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On the tautomerism of pyrazolones: the geminal ^2J[pyrazole C-4,H-3(5)] spin coupling constant as a diagnostic tool☆

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Abstract—The tautomerism of pyrazolones unsubstituted at position 3(5) has been investigated by ^{13}C- and ^{1}H NMR spectroscopic methods. Apart from chemical shift considerations and NOE effects the magnitude of the geminal ^2J[pyrazole C-4,H3(5)] spin coupling constant permits the unambiguous differentiation between 1*H*-pyrazol-5-ol (OH) and 1,2-dihydro-3*H*-pyrazol-3-one (NH) forms. Whereas 1*H*-pyrazol-5-ols and 2,4-dihydro-3*H*-pyrazol-3-ones (CH-form) exhibit ^2J values of approximately 9–11 Hz, in 1,2-dihydro-3*H*-pyrazol-3-ones this coupling constant is considerably reduced to 4–5 Hz. This can be mainly attributed to the removal of the lone-pair at pyrazole $N-1$ in the latter due to protonation or alkylation. According to the data obtained, 2-substituted 4-acyl-1,2-dihydro-3*H*-pyrazol-3-ones exist predominantly as pyrazol-5-ols in $CDCl_3$ or benzene-d_6 solution, whereas in DMSO-d_6 also minor amounts of NH tautomer may contribute to the tautomeric composition. 2,4-Dihydro-2-phenyl-3*H*-pyrazol-3-one (1-phenyl-2-pyrazolin-5-one) exists in benzene-d_6 solely in the CH-form, in $CDCl_3$ as a mixture of CH and OH-form, whereas in DMSO-d_6 a fast equilibrium between OH and NH isomer (with the former far predominating) is probable. For 11 compounds, including neutral and protonated molecules, we have calculated at the B3LYP/6-311++G** level, the $^2J(^1H,^{13}C)$ coupling constants which are in good agreement with those measured experimentally.

1. Introduction

The tautomerism of pyrazolones is an old problem of pyrazole chemistry and thus it has been the subject of a considerable number of studies.[2–13] In principle, for compounds unsubstituted at pyrazole C-4, OH- (**A**), CH- (**B**) and NH-isomers (**C**) are possible (Fig. 1, upper line), assigned as 1*H*-pyrazol-5-ols, 2,4-dihydro-3*H*-pyrazol-3-ones and 1,2-dihydro-3*H*-pyrazol-3-ones according to *Chemical Abstracts* nomenclature. In the case of 4-acyl congeners, which are popular chelating and extracting ligands for metal ions[14] as well as starting materials for biologically active compounds,[15] additional species (**D**, **E**, middle line) have to be considered since in this case the 4-substituent can participate in tautomerism and also stabilization by intramolecular hydrogen bonds may occur (**A′**, **D′**, Fig. 1, lower line). Whereas in the solid state unambiguous results were obtained on the basis of X-ray crystallographic data,[8–12] the situation in solution is much more complicated and the determination of the tautomeric composition can be difficult. The simultaneous presence of several tautomeric forms can either result in distinct signal sets in the NMR spectra due to the individual isomers (slow interconversion rate on the NMR timescale) or in the observation of one averaged signal set in case of rapid chemical exchange. Fast exchange frequently occurs between OH- and NH-tautomers, whereas those equilibria which involve a proton moving from a carbon atom (CH-tautomers) are normally slow.[16]

Nearly all investigations regarding pyrazolone tautomerism were carried out with 3(5)-methyl substituted model compounds (R^3=Me) due to the easy availability of the latter upon reaction of alkyl acetoacetates with substituted hydrazines. In a recent study, we concluded that 4-acyl-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones (Fig. 1: R^1=Ph, R^3=Me, R^4=Me, Ph, 2-thienyl, styryl) are present in the chelated 5-hydroxypyrazole form (**A′**) in apolar solvents such as $CDCl_3$ or benzene-d_6, whereas in

☆ See Ref. 1.

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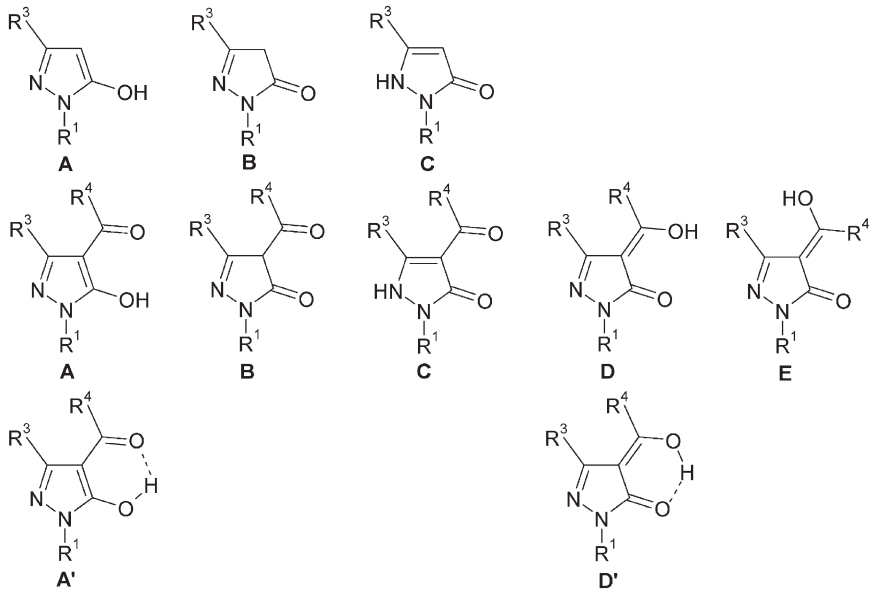

Figure 1. Tautomeric forms of (4-acyl)pyrazolones.

DMSO-d_6 solution additionally, some NH-tautomer (**C**) seems to contribute to the tautomeric composition.[12] Continuing with our previous studies[12,15,17–23] on pyrazolones (hydroxypyrazoles) we here present detailed NMR spectroscopic investigations with representatives **2** unsubstituted at C-3(5), as well as with corresponding 'fixed' tautomers—such as *O*-methyl (**3**) and *N*-methyl derivatives (**4**) (Fig. 2) or suitable condensed systems—in order to obtain insight into the tautomeric behavior of the title compounds **2**. In compounds **2**-**4**, the hydrogen atom at pyrazole H-3(5) on one hand can act as an irradiation target or as a probe in NOE experiments, on the other hand this proton is involved in different $^{13}C,^{1}H$ spin couplings. The value of the corresponding coupling constants and their changes upon structural alterations may help to answer the questions raised.

2. Results and discussion

2.1. Chemistry

Compound **1** was prepared in two steps from diethyl ethoxymethylenemalonate and phenylhydrazine according to literature,[24,25] 4-acylpyrazolones **2b**-**e** were obtained from **1** and the corresponding carboxylic acid chlorides via the method described by Jensen (RCOCl, $Ca(OH)_2$, dioxane).[26] Treatment of **1** with methyl 4-toluenesulfonate in DMF in the presence of potassium carbonate afforded 5-methoxy-1-phenyl-1*H*-pyrazole (**3a**); in contrast, the use of xylene as solvent and performing the reaction without addition of a base led to the corresponding *N*-methyl derivative **4a**. Products **3b**-**e** and **4b**-**e** were obtained by methylation of compounds **2b**-**e**: whereas heating of the starting materials with dimethyl sulfate in alkaline medium mainly afforded *N*-methyl derivatives **4**, upon treatment with trimethylsilyl-diazomethane/HBF_4 in dichloromethane isomeric mixtures were obtained, with the *O*-methyl derivatives **3** far predominating.[19] The 4-cinnamoyl-5-methoxypyrazole **3e** was synthesized from **2e** via Mitsunobu reaction (diethyl azodicarboxylate, triphenylphosphine, methanol).[20] All syntheses were devoted to obtain material for the NMR-spectroscopic investigations, thus no efforts were undertaken to optimize yields.

2.2. NMR spectroscopic investigations

The NMR data of the compounds investigated are presented in Tables 1–7. It should be mentioned that for all proton and carbon resonances complete and unambiguous assignments were achieved by combined application of standard NMR techniques (^{1}H-coupled ^{13}C NMR, APT,[27] NOE-difference,[28] 1D-TOCSY,[29] 1D-HETCOR,[30] HMQC,[31] and long-range INEPT experiments with selective excitation in a 1D[32] and a 2D-version[33]) without relying on empirical rules.

2.2.1. Chemical shift considerations. The *O*-methyl (**3**) and *N*-methylpyrazoles (**4**) can be seen as fixed OH or NH-tautomers and thus can provide valuable data for the

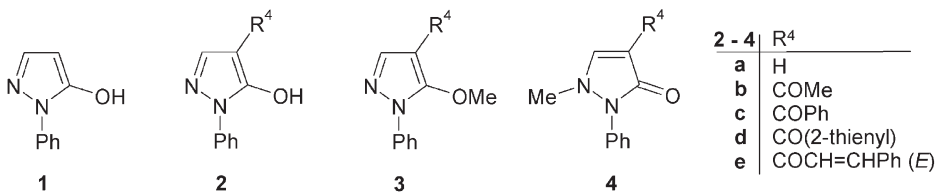

Figure 2. Investigated pyrazolone (**1**≡**2a**) and 4-acylpyrazol-5-ones (**2b**-**e**)≡(4-acyl)-5-hydroxypyrazoles and their fixed *O*-Me (**3**) and *N*-Me (**4**) derivatives.

