HETEROCYCLES, Vol. 63, No. 6, 2004, pp. 1311 - 1334
Received, 20th February, 2004, Accepted, 5th April, 2004, Published online, 9th April, 2004

SYNTHESIS AND NMR SPECTROSCOPIC INVESTIGATIONS WITH 3-AMINO-, 3-HYDROXY-, AND 3-METHOXY-4-ACYL-1-PHENYL-2-PYRAZOLIN-5-ONES

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Abstract – Reaction of 3-amino-, 3-hydroxy- and 3-methoxy-1-phenyl-2-pyrazolin-5-one with carboxylic acid chlorides / calcium hydroxide in 1,4-dioxane mainly affords the corresponding 4-acyl-2-pyrazolin-5-ones. 3-Methoxy-1-phenyl-2-pyrazolin-5-one reacts with dimethylformamide diethyl acetal to give an (*E*)/(*Z*)-mixture of the 4-dimethylaminomethylene product, with tetracyanoethylene the 4-dicyanomethylene product is obtained, whereas with nitrous acid the 4-hydroximino derivative results. NMR-spectroscopic investigations (^{1}H, ^{13}C, ^{15}N) with the obtained reaction products are presented.

INTRODUCTION

A considerable number of studies have been undertaken to investigate prototropic tautomerism of 2-pyrazolin-5-ones.[1-13] With 4-unsubstituted systems CH- (**A**), OH (**B**) and NH-isomers (**C**) result, which - according to Chemical Abstracts nomenclature - confusingly are designated as 2,4-dihydro-3*H*-pyrazol-3-ones (**A**), 1*H*-pyrazol-5-ols (**B**), and 1,2-dihydro-3*H*-pyrazol-3-ones (**C**) (Figure 1, upper trace). Species with an acyl or aroyl group attached at position 4 of the heterocyclic moiety are particularly challenging as such substituents can participate to tautomerism and thus enable a wide variety of – theoretically – possible tautomers, some of them being stabilized by intramolecular hydrogen bonds (Figure 1, lower trace).[1] Whereas for solid pyrazolones single crystal X-Ray analysis enables unambiguous

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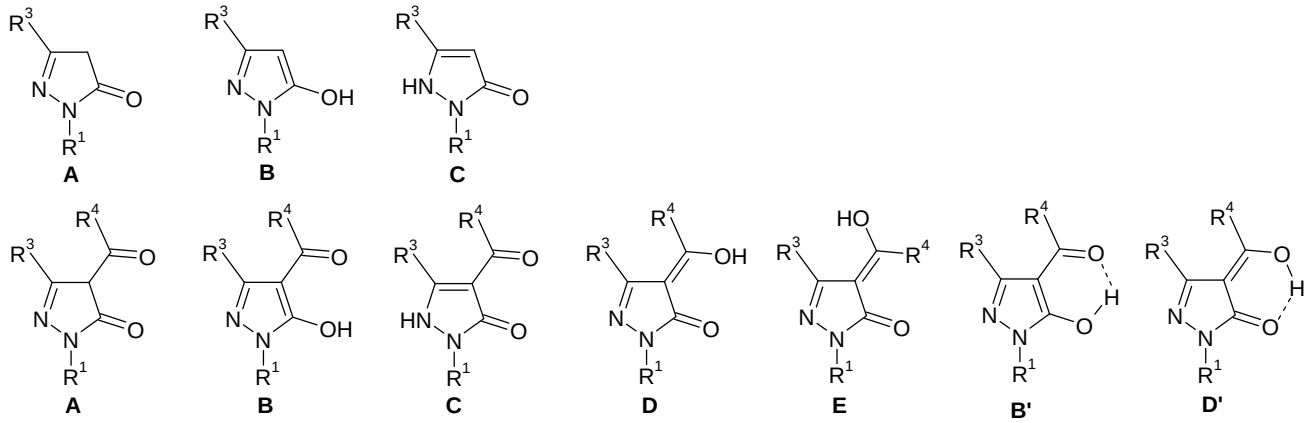
Dedicated to Prof. Peter Stanetty on the occasion of his 60th anniversary

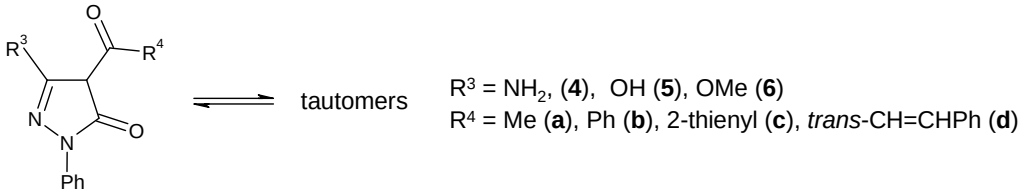
assignment to one of the tautomeric forms,[8-13] this task is more difficult in solution. Here, the – possible – simultaneous presence of several tautomeric forms can either lead to different signal sets in the NMR spectra due to the individual species (in the case of slow exchange) or to the observation of only one average signal set in case of rapid chemical exchange between the tautomers (rapid compared to the NMR timescale). From recent NMR spectral investigations with some simple 4-acylpyrazolones (R^1 = Ph; R^3 = Me, H; R^4 = Me, Ph, 2-thienyl, CH=CHPh) it was concluded that these species exist solely or far predominantely as OH tautomer (**B'**) in apolar $CDCl_3$ or benzene-d_6 solution, whereas in DMSO-d_6 beneath the OH-form also some amount of NH-isomer is probable (Figure 1).[13] Also the tautomerism of oximes derived from 4-acylpyrazolones has been investigated, what decisively helped to explain the particular reactivity of such compounds.[14,15]

Figure 1. Tautomeric forms of 4-acylpyrazolones



However, little is hitherto known about 4-acylpyrazolones carrying an R^3 substituent which can be additionally involved into tautomerism such as hydroxy or amino groups. Thus, the present study is devoted to the synthesis and to NMR spectroscopic investigations with 3-amino- and 3-hydroxy-2-pyrazolin-5-ones, especially to gain insight into the tautomeric behavior of such compounds in solution. Moreover, the synthesis of congeners with a methoxy function as R^3 substituent, which can be seen as 'fixed' hydroxy tautomers, was envisaged. As model pyrazolones species with R^1 = Ph and with four representative 4-acyl(aroyl) moieties should serve (R^4 = Me, Ph, 2-thienyl, *trans*-CH=CHPh) (Figure 2).

Figure 2. Compounds investigated

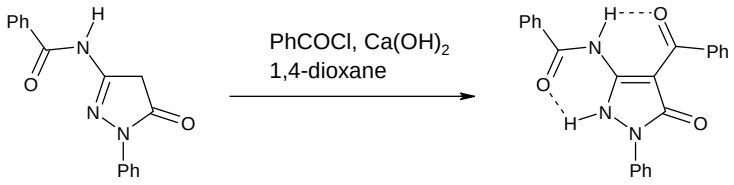


RESULTS AND DISCUSSION

Chemistry

According to the procedure of *Jensen*[16] for the transformation of 1-substituted 2-pyrazolin-5-ones into the corresponding 4-acyl products, treatment of **1**, **2** or **3** with the appropriate carboxylic acid chloride in refluxing dioxane in the precence of excess calcium hydroxide gave the acylation products **4**, **5** and **6** in moderate to good yields. The aromatic electrophilic substitution has been confirmed in acylation of *N*-benzoylpyrazolinone (**10**), the product (**11**) of which was established by single-crystal X-Ray structural analysis (Scheme 1).[17]

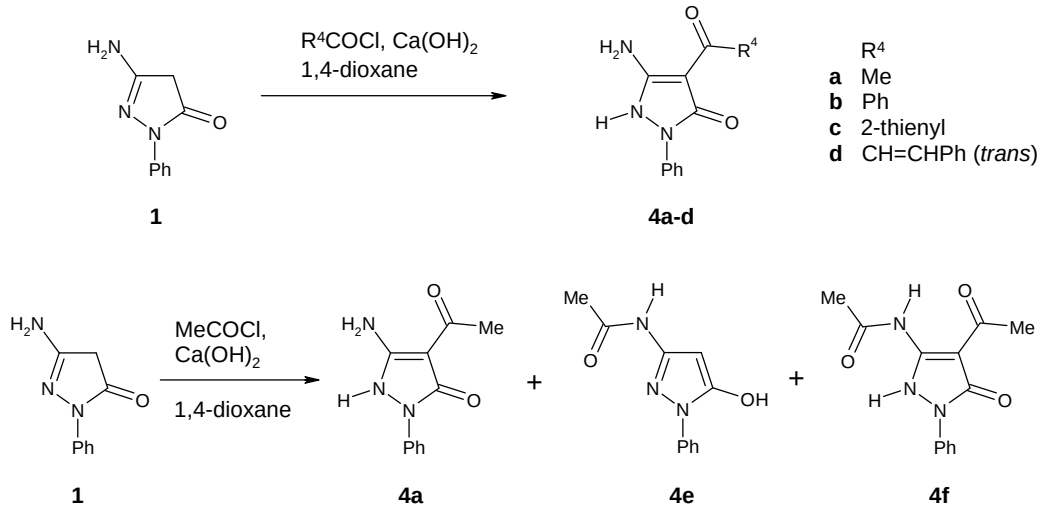
Scheme 1



10 **11**

Whereas upon treatment of **1** with benzoyl, 2-thenoyl or cinnamoyl chloride the formation of only moderate amounts of by-products was observed, the reaction of **1** with acetyl chloride gave an unisolable mixture of **1**, **4a**, **4e** and **4f** (Scheme 2), from which a part of **4f** could be isolated. Compound (**4e**) was identified by comparison with ^{1}H- and ^{13}C-NMR spectral data of the compound reported recently.[18]

Scheme 2. Synthesis of compounds (**4a**-**d**)

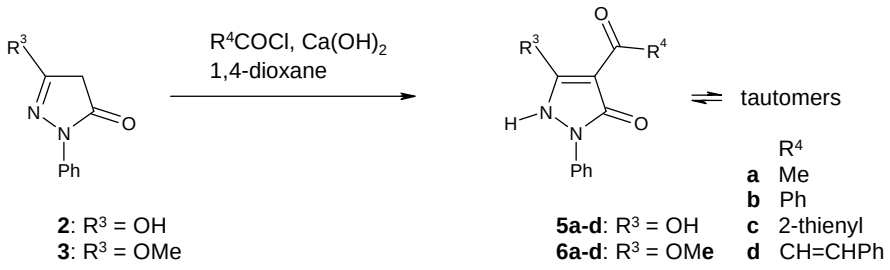


1 **4a-d**

1 **4a** **4e** **4f**

Acylation of **2** and **3** under similar conditions led to the corresponding 4-acylpyrazolones (**5**) and (**6**) in moderate to good yields (Scheme 3), the formation of larger amounts of by-products was not observed. The synthesis of **5a** and **5b** according to a similar protocol has been already reported in the literature.[19,20]

Scheme 3. Synthesis of 4-Acylpyrazolones (**5a**-**d**) and (**6a**-**d**)



