# On the Synthesis and Reactivity of the *Z*-2,4-Dinitrophenylhydrazone of 5-Amino-3-benzoyl-1,2,4-oxadiazole

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The synthesis of the title compound (**4b**) has been completed: its rearrangement (in dioxane/water; 1:1, v/v) into *N*-(2,4-dinitrophenyl)-5-phenyl-2*H*-1,2,3-triazol-4-ylurea (**7**) has been quantitatively studied in a wide reactivity (at 293 K, $k_A$ $10^{-8}$ −4 $s^{-1}$) and p$S^+$ (4.5−14.1) range and compared with that of the *Z*-2,4-dinitrophenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**10**), of the 3-(*p*-nitro)phenylureine of 5-phenyl-1,2,4-oxadiazole (**13**), and of *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N*′-*p*-nitrophenylformamidine (**14**). The results (reactivity, occurrence of specific or general base-catalysis, evidence for or absence of rate-limiting constants) have been well interpreted considering the structure of the side-chains involved and the stability of the final rings obtained in the rearrangements.

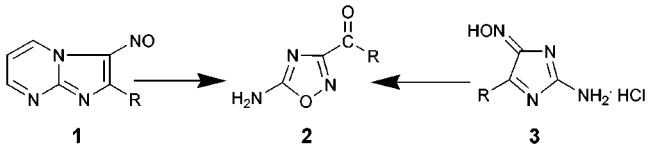
## Introduction

Recently we studied the reactivity of nitrosoimidazoles with hydrochloric acid (the Cusmano and Ruccia reaction),[1] examining the effect of some rings condensed at N-1 and C-2 of the imidazole.[2]In the case of 2-aryl-3-nitrosoimidazo[1,2-*a*]pyrimidines (**1a**,**b**) we observed[2d] (Scheme 1) a ring−ring interconversion occurring with elimination of ammonia and loss of a three-carbon fragment, obtaining the known 5-amino-3-aroyl-1,2,4-oxadiazoles (**2a**,**b**).[3,4]

As a matter of fact Cavalleri et al. described the synthesis of **2b**−**d**[3] and of **2a**,**e**−**m**[4] by applying the Cusmano and Ruccia reaction to several 4(5)-substituted 2-amino-5(4)-hydroxyimino-5(4)-*H*-imidazoles (**3**) (Scheme 1) and then studied their pharmacological properties, observing an interesting depressant activity on the central nervous system.[4]

Cavalleri et al. confirmed[3] the structure of **2b**−**d** by using chemical and spectroscopic methods.[5] Thus, inter alia, they tried to evidence the presence of the carbonyl group by reaction with 2,4-dinitrophenylhydrazine (DNPH) and hydroxylamine, claiming the isolation of the corresponding 2,4-dinitrophenylhydrazones (**4b**−**d**) and oximes (**5b**−**d**) (Scheme 2).

**Scheme 1**




**a** R = $C_6H_4$-Cl (*p*)
**b** R = $C_6H_5$
**c** R = Me
**d** R = *n*-$C_3H_7$
**e** R = $C_6H_4$-Me (*p*)
**f** R = $C_6H_4$-F (*p*)
**g** R = $C_6H_4$-Br (*p*)
**h** R = $C_6H_4$-OMe (*p*)
**i** R = $C_6H_4$-$NO_2$ (*p*)
**j** R = $C_6H_3$-$Cl_2$ (*3,4*)
**k** R = $C_6H_3$-$Cl_2$ (*2,4*)
**l** R = $C_6H_4$-$C_6H_5$ (*p*)
**m** R = 2-$C_{10}H_7$

Vice-versa we have shown that the derivatives obtained were not always the alleged ones. Actually, an accurate examination of the $^1$H NMR spectra reported[3] evidenced some striking discrepancies in the resonances of the exchangeable protons of **4b**,**c** as compared to **4d**. Thus, the signals of −N*H*$_2$ and of >N*H* were reported at 6.34 and 8.90 ppm for **4b** and at 6.55 and 9.25 ppm for **4c**, respectively, but at 8.35 and 13.40 ppm for **4d**: such large chemical shift variations for protons of the same

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(1) (a) Spinelli, D. Thesis, University of Bari, 1955 (Tutor: Professor S. Cusmano). (b) Cusmano, S.; Ruccia, M. *Gazz. Chim. Ital.* **1955**, *85*, 1686−1697. (c) Cusmano, S.; Ruccia, M. *Gazz. Chim. Ital.* **1958**, *88*, 463−481.

(2) (a) Spinelli, D.; Mugnoli, A.; Andreani, A.; Rambaldi, M.; Frascari, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1394−1395. (b) Andreani, A.; Billi, R.; Cosimelli, B.; Mugnoli, A.; Rambaldi, M.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2407−2410. (c) Billi, R.; Cosimelli, B.; Spinelli, D.; Rambaldi, M. *Tetrahedron* **1999**, *55*, 5433−5440. (d) Billi, R.; Cosimelli, B.; Spinelli, D.; Andreani, A.; Leoni, A. *Tetrahedron* **2000**, *56*, 6527−6532. (e) Billi, R.; Cosimelli, B.; Spinelli, D.; Leoni, A. *J. Heterocycl. Chem.* **2000**, *37*, 875−878.

(3) Cavalleri, B.; Bellani, P.; Lancini, G. *J. Heterocycl. Chem.* **1973**, *10*, 357−362.

(4) Cavalleri, B.; Volpe, G.; Rosselli del Turco, B.; Diena, A. *Il Farmaco Ed. Sci* **1976**, *66*, 393−402.

