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NEW 1-SUBSTITUTED 4-CINNAMOYL-5-HYDROXYPYRAZOLES AND PRECURSORS THEREOF: SYNTHESIS, RING CLOSURE REACTIONS AND NMR-SPECTROSCOPIC INVESTIGATIONS

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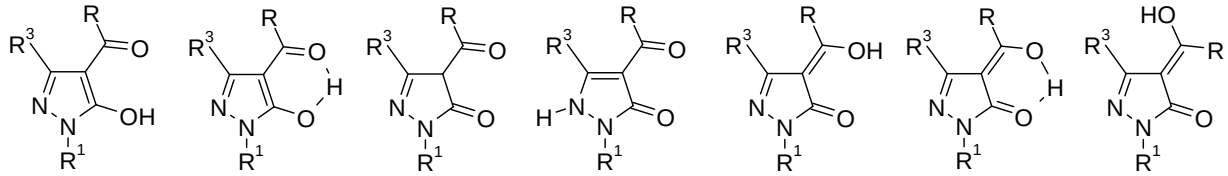
Abstract – Reaction of 1-substituted 5-hydroxy-1*H*-pyrazoles (pyrazolones) with *trans*-cinnamoyl chloride / calcium hydroxide in dioxane affords the corresponding 4-cinnamoyl-5-hydroxy-1*H*-pyrazoles. Cyclization of the latter into 5,6-dihydropyrano[2,3-*c*]pyrazol-4-ones proceeds in very low yields upon treatment with concentrated sulfuric acid. 1,6-Diphenyl-1*H*-pyrano[2,3-*c*]pyrazol-4-one was synthesized by reaction of of 4-acetyl-5-hydroxy-1-phenyl-1*H*-pyrazole with benzoyl chloride and lithium bis(trimethylsilyl)amide and subsequent cyclization of the thus obtained 1,3-diketone. NMR-spectroscopic investigations with the obtained 4-substituted 5-hydroxypyrazoles and their precursors regarding their tautomeric behavior in various solvents are presented.

INTRODUCTION

Prototropic tautomerism of heteroaromatic compounds has been extensively studied for a long period.[1,2] Within this field there is ongoing interest in the tautomerism of pyrazolones (2,4-dihydro-3*H*-pyrazol-3-ones, 1,2-dihydro-3*H*-pyrazol-3-ones, 1*H*-pyrazol-5-ols, according to Chemical Abstracts nomenclature) and a considerable number of studies have been devoted to this problem. Pyrazolones with an acyl or aroyl group attached at position 4 of the heterocyclic moiety represent a particular challenge 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 (Scheme 1).[1-9]

Scheme 1. Tautomeric forms of 4-acylpyrazolones

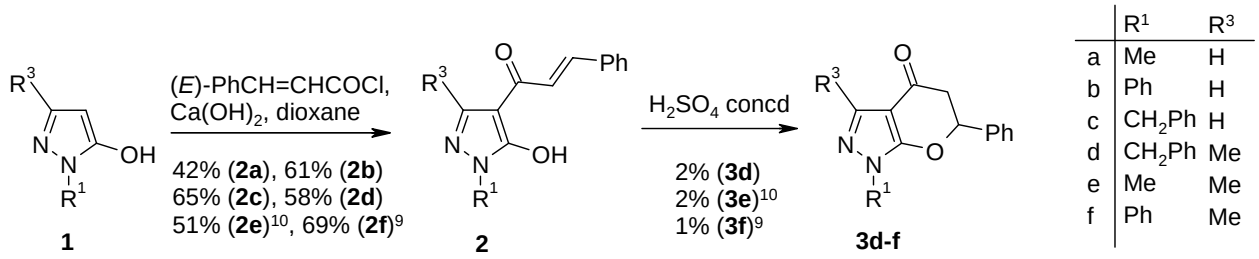


Among such 4-acylpyrazolones the 4-cinnamoyl substituted congeners (R = CH=CH-Ph) turned out to be of special interest. Thus, for instance, with 4-cinnamoyl-1,3-dimethyl-5-hydroxy-1*H*-pyrazole (**2e** in Scheme 2) the phenomenon of desmotropy was observed in the solid state.[8,10] X-Ray structure analyses revealed orange crystals of **2e** – obtained by recrystallization from light petroleum – to be the OH-tautomer stabilized by an intramolecular hydrogen bond (form **A'** in Scheme 1), whereas yellow **2e** crystallized from 96% ethanol exists as hydrate in the NH-form (form **C**).[8] In contrast, crystals of 4-cinnamoyl-3-methyl-1-phenyl-5-hydroxy-1*H*-pyrazole (**2f** in Scheme 2), obtained from $CDCl_3$, showed an exocyclic enol structure of type **D'**, the completely flat molecule again stabilized by a strong intramolecular hydrogen bond.[9] The latter compound was the first and only proven example for a crystalline pyrazolone to be present in such an isomeric form. The situation in solution is more complicated as such pyrazolones can simultaneously exist as a mixture of two or more tautomers. Detailed NMR spectroscopic investigations revealed pyrazolone (**2f**) to exist solely or far predominantely as OH tautomer (**A'**) in $CDCl_3$ or benzene-d_6 solution, whereas in DMSO-d_6 beneath the OH-form also some amount of NH-isomer is probable.[9] For compound (**2e**) existence in form **A'** in $CDCl_3$ and as isomer **B** in DMSO-d_6 was suggested.[8] As the distribution of isomeric pyrazolone forms was found to be strongly dependent from substituents, concentration and temperature[7] it seemed appropriate to synthesize novel 4-cinnamoylpyrazolones of type (**2**) in order to study their tautomerism in solution. Moreover, it was found that compounds (**2e**)[10] as well as (**2f**)[9,11] can be cyclized into the corresponding 3-methyl-5,6-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-4-ones (**3e**, **3f**) in only low yields (Scheme 2).[9,10] Thus, it was also of interest for us if other pyrazolones (**2**) show a similar reaction behavior.

RESULTS AND DISCUSSION

The synthesis of the novel 4-cinnamoylpyrazolones (**2a-d**) was carried out according to the method described by Jensen.[12] Reaction of 5-hydroxypyrazoles (**1a-d**) with *trans*-cinnamoyl chloride and calcium hydroxide in dioxane afforded the mostly orange products of type (**2**) in reasonable yields (Scheme 2).

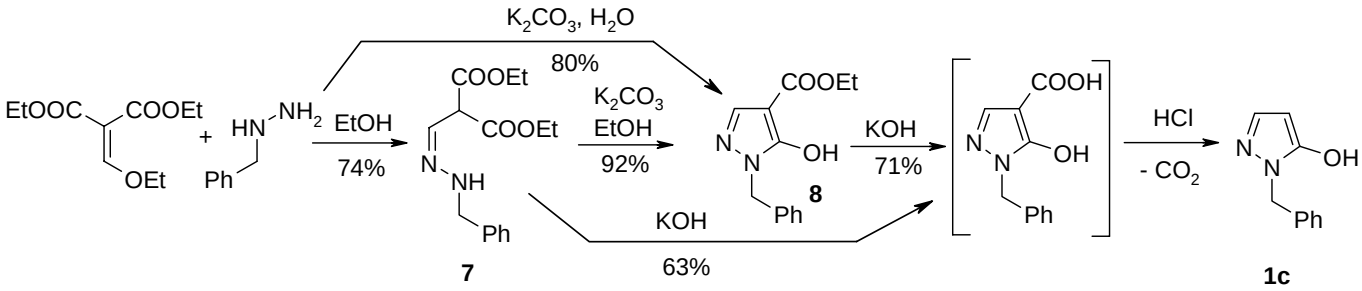
Scheme 2. Synthesis of 4-cinnamoyl-5-hydroxypyrazoles and cyclization into 5,6-dihydropyrano[2,3-*c*]pyrazol-4-ones



	R^1	R^3
a	Me	H
b	Ph	H
c	CH_2Ph	H
d	CH_2Ph	Me
e	Me	Me
f	Ph	Me

The required educts (**1a**), (**1b**) and (**1d**) were synthesized according to known procedures,[13-15] however, as the described syntheses for **1c** appeared tedious or complicated[16-19] this compound was prepared according to Scheme 3. Reaction of diethyl ethoxymethylenemalonate with benzylhydrazine led to hydrazone (**7**), which – in a one-pot reaction comprising cyclization, ester hydrolysis and decarboxylation – was converted into 1-benzyl-5-hydroxy-1*H*-pyrazole (**1c**). Alternatively, the ester (**8**) – available in good yields upon reaction of diethyl ethoxymethylenemalonate with benzylhydrazine in aqueous potassium carbonate[20] or by treatment of **7** with potassium carbonate in dry ethanol – was transformed into **1c** by prolonged heating with potassium hydroxide in methanol - water followed by treatment with concentrated hydrochloric acid (Scheme 3).

