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THE 4-METHOXYBENZYL (PMB) FUNCTION AS A VERSATILE PROTECTING GROUP IN THE SYNTHESIS OF *N*-UNSUBSTITUTED PYRAZOLONES

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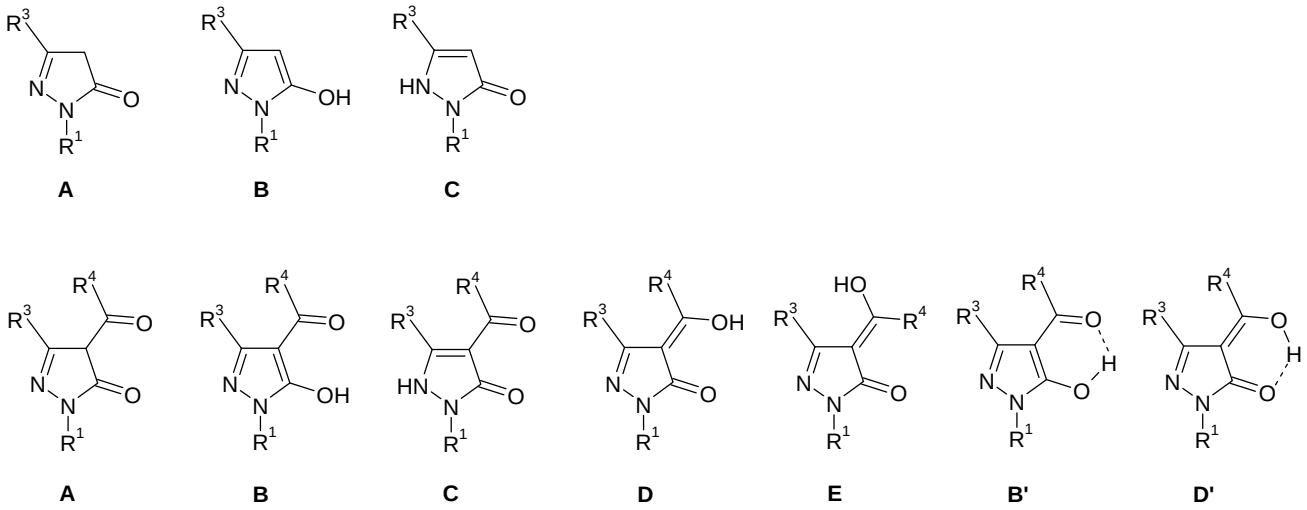
Abstract – Starting from diethyl ethoxymethylenemalonate and 4-methoxybenzylhydrazine (PMB-$NHNH_2$) 2-(4-methoxybenzyl)-2,4-dihydro-3*H*-pyrazol-3-one was prepared. Reaction of the latter with carboxylic acid chlorides / calcium hydroxide in 1,4-dioxane afforded 4-acyl-5-hydroxy-1-PMB-1*H*-pyrazoles, whereas with dimethylformamide diethyl acetal or benzaldehyde the corresponding (*E*)-4-dimethylaminomethylene or (*E*)-4-benzylidene products, respectively, were obtained. The PMB protecting group could be conveniently removed from the pyrazole nucleus by treatment with trifluoroacetic acid to give the *N*-unsubstituted pyrazolones. Detailed NMR spectroscopic investigations (^{1}H, ^{13}C, ^{15}N) with the obtained compounds are presented.

INTRODUCTION

N1-Substituted 2-pyrazolin-5-ones are important synthetic targets as a consequence of their prevalence in numerous pharmaceuticals, agrochemicals, dyes and pigments as well as in chelating and extracting agents.[1,2] Moreover, they are capable of prototropic tautomerism and can be present as CH- (**A**), OH- (**B**) and NH-isomers (**C**) (Figure 1, upper line),[3-5] which - according to systematic nomenclature - are designated as 2,4-dihydro-3*H*-pyrazol-3-ones (**A**), 1*H*-pyrazol-5-ols (**B**), and 1,2-dihydro-3*H*-pyrazol-3-ones (**C**). For species with an acyl or aroyl group attached at position 4 of the heterocyclic moiety the number of possible tautomeric forms increases since now the 4-substituent can participate in tautomerism and also stabilization by intramolecular hydrogen bonds may occur (Figure 1, lower line).[3] Whereas

numerous investigations have been devoted to the chemistry and also to the tautomeric behavior of *N*-substituted 4-acylpyrazolones (R^1 = alkyl, aryl)[6-10] relatively little is known about corresponding species lacking a substituent at the pyrazole nitrogen atom (R^1 = H). Occasionally, ring transformation reactions have been employed for the synthesis of such compounds.[11] This prompted us to develop a new synthetic methodology for the synthesis of the latter 4-acylpyrazolones (Figure 1, lower line, R^1 = H, R^3 = H, R^4 = Me, Et, Ph, 2-thienyl, *trans*-styryl) and some related compounds. Species with R^3 = H seemed especially interesting for investigations regarding tautomerism as the geminal ^2J(C-4,H-3) coupling constant has proven to be a valuable tool for this purpose.[10]

Figure 1. Tautomeric forms of pyrazolones and 4-acylpyrazolones



RESULTS AND DISCUSSION

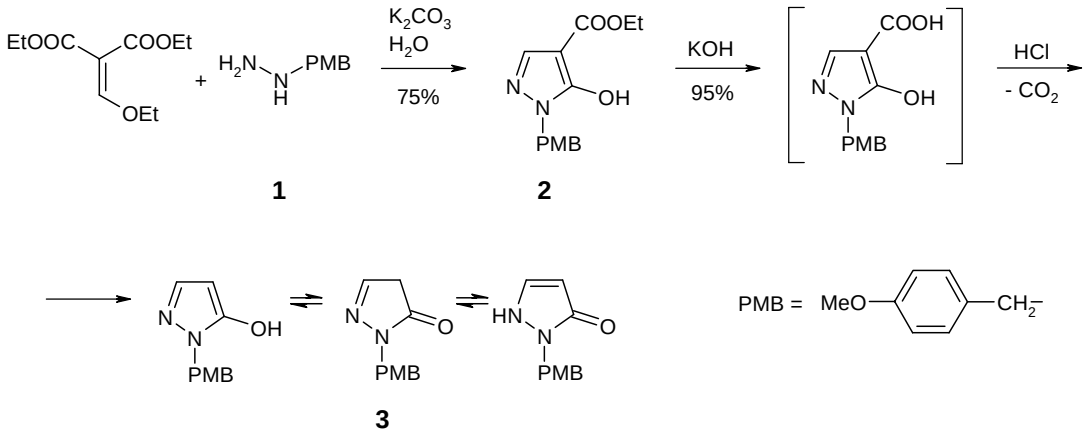
Chemistry

N1-Substituted 4-acyl-2-pyrazolin-5-ones are typically prepared by treatment of 1-substituted 2-pyrazolin-5-ones with carboxylic acid chlorides / calcium hydroxide in refluxing dioxane according to the procedure of *Jensen.*[12] As this approach obviously is not suitable for the acylation of *N*-unsubstituted pyrazolones, employment of appropriately N1 protected 2-pyrazolin-5-ones and subsequent removal of the *N*-substituent should provide an access to *N*-unsubstituted 4-acylpyrazolones. Such an assistant group on one hand should resist the conditions of primary pyrazole ring synthesis (i.e. condensation of 1,3-dicarbonyl compounds or their synthetic equivalents with substituted hydrazines), on the other hand deprotection should proceed under mild and simple conditions. We anticipated the 4-methoxybenzyl (*para*-methoxybenzyl = PMB) group to meet these requirements as this system has been successfully

employed under different reaction conditions in pyrazole,[13-17] but also in imidazole[18] or 1,2,3-triazole chemistry[19] and can be removed from the azole nitrogen atom by the action of trifluoroacetic acid[13-15,17,19] as well as by hydrogenolytic or oxidative methods.[13,18]

Following a well known synthetic strategy for the synthesis of 1-substituted pyrazolones,[8,20,21] diethyl ethoxymethylenemalonate was treated with PMB-hydrazine (**1**) (prepared by reaction of hydrazine with PMB-chloride) in aqueous potassium carbonate to afford the ester (**2**), which was transformed into the key pyrazolone (**3**) by alkaline hydrolysis followed by decarboxylation of the intermediate carboxylic acid under acidic conditions (Scheme 1).

