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Short Note

Synthesis of 4,4'-(Cyclohexane-1,1-diyl)bis(1-methyl-1*H*-pyrazol-5-ol)

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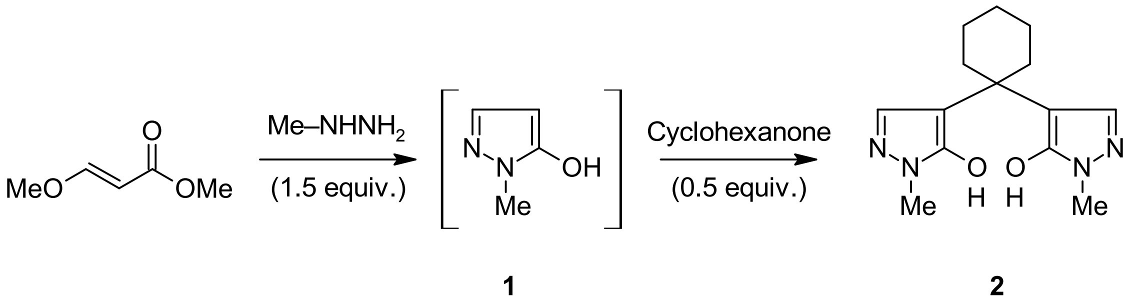
Abstract: Methyl (2*E*)-3-methoxyacrylate and excess methylhydrazine yield crude 1-methyl-2-pyrazolin-5-one which is reacted with cyclohexanone to obtain the title compound in 86% yield. Detailed spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, and MS) are presented.

Keywords: Pyrazolones, cyclohexanone adduct, NMR spectroscopy.

1. Introduction

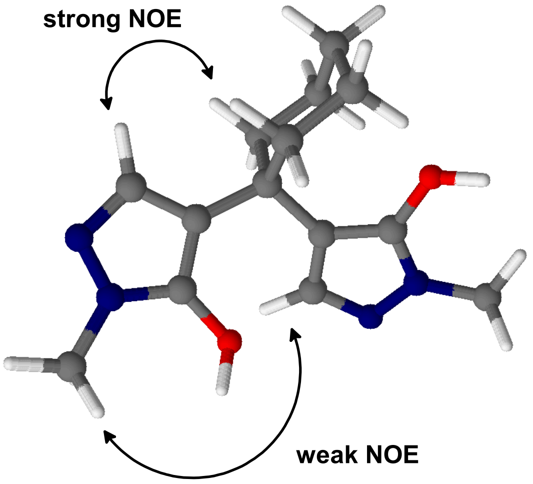
During our ongoing research on pyrano[2,3-*c*]pyrazol-4(1*H*)-ones [1–5] we were interested in the not yet commercially available methylpyrazolone **1**. Although dozens of patents and journal articles deal with its synthesis, most of them include multi-step reactions or seem to be less suited for laboratory scale preparations. Thus, we chose to follow a patent protocol, which starts from alkoxyacrylic alkyl esters and alkylhydrazines [6]. Recently, we have successfully applied that procedure to yield the unsubstituted pyrazolone [7]. Unfortunately, no work up for the crude methylpyrazolone **1** is published in the original patent (only GC/MS analysis is carried out). When we tried to find a proper solvent to precipitate the desired methylpyrazolone from the oily reaction syrup, we found that ketones – such as acetone or cyclohexanone – readily react and give colourless precipitates as the analysis of such a precipitate revealed. A representative procedure with cyclohexanone is presented in the experimental part [Scheme 1].

Scheme 1. Synthesis of the title compound **2**



It should be noted that according to NMR data in DMSO-d_6 solution, we presume a rather unsymmetrical conformation as outlined in Scheme 2. Consistent with this suggestion, we achieved no intramolecular cyclization to the corresponding pyrano[2,3-*c*:6,5-*c*']dipyrazole upon treatment with conc. sulfuric acid or polyphosphoric acid, that would be expected if the hydroxy groups were spatially close.