Table 1. ^{1}H NMR chemical shifts (δ, ppm) of compounds **1** and **2** (numbering of atoms for the hydroxypyrazole form)

No.	Solvent	H-3	*N*-phenyl			OH	H of 4-substituent R
			H-2,6	H-3,5	H-4		
1[a]	$CDCl_3$	7.46	7.85	7.41	7.22	—	3.47 (d, ^3J=1.1 Hz, 2H, H-4)
1[b]	$CDCl_3$	7.24	7.58	7.35	7.24	9.78	5.38 (d, ^3J=2.2 Hz, 1H, H-4)
1[a]	C_6D_6	6.30	8.26	7.22	6.95	—	2.19 (d, ^3J=1.3 Hz, 2H, H-4)
1[b]	DMSO-d_6	7.40	7.75	7.44	7.24	11.57	5.54 (d, ^3J=1.9 Hz, 1H, H-4)
2b	$CDCl_3$	7.79	7.83	7.46	7.32	10.18	2.43 (Me)
2b	DMSO-d_6	8.06	7.71	7.49	7.33	10.32	2.38 (Me)
2c	$CDCl_3$	7.97	7.90	7.49	7.34	11.80	7.96 (Ph-2,6), 7.55 (Ph-3,5), 7.64 (Ph-4)
2c	C_6D_6	7.67	8.07	7.15	6.96	10.68	7.73 (Ph-2,6), 7.03 (Ph-3,5), 7.12 (Ph-4)
2c	DMSO-d_6	7.97	7.77	7.52	7.37	9.12	7.88 (Ph-2,6), 7.56 (Ph-3,5), 7.65 (Ph-4)
2d	$CDCl_3$	8.12	7.88	7.48	7.33	11.10	7.98 (Th-3), 7.23 (Th-4), 7.73 (Th-5)[c]
2d	C_6D_6	7.84	8.02	7.13	6.96	11.68	7.46 (Th-3), 6.54 (Th-4), 6.89 (Th-5)[c]
2d	DMSO-d_6	8.29	7.76	7.52	7.37	10.63	8.13 (Th-3), 7.29 (Th-4), 8.02 (Th-5)[c]
2e	$CDCl_3$	7.93	7.93	7.46	7.29	12.05	7.05 (COCH)[d], 7.88 (C*H*Ph)[d], 7.64 (Ph-2,6), 7.44 (Ph-3,5), 7.44 (Ph-4)
2e	C_6D_6	7.50	8.23	7.18	6.96	10.75	6.57 (COCH)[d], 7.81 (C*H*Ph)[d], 7.13 (Ph-2,6), 7.04 (Ph-3,5), 7.04 (Ph-4)
2e	DMSO-d_6	8.42	7.81	7.49	7.31	11.79	7.75 (COCH)[d], 7.73 (C*H*Ph)[d], 7.82 (Ph-2,6), 7.46 (Ph-3,5), 7.46 (Ph-4)

[a] CH-isomer.
[b] OH-isomer.
[c] Thiophene ring: ^3J(3,4)=3.8 Hz, ^3J(4,5)=5.0 Hz, ^4J(3,5)=1.1 Hz.
[d] ^3J=15.9 Hz.

Table 2. ^{1}H NMR chemical shifts (δ, ppm) of 5-methoxy-1-phenyl-1*H*-pyrazoles **3**

No.	Solvent	H-3	*N*-phenyl			OMe	H of 4-substituent R
			H-2,6	H-3,5	H-4		
3a	$CDCl_3$	7.50	7.72	7.42	7.27	3.93	5.66 (d, ^3J=2.0 Hz, H-4)
3a	DMSO-d_6	7.50	7.66	7.46	7.29	3.92	5.87 (d, ^3J=2.0 Hz, H-4)
3b	$CDCl_3$	7.92	7.63	7.46	7.35	4.05	2.46 (Me)
3c	$CDCl_3$	7.78	7.70	7.48	7.37	4.10	7.89 (Ph-2,6), 7.50 (Ph-3,5), 7.59 (Ph-4)
3c	DMSO-d_6	7.85	7.68	7.55	7.43	4.01	7.84 (Ph-2,6), 7.56 (Ph-3,5), 7.65 (Ph-4)
3d	$CDCl_3$	8.00	7.69	7.48	7.37	4.10	7.81 (Th-3), 7.19 (Th-4), 7.69 (Th-5)[a]
3d	C_6D_6	7.91	7.71	7.10	6.97	3.68	7.48 (Th-3), 6.62 (Th-4), 6.96 (Th-5)[a]
3d	DMSO-d_6	8.17	7.67	7.55	7.44	4.02	7.93 (Th-3), 7.28 (Th-4), 8.05 (Th-5)[a]
3e	$CDCl_3$	8.08	7.70	7.48	7.37	4.11	7.34 (COCH)[b], 7.80 (C*H*Ph)[b], 7.64 (Ph-2,6), 7.41 (Ph-3,5), 7.41 (Ph-4)
3e	DMSO-d_6	8.52	7.66	7.55	7.45	4.11	7.68 (COCH)[b], 7.68 (C*H*Ph)[b], 7.85 (Ph-2,6), 7.45 (Ph-3,5), 7.45 (Ph-4)

[a] Thiophene ring: ^3J(3,4)=3.8 Hz, ^3J(4,5)=5.0 Hz, ^4J(3,5)=1.1 Hz.
[b] ^3J=15.8 Hz.

Table 3. ^{1}H NMR chemical shifts (δ, ppm) of 1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones **4**

No.	Solvent	H-5	*N*-phenyl			NMe	H of 4-substituent R
			H-2,6	H-3,5	H-4		
4a	$CDCl_3$	7.36	7.36	7.45	7.30	3.11	5.56 (d, ^3J=3.5 Hz, H-4)
4a	DMSO-d_6	7.91	7.33	7.48	7.31	3.11	5.42 (d, ^3J=3.5 Hz, H-4)
4b	$CDCl_3$	8.01	7.32	7.53	7.45	3.42	2.55 (Me)
4c	$CDCl_3$	8.09	7.31	7.48	7.40	3.41	7.98 (Ph-2,6), 7.40 (Ph-3,5), 7.49 (Ph-4)
4c	DMSO-d_6	8.52	7.41	7.55	7.46	3.45	7.83 (Ph-2,6), 7.46 (Ph-3,5), 7.56 (Ph-4)
4d	$CDCl_3$	8.23	7.36	7.53	7.45	3.46	8.95 (Th-3), 7.12 (Th-4), 7.60 (Th-5)[a]
4d	DMSO-d_6	8.66	7.44	7.57	7.49	3.47	8.69 (Th-3), 7.20 (Th-4), 7.91 (Th-5)[a]
4e	$CDCl_3$	8.17	7.34	7.53	7.45	3.45	8.21 (COCH)[b], 7.79 (C*H*Ph)[b], 7.65 (Ph-2,6), 7.33 (Ph-3,4,5)
4e	DMSO-d_6	8.64	7.43	7.54	7.52	3.46	8.05 (COCH)[c], 7.63 (C*H*Ph)[c], 7.64 (Ph-2,6), 7.41 (Ph-3,5), 7.40 (Ph-4)

[a] Thiophene ring: ^3J(3,4)=3.8 Hz, ^3J(4,5)=5.0 Hz, ^4J(3,5)=1.1 Hz.
[b] ^3J=15.9 Hz.
[c] ^3J=16.0 Hz.

assignment of the tautomeric composition in the pyrazolones **1** or **2**. As a representative set of compounds, the thenoyl substituted pyrazoles **2d**, **3d**, and **4d** may serve for the following discussion. A comparison of the ^{13}C chemicals shifts (in $CDCl_3$) between these compounds shows, that the data of the tautomeric pyrazolone **2d**—in comparable parts such as the 1-phenyl moiety—resemble somewhat more those of the *O*-methyl **3d** than those of the

Table 4. ^{13}C NMR chemical shifts (δ, ppm) of compounds **1-3**

No.	Solvent	Pyrazole–C			OMe	C of *N*-phenyl				C=O	C of 4-substituent R
		C-3	C-4	C-5		C-1	C-2,6	C-3,5	C-4		
1[a]	$CDCl_3$	147.0	40.9	170.0	—	137.8	118.9	128.8	125.4	—	—
1[b]	$CDCl_3$	138.6	90.3	156.8	—	137.2	122.3	128.8	126.6	—	—
1[a]	C_6D_6	146.3	40.1	169.4	—	139.2	118.4	129.1	125.0	—	—
1[b]	DMSO-d_6	139.6	87.9	153.1	—	138.9	121.0	128.8	125.5	—	—
2b	$CDCl_3$	138.7	105.0	158.2	—	137.3	120.9	129.1	127.0	195.1	25.8 (Me)
2b	DMSO-d_6	140.4	106.1	155.7	—	137.4	121.6	129.0	126.6	191.1	26.6 (Me)
2c	$CDCl_3$	139.6	103.2	160.8	—	137.3	120.9	129.1	127.0	189.4	136.7 (Ph-1), 128.5 (Ph-2,6), 128.9 (Ph-3,5), 133.0 (Ph-4)
2c	C_6D_6	139.4	103.6	161.7	—	138.2	120.8	129.2	126.7	188.7	136.9 (Ph-1), 128.77 (Ph-2,6), 128.8 (Ph-3,5), 132.7 (Ph-4)
2c	DMSO-d_6	141.0	104.0	156.9	—	137.3	121.8	129.1	127.0	187.7	137.8 (Ph-1), 128.4 (Ph-2,6), 128.6 (Ph-3,5), 132.3 (Ph-4)
2d	$CDCl_3$	138.4	102.3	160.2	—	137.3	121.0	129.1	127.0	180.5	141.2 (Th-2), 132.3 (Th-3), 128.4 (Th-4), 133.7 (Th-5)
2d	C_6D_6	138.4	102.6	161.0	—	138.2	120.9	129.2	126.8	180.5	141.6 (Th-2), 132.3 (Th-3), 128.2 (Th-4), 133.6 (Th-5)
2d	DMSO-d_6	140.0	103.3	156.7	—	137.2	121.8	129.1	127.0	179.0	143.2 (Th-2), 132.7 (Th-3), 128.8 (Th-4), 134.2 (Th-5)
2e	$CDCl_3$	137.9	105.2	162.3	—	137.6	120.2	129.0	126.4	180.4	119.6 (COCH), 144.0 (CHPh), 134.2 (Ph-1), 128.6 (Ph-2,6), 129.0 (Ph-3,5), 131.0 (Ph-4)
2e	C_6D_6	137.9	105.7	163.5	—	138.7	120.1	129.2	126.3	179.7	119.9 (COCH), 143.6 (CHPh), 134.7 (Ph-1), 128.8 (Ph-2,6), 129.0 (Ph-3,5), 130.8 (Ph-4)
2e	DMSO-d_6	140.1	106.1	159.4	—	137.5	120.6	128.9	126.2	178.9	121.8 (COCH), 142.1 (CHPh), 134.5 (Ph-1), 128.7 (Ph-2,6), 129.0 (Ph-3,5), 130.6 (Ph-4)
3a	$CDCl_3$	139.6	85.7	155.5	58.8	138.6	122.0	128.7	126.2	—	—
3a	DMSO-d_6	139.6	86.4	155.3	59.2	138.3	121.5	128.9	126.1	—	—
3b	$CDCl_3$	141.6	109.7	154.7	62.6	137.5	123.2	129.1	127.8	191.1	28.4 (Me)
3c	$CDCl_3$	142.8	107.4	156.1	62.4	137.6	123.2	129.0	127.7	188.4	139.1 (Ph-1), 129.1 (Ph-2,6), 128.4 (Ph-3,5), 132.3 (Ph-4)
3c	DMSO-d_6	142.3	107.1	155.6	62.3	137.1	123.2	129.2	127.8	187.4	138.6 (Ph-1), 128.8 (Ph-2,6), 128.5 (Ph-3,5), 132.4 (Ph-4)
3d	$CDCl_3$	141.7	107.1	155.8	62.3	137.6	123.2	129.0	127.7	179.5	145.0 (Th-2), 132.7 (Th-3), 127.9 (Th-4), 133.3 (Th-5)
3d	C_6D_6	141.8	107.6	156.1	61.9	138.5	123.3	129.0	127.4	179.0	145.9 (Th-2), 132.5 (Th-3), 127.8 (Th-4), 132.9 (Th-5)
3d	DMSO-d_6	141.4	106.6	155.3	62.2	137.1	123.2	129.2	127.9	178.6	144.2 (Th-2), 133.4 (Th-3), 128.6 (Th-4), 134.5 (Th-5)
3e	$CDCl_3$	141.2	110.0	155.4	62.7	137.6	123.1	129.0	127.8	182.9	123.7 (COCH), 143.0 (CHPh), 134.8 (Ph-1), 128.3 (Ph-2,6), 128.9 (Ph-3,5), 130.3 (Ph-4)
3e	DMSO-d_6	141.9	109.7	155.1	62.6	137.1	123.2	129.2	127.9	181.9	124.1 (COCH), 142.0 (CHPh), 134.6 (Ph-1), 128.6 (Ph-2,6), 128.8 (Ph-3,5), 130.3 (Ph-4)