(5) The $^1$H NMR in DMSO-$d_6$ of **2b** obtained by us does not fit reported data,[3] where the assignment of aminic protons was definitely unlikely as compared with data for **2c**−**e** (Cavalleri et al.)[3,4] and for **2a** and **2b** (Cosimelli et al.):[2d] in every case the 5-aminic protons of 1,2,4-oxadiazole derivatives resonate in the range 7.8−8.5 ppm and not at 6.7 ppm.

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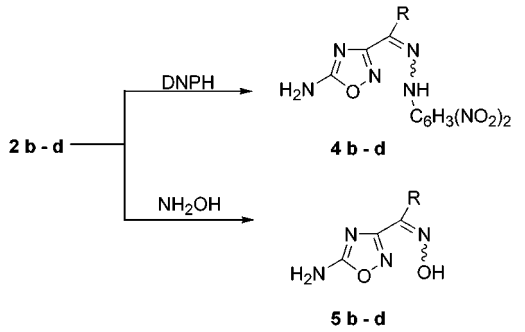
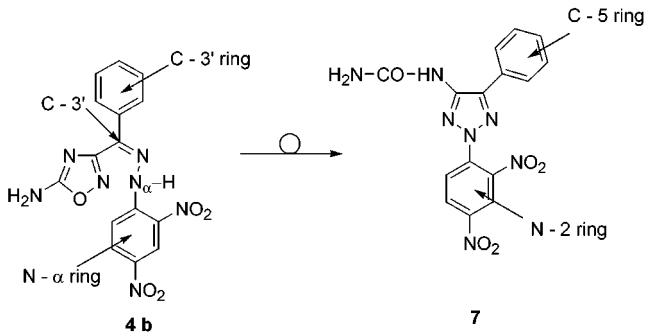
**Scheme 2**



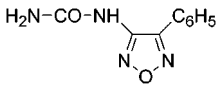

**Scheme 3**




type could be hardly related to structural differences in the remote 3-acyl group.

Similar discrepancies have been observed for the exchangeable protons ($-NH_2$ and $-OH$) of the claimed oxime **5b** (6.55 and 9.05 ppm) as compared to **5c**,**d** (7.80 and 7.88 for aminic protons and 11.86 and 11.80 ppm for oxyiminic protons, respectively).

In the framework of their excellent studies on mononuclear heterocyclic rearrangements (MHR) Vivona et al. reinvestigated[6] the oximation reaction of some 3-acylisoxazoles and 3-acyl-1,2,4-oxadiazoles, observing in particular that **2b** with hydroxylamine "gave a mixture of the furazan **6**, the NMR spectrum of which was identical to that for the alleged "oxime",[3] and the (*E*)-oxime *E*-**5b**. In the NMR spectrum of the latter compound the oximino proton resonates at $\delta$ 12.2".[6b]



**6**

Thus, supposing that also the structures assigned to *Z*-dinitrophenylhydrazones **4b**,**c** were uncorrect and on the grounds of our previous large experience in ring−ring interconversions of azoles,[7] we reexamined the reaction of **2b** with DNPH:[8] the $^1$H NMR spectrum of the crude *Z*-dinitrophenylhydrazone **4b** (obtained in a high purity degree: see Experimental Section) showed $-NH_2$ and >NH signals at 8.48 and 13.52 ppm (cf. the data for **4d** above), as expected by comparison with the whole of the data on 5-amino-1,2,4-oxadiazoles[2d,3,4,6b] and on *Z*-2,4-dinitrophenylhydrazones.[9] MS data confirmed its structure.

With the aim of understanding the reasons of the inaccuracies contained in Cavalleri's paper,[3] which represent, though, a minor point in an otherwise excellent work indeed, we investigate herein the reactivity of **4b**.

## Results and Discussion

**Reactivity of the *Z*-2,4-Dinitrophenylhydrazone of 5-Amino-3-benzoyl-1,2,4-oxadiazole (4b). Qualitative Features.** An attempt to purify **4b** by crystallization from ethanol, the solvent suggested by Cavalleri et al.,[3] caused its complete conversion into a new product: i.e., *a few minutes heating in ethanol determined a complete transformation of **4b***, an observation which makes Cavalleri's mistake understandable.[3] As expected, physical (mp) and spectral ($^1$H NMR) data of the new product compared well with those reported by Cavalleri for the alleged **4b**.[3] An accurate interpretation of $^1$H NMR data indicated that the "claimed"[3] hydrazone really was the isomeric *N*-(2,4-dinitrophenyl)-5-phenyl-2*H*-1,2,3-triazol-4-ylurea **7**, obtained through a MHR (Scheme 3) from the "true" hydrazone by short heating in ethanol.

As MHR processes are faster in aprotic dipolar solvents[10−12] than in ethanol, we have monitored the conversion of **4b** in DMSO-$d_6$ to **7** by $^1$H NMR. At room temperature after only 2 h the spectrum already showed the presence of resonances at 6.34 and 8.90 ppm, while in 12 h the conversion **4b** → **7** was complete.

The rearrangement of **4b** could be easily achieved also by heating above its melting point, as already observed for all arylhydrazones of 3-acyl-1,2,4-oxadiazoles.[7]

**Quantitative Features: An Introduction.** *Z*-Arylhydrazones of 3-benzoyl-1,2,4-oxadiazole rearrange with high yields into *N*-aryl-4-acylamino-5-phenyl-2*H*-1,2,3-triazoles.[7] Derivatives of isoxazole[11] also undergo rearrangement, although more slowly than the corresponding 1,2,4-oxadiazoles.

