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Synthesis and Reactions of Some Nitrone Derivatives

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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: Arylnitroso compounds easily react as nucleophiles with conjugated azoalkenes to give α-(arylimino-*N*-oxide)hydrazones by their 1,4-addition to the azo-ene system. These adducts undergo an internal heterocyclization process with pyrazole ring formation to produce 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones stereoselectively in *Z* form by loss of an alcohol molecule. Deoxygenation of these compounds with triphenylphosphine affords 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones. Basic treatment with triethylamine of the same compounds leads to 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones by removal of the substituents on N(1) heteroatom of the pyrazole ring. Both deoxygenation and basic treatment of 1-alkoxycarbonyl- and 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones have been realized sequentially, providing 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones. The same products were succesfully obtained by reversing the order of these processes.

INTRODUCTION

During the last few years, nitrones have been subjected to increasing attention as they are very important synthetic tools in organic chemistry. In fact, numerous reports dealing with their preparations and reactions have appeared, especially concerning 1,3-dipolar cycloadditions.[1] These reagents are mainly prepared by oxidation of imines or by dehydrogenation of hydroxylamine or related methods,[2] and are used in the preparation of various products *e.g.* heterocycles, carbohydrates, amino acids, and alkaloids.[1-3]

Conjugated azoalkenes are interesting materials known to be particularly active towards nucleophilic agents. They give firstly hydrazonic derivatives by 1,4-conjugated addition of such reagents to the azo-ene system and then polysubstituted pyrrole and pyrazole rings by internal cyclization.[4]

Nitroso derivatives exhibit different chemical properties. Sometimes, they serve as electrophiles *i.e.* in condensation reactions with compounds containing activated methylene groups (Ehrlich-Sachs reaction).[5] Sometimes, nitroso compounds act in an ambiphilic way, *i.e.* in the dimerization process where the nitrogen atom of a nitroso group attacks as a nucleophile and the nitrogen atom of another nitroso group as an electrophile.[6] In other reactions the nitroso nitrogen behaves as a nucleophile with formaldehyde, glyoxylic acid, and pyruvic acid.[7] In other cases, the nitroso group is used as an efficient dienophile moiety in hetero Diels-Alder reactions.[8]

Our efforts have been thus directed to the investigation of the reaction between conjugated azoalkenes and arylnitroso compounds in an attempt to find a new and convenient entry to useful nitrone derivatives. Although conjugated azoalkenes are also described as effective substrates able to undergo [2+2]-, [3+2]-, as well as [4+2]-cycloadditions,[4,9] we have never observed, to a significant extent, such behaviour in our reaction conditions.

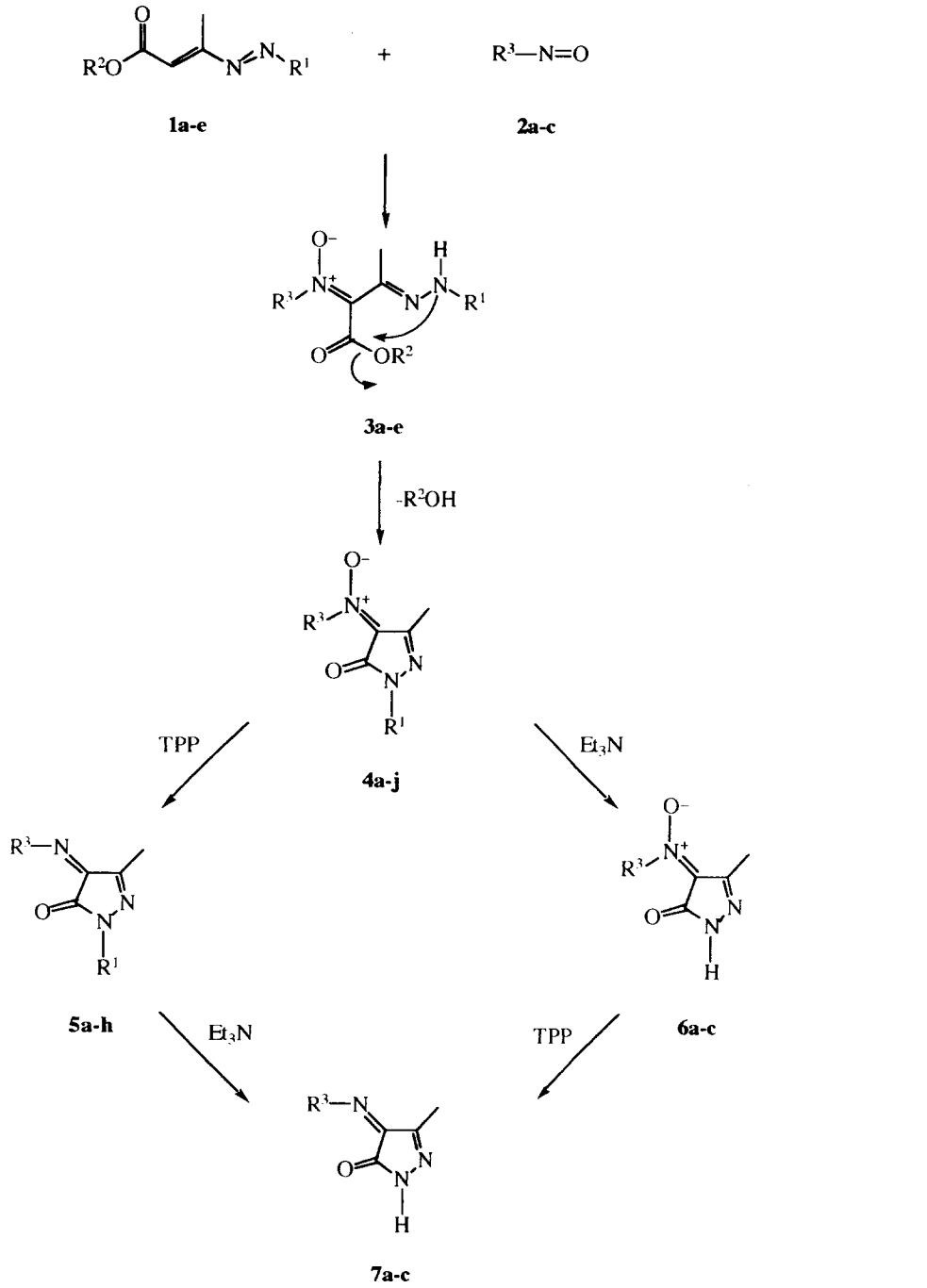
We now report a simple one-flask method for the synthesis of interesting nitrone derivatives, in some of which the carbon atom in α-position is a member of a pyrazole ring. In fact, the reaction between conjugated azoalkenes and arylnitroso compounds affords first α-(arylimino-*N*-oxide)hydrazones and then 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones stereoselectively in *Z* form. The successive deoxygenation of these latter products with triphenylphosphine gives 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones, while the independent basic treatment with triethylamine of 1-alkoxycarbonyl- or 1-aminocarbonyl-group of the same materials provides 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones by removal of the substituents present on the N(1) heteroatom of the pyrazole ring. The consecutive execution of both the above-mentioned reactions leads to 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones, with analogous success even by inversion of the order of these processes.