[a] CH-isomer.
[b] OH-isomer.

Table 5. ^{13}C NMR chemical shifts (δ, ppm) of compounds **4**

No.	Solvent	Pyrazole–C			NMe	C of N-phenyl				C=O	C of 4-substituent R
		C-5	C-4	C-3		C-1	C-2,6	C-3,5	C-4		
4a	$CDCl_3$	145.8	98.8	166.3	37.7	134.2	124.6	129.2	127.0	—	—
4a	DMSO-d_6	147.7	96.5	165.5	37.3	134.4	124.1	128.9	126.4	—	—
4b	$CDCl_3$	142.5	109.4	163.1	37.4	132.9	127.0	129.7	129.1	193.1	28.4 (Me)
4c	$CDCl_3$	145.1	108.3	161.8	37.4	132.9	127.0	129.5	128.9	188.1	137.9 (Ph-1), 129.3 (Ph-2,6), 127.8 (Ph-3,5), 132.1 (Ph-4)
4c	DMSO-d_6	145.2	105.5	161.2	36.9	133.0	127.4	129.3	128.7	186.8	138.6 (Ph-1), 128.7 (Ph-2,6), 127.9 (Ph-3,5), 131.6 (Ph-4)
4d	$CDCl_3$	145.3	108.6	161.4	37.5	133.0	127.2	129.7	129.2	178.8	144.7 (Th-2), 135.0 (Th-3), 128.2 (Th-4), 133.4 (Th-5)
4d	DMSO-d_6	144.7	105.5	160.5	37.0	132.8	127.7	129.3	128.8	177.6	144.9 (Th-2), 133.4 (Th-3), 128.2 (Th-4), 133.6 (Th-5)
4e	$CDCl_3$	143.3	109.4	163.0	37.4	132.8	127.1	129.7	129.2	183.5	124.2 (COCH), 142.0 (CHPh), 135.3 (Ph-1), 128.6 (Ph-2,6), 128.64 (Ph-3,5), 130.0 (Ph-4)
4e	DMSO-d_6	143.0	106.9	161.9	37.0	132.7	127.7	129.3	128.9	181.5	124.4 (COCH), 140.2 (CHPh), 135.0 (Ph-1), 128.0 (Ph-2,6), 128.9 (Ph-3,5), 130.0 (Ph-4)

N-methyl derivative **4d** (Fig. 3). This is also the case considering the data in DMSO-d_6 (Tables 4 and 5). However, based on these data an unambiguous assignment of **2d** to one of the tautomeric forms seems questionable. Moreover, occasional line broadening in the spectra of **2**, particularly in DMSO-d_6 solution, points to a dynamic behavior.

Also, the comparison of ^{1}H NMR chemical shifts in **2d**, **3d**, and **4d** shows some remarkable features. Whereas the data of **3d** and **2d** do not differ substantially, with **4d** a drastic downfield shift is observed for the signal due to thiophene H-3 (Fig. 4). Thus, for instance, in benzene-d_6 the difference for thiophene H-3 proton shift between **2d** and **4d** is found to be 2.3 ppm (Fig. 4). This can be explained by a substantial contribution of conformational isomers having the pyrazolone C═O group close to the thiophene H-3 proton (similar to conformer Y), which would be markedly deshielded due to the anisotropy of the bond magnetic susceptibility of the C═O bond. The contribution of conformer X is less probable due to the absence of an NOE between pyrazole H-5 and thiophene H-3 in the NOE difference spectrum of **4d** (Fig. 4). In contrast, such a through-space interaction can be clearly observed in similar experiments with compounds **2d** and **3d** indicating also that those conformers displayed in Figure 4 contribute to the overall situation.

Amongst the tautomeric pyrazolones investigated, compound **1** occupies an exceptional position due to the lack of a substituent at the 4-position of the heterocyclic ring. Whereas in benzene-d_6 solution the compound solely exists as the CH-isomer [CH_2-substructure with δ(^{1}H) 2.19 ppm and δ (^{13}C) 40.1 ppm], in $CDCl_3$ solution (c~0.2 mol/l) a mixture of CH and—mainly—OH form (~1.7:1) was found at 28 °C, confirming a sufficiently slow interconversion of the CH-isomer compared to the NMR timescale. In contrast, in polar aprotic DMSO-d_6 only one signal set emerged, which can be attributed to the OH form—possibly being in fast exchange with the NH isomer. However, on the basis of chemical shift considerations[7] (δ pyrazole C-5 153.1 ppm), NOEs (only very weak NOE between acidic proton and Ph H-2,6), and considering ^{1}H,^{1}H as well as ^{13}C,^{1}H spin coupling constants (see below) dominance of the OH-form can be concluded. These results are in accordance with those reported for related 3-methyl-1-phenyl-2-pyrazolin-5-one.[34,35]

2.2.2. NOE-difference experiments. NOE-difference experiments show some differences between recordings in apolar solvents such as $CDCl_3$ or benzene-d_6 compared to those in polar ones such as DMSO-d_6. In the latter solvent, for **2d** through-space connectivities can be observed between the XH-proton and pyrazole H-3(5) as well as to H-2/6 of *N*-phenyl (Fig. 5). A possible explanation of this phenomenon is some contribution of the NH-isomer to the tautomeric composition or the presence of intermolecular effects. In contrast, in $CDCl_3$ and benzene-d_6 a spatial closeness of XH and pyrazole H-3 is not detectable (Fig. 6) indicating the absence of NH-tautomer. We believe compounds **2** in these non-polar solvents to be present in a chelated hydroxypyrazole form (isomer **A**′ in Fig. 1). NOE-difference experiments with pyrazolone **1** in $CDCl_3$ are characterized by strong saturation transfer effects (e.g.,