(6) (a) Vivona, N.; Macaluso, G.; Frenna, V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 483−486. (b) Vivona, N.; Buscemi, S.; Frenna, V.; Ruccia, M.; Condò, M. *J. Chem. Res.* **1985**, (*S*) 190, (*M*) 2184−2197.

(7) (a) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141−169. (b) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49−154. (c) Frenna, V.; Vivona, N.; Consiglio, G.; Corrao, A.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1325−1328. (d) Frenna, V.; Macaluso, G.; Consiglio, G.; Cosimelli B.; Spinelli, D. *Tetrahedron* **1999**, *55*, 12885−12896 and references therein.

(8) This reaction has been carried out in strongly acidic conditions to maximize the yield of the *Z*-isomer. Thus, in the reported conditions (see Experimental Section) we obtained only the *Z*-isomer in 69% yield (purity degree >95%); in contrast an isomeric mixture (*Z*:*E* = 3:1) was obtained operating in weakly acidic EtOH. The characterization of the two isomers is based on spectroscopic data. The UV/VIS spectra in water/dioxane afforded $\lambda_{max}$ 390 nm for the *Z*-isomer and $\lambda_{max}$ 360 for the *E*-isomer. In DMSO-$d_6$, the NH proton resonates at 13.52 and 11.26 ppm for the *Z*- and the *E*-isomer, respectively. Moreover in DMSO the *Z*-isomer rearranged in a few hours into **7**, while the *E*-isomer remained unchanged also for long times.

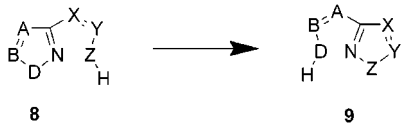
(9) (a) Venien, F. *Org. Magn. Reson.* **1973**, *5*, 113−117. (b) Tayyari, S. F.; Speakman, J. L.; Arnold, M. B.; Cai, W.; Behforouz, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2195−2200. (c) Vivona, N.; Ruccia, M.; Frenna, V.; Spinelli, D. *J. Heterocycl. Chem.* **1980**, *17*, 401−402.

(10) (a) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1199−1202. (b) Frenna, V.; Vivona, N.; Cannella, L.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1183−1187. (c) Frenna, V.; Buscemi, S.; Arnone, C. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1683−1686.

(11) (a) Frenna, V.; Vivona, N.; Macaluso, G.; Spinelli, D.; Consiglio, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 537−540. (b) Kamiya, M. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3344−3353. (c) Paoloni, L.; Cignitti, M. *Tetrahedron* **1968**, *24*, 485−495. (d) Adam, W.; Grimison, A. *Theor. Chim. Acta* **1967**, *7*, 342−351.

(12) (a) Korbonits, D.; Kanzel-Szvoboda, I.; Horváth, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 759−766. (b) Horváth, K.; Korbonits, D.; Náray-Szabó, G.; Simon, K. *J. Mol. Struct. (THEOCHEM)* **1986**, *136*, 215−227.

**Scheme 4**



**8** **9**

These reactions represent examples of ring−ring rearrangements, that can be referred to the more general topic of azole−azole interconversions; the latter are in turn a peculiar case of the "monocyclic rearrangements of heterocycles" recognized by Boulton, Katritsky, and Majid-Hamid[13a−c] as a general class of rearrangements (Scheme 4) showing interesting synthetic applications[13,14] as well as intriguing mechanistic aspects.[7,12,13]

Many facets of MHR have been thoroughly investigated by us[7] both in dioxane/water (D/W; 1:1, v/v) in the presence of buffers and in benzene (as well as in other organic solvents) in the presence of several amines. The process can be depicted as an internal (intramolecular) nucleophilic substitution, and therefore the reactivity can be related to the main factors normally affecting $S_N$ reactivity, i.e., (i) the nucleophilic power of the arylhydrazonic α-nitrogen, (ii) the electrophilic character of the heterocyclic N-2 atom, and (iii) the strength of the N-2/O-1 bond to be cleaved in the starting ring (1,2,4-oxadiazole or isoxazole) and hence the leaving group ability of O-1.

The last factors can be modulated in several manners: e.g., by changing the starting ring[11a] both the strength of the N-2/O-1 bond and the ability of the leaving group to carry the negative charge can be varied (on going from 1,2,4-oxadiazole to isoxazole, the strength of the cleaving bond increases with the aromatic character of the ring[11b−d] and, moreover, the leaving group ability decreases, as −N=C−O$^-$ is much more resonance-stabilized than >C=C−O$^-$).[11a]

On the other hand, when keeping the starting ring constant (e.g., 1,2,4-oxadiazoles), by changing the nature of the substituent (electron-repelling or -attracting) at C-5,[12,15,16] the delocalization of the negative charge in −N=C−O$^-$ can be affected. This effect has been deeply investigated studying both a series of 5-alkyl[15] and of 5-aryl[16] derivatives.

In all the *Z*-arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles (with the substituent in the arylhydrazono moiety ranging from the strongly electron-donating *p*-methoxy to the strongly electron-withdrawing *p*-nitro) previously studied by us, a large dependence of the reactivity on the base concentration has been observed. Moreover the occurrence of two different pathways was evidenced:[7a,b] an uncatalyzed, p$S^+$-independent route (at low p$S^+$ values)[17] and a catalyzed, p$S^+$-dependent one (at high p$S^+$ values).

