HETEROCYCLES, Vol. 83, No. 7, 2011, pp. 1567 - 1585. © The Japan Institute of Heterocyclic Chemistry
Received, 10th March, 2011, Accepted, 25th April, 2011, Published online, 10th May, 2011
DOI: 10.3987/COM-11-12206

REACTIONS AND TAUTOMERIC BEHAVIOR OF 1-(2-PYRIDINYL)-1*H*-PYRAZOL-5-OLS

Peter Pfaffenhuemer, Christian Laggner, Stefan Deibl, Barbara Datterl, and Wolfgang Holzer*

Department of Drug and Natural Product Synthesis, Faculty of Life Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria
E-mail: wolfgang.holzer@univie.ac.at

Abstract – The tautomeric behavior of 1-(2-pyridinyl)-2-pyrazolin-5-one (**1a**) and its 3-methyl derivative (**1b**) in different solvents was investigated by means of NMR spectroscopy (^{1}H, ^{13}C, ^{15}N). Moreover, studies regarding the reactions of the title compounds with trimethylsilyldiazomethane, carboxylic acid chlorides, different orthoesters, dimethylformamide diethyl acetal and benzaldehyde are presented. Involvement of pyridine-N atoms in hydrogen bondings was investigated by means of ^{15}N-NMR spectroscopy.

INTRODUCTION

Pyrazolones (2-pyrazolin-5-ones) are compounds of significant importance due to their role as core structural element in a number of drug molecules, complexing agents, dyestuffs and agrochemicals.[1-5] Moreover, pyrazolones are inasmuch interesting structures as they are capable of prototropic tautomerism. In principle, for compounds unsubstituted at pyrazole C-4, OH (**A**), CH (**B**), and NH (**C**) forms are possible (Figure 1), designated as 1*H*-pyrazol-5-ols, 2,4-dihydro-3*H*-pyrazol-3-ones and 1,2-dihydro-3*H*-pyrazol-3-ones according to Chemical Abstracts nomenclature. The tautomerism of pyrazolones has been the subject of a considerable number of studies,[6,7] in recent years we have also presented some contributions concerning the tautomerism, reactivity and synthetic potential of pyrazolones and 4-acylpyrazolones.[8-15] In continuation of these studies we here want to present investigations with 2-pyrazolin-5-ones having a 2-pyridinyl moiety attached to pyrazole N-1, *i.e.* compounds of type **1** (Figure 1). Such compounds have been very rarely studied and provide the possibility to form additional tautomeric forms characterized by intramolecular hydrogen bonds between the pyridine nitrogen atom and the OH proton (form **A'**) or the NH proton (form **C'**) (Figure 1). Naturally, also the tautomerism of 4-acyl derivatives of compounds **1** is

expected to be more complex compared to that of congeners carrying an 1-phenyl group instead of an 1-(2-pyridinyl) moiety. Moreover, preliminary tests showed different reactivities of the title compounds **1a** and **1b** compared to their 1-phenyl congeners 1-phenyl-2-pyrazolin-5-one and 3-methyl-1-phenyl-2-pyrazolin-5-one.

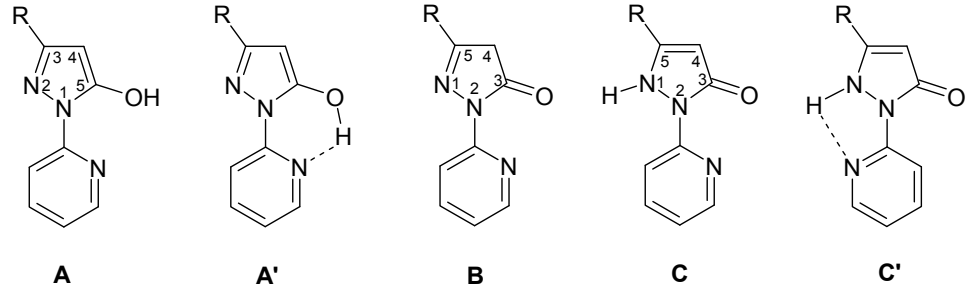


Figure 1. Possible tautomeric forms of title compounds **1**

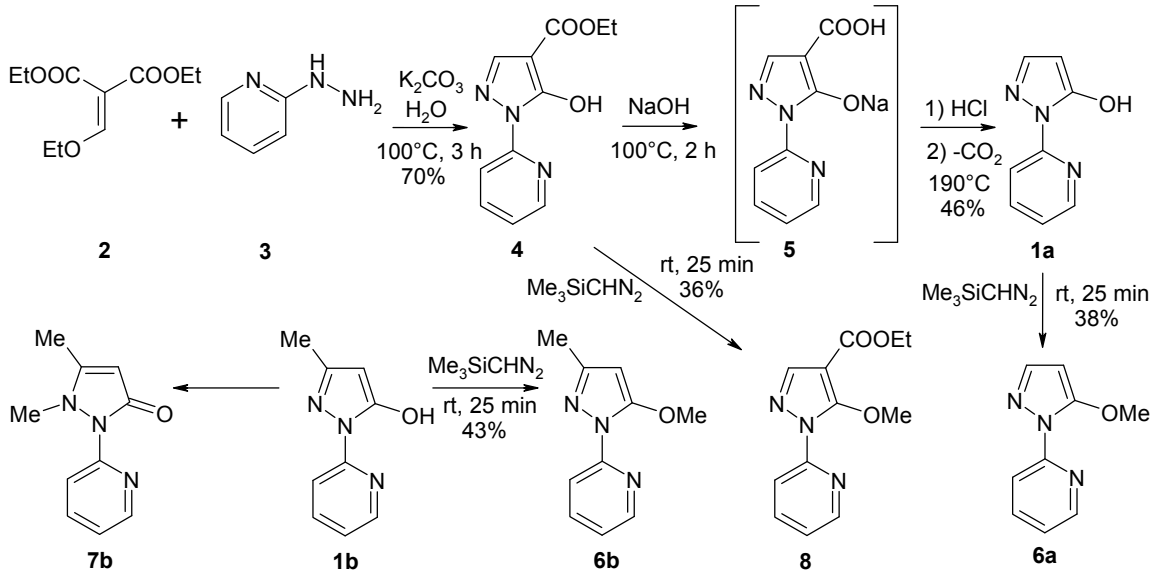
RESULTS AND DISCUSSION

Synthesis of title compounds **1**

The synthesis of pyrazolones **1** was accomplished by known methods. Reaction of diethyl ethoxymethylenemalonate (**2**) with 2-hydrazinopyridine (**3**) in aqueous potassium carbonate led to ester **4**, which was transformed into the corresponding acid **5** by heating with 4M sodium hydroxide (Scheme 1).[16] Decarboxylation of the latter afforded **1a**, which was purified by sublimation.[16] Pyrazolone **1b** resulted from reaction of ethyl acetoacetate with 2-hydrazinopyridine.[17,18] For the investigation of tautomeric equilibria the concept of fixed or blocked derivatives is important – compounds in which the moveable proton is replaced by a methyl group. Such blocked derivatives are not capable of tautomerism and can act as model compounds for comparison purposes.[6,7,19] Thus, pyrazolones **1a,b** as well as **4** were reacted with trimethylsilyldiazomethane in order to obtain the corresponding *O*-methyl derivatives **6a,b** and **8**. The formation of corresponding *N*-methyl products was not observed during these reactions. This regioselective behavior can be rationalized by the 'soft-hard' reagent rule: the substituted diazomethane is a hard electrophile and thus attacks the harder nucleophilic site, *i.e*. the pyrazolone O-atom.[19] *N*-Methyl derivative **7b**, obtained by reaction of **1b** with dimethyl sulfate, is already described in the literature.[20]

Tautomeric behavior of pyrazolones **1a**,**b** in solution

For pyrazolone **1a** in $CDCl_3$ solution a single signal set was observed, which can be attributed best to the OH-form fixed by an intramolecular hydrogen bond between OH and pyridine-N (form **A'** in Figure 1). The ^{1}H, ^{13}C and ^{15}N-NMR chemical shifts for **1a** and its fixed derivative **6a** are given in Figure 2. The shifts of



Scheme 1. Synthesis of pyrazolone **1a** and 'fixed' forms **6a,b, 7b** and **8**

1a and **6a** (in $CDCl_3$) resemble closely, except that of the pyridine N-atom which is markedly shifted downfield when switching from **1a** (δ –129.6 ppm) to **6a** (δ –93.1 ppm). This explicit difference can be explained by the involvement of the concerning pyridine N-atom of **1a** in an intramolecular hydrogen bond (Figures 1 and 2). The so-caused stress of the nitrogen's lone-pair leads to a decrease of its chemical shift.[21-23] In **6a** (and also in **8**) such an interaction is not possible and hence the pyridine-N atom appears at markedly larger chemical shifts (**6a**: δ –93.1 ppm; **8**: δ –87.5 ppm). In contrast, the ^{1}H and ^{13}C-NMR spectra of **1a** in DMSO-d_6 solution (0.2 M) at 25 °C show broad to very broad lines indicating a dynamic behavior and preventing the detection of signals due to quaternary carbon atoms as well as of nitrogen atoms. However, due to the similarity of chemical shifts in DMSO-d_6 compared to those found for $CDCl_3$ it is assumed that **1a** is also present in the OH form in DMSO-d_6 solution at room temperature (Figure 1).