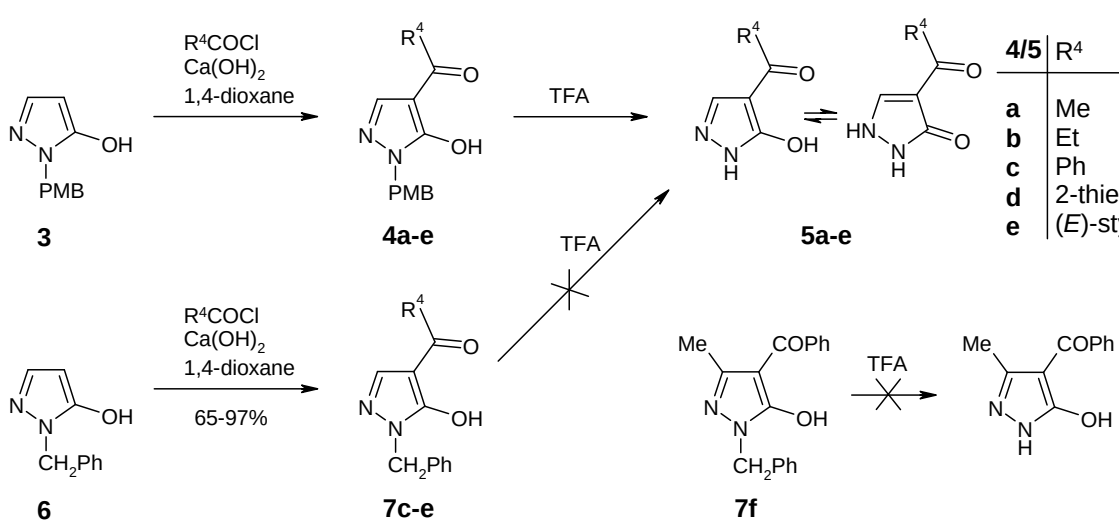
Scheme 1. Synthesis of 1-PMB-2-pyrazolin-5-one (**3**) (tautomer to 5-hydroxy-1-PMB-pyrazole)



Applying the above mentioned acylation conditions (R^4COCl / $Ca(OH)_2$ / dioxane), the transformation of pyrazolone (**3**) into the corresponding 4-acyl derivatives (**4a-d**) proceeded in good yields (Scheme 2). However, upon reaction of **3** with *trans*-cinnamoyl chloride the desired product (**4e**) was obtained in lower yield (34%) for some unknown reasons. Removal of the PMB protecting group was achieved by prolonged (*ca*. 24 h) heating of compounds (**4**) in trifluoroacetic acid (TFA) at 70 °C (Scheme 2). Application of the system TFA / anisole in refluxing dichloroethane according to ref.[16] turned out to be disadvantageous owing to incomplete deprotection and problems arising with the removal of excess anisole. Deprotection of the starting pyrazolone (**3**) to afford 2-pyrazolin-5-one required markedly longer reaction times compared to those for the 4-acyl derivatives (**4a-e**).

Under comparable conditions (TFA, 70 °C, 24 h) neither the *N*-benzyl substituted 4-acylpyrazolones (**7c-e**) - obtained from 1-benzylpyrazolone (**6**) and R^4COCl / $Ca(OH)_2$ / dioxane - could not be transformed into the corresponding NH-pyrazolones (**5c-e**), nor deprotection of the 1-benzyl derivative (**7f**)[22] could be achieved (Scheme 2).

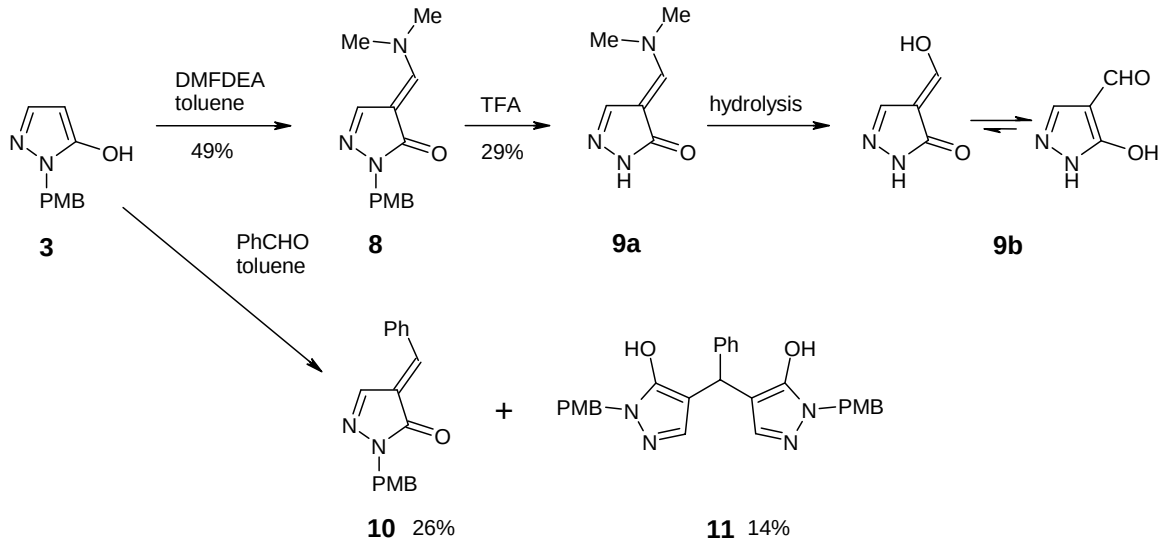
Scheme 2. Synthesis of 4-acyl-1-PMB-pyrazolones (**4a-e**) and deprotection into 4-acylpyrazolones (**5a-e**)



4/5	R^4	% yield of 4	5
a	Me	75	60
b	Et	86	66
c	Ph	61	57
d	2-thienyl	57	83
e	(*E*)-styryl	34	14

The 'active' methylene group in the pyrazole system of **3** permits classical C-C bond formation as shown by condensation of **3** with dimethylformamide diethyl acetal (DMFDEA) to afford the (*E*)-configurated dimethylaminomethylene compound (**8**), the formation of corresponding (*Z*)-isomer was not observed**.** Accordingly, reaction of **3** with benzaldehyde gave the (*E*)-4-benzylidenepyrazolone (**10**) accompanied by minor amounts of the dimer (**11**), the latter obviously resulting from *Michael*-type addition of a second unit of **3** to the primary reaction product (**10**) (Scheme 3) (the determination of the stereochemistry for **8** and **10** is described in detail in the chapter NMR spectroscopic investigations). Treatment of **8** with TFA led to the pyrazolone (**9a**) which partially hydrolyzed into aldehyde (**9b**) during workup. When recording NMR spectra of **9a** in DMSO-d_6 (containing trace water) also successive formation of **9b** was observed.

Scheme 3. Reaction of **3** with DMFDEA and benzaldehyde



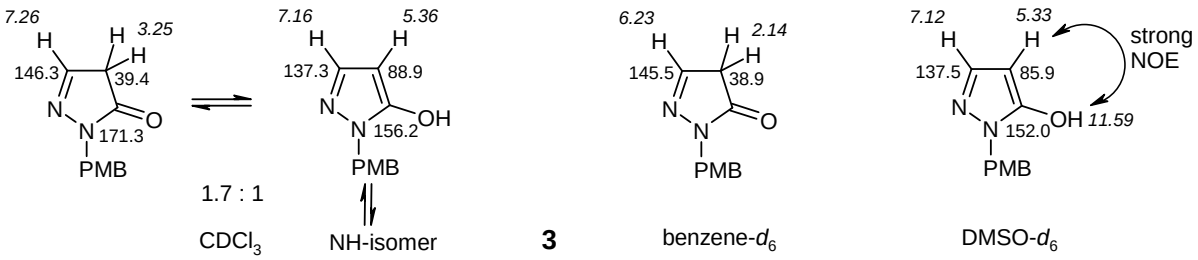
NMR SPECTROSCOPIC INVESTIGATIONS

Unambiguous assignment for all proton and carbon resonances was achieved by combined application of some standard NMR spectroscopic techniques, such as NOE-difference experiments, fully ^{1}H-coupled ^{13}C-NMR spectra, APT, HMQC and HMBC spectra as well as experiments with selective excitation such as 1D-TOCSY,[23] 1D-HETCOR[24] and selective long-range INEPT.[25,26] The ^{15}N-NMR spectra were recorded using the refocused INEPT technique[27,28] with proton decoupling and - especially - gradient selected, sensitivity enhanced HSQC[29-31] and HMBC sequences.[32] It should be emphasized that - owing to the dynamic behavior of most substances investigated and the thus resulting (massive) line broadening - it was sometimes difficult or impossible to observe all expected ^{15}N-NMR signals.

Pyrazolone (**3**)

The possible tautomeric forms of pyrazolone (**3**) are displayed in the upper line of Figure 1 or in Scheme 1, respectively. In $CDCl_3$ solution two sets of signals emerged (ratio 1.7 : 1) with the major component being easily assignable as the CH-isomer (CH_2 partial structure in the heterocyclic ring) and the minor species as the OH-isomer (possibly in fast exchange with some NH-isomer) (Figure 2). In benzene-d_6 compound (**3**) has a very low solubility, in a saturated solution predominance of the CH-form (90%) over the OH-form (10%) was detected. In more polar DMSO-d_6 only one signal set emerged which can be attributed to the OH-isomer or to a mixture of OH (far predominating) and NH-isomer (low amount) in fast exchange (Figure 2). Marked line broadening of certain resonances in the spectra of **3** hints to a dynamic behavior. Investigations regarding the tautomerism of pyrazolone (**3**) and related compounds in protic solvents such as methanol-d_4 or trifluoroacetic acid-d_1 will be reported elsewhere.[33]

Figure 2. Selected ^{1}H-NMR (*italics*) and ^{13}C-NMR chemical shifts of pyrazolone (**3**) in $CDCl_3$, benzene-d_6 and DMSO-d_6 solution



4-Acylpyrazolones (**4a-e**) and (**7c-e**)

The tautomeric behavior of closely related 4-acylpyrazolones has been extensively investigated in some recent publications.[6-10] Accordingly, it can be assumed that in $CDCl_3$ solution the novel compounds (**4a-e**),

