NMR Study of the (*Z*)-Phenylhydrazones of 5-Alkyl- and 5-Aryl-3-benzoyl-1,2,4-oxadiazoles: Support for the Interpretation of Kinetic Results on the Rearrangement of 1,2,4-Oxadiazoles to 1,2,3-Triazoles

Elisabetta Mezzina,[a] Domenico Spinelli,*[a] Liliana Lamartina,[b] Francesca D'Anna,[c] Vincenzo Frenna,[c] and Gabriella Macaluso[c]

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An analysis of the ^{1}H, ^{13}C, and ^{15}N NMR substituent chemical shifts (SCSs) of the title compounds in $CDCl_3$ solution has been carried out by using the SCSs of other classes of compounds (arenes, methyl esters or amides), Hammett substituent constants or kinetic data. The results obtained provide information concerning the ground-state electronic distribution of the compounds examined. The results relevant to the carbon and nitrogen atoms of the 1,2,4-oxadiazole ring can be considered of special interest, as the effects of the substituents on the chemical shifts of N-4 and C-5 appear in line with kinetic results collected in the study of the rearrangement (Boulton–Katritzky reaction) of the title compounds into the relevant 1,2,3-triazoles, thereby strongly supporting the importance of the leaving-group ability of the N-4/C-5/O-1 system.

Introduction

For several years our research group has been involved in the use of NMR spectroscopic data (^{1}H, ^{13}C, ^{15}N, and ^{17}O) to obtain information about the ground-state electronic distribution of different classes of organic compounds and to evaluate the influence of substituents on this distribution in order to correlate NMR and reactivity data.[1,2]

Thus, the study of the SCSs (substituent-induced chemical shifts) of aryl (or heteroaryl) carboxylic acids[1a–1c] and their derivatives (esters[1d–1g] and amides[1f]) or ketones,[1d,1i] arylhydrazines[2a–2c] or (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole[2d] by using both the one- and the two-parameter [DSP (dual substituent parameter)] treatment, has furnished free-energy relationships (FERs) that are useful for an analysis of substituent effects.

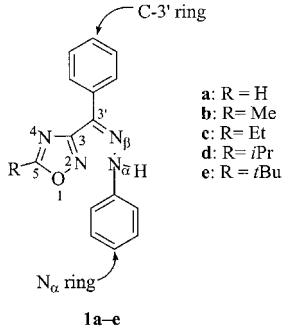
At the same time, we have deeply investigated the mechanisms of the "monocyclic rearrangement of heterocycles" (MRH or Boulton–Katritzky reaction, BKR)[3] by collecting large series of kinetic data for the rearrangement of several (*Z*)-arylhydrazones of 5-substituted 3-benzoyl-1,2,4-oxadiazoles to the relevant 1,2,3-triazoles in different solvents (water/dioxane, dioxane, benzene, toluene, ethyl acetate, acetonitrile, methanol and water in the presence of micelles or of β-cyclodextrin[4]). The BKR is an important and well-studied example of an azole-to-azole interconversion whose general applicability has been largely evidenced by the papers of Katritzky,[3a,3b,5] Korbonits,[6a] and of several[6b,6c] other research groups, as well as by our own contribution.[3c,3d,4]

In this framework, we have found that in water/dioxane (W/D, the most studied solvent system), in the presence of buffers, at least two different intramolecular nucleophilic substitution (S_Ni) pathways of nitrogen N-α onto nitrogen N-2 occur: an uncatalysed and a base-catalysed one.[3c,3d,4] Furthermore, in the case of the arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole an acid-catalysed pathway has also been evidenced in W/D as well as in toluene.[4m,4n] Finally, a DFT study of the uncatalysed MRH pathway[7] has provided results that are convergent with the experimental ones, thus definitively supporting the proposed mechanism.[3c,3d,4]

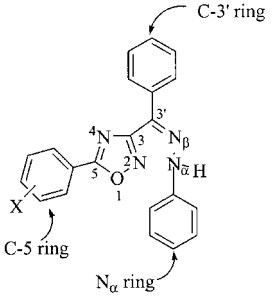
As far as the nature of the 5-substituent and its influence on the rearrangement are concerned, a thorough comparison between kinetic results obtained when C-5 bears a hydrogen or a phenyl group[3c,3d,4] has shown, for example, the importance of the so-called "biaryloid effect".[3c,3d,4a,8] The influence of some alkyl groups with different steric constraints[4g] and of several aryl substituents[4h] has also been investigated.