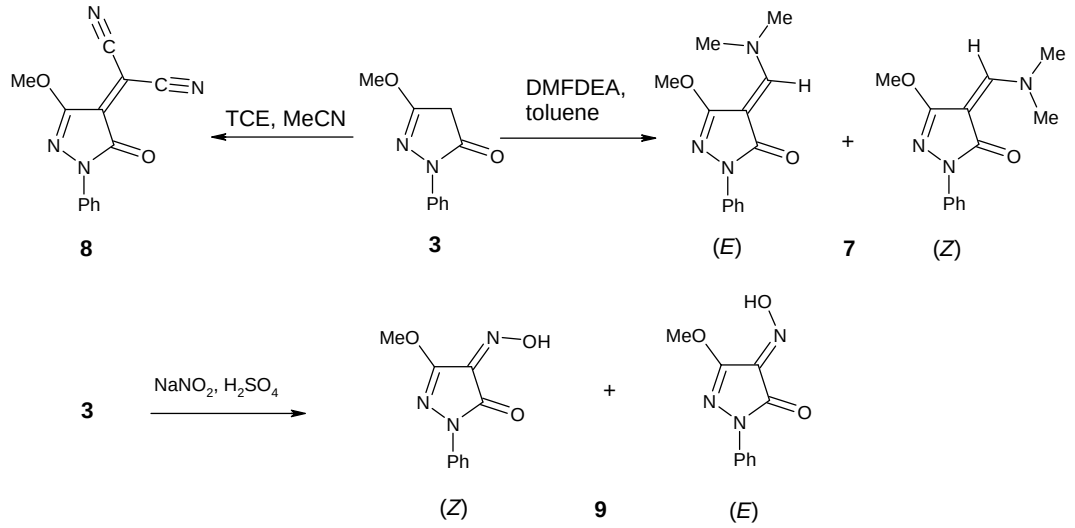
Regarding the reactivity of **3** only its reaction with carbon disulfide and alkyl bromides to give the corresponding alkyl 5-hydroxy-3-methoxy-1-phenylpyrazole-4-dithiocarboxylates has been described in the literature.[21] As comparable 1-substituted 2-pyrazolin-5-ones (R^3 = Me, Ph, H) are characterized by a reactive methylene group at pyrazole C-4 and thus many reactions employing this specificic reactivity have been reported, we investigated the behavior of **3** against dimethylformamide diethyl acetal (DMFDEA), tetracyanoethylene (TCE) and nitrous acid (Scheme 4). Thus, refluxing **3** with DMFDEA in toluene afforded a 1:1 mixture of stereoisomeric dimethylaminomethylene compounds ((*E*)-**7**) and ((*Z*)-**7**). Owing to their similar chromatographic behavior no attemps were made to separate these two species. Nevertheless, careful NMR spectroscopic analysis enabled us to perform a complete and unambiguous spectral assignment using the (*E*)/(*Z*) mixture (see NMR spectroscopic investigations).

In a similar manner as found with various 3-substituted 1-phenyl-2-pyrazolin-5-ones,[22] **3** also reacted with tetracyanoethylene (TCE) in acetonitrile to afford the corresponding dicyanomethylene compound (Scheme 4). The reaction product (**8**) forms deeply colored (black-violet) crystals and exhibits interesting spectral properties with respect to the highly polarized exocyclic C=C double bond.[22]

Nitrosation of 1*H*-pyrazoles proceeds smoothly in 4-postion of the heterocyclic nucleus when the electron density at C-4 is enhanced by the presence of electron-donating functions at position 5, such as NH_2, NHR, OH, OR or SR groups.[23] In case of pyrazolones (tautomer to 5-OH) the primary formed nitrosopyrazoles isomerize into the corresponding isonitroso compounds (oximes). Several examples are known, starting, for instance, from various 3-substituted 1-phenyl-2-pyrazolin-5-ones.[24-26] The stereochemistry of the thus obtained oximes was found to be dependent on the substituent attached to pyrazole C-3.[26] In our case, i.e. reaction of **3** with sodium nitrite in aqueous sulfuric acid, a 1:1 mixture of

isomeric oximes ((***E***)-**9**) and ((***Z***)-**9**) was obtained (Scheme 4). The dark red products could not be separated, however, unequivocal spectral assignment was possible.

Scheme 4. Reaction of **3** with DMFDEA, TCE and HNO_2



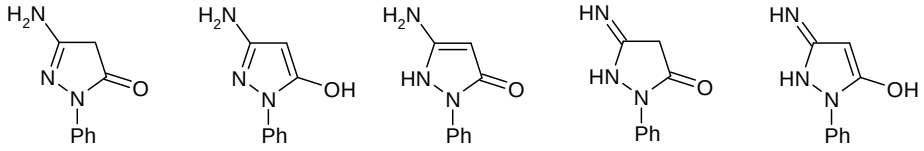
NMR SPECTROSCOPIC INVESTIGATIONS

Unambiguous assignment for all proton and carbon resonances was achieved on basis of homonuclear[27] and heteronuclear $^{13}C\{^1H\}$NOE-difference experiments,[27-29] 1D-TOCSY,[30] fully ^1H-coupled ^{13}C-NMR spectra, APT,[31] HMQC,[32] HMBC,[33] 1D-HETCOR,[34] and long-range INEPT spectra with selective excitation.[35,36] The ^{15}N-NMR spectra were recorded using the refocused INEPT technique[37,38] with proton decoupling and - especially - gradient selected, sensitivity enhanced HSQC[39-41] and HMBC sequences.[42] In some cases, one-pulse sequences with long relaxation delays and no decoupling had to be applied. In this regard it should be emphasized that owing to the dynamic behavior of many substances and the thus resulting (massive) line broadening it was often difficult to obtain sufficient ^{15}N-NMR spectra although relatively concentrated solutions were used for the recordings. Thus, in some cases, not all expected ^{15}N signals could be detected unequivocally.

5-Amino-2,4-dihydro-2-phenyl-3*H*-pyrazol-3-one (**1**)

In principle, with aminopyrazolone (**1**) tautomeric forms **A**-**E** are possible (Figure 3). As the ^1H- and ^{13}C-NMR spectra exhibit the presence of a CH_2-substructure (^1H: singlet with relative intensity 2 at 3.59 ppm; ^{13}C: triplet multiplicity of the signal located at 38.7 ppm) forms **B**, **C**, and **E** can be ruled out. In the ^1H-NMR spectrum one average signal of relative intensity 2 is found for the acidic protons and, moreover, the ^{15}N-NMR spectrum shows an NH_2-group in the typical range (–314.4 ppm) and signals due to two

Figure 3

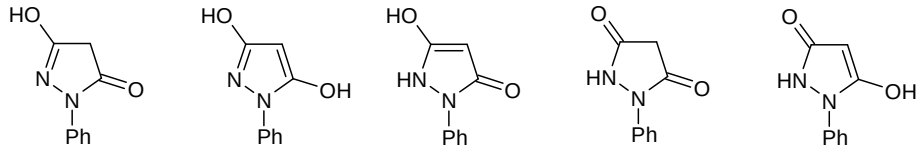


1

markedly different pyrazole nitrogen atoms (–201.3 ppm, –131.4 ppm). Accordingly it can be assumed that **1** is predominantely present as aminopyrazolone (**A**). However, there are unequivocal hints for a dynamic behavior of pyrazolone (**1**) in DMSO-d_6 solution. Thus, the signals due to pyrazole H-4 and pyrazole C-4 are significantly broadened. In NOE-difference experiments irradiation of the pyrazole H-4 resonance leads to saturation transfer to the NH_2 protons and also to a clear NOE on the signal of NPh H-2,6; the latter observation cannot be explained by the exclusive presence of species **A**. From these findings, a tautomeric equilibrium with fast proton exchange (fast compared to the NMR-timescale) involving also - minor contributions - of other isomeric forms such as **B** or **C** cannot be excluded. It should be mentioned that ^{1}H- and ^{13}C-NMR spectral data for this compound have been already provided by *Frigola*,[43] the values being in good accordance to those found by us.

1-Phenyl-3,5-pyrazolidindione (**2**)

Figure 4



2

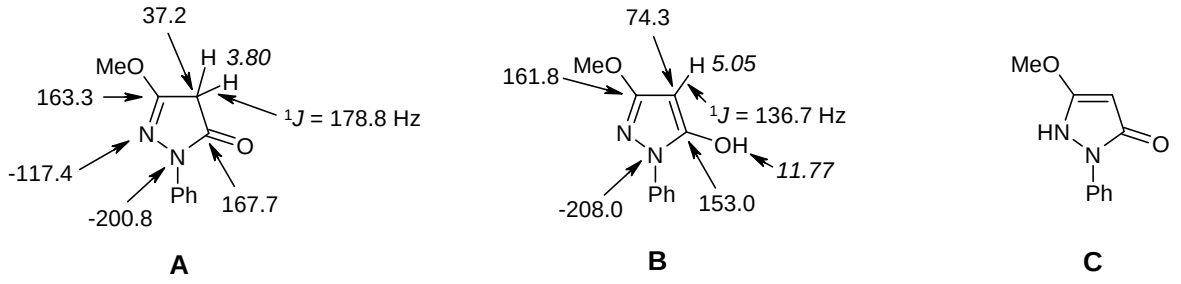
For compound (**2**) five tautomeric forms (**A**-**E**) are possible (Figure 4). NMR spectra of **2** show similar chemical shifts in DMSO-d_6 and in $CDCl_3$ solution, although in the latter the solubility is very low. In both solvents the appearance of a CH_2 substructure at position 4 of the pyrazole system narrows the possible main components to species **A** and **D**, respectively. As found with compound (**1**), also in the spectra of **2** chemical exchange between pyrazole H-4 and the acidic protons was found (saturation transfer in NOE-difference experiments) and again a clear NOE beween the acidic protons and Ph H-2,6 rules out the sole and 'static' presence of isomer **A**. Obviously owing to the dynamic behavior it was not possible to obtain satisfying ^{15}N-NMR spectra of **2**. Although an HMBC experiment showed a correlation

beween pyrazole H-4 as well as Ph H-2,6 to a nitrogen signal at δ –216.9 ppm (the latter signal thus originating from the nitrogen atom directly attached to the phenyl ring), the second pyrazole-N signal could not be observed employing different experiments (HSQC, HMBC, inverse gated decoupling, 20000 scans). In conclusion, on basis of the present data no clear decision beween isomers (**A**) and (**D**) can be made.

2,4-Dihydro-5-methoxy-2-phenyl-3*H*-pyrazol-3-one (**3**)

With compound (**3**), the possible tautomers are reduced to **A**-**C** (Figure 5). In apolar solvents such as $CDCl_3$ and benzene-d_6 only a single species was detected which had to be isomer (**A**) due to the appearance of a CH_2-fragment in the ^{1}H- as well as in the ^{13}C-NMR spectrum. In more polar DMSO-d_6, which has also strong acceptor properties, the main isomer (**A**) (δ pyrazole C-4 = 37.2 ppm, triplet in the ^{1}H-coupled ^{13}C-NMR spectrum, ^1J(C4,H4) = 136.7 Hz) is accompanied by ~20% of the OH-form (**B**). The latter can be identified considering the data of the pyrazole-CH fragment in 4-position (δ H-4 = 5.05 ppm, saturation transfer to H-4 of **A**, δ C-4 = 74.3 ppm, dublet in the ^{1}H-coupled ^{13}C-NMR spectrum with ^1J(C4,H4) = 178.8 Hz) as well as the chemical shift of pyrazole C-5 (153.0 ppm) (Figure 5). In contrast to pyrazolones (**1**) and (**2**) the spectra of **3** exhibit no significant line-broadening. The ^{15}N-NMR spectrum of form (**A**) (in DMSO-d_6) shows two well separated nitrogen signals which can be attributed to pyrazole N-2 (–200.8 ppm) and to pyrazole N-1 (–117.4 ppm) (Figure 5).