Table 6. $^{13}C,^{1}H$ spin coupling constants (Hz) of compounds **1**-**3**

No.	Solvent	^{1}J(C3,H3)	^{2}J(C4,H3)	^{3}J(C5,H3)	^{1}J(OMe)	Other couplings
1[a]	$CDCl_3$	196.2	11.1	[b]	—	^{1}J(C4,H4)=134.6 Hz; ^{2}J(C3,H4)=5.4 Hz
1[c]	$CDCl_3$	185.4	8.1	[b]	—	^{1}J(C4,H4)=180.2 Hz; ^{2}J(C3,H4)=6.0 Hz
1[a]	C_6D_6	195.5	11.1	[b]	—	^{1}J(C4,H4)=134.4 Hz; ^{2}J(C3,H4)=5.5 Hz
1[c]	DMSO-d_6	184.1	[d]	[b]	—	^{1}J(C4,H4)=177.2 Hz; ^{2}J(C3,H4)=4.9 Hz
2b	$CDCl_3$	188.6	10.7	4.8	—	^{1}J(Me)=127.9 Hz
2b	DMSO-d_6	189.3	9.5	[b]	—	^{1}J(Me)=127.3 Hz; ^{3}J(C4,Me)=1.5 Hz
2c	$CDCl_3$	190.7	11.0	4.8	—	^{3}J(CO,Ph-2,6)=4.0 Hz
2c	C_6D_6	190.4	11.0	4.7	—	
2c	DMSO-d_6	190.1	10.6	4.8	—	
2d	$CDCl_3$	189.6	11.1	4.9	—	Th: ^{2}J(C2,H3)=6.5 Hz; ^{3}J(C2,H4)=9.2 Hz; ^{3}J(C2,H5)=5.8 Hz; ^{1}J(C3,H3)=168.6 Hz; ^{2}J(C3,H4)=5.7 Hz; ^{3}J(C3,H5)=9.2 Hz; ^{1}J(C4,H4)=170.5 Hz, ^{2}J(C4,H3)=^{3}J(C4,H5)=4.4 Hz; ^{1}J(C5,H5)=186.1 Hz; ^{2}J(C5,H4)=7.2 Hz; ^{3}J(C5,H3)=10.9 Hz
2d	C_6D_6	189.4	11.2	4.9	—	Th: ^{2}J(C2,H3)=6.6 Hz; ^{3}J(C2,H4)=9.2 Hz; ^{3}J(C2,H5)=5.7 Hz; ^{1}J(C3,H3)=168.6 Hz; ^{2}J(C3,H4)=5.6 Hz; ^{3}J(C3,H5)=9.3 Hz; ^{1}J(C4,H4)=169.6 Hz, ^{2}J(C4,H3)=^{3}J(C4,H5)=4.5 Hz; ^{1}J(C5,H5)=185.5 Hz; ^{2}J(C5,H4)=7.6 Hz; ^{3}J(C5,H3)=10.8 Hz
2d	DMSO-d_6	190.0	10.6	5.0	—	Th: ^{2}J(C2,H3)=7.3 Hz; ^{3}J(C2,H4)=9.0 Hz; ^{3}J(C2,H5)=5.8 Hz; ^{1}J(C3,H3)=169.4 Hz; ^{2}J(C3,H4)=5.8 Hz; ^{3}J(C3,H5)=9.3 Hz; ^{1}J(C4,H4)=170.4 Hz, ^{2}J(C4,H3)=^{3}J(C4,H5)=4.4 Hz; ^{1}J(C5,H5)=188.0 Hz; ^{2}J(C5,H4)=7.3 Hz; ^{3}J(C5,H3)=10.6 Hz
2e	$CDCl_3$	189.8	10.4	4.6	—	^{1}J(COCH)=157.9 Hz; ^{2}J=2.3 Hz; ^{1}J(CHPh)=156.5 Hz
2e	C_6D_6	189.7	10.7	4.3	—	^{1}J(COCH)=158.0 Hz; ^{2}J=2.4 Hz; ^{1}J(CHPh)=156.0 Hz
2e	DMSO-d_6	191.6	9.8	4.5	—	^{1}J(COCH)=161.9 Hz; ^{2}J=4.3 Hz; ^{1}J(CHPh)=157.6 Hz
3a	$CDCl_3$	185.9	10.7	[b]	146.0	^{1}J(C4,H4)=177.7 Hz; ^{2}J(C3,H4)=4.1 Hz
3a	DMSO-d_6	186.0	10.7	[b]	146.8	^{1}J(C4,H4)=179.2 Hz; ^{2}J(C3,H4)=4.2 Hz
3b	$CDCl_3$	188.1	9.6	4.4	147.8	^{1}J(CO*Me*)=127.5 Hz; ^{2}J(CO,COMe)=5.9 Hz; ^{3}J(C4,COMe) 1.3 Hz; ^{3}J(C5,OMe)=4.4 Hz
3c	$CDCl_3$	189.8	9.8	4.9	147.9	^{3}J(C5,OMe)=4.4 Hz
3c	DMSO-d_6	190.5	9.9	4.4	148.2	^{3}J(C5,OMe)=4.4 Hz
3d	$CDCl_3$	190.0	9.9	5.1	147.9	Th: ^{2}J(C2,H3)=6.6 Hz; ^{3}J(C2,H4)=8.8 Hz; ^{3}J(C2,H5)=5.6 Hz; ^{1}J(C3,H3)=168.5 Hz; ^{2}J(C3,H4)=5.7 Hz; ^{3}J(C3,H5)=9.1 Hz; ^{1}J(C4,H4)=169.6 Hz, ^{2}J(C4,H3)=4.9 Hz; ^{3}J(C4,H5)=4.0 Hz; ^{1}J(C5,H5)=185.4 Hz; ^{2}J(C5,H4)=7.2 Hz; ^{3}J(C5,H3)=10.9 Hz; ^{3}J(C5,OMe)=4.2 Hz
3d	C_6D_6	189.2	10.1	4.4	147.8	Th: ^{2}J(C2,H3)=6.8 Hz; ^{3}J(C2,H4)=8.8 Hz; ^{3}J(C2,H5)=5.5 Hz; ^{1}J(C3,H3)=168.2 Hz; ^{2}J(C3,H4)=5.6 Hz; ^{3}J(C3,H5)=9.2 Hz; ^{1}J(C4,H4)=169.2 Hz, ^{2}J(C4,H3)=4.6 Hz; ^{3}J(C4,H5)=4.6 Hz; ^{1}J(C5,H5)=184.8 Hz; ^{2}J(C5,H4)=7.5 Hz; ^{3}J(C5,H3)=11.0 Hz; ^{3}J(C5,OMe)=4.4 Hz
3d	DMSO-d_6	190.8	10.1	4.5	148.2	Th: ^{2}J(C2,H3)=7.0 Hz; ^{3}J(C2,H4)=8.7 Hz; ^{3}J(C2,H5)=5.6 Hz; ^{1}J(C3,H3)=169.6 Hz; ^{2}J(C3,H4)=5.7 Hz; ^{3}J(C3,H5)=9.2 Hz; ^{1}J(C4,H4)=170.7 Hz, ^{2}J(C4,H3)=4.5 Hz; ^{3}J(C4,H5)=4.5 Hz; ^{1}J(C5,H5)=188.0 Hz; ^{2}J(C5,H4)=7.3 Hz; ^{3}J(C5,H3)=10.6 Hz; ^{3}J(C5,OMe)=4.5 Hz
3e	$CDCl_3$	188.5	9.6	4.3	147.8	^{1}J(COCH)=155.9 Hz; ^{2}J=1.9 Hz; ^{1}J(CHPh)=154.9 Hz; ^{3}J(C5,OMe)=4.3 Hz
3e	DMSO-d_6	190.3	9.7	4.4	148.1	^{1}J(COCH)=160.1 Hz; ^{2}J=4.5 Hz; ^{1}J(CHPh)=156.9 Hz; ^{3}J(C5,OMe)=4.3 Hz

[a] CH-isomer.
[b] Not unequivocally determined.
[c] OH-isomer.
[d] Small couplings not resolved due to marked line broadening.

of pyrazole H-4 between forms **A** and **B**) confirming interconversion between the tautomeric forms. In DMSO-d_6, where only one (averaged) signal set appeared, the observed saturation transfer between pyrazole H-4 and the acidic proton provides a possible hint for the involvement of the CH-isomer into the proton transfer reactions. Due to an NOE observed for the signal of NPh H-2,6 upon irradiation of the transition of the acidic proton (11.57 ppm) also the presence of a certain percentage of NH-tautomer cannot be excluded.

2.2.3. The geminal ^{2}J[pyrazole C4,H3(5)] spin coupling constant as a structural probe. Comparing a variety of $^{13}C,^{1}H$ spin coupling constants of compounds **3** and **4** it is noticeable that ^{2}J[pyrazole C-4,H3(5)] suffers the most remarkable change when switching from *O*-methyl compounds **3** to the corresponding *N*-methyl derivatives **4**. Comparing compounds within the thenoyl series **d** reveals the magnitude of this coupling to be reduced from ~10 Hz in **3d** to 4–5 Hz in **4d**, very similar results were obtained for 4-acetyl (**b**), 4-benzoyl (**c**) and 4-cinnamoyl (**e**) congeners (Tables 6 and 7). The tautomeric pyrazolones **2b**-**d** showed values in the range of 9.5 Hz (**2b** in DMSO-d_6) to 11.2 Hz (**2d** in benzene-d_6), again giving a strong hint for the preferential presence of compounds **2** in the hydroxy form.

A possible explanation for the remarkable changes in the magnitude of ^{2}J[C4,H3(5)] between structures **3** and **4** as

Table 7. $^{13}C,^{1}H$ spin coupling constants (Hz) of compounds **4**

No.	Solvent	^{1}J(C5,H5)	^{2}J(C4,H5)	^{3}J(C3,H5)	^{1}J(NMe)	Other couplings
4a	$CDCl_3$	186.3	6.3	8.6	140.6	^{1}J(C4,H4)=182.4 Hz; ^{2}J(C3,H4)=5.3 Hz; ^{2}J(C5,H4)=7.1 Hz; ^{3}J(C5,NMe)=3.5 Hz; ^{3}J(NMe,H5)=1.6 Hz
4a	DMSO-d_6	189.0	6.7	8.6	140.8	^{1}J(C4,H4)=181.3 Hz; ^{2}J(C3,H4)=5.8 Hz; ^{2}J(C5,H4)=7.0 Hz; ^{3}J(C5,NMe)=3.5 Hz; ^{3}J(NMe,H5)=1.6 Hz
4b	$CDCl_3$	190.1	4.2	7.0	142.4	^{1}J(Me)=128.0 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4c	$CDCl_3$	190.7	4.6	6.8	142.6	^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4c	DMSO-d_6	192.9	5.3	6.9	143.0	^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4d	$CDCl_3$	191.3	4.0	6.6	142.5	Th: ^{2}J(C2,H3)=6.3 Hz; ^{3}J(C2,H4)=8.9 Hz; ^{3}J(C2,H5)=6.3 Hz; ^{1}J(C3,H3)=172.0 Hz; ^{2}J(C3,H4)=5.8 Hz; ^{3}J(C3,H5)=8.8 Hz; ^{1}J(C4,H4)=169.2 Hz, ^{2}J(C4,H3)=5.0 Hz; ^{3}J(C4,H5)=4.0 Hz; ^{1}J(C5,H5)=183.8 Hz; ^{2}J(C5,H4)=7.1 Hz; ^{3}J(C5,H3)=11.1 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4d	DMSO-d_6	193.7	5.0	6.7	143.3	Th: ^{2}J(C2,H3)=6.5 Hz; ^{3}J(C2,H4)=8.8 Hz; ^{3}J(C2,H5)=5.8 Hz; ^{1}J(C3,H3)=171.1 Hz; ^{2}J(C3,H4)=6.0 Hz; ^{3}J(C3,H5)=9.0 Hz; ^{1}J(C4,H4)=169.6 Hz, ^{2}J(C4,H3)=5.2 Hz; ^{3}J(C4,H5)=4.3 Hz; ^{1}J(C5,H5)=186.8 Hz; ^{2}J(C5,H4)=7.3 Hz; ^{3}J(C5,H3)=10.8 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4e	$CDCl_3$	190.6	4.4	6.9	142.3	^{1}J(COCH)=159.9 Hz; ^{2}J(COCH=CH)=2.1 Hz; ^{1}J(CHPh)=154.4 Hz; ^{3}J(=CHPh,Ph-2,6)=4.7 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H-5)=2.0 Hz
4e	DMSO-d_6	193.2	5.1	6.9	143.2	^{1}J(COCH)=158.3 Hz; ^{2}J(COCH=CH)=2.0 Hz; ^{1}J(CHPh)=154.4 Hz; ^{3}J(=CHPh,Ph-2,6)=4.6 Hz; ^{3}J(C5,NMe)=3.4 Hz; ^{3}J(NMe,H-5)=2.0 Hz