The structure of **1b** in the solid state has been determined by X-ray crystallography and showed the compound to exist as 5-methyl-2-(2-pyridinyl)-1,2-dihydro-3*H*-pyrazol-3-one (NH-form **C**, Figure 1) stabilized by intermolecular hydrogen bonds of N1-H···O=C type.[24,25] For **1b** in $CDCl_3$ solution, ^{1}H and ^{13}C-NMR chemical shifts are provided in several publications,[18,26] however without signal assignment. These data denote the presence of only one signal set with one proton attached to pyrazole C-4. This hints either to the presence of the OH-form or the NH-form, or to a mixture of both forms being in fast exchange. The results of our ^{1}H-, ^{13}C- and ^{15}N-NMR recordings with **1b** in $CDCl_3$ solution are displayed in Figure 2 (lower trace). According to our data, **1b** exists as a ~ 10:1 mixture of OH-form and CH form in $CDCl_3$ (0.2 M solution) at 25 °C. The two signal sets can be easily distinguished considering the pyrazole C-4 signals in the ^{1}H-coupled ^{13}C-NMR spectrum. The main form shows a double quartet (^{1}J(C4,H4) = 177.3 Hz,

^3J(C4,Me) = 3.4 Hz) whereas the C-4 signal of the minor component is split into a triple quartet (^1J(C4,H4) = 133.7 Hz, ^3J(C4,Me) = 2.9 Hz). As found with **1a**, also for the OH-form of **1b** in $CDCl_3$ the presence of an intramolecular hydrogen bond is assumed as in principle the same phenomena were observed as described above (for instance pyridine-N: **6b** δ – 94.4 ppm, **1b** δ – 130.5 ppm). In contrast, in DMSO-d_6 solution only a single signal set is present. However, some broad signals (pyridine H-3, pyrazole C-O, pyrazole C-4) hint to an explicit dynamic behavior. A marked saturation transfer between the acidic proton and the H-4 signal indicates the involvement of the CH-isomer into the exchange process, the lack of an NOE between pyridine H-3 and the acidic proton rules out the presence of significant amounts of NH-form (form **C** in Figure 1).

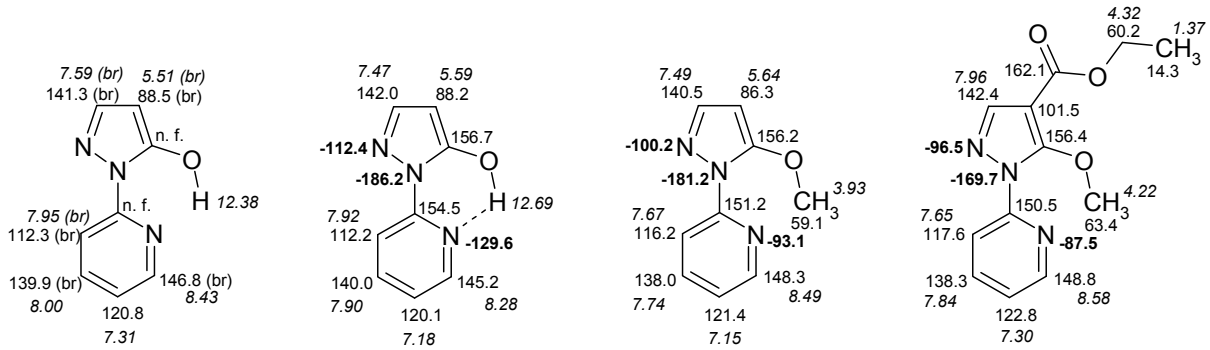
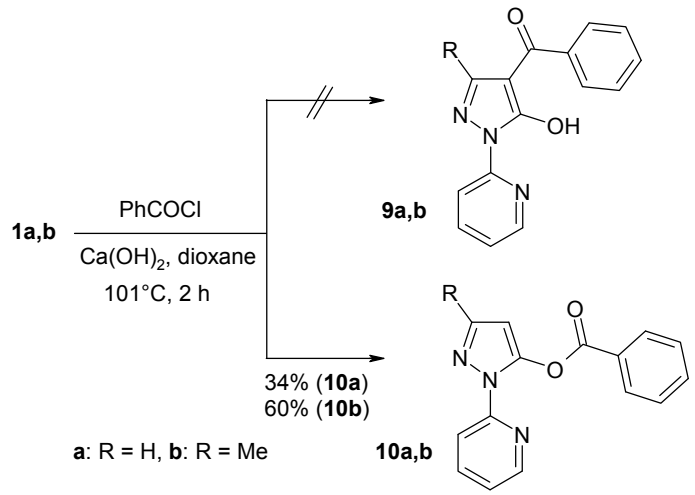


Figure 2. ^{1}H (italics), ^{13}C and ^{15}N-NMR (bold) chemical shifts in **1a**,**b** and fixed derivatives **6a,b**, **7b** and **8** (n. f. = not found, br = broad signal)

Reaction of **1a,b** with carboxylic acid chlorides

For the introduction of an acyl or aroyl group in position 4 of a pyrazolone system, the standard procedure consists in reaction of the pyrazolone with an appropriate acid chloride in the presence of excess calcium

hydroxide in boiling 1,4-dioxane ('Jensen'-method) (Scheme 2).[27] However, we observed that this approach is not suitable when using **1a** or **1b** as starting pyrazolones. Thus, reaction of **1a** or **1b** with benzoyl chloride under the above mentioned conditions did not afford the desired 4-benzoylpyrazol-5-ols of type **9**, instead the isomeric *O*-benzoyl products **10a,b** were isolated as the sole reaction products. Such a reaction behavior has been also found with 1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol.[14] The structure of compounds **10** easily follows from the NMR spectra, they show the presence of a C-H moiety within the pyrazole system, relative small ^{13}C-NMR chemical shifts of pyrazole C-5 (~145 ppm) and the ester C=O atom (~163 ppm).



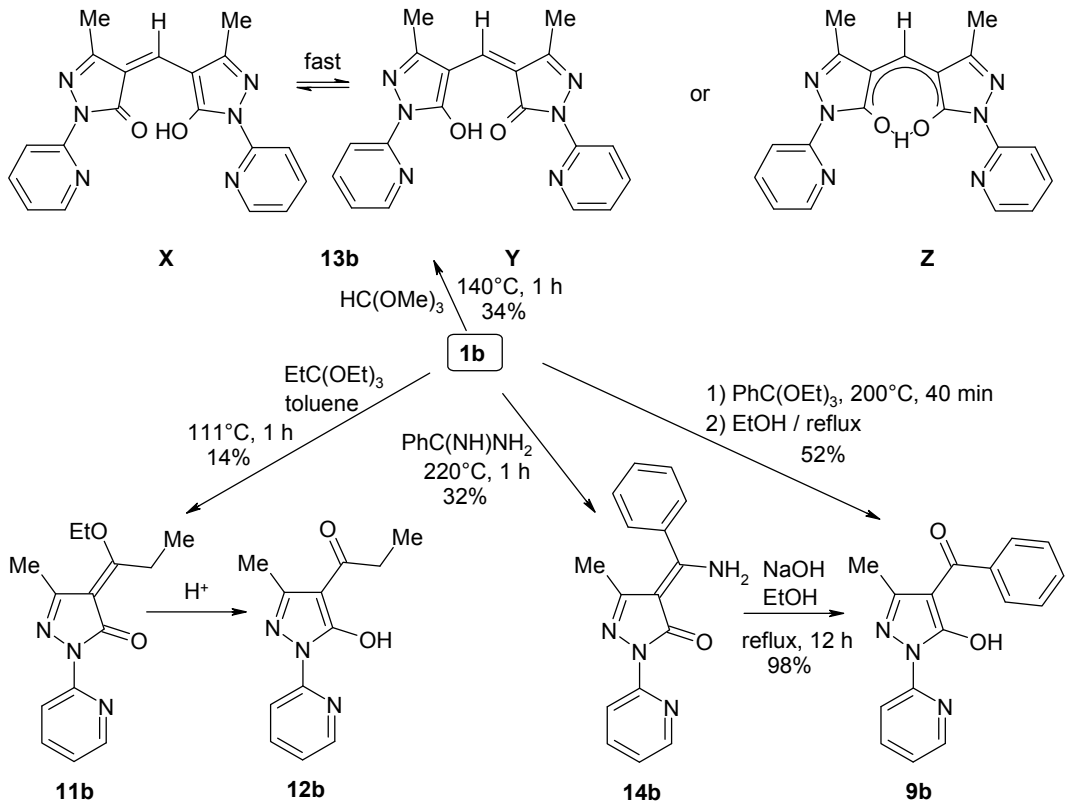
Scheme 2. Reaction of **1a,b** with benzoyl chloride / $Ca(OH)_2$

Reaction of **1a,b** with orthoesters and benzamidine

An alternative method for the introduction of an aroyl or acyl substituent into position 4 of a 2-pyrazolin-5-one should be condensation with appropriate orthoesters, primarily leading to enol ethers of type **11** (Scheme 3). The latter can be easily hydrolized into the corresponding enols which tautomerize into the desired ketones (Scheme 3). This approach has been demonstrated by means of some examples,[14,28,29] however it is very limited to a few available orthoesters.

