On the Dichotomic Behavior of the *Z*-2,4-Dinitrophenylhydrazone of 5-Amino-3-benzoyl-1,2,4-oxadiazole with Acids in Toluene and in Dioxane/Water: Rearrangement versus Hydrolysis

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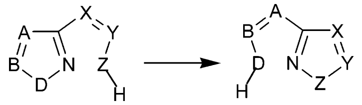
The mononuclear rearrangement (MRH) of the *Z*-2,4-dinitrophenylhydrazone (**4a**) and of the *Z*-phenylhydrazone (**4b**) of 5-amino-3-benzoyl-1,2,4-oxadiazole into the relevant triazoles **5a** and **5b** in toluene has been quantitatively investigated in the presence of trichloroacetic acid (TCA) and of piperidine at 313.1 K. While the behavior in the presence of piperidine recalls the one previously evidenced for some *Z*-hydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, the study of the reactivity in the presence of TCA has most interestingly evidenced a general-acid-catalyzed rearrangement for "both" **4a** and **4b**. Thus, **4a** offers the first example of a solvent-dependent dichotomic behavior in MRH processes on 1,2,4-oxadiazole derivatives as far as it undergoes an "*acidic hydrolysis*" in dioxane/water and a *"rearrangement"* in toluene.

Introduction

Our research group has been long involved in the study of the synthetic applications[1] and of the mechanisms (either collecting kinetic data[1a,b,2] or by means ab initio calculations,[3] thus definitively identifying the reaction as a S_{Ni} process) of *m*onocyclic *r*earrangements of *h*eterocycles[4] (Scheme 1, MRH or Boulton−Katritzky reaction), especially devoting the attention to 1,2,4-oxadiazoles.[2] As a matter of fact, ring-to-ring interconversions are useful tools for the synthesis of heterocycles to be used as such[1,5] (in medicinal and veterinary chemistry or in the field of materials) or as masked functionalities[1,5−7] for the attainment of several target functional groups.

SCHEME 1



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(7) The widespread importance of synthetic methodologies based on the use of heterocycles could be easily envisaged by looking at the symposia-in-print on this topic. E.g., in the past decade, *Tetrahedron* published four symposia-in-print: (1) Katritzky, A. R., Ed. Novel applications of heterocycles in synthesis. *Tetrahedron* **1996**. (2) Alexakis, A., Ed. Heterocycles in asymmetric synthesis. *Tetrahedron* **1998**. (3) Howell, A. R., Ed. Strained heterocycles as intermediates in organic synthesis. *Tetrahedron* **2002**. (4) Florio, S., Ed. Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry. *Tetrahedron* **2003**. Very recently, *Chemical Reviews* dedicated an entire issue to heterocycles (Katritzky, A. R., Ed. *Chem. Rev.* **2004**, *104* (5)), and several papers were concerned with syntheses of heterocycles as well as their uses as synthones.

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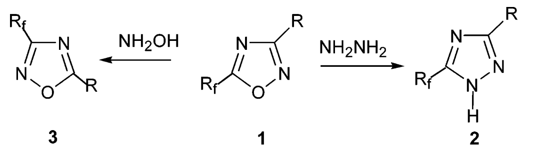
SCHEME 2



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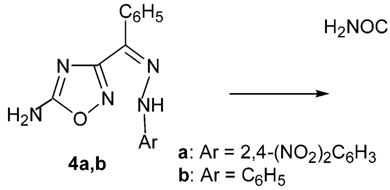

In this framework, we have more recently addressed our attention to the behavior of 1,2,4-oxadiazoles characterized by substituents at C-5 endowed with electronic effects of particular significance, such as the strongly electron-withdrawing trifluoromethyl (or perfluoroalkyl) group[1c,e] or the strongly electron-donating amino group.[2h,i]

Thus, we observed that 5-perfluoroalkyl-1,2,4-oxadiazoles (**1**) react with bidentate nucleophiles (Scheme 2) giving interconversions into 5-perfluoroalkyl-1,2,4-triazoles (**2**)[1c] or 3-perfluoroalkyl-1,2,4-oxadiazoles (**3**)[1e] via an ANRORC-like pattern.[8]