Scheme 3. Synthesis of 1-benzyl-5-hydroxypyrazole (**1c**)

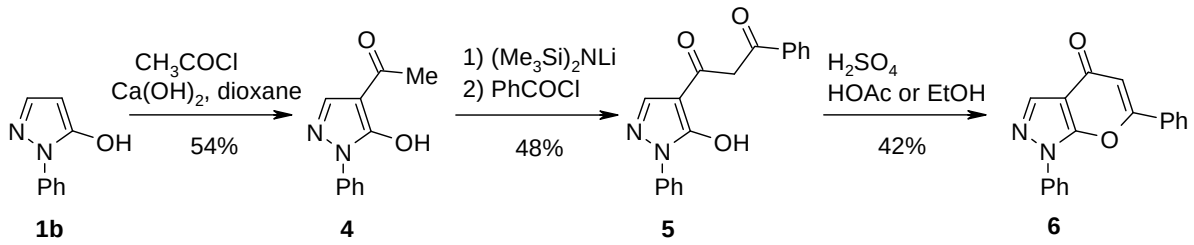


As mentioned above, the cyclization of cinnamoylpyrazolones (**2e, f**) into the corresponding bicyclic systems (**3e, f**) in concentrated sulfuric acid is characterized by very low yields.[9,10] Although unchanged educt can be recovered nearly quantitatively and used for another cyclization run, it is tedious to produce appropriate quantities of compounds (**3**) in such a way. In the light of these findings model compounds (**2b**), (**2d**) and (**2f**) were subjected to a number of reaction conditions which were found to be suitable for the cyclization of 2'-hydroxychalcones into flavanones.[21] In addition to the 'classical' conditions

(treatment of the educts with various diluted acids or bases, such as hydrochloric or phosphoric acid in ethanol, treatment with aqueous sodium hydroxide, sodium acetate in aqueous ethanol)[21] also the more recently used systems NH_4OH / tetraethylammonium hydroxide in benzene - water,[22] or treatment with activated silica gel in dichloromethane[23] were applied, however, without any success. Only by treatment with concentrated sulfuric acid the novel 4-cinnamoylpyrazolone (**2d**) could be converted into the corresponding 'flavanone' (**3d**), however, in the usual low yield (Scheme 2).

One of the most relevant methods for the synthesis of pyrano[2,3-*c*]pyrazol-4-ones consists in transformation of 4-acetyl-5-hydroxypyrazoles into the corresponding 4-acylacetyl congeners *via* base-induced Claisen condensation and subsequent cyclization of thus obtained β-diketones under acidic conditions.[24-26] Employing a similar synthetic route the synthesis of a series of biologically active 3-methyl-1-phenylpyrano[2,3-*c*]pyrazol-4-ones starting from 3-methyl-5-hydroxy-1-phenyl-1*H*-pyrazole (**1f**) was accomplished recently.[27] To obtain a – hitherto unknown – representative having no substituent attached at position 3 of the bicyclic system we adopted the latter synthesis[27] starting with 5-hydroxy-1-phenylpyrazole (**1b**) as the educt (Scheme 4). Reaction of **1b** with acetyl chloride and calcium hydroxide in dioxane furnished the 4-acetyl-5-hydroxypyrazole (**4**), which was transformed into the β-diketone (**5**) by treatment with lithium bis(trimethylsilyl)amide followed by addition of benzoyl chloride. Cyclization of **5** with sulfuric acid in glacial acetic acid or in dry ethanol finally afforded the desired pyrano[2,3-*c*]pyrazole (**6**) (Scheme 4).

Scheme 4. Synthesis of pyrano[2,3-*c*]pyrazole (**6**)



NMR SPECTROSCOPIC INVESTIGATIONS

Unambiguous assignment for all proton and carbon resonances was achieved on basis of NOE-difference[28] and 1D-TOCSY[29] experiments, fully ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling), APT,[30] HMQC,[31] 1D-HETCOR,[32] and long-range INEPT spectra with selective excitation.[33,34]

4-Cinnamoyl-5-hydroxypyrazoles (2)

From detailed NMR spectroscopic investigations with **2f** its occurrence as OH-tautomer (**A'**) in $CDCl_3$ or benzene-d_6 solution (a minor amount of **D'** cannot be excluded) and, probably, a mixture of OH and NH-tautomer in DMSO-d_6 solution (fast exchange compared to the NMR timescale) with the former species predominating was concluded.[9] The presence of CH-isomer (**B**) is not probable for it is known that proton transfer between pyrazole C-4 and OH or NH is usually slow[35] and thus an additional signal set would be expected for isomer (**B**) which, however, was not observed. In the light of these findings similar NMR investigations were also performed with 4-cinnamoylpyrazolones (**2a-e)**. In Table 1, relevant ^{1}H-NMR spectral and ^{13}C-NMR chemical shifts of **2a-f** are summarized revealing consistency of the obtained data. As reported for **2f**, also in the spectra of **2a-e** line broadening was observed for a number of signals, especially in DMSO-d_6 solution (see Experimental), indicating a dynamic behavior.

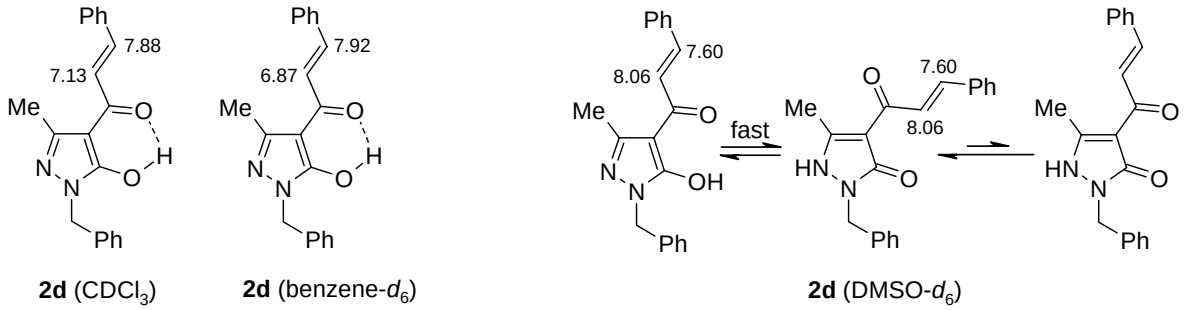
Table 1. Selected ^{1}H and ^{13}C-NMR chemical shifts of 4-cinnamoyl-5-hydroxypyrazoles (**2**)

	comp.	δ (^{1}H)			δ (^{13}C)				
	No.	OH	COC**H**=	=C**H**Ph	C-5	C-4	C=O	CO**C**H=	=**C**HPh
$CDCl_3$	**2a**	10.53	7.04	7.81	160.1	104.1	183.4	121.0	143.3
	2b	12.05	7.05	7.88	162.3	105.2	180.4	119.6	144.0
	2c	7.65	7.05	7.84	160.6	104.3	182.9	120.8	143.6
	2d	11.73	7.13	7.88	163.8	103.6	180.3	120.3	143.5
	2e	10.20	7.14	7.87	162.9	103.1	180.7	120.3	143.0
	2f	13.72	7.10	7.89	165.2	104.7	177.7	119.1	143.9
DMSO-d_6	**2a**	7.18	7.60	7.62	155.9	105.6	181.7	123.6	140.8
	2b	11.79	7.75	7.73	159.4	106.1	178.9	121.8	142.1
	2c	6.11	7.63	7.63	156.2	105.7	181.5	123.5	140.9
	2d	11-14	8.06	7.60	160.5	104.3	182.6	124.9	139.7
	2e	10.70	7.95	7.58	159.9	104.3	182.6	124.9	139.7
	2f	9-12	7.90	7.69	161.8	104.8	180.6	123.3	140.9
benzene-d_6	**2a**	11.10	6.78	7.92	160.7	104.4	183.6	121.7	143.1
	2b	10.75	6.57	7.81	163.5	105.7	179.7	119.9	143.6
	2c	10.02	6.71	7.87	161.2	104.6	182.9	121.3	143.2
	2d	13.91	6.87	7.92	164.4	104.0	180.3	121.0	143.1
	2f	10-12	6.75	7.85	166.4	105.3	177.0	119.6	143.4

With **2a-f** in $CDCl_3$ or in benzene-d_6 solution the signal of the proton α to the carbonyl moiety (COC**H**=) shows a markedly smaller chemical shift than that of the corresponding β-proton (=C**H**Ph). However, in DMSO-d_6 a reverse order was observed for 3-methyl substituted pyrazoles (**2d-f**) and similar chemical

shift values for α– and β-protons were found with 3-unsubstituted congeners (**2a-c**). A possible explanation for this phenomenon is the occurrence of NH-isomer in DMSO-d_6 solution with the α-proton receiving a downfield shift due to the magnetic anisotropy of the spatially close pyrazolone C=O moiety considering the most stable rotamer (Figure 1).[9] The corresponding ^{13}C-NMR chemical shifts of the alkene carbon atoms cannnot be affected in such a way, expectedly δ (CO**C**H=) is always smaller than δ (=**C**HPh). Nevertheless, ^{13}C chemical shifts of =**C**HPh decrease and those of CO**C**H= increase when switching from $CDCl_3$ (or benzene-d_6) to DMSO-d_6 solutions (Table 1).

Figure 1. Diagnostic ^{1}H-NMR chemical shifts in **2d**



2d ($CDCl_3$) **2d** (benzene-d_6) **2d** (DMSO-d_6)

The presence of NH-isomer in DMSO-d_6 is also indicated by the results of NOE-difference experiments. Thus, for instance, in this solvent irradiation of the transition due to the acidic proton of **2b** leads to a clear NOE to the characteristic singlet signal of pyrazole H-3 (and to that of N-Ph H-2,6) (Figure 2), whereas in $CDCl_3$ such a through-space interaction was not observed (Figure 3). As spatial closeness of acidic proton and pyrazole H-3 is only the case in the NH-form the observed NOE hints to a contribution of this species to the overall tautomeric composition in DMSO-d_6.

