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Synthesis, Reaction, Theoretical Calculation, NMR Study and X-Ray Crystal Structure of 1-Substituted and 1-Unsubstituted 1H-Pyrazol-5(2H)-ones

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This work is dedicated to the memory of our long time friend and colleague Franco Serra-Zanetti († October 10, 1995).

Non omnis moriar,.....
(Quintus Horatius Flaccus, Carmina, III, XXX, VI)

Abstract: 1-Substituted 4-alkoxy-, 4-alkylthio-, and 4-aryloxy-1*H*-pyrazol-5(2*H*)-ones have been prepared by the reaction of conjugated azoalkenes with alcohols, thiols, and phenols. In some cases the intermediate hydrazones were isolated, while in others the products were obtained in one step. 1-Unsubstituted 4-alkoxy-, 4-alkylthio-, and 4-aryloxy-1*H*-pyrazol-5(2*H*)-ones were produced by methanolysis of the corresponding 1-substituted derivatives under reflux. Some of these compounds were studied by molecular mechanics calculations, as well as deuterium induced shifts (DIS) on ^{13}C chemical shifts, and tentative conclusion was drawn about their tautomerism and conformations. X-Ray crystal structure determinations of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one **4e** and 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one **5a** demonstrated that both molecules exist in the crystal exclusively in the HN-CO tautomeric form. Some previously reported structural assignments in some pyrazolones and hydroxypyrazoles were corrected.

INTRODUCTION

Previous papers from one of our groups dealt with the synthesis and reactions of some 1*H*-pyrazol-5(2*H*)-ones,[1,2] which are of great interest both as products and intermediates in organic,[3] biological (muscimol analogs, and bacterial metabolites of antipyrine),[4] pharmaceutical [antipyretics, analgesics, antiinflammatories, antirheumatics, antiphlogistics (*e.g.* antipyrine, aminopyrine or aminophenazone, isopyrine, nifenazone,

aminopropylon, propylphenazone or isopropylantipyrine, mofebutazone, piperylone, noramidopyrine or metamizole or dipyrone, epirizole or mepirizole), diuretics (*e.g.* muzolimine), ulcer inhibitors, and cardiovascular agents],[5] analytical (*e.g.* antipyrine, 4-aminoantipyrine)[6] and agricultural chemistry (herbicides, and carbamate insecticides).[7] During the spectroscopic investigations of 1*H*-pyrazol-5(2*H*)-ones, several problems emerged concerning the tautomerism of these compounds.[1,2] 1-Substituted 1*H*-pyrazol-5(2*H*)-ones can exist in three tautomeric structures which are designated as the HN-CO, the HC-CO and the HO-NR forms (Figure 1). 1-Unsubstituted 1*H*-pyrazol-5(2*H*)-ones present a more complex tautomerism due to one further important tautomer (designated as the HN-OH form) and four other possible structures.

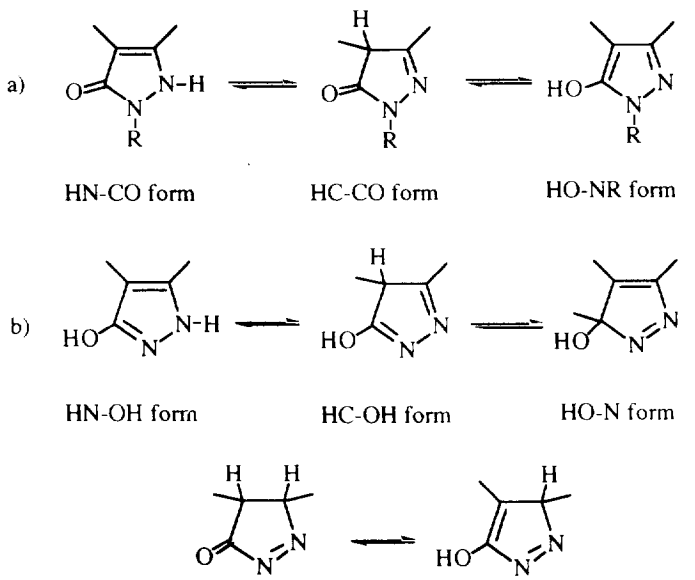


Figure 1. Tautomeric forms for a) 1-substituted and b) extra forms for 1-unsubstituted 1*H*-pyrazol-5(2*H*)-ones (note that the last two structures are considered highly unstable and are not considered further in this paper).

Early confusion as to the relative importance of the tautomeric forms of pyrazolones was clarified by two early independent investigations by the groups of Katritzky and Jacquier.[8] A complete overview of the tautomerism of these derivatives, placed in perspective in the scheme of heteroaromatic tautomerism in general, was provided by Elguero et al. [9a] which summarizes the literature up to 1975 (for more recent reviews, see.[9b,c] The effect of the medium, and in particular the dielectric constant of the solvent, on the tautomeric equilibria of heterocycles was studied experimentally and theoretically.[9,10]

In general, the HC-CO form is found in non-polar solvents, while the HN-CO form is favored in polar ones.[8-11] The HC-CO form can be easily identified by NMR spectroscopy, but discrimination between the HN-CO and HO-NR forms is more difficult. In some cases, limited solubilities hinder structure determination.

Therefore, it is not surprising that, even in the more recent literature, confusion still exists.[3,5,7,12] The 1-substituted derivatives are designated as HC-CO (also named 2-pyrazolin-5-ones) and HO-NR (also named 5-hydroxypyrazoles) forms in most cases, while the HN-CO (also named 3-pyrazolin-5-ones) forms are less frequent. Thus, the majority of authors have reported the synthesis and use of 3- and/or 5-hydroxypyrazoles,[7h,j,k-m,q;12c-e,g,h,n,o-u] while a lesser number of 2-pyrazolin-5-ones were reported.[12e,j-l,n-p,r,t,u] The citation of these products as 3-pyrazolin-5-ones is the least frequent.[12t,u] Different structures and nomenclatures were often adopted in the same paper.[12e,o,p,r,t] In pharmaceutical texts and handbooks identical products or intermediates are reported variously in HC-CO or HN-CO form, with consequent nomenclature confusion.[5c,k] In chemical catalogues the same methylpyrazolone has been presented with different structures and names, for instance 3-methyl-2-pyrazolin-5-one (Lancaster, Avocado, Acros, TCI) or 3-methyl-3-pyrazolin-5-one (Aldrich). 1,3-Dimethyl-2-pyrazolin-5-one is named 1,3-dimethyl-5-pyrazolinone (Acros, TCI) but also 2,4-dihydro-2,5-dimethyl-3*H*-pyrazol-3-one (TCI).

In an attempt to increase our knowledge of the structure, conformation and tautomerism of 1*H*-pyrazol-5(2*H*)-ones, we have synthesized relatively simple 1-substituted and 1-unsubstituted derivatives and carried out an integrated study by theoretical calculation, NMR spectroscopy and X-ray diffraction.