Table 1. ^{1}H-NMR chemical shifts (δ, ppm) of **4a-e**, **5a-e** and **7c-e**

No.	solvent	H-3	N-PMB / N-benzyl NCH_2	H-2,6	H-3,5	OMe (H-4)	OH NH	H of 4-substituent R
4a	$CDCl_3$	7.61	5.06	7.26	6.86	3.77	9.08	2.35 (Me)
4a	DMSO-d_6	7.79	5.00	7.13	6.88	3.71	8.64	2.28 (Me)
4b	$CDCl_3$	7.60	5.04	7.24	6.84	3.77	9.06	2.67 (CH_2),[a] 1.18 (CH_3)[a]
4b	DMSO-d_6	7.79	5.00	7.14	6.87	3.71	6.90	2.68 (CH_2),[a] 1.02 (CH_3)[a]
4c	$CDCl_3$	7.77	5.13	7.31	6.88	3.79	9.90	7.90 (Bz H-2,6), 7.59 (Bz H-4), 7.51 (Bz H-3,5)
4c	DMSO-d_6	7.68	5.07	7.20	6.90	3.72	7.20	7.80 (Bz H-2,6), 7.60 (Bz H-4), 7.52 (Bz H-3,5)
4d	$CDCl_3$	7.94	5.12	7.30	6.87	3.78	10.09	7.90 (Th H-3),[b] 7.68 (Th H-5),[b] 7.19 (Th H-4)[b]
4d	DMSO-d_6	8.02	5.07	7.19	6.89	3.71	8.00	8.02 (Th H-3),[c] 7.96 (Th H-5),[c] 7.24 (Th H-4)[c]
4e	$CDCl_3$	7.77	5.09	7.29	6.87	3.79	7.07	7.83 (PhCH),[d] 7.04 (COCH=),[d] 7.62 (Cm H-2,6), 7.42 (Cm (H-3,4,5)
4e	DMSO-d_6	8.14	5.02	7.17	6.89	3.72	4.54[e]	7.78 (Cm H-2,6), 7.62 (PhCH, COCH=), 7.43 (Cm H-3,4,5)
5a	DMSO-d_6	8.00	---	---	---	---	9-14	2.29 (Me)
5b	DMSO-d_6	8.01	---	---	---	---	9-16	2.69 (CH_2), 1.01 (CH_3)
5c	DMSO-d_6	8.01	---	---	---	---	9-14	7.79 (Bz H-2,6), 7.60 (Bz H-4), 7.50 (Bz H-3,5)
5d	DMSO-d_6	8.29	---	---	---	---	9-14	8.03 (Th H-3),[c] 7.97 (Th H-5),[c] 7.24 (Th H-4)[c]
5e	DMSO-d_6	8.31	---	---	---	---	4.03[e]	7.74 (Cm H-2,6), 7.63 (PhCH, COCH=), 7.43 (Cm H-3,4,5)
7c	$CDCl_3$	7.80	5.20	7.35	7.35	7.33	9.23	7.91 (Bz H-2,6), 7.60 (Bz H4), 7.52 (Bz H-3,5)
7c	DMSO-d_6	7.70	5.16	7.23	7.35	7.30	5.20[e]	7.80 (Bz H2,6), 7.61 (Bz H-4), 7.52 (Bz H-3,5)
7d	$CDCl_3$	7.96	5.20	7.34	7.34	7.33	8.83	7.92 (Th H-3),[b] 7.70 (Th H-5),[b] 7.20 (Th H-4)[b]
7d	DMSO-d_6	8.04	5.15	7.23	7.34	7.30	5.56	8.04 (Th H-3),[c] 7.97 (Th H-5),[c] 7.25 (Th H-4)[c]
7e[f]	$CDCl_3$	7.79	5.16	7.34	7.28 - 7.36		7.65	7.84 (PhCH),[d] 7.05 (COCH=),[d] 7.63 (Cm H-2,6), 7.43 (Cm (H-3,4,5)
7e[f]	DMSO-d_6	8.17	5.11	7.21	6.89	7.34	6.11	7.79 (Cm H-2,6), 7.63 (PhCH, COCH=), 7.44 (Cm H-3,4,5)

[a] ^{3}J(CH_3, CH_2) = 7.4 Hz. [b] ^{3}J(Th H-4,Th H-5) = 4.9 Hz, ^{3}J(Th H-3,Th H-4) = 3.8 Hz, ^{4}J(Th H-3,Th H-5) = 1.1 Hz. [c] ^{3}J(Th H-4,Th H-5) = 5.0 Hz, ^{3}J(Th H-3,Th H-4) = 3.8 Hz, ^{4}J(Th H-3,Th H-5) = 1.1 Hz.
[d] ^{3}J(PhCH,COCH=) = 15.7 Hz. [e] Together with trace H_2O. [f] See ref. 8.

Table 2. ^{15}N-NMR chemical shifts (δ, ppm) of **4a-e** and **7c,d**

No.	Solvent	PMB-N / Bn-N	N
4a	$CDCl_3$	-189.5	-99.1
4b	$CDCl_3$	-189.8	-100.3
4b	DMSO-d_6	-186.6	[a]
4c	$CDCl_3$	-189.8	-97.7
4c	DMSO-d_6	-185.2	[a]
4d	$CDCl_3$	-189.7	-97.7
4d	DMSO-d_6	-186.5	[a]
4e	$CDCl_3$	-189.9	-94.6
7c	DMSO-d_6	-186.9	[a]
7d	DMSO-d_6	-187.6	[a]

[a] Not found.

Table 3. ^{13}C-NMR chemical shifts (δ, ppm) of **4a-e**, **5a-e** and **7c-e**

		pyrazole			N-PMB / N-benzyl							
No.	solvent	C-3	C-4	C-5	NCH_2	Ph C-1	Ph C-2,6	Ph C-3,5	Ph C-4	OMe	C=O	C of 4-substituent R
4a	$CDCl_3$	138.1	104.2	157.2	49.7	127.5	129.5	114.1	159.4	55.2	195.3	26.0 (Me)
4a	DMSO-d_6	139.0	105.5	154.2	48.4	128.6	128.8	113.9	158.7	55.0	191.3	27.2 (Me)
4b	$CDCl_3$	137.8	103.4	157.5	49.6	127.7	129.4	114.1	159.4	55.2	198.8	32.1 (CH_2), 8.4 (CH_3)
4b	DMSO-d_6	138.6	104.7	154.2[a]	48.4[a]	128.7	128.8	113.9	158.6	55.0	194.5	32.0 (CH_2), 8.2 (CH_3)
4c	$CDCl_3$	138.9	102.4	159.6	49.7	127.6	129.5	114.2	159.5	55.2	190.0	137.3 (Bz C-1), 132.6 (Bz C-4), 128.7 (Bz C-3,5), 128.4 (Bz C-2,6)
4c	DMSO-d_6	139.7	103.2	155.6	48.8	128.4	129.0	113.9	158.7	55.1	187.7	138.4 (Bz C-1), 131.9 (Bz C-4), 128.5 (Bz C-3,5), 128.3 (Bz C-2,6)
4d	$CDCl_3$	137.8	101.6	159.3	49.7	127.5	129.5	114.2	159.4	55.2	180.9	141.8 (Th C-2), 133.2 (Th C-5), 131.9 (Th C-3), 128.2 (C-4)
4d	DMSO-d_6	138.7	102.7	155.7	48.7	128.4	129.0	113.9	158.7	55.1	178.8	143.7 (Th C-2), 133.6 (Th C-5), 132.2 (Th C-3), 128.6 (C-4)
4e	$CDCl_3$	137.3	104.3	160.2	49.4	127.8	129.5	114.2	159.4	55.3	183.1	143.5 (PhCH), 134.4 (Cm C-1), 130.8 (Cm C-4), 129.0 (Cm C-3,5), 128.5 (Cm C-2,6), 120.9 (COCH=)
4e	DMSO-d_6	138.9	105.7	156.1[a]	48.3	128.6	128.9	113.9	158.7	55.1	181.6[a]	140.8 (PhCH), 134.7 (Cm C-1), 130.2 (Cm C-4), 128.8 (Cm C-3,5), 128.5 (Cm C-2,6), 123.5 (COCH=)
5a	DMSO-d_6	133.5	107.2[a]	160.3[a]	---	---	---	---	---	---	192.2	28.0 (Me)
5b	DMSO-d_6	133.3	106.5	160.3	---	---	---	---	---	---	195.4	32.8 (CH_2), 8.2 (CH_3)
5c	DMSO-d_6	135.1[a]	104.6	161.4[a]	---	---	---	---	---	---	189.0	138.7 (Bz C-1), 131.9 (Bz C-4), 128.4 (Bz C-3,5), 128.3 (Bz C-2,6)
5d	DMSO-d_6	134.2[a]	104.0	161.2	---	---	---	---	---	---	179.9	143.9 (Th C-2), 133.7 (Th C-5), 132.4 (Th C-3), 128.5 (C-4)
5e	DMSO-d_6	134.1	107.8	161.1	---	---	---	---	---	---	183.1	140.8 (PhCH), 134.8 (Cm C-1), 130.2 (Cm C-4), 128.9 (Cm C-3,5), 128.3 (Cm C-2,6), 124.2 (COCH=)
7c	$CDCl_3$	139.0	102.4	159.9	50.2	135.4	128.0	128.8	128.1	---	190.0	137.2 (Bz C-1), 132.7 (Bz C-4), 128.7 (Bz C-3,5), 128.4 (Bz C-2,6)
7c	DMSO-d_6	139.9	103.3	155.8	49.2	136.6	127.4	128.5	127.5	---	187.7	138.4 (Bz C-1), 131.9 (Bz C-4), 128.5 (Bz C-3,5), 128.3 (Bz C-2,6)
7d	$CDCl_3$	137.9	101.6	159.6	50.2	135.4	128.0	128.8	128.1	---	180.9	141.8 (Th C-2), 133.2 (Th C-5), 131.9 (Th C-3), 128.2 (C-4)
7d	DMSO-d_6	138.8	102.7	155.8	49.2	136.5	127.4	128.5	127.5	---	178.8	143.8 (Th C-2), 133.6 (Th C-5), 132.2 (Th C-3), 128.6 (C-4)
7e	$CDCl_3$	137.4	104.3	160.6	49.9	135.6	128.6	128.8	128.0	---	182.9	143.6 (PhCH), 134.4 (Cm C-1), 130.8 (Cm C-4), 129.0 (Cm C-3,5), 128.0 (Cm C-2,6), 120.8 (COCH=)
7e	DMSO-d_6	139.0	105.7	156.2	48.8	136.7	127.3	128.5	127.5	---	181.5	140.9 (PhCH), 134.7 (Cm C-1), 130.2 (Cm C-4), 128.8 (Cm C-3,5), 128.5 (Cm C-2,6), 123.5 (COCH=)