Hence, the reaction of **1a** and **1b** with trimethyl orthoacetate, trimethyl orthopropionate, trimethyl orthobenzoate and trimethyl orthoformate was investigated in a series of experiments under different reaction conditions. These consisted in heating of molar amounts of the neat reactants to temperatures between 100 and 180 °C for times between 2 minutes and several hours, or performing the reaction in boiling toluene. It turned out that these reactions are very difficult to control and do not take place uniformly. Whereas upon somewhat too low temperatures and/or too short reaction times no conversion was observed, higher temperatures and longer reaction times led to complete decomposition. In general,

with **1a** no defined reaction products could be obtained at all. Whereas heating of **1b** with triethyl orthopropionate to 120–150 °C without a solvent led to decomposition, in boiling toluene the formation of some condensation product **11b** was observed (Scheme 3). The latter was isolated for spectroscopic investigations, but rather quickly converted into ketone **12b** upon standing. Whereas heating of **1b** with trimethyl orthobenzoate in boiling toluene brought no reaction, with neat diethyl orthobenzoate at 200 °C condensation was observed. After refluxing the obtained material with ethanol for one hour the desired 4-benzoylpyrazol-5-ol **9b** was obtained in acceptable yield (45%) (Scheme 3).



Scheme 3. Reaction of **1a,b** with orthoesters and benzamidine

Alternatively, an access to **9b** is possible by melting **1b** together with benzamidine hydrochloride at 220 °C (as described for a similar example in lit.,[30]) which produces **14b**. The latter was converted into **9b** by refluxing in aqueous/ethanolic NaOH. Detailed NMR spectroscopic investigations revealed **14b** to exist exclusively as an enamine (as given in Scheme 3) and not in the corresponding imino form. This finding is supported by the following facts (Figure 3). The methyl protons (δ 1.66 ppm) are significantly shifted upfield compared to those in corresponding **1b** or **6b** (δ ~2.2 ppm) and exhbit a marked NOE to the protons H-2,6 of the phenyl ring. Furthermore, the existence of an amino function is proved by an $^{15}N,^{1}H$-HSQC spectrum, showing two different amino protons attached to the nitrogen atom resonating at –269.7 ppm (in $CDCl_3$). The non-equivalence of the diastereotopic amino protons can be explained by restricted rotation

around the C-N bond (vinylogous carboxamide substructure), the involvement of one NH proton into an intramolecular hydrogen bond to the pyrazolone O-atom explains its markedly larger chemical shift (δ 10.30 ppm) compared to the other being not affected (δ 6.65 ppm). Interestingly, in the course of NOE-difference experiments no chemical exchange between the two amino protons was observed, indicating strong hydrogen bonding and also highly restricted rotation around the C-N bond under the recording conditions (Figure 3). In addition, considering the chemical shift of the pyridin-N atom in **14b** (δ –99.5 ppm) involvement of this nitrogen into an intramolecular hydrogen bond as found in **1a** or of **1b** in $CDCl_3$ (OH-form) is improbable.

For **9b**, in principle numerous different tautomeric forms are possible. Considering the reflexions given above, the presence of **9b** as OH-isomer stabilized by an intramolecular hydrogen bond between OH and pyridine-N atom (Figure 3) is supposable. This again is supported by the relatively small chemical shift of the pyridine-N atom (δ –134.2 ppm), closely resembling those of **1a** and **1b** in $CDCl_3$ and being in clear contrast to the corresponding pyridine-N chemical shifts in related derivatives without such an interaction, for instance in **6b** and **8** (δ ~ –90 ppm, see Figure 2). Moreover, structure **9b** is confirmed by a midsize NOE observed on the signal of pyridine H-6 (8.21ppm) upon irradiation of the OH transition (Figure 3). Another midsize NOE detected between methyl protons and H-2,6 of C-phenyl gives a hint that also that rotamer depicted in Figure 3 contributes to the overall situation.

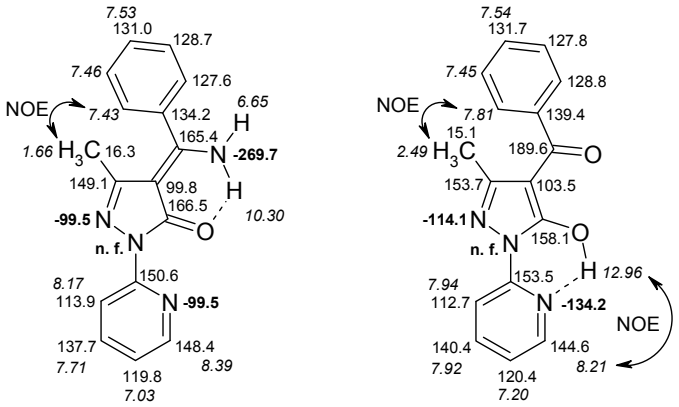


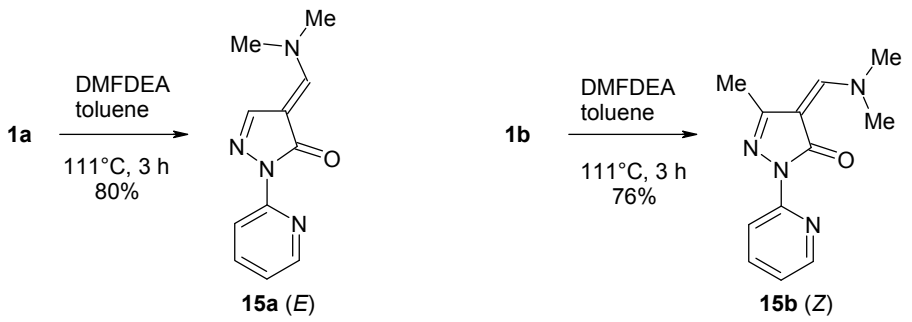
Figure 3. ^{1}H (italics), ^{13}C and ^{15}N-NMR (bold) chemical shifts in **14b** and **9b** (n. f. = not found)

Furthermore, reaction of **1b** with trimethyl orthoformate expectedly led to the dimeric product **13b**, resulting from addition of a second unit of **1b** to the primarily formed condensation product. In all NMR spectra of **13b** the two 1-(2-pyridinyl)pyrazole units are completely equivalent, what can be explained by fast exchange of tautomers **X** and **Y** (Scheme 3) or by the presence of a species of type **Z**. Investigations with closely related compounds including also X-ray crystal structure analysis revealed forms of type **Z** to

be valid.[14,31-33] Such species are stabilized by a strong intramolecular hydrogen bond with double minimum potential. The extraordinaryly large chemical shift of the OH proton in **13b** (δ 17.87 ppm in $CDCl_3$) hints to a comparable situation. On basis of the above considerations, especially due to the chemical shift of the pyridine-N atom in **13b** (δ –92.9 ppm, in $CDCl_3$) it can be concluded that the latter is not involved in hydrogen bonding.

Reaction of **1a,b** with *N*,*N*-dimethylformamide diethyl acetal

It is known from the literature that the active methylene group in 4-position of 2-pyrazolin-5-ones smoothly reacts with dimethylformamide acetals to form the corresponding 4-enaminopyrazolones.[12,34,35] Thus, **1a** and **1b** were heated with one equivalent of dimethylformamide diethyl acetal (DMFDEA) in boiling toluene to afford the colored condensation products **15a** and **15b** in good yields (Scheme 4).