[a] Dipartimento di Chimica Organica "A. Mangini", Università di Bologna,
Via San Giacomo 11, 40126 Bologna, Italy
Fax: + 39-051-209-5688
E-mail: domenico.spinelli@unibo.it
[b] Dipartimento di Chimica e Tecnologie Farmaceutiche, Università di Palermo,
Via Archirafi 32, 90123 Palermo, Italy
[c] Dipartimento di Chimica Organica "E. Paternò", Università di Palermo,
Viale delle Scienze, Parco d'Orleans II, 90128 Palermo, Italy

The results obtained indicate that, inter alia, the substituent at C-5 affects the leaving group ability of the N-4/C-5/O-1 system[4h] in the S_Ni-like process. Thus, for example, the MRH process of the (*Z*)-phenylhydrazones **1b**–**e** of 5-alkyl-3-benzoyl-1,2,4-oxadiazoles[4g] shows only a small rate variation in benzene (5%), acetonitrile (50%) and W/D in the uncatalysed pS^+[9] range (30%). In contrast, in the base-catalysed region (in W/D) significant variations of the reactivity have been measured as a function of the structure of the alkyl substituent, and thus a significant linear FER has been calculated for the series **1a**–**e** vs. steric parameters.[4g]



1a–e



2p: X = *p*-OMe, *p*-Me, H, *p*-Cl, *p*-Br, *p*-CN, *p*-NO_2
2m: X = *m*-Me, H, *m*-Cl, *m*-Br, *m*-NO_2

On the other hand, significant and large reactivity variations have been observed in the uncatalysed and in the base-catalysed range, respectively, for the *para*- and *meta*-substituted 5-phenyl derivatives **2p** and **2m**, and excellent ($r >$ 0.995) linear FERs have been found with positive susceptibility constants (in the 3.8–6.0 pS^+ range: $\rho = 0.85$; in the 9.0–12.0 pS^+ range: $\rho_n = 1.71$–1.74).[4h]

More recently, we have measured the ^1H, ^{13}C and ^{15}N SCSs of several *para*- and *meta*-substituted (*Z*)-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in $CDCl_3$ solutions, thus obtaining a map of the ground-state electronic distribution in such compounds.[2d] We have thus been able to evaluate the influence of the substituents on the electronic density in the sites involved in the rearrangement, i.e. the proton bound to N_α (the nucleophilic atom), the N-2 atom (the electrophilic centre) and the C-5 atom (whose electronic density affects the nucleofugacity of the N-4/C-5/O-1 system).

We now report the results of a complete ^1H and ^{13}C NMR study of some 5-alkyl (**1b**–**e**: R = Me, Et, *i*Pr, *t*Bu; for comparison, the data for the C-5-unsubstituted derivative **1a** have been collected) and of some *para*- and *meta*-substituted 5-phenyl- (**2p** and **2m**) (*Z*)-phenylhydrazones of 3-benzoyl-1,2,4-oxadiazole in $CDCl_3$. Some ^{15}N NMR spectroscopic data have also been gathered.

The spectra were recorded in $CDCl_3$, a solvent that is not able to give significant interactions with the studied compounds. The numbering of the atoms and the identification of the rings are indicated in the formulae.

Interest in the determination of properties of 1,2,4-oxadiazoles has increased greatly in the last few decades with the discovery that several of them show peculiar biological activities: their development appears linked to the idea that they can be seen as hydrolysis-resistant bioisosters of an ester or an amide (in its imidic form) functionality.[10] Moreover, the discovery[11] of the neuroexcitatory activity of L-quisqualic acid (a naturally occurring α-amino acid, which is a 1,2,4-oxadiazolidine derivative) has directed the interest also towards the study of saturated 1,2,4-oxadiazoles.

Results and Discussion

An Examination of NMR Data for Compounds 1

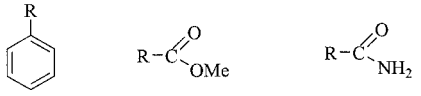
Looking at the ^{13}C NMR spectroscopic data for compounds **1a**–**e** (Table 1), only small variations of chemical shifts are observed for all carbon atoms except C-5, which shows a chemical-shift variation similar to that reported for the C-1 atom of the corresponding alkylbenzenes (**3**), i.e. the chemical shifts of C-5 of **1** as well as of C-1 of **3** increase

Table 1. ^1H and ^{13}C NMR substituent-induced chemical shifts [SCS = $\delta_X - \delta_H$] for compounds **1**.