**Table 1. Calculated or Measured Apparent Kinetic Constants (at 293 K) and Activation Parameters for the Rearrangement of 4b into 7 at Various p$S^+$ in D/W**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| p$S^+$[a] | 4.52 | 4.95 | 5.55 | 6.02 | 6.47 | 7.21 | 7.60 | 7.90 |
| $10^7(k_{A,R})_{4b}$[b] | 0.0930 | 0.239 | 0.742 | 2.03 | 4.79 | 27.5 | 57.2 | 118 |
| $\Delta H^{\ddagger}$[c] | 97 | 96 | 97 | 97 | 97 | 98 | 100 | 96 |
| $\Delta S^{\ddagger}$[d] | −68 | −64 | −51 | −41 | −33 | −15 | −3 | −10 |
| p$S^+$[e] | 8.95 | 9.45 | 9.78 | 10.13 | 10.33 | 10.58 | 10.79 | 11.02 |
| $10^5(k_{A,R})_{4b}$[b] | 15.2 | 43.7 | 89.5 | 186 | 282 | 468 | 748 | 1219 |
| $\Delta H^{\ddagger}$[c] | 81 | 81 | 79 | 79 | 80 | 81 | 78 | 78 |
| $\Delta S^{\ddagger}$[d] | −41 | −33 | −32 | −26 | −22 | −14 | −18 | −15 |
| p$S^+$[e] | 11.21 | 11.52 | 11.64 | 11.78 | 11.98 | 12.10 | 12.11 | 12.24 |
| $10(k_{A,R})_{4b}$[f] | 0.168 | 0.354 | 0.426 | 0.499 | 0.849 | 0.939 | 1.08 | 1.36 |
| p$S^+$[e] | 12.26 | 12.30 | 12.35 | 12.39 | 12.52 | 12.57 | 12.58 | 12.64 |
| $10(k_{A,R})_{4b}$[f] | 1.38 | 1.51 | 1.80 | 1.97 | 2.37 | 2.91 | 2.90 | 3.16 |
| p$S^+$[e] | 12.66 | 12.69 | 12.73 | 12.85 | 12.97 | 13.04 | 13.20 | 13.22 |
| $10(k_{A,R})_{4b}$[f] | 3.17 | 3.47 | 3.65 | 4.38 | 5.45 | 6.47 | 7.53 | 10.2 |
| p$S^+$[e] | 13.56 | 13.48 | 13.68 | 13.81 | 14.05 | | | |
| $10(k_{A,R})_{4b}$[f] | 12.5 | 15.7 | 19.4 | 25.8 | 39.7 | | | |

[a] Citrate buffer; total buffer concentration 0.0125 M. [b] $s^{-1}$, values calculated by activation parameters at 293 K. The experimental rate constants were measured in the range 283−334 K and were reproducible within ±3%. [c] kJ mol$^{-1}$. At 313 K the maximum error is 3 kJ mol$^{-1}$. [d] J K$^{-1}$ mol$^{-1}$. At 313 K the maximum error is 8 J K$^{-1}$ mol$^{-1}$. [e] Borate buffer; total buffer concentration 0.0125 M. [f] $s^{-1}$, values directly measured at 293 K.

The $S_N$ reaction appears to be the *push−pull* type (where the progress of the bond-forming step affects the bond-breaking step and vice-versa): the different effects of the nature of the substituents in the arylhydrazono moiety[7a,b] as well as in the 5-aryl group[16] on the reactivity in the two reaction pathways provide evidence for a concerted mechanism.

**Quantitative Features: Kinetic Study of the Rearrangement of 4b into 7.** In this line we have determined the apparent first-order rate constant for the rearrangement of **4b** into **7** in D/W ($k_{A,R})_{4b}$ (apparent first-order kinetic constant for the rearrangement of **4b**), in the presence of buffers in the p$S^+$ range 4.5−14.1 (Table 1). Under these conditions, the only reaction observed was the expected rearrangement, while at lower p$S^+$ (e.g., at p$S^+ \leq 3.5$) there was a significant competitive acidic hydrolysis of **4b** to **2b** and DNPH,[20] which obviously prevented a kinetic investigation at such p$S^+$ values and did not allow us to detect evidence for the occurrence of an uncatalyzed pathway. Kinetic data at 293 K have been calculated from activation parameters[22] or directly mea-

(13) (a) Boulton, A. J. *Lectures in Heterocyclic Chemistry;* Hetero-Corporation: Provo, Utah 1973. (b) Boulton, A. J.; Katritzky, A. R.; Majid-Hamid, A. *J. Chem. Soc. C* **1967**, 2005−2007. (c) Katritzky, A. R.; Gordeev, M. F. *Heterocycles* **1993**, *35*, 483−518. (d) Van der Plas, H. C. *Ring Transformations of Heterocycles*; Academic Press: London, 1973; vols. 1 and 2. (e) L'abbé, G. *J. Heterocycl. Chem.* **1984**, *21*, 627−638.

(14) On the use of heterocycles as masked functionalities, see: (a) Dondoni, A.; Marino, P. *J. Org. Chem.* **1991**, *56*, 5294−5301. (b) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, Switzerland, 1992; pp 377−437. (c) Dondoni, A.; Marra, A. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; Chapter 9, pp 173−205. (d) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585−4595.

(15) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 541−545.

(16) Frenna, V.; Vivona, N.; Caronia, A.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 785−789.

(17) An operational p*H* scale, p$S^+$,[18] was established in aqueous dioxane by employing the p$K_a$ values of acids determined by interpolation from the data reported by Harned and Owen.[19] For dioxane−water (1:1, v/v) the meter reading after calibration against buffers was not significantly different from p$S^+$, requiring a correction of only +0.16 to the meter reading.