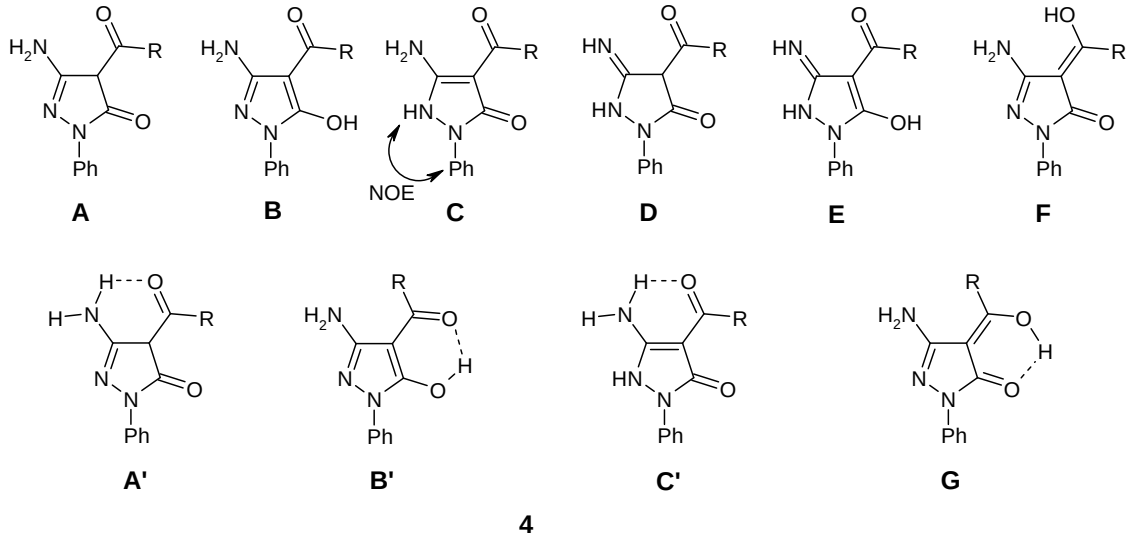
Figure 5. ^{1}H- (italics), ^{13}C- and ^{15}N-NMR chemical shifts for **3** in DMSO-d_6



Compounds (**4b**-**d**)

Attachment of an acyl or aroyl group to the 4-position of a pyrazolone systems in principle increases the number of possible isomeric forms as now also the 4-substituent can participate to tautomerism. Moreover, a variety of forms stabilized by intramolecular hydrogen bonds (for instance **A'**, **B'**, **G**) have to be considered. In case of aminopyrazolones of type (**4**) the most important tautomers are given in Figure 6.

Figure 6



^{15}N-NMR spectroscopic experiments (INEPT, HSQC) with **4c** prove the amino function attached to the pyrazole nucleus to be intact (NH_2: δ –306.3 ppm) and thus imino forms can be ruled out. In the HSQC-spectrum a second, although weaker N-H correlation can be found between the acidic H (δ 11.10 ppm) and an ^{15}N signal at δ –253.7 ppm; the HMBC spectrum correlates the Ph H-2,6 signal (δ 7.58 ppm) with that of N-Ph (δ –228.6 ppm). Similar results were obtained with **4a**, **4b** and **4d**. As CH-forms of type **A** are not relevant with respect to the lack of a CH-fragment at the 4-position of the pyrazole nucleus (pyrazole C-4 is a quarternary C-atom with δ ~ 90 ppm) these findings provide a strong hint that for compounds (**4**) in DMSO-d_6 solution the NH-isomer (**C**) provides the substantial contribution to the overall tautomeric composition. This assumption is confirmed by clear NOEs on the signal due to the phenyl H-2,6 protons upon irradiation of the transition originating from the acidic H (~ 11 ppm, relative intensity 1) (Figure 6).

A difficult task with compounds (**4**) is the unambiguous differentiation between the resonances of pyrazole C-3 and pyrazole C-5, which are close together (often less than 1 ppm difference) and lack suitable C,H-couplings which would enable their assignment. However, in a heteronuclear ^{13}C{^{1}H} NOE-difference experiment[27,29] irradition of the NH_2-resonance of **4c** enhances the signal of the spatially close pyrazole C-5, whereas the signal of the more distant pyrazole C-3 remains unaffected (Figure 7).

An interesting phenomenen was observed in the ^{1}H-NMR spectrum of the thenoyl derivative (**4c**). The unusually large chemical shift of the signal due to thiophene H-3 can be attributed to the preferential presence in conformation (**Y**) in which this proton receives deshielding due to an anisotropy effect of pyrazolone C=O and thus a marked downfield shift compared to conformation (**X**), which is less probable owing to two '*cis*'-configurated carbonyl moieties providing an electrostatic obstacle (Figure 8). A similar

effect was observed with the COC<u>H</u>=C signal (δ 8.16 ppm) in **4d**.

Figure 7. Upper trace: ^{13}C-NMR spectrum of **4c** (133-193 ppm). Lower trace: Identification of the signal due to C-5 *via* a heteronuclear $^{13}C\{^1H\}$ NOE-difference experiment (irradiation of the NH_2 resonance)

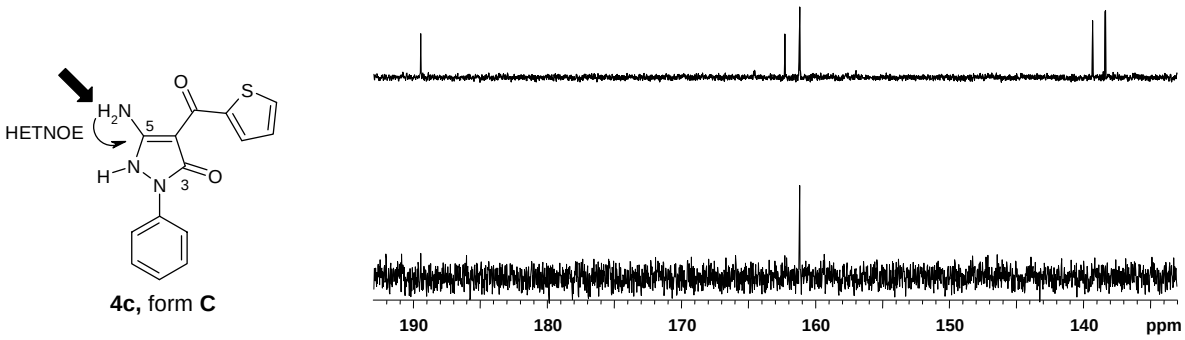
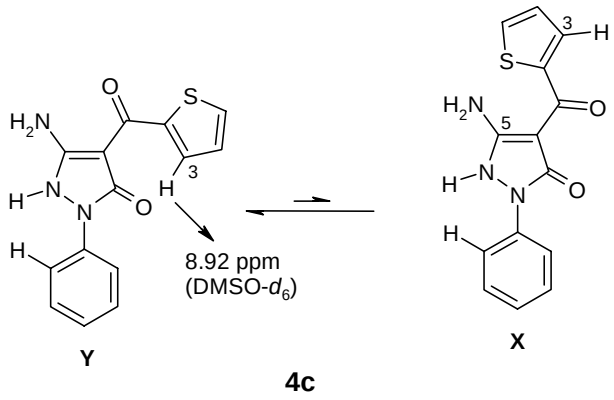


Figure 8



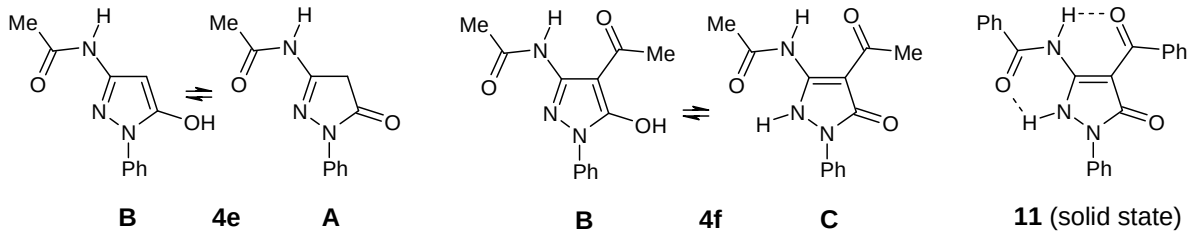
Compounds (**4e**) and (**4f**)

The NMR spectroscopic data of the diacetyl derivative (**4f**) - obtained as a minor product upon reaction of **1** with acetyl chloride - are in agreement with a structure similar as found for **11** (Figure 9). In contrast to aminopyrazolones (**4a**-**d**) which have chemical shifts of δ 159.4-161.3 ppm for the pyrazole C-5 signal (adjacent to NH_2), in **4f** the corresponding signal is shifted upfield to δ 147.7 ppm. In addition, the *N*-acetyl moiety in **4f** shows typical values for such a group (δ C<u>H</u>$_3$ 2.24 ppm, δ <u>C</u>H$_3$ 23.8 ppm, δ <u>C</u>=O 169.5 ppm, δ <u>N</u>H –253.9 ppm)). As a CH-isomer again can be ruled out **4f** can be present as NH (**C**) or OH (**B**) tautomer (or a mixture of both with rapid exchange) (Figure 9).

Compound (**4e**), which was not attempted to isolate, is mainly present in the 5-hydroxy form (**B**)[18] in order to the chemical shift of C-5 (δ 152.2 ppm) which is not in good accordance with a pyrazolone structure. However, also a minor amount of the corresponding CH-isomer (**A**) could be detected in

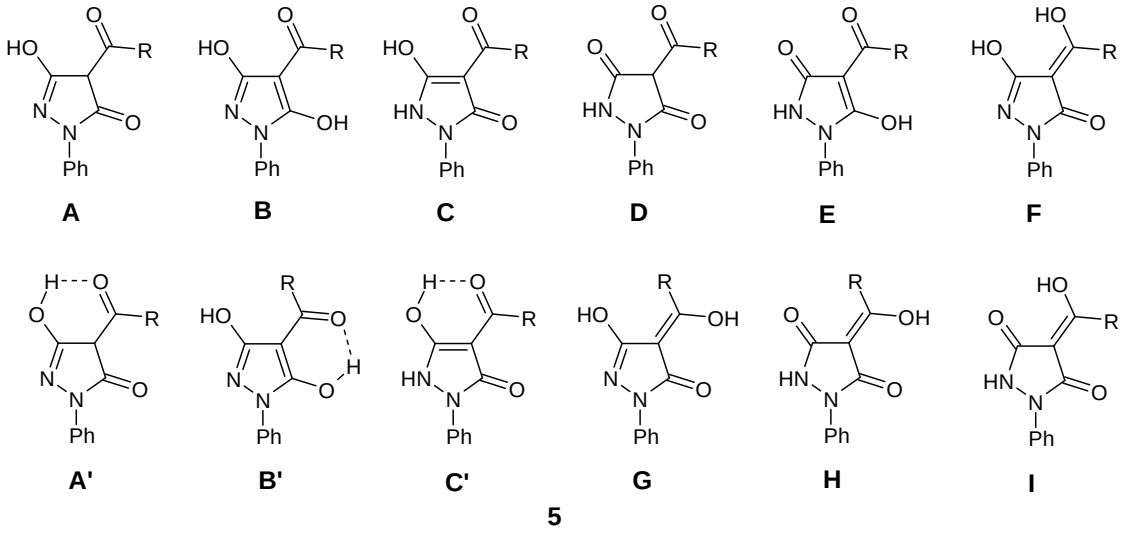
DMSO-d_6 (δ pyrazolone C=O: 168.9 ppm). In NOE-difference experiments chemical exchange between pyrazole H-4 in 5-hydroxypyrazole (**B**) (δ 5.92 ppm) and those in the corresponding CH-isomer (**A**) (δ 4.04 ppm) was observed.