	Carbon atom: X	3	5	3′	1 (C-3′ ring)	2,6 (C-3′ ring)	3,5 (C-3′ ring)	4 (C-3′ ring)	1 (N_α ring)	2,6 (N_α ring)	3,5 (N_α ring)	4 (N_α ring)	HN_α
1a[a]	5-H	162.37	163.13	125.46	136.34	128.22	127.96	127.96	143.49	113.91	129.22	121.90	11.24
1b	5-Me[b]	+1.10	+12.06	+0.73	+0.26	+0.04	0.00	–0.03	+0.26	–0.04	0.00	–0.23	0.03
1c	5-Et[c]	+1.00	+16.27	+0.83	+0.34	+0.08	+0.03	–0.02	+0.34	–0.04	+0.04	–0.25	0.12
1d	5-*i*Pr[d]	+0.84	+19.4	+0.79	+0.33	+0.03	–0.04	–0.11	+0.31	–0.14	0.00	–0.35	0.20
1e	5-*t*Bu[e]	+0.83	+21.87	+0.83	+0.40	+0.07	–0.02	–0.09	+0.38	–0.13	+0.05	–0.35	0.29
	ΔSCS[f]	1.10	21.87	0.83	0.40	0.08	0.07	0.11	0.38	0.14	0.05	0.35	0.29

[a] ^{13}C chemical shifts (ppm) for the parent compound **1a** are relative to $CDCl_3$ (δ = 77.00 ppm with respect to TMS). [b] CH_3 (δ = 12.22 ppm). [c] CH_2 (δ = 20.21 ppm), CH_3 (δ = 10.75 ppm). [d] CH (δ = 27.41 ppm), CH_3 (δ = 20.04 ppm). [e] CMe_3 (δ = 33.69 ppm), CH_3 (δ = 28.35 ppm). [f] SCS range of the substituent effect on chemical shift.

with increasing the methyl substitution at C-α (the so called β-effect[12]), furnishing an excellent cross-correlation (Table 2, Entry 1, β = 0.94); it should be noted that the chemical shifts of the side-chain carbon atoms of **1b**–**e** also show a trend strictly similar to that of compounds **3b**–**e**. Moreover, excellent cross-correlations with almost unitary slopes (Table 2, Entries 2–3) can be calculated for the C-5 SCSs of **1** vs. the carbonyl chemical shifts of the corresponding aliphatic methyl esters (**4a**–**e**, β = 1.3) or amides (**5a**–**e**, β = 1.1).[13] An excellent structure vs. reactivity correlation [SCS for C-5 atoms vs. $\log(k_{A,R})$**1b–e**/$(k_{A,R})$**1a** at pS^+ = 11.0,[4g] where $k_{A,R}$ represents the apparent first-order rate constant for the rearrangement] has been observed (Table 2, Entry 4, β = –14.9).



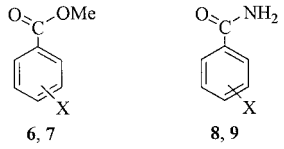
3a–e **4a–e** **5a–e**

a: R = H; **b**: R = Me; **c**: R = Et; **d**: R = *i*Pr; **e**: R = *t*Bu

The small variations of chemical shifts occurring at C-3, C-3′, C-1(C-3′), C-1(N_α), C-4(N_α) and H-N_α can be related to the inductive effect of the alkyl groups, which can be estimated by using the relevant σ_m Hammett constants (for example, see Table 2, Entries 5–10, r = 0.87–0.998), although the small range of the electronic substituent constants for the alkyl series examined, and the relatively small variation of chemical shifts caused by the 5-substituent on other atoms of the molecule, suggest that these kinds of relationships should be considered with caution.

An Examination of NMR Data for Compounds 2

Looking at the ^{13}C NMR spectroscopic data of compounds **2p** and **2m** (Table 3), large variations of chemical shifts are observed for carbons *ipso*, *ortho* or *para* to the substituent in the 5-phenyl ring. Their SCSs give good or excellent cross-correlations with the SCSs of monosubstituted benzenes (not reported),[14] or of 3- or 4-substituted methyl benzoates (**6** and **7**, respectively)[1d–1g] or benzamides (**8** and **9**, respectively),[1f] in line with the expectations based on the resemblance between 5-aryl-1,2,4-oxadiazoles and methyl benzoates or benzamides (see Tables 5 and 6, Entries 18 and 19 or 14 and 15, respectively).



6, 7 **8, 9**

6, 8: X = *p*-OMe, *p*-Me, H, *p*-Cl, *p*-Br, *p*-CN, *p*-NO_2

7, 9: X = *m*-Me, H, *m*-Cl, *m*-Br, *m*-NO_2

Interestingly, in the case of **2p** the susceptibility constants for C-5 ($\rho_p < 0$) and for C-1(C-5) ($\rho_p > 0$; Table 5: Entries 3 and 7, respectively) once more show the occurrence of the alternate polarization which is characteristic of benzoates and benzamides.[1d–1g,16,17] Furthermore, the significant SCS variations measured for C-5 ($\rho_p < 0$), N-4 ($\rho_p > 0$), C-3 ($\rho_p > 0$) and C-3′ ($\rho_p < 0$; Table 5, Entries 3, 9, 2, and 4, respectively) confirm the expectation[2d] for an extended alternate polarisation pattern.