An additional hint concerning the tautomeric behavior can be extracted from the magnitude of the geminal ^2J(pyrazole C-4, pyrazole H-3) coupling constant in compounds (**2a-c**). In pyrazoles having an intact lone-pair adjacent the the coupled pyrazole H-3 atom this coupling constant was found to be approximately 10 Hz, whereas in 1-alkyl-1,2-dihydro-3*H*-pyrazol-3-ones values in the range of 4-5 Hz were observed (detailed investigations regarding this phenomenon will be published elsewhere). As **2a-c** in $CDCl_3$ or benzene-d_6 solution showed values for ^2J(C-4,H-3) of 10.4-11.1 Hz the presence of NH-form can be practically excluded. In DMSO-d_6 this coupling constant is somewhat reduced (9.7-9.8 Hz), what is in accordance with the above findings indicating a mixture of NH and OH form (fast exchange) with the latter predominating. It shall be emphasized that for pyrano[2,3-*c*]pyrazol-4-one (**6**), which can be seen as 'fixed' OH-tautomer, ^2J(C-4,H-3) was found to be 10.3 Hz what fully supports the above considerations.

Figure 2. NOE-difference spectrum of **2b** obtained upon irradiation of the transition due to the acidic proton (in DMSO-d_6)

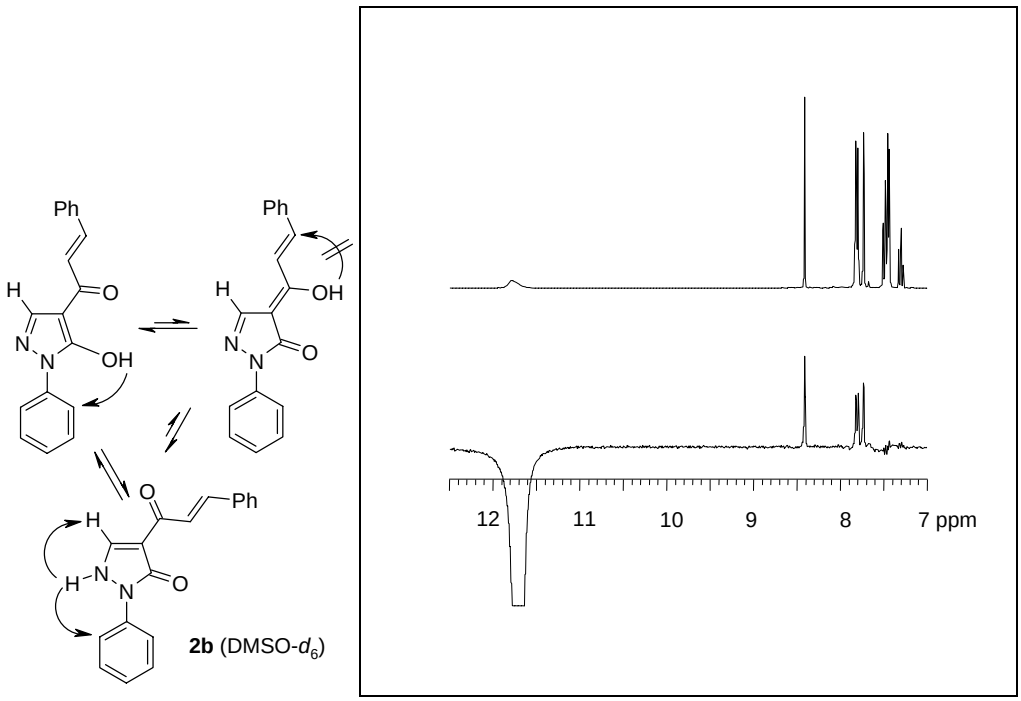


Figure 3. NOE-difference spectrum of **2b** obtained upon irradiation of the transition due to the acidic proton (in $CDCl_3$)

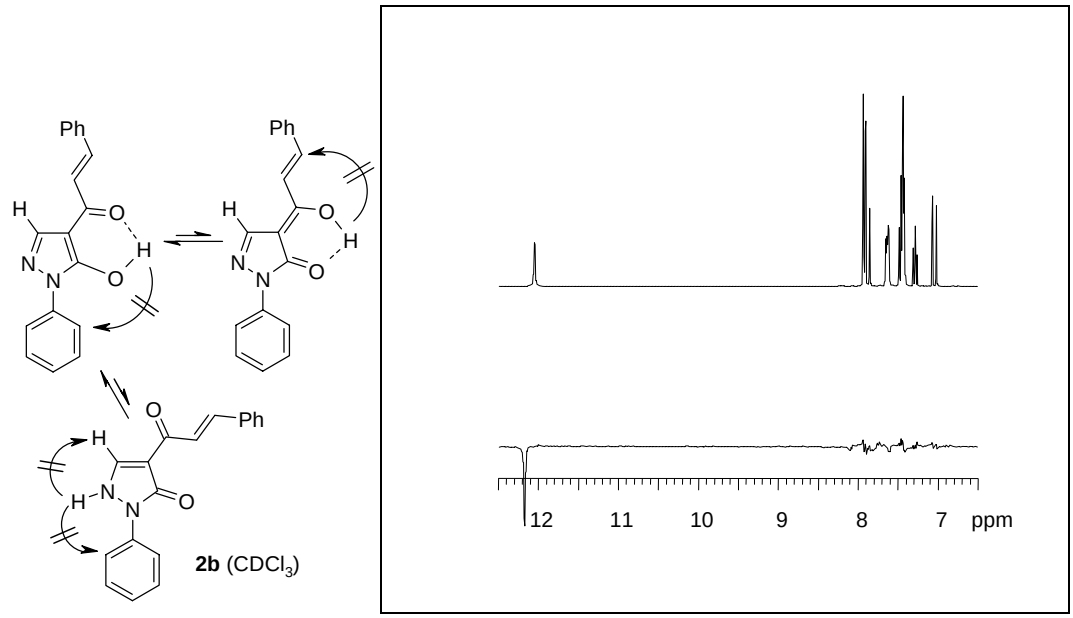
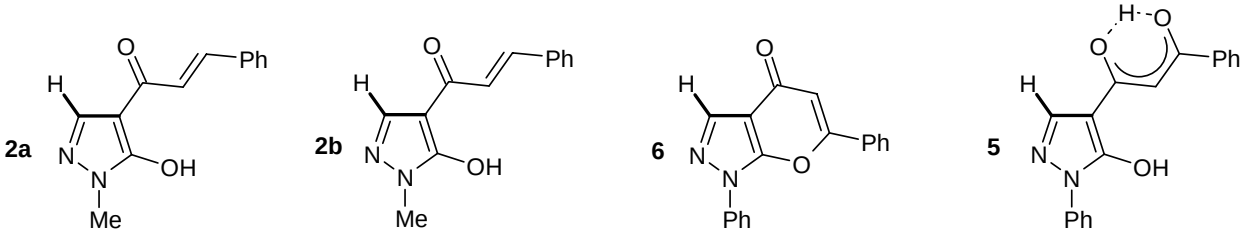


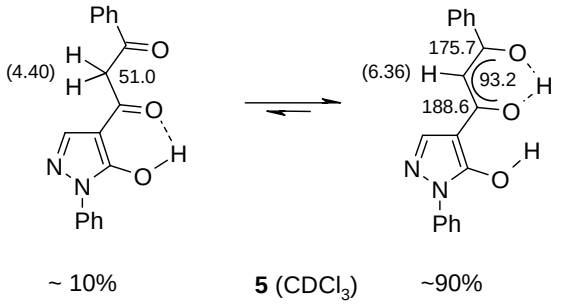
Figure 4. Diagnostic ^{2}J(pyrazole C-4, pyrazole H-3) coupling constants



1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylpropane-1,3-dione (5)

For hydroxypyrazole (**5**) additionally to tautomeric forms (**A**-**D**) also enol forms concerning the β-diketone substructure have to be considered. As observed for a number of similar structures[25,27,36] compound (**5**) is mainly present as 5-hydroxypyrazole with the 4-substituent in an enol form being stabilized by intramolecular hydrogen bonds (Figure 5). However, also the 1,3-diketo form can be detected on account of the occurrence of an isolated methylene fragment in the ^{1}H and ^{13}C-NMR spectra (δ 4.40 (^{1}H) and δ 51.0 (^{13}C) in $CDCl_3$). According to the integrals the amount of diketo form is estimated 10% in $CDCl_3$, 6% in benzene-d_6 and 17% in DMSO-d_6 solution. The higher percentage of diketo form in the latter can be explained by the strong acceptor properties of this solvent reducing the probability of intramolecular hydrogen bonds.

