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Mononuclear Heterocyclic Rearrangements. Effect of the Structure of the Side Chain on the Reactivity. Part 3.[1] Rearrangement of Some *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-arylformamidines into 1-Aryl-3-benzoylamino-1,2,4-triazoles in Acetonitrile in the Presence of Triethylamine

Vincenzo Frenna, Gabriella Macaluso and Nicolò Vivona

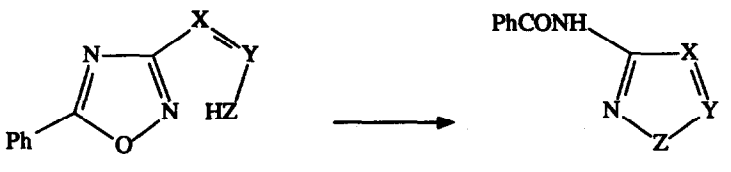
Dipartimento di Chimica Organica, Via Archirafi 20, Palermo, I-90123, Italy

Domenico Spinelli, Giovanni Consiglio and Elisabetta Mezzina

Dipartimento di Chimica Organica 'A. Mangini', Via S. Donato 15, Bologna, I-40127, Italy

Abstract: The apparent pseudo-first-order rate constants for the title reaction give a curvilinear plot *versus* tertiary amine concentration, according to the equation $k_A = (k_u + K_1k_2[TEA])/(1 + K_1[TEA])$. This shows the occurrence of two different reaction pathways; the one, independent of [TEA] and the other, dependent on [TEA], which involves a fast conversion of the substrate into an acid-base adduct or an ion pair followed by its slow conversion into the corresponding triazole. The substituent effects on these reactions have also been studied.

In the framework of our synthetic[2] and mechanistic[1,3] studies on heterocyclic rearrangements we have recently examined the effect of the structure of the side chain on the reactivity[1,3,4] in mononuclear heterocyclic rearrangements (MHRs).[5] For example, the rearrangements of some derivatives of 1,2,4-oxadiazole were studied in dioxane-water (DIOX-W) in a large range of pS^+ (Scheme 1).[1] The side chains considered were



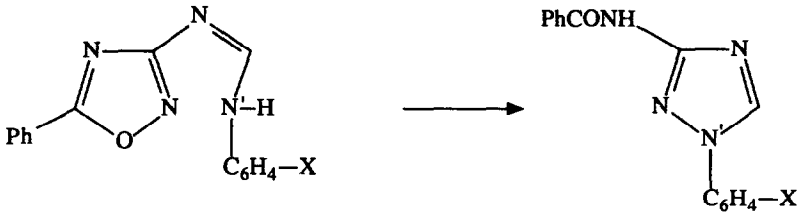
1 2

Scheme 1

CNN (>C=N-NH-Ar)[3] and NCN (-NH-CO-NH-Ar[4] and -N=CH-NH-Ar[1]). For these MHRs different reaction mechanisms were observed as a function of the chemical structure of the side chain, of the nature and of the concentration of the bases used and of the nature of the reaction solvent.

On the assumption that MHRs follow a S_Ni mechanism[1,3-5] and considering the rearrangements for derivatives of the same starting heterocycle (*e.g.*, MHRs of various derivatives of 1,2,4-oxadiazole) one can regard as practically constant both the electrophilic character of N(2), weakly bonded to O(1) in the starting ring, and the nucleofugality of the leaving group. Therefore, by varying the nature of the considered side chain, the observed reactivity could be related to the nucleophilicity of Z atom (Scheme 1) and to the acidic character of the hydrogen atom bound to it. The nature of the solvent and of the base used can determine the reactivity by affecting both the kind of the interactions with the base (acid-base adduct, ion-pair or anion formation) and the possible occurrence of an uncatalysed pathway, which is favoured by the features (*e.g.*, nucleophilic character) of the solvent used.

In order to gain information on the way in which the solvent and the base used can affect the reaction mechanism we have studied the rearrangement of some *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-arylformamidines (**3**), containing both electron-donating and -withdrawing substituents, into 1-aryl-3-benzoylamino-1,2,4-triazoles (**4**) at 313.15 K in acetonitrile (ACN) in the presence of triethylamine (TEA).