In some cases the ^{13}C SCS ranges are quite narrow (0.3–0.7 ppm on going from *p*-OMe to *p*-NO_2 or from *m*-Me to *m*-NO_2), but nonetheless they generally give significant or good FERs, thus clearly indicating the sign of the induced polarisation. In contrast, the ^{15}N SCS ranges (Table 4) are appreciably wider, always leading in turn to significant, if not excellent, FERs (Tables 5 and 6, Entries 9–11 and 7–10, respectively).

For the sake of clarity, and in order to gain more sound information about the electronic distribution caused by the substituents on the phenyl ring at C-5, and hence about their influence on the reactivity in the studied ring-ring interconversion, the relevant susceptibility constants are reported in formulas **P** and **M**. Their values actually deserve some comment in light of the kinetic results observed previously.

Table 2. Statistical data[a] for the cross-correlations and for the Hammett analysis of SCS values of proton and carbon atoms of compounds **1**.

Entry	Probe atom	$\rho \pm s_\rho$ (or $\beta \pm s_\beta$)	Cross-correlated atom (SCS), kinetic constant or substituent constant	$i \pm s_i$	n	r
1	C-5	0.935 ± 0.083	C-1(**3**)	1.24 ± 1.32	5	0.99
2	C-5	1.29 ± 0.02	C=O (**4**)[b]	–0.05 ± 0.22	5	0.9997
3	C-5	1.11 ± 0.02	C=O (**5**)[c]	0.14 ± 0.32	5	0.9994
4	C-5	–14.9 ± 0.7	$\log(k_{A,R})_{Alk}/(k_{A,R})_H$[d]	–0.26 ± 0.79	5	0.996
5	C-3	9.0 ± 3.7	σ_m	1.64 ± 0.29	4[e]	0.87
6	C-3′	–9.65 ± 1.15	σ_m	0.04 ± 0.08	5	0.98
7	C-1(3′)	–4.31 ± 0.16	σ_m	0.00 ± 0.01	5	0.998
8	C-1(N_α)	–4.13 ± 0.21	σ_m	0.00 ± 0.01	5	0.996
9	C-4(N_α)	3.81 ± 0.57	σ_m	0.00 ± 0.04	5	0.968
10	H-N_α	–8.21 ± 2.29	σ_m	–0.48 ± 0.18	4[e]	0.93

[a] ρ: susceptibility constant for the single-parameter analysis; β: slope of the cross-correlation; i: intercept; s_ρ, s_β and s_i: standard deviations; n: number of points; r: correlation coefficient. [b] Data of probe atoms in $CDCl_3/CCl_4$ (see ref.[13]). [c] Data of probe atoms in D_2O/H_2O/dioxane (see ref.[13]). [d] At pS^+ 11.0. [e] The datum for compound **1a** is excluded from the correlation.

Table 3. ^{13}C NMR substituent-induced chemical shifts [SCS = $\delta_X - \delta_H$] for compounds **2p**[a] and **2m**.[a]

