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Acid- and Base-Catalysis in the Mononuclear Rearrangement of Some (*Z*)-Arylhydrazones of 5-Amino-3-benzoyl-1,2,4-oxadiazole in Toluene: Effect of Substituents on the Course of Reaction

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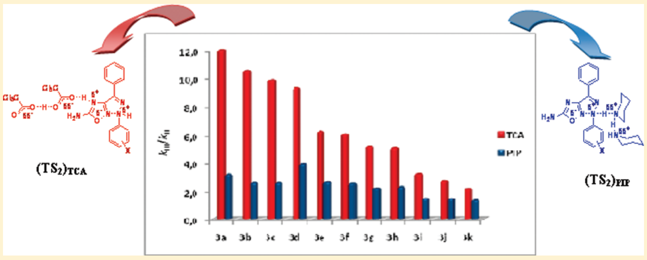
S *Supporting Information*

ABSTRACT: The reaction rates for the rearrangement of eleven (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole **3a**−**k** into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas **4a**−**k** in the presence of trichloroacetic acid or of piperidine have been determined in toluene at 313.1 K. The results have been related to the effect of the aryl substituent by using Hammett and/or Ingold−Yukawa−Tsuno correlations and have been compared with those previously collected in a protic polar solvent (dioxane/water) as well as with those on the analogous rearrangement of the corresponding (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **1a**−**k** in benzene. Some light can thus be shed on the general differences of chemical reactivity between protic polar (or dipolar aprotic) and apolar solvents.



INTRODUCTION

Heterocyclic compounds play a central role in chemistry; from medicinal[1] to organic chemistry[2] and from materials science[3] to biochemistry[4] every branch of chemistry is in debt to heterocycles.

Several drugs (from antibiotics to calcium channel blockers),[5] many organic syntheses (from those of aldehydes and acids to those of amines and aminoacids)[6] and studies on reaction mechanisms (from ANRORC to azole-into-azole interconversions),[7] a number of nanomaterials (from molecular devices and machines to noncarbon nanotubes),[8] and numberless biological processes (from the chlorophyllian synthesis to biological oxidation, from the hemoglobin-mediated oxygen transfer to DNA/RNA function in protein syntheses, and so on)[9] exploit heterocyclic systems, very often containing nitrogen atom(s) in the heteroring.[10]

Syntheses and mechanistic studies concerning modifications of heterocycles represent an important part of today's chemistry: special interest must be attributed to nitrogen-containing heterocycles, with both five- or six-membered rings, especially in the instance of biological processes.[5,9] For all of these reasons we have addressed our interest to synthetic applications[7d,e,j,k,11] and mechanistic studies of mononuclear rearrangements of heterocycles (MRHs, see Scheme 1),[7j−l,12a−12d,12e−12o] a class of azole-into-azole interconversion classified in the 1960s by Boulton and Katritzky.[7h,i] MRHs involve a side chain (frequently joined to the starting heterocycle through a continuous π-electron system) and cover the synthesis of a large number of five-membered, nitrogen-containing heterocycles.[7h−k,11]

Looking at the mechanism of MRHs, we have investigated the rearrangement of several (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1**) into the relevant 2-aryl-4-benzoylamino-5-phenyl-2*H*-1,2,3-triazoles (**2**) (Scheme 2)[7j,k,12a−12d,12e−12o] and have observed that the reaction (typically a S_Ni process with a quasi-aromatic transition state, 10 π-electrons in a bicyclic structure being involved)[7l,12k,12n] can take place via different pathways not only structure- but also solvent-dependent. Thus in a solvent such as a dioxane/water mixture (D/W, a polar medium able to interact with starting and final products by means of both donor and acceptor hydrogen bonds, thus behaving as actor in the process through the exploitation of its amphiprotic character)[12k] two different paths (general-base-catalyzed and uncatalyzed)[12a,b,d] can be observed (Figure 1). Interestingly enough, also aprotic dipolar solvents such as DMSO do favor the rearrangement of (*Z*)-arylhydrazones; for example, we have observed that during the time required for the registration of the ^{13}C NMR spectra (*Z*)-arylhydrazones **3a**−**k** can rearrange into the relevant triazoles **4a**−**k**. This peculiar behavior could be related to different factors linked to the particular nature of DMSO, from the general ability of an aprotic dipolar solvent in favoring some nucleophilic substitutions, to its specific capability in behaving as proton shuttle due to its hydrogen-bond acceptor (HBA) character, to