[a] Broad signal.

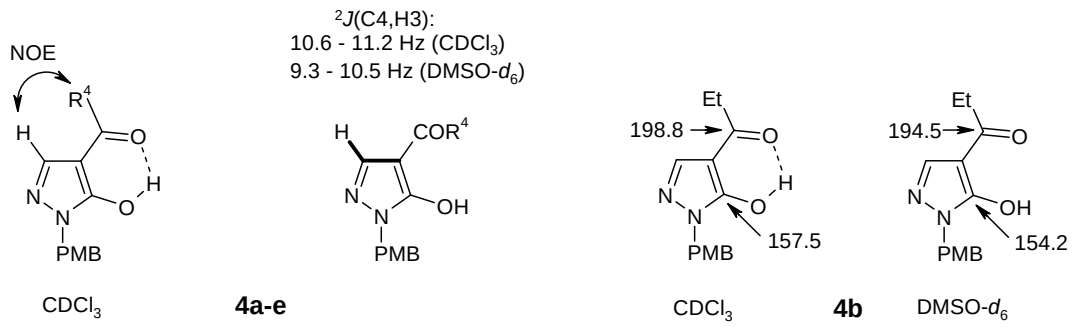
Table 4. Selected ^{13}C, ^{1}H spin coupling constants (Hz) of **4a-e**, **5a-e** and **7c-e**

No.	solvent	^{1}J(C-3,H-3)	^{2}J(C-4,H-3)	^{1}J(NCH_2)	^{1}J(OMe)	other couplings (R)
4a	$CDCl_3$	188.0	10.6	140.4	143.8	^{1}J(Me) = 127.7, ^{3}J(NCH_2,Ph H-2,6) = 4.4, ^{3}J(C-4,Me) = 1.8
4a	DMSO-d_6	187.7	9.3	140.2	144.1	^{1}J(Me) = 127.1
4b	$CDCl_3$	187.7	10.6	140.1	143.8	^{1}J(CH_3) = 128.5, ^{1}J(CH_2) = 126.3, ^{2}J(CH_3,CH_2) = 4.7, ^{3}J(NCH_2,Ph H-2,6) = 4.5, ^{2}J(CH_2,CH_3) = 4.4
4b	DMSO-d_6	187.7	9.6	144.4	144.2	^{1}J(CH_3) = 127.3, ^{1}J(CH_2) = 125.9, ^{2}J(CH_3,CH_2) = 4.6, ^{2}J(CH_2,CH_3) = 4.5
4c	$CDCl_3$	189.7	11.0	140.5	143.8	^{3}J(C-5,H-3) = 4.9, ^{3}J(NCH_2,Ph H-2,6) = 4.5, ^{3}J(C-5,NCH_2) = 2.5
4c	DMSO-d_6	188.8	10.4	140.8	144.2	
4d	$CDCl_3$	189.0	11.2	140.3	143.9	^{1}J(Th C-5) = 185.9, ^{1}J(Th C-4) = 170.2, ^{1}J(Th C-3) = 168.5, ^{3}J(Th C-5,Th H-3) = 10.9, ^{3}J(Th C-3,Th H-5) = 9.3, ^{3}J(Th C-2,Th H-4) = 9.1, ^{2}J(Th C-5,Th H-4) = 7.2, ^{2}J(Th C-2,Th H-3) = 6.5, ^{2}J(Th C-3,Th H-4) = 5.7, ^{3}J(Th C-2,Th H-5) = 5.6, ^{2}J(Th C-4,Th H-3) = 4.7, ^{3}J(NCH_2,Ph H-2,6) = 4.5, ^{2}J(Th C-4,Th H-5) = 4.1
4d	DMSO-d_6	189.2	10.5	140.3	144.2	^{1}J(Th C-5) = 187.7, ^{1}J(Th C-4) = 170.2, ^{1}J(Th C-3) = 169.3, ^{3}J(Th C-5,Th H-3) = 10.6, ^{3}J(Th C-3,Th H-5) = 9.1, ^{3}J(Th C-2,Th H-4) = 8.7, ^{2}J(Th C-5,Th H-4) = 7.4, ^{2}J(Th C-2,Th H-3) = 7.2, ^{2}J(Th C-3,Th H-4) = 5.8, ^{3}J(Th C-2,Th H-5) = 5.6, ^{2}J(Th C-4,Th H-3) = 4.5, ^{2}J(Th C-4,Th H-5) = 4.5
4e	$CDCl_3$	188.5	10.6	140.3	143.8	^{1}J(PhCH) = 156.0, ^{1}J(COCH=) = 157.1, ^{2}J(COCH=,PhCH) = 2.3, ^{3}J(C-5,NCH_2) = 4.2
4e	DMSO-d_6	189.0	9.7	[a]	144.1	
5a	DMSO-d_6	[a]	[a]	---	---	^{1}J(Me) = 127.1, ^{2}J(CO,Me) = 5.5
5b	DMSO-d_6	188.7	[a]	---	---	^{1}J(CH_3) = 127.3, ^{1}J(CH_2) = 126.4, ^{2}J(CH_3,CH_2) = 4.4, ^{2}J(CH_2,CH_3) = 4.4
5c	DMSO-d_6	[a]	[a]	---	---	
5d	DMSO-d_6	[a]	8.8	---	---	^{1}J(Th C-5) = 187.7, ^{1}J(Th C-4) = 170.1, ^{1}J(Th C-3) = 169.4, ^{3}J(Th C-5,Th H-3) = 10.7, ^{3}J(Th C-3,Th H-5) = 9.2, ^{3}J(Th C-2,Th H-4) = 8.7, ^{2}J(Th C-5,Th H-4) = 7.3, ^{2}J(Th C-2,Th H-3) = 7.2, ^{2}J(Th C-3,Th H-4) = 5.8, ^{3}J(Th C-2,Th H-5) = 5.6, ^{2}J(Th C-4,Th H-3) = 4.4, ^{2}J(Th C-4,Th H-5) = 4.4
5e	DMSO-d_6	[a]	[a]	---	---	
7c	$CDCl_3$	189.7	11.0	140.3	---	^{3}J(C-5,H-3) = 5.0, ^{3}J(C-5,NCH_2) = 2.5
7c	DMSO-d_6	188.6	10.4	141.1	---	^{2}J(Ph C-1,NCH_2) = 5.0, ^{3}J(NCH_2,Ph H-2,6) = 4.1, ^{3}J(C-5,NCH_2) = 2.2, ^{3}J(C-5,H-3) = 5.0
7d	$CDCl_3$	189.0	11.2	140.5	---	^{1}J(Th C-5) = 185.9, ^{1}J(Th C-4) = 170.3, ^{1}J(Th C-3) = 168.5, ^{3}J(Th C-5,Th H-3) = 10.9, ^{3}J(Th C-3,Th H-5) = 9.3, ^{3}J(Th C-2,Th H-4) = 9.1, ^{2}J(Th C-5,Th H-4) = 7.2, ^{2}J(Th C-2,Th H-3) = 6.5, ^{2}J(Th C-3,Th H-4) = 5.6, ^{3}J(Th C-2,Th H-5) = 5.6, ^{3}J(C-5,H-3) = 4.8, ^{2}J(Th C-4,Th H-3) = 4.7, ^{2}J(Th C-4,Th H-5) = 4.1, ^{3}J(C-5,NCH_2) = 2.6
7d	DMSO-d_6	189.2	10.5	140.9	---	^{1}J(Th C-5) = 187.7, ^{1}J(Th C-4) = 170.3, ^{1}J(Th C-3) = 169.4, ^{3}J(Th C-5,Th H-3) = 10.6, ^{3}J(Th C-3,Th H-5) = 9.2, ^{3}J(Th C-2,Th H-4) = 8.8, ^{2}J(Th C-5,Th H-4) = 7.4, ^{2}J(Th C-2,Th H-3) = 7.3, ^{2}J(Th C-3,Th H-4) = 5.8, ^{3}J(Th C-2,Th H-5) = 5.6, ^{3}J(C-5,H-3) = 5.3, ^{2}J(Th C-4,Th H-3) = 4.4, ^{2}J(Th C-4,Th H-5) = 4.4
7e	$CDCl_3$	188.6	10.8	140.2	---	^{1}J(PhCH) = 156.2, ^{1}J(COCH=) = 157.2, ^{2}J(COCH=,PhCH) = 2.3
7e	DMSO-d_6	189.1	9.7	[a]	---	^{1}J(COCH=) = 160.4, ^{2}J(CO<u>C</u>H=,PhC<u>H</u>) = 4.0

[a] Not unambiguously determined.