3 **4**

a; X = *p*-MeO
b; X = *p*-Me
c; X = H
d; X = *p*-Cl
e; X = *m*-Cl
f; X = *m*-NO_2
g; X = *p*-NO_2

Scheme 2

For the sake of comparison the rearrangement of **3g** has also been studied in the presence of diazabicyclo[2.2.2]octane (DABCO), a base less strong and less bulky than TEA.[6] ACN as other dipolar aprotic solvents (*e.g.*, dimethylsulphoxide or dimethylformamide) is a very good solvent for MHRs.[3e] The results obtained can be compared with those referring to for the rearrangements of *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole[3] and of *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-arylureines in ACN and in the presence of TEA.[4]

The study of the rearrangement of **3** in DIOX-W at various pS^+ showed the occurrence of an uncatalysed (pS^+-independent) range at low pS^+ values and of a catalysed (pS^+-dependent and then pS^+-independent) range at high pS^+ values.[1]

On the other hand it is known that diarylformamidines are easily hydrolysed[7] in water in the presence of either acids or bases while in acetic acid, in the presence of some derivatives of ammonia[8] (hydroxylamine, hydrazine, primary or secondary amines but not a tertiary amine), they give a transamination reaction, probably through an addition-elimination mechanism. In order to test this behaviour we have studied the reaction of **3g** with piperidine (PIP), TEA and DABCO in ACN at 313.15 K. In the case of the tertiary amines only the rearrangement product was obtained, whereas in the case of PIP the reaction mixture, separated by column chromatography, showed hydrolysis products such as *p*-nitroaniline and 3-amino-5-phenyl-1,2,4-oxadiazole in addition to the rearrangement product, thus indicating that in the presence of the secondary amine a fast addition reaction occurs and this is followed by a hydrolysis reaction.

RESULTS AND DISCUSSION

Rearrangement of N-(5-phenyl-1,2,4-oxadiazol-3-yl)-N'-arylformamidines 3a-g in ACN in the Presence of TEA: Reaction Mechanism and Substituent Effects

The apparent pseudo-first-order rate constants (k_A) have been measured at 313.15 K at various TEA concentrations and are shown in Table 1. A plot of experimental rate constants *versus* [TEA] shows a downward curvilinear trend (see Figure 1 for **3c** - **3f** and Figure 2 for **3g**): a large and a small increase of the reactivity with increasing [TEA] is observed at low and at large [TEA], respectively, with an intercept (*i.e.*, the rate constant at [TEA] 0) different from zero. The plot observed shows clearly a significant contribution to rate constants from *i*) an uncatalysed pathway, in accord with both the nature of the solvent used and the significant nucleophilicity of N' (notwithstanding that **3g** bears in the aryl group a strong electron-withdrawing substituent) and *ii*) a catalysed pathway which tends to a limiting rate in accord with the acidity of the hydrogen atom (N'-H) of **3**.

$$\underset{\mathbf{3}}{\text{AFH}} \xrightarrow{k_u} \text{products} \qquad (1)$$

$$\text{AFH} + \text{TEA} \underset{\text{(fast)}}{\overset{K_1}{\rightleftharpoons}} \text{AFH.TEA} \qquad (2)$$

$$\text{AFH.TEA} \xrightarrow[\text{(slow)}]{k_2} \text{products} \qquad (3)$$

AFH.TEA: AFH$\cdots$TEA or $AF^-//HTEA^+$

Scheme 3

Scheme 3, where the product deriving from the interaction between **3** and TEA can have the structure of an acid-base adduct or of an ion-pair (a true anionic structure for AFH.TEA can be excluded, see below), agrees

Table 1. Apparent Pseudo-first-order Rate Constants[a] for the Rearrangement (3a-g) → (4a-g) in ACN in the Presence of TEA at 313.15 K