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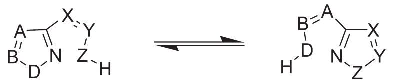
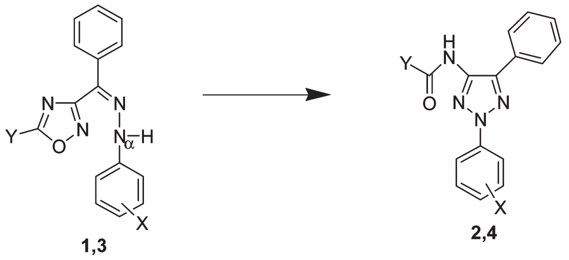
Scheme 1. Representation of the Mononuclear Rearrangement of Heterocycles as Proposed by Boulton, Katritzky, and Majid-Hamid[7h]



Scheme 2. MRH of 1 or 3 into 2 or 4, Respectively



1,3

2,4

1, 2: Y = Ph
3, 4: Y = NH_2

a: X = 4-OCH_3
b: X =4-CH_3
c: X = 3-CH_3
d: X = H
e: X = 4-Cl
f: X = 4-Br
g: X = 3-Cl
h: X = 3-Br
i: X = 4-CN
j: X = 3-NO_2
k: X = 4-NO_2

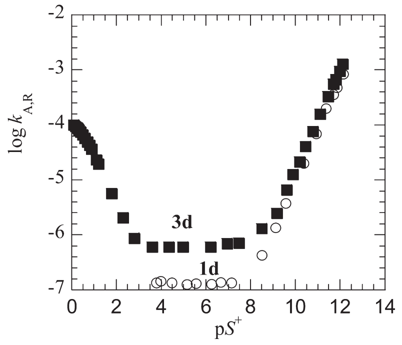


Figure 1. Plot of log $k_{A,R}$ vs pS^+ (an operational scale of proton concentration in the considered D/W mixture)[12a] for the rearrangement of **1d** (○) and **3d** (■) into **2d** and **4d** in D/W (1:1; v/v) at 293.1 K.

its global solvent characteristics (values of relative permittivity, of dipole moment, of E_T or $E^N{}_T$, and so on).

An in-depth computational study at the density functional theory (DFT) level of the uncatalyzed path for the rearrangement of the (*Z*)-hydrazone of 3-formyl-1,2,4-oxadiazole has brought to evidence the active role of water molecules able to behave as proton shuttles.[12k] As a matter of fact, it has been found that in the gas phase one or two molecules of water, because of their amphiprotic properties, would cause an increase of the rate constant by a factor of 10^{15} and 10^{18}, respectively, rendering possible a rearrangement otherwise practically impossible in the gas phase (a half-life of ca. 10^{10} years was calculated for the more favorable reaction pathway in the gas phase).

In line with previsions based on the DFT calculations in the gas phase and at variance with the in-presence-of-water behavior, in solvents such as benzene (PhH) or toluene (TOL) (solvents typically apolar and unable to give significant interactions with starting and final products) only one reaction path for (*Z*)-arylhydrazones **1** is possible. Thus, in the presence of quite strong bases[12p] (several primary, secondary, and tertiary amines have been tested, with special attention devoted to the use of piperidine (PIP)) the general-base-catalyzed path can occur.[12c,e] In fact, the uncatalyzed path does not occur at all, in line both with the above DFT results and with the observation that compounds **1** in the solid state at room temperature stay unchanged for very long time (years).

Furthermore, by examining the rearrangement in D/W mixture of some (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole (**3**) into the relevant (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (**4**) (see Scheme 2), we have observed that now the reaction can occur via three different pathways, again structure- and solvent-dependent (see Figure 1, where the course of the MRH of **1d** and **3d** in D/W are compared as a function of proton concentration).[12g,m]

Thus in a solvent such as D/W mixture, thanks to the presence of the amino group, three different paths can be observed (as a new specific-acid-catalyzed path is now possible),[12g,m] whereas in an apolar solvent such as TOL only two paths are possible (a general-base- or a general-acid-catalyzed path in the presence of quite strong bases or acids, respectively).[12j] Interestingly the (*Z*)-2,4-dinitrophenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole and of 5-amino-3-benzoyl-1,2,4-oxadiazole in D/W rearrange only via the base-catalyzed pathway, as at high proton concentration (e.g., at pS^+ < 3.5) in both cases only a hydrolysis of the substrates can occur.[13] In contrast, in an apolar and anhydrous solvent (TOL) the (*Z*)-2,4-dinitrophenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole in the presence of trichloroacetic acid (TCA) rearranges also via a general-acid-catalyzed path.[12j]

Thus, the use of an apolar solvent (TOL) has been particularly fruitful, and for this reason the MRH of **3d** has been examined in the presence of several halogenated acetic acids (HAAs) or of PIP, providing interesting information on the above two reaction paths. In both cases the reaction requires either one or two molecules of HAA or of PIP, according to eqs 1 and 2,[14a] clearly indicating the efficacy of catalysis-of-catalysis in an apolar solvent.[12c,e] Once more in TOL the uncatalyzed path was not observed.