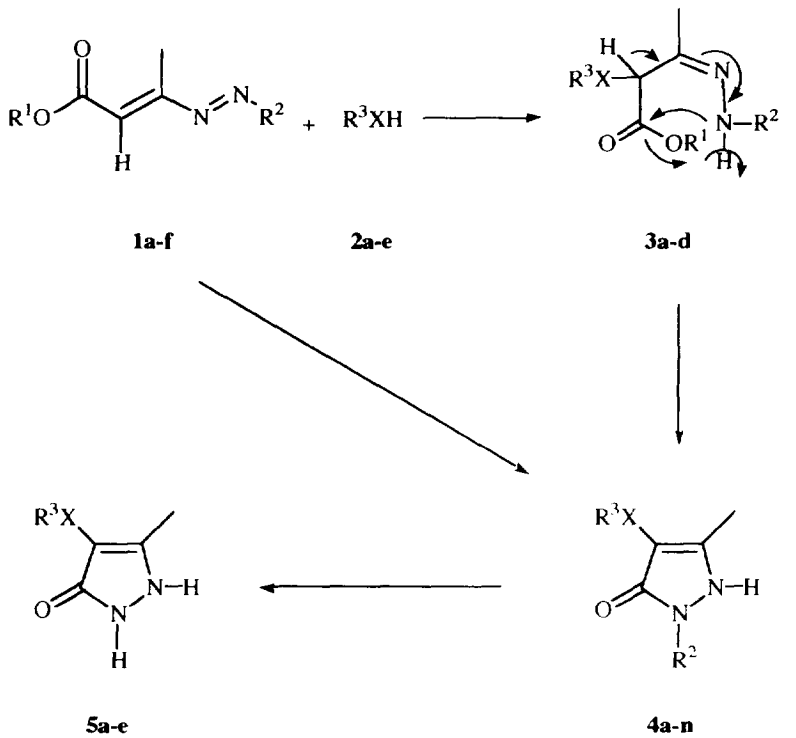
RESULTS AND DISCUSSION

New 1-substituted 4-alkoxy-, 4-alkylthio-, and 4-aryloxy-1*H*-pyrazol-5(2*H*)-ones **4a-n** were obtained by the reaction of conjugated azoalkenes **1a-f** with alcohols, phenols and thiols **2a-e**. In the case of the 1*H*-pyrazol-5(2*H*)-ones **4a-d**, hydrazone intermediates **3a-d** produced by 1,4-addition of the reagents **2a-e** to the azo-ene system of the azoalkene substrates were isolated. The 1*H*-pyrazol-5(2*H*)-ones **4e-n** were produced directly in one pot. The 1-unsubstituted 4-alkoxy-, 4-alkylthio-, and 4-aryloxy-1*H*-pyrazol-5(2*H*)-ones **5a-e** were prepared by mild solvolytic cleavage of the relevant 1-substituted 4-alkoxy-, 4-alkylthio-, and 4-aryloxy-1*H*-pyrazol-5(2*H*)-ones **4a-n** in methanol under reflux. Thus, the N(1) substituents used as protective groups, were easily replaced (Scheme 1 and Tables 1-4).[2,13]

The present investigation confirms once again the utility of conjugated azoalkenes in the construction of polyfunctionalized heterocyclic systems.[2,3,14-16]

Molecular mechanics calculations using the MMX[17,18] force field applied to 1-substituted 1*H*-pyrazol-5(2*H*)-ones **4a-b,e-f** in the HN-CO, HC-CO, and HO-NR forms, for both *syn* and *anti* conformers respectively (Figure 2), result in the relative energy values and the *syn/anti* ratios[19] presented in Table 5.

For compounds **4a** and **4b** the stability order is HC-CO$_{anti}$>HC-CO$_{syn}$>HN-CO$_{anti}$>HN-CO$_{syn}$>HO-NR$_{syn}$>HO-NR$_{anti}$, while for compounds **4e** and **4f** the following stability order can be deduced: HC-CO$_{anti}$>HC-CO$_{syn}$>HN-CO$_{anti}$>HO-NR$_{syn}$>HN-CO$_{syn}$>HO-NR$_{anti}$. The major conclusion from these data is that HC-CO forms in the *anti* conformation are the most stable. For compounds **4e** and **4f**, the intramolecular hydrogen bonds between the $CONH_2$ and CONHPh protons of the substituent on the N(1) and the carbonyl group of the pyrazole ring seems to stabilize the *anti* conformers. For compound **4a** and especially for



1a-f **2a-e** **3a-d**

5a-e **4a-n**

R^1 = Me, Et

R^2 = CO_2Me, CO_2Bu^t, $CONH_2$, CONHPh

R^3 = Me, Et, Ph, 4-$NO_2C_6H_4$, CH_2CO_2Et

X = O, S

Scheme 1

Table 1. Yields and reaction times of hydrazones **3a-d**.

Azoalkene **1**	R^1	R^2	Alcohol **2**	R^3	X	Hydrazone **3**	Yields (%)	Reaction Times (h)
1a	Me	CO_2Me	**2a**	Me	O	**3a**	93	0.2
1b	Et	CO_2Bu^t	**2a**	Me	O	**3b**	70	0.1
1c	Et	$CONH_2$	**2b**	4-$NO_2C_6H_4$	O	**3c**	49	10.0
1d	Et	CONHPh	**2b**	4-$NO_2C_6H_4$	O	**3d**	42	2.0

Table 2. Yields and reaction times of 1-substituted 1*H*-pyrazol-5(2*H*)-ones **4a-d**.

Hydrazone 3	R^1	R^2	R^3	X	Pyrazolone 4	Yield (%)	Reaction Times (h)
3a	Me	CO_2Me	Me	O	**4a**	82	8.0
3b	Et	CO_2Bu^t	Me	O	**4b**	93	4.0
3c	Et	$CONH_2$	$4\text{-}NO_2C_6H_4$	O	**4c**	94	0.2
3d	Et	CONHPh	$4\text{-}NO_2C_6H_4$	O	**4d**	82	0.1

Table 3. Yields and reaction times of one-pot preparation of 1-substituted 1*H*-pyrazol-5(2*H*)-ones **4e-n**.

Azoalkene 1	R^1	R^2	Alcohol 2	R^3	X	Pyrazolone 4	Yields (%)	Reaction Times (h)
1c	Et	$CONH_2$	**2a**	Me	O	**4e**	76	0.1
1d	Et	CONHPh	**2a**	Me	O	**4f**	88	0.1
1e	Me	$CONH_2$	**2c**	Et	O	**4g**	66	0.1
1f	Me	CONHPh	**2c**	Et	O	**4h**	67	0.1
1e	Me	$CONH_2$	**2d**	Ph	O	**4i**	62	0.1
1f	Me	CONHPh	**2d**	Ph	O	**4j**	60	0.1
1a	Me	CO_2Me	**2e**	CH_2CO_2Et	S	**4k**	90	15.0
1b	Me	CO_2Bu^t	**2e**	CH_2CO_2Et	S	**4l**	97	10.0
1c	Et	$CONH_2$	**2e**	CH_2CO_2Et	S	**4m**	95	12.0
1f	Me	CONHPh	**2e**	CH_2CO_2Et	S	**4n**	93	2.0

compound **4b** the *syn* conformers should be favored due to the absence of such bonds and the presence of steric effects.[1,2]

In the case of 1-unsubstituted 1*H*-pyrazol-5(2*H*)-one **5a**, molecular mechanics calculations of the relative E values using MMX force field and extended to all six forms pictured in Figure 1 were as follows: HC-CO E = 0.00 kcal/mol, HO-N E = 0.33 kcal/mol, HO-NR E = 2.81 kcal/mol, HN-CO E = 3.81 kcal/mol, HN-OH E = 6.65 kcal/mol, HC-OH E = 12.14 kcal/mol. In conclusion, the HC-CO form is the most stable one, in agreement with the results for 1-substituted 1*H*-pyrazol-5(2*H*)-ones.

Table 4. Preparation of 1-unsubstituted 1*H*-pyrazol-5(2*H*)-ones **5a-e**.

Pyrazolone **4**	R^2	R^3	X	Pyrazolone **5**	Yields (%)	Reaction Times (h)
4a	CO_2Me	Me	O	**5a**	81	7.0
4b	CO_2t-Bu	Me	O	**5a**	85	7.5
4e	$CONH_2$	Me	O	**5a**	77	12.0
4f	CONHPh	Me	O	**5a**	78	3.5
4c	$CONH_2$	4-$NO_2C_6H_4$	O	**5b**	87	5.0
4d	CONHPh	4-$NO_2C_6H_4$	O	**5b**	88	4.0
4g	$CONH_2$	Et	O	**5c**	71	12.0
4h	CONHPh	Et	O	**5c**	78	4.0
4i	$CONH_2$	Ph	O	**5d**	92	9.0
4j	CONHPh	Ph	O	**5d**	91	5.0
4k	CO_2Me	CH_2CO_2Et	S	**5e**	78	5.5
4l	CO_2t-Bu	CH_2CO_2Et	S	**5e**	74	6.5
4m	$CONH_2$	CH_2CO_2Et	S	**5e**	67	12.0
4n	CONHPh	CH_2CO_2Et	S	**5e**	77	4.0

Computational methods thus indicated that all these molecules exist preferentially in the HC-CO form, and in *anti* conformations when carbonyl groups are present on N(1). We have previously demonstrated by comparative crystallographic analysis that not only 1-(aminocarbonyl)-3-methyl-4-((pyrimid-2-yl)thio)-1*H*-pyrazol-5(2*H*)-one,[1] 1-(aminocarbonyl)-3-methyl-4-benzoylthio-1*H*-pyrazol-5(2*H*)-one[2] and 1-(anilinocarbonyl)-3-methyl-4-benzoylthio-1*H*-pyrazol-5(2*H*)-one,[2] but also 1-(*tert*-butoxycarbonyl)-3-methyl-4-benzoylthio-1*H*-pyrazol-5(2*H*)-one[2] exist in the HN-CO form, notwithstanding the absence of intramolecular hydrogen bonding, although exhibiting the preference for the *syn* conformation, probably due to the considerable steric hindrance of the *tert*-butyl group. Crystallographic study of related 1-unsubstituted 1*H*-pyrazol-5(2*H*)-one was not possible because of unsuitable crystals. The results of this theoretical approach are, as a whole, in good agreement with analogous results by Elguero *et al.* for similar molecules.[20] However, in these calculations the molecules examined are considered at infinite dilution in the gas phase. In solution, the inter- and intramolecular forces are frequently overwhelmed by the solute-solvent interactions (mainly dielectric), which may play the dominant role in the relative energy of the tautomers. In general, high dielectric constant media favor species with greater charge separation.[10,11] In solids, only the inter- and intramolecular forces, depending exclusively upon the intrinsic electron densities, determine structure and conformation.