RESULTS AND DISCUSSION

Conjugated azoalkenes **1a-e** react with arylnitroso compounds **2a-c** in methanol at room temperature to form the relevant α-(arylimino-*N*-oxide)hydrazone intermediates that directly cyclize to 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **4a-j** in overall good to excellent yields (see Scheme and Table 2). When the reaction between conjugated azoalkenes **1a-e** and *N*,*N*-dimethyl-4-nitrosoaniline **2c** is carried out in benzene, only the corresponding α-(arylimino-*N*-oxide)hydrazones **3a-e** are recovered in high yields. Yields, melting points, and reaction times of α-(arylimino-*N*-oxide)hydrazones **3a-e** are listed in Table 1.

Table 1. Yields, melting points, and reaction times of α-(arylimino-*N*-oxide)hydrazones **3a-e**.

Azoalkene **1**	R^1	R^2	Arylnitroso **2**	R^3	Hydrazone **3**	Yields (%)	Mps (°C)	Reaction Times (h)
1a	COOMe	Et	**2c**	4-$Me_2NC_6H_4$	**3a**	68	168-173	10
1b	COOEt	Et	**2c**	4-$Me_2NC_6H_4$	**3b**	65	120-121	3
1c	$COOBu^t$	Me	**2c**	4-$Me_2NC_6H_4$	**3c**	78	140-142	28
1d	$CONH_2$	Me	**2c**	4-$Me_2NC_6H_4$	**3d**	88	151-154	30
1e	CONHPh	Me	**2c**	4-$Me_2NC_6H_4$	**3e**	88	175-177	4



Scheme

The mechanism of this reaction clearly implies the nucleophilic attack by the nitroso nitrogen of the arylnitroso reagents on the azo-ene moiety of conjugated azoalkenes, resulting in a Michael-type addition of these reagents to the heterodiene system with production of α-(arylimino-*N*-oxide)hydrazone derivatives. As a second step, an internal nucleophilic attack by the >C=N-NH nitrogen atom to the ester function in the β-position determines the heterocyclization process with pyrazole ring formation. The successive elimination of an alcohol molecule gives the final 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-one **4a-j**. Yields, melting points, and reaction times of 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **4a-j** are listed in Table 2.

Table 2. Yields, melting points, and reaction times of 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **4a-j**.

Azoalkene	R^1	R^2	Arylnitroso	R^3	Pyrazolone	Yields	Mps	Reaction Times
1			**2**		**4**	(%)	(°C)	(h)
1a	COOMe	Et	**2a**	C_6H_5	**4a**	55	160-162	7
1a	COOMe	Et	**2c**	4-$Me_2NC_6H_4$	**4b**	75	183-185	2
1b	COOEt	Et	**2a**	C_6H_5	**4c**	65	172-175	8
1b	COOEt	Et	**2c**	4-$Me_2NC_6H_4$	**4d**	75	163-166	1
1c	$COOBu^t$	Me	**2a**	C_6H_5	**4e**	56	132-135	7
1c	$COOBu^t$	Me	**2c**	4-$Me_2NC_6H_4$	**4f**	70	163-165	2
1d	$CONH_2$	Me	**2b**	2-MeC_6H_4	**4g**	52	148-150	11
1d	$CONH_2$	Me	**2c**	4-$Me_2NC_6H_4$	**4h**	98	162-164	2
1e	CONHPh	Me	**2b**	2-MeC_6H_4	**4i**	54	160-162	11
1e	CONHPh	Me	**2c**	4-$Me_2NC_6H_4$	**4j**	93	208-209	20

The easy deoxygenation of 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **4a-f,h,j** takes place rapidly with triphenylphosphine in methanol at room temperature, affording 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **5a-h** in good yields. In the cases of **4g** and **4i**, complicated reaction mixtures were observed. Yields, melting points, and reaction times of 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **5a-h** are listed in Table 3.