Moreover we have very recently observed that **3d** rearranges in TOL in the presence of some 2,2-dichloroalkanoic acids (HAs; carboxylic acids with linear and branched chains containing 3−8 atoms have been examined) requiring only one molecule of HA.[14b] This peculiar behavior has been attributed to both steric and electronic effects.[15]

$$[(k_{A,R})_{HAA}] = k_{II}[HAA] + k_{III}[HAA]^2 \qquad (1)$$

$$[(k_{A,R})_{PIP}] = k_{II}[PIP] + k_{III}[PIP]^2 \qquad (2)$$

The obtained results have brought to evidence that the reactivity dependence on one or two molecules of the catalyst is linked to the structure of the arylhydrazono moiety and to the very nature of the catalyst itself. Moreover, depending on the acidic or basic catalyst used, different k_{III}/k_{II} ratios can be calculated.[14a]

To get further information on the mechanisms involved, we examine herein the MRH of a series of eleven *meta*- or *para*-substituted (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole (Scheme 2; **3a**−**k**, X = 4-OCH_3, 4-CH_3, 3-CH_3, H, 4-Cl, 4-Br, 3-Cl, 3-Br, 4-CN, 3-NO_2, 4-NO_2) into the relevant

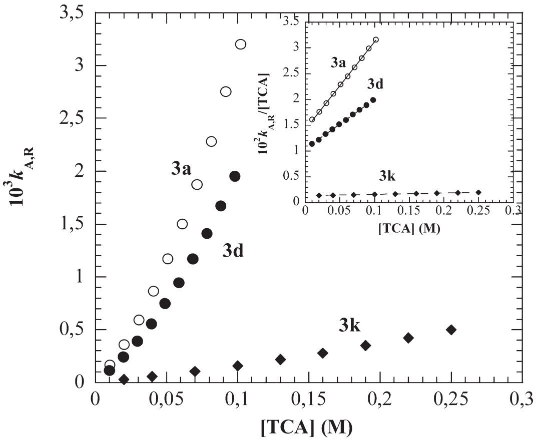


Figure 2. Plot of $k_{A,R}$ for the rearrangements of **3a**, **3d**, and **3k** into **4a**, **4d**, and **4k** at 313.1 K in TOL versus [TCA]. Inset: plot of $k_{A,R}$/[TCA] for the rearrangements of **3a**, **3d**, and **3k** into **4a**, **4d**, and **4k** at 313.1 K in TOL versus [TCA].

(2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas (**4a**−**k**) in the presence of TCA or of PIP in TOL by means of free-energy relationships. The results will be also compared with those previously collected on the rearrangement of the corresponding (*Z*)-arylhydrazones **1a**−**k** into **2a**−**k** in the presence of PIP in PhH.[12f]

We have chosen a large set of substrates containing *meta* and *para* substituents able to cover a significant range of resonance and inductive effects:[16] from the strong electron-donating *p*-methoxy to the strong electron-withdrawing *p*-cyano and *p*-nitro groups, from the electron-repelling *m*- and *p*-methyl groups to the electron-attracting *m*-halogens or *m*-nitro group. In the whole the examined substituents cover ca. one unity in terms of Hammett substituent constants[16] and ca. two units in terms of resonance substituent constants.[16] Therefore the results of the obtained free energy relationships (FER) are foreseen to be highly significant.

Considering the different aspects examined in our studies on MRH, we think that because of their versatility (possible pathways, usable catalysts, effects of the used solvents (protic polar or aprotic), variable structures of the starting (*Z*)-arylhydrazones) the considered rearrangements could be used as reference reaction to gain general information on the reactivity as a function of several parameters. In this line we are collecting these new kinetic data that as a matter of fact could be compared to results in protic polar solvents to gain general information on reactivity as a function of different parameters.

RESULTS AND DISCUSSION

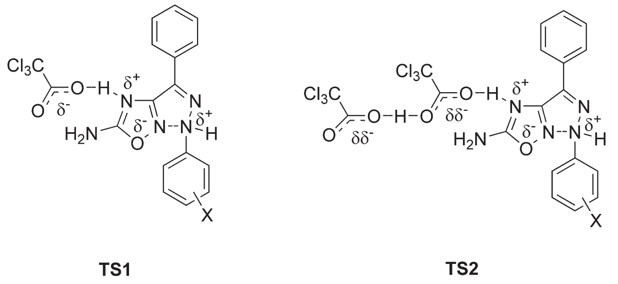
Rearrangement of (*Z*)-Arylhydrazones 3a−k in the Presence of TCA in TOL: General Acid-Catalyzed Pathway. The rate constants of the MRH of the (*Z*)-arylhydrazones **3a**−**k** have been measured at 313.1 K at different concentrations of TCA. As in the instance of **3d**[12j] we always observed an upward curvilinear dependence of apparent first-order rate constants $[(k_{A,R})_{TCA}]$ versus [TCA] (indicating that complex acid-catalyzed pathways concur; see Figure 2, where zero-intercepts are anyway always observed) and, in contrast, an excellent linear plot of $[(k_{A,R})_{TCA}]$/[TCA] versus [TCA] (see inset of Figure 2, the relevant values are collected in Table A of the Supporting Information). The intercepts and the slopes of eq 3 (see data in Table 1) allow calculation of the second- (k_{II}) and the third-order (k_{III}) rate constants, once more showing that the rearrangement in TOL occurs via two different reaction pathways, requiring one or two molecules of TCA, respectively. The two relevant transition states (TS) are reported in Scheme 3.