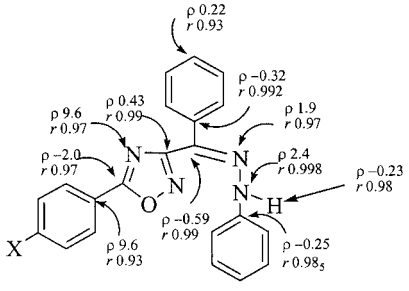
Carbon atom: X	3	5	1 (C-5 ring)	2 (C-5 ring)	3 (C-5 ring)	4 (C-5 ring)	5 (C-5 ring)	6 (C-5 ring)	3′	1 (C-3′ ring)	2, 6 (C-3′ ring)	3, 5 (C-3′ ring)	4 (C-3′ ring)	1 (N_α ring)	2, 6 (N_α ring)	3, 5 (N_α ring)	4 (N_α ring)
H	163.87	174.22	123.43	128.26	129.12	133.16	129.12	128.26	126.22	136.70	128.34	127.93	127.86	143.81	113.91	129.24	121.69
p-Me[b]	–0.04	+0.17	–2.75	+0.01	+0.76	+11.0	+0.76	+0.01	+0.10	+0.03	+0.01	+0.03	+0.03	+0.02	–0.04	+0.02	–0.06
p-Cl	+0.10	–0.85	–1.57	+1.37	+0.51	+6.64	+0.51	+1.37	–0.14	–0.11	+0.02	+0.08	+0.15	–0.09	+0.06	+0.07	+0.17
p-Br	+0.11	–0.74	–1.10	+1.43	+3.49	–4.80	+3.49	+1.43	–0.16	–0.11	+0.02	+0.08	+0.15	–0.10	+0.07	+0.07	+0.18
p-CN[c]	+0.30	–1.71	+3.73	+0.61	+3.82	–16.42	+3.82	+0.61	–0.42	–0.26	+0.03	+0.15	+0.22	–0.21	+0.18	+0.14	+0.46
p-NO_2	+0.41	–1.95	+5.34	+1.26	–4.65	+17.37	–4.65	+1.26	–0.42	–0.26	+0.06	+0.18	+0.25	–0.20	+0.23	+0.16	+0.52
p-OMe[d]	–0.07	–0.06	–7.53	+2.02	–14.51	+30.39	–14.51	+2.02	+0.23	+0.07	+0.02	+0.04	+0.04	+0.06	–0.05	+0.04	–0.09
ΔSCS[e]	0.48	2.12	12.87	2.02	18.33	46.81	18.33	2.02	0.65	0.33	0.06	0.18	0.25	0.27	0.28	0.16	0.61
X																	
m-Me[f]	+0.02	+0.24	–0.10	+0.52	+10.04	+0.92	–0.04	–2.75	+0.12	+0.02	+0.03	+0.06	+0.06	+0.02	+0.01	+0.04	0.00
m-Cl	+0.11	–1.21	+1.60	+0.02	+6.27	+0.11	+1.43	–1.86	–0.23	–0.15	+0.02	+0.09	+0.13	–0.12	+0.10	+0.07	+0.22
m-Br	+0.12	–1.32	+1.83	+2.91	–5.88	+3.04	+1.63	–1.40	–0.20	–0.15	+0.03	+0.11	+0.14	–0.11	+0.11	+0.08	+0.23
m-NO_2	+0.28	–2.04	+1.68	–4.93	+19.53	–5.61	+1.50	+5.58	–0.45	–0.28	+0.03	+0.19	+0.26	–0.13	+0.21	+0.15	+0.48
ΔSCS[e]	0.28	2.28	1.93	7.84	25.41	8.65	1.67	8.33	0.57	0.30	0.03	0.19	0.26	0.15	0.21	0.15	0.48

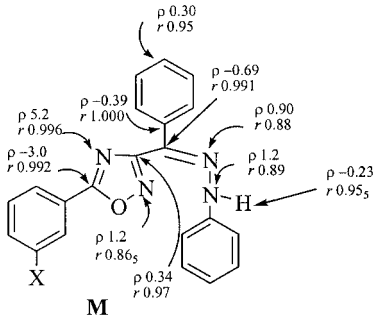
[a] ^{13}C chemical shifts (ppm) for the parent compound **1a** are relative to $CDCl_3$ (δ = 77.00 ppm with respect to TMS). [b] CH_3 (δ = 21.76 ppm). [c] *C*N (δ = 117.54 ppm). [d] OCH_3 (δ = 55.50 ppm). [e] SCS range of the substituent effect on chemical shift. [f] CH_3 (δ = 21.29 ppm).

Table 4. ^1H and ^{15}N NMR substituent-induced chemical shifts [SCS = $\delta_X - \delta_H$] for compounds **2p** and **2m** in $CDCl_3$.

X	N-2	N-4	N_α	N_β	H-N_α
H[a]	–26.24	–148.58	–225.42	–44.38	11.45
p-Me	–0.97	–2.00	–0.26	–0.46	+0.01
p-Cl	–0.19	+0.94	+0.55	+0.18	–0.10
p-Br	–0.14	+1.10	+0.56	+0.19	–0.11
p-CN[b]					–0.19
p-NO_2[c]					–0.20
p-OMe	+1.77	–4.04	–0.65	–0.79	+0.04
ΔSCS[d]	2.74	5.14	1.21	0.98	0.24
m-Me	–0.65	+0.08	–0.05	–0.39	–0.03
m-Cl	+0.20	+2.18	+0.77	+0.32	–0.13
m-Br	+0.15	+2.00	+0.77	+0.29	–0.14
m-NO_2[e]	+0.47	+3.93	+0.76	+0.39	–0.18
ΔSCS[d]	1.12	3.93	0.82	0.78	0.18

[a] ^1H and ^{15}N chemical shifts (ppm) for parent compound (X = H) are relative to TMS and to external $CH_3{}^{15}NO_2$, respectively. [b] The compound undergoes rearrangement to the triazole during the data acquisition. [c] The compound has very low solubility in $CDCl_3$. [d] SCS range of the substituent effect on chemical shifts. [e] NO_2 (δ = –12.83 ppm).





