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Isomerization and rearrangement of (*E*)- and (*Z*)-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole: evidence for a 'new' type of acid-catalysis by copper(II) salts in mononuclear rearrangement of heterocycles

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A kinetic investigation in methanol of the title reaction has evidenced the occurrence of two processes: the 1-$E \rightleftarrows$ 1-Z isomerization and the rearrangement of the (*Z*)-isomer into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (1-$Z \rightarrow$ T). The latter reaction is in line with the ability of the (*Z*)-phenylhydrazones of 3-benzoyl-1,2,4-oxadiazoles to undergo the so called mononuclear rearrangement of heterocycles (MRH). The occurrence of both the examined reactions is dependent on a Lewis-acid-catalysis. The obtained results have shown the possibility of a 'new' type of acid-catalysis (bifunctional catalysis by Lewis salts) in the MRH. This catalysis operates through a completely different mechanism with respect to the one recently observed, and deeply investigated, in the presence of protic acids for the (*Z*)-phenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole, in both dioxane/water and toluene, for which the catalytic process was dependent on the protonation of N(4) ring-nitrogen of the 1,2,4-oxadiazole. As a matter of fact, the copper salts seem able to interact with the $>C{=}N{-}NH{-}C_6H_5$ moiety, yielding adducts which, in some cases, are prone to both isomerize and rearrange. Therefore, a similar behaviour in some manner parallel to that already observed in benzene in the presence of aliphatic amines (base-catalysis) has been evidenced. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: azole-to-azole interconversion; copper salts catalysis; *E*,*Z*-Isomerization; Lewis-acids-catalysis

INTRODUCTION

Transition metal catalysis has attracted much attention in chemistry.[1–8] This is not surprising as several examples of efficient natural reactions catalyzed by metal enzymes are known, and nature itself represents an 'infinite' source of teaching and inspiration for researchers.

In order to perform metal catalysis, it is important to consider both the characteristics of the metal (or of the ion, if salts are used) and the structure of the involved substrate. Several reports in literature have shown that copper(II) salts are able to form complexes with organic *p*- or π-donor ligands having both heterocyclic units[9–17] (e.g. azoles, azines etc.) and various kinds of nitrogen atoms.[18–20] The interest in this area is also related to the biological importance of interactions of copper ions with the imidazole of histidine in several biological molecules and metallo proteins[21–23] as well as with pyrrole ring in porphyrins.[24–27] Indeed, these interactions represent the prerequisite for their reactivity.

Due to our interest in the study of the reactivity of five-membered heterocyclic compounds, we decided to investigate the effect of metal catalysis on heterocyclic rearrangements. In particular, for a long time we have been involved in the study of synthesis and reactivity of the (*E*)- and (*Z*)-arylhydrazones of 3-benzoyl-5-X-1,2,4-oxadiazole.[28–35] In principle, these hydrazones might be able to show a dichotomic behaviour. On one hand, in both polar and apolar solvents (acetonitrile, dioxane and benzene), and in the presence of organic bases (e.g. piperidine) the $E \rightarrow Z$ isomerization around the imino bond has been observed.[33] This isomerization has been also investigated on a series of *meta*- and *para*-substituted phenylhydrazones eviden-

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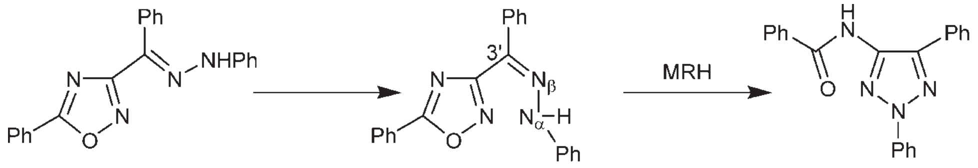


(1-*E*) **(1-*Z*)** **(T)**

Scheme 1. Isomerization of **1-*E*** and rearrangement of **1-*Z***.

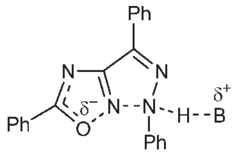
cing the occurrence of an unusual substituent effect.[33] On the other hand, the (*Z*)-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, under the same experimental conditions used for the isomerization, rearrange into the relevant 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles by means of a mononuclear rearrangement of heterocycles (MRH; as named by Boulton and Katritzky; Scheme 1).[29,36–39] In contrast, the (*E*)-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1-*E***) remains unchanged in benzene either at room temperature or by heating in the presence of an excess of acetic acid (48 h at 333 K).[33]

MRHs are intramolecular nucleophilic substitutions (S_Ni). They proceed via a 'quasi-aromatic' transition state (TS)[40] and show reaction rates largely influenced by both the acidity of the hydrogen of the N_α—$\underline{H}$ on the arylhydrazonic nitrogen and the nucleophilicity of the $\underline{N}_\alpha$.[29,34]