Table 1. Linear Regression Analysis[a] of the Apparent Rate Constants for the Rearrangement of 3a−k into 4a−k at 313.1 K in the Presence of TCA

compd	$k_{II} \pm s_{II}$ (L mol^{-1} s^{-1})	$k_{III} \pm s_{III}$ (L mol^{-1})^2 s^{-1}	k_{III}/k_{II}
3a	$(1.42 \pm 0.01) \times 10^{-2}$	$(1.70 \pm 0.01) \times 10^{-1}$	12.0
3b	$(1.33 \pm 0.01) \times 10^{-2}$	$(1.40 \pm 0.01) \times 10^{-1}$	10.5
3c	$(1.23 \pm 0.00) \times 10^{-2}$	$(1.21 \pm 0.01) \times 10^{-1}$	9.84
3d	$(1.04 \pm 0.00) \times 10^{-2}$	$(9.67 \pm 0.07) \times 10^{-2}$	9.30
3e	$(5.49 \pm 0.04) \times 10^{-3}$	$(3.42 \pm 0.03) \times 10^{-2}$	6.23
3f	$(5.25 \pm 0.02) \times 10^{-3}$	$(3.18 \pm 0.02) \times 10^{-2}$	6.06
3g	$(4.59 \pm 0.02) \times 10^{-3}$	$(2.35 \pm 0.02) \times 10^{-2}$	5.12
3h	$(4.31 \pm 0.02) \times 10^{-3}$	$(2.17 \pm 0.02) \times 10^{-2}$	5.03
3i	$(2.04 \pm 0.00) \times 10^{-3}$	$(6.50 \pm 0.03) \times 10^{-3}$	3.19
3j	$(1.79 \pm 0.00) \times 10^{-3}$	$(4.86 \pm 0.01) \times 10^{-3}$	2.72
3k	$(1.30 \pm 0.00) \times 10^{-3}$	$(2.81 \pm 0.02) \times 10^{-3}$	2.16

[a] s_{II} and s_{III} are the standard deviations of the regression parameters k_{II} and k_{III}, respectively. $r \geq 0.9998$. Number of experimental points $[(k_{A,R})_{TCA}]$: 9−10. The confidence levels for significance of regression parameters are all better than 99.9%.

Scheme 3. Representation of the TS[a] for the Second- and Third-Order General Acid-Catalyzed Pathways



[a] Please take note of their quasi-aromatic structure, as ten π-electrons are involved in a biclycic system.

$$[(k_{A,R})_{HAA}]/[TCA] = k_{II} + k_{III}[TCA] \quad (3)$$

An examination of kinetic data concerning the rearrangement of **3a**−**k** in the presence of TCA brings to evidence the following points:

(i) The reactivity increases on going from (*Z*)-arylhydrazones containing electron-withdrawing to those containing electron-donating substituents for both reaction paths (the ranges of k_{II} and k_{III} values are 1.30×10^{-3} to 1.42×10^{-2} L mol^{-1} s^{-1} and 2.81×10^{-3} to 0.170 L^2 mol^{-2} s^{-1}, respectively). This trend depends on the two main effects exerted by the substituents on the (*Z*)-arylhydrazones **3**, whereby electron repulsion/donation by the substituent increases both the basicity of the N-4 atom of the 1,2,4-oxadiazole ring (which favors the protonation and then the acidic catalysis) and the nucleophilic character of N_α of the arylhydrazono moiety (which favors the S_Ni process).