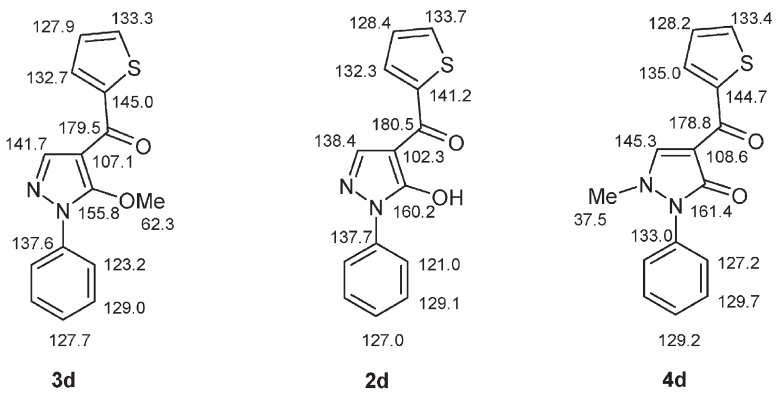

Figure 3. ^{13}C NMR chemical shifts of **2d**, **3d**, and **4d** ($CDCl_3$).

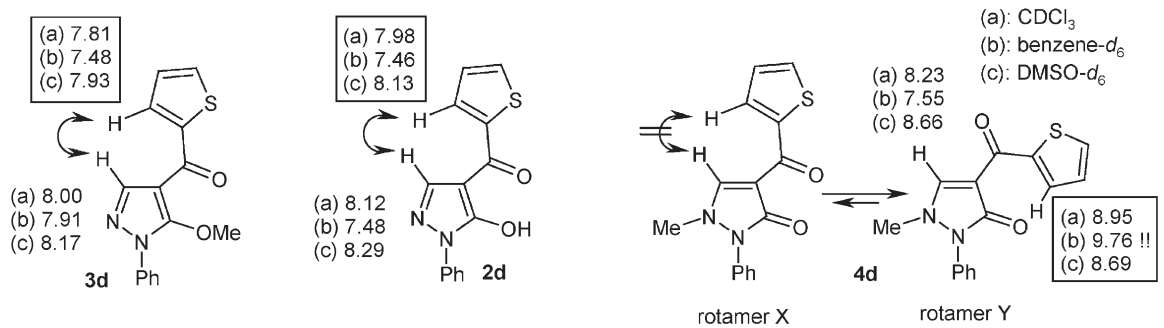

Figure 4. ^{1}H NMR chemical shifts (δ, ppm) for pyrazole H-3(5) and thiophene H-3 (framed) and observed NOEs (arrows) with compounds **2d**, **3d**, and **4d**.

well as between OH (CH) isomers (**A**, **B** in Fig. 1) on the one hand, and NH-forms (**C** in Fig. 1) on the other hand can be given on the basis of lone-pair effect considerations. It is well known from the literature that lone-pair effects can drastically influence a large variety of different spin coupling constants.[36] In the case of pyrazole ^{2}J[C4,H3(5)] the H-C−C axis is coplanar with the sp^2-hybridized lone-pair in α-position at pyrazole N2(1), what according to theory should lead to a positive effect and, inversely, to a decrease in magnitude upon removal of such a lone-pair by alkylation, protonation, oxidation or complexation.[36] A related, well known example is the reduction of ^{2}J(C3,H2) in pyridine (+8.5 Hz) to 5.1 Hz on protonation and to 4.2 Hz on *N*-oxide formation (Fig. 7, upper trace).[37,38] The

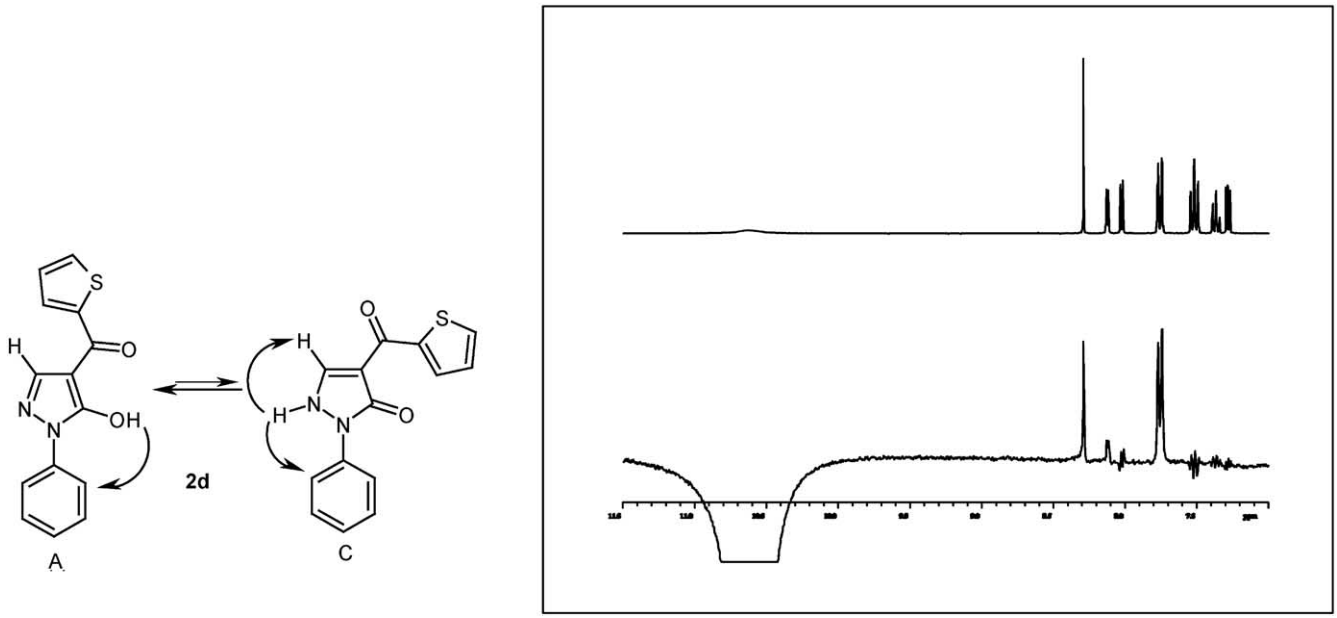

Figure 5. NOE-difference spectrum of **2d** obtained upon irradiation of the XH-resonance (7.0–11.5 ppm, in DMSO-d_6).

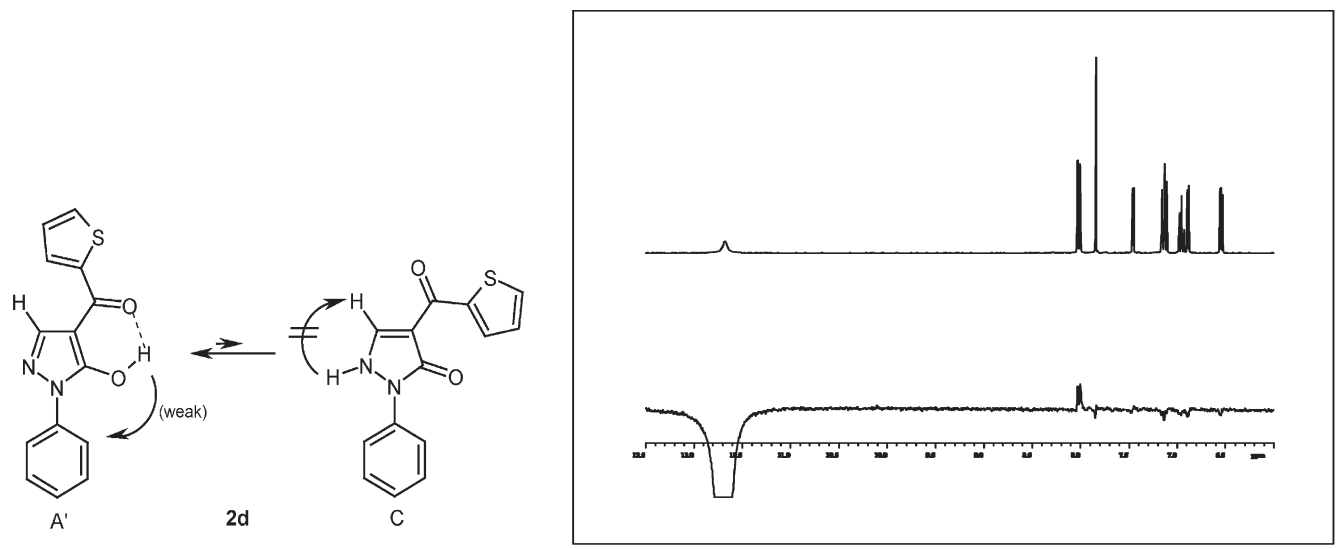

Figure 6. NOE-difference spectrum of **2d** obtained upon irradiation of the XH-resonance (6.0–12.5 ppm, in benzene-d_6).

value of this coupling indicates that 2-aminopyridines are present in the NH_2-form (^2J=7 Hz), but 2-hydroxypyridines exist as pyridones (^2J=3 Hz), whereas in the fixed 2-methoxypyridine the 'intact' coplanar lone-pair increases ^2J(C5,H6) again to 8 Hz (Fig. 7, middle trace).[39] Similarly, all pyrazole derivatives investigated in the present study characterized by an intact lone-pair at pyrazole N–2(1) (a 'pyridine'-type nitrogen atom) exhibit a large value for ^2J[(C4,H3(5)], whereas *N*-methyl compounds of type **4** show markedly lower ones (Fig. 7, lower trace). Similar sp^2-hybridized nitrogen atoms are not only present in 5-alkoxy or 5-hydroxypyrazoles, but also in 2,4-dihydro-3*H*-pyrazol-3-ones (e.g., the CH-isomer of **1**), the latter exhibiting even slightly larger values. Thus, in **1B**—the CH-isomer of **1**—this ^2J coupling constant was found to be 11.1 Hz in $CDCl_3$ or benzene-d_6 solution (Fig. 7, lower trace).