Figure 5. Tautomeric forms and some characteristic ^{13}C-NMR and ^{1}H-NMR (in parentheses) chemical shifts of compound (**5**)

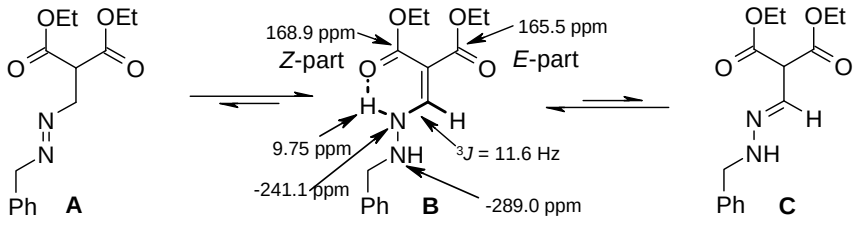


Diethyl 2-[(2-benzylhydrazino)methylidene]malonate (7)

As observed with related compounds[37] the reaction product (**7**) of diethyl ethoxymethylenemalonate with

benzylhydrazine can exist in several tautomeric forms which are depicted in Figure 6. In $CDCl_3$ solution the NMR data confirm the exclusive presence of form **B**, the occurrence of a CH-CH= partial structure (form **C**) or a CH-CH_2 fragment (form **A**) can be definitely excluded. Evidence for form **B** follows from the appearance of two signal sets originating from two different ester functions in the ^{1}H as well as in the ^{13}C-NMR spectra. Moreover, the vicinal coupling (^3J = 11.6 Hz in $CDCl_3$, 12.3 Hz in DMSO-d_6) in the =CH-NH fragment is worth to mention, which leads to a (sharp) dublet signal for the low-field NH signal (δ 9.75 ppm in $CDCl_3$, 6.07 ppm in DMSO-d_6), whereas the other NH signal is characterized by a much smaller chemical shift (δ 4.50 ppm). The large chemical shift of =CH-N**H** can be explained by its involvement in an intramolecular hydrogen bond with the '*cis*'-ester carbonyl *O*-atom as the acceptor (Figure 6). This is supported by the larger ^{13}C-NMR chemical shift for the ester carbonyl *C*-atom involved in the hydrogen bond (δ 169.0 ppm, *Z*-part) compared to the other (*trans*) ester carbonyl *C*-atom (δ 165.5 ppm, *E*-part). These two ester carbonyl *C*-atoms can be unambiguously distinguished *via* their vicinal coupling to the olefinic proton. Thus, the *Z*-part CO shows a coupling constant of 10 Hz (*trans*-coupling), whereas the *E*-part CO signal is only split with 4 Hz. An additional hint for the different C=O functions is provided by the IR spectrum which exhibits two ester C=O bands (1704 and 1654 cm^{-1}), both appearing at low frequencies due to conjugation, but one having an additional low-frequency shift by involvement in a hydrogen bond. Expectedly, in the ^{15}N-NMR spectrum the =CH-**N**H resonance shows a remarkably larger chemical shift (δ –241.1 ppm) as well as a larger one-bond coupling (^1J = 99.4 Hz) than the CH_2**N**H signal (δ –289.0 ppm, ^1J = 69.9 Hz) (Figure 6, assignment veryfied via ^{15}N,^{1}H HSQC spectrum).

Figure 6. Possible tautomeric forms and some characteristic NMR spectral data of **7** (in $CDCl_3$)



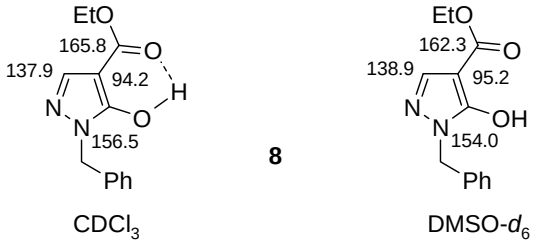
7

Ethyl 1-benzyl-5-hydroxy-1*H*-pyrazol-4-carboxylate (8)

For compound (**8**) in $CDCl_3$ solution occurrence in the chelated 5-hydroxypyrazole form can be assumed whereas in DMSO-d_6 the intramolecular hydrogen bond is obviously disrupted what is evidenced by a markedly smaller ^{13}C chemical shift of the ester carbonyl *C*-atom in the latter solvent compared to that

found in $CDCl_3$ (Figure 7).[37]

Figure 7. Important ^{13}C-NMR chemical shifts for compound (**8**)



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 ^1H, 75.43 MHz for ^{13}C) at 28°C. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^1H in $CDCl_3$), δ 2.49 ppm (^1H in DMSO-d_6), δ 7.16 ppm (^1H 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 and were referenced against neat, external nitromethane (coaxial capillary). Digital resolutions were 0.25 Hz/data point in the ^1H and 0.4 Hz/data point in the ^1H-coupled ^{13}C-NMR spectra (gated decoupling). 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 the described syntheses were mainly devoted to obtain material for the NMR spectroscopic investigations no attempts were made to optimize the yields.

1-Benzyl-5-hydroxy-1*H*-pyrazole (1c)

a) A mixture of compound (**7**) (1.0 g, 3.42 mmol) and 35% aqueous KOH (6 mL, 37 mmol) was heated to reflux for 24 h. Under cooling with an ice bath, the mixture was then acidified to pH ~ 2 with concd HCl and refluxed for additional 5 h to complete decarboxylation. Then water (5 mL) was added and the whole was extracted with AcOEt (3 × 50 mL). The combined organic phases were washed with water (3 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford 377 mg (63%) of a yellowish solid, pure according to TLC and ^1H-NMR spectroscopy. An analytical sample was obtained by recrystallization from toluene affording yellow crystals of mp 158-160°C, crystal modifications beginning

at ~ 140°C) (lit.,[15] mp 160-162°C); ^{1}H-NMR ($CDCl_3$): (CH-isomer) δ (ppm) 7.34-7.20 (m, 5H. Ph-H), 7.27 (t, ^3J = 1.3 Hz, 1H, pyrazole H-3), 4.85 (s, 2H, NCH_2), 3.28 (d, ^3J = 1.3 Hz, 2H, pyrazole H-4); ^{1}H-NMR (DMSO-d_6): (OH/NH-isomer) δ (ppm) 10.96 (br s, 1H, OH), 7.30 (m, 2H, Ph H-3,5), 7.26 (m, 1H, Ph H-4), 7.17 (d, ^3J = 2.0 Hz, pyrazole H-3), 7.14 (m, 2H, Ph H-2,6), 5.37 (d, ^3J = 2.0 Hz, pyrazole H-4), 5.05 (s, 2H, NCH_2); ^{13}C-NMR ($CDCl_3$): (CH-isomer) δ (ppm) 171.4 (pyrazole C-5), 146.3 (pyrazole C-3), 136.3 (Ph C-1), 128.7 (Ph C-3,5), 128.2 (Ph C-2,6), 127.8 (Ph C-4), 48.0 (NCH_2), 39.3 (pyrazole C-4); ^{13}C-NMR (DMSO-d_6): (OH/NH-isomer) δ (ppm) 152.5 (br, C-5), 138.0 (Ph C-1), 137.7 (C-3, ^1J = 183.0 Hz, ^2J(C3,H4) = 5.0 Hz), 128.3 (Ph C-3,5), 127.1 (Ph C-2,6 and Ph C-4), 86.1 (C-4, ^1J = 176.0 Hz, ^2J(C4,H3) = 10.0 Hz), 49.2 (NCH_2, ^1J = 139.3 Hz).

b) A mixture of ester (**8**) (2.463 g, 10 mmol), 35% aqueous KOH (12 mL, 75 mmol) and MeOH (5 mL) was heated to reflux for 24 h. Under cooling with an ice bath, the mixture was then acidified to pH ~ 2 with concd HCl and refluxed for additional 12 h to complete decarboxylation. Then the solvents were removed under reduced pressure, the residue was taken up in water (20 mL) and extracted with AcOEt (3 × 40 mL). The combined organic phases were washed with water (3 × 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford 1.23 g (71%) of a yellowish solid, pure according to TLC and ^{1}H-NMR spectroscopy. Recrystallization from toluene afforded 1.03 g (59%) of yellow crystals, mp 158-160°C (crystal modifications beginning at ~ 140°C) (lit.,[15] mp 160-162°C).

(*E*)-1-(5-Hydroxy-1-methyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (2a)

Under stirring and cooling, to a mixture of 1-methyl-5-hydroxy-1*H*-pyrazole (**1a**)[13] (981 mg, 10 mmol) and $Ca(OH)_2$ (1.482 g, 20 mmol) in dioxane (25 mL, stored over 4Å molsieve) was added *trans*-cinnamoyl chloride (1.666 g, 10 mmol) within 5 min and the mixture was then heated to reflux for 2 h. After it was allowed to cool to rt 2M HCl (30 mL) was added, the mixture was stirred for one additional h and poured onto water (200 mL). The mixture was extracted with AcOEt (3 × 20 mL), the combined organic phases were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated under reduced pressure. The residue (1.30 g) was recrystallized from diisopropyl ether to afford 950 mg (42%) of brown-yellow crystals, mp 140-142°C; IR (KBr): 1652 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 10.53 (s, 1H, OH), 7.81 (d, ^3J = 15.8 Hz, 1H, =C<u>H</u>Ph), 7.75 (s, 1H, pyrazole H-3), 7.60 (m, 2H, Ph H-2,6), 7.40 (m, 3H, Ph H-3,4,5), 7.04 (d, ^3J = 15.8 Hz, 1H, COCH), 3.64 (s, 3H, NMe); ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.10 (s, 1H, pyrazole H-3), 7.78 (m, 2H, Ph H-2,6), 7.62* (A-part of an AB-system, ^3J = 15.9 Hz, 1H, =C<u>H</u>Ph), 7.60* (B-part of an AB-system, ^3J = 15.9 Hz, 1H, COCH), 7.42 (m, 3H, Ph H-3,4,5), 7.18 (br s, 1H, OH), 3.53 (s, 3H, NMe); ^{1}H-NMR (benzene-d_6): δ (ppm) 11.10 (s, 1H, OH), 7.92 (d, ^3J = 15.7 Hz, 1H, =C<u>H</u>Ph), 7.51 (s, 1H, pyrazole H-3), 7.17 (m, 2H, Ph H-2,6), 7.03 (m, 3H, Ph H-3,4,5), 6.78 (d, ^3J = 15.7 Hz, COCH), 3.10 (s, 3H, NMe); ^{13}C-NMR ($CDCl_3$): δ (ppm) 183.4 (C=O), 160.1 (C-5), 143.3