(ii) The reactivity increase observed with electron-donating susbstituents is higher for the path requiring two than for that requiring one molecule of TCA [the k_{III}/k_{II} ratios ranging from 2.16 for **3k** ($X = 4\text{-}NO_2$) to 12.0 for **3a** ($X = 4\text{-}OCH_3$), respectively]. That is, the more basic[17] is the substrate (whose principal basic center is N-4 of the 1,2,4-oxadiazole ring),[12g] the more significant becomes the complex path. This observation agrees with some of our previous results. For example, measuring the acidity in TOL (constants of ion-pair formation with 4-nitroaniline) of several HAAs, we observed that the stronger are the acids, the higher are the relevant K_3/K_2 ratios;[14a] moreover measuring the rearrangement rates of the (*Z*)-phenylhydrazone **3d** with different HAAs we have again observed that the stronger are the acids, the higher are the relevant k_{III}/k_{II} ratios.[14a] Finally, measuring the basicity of some nitroanilines with trifluoroacetic acid, we observed that the stronger are the bases, the higher are the relevant K_3/K_2 ratios.[14a] In conclusion, the stronger are the bases and/or the acids involved, the higher is the weight of the complex acid−base process or of the catalysis-of-catalysis.

(iii) At low [TCA] the more important path is the simple one, whereas at high [TCA] the two paths could have comparable importance or the complex one could be pre-eminent.

(iv) The calculated k_{II} and k_{III} values and the relevant k_{III}/k_{II} ratios have been tentatively correlated with the electronic effects of the substituents by using the simple Hammett equation,[18a] obtaining only good relationships ($\rho = -1.00 \pm 0.05, -1.69 \pm 0.09$, and -0.686 ± 0.037; $i = 0.01 \pm 0.02, -0.08 \pm 0.04$, and -0.03 ± 0.02 ; $n = 11$; $r = 0.988$, 0.988, and 0.987, respectively). Remembering the results obtained in a previous study of the substituent effects for the acidic path in D/W mixture,[12m] we have attempted a relationship versus the relevant $k_{A,R}$ measured (or the substituent constants calculated at $pS^+ = 1.0$) in D/W as well as by using an Ingold−Yukawa−Tsuno (IYT) treatment,[18b] thus obtaining excellent statistical results ($r \geq 0.999$; see details in Table C of Supporting Information. In eqs 4−6 the results of the IYT treatment are reported (the used substituent constants derive from ref 16).

$$\log(k_{II})_X/(k_{II})_H = (0.988 \pm 0.007)\sigma^n + (0.07 \pm 0.01)\Delta\sigma_R^+ + (0.28 \pm 0.04)\Delta\sigma_R^-$$
$$R = 0.9998;\ n = 11;\ i = 0.01 \pm 0.03 \tag{4}$$

$$\log(k_{III})_X/(k_{III})_H = -(1.62 \pm 0.01)\sigma^n + (0.09 \pm 0.02)\Delta\sigma_R^+ + (0.34 \pm 0.03)\Delta\sigma_R^-$$
$$R = 0.9998;\ n = 11;\ i = -0.01 \pm 0.00 \tag{5}$$

$$\log[(k_{III})_X/(k_{II})_X]/[(k_{III})_H/(k_{II})_H] = (0.644 \pm 0.008)\sigma^n + (0.13 \pm 0.02)\Delta\sigma_R + (0.39 \pm 0.01)\Delta\sigma_R^-$$
$$R = 0.9994;\ n = 11;\ i = -0.012 \pm 0.004 \tag{6}$$

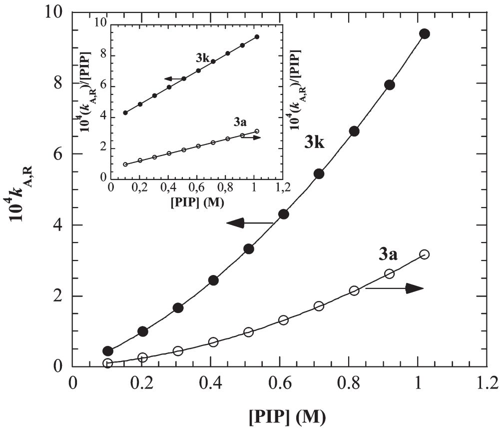


Figure 3. Plot of $k_{A,R}$ for the rearrangements of **3a** and **3k** into **4a** and **4k** at 313.1 K in TOL versus [PIP]. Inset: Plot of $k_{A,R}$/[PIP] for the rearrangements of **3a** and **3k** into **4a** and **4k** at 313.1 K in TOL versus [PIP].

Table 2. Linear Regression Analysis[a] of the Apparent Rate Constants for the Rearrangement of 3a−k into 4a−k at 313.1 K in the Presence of Piperidine