Moreover, we synthesized the *Z*-2,4-dinitrophenylhydrazone (**4a**)[2h] and the *Z*-phenylhydrazone (**4b**)[2i] of 5-amino-3-benzoyl-1,2,4-oxadiazole to study their rearrangement into the relevant 1,2,3-triazoles (**5a**,**b**, see Scheme 3) in dioxane/water in a wide pS^+ range,[9] observing remarkable differences in their behavior. In the first case (**4a**), in the 4.5−14.1 pS^+ range only a pS^+-dependent reactivity is shown (general-base catalysis, Figure 1),[2h] while at high proton concentrations (p$S^+ < 3.5$) a fast hydrolysis becomes the prevailing process. In contrast, in the case of **4b**[2i] (Figure 1) the occurrence of specific-acid catalysis (pS^+ 0.1−3.5), of an uncatalyzed process (pS^+ 3.5−8.0)[1a,b,2a,d] and of general-base catalysis (pS^+ 8.0−14.9)[2c] was evidenced, for the first time observing an acid-catalyzed rearrangement in place of the acidic hydrolysis of the hydrazono group which takes over in more polar solvents.[2a,h]

This new behavior has been related to the protonation of the 5-amino-1,2,4-oxadiazole ring at N(4),[10] which modifies the leaving-group ability of the A = B − D moiety of the starting ring (Scheme 1), probably opening the way to rearrangement pathways not foreseeable on the grounds of the scheme initially proposed by Boulton and Katritzky.[4]

The presence in **4a** of the two strong electron-withdrawing nitro groups is obviously responsible for the differential behavior between **4a** and **4b** in the neutral as well as in the acidic range as a consequence of a decrease both in the nucleophilic character of the hydrazono *N*H atom and in the basicity of N(4) of the 1,2,4-oxadiazole ring, which should also affect the leaving group ability of the A = B − D group and the electrophilic character of N(2), such factors suppressing the uncatalyzed MRH pathway of **4a** and making its acidic hydrolysis the only possible pathway at high proton concentration.

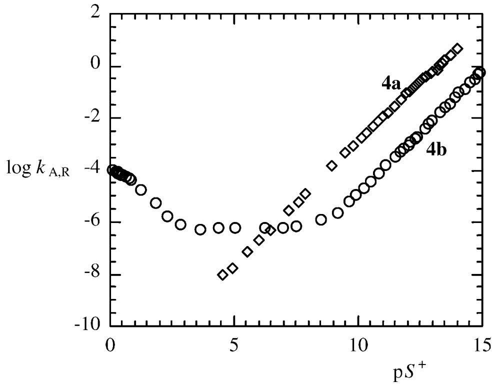

FIGURE 1. Plot of log $k_{\mathrm{A,R}}$ for the rearrangement of **4a** and **4b** into **5a** and **5b**, respectively, in dioxane/water at 293.1 K versus pS^+.

These considerations induced us to look for experimental conditions capable to prevent the hydrolysis of **4a** and to ascertain if in such a way an acid-catalyzed rearrangement could be observed instead. With this aim we have followed the rearrangement of **4a** and **4b** in anhydrous toluene (a nonprotic, nonpolar solvent: $E^{\mathrm{T}}_{\mathrm{N}}$ 0.099),[11] in the presence of a strong organic acid such as trichloroacetic acid (TCA). First, it should be noticed that **4a** and **4b** are long stable in pure toluene, both at room temperature (with apparent rearrangement rate constants lower than 10^{-10} and 10^{-7} s^{-1}, respectively) and at higher (323.1 K) temperatures: this clearly indicates that in toluene, as we have already observed in benzene,[2f,g] the uncatalyzed rearrangement does not contribute effectively,[12] at variance with what happens in polar oxygenated solvents[2e−g] or in aprotic dipolar solvents.[2e,g,h]

Moreover, to gain also information about the base-catalyzed pathways and to make a comparison with the already studied rearrangement in benzene of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**6a**) in the presence of piperidine[2b] we have carried out a study of the rearrangement of **4a** and **4b** in toluene in the presence of the same amine.