Usually this ring-to-ring interconversion can occur via a general-base-catalyzed and/or a uncatalyzed pathway.[28,30] Moreover, a specific-acid-catalyzed pathway has been observed if an amino group is present at the C-5 of the 1,2,4-oxadiazole ring, thus rendering the N-4 atom so basic to undergo a protonation: an example is given by the behaviour of the (*Z*)-phenylhydrazone of 5-amino-3-benzoyl-1,2,4-oxadiazole in water/dioxane or in toluene in the presence of protic acids.[41–43]

Also in non-aqueous solvents the MRHs can occur by base-catalyzed or uncatalyzed pathways. They have been studied in conventional solvents (acetonitrile, benzene, dioxane, ethyl acetate and methanol),[31,32] and in organized and pre-organized systems (micelles[44] and β-cyclodextrin[45]) and recently in room temperature ionic liquids.[46–48]

However, it has been qualitatively outlined that in methanol and in the presence of copper acetate (Lewis acids),[49] the (*E*)- and the (*Z*)-phenylhydrazones of the 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1-*E*** and **1-*Z***) give both the **1-*E*** ⇄ **1-*Z*** isomerization and the **1-*Z*** → **T** rearrangement into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole. Considering all these information and particularly the last intriguing behaviour (see above the stability of **1-*E*** in benzene in the presence of acetic acid[33]), we started with a quantitative examination of the reactivity of **1-*E*** and **1-*Z*** in methanol in the presence of some Cu(II) salts to gain mechanistic information. Thus, we carried out a study by using several Cu(II) salts [$CuSO_4 \cdot 5H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2 \cdot H_2O$] having different characteristics, that is, anions showing different coordinating ability as well as different basic and nucleophilic aptitude.



TS

$$\mathbf{1\text{-}}\boldsymbol{E} \underset{k_{Z,E}}{\overset{k_{E,Z}}{\rightleftharpoons}} \mathbf{1\text{-}}\boldsymbol{Z} \xrightarrow{k_{Z,\mathrm{T}}} \mathbf{T}$$

Scheme 2. **1-*E*** ⇄ **1-*Z*** isomerization and **1-*Z*** → **1-T** rearrangement

RESULTS AND DISCUSSION

A qualitative approach

In order to verify the ability of the above Cu(II) salts to induce the isomerization and/or the rearrangement, we have checked the reactivity of **1-*E*** and **1-*Z*** in methanol in the presence of equimolar amounts of the salt. All the reactions were monitored for 8 h (refer to Experimental section).

Moreover, for comparison, we have carried out a blank test on a methanol solution of **1-*Z*** since its rearrangement into the relevant triazole can significantly proceed via an uncatalyzed pathway in a protic solvent.[30,31] The same blank reaction has been carried out also with **1-*E*** which appeared to remain unchanged. The results are reported in Table 1.

An analysis of data evidenced that the outcome of the reactions is affected by the nature of the anion of the copper salts. In particular, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2 \cdot H_2O$ were able to promote both the **1-*E*** ⇄ **1-*Z*** isomerization and the **1-*Z*** → **T** rearrangement. With these salts, increasingly higher yields in triazole (from 24 ± 3% to 91 ± 3%), with respect to the blank test (17 ± 3%), were obtained showing the occurrence of catalysis.

At first sight some results concerning the yields in **T** from **1-*E*** and **1-*Z*** (comparable or higher yields from **1-*E***, which gives the MRH only after the isomerization into **1-*Z***) could appear unexpected, but they can be easily related to the different solubility in methanol of the two isomers (refer to Experimental section).

In contrast, $CuSO_4 \cdot 5H_2O$ and $Cu(ClO_4)_2 \cdot 6H_2O$ seem able to induce only the **1-*E*** ⇄ **1-*Z*** isomerization as indicated by yields in triazole strictly comparable to that observed in pure methanol [(17.5–18.0) ± 3% vs. 17 ± 3%].

Data in Table 1 indicate that the nature of the anion in the salts affects the reactivity. Among acetate, bromide and chloride the former is the best catalyst for the **1-*Z*** → **T** rearrangement, while the chloride anion seems to be the worst. In contrast, sulphate and perchlorate did not favour any rearrangement.

Table 1. Data concerning the isomerization (**1-*E*** ⇄ **1-*Z***) and the rearrangement (**1-*Z*** → **T**) in methanol at 313 K and in the presence of some copper salts[a]

Substrate	Copper salt	Reaction time	Substrate unchanged (%)	Yield in 1-*E*(%)	Yield in 1-*Z*(%)	Yield in (T)(%)
1-*Z*	None	8 h	83.0			17.0
1-*E*		8 h	100			
1-*Z*	$CuCl_2$	8 h	54.7	11.9		23.8
1-*E*		8 h	12.5		56.2	27.0
1-*Z*	$CuBr_2$	8 h	21.7	17.3		52.1
1-*E*		8 h	1		26.7	66.7
1-*Z*	$Cu(OAc)_2{\cdot}H_2O$	8 h	4.7			88.4
1-*E*		8 h				91.0
1-*Z*	$CuSO_4{\cdot}5H_2O$	8 h	65.0	12.5		17.5
1-*E*		8 h	20.0		60.0	18.0
1-*Z*	$Cu(ClO_4)_2$	8 h	51.2	23.2		18.0
1-*E*		8 h	26.4		54.5	18.0

[a] The yields are reproducible within ±3%.