(**7c**) and (**7d**) are present as 5-hydroxypyrazoles stabilized by an intramolecular hydrogen bond (form (**B'**) in Figure 1) whereas in DMSO-d_6 form (**B**) - possibly in fast (compared to the NMR-timescale) exchange with minor amounts of NH-isomer (**C**) - dominates. Again, the dynamic behavior becomes apparent upon line broadening effects, especially in the ^{13}C-NMR spectra. Compounds (**4**) and (**7**) exhibit very consistent ^{15}N-NMR chemical shift data with δ (N-1) *ca*. -190 (pyrrole-type) and δ (N-2) in the range from -95 to -100 (pyridine type nitrogen) (Table 2). In Figure 3, some diagnostic NMR spectroscopic data which support the above considerations are presented. The NMR data of compounds (**4**) and (**7**) are collected in Tables 1-4.

Figure 3. Some diagnostic NMR spectroscopic data for 4-acylpyrazolones (**4**)



4-Acylpyrazolones (**5**)

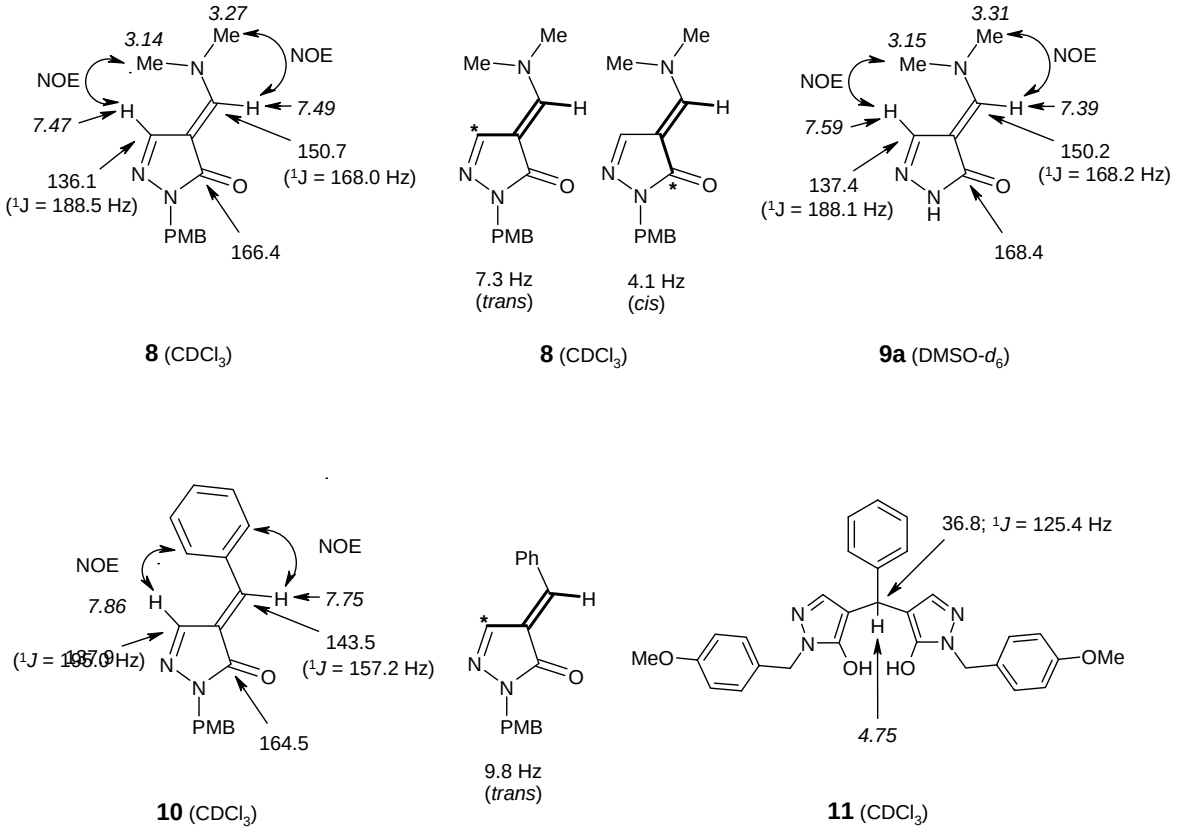
Recordings of pyrazolones (**5**) were carried out in DMSO-d_6 solution due to solubility reasons. In all spectra marked line broadening effects can be observed which prevent the accurate determination of, for instance, ^{13}C,^{1}H spin coupling constants. Thus, only in case of **5d** the diagnostic pyrazole ^2J(C-4, H-3) coupling constant could be determined. Its magnitude of 8.8 Hz hints to the predominance of the OH-isomer, however, some contribution of NH-isomer is probable.

Compounds (**8-11**)

(*E*)-Configuration regarding the exocyclic C=C bond of **8** unambiguously follows from the ^{1}H-coupled ^{13}C-NMR spectrum. Thus, the pyrazole C-5 signal (δ 136.1) exhibits a ^3J coupling of 7.3 Hz to the alkene proton (*trans*-coupling) whereas the pyrazole C-3 (≡ pyrazolone C=O, δ 166.4) signal is split by a markedly smaller coupling to the latter proton (^3J = 4.1 Hz, *cis*-coupling) (Figure 4). This assignment is confirmed by a strong NOE between pyrazole H-5 and NMe (3.14 ppm) (Figure 4) and the complete absence of an NOE between pyrazole H-5 and alkene-H [in (*Z*)-configuration these protons should be spatially close]. Moreover, the ^{13}C-NMR chemicals shifts of the pyrazole carbon atoms in **8** are in good agreement with those reported for related compounds with unambiguously assigned stereochemistry[9] and reflect well the

influence of the enamino N-atom (shielding of pyrazole C-5 due to γ-effects). As the data of **9a** closely resemble those of **8** (Figure 4) also (*E*)-configuration can be attributed to the former. Both **8** and **9a** show two well separated signals for each methyl group within the NMe_2 moiety due to hindered rotation around the C–N bond.[9] Determination of the stereochemistry of the 4-benzylidene derivative (**10**) was based on similar experiments: the strong NOEs between pyrazole H-5 and the phenyl protons, the magnitude of the vicinal (pyrazole C-5,alkene-H) coupling (^3J = 9.8 Hz) as well as the ^{13}C-NMR chemical shifts of pyrazole C-5 and pyrazole C-3 clearly assign (*E*)-configuration at the excocyclic C=C bond. Expectedly, in the NMR spectra of **11** the two 1-PMB-5-hydroxypyrazol-4-yl units give rise to one signal set (2:1 ratio to the central Ph-CH substructure) (Figure 4). An interesting phenomenon is the non-equivalence of the methylene protons in the PMB substructure of (AB-system, ^2J = 15.1 Hz) which can be attributed to the fact that the central sp^3-hybridized carbon atom in **11** represents a prochiral center. According to its ^{1}H and ^{13}C-NMR data compound (**9b**), resulting from hydrolysis of **9a**, is present as aldehyde (CHO partial structure: H 9.86 ppm, C 183.2 ppm, in DMSO-d_6) and not as hydroxymethylene compound (see Scheme 1).

Figure 4. Characteristic ^{1}H-NMR (*italics*) and ^{13}C-NMR chemical shifts, ^{13}C,^{1}H coupling constants (Hz) and NOEs used for structural assignments of **8**, **9a**, **10**, and **11**



8 ($CDCl_3$) **8** ($CDCl_3$) **9a** (DMSO-d_6)

10 ($CDCl_3$) **11** ($CDCl_3$)

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 (ESI-TOF) on a Biosystem Q-Star and 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) 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 (^{1}H in $CDCl_3$), δ 2.49 ppm (^{1}H in DMSO-d_6), δ 7.16 ppm (^{1}H in benzene-d_6) δ 77.0 ppm (^{13}C in $CDCl_3$), δ 39.5 ppm (^{13}C in DMSO-d_6) and δ 128.4 ppm (^{13}C in benzene-d_6). ^{15}N-NMR spectra (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a 'directly' detecting broadband observe probe and were referenced against neat, external nitromethane (coaxial capillary). Digital resolutions were 0.25 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling) and ≤ 59 Hz/data point in the ^{15}N-NMR spectra. In the description of the ^{13}C-NMR spectra the terms C-3, C-4 and C-5 refer to the carbon atoms of the pyrazole nucleus. As syntheses were mainly devoted to obtain material for the NMR-spectroscopic investigations no attempts were made to optimize the yields. Systematic names according to IUPAC recommendations were generated with ACD/Name and checked manually.[34]

4-Methoxybenzylhydrazine (1)[35]

To hydrazine hydrate (80.0 g, 1.6 mol, purity > 98%) was added 4-methoxybenzyl chloride (25.0 g, 0.16 mol) in MeOH (150 mL) at 0 °C and the mixture was then stirred at rt for 2 h. After removal of MeOH under reduced pressure, the residue was extracted with Et_2O (3 × 30 mL), the combined etheral phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was subjected to vacuum distillation to afford 12.61 g (52%) of a colorless oil, bp 145 °C / 16 mbar (lit.,[35] bp 139 °C / 5 Torr), which solidified on standing (mp 30-35 °C). ^{1}H-NMR (DMSO-d_6): δ (ppm) 7.21 (m, 2H, Ph H-2,6), 6.86 (m, 2H, Ph H-3,5), 3.72 (s, 3H, OMe), 3.71 (s, 2H, CH_2), 3.34 (s, 3H, NH, NH_2); ^{13}C-NMR (DMSO-d_6): δ (ppm) 158.2 (Ph C-4), 131.1 (Ph C-1), 129.7 (Ph C-2,6), 113.5 (Ph C-3,5), 58.3 (CH_2), 55.0 (OMe).