(=CHPh, ^1J =155.9 Hz), 137.0 (C-3, ^1J = 188.4 Hz), 134.3 (Ph C-1), 130.7 (Ph C-4), 128.9 (Ph C-3,5), 128.4 (Ph C-2,6), 121.0 (COCH, ^1J = 157.1 Hz, ^2J = 2.0 Hz), 104.1 (C-4, ^2J(C4,H3) = 10.4 Hz), 32.7 (NMe, ^1J = 140.8 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 181.7 (C=O), 155.9 (C-5), 140.8 (=CHPh), 138.5 (C-3, ^1J = 189.0 Hz), 134.7 (Ph C-1), 130.1 (Ph C-4), 128.8 (Ph C-3,5), 128.4 (Ph C-2.6), 123.6 (COCH, ^1J = 159.9 Hz, ^2J = 4.3 Hz), 105.6 (C-4, ^2J(C4,H3) = 9.8 Hz), 32.7 (NMe, ^1J = 140.5 Hz); ^{13}C-NMR (benzene-d_6): δ (ppm) 183.6 (C=O), 160.7 (C-5, ^3J(C5,NMe) = 2.4 Hz, ^3J(C5,H3) = 4.8 Hz), 143.1 (=CHPh, ^1J = 156.0 Hz), 136.9 (C-3, ^1J = 188.0 Hz), 134.9 (Ph C-1), 130.5 (Ph C-4), 128.9 (Ph C-3,5), 128.7 (Ph C-2,6), 121.7 (COCH, ^1J = 156.9 Hz, ^2J = 2.4 Hz), 104.4 (C-4, ^2J(C4,H3) = 11.1 Hz), 32.2 (NMe, ^1J = 140.7 Hz); MS: *m/z* (%) 229 (M^++1, 13), 228 (M^+, 72), 131 (35), 128 (22), 125 (35), 124 (85), 104 (100), 103 (44), 77 (46), 53 (53), 51 (52), 43 (34). *Anal*. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.17; H, 5.23; N, 12.11.

(*E*)-1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (2b)

Compound (**2b**) was prepared from 5-hydroxy-1-phenyl-1*H*-pyrazole (**1b**)[14] (1.602 g, 10 mmol) and *trans*-cinnamoyl chloride (1.666 g, 10 mmol) similarly as described for the synthesis of **2a**. After the reaction mixture was allowed to cool to rt 2M HCl (30 mL) was added, the mixture was stirred for one additional h and poured onto water (200 mL). The precipitate was filtered off, washed with water and recrystallized from ethanol to afford 1.771 g (61%) of orange needles, mp 182-183°C; ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.05 (s, 1H, OH), 7.93 (s, 1H, pyrazole H-3), 7.93 (m, 2H, N-Ph H-2,6), 7.88 (d, ^3J = 15.8 Hz, 1H, =CHPh), 7.64 (m, 2H, C-Ph H-2,6), 7.46 (m, 2H, N-Ph H-3,5), 7.44 (m, 3H, C-Ph H-3,4,5), 7.29 (m, 1H, N-Ph H-4), 7.05 (d, ^3J = 15.8 Hz, 1H, COCH); ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.79 (br s, 1H, OH), 8.42 (s, 1H, pyrazole H-3), 7.82 (m, 2H, C-Ph H-2,6), 7.81 (m, 2H, C-Ph H-2,6), 7.75 (A-part of an AB-system, ^3J = 15.9 Hz, 1H, COCH), 7.73 (B-part of an AB-system, ^3J = 15.9 Hz, 1H, =CHPh), 7.49 (m, 2H, N-Ph H-3,5), 7.46 (m, 2H, C-Ph H-3,5), 7.46 (m, 1H, C-Ph H-4), 7.31 (m, 1H, N-Ph H-4); ^{1}H-NMR (benzene-d_6): δ (ppm) 10.75 (s, 1H, OH), 8.23 (m, 2H, N-Ph H-2,6), 7.81 (d, ^3J = 15.7 Hz, 1H, =CHPh), 7.50 (s, 1H, pyrazole H-3), 7.18 (m, 2H, N-Ph H-3,5), 7.13 (m, 2H, C-Ph H-2,6), 7.04 (m, 2H, C-Ph H-3,5), 7.04 (m, 1H, C-Ph H-4), 6.96 (m, 1H, N-Ph H-4), 6.57 (d, ^3J = 15.7 Hz, 1H, COCH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 180.4 (C=O), 162.3 (C-5, ^3J(C5,H3) = 4.6 Hz), 144.0 (=CHPh, ^1J = 156.5 Hz), 137.9 (C-3, ^1J = 189.8 Hz), 137.6 (N-Ph C-1), 134.2 (C-Ph C-1), 131.0 (C-Ph C-4), 129.0 (N-Ph C-3,5), 129.0 (C-Ph C-3,5), 128.6 (C-Ph C-2,6), 126.4 (N-Ph C-4), 120.2 (N-Ph C-2,6), 119.6 (COCH, ^1J = 157.9 Hz, ^2J =2.3 Hz), 105.2 (C-4, ^2J(C4,H3) = 10.4 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 178.9 (C=O), 159.4 (C-5, ^3J(C5,H3) = 4.5 Hz), 142.1 (=CHPh, ^1J = 157.6 Hz), 140.1 (C-3, ^1J = 191.6 Hz), 137.5 (N-Ph C-1), 134.5 (C-Ph C-1), 130.6 (C-Ph C-4), 129.0 (C-Ph C-3,5), 128.9 (N-Ph C-3,5), 128.7 (C-Ph C-2,6), 126.2 (N-Ph C-4), 121.8 (COCH, ^1J = 161.9 Hz, ^2J = 4.3 Hz), 120.6 (N-Ph C-2,6), 106.1 (C-4, ^2J(C4,H3) = 9.8 Hz);

^{13}C-NMR (benzene-d_6): δ (ppm) 179.7 (C=O), 163.5 (C-5, ^{3}J(C5,H3) = 4.3 Hz), 143.6 (=CHPh, ^{1}J = 156.0 Hz), 138.7 (N-Ph C-1), 137.9 (C-3, ^{1}J = 189.7 Hz), 134.7 (C-Ph C-1), 130.8 (C-Ph C-4), 129.2 (N-Ph C-3,5), 129.0 (C-Ph C-3,5), 128.8 (C-Ph C-2,6), 126.3 (N-Ph C-4), 120.1 (N-Ph C-2,6), 119.9 (COCH, ^{1}J = 158.0 Hz, ^{2}J =2.4 Hz), 105.7 (C-4, ^{2}J(C4,H3) = 10.7 Hz); MS: *m/z* (%) 290 (M^+, 37), 186 (55), 131 (46), 103 (42), 77 (100), 53 (29), 51 (70). *Anal*. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.26; H, 4.84; N, 9.54.

(*E*)-1-(1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (2c)