The largest effect on a carbon atom of the 1,2,4-oxadiazole ring has been evidenced at C-5 (ρ_p = –2.0, Entry 3 of Table 5; ρ_m = –3.0, Entry 3 of Table 6), where electron-withdrawing and -repelling substituents cause an increase and a decrease of electronic density, respectively; moreover, a DSP treatment of the data for **2p** once more shows the occurrence of reverse polar and resonance contributions.[1d–1g]

The large chemical-shift variations observed for N-4 in **2p** and **2m** appear to be of particular significance: as a matter of fact, they well evidence the electronic density changes at N-4 caused by a substituent on the aryl group at C-5 (in the frame of the alternate polarisation already observed along the C-5/N-4 bond[2d]) and thus provide a direct indication of how such a substituent affects the leaving-group ability of the N-4/C-5/O-1 system. Since the SCSs for N-4 of **2p** and **2m** give good or excellent linear FERs (r = 0.97 and 0.996, respectively) with Hammett substituent constants (ρ_p = 9.6, Entry 9 of Table 5; ρ_m = 5.2, Entry 8 of Table 6) as well as with $\log(k_{A,R})_X/(k_{A,R})_H$ [in the uncatalysed (pS^+ = 3.80: β_p = 10.9, Entry 21 of Table 5; β_m = 5.6_5, Entry 17 of Table 6) and in the base-catalysed range (pS^+ = 11.0: β_p = 5.4, Entry 23 of Table 5; β_m = 3.0, Entry 19 of Table 6)], this result well corroborates the interpretation we have proposed for kinetic data and stresses the importance of the electronic density at C-5 and N-4 in affecting the rate for the rearrangement of **2p** and **2m** into the relevant 1,2,3-triazoles.[15]

Table 5. Statistical data for the cross-correlations and for the Hammett and DSP analysis of SCS values of proton, carbon and nitrogen atoms of compounds **2p**.

Entry	Probe atom	$\rho \pm s_\rho$ (or $\beta \pm s_\beta$)[a]	Cross-correlated atom (SCS), kinetic constant or substituent constant	$i \pm s_i$	n	r or R
1	H-N_α	–0.23 ± 0.02	σ_p	–0.03 ± 0.01	7	0.98
2	C-3	0.43 ± 0.03	σ_p	0.02 ± 0.01	7	0.99
3	C-5	–1.99 ± 0.22	σ_p	–0.30 ± 0.10	7	0.97
4	C-3′	–0.59 ± 0.04	σ_p	0.02 ± 0.02	7	0.99
5	C-1(C-3′)	–0.32 ± 0.02	σ_p	–0.02 ± 0.01	7	0.992
6	C-4(C-3′)	0.22 ± 0.04	σ_p	0.07 ± 0.02	7	0.93
7	C-1(C-5)	9.58 ±1.72	σ_p	–2.66 ± 0.76	7	0.93
8	C-1(N_α)	–0.25 ± 0.02	σ_p	–0.02 ± 0.01	7	0.98_5
9	N-4	9.63 ± 1.40	σ_p	–0.84 ± 0.28	5	0.97
10	N_α	2.37 ± 0.07	σ_p	0.03 ± 0.01	5	0.998
11	N_β	1.90 ± 0.29	σ_p	–0.18 ± 0.05	5	0.97
12	C-1(C-5)	ρ_I 8.53 ± 1.50 ρ_{R° 17.39 ± 1.99	σ_I, σ_{R°	–0.33 ± 0.74	7	0.98
13[b]	C-3′	–1.33 ± 0.17	C-3	0.04 ± 0.03	7	0.96
14[b]	C-3′	1.84 ± 0.10	C-1(C-3′)	0.05 ± 0.02	7	0.992
15[b]	C-3′	–0.37 ± 0.05	N_β	–0.06 ± 0.02	5	0.98
16[b]	C-1(C-3′)	–1.30 ± 0.18	C-4(C-3′)	0.06 ± 0.03	7	0.95
17[b]	C-1(C-5)	–4.1 ± 1.3	C-5	–3.6 ± 1.4	7	0.82
18	C-5	1.07 ± 0.03	C=O (**6**)[c]	0.09 ± 0.03	7	0.998
19	C-5	1.27 ± 0.15	C=O (**7**)[d]	0.29 ± 0.15	7	0.97
20	C-5	–1.18 ± 0.27	$\log(k_{A,R})_X/(k_{A,R})_H$[e]	–0.34 ± 0.12	7	0.95
21	N-4	10.87 ± 1.36	$\log(k_{A,R})_X/(k_{A,R})_H$[e]	–0.23 ± 0.25	5	0.98
22	C-5	–1.33 ± 0.17	$\log(k_{A,R})_X/(k_{A,R})_H$[f]	–0.10 ± 0.05	7	0.994
23	N-4	5.39 ± 1.92	$\log(k_{A,R})_X/(k_{A,R})_H$[f]	–1.59 ± 0.66	5	0.85

[a] ρ: susceptibility constant for the single-parameter or for the DSP analysis; β: slope of the cross-correlation; i: intercept; s_ρ, s_β and s_i: standard deviations; n: number of points; r or R: correlation coefficients. [b] Cross-correlations between SCSs of probe atoms within compounds **2p**. [c] Data of probe atoms in $CDCl_3$ (see ref.[16]). [d] Data of probe atoms in [D_6]DMSO (see ref.[17]). [e] At $pS^+ = 3.8$. [f] At $pS^+ = 11.0$.