Table 5. The relative calculated MMX steric energies and syn/anti ratios at 298 K for compounds 4a-f.

Pyrazolone	E(kcal/mol)		*syn/anti*	E(kcal/mol)		*syn/anti*	E(kcal/mol)		*syn/anti*
4	HN-CO *syn*	HN-CO *anti*	HN-CO form	HC-CO *syn*	HC-CO *anti*	HC-CO form	HO-NR *syn*	HO-NR *anti*	HO-NR form
4a	8.58	7.81	22:78	0.23	0.00	40:60	9.29	11.71	98:2
4b	8.60	7.75	19:81	0.37	0.00	35:65	17.74	20.23	98.5:1.5
4e	13.34	7.59	0:100	3.00	0.00	0.5:99.5	8.73	16.08	100:0
4f	13.25	6.20	0:100	3.12	0.00	0.5:99.5	10.96	14.31	100:0

Table 6. The relative calculated MMX steric energies and syn/anti ratios at 298 K for compounds 6-8.

Pyrazolone	E(kcal/mol)		*syn/anti*	E(kcal/mol)		*syn/anti*	E(kcal/mol)		*syn/anti*
	HN-CO *syn*	HN-CO *anti*	HN-CO form	HC-CO *syn*	HC-CO *anti*	HC-CO form	HO-NR *syn*	HO-NR *anti*	HO-NR form
6	13.85	6.81	0:100	3.04	0.00	1:99	12.83	19.83	100:0
7	10.65	9.64	16:84	0.46	0.00	32:68	18.12	23.30	97.5:2.5
8	13.58	8.27	0:100	2.70	0.00	1:99	11.13	17.89	100:0

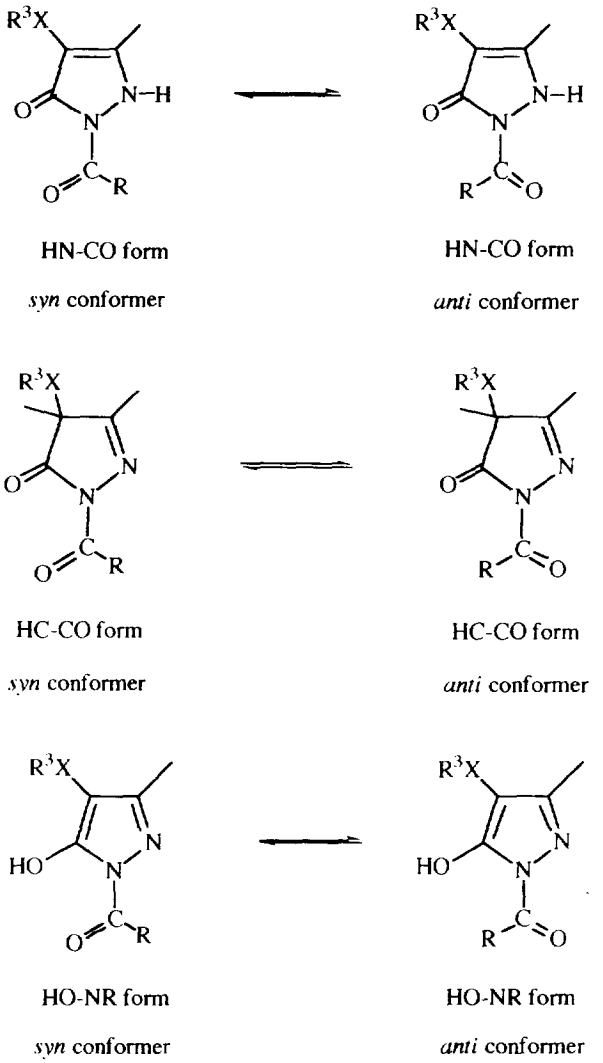
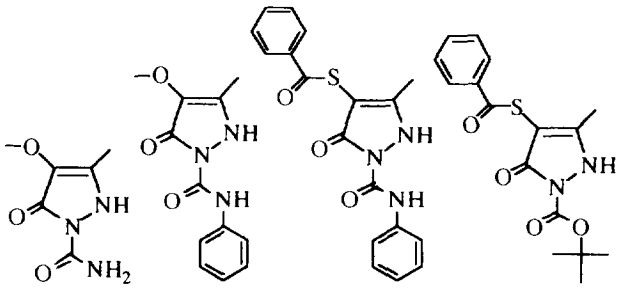


Figure 2. Tautomeric forms and *syn-anti* conformers for 1-substituted 1*H*-pyrazol-5(2*H*)-ones.

Molecular mechanics calculations using the MMX force field of the relative energy values for 1-substituted 4-benzoylthio-1*H*-pyrazol-5(2*H*)-ones **6** and **7** (Figure 3) in the HN-CO, HC-CO, and HO-NR forms, for both *syn* and *anti* conformers respectively, reached the values and the *syn/anti* ratios depicted in Table 6.[2]

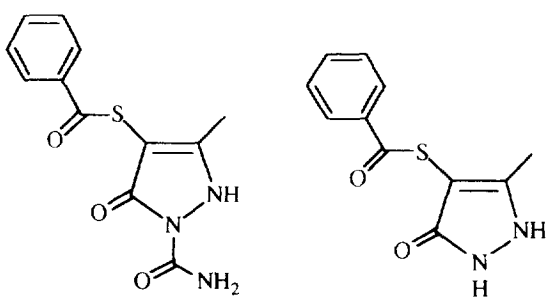


4e **4f** **6** **7**

Figure 3. Compounds **4e**, **4f**, **6**, and **7**.

According to these data the stability order is: (*i*) for compound **6** HC-CO*anti*>CH-CO*syn*>HN-CO*anti*>HO-NR*syn*>HN-CO*syn*>HO-NR*anti* (in agreement with the above-reported stability order for analogous compounds **4e** and **4f**); (*ii*) for compound **7** HC-CO*anti*>HC-CO*syn*>HN-CO*anti*>HN-CO*syn*>HO-NR*syn*>HO-NR*anti* (concordant with the above stability order for compounds **4a** and **4b**). Even in this case, the only reasonable conclusion that can be drawn is the high stability of the HC-CO forms, in both cases with preference towards the anti conformation. These conclusions are in disagreement with previous crystallographic results.[2] Furthermore, the behavior of compounds **6** and **7** is similar to that obtained from molecular mechanics calculations using the MMX force field for the analogous compound **8** (Figure 4) for which the stability order is qualitatively the same as for compounds **4e**, **4f** and **6**.

Molecular mechanics calculations of the relative E values using the MMX force field applied to the first six forms in Figure 1 of 1-unsubstituted 4-benzoylthio-1*H*-pyrazol-5(2*H*)-one **9** (Figure 4) afforded slightly different results as compared to compound **5a**, as follows: HC-CO E = 0.00 kcal/mol, HO-N E = 3.15 kcal/mol, HN-CO E = 5.07 kcal/mol, HO-NR E = 5.44 kcal/mol, HN-OH E = 7.67 kcal/mol, HC-OH E = 14.68 kcal/mol. In conclusion, the CH-CO form is still the most stable one.



8 **9**

Figure 4. Compounds **8** and **9**.

