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A one-step synthesis of pyrazolone

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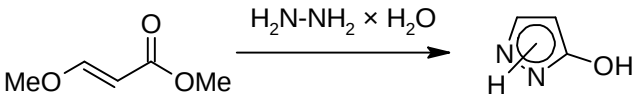
Abstract: The fully unsubstituted pyrazolone (= 2-pyrazolin-5-one, which is tautomer to 1*H*-pyrazol-3-ol and 1*H*-pyrazol-5-ol) was prepared from hydrazine hydrate and methyl (2*E*)-3-methoxyacrylate in almost quantitative yield. Detailed spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, MS) for this compound are presented.

Substituted 2-pyrazolin-5-ones play an important role as substructures of numerous pharmaceuticals, agrochemicals, dyes, pigments, as well as chelating agents and thus attract remarkable attention [1,2].

Recently, we investigated the synthesis of some N1-unsubstituted pyrazolones by use of the PMB (*p*-methoxybenzyl) protecting group [3,4]. Although this substituent proved to be conveniently removable from various 4-substituted pyrazolones upon treatment with refluxing trifluoroacetic acid only poor results were obtained when the parent 1-PMB-pyrazolone (= 2-(4-methoxybenzyl)-2,4-dihydro-3*H*-pyrazol-3-one [3]) was subjected to these conditions. Even prolonged heating (1 week instead of 1 day) did not effect full deprotection (1 day ~ 15%, 2 days ~ 35%, 7 days ~ 75%; monitored by mean of ^{1}H NMR). Hence, there is need for other and more suitable methods for the synthesis of the unsubstituted pyrazolone **1**.

With respect to the fact that other hitherto described syntheses of **1** are characterized by multi-step procedures and/or low yields [5,6], we report here an almost quantitative one-step preparation of the fully unsubstituted pyrazolone system from hydrazine hydrate and methyl (2*E*)-3-methoxyacrylate following an already known procedure for the synthesis of 1-alkyl pyrazolones [7] (Scheme 1).



1

Scheme 1. One-step procedure for the preparation of 'pyrazolone' 1.

A considerable number of studies deal with the prototropic tautomerism of pyrazolones [8].

Determination of the tautomeric composition of compound **1** is quite challenging as eight possible tautomeric forms have to be considered. This may also be a reason why in the Chemical Abstracts Service (CAS) references are cited for all possible tautomeric forms of compound **1** (Figure 1) except for form **E**. From the signal multiplicities in the carbon NMR spectra tautomeric forms **B**, **C**, **F**, **G**, and **H** can be excluded. Moreover, the ^{15}N NMR chemical shifts found for compound **1** (–126.5 ppm and –192.0 ppm) rule out form **A**, as for this tautomer a much smaller chemical shift for the =CH–NH– atom has to be expected (for instance, in phenazone – 1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one – which is structurally related to form **A** this atom exhibits a chemical shift of –245.1 ppm [9]). The differentiation between forms **D** and **E** is not a trivial task. However, from comparison of the ^{13}C chemical shifts, the ^{15}N chemical shifts, the ^{3}J(H,H) coupling constants, and the different ^{13}C,^{1}H-coupling constants of **1** with those of the corresponding N-phenyl analogues (1-phenyl-1*H*-pyrazol-3-ol, 1-phenyl-1*H*-pyrazol-5-ol) [10,11] we assume that form **D** is predominating in DMSO-d_6 solution. Nevertheless an additional contribution of other isomers (in minor amounts) can not be ruled out.

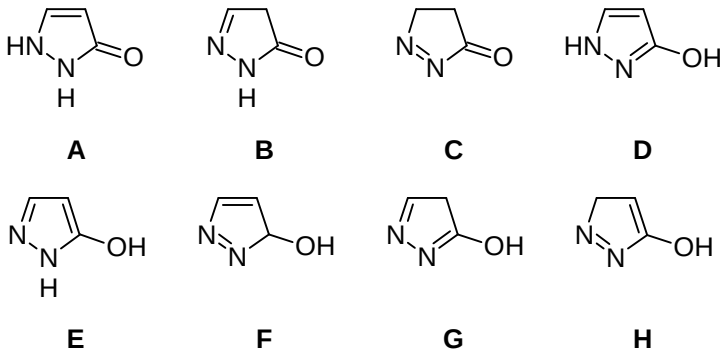


Figure 1. Possible tautomeric forms of 'pyrazolone' 1.

Compound **1**: Under stirring, to a solution of 5.81 g (50 mmol) of methyl (2*E*)-3-methoxyacrylate in methanol (5 mL) was hydrazine hydrate (2.75 g, 55 mmol) added and the mixture was refluxed for 1h. Evaporation under reduced pressure to dryness gave 4.13 g (98%) of a slightly yellowish powder, pure according to ^{1}H NMR spectroscopy.

Melting point: 160–162 °C, crystal modifications starting at ~140 °C, (lit. [12] 162–164 °C).

^{1}H-NMR (300 MHz, DMSO-d_6, 28 °C, numbering for 1*H*-pyrazol-3-ol = form **D**) [13]: δ= 9.82 (br s, 2H, XH); 7.33 (d, $^{3}J_{(H5,H4)}$= 2.3 Hz, 1H, H5); 5.43 (d, $^{3}J_{(H4,H5)}$= 2.3 Hz, 1H, H4).

^{13}C-NMR (75 MHz, DMSO-d_6, 28 °C, numbering for 1*H*-pyrazol-3-ol = form **D**) [13]: δ= 161.0 (C3, $^{2}J_{(C3,H4)}$= 3.4 Hz, $^{3}J_{(C3,H5)}$= 9.2 Hz); 130.1 (C5, ^{1}J = 184.0 Hz, $^{2}J_{(C5,H4)}$= 8.2 Hz); 89.3 (C4, ^{1}J = 175.6 Hz, $^{2}J_{(C4,H5)}$= 8.7 Hz).

^{15}N-NMR (50 MHz, DMSO-d_6, 294 K) [14]: δ= –126.5; –192.0.

MS (m/z, %) [15]: 84 (M^+, 100); 55 (24).

Elemental Analysis: Calculated for $C_3H_4N_2O$ (84.08): C, 42.86%; H, 4.80%; N, 33.32%. Found: C, 42.75%; H, 4.65%; N, 33.15%.

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13. The spectrum was obtained on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C). The center of the solvent signal was used as an internal standard which was related to TMS with δ 2.49 ppm (^{1}H NMR) and δ 39.5 ppm (^{13}C NMR).
14. The spectrum was obtained on a Bruker Avance 500 spectrometer and was referenced against neat, external nitromethane (coaxial capillary). The signals were not unequivocally assigned to the N atoms.
15. The spectrum was obtained on a Shimadzu QP 1000 instrument (EI, 70eV).

Sample Availability: Available from MDPI.