Results and Discussion

Rearrangement of 4a and 4b in Toluene in the Presence of TCA. The *a*pparent first-order rate constants for the *r*earrangement at different [TCA] values [$(k_{\mathrm{A,R}})_{\mathrm{TCA}}$] and at 313.1 K are collected in Table 1 together with the calculated $(k_{\mathrm{A,R}})_{\mathrm{TCA}}$/[TCA] ratios: these ratios strongly increase with [TCA], indicating for both **4a** and **4b** the occurrence of complex acid-catalyzed pathways. Accordingly, a plot of log$(k_{\mathrm{A,R}})_{\mathrm{TCA}}$ versus [TCA] (Figure 2, curves **a** and **b**) shows a strong upward curvilinear dependence of the reactivity on [TCA] and the excellent (see Table 2) linear plots of $(k_{\mathrm{A,R}})_{\mathrm{TCA}}$/[TCA] versus [TCA]

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(8) Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 1−253.

(9) pS^+ is an operational proton-concentration scale used in dioxane/water (for details, see ref 2a).

(10) By using computations at the DFT level, we have confirmed that in 5-amino-1,2,4-oxadiazole the most basic center is N(4).[2i]

(11) Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2003; pp 416−425.

(12) The *Z*-hydrazones are stable at room temperature in the solid state for years, in accordance with the high energy barrier calculated at DFT level in the gas phase for the rearrangement of the *Z*-hydrazone of 3-formyl-1,2,4-oxadiazole.[3]

TABLE 1. Apparent First-Order Rate Constants,[a] $(k_{A,R})_{TCA}$ and $(k_{A,R})_{PIP}$, and Ratio Values, $(k_{A,R})_{TCA}$/[TCA] and $(k_{A,R})_{PIP}$/[Piperidine], for the Rearrangement of 4a and 4b into 5a and 5b in Toluene in the Presence of TCA[b] and Piperidine,[c] Respectively, at 313.1 K

	[TCA], M								
4a	0.200	0.300	0.400	0.500	0.600	0.700	0.800	0.900	1.00
$10^5(k_{A,R})_{TCA}$, s^{-1}	0.253	0.510	0.840	1.25	1.77	2.40	3.06	3.81	4.68
$10^5(k_{A,R})_{TCA}$/[TCA], L mol^{-1} s^{-1}	1.27	1.70	2.10	2.50	2.95	3.43	3.83	4.23	4.68

	[TCA], M									
4b	0.00980	0.0196	0.0294	0.0392	0.0490	0.0588	0.0686	0.0784	0.0882	0.0980
$10^5(k_{A,R})_{TCA}$, s^{-1}	1.12	2.40	3.90	5.56	7.46	9.42	11.7	14.1	16.7	19.5
$10^5(k_{A,R})_{TCA}$/[TCA], L mol^{-1} s^{-1}	1.14	1.22	1.33	1.42	1.52	1.60	1.71	1.80	1.89	1.99

	[piperidine], M									
4a	0.100	0.200	0.300	0.400	0.500	0.600	0.700	0.800	0.900	1.00
$10^4(k_{A,R})_{PIP}$, s^{-1}	0.368	0.766	1.20	1.67	2.16	2.69	3.25	3.86	4.50	5.17
$10^4(k_{A,R})_{PIP}$/[piperidine], L mol^{-1}s^{-1}	3.68	3.83	4.00	4.18	4.32	4.48	4.64	4.83	5.00	5.17

	[piperidine], M										
4a[d]	0.104	0.166	0.250	0.333	0.416	0.499	0.582	0.666	0.749	0.874	1.04
$10^4(k_{A,R})_{PIP}$, s^{-1}	0.345	0.565	0.875	1.20	1.55	1.91	2.30	2.70	3.12	3.80	4.74
$10^4(k_{A,R})_{PIP}$/[piperidine], L mol^{-1}s^{-1}	3.32	3.40	3.50	3.60	3.73	3.83	3.95	4.05	4.17	4.35	4.56

	[piperidine], M									
4b	0.101	0.202	0.303	0.404	0.505	0.606	0.707	0.808	0.909	1.01
$10^4(k_{A,R})_{PIP}$, s^{-1}	0.0702	0.180	0.329	0.517	0.757	1.01	1.32	1.66	2.05	2.50
$10^4(k_{A,R})_{PIP}$/[piperidine], L mol^{-1}s^{-1}	0.695	0.891	1.09	1.28	1.50	1.67	1.87	2.05	2.26	2.48

[a] The kinetic constants were reproducible to within ±3%. [b] [**4a**] 5.64×10^{-5} M (at λ 410 nm, log ϵ 4.25 ± 0.02) and [**4b**] 5.05×10^{-5} M (at λ 360 nm, log ϵ 4.24 ± 0.02). [c] [**4a**] 5.46×10^{-5} M and [**4b**] 5.15×10^{-5} M. [d] In benzene. [**4a**] 6.46×10^{-5} M (at λ 410 nm, log ϵ 4.25 ± 0.02).