(18) Bates, R. G. *Solute−Solvent Interaction*; Coetzee, J. F., Ritchie, C. D., Eds.; New York, 1969; p 46.

(19) Harned, H. S.; Owen, B. B. *The Physical Chemistry of Electrolytic Solution*, 3rd ed.; ACS Monograph No. 137, Reinhold: New York, 1970, pp 716, 755.

(20) Hydrolysis represents an usual behavior of arylhydrazones in acidic conditions: moreover we had previously pointed out[21] that in the case of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in D/W at p$S^+ < 3.8$ this reaction becomes a significant competitive one with respect to MHR, thus preventing the kinetic investigation of the rearrangement at low p$S^+$ values.

(21) Spinelli, D.; Corrao, A.; Frenna, V.; Vivona, N.; Ruccia, M.; Cusmano, G. *J. Heterocycl. Chem.* **1976**, *13*, 357−360.

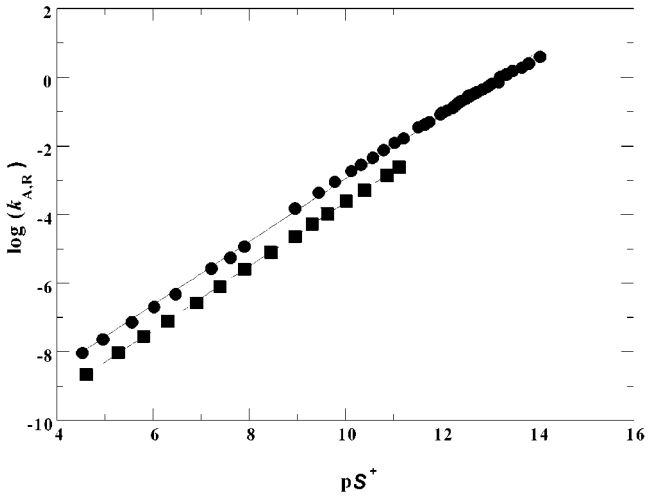
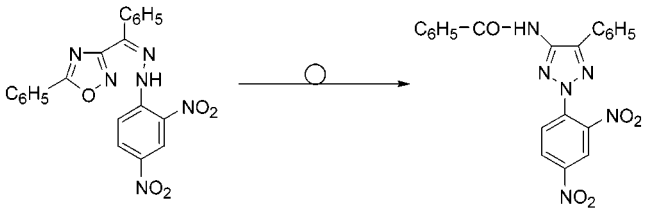



**Figure 1.** Plot of $\log(k_{A,R})_{\mathbf{4b}}$ ond of $\log(k_{A,R})_{\mathbf{10}}$ for the rearrangement of **4b** (●) and **10** (■; ref 23) into **7** and **11**, respectively, in D/W at 293 K versus p$S^+$.

**Scheme 5**



**10** **11**

sured: a logarithmic plot versus p$S^+$ is reported in Figure 1 (*s* 0.921 ± 0.004; *n* 45; *r* 0.9995) together with data concerning the rearrangement of the *Z*-2,4-dinitrophenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**10**) into *N*-[2-(2,4-dinitrophenyl)-5-phenyl-2*H*-1,2,3-triazol-4-yl]benzenecarboxamide (**11**) (Scheme 5).[23]

An examination of Figure 1 provides evidence for a large influence of the p$S^+$ on the reactivity for both substrates: **4b** and **10** have similar structures, both containing the same arylhydrazono moiety (i.e., the same nucleophile) and the same five-member ring system, the only difference being the substituent at C-5 of the 1,2,4-oxadiazole ring. They show similar reactivities [$(k_{A,R})_{\mathbf{4b}}/(k_{A,R})_{\mathbf{10}}$ = ca. 4], and the difference observed can be related to the "diaryloid effect"[21,24] (which stabilizes **10**, lowering its reactivity) and/or to some specific effect of the 5-amino group (which interacts with N-4[25] of the 1,2,4-oxadiazole ring, both lowering its aromaticity and increasing the leaving group ability of ring oxygen in **4b**).

**Quantitative Features: A Deep Insight on the Mechanism of MHR's.** The $\log(k_{A,R})_{\mathbf{4b}}$ versus p$S^+$ plot does not show a limiting value at high p$S^+$, notwithstanding the fact that at the highest p$S^+$ values **4b** is largely converted into its conjugate base.[26] Considering the general scheme of base-catalyzed reactions, two standard situations can be envisaged, namely the occurrence of an Arrhenius or of a van't Hoff complex.[27] In kinetic terms such situations correspond to a rate-determining decomposition or formation of the intermediate complex, respectively, causing the attainment or not of a limiting rate constant value (i.e., a "plateau") at high base concentrations. It must be remembered that the two different complexes also cause two different outcomes as far as base-catalysis is concerned: "specific" or "general" base-catalysis being expected and observed, respectively.