Scheme 4. Recation of **1a,b** with DMFDEA

Careful NMR spectroscopic investigations revealed **15a** to have *E*-configuration regarding the exocyclic double bond, whereas **15b** has the opposite *Z*-configuration (Scheme 4, Figure 4). These findings are based on NOE-difference experiments, chemical shift considerations and bearing in mind some diagnostic $^{13}C,^{1}H$ coupling constants (Figure 4). Hence, for **15a** a clear NOE between pyrazole CH and NMe protons and no NOE between pyrazole CH and alkene-H is observed, quite contrary to **15b** (NOE between C-methyl and alkene-H, no NOE between C-methyl and NMe protons, Figure 4). The alkene-H in **15a** exhibits a markedly larger chemical shift (δ 7.53 ppm) compared to that in **15b** (δ 7.00 ppm) due to the magnetic anisotropy effect of the *cis*-positioned C=O moiety. The pyrazolone C=O atom in **15b** is more shielded (δ 162.6 ppm) than that in **15a** (δ 166.4 ppm) what can be attributed to γ-effects caused by the amino-N atom in *cis* position (Figure 4). Moreover, the configurational differences between **15a** and **15b** are impressively confirmed on the basis of the vicinal coupling constants ^{3}J(C=O,=CH) and ^{3}J(C5,=CH) which show opposite trends (Figure 4). A characteristic feature with both compounds is the non-equivalence of the two methyl groups attached to the amino nitrogen atom leading to distinctly separated signals in the ^{1}H and

^{13}C-NMR spectra. This phenomenon can be explained by hindered rotation around the C–N bond which has partial double bond character (vinylogous carboxamide character of compounds **15**).

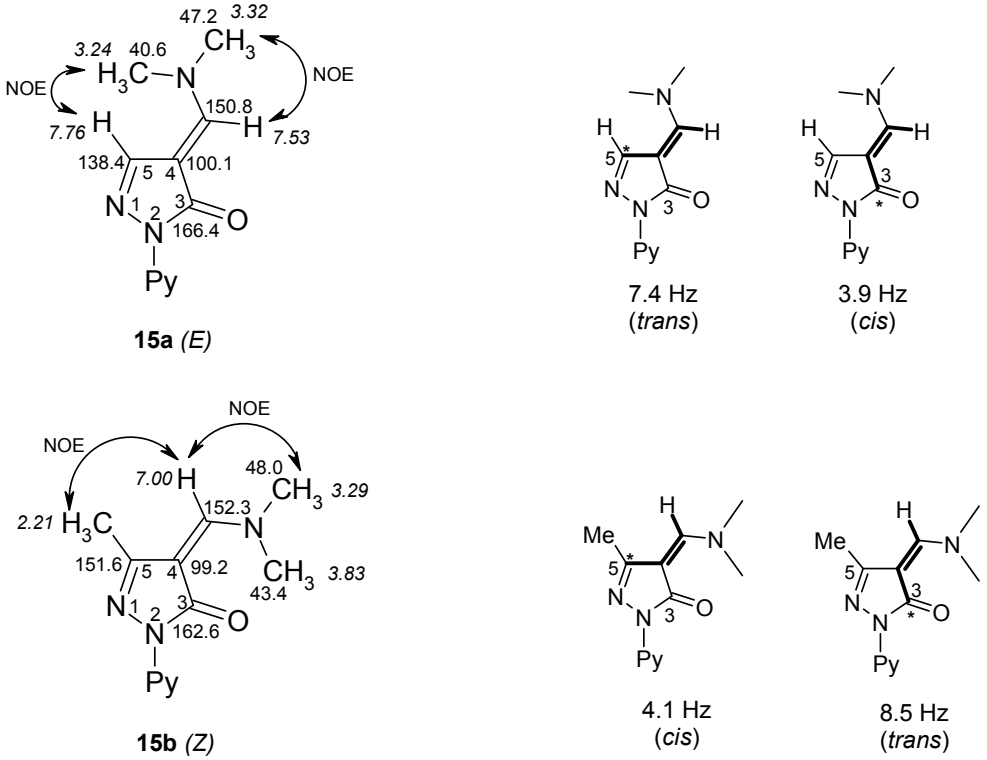
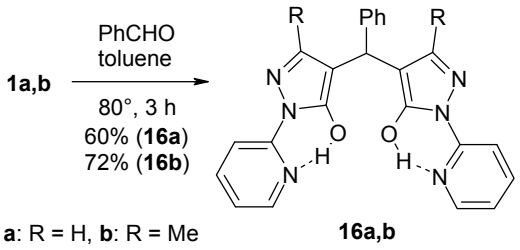


Figure 4. Determination of the stereochemistry of compounds **15** *via* NOEs (arrows), ^{1}H (italics) and ^{13}C-NMR chemical shifts as well as ^{13}C,^{1}H coupling constants

Investigations concerning the hydrolytic cleavage of the exocyclic C-N bond in compounds **15** in order to access the corresponding 5-hydroxypyrazole-4-carbaldehydes and regarding the chemistry of the latter compounds are in progress and will be published elsewhere.

Reaction of **1a,b** with benzaldehyde

Another possibility for C–C bond formation at position 4 of the pyrazolone system consists in condensation with aldehydes, which again utilizes the CH acidity of pyrazolones.[3] However, reaction of **1a** or **1b** did not afford the corresponding 1:1 condensation products but led to dimeric species of type **16** (Scheme 5). Obviously, under the employed conditions the primary product is very reactive and immediately adds a second pyrazolone unit to afford compounds **16**. In contrast to dimer **13b**, the pyridine-N atom in **16a** (or **16b**) is involved into an intramolecular hydrogen bond what is reflected by the corresponding ^{15}N chemical shifts (**16a**: δ –129.4 ppm ; **16b**: δ –130.6 ppm, in $CDCl_3$) (Scheme 5).



Scheme 5. Reaction of **1a,b** with benzaldehyde

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), HRMS spectra (EI) on a Finnigan MAT 8230 instrument. IR spectra were recorded 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) or on a Bruker Avance 500 (500.14 MHz for ^{1}H, 125.77 MHz for ^{13}C) spectrometer. 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 77.0 ppm (^{13}C in $CDCl_3$), δ 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N-NMR spectra (gs-HMBC, gs-HSQC) (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a 'directly' detecting broadband observe (BBFO) probe and were referenced against neat, external nitromethane. 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). Except as noted otherwise the NMR spectra were taken at 25 °C. Unequivocal assignment of signals was carried out by the combined application of standard NMR spectroscopic techniques such as ^{1}H-coupled ^{13}C-NMR spectra, APT, HMQC, gs-HSQC, gs-HMBC, COSY, TOCSY, NOESY and NOE-difference spectroscopy.[36] Moreover, in some cases experiments with selective excitation (DANTE) of certain ^{1}H-resonances were performed, such as long-range INEPT[37] and 2D(δ,*J*) long-range INEPT.[38] Especially the latter experiments were indispensable for the unambiguous mapping of long-range ^{13}C,^{1}H coupling constants. Reliable and unambiguously assigned chemical shift data such as those presented here can be considered as important reference material for NMR prediction programs, such as CSEARCH[39]/NMRPREDICT[40] and ACD/C + H predictor[41] – programs which have become very popular in the last few years, particularly for predicting ^{13}C-NMR chemical shifts.

1-(2-Pyridinyl)-1*H*-pyrazol-5-ol (1a)[16]

^{1}H-NMR ($CDCl_3$): δ (ppm) 12.69 (s, 1H, OH), 8.28 (m, 1H, py H-6), 7.92 (m, 1H, py H-3), 7.90 (m, 1H, py H-4), 7.47 (d, 1H, H-3, ^{3}J(H3,H4) = 2.0 Hz), 7.18 (m, 1H, py H-5), 5.59 (d, 1H, H-4, ^{3}J(H4,H3) = 2.0 Hz);

^{13}C-NMR ($CDCl_3$): δ (ppm) 156.7 (C5, ^2J(C5,H4) = 5.8 Hz, ^3J(C5,H3) = 5.8 Hz), 154.5 (py C-2), 145.2 (py C-6), 142.0 (C-3, ^1J = 185.0 Hz, ^2J(C3,H4) = 4.9 Hz), 140.0 (py C-4), 120.1 (py C-5), 112.2 (py C-3), 88.2 (C-4, ^1J = 179.2 Hz, ^2J(C4,H3) = 10.3 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −112.4 (N-2), −129.6 (py N), −186.2 (N-1).

^{1}H-NMR (DMSO-d_6): δ (ppm) 12.38 (br s, 1H, OH), 8.43 (m, 1H, py H-6), 8.00 (br s, 1H, py H-4), 7.95 (br s, 1H, py H-3), 7.59 (br s, 1H, H-3), 7.31 (br s, 1H, py H-5), 5.51 (br s, 1H, H-4); ^{13}C-NMR (DMSO-d_6): δ (ppm) 146.8 (py C-6), 141.3 (C-3), 139.9 (py C-4), 120.8 (py C-5), 112.3 (py C-3), 88.5 (C-4), signals of C-5 and py C-2 were not found.