Figure 9



Compounds (**5a-d**)

Figure 10



The most important, possible tautomeric forms of compounds (**5**) are displayed in Figure 10. CH-Isomers like **A**, **A'** or **D** can be ruled out due to the lack of an sp^3-hybridized pyrazole C-4 atom. Similarly as observed with **4c**, also in the ^{1}H-NMR spectrum of **5c** a marked downfield shift for the thiophene H-3 signal (δ 9.19 ppm in DMSO-d_6) was found. Again, this phenomenon can be explained considering the local environment of thiophene H-3 as in the most relevant rotameric forms this proton is brought into the deshielding zone of a pyrazolone C=O group. As the ^{13}C-NMR spectra of **5** exhibit an 'intact' carbonyl C-atom of the 4-acyl (aroyl) moiety (δ in the expected range for a C=O) a significant amount of tautomeric forms with an exocyclic double bond (**F**, **G**, **H**, **I**) is improbable. Signals due to pyrazole C-3

and C-5 were distinguished by heteronuclear $^{13}C\{^{1}H\}$ NOE-difference experiments irradiating the phenyl H-2/6 transition (NOE to the spatially closer pyrazole C-3). In the ^{15}N-NMR spectra of compounds (**5**) in each case only the signal due to the *N*-phenyl nitrogen atom could be observed. In summary, an unequivocal assignment of compounds (**5**) to one of the remaining isomers **B**, **C**, or **E** is not possible on basis of the NMR spectral data, however, a marked dynamic behavior can be assumed.

Compounds (**6a-d**)

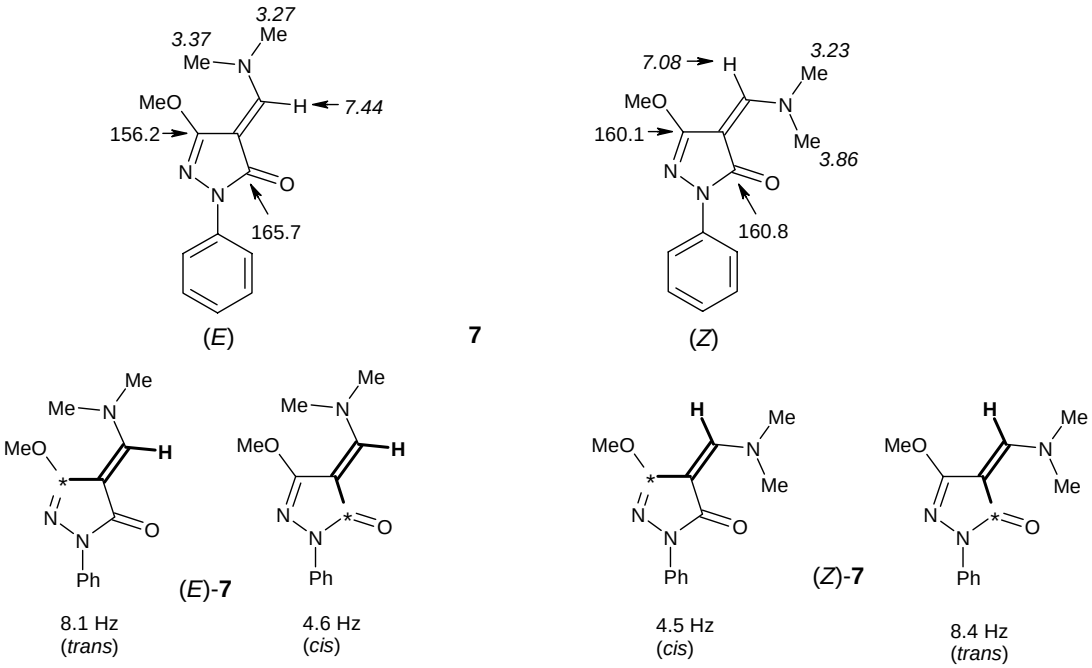
As the methoxy group in compounds (**6**) cannot be involved into tautomerism, the number of possible isomers is reduced when compared to **4** or **5** and corresponds to those given for already known 3-methyl- and 3-H congeners (Figure 1).[1,13,44] In contrast to **4** and **5** compounds (**6**) are well soluble in $CDCl_3$ and thus all NMR spectroscopic investigations were carried out also in this solvent. The data in $CDCl_3$ and DMSO-d_6 solutions do not show marked differences. Whereas the thiophene H-3 signal with **4c** (δ 8.92 ppm in DMSO-d_6) and **5c** (δ 9.19 ppm in DMSO-d_6) exhibits a marked downfield shift due to the above mentioned anisotropy effect, this is not (or only in a much smaller extent) the case with **6c** (δ 8.31 ppm in DMSO-d_6). With respect to the similarity in the spectra of compounds (**6**) and the above mentioned 3(5)-methyl and 3(5)-H analogues[13,44] we believe that the former are mainly present as 5-hydroxy isomers of type **B**, with intramolecular hydrogen bonds (**B'**) in $CDCl_3$-solutions.

(*E*/*Z*)-4-(Dimethylaminomethylene)-2,4-dihydro-5-methoxy-2-phenyl-3*H*-pyrazol-3-one (**7**)

Discrimination of the (*E*)- and (*Z*)-form of **7** was achieved on the following considerations. The exocyclic enamino *N*-atom gives the γ-C-atom in *cis*-position a marked shielding effect resulting in an upfield shift for the latter. Thus, pyrazole C-5 (= -C-OMe) in (*E*)-**7** has a smaller chemical shift (δ 156.2 ppm) than the corresponding pyrazole C-5 in (*Z*)-**7** (δ 160.1 ppm), whereas - reversely - the pyrazolone C=O (= pyrazole C-3) in (*Z*)-**7** (δ 160.8 ppm) is shifted upfield compared to the signal due to pyrazolone C=O in (*E*)-**7** (δ 165.7 ppm) (Figure 11, upper trace). Further, the alkene-H signal in (*E*)-**7** (δ 7.44 ppm) is deshielded compared to that in (*Z*)-**7** (δ 7.08 ppm) due to the anisotropy effect of the *cis*-positioned pyrazolone C=O moiety (Figure 11, upper trace). In (*E*)-**7** the pyrazolone C=O shows a vicinal coupling constant to the alkene H of ^{3}J(CO,=CH) = 4.6 Hz ('*cis*'-coupling), whereas ^{3}J(C-5,=CH) = 8.1 Hz ('*trans*'-coupling). Reversely, in the ^{1}H-coupled ^{13}C-NMR spectrum of (*Z*)-**7** the corresponding vicinal couplings are ^{3}J(CO,=CH) = 8.4 Hz ('*trans*'-coupling), whereas ^{3}J(C-5,=CH) = 4.5 Hz ('*cis*'-coupling) (Figure 11, lower trace). A characteristic phenomenon observed in the NMR spectra of (*E*)-**7** and (*Z*)-**7** is the non-equivalence of the two methyl groups within each NMe_2 moiety giving rise to two well separated singlet signals for each isomer. This can be explained by the partial double bond character of the C–N bond in **7**. Hindered rotation around the C-N bond is well known for carboxamides (and peptides), compounds (**7**)

can be seen as vinylogous carboxamides (hydrazides). Similar effects have been also observed for related 4-enaminopyrazolones.[14, 45-47]

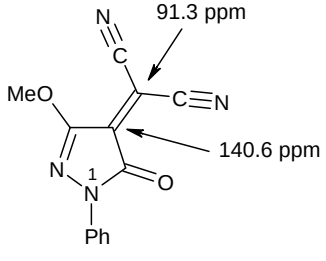
Figure 11



Compound (**8**)

The dicyanomethylenepyrazolone (**8**) is another compound with interesting spectral properties. As found with related pyrazolones,[22] also the C=C double bond in **8** is highly polarized. Whereas the pyrazole C-4 atom suffers a drastic downfield shift (δ 140.6 ppm in $CDCl_3$) the adjacent **C**$(CN)_2$ atom is highly shielded (δ 91.3 ppm in $CDCl_3$) by the two directly attached nitrile functions (Figure 12). The signals of the latter (δ 109.2 and 108.7 ppm) cannot be distinguished unequivocally.

Figure 12

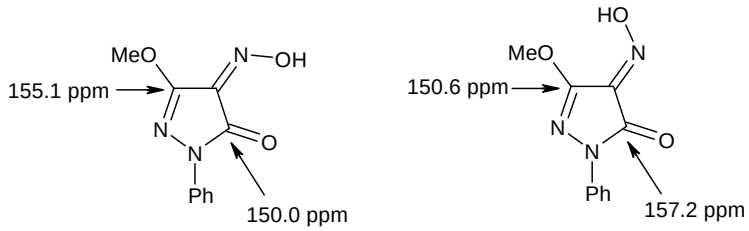


8

Oximes (**9**)

Oximes (**9**) were obtained as a mixture of stereoisomers. The unambiguous discrimination of (*E*)- and (*Z*)-isomer again was possible considering γ-effects. Carbons atoms in γ-position (α to C=N) to a *syn*-located oxime oxygen atom suffer a characteristic upfield shift compared to the γ-atoms in *anti*-position due to steric compression.[48,49] Thus, the pyrazolone carbonyl C-atom in (*Z*)-**9** shows a smaller chemical shift (δ 150.0 ppm in DMSO-d_6) than that in (*E*)-**9** (δ 157.2 ppm in DMSO-d_6), whereas pyrazole C-3 in (*E*)-**9** (δ 150.6 ppm in DMSO-d_6) is more shielded than the corresponding signal in (Z)-**9** (δ 155.1 ppm in DMSO-d_6) due to the *syn*-located hydroximino group (Figure 13).