**Table 2. Calculated Apparent Kinetic Constants (at 298 K) and Activation Parameters for the Rearrangement of 4b into 7 at Various p$S^+$ and Borate Buffer Concentrations in D/W**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| p$S^+$ [a] | 8.95 | 9.45 | 9.78 | 10.13 | 10.33 | 10.58 | 10.79 | 11.02 |
| $10^4(k_{A,R})_{\mathbf{4b}}$ [b] | 2.70 | 7.76 | 15.8 | 32.6 | 49.7 | 83.1 | 131 | 212 |
| p$S^+$ [c] | 9.24 | 9.75 | 10.05 | 10.30 | 10.64 | 10.82 | 11.02 | |
| $10^4(k_{A,R})_{\mathbf{4b}}$ [b] | 5.76 | 18.1 | 32.9 | 63.4 | 132 | 190 | 285 | |
| $\Delta H^{\ddagger}$ [d] | 84 | 83 | 85 | 82 | 83 | 84 | 84 | |
| $\Delta S^{\ddagger}$ [e] | −25 | −19 | −8 | −12 | −2 | +3 | +6 | |
| p$S^+$ [f] | 9.27 | 9.74 | 10.04 | 10.30 | 10.62 | 10.83 | | |
| $10^4(k_{A,R})_{\mathbf{4b}}$ [b] | 10.1 | 28.8 | 56.9 | 102 | 198 | 304 | | |
| $\Delta H^{\ddagger}$ [d] | 85 | 85 | 83 | 85 | 85 | 84 | | |
| $\Delta S^{\ddagger}$ [e] | −17 | −11 | −9 | +0.5 | +6 | +8 | | |

[a] Total buffer concentration 0.0125 M. [b] $s^{-1}$, values calculated by activation parameters. The experimental rate constants were measured in the range 283−313 K and were reproducible within ±3%. [c] Total buffer concentration 0.0250 M. [d] kJ $mol^{-1}$. At 313 K the maximum error is 3 kJ $mol^{-1}$. [e] J $K^{-1}$ $mol^{-1}$. At 313 K the maximum error is 8 J $K^{-1}$ $mol^{-1}$. [f] Total buffer concentration 0.0500 M.

The plot of Figure 1 suggests the formation of a van't Hoff complex and accordingly the occurrence of general base-catalysis. To confirm this outcome we have studied the rearrangement in sodium borate−boric acid buffers, at various p$S^+$ and buffer concentrations, observing a $(k_{A,R})_{\mathbf{4b}}$ increase with buffer concentration at constant p$S^+$.[28] Fitting the $(k_{A,R})_{\mathbf{4b}}$ values measured at 298 K in the p$S^+$ range 9.0−11.0 (Table 2) to eq 1 (where $k_{OH}[OH^-]$, $k_B[B]$, and $k_A[A]$ represent the bimolecular reaction pathway with catalysis by hydroxide ion and by the basic (B) and the acidic (A) component of the buffer, respectively; whereas $k_{A,B}[A][B]$ and $k_{B,OH}[B][OH^-]$ imply a termolecular reaction pathway with catalysis by both A and B or both B and $OH^-$, respectively), which represents the most general form for a base-catalyzed reaction, we obtained the results collected in Table 3. While the statistical data give indication of the probable occurrence of the uncatalyzed ($k_u$) pathway, $k_A$, $k_{A,B}$, and $k_{B,OH}$ are clearly shown to give no significant contribution to $(k_{A,R})_{\mathbf{4b}}$, pointing out the occurrence of simple (bimolecular) general base-catalysis ($k_{OH}$ 445 and $k_B$ 2.13 $lmol^{-1}$

(22) Since in the p$S^+$ range studied the rate constants are composite values (see text) a discussion on the activation parameters is not meaningful. One can only observe that the reactivity variation is more entropy-dependent than enthalpy-dependent, as already observed in the rearrangement of other arylhydrazones of 5-substituted 3-benzoyl-1,2,4-oxadiazoles.[15,16,21]

(23) Frenna, V.; Macaluso, G.; Cosimelli, B.; Spinelli, D. Unpublished results. In the rearrangement of **10** general base-catalysis and absence of a limiting rate constant value have been observed.

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(25) (a) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: London, 1976. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Amsterdam, 2000; p 450.

(26) (a) Jones, L. A.; Mueller, N. L. *J. Org. Chem.* **1962**, *27*, 2356−2360. (b) Rajasekaran, K.; Baskaran, T.; Gnanasekaran, C. *Ind. J. Chem.* **1985**, *24A*, 82−84.

(27) For the definition of Arrhenius or van't Hoff complexes, see (a) Laidler, K. J. *Chemical Kinetics*; McGraw-Hill: London, 1965; p 457. (b) Laidler, K. J.; Bunting, P. S. *The Chemical Kinetics of Enzime Action*; Clarendon Press: Oxford, 1973; p 60.

(28) This outcome fits Hammett's criterion well (Hammett, L. P. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970, pp 322−323) for identification of the kind of catalysis.

**Table 3. Multiple Linear Regression Analysis[a] of Kinetic Data According to Eq 1 at 298 K**

| $10^5 k_u$, $s^{-1}$ | $k_{OH} \pm s_{k_{OH}}$, $lmol^{-1}\ s^{-1}$ | $k_B \pm s_{k_B}$, $lmol^{-1}\ s^{-1}$ | $k_A \pm s_{k_A}$, $lmol^{-1}\ s^{-1}$ | $k_{A,B} \pm s_{k_{A,B}}$, $l^2mol^{-2}\ s^{-1}$ | $k_{B,OH} \pm s_{k_{B,OH}}$, $l^2mol^{-2}\ s^{-1}$ | $R$ |
|---|---|---|---|---|---|---|
| $7 \pm 4$ | $445 \pm 5$ | $2.13 \pm 0.02$ | 0 | 0 | 0 | 0.9999 |
| $13 \pm 8$ | $442 \pm 6$ | $2.14 \pm 0.02$ | $-0.002 \pm 0.003$ | 0 | 0 | 0.9999 |
| $5 \pm 5$ | $449 \pm 7$ | $2.15 \pm 0.03$ | 0 | 0 | $-1311 \pm 1592$ | 0.9999 |
| $7 \pm 4$ | $462 \pm 10$ | $1.99 \pm 0.08$ | 0 | $3 \pm 1$ | 0 | 0.9990 |

[a] $s_{k_{OH}}$, $s_{k_B}$, $s_{k_A}$, $s_{k_{A,B}}$ and $s_{k_{B,OH}}$, standard deviations of $k_{OH}$, $k_B$, $k_A$, $k_{A,B}$, and $k_{B,OH}$, respectively. $R$, multiple correlation coefficient. The number of points is 21 throughout.