3-Methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **6a-c** are isolated in nearly quantitative yields by treatment of 1-methoxycarbonyl-3-methyl-4-(phenylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-one **4a** and 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **4g** and **4h**, respectively, with triethylamine in methanol under reflux. These products arise as a consequence of the basic cleavage of the R^1 group present on the N(1) heteroatom of the pyrazole ring. Yields, melting points, and reaction times of 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **6a-c** are listed in Table 4.

The structures of the 4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **4a-j** and **6a-c** were assigned by spectral methods on the pure isolated products. In particular, the presence in the mass spectrum of each

compound of the $(M-16)^+$ ion in very high relative abundance is characteristic of nitrones and represents the most convincing evidence for the structure. The assignment of stereochemistry to the compounds **4a-j** were based upon a comparison of the chemical shift values with those exhibited from the relevant deoxygenated compounds **5a-h**. In particular, the ^{1}H-NMR spectra of the nitrones **4a-j** show only a neat singlet ascribable to the methyl group in the position 3 of the pyrazole ring at a field lower than that of the same signal in the corresponding deoxygenated compounds **5a-h**. This occurrence is clearly imputable to the deshielding effect of the nitrone oxygen. These spectral evidences support the *Z* configuration of the compounds **4a-j**, while *E* isomers of the same compounds are not detected in these reactions.

Indeed, compounds similar to those reported here have previously been prepared by the reaction between nitroso aromatics and pyrazol-5-ones.[10] However, the procedure reported here represents a ready one-pot method that permits the direct synthesis of heterocyclic nitrone derivatives starting from acyclic precursors.

Table 3. Yields, melting points, and reaction times of 1-alkoxycarbonyl- or 1-aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **5a-h**.

Pyrazolone **4**	R^1	R^3	Pyrazolone **5**	Yields (%)	Mps (°C)	Reaction Times (h)
4a	COOMe	C_6H_5	**5a**	50	110-112	2
4b	COOMe	4-$Me_2NC_6H_4$	**5b**	88	138-140	0.4
4c	COOEt	C_6H_5	**5c**	52	122-124	2
4d	COOEt	4-$Me_2NC_6H_4$	**5d**	90	149-151	0.4
4e	COOBu^t	C_6H_5	**5e**	55	135-136	2
4f	COOBu^t	4-$Me_2NC_6H_4$	**5f**	92	160-161	0.4
4h	$CONH_2$	4-$Me_2NC_6H_4$	**5g**	90	167-169	0.4
4j	CONHPh	4-$Me_2NC_6H_4$	**5h**	95	218-220	0.4

Table 4. Yields, melting points, and reaction times of 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **6a-c**.

Pyrazolone **4**	R^1	R^3	Pyrazolone **6**	Yields (%)	Mps (°C)	Reaction Times (h)
4a	COOMe	C_6H_5	**6a**	90	165-167	0.3
4g	$CONH_2$	2-MeC_6H_4	**6b**	88	121-123	0.3
4h	$CONH_2$	4-$Me_2NC_6H_4$	**6c**	98	190-192	3

3-Methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **7a-c** were obtained by two different pathways. 3-Methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones **6a-c** were reacted with triphenylphosphine in methanol at room temperature to afford 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **7a-c**, or 1-methoxycarbonyl- and 1-

aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(2*H*)-ones **5a** and **5g** were heated with triethylamine in methanol under reflux to form in high yields 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **7a** and **7c**, respectively. Yields, melting points, and reaction times of 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **7a-c** are listed in Table 5.

Although both sequences are satisfactory, the pathway involving the preliminary basic treatment followed by deoxygenation (route **4-6-7**) is more convenient than the other (route **4-5-7**), both in terms of smoothness and yields. Finally, it is noteworthy that 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **5** and **7** are attractive products and versatile intermediates mainly because of the presence of a heterodienic system capable of making these molecules suitable for further organic transformation *i.e.* by means of Michael-like or hetero Diels-Alder type reactions.[8,11]

In conclusion, we report here an interesting study of the reaction between conjugated azoalkenes and arylnitroso compounds where the nitroso nitrogen acts as a nucleophile. Conjugated azoalkenes are readily synthesised and nitroso aromatics are commercial materials.

Table 5. Yields, melting points, and reaction times of 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones **7a-c**.

Pyrazolone **5** or **6**	R^1	R^3	Pyrazolone **7**	Yields (%)	Mps (°C)	Reaction Times (h)
5a	COOMe	C_6H_5	**7a**	80	165-167	7
6a	H			84		3
6b	H	2-MeC_6H_4	**7b**	85	170-172	4
5g	$CONH_2$	4-$Me_2NC_6H_4$	**7c**	88	197-199	6
6c	H			91		0.4

Unknown and useful α-(arylimino-*N*-oxide)hydrazones, as pyrazole and nitrone derivatives have been synthesised. Simple procedures for deoxygenation and/or basic treatment of these latter products permit access to unusual aryliminopyrazolones. Mild reaction conditions have generally been used and all products obtained are susceptible to further transformations. Therefore, the above-described reactions are significant in terms of both reactivity and preparation.