Scheme 2. Proposed conformation of compound **2** in DMSO solution [8]



2. Experimental

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV). Elemental analysis was performed at the Microanalytical Laboratory, University of Vienna. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The centre of the solvent signal was used as an internal standard which was related to TMS with $\delta = 7.26$ ppm (^{1}H in CDCl$_3$), $\delta = 2.49$ ppm (^{1}H in DMSO-d_6), $\delta = 77.0$ ppm (^{13}C in CDCl$_3$), and $\delta = 39.5$ ppm (^{13}C in DMSO- d_6). The digital resolutions were 0.2 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling). ^{15}N NMR spectra were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary).

2.1. 4,4'-(Cyclohexane-1,1-diyl)bis(1-methyl-1H-pyrazol-5-ol) (2)

CAUTION: Methylhydrazine is a potentially highly toxic compound and must be used with great care under a well-ventilated hood.

To a well stirred solution of methyl 3-methoxyacrylate (50 mmol, 5.80 g) in dry MeOH (5 mL) methylhydrazine (75 mmol, 3.46 g) was added dropwise and the mixture was stirred at room temperature for 3 h. Then the excess solvent and reagents were distilled off using a rotary evaporator to obtain the crude methylpyrazolone **1** as a yellowish honey-like mass [9]. Cyclohexanone (25 mmol, 2.45 g) was added to the residue and the mixture was refluxed for 5 min. The formed precipitate was filtered off and washed subsequently with petroleum ether and acetone to yield the pure title compound **2** (5.91 g, 86%).

Mp: 186–191 °C, colourless powder.

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 13.77 (br s, 2H, OH), 7.16 (s, 2H, pyrazole H-3), 3.38 (s, 6H, NMe), 2.07 (m, 4H, cyclohexane H-2,6), 1.38 (m, 6H, cyclohexane H-3,4,5).

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 156.0 (pyrazole C-5), 132.6 (pyrazole C-3, $^{1}J = 183.8$ Hz), 110.9 (pyrazole C-4), 33.5 (cyclohexane C-1), 33.2 (cyclohexane C-2,6), 31.6 (NMe, $^{1}J = 140.0$ Hz), 26.0 (cyclohexane C-4), 21.9 (cyclohexane C-3,5).

^{15}N NMR (50 MHz, DMSO-d_6): δ (ppm) –210.0 (N-1); N-2 was not found.

MS (*m/z*, %): 276 (M^+, 3), 179 (42), 178 (100), 163 (50), 149 (34), 135 (33), 124 (28), 111 (48), 99 (26), 98 (53), 79 (36), 55 (45), 43 (46).

Elemental Analysis: Calculated for $C_{14}H_{20}N_4O_2$ (276.33): C, 60.85%; H, 7.30%; N, 20.28%. Found: C, 60.66%; H, 7.24%; N, 20.34%.

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9. Upon trituration and subsequent recrystallization of the oily residue with/from i.e. diethyl ether, pure methylpyrazolone **1** can be obtained as colourless crystals. Mp 108.5–111 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 10.90 (br s, 1H, OH), 7.09 (d, ^{3}J(H-3,H-4) = 1.9 Hz, 1H, H-3), 5.30 (d, ^{3}J(H-4,H-3) = 1.9 Hz, 1H, H-4), 3.47 (s, 3H, NMe). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 152.6 (C-5, ^{2}J(C-5,H-4) = 5.7 Hz, ^{3}J(C-5,H-3) = 10.5 Hz, ^{3}J(C-5,NMe) = 1.9 Hz), 137.1 (C-3, ^{1}J = 182.7 Hz, ^{2}J(C-4,H-3) = 5.1 Hz), 86.1 (C-4, ^{1}J = 176.1 Hz), 32.9 (NMe, ^{1}J = 139.3 Hz). ^{15}N NMR (50 MHz, DMSO-d_6): δ (ppm) −201.9 (N-1); N-2 was not found.

Sample Availability: Compounds **1** and **2** are available from MDPI.