3a[b]														
[TEA]/mol dm^{-3}	0.000	0.040	0.080	0.120	0.200	0.310	0.400	0.520	0.640	0.740	0.860	1.000		
$10^5 k_A$/s^{-1}	3.20	3.36	3.57	3.73	4.15	4.75	5.00	5.35	5.79	6.17	6.47	6.83		
3b[c]														
[TEA]/mol dm^{-3}	0.000	0.060	0.120	0.180	0.240	0.320	0.400	0.500	0.600	0.720	0.840	1.000		
$10^5 k_A$/s^{-1}	2.70	3.04	3.40	3.64	3.96	4.34	4.65	5.10	5.42	5.85	6.20	6.60		
3c[d]														
[TEA]/mol dm^{-3}	0.000	0.040	0.080	0.120	0.200	0.280	0.400	0.520	0.640	0.800	0.900	1.000		
$10^5 k_A$/s^{-1}	2.30	2.70	3.05	3.38	3.97	4.55	5.30	5.85	6.52	7.15	7.56	8.10		
3d[e]														
[TEA]/mol dm^{-3}	0.000	0.041	0.055	0.080	0.105	0.165	0.205	0.240	0.360	0.480	0.580	0.720		
$10^4 k_A$/s^{-1}	0.195	0.440	0.540	0.656	0.781	1.04	1.19	1.32	1.62	1.85	2.02	2.25		
3e[f]														
[TEA]/mol dm^{-3}	0.000	0.0202	0.0404	0.0505	0.0606	0.0808	0.101	0.121	0.162	0.202	0.242	0.303	0.404	0.505
$10^4 k_A$/s^{-1}	0.178	0.379	0.561	0.642	0.721	0.873	1.01	1.12	1.38	1.55	1.69	1.93	2.24	2.45
3f[g]														
[TEA]/mol dm^{-3}	0.000	0.0202	0.0404	0.0606	0.0808	0.101	0.141	0.182	0.212	0.242	0.303	0.404	0.505	
$10^4 k_A$/s^{-1}	0.140	1.12	1.87	2.45	3.00	3.45	4.14	4.64	4.95	5.27	5.65	6.20	6.55	
3g[h]														
[TEA]/mol dm^{-3}	0.000	0.00147	0.00294	0.00490	0.00735	0.0098	0.0137	0.0176	0.0216	0.0255	0.0294	0.0392	0.0490	0.100
$10^4 k_A$/s^{-1}	0.131	0.641	1.12	1.73	2.42	3.06	3.97	4.78	5.52	6.17	6.75	7.98	8.96	12.4
[TEA]/mol dm^{-3}	0.200	0.400	0.600	0.800	1.000									
$10^4 k_A$/s^{-1}	14.8	16.0	16.7	17.0	17.2									

[a] The rate constants are accurate to within ±3% . [b] [**3a**] 3.70x10^{-4}mol dm^{-3}. At λ 300 nm, log ε_{3a} 4.29 ± 0.02 and log ε_{4a} 2.93 ± 0.02. [c] [**3b**] 3.70x10^{-4}mol dm^{-3}. At λ 300 nm, log ε_{3b} 4.32 ± 0.02 and log ε_{4b} 3.14 ± 0.02. [d] [**3c**] 3.95x10^{-4}mol dm^{-3}. At λ 300 nm, log ε_{3c} 4.30 ± 0.02 and log ε_{4c} 2.93 ± 0.02. [e] [**3d**] 3.45x10^{-4}mol dm^{-3}. At λ 300 nm, log ε_{3d} 4.37 ± 0.02 and log ε_{4d} 3.57 ± 0.02. [f] [**3e**] 3.55x10^{-4}mol dm^{-3}. At λ 300 nm, log ε_{3e} 4.33 ± 0.02 and log ε_{4e} 2.90 ± 0.02. [g] [**3f**] 3.44x10^{-4}mol dm^{-3}. At λ 300 nm, log ε_{3f} 4.22 ± 0.02 and log ε_{4f} 3.62 ± 0.02. [h] [**3g**] 8.20x10^{-5}mol dm^{-3}. At λ 360 nm, log ε_{3g} 4.18 ± 0.02 and log ε_{4g} 3.46 ± 0.02.