Ethyl 5-Hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-carboxylate (2)

To a mixture of **1** (11.50 g, 75.5 mmol) and K_2CO_3 (10.46 g, 75.5 mmol) in water (300 mL) was added diethyl ethoxymethylenemalonate (16.30 g, 75.5 mmol). The mixture was refluxed for 3 h and then let to reach rt. After washing with AcOEt (3 × 50 mL) the aqueous phase was acidified to pH 2 with concd HCl and was then extracted with AcOEt (3 × 100 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 14.55 g

(75%) of a yellow solid, pure according to ^{1}H-NMR spectrum. For analytical purposes some material was recrystallized from EtOH/H_2O to give yellowish crystals of mp 105-106 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 6.7-9.3 (very br s, 1H, OH), 7.59 (s, 1H, H-3), 7.24 (m, 2H, Ph H-2,6), 6.85 (m, 2H, Ph H-3,5), 5.08 (s, 2H, NCH_2), 4.30 (q, J = 7.1 Hz, 2H, OCH_2), 3.77 (s, 3H, OMe), 1.34 (t, J = 7.1 Hz, 3H, CH_3): ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.62 (s, 1H, OH), 7.57 (s, 1H, H-3), 7.13 (m, 2H, Ph H-2,6), 6.87 (m, 2H, Ph H-3,5), 5.01 (s, 2H, NCH_2), 4.16 (q, J = 7.1 Hz, 2H, OCH_2), 3.71 (s, 3H, OMe), 1.23 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ (ppm) 165.9 (C=O, ^3J(CO,C$\underline{H}_2$) = 3.4 Hz), 159.4 (Ph C-4, ^2J(Ph C-4,OMe) = 4.2 Hz), 156.2 (C-5), 137.8 (C-3, ^1J = 190.8 Hz, ^2J(C-4,H-3) = 9.6 Hz), 129.3 (Ph C-2,6), 127.8 (Ph C-1), 114.1 (Ph C-3,5), 94.1 (C-4), 60.4 (OCH_2, ^1J = 147.8, ^2J(O$\underline{C}$H$_2$,C$\underline{H}_3$) = 4.4 Hz), 55.2 (OMe, ^1J = 143.8 Hz), 50.1 (NCH_2, ^1J = 140.2 Hz, ^3J(N$\underline{C}$H$_2$,Ph H-2,6) = 4.5 Hz), 14.3 (CH_3, ^1J = 127.2 Hz, ^2J($\underline{C}$H$_3$,C$\underline{H}_2$) = 2.6 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 162.4 (C=O, ^3J(CO,C$\underline{H}_2$) = 3.4 Hz), 158.6 (Ph C-4), 153.8 (C-5), 138.8 (C-3, ^1J = 190.0 Hz), 128.8 (Ph C-1), 128.8 (Ph C-2,6), 113.9 (Ph C-3,5), 95.2 (C-4, ^2J(C-4,H-3) = 9.2 Hz), 58.9 (OCH_2, ^1J = 147.1 Hz, ^2J(O$\underline{C}$H$_2$,C$\underline{H}_3$) = 4.5 Hz), 55.0 (OMe, ^1J = 144.2 Hz), 48.9 (NCH_2, ^1J = 140.2 Hz, ^3J(N$\underline{C}$H$_2$,Ph H-2,6) = 4.4 Hz), 14.4 (CH_3, ^1J = 126.7 Hz, ^2J($\underline{C}$H$_3$,C$\underline{H}_2$) = 2.6 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) -100.6 (N-2), -189.7 (N-1); ^{15}N-NMR (DMSO-d_6): δ (ppm) -98.6 (N-2), -184.3 (N-1); IR (KBr): ν (cm^{-1}) 1700 (C=O); MS (m/z , %): 276 (M^+, 5), 230 (4), 202 (14), 174 (8), 121 (100), 91 (9), 77 (14). *Anal*. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.95; H, 5.86; N, 10.12.

2-(4-Methoxybenzyl)-2,4-dihydro-3*H*-pyrazol-3-one [tautomer to 1-(4-Methoxybenzyl)-1*H*-pyrazol-5-ol] (3)

A mixture of ester (**2**) (13.40 g, 48.5 mmol), 35% aqueous KOH (57.4 mL, 358 mmol) and MeOH (25 mL) was heated to reflux for 8 h and was then stirred at rt for further 12 h. Under cooling with an ice-bath, the mixture was brought to pH 2-3 by careful addition of 2N HCl and was then refluxed for 6 h to complete decarboxylation. Then MeOH was removed under reduced pressure and the residue was extracted with AcOEt (3 × 100 mL). The combined ethyl acetate phases were washed several times with H_2O, dried (Na_2SO_4) and evaporated under reduced pressure to afford 9.41 g (95%) of a yellowish powder, pure according to the ^{1}H-NMR spectrum. For analytical purposes some material was recrystallized from EtOH/H_2O to give yellowish crystals of mp 135-137 °C. ^{1}H-NMR ($CDCl_3$): (ratio CH-Isomer to OH-Isomer 1.7 : 1): CH-isomer: δ (ppm) 7.28 (m, 2H, Ph H-2,6), 7.26 (s, 1H, H-3), 6.86 (m, 2H, Ph H-3,5), 4.78 (s, 2H, NCH_2), 3.79 (s, 3H, OMe), 3.25 (s, 2H, C-4); (OH-isomer): δ (ppm) 7.8-9.2 (very br s, 1H, OH), 7.16 (d, ^3J = 2.0 Hz, 1H, H-3), 7.12 (m, 2H, Ph H-2,6), 6.77 (m, 2H, Ph H-3,5), 5.36 (d, ^3J = 2.0 Hz, 1H, H-4), 4.98 (s, 2H, NCH_2), 3.74 (s, 3H, OMe); ^{1}H-NMR (DMSO-d_6): OH-isomer: δ (ppm) 10.89 (s, 1H, OH), 7.12 (d, J = 1.8 Hz, 1H, H-3), 7.10 (m, 2H, Ph H-2,6), 6.86 (m, 2H, Ph H-3,5), 5.33 (d, J = 1.8 Hz, 1H, H-4), 4.96 (s, 2H, NCH_2), 3.70 (s, 3H, OMe); ^{1}H-NMR (benzene-d_6): (ratio CH-isomer to OH-isomer 10 :1): CH-isomer: δ (ppm) 7.33 (m, 2H, Ph H-2,6), 6.74 (m, 2H, Ph H-3,5), 6.23 (t, J = 1.3 Hz, 1H, H-3), 5.00 (s,

2H, NCH_2), 3.24 (s, 3H, OMe), 2.14 (d, *J* = 1.3 Hz, 2H, H-4); OH-isomer: δ (ppm) 5.35 (d, *J* = 1.9 Hz, 1H, H-4), 5.01 (s, 2H, NCH_2), 3.23 (s, 3H, OMe); ^{13}C-NMR ($CDCl_3$): (ratio CH-isomer to OH-Isomer 1.7 : 1): CH-isomer: δ (ppm) 171.3 (C-5), 159.2 (Ph C-4), 146.3 (C-3, ^1J = 196.0 Hz, ^2J(C-3,H-4) = 5.5 Hz), 129.7 (Ph C-2,6), 128.5 (Ph C-1), 114.0 (Ph C-3,5), 55.2 (OMe, ^1J = 143.7 Hz), 47.5 (NCH_2, ^1J = 139.2 Hz, ^3J(NCH_2,Ph H-2,6) = 4.4 Hz), 39.4 (C-4, ^1J = 134.1 Hz, ^2J(C-4,H-3) = 11.3 Hz); OH-isomer: δ (ppm) 159.1 (Ph C-4), 156.2 (C-5), 137.3 (C-3, ^1J = 182.9 Hz, ^2J(C-3,H-4) = 5.1 Hz), 129.1 (Ph C-2,6), 128.7 (Ph C-1), 114.0 (Ph C-3,5), 88.9 (C-4, ^1J = 179.6 Hz, ^2J(C-4,H-3) = 8.9 Hz), 55.2 (OMe, ^1J = 143.7 Hz), 48.6 (NCH_2); ^{13}C-NMR (DMSO-d_6): OH-isomer: δ (ppm) 158.4 (Ph C-4), 152.0 (C-5), 137.5 (C-3, ^1J = 182.9 Hz, ^2J(C-3,H-4) = 5.1 Hz), 129.9 (Ph C-1), 128.6 (Ph C-2,6), 113.7 (Ph C-3,5), 85.9 (C-4), 55.0 (OMe, ^1J = 144.1 Hz), 48.7 (NCH_2); ^{13}C-NMR (benzene-d_6): CH-isomer: δ (ppm) 160.2 (Ph C-4), 145.5 (C-3, ^1J = 194.9 Hz, ^2J(C-3,H-4) = 5.6 Hz), 130.6 (Ph C-2,6), 130.1 (Ph C-1), 114.7 (Ph C-3,5), 55.1 (OMe, ^1J = 143.7 Hz), 48.0 (NCH_2), 38.9 (C-4, ^1J = 134.1 Hz, ^2J(C-4,H-3) = 5.6 Hz); ^{15}N-NMR ($CDCl_3$): CH-isomer: δ (ppm) -39.4 (N-2), -189.8 (N-1); OH-isomer: δ (ppm) -150.5 (N-2), -196.9 (N-1); ^{15}N-NMR (DMSO-d_6): OH-isomer: δ (ppm) -99.0 (N-2), -189.9 (N-1); ^{15}N-NMR (benzene-d_6): CH-isomer: δ (ppm) -37.7 (N-2), -190.9 (N-1); MS (m/z, %): 203 (M^+-1, 14), 176 (15), 146 (21), 134 (12), 121 (100), 91 (13), 77 (21). *Anal*. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.90; H, 5.93; N, 13.54.