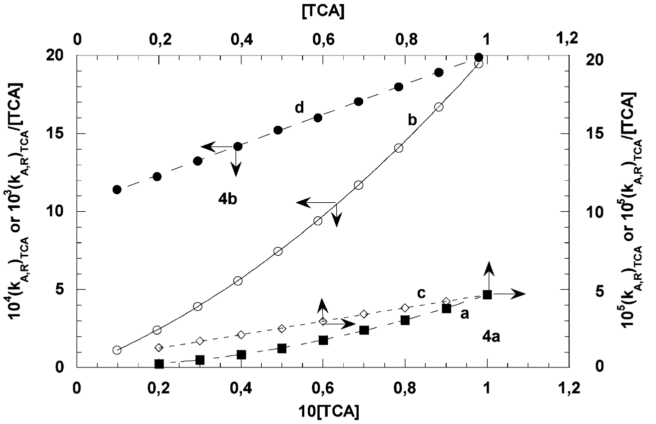


FIGURE 2. Plot of $\log(k_{A,R})_{TCA}$ for the rearrangement of **4a** and **4b** [lines **a** (■) and **b** (○)] and of the relevant $\log(k_{A,R})_{TCA}$/[TCA] ratios [lines **c** (◊) and d (●)] in toluene at 313.1 K vs [TCA].

observed (Figure 2, curves **c** and **d**) evidence, for both substrates, the occurrence of an acid-catalyzed pathway whose second- (k_{II}) and third-order (k_{III}) rate constants can be calculated from the intercept and the slope of eq 1. Thus, our expectations have been clearly fulfilled as the hydrolysis of **4a** has been superseded by an acid-catalyzed rearrangement, which is now undergone by "both" **4a** and **4b**.

$$(k_{A,R})_{TCA}/[TCA] = k_{II} + k_{III}[TCA] \qquad (1)$$

It should first of all be remarked that, well in agreement with both the expected higher basic character of N(4) and the well-known higher nucleophilic character of the hydrazono *N*H atom of **4b** compared to that of **4a**, the former is more than 3 orders of magnitude more reactive than the latter.

Some further comments on the behavior of **4b** come from the analysis of the mechanistic course of the rearrangement. Although the observed second-order term in toluene recalls the situation observed for the rearrangement of **4b** in dioxane/water, we must consider that the large differences between the two media could enforce different pathways for the overall MRH process. As a matter of fact, in dioxane/water at high proton concentration a specific-acid catalysis was observed in agreement with the occurrence of a two-step mechanism.[2i] In contrast, in toluene and in the presence of TCA only one-step S_{Ni} processes via a general-acid catalysis can occur, the protonation at N(4) and the nucleophilic attack of *N*H onto N(2) taking place in a single multiconcerted step (see Scheme 4), with a significant charge separation in the transition state. In fact, the interaction between TCA and N(4) of **4a** or of **4b** causes a partial negative charge on the oxygens of TCA and a partial positive charge on N(4) and on N(2).[2i] Because of the significant increase in its electrophilic character, N(2) can now undergo nucleophilic attack by the *N*H atom of the hydrazono moiety (on which a partial positive charge is developing) also in a solvent such as toluene, per se "not" capable of assistance through solvation.

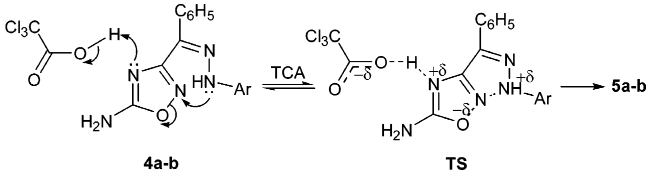
As a consequence of the nonsolvation of the incipient charges, the "assistance" to the rearrangement by a second molecule of TCA becomes significant as it can help in the formation of the negative charge on the oxygens of TCA, dispersing it by means of a catalysis-of-catalysis mechanism. The observed k_{III}/k_{II} ratios are quite high (ca. 10) evidencing the importance of such a charge disper-