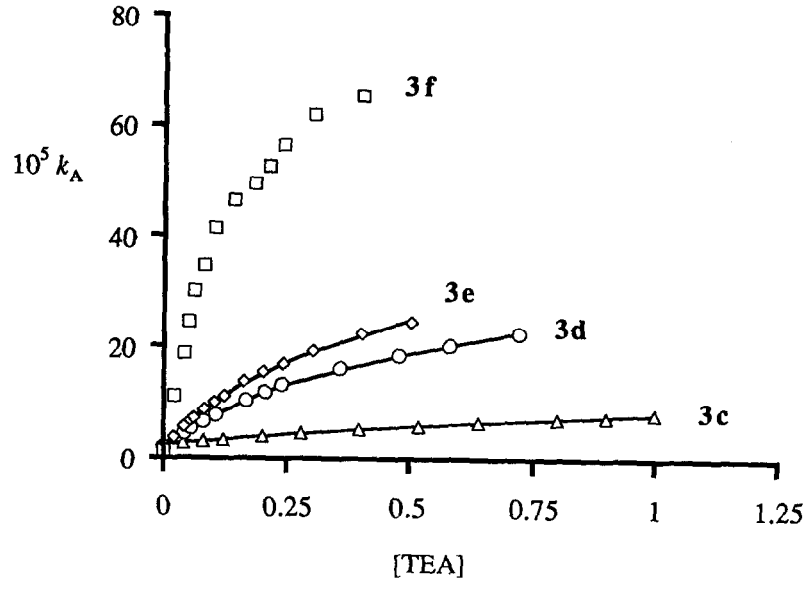


Fig. 1. Plot of log k_A of **3c-f** in ACN at 313.5 K *versus* [TEA]

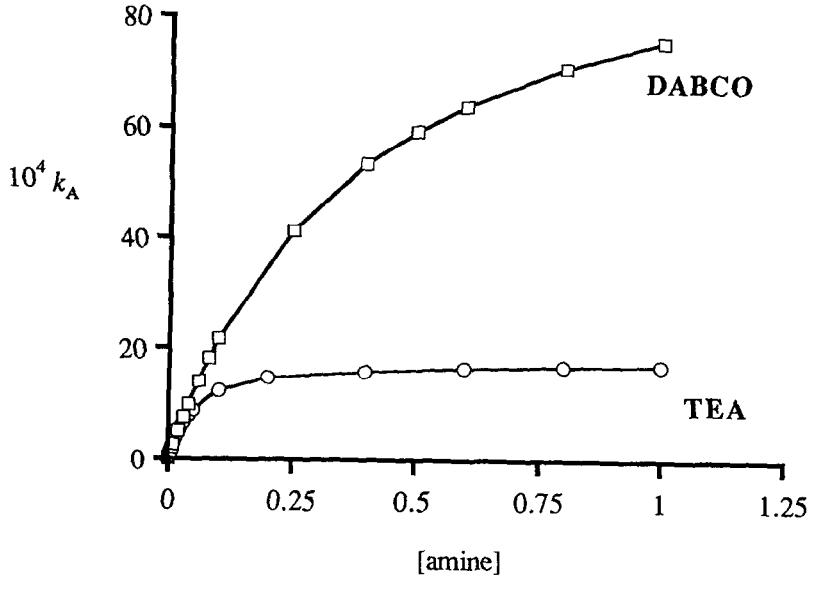


Fig. 2. Plot of log k_A of **3g** in ACN at 313.15 K *versus* [amine]

with experimental kinetic data and by using a steady state treatment one obtains the following equation at a constant concentration of **3**.

$$k_A = (k_u + K_1k_2[TEA])/(1 + K_1[TEA]) \qquad \text{eqn. 1}$$

The various rate constants calculated according to eqn. 1 by regression analysis are shown in Table 2. Equation 1 implies that at [TEA] 0 the uncatalysed pathway can be operative ($k_A = k_u$; step 1 of Scheme 3): the experimental data collected show that this pathway gives a contribution to the global reactivity also at high [TEA] and this is more or less relevant as a function of the present substituent (e.g., at [TEA] 0.5 mol dm^{-3} for X = *p*-MeO, H and *p*-Cl the observed k_u contributions were 60, 42 and 10%, respectively, and for X = *p*-NO_2 the calculated contribution was 0.8%).