compd	$k_{II} \pm s_{II}$ (L mol^{-1} s^{-1})	$k_{III} \pm s_{III}$ (L mol^{-1})^2 s^{-1}	k_{III}/k_{II}
3a	$(7.31 \pm 0.07) \times 10^{-6}$	$(2.31 \pm 0.01) \times 10^{-5}$	3.16
3b	$(6.31 \pm 0.06) \times 10^{-6}$	$(1.65 \pm 0.01) \times 10^{-5}$	2.61
3c	$(5.45 \pm 0.06) \times 10^{-6}$	$(1.42 \pm 0.01) \times 10^{-5}$	2.61
3d	$(4.99 \pm 0.08) \times 10^{-6}$	$(1.94 \pm 0.01) \times 10^{-5}$	3.89
3e	$(1.97 \pm 0.02) \times 10^{-5}$	$(5.22 \pm 0.04) \times 10^{-5}$	2.65
3f	$(2.18 \pm 0.02) \times 10^{-5}$	$(5.56 \pm 0.03) \times 10^{-5}$	2.55
3g	$(3.91 \pm 0.03) \times 10^{-5}$	$(8.61 \pm 0.06) \times 10^{-5}$	2.20
3h	$(4.10 \pm 0.03) \times 10^{-5}$	$(9.35 \pm 0.05) \times 10^{-5}$	2.28
3i	$(2.30 \pm 0.02) \times 10^{-4}$	$(3.45 \pm 0.03) \times 10^{-4}$	1.50
3j	$(1.79 \pm 0.01) \times 10^{-4}$	$(2.67 \pm 0.02) \times 10^{-4}$	1.49
3k	$(3.81 \pm 0.02) \times 10^{-4}$	$(5.30 \pm 0.03) \times 10^{-4}$	1.39

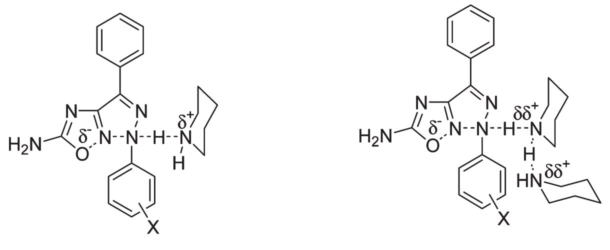
[a] s_{II} and s_{III} are the standard deviations of the regression parameters k_{II} and k_{III}, respectively. $r \geq 0.9998$. Number of experimental points $[(k_{A,R})_{PIP}]$: 10. The confidence levels for significance of regression parameters are all better than 99.9%.

Rearrangement of (*Z*)-Arylhydrazones 3a−k in the Presence of PIP in TOL: General-Base-Catalyzed Pathway. The rate constants of the MRH of the (*Z*)-arylhydrazones **3a**−**k** have been measured in TOL at different concentrations of PIP and at 313.1 K; $(k_{A,R})_{PIP}$ values, together with the calculated $[(k_{A,R})_{PIP}]$/[PIP] ratios are collected in Table B of the Supporting Information. The nonlinear increase (upward curvilinear dependence) of $(k_{A,R})_{PIP}$ versus [PIP] once more[12j] indicates that a complex base-catalyzed pathway occurs with all of the examined substrates, related to a catalysis-of-catalysis process.[12c,e,j]

Following the above calculation procedures previously used by some of us,[12c,e,j] we have calculated the second- (k_{II}) and the third-order (k_{III}) rate constants by using eq 2 (see Figure 3 and data in Table 2), once more showing that the rearrangement in TOL occurs via two different reaction pathways, whose TSs are reported in Scheme 4.

Concerning the substituent effect on the rearrangement rates we have observed that second- (k_{II}) as well as third-order (k_{III}) rate constants show a nonlinear substituent-dependent behavior:

Scheme 4. Representation of the TSs[a] for the Second- and Third-Order General-Base-Catalyzed Pathways



TS1 **TS2**

[a] Once more their quasi-aromatic character can be evidenced.

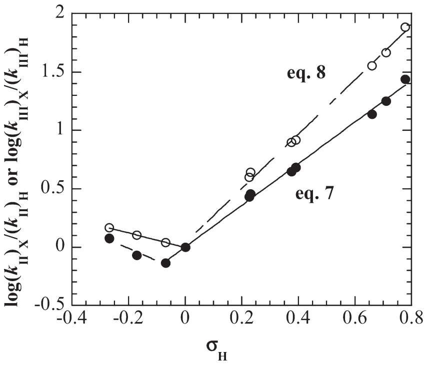


Figure 4. Plot of $\log(k_{II})_X/(k_{II})_H$ (○) or $\log(k_{III})_X/(k_{III})_H$ (●) versus σ_H for the rearrangement of **3a**−**k** into **4a**−**k**, at 313.1 K in TOL in the presence of PIP.

both of them give concave-upward Hammett plots (see Figure 4) with the reactivity minimum centered on the unsubstituted **3d** or on the *m*-methyl-substituted **3c** (*Z*)-arylhydrazones for k_{II} and k_{III}, respectively. This behavior parallels those observed studying the rearrangement of the (*Z*)-arylhydrazones **1**[12d] and **3**[12m] in D/W as well as of **1** in PhH.[12f]