$s^{-1}$, respectively) and definitively supporting the formation of a van't Hoff complex.

$$(k_{A,R})_{\mathbf{4b}} = k_u + k_{OH}[OH^-] + k_B[B] + k_A[A] + k_{A,B}[A][B] + k_{B,OH}[B][OH^-] \quad (1)$$

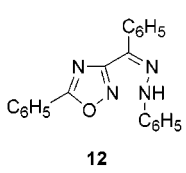
Some interesting and enlightening comparisons with our previous results can thus be made. First of all we can compare the behavior of **4b** with that of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**12**), for which the occurrence of "general" base-catalysis has likewise been shown:[7c] on going from **12** to **4b** a large increase of the rate constants for the two base-catalyzed pathways is observed [$(k_{OH})_{\mathbf{4b}}/(k_{OH})_{\mathbf{12}}$ and $(k_B)_{\mathbf{4b}}/(k_B)_{\mathbf{12}}$ being ca. 120 and 220, respectively], in good agreement with the stronger acidic character of the arylhydrazono proton of **4b** with respect to that of **12**.

More interestingly, unlike **4b** and **10**, both the 3-(*p*-nitrophenyl)ureine of 5-phenyl-1,2,4-oxadiazole (**13**)[29] and *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N*′-(*p*-nitrophenyl)formamidine (**14**)[30] rearrange showing "specific" base-catalysis and a limiting rate-constant value at p$S^+$ values where the starting material is quantitatively transformed into its conjugate base. As compounds **4b**, **10**, **13**, and **14** are characterized by the same starting heteroaromatic ring but by different side chains, the question arises of how the nature of the latter affect the nature of the intermediate complex (Arrhenius or van't Hoff) which is formed along the MHR coordinate.

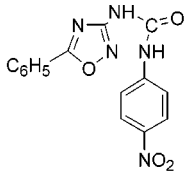
In this regard it must first of all be remarked that complete deprotonation of substrate in the p$S^+$ range examined requires only *one* activating nitro group for **13** or **14**, as compared to the *two* nitro groups necessary in **4b** or **10**. As a matter of fact, in the case of **13** and **14** the conjugation with the nitrophenyl ring as well as with the upper portion of the side chain of the oxadiazole ring (typical ureine and formamidine resonance, respectively) contribute to the acidic character of the $N_\alpha$-H proton, stabilizing by resonance the conjugate base and hence furthermore lowering its nucleophilicity, so giving a true Arrhenius intermediate.

Such effects on both acidity and nucleophilicity surely play a less important role in **4b** as well as in **10**, whose less resonance-stabilized conjugate bases are rendered even more reactive toward electrophiles by the α-effect[31] typical of hydrazono moieties.

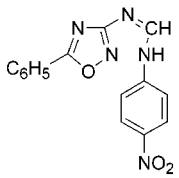
Moreover, the peculiar characteristics of MHR processes are, at least in part, linked to the fact that these ring−ring interconversions occur as internal (intramolecular) nucleophilic substitutions: because in $S_N2$ reactions the energy necessary to break the starting bond is supplied by the simultaneous formation of the new bond, the aromaticity of both the starting and the final ring represents herein a further important aspect. Thus the MHR reactivity of **10**, **13**, and **14** (which are characterized by the same 5-phenyl-1,2,4-oxadiazole "starting" ring) is differentially affected by the aromaticity of the relevant final rings (2*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, and 1*H*-1,2,4-triazolin-5-one, respectively).




**12**




**13**




**14**

As a result, both factors identified as relevant in the discussion above, i.e., nucleophilicity of the attacking $N_\alpha$ atom (arylhydrazono > arylformamidino and arylureino) and aromaticity (and hence stability) of the resulting heteroring (2*H*-1,2,3-triazole > 1*H*-1,2,4-triazole and 1*H*-1,2,4-triazolin-5-one) cooperatively justify the behavior observed.

Of course, both the higher aromatic character of the final triazole ring[32,33] with respect to the initial oxadiazole heterocycle[32,33] and the formation of a strongly resonance-stabilized amido group[12] definitely contribute to the general high stability of the final products of the MHR processes discussed herein.

It should be also stressed that the reactivity comparisons above clearly identify the aromaticity of the starting and of the final ring as important factors affecting the MHR behavior of suitably functionalized heterocyclic derivatives with respect to usual nucleophilic substitutions.

Finally, one can reasonably suppose that all the factors discussed affect not only the reaction rate but also its mechanism: a high or low reactivity causing an early or late transition state, respectively, and hence the occurrence of general or specific base-catalyis, well in agreement with the experimental data herein.

## Experimental Section

**General Methods.** $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini 300 Instrument in the Fourier transform mode at 21.0 ± 0.5 °C in DMSO-$d_6$. Chemical shifts ($\delta$) in ppm

(29) Frenna, V.; Spinelli, D.; Consiglio, G. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1289−1295.

(30) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D.; Mezzina, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1339−1343.

(31) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1988, p 212 and references therein.

