of acrylic acid [4] and methyl vinyl ketone [1]: when heated in bulk in the absence of any catalyst, they yielded the corresponding (pyrazol-1-yl)succinic acids **IV–VI** (Scheme 1).

Yields of aza-Michael adducts **IV–VI** depended strongly on the azoles basicity. When maleic acid reacted with 3,5-dimethylpyrazole **III** ($pK_b = 4.38$), yield of compound **VI** was of 96%, whereas in the case

of less basic pyrazole **I** ($pK_b = 2.53$) the reaction proceeded with yield of 65%. In the case of 3(5)-methylpyrazole **II** ($pK_b = 3.55$), the desired product was obtained in yield of 80% as a mixture of two isomers **Va** and **Vb** in the ratio of 9 : 1. Isomer **5a** was isolated via fractional crystallization from water.

2-(1H-Pyrazol-1-yl)butanedioic acid (IV). A mixture of 1.5 g (0.022 mol) of pyrazole **I** and 3.0 g (0.024 mol) of maleic acid was heated to 110°C. The reaction temperature spontaneously went up to 130°C. Heating was continued at 110°C for 2.5 h. The resulting mixture was recrystallized from water. Yield 2.6 g (65%), mp 170°C. IR spectrum, ν , cm^{-1} : 1520 (ring), 1570 (COOH). ^1H NMR spectrum, δ , ppm (J , Hz): 2.99 d.d (1H, CH_2 , J 17.0, 7.6), 3.14 d.d (1H, CH_2 , J 17.0, 6.2), 5.27 d.d (1H, CH , J 7.6, 6.2), 6.18 d.d (1H, $=\text{CH}$, J 2.3, 1.8), 7.37 d.d (1H, $=\text{CH}$, J 1.8, 0.8), 7.65 d.d (1H, $=\text{CH}$, J 2.3, 0.8), 12.20 br.s (2H, COOH). Found, %: C 45.85; H 4.75; N 15.56. $\text{C}_7\text{H}_8\text{N}_2\text{O}_4$. Calculated, %: C 45.66; H 4.38; N 15.21.

Scheme 1.



$\text{R}^1 = \text{R}^2 = \text{H}$ (**I**, **IV**); $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$ (**IIa**, **Va**); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$ (**IIb**, **Vb**); $\text{R}^1 = \text{R}^2 = \text{CH}_3$ (**III**, **VI**).

2-[3(5)-Methyl-1H-pyrazol-1-yl]butanedioic acid (Va, Vb) was obtained similarly from 8.2 g (0.1 mol) of 3(5)-methylpyrazole **II** and 7.7 g (0.11 mol) of maleic acid. Yield 15.8 g (80%), mp 200°C. IR spectrum, ν , cm^{-1} : 1530 (ring), 1680 (COOH). ^1H NMR spectrum, δ , ppm (J , Hz): 2.19 s (3H, CH_3), 2.20 s (3H, CH_3), 2.93 m (1H, CH_2), 3.11 m (1H, CH_2), 5.14 m (2H, NCH_2), 5.94 d (1H, $=\text{CH}$, J 2.2), 7.21 d (1H, $=\text{CH}$, J 2.4), 7.49 d (1H, $=\text{CH}$, J 2.2), 12.20 br.s (2H, COOH). Found, %: C 48.80; H 5.49; N 14.38. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_4$. Calculated, %: C 48.49; H 5.09; N 14.14.

After fractional recrystallization of a mixture of isomers **Va** and **Vb** from water, isomer **Va** (50%) was isolated, mp. 215–218°C. ^1H NMR spectrum, δ , ppm (J , Hz): 2.19 s (3H, CH_3), 2.93 d.d (1H, CH_2 , J 16.9, 7.2), 3.11 d.d (1H, CH_2 , J 16.9, 6.7), 5.14 d.d (1H, CH , J 7.2, 6.7), 5.93 d (1H, $=\text{CH}$, J 2.2), 7.48 d (1H, $=\text{CH}$, J 2.2), 12.4 br.s (2H, COOH).

2-(3,5-Dimethyl-1H-pyrazol-1-yl)butanedioic acid (VI) was obtained similarly from 9.6 g (0.1 mol) of 3,5-dimethylpyrazole **III** and 7.7 g (0.11 mol) of maleic acid. Yield 20.4 g (96%), mp 220°C [5]. IR spectrum, ν , cm^{-1} : 1540 (ring), 1690 (COOH). ^1H NMR spectrum, δ , ppm (J , Hz): 2.12 s (3H, CH_3), 2.28 s (3H, CH_3), 3.00 d.d (1H, CH_2 , J 17.1, 8.0), 3.15 d.d (1H, CH_2 , J 17.1, 5.8), 5.03 d.d (1H, CH , J 8.0, 5.8), 5.7 q (1H, $=\text{CH}$, J 0.7), 12.30 br.s (2H, COOH). Found, %: C 50.45; H 5.38; N 13.56. $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_4$. Calculated, %: C 50.94; H 5.70; N 13.20.

IR spectra were obtained using a Nexus instrument (Thermo Nicolet Corporation, USA). ^1H NMR spectra of the solutions in $\text{DMSO}-\text{CCl}_4$ (1 : 3) were recorded with a Varian Mercury spectrometer (300 MHz). Elemental analysis was performed using a Korshun–Klimova apparatus.

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