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LETTERS TO THE EDITOR

Addition of 2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)ethanamine to Methyl Acrylate and Cyclization of the Adducts

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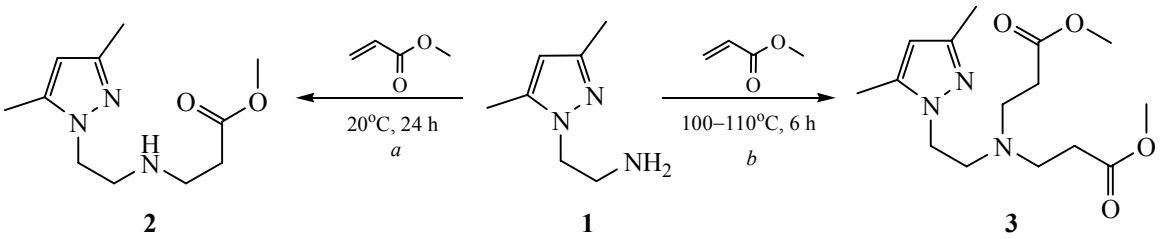
Development of new methods for the synthesis of pyrazole derivatives constitutes an important problem due to prospects in their use as synthons for the design of new biologically active compounds [1–3]. In continuation of our studies on the aza-Michael additions of azoles to α,β-unsaturated carbonyl compounds [4, 5], including noncatalytic reactions, we examined the addition of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethanamine (**1**) [6] to methyl acrylate with the goal of obtaining pyrazolylpyrimidine and pyrazolylpiperidine derivatives.

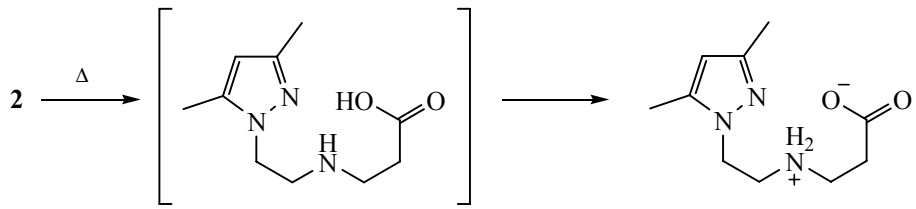
Compound **1** chemoselectively reacted with methyl acrylate under mild conditions (20°C, 24 h) to give the corresponding monoadduct **2** (Scheme 1, path *a*). When the reaction was carried out under more severe conditions (100–110°C), bis-adduct **3** was formed in quantitative yield (path *b*). Distillation of ester **2** was accompanied by partial hydrolysis by the action of atmospheric moisture to afford compound **5** which was found to exist as zwitterionic structure **5a** [7] (Scheme 2). Distillation of **3** was accompanied by β-elimination of methyl acrylate with formation of monoadduct **2**, and the latter underwent further partial β-elimination and hydrolysis. Therefore, compound **3** was brought into subsequent transformations without additional purification.

Scheme 1.



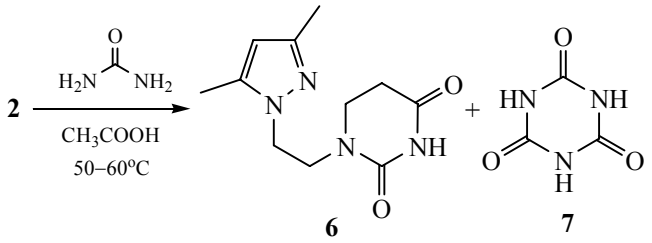
2 **1** **3**

Scheme 2.

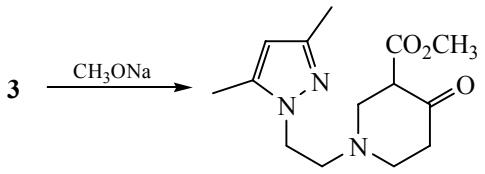


5 **5a**

Scheme 3.



Scheme 4.



By heating compound **2** with urea in glacial acetic acid for 12 h at 50–60°C we obtained 55% of 1-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]hexahydropyrimidine-2,4-dione (**6**), and cyanuric acid (**7**) was also isolated as by-product (Scheme 3). Cyclization of bis-adduct **3** in the presence of sodium methoxide afforded 40% of methyl 1-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]-4-oxopiperidine-3-carboxylic acid (**8**).

The structure of the newly synthesized compounds was confirmed by IR and ^{1}H NMR spectra and elemental analyses.

Methyl 3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethylamino]propanoate (2) and 3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethylamino]propanoic acid (5). Methyl acrylate, 25.8 g (0.3 mol), was added dropwise at 10–20°C to 13.9 g (0.1 mol) of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethanamine (**1**), and the mixture was kept for 24 h at room temperature. Excess methyl acrylate was removed, and the residue was distilled under reduced pressure. A fraction boiling in the range from 150 to 160°C (1 mmHg), 15.3 g, was collected. The product was treated with 50 mL of isopropyl alcohol left overnight, and the precipitate of **5** was filtered off and dried. Yield of **5** 1.5 g (7.1%), mp 181°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 1550 (ring), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15 s (3H, 3-CH_3), 2.21 s (3H, 5-CH_3), 2.30 t (2H, CH_2CO, *J* = 6.6), 2.74 t (2H, NHC$\underline{H}_2CH_2CO$, *J* = 6.6), 2.91 t (2H, NHC$\underline{H}_2CH_2N$, *J* = 6.3), 4.08 t (2H, CH_2N, *J* = 6.3), 4.36 m (2H, NH, COOH), 6.0 s (1H, 4-H). Found, %: C 56.41; H 7.85; N 20.40. $C_{10}H_{17}N_3O_2$. Calculated, %: C 56.85; H 8.11; N 19.89.