The computational findings for the compounds considered are difficult to rationalize as a whole, and this inconsistency can be ascribed to the unreliability of MMX in the study of molecules in solution or solid state.[10,11,17-19]

To determine the dominant tautomer of the equilibrium of the HN-CO, HC-CO and HO-NR forms in solution, a detailed NMR study was carried out by using the deuterium induced shifts on ^{13}C (DIS) technique. DIS have provided a wealth of information on hydrogen bonding and tautomerism, as well as unique information about the influence on the equilibrium of a hydrogen bond pointing to a heteroatom involved in tautomerism.[21]

Compounds of this work (**4f**) and the previously reported [6,2] were found suitable for DIS measurements, having good solubility in $CDCl_3$. Complete assignment of the ^1H and ^{13}C chemical shifts, made on basis of ^1H-^{13}C direct and long-range correlations in compounds **4f** and **6**, are given in Figure 5.

Compounds **4f** and **6** each exhibited one broad signal and one sharp signal for the two exchangeable protons. It was impossible to deuterate selectively the proton displaying the broad signal. However DIS due to deuterium exchange of proton H_A displaying the sharp signal (DIS_A) and DIS due to deuterium exchange of proton H_B displaying the broad signal (DIS_B) were measured in a partially deuterated sample using an original method, described in the experimental section. DIS values in ppb for compounds **4f** and **6** are shown in Figure 5, DIS_A on the first row and DIS_B on the second. The magnitude and location of DIS_A clearly indicate that these effects are intrinsic and that proton A is localized on the amidic nitrogen in both compounds **4f** and **6**. DIS_B can be interpreted as intrinsic effects, equilibrium effects or a combination of both. For compound **6**, DIS_A on the aniline ring are large enough to be reliable and are consistent with equilibrium effects. The predicted chemical shifts[21k] for the HN-CO and the HO-NR tautomers of **6** are shown in Figure 6.

DIS_B on the aniline ring (negative value for the quaternary carbon and positive values for the *ortho* and *para* positions) indicate that deuteration of H_B produces a shift of the equilibrium towards the HN-CO form. Since deuteration increases the concentration of the most stable tautomer, the equilibrium of compound **6** appears to be dominated by the HN-CO form.[21a] DIS_B values in position 3, 4, and 6 are consistent with intrinsic effects in the HN-CO form. They cannot be interpreted as equilibrium effects because DIS_B in position 3 and 4 should have a different sign from DIS_B in position 6. We cannot provide any explanation for DIS_B in position 7. DIS_A in position 3 are consistent with both *i*) intrinsic effects due to a hydrogen bond formed by H_A with N(2) or *ii*) effect of deuteration of H_A on the equilibrium between the HN-CO and the HO-NR forms. In case *ii*) deuteration of H_A produces a shift of the equilibrium towards the form in which N(2) is a weaker hydrogen bond acceptor, namely the HO-NR form. This is consistent with different signs for DIS_A and DIS_B in position 3. Meanwhile, the similarity of the DIS_A and δH_A in position 3 of compounds **4f** and **6** supports case *i*). The small magnitude of DIS_B in compound **4f** is consistent with an insignificant shift of the equilibrium upon deuteration when one form is present in large excess. However, intrinsic DIS_B expected for such a situation have not been observed.

Thus, the DIS clearly indicate that in both **4f** and **6** the proton displaying the sharp line is localized on the amidic nitrogen. For compound **6**, DIS suggest that in chloroform solution an equilibrium between the HN-CO and HO-NR forms, in which HN-CO form is in excess, takes place. The interpretation of equilibrium effects relied on the predicted ^{13}C chemical shifts and, as a consequence, depends on the accuracy of these predictions. DIS provided no information about the equilibrium of compound **4f**.

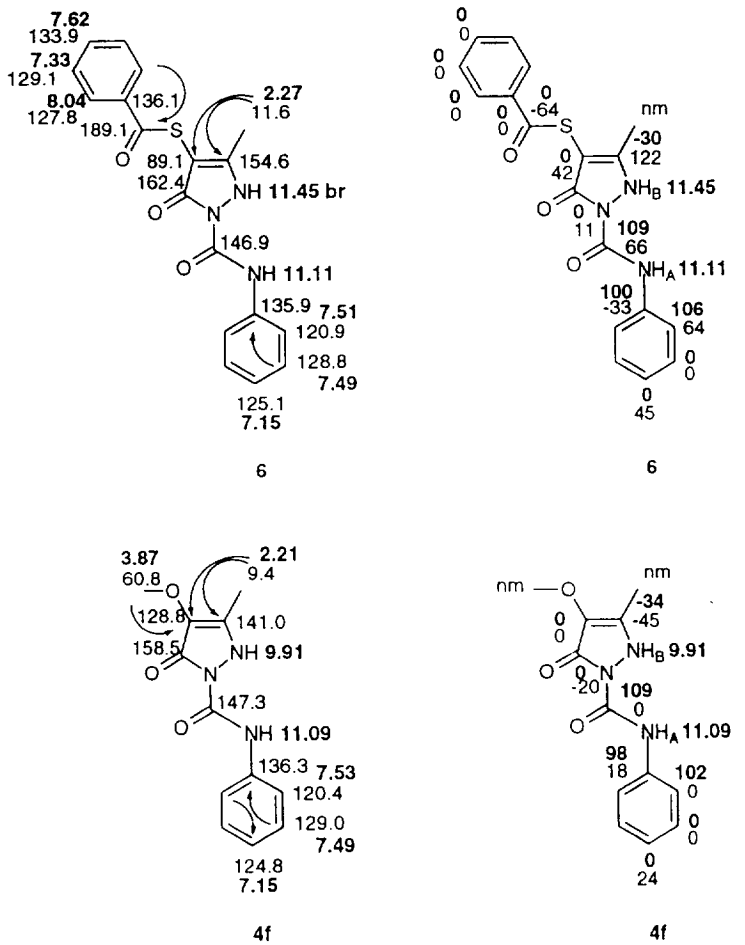


Figure 5. Assignments of ^{1}H and ^{13}C chemical shifts and DIS values in ppb for compounds **4f** and **6**; DIS_A on the first row and DIS_B on the second.

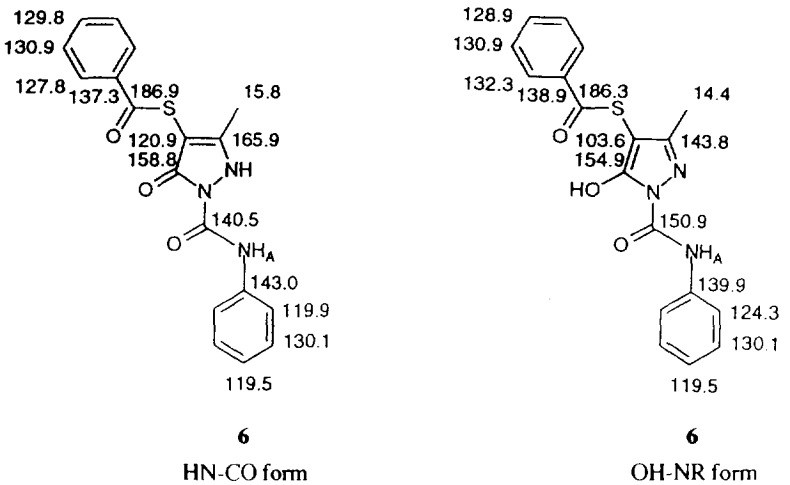


Figure 6. The predicted chemical shifts for the HN-CO and the HO-NR tautomers of **6**.

Considering the uncertain results deriving both from the computational approach and the NMR study, we carried out X-ray diffraction analyses of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one **4e** and 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one **5a**, as models for other similar molecules.

The crystal structure of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (**4e**) (Figure 7) shows interatomic distances consistent with the HN-CO tautomeric form. The bond length C(5)-O(9) is 1.236(4) Å, close to that of a nearly pure C=O double bond (average length of C=O sp^2-O bond is 1.20 Å and of C-O sp^3-O single bond is 1.34 Å). The C(3)-C(4) distance of 1.346(4) Å is consistent with a C=C double bond (average for C=C sp^2-sp^2 bond is 1.34 Å). The length of C(4)-C(5) is 1.425(4) Å, similar to C-C sp^2-sp^2 single bond (average length for such a bond is 1.48 Å). The 1*H*-pyrazol-5(2*H*)-one ring is planar with a maximum deviation from the least-squares plane passing through the five atoms of -0.0271 Å at N(2). An intramolecular hydrogen contact N(12)-H(122)---O(9)-C(5) (length 2.710(1) Å, angle 126.9°) is detected, as seen for similar cases.[1,2] This intramolecular organization is strengthened by three intermolecular hydrogen bondings that determine the molecular packing: N(12)-H(122)---O(9)-C(5) (2.853(1) Å), N(12)-H(121)---O(11)-C(10) (2.898(1) Å), and N(2)-H(2)---O(11)-C(10) (2.922(1) Å).