EXPERIMENTAL

Alkoxycarbonylazoalkenes (**1a-c**)[12] and aminocarbonylazoalkenes (**1d-e**)[13] were synthesized as previously reported. Nitrosobenzene (**2a**), 2-nitrosotoluene (**2b**), and *N*,*N*-dimethyl-4-nitrosoaniline (**2c**) were commercial materials (Aldrich) 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 5995 C spectrometer. Elemental analyses were performed with a Fisons EA 1108 instrument. ^{1}H-NMR spectra at 60 MHz were recorded on Varian EM 360 L, while ^{1}H- and ^{13}C-NMR spectra at 200 MHz were recorded on Bruker AC 200 spectrometers and performed in $CDCl_3$ or in DMSO-d_6. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (J) 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 ex, D_2O exchange. Densitometric analysis was made with a Scanning Densitometer Shimadzu CS-9000. Macherey-Nagel precoated silica gel SIL G-25UV$_{254}$ plates (0.25 mm) were employed for analytical thin layer chromatography (TLC) and silica gel Amicon LC 60 Å (35-70 mμ) for column chromatography. All new compounds showed satisfactory elemental analysis (C ±0.35, H ±0.30, N ±0.30).

General procedure for the synthesis of α-(arylimino-*N*-oxide)hydrazones (3a-e).

To a stirred solution of conjugated azoalkene **1a-e** (2 mmol) in benzene (5 ml) was added dropwise *N*,*N*-dimethyl-4-nitrosoaniline **2c** (1mmol) in benzene (5 ml). The mixture was stirred at room temperature (except for the formation of hydrazone **3d** where the reaction was heated under reflux) for the time reported in Table 1, left overnight and the products **3a-e** precipitated out in adequate purity as pale green solids. Yields and melting points are reported in Table 1.

Compound (3a).

IR: 3230, 3160, 1725, 1695, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.00 (t, 3H, J=7.0 Hz, Me), 2.13 (s, 3H, Me), 2.97 (s, 6H, NMe_2), 3.66 (s, 3H, OMe), 4.02 (q, 2H, J=7.0 Hz, OCH_2), 6.69 (d, 2H, J=9.4 Hz, Ar), 7.29 (d, 2H, J=9.4 Hz, Ar), 10.52 (bs, 1H, NH, D_2O ex).^{13}C-NMR (DMSO-d_6): δ 13.4 (Me), 14.2 (Me), 39.7 (NMe_2), 52.0 (OMe), 61.3 (OCH_2), 110.9, 124.0, 124.9 and 136.3 (Ar), 145.0, 151.7, 153.9, 162.7. MS: m/z (%) = 350 (20) [M$^+$], 335 (35), 289 (100), 275 (19), 247 (30), 231 (33). Anal. Calcd. for $C_{16}H_{22}N_4O_5$: C, 54.85; H, 6.33; N, 15.99. Found: C, 54.68; H, 6.45; N, 15.91.

Compound (3b).

IR: 3230, 3140, 1735, 1695, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.01 (t, 3H, J=7.0 Hz, Me), 1.22 (t, 3H, J=7.0 Hz, Me), 2.14 (s, 3H, Me), 2.97 (s, 6H, NMe_2), 4.02 (q, 2H, J=7.0 Hz, OCH_2), 4.14 (q, 2H, J=7.0 Hz, OCH_2), 6.69 (d, 2H, J=9.1 Hz, Ar), 7.30 (d, 2H, J=9.1 Hz, Ar), 10.49 (bs, 1H, NH, D_2O ex).^{13}C-NMR (DMSO-d_6): δ 13.4 (Me), 14.1 (Me), 14.3 (Me), 39.8 (NMe_2), 60.7 (OCH_2), 61.3 (OCH_2), 110.9, 124.6, 125.3 and 136.9 (Ar), 144.1, 151.9, 152.3, 162.9. MS: m/z (%) = 364 (6) [M$^+$], 348 (15), 318 (24), 303 (100), 287 (5). Anal. Calcd. for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 56.10; H, 6.37; N, 15.52.

Compound (3c).

IR: 3260, 3160, 1735, 1685, 1595 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.45 (s, 9H, Bu^t), 2.13 (s, 3H, Me), 2.97 (s, 6H, NMe_2), 3.55 (OMe), 6.69 (d, 2H, J=9.1 Hz, Ar), 7.29 (d, 2H, J=9.1 Hz, Ar), 10.22 (bs, 1H, NH, D_2O ex).^{13}C-NMR (DMSO-d_6): δ 14.2 (Me), 27.9 (C<u>Me</u>$_3$), 39.7 (NMe_2), 52.4 (OMe), 79.9 (<u>C</u>Me$_3$), 111.0, 123.9, 124.9 and 136.3 (Ar), 144.3, 151.6, 152.3, 163.5. MS: m/z (%) = 378 (5) [M$^+$], 363 (27), 347 (7), 331 (16), 261 (50), 232 (60), 200 (65), 173 (100). Anal. Calcd. for $C_{18}H_{26}N_4O_5$: C, 57.13; H, 6.93; N, 14.81. Found: C, 57.27; H, 6.78; N, 15.01.

Compound (3d).