Figure 13



(*Z*)-**9** (*E*)-**9**

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. MS spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), IR spectra on a Perkin-Elmer FTIR 1605 spectrophotometer. The NMR spectra were obtained on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28°. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$, δ 2.49 ppm (^{1}H in DMSO-d_6), δ 7.16 ppm (^{1}H in benzene-d_6), δ 77.0 ppm (^{13}C in $CDCl_3$), δ 39.5 ppm (^{13}C in DMSO-d_6) and δ 128.4 ppm (^{13}C in benzene-d_6). ^{15}N-NMR spectra (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a 'directly' detecting broadband observe probe and were referenced against neat, external nitromethane (coaxial capillary). Digital resolutions were 0.25 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling) and ≤ 59 Hz/data point in the ^{15}N-NMR spectra. In the description of the ^{13}C-NMR spectra the terms C-3, C-4 and C-5 refer to the carbon atoms of the pyrazole nucleus. As syntheses were mainly devoted to obtain material for the NMR spectroscopic investigations no attempts were made to optimize the yields. Compound (**1**) is commercially available, starting materials (**2**)[50] and (**3**)[51] were prepared according to procedures given in the literature.

5-Amino-2,4-dihydro-2-phenyl-3*H*-pyrazol-3-one (1)

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.59 (br s, 2H, H-4), 6.40 (s, 2H, NH_2), 7.04 (m, 1H, Ph H-4), 7.33 (m, 2H, Ph H-3,5), 7.83 (m, 2H, Ph H-2,6); ^{13}C-NMR (DMSO-d_6): δ (ppm) 38.7 (br, C-4), 117.5 (Ph C-2,6), 123.1 (Ph C-4), 128.5 (Ph C-3,5), 138.9 (Ph C-1), 157.1 (C-5), 167.9 (C-3); ^{15}N-NMR (DMSO-d_6): δ (ppm) –314.4 (5-NH_2, ^{1}J = 88.1 Hz), –201.3 (N-2), –131.4 (N-1).

1-Phenyl-3,5-pyrazolidindione (2)[50]

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.58 (s, 2H, H-4), 7.16 (m, 1H, Ph H-4), 7.40 (m, 2H, Ph H-3,5), 7.64 (m, 2H, Ph H-2,6), 11.44 (s, 1H, NH or OH); ^{1}H-NMR ($CDCl_3$) (low solubility): δ (ppm) 3.46 (s, 2H, H-4), 7.26 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 7.57 (m, 2H, Ph H-2,6), 8.60 (very br s, 1H, NH or OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 37.7 (C-4, ^{1}J = 136.1 Hz), 118.4 (Ph C-2,6), 124.5 (Ph C-4), 128.8 (Ph C-3,5), 136.8 (Ph C-1), 166.0 and 167.4 (br, C-3 and C-5, not unambiguously assignable); ^{13}C-NMR ($CDCl_3$) (low solubility): δ (ppm) 37.7 (C-4, ^{1}J = 136.8 Hz), 119.1 (Ph C-2,6), 126.3 (Ph C-4), 129.4 (Ph C-3,5), 135.5 (Ph C-1), 163.5 and 169.0 (C-3 and C-5, not unambiguously assignable); ^{15}N-NMR (DMSO-d_6): δ (ppm) –216.8 (N-Ph), N-2 not found.

2,4-Dihydro-5-methoxy-2-phenyl-3*H*-pyrazol-3-one (3)[51]

^{1}H-NMR (DMSO-d_6): Isomer (**A**): δ (ppm) 3.80 (s, 2H, H-4), 3.90 (s, 3H, OMe), 7.13 (m, 1H, Ph H-4), 7.39 (m, 2H, Ph H-3,5), 7.80 (m, 2H, Ph H-2,6); Isomer (**B**): δ (ppm): 3.78 (s, 3H, OMe), 5.05 (s, 1H, H-4), 7.15 (m, 1H, Ph H-4), 7.39 (m, 2H, Ph H-3,5), 7.67 (m, 2H, Ph H-2,6); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.49 (s, 2H, H-4), 3.97 (s, 3H, OMe), 7.15 (m, 1H, Ph H-4), 7.37 (m, 2H, Ph H-3,5), 7.86 (m, 2H, Ph H-2,6); ^{1}H-NMR (benzene-d_6): δ (ppm) 2.47 (s, 2H, H-4), 3.36 (s, 3H, OMe), 6.97 (m, 1H, Ph H-4), 7.26 (m, 2H, Ph H-3,5), 8.25 (m, 2H, Ph H-2,6); ^{13}C-NMR (DMSO-d_6): Isomer (**A**): δ (ppm) 37.2 (C-4, ^{1}J = 136.7 Hz), 55.3 (OMe, ^{1}J = 147.7 Hz), 117.8 (Ph C-2,6), 124.0 (Ph C-4), 128.7 (Ph C-3,5), 138.3 (Ph C-1), 163.3 (C-5, ^{2}J(C5,H4) = 6.6 Hz, ^{3}J(C5,OMe) = 3.9 Hz), 167.7 (C-3, ^{2}J(C3,H4) = 5.5 Hz); ^{13}C-NMR ($CDCl_3$): δ (ppm) 37.5 (C-4, ^{1}J = 136.0 Hz), 55.5 (OMe, ^{1}J = 147.5 Hz), 118.7 (Ph C-2,6), 124.6 (Ph C-4), 128.7 (Ph C-3,5), 138.3 (Ph C-1), 162.3 (C-5, ^{2}J(C5,H4) = 6.6 Hz, ^{3}J(C5,OMe) = 3.9 Hz), 167.0 (C-3, ^{2}J(C3,H4) = 5.4 Hz); Isomer (**B**): δ (ppm) 56.0 (OMe), 74.3 (C-4, ^{1}J = 179.1 Hz), 119.4 (Ph C-2,6), 124.3 (Ph C-4), 129.6 (Ph C-3,5), 138.9 (Ph C-1), 153.0 (C-5), 161.8 (C-OMe); ^{13}C-NMR ($CDCl_3$): δ (ppm) 37.5 (C-4, ^{1}J = 136.0 Hz), 55.5 (OMe, ^{1}J = 147.5 Hz), 118.7 (Ph C-2,6), 124.6 (Ph C-4), 128.7 (Ph C-3,5), 138.3 (Ph C-1), 162.3 (C-5, ^{2}J(C5,H4) = 6.6 Hz, ^{3}J(C5,OMe) = 3.9 Hz), 167.0 (C-3, ^{2}J(C3,H4) = 5.4 Hz); ^{13}C-NMR (benzene-d_6): δ (ppm) 37.0 (C-4, ^{1}J = 135.8 Hz), 55.0 (OMe, ^{1}J = 147.1 Hz), 118.8 (Ph C-2,6), 124.6 (Ph C-4), 129.4 (Ph C-3,5), 140.0 (Ph C-1), 162.4 (C-5, ^{2}J(C5,H4) = 6.7 Hz, ^{3}J(C5,OMe) =

3.8 Hz), 167.1 (C-3, ^{2}J(C3,H4) = 5.5 Hz); ^{15}N-NMR (DMSO-d_6): Isomer (**A**): δ (ppm) –200.8 (N-Ph), –117.4 (N-1); Isomer (**B**): δ (ppm) –208.0 (N-Ph); ^{15}N-NMR ($CDCl_3$): δ (ppm) –200.2 (N-Ph), –115.3 (N-1).

4-Acylation of Pyrazolones (1)-(3): Synthesis of Compounds (4)-(6) (General Procedure)

With stirring, to a mixture of pyrazolone (**1**), (**2**) or (**3**) (22.70 mmol) and $Ca(OH)_2$ (5.38 g, 72.60 mmol) in dry 1,4-dioxane (70 mL) was added the appropriate carboxylic acid chloride (22.70 mmol) and the mixture was refluxed at 100 °C for 3 h. After cooling to rt, 2N HCl (90 mL) was added and stirring was continued for further 2 h. Then water (300 mL) was added and the mixture was stirred for another 10 min. The precipitate was filtered off, washed several times with water, dried and purified as described below. In cases when no precipitate was formed the mixture was extracted several times with ethyl acetate, the combined organic phases were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified as described below.

Reaction of 1 with acetyl chloride: 4-Acetyl-5-amino-1,2-dihydro-2-phenyl-3*H*-pyrazol-3-one (4a), *N*-(5-Hydroxy-1-phenyl-1*H*-pyrazol-3-yl)acetamide (4e), and *N*-(4-Acetyl-4,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetamide (4f)

The precpitated product was filtered off and dried to afford 0.64 g (11%) of **4f** as yellow-brown crystals, mp 215–222 °C. The filtrate was extracted with ethyl acetate, the combined ethyl acetate phases were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. Upon trituration with diisopropyl ether a brown solid was obtained which was washed with diisopropyl ether and dried to yield 4.2 g of a light-brown powder consisting in an unisolable mixture of **1**, **4a, 4e** and **4f**.

Compound (**4a**): ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.30 (s, 3H, 4-Ac), 7.11 (m, 1H, Ph H-4), 7.38 (m, 2H, Ph H-3,5), 7.55 (m, 2H, Ph H-2,6), 7.81 (s, 2H, NH_2), 10.85 (br s, NH(OH)); ^{13}C-NMR (DMSO-d_6): δ (ppm) 27.1 (4-CO<u>Me</u>, ^{1}J = 127.3 Hz), 91.1 (C-4), 118.4 (Ph C-2,6), 123.6 (Ph C-4), 128.6 (Ph C-3,5), 138.4 (Ph C-1), 159.4 (C-5), 163.6 (C-3), 192.6 (4-CO); ^{15}N-NMR (DMSO-d_6): δ (ppm) –307.4 (NH_2), –227.0 (N-Ph), N-1 not found.

Compound (**4e**): ^{1}H-NMR (DMSO-d_6): 5-OH isomer (main component): δ (ppm) 1.98 (s, 3H, N-Ac), 5.92 (s, 1H, H-4), 7.19 (m, 1H, Ph H-4), 7.41 (m, 2H, Ph H-3,5), 7.69 (m, 2H, Ph H-2,6), 10.40 (s, 1H, CONH), 11.75 (br s, 1H, OH); CH-isomer (minor component): δ (ppm) 2.04 (s, 3H, N-Ac), 4.04 (s, 2H, H-4), 7.14 (m, 1H, Ph H-4), 7.40 (m, 2H, Ph H-3,5), 7.78 (m, 2H, Ph H-2,6), 11.18 (s, 1H, CONH); ^{13}C-NMR (DMSO-d_6): 5-OH isomer (main component): δ (ppm) 23.2 (NAc, ^{1}J = 127.9 Hz), 80.6 (C-4, ^{1}J = 183.8 Hz, ^{3}J(C4,NH) = 4.2 Hz), 120.4 (Ph C-2,6), 124.9 (Ph C-4), 128.9 (Ph C-3,5), 138.8 (Ph C-1), 147.1 (C-3, ^{2}J(C3,H4) = 1.8 Hz), 152.2 (C-5, ^{2}J(C5,H4) = 7.6 Hz), 167.7 (amide CO); CH-isomer (minor

component): δ (ppm) 23.3 (NAc), 40.1 (C-4), 117.8 (Ph C-2,6), 124.2 (Ph C-4), 128.9 (Ph C-3,5), 138.1 (Ph C-1), 151.7 (C-5 (= NHC=N)), 168.2 (amide CO), 168.9 (pyrazolone C=O); ^{15}N-NMR (DMSO-d_6): 5-OH isomer (main component): δ (ppm) –252.1 (NHAc), –202.0 (N-Ph), N-2 not found; CH-isomer (minor component): δ (ppm) –244.5 (NHAc), –101.9 (C=N).