Compound (**2c**) was prepared from 1-benzyl-5-hydroxy-1*H*-pyrazole (**1c**) (1.742 g, 10 mmol) and *trans*-cinnamoyl chloride (1.666 g, 10 mmol) similarly as described for the synthesis of **2b**. Recrystallization from diisopropyl ether - ethanol afforded 1.978 g (65%) of red-brown crystals, mp 155°C; IR (KBr): 1650 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.84 (d, ^{3}J = 15.7 Hz, 1H, =CHPh), 7.79 (s, 1H, pyrazole H-3), 7.65 (br s, 1H, OH), 7.63 (m, 2H, =CHPh H-2,6), 7.43 (m, 3H, =CHPh H-3,4,5), 7.34 (m, 2H, CH_2Ph H-2,6), 7.28-7.36 (m, 3H, CH_2Ph H-3,4,5), 7.05 (d, ^{3}J = 15.7 Hz, 1H, COCH), 5.16 (s, 2H, NCH_2); ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.17 (s, 1H, pyrazole H-3), 7.79 (m, 2H, =CHPh H-2,6), 7.63 (s, 2H, =CHPh and COCH), 7.44 (m, 3H, =CHPh H-3,4,5), 7.34 (m, 2H, CH_2Ph H-3,5), 7.27 (m, 1H, CH_2Ph H-4), 7.21 (m, 2H, CH_2Ph H-2,6), 6.11 (br s, 1H, OH), 5.11 (s, 2H, NCH_2); ^{1}H-NMR (benzene-d_6): δ (ppm) 10.02 (s, 1H, OH), 7.87 (d, ^{3}J = 15.7 Hz, 1H, =CHPh), 7.49 (s, 1H, pyrazole H-3), 7.25 (m, 2H, CH_2Ph H-2,6), 7.14 (m, 2H, =CHPh H-2,6), 7.07 (m, 2H, CH_2Ph H-3,5), 7.03 (m, 4H, =CHPh H-3,4,5 and CH_2Ph H-4), 6.71 (d, ^{3}J = 15.7 Hz, 1H, COCH), 4.85 (s, 2H, NCH_2); ^{13}C-NMR ($CDCl_3$): δ (ppm) 182.9 (C=O), 160.6 (C-5), 143.6 (=CHPh, ^{1}J = 156.2 Hz), 137.4 (C-3, ^{1}J = 188.6 Hz), 135.6 (CH_2Ph C-1), 134.4 (=CHPh C-1), 130.8 (=CHPh C-4), 129.0 (=CHPh C-3,5), 128.8 (CH_2Ph C-3,5), 128.6 (=CHPh C-2,6), 128.04 (CH_2Ph C-4), 128.01 (CH_2Ph C-2,6), 120.8 (COCH, ^{1}J = 157.2 Hz, ^{2}J = 2.3 Hz), 104.3 (C-4, ^{2}J(C4,H3) = 10.8 Hz), 49.9 (NCH_2, ^{1}J = 140.2 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 181.5 (C=O), 156.2 (C-5), 140.9 (=CHPh), 139.0 (C-3, ^{1}J = 189.1 Hz), 136.7 (CH_2Ph C-1), 134.7 (=CHPh C-1), 130.2 (=CHPh C-4), 128.8 (=CHPh C-3,5), 128.5 (CH_2Ph C-3,5), 128.46 (=CHPh C-2,6), 127.5 (CH_2Ph C-4), 127.3 (CH_2Ph C-2,6), 123.5 (COCH, ^{1}J = 160.4 Hz, ^{2}J = 4.0 Hz), 105.7 (C-4, ^{2}J(C4,H3) = 9.7 Hz), 48.8 (NCH_2); ^{13}C-NMR (benzene-d_6): δ (ppm) 182.9 (C=O), 161.2 (C-5), 143.2 (=CHPh, ^{1}J = 156.7 Hz), 137.3 (C-3, ^{1}J = 188.2 Hz), 136.5 (CH_2Ph C-1), 134.9 (=CHPh C-1), 130.5 (=CHPh C-4), 129.1 (=CHPh C-3,5), 128.8 (CH_2Ph C-3,5), 128.7 (=CHPh C-2,6), 128.4 (CH_2Ph C-2,6), 128.0 (CH_2Ph C-4), 121.3 (COCH, ^{1}J = 157.2 Hz, ^{2}J = 2.4 Hz), 104.6 (C-4, ^{2}J(C4,H3) = 10.7 Hz), 49.9 (NCH_2, ^{1}J = 139.9 Hz, ^{3}J(NCH_2,NCH_2Ph H-2,6) = 4.6 Hz); MS: *m/z* (%) 305 (M^++1, 9), 304 (M^+, 42), 172 (18), 144 (17), 131 (20), 128 (24), 127 (10), 106 (13), 104 (18), 103 (23), 91 (100), 77 (21), 65 (29), 53 (19), 51 (17). *Anal*. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.77; H, 5.45; N, 9.30.

(*E*)-1-(1-Benzyl-5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (2d)

Compound (**2d**) was prepared from 1-benzyl-5-hydroxy-3-methyl-1*H*-pyrazole (**1d**)[15] (1.882 g, 10 mmol) and *trans*-cinnamoyl chloride (1.666 g, 10 mmol) similarly as described for the synthesis of **2b**. Recrystallization from diisopropyl ether - ethanol afforded 1.847 g (58%) of orange red crystals, mp 139°C; IR (KBr): 1640 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 11.73 (m, 1H, OH), 7.88 (d, ^3J = 15.7 Hz, 1H, =CHPh), 7.60 (m, 2H, =CHPh H-2,6), 7.43 (m, 3H, =CHPh H-3,4,5), 7.33 (m, 2H, CH_2Ph H-2,6), 7.28-7.35 (m, 3H, CH_2Ph H-3,4,5), 7.13 (d, ^3J = 15.7 Hz, 1H, COCH), 5.07 (s, 2H, NCH_2), 2.49 (s, 3H, CH_3); ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.0-14.0 (very br s, 1H, OH), 8.06 (br d, ^3J = 15.9 Hz, 1H, COCH), 7.67 (m, 2H, =CHPh H-2,6), 7.60 (d, ^3J = 15.9 Hz, 1H, =CHPh), 7.42 (m, 1H, =CHPh H-4), 7.41 (m, 2H, =CHPh H-3,5), 7.35 (m, 2H, CH_2Ph H-3,5), 7.28 (m, 1H, CH_2Ph H-4), 7.24 (m, 2H, CH_2Ph H-2,6), 4.99 (s, 2H, NCH_2), 2.40 (s, 3H, Me); ^{1}H-NMR (benzene-d_6): δ (ppm) 13.91 (s, 1H, OH), 7.92 (d, ^3J = 15.6 Hz, 1H, =CHPh), 7.32 (m, 2H, CH_2Ph H-2,6), 7.23 (m, 2H, =CHPh H-2,6), 7.09 (m, 2H, CH_2Ph H-3,5), 7.04 (m, 1H, =CHPh H-4), 7.03 (m, 2H, =CHPh H-3,5), 7.01 (m, 1H, CH_2Ph H-4), 6.87 (d, ^3J = 15.6 Hz, 1H, COCH), 4.86 (s, 2H, NCH_2), 2.10 (s, 3H, Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 180.3 (C=O, ^2J = 6.9 Hz, ^3J = 6.9 Hz), 163.8 (C-5, ^3J(C5,NCH_2) = 2.5 Hz), 146.2 (C-3, ^2J(C3,3-Me) = 6.9 Hz), 143.5 (=CHPh, ^1J = 156.4 Hz), 136.0 (CH_2Ph C-1), 134.5 (=CHPh C-1), 130.8 (=CHPh C-4), 129.0 (=CHPh C-3,5), 128.7 (CH_2Ph C-3,5), 128.4 (=CHPh C-2,6), 127.9 (CH_2Ph C-2,6), 120.3 (COCH, ^1J = 157.4 Hz, ^2J = 2.3 Hz), 103.6 (C-4, ^3J(C4,3-Me) = 2.6 Hz), 49.0 (NCH_2, ^1J = 139.7 Hz), 16.2 (3-Me, ^1J = 128.3 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 182.6 (C=O), 160.5 (C-5), 148.7 (C-3), 139.7 (=CHPh), 136.6 (CH_2Ph C-1), 135.1 (=CHPh C-1), 129.9 (=CHPh C-4), 128.9 (=CHPh C-3,5), 128.5 (CH_2Ph C-3,5), 128.0 (=CHPh C-2,6), 127.5 (CH_2Ph C-4), 127.3 (CH_2Ph C-2,6), 124.9 (COCH), 104.3 (C-4, ^3J(C4,3-Me) = 2.4 Hz), 46.8 (NCH_2, ^1J = 140.3 Hz), 14.1 (3-Me, ^1J = 129.7 Hz); ^{13}C-NMR (benzene-d_6): δ (ppm) 180.3 (C=O, ^2J = 6.9 Hz, ^3J = 6.9 Hz), 164.4 (C-5, ^3J(C5,NCH_2) = 2.5 Hz), 145.6 (C-3, ^2J(C3,3-Me) = 7.0 Hz), 143.1 (=CHPh, ^1J = 157.0 Hz, ^2J = 1.4 Hz, ^3J = 4.7 Hz), 137.0 (CH_2Ph C-1), 135.1 (=CHPh C-1), 130.5 (=CHPh C-4), 129.1 (=CHPh C-3,5), 128.8 (CH_2Ph C-3,5), 128.6 (=CHPh C-2,6), 128.5 (CH_2Ph C-2,6), 127.9 (CH_2Ph C-4), 121.0 (COCH, ^1J = 157.3 Hz, ^2J = 2.6 Hz), 104.0 (C-4, ^3J(C4,3-Me) = 2.6 Hz), 49.1 (NCH_2, ^1J = 139.5 Hz, ^3J(NCH_2,Ph-2,6) = 4.7 Hz), 15.9 (3-Me, ^1J = 128.0 Hz); MS: *m/z* (%) 318 (M^+, 5), 131 (15), 104 (11), 103 (19), 91 (100), 77 (15), 67 (10), 65 (21). *Anal*. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.44; H, 5.70; N, 8.80.

1-Benzyl-3-methyl-6-phenyl-5,6-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-4-one (3d)

A mixture of **2d** (955 mg, 3 mmol) and concd H_2SO_4 (35 mL) was left at rt for 24 h. Then the mixture was poured onto ice - water (100 mL) and extracted with dichloromethane (3 × 50 mL). The combined

organic phases were washed with saturated Na_2CO_3 solution (until the yellow color disappeared), dried (Na_2SO_4) and evaporated. The residue was subjected to preparative TLC (silica gel, eluent: dichloromethane – ethyl acetate, 1:1) to afford 20 mg (2%) of a slightly tan oil. Acidification of the combined carbonate extracts gave unreacted **2d** with a nearly quantitative recovery rate. Compound (**3d**) had IR (KBr): 1674 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.40 (m, 5H, 6-Ph), 7.31 (m, 3H, CH_2Ph H-3,4,5), 7.26 (m, 2H, CH_2Ph H-2,6), 5.65 (X-part of an ABX-system, ^3J = 12.1 Hz and 3.4 Hz, 1H, H-6), 5.09 (s, 2H, NCH_2), 2.92 (B-part of an ABX-system, ^2J = 17.0 Hz, ^3J = 12.1 Hz, 1H, H-5), 2.69 (A-part of an ABX-system, ^2J = 17.0 Hz, ^3J = 3.4 Hz, 1H, H-5'), 2.43 (s, 3H, Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 185.3 (C=O), 158.7 (C-7a), 147.6 (C-3, ^2J(C3,3-Me) = 7.0 Hz), 137.4 (6-Ph C-1), 135.6 (CH_2Ph C-1), 129.1 (6-Ph C-4), 128.9 (6-Ph C-3,5), 128.8 (CH_2Ph C-3,5), 128.0 (CH_2Ph C-4), 127.7 (CH_2Ph C-2,6), 126.2 (6-Ph C-2,6), 102.0 (C-3a), 84.5 (C-6, ^1J = 149.4 Hz), 50.5 (NCH_2, ^1J = 140.1 Hz), 43.8 (C-5), 14.0 (Me, ^1J = 128.7 Hz); MS: *m/z* (%) 319 (M^++1, 5), 318 (M^+, 18), 214 (26), 186 (26), 158 (26), 104 (28), 103 (13), 91 (100), 78 (13), 77 (17), 67 (29), 65 (29), 55 (18), 51 (12). *Anal*. Calcd for $C_{20}H_{18}N_2O_2$•0.2 H_2O: C, 74.61; H, 5.76; N, 8.70. Found: C, 74.59; H, 5.99; N, 8.67.