IR: 3470, 3190, 3090, 1730, 1685, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, Me), 2.98 (s, 6H, NMe_2), 3.58 (s, 3H, OMe), 6.32 (bs, 2H, NH_2, D_2O ex), 6.69 (d, 2H, J=9.1 Hz, Ar), 7.29 (d, 2H, J=9.1 Hz, Ar), 9.84 (bs, 1H, NH, D_2O ex).^{13}C-NMR (DMSO-d_6): δ 13.8 (Me), 39.7 (NMe_2), 52.5 (OMe), 110.7, 123.7, 124.7 and 136.4 (Ar), 140.6, 151.6, 155.9, 163.5. MS: m/z (%) = 321 (5) [M^+], 290 (6), 246 (11), 237 (12), 230 (100). Anal. Calcd. for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.68; H, 5.55; N, 21.91.

Compound (3e).

IR: 3395, 3205, 3090, 1715, 1705, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.18 (s, 3H, Me), 2.99 (s, 6H, NMe_2), 3.61 (s, 3H, OMe), 6.50-7.55 (m, 9H, Ar), 8.59 (bs, 1H, NH, D_2O ex), 10.23 (bs, 1H, NH, D_2O ex).^{13}C-NMR (DMSO-d_6): δ 14.0 (Me), 39.6 (NMe_2), 52.6 (OMe), 110.9, 119.7, 124.0, 124.7, 128.6, 136 and 138.4 (Ar), 142.1, 152.1, 152.5, 164.0. MS: m/z (%) = 397 (2) [M^+], 381 (2), 261 (24), 232 (18), 200 (20), 173 (33), 119 (100). Anal. Calcd. for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N, 17.62. Found: C, 60.68; H, 5.65; N, 17.81.

General procedure for the synthesis of 1-alkoxycarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (4a-f) and 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (4g-j).

To a stirred solution of azoalkene **1a-e** (2 mmol) in methanol (5 ml) was added arylnitroso derivative **2a-c** (1 mmol) in methanol (5ml). The reaction mixture was stirred at room temperature for the times reported in Table 2 until conjugated azoalkene completely disappeared (monitored by silica gel TLC). The solvent was evaporated under reduced pressure and the products **4a-j** were purified by chromatography on a silica gel column (elution with cyclohexane-ethyl acetate mixtures). The products were further purified by crystallization from ethyl acetate-petroleum ether (30-60 °C). For the preparation of products **4g** and **4i**, benzene was used as solvent instead of methanol and the reactions were heated under reflux. Yields and melting points of pure isolated products are reported in Table 2.

Compound (4a).

IR: 1765, 1690, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.58 (s, 3H, Me), 3.97 (s, 3H, OMe), 7.35-7.70 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$): δ 16.8 (Me), 54.2 (OMe), 123.7, 129.2, 132.5 and 133.4 (Ph), 146.0, 148.0, 149.2 155.1. MS: m/z (%) = 261 (53) [M^+], 245 (64), 200 (10), 130 (100). Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 54.98; H, 4.45; N, 15.93.

Compound (4b).

IR: 1770, 1670, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.50 (s, 3H, Me), 3.14 (s, 6H, NMe_2), 3.98 (s, 3H, OMe), 6.64 (d, 2H, J=9.2 Hz, Ar), 7.63 (d, 2H, J=9.2 Hz, Ar).^{13}C-NMR ($CDCl_3$): δ 16.5 (Me), 40.3 (NMe_2), 54.0 (OMe), 110.6, 127.6, 129.4 and 134.3 (Ar), 147.3, 148.4, 154.1, 155.7. MS: m/z (%) = 305 (15) [M^+], 289 (100), 231 (9), 173 (50), 136 (46). Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.38; H, 5.45; N, 18.31.

Compound (4c).
IR: 1770, 1690, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, J=7.0 Hz, Me), 2.57 (s, 3H, Me), 4.44 (q, 2H, J=7.0 Hz, OCH_2), 7.35-7.75 (m, 5H, Ph). ^{13}C-NMR ($CDCl_3$): δ 14.2 (Me), 16.8 (Me), 63.8 (OCH_2), 123.7, 129.2, 132.4 and 136.8 (Ar), 146.0, 147.8, 148.7, 155.1. MS: m/z (%) = 275 (18) [M^+], 259 (100), 186 (18), 130 (52). Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.37; H, 4.45; N, 15.51.

Compound (4d).
IR: 1770, 1710, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.26 (t, 3H, J=7.0 Hz, Me), 2.30 (s, 3H, Me), 3.10 (s, 6H, NMe_2), 4.27 (q, 2H, J=7.0 Hz, OCH_2), 6.75 (d, 2H, J=9.2 Hz, Ar), 7.63 (d, 2H, J=9.2 Hz, Ar). ^{13}C-NMR (DMSO-d_6): δ 13.9 (Me), 15.8 (Me), 39.7 (NMe_2), 62.3 (OCH_2), 110.4, 127.2, 129.4 and 134.2 (Ar), 147.8, 148.4, 153.9, 155.4. MS: m/z (%) = 319 (22) [M^+], 303 (100), 231 (15), 173 (60), 136 (50). Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.90; H, 5.55; N, 17.30.