Compound (**4f**): ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.24 (s, 3H, NAc), 2.37 (s, 3H, 4-Ac), 5.89 (very br s, 1H, NH(OH)), 7.25 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 7.54 (m, 2H, Ph H-2,6), 10.82 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 23.8 (NAc, ^{1}J = 129.2 Hz), 27.3 (4-COMe, ^{1}J = 127.7 Hz), 94.0 (C-4), 121.0 (Ph C-2,6), 125.5 (Ph C-4), 128.6 (Ph C-3,5), 136.9 (Ph C-1), 147.6 (C-3), 160.2 (C-5), 169.5 (NHCO, ^{2}J(CO,Me) = 6.5 Hz, ^{2}J(CO,NH) = 3.3 Hz), 193.6 (4-CO); ^{15}N-NMR (DMSO-d_6): δ (ppm) –253.9 (NHAc), N-1 and N-2 not found; MS (m/z, %): 259 (M^+, 36), 218 (27), 217 (100), 202 (34), 200 (11), 199 (41), 175 (30), 158 (10), 108 (42), 107 (24), 93 (13), 92 (21), 91 (48), 84 (14), 78 (14), 77 (64), 68 (35), 66 (13), 65 (17), 64 (15), 51 (28), 43 (90); IR (KBr): ν (cm^{-1}) 3253, 3044, 1712, 1657. *Anal*. Calcd for $C_{13}H_{13}N_3O_2$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.20; H, 5.11; N, 16.32.

5-Amino-4-benzoyl-1,2-dihydro-2-phenyl-3*H*-pyrazol-3-one (4b)

The reaction mixture was extracted with EtOAc, the combined organic phases were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The remaining sticky syrup was triturated with diisopropyl ether to afford a yellowish solid (5.29 g, 83%). For analytical purposes some material was recrystallized from toluene to give pale yellow crystals of mp 96-98 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 7.11 (m, 1H, NPh H-4), 7.37 (m, 2H, NPh H-3,5), 7.38 (m, 2H, CPh H-3,5), 7.46 (m, 1H, CPh H-4), 7.53 (m, 2H, NPh H-2,6), 7.69 (m, 2H, CPh H-2,6), 8.07 (s, 2H, NH_2), 11.02 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 90.3 (C-4), 118.6 (NPh C-2,6), 123.6 (NPh C-4), 127.1 (CPh C-3,5), 128.4 (CPh C-2,6), 128.6 (NPh C-3,5), 130.5 (CPh C-4), 138.4 (NPh C-1), 139.4 (CPh C-1), 161.2 (C-5), 162.3 (C-3), 189.5 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –306.3 (NH_2), –254.5 (N-1), – 228.1 (N-Ph); MS (m/z, %): 279 (M^+, 43), 201 (59), 105 (94), 91 (15), 77 (100), 68 (51), 51 (33). *Anal*. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.61; H, 4.69; N, 14.82.

5-Amino-1,2-dihydro-2-phenyl-4-(2-thienoyl)-3*H*-pyrazol-3-one (4c)

The crude product was washed with some cold CH_2Cl_2 to give 6.51g (81%) brownish crystals of mp 140-145°C. For analytical purposes some product was recrystallized from MeCN to afford beige crystals of mp 142-145 °C.^{1}H-NMR (DMSO-d_6): δ (ppm) 7.15 (m, 1H, Ph H-4), 7.16 (dd, ^{3}J(H3,H4) = 3.8 Hz, ^{3}J(H4,H5) = 5.0 Hz, 1H, Th H-4), 7.41 (m, 2H, Ph H-3,5), 7.58 (m, 2H, Ph H-2,6), 7.81 (dd, ^{3}J(H4,H5) = 5.0 Hz, ^{4}J(H3,H5) = 1.2 Hz, 2H, Th H-5), 8.11 (s, 2H, NH_2), 8.92 (dd, ^{3}J(H3,H4) = 3.8 Hz, ^{4}J(H3,H5) = 1.2 Hz, 1H, Th H-3), 11.10 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 90.3 (C-4), 119.1 (Ph C-2,6),

124.0 (Ph C-4), 127.9 (Th C-4, ^{1}J(C4,H4) = 168.8 Hz, ^{2}J(C4,H3) = 5.6 Hz, ^{2}J(C4,H5) = 4.1 Hz), 128.7 (Ph C-3,5), 132.6 (Th C-5, ^{1}J(C5,H5) = 185.9 Hz, ^{2}J(C5,H4) = 7.3 Hz, ^{3}J(C5,H3) = 11.0 Hz), 132.7 (Th C-3, ^{1}J(C3,H3) = 171.8 Hz, ^{2}J(C3,H4) = 6.1 Hz, ^{3}J(C3,H5) = 8.9 Hz), 138.3 (Ph C-1), 145.7 (Th C-2, ^{2}J(C2,H3) = 6.1 Hz, ^{3}J(C2,H4) = 8.9 Hz, ^{3}J(C2,H5) = 6.1 Hz), 161.3 (C-5), 162.0 (C-3), 179.6 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –305.3 (NH_2), –253.7 (N-1), –228.6 (N-Ph); MS (m/z, %): 285 (M^+, 2), 201 (22), 111 (27), 88 (100), 68 (23), 58 (99), 57 (49), 45 (25), 44 (29), 43 (59). *Anal*. Calcd for $C_{14}H_{11}N_3O_2S$•0.2 H_2O: C, 58.20; H, 3.98; N, 14.54. Found: C, 58.33; H, 3.93; N, 14.28.

(*E*)-5-Amino-1,2-dihydro-2-phenyl-4-(3-phenylprop-2-enoyl)-3*H*-pyrazol-3-one (4d)

The reaction mixture was extracted with ethyl acetate, the combined organic phases were washed with water, dried and evaporated under reduced pressure. The remaining sticky syrup was triturated with diisopropyl ether to afford 6.80 g (98%) of a yellowish solid. For analytical purposes some material was recrystallized from (large amounts of) diisopropyl ether to give pale yellow crystals of mp 123-127 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 7.14 (m, 1H, NPh H-4), 7.40 (m, 3H, CPh H-3,4,5), 7.41 (m, 2H, NPh H-3,5), 7.58 (d, ^{3}J = 15.9 Hz, PhC<u>H</u>=), 7.60 (m, 2H, NPh H-2,6), 7.64 (m, 2H, CPh H-2,6), 8.07 (br s, 2H, NH_2), 8.16 (d, ^{3}J = 15.9 Hz, COC<u>H</u>=), 11.07 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 91.5 (C-4), 118.6 (NPh C-2,6), 123.8 (NPh C-4), 124.8 (CO<u>C</u>H=), 127.9 (CPh C-2,6), 128.6 (CPh C-3,5), 128.9 (NPh C-3,5), 129.7 (CPh C-4), 135.3 (CPh C-1), 138.2 (NPh C-1), 138.6 (Ph<u>C</u>H=), 160.2 (C-5), 163.2 (C-3), 183.1 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –305.9 (NH_2), –254.3 (N-1), –227.3 (N-2); MS (m/z, %): 305 (M^+, 9), 148 (68), 147 (100), 131 (35), 103 (41), 102 (21), 97 (24), 91 (26), 83 (31), 81 (24), 77 (49), 71 (33), 69 (48), 68 (20), 67 (21), 57 (62), 55 (60), 51 (59), 45 (33), 43 (91); IR (KBr): ν (cm^{-1}) 3421, 3106, 2940, 2861, 2763, 1660. *Anal*. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.55; H, 4.89; N, 13.48.

4-Acetyl-1,2-dihydro-5-hydroxy-2-phenyl-3*H*-pyrazol-3-one (5a)[19,20,52]

The crude product was recrystallized from chloroform to afford 3.07g (62%) of brown crystals, mp 180-182 °C (lit.,[52] mp 185-186 °C). ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.43 (s, 3H, 4-Ac), 4.81 (br s, OH, NH, H_2O), 7.19 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.62 (m, 2H, Ph H-2,6); ^{13}C-NMR (DMSO-d_6): δ (ppm) 21.4 (4-CO<u>Me</u>, ^{1}J = 129.3 Hz), 95.5 (C-4, ^{3}J(C4,Me) = 2.2 Hz), 119.1 (Ph C-2,6), 124.9 (Ph C-4), 128.9 (Ph C-3,5), 136.9 (Ph C-1), 161.3 (C-3), 164.4 (br, C-5), 187.6 (4-CO, ^{2}J(CO,Me) = 6.1 Hz); ^{15}N-NMR (DMSO-d_6): δ (ppm) –223.9 (N-Ph), N-1 not found; MS (m/z, %): 219 (M^++1, 11), 218 (M^+, 73), 134 (17), 108 (47), 107 (65), 85 (28), 83 (25), 81 (39), 77 (38), 73 (35), 71 (28), 69 (86), 67 (22), 60 (28), 57 (51), 55 (54), 51 (20), 43 (100).

4-Benzoyl-1,2-dihydro-5-hydroxy-2-phenyl-3*H*-pyrazol-3-one (5b)[19,20]

The crude product 5.60 g (88%) was recrystallized from ethanol to yield 2.54 g (40%) of yellowish crystals, mp 234-237 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 7.23 (m, 1H, NPh H-4), 7.45 (m, 2H, NPh H-3,5), 7.53 (m, 2H, CPh H-3,5), 7.64 (m, 1H, CPh H-4), 7.67 (m, 2H, NPh H-2,6), 8.15 (m, 2H, CPh H-2,6), 9.49 (br s, 2H, NH, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 93.7 (C-4), 119.6 (NPh C-2,6), 125.2 (NPh C-4), 128.0 (CPh C-3,5), 128.9 (NPh C-3,5), 129.4 (CPh C-2,6), 133.2 (CPh C-4), 133.6 (CPh C-1), 136.7 (NPh C-1), 161.2 (C-3), 164.1 (br, C-5), 184.2 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –222.3 (N-Ph), N-1 not found; MS (m/z, %): 280 (M^+, 6), 105 (12), 95 (12), 81 (60), 69 (100), 68 (13), 55 (12); IR (KBr): ν (cm^{-1}) 3068, 2768, 1668, 1589.