The crystal structure of 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (**5a**) (Figure 8) with bond lengths of [C(5)-O(9) 1.279(2) Å, C(3)-C(4) 1.375(3) Å, and C(4)-C(5) 1.245(3) Å] supports the HN-CO tautomeric form. The maximum deviation from the least-squares plane passing through the five atoms is at N(1), of -0.0128 Å. In compound **5a**, both the hydrogen atoms of the pyrazolone heterocycle are available only for intermolecular hydrogen bondings. Two intermolecular hydrogen contacts (determining the molecular packing) N(2)-H(2)---O(9)-C(5) (2.660(1) Å) and N(1)-H(1)---O(9)-C(5) (2.730(1) Å) are detected.

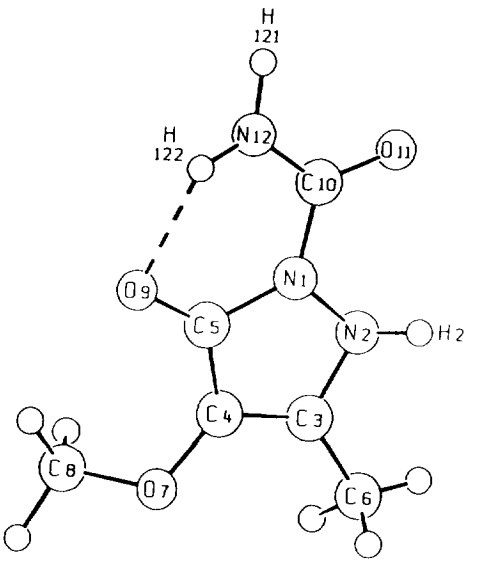


Figure 7. X-ray molecular structure of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (**4e**) with the atom numbering system used in the crystallographic analysis.

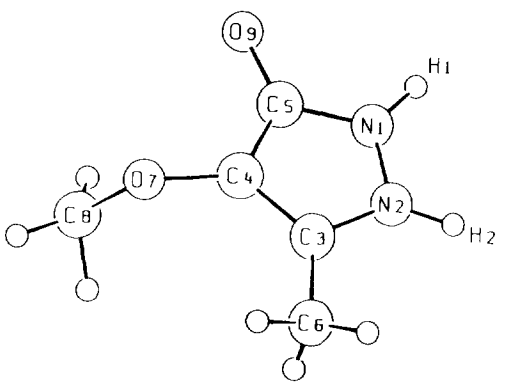


Figure 8. X-ray molecular structure of 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (**5a**) with the atom numbering system used in the crystallographic analysis.

In accordance with our previous reports,[1,2] these data demonstrate limitations in the applicability of the usual computational and spectroscopic methods in the assignment of the tautomeric structures of pyrazolones. Our results demonstrate errors in some literature structural assignments for 5- and 3-hydroxypyrazole derivatives.[3,5,7,12] In doubtful cases, structure determinations can conveniently be supported by X-ray diffraction investigations.

EXPERIMENTAL

(Alkoxycarbonyl)azoalkenes **1a,b**, (aminocarbonyl)azoalkenes **1c,e**, and (anilinocarbonyl)azoalkenes **1d,f** were prepared as previously reported.[22,23] Starting materials of the above-mentioned reagents, as well as 4-nitrophenol **2b**, phenol or sodium phenoxide trihydrate **2d**, ethyl 2-mercaptoacetate **2e**, methanol-sodium methoxide (30% solution), ethanol-sodium ethoxide (30% solution), sodium hydride, sodium methoxide, sodium ethoxide, and trifluoroacetic acid are commercial materials (Aldrich, Acros or Lancaster) and were used without further purification. Melting points were determined in open capillary tubes with a Büchi (Tottoli) or Gallenkamp apparatus and are uncorrected. The products often decompose at melting point. IR spectra were obtained as liquid film or Nujol mull with a Perkin-Elmer 298 spectrophotometer. IR-FT spectra were performed with a Nicolet Impact 400 spectrophotometer. MS spectra were made with a Hewlett Packard 5995C spectrometer. Elemental analyses were performed with a Fisons EA 1108 instrument. NMR spectra were performed with DMSO-d_6. ^{1}H NMR spectra at 60 MHz were recorded on Varian EM 360 L and at 200 MHz on Bruker AC 200 spectrometers and ^{13}C NMR spectra at 50 MHz on Bruker AC 200 spectrometer. Chemical shifts (δ) are in ppm and are referred to internal TMS. The coupling constants (J) are given in Hz. The abbreviations used are as follows: s, singlet; d, doublet, dd, doublet-doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O-exch, D_2O exchange. Macherey-Nagel precoated silica gel SIL G-25 UV_{254} plates (0.25 mm) were employed for analytical thin layer chromatography and silica gel Amicon LC 60 Å (35-70 mμ) for column chromatography.

Preparation of α-(methoxy) hydrazones 3a-b. To a magnetically stirred solution of azoalkene **1a-b** (1 mmol) in methanol **2a** (10 ml) was added a catalytic amount of sodium methoxide (0.1 mmol). The reaction was stirred at room temperature for 0.1-0.2 h until the azoalkene **1** disappeared (checked by TLC). After evaporation of solvent under reduced pressure, the prodocts **3a-b** were obtained by chromatography separation on a silica gel column (elution with ethyl acetate-cyclohexane mixtures) and were crystallized from ethyl acetate/petroleum ether (40-60 °C).

Methyl 2-(methoxy)acetoacetate (methoxycarbonyl)hydrazone (3a): mp 90-91 °C; IR ν_{max} 3230, 1760, 1735, 1715, 1535, 1375 cm^{-1}; ^{1}H NMR δ 1.94 (s, 3 H, Me), 3.26 (s, 3 H, OMe), 3.66 (s, 6 H, 2 CO_2Me), 4.39 (s, 1 H, CH), 10.13 (s, 1 H, NH, D_2O-exch). Anal. Calcd for $C_8H_{14}N_2O_5$: C, 44.03; H, 6.47; N, 12.84. Found: C, 44.14; H, 6.56; N, 12.66.

Ethyl 2-(methoxy)acetoacetate (*t*-buthoxycarbonyl)hydrazone (3b): mp 106-108 °C; IR ν_{max} 3220, 1745, 1725, 1700, 1530, 1370 cm^{-1}; ^{1}H NMR δ 1.19 (t, 3 H, J = 7 Hz, $CO_2CH_2\mathit{Me}$), 1.45 (s, 9 H, CO_2Bu^t),

1.75 (s, 3 H, Me), 3.25 (s, 3 H, OMe), 4.14, (q, 2 H, J = 7 Hz, CO_2CH_2Me), 4.33 (s, 1 H, CH), 9.78 (s, 1 H, NH, D_2O-exch). Anal. Calcd for $C_{12}H_{22}N_2O_5$: C, 52.54; H, 8.08 N, 10.21. Found: C, 52.41; H, 8.20; N, 10.06.

Preparation of α-(4-nitrophenoxy) hydrazones 3c-d. To a magnetically stirred solution of 4-nitrophenol **2b** (1 mmol) and sodium methoxide (0.1 mmol) in tetrahydrofuran (3 ml) was added a solution of azoalkene **1c-d** (1 mmol) in tetrahydrofuran (3 ml). The reaction was stirred at room temperature for 2.0-10.0 h until the azoalkene **1** disappeared (checked by TLC). After evaporation of solvent under reduced pressure, the prodocts **3c-d** were obtained by chromatography separation on a silica gel column (elution with ethyl acetate-cyclohexane mixtures) and were crystallized from ethyl acetate/petroleum ether (40-60 °C).

Ethyl 2-(4-nitrophenoxy)acetoacetate (aminocarbonyl)hydrazone (3c): mp 149-151 °C; IR ν_{max} 3470, 3180, 1735, 1690, 1670, 1610, 1580, 1510, 1370, 1340 cm^{-1}; ^1H NMR δ 1.20 (t, 3 H, J = 7 Hz, CO_2CH_2Me), 1.85 (s, 3 H, Me), 4.22 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 5.67 (s, 1 H, CH), 6.42 (br s, 2 H, NH_2, D_2O-exch), 7.20 (d, 2 H, J = 9 Hz, Ph), .8.20 (d, 2 H, J = 9 Hz, Ph), 9.58 (s, 1 H, NH, D_2O-exch.). Anal. Calcd for $C_{13}H_{16}N_4O_6$: C, 48.15; H, 4.97; N, 17.28. Found: C, 48.26; H, 4.84; N, 17.39.