It should be noted that the magnitude of the considered geminal $^{13}C,^1H$ spin coupling constant is also dependent from additional factors such as bond lengths, bond angles and substituents.[37] However, within the different types of pyrazoles investigated the changes within these parameters are not anticipated to lead to such drastic changes. Thus, we believe the described lone-pair effects to play the dominant role here.

In Figure 8, the pyrazole ^2J[C4,H3(5)] spin coupling constants for a variety of pyrazole derivatives are displayed.[40–49] In the two lowest rows, the effects of protonation, alkylation, *N*-oxidation and complexation are presented for pyrazole (**16**), 1-methyl (**18**), and 1-phenylpyrazole (**22**), respectively. Thus, pyrazole (**16**) in $CDCl_3$ or acetone-d_6 exhibits ^2J(C4,H3)=9.9 Hz,[40,41] being identical

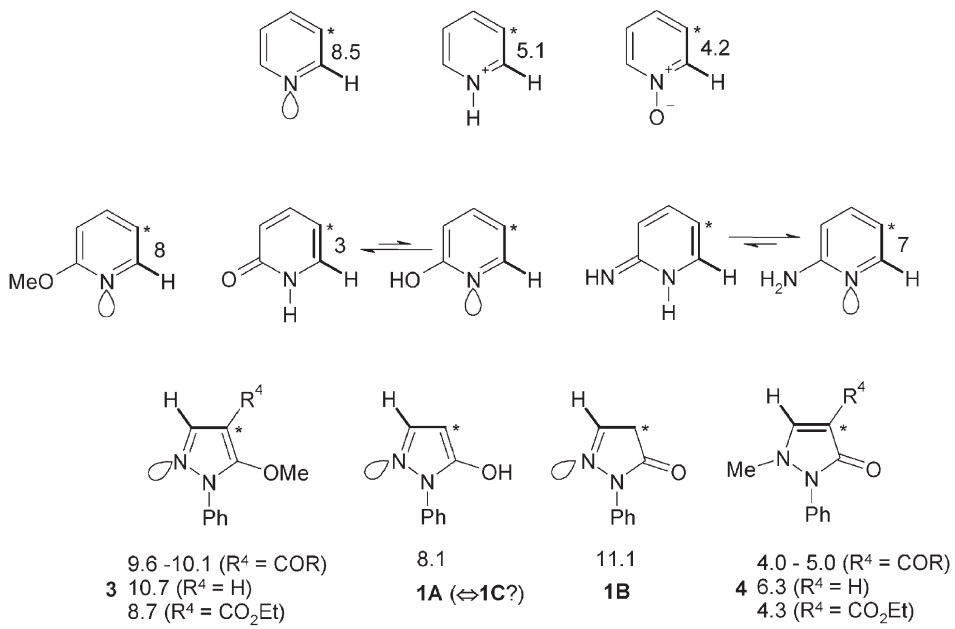

Figure 7. Geminal spin coupling constants in pyridine and pyrazole derivatives (in Hz).

with ^2J(C4,H5) due to fast prototropic exchange at room temperature. According to this situation, the observed 9.9 Hz represent a mean value between the larger ^2J(C4,H3) coupling and the smaller ^2J(C4,H5) one. In fixed 1-methylpyrazole (**18**) the different magnitudes of these geminal couplings clearly emerge [^2J(C4,H3)=10.5 Hz; ^2J(C4,H5)=8.7 Hz].[42] However, switching from pyrazole (**16**) to its cation **17** (in H_2SO_4) reduces ^2J(C4,H3) [and also ^2J(C4,H5)] from 9.9 to 6.7 Hz.[43] The same or a similar value of ^2J was found in *N*-methylpyrazolium salt **19** (6.7 Hz in H_2SO_4,[44] 7.2 Hz in CF_3CO_2H[45]) and in 1,2-dimethyl-pyrazolium cation **20** (7.1 Hz in DMSO-d_6, 6.8 Hz in TFA).[45] The effect caused by involvement of the lone-pair in the complexation is obviously somewhat smaller than that of protonation, as ^2J(C4,H3) in the ruthenium complexes **21** was found to be 7.6 and 9.1 Hz, respectively.[46] Comparison of ^2J(C4,H3) in 1-phenylpyrazole (**22**) (10.5 Hz),[45] and in the corresponding cations **23** (6.7 Hz in conc. H_2SO_4),[43] and **24** (7.0 Hz in CF_3CO_2D) support the above considerations, as well as the value found for *N*-oxide **25**.[47]

2.2.4. The vicinal ^3J[pyrazole H3(5),H4] spin coupling constant in compounds 1, 3a and 4a. The 4-unsubstituted compounds **1**, **3a** and **4a** exhibit interesting differences regarding the magnitude of the vicinal pyrazole H3(5),H4 coupling constant.[6] Whereas this coupling constant in *N*-methyl derivative **4a** was found to be 3.5 Hz (in $CDCl_3$ as well as in DMSO-d_6), for the corresponding *O*-methyl isomer **3a** a considerably reduced value of 2.0 Hz was determined (Fig. 9). Thus, the observed values for pyrazolone **1** (2.2 Hz in $CDCl_3$, 1.9 Hz in DMSO-d_6) suggest the predominance of the OH-form **1A**, what is in full accordance with the findings based on other criteria. In the CH-isomer **1B** the corresponding coupling is further reduced to 1.1 Hz ($CDCl_3$) and 1.3 Hz (benzene-d_6), respectively (Fig. 9).

2.3. DFT-calculations

Having thus collected a large number of $^{13}C,^1H$ coupling constants we decided to complete them with some literature data and carry out DFT calculations to determine the generality of our assumptions. In Table 8 are collected the experimental values and their origin.

For all these situations we carried out DFT calculations of the four terms (see Table 9) that are involved in coupling constants: diamagnetic spin orbit (DSO), Fermi contact (FC), paramagnetic spin orbit (PSO) and spin dipole (SD) terms. As it is well known for atoms of the first rows excluding ^{19}F, the FC largely dominates.[52]

We should note that according to the calculations, $^2J(^{13}C,^1H)$ is always positive and that the calculated sign is in general correct[52] (this is known experimentally for benzene).[37]

The line corresponds to Experimental J=(0.90±0.03), Calculated J, n=11, r^2=0.988. The effect of the lone pair on the adjacent $^{13}C,^1H$ coupling constant is clearly observed in the upper corner of Figure 10.

3. Conclusion

Considering the—easily obtainable—magnitude of the geminal pyrazole C-4,H-3(5) spin coupling constant, the observed NOEs as well as the chemical shifts it can be concluded that *N*-phenyl-4-acylpyrazolones **2** are present as 5-hydroxypyrazoles in $CDCl_3$ or benzene-d_6 solution. In polar DMSO-d_6, a minor contribution of the NH-forms seems to be probable. In contrast, the NMR recordings unambiguously assign compound **1** to be present solely as the CH-isomer in benzene-d_6 solution. In $CDCl_3$ solution, a mixture of CH-isomer and—probably—OH-form [^2J(C4,H3)=8.1 Hz] was found, whereas **1** occurs mainly as hydroxypyrazole in DMSO-d_6. Theoretical calculations of the ^2J(C4,H3) coupling constants for a wide variety of compounds assess that they always have a positive sign and