3-Methyl-1-(2-pyridinyl)-1*H*-pyrazol-5-ol (1b)[17,18]

^{1}H-NMR ($CDCl_3$): δ (ppm) (major isomer) 12.70 (s, 1H, OH), 8.21 (m, 1H, py H-6), 7.83 (m, 1H, py H-3), 7.82 (m, 1H, py H-4), 7.09 (m, 1H, py H-5), 5.41 (s, 1H, H-4), 2.24 (s, 3H, 3-Me); δ (ppm) (minor isomer) 8.51 (m, 1H, py H-6), 7.99 (m, 1H, py H-3), 7.44 (m, 1H, py H-4), 7.11 (m, 1H, py H-5), 3.48 (s, 2H, H-4), 2.22 (s, 3H, 3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) (major isomer) 156.9 (C5, ^2J(C5,H4) = 5.5 Hz), 151.5 (C-3, ^2J(C3,3-Me) = 6.8 Hz, ^2J(C3,H4) = 4.4 Hz), 145.0 (py C-6), 139.8 (py C-4), 119.4 (py C-5), 111.7 (py C-3), 88.3 (C-4, ^1J = 177.3 Hz, ^3J(C4,3-Me) = 3.4 Hz), 14.6 (3-Me, ^1J = 127.5 Hz), py C-2 was not unambiguously assigned; δ (ppm) (minor isomer) 170.9 (C-5 = C=O), 154.5 (C-3), 148.6 (py C-6), 138.0 (py C-4), 120.7 (py C-5), 114.0 (py C-3), 43.1 (C-4, ^1J = 133.7 Hz, ^3J(C4,3-Me) = 2.9 Hz), 17.1 (3-Me, ^1J = 129.2 Hz), py C-2 was not found; ^{15}N-NMR ($CDCl_3$): (major isomer) δ (ppm) −116.9 (N-2), −130.5 (py N), −190.0 (N-1); ^{15}N-NMR ($CDCl_3$): (minor isomer) δ (ppm) −59.1 (N-2), py N and N-1 were not found.

^{1}H-NMR (DMSO-d_6): δ (ppm) 12.17 (s, 1H, OH), 8.39 (m, 1H, py H-6), 8.17 (m, 1H, py H-3), 7.91 (m, 1H, py H-4), 7.21 (m, 1H, py H-5), 5.20 (s, 1H, H-4), 2.15 (s, 3H, 3-Me); ^{13}C-NMR (DMSO-d_6): δ (ppm) 160.3 (br, C-5), 149.8 (C-3, ^2J(C3,3-Me) = 6.5 Hz, ^2J(C3,H4) = 6.5 Hz), 147.0 (py C-6), 139.3 (py C-4), 120.0 (py C-5), 111.4 (py C-3), 91.0 (br, C-4), 12.8 (3-Me, ^1J = 128.5 Hz), py C-2 was not found; ^{15}N-NMR (DMSO-d_6): δ (ppm) −112.5 (py N), −196.5 (N-1), N-2 was not found.

2-(5-Methoxy-1*H*-pyrazol-1-yl)pyridine (6a)

To a solution of **1a** (161 mg, 1 mmol) in a mixture of EtOAc (7.5 mL) and MeOH (2.5 mL) was added a solution of trimethylsilyldiazomethane (2.0 M in hexane, 1.63 mL, 3.25 mmol) within a peroid of 10 min and the mixture was stirred for further 15 min. Then the solvents were removed under reduced pressure and the residue was subjected to column chromatography (eluent: EtOAc) to afford 67 mg (38%) of **6a** as a brownish oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.49 (ddd, 1H, py H-6, ^3J(H5,H6) = 4.9 Hz, ^4J(H4,H6) = 1.9 Hz, ^5J(H3,H6) = 0.9 Hz), 7.74 (m, 1H, py H-4, ^3J(H3,H4 = 8.3 Hz, ^3J(H4,H5) = 7.3 Hz, ^4J(H4,H6) = 1.9 Hz), 7.67 (ddd, 1H, py H-3, ^3J(H3,H4) = 8.3 Hz, ^4J(H3,H5) = 1.1 Hz, ^5J(H3,H6) = 0.9 Hz), 7.49 (d, 1H, H-3,

^3J(H3,H4) = 1.9 Hz), 7.15 (ddd, 1H, py H-5, ^3J(H4,H5) = 7.3 Hz, ^3J(H5,H6) = 4.9 Hz, ^4J(H3,H5) = 1.1 Hz), 5.64 (d, 1H, H-4, ^3J(H4,H3) = 1.9 Hz), 3.93 (s, 3H, OMe); ^{13}C-NMR ($CDCl_3$): δ (ppm) 156.2 (C5, ^2J(C5,H4) = 5.7 Hz, ^3J(C5,H3) = 5.9 Hz, ^3J(C5,OMe) = 4.9 Hz), 151.2 (py C-2), 148.3 (py C-6, ^1J = 180.5 Hz, ^2J(C6,H5) = 3.6 Hz, ^3J(C6,H4) = 7.4 Hz), 140.5 (C-3, ^1J = 186.5 Hz, ^2J(C3,H4) = 4.1 Hz), 138.0 (py C-4, ^1J = 163.8 Hz, ^2J(C4,H5) = 1.2 Hz, ^3J(C4,H6) = 6.8 Hz), 121.4 (py C-5, ^1J = 165.1 Hz, ^2J(C5,H4) = 0.9 Hz, ^3J(C5,H6) = 8.0 Hz, ^3J(C5,H3) = 6.4 Hz), 116.2 (py C-3, ^1J = 169.5 Hz, ^2J(C3,H4) = 1.3 Hz, ^3J(C3,H5) = 6.8 Hz, ^4J(C3,H6) = 1.3 Hz), 86.3 (C-4, ^1J = 178.2 Hz, ^2J(C4,H3) = 10.7 Hz), 59.1 (OMe, ^1J = 146.3 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −93.1 (py N), −100.2 (N-2), −181.2 (N-1); MS (m/z, %): 175 (M^+, 25), 146 (25), 79 (26), 78 (100), 63 (69); HRMS: Calcd for $C_9H_9N_3O$: 175.0746. Found: 175.0744.

2-(5-Methoxy-3-methyl-1*H*-pyrazol-1-yl)pyridine (6b)[42]

Similarly as described for the preparation of **6a**, from **1b** (175 mg, 1 mmol) and trimethylsilyldiazomethane (2.0 M in hexane, 1.63 mL, 3.25 mmol) 81 mg (43%) of **6b** were obtained as a yellowish oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.45 (ddd, 1H, py H-6, ^3J(H5,H6) = 4.9 Hz, ^4J(H4,H6) = 1.9 Hz, ^5J(H3,H6) = 0.9 Hz), 7.66 (m, 1H, py H-4, ^3J(H3,H4 = 8.3 Hz, ^3J(H4,H5) = 7.3 Hz, ^4J(H4,H6) = 1.9 Hz), 7.60 (ddd, 1H, py H-3, ^3J(H3,H4) = 8.3 Hz, ^4J(H3,H5) = 1.1 Hz, ^5J(H3,H6) = 0.9 Hz), 7.06 (ddd, 1H, py H-5, ^3J(H4,H5) = 7.3 Hz, ^3J(H5,H6) = 4.9 Hz, ^4J(H3,H5) = 1.1 Hz), 5.45 (s, 1H, H-4), 3.86 (s, 3H, OMe), 2.22 (s, 3H, 3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 156.3 (C5, ^2J(C5,H4) = 5.7 Hz, ^3J(C5,OMe) = 4.9 Hz), 150.9 (py C-2), 149.7 (C-3, ^2J(C3,3-Me) = 6.7 Hz, ^2J(C3,H4) = 3.6 Hz), 148.3 (py C-6, ^1J = 180.2 Hz, ^2J(C6,H5) = 3.6 Hz, ^3J(C6,H4) = 7.4 Hz), 137.8 (py C-4, ^1J = 163.5 Hz, ^2J(C4,H5) = 1.2 Hz, ^3J(C4,H6) = 6.7 Hz), 120.7 (py C-5, ^1J = 165.1 Hz, ^2J(C5,H4) = 1.0 Hz, ^3J(C5,H6) = 8.1 Hz, ^3J(C5,H3) = 6.3 Hz), 115.5 (py C-3, ^1J = 169.2 Hz, ^2J(C3,H4) = 1.3 Hz, ^3J(C3,H5) = 6.8 Hz, ^4J(C3,H6) = 1.4 Hz), 86.4 (C-4, ^1J = 176.3 Hz, ^3J(C4,3-Me) = 3.4 Hz), 58.9 (OMe, ^1J = 146.2 Hz), 14.4 (3-Me, ^1J = 127.5 Hz, ^3J(3-Me,H4) = 0.7 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −94.4 (py N), −105.7 (N-2), −185.7 (N-1); MS (m/z, %): 189 (M^+, 59), 188 (26), 160 (31), 119 (42), 118 (30), 117 (59), 111 (27), 93 (28), 83 (21), 79 (33), 78 (100), 67 (21), 52 (36), 51 (81).