Ethyl 2-(4-nitrophenoxy)acetoacetate (anilinocarbonyl)hydrazone (3d): mp 184-185 °C; IR ν_{max} 3370, 3190, 1750, 1720, 1590, 1530, 1370, 1335 cm^{-1}; ^1H NMR δ 1.92 (s, 3 H, Me), 3.77 (s, 3 H, CO_2Me), 5.86 (s, 1 H, CH), 6.98-7.34 (m, 5 H, Ph), 7.55 (d, 2 H, J = 9 Hz, Ph), 8.23 (d, 2 H, J = 9 Hz, Ph), 8.86 (s, 1 H, NH, D_2O-exch), 10.07 (s, 1 H, NH, D_2O-exch). Anal. Calcd for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 55.91; H, 4.79; N, 14.61.

Procedure for the Synthesis of 4-Methoxy-1*H*-pyrazol-5(2*H*)-ones 4a-b. To a magnetically stirred solution of hydrazone **3a-b** (1 mmol) in methanol (6 ml) at 0-5 °C was added a solution of sodium methoxide (1 mmol) in methanol (30% wt.). The reaction mixture was continued at the same conditions for 4.0-8.0 h until the hydrazone **3** disappeared (checked by TLC) and then was acidified by addition of trifluoroacetic acid (2 mmol). After evaporation of the reaction solvent under reduced pressure, the products **4a-b** were obtained by crystallization from ethyl acetate/petroleum ether (40-60 °C).

1-(Methoxycarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4a): mp 125-127 °C; IR ν_{max} 3420, 1720, 1610, 1375, 1340, 1295 cm^{-1}; ^1H NMR δ 2.04 (s, 3 H, Me), 3.47 (s, 3 H, OMe), 3.68 (s, 3 H, CO_2Me), 10.23 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.59 (Me), 53.55 (OMe), 59.93 (OMe), 127.78 (C4), 143.82 (C3), 148.83 (C=O), 156.70 (C5). Anal. Calcd for $C_7H_{10}N_2O_4$: C 45.16; H, 5.41; N, 15.05. Found: C, 45.23; H, 5.38; N, 15.23.

1-(*t*-Buthoxycarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4b): mp 119-121 °C; IR ν_{max} 3440, 1760, 1690, 1590, 1370, 1330, 1310 cm^{-1}; ^1H NMR δ 1.47 (s, 9 H, CO_2Bu), 2.04 (s, 3 H, Me), 3.63 (s, 3 H, OMe), 10.31 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.52 (Me), 27.58 (CMe_3), 59.97 (OMe), 83.61 (CMe_3), 127.82 (C4), 143.00 (C3), 146.70 (C=O), 157.92 (C5). Anal. Calcd for $C_{10}H_{16}N_2O_4$: C 52.62; H, 7.07; N, 12.27. Found: C, 52.68; H, 7.18; N, 12.21.

Procedure for the synthesis of 4-(4-nitrophenoxy)-1*H*-pyrazol-5(2*H*)-ones 4c-d. To a magnetically stirred solution of hydrazone **3c-d** (1 mmol) in methanol (6 ml) was added at room temperature sodium hydride (1mmol). The conversion rapidly occurred (0.1-0.2 h) and the 1*H*-pyrazol-5(2*H*)-ones **4c-d** formed (monitored by TLC). The reaction mixture was acidified by addition of trifluoroacetic acid (2 mmol) and evaporated under reduced pressure. Product **4c** was obtained by crystallization from ethyl ether/petroleum ether (40-60 °C), while product **4d** by crystallization from ethyl acetate/petroleum ether (40-60 °C).

1-(Aminocarbonyl)-3-methyl-4-(4-Nitrophenoxy)-1*H*-pyrazol-5(2*H*)-one (4c): mp 263-264 °C; IR ν_{max} 3310, 3170, 1720, 1655, 1590, 1370, 1340, 1290 cm^{-1}; ^1H NMR δ 2.10 (s, 3 H, Me), 7.20 (d, 2 H, J = 9 Hz, Ph), 7.69, 8.12 (2 s, 2 H, NH_2, D_2O-exch), 8.21 (d, 2 H, J = 9 Hz, Ph), 12.57 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.07 (Me), 115.64, 126.00 and 162.69 (Ph), 119.64 (C4), 141.84 (Ph or C3), 142.17 (C3 or Ph), 148.94 (C=O), 155.63 (C5). Anal. Calcd for $C_{11}H_{10}N_4O_5$: C 47.49; H, 3.62; N, 20.14. Found: C, 47.53; H, 3.58; N, 20.19.

1-(Anilinocarbonyl)-3-methyl-4-(4-Nitrophenoxy)-1*H*-pyrazol-5(2*H*)-one (4d): mp 258-260 °C; IR ν_{max} 3340, 1730, 1660, 1600, 1590, 1560, 1360, 1340, 1300 cm^{-1}; ^1H NMR δ 2.16 (s, 3 H, Me), 7.10-7.42 (m, 5 H, Ph), 7.54 (d, 2 H, J = 9 Hz, Ph), 8.22 (d, 2 H, J = 9 Hz, Ph), 11.05 (s, 1 H, NH, D_2O-exch), 12.89 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.06 (Me), 115.72, 119.58, 124.08, 125.77, 129.08, 136.75, and 162.52 (Ph), 119.66 (C4), 142.27 (Ph or C3), 142.72 (C3 or Ph), 146.07 (C=O), 155.88 (C5). Anal. Calcd for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.72; H, 3.91; N, 15.71.

Procedure for the synthesis of 4-methoxy- and 4-ethoxy-1*H*-pyrazol-5(2*H*)-ones 4e-h. To a magnetically stirred solution of sodium methoxide **2a** (1 mmol) or ethoxide **2c** (1 mmol) in methanol or ethanol (30% wt.), respectively, was added at room temperature a solution of azoalkene **1c-f** (1 mmol) dissolved in methanol (6 ml) or ethanol (6 ml), respectively. The azoalkene **1** rapidly disappeared (0.1 h) (checked by TLC) and the reaction mixture was acidified by addition of trifluoroacetic acid (2 mmol). After evaporation of solvent under reduced pressure, products **4e-h** were obtained by flash chromatography separation on a silica gel column (elution with ethyl acetate-cyclohexane mixtures). Products **4e** and **4g-h** were recrystallized from ethyl acetate, while product **4f** from methanol.

1-(Aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4e): mp 131-132 °C; IR ν_{max} 3360, 3080, 1690, 1625, 1560, 1400, 1375, 1290 cm^{-1}; ^1H NMR δ 2.08 (s, 3 H, Me), 3.66 (s, 3 H, OMe), 7.78, 8.22 (2 s, 2 H, NH_2, D_2O-exch) 11.34 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 8.98 (Me), 60.05 (OMe), 126.78 (C4), 140.40 (C3), 149.22 (C=O), 157.26 (C5). Anal. Calcd for $C_6H_9N_3O_3$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.31; H, 5.37; N, 24.41.

1-(Anilinocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4f): mp 158-160 °C; IR ν_{max} 3200, 1730, 1640, 1570, 1380, 1360, 1295 cm^{-1}; ^1H NMR δ 2.14 (s, 3 H, Me), 3.72 (s, 3 H, OMe), 7.08-7.56 (m, 5 H, Ph), 11.20 (s, 1 H, NH, D_2O-exch), 12.01 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.03 (Me), 60.16 (OMe), 119.87, 123.95, 129.06 and 136.93 (Ph), 126.60 (C4), 141.32 (C3), 146.30 (C=O), 157.47 (C5). Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.41; H, 5.28; N, 16.78.

1-(Aminocarbonyl)-3-methyl-4-ethoxy-1*H*-pyrazol-5(2*H*)-one (4g): mp 132-135 °C; IR ν_{max} 3350, 3180, 1715, 1660, 1585, 1375, 1350, 1290 cm^{-1}; ^1H NMR δ 1.19 (t, 3 H, J = 7 Hz, OCH_2Me), 2.09 (s, 3 H, Me), 3.92 (q, 2 H, J = 7 Hz, OCH_2Me), 7.77, 8.26 (2 s, 2 H, NH_2, D_2O-exch.), 11.45 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.02 (Me), 15.02 (Me), 67.74 (OCH_2), 125.22 (C4), 140.93 (C3), 149.17 (C=O), 157.48 (C5). Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.63; H, 6.21; N, 22.61.