TABLE 2. Linear Regression Analysis[a] of Apparent Rate Constants for the Rearrangements of 4a and 4b into 5a and 5b at 313.1 K, According to eqs 1 and 2

substrate	$k_{II} \pm s_{II}$ (L mol^{-1} s^{-1})	$k_{III} \pm s_{III}$ (L mol^{-1})^2 s^{-1}	r	n	k_{III}/k_{II}
4a[b]	$(4.1 \pm 0.1) \times 10^{-6}$	$(4.26 \pm 0.02) \times 10^{-5}$	0.9999	9	10.4
4b[b]	$(1.04 \pm 0.00) \times 10^{-2}$	$(9.67 \pm 0.07) \times 10^{-2}$	0.9998	10	9.30
4a[c]	$(3.50 \pm 0.01) \times 10^{-4}$	$(1.65 \pm 0.01) \times 10^{-4}$	0.9997	10	0.47
4a[d]	$(3.17 \pm 0.01) \times 10^{-4}$	$(1.34 \pm 0.01) \times 10^{-4}$	0.9998	11	0.42
4b[c]	$(4.99 \pm 0.08) \times 10^{-6}$	$(1.94 \pm 0.01) \times 10^{-5}$	0.9998	10	3.89

[a] s_{II} and s_{III} are the standard deviations of the regression parameters k_{II} and k_{III}, respectively. r is the correlation coefficient and n the number of points. The confidence levels for significance of regression parameters are all better than 99.9%. [b] TCA in toluene. [c] Piperidine in toluene. [d] Piperidine in benzene.

SCHEME 4



sion:[13] the practically constant ratios observed indicate that these values are dependent on the structure of the 5-amino-1,2,4-oxadiazol-3-yl moiety and much less affected by the nature of the arylhydrazono moiety.

This behavior strictly recalls that observed by us studying the base catalysis in the rearrangement of the *Z*-phenylhydrazone (or of the *Z*-*p*-nitrophenylhydrazone) of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**6a**) in benzene in the presence of amines:[2b,f] with secondary and primary amines the formation of the transition state causes the presence of an incipient positive charge on nitrogen and its dispersion is assisted by other molecules of base and third- and fourth-order pathways could be observed.[2f]

Once more the use of a solvent such as benzene or toluene enforces a catalysis-of-catalysis to support the charge dispersion as the solvent itself is not able to pay assistance to the progress of the reaction.

Rearrangement of 4a and 4b in Toluene in the Presence of Piperidine. The apparent first-order rate constants, $(k_{A,R})_{PIP}$, for the rearrangement at different piperidine concentrations have been measured at 313.1 K and the data collected in Table 1 together with the calculated $(k_{A,R})_{PIP}$/[piperidine] ratios: also these ratios significantly increase with [piperidine], indicating for both **4a** and **4b** the occurrence of complex base-catalyzed pathways. Accordingly, a plot of log$(k_{A,R})_{PIP}$ versus [piperidine] (Figure 3, curves **a** and **b**) shows a strong upward curvilinear dependence of the reactivity on [piperidine]. Once more (see data in the presence of TCA above) the excellent (see Table 2) linear plots of $(k_{A,R})_{PIP}$/[piperidine] versus [piperidine] (Figure 3, curves **c** and **d**) evidence the occurrence, for both substrates, of a base-catalyzed reaction pathway whose second- and third-order rate constants can be obtained from the intercept and the slope of eq 2.

$$(k_{A,R})_{PIP}/[\text{piperidine}] = k_{II} + k_{III}[\text{piperidine}] \quad (2)$$