1,5-Dimethyl-2-(2-pyridinyl)-1,2-dihydro-3*H*-pyrazol-3-one (7b)[20]

^{1}H-NMR (DMSO-d_6): δ (ppm) 8.45 (m, 1H, py H-6), 7.89 (m, 1H, py H-3), 7.78 (m, 1H, py H-4), 7.11 (m, 1H, py H-5), 5.33 (s, 1H, H-4), 3.29 (s, 3H, NMe), 2.23 (s, 3H, 5-Me); ^{13}C-NMR (DMSO-d_6): δ (ppm) 166.3 (C-3), 158.4 (C-5), 148.7 (py C-2), 148.0 (py C-6), 138.0 (py C-4), 129.2 (py C-5), 117.6 (py C-3), 97.9 (C-4), 36.3 (NMe), 12.9 (5-Me).

Ethyl 5-methoxy-1-(2-pyridinyl)-1*H*-pyrazole-4-carboxylate (8)

Similarly as described for the preparation of **6a**, from **4** (233 mg, 1 mmol) and trimethylsilyldiazomethane (2.0 M in hexane, 1.63 mL, 3.25 mmol) 88 mg (36%) of **8** were obtained as a yellowish oil. ^{1}H-NMR

($CDCl_3$): δ (ppm) 8.58 (m, 1H, py H-6), 7.96 (s, 1H, H-3), 7.84 (m, 1H, py H-4), 7.65 (m, 1H, py H-3), 7.30 (m, 1H, py H-5), 4.32 (q, 2H, OCH_2, ^3J = 7.2 Hz), 4.22 (s, 3H, OMe), 1.37 (t, 3H, Me, ^3J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$): δ (ppm) 162.1 (C=O, ^3J(CO,CH_2) = 3.2 Hz), 156.4 (C-5), 150.5 (py C-2), 148.8 (py C-6, ^1J = 181.2 Hz, ^2J(C6,H5) = 3.5 Hz, ^3J(C6,H4) = 7.6 Hz), 142.4 (C-3, ^1J = 192.1 Hz), 138.3 (py C-4, ^1J = 165.8 Hz, ^3J(C4,H6) = 6.7 Hz), 122.8 (py C-5, ^1J = 165.2 Hz, ^2J(C5,H4) = 1.0 Hz, ^2J(C5,H6) = 8.2 Hz, ^3J(C5,H3) = 6.4 Hz), 117.6 (py C-3, ^1J = 170.0 Hz, ^3J(C3,H5) = 6.9 Hz), 101.5 (C-4, ^2J(C4,H3) = 8.7 Hz), 63.4 (OMe, ^1J = 147.8 Hz), 60.2 (OCH_2, ^1J = 147.4 Hz, ^2J(CH_2,CH_3) = 4.5 Hz), 14.3 (Me, ^1J = 127.0 Hz, ^2J(CH_3,CH_2) = 2.6 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −87.5 (py N), −96.5 (N-2), −169.7 (N-1); IR (KBr): ν (cm^{-1}) 1716 (C=O); MS (m/z, %): 247 (M^+, 48), 218 (40), 202 (56), 201 (24), 200 (30), 174 (25), 145 (22), 125 (33), 92 (27), 79 (67), 78 (100), 53 (36), 51 (47). HRMS: Cald for $C_{12}H_{13}N_3O_3$: 247.0956. Found: 247.0959.

[5-Hydroxy-3-methyl-1-(2-pyridinyl)-1*H*-pyrazol-4-yl](phenyl)methanone (9b)

Method a: Under a nitrogen atmosphere, a mixture of **1b** (876 mg, 5 mmol) and triethyl orthobenzoate (4.5 mL, 4.46 g, 19.9 mmol) was heated to 200 °C for 40 min. After cooling to room temperature, 96% EtOH (15 mL) was added and the mixture was heated to reflux for 1 h. Then the solvents were removed under reduced pressure, the residue was digested with ice-cold EtOAc (35 mL) and washed with cold Et_2O to afford 999 mg (52%) of colorless crystals of mp 182–183 °C.

Method b: Under a nitrogen atmosphere, a mixture of **1b** (526 mg, 3 mmol) and benzamidine hydrochloride (705 mg, 4. mmol) was heated to 220 °C for 40 minutes. After cooling to room temperature, 96% EtOH (12 mL) and 2M NaOH (5 mL) was added and the mixture was heated to reflux for 12 h. Then H_2O was added (40 mL), the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The aqueous phase was brought to pH 5 by addition of 2M HCl and then exctracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was digested with ice-cold Et_2O (5 mL) to afford, after drying, 260 mg (31%) of **9b**. ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.96 (s, 1H, OH), 8.21 (m, 1H, py H-6), 7.94 (m, 1H, py H-3), 7.92 (m, 1H, py H-4), 7.81 (m, 2H, Ph H-2,6), 7.54 (m, 1H, Ph H-4), 7.45 (m, 2H, Ph H-3,5), 7.20 (m, 1H, py H-5), 2.49 (s, 3H, 3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 189.6 (C=O), 158.1 (C-5), 153.7 (C-3, ^2J(C3,3-Me) = 7.0 Hz), 153.5 (py C-2), 144.6 (py C-6), 140.4 (py C-4), 139.3 (Ph C-1), 131.7 (Ph C-4), 128.8 (Ph C-2,6), 127.8 (Ph C-3,5), 120.4 (py C-5), 112.7 (py C-3), 103.5 (C-4, ^3J(C4,3-Me) = 2.3 Hz), 15.1 (3-Me, ^1J = 129.0 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −114.1 (N-2), −134.2 (py N), N1 was not found; MS (m/z, %): 279 (M^+, 54), 278 (100), 202 (46), 134 (29), 105 (32), 77 (45). *Anal.* Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.76; H, 4.80; N, 15.03.

1-(2-Pyridinyl)-1*H*-pyrazol-5-yl benzoate (10a)

Under anhydrous conditions, to a suspension of **1a** (161 mg, 1 mmol) and $Ca(OH)_2$ (148 mg, 12 mmol) in

dry 1,4-dioxane (2 mL) a solution of benzoyl chloride (141 mg, 1 mmol) in dry 1,4-dioxane (2 mL) was added. The reaction mixture was heated at reflux for 2 h under stirring. After cooling to room temperature, the mixture was treated with 2 M HCl (8 mL), stirred for 1 h, and poured into H_2O (20 mL). Then the mixture was neutralized with aqueous Na_2CO_3 and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel, eluent: EtOAc–CH_2Cl_2, 1:1) to afford 91 mg(34 %) of colorless crystals of mp 69 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.21 (m, 3H, py H-6 and Ph H-2,6), 7.86 (m, 1H, py H-3), 7.80 (m, 1H, py H-4), 7.70 (d, 1H, H-3, ^3J(H3,H4) = 1.8 Hz), 7.66 (m, 1H, Ph H-4), 7.52 (m, 2H, Ph H-3,5), 7.15 (m, 1H, py H-5), 6.37 (d, 1H, H-4, ^3J(H3,H4) = 1.8 Hz); ^{13}C-NMR ($CDCl_3$): δ (ppm) 163.4 (C=O), 151.9 (py C-2), 147.9 (py C-6), 145.6 (C-5), 140.5 (C-3, ^1J = 188.4 Hz, ^2J(C3,H4) = 4.6 Hz), 138.4 (py C-4), 133.9 (Ph C-4), 130.6 (Ph C-2,6), 128.62 (Ph C-1), 128.56 (Ph C-3,5), 121.7 (py C-5), 115.4 (Py C-3), 98.3 (C-4, ^1J = 182.3 Hz, ^2J(C4,H3) = 10.4 Hz; ^{15}N-NMR ($CDCl_3$): δ (ppm) −93.3 (N-2), −94.9 (py N), −174.3 (N-1); IR (KBr): ν (cm^{-1}) 1747 (C=O); MS (m/z, %): 265 (M^+, 7), 105 (100), 77 (20), 51 (11). *Anal.* Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.08; H, 4.26; N, 15.56.