1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (4)

Compound (**4**) was prepared from 5-hydroxy-1-phenylpyrazole (**1b**)[14] (1.601 g, 10 mmol) and acetyl chloride (785 mg, 10 mmol) similarly as described for the synthesis of **2b**. Recrystallization from ethanol afforded 1.092 g (54%) of colorless crystals, mp 124°C; IR (KBr): 1664 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 10.18 (s, 1H, OH), 7.83 (m, 2H, Ph H-2,6), 7.79 (s, 1H, pyrazole H-3), 7.46 (m, 2H, Ph H-3,5), 7.32 (m, 1H, Ph H-4), 2.43 (s, 3H, Me); ^{1}H-NMR (DMSO-d_6): δ (ppm) 10.32 (br s, 1H, OH), 8.06 (s, 1H, pyrazole H-3), 7.71 (m, 2H, Ph H-2,6), 7.49 (m, 2H, Ph H-3,5), 7.33 (m, 1H, Ph H-4), 2.38 (Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 195.1 (C=O), 158.2 (C-5, ^3J(C5,H3) = 4.8 Hz), 138.7 (C-3, ^1J = 188.6 Hz), 137.3 (Ph-1), 129.1 (Ph C-3,5), 127.0 (Ph C-4), 120.9 (Ph C-2,6), 105.0 (C-4, ^2J(C4,H3) = 10.7 Hz), 25.8 (Me, ^1J = 127.9 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 191.1 (C=O), 155.7 (C-5), 140.4 (C3, ^1J = 189.3 Hz), 137.4 (Ph C-1), 129.0 (Ph C-3,5), 126.6 (Ph C-4), 121.6 (Ph C-2,6), 106.1 (C-4, ^2J(C4,H3) = 9.5 Hz, ^3J(C4,Me) =1.5 Hz), 26.6 (Me, ^1J = 127.3 Hz); MS: *m/z* (%) 203 (M^++1, 17), 202 (M^+, 100), 187 (77), 77 (40), 51 (34), 43 (48). *Anal*. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.37; H, 5.26; N, 13.95.

1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylpropan-1,3-dione (5)

Under Ar, to a cooled (–70°) solution of 4-acetylpyrazolone (**4**) (1.011 g, 5 mmol) in dry THF (55 mL) was added 1M lithium bis(trimethylsilyl)amide solution in THF (10 mL, 10 mmol) within 45 min. After the addition was complete the mixture was stirred for 2 h at –70°C, then a solution of benzoyl chloride

(703 mg, 5 mmol) in THF (3 mL) was slowly added and stirring was continued for one additional h at –70°C. Then the cooling bath was removed, the mixture was allowed to reach rt and was then stirred for another 22 h. After addition of 5% aqueous HCl (90 mL) a brownish material precipitated, which was filtered off, washed with water and recrystallized from diisopropyl ether to afford 730 mg (48%) of brownish crystals, mp 181-183°C; IR (KBr): 1622 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 15.13 (s, 1H, enol OH), 7.92 (m, 2H, C-Ph H-2,6), 7.87 (s, 1H, pyrazole H-3), 7.85 (m, 2H, N-Ph H-2,6), 7.55 (m, 1H, C-Ph H-4), 7.49 (m, 2H, N-Ph H-3,5), 7.48 (m, 2H, C-Ph H-3,5), 7.34 (m, 1H, N-Ph H-4), 6-10 (very br s, 1H, 5-OH), 6.36 (s, 1H, COCH); ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.34 (s, 1H, pyrazole H-3), 7.97 (m, 2H, C-Ph H-2,6), 7.74 (m, 2H, N-Ph H-2,6), 7.56 (m, 1H, C-Ph H-4), 7.53 (m, 2H, C-Ph H-3,5), 7.50 (m, 2H, N-Ph H-3,5), 7.34 (m, 1H, N-Ph H-4), 7.09 (s, 1H, COCH); ^{1}H-NMR (benzene-d_6): δ (ppm) 15.49 (s, 1H, enol OH), 7.97 (m, 2H, N-Ph H-2,6), 7.73 (m, 2H, C-Ph H-2,6), 7.52 (s, 1H, pyrazole H-3), 7.11 (m, 4H, C-Ph H-3,5 and N-Ph H-3,5), 7.09 (m, 1H, C-Ph H-4), 6.95 (m, 1H, N-Ph H-4), 6.00 (s, 1H, COCH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 188.6 (4-C=O), 175.7 (C-Ph), 157.2 (C-5, ^{3}J(C5,H3) = 5.0 Hz), 137.7 (C-3, ^{1}J = 188.3 Hz), 137.4 (N-Ph C-1), 133.4 (C-Ph C-1), 132.2 (C-Ph C-4), 129.2 (N-Ph C-3,5), 128.7 (C-Ph C-3,5), 127.1 (N-Ph C-4), 126.7 (C-Ph C-2,6), 121.2 (N-Ph C-2,6), 102.7 (C-4, ^{2}J(C4,H3) = 10.3 Hz), 93.2 (COCH, ^{1}J = 163.6 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 184.0 (4-C=O), 178.5 (C-Ph), 139.4 (C-3, ^{1}J = 190.0 Hz), 137.1 (N-Ph C-1), 134.3 (C-Ph C-1), 132.0 (C-Ph C-4), 129.0 (N-Ph C-3,5), 128.7 (C-Ph C-3,5), 126.5 (N-Ph C-4), 126.4 (C-Ph C-2,6), 121.6 (N-Ph C-2,6), 103.1 (C-4, ^{2}J(C4,H3) = 8.3 Hz), 93.2 (COCH, ^{1}J = 166.2 Hz); ^{13}C-NMR (benzene-d_6): δ (ppm) 189.0 (4-C=O), 175.8 (C-Ph), 157.7 (C-5), 138.2 (N-Ph C-1), 137.8 (C-3, ^{1}J = 188.2 Hz), 133.8 (C-Ph C-1), 132.1 (C-Ph C-4), 129.2 (N-Ph C-3,5), 128.8 (C-Ph C-3,5), 127.0 (C-Ph C-2,6), 126.9 (N-Ph C-4), 121.1 (N-Ph C-2,6), 103.1 (C-4), 93.5 (COCH, ^{1}J = 163.0 Hz); MS: *m/z* (%) 306 (M^{+}, 21), 186 (13), 105 (100), 91 (31), 77 (50), 51 (22). *Anal*. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.52; H, 4.66; N, 9.15.

1,6-Diphenyl-1*H*-pyrano[2,3-*c*]pyrazol-4-one (6)

A solution of **5** (61 mg, 0.2 mmol) in glacial acetic acid (0.3 mL) and concd H_2SO_4 (0.07 mL) was heated to reflux for 1 h. After cooling, the mixture was poured onto ice-water (4 mL) and was then exhaustively extracted with dichloromethane. The combined organic phases were carefully washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to afford 24 mg (42%) of a beige solid, mp 177-180°C. Further purification by preparative TLC (silica gel, eluent: dichloromethane – ethyl acetate, 1:1) gave crystals of mp 190°C; IR (KBr): 1656 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.18 (s, 1H, H-3), 7.89 (m, 2H, N-Ph H-2,6), 7.82 (m, 2H, C-Ph H-2,6), 7.59 (m, 2H, N-Ph H-3,5), 7.54 (m, 2H, C-Ph H-3,5), 7.53 (m, 1H, C-Ph H-4), 7.45 (m, 1H, N-Ph H-4), 6.77 (s, 1H, H-5); ^{13}C-NMR ($CDCl_3$): δ (ppm) 174.8 (C=O, ^{3}J(CO,H3) = 2.1 Hz), 160.5 (C-6), 153.1 (C-7a, ^{3}J(C-7a,H3) = 5.0 Hz), 137.0 (N-Ph C-1), 135.7 (C-3, ^{1}J =

194.9 Hz, ^{4}J(C3,H5) = 1.5 Hz), 131.7 (C-Ph C-4), 130.7 (C-Ph C-1), 129.6 (N-Ph C-3,5), 129.3 (C-Ph C-3,5), 127.9 (N-Ph C-4), 126.1 (C-Ph C-2,6), 121.3 (N-Ph C-2,6), 109.8 (C-5, ^{1}J = 165.8 Hz), 108.9 (C-3a, ^{2}J(C-3a,H3) = 10.3 Hz, ^{3}J(C-3a,H5) = 4.4 Hz); MS: *m/z* (%) 289 (M^{+}+1, 12), 288 (M^{+}, 60), 187 (14), 186 (100), 118 (13), 91 (35), 77 (25), 51 (10); HRMS: Calcd for $C_{18}H_{12}N_2O_2$: 288.0899. Found: 288.0904±0.0014. *Anal*. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.68; H, 4.66; N, 9.31.