1,2-Dihydro-5-hydroxy-2-phenyl-4-(2-thienoyl)-3*H*-pyrazol-3-one (5c)

After work-up 4.68 g (72%) of crude **5c** were obtained. For analytical purposes 1.00 g of the latter was recrystallized from EtOH/H_2O to afford 358 mg of brown-yellow crystals, mp 254-257 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 7.23 (m, 1H, Ph H-4), 7.34 (dd, ^{3}J(H3,H4) = 3.9 Hz, ^{3}J(H4,H5) = 4.9 Hz, 1H, Th H-4), 7.46 (m, 2H, Ph H-3,5), 7.66 (m, 2H, Ph H-2,6), 8.15 (dd, ^{3}J(H4,H5) = 4.9 Hz, ^{4}J(H3,H5) = 1.1 Hz, 1H, Th H-5), 9.19 (dd, ^{3}J(H3,H4) = 3.9 Hz, ^{4}J(H3,H5) = 1.1 Hz, 1H, Th H-3), 8.90 (very br s, 2H, NH, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 91.7 (C-4), 119.7 (Ph C-2,6), 125.2 (Ph C-4), 128.9 (Ph C-3,5), 129.0 (Th C-4), 136.35 (Th C-3), 136.42 (Th C-5), 136.5 (Ph C-1), 138.0 (Th C-2), 161.5 (br, C-3), 164.9 (br, C-5), 175.8 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –226.3 (N-Ph), N-1 not found; MS (m/z, %): 286 (M^+, 48), 202 (70), 134 (20), 111 (100), 107 (29), 77 (40), 69 (27), 51 (22); IR (KBr): ν (cm^{-1}) 3088, 1674, 1587. *Anal*. Calcd for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78. Found: C, 58.50; H, 3.80; N, 9.56.

(*E*)-1,2-Dihydro-5-hydroxy-2-phenyl-4-(3-phenylprop-2-enoyl)-3*H*-pyrazol-3-one (5d)

After work-up 5.08 g (73%) of crude **5d** was obtained. An analytical sample was prepared by recrystallization from (large amounts) of EtOH to afford fine red crystals of mp 257-260 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 6.30 (very br s, 2H, NH, OH), 7.20 (m, 1H, NPh H-4), 7.44 (m, 2H, NPh H-3,5), 7.48 (m, 3H, CPh H-3,4,5), 7.67 (m, 2H, NPh H-2,6), 7.72 (m, 2H, CPh H-2,6), 7.75 (d, ^{3}J = 15.9 Hz, COC<u>H</u>=), 7.90 (d, ^{3}J = 15.9 Hz, PhC<u>H</u>=); ^{13}C-NMR (DMSO-d_6): δ (ppm) 95.5 (C-4), 117.6 (CO<u>C</u>H=), 118.7 (NPh C-2,6), 124.8 (NPh C-4), 128.7 (CPh C-2,6), 128.9 (NPh C-3,5), 129.2 (CPh C-3,5), 131.3 (CPh C-4), 134.1 (CPh C-1), 136.6 (NPh C-1), 143.6 (Ph<u>C</u>H=), 162.3 (br) and 165.3 (br) (C-3 and C-5), 174.5 (4-C=O); MS (m/z, %): 307 (M^++1, 15), 306 (M^+, 67), 202 (92), 131 (100), 115 (21), 111 (49), 103 (55), 77 (63); IR (KBr): ν (cm^{-1}) 1693, 1632. *Anal*. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.33; H, 4.67; N, 9.04.

1-(5-Hydroxy-3-methoxy-1-phenyl-1*H*-pyrazol-4-yl)ethanone (6a)

Yield: 3.00 g (57%); an analytical sample was obtained upon recrystallization from EtOH/H_2O to give brown needles of mp 103-105 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.37 (s, 3H, 4-Ac), 3.95 (s, 3H, OMe), 6.29 (br s, 1H, OH), 7.23 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 7.77 (m, 2H, Ph H-2,6); ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.41 (s, 3H, 4-Ac), 4.03 (s, 3H, OMe), 7.21 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.86 (m, 2H, Ph H-2,6), 10.94 (br s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 24.8 (br, 4-CO<u>Me</u>, ^1J = 128.5 Hz), 55.2 (OMe, ^1J = 147.0 Hz), 94.8 (C-4), 119.8 (Ph C-2,6), 125.3 (Ph C-4), 128.9 (Ph C-3,5), 137.6 (Ph C-1), 158.8 (C-3, ^3J(C3,OMe) = 3.8 Hz), 188.3 (br, 4-CO), C-5 not observed; ^{13}C-NMR ($CDCl_3$): δ (ppm) 24.2 (4-CO<u>Me</u>, ^1J = 128.8 Hz), 55.4 (OMe, ^1J = 146.8 Hz), 95.4 (C-4, ^3J(C4,COMe) = 2.1 Hz), 119.7 (Ph C-2,6), 125.5 (Ph C-4), 128.9 (Ph C-3,5), 137.7 (Ph C-1), 159.1 (C-3, ^3J(C3,OMe) = 3.8 Hz), 160.9 (C-5), 190.3 (4-CO, ^2J(CO,Me) = 6.1 Hz); ^{15}N-NMR (DMSO-d_6): δ (ppm) –205.9 (N-Ph), N-1 not found; MS (m/z, %): 233 (M^++1, 14), 232 (M^+, 97), 217 (32), 107 (55), 91 (29), 77 (77), 69 (20), 51 (34), 43 (100); IR (KBr): ν (cm^{-1}) 1653 (br). *Anal*. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.06; H, 5.26; N, 12.28.

1-(5-Hydroxy-3-methoxy-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (6b)

Yield: 6.21 g (93%); an analytical sample was obtained upon recrystallization from EtOH to give yellow crystals of mp 113-115 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.85 (s, 3H, OMe), 6.97 (br s, OH and H_2O), 7.29 (m, 1H, NPh H-4), 7.49 (m, 2H, NPh H-3,5), 7.51 (m, 2H, CPh H-3,5), 7.62 (m, 1H, CPh H-4), 7.80 (m, 2H, NPh H-2,6), 7.83 (m, 2H, CPh H-2,6); ^{1}H-NMR ($CDCl_3$): δ (ppm) 4.01 (s, 3H, OMe), 7.25 (m, 1H, NPh H-4), 7.46 (m, 2H, NPh H-3,5), 7.50 (m, 2H, CPh H-3,5), 7.60 (m, 1H, CPh H-4), 7.95 (m, 2H, NPh H-2,6), 8.00 (m, 2H, CPh H-2,6), 12.60 (br s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 55.3 (OMe, ^1J = 146.9 Hz), 93.2 (C-4), 120.5 (NPh C-2,6), 125.9 (NPh C-4), 128.0 (CPh C-3,5), 128.8 (CPh C-2,6), 129.0 (NPh C-3,5), 132.4 (CPh C-4), 136.4 (CPh C-1), 137.3 (NPh C-1), 158.2 (C-3, ^3J(C3,OMe) = 3.9 Hz), 158.9 (C-5), 186.2 (4-C=O); ^{13}C-NMR ($CDCl_3$): δ (ppm) 55.5 (OMe, ^1J = 146.9 Hz), 93.8 (C-4), 119.8 (NPh C-2,6), 125.6 (NPh C-4), 128.0 (CPh C-3,5), 129.0 (NPh C-3,5), 129.2 (CPh C-2,6), 132.7 (CPh C-4), 135.0 (CPh C-1), 137.7 (NPh C-1), 158.0 (C-3, ^3J(C3,OMe) = 3.9 Hz), 163.1 (C-5), 186.0 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –205.2 (N-Ph), –142.1 (N-2); MS (m/z, %): 294 (M^+, 33), 105 (100), 77 (62), 43 (31); IR (KBr): ν (cm^{-1}) 1589 (br). *Anal*. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.34; H, 4.88; N, 9.63.

1-(5-Hydroxy-3-methoxy-1-phenyl-1*H*-pyrazol-4-yl)(2-thienyl)methanone (6c)

Yield: 4.64 g (68%); an analytical sample was obtained upon recrystallization from a little amount of EtOH to give yellow-brown crystals of mp 89-90 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.99 (s, 3H, OMe),

6.21 (br s, OH and H_2O), 7.29 (m, 1H, NPh H-4), 7.29 (dd, ^3J(H3,H4) = 3.9 Hz, ^3J(H4,H5) = 4.9 Hz, 1H, Th H-4), 7.49 (m, 2H, NPh H-3,5), 7.79 (m, 2H, NPh H-2,6), 8.07 (dd, ^3J(H4,H5) = 4.9 Hz, ^4J(H3,H5) = 1.0 Hz, 1H, Th H-5), 8.31 (dd, ^3J(H3,H4) = 3.9 Hz, ^4J(H3,H5) = 1.0 Hz, 1H, Th H-3); ^{1}H-NMR ($CDCl_3$): δ (ppm) 4.13 (s, 3H, OMe), 7.21 (dd, ^3J(H3,H4) = 3.9 Hz, ^3J(H4,H5) = 4.9 Hz, 1H, Th H-4), 7.26 (m, 1H, NPh H-4), 7.45 (m, 2H, NPh H-3,5), 7.73 (dd, ^3J(H4,H5) = 4.9 Hz, ^4J(H3,H5) = 1.1 Hz, 1H, Th H-5), 7.91 (m, 2H, NPh H-2,6), 8.55 (dd, ^3J(H3,H4) = 3.9 Hz, ^4J(H3,H5) = 1.1 Hz, 1H, Th H-3), 10.0-15.0 (very br s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 55.5 (OMe, ^1J = 147.2 Hz), 91.6 (C-4), 120.5 (Ph C-2,6), 126.0 (Ph C-4), 128.7 (Th C-4, ^1J(C4,H4) = 170.9 Hz, ^2J(C4,H3) = 4.4 Hz, ^2J(C4,H5) = 4.4 Hz), 129.0 (Ph C-3,5), 134.2 (Th C-3, ^1J(C3,H3) = 171.0 Hz, ^2J(C3,H4) = 5.9 Hz, ^3J(C3,H5) = 9.0 Hz), 135.3 (Th C-5, ^1J(C5,H5) = 188.0 Hz, ^2J(C5,H4) = 7.3 Hz, ^3J(C5,H3) = 10.7 Hz), 137.2 (Ph C-1), 141.3 (Th C-2, ^2J(C2,H3) = 6.4 Hz, ^3J(C2,H4) = 9.1 Hz, ^3J(C2,H5) = 6.4 Hz), 157.7 (C-3, ^3J(C3,OMe) = 3.9 Hz), 159.2 (C-5), 177.6 (4-C=O); ^{13}C-NMR ($CDCl_3$): δ (ppm) 55.7 (OMe, ^1J = 147.0 Hz), 91.8 (C-4), 120.1 (Ph C-2,6), 125.8 (Ph C-4), 128.4 (Th C-4, ^1J(C4,H4) = 169.8 Hz, ^2J(C4,H3) = 4.9 Hz, ^2J(C4,H5) = 4.0 Hz), 129.0 (Ph C-3,5), 134.37 (Th C-5, ^1J(C5,H5) = 184.8 Hz, ^2J(C5,H4) = 7.0 Hz, ^3J(C5,H3) = 11.0 Hz), 134.40 (Th C-3, ^1J(C3,H3) = 171.8 Hz, ^2J(C3,H4) = 6.0 Hz, ^3J(C3,H5) = 9.0 Hz), 137.7 (Ph C-1), 140.7 (Th C-2, ^2J(C2,H3) = 6.4 Hz, ^3J(C2,H4) = 9.4 Hz, ^3J(C2,H5) = 6.4 Hz), 157.7 (C-3, ^3J(C3,OMe) = 3.9 Hz), 162.6 (C-5), 178.1 (4-C=O); ^{15}N-NMR (DMSO-d_6): δ (ppm) –205.8 (N-Ph), –143.4 (N-2); MS (m/z, %): 300 (M^+, 49), 216 (100), 111 (97), 83 (25), 77 (45); IR (KBr): ν (cm^{-1}) 1568 (br). *Anal*. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 59.87; H, 4.10; N, 9.35.