3-Methyl-1-(2-pyridinyl)-1*H*-pyrazol-5-yl benzoate (10b)

Similarly as described for the preparation of **10a**, from **1b** (175 mg, 1 mmol) and benzoyl chloride (141 mg, 1 mmol) 168 mg (60%) of **10b** were obtained as colorless crystals of mp 59–61 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.20 (m, 2H, Ph H-2,6), 8.19 (m, 1H, py H-6), 7.80 (m, 1H, py H-3), 7.75 (m, 1H, py H-4), 7.65 (m, 1H, Ph H-4), 7.51 (m, 2H, Ph H-3,5), 7.09 (m, 1H, py H-5), 6.19 (s, 1H, H-4), 2.37 (s, 3H, Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 163.3 (C=O), 151.8 (py C-2), 149.8 (C-3, ^2J(C3,3-Me) = 6.8 Hz, ^2J(C3,H4) = 4.1 Hz), 147.9 (py C-6), 145.5 (C-5), 138.2 (py C-4), 133.8 (Ph C-4), 130.5 (Ph C-2,6), 128.7 (Ph C-1), 128.6 (Ph C-3,5), 121.2 (py C-5), 115.1 (Py C-3), 98.2 (C-4, ^1J = 180.3 Hz, ^3J(C4,3-Me) = 3.4 Hz), 14.6 (3-Me, ^1J = 127.8 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −95.4 (py N), −98.2 (N-2), −178.8 (N-1); IR (KBr): ν (cm^{-1}) 1755 (C=O); MS (m/z, %): 279 (M^+, 5), 105 (100), 78 (22), 77 (67), 51 (35). *Anal.* Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.95; H, 4.87; N, 15.03.

Reaction of 1b with triethyl orthopropionate – compounds 11b and 12b

A mixture of **1b** (175 mg, 1 mmol) and triethyl orthopropionate (176 mg, 1 mmol) in toluene (2 mL) was was heated to reflux for 1 h. Then the solvent was removed under reduced pressure and the residue was washed with diisopropyl ether to afford 36 mg (14%) of (4*E*)-4-(1-ethoxypropylidene)-5-methyl-2-(2-pyridinyl)-2,4-dihydro-3*H*-pyrazol-3-one (**11b**) as red crystals of mp 92 °C. The product hydrolized to 1-[5-hydroxy-3-methyl-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-1-propanone (**12b**) on treatment with 96% EtOH to give 23 mg (10%) of colorless crystals of mp 115–118 °C (EtOH).

Compound **11b**: ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.50 (m, 1H, py H-6), 8.14 (m, 2H, py H-3, py H-4), 7.04 (m, 1H, py H-5), 4.37 (q, 2H, OCH_2, ^{3}J = 7.0 Hz), 3.21 (q, 2H, CCH_2, ^{3}J = 7.5 Hz), 2.39 (s, 3H, 5-Me), 1.47 (t, 3H, $OCH_2C\underline{H}_3$, ^{3}J = 7.0 Hz), 1.28 (t, 3H, $CCH_2C\underline{H}_3$, ^{3}J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$): δ (ppm) 182.3 (C=$\underline{C}$-O), 165.7 (C-3), 149.8 (C-5, ^{2}J(C5,5-Me) = 7.6 Hz), 149.8 (py C-2), 148.5 (py C-6), 137.6 (py C-4), 119.7 (py C-5), 114.0 (py C-3), 107.3 (C-4), 64.7 (OCH_2), 20.6 ($C\underline{C}H_2$), 17.9 (5-Me, ^{1}J = 129.3 Hz), 14.8 ($OCH_2\underline{C}H_3$), 11.6 ($CCH_2\underline{C}H_3$).

Compound **12b**: ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.28 (m, 1H, py H-6), 7.91 (m, 2H, py H-3, py H-4), 7.20 (m, 1H, py H-5), 2.84 (q, 2H, CH_2, ^{3}J = 7.2 Hz), 2.47 (s, 3H, 3-Me), 1.16 (t, 3H, $CH_2C\underline{H}_3$, ^{3}J = 7.2 Hz), OH was not unambiguously assigned; ^{13}C-NMR ($CDCl_3$): δ (ppm) 195.7 (C=O), 159.1 (C-5), 152.9 (C-3), 150.5 (py C-2), 144.8 (py C-6), 140.3 (py C-4), 120.4 (py C-5), 112.6 (py C-3), 104.1 (C-4), 34.5 (CH_2, ^{1}J = 126.4 Hz, , ^{2}J(CH_2,CH_3) = 7.0 Hz), 15.5 (3-Me, ^{1}J = 128.9 Hz), 8.0 ($CH_2\underline{C}H_3$, ^{1}J = 127.5 Hz, ^{2}J(CH_3,CH_2) = 4.4 Hz); MS (m/z, %): 231 (M^+, 19), 202 (100), 134 (20), 104 (40), 93 (16), 78 (11), 67 (13), 49 (27). HRMS: Cald for $C_{12}H_{13}N_3O_2$: 231.1008. Found: 231.1003.

(4*Z*)-4-{[5-Hydroxy-3-methyl-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]methylene}-5-methyl-2-(2-pyridinyl)-2,4-dihydro-3*H*-pyrazol-3-one (13b)

A mixture of **1b** (175 mg, 1 mmol) and triethyl orthoformate (106 mg, 1mmol) was heated to 140 °C for 1 h. The solid material obtained after cooling was washed with diisopropyl ether and recrystallized from EtOH to afford 61 mg (34%) of orange needles, mp 237 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 17.87 (1H, OH), 8.60 (m, 2H, py H-6), 7.99 (m, 2H, py H-3), 7.81 (m, 2H, py H-4), 7.29 (s, 1H, CH), 7.23 (m, 2H, py H-5), 2.42 (s, 6H, 3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 162.2 (C-5, ^{3}J(C5,CH) = 10.0 Hz), 153.5 (C-3, ^{2}J(C3,3-Me) = 6.9 Hz, ^{3}J(C3,CH) = 5.7 Hz), 149.5 (py C-2), 148.9 (py C-6), 138.9 (alkene C-H, ^{1}J = 148.2 Hz), 138.1 (py C-4), 122.0 (py C-5), 116.1 (py C-3), 109.7 (C-4, ^{3}J(C4,3-Me) = 2.4 Hz, ^{2}J(C4,CH) = 2.4 Hz), 13.0 (3-Me, ^{1}J = 128.7 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −92.9 (py N), −93.6 (N-2), −180.4 (N-1); IR (KBr): ν (cm^{-1}) 3430 (OH), 1628 (C=O); MS (m/z, %): 360 (M^+, 40), 345 (88), 343 (76), 230 (20), 79 (46), 78 (100). *Anal.* Calcd for $C_{19}H_{16}N_6O_2$: C, 63.33; H, 4.47; N, 23.32. Found: C, 63.27; H, 4.41; N, 23.21.

(4*Z*)-4-[Amino(phenyl)methylene]-5-methyl-2-(2-pyridinyl)-2,4-dihydro-3*H*-pyrazol-3-one (14b)

Under a nitrogen atmosphere, a mixture of **1a** (350 mg, 2 mmol) and benzamidine hydrochloride (329 mg, 2.1 mmol) was heated to 220 °C for 1 h. After cooling to room temperature, 96% EtOH (3 mL) was added and the mixture was refluxed for 5 min, before it was stored in the deep freezer for some hours. The precipitate was filtered off and washed with a few ice-cold EtOH to afford **14b**•HCl as a yellow powder. The latter was dissolved in H_2O (20 mL), the solution was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and

evaporated under reduced pressure. The residue was recrystallized from MeCN to give 178 mg (32 %) of apricot-colored crystals with mp 223–228 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 10.30 (s, 1H, NH···O), 8.39 (m, 1H, py H-6), 8.17 (m, 1H, py H-3), 7.71 (m, 1H, py H-4), 7.53 (m, 1H, Ph H-4), 7.46 (m, 2H, Ph H-3,5), 7.43 (m, 2H, Ph H-2,6), 7.03 (m, 1H, py H-5), 6.65 (s, 1H, NH), 1.66 (s, 3H, 5-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 166.5 (C-3), 165.4 (N-C-Ph), 150.6 (py C-2), 149.1 (C-5, ^{2}J(C5,5-Me) = 7.0 Hz), 148.4 (py C-6), 137.7 (py C-4), 134.2 (Ph C-1), 131.0 (Ph C-4), 128.7 (Ph C-3,5), 127.6 (Ph C-2,6), 119.8 (py C-5), 113.9 (py C-3), 99.8 (C-4), 16.3 (5-Me, ^{1}J = 128.7 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −99.5 (N-1 and py N), −269.7 (NH_2), N-2 was not found; MS (m/z, %): 279 (M^+, 9), 278 (54), 277 (100), 134 (11), 104 (12), 78 (16), 66 (16). *Anal.* Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.94; H, 5.19; N, 20.34.