Table 6. Statistical data for the cross-correlations and for the Hammett analysis of SCS values of proton, carbon and nitrogen atoms of compounds **2m**.

Entry	Probe atom	$\rho \pm s_\rho$ (or $\beta \pm s_\beta$)[a]	Cross-correlated atom (SCS), kinetic constant or substituent constant	$i \pm s_i$	n	r
1	H-N_α	–0.23 ± 0.04	σ_m	–0.03 ± 0.02	5	0.95_5
2	C-3	0.34 ± 0.05	σ_m	0.01 ± 0.02	5	0.97
3	C-5	–3.03 ± 0.23	σ_m	–0.03 ± 0.09	5	0.992
4	C-3′	–0.69 ± 0.05	σ_m	0.04 ± 0.02	5	0.991
5	C-1(C-3′)	–0.39 ± 0.04	σ_m	0.00 ± 0.00	5	1.000
6	C-4(C-3′)	0.30 ± 0.05	σ_m	0.04 ± 0.02	5	0.95
7	N-2	1.15 ± 0.39	σ_m	–0.29 ± 0.15	5	0.86_5
8	N-4	5.20 ± 0.28	σ_m	0.19 ± 0.11	5	0.996
9	N_α	1.23 ± 0.36	σ_m	0.11 ± 0.14	5	0.89
10	N_β	0.90 ± 0.28	σ_m	–0.13 ± 0.11	5	0.88
11[b]	C-3′	1.76 ± 0.15	C-1(C-3′)	0.05 ± 0.02	5	0.990
12[b]	C-3′	–0.63 ± 0.16	N_β	–0.08 ± 0.05	5	0.92
13[b]	C-1(C-3′)	–1.21 ± 0.22	C-4(C-3′)	0.03 ± 0.03	5	0.95
14	C-5	0.98 ± 0.02	C=O (**8**)[c]	0.03 ± 0.02	5	0.9995
15	C-5	0.93 ± 0.04	C=O (**9**)[d]	0.05 ± 0.06	5	0.997
16	C-5	–3.33 ± 0.38	$\log(k_{A,R})_X/(k_{A,R})_H$[e]	–0.26 ± 0.12	5	0.98
17	N-4	5.65 ± 0.79	$\log(k_{A,R})_X/(k_{A,R})_H$[e]	0.61 ± 0.25	5	0.97
18	C-5	–1.72 ± 0.14	$\log(k_{A,R})_X/(k_{A,R})_H$[f]	–0.03 ± 0.10	5	0.990
19	N-4	2.96 ± 0.16	$\log(k_{A,R})_X/(k_{A,R})_H$[f]	0.19 ± 0.11	5	0.996

[a] ρ: susceptibility constant for the single-parameter analysis; β: slope of the cross-correlation; i: intercept; s_ρ, s_β and s_i: standard deviations; n: number of points; r: correlation coefficients. [b] Cross-correlations between SCSs of probe atoms within compounds **2**. [c] Data of probe atoms in $CDCl_3$ (see ref.[16]). [d] Data of probe atoms in [D_6]DMSO (see ref.[17]). [e] At $pS^+ = 3.8$. [f] At $pS^+ = 11.0$.

As a matter of fact, other things being equal, the reactivity in the ring-to-ring interconversion, which requires the breaking of the O-1/N-2 bond, depends on the leaving group ability (nucleofugacity) of the N-4/C-5/O-1 system, and therefore essentially on the electron-attracting power of N-4 which, whilst the O-1/N-2 bond breaks, largely contributes to the dispersion of the incipient negative charge. Thus, the effect of the substituents on the ground-state electron

density is in perfect agreement with the kinetic results, as also indicated by the above reported correlation between the SCS values and reactivity data.

The substituents of the 5-phenyl group are also able to cause variations of chemical shifts in the remote nitrogen (N_α, $\rho > 0$) and hydrogen (N_α-*H*, $\rho < 0$) atoms of the (*Z*)-phenylhydrazone moiety. The calculated values of the susceptibility constants agree well with their effects on the reactivity and once more indicate an alternate polarization along the N_α–H bond.