Compound (4e).
IR: 1735, 1710, 1625 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.52 (s, 9H, Bu^t), 2.39 (s, 3H, Me), 7.50-7.65 (m, 5H, Ph). ^{13}C-NMR (DMSO-d_6): δ 16.3 (Me), 27.5 ($C\underline{Me}_3$), 83.2 ($\underline{C}Me_3$), 123.7, 128.8, 131.5 and 134.0 (Ph), 145.9, 146.5, 146.6, 154.7. MS: m/z (%) = 303 (18) [M^+], 287 (20), 230 (10), 203 (100), 186 (93). Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.15; H, 5.45; N, 13.98.

Compound (4f).
IR: 1770, 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.59 (s, 9H, Bu^t), 2.48 (s, 3H, Me), 3.12 (s, 6H, NMe_2), 6.63 (d, 2H, J=9.2 Hz, Ar), 7.60 (d, 2H, J=9.2 Hz, Ar). ^{13}C-NMR ($CDCl_3$): δ 16.5 (Me), 28.1 ($C\underline{Me}_3$), 40.2 (NMe_2), 84.2 ($\underline{C}Me_3$), 110.5, 127.4, 130.2 and 134.9 (Ar), 147.9, 148.6, 154.3, 155.9. MS: m/z (%) = 347 (20) [M^+], 331 (11), 246 (48), 230 (100). Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 58.70; H, 6.55; N, 15.97.

Compound (4g).
IR: 3450, 3390, 3180, 1740, 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.26 (s, 3H, Me), 2.61 (s, 3H, Me), 5.70 (bs, 2H, NH_2, D_2O ex), 7.15-7.60 (m, 4H, Ar). ^{13}C-NMR ($CDCl_3$): δ 16.4 (Me), 16.6 (Me), 123.2, 127.1, 131.1, 131.3, 131.7 and 135.1 (Ar), 145.9, 146.4, 149.3, 157.1. MS: m/z (%) = 260 (2) [M^+], 244 (2), 217 (100), 200 (95), 186 (24). Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.68; H, 4.45; N, 21.30.

Compound (4h).
IR: 3480, 3380, 3100, 1760, 1730, 1690, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3H, Me), 3.32 (s, 6H, NMe_2), 6.75 (d, 2H, J=9.3 Hz, Ar), 7.43 (bs, 1H, NH_2, D_2O ex), 7.47 (bs, 1H, NH_2, D_2O ex), 7.77 (d, 2H, J=9.3 Hz, Ar). ^{13}C-NMR (DMSO-d_6): δ 15.7 (Me), 39.8 (NMe_2), 110.4, 127.5, 129.8 and 134.3 (Ar), 146.2, 147.5, 154.1, 157.4. MS: m/z (%) = 289 (2) [M^+], 273 (5), 246 (25), 230 (100). Anal. Calcd. for $C_{13}H_{15}N_5O_3$: C, 53.97; H, 5.23; N, 24.21. Found: C, 54.18; H, 5.47; N, 24.51.

Compound (4i).

IR: 3240, 1745, 1695, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.28 (s, 3H, Me), 2.63 (s, 3H, Me), 7.00-7.65 (m, 9H, Ar), 9.55 (bs, 1H, NH, D_2O ex.). ^{13}C-NMR ($CDCl_3$): δ 16.5 (Me), 16.6 (Me), 120.3, 123.3, 124.5, 127.3, 129.0, 131.1, 131.3, 131.8, 135.3 and 136.7 (Ar), 145.9, 146.2, 146.4, 157.3. MS: m/z (%) = 336 (10) [M^+], 320 (8), 217 (14), 201 (28), 144 (32), 119 (100). Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.58; H, 4.56; N, 16.81.

Compound (4j).

IR: 3450, 3260, 1740, 1680, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.51 (s, 3H, Me), 3.19 (s, 6H, NMe_2), 6.55-7.75 (m, 9H, Ar), 10.15 (bs, 1H, NH, D_2O ex). ^{13}C-NMR ($CDCl_3$): δ 16.1 (Me), 40.3 (NMe_2), 110.6, 120.2, 124.1, 127.9, 129.0, 134.4 and 137.4 (Ar), 146.9, 147.1, 154.8, 158.1. MS: m/z (%) = 365 (2) [M^+], 350 (4), 336 (2), 246 (20), 230 (100). Anal. Calcd. for $C_{19}H_{19}N_5O_3$: C, 62.46; H, 5.24; N, 19.17. Found: C, 62.37; H, 5.43; N, 19.40.

Conversion of 1-alkoxycarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (4a-f) and 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (4h, 4j) into 1-alkoxycarbonyl- and 1-aminocarbonyl-3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones (5a-h).

To a stirred solution of 1-alkoxycarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-one **4a-f** or 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-one **4h**, **4j** (1 mmol) in methanol (10 ml) triphenylphosphine (1mmol) was added and the reaction mixture was stirred at room temperature for the times reported in Table 3. Then the solvent was evaporated under reduced pressure affording the crude products **5a-h** that were purified by crystallization from ethyl ether or ethyl acetate-petroleum ether (30-60 °C).

Compound (5a).

IR: 1735, 1650, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.35 (s, 3H, Me), 3.99 (s,3H, OMe), 7.40 (s, 5H, Ph). ^{13}C-NMR ($CDCl_3$): δ 12.3 (Me), 54.2 (OMe), 122.7, 128.7, 129.7 and 133.0 (Ph), 141.5 , 149 2 , 150.7 , 153.3. MS: m/z (%) = 246 (100) [M^+], 214 (15), 186 (45). Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.65; H, 4.75; N, 17.38.