Looking at the right side of the Hammett plot in Figure 4, one can observe, for both k_{II} and k_{III}, the occurrence of excellent linear FERs ($r = 0.998$) with positive susceptibility constants (see eqs 7 and 8) with a strong increase of the reactivity on going toward (*Z*)-arylhydrazones containing stronger and stronger electron-withdrawing groups. This is in line with the expected electronic effects of the substituents that, by increasing the acidic character of the arylhydrazonic proton, favor the base-catalysis. In the instance of k_{II} the substituents range from hydrogen to *p*-nitro (**3d**−**k**), whereas in the instance of k_{III} they range from *m*-methyl to *p*-nitro (**3c**−**k**).

$$\log(k_{II})_X/(k_{II})_H = (2.33 \pm 0.06)\sigma_H + (0.04 \pm 0.03) \quad r = 0.998;\ n = 8 \tag{7}$$

$$\log(k_{III})_X/(k_{III})_H = (1.81 \pm 0.05)\sigma_H + (0.00 \pm 0.02) \quad r = 0.998;\ n = 9 \tag{8}$$

Looking at the left side of the Hammett plot in Figure 4 one can observe the occurrence of excellent or good linear FERs ($r = 0.9994$ and 0.97, respectively) with negative susceptibility constants (see eqs 9 and 10) with a moderate increase of the reactivity on going toward (*Z*)-arylhydrazones containing stronger and stronger electron-donating or -repelling groups. In the instance of k_{II} the substituents range from hydrogen to *p*-methoxy (**3a**−**d**), while in the instance of k_{III} they range from *m*-methyl to *p*-methoxy (**3a**−**c**). In both cases, notwithstanding the small number of the considered substrates, the results of FER appear significant and agreeable.

$$\log(k_{II})_X/(k_{II})_H = (-0.622 \pm 0.014)\sigma_H + (-0.002 \pm 0.002)\ r = 0.9995;\ n = 4 \tag{9}$$

$$\log(k_{III})_X/(k_{III})_H = (-1.06 \pm 0.24)\sigma_H + (-0.22 \pm 0.05)\ r = 0.97;\ n = 3 \tag{10}$$

The kinetic results obtained with (*Z*)-arylhydrazones **3a**−**k** in TOL at 313.1 K have been compared with those observed with the (*Z*)-arylhydrazones **1a**−**k** in PhH. Both (k_{II}) and (k_{III}) gave excellent relationships ($r \geq 0.9985$).[12f]

An examination of kinetic data concerning the rearrangement in the presence of PIP puts in evidence the following points:

(i) The reactivity as a function of the substituent shows a concave-upward Hammett trend, once more confirming a changeover of the reaction mechanism that is substituent-dependent in the base-catalyzed path (variable structure of the TS as a function of the substituent).[19] In fact, on the one hand electron-withdrawing substituents increase the acidity of the proton bound to N_α, thus facilitating the proton interaction with PIP in the TS (but decreasing the nucleophilicity of N_α),[20] whereas on the other hand electron-releasing substituents decrease the acidity of the above proton and then its interaction with PIP in the TS (but increasing the nucleophilic character of the N_α). Therefore, in the whole the substituent with its opposite effects influences the TS structure, and this can show different degrees of N_α−H bond breaking and N_α−N_2 bond forming and different position along the reaction coordinates. Globally this fact causes quite low susceptibility constants in the presence of electron-repelling substituents. The sign of susceptibility constants (positive and negative with electron-withdrawing and -repelling substituents, respectively) depends on different balancing of the former or of the latter effect.

(ii) With all of the substituents both PIP-catalyzed paths are present [the k_{III}/k_{II} ratios ranging from 3.2 for **3a** (X = 4-OCH_3) to 2.6 for **3b**,**c** and to 3.9 for **3d**, then regularly decreasing with the electron-withdrawing effect of the present substituent to 1.4 for **3k** (X = 4-NO_2), respectively]. The above ratios are lower than those calculated in the TCA-catalyzed paths, and this can be related to the different entity of the positive and negative charge present in the relevant transition state and then on the necessary assistance from a second molecule of catalyst for realizing the catalysis-of-catalysis process.[14a] In summary we can say that the involved (*Z*)-arylhydrazones contain centers feebly nucleophilic as well as acidic,: but TCA is a quite strong acid while PIP is not a so strong a base in TOL.

(iii) A comparison between k_{II} and k_{III} values for the base-catalyzed rearrangement of the (*Z*)-arylhydrazones **3a**−**k** and **1a**−**k** appears of interest. First the path catalyzed by

1 mol of PIP is present in all of the **3a**−**k** derivatives and in contrast only for **1a**−**d**. Interestingly the k_{II} and k_{III} values for the (*Z*)-arylhydrazones **3** are higher and lower, respectively, than those of **1**.[12f] Both of these facts could be related to the better leaving group ability of the N(4)−C(5)−O(1) system in compounds **3** in comparison with the relevant **1**, and this makes possible the 1 mol PIP-catalyzed path with all of the examined **3**. For **3a**−**k** the calculated k_{II} and k_{III} values and the relevant k_{III}/k_{II} ratios have been well correlated with the electronic effects of the present substituents as well as with the relevant kinetic constants for the PIP-catalyzed path of **1a**−**k** obtaining good or excellent relationships (eqs 7−10 and data in Table C). Taking into account the [PIP] used, we can advance comments similar to those presented in the instance of the acid-catalyzed path on the contribution of the two paths.

