A one-step synthesis of pyrazolone

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Abstract: The fully unsubstituted pyrazolone (= 2-pyrazolin-5-one, which is tautomer to 1H-pyrazol-3-ol and 1H-pyrazol-5-ol) was prepared from hydrazine hydrate and methyl (2E)-3-methoxyacrylate in almost quantitative yield. Detailed spectroscopic data (1H NMR, 13C NMR, 15N 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-3H-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 1H NMR). Hence, there is need for other and more suitable methods for the synthesis of the unsubstituted pyrazolone

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 (2E)-3-methoxyacrylate following an already known procedure for the synthesis of 1-alkyl pyrazolones [7] (Scheme 1).

![Scheme 1. One-step procedure for the preparation of 'pyrazolone' 1.](http://www.mdpi.net/molbank/molbank2006/m464.htm)

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 15N 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-3H-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 $^3J(H,H)$ coupling constants, and the different $^{13}$C,$^1$H-coupling constants of I 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 I: 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.


$^1$H-NMR (300 MHz, DMSO-$d_6$, 28 °C, numbering for 1$H$-pyrazol-3-ol = form D) [13]: $\delta$= 9.82 (br s, 2H, XH); 7.33 (d, $^3J(H5,H4)$= 2.3 Hz, 1H, H5); 5.43 (d, $^3J(H4,H5)$= 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]: $\delta$= 161.0 (C3, $^2J(C3,H4)$= 3.4 Hz, $^3J(C3,H5)$= 9.2 Hz); 130.1 (C5, $^1J$= 184.0 Hz, $^2J(C5,H4)$= 8.2 Hz); 89.3 (C4, $^1J$= 175.6 Hz, $^2J(C4,H5)$= 8.7 Hz).

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

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

Elemental Analysis: Calculated for C$_3$H$_4$N$_2$O (84.08): C, 42.86%; H, 4.80%; N, 33.32%. Found: C, 42.75%; H, 4.65%; N, 33.15%.

References and Notes:
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.

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