Compound (5b).

IR: 1755, 1640, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.29 (s, 3H, Me), 3.19 (s, 6H, NMe_2), 4.01 (s, 3H, OMe), 6.70 (d, 2H, J=9.2 Hz, Ar), 8.28 (d, 2H, J=9.2 Hz, Ar). ^{13}C-NMR ($CDCl_3$): δ 12.6 (Me), 40.3 (NMe_2), 53.9 (OMe), 111.4, 134.2, 136.8 and 141.6 (Ar), 149.1, 154.0, 154.1, 155.0. MS: m/z (%) = 289 (100) [M^+], 230 (12), 173 (46). Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.10; H, 5.75; N, 19.70.

Compound (5c).

IR: 1740, 1640, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 1.24 (t, 3H, J=7.0 Hz, Me), 2.18 (s, 3H, Me), 4.18 (q, 2H, J=7.0 Hz, OCH_2), 7.15-7.52 (m, 5H, Ph). ^{13}C-NMR (DMSO-d_6): δ 16.4 (Me), 18.1 (Me), 58.8 (OCH_2), 108.0, 112.8, 114.1 and 116.3 (Ph), 140.8, 151.0, 153.7, 155.6. MS: m/z (%) = 259 (100) [M^+],

213 (5), 130 (45). Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.47; H, 4.75; N, 16.00.

Compound (5d).
IR: 1750, 1645, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.44 (t, 3H, J=7.0 Hz, Me), 2.29 (s, 3H, Me), 3.19 (s, 6H, NMe_2), 4.48 (q, 2H, J=7.0 Hz, OCH_2), 6.70 (d, 2H, J=9.2 Hz, Ar), 8.27 (d, 2H, J=9.2 Hz, Ar). ^{13}C-NMR (DMSO-d_6): δ 12.6 (Me), 14.4 (Me), 40.3 (NMe_2), 63.3 (OCH_2), 111.4, 134.2, 136.8 and 139.6 (Ar), 148.4, 153.9, 154.0, 154.1. MS: m/z (%) = 302 (100) [M^+], 257 (2), 230 (8), 173 (44). Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.70; H, 6.25; N, 18.71.

Compound (5e).
IR: 1750, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.58 (s, 9H, Bu^t), 2.31 (s, 3H, Me), 7.20-7.75 (m, 5H, Ph). ^{13}C-NMR (DMSO-d_6): δ 12.1 (Me), 27.6 ($C\underline{Me}_3$), 82.5 ($\underline{C}Me_3$), 111.4, 132.9, 135.3 and 138.4 (Ph), 140.5, 147.3, 152.8, 153.4. MS: m/z (%) = 287 (15) [M^+], 230 (100), 214 (5), 186 (40). Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.43; H, 6.15; N, 14.43.

Compound (5f).
IR: 1760, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.63 (s, 9H, Bu^t), 2.27 (s, 3H, Me), 3.17 (s, 6H, NMe_2), 6.69 (d, 2H, J=9.2 Hz, Ar), 7.25 (d, 2H, J=9.2 Hz, Ar). ^{13}C-NMR ($CDCl_3$): δ 12.6 (Me), 28.1 ($C\underline{Me}_3$), 40.2 (NMe_2), 83.9 ($\underline{C}Me_3$), 111.3, 133.8, 136.6 and 139.8 (Ar), 148.3, 153.7, 154.0, 154.1. MS: m/z (%) = 330 (13) [M^+], 230 (100), 174 (55). Anal. Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.57; H, 6.49; N, 17.26.

Compound (5g).
IR: 3480, 3360, 3195, 1760, 1705, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.13 (s, 3H, Me), 3.17 (s, 6H, NMe_2), 6.85 (d, 2H, J=9.5 Hz, Ar), 7.47 (bs, 2H. NH_2, D_2O ex), 8.12 (d, 2H, J=9.3 Hz, Ar). ^{13}C-NMR (DMSO-d_6): δ 12.0 (Me), 39.9 (NMe_2), 111.6, 133.4, 135.0 and 138.5 (Ar), 149.6, 151.7, 153.8, 154.9. MS: m/z (%) = 273 (2) [M^+], 246 (30), 231 (100), 216 (10). Anal. Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.33; H, 5.35; N, 25.85.

Compound (5h).
IR: 3460, 3190, 1725, 1670, 1620, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.31 (s, 3H, Me), 3.18 (s, 6H, NMe_2), 6.74 (d, 2H, J=9.5 Hz, Ar), 7.00-7.72 (m, 5H, Ar), 8.23 (d, 2H, J=9.5 Hz, Ar), 10.18 (bs, 1H, NH, D_2O ex). ^{13}C-NMR ($CDCl_3$): δ 12.5 (Me), 40.3 (NMe_2), 110.8, 111.8, 120.0, 124.0, 129.0, 134.5, 137.0 and 137.8 (Ar), 147.4, 153.8, 154.3, 155.8. MS: m/z (%) = 349 (7) [M^+], 299 (2), 230 (100). Anal. Calcd. for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04. Found: C, 65.62; H, 5.25; N, 20.31.

Conversion of 1-methoxycarbonyl-3-methyl-4-(phenylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-one (4a), 1-aminocarbonyl-3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (4g, 4h) into 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (6a-c).