(*E*)-1-(5-Hydroxy-3-methoxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-2-propen-1-one (6d)

Yield: 6.40 g (88%); an analytical sample was obtained upon recrystallization from a large amount of EtOH to give dark-red crystals of mp 120-121 °C. ^{1}H-NMR (DMSO-d_6): δ (ppm) 4.05 (s, 3H, OMe), 5.19 (br s, OH and H_2O), 7.21 (m, 1H, NPh H-4), 7.34 (d, ^3J = 15.9 Hz, COC<u>H</u>=), 7.44 (m, 2H, NPh H-3,5), 7.48 (m, 3H, CPh H-3,4,5), 7.73 (m, 2H, CPh H-2,6), 7.85 (m, 2H, NPh H-2,6), 7.86 (d, ^3J = 15.9 Hz, PhC<u>H</u>=); ^{1}H-NMR ($CDCl_3$): δ (ppm) 4.12 (s, 3H, OMe), 7.18 (m, 1H, NPh H-4), 7.30 (d, ^3J = 15.9 Hz, COC<u>H</u>=), 7.42 (m, 2H, NPh H-3,5), 7.43 (m, 3H, CPh H-3,4,5), 7.63 (m, 2H, CPh H-2,6), 7.87 (d, ^3J = 15.9 Hz, PhC<u>H</u>=), 7.96 (m, 2H, NPh H-2,6), 11.24 (very br s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 55.6 (OMe, ^1J = 147.3 Hz), 95.6 (C-4), 118.7 (NPh C-2,6), 119.0 (CO<u>C</u>H=), 124.9 (NPh C-4), 128.7 (CPh C-2,6), 128.9 (NPh C-3,5), 129.1 (CPh C-3,5), 131.2 (CPh C-4), 134.0 (CPh C-1), 137.7 (NPh C-1), 143.3 (Ph<u>C</u>H=), 158.1 (C-3, ^3J(C3,OMe) = 3.9 Hz), 163.1 (C-5), 174.0 (4-C=O); ^{13}C-NMR ($CDCl_3$): δ (ppm) 55.5 (OMe, ^1J = 147.0 Hz), 96.3 (C-4), 119.0 (NPh C-2,6), 119.1 (CO<u>C</u>H=), 124.8 (NPh C-4), 128.7 (CPh C-2,6), 128.85 (NPh C-3,5), 129.0 (CPh C-3,5), 130.9 (CPh C-4), 134.6 (CPh C-1), 138.2 (NPh C-1), 143.5 (Ph<u>C</u>H=), 158.3 (C-3, ^3J(C3,OMe) = 3.8 Hz), 164.8 (C-5), 174.2 (4-C=O); MS (m/z,

%): 320 (M^+, 40), 294 (36), 216 (100), 131 (43), 105 (90), 103 (28), 77 (77), 69 (26), 51 (25), 44 (21), 43 (26); IR (KBr): ν (cm^{-1}) 1652. *Anal*. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.05; H, 5.17; N, 8.79.

(*E*/*Z*)-4-(Dimethylaminomethylene)-2,4-dihydro-5-methoxy-2-phenyl-3*H*-pyrazol-3-one (7)

To a mixture of **3** (200 mg, 1.05 mmol) and 6 mL of toluene was added dimethylformamide diethyl acetal (DMFDEA, 155 mg, 1.05 mmol). The solution was refluxed for 3 h, then the solvents were evaporated under reduced pressure. The residue was subjected to column chromatography (silca gel, eluent: EtOAc) giving 228 mg (88%) of yellowish crystals of mp 93-95 °C, ratio (*Z*) : (*E*) ~ 1.1 : 1 according to ^{1}H-NMR). (*Z*)-isomer: ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.23 (s, 3H, NMe *cis* to =CH), 3.86 (s, 3H, NMe *trans* to =CH), 3.95 (s, 3H, OMe), 7.06 (m, 1H, Ph H-4), 7.08 (s, 1H, =CH), 7.34 (m, 2H, Ph H-3,5), 7.97 (m, 2H, Ph H-2,6); (*Z*)-isomer: ^{13}C-NMR ($CDCl_3$): δ (ppm) 43.1 (NMe *trans* to =CH, ^1J = 140.0 Hz, ^3J(NMe,=CH) = 8.1 Hz, ^3J(N$\underline{C}$H$_3$,NC$\underline{H}_3$) = 2.9 Hz), 47.6 (NMe *cis* to =CH, ^1J = 140.0 Hz), 54.5 (OMe, ^1J = 146.4 Hz), 89.7 (C-4), 118.9 (Ph C-2,6), 123.2 (Ph C-4), 128.4 (Ph C-3,5), 139.9 (Ph C-1), 150.8 (=CH, ^1J = 165.3 Hz, ^3J(=CH,NMe) = 3.7 Hz), 160.1 (C-5, ^3J(C5,=CH) = 4.5 Hz, ^3J(C5,OMe) = 3.8 Hz), 160.8 (C-3, ^3J(C3,=CH) = 8.4 Hz); (*E*)-isomer: ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.27 (s, 3H, NMe *cis* to =CH), 3.37 (s, 3H, NMe *trans* to =CH), 3.98 (s, 3H, OMe), 7.06 (m, 1H, Ph H-4), 7.35 (m, 2H, Ph H-3,5), 7.44 (s, 1H, =CH), 8.01 (m, 2H, Ph H-2,6); (*E*)-isomer: ^{13}C-NMR ($CDCl_3$): δ (ppm) 41.7 (NMe *trans* to =CH, ^1J = 140.0 Hz, ^3J(NMe,=CH) = 8.0 Hz, ^3J(N$\underline{C}$H$_3$,NC$\underline{H}_3$) = 2.9 Hz), 47.6 (NMe *cis* to =CH, ^1J = 140.0 Hz, ^3J(NMe,=CH) = 6.1 Hz), 54.9 (OMe, ^1J = 146.6 Hz), 89.7 (C-4), 118.4 (Ph C-2,6), 123.1 (Ph C-4), 128.5 (Ph C-3,5), 139.8 (Ph C-1), 151.6 (=CH, ^1J = 166.2 Hz, ^3J(=CH,NMe) = 3.8 Hz), 156.2 (C-5, ^3J(C5,=CH) = 8.1 Hz, ^3J(C5,OMe) = 3.8 Hz), 165.7 (C-3, ^3J(C3,=CH) = 4.6 Hz); MS (*E*/*Z*-mixture) (m/z, %): 246 (M^++1, 16), 245 (M^+, 100), 230 (25), 201 (17), 105 (25), 77 (70), 69 (19), 43 (33); IR (KBr): ν (cm^{-1}) 1669. *Anal*. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.60; H, 5.91; N, 17.08.

(1,5-Dihydro-3-methoxy-5-oxo-1-phenyl-4*H*-pyrazol-4-ylidene)propanedinitrile (8)

Tetracyanethylene (TCE, 256 mg, 2 mmol) was dissolved in 4 mL of acetonitrile and the solution warmed to 40 °C. Under stirring, 190 mg (1 mmol) of **3** was added slowly and stirring was continued for 1 h. The mixture was then cooled to rt and 20 mL of water were added. A dark precipitate formed which was filtered off and washed several times with water. After drying, 144 mg (57%) of dark violet crystals were obtained, mp 165-169°C. An analytical sample was obtained by recrystallization from $CDCl_3$. ^{1}H-NMR ($CDCl_3$): δ (ppm) 4.17 (s, 3H, OMe), 7.25 (m, 1H, Ph H-4), 7.43 (m, 2H, Ph H-3,5), 7.84 (m, 2H, Ph H-2,6); ^{13}C-NMR ($CDCl_3$): δ (ppm) 57.0 (OMe, ^1J = 149.1 Hz), 91.3 ($\underline{C}$-CN), 108.7 and 109.2 (C≡N), 118.4 (Ph C-2,6), 126.0 (Ph C-4), 129.2 (Ph C-3,5), 136.6 (Ph C-1), 140.6 (C-4), 153.6 (C-3), 154.8 (C-5); MS

(m/z, %): 252 (M^+, 35), 105 (24), 91 (22), 77 (100), 51 (34); IR (KBr): ν (cm^{-1}) 2230 (weak), 1713, 1601. *Anal*. Calcd for $C_{13}H_8N_4O_2$: C, 61.90; H, 3.20; N, 22.21. Found: C, 61.71; H, 3.34; N, 21.93.

***(E*/*Z*)-3-Methoxy-1-phenyl-1*H*-pyrazol-4,5-dione-4-oxime (9)**

A solution of **3** (190 mg, 1 mmol) in 1.5 mL of 10% H_2SO_4 was cooled to 0 °C using an ice-salt bath. Then a solution of $NaNO_2$ (69 mg, 1 mmol) in a minimum amount of water was added dropwise with stirring at 0 °C. After the addition was complete the mixture was stirred at 0 °C for further 30 min, then the precipitate was filtered off and washed with water. Recrystallization from AcOH/H_2O afforded 189 mg (86%) of reddish-brown crystals, mp 140-150 °C, ratio (*Z*) : (*E*) = 1 : 1 according to ^{1}H-NMR. (*Z*)-isomer: ^{1}H-NMR (DMSO-d_6): δ (ppm) 4.00 (s, 3H, OMe), 7.17 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.81 (m, 2H, Ph H-2,6), 14.66 (s, 1H, OH); (*Z*)-isomer: ^{13}C-NMR (DMSO-d_6): δ (ppm) 55.4 (OMe, ^1J = 148.1 Hz), 117.7 (Ph C-2,6), 124.5 (Ph C-4), 128.8 (Ph C-3,5), 137.2* (C-4), 137.8 (Ph C-1), 150.0 (C-5), 155.1 (C-3, ^3J(C3,OMe) = 3.9 Hz); (*E*)-isomer: ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.97 (s, 3H, OMe), 7.17 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.82 (m, 2H, Ph H-2,6), 14.66 (s, 1H, OH); (*E*)-isomer: ^{13}C-NMR (DMSO-d_6): δ (ppm) 55.5 (OMe, ^1J = 148.1 Hz), 117.8 (Ph C-2,6), 124.5 (Ph C-4), 128.8 (Ph C-3,5), 137.3* (C-4), 137.8 (Ph C-1), 150.6 (C-3, ^3J(C3,OMe) = 3.9 Hz), 157.2 (C-5) (* = not unequivocally distinguished); MS (m/z, %): 220 (M^++1, 11), 219 (M^+, 79), 105 (47), 77 (100), 51 (36); IR (KBr): ν (cm^{-1}) 3143, 3027, 2852, 1683, 1595. *Anal*. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 54.47; H, 4.15; N, 19.19.

ACKNOWLEDGEMENTS

We thank Dr. Csaba Szantay Jr. for providing a pulse sequence for the ^{13}C{^{1}H} NOE-difference experiments. Linda Hallak thanks for a grant obtained in the course of the ‘Erasmus Student Exchange Programme’.

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