This behaviour depends on the low ratio between catalysed and uncatalysed kinetic constants (*e.g.* for X = *p*-OMe k_2/k_u 4.5) which reaches a relatively high value only for X = NO_2 (137). A comparison with the corresponding ratios observed in DIOX /W in the presence of buffers,[1] 390 and 4080, respectively, brings to evidence the strong differences shown by the two different bases and solvents. The relatively low values of k_2 (10^{-4}—$10^{-3}s^{-1}$) indicate that the products of the equilibrium reaction (step 2 of Scheme 3) neither have an

Table 2. Linear Regression Analysis of Apparent Pseudo-first-order Rate Constants for the Rearrangement (3a-g) → (4a-g) in ACN in the Presence of TEA at 313.15 K according to Eqn. 1

Compound	$10^5k_u/s^{-1}$ [a]	K_1/dm^3mol^{-1}	$10^4k_2/s^{-1}$
3a	3.16±0.04 (3.20)	0.491±0.075	1.43±0.10
3b	2.69±0.02 (2.70)	0.526±0.033	1.41±0.04
3c	2.35±0.04 (2.30)	0.598±0.058	1.67±0.08
3d	1.95±0.12 (1.95)	1.93±0.09	3.68±0.10
3e	1.84±0.09 (1.78)	2.52±0.08	4.23±0.07
3f	1.46±0.18 (1.40)	6.38±0.09	8.54±0.09
3g[b]	1.31±0.02 (1.31)	20.0±0.0$_5$	18.0±0.20

[a] In parenthesis are reported the rate constants (accurate to within ±3%) measured in absence of TEA. [b] k_u, K_1 and k_2 values calculated using apparent first-order rate constants measured at [TEA] -0.0490 mol dm^{-3}. *Viceversa* using all the experimental rate constants of Table 1 the following values have been calculated (0.952±0.617)10^{-5}, (20.1±0.0$_5$) and (1.82±0.03)10^{-3}, respectively. The use of the rate constants measured at high [TEA] causes a large increase in the uncertainty of the k_u value.

anion character since an anion would fast rearrange [*e.g.* see the behaviour of **3a-g** in DIOX/W in buffer solutions (k_2 2.5-10.7x10^{-2}s^{-1})] nor an ion-pair character, but they represent an acid-base hydrogen-bonded adduct.

The rate of the uncatalysed pathway (3.16-1.31x10^{-5}s^{-1}) depends on the nucleophilicity of *N'* and on the strength of the *N'*-H bond, which are affected by the nature of the substituent present in opposite ways:[1] the balancing between the two factors, as expected, causes *a small substituent effect* with a prevalence of the first factor, for which reason electron-repelling and -withdrawing substituents increase and decrease, respectively, the k_u values, [$(k_u)_{p\text{-MeO}}/(k_u)_{p\text{-NO}_2} \cong 2.4$],[9] and determine *a low susceptibility constant* [ρ -0.34(±0.02), *i* 0.01(±0.01), *n* 7, *r* 0.992] in the linear free energy correlation (LFEC) with Hammett σ constants.[10] The result obtained (small negative susceptibility constant) strictly recalls that observed for the same MHRs in DIOX-W in the uncatalysed range (ρ -0.37).[1]

Both K_1 (0.5-20 dm^3 mol^{-1}) and k_2 (1.4-18x10^{-4}s^{-1}) values (steps 2 and 3 of Scheme 3) show similar substituent effects: electron-repelling and -withdrawing substituents decrease and increase, respectively, both the equilibrium and the kinetic constants. Thus a Hammett plot[10] gives positive susceptibility constants [ρ 1.44 (±0.16) and 1.00 (±0.11), respectively]. The statistical results (*r* 0.970 and 0.972, for K_1 and k_2, respectively) are poor because of some scattering of both strong electron-donating (*e.g.*, X = *p*-MeO) and electron-withdrawing (*e.g.*, X = *p*-NO_2) substituents, which show a reactivity higher than that estimated by the LFEC involving only X = H, *m*-Cl and *m*-NO_2, *i.e.*, substituents which cannot give conjugative interactions. This behaviour for electron-donating substituents can be *corrected* by using σ^n values.[11] In fact a plot of reactivity data versus σ^n values clearly shows that all the substituents but the strongly electron-withdrawing *p*-nitro substituent well fit the new correlations. For this substituent the correlations would require the use of a value of the substituent constant intermediate between σ^n and σ_p^-. On exclusion of the point for *p*-nitrosubstituted formamidine (**3g**) excellent LFEC's have been observed for both K_1 and k_2 [ρ 1.42 (±0.06) and 0.99 (±0.03), *n* 6, *i* 0.06 (±0.02) and 0.02 (±0.01), *r* 0.996 and 0.998, respectively].[12]