Removal of isopropyl alcohol from the filtrate gave 16.9 g (75%) of ester **2**, n_D^{20} = 1.4950. IR spectrum, ν, cm^{-1}: 1540 (ring), 1670 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.65 br. s (1H, NH), 2.19 s (3H, 3-CH_3), 2.22 s (3H, 5-CH_3), 2.38 t (2H, CH_2CO, *J* = 6.6), 2.82 t (2H, NHC$\underline{H}_2CH_2CO$, *J* = 6.2), 2.92 t (2H, NHC$\underline{H}_2$, *J* = 6.2), 3.60 s (3H, OCH_3), 4.00 t (2H, CH_2N, *J* = 6.2), 5.98 s (1H, 4-H). Found, %: C 58.88; H 8.21; N 18.10. $C_{11}H_{19}N_3O_2$. Calculated, %: C 58.64; H 8.50; N 18.65.

Dimethyl 3,3′-{[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]azanediyl}dipropanoate (3). Methyl acrylate, 43 g (0.5 mol), was added dropwise at 5–10°C to 13.9 g (0.1 mol) of pyrazole **1**, and the mixture was left to stand for 24 h at room temperature and then heated for 6 h under reflux. Excess methyl acrylate was removed to leave 30.4 g (98%) of **3** with a purity of ~97% (according to the ^{1}H NMR data), n_D^{20} = 1.4870. IR spectrum, ν, cm^{-1}: 1530 (ring), 1750 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 s (3H, 3-CH_3), 2.22 s (3H, 5-CH_3), 2.32 t (4H, CH_2CO, *J* = 6.9), 2.72 t (4H, NC$\underline{H}_2CH_2CO$, *J* = 6.9), 2.79 t (2H, 1-$CH_2C\underline{H}_2N$, *J* = 6.9), 3.60 s (6H, OCH_3), 4.00 t (2H, 1-C$\underline{H}_2CH_2N$, *J* = 6.9), 6.00 s (1H, 4-H). Found, %: C 57.45; H 8.71; N 13.20. $C_{15}H_{25}N_3O_4$. Calculated, %: C 57.86; H 8.09; N 13.49.

Compound **3** was distilled under reduced pressure, and a fraction boiling in the range from 170 to 200°C (1 mmHg) was collected, 18 g. Crystals of **5** with mp 181°C separated from that fraction on storage. Repeated distillation of the filtrate gave 4.0 g of initial pyrazole **1**, bp 60°C (1 mmHg), n_D^{20} = 1.5030 [6] and 8.5 g of a mixture of compounds **2** and **5** at a ratio of 9:1 (^{1}H NMR), bp 140–190°C (1 mmHg).

1-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)ethyl]hexahydropyrimidine-2,4-dione (6). A mixture of 11.3 g (0.05 mol) of ester **2** and 12 g (0.2 mol) of urea in 15 mL of glacial acetic acid was heated for 24 h at 145–150°C. The mixture was cooled to 20°C, 10 mL of aqueous HCl was added, and the mixture was again heated under reflux for 8 h more. The precipitate of cyanuric acid **7** (mp 145–148°C [8]) was filtered off, and the filtrate was treated with a solution of sodium carbonate until weakly alkaline reaction, extracted with chloroform, and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized from isopropyl alcohol. Yield 6.5 g (55%), mp 165–167°C. IR spectrum, ν, cm^{-1}: 1540 (ring), 1720 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 s (3H, 3-CH_3), 2.28 s (3H, 5-CH_3), 2.35 t (2H, CH_2CO, *J* = 6.8), 3.03 t

(2H, NCH_2CH_2CO, J = 6.8), 3.68 t and 4.22 t (2H each, NCH_2CH_2N, J = 5.9), 6.00 s (1H, 4-H), 9.91 br.s (1H, NH). Found, %: C 55.48; H 6.91; N 23.41. $C_{11}H_{16}N_4O_2$. Calculated, %: C 55.92; H 6.83; N 23.71.

Methyl 1-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl]-4-oxopiperidine-3-carboxylate (8). Compound **3**, 15.5 g (0.05 mol), was added under stirring to a suspension of 3.0 g (0.055 mol) of sodium methoxide in benzene. The mixture warmed up to 50°C and was stirred for 3 h at 50–60°C, cooled to 10°C, and treated with 50 mL of water. After complete dissolution of the sodium derivative, the organic layer was separated, and the aqueous layer was neutralized with aqueous HCl and extracted with benzene (3×25 mL). The solvent was removed, and the residue was recrystallized from carbon tetrachloride. Yield 4.7 g (34%), mp 50–51°C. IR spectrum, ν, cm^{-1}: 1540 (ring), 1710 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 2.15 s (3H, 3-CH_3), 2.22 s (3H, 5-CH_3), 2.38 m (3H, CH_2COCH), 3.43 t (2H, NCH_2CH_2CO, J = 6.7), 3.58 s (3H, OCH_3), 3.62 d (2H, NCH_2CH, J = 6.2), 3.85 t (2H, $NNCH_2$, J = 5.8), 4.38 t (2H, $NNCH_2CH_2$, J = 5.8), 5.95 s (1H, 4-H). Found, %: C 57.45; H 8.71; N 13.20. $C_{12}H_{19}N_3O$. Calculated, %: C 65.13; H 8.65; N 18.99.

The IR spectra were recorded on a Thermo Nicolet Nexus spectrometer (USA). The ^1H NMR spectra were measured on a Varian Mercury instrument at 300 MHz using DMSO-d_6–CCl_4 (1 : 3) as solvent. The elemental analyses were obtained with a Korshun–Klimova apparatus.

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