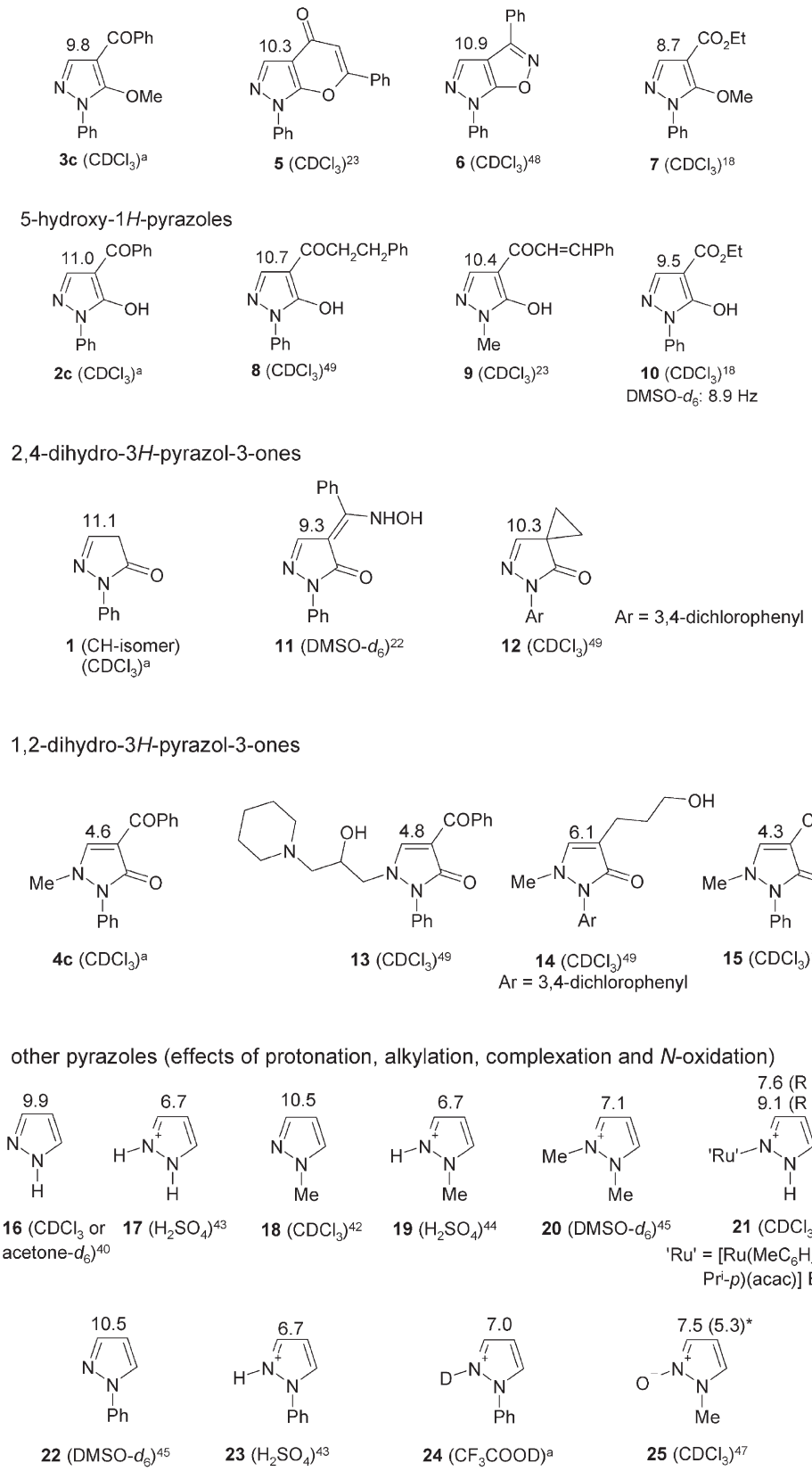

Figure 8. Pyrazole ^{2}J[C4,H3(5)] spin coupling constants (Hz) in different pyrazole derivatives.

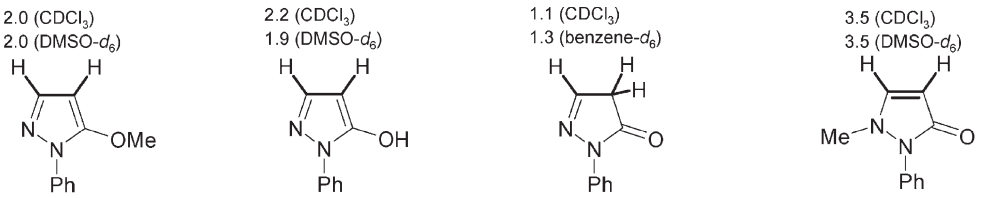

Figure 9. The vicinal ^{3}J[pyrazole H3(5),H4] spin coupling constant in compounds **1**, **3a** and **4a**.

Table 8. Experimental values

Molecule	Point	$^{2}J(^{13}C,^{1}H)$	Source
C_6H_6	**1**	1.15	Ref. 50
Pyridine (C3–H2)	**2**	8.47	Ref. 51
Pyridine (C2–H3)	**3**	3.12	Ref. 51
Pyridinium^{+} (C3–H2)	**4**	4.09	Ref. 51
Pyridinium^{+} (C2–H3)	**5**	4.62	Ref. 51
Pyridinium N–O	**6**	4.2	This work
Pyrazole	**7**	10.5	Ref. 42
Pyrazolium (H^{+})	**8**	6.7	Refs. 42,44
5-OH Pyrazole	**9**	10	This work
4*H*-Δ^{2}-Pyrazolinone	**10**	10	This work
2*H*-Δ^{3}-Pyrazolinone	**11**	4.5	This work

recorded on an ATI Mattson Genesis Series FTIR™ spectrophotometer. Mass spectra were obtained on a Shimadzu DI-QP1000 instrument (EI, 70 eV). The NMR spectra were recorded on a Varian Unity Plus 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, $CDCl_3$), δ 2.49 ppm (^{1}H, DMSO-d_6), δ 7.16 ppm (^{1}H, benzene-d_6), δ 77.0 ppm (^{13}C, $CDCl_3$), δ 39.5 ppm (^{13}C, DMSO-d_6), δ 128.0 ppm (^{13}C, benzene-d_6). The digital resolutions in the gated-decoupled ^{13}C NMR spectra were 0.33 Hz/data point. Preparative layer chromatography was performed on Merck $60F_{254}$ 20×20 cm glass plates (2 mm thickness). Column chromatographic separations were performed on Merck Kieselgel 60 (70–230 mesh). As not otherwise indicated all reagents are commercially available,

Table 9. Calculations of the four terms that contribute to the total $^{2}J(^{13}C,^{1}H)$

Molecule (Point)	DSO	FC	PSO	SD
C_6H_6 (**1**)	−0.35	3.12	−0.90	0.00
Pyridine (C3–H2) (**2**)	−0.34	10.13	−0.75	0.03
Pyridine (C2–H3) (**3**)	−0.31	5.04	−0.97	−0.02
Pyridinium^{+} (C3–H2) (**4**)	−0.41	5.08	−0.74	−0.02
Pyridinium^{+} (C2–H3) (**5**)	−0.32	6.91	−0.95	−0.05
Pyridinium *N*-oxide (**6**)	−0.38	5.87	−0.68	0.00
Pyrazole (**7**)	−0.44	12.21	−0.42	0.03
Pyrazolium (H^{+}) (**8**)	−0.50	7.58	−0.43	−0.02
5-OH Pyrazole (**9**)	−0.39	12.20	−0.41	0.02
4*H*-Δ^{2}-Pyrazolinone (**10**)	−0.35	11.62	0.11	0.06
2*H*-Δ^{3}-Pyrazolinone (**11**)	−0.49	6.24	−0.62	−0.03
	Total *J*	Experimental *J* (Table 1)	Fitted	
C_6H_6 (**1**)	1.87	1.15	1.69	
Pyridine (C3–H2) (**2**)	9.07	8.47	8.18	
Pyridine (C2–H3) (**3**)	3.74	3.12	3.37	
Pyridinium^{+} (C3–H2) (**4**)	3.91	4.09	3.52	
Pyridinium^{+} (C2–H3) (**5**)	5.59	4.62	4.34	
Pyridinium N–O (**6**)	4.81	4.2	5.04	
Pyrazole (**7**)	11.38	10.5	10.26	
Pyrazolium (H^{+}) (**8**)	6.63	6.7	5.98	
5-OH Pyrazole (**9**)	11.42	10	10.29	
4*H*-Δ^{2}-Pyrazolinone (**10**)	11.44	10	10.31	
2*H*-Δ^{3}-Pyrazolinone (**11**)	5.10	4.5	4.61	

that the adjacent lone pair makes an important contribution to their value.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The IR spectra were

the yields given below are not optimized and refer to analytically pure compounds.

4.2. 4-Acylpyrazolones 2; general procedure

To a mixture of pyrazolone **1** (3.204 g, 20 mmol) and $Ca(OH)_2$ (2.932 g, 40 mmol) in dioxane (35 mL, stored over 4 Å molsieve) was added the appropriate carboxylic acid chloride (20 mmol) in dioxane (10 mL) within 5 min. The resulting mixture was heated to reflux for 2 h and then

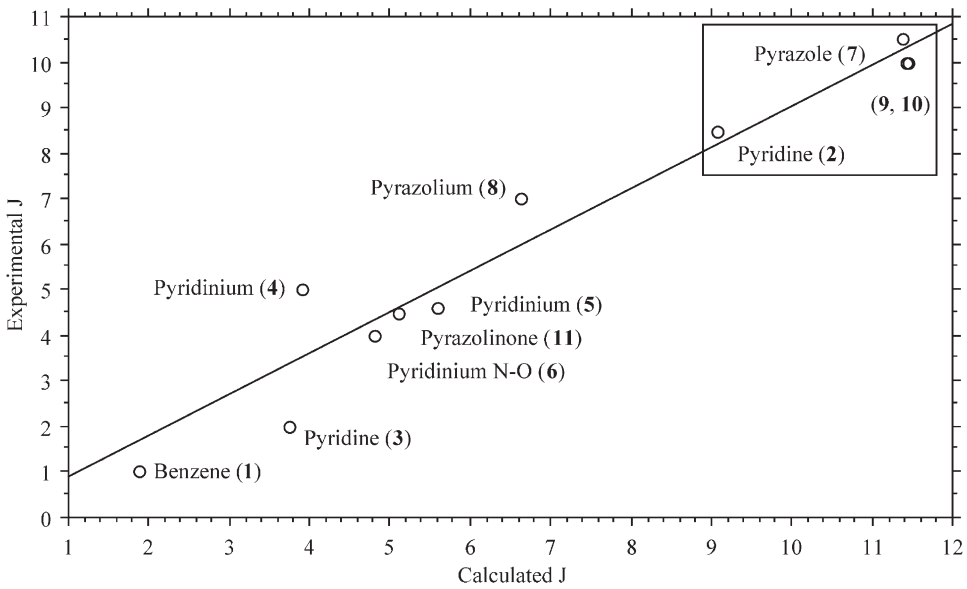

Figure 10. Plot of experimental versus calculated $^{2}J(^{13}C,^{1}H)$ coupling constants (Hz).

allowed to cool to room temperature. After addition of 2 N HCl (50 mL) the mixture was stirred for 1 h, then poured onto H_2O (150 mL). The precipitated product was filtered off, washed several times with H_2O and recrystallized from the solvent given below.

4.2.1. 1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (2b).[53] Yield 2.18 g (54%) of colorless crystals, mp 124 °C (EtOH). IR: 1664 cm^{-1} (C═O). MS (Th, %): 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.

4.2.2. 1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)-methanone (2c). Yield 4.02 g (76%) of yellowish leaflets, mp 159–161 °C (EtOH) (lit.[54] mp 160–161 °C). MS (Th, %): 265 (M^++1, 13), 264 (M^+, 68), 186 (39), 105 (100), 91 (89), 77 (98), 69 (32), 55 (25), 53 (68), 51 (62), 43 (27). Anal. calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.42; H, 4.65; N, 10.50.