Concerning the equilibrium reaction (step 2 in Scheme 3) the positive susceptibility constant calculated fulfils the expectation that K_1 values depend on both the acidity of the hydrogen atom (>N'-H) which interacts with the base and the stability of the obtained adduct, which factors are increased and decreased by electron-withdrawing and -donating substituents, respectively.

The positive susceptibility constant calculated for the rearrangement reaction (step 3 in Scheme 3) agrees with the structure of the transition state where a negative charge must be spread out. Moreover electron-withdrawing and -donating substituents can stabilize and destabilize, respectively, the final products **4** by means of an electronic interaction between N(1) and the substituted N(1)-aryl groups, which would affect also the stability of the relevant transition states.

The calculated K_1 and k_2 values (large and low, respectively) are consistent with the mechanism proposed. In fact, large substituent-dependent K_1/k_2 ratios are observed: they range between 3.4x10^3 (for X = *p*-MeO) and 11.1x10^3/s dm^{3}mol^{-1} (for X = *p*-NO_2) in accord with a positive susceptibility constant larger for the equilibrium step (ρ 1.42) than for the rearrangement step (ρ 0.99). As already observed in other MHRs with a multistep mechanism for the catalysed pathway, the equilibrium step shows a larger substituent effect (*i.e.* a larger susceptibility constant) than the rearrangement step,[1,4] in accord with the different electronic requirements of the two steps.

Rearrangement of N-(5-phenyl-1,2,4-oxadiazol-3-yl)-N'-p-nitrophenyl-formamidine 3g in ACN in the presence of DABCO

This reaction has been studied at 313.15 K at various concentrations of DABCO to gain information about the effect of the base used. The rate constants obtained are shown in Table 3 and in Figure 2. Once again a downward curvilinear trend has been observed. The various rate constants calculated by regression analysis are as follows: k_u/s^{-1} (1.29±0.13)x10^{-5}, K_1/dm^3mol^{-1} (2.60±0.00) and k_2/s^{-1} (1.05±0.01)x10^{-2}.

Table 3. Apparent Pseudo-first-order Rate Constants[a] for the Rearrangement (3g) → (4g) in ACN in the Presence of DABCO at 313.15 K

[DABCO]/mol dm^{-3}	0.000	0.0015	0.0030	0.0050	0.0075	0.0100
$10^4k_A/s$	0.131	0.538	0.943	1.48	2.14	2.79
[DABCO]/mol dm^{-3}	0.0200	0.0300	0.0400	0.0600	0.0800	0.100
$10^4k_A/s$	5.31	7.72	10.0	14.2	18.2	21.8
[DABCO]/mol dm^{-3}	0.250	0.400	0.500	0.600	0.800	1.000
$10^4k_A/s$	41.4	53.6	59.4	64.0	71.0	75.8

[a] As notes *a* and *h* of Table 1.

A comparison with the data obtained in the presence of TEA are of some interest: the k_u values calculated in ACN in the presence of the two bases, considering the uncertainties calculated, are coincident (1.31 and 1.29x$10^{-5}/s^{-1}$, respectively: in the same solvent the rates of the uncatalysed pathway are, by definition, unaffected by the used bases), whereas K_1 and k_2 values change according to the proposed mechanisms. In fact a lower value of K_1 for DABCO has been calculated, in accord with the lower basicity of DABCO with respect to TEA in polar solvents [compare, e.g., the pK_a values in water: $(pK_a)_{TEA}$ 10.68 and $(pK_a)_{DABCO}$ 8.72].[6] In contrast a higher value for k_2 has been calculated and this clearly confirms the acid-base hydrogen-bonded adduct nature for AFH.TEA (see Scheme 4), whose reactivity in the further rearrangement is affected by the steric requirements of the linked amine (DABCO is less bulky than TEA).