1-(Anilinocarbonyl)-3-methyl-4-ethoxy-1*H*-pyrazol-5(2*H*)-one (4h): mp 128-129 °C; IR ν_{max} 3240, 1700, 1650, 1600, 1565, 1375, 1290 cm^{-1}; ^1H NMR δ 1.22 (t, 3 H, J = 7 Hz, OCH_2Me), 2.15 (s, 3 H, Me), 3.97 (q, 2 H, J = 7 Hz, OCH_2Me), 7.10-7.57 (m, 5 H, Ph), 11.24 (s, 1 H, NH, D_2O-exch), 11.98 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.05 (Me), 15.02 (Me), 67.79 (OCH_2), 119.52, 123.94, 129.07 and 136.90 (Ph), 125.06 (C4), 141.96 (C3), 146.30 (C=O), 157.52 (C5). Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.53; H, 5.82; N, 16.11.

Procedure for the synthesis of 4-phenoxy-1*H*-pyrazol-5(2*H*)-ones 4i-j. To a magnetically stirred solution of sodium phenoxide trihydrate **2d** (1mmol) in tetrahydrofuran (3 ml) was added at 0-5 °C a solution of azoalkene **1e-f** (1mmol) dissolved in tetrahydrofuran (3 ml). The azoalkene **1** rapidly disappeared (0.1 h) (checked by TLC) and the reaction mixture was acidified by addition of trifluoroacetic acid (2 mmol). After evaporation of solvent under reduced pressure, products **4i-j** were obtained by flash chromatography separation on a silica gel column (elution with ethyl acetate-cyclohexane mixtures) and were recrystallized from ethyl acetate.

1-(Aminocarbonyl)-3-methyl-4-phenoxy-1*H*-pyrazol-5(2*H*)-one (4i): mp 169-171 °C; IR ν_{max} 3340, 3220, 1730, 1640, 1565, 1375, 1340, 1300 cm^{-1}; ^1H NMR δ 2.08 (s, 3 H, Me), 6.93-7.34 (m, 5 H, OPh), 7.89, 8.19 (2 s, 2 H, NH_2, D_2O-exch), 12.17 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.05 (Me), 114.78, 121.99, 129.47 and 157.77 (Ph), 120.71 (C4), 142.12 (C3), 148.97 (C=O), 156.46 (C5). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.53; H, 4.82; N, 18.19.

1-(Anilinocarbonyl)-3-methyl-4-phenoxy-1*H*-pyrazol-5(2*H*)-one (4j): mp 163-164 °C; IR ν_{max} 3240, 1730, 1640, 1600, 1575, 1545, 1370, 1295 cm^{-1}; ^1H NMR δ 2.14 (s, 3 H, Me), 6.99-7.59 (m, 10 H, OPh and Ph), 11.13 (s, 1 H, NH, D_2O-exch), 11.33 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 9.17 (Me), 114.88, 119.56, 122.15, 124.03, 129.08, 129.49, 136.80 and 157.68 (Ph), 120.60 (C4), 143.08 (C3), 146.18 (C=O), 156.68 (C5). Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 66.18; H, 4.73; N, 13.42.

Procedure for the synthesis of 4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-ones 4k-n. To a magnetically stirred solution of ethyl 2-mercaptoacetate **2e** (1 mmol) in tetrahydrofuran (3 ml) was added at room temperature a solution of azoalkene **1a-c,f** (1 mmol) dissolved in tetrahydrofuran (3 ml). The reaction was continued until the azoalkene **1** disappeared (2.0-15.0 h) (checked by TLC) and then sodium hydride (1 mmol) was added at the same temperature. The reaction mixture was acidified by addition of trifluoroacetic acid (2 mmol) and, after evaporation of solvent under reduced pressure, products **4k-n** were obtained by

chrmatography separation on a silica gel column (elution with ethyl acetate-cyclohexane mixtures) and were recrystallized from ethyl acetate/petroleum ether (40-60 °C).

1-(Methoxycarbonyl)-3-methyl-4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-one (4k): mp 141-143 °C; IR ν_{max} 3400, 1765, 1710, 1630, 1400, 1375, 1300 cm^{-1}; ^1H NMR δ 1.12 (t, 3 H, J = 7 Hz, CO_2CH_2*Me*), 2.15 (s, 3 H, Me), 3.25 (s, 2 H, CH_2), 3.87 (s, 3 H, CO_2Me), 4.00 (q, 2 H, J = 7 Hz, CO_2*C*H_2Me), 12.30 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.36 (Me), 13.67 (Me), 35.45 (S-CH_2), 53.70 (OMe), 60.46 (OCH_2), 90.90 (C4), 148.52 (N-C=O), 156.36 (C3), 160.58 (C5), 169.36 (C=O). Anal Calcd for $C_{10}H_{14}N_2O_5$: C, 43.79; H, 5.14; N, 10.21. Found: C, 43.84; H, 5.28; N, 10.33.

1-(*t*-Buthoxycarbonyl)-3-methyl-4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-one (4l): mp 109-112 °C; IR ν_{max} 3420, 1760, 1720, 1630, 1375, 1320, 1300 cm^{-1}; ^1H NMR δ 1.13 (t, 3 H, J = 7 Hz, CO_2CH_2*Me*), 1.51 (s, 9 H, CO_2Bu^t), 2.15 (s, 3 H, Me), 3.25 (s, 2 H, CH_2), 4.00 (q, 2 H, J = 7 Hz, CO_2*C*H_2Me), 12.20 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 12.17 (Me), 13.80 (Me), 27.73 (*C*Me_3), 36.55 (S-CH_2), 60.45 (OCH_2), 82.71 (*C*Me_3), 89.76 (C4), 148.35 (N-C=O), 155.44 (C3), 160.78 (C5), 169.91 (C=O). Anal. Calcd for $C_{13}H_{20}N_2O_5S$: C, 49.35; H, 6.37; N, 8.85. Found: C, 49.42; H, 6.51; N, 8.79.

1-(Aminocarbonyl)-3-methyl-4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-one (4m): mp 142-144 °C; IR ν_{max} 3310, 3120, 1735, 1710, 1675, 1645, 1575, 1540, 1370 cm^{-1}; ^1H NMR δ 1.11 (t, 3 H, J = 7 Hz, CO_2CH_2*Me*), 2.17 (s, 3 H, Me), 3.26 (s, 2 H, CH_2), 4.00 (q, 2 H, J = 7 Hz, CO_2*C*H_2Me), 7.89, 8.20 (2 s, 2 H, NH_2, D_2O-exch), 12.97 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 10.82 (Me), 13.72 (Me), 35.51 (S-CH_2), 60.48 (OCH_2), 90.70 (C4), 148.99 (N-C=O), 153.06 (C3), 161.95 (C5), 169.39 (C=O). Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21. Found: C, 41.58; H, 5.17; N, 16.34.

1-(Anilinocarbonyl)-3-methyl-4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-one (4n): mp 143-145 °C; IR ν_{max} 3420, 3100, 1720, 1670, 1610, 1565, 1540, 1375 cm^{-1}; ^1H NMR δ 1.11 (t, 3 H, J = 7 Hz, CO_2CH_2*Me*), 2.23 (s, 3 H, Me), 3.31 (s, 2 H, CH_2), 4.02 (q, 2 H, J = 7 Hz, CO_2CH_2Me), 7.10-7.56 (m, 5 H, Ph), 11.19 (s, 1 H, NH, D_2O-exch), 13.27 (br s, 1 H, NH, D_2O-exch); ^{13}C NMR δ 11.06 (Me), 13.75 (Me), 35.75 (S-CH_2), 60.60 (OCH_2), 90.61 (C4), 120.12, 124.01, 129.10 and 136.94 (Ph), 146.44 (N-C=O), 154.14 (C3), 162.56 (C5), 169.48 (C=O). Anal. Calcd for $C_{15}H_{17}N_3O_4S$: C, 53.72; H, 5.11; N, 12.53. Found: C, 53.69; H, 5.18; N, 12.41.