Thus, the outcome in toluene closely parallels the one evidenced in benzene for **6a** in the presence of piperidine (incidentally **6a** in benzene[2b] and **4b** in toluene as well as **4a** in toluene or in benzene show similar reactivities, see data in Table 1): the mechanism and the structure of the relevant transition states having been deeply investigated and ascertained.[2b,f] An examination of the k_{II} and k_{III} values for **4a** and **4b** evidences, in the presence of piperidine, a relative behavior opposite with respect to that observed in the presence of TCA: as a matter of fact (see data in Figure 3 and in Table 2) **4a** is now significantly more reactive than **4b**[14] $[(k_{II})_{\mathbf{4a}}/(k_{II})_{\mathbf{4b}} = 70$ and $(k_{III})_{\mathbf{4a}}/(k_{III})_{\mathbf{4b}} = 8.5]$ and this agrees with the expected higher acidic character of the N*H* hydrogen of **4a** with respect to that of **4b**, then rendering the *N*H nitrogen atom more nucleophilic with respect to that of **4b** by interaction with the base. Consequently, for **4a** the assistance of a second molecule of piperidine is less important than for **4b** (see the k_{III}/k_{II} ratios: 0.5 and 3.9, respectively), suggesting a different position of the rate-determining transition state along the reaction coordinate in the two cases. Then the role of the dispersion of the rising positive charge on the piperidine nitrogen has a different weight on the progress of the reaction in the two cases, leading to an inverse relationship between reactivities and k_{III}/k_{II} ratios.

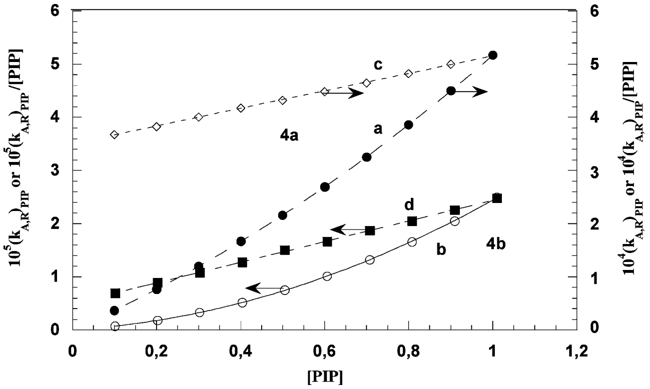


FIGURE 3. Plot of log$(k_{A,R})_{PIP}$ for the rearrangement of **4a** and **4b** into **5a** and **5b** [lines **a** (●) and **b** (○)], respectively, and of the relevant log$(k_{A,R})_{PIP}$/[piperidine] ratios [lines **c** (◇) and **d** (■)] in toluene at 313.1 K vs [piperidine].

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[13] In principle, the presence of the third-order pathway could perhaps be in some way favored by the significant association between TCA molecules in toluene, but the direct intervention of the dimeric acid as such could be reasonably excluded considering its very low effective acidic character. The behavior of organic acids in water and in benzene or toluene has been investigated by several authors (see: Gelb, R. I.; Alper, J. S. *Anal. Chem.* **2000**, *72*, 1322−1327. Steigman, J.; Cronkright, W. *J. Am. Chem. Soc.* **1970**, *92*, 6729−6736; *Spectrochim. Acta*, *Part A* **1970**, *26*, 1805−1811).

[14] This behavior recalls that one observed by comparing the reactivity of **4a** and **4b** in the general-base-catalyzed range in D/W [e.g., at pS^+ = 10.8 a ratio $(k_{A,R})_{\mathbf{4a}}/(k_{A,R})_{\mathbf{4b}} = 82$ has been calculated].[2h,i]

Conclusions

The kinetic study of the rearrangement of **4a** and **4b** in toluene in the presence of TCA has evidenced the dichotomic behavior of **4a** in the presence of acids: acidic hydrolysis in dioxane/water and general-acid-catalyzed MRH in anhydrous toluene. Thus, in the absence of water, thanks to suppression of hydrolysis, the occurrence of the characteristic MRH process of azoles[1−4] can be observed. Also in the presence of piperidine the above rearrangements show the expected general-base-catalyzed pathways.[2b,c,f] Similarities and differences have been evinced in two cases: (a) in both acid- and base-catalyzed rearrangements assistance by a second molecule of the catalyst has been observed, and (b) in the presence of TCA **4b** is much more reactive than **4a**; in contrast, in the presence of piperidine **4a** is significantly more reactive than **4b**.

Experimental Section

Synthesis and Purification of Compounds. Compounds **4a**[2h] and **4b**,[2i] piperidine,[15] benzene,[16] and toluene[16] were prepared and/or purified according to the methods reported. Commercial TCA was used without further purification.

Kinetic Measurements. The kinetics were followed spectrophotometrically, as previously described[2] by measuring the disappearance of **4a** and **4b** at the wavelengths reported in Table 1.

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