Comparison of the Reactivity of 3a-g in ACN with that in DIOX-W and with the Reactivity of N-(5-phenyl-1,2,4-oxadiazol-3-yl)-N'-arylureines (5) and of Z-Arylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole (6) in ACN

The rearrangement of arylformamidines **3a-g** proceeds with much the same mechanism in ACN and in DIOX-W[1] following both an uncatalysed and a catalysed pathway, with this latter reaching a limiting rate. Bearing in mind that different bases are involved in the two solvents (OH^- in DIOX-W and TEA in ACN) a direct comparison between the results in the two solvents is possible only for the uncatalysed pathway, for

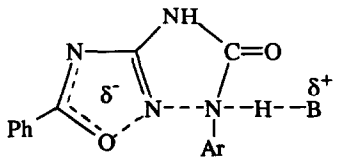
which quite similar rate constants are observed[1] [*e.g.*, for X = H: $(k_u)_{DIOX\text{-}W}/(k_u)_{ACN}$ 2.1] and similar susceptibility constants are calculated [$(\rho)_{DIOX\text{-}W}$ -0.37[1] and $(\rho)_{ACN}$ -0.34)].

The results obtained (similar k_u values and small negative susceptibility constants) indicate that the reaction pathway is much the same in the two solvents. Moreover the fact that the rate constants are scarcely affected by the nature of the solvents used (the one dipolar aprotic, the other dipolar protic) confirms that MHRs occur through an uncatalysed internal nucleophilic substitution and therefore that the two basic solvent systems (DIOX-W and ACN) behave similarly.

The K_1 and k_2 values are significantly larger in DIOX-W[1] than in ACN: apart from the solvent effect, in the case of K_1 (step 2 of Scheme 3; for X = H, $(K_1)_{DIOX\text{-}W}/(K_1)_{ACN}$ 86) this agrees with a larger efficiency as a base of hydroxide ion compared to TEA whereas in the case of k_2 (step 3 of Scheme 4; for X=H, $(k_2)_{DIOX\text{-}W}/(k_2)_{ACN}$ 172) this can be clearly related to the different nature of the product deriving from the acid-base interaction (anion in DIOX-W, more probably acid-base hydrogen-bonded adduct or ion-pair in ACN), which gives the rearrangement.

At variance with the uncatalysed pathway which shows the same substituent effect in the two solvents (see above), the two steps of the catalysed pathway (equilibrium and rearrangement steps) show a larger substituent effect in ACN than in DIOX/W. The higher polarity of DIOX-W compared to ACN, the larger basicity of hydroxide ion compared to TEA and the different reactivities observed (which obey the selectivity-reactivity principle) well account for this behaviour: in fact, polar transition states, as those expected for steps 2 and 3 of Scheme 3, require a higher and higher help from substituents (*i.e.* they show higher and higher susceptibility constants) as the solvent becomes *less polar* and the base used *less effective*.

In compounds **3**, **5** and **6** the starting ring (1,2,4-oxadiazole) is the same and the side chain is variable: *i.e.*, in the rearrangement (a S_Ni reaction) the leaving group is the same and the nucleophile is variable and its nature affects the mechanism of the rearrangement and its reactivity. In the rearrangements of *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-arylureines (**5**) into 1-aryl-3-benzoylamino-1,2,4-triazolin-5-one[4] the side chain involved in the rearrangement contains the same atoms (NCN) present in the now studied N-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-arylformamidines **3** but they are combined to give different functionalities (-NH-CO-NH-Ar and -N=CH-NH-Ar, respectively) with different features. E.g., in **5** the high internal conjugation characteristic of ureines lowers so much the nucleophicility of the nitrogen atom that arylureines **5** do not rearrange either by melting nor by an uncatalysed pathway in solution.[4,5] Moreover compounds **5** rearrange in ACN in the presence of amines (*n*-butylamine, piperidine, TEA or DABCO) following a clean second-order kinetic law ($k_A = k_{II}[S][B]$).[4] Therefore both the acidic hydrogen/base interaction and the nucleophilic attack of the nitrogen atom of the side chain on N(2) of the 1,2,4-oxadiazole ring occur in the unique transition state (**7**) of this MHR.