Procedure for the synthesis of 4-methoxy-, 4-ethoxy-, 4-phenoxy-, 4-(4-nitrophenoxy), 4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-ones 5a-e. A solution of 1-substituted pyrazolone **4a-n** (1 mmol) in methanol (8 ml) was heated under reflux for 3.5-12.0 h until complete conversion into 1-unsubstituted pyrazolone **5a-e** was detected (checked by TLC). After evaporation of the solvent under reduced pressure, products **5a-b** were obtained by addition to the residue of ethyl ether/petroleum ether (40-60 °C), while probucts **5c-d** by addition of ethyl acetate/petroleum ether (40-60 °C).

3-Methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (5a): mp 188-119 °C; IR ν_{max} 3420, 2640, 1615, 1580, 1530, 1370 cm^{-1}; ^1H NMR δ 2.02 (s, 3 H, Me), 3.58 (s, 3 H, OMe), 10.23 (br s, 2 H, 2 NH, D_2O-exch); ^{13}C

NMR δ 8.71 (Me), 60.75 (OMe), 126.55 (C4), 128.47 (C3), 152.23 (C5). Anal. Calcd for $C_5H_8N_2O_2$: C 46.87; H, 6.29; N, 21.86. Found: C, 46.71; H, 6.31; N, 21.93.

3-Methyl-4-(4-nitrophenoxy)-1*H*-pyrazol-5(2*H*)-one (5b): mp 283-284 °C; IR ν_{max} 3440, 2640, 1610, 1590, 1510, 1370, 1340 cm^{-1}; ^1H NMR δ 2.00 (s, 3 H, Me), 7.08 (d, 2 H, J = 9 Hz, Ph), 7.72 (d, 2 H, J = 9 Hz, Ph), 10.79 (br s, 2 H, 2 NH, D_2O-exch); ^{13}C NMR δ 8.66 (Me), 115.40, 125.84, 141.78 and 163.66 (Ph), 119.57 (C4), 130.47 (C3), 151.80 (C5). Anal. Calcd for $C_{10}H_9N_3O_4$: C 51.07; H, 3.86; N, 17.87. Found: C, 51.18; H, 3.91; N, 17.73.

3-Methyl-4-ethoxy-1*H*-pyrazol-5(2*H*)-one (5c): mp 166-168 °C; IR ν_{max} 3340, 2660, 1620, 1590, 1510, 1370 cm^{-1}; ^1H NMR δ 1.16 (t, 3 H, J = 7 Hz, $OCH_2\mathit{Me}$), 2.01 (s, 3 H, Me), 3.80 (q, 2 H, J = 7 Hz, $OC\mathit{H}_2Me$), 10.17 (br s, 2 H, 2 NH, D_2O-exch); ^{13}C NMR δ 8.69 (Me), 15.12 (Me), 68.23 (OCH_2), 124.67 (C4), 128.67 (C3), 152.41 (C5). Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.53; H, 7.14; N, 19.83.

3-Methyl-4-phenoxy-1*H*-pyrazol-5(2*H*)-one (5d): mp 213-215 °C; IR ν_{max} 3430, 2610, 1620, 1590, 1520, 1370 cm^{-1}; ^1H NMR δ 1.97 (s, 3 H, Me), 6.84-7.31 (m, 5 H, OPh), 10.54 (br s, 2 H, 2 NH, D_2O-exch); ^{13}C NMR δ 8.68 (Me), 114.64, 121.32, 129.28 and 158.64 (Ph), 120.24 (C4), 130.32 (C3), 152.28 (C5). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.09; H, 5.41; N, 14.92.

3-Methyl-4-((ethyl acetate)-2-thio)-1*H*-pyrazol-5(2*H*)-one (5e). mp 167-169 °C; IR ν_{max} 3440, 2650, 1730, 1610, 1580, 1550, 1375 cm^{-1}; ^1H NMR δ 1.12 (t, 3 H, J = 7 Hz, $CO_2CH_2\mathit{Me}$), 2.10 (s, 3 H, Me), 3.22 (s, 2 H, CH_2), 4.00 (q, 2 H, J = 7 Hz, $CO_2\mathit{CH}_2Me$), 10.90 (br s, 2 H, 2 NH, D_2O-exch); ^{13}C NMR δ 10.01 (Me), 13.74 (Me), 37.17 (S-CH_2), 60.41 (OCH_2), 89.37 (C4), 143.91 (C3), 161.85 (C5), 169.67 (C=O). Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.52; H, 5.63; N, 12.83.

Method for DIS_A/DIS_B measurement. The chemical shifts of a carbon in the protium (δ_H) and the deuterium isotopomers (δ_D) were identified on the basis of the intensity of the signals corroborated with the deuteration ratio [ρ=D/(H+D)] measured in the proton spectrum. DIS due to the proton displaying the sharp signal were calculated as $DIS_A=\delta_H-\delta_D$. DIS due to the proton displaying the broad signal were calculated using the formula $DIS_B=(\delta_C-\delta_H)/\rho$, were δ_C is the chemical shift of the corresponding carbon in a non-deuterated sample. Measurements of DIS using two different solutions for the protium and the deuterium isotopomers are normally less reliable, due to the dependence of chemical shifts on concentration and therefore we used in our measurements only saturated solutions. The chemical shifts were referred to the signal of $CDCl_3$ (77.000 ppm), which had to be kept in the spectral window, reducing thus the digital resolution to 8 ppb.

X-ray Analysis of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4e). Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-Ka radiation, $\omega/2\vartheta$ scan mode, range 2.94°<ϑ<24.99°. The unit cell parameters were determined by least-squares refinement on diffractometer angles for 25 automatically centered reflections 7.50°<ϑ<16.81°.

Crystal data of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4e). $C_6H_9N_3O_3$; mol. wt. 171.2; monoclinic; space group $P2_1/n$; a = 7.711(2) Å, b = 7.301(5) Å, c = 13.868(6) Å, β = 92.55(3)°, U = 779.9(7) Å^3, Z = 4, D_c = 1.458 Mg/m^3, F(000) = 360, λ = 0.71069 Å, T = 298 K; μ(Mo-Kα) = 0.11 mm^{-1}. Of 1382 independent reflections [R(int) = 0.0462], 1046 having I>2σ(I) were considered observed.

Structure determination and refinement of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (4e). The structure was solved by direct method, and refined by full-matrix least-squares on F^2 using the SHELX program packages.[24] In refinements were used weights in accordance with the scheme $w = 1/[\sigma^2(F_o^2) + (0.0872P)^2 + 0.7438P]$ where $P = (F_o^2 + 2F_c^2)/3$. All the hydrogen atoms were revealed on the Fourier difference maps, but not refined. The final agreement indices were $R_1 = 0.0585$ and $wR_2 = 0.1659$. Goodness of fit on $F^2 = 1.086$. Largest difference peak and hole was 0.751 and -0.321 eÅ^{-3}.

X-ray Analysis of 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (5a). Intensity data were collected with on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-Kα radiation, ω/2ϑ scan mode, range 2.62°<ϑ<24.96°. The unit cell parameters were determined by least-squares refinement on diffractometer angles for 25 automatically centered reflections 7.81°<ϑ<13.78°.

Crystal data of 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (5a). $C_5H_6N_2O_2$; mol. wt. 126.1; monoclinic; space group $P2_1/c$; a = 8.077(2) Å, b = 6.972(1) Å, b = 11.114(4) Å, β = 105.94(2)°, U = 601.8(3) Å^3, Z = 4, D_c = 1.39 Mg/m^3, F(000) = 264, λ = 0.71069 Å , T = 298 K, μ(Mo-Kα) = 0.110 mm^{-1}. Of 1062 indipendent reflections [R(int) = 0.0109], 838 having I>2σ(I) were considered observed.

Structure determination and refinement of 3-methyl-4-methoxy-1*H*-pyrazol-5(2*H*)-one (5a). The structure was solved by direct method, and refined by full-matrix least-squares on F^2 using the SHELX program packages.[24] In refinements were used weights in accordance with the scheme $w = 1/[\sigma^2(F_o^2) + (0.0661P)^2 + 0.2525P]$ where $P = (F_o^2 + 2F_c^2)/3$. All the hydrogen atoms were revealed on the Fourier difference maps, but not refined. The final agreement indices were $R_1 = 0.0434$, $wR_2 = 0.1127$. Goodness of fit on $F^2 = 1.129$. Largest difference peak and hole was 0.241 and -0.319 eÅ^{-3}.

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18. The MMX force field is an improved version of MM2. In this force field the VESCF pi routine from MMPI and the concept of generalized parameters from C. Still are added.
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