CONCLUSIONS

On the whole, the data collected definitively show that in TOL at 313.1 K the (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole **3a**−**k** rearrange, in the presence of both TCA or PIP, via two different pathways: a simple and a complex one, characterized by the participation of one or two molecules (catalysis-of-catalysis) of catalyst, respectively.

In general, the trends of k_{III}/k_{II} ratios (see Tables 1 and 2) evidence that the relevance of catalysis-of-catalysis depends on the nature of both catalyst and substituent. This result makes it possible to pinpoint the different amount of charge distribution in the two transition states, underlining that the role played by the second molecule of catalyst is a function of the strength of the acid−base pair interaction.

In both cases (general-acid- and general-base-catalysis) the k_{II} and k_{III} values well correlate with the electronic effect of the substituents. Once again, in the case of TCA and of PIP linear and nonlinear substituent-dependence have been, respectively, observed.

The electronic effects exerted by the substituents on the rearrangement rates of **3a**−**k** and of **1a**−**k** in apolar solvents for the complex general-base-catalyzed pathway appear strictly comparable, by using the same set of substituent constants (σ_H).

The kinetic data concerning the rearrangement of **3a**−**k** in D/W mixture and in TOL evidence the occurrence of similar electronic effects of the substituents in the two solvents. For example, looking at the acid-catalyzed path (specific in D/W and general in TOL) in both cases the used Ingold−Yukawa−Tsuno treatment of data gives comparable susceptibility constants with (small) through-resonance contributions from both electron-repelling and -withdrawing substituents. Similarly, in the general-base-catalyzed pathways in both solvents, concave-upward Hammett plots have been observed with similar susceptibility constants, considering the simple base-catalyzed path in TOL.

In both (*Z*)-arylhydrazones **1** and **3** the MRH reactivity in protic polar (or dipolar aprotic) and apolar solvents confirms the roles that these different solvents can or cannot exert. As a matter of fact (*Z*)-arylhydrazones **3a**−**k** in TOL do not show the spontaneous (uncatalyzed pathway) rearrangement (**3a**−**k** → **4a**−**k**), replicating the situation observed with **1a**−**k** in PhH and in line with results of DFT calculations in the gas phase. Therefore, in apolar solvents with both the (*Z*)-arylhydrazones **1** and **3** the rearrangements can occur only in the presence of catalyst (bases, or bases as well as acids, respectively). In contrast, in polar and dipolar aprotic solvents the rearrangement of **1** and **3** can occur via both uncatalyzed pathway and catalyzed pathways, in line with the ability of protic polar and dipolar aprotic solvents to act as proton-shuttle.

In conclusion, we hope that the results herein collected have allowed us to shed light on the influence that different solvents, protic polar as well as dipolar aprotic solvents in one side and apolar solvents in the other side, and catalysts can exert on the occurrence of some reactions, thus helping chemists to choose the best experimental conditions to carry out organic reactions and at the same time to understand their intimate course.

EXPERIMENTAL SECTION

Chemistry. Compounds **3a**−**k** were prepared according to known procedures.[12m] TOL was purified as reported.[21] TCA was purchased and used without any other purification. PIP was freshly distilled before use.

Kinetic Measurements. The kinetics were carried out at 313.1 K and followed spectrophotometrically as previously described[12j] by measuring the disappearance of **3a**−**k** at the suitable wavelength (see Tables A and B in Supporting Information). The sample for a typical run was prepared by mixing into a quartz cuvette (optical path 1 cm) 2 mL of a TOL solution of **3** with 1 mL of a TOL solution of TCA or PIP, both previously thermostatted. The concentration of **3** in the reaction mixture was constant. The TCA or PIP concentrations ranged as reported in Tables A and B. The absorbances measured at the suitable wavelenght were plotted versus time and showed an exponential dependence. The courses of the reaction were all studied over three half-lives or more. In all cases the correlation coefficients were >0.9998. The apparent first-order rate constants obtained were reproducible within ±3%.

ASSOCIATED CONTENT

Ⓢ Supporting Information. Apparent kinetic constants, second- and third-order kinetic constants, free energy relationships. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The TOC and abstract graphic were incomplete in the version published ASAP March 15, 2011; the correct version reposted March 17, 2011.