Diethyl 2-[(2-Benzylhydrazino)methylidene]malonate (7)

Under cooling, to diethyl ethoxymethylenemalonate (2.162 g, 10 mmol) in dry ethanol (1 mL) was added dropwise (*via* a syringe) a solution of benzylhydrazine (1.221 g, 10 mmol) in dry ethanol (1 mL) and the mixture was then heated to reflux for 2 h. After reaching rt crystals appeared on scratching. The flask was stored in a deep freezer overnight, then the precipitate was filtered off, washed with a few ice-cold ethanol and dried to afford 1.55 g of colorless crystals, mp 67-68°C. From the mother liquor a further crop of 610 mg was obtained. Overall yield 2.16 g (74%); IR (KBr): 3282 cm^{-1} (NH), 1704 (C=O), 1654 (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 9.75 (d, ^{3}J(NH,=CH) = 11.6 Hz, 1H, =CHN<u>H</u>), 8.15 (d, ^{3}J(NH,=CH) = 11.6 Hz, 1H, =C<u>H</u>NH), 7.38-7.27 (m, 5H, Ph-H), 4.50 (t, ^{3}J(NH,CH_2) = 5.9 Hz, 1H, CH_2N<u>H</u>), 4.19 (q, ^{3}J = 7.2 Hz, OCH_2 (*Z*-part)), 4.14 (q, ^{3}J = 7.1 Hz, OCH_2 (*E*-part)), 4.01 (d, ^{3}J(CH_2,NH) = 5.9 Hz, 2H, PhC<u>H</u>$_2$), 1.29 (t, ^{3}J = 7.1 Hz, Me (*Z*-part)), 1.25 (t, ^{3}J = 7.1 Hz, Me (*E*-part); ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.76 (d, ^{3}J(NH,=CH) = 12.3 Hz, 1H, =CHN<u>H</u>), 7.92 (d, ^{3}J(NH,=CH) = 12.3 Hz, 1H, =C<u>H</u>NH), 7.33 (m, 4H, Ph H-2,3,5,6), 7.28 (m, 1H, Ph H-4), 6.07 (dt, ^{3}J(NH,CH_2) = 5.3 Hz, ^{3}J(NH,NH) = 1.9 Hz, 1H, CH_2N<u>H</u>), 4.06 (q, ^{3}J = 7.1 Hz, OCH_2 (*Z*-part)), 3.99 (q, ^{3}J = 7.1 Hz, OCH_2 (*E*-part)), 3.93 (d, ^{3}J(CH_2,NH) = 5.2 Hz, 2H, PhC<u>H</u>$_2$), 1.17 (t, ^{3}J = 7.1 Hz, Me (*Z*-part)), 1.14 (t, ^{3}J = 7.1 Hz, Me (*E*-part)); ^{13}C-NMR ($CDCl_3$): δ (ppm) 168.9 (ester C=O, *Z*-part, ^{3}J(CO,=CH) = 10.2 Hz, ^{3}J(CO,OCH_2) = 3.2 Hz), 165.5 (ester C=O, *E*-part, ^{3}J(CO,=CH) = 4.1 Hz, ^{3}J(CO,OCH_2) = 3.0 Hz), 160.6 (=<u>C</u>HNH, ^{1}J = 170.8 Hz, ^{2}J(=CH,NH) = 3.0 Hz, ^{3}J(=CH,NH) = 5.2 Hz), 136.1 (Ph C-1), 128.8 (Ph C-3,5), 128.7 (Ph C-2,6), 128.1 (Ph C-4), 88.7 (=<u>C</u>$(COOEt)_2$), 59.9 (OCH_2, *Z*-part, ^{1}J = 147.1 Hz, ^{2}J = 4.4 Hz), 59.5 (OCH_2, *E*-part, ^{1}J = 146.8 Hz, ^{2}J = 4.4 Hz), 57.2 (Ph<u>C</u>H_2, ^{1}J = 137.1 Hz), 14.34 (Me, *E*-part, ^{1}J = 126.8 Hz, ^{2}J = 2.6 Hz), 14.25 (Me, *Z*-part, ^{1}J = 126.6 Hz, ^{2}J =2.5 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 167.4 (ester C=O, *Z*-part, ^{3}J(CO,=CH) = 10.0 Hz, ^{3}J(CO,OCH_2) = 3.3 Hz), 164.7 (ester C=O, *E*-part, ^{3}J(CO,=CH) = 4.2 Hz, ^{3}J(CO,OCH_2) = 3.1 Hz), 159.4 (=<u>C</u>HNH, ^{1}J = 169.0 Hz, ^{2}J(=CH,NH) = 3.4 Hz, ^{3}J(=CH,NH) = 5.7 Hz), 137.3 (Ph C-1), 128.3 (Ph C-3,5), 128.3 (Ph C-2,6), 127.3 (Ph C-4), 86.3 (=<u>C</u>$(COOEt)_2$), 58.9 (OCH_2, *Z*-part, ^{1}J = 147.0 Hz, ^{2}J = 4.5 Hz), 58.6 (OCH_2, *E*-part, ^{1}J = 146.7 Hz, ^{2}J = 4.5 Hz), 55.6 (Ph<u>C</u>H_2, ^{1}J = 136.6 Hz), 14.26 (Me, *E*-part, ^{1}J = 126.5 Hz, ^{2}J = 2.6 Hz), 14.23 (Me, *Z*-part, ^{1}J = 126.5 Hz, ^{2}J =2.5 Hz); ^{15}N-NMR ($CDCl_3$): –241.1 (=CHNH), –289.0 (CH_2NH); MS: *m/z* (%) 292 (M^{+}, 1), 246 (3), 91 (100), 65

(7), 53 (4). *Anal*. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.86; H, 6.85; N, 9.37.

Ethyl 1-Benzyl-5-hydroxy-1*H*-pyrazol-4-carboxylate (8)

a) To a mixture of benzylhydrazine (3.24 g, 26.5 mmol) and K_2CO_3 (3.66 g, 26.5 mmol) in water (150 mL) was added diethyl ethoxymethylenemalonate (5.73 g, 26.5 mmol). The mixture was refluxed for 3 h and then stirred at rt overnight. After washing with AcOEt (3 × 30 mL) the aqueous phase was acidified to pH ~ 2 with concd HCl and then extracted with AcOEt (3 × 30 mL). The latter ethyl acetate phases were washed several times with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dried to afford 5.20 g (80%) of a yellow solid, mp 88-90°C (lit.,[20] mp 79-81°C), pure according to TLC and ^{1}H-NMR spectroscopy.

b) A mixture of hydrazone (**7**) (292 mg, 1 mmol) and K_2CO_3 (138 mg, 1 mmol) in dry ethanol (8 mL) was heated to reflux for 6 h. Then the solvent was removed under reduced pressure, the remaining solid was taken up in water (20 mL) and the mixture was acidified to pH 2 with diluted HCl. After extraction with AcOEt (3 × 15 mL) the combined organic phases were washed with water (3 × 5 mL), dried (Na_2SO_4) and evaporated to afford 227 mg (92%) of a brown-yellow solid, mp 88-90°C (lit.,[20] mp 79-81°C); IR (KBr): 1708 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.75 (br s, 1H, OH), 7.56 (s, 1H, pyrazole H-3), 7.28-7.18 (m, 5H, Ph-H), 5.09 (s, 2H, CH_2), 4.24 (q, ^3J = 7.1 Hz, 2H, OCH_2), 1.28 (t, ^3J = 7.1 Hz, 3H, Me); ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.72 (br s, 1H, OH), 7.59 (s, 1H, pyrazole H-3), 7.32 (m, 1H, Ph H-4), 7.30 (m, 2H, Ph H-3,5), 7.16 (m, 2H, Ph H-2,6), 5.09 (s, 2H, CH_2), 4.17 (q, ^3J = 7.0 Hz, 2H, OCH_2), 1.23 (t, ^3J = 7.0 Hz, 3H, Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 165.8 (ester C=O), 156.2 (C-5), 137.9 (C-3, ^1J = 191.0 Hz), 135.6 (Ph C-1), 128.7 (Ph C-3,5), 128.0 (Ph C-4), 127.8 (Ph C-2,6), 94.2 (C-4, ^2J(C4,H3) = 9.7 Hz), 60.4 (OCH_2, ^1J = 148.0 Hz, ^2J = 4.4 Hz), 50.5 (NCH_2), 14.3 (Me, ^1J = 127.1 Hz, ^2J = 2.6 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 162.3 (ester C=O), 154.0 (C-5), 138.9 (C-3, ^1J = 189.1 Hz), 136.9 (Ph C-1), 128.4 (Ph C-3,5), 127.4 (Ph C-4), 127.2 (Ph C-2,6), 95.2 (C-4, ^2J(C4,H3) = 9.1 Hz), 58.8 (OCH_2, ^1J = 147.3 Hz, ^2J = 4.5 Hz), 49.4 (NCH_2, ^1J = 141.0 Hz), 14.4 (Me, ^1J = 126.6 Hz, ^2J = 2.6 Hz); MS: *m/z* (%) 247 (M^++1, 15), 246 (M^+, 81), 200 (52), 172 (75), 144 (36), 91 (100), 65 (56), 53 (63). *Anal*. Calcd for $C_{13}H_{14}N_2O_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.32; H, 5.87; N, 11.49.

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