4-Acylation of Pyrazolones (3) and (6): Synthesis of Compounds (4) and (7) (General Procedure)

With stirring, to a mixture of pyrazolone (**3**) (1.02 g, 5 mmol) or (**6**)[8] (871 mg, 5 mmol) and $Ca(OH)_2$ (0.73 g, 10 mmol) in dry 1,4-dioxane (5 mL) was added a solution of the appropriate carboxylic acid chloride (5 mmol) in 1,4-dioxane (5 mL) and the mixture was refluxed for 2 h. After cooling to rt, 2N HCl (20 mL) was added and stirring was continued for further 1 h. Then the mixture was poured onto water (50 mL). After standing for 30 min the precipitate was filtered off, washed several times with water, dried and purified as described below.

1-[5-Hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]ethanone (4a)

From **3** and acetyl chloride 0.92 g (75%) of yellow-brownish leaves were obtained, pure according to ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from EtOH/H_2O affording slightly yellowish crystals of mp 121-122 °C. IR (KBr): ν (cm^{-1}) 1651 (C=O); MS (m/z, %): 246 (M^+, 21), 121 (100), 112 (20). *Anal*. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.13; H, 5.64; N, 11.37.

1-[5-Hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]propan-1-one (4b)

Reaction of **3** with propionyl chloride gave 1.12 g (86%) of a yellow solid, pure according to ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from diisopropyl ether affording a

slightly yellowish powder of mp 86-89 °C, crystal modifications starting at ~ 75 °C. IR (KBr): ν (cm^{-1}) 1663 (C=O); MS (m/z, %): 260 (M^+, 46), 245 (19), 136 (32), 121 (100), 77 (32). *Anal*. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.31; H, 6.31; N, 10.85.

[5-Hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl](phenyl)methanone (4c)

From reaction of **3** with benzoyl chloride 0.94 g (61%) of a brownish was obtained, pure according to ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from EtOH affording beige crystals of mp 98-99 °C. IR (KBr): ν (cm^{-1}) 1625 (C=O); MS (m/z, %): 308 (M^+, 1), 260 (4), 136 (9), 121 (100), 77 (26). *Anal*. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.85; H, 5.31; N, 9.16.

[5-Hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl](2-thienyl)methanone (4d)

Reaction of **3** with thiophene-2-carbonyl chloride afforded 0.89 g (57%) of a beige solid, pure according to ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from EtOH affording yellowish needles of mp 111-114 °C. IR (KBr): ν (cm^{-1}) 1604 (C=O); MS (m/z, %): 314 (M^+, 5), 202 (5), 180 (8), 136 (10), 121 (100), 77 (17). *Anal*. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.28; H, 4.42; N, 9.20.

(2*E*)-1-[5-Hydroxy-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl]-3-phenylprop-2-en-1-one (4e)

The raw product obtained from reaction of **3** with *trans*-cinnamoyl chloride was recrystallized from EtOH to yield 0.57 g (34%) of yellow crystals, mp 128-131 °C. IR (KBr): ν (cm^{-1}) 1662 (C=O); MS (m/z, %): 334 (M^+, 4), 136 (21), 121 (100), 77 (31). *Anal*. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.60; H, 5.55; N, 8.40.

(1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl)(phenyl)methanone (7c)

Reaction of **6** and benzoyl chloride gave 1.35 g (97%) of a yellow solid, pure according to ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from EtOH affording beige crystals of mp 100-101 °C. MS (m/z, %): 278 (M^+, 62), 174 (26), 105 (48), 91 (100), 77 (26). *Anal*. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.36; H, 5.19; N, 10.13.

(1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl)(2-thienyl)methanone (7d)

Reaction of **6** and thiophene-2-carbonyl chloride gave 1.11 g (78%) of a yellow solid, pure according to ^{1}H-NMR spectrum. An analytical sample was obtained by recrystallization from EtOH affording slightly

mauve crystals of mp 132-135 °C. MS (m/z, %): 284 (M^+, 31), 172 (30), 144 (23), 111 (38), 91 (100). *Anal*. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.09; H, 4.21; N, 9.75.

(2*E*)-1-[1-Benzyl-5-hydroxy-1*H*-pyrazol-4-yl]-3-phenylprop-2-en-1-one (7e)

Compound (**7e**) was prepared according to ref.[8]

Deprotection of 4-Acyl-1-PMB-pyrazolones (4a-e): Synthesis of Compounds (5a-e) (General Procedure)

With stirring, a mixture of 4-acylpyrazolones (**4a-e**) (1 mmol) and 2.85 g (25 mmol) of trifluoroacetic acid (TFA) was heated at 70-75 °C for 24 h. After removal of excess TFA under reduced pressure the residue was dried and worked-up as described below.

1-(5-Hydroxy-1*H*-pyrazol-4-yl)ethanone (5a)

The residue obtained upon treatment of **4a** (246 mg, 1.0 mmol) with TFA was washed with acetone and recrystallized from glacial acetic acid to give 76 mg (60%) of colorless crystals, mp 205-209 °C, crystal modifications beginning at ~ 155 °C. MS (m/z, %): 126 (M^+, 65), 111 (100). *Anal*. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.65; H, 4.57; N, 21.96.

1-(5-Hydroxy-1*H*-pyrazol-4-yl)propan-1-one (5b)

The residue obtained upon treatment of **4b** (260 mg, 1 mmol) with TFA was washed with acetone and recrystallized from glacial acetic acid to give 93 mg (66%) of colorless crystals, mp 185-186 °C, crystal modifications beginning at ~ 160 °C. IR (KBr): ν (cm^{-1}) 1695, 1657 (C=O); MS (m/z, %): 140 (M^+, 30), 111 (100), 43 (30). *Anal*. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.43; H, 5.77; N, 19.59.

(5-Hydroxy-1*H*-pyrazol-4-yl)(phenyl)methanone (5c)

The residue obtained upon treatment of **4c** (308 mg, 1 mmol) with TFA was washed with ethyl acetate and recrystallized from glacial acetic acid to give 107 mg (57%) of colorless crystals, mp 218-221 °C, crystal modifications starting at ~ 170 °C, (lit.,[11] mp 265-270 °C). IR (KBr): ν (cm^{-1}) 1645 (C=O); MS (m/z, %): 188 (M^+, 51), 110 (100), 105 (68), 77 (76), 53 (66). *Anal*. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.55; H, 4.09; N, 14.85.

(5-Hydroxy-1*H*-pyrazol-4-yl)(2-thienyl)methanone (5d)

The residue obtained upon treatment of **4d** (314 mg, 1 mmol) with TFA was washed with ethyl acetate and recrystallized from glacial acetic acid to give 161 mg (83%) of almost colorless crystals, mp 247-249 °C,

crystal modifications starting at ~ 185 °C. IR (KBr): ν (cm^{-1}) 1628 (C=O); MS (m/z, %): 194 (M^+, 35), 110 (38), 84 (32). *Anal*. Calcd for $C_8H_6N_2O_2S$: C, 49.47; H, 3.11; N, 14.42. Found: C, 49.50; H, 3.19; N, 14.21.

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

The residue obtained upon treatment of **4e** (334 mg, 1 mmol) with TFA was washed with toluene to give 30 mg (14%) of a grey powder, mp 194-196 °C, crystal modifications starting at ~ 185 °C. IR (KBr): ν (cm^{-1}) 1661 (C=O); MS (m/z, %): 214 (M+, 64), 131 (14), 111 (27), 104 (100), 77 (22). HRMS: Calcd for $C_{12}H_{10}N_2O_2$: 214.0742. Found: 214.0749.