(32) Several indexes have been used to evaluate the aromaticity of five-membered heterocycles.[33−35] "The relative "diene character" or "bond fixation" .... may be considered a measure of their lack of aromaticity."[34] In line with these considerations "a new index of aromatic character has been devised upon a statistical evaluation of the deviation in peripheral bond orders" by Bird.[33] His results, strengthened by Katritzky et al.[35] and Bean[34] considerations, indicate the following aromaticity sequence: 2*H*-1,2,3-triazole > 1*H*-1,2,4-triazole ≫ 1,2,4-oxadiazole (Bird's $I_5$ indexes: 88, 81, and 39, respectively). The higher aromaticity of isoxazole ($I_5$ = 47) with respect to 1,2,4-oxadiazole is in turn confirmed (also compare data in ref 11).

(33) Bird, C. W. *Tetrahedron* **1985**, *41*, 1409−1414.

from tetramethylsilane and coupling constants in Hz, respectively, are reported. Mass spectra were recorded on a VG70 70E apparatus. All melting points were obtained with a Reichert Termovar apparatus. Solvents were removed under reduced pressure.

**(*Z*)-(5-Amino-1,2,4-oxadiazol-3-yl)(phenyl)methanone *N*-(2,4-dinitrophenyl)hydrazone (4b).** A solution of 2,4-dinitrophenylhydrazine (2.40 g, 12 mmol) in concentrated $H_2SO_4$ (18 mL) was added carefully, under stirring, to ethanol (78 mL). A solution of 5-amino-3-benzoyl-1,2,4-oxadiazole (0.76 g; 4 mmol) in ethanol (85 mL) was added dropwise under stirring to the previous one. After standing 24 h at room temperature in the dark, the orange precipitate was collected and characterized (mp 190 °C with dec, 0.95 g; 64%).[8] Neutralization of mother liquors with bases afforded, by extraction with $CHCl_3$, a second portion (0.08 g; 5%) of **4b**. $\delta_H$ 13.52 (s, exch., 1H, NH); 8.92 [d, $^4J$ = 2.6 Hz, 1H, H-3($N_\alpha$)]; 8.48 (s, exch., 2H, $NH_2$); 8.47 [dd, $^3J$ = 9.5, $^4J$ = 2.6 Hz, 1H, H-5($N_\alpha$)]; 8.22 [d, $^3J$ = 9.5 Hz, 1H, H-6($N_\alpha$)]; 7.89−7.87 [m, 2H, H-2(C-3′) and H-6(C-3′)]; 7.50−7.48 [m, 3H, H-3(C-3′), H-4(C-3′) and H-5(C-3′)]. $\delta_C$ 171.5; 162.1; 144.1; 138.4; 138.4; 134.9; 130.7; 130.0; 129.7; 128.6; 128.1; 122.5; 116.9. MS *m*/*z* 352 ($M^+$ − 17, 100%); 326 (77); 260 (12); 129 (13); 104 (31); 77 (37).

***N*-(2,4-Dinitrophenyl)-5-phenyl-2*H*-1,2,3-triazol-4-ylurea (7).** A solution of **4b** (0.74 g, 2 mmol) in dimethyl sulfoxide (8 mL) was kept, under stirring, at room temperature for 2 days. Then water (15 mL) was added, and the yellowish precipitate was collected by filtration and characterized [mp 212−213 °C, from ethanol (lit.[3] mp 212−213 °C), 0.61 g; 82%]. $\delta_H$ 8.98 [d, $^4J$ = 2.5 Hz, 1H, H-3(N-2)]; 8.85 (s, exch., 1H, NH); 8.65 [dd, $^3J$ = 9.0, $^4J$ = 2.5 Hz, 1H, H-5(N-2)]; 8.36 [d, $^3J$ = 9.0 Hz, 1H, H-6(N-2)]; 7.80−7.77 [m, 2H, H-2(C-5) and H-6(C-5)]; 7.56−7.48 [m, 3H, H-3(C-5), H-4(C-5) and H-5(C-5)]; 6.34 (s, exch., 2H, $NH_2$). $\delta_C$ 155.4; 145.4; 145.1; 144.1; 140.8; 133.7; 129.4; 128.7; 128.4; 127.9; 126.9; 123.9; 121.1. MS *m*/*z* 352 ($M^+$ − 17, 37%); 326 (100); 131 (15); 119 (10); 105 (12); 104 (42); 103 (17); 89 (11); 77 (47); 76 (21); 75 (24); 74 (11); 63 (14); 62 (22); 51 (15).

**p$S^+$ Scale Definition and Kinetic Measurements.** Water and dioxane were purified according to the methods previously reported.[36] Details on operational pH scale used (p$S^+$) have already been reported.[17,21] The kinetics were followed spectrophotometrically as previously described[21] by measuring the disappearance of **4b** at 400 nm (where the observed optical density difference between starting and final products is largest) by using a UV−vis spectrophotometer ZEISS PMQ II (p$S^+$ 4.5−11.2) or Varian Cary 1E equipped with the rapid kinetic accessory SFA-11 (p$S^+$ 11.2−14.1). The rate constants are accurate within ±3%. Apparent first-order kinetic constants in D/W directly measured (p$S^+$ 11.2−14.1) or calculated (p$S^+$ 4.5−11.2) at 293 K together with thermodynamic parameters are reported in Table 1.

The values of $(k_{A,R})_{\mathbf{4b}}$ for general base-catalysis determination have been calculated at 298 K from thermodynamic parameters in the p$S^+$ range 9.0−11.0 (Table 2) and managed as previously described.[7c]

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