Conclusions

The study of ^{1}H, ^{13}C and ^{15}N chemical shifts of the (*Z*)-phenylhydrazones of some 5-alkyl- or 5-aryl-3-benzoyl-1,2,4-oxadiazoles (**1**, **2p**, and **2m**) in $CDCl_3$ has furnished a map of ground-state electron densities in such compounds.

Concerning the effects of the substituents at C-5 the following considerations can be made:

a) Alkyl substituents cause significant SCSs only at C-5 itself within the heterocyclic moiety while, as expected, large variations at the carbon atoms of the alkyl chain have been observed; the measured C-5 SCS values can be well correlated with the SCSs at C-1 of alkylbenzenes **3**[12] or SCSs of the carbonyl groups of methyl esters **4** or amides **5**, as well as with the kinetic data concerning the rearrangement rates in the base-catalysed region.

b) Aryl substituents cause significant SCSs at all the carbon and nitrogen atoms of the 1,2,4-oxadiazole ring. Of course, different SCSs have been measured for the aromatic carbon atoms of the 5-aryl groups (large SCSs) or of the C-3′ ring as well as of the hydrazonic phenyl rings (small SCSs). Thus, the remote substituent is able to affect the chemical shifts of the whole molecule to different extents, thus evidencing its ability to exert long-range electronic effects. The calculated susceptibility constants (see figures in formulas **P** and **M**) once more evidence the occurrence of alternate polarization in the case of a single-bonded ring substituent [for example, C-5/C-1(C-5) or C-3/C-3′], between atoms of different electronegativity (for example N_α-H) or those involved in double-bond formation (for example C-5/N-4 or C-3′/N_β).

The very nature of the rearrangement − it is an intramolecular nucleophilic substitution − attributes an important role to electronic densities on the N-4/C-5/O-1 system on the course of the reaction. Accordingly, the picture of electronic densities for the (*Z*)-phenylhydrazones **1**, **2p** and **2m** provided by NMR spectroscopic data appears truthful and correct. As a matter of fact, the substituents on the 5-aryl moiety strongly affect the electronic density at N-4, determining high susceptibility constants (ρ_p and ρ_m: 9.6 and 5.2, respectively): accordingly, the leaving-group ability of the N-4/C-5/O-1 system and hence the reactivity in the S_Ni mononuclear rearrangement[3,4,7] are heavily influenced, as evidenced by the occurrence of acceptable or good correlations between SCS at N-4 and $\log(k_{A,R})_X/(k_{A,R})_H$ ratios with large and positive slopes (β_p and β_m: 3.0–10.9). Of course, good correlations between the SCS at C-5 and kinetic data have also been observed, in this case with negative slopes (β_p and β_m: –1.2 to –3.3) because of the aforementioned alternate polarization observed between N-4 and C-5.

Moreover, in line with the idea that 1,2,4-oxadiazoles can be considered as hydrolysis-resistant isosters of esters or amides, the SCSs of C-5 correlate well with the SCSs of the carbonyl group of the relevant methyl esters (**6** and **7**) and amides (**8** and **9**), and in the case of **2p** evidence the alternate polarization between C-5 and C-1(C-5) already observed in *para*-substituted benzoates and benzamides.

Experimental Section

Spectroscopic Measurements: All the NMR spectra were recorded with a Varian Gemini 300 spectrometer in $CDCl_3$. ^{1}H (300.07 MHz, 0.02 M) and ^{13}C (75.43 MHz, 0.1 M) chemical-shift values are given in ppm relative to $SiMe_4$ (internal standard) and $CDCl_3$ (centred at δ = 77.00 ppm), respectively. ^{13}C chemical-shift values were measured from fully decoupled spectra. Signal assignments were made on the grounds of both known substituent effects and of multiplicities determined by proton-gated decoupled experiments. The ^{15}N NMR spectra (30.40 MHz) were acquired at natural abundance for 0.5 M solutions in $CDCl_3$ containing a 0.01 M addition of $Cr(acac)_3$ for each N atom present in the sample molecule. The spectra were recorded at 20 ± 1 °C using a 10-mm broadband probe. Chemical shifts are referred to external neat $CH_3{}^{15}NO_2$. Typical operating conditions employed a delay between pulses of 5 s (acquisition time 1 s), spectral width of 10 kHz, 15 μs pulse width (ca. 60° flip angle). The signal-to-noise ratio was improved by applying a 2 Hz line-broadening factor to the FID prior to Fourier transformation. The digital resolution was improved to 0.02 ppm by zero-filling to 32 k data points.

Materials: The (*Z*)-arylhydrazones **1**,[4g] **2p** and **2m**[4h] were synthesised and purified according to literature methods.

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