(4*E*)-4-[(Dimethylamino)methylene]-2-(2-pyridinyl)-2,4-dihydro-3*H*-pyrazol-3-one (15a)

A mixture of **1a** 161 mg (1 mmol) and dimethylformamide diethyl acetal (147 mg, 1 mmol) in toluene (5 mL) was heated to reflux for 3 h. On cooling, an orange solid precipitated which was filtered off and recrystallized from toluene to afford 172 mg (80%) of orange-yellow crystals, mp 193 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.48 (m, 1H, py H-6), 8.25 (m, 1H, py H-3), 7.76 (s, 1H, H-5), 7.71 (m, 1H, py H-4), 7.53 (s, 1H, =CH), 7.05 (m, 1H, py H-5), 3.32 (s, 3H, NMe *cis* to =CH), 3.24 (s, 3H, NMe *trans* to =CH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 166.4 (C-3, ^{3}J(C3,H5) = 4.7 Hz, ^{3}J(C3,=CH) = 3.9 Hz), 150.8 (=CH, ^{1}J = 168.3 Hz, ^{3}J(=CH,NMe_{cis}) = 4.0 Hz, ^{3}J(=CH,NMe_{trans}) = 3.4 Hz), 150.8 (py C-2, ^{3}J(C2,H6) = 12.3 Hz, ^{3}J(C2,H4) = 9.1 Hz, ^{4}J(C2,H5) = 1.1 Hz), 148.4 (py C-6, ^{1}J = 179.4 Hz, ^{2}J(C6,H5) = 3.6 Hz, ^{3}J(C6,H4) = 7.6 Hz), 138.4 (C-5 ^{1}J = 189.2 Hz, ^{3}J(C5,=CH) = 7.4 Hz), 137.7 (py C-4, ^{1}J = 162.1 Hz, ^{2}J(C4,H5) = 1.2 Hz, ^{3}J(C4,H6) = 6.7 Hz), 119.9 (py C-5, ^{1}J = 164.5 Hz, ^{2}J(C5,H6) = 8.0 Hz, ^{3}J(C5,H3) = 6.6 Hz), 114.0 (py C-3, ^{1}J = 169.7 Hz, ^{2}J(C3,H4) = 1.8 Hz, ^{3}J(C3,H5) = 6.7 Hz, ^{4}J(C3,H6) = 1.8 Hz), 100.1 (C-4, ^{2}J(C4,H5) = 11.2 Hz, ^{2}J(C4,=CH) = 1.8 Hz), 47.2 (NMe *cis* to =CH, ^{1}J = 139.8 Hz, ^{3}J(NMe,=CH) = 5.2 Hz, ^{3}J(NMe,NMe) = 3.2 Hz), 40.6 (NMe *trans* to =CH, ^{1}J = 139.4 Hz, ^{3}J(NMe,=CH) = 7.3 Hz, ^{3}J(NMe,NMe) = 3.5 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −90.2 (N-1), −99.2 (py N), −180.5 (N-2), −269.9 (NMe_2); IR (KBr): ν (cm^{-1}) 1684 (C=O). MS (m/z, %): 216 (M^+, 100), 201 (39), 145 (40), 82 (20), 78 (22), 51 (16), 42 (44). *Anal.* Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 60.89; H, 5.35; N, 25.68.

(4*Z*)-4-[(Dimethylamino)methylene]-5-methyl-2-(2-pyridinyl)-2,4-dihydro-3*H*-pyrazol-3-one (15b)

Similarly as described for the preparation of **15a**, from **1b** (175 mg, 1 mmol) and dimethylformamide diethyl acetal (147 mg, 1 mmol) 174 mg (76%) of **15b** were obtained as yellow crystals of mp 181 °C (toluene) (lit.[43]: mp 180 °C). ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.49 (m, 1H, py H-6), 8.16 (m, 1H, py H-3), 7.67 (m, 1H, py H-4), 7.01 (m, 1H, py H-5), 7.00 (s, 1H, =CH), 3.83 (s, 3H, NMe *trans* to =CH), 3.29 (s, 3H, NMe *cis* to =CH), 2.21 (s, 3H, 5-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 162.6 (C-3, ^{3}J(C3,=CH) = 8.5 Hz), 152.3

(=CH, ^1J = 162.5 Hz, ^3J(=CH,NMe) = 3.8 Hz), 151.6 (C-5, ^2J(C5,5-Me) = 6.9 Hz, ^3J(C5,=CH) = 4.1 Hz), 151.0 (py C-2), 148.4 (py C-6), 137.4 (py C-4), 119.4 (py C-5), 114.1 (py C-3), 99.2 (C-4, ^2J(C4,=CH) = 2.4 Hz, ^3J(C4,5-Me) = 2.4 Hz), 48.0 (NMe *cis* to =CH, ^1J = 139.3 Hz, ^3J(NMe,=CH) = 5.5 Hz, ^3J(NMe,NMe) = 3.8 Hz), 43.4 (NMe *trans* to =CH, ^1J = 140.3 Hz, ^3J(NMe,=CH) = 7.7 Hz, ^3J(NMe,NMe) = 3.0 Hz), 13.6 (5-Me, ^1J = 127.8 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −98.8 (py N), −100.6 (N-1), −182.0 (N-2), −264.7 (NMe_2); IR (KBr): ν (cm^{-1}) 1671 (C=O). MS (m/z, %): 230 (M^+, 100), 215 (76), 188 (28), 186 (26), 145 (38), 107 (30), 96 (29), 78 (57), 53 (31), 51 (24).

4,4'-(Phenylmethylene)bis[1-(2-pyridinyl)-1*H*-pyrazol-5-ol] (16a)

A mixture of **1a** (161 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol) in toluene (1 mL) was stirred at 80 °C for 3 h. Then the solvent was largely removed under reduced pressure and the residue was cooled to 5 °C. The precipitated crystals were washed with cold ether and dried to give 123 mg (60%) of colorless crystals, mp 179 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.63 (s, 2H, OH), 8.22 (m, 2H, py H-6), 7.90 (m, 2H, py H-3), 7.85 (m, 2H, py H-4), 7.44 (s, 2H, H-3), 7.40 (m, 2H, Ph H-2,6), 7.31 (m, 2H, Ph H-3,5), 7.21 (m, 1H, Ph H-4), 7.13 (m, 2H, py H-5), 5.24 (s, 1H, CH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 154.5 (py C-2), 152.7 (C-5), 145.1 (py C-6), 143.2 (Ph C-1), 142.3 (C-3, ^1J = 184.4 Hz, ^3J(C3,CH) = 5.0 Hz), 139.8 (py C-4), 128.3 (Ph C-3,5), 127.9 (Ph C-2,6), 126.2 (Ph C-4), 120.0 (py C-5), 112.1 (py C-3), 104.1 (C-4, ^2J(C4,H-3) = 8.6 Hz, ^2J(C4,CH) = 8.6 Hz), 33.8 (CH, ^1J =127.4 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −116.4 (N-2), −129.4 (py N), −186.4 (N-1); IR (KBr): ν (cm^{-1}) 1599; MS (m/z,%): 410 (M^+, 3), 250 (61), 249 (68), 221 (45), 220 (51), 161 (72), 120 (43), 115 (37), 94 (25), 79 (69), 78 (100), 67 (21), 52 (30), 51 (42). *Anal.* Calcd for $C_{23}H_{18}N_6O_2$: C, 67.31; H, 4.42; N, 20.48. Found: C, 67.25; H, 4.35; N, 20.26.

4,4'-(Phenylmethylene)bis[3-methyl-1-(2-pyridinyl)-1*H*-pyrazol-5-ol] (16b)

Similarly as described for the preparation of **16a**, from **1b** (175 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol) were obtained 158 mg (72 %) of colorless crystals, mp 168–173 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.68 (broad s , 2H, OH), 8.16 (m, 2H, py H-6), 7.85 (m, 2H, py H-3), 7.80 (m, 2H, py H-4), 7.34 (m, 2H, Ph H-2,6), 7.30 (m, 2H, Ph H-3,5), 7.22 (m, 1H, Ph H-4), 7.06 (m 1H, py H-5), 5.28 (s, 1H, CH), 2.10 (s, 3H, 3-Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 154.4 (py C-2), 153.5 (C-5, ^3J(C5,CH) = 5.6 Hz), 151.4 (C-3), 144.9 (py C-6), 141.4 (Ph C-1), 139.6 (Ph C-4), 128.2 (Ph C-2,6), 128.0 (Ph C-3,5), 126.0 (Ph C-4), 119.2 (py C-5), 111.7 (py C-3), 101.0 (C-4), 33.7 (CH, ^1J = 124.3 Hz, ^3J(CH,PhC-2,6) = 4.0 Hz), 13.7 (3-Me, ^1J = 127.5 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −121.1 (N-2), −130.6 (Py N), −199.1 (N-1); IR (KBr): ν (cm^{-1}) 1599; MS (m/z,%): 438 (M^+, 1), 264 (24), 263 (81), 262 (23), 248 (32), 234 (39), 221 (30), 220 (34), 175 (100), 160 (22), 134 (37), 128 (47), 127 (23), 91 (27), 79 (78), 78 (78), 52 (35), 51 (44). *Anal.* Calcd for $C_{25}H_{22}N_6O_2$: C, 68.48; H, 5.06; N, 19.17. Found: C, 68.50; H, 5.13; N, 18.88.

ACKNOWLEDGEMENTS

We are grateful to Dr. L. Jirovetz for recording the MS spectra.

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