(4*E*)-4-Dimethylaminomethylene-2-(4-methoxybenzyl)-2,4-dihydro-3*H*-pyrazol-3-one (8)

A mixture of pyrazolone (**3**) (1.02 g, 5 mmol), DMFDEA (0.74 g, 5 mmol) and toluene (20 mL) was refluxed for 3 h and then allowed to cool to rt. The precipitate was filtered off and washed with toluene to afford 0.63 g (49%) of yellow crystals, mp 171-172 °C. After concentration of the combined mother liquors additional 0.59 g (46%) of pure **8** were obtained, giving a total yield of 1.22 g (95%). ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.49 (s, 1H, =CH), 7.47 (s, 1H, H-5), 7.24 (m, 2H, Ph H-2,6), 6.80 (m, 2H, Ph H-3,5), 4.89 (s, 2H, NCH_2), 3.73 (s, 3H, OMe), 3.27 (s, 3H, NMe *cis* to =CH), 3.14 (s, 3H NMe *trans* to =CH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 166.4 (C-3, ^3J(C-3,NCH_2) = 2.2 Hz, ^3J(C-3,H-5) = ^3J(C-3,=CH) = 4.1 Hz), 158.7 (Ph C-4), 150.7 (=CH, ^1J = 168.0 Hz, ^3J(=CH,NMe_2) = 3.7 Hz), 136.1 (C-5, ^1J = 188.5 Hz, ^3J(C-5,=CH) = 7.3 Hz), 130.1 (Ph C-1), 129.2 (Ph C-2,6), 113.8 (Ph C-3,5), 99.6 (C-4, ^2J(C-4,H-5) = 11.1 Hz, ^2J(C-4,=CH) = 1.8 Hz), 55.2 (OMe, ^1J = 143.6 Hz), 47.3 (NCH_2, ^1J = 138.3 Hz, ^3J(NCH_2,Ph H-2,6) = 4.4 Hz), 46.9 (NMe *cis* to =CH, ^1J = 139.6 Hz, ^3J(NMe,=CH) = 5.2 Hz, ^3J(NMe,NMe) = 3.3 Hz), 40.3 (NMe *trans* to =CH, ^1J = 139.3 Hz, ^3J(NMe,=CH) = 7.4 Hz, ^3J(NMe,NMe) = 3.5 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) -84.4 (N-1), -191.8 (N-2), -272.5 (NMe_2); IR (KBr): ν (cm^{-1}) 1663 (C=O); MS (m/z, %): 259 (M^+, 8), 216 (17), 121 (100). *Anal*. Calcd for $C_{14}H_{17}N_2O_3$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.83; H, 6.66; N, 16.09.

(4*E*)-4-Dimethylaminomethylene-2,4-dihydro-3*H*-pyrazol-3-one (9a) and 5-Hydroxy-1*H*-pyrazole-4-carbaldehyde (9b)

Compound (**8**) (259 mg, 1.0 mmol) was treated with TFA as described for the synthesis of compounds (**5**). After removal of excess TFA the residue was taken up in ethyl acetate and extracted twice with 2N HCl. The aqueous layers were collected and evaporated under reduced pressure to afford 105 mg of a yellowish oil, containing **9a**•HCl and 20% of the aldehyde (**9b**) according to ^{1}H- and ^{13}C-NMR data (later NMR experiments in DMSO-d_6 solution confirmed a continuously ongoing hydrolysis of **9a** into **9b**). To obtain pure **9a** the residue was subjected to preparative TLC (silica gel, eluent: EtOAc / MeOH, 1:1) to give 26 mg (29%) of yellow crystals, mp 205-208 °C (dec). Compound (**9a**): ^{1}H-NMR (DMSO-d_6): δ (ppm) 10.77 (br s,

1H, NH), 7.59 (d, ^4J(H-5,NH) = 1.3 Hz, 1H, H-5), 7.39 (s, 1H, =CH), 3.31 (s, 3H, NMe *cis* to =CH), 3.15 (s, 3H, NMe *trans* to =CH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 168.4 (C-3), 150.2 (=CH, ^1J = 168.2 Hz), 137.4 (C-5, ^1J = 188.1 Hz, ^3J(C-5,=CH) = 7.6 Hz, ^3J(C-5,NH) = 7.6 Hz), 98.3 (C-4), 46.4 (NMe *cis* to =CH), 40.3 (NMe *trans* to =CH); IR (KBr): ν (cm^{-1}) 1670 (C=O); MS (m/z, %): 139 (M$^+$, 100), 124 (20), 95 (38), 82 (29). HRMS (ESI-TOF): Calcd for $C_6H_9N_3O$•H$^+$: 140.0818. Found: 140.0823. **9a**•HCl:[36] ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.90 (br s, 1H, NH), 8.54 (s, 1H, =CH), 8.34 (s, 1H, H-5), 3.58 (s, 3H, NMe *cis* to =CH), 3.44 (s, 3H, NMe *trans* to =CH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 163.9 (C-3), 157.1 (=CH), 136.8 (C-5), 97.6 (C-4), 48.7 (NMe *cis* to =CH), 42.2 (NMe *trans* to =CH).

Compound (**9b**):[37] ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.68 (s, 1H, CHO), 8.90 (br s, 2H, NH, OH), 7.94 (s, 1H, H-3); ^{13}C-NMR (DMSO-d_6): δ (ppm) 183.2 (CHO, ^1J = 171.8 Hz), 160.8 (C-5), 134.1 (C-3, ^1J = 189.0 Hz), 107.6 (C-4, ^2J(C-4,CHO) = 24.1 Hz, ^2J(C-4,H-3) = 8.2 Hz).

(4*E*)-4-Benzylidene-2-(4-methoxybenzyl)-2,4-dihydro-3*H*-pyrazol-3-one (10) and 4,4'-(Phenylmethylene)bis[1-(4-methoxybenzyl)-1*H*-pyrazol-5-ol] (11)

A solution of pyrazolone (**3**) (204 mg, 1 mmol) and distilled benzaldehyde (111 mg, 1.05 mmol) in toluene (2 mL) was stirred for 2 h at 80 °C. After removal of the solvent the oily residue was subjected to preparative TLC (silica gel, eluent: EtOAc) to afford 77 mg (26%) of **10** (faster eluted component, Rf ~ 0.9) as yellow crystals of mp 118-119 °C and 36 mg (14%) of **11** (slower eluted component, Rf ~ 0.3) as brownish oil.

Compound (**10**): ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.86 (s, 1H, H-5), 7.75 (s, 1H, =CH), 7.67 (m, 2H, =CHPh H-2,6), 7.50 (m, 3H, =CHPh H-3,4,5), 7.31 (m, 2H, Ph H-2,6), 6.87 (m, 2H, Ph H-3,5), 4.91 (s, 2H, NCH_2), 3.79 (s, 3H, OMe); ^{13}C-NMR ($CDCl_3$): δ (ppm) 164.5 (C-3), 159.2 (Ph C-4), 143.5 (=CH, ^1J = 157.2 Hz, ^3J(=C<u>H</u>,=CHPh H-2,6) = 4.9 Hz), 137.9 (C-5, ^1J = 195.0 Hz, ^3J(C-5,=C<u>H</u>) = 9.8 Hz), 133.8 (=CHPh C-1), 132.2 (=CHPh C-4), 131.2 (=CHPh C-2,6), 129.6 (Ph C-2,6), 129.4 (=CHPh C-3,5), 128.8 (Ph C-1), 126.0 (C-4, ^2J(C-4,H-5) = 11.4 Hz, ^2J(C-4,=C<u>H</u>) = 2.9 Hz), 114.1 (Ph C-3,5), 55.3 (OMe, ^1J = 143.7 Hz), 47.8 (NCH_2, ^1J = 139.0 Hz, ^3J(NCH_2,Ph H-2,6) = 4.4 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) -48.9 (N-1), -193.0 (N-2); IR (KBr): ν (cm^{-1}) 1680 (C=O); MS (m/z, %): 292 (M$^+$, 20), 121 (100), 77 (19). HRMS (EI): Calcd for $C_{18}H_{16}N_2O_2$ 292.1212. Found: 292.1219.

Compound (**11**): ^{1}H-NMR ($CDCl_3$): δ (ppm) 9.0-10.0 (br s, 2H, OH), 7.25 (m, 5H, CHPh H-2,3,4,5,6,), 7.00 (m, 4H, Ph H-2,6), 6.83 (s, 2H, H-3), 6.71 (m, 4H, Ph H-3,5), 4.84 and 4.79 (AB-system, ^2J(A,B) = 15.1 Hz, 4H, NCH_2), 4.75 (s, 1H, CH), 3.69 (s, 6H, OMe); ^{13}C-NMR ($CDCl_3$): δ (ppm) 159.3 (Ph C-4), 157.2 (C-5), 141.7 (CHPh C-1), 135.3 (C-3, ^1J = 182.0 Hz, ^3J(C-3,CH) = 5.2 Hz), 129.1 (Ph C-2,6), 128.4 (CHPh C-3,5), 128.2 (Ph C-1), 127.8 (CHPh C-2,6), 126.5 (CHPh C-4), 114.0 (Ph C-3,5), 106.7 (C-4, ^2J(C-4,H-3) = 7.5 Hz, ^2J(C-4,CH) = 7.5 Hz), 55.2 (OMe, ^1J = 143.8 Hz), 48.2 (NCH_2, ^1J = 140.2 Hz), 36.8

(CH, ^{1}J = 125.4 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) -198.5 (N-1), -176.8 (N-2); MS (ESI) (m/z, %): 497 ($M+1^+$, 100), 293 (29), 205 (53), 185 (19). HRMS (ESI-TOF): Calcd for $C_{29}H_{28}N_4O_4 \bullet H^+$: 497.2183. Found: 497.2170.

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