4.2.3. (5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)(2-thienyl)-methanone (2d). Yield 3.53 g (65%) of yellowish crystals, mp 161 °C (EtOH). MS (Th, %): 270 (M^+, 48), 186 (100), 118 (35), 111 (86), 91 (38), 81 (24), 77 (34), 69 (51), 57 (20), 55 (27), 53 (92), 51 (39), 43 (24), 41 (39). Anal. calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.37; N, 10.36. Found: C, 62.07; H, 3.95; N, 10.40.

4.2.4. (*E*)-1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (2e).[23] Yield 3.52 g (61%) of orange needles, mp 182–183 °C (EtOH).[23]

4.3. Preparation of *O*-methyl (3) and *N*-methyl derivatives (4)

4.3.1. 5-Methoxy-1-phenyl-1*H*-pyrazole (3a).[55] To a stirred mixture of pyrazolone **1** (250 mg, 1.561 mmol), K_2CO_3 (432 mg, 3.126 mmol) and dry DMF (3 mL) was added dropwise methyl 4-toluenesulfonate (291 mg, 1.563 mmol). After stirring for 15 h at room temperature the mixture was poured onto 2 N HCl (20 mL) and washed with light petroleum (3 times). The aqueous phase was made alkaline with solid Na_2CO_3 and extracted with Et_2O (3 times). The combined etheral phases were washed with H_2O and brine, dried (Na_2SO_4) and evaporated under reduced pressure to afford a nearly colorless oil. Yield: 152 mg (56%).

4.3.2. (5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (3b) and 4-acetyl-1,2-dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-one (4b). Under vigorous stirring, to a solution of **2b** (1.011 g, 5 mmol) in CH_2Cl_2 (20 mL) was added a 40% aqueous solution of HBF_4 (1.100 g, 5 mmol) at 0 °C. Then a 2 M solution of trimethylsilyldiazomethane in *n*-hexane (2.5 mL, 5 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. After a second portion of reagent (2.5 mL, 5 mmol) had been added and stirring was continued for another 1 h, the mixture was poured onto H_2O (45 mL). After extraction with CH_2Cl_2 (3×50 mL) the combined organic phases were washed with 2 N NaOH (2×75 mL) and H_2O (2×75 mL), dried (Na_2SO_4) and evaporated. The residual tan oil (531 mg), which crystallized on standing, was subjected to preparative layer chromatography (silica gel, CH_2Cl_2/EtOAc 7:3) giving **3b** as the less retarded and **4b** as the more polar fraction. The compounds were removed from the stationary phase by repeated extraction with warm EtOAc.

Compound **3b**. Yield: 299 mg (28%) of tan crystals, mp 63 °C. IR: 1656 cm^{-1} (C═O). MS (Th, %): 216 (M^+, 7), 201 (20), 91 (22), 77 (33), 51 (26), 43 (100), 41 (20). Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.94; H, 5.55; N, 12.77.

Compound **4b**. Yield: 50 mg (5%) of colorless crystals after recrystallization from diisopropyl ether, mp 220–222 °C (lit.[56] mp 216–217 °C). HRMS: Th (M^+); calcd for $C_{12}H_{12}N_2O_2$: 216.0900. Found: 216.0903±0.0011.

4.3.3. (5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)-methanone (3c). Compound **3c** was obtained from **2c** (1.321 g, 5 mmol) and Me_3SiCHN_2/HBF_4 similarly as described for the synthesis of **3b** from **2b**. Preparative layer chromatography (CH_2Cl_2/EtOAc 7:3) afforded **3c** as the less retarded component accompanied by small amounts (5%) of isomer **4c**.

Compound **3c**. Yield: 473 mg (34%) of a reddish oil. IR: 1656 cm^{-1} (C=O). MS (Th, %): 278 (M^+, 5), 105 (41), 91 (36), 77 (100), 51 (29). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.02; H, 5.00; N, 9.82.

4.3.4. (5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)(2-thienyl)-methanone (3d). Compound **3d** was obtained from **2d** (1.352 g, 5 mmol) and Me_3SiCHN_2/HBF_4 similarly as described for the synthesis of **3b** from **2b**. Preparative layer chromatography (CH_2Cl_2/EtOAc 3:2) afforded **3d** as the less retarded component accompanied by traces of isomer **4d**. The product was crystallized from diisopropyl ether with addition of charcoal. Yield: 341 mg (24%) of yellowish crystals, mp 105 °C. IR: 1622 cm^{-1} (C=O). MS (Th, %): 285 (M^++1, 11), 284 (M^+, 55), 144 (23), 111 (100), 91 (53), 77 (74), 53 (34), 51 (64). Anal. calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.06; H, 4.33; N, 9.82.

4.3.5. (*E*)-1-(5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-2-propen-1-one (3e). To a mixture of **2e** (871 mg, 3 mmol), PPh_3 (1.179 g, 4.5 mmol) and MeOH (120 mg, 3.75 mmol) in CH_2Cl_2 (60 mL) was added dropwise diethyl azodicarboxylate (783 mg, 4.5 mmol). After stirring for 20 h at room temperature, MeOH (3 mL) was added and the mixture was poured onto H_2O (60 mL). After exhaustive extraction with CH_2Cl_2, the combined organic phases were washed several times with 2 N NaOH and then with H_2O. After drying (Na_2SO_4), the solvent was evaporated and the residue was subjected to preparative layer chromatography (CH_2Cl_2/EtOAc 3:2). The less retarded zone was removed and extracted several times with warm EtOAc. The residue obtained after filtration and evaporation of the solvent was recrystallized from diisopropyl ether. Yield: 307 mg (34%) of colorless crystals, mp 165 °C. IR: 1654 cm^{-1} (C=O). MS (Th, %): 304 (M^+, 24), 213 (19), 187 (28), 186 (21), 131 (16), 103 (32), 91 (33), 77 (100), 51 (42). Anal. calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.80; H, 5.33; N, 9.12.

4.3.6. 1,2-Dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-one (4a). A mixture of pyrazolone **1** (250 mg, 1.561 mmol), methyl 4-toluenesulfonate (291 mg, 1.561 mmol) and dry xylene (5 mL) was heated to reflux for 24 h under anhydrous conditions. After cooling, to the mixture was added light petroleum (3 mL), the organic phase was cautiously removed, the remaining oil was taken up in 2 N NaOH (3 mL) and exhaustively extracted with $CHCl_3$ (6 times). The combined $CHCl_3$ phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from EtOAc to afford cream crystals. Yield: 183 mg (67%); mp 115–117 °C (lit.[57] mp 117–118 °C).

4.3.7. 4-Benzoyl-1,2-dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-one (4c). A mixture of **2c** (300 mg, 1.135 mmol) and dimethyl sulfate (430 mg, 3.41 mmol) was heated to reflux on an oil bath (T=190–200 °C) for 15 min. Then, the mixture was poured onto hot H_2O (5 mL), stirred for 20 min, made alkaline with solid Na_2CO_3 and 2 N NaOH and extracted exhaustively with CH_2Cl_2. The combined organic phases were washed twice with H_2O and then brine, dried (Na_2SO_4) and evaporated. The residue was recrystallized from toluene (ca. 30 mL) to afford a colorless solid; yield: 148 mg (47%); mp 157–159 °C. MS (Th, %): 279 (M^++1, 10), 278 (M^+, 52), 201 (15), 158 (47), 121 (74), 105 (100), 91 (12), 77 (85), 51 (23). HRMS: Th (M^+); calcd for $C_{17}H_{14}N_2O_2$: 278.1055. Found: 278.1049±0.0014. Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.11; H, 5.33; N, 10.02.

4.3.8. 1,2-Dihydro-1-methyl-2-phenyl-4-(2-thienylcarbonyl)-3*H*-pyrazol-3-one (4d). A mixture of **2d** (811 mg, 3 mmol), 1 N aq. NaOH (9 mL), H_2O (6 mL), and dimethyl sulfate (756 mg, 6 mmol) was heated to reflux for 4 h before it was stirred at rt for additional 16 h. The combined organic phases obtained after extraction with CH_2Cl_2 (3×10 mL) were washed with H_2O, dried (Na_2SO_4) and evaporated. The residue (610 mg) was subjected to preparative layer chromatography (CH_2Cl_2/EtOAc 1:9). From the central area the product was desorbed by repeated extraction with EtOAc. Yield: 40 mg (5%) of colorless crystals; mp 209 °C. MS (Th, %): 285 (M^++1, 10), 284 (M^+, 51), 111 (100), 97 (29), 77 (33), 53 (14). Anal. calcd for $C_{15}H_{12}N_2O_2S\cdot0.5H_2O$: C, 61.42; H, 4.47; N, 9.55. Found: C, 61.31; H, 4.32; N, 9.36.

4.3.9. (*E*)-1,2-Dihydro-1-methyl-2-phenyl-4-(3-phenylacryloyl)-3*H*-pyrazol-3-one (4e). A mixture of **2e** (450 mg, 1.55 mmol) and dimethyl sulfate (1.95 g, 15.45 mmol) was heated to 100 °C for 24 h with stirring. Then the excess reagent was removed by bulb-to-bulb distillation (75 °C). The residue was stirred with sat. aqueous Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined CH_2Cl_2-phases were dried (Na_2SO_4) and evaporated to dryness. The oily residue crystallized upon treatment with water, and was washed with cold ethanol and then recrystallization from EtOH. Yield: 179 mg (38%) of nearly colorless crystals; mp 201 °C [lit.[58] mp 234 °C, Beilstein (Reg. Nr. 30915) mp 198–199 °C, lit.[59] mp 190–192 °C]. MS (Th, %): 305 (M^++1, 21), 304 (M^+, 100), 303 (30), 275 (31), 193 (19), 184 (63), 174 (22), 131 (32), 121 (65), 103 (45), 77 (38). HRMS: Th (M^+); calcd for $C_{19}H_{16}N_2O_2$: 304.1212. Found: 304.1208±0.0015.

Computational part. The optimization was carried out at the B3LYP/6-311++G** level[60,61] and the calculation of the four components of the coupling constant at the same level using the facilities provided by the Gaussian 03 package.[62,63]

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