Compounds **4a**, **4g** and **4h** (1 mmol) were dissolved in methanol (20 ml) and triethylamine (2mmol) was added. The reaction mixture was heated under reflux for the times reported in Table 4. The evaporation of the solvent under reduced pressure afforded crude compounds **6a-c** in good purity that were crystallized from ethyl acetate-petroleum ether (30-60 °C).

Compound (6a).
IR: 3420, 1740, 1705 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.32 (s, 3H, Me), 7.40-7.65 (m, 5H, Ph), 11.50 (bs, 1H, NH, D_2O ex). ^{13}C-NMR (DMSO-d_6): δ .16.2 (Me), 123.8, 128.7, 131.2 and 134.4 (Ph), 143.4, 145 9, 155.1. MS: m/z (%) = 203 (80) [M^+], 187 (90), 130 (70), 103 (100). Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.27; H, 4.27; N, 20.41.

Compound (6b).
IR: 3360, 3190, 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.14 (s, 3H, Me), 2.35 (s, 3H, Me), 7.25-7.50 (m, 4H, Ar), 11.53 (bs, 1H, NH, D_2O ex) ^{13}C-NMR (DMSO-d_6): δ 15.7 (Me), 16.2 (Me), 123.5, 123.9, 126.6, 129.0 and 134.9 (Ar), 142.8, 145 7, 158.0. MS: m/z (%) = 217 (70) [M^+], 201 (100), 145 (66). Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.63; H, 5.27; N, 19.50.

Compound (6c).
IR: 3450, 3190, 1665, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.25 (s, 3H, Me), 3.05 (s, 6H, NMe_2), 6.69 (d, 2H, J=9.2 Hz, Ar), 7.54 (d, 2H, J=9.2 Hz, Ar), 11.31 (bs, 1H, NH, D_2O ex). ^{13}C-NMR (DMSO-d_6): δ 15.9 (Me), 39.7 (NMe_2), 110.1, 126.5, 132.5 and 134.2 (Ar), 144.2, 153.2, 158.4. MS: m/z (%) = 246 (33) [M^+], 231 (100), 216 (5), 174 (45). Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.73; H, 5.45; N, 22.47.

Preparation of 3-methyl-4-phenylimino-1*H*-pyrazol-5(4*H*)-one (7a) and 3-methyl-4-(4-*N*,*N*-dimethylphenylimino)-1-*H*-pyrazol-5(4*H*)-one (7c) from 1-methoxy-3-methyl-4-phenylimino-1*H*-pyrazol-5(4*H*)-one (5a) and 1-aminocarbonyl-3-methyl-4-(4-*N*,*N*-dimethylphenylimino)-1*H*-pyrazol-5(4*H*)-one (5g).
Compounds **5a** and **5g** (1mmol) were dissolved in methanol (20 ml) and triethylamine (2mmol) was added. The mixture was heated under reflux for the times reported in Table 5. The evaporation of the solvent under reduced pressure afforded the crude products **7a** and **7c**, respectively, that were crystallized from ethyl acetate-petroleum ether (30-60 °C).

Preparation of 3-methyl-4-arylimino-1*H*-pyrazol-5(4*H*)-ones (7a-c) from 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(4*H*)-ones (6a-c).
To a stirred solution of 3-methyl-4-(arylimino-*N*-oxide)-1*H*-pyrazol-5(2*H*)-one **6a-c** (1 mmol) in methanol (10 ml) was added triphenylphosphine (1mmol). The reaction mixture was stirred for the times reported in Table 5 and then the solvent was evaporated under reduced pressure affording the crude products **7a-c** that were purified by crystallization from ethyl acetate-petroleum ether (30-60 °C).

Compound (7a).
IR: 3200, 1690, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.14 (s, 3H, Me), 7.10-7.45 (m, 5H, Ph), 8.88 (bs, 1H, NH, D_2O ex). ^{13}C-NMR ($CDCl_3$): δ 12.2 (Me), 116.7, 122.4, 128.6 and 128.8 (Ph), 147.9, 150.8, 152.6. MS: m/z (%) = 187 (100) [M^+], 128 (35), 102 (44). Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.46; H, 4.60; N, 22.18.

Compound (7b).
IR: 3225, 1685, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.16 (s, 3H, Me), 2.22 (s, 3H, Me), 7.05-7.30 (m, 4H, Ar), 8.72 (bs, 1H, NH, D_2O ex). ^{13}C-NMR ($CDCl_3$): δ 12.2 (Me), 14.0(Me), 118.7, 125.1, 128.7, 130.6, 131.9 and 132.5 (Ar), 150.6, 150.8, 154.8. MS: m/z (%) = 201 (100) [M^+], 142 (42), 116 (25). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.43 H, 5.75; N, 20.64.

Compound (7c).
IR: 3180, 1670, 1610 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.20 (s, 3H, Me), 3.16 (s, 6H, NMe_2), 6.70 (d, 2H, J=9.4 Hz, Ar), 8.50 (d, 2H, J=9.4 Hz, Ar), 8.56 (bs, 1H, NH, D_2O ex). ^{13}C-NMR (DMSO-d_6): δ 11.9 (Me), 39.6 (NMe_2), 111.0, 131.9, 134.4 and 135.4 (Ar), 142.8, 148.7, 156.8. MS: m/z (%) = 230 (100) [M^+], 171 (50), 159 (25), 145 (45). Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.71; H, 6.40; N, 24.08.

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