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This behaviour well accounts for the high susceptibility constant (ρ 2.45) observed for the amine (e.g., piperidine) catalysed rearrangement of **5**:[4] in fact, the calculated constant in some way combines the electronic effects observed in the case of compounds **3** in the equilibrium and rearrangement steps.

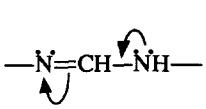
In the rearrangement of *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**6**) into 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazole a different side chain (CNN: >C=N-NH-Ar) was investigated. The substituent effect on the rearrangement rate of **6** in ACN was studied in the presence of piperidine and no LFER could be obtained.[3f] In fact, a strong electron-donating substituent practically did not affect the reactivity {at [PIP] 0.5 mol dm^{-3} and at 283.15 K $(k_A)_{MeO}/(k_A)_H$ 0.97}; in contrast, a strong electron-withdrawing substituent caused a large increase of the reactivity [$(k_A)_{NO_2}/(k_A)_H$ 62]. Bearing in mind the course of the rearrangement in less polar solvents (benzene or DIOX), in which both electron-donating and -withdrawing substituents cause an increase of the reactivity, the observed behaviour indicates clearly a changeover of mechanism with changing substituent. For this reason no comparison concerning the global substituent effect on the rearrangement of **3** and **6** in ACN can be made.

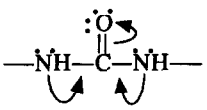
Only a rough comparison concerning the effect of the strong electron-withdrawing *p*-nitro substituent and that of hydrogen in ACN can be made: for compounds **3** (at [TEA] 0.5 mol dm^{-3} and at 313.15 K), **5** and **6** (in both cases in the presence of [PIP] 0.5 mol dm^{-3} and at 313.15 and 283.15 K, respectively) $(k_A)_{NO_2}/(k_A)_H$ 29, 222[4] and 62,[3f] have been observed which indicate that in each case such a substituent causes reactivity increases of a comparable extent.

A comparison, between the apparent reactivity at 313.15 K in ACN of the *p*-nitrosubstituted N-(5-phenyl-1,2,4-oxadiazol-3-yl)-N'-*p*-nitrophenylformamidine **3g**,[4] *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)-*N'*-*p*-nitrophenylureine **5** and *Z*-*p*-nitrophenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **6**[3e] gives the following figures

$(k_A)_3$	3.1×10^{-4} s^{-1}	[in the presence of TEA (0.01 mol dm^{-3})]
$(k_A)_5$	6.8×10^{-5} s^{-1}	[in the presence of TEA (0.01 mol dm^{-3})]
$(k_A)_6$	*ca.* 0.6 s^{-1}	[in the presence of PIP (0.01 mol dm^{-3}), value estimated from data at 283.15 K]
$(k_A)_6$	*ca.* 9×10^{-2} s^{-1}	[in the presence of TEA (0.01 mol dm^{-3}), value estimated from data in the presence of PIP]

which indicate the sequence of reactivity **6** >> **3** > **5**. In this sequence the striking point is the very high reactivity of **6** with respect to **3** and **5**. In all the compounds considered an electronic interaction between the nucleophilic nitrogen and the aryl is possible (). Moreover in **3** (side chain, formamidine) and in





5 (side chain, ureine) there is a strong internal conjugation, which lowers the nucleophilic character of the nitrogen atom. In **6**, *viceversa*, a similar interaction is disfavoured and, furthermore, the two adjacent nitrogen atoms can give some repulsive stereoelectronic interactions between their lone pairs, which increases the nucleophilicity of the nitrogen atom involved in the internal nucleophilic substitution.

EXPERIMENTAL SECTION

Synthesis and Purification of Compounds

3a-g,[1] **4a-g**[1] and ACN[13] were synthesised and/or purified according to literature methods. TEA[6] was purified by standing over potassium hydroxide (24h) and twice fractionally distilled. DABCO[6] was purified by sublimation.

Kinetic Measurements

The kinetics were followed spectrophotometrically as previously described[1,3,4] by measuring the disappearance of (**3a-g**) at suitable wavelengths, where the differences of the absorption between **3a-g** and **4a-g** were highest. The measured apparent first-order rate constants, the used wavelengths and the log ε values are reported in Tables 1 and 3.

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