A quantitative approach: the mechanism of the conversion processes

To better interpret the above results we have measured the reactivity in methanol as a function of copper salts concentration. As the hydrazones **1-*E*** and **1-*Z*** and the relevant triazole **T** are active in different region of UV–Vis spectrum, the kinetic investigation was carried out at 313.1 K by means of UV–Vis measurements. At the used kinetic concentrations, **1-*E*** and **1-*Z*** (as well as **T**) are soluble in methanol and we have ascertained that the presence of a small quantity of water (crystallization water of used salts, always lower than 1%) does not affect the nature of the solvent. The overall reactivity of hydrazones **1** is illustrated in Scheme 2:

where $k_{E,Z}$ and $k_{Z,E}$ are the rate constants related to the reversible isomerization and $k_{Z,\mathrm{T}}$ is the rate constant for the rearrangement, respectively. Details concerning the reaction mixture analysis and the determination of the rate constants have been reported in the Experimental section.

The 1-E ⇄ 1-Z isomerization

In all of the cases considered, the plot of the observed rate constants ($k_{E,Z}$ or $k_{Z,E}$) versus Cu(II) concentration showed an hyperbolic trend: in Fig. 1 data concerning the isomerization in the presence of $Cu(ClO_4)_2$ are shown. Data at different concentrations of all the copper salts are reported in Supplementary Material (Tables 4–8 and Figures 7–14). Collected data indicate that, in the presence of copper salts, the reaction proceeds via a two steps mechanism: a first fast equilibrium [the coordination between the substrate and Cu(II)], followed by the rate determining step (the isomerization around the imino bond), as reported in Scheme 3 considering **1-*E*** as substrate.

Analogous equilibria apply to **1-*Z*** as starting material. The fit of experimental data by means of equations such as:

$$k_{E,Z} = \frac{(k_{E,Z})_{\mathrm{Cu}}\,(K_E)_{\mathrm{Cu}}[\mathrm{Cu(II)}]}{1 + (K_E)_{\mathrm{Cu}}[\mathrm{Cu(II)}]}$$
$$k_{Z,E} = \frac{(k_{Z,E})_{\mathrm{Cu}}\,(K_Z)_{\mathrm{Cu}}[\mathrm{Cu(II)}]}{1 + (K_Z)_{\mathrm{Cu}}[\mathrm{Cu(II)}]} \quad (1)$$

[$(K_E)_{\mathrm{Cu}}$ and $(K_Z)_{\mathrm{Cu}}$ are the binding equilibrium constants for the formation of the adducts between **1-*E*** and **1-*Z*** and Cu(II) and $(k_{E,Z})_{\mathrm{Cu}}$, and $(k_{Z,E})_{\mathrm{Cu}}$ the rate constants for the isomerization, respectively] gave the results in Table 2.

Data in Table 2 show that all of the copper salts tested are able to promote the **1-*E*** ⇄ **1-*Z*** isomerization. For both isomers, two parallel pathways furnishing the same TS can be depicted as shown in Scheme 4.

In both cases the coordination of the Cu(II) cation must occur at the imino nitrogen in order to cause the isomerization: it lowers the carbon-nitrogen [$C(3')_\alpha$—N_β] double bond character and allows the occurrence of the rotation around the 'ex-double bond' in the TS. In the TS the imino nitrogen would have a trigonal structure with Cu(II) and NH_α—Ph substituents orthogonal to the plane individuated by $N(2)_\alpha$—$C(3)_\alpha$—$C(3')_\alpha$—N_β.

This hypothesis appears in line with literature data[50] about the ability of ions of transition metals, for example Zn(II), to catalyze the isomerization around a >C=N—. Furthermore, a similar function of Cu(II) salts was previously suggested also by Gokhale *et al.*[51] and by some of us.[49]

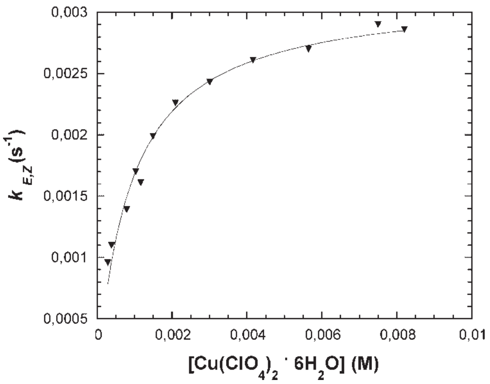


Figure 1. Observed rate constant ($k_{E,Z}$) versus [$Cu(ClO_4)_2{\cdot}6H_2O$] for the 1-E ⇄ 1-Z isomerization in methanol at 313.1 K

$$\mathbf{1}\text{-}\boldsymbol{E} + \mathrm{Cu(II)} \xrightleftharpoons{(K_E)_{Cu}} \mathbf{1}\text{-}\boldsymbol{E}/\mathrm{Cu(II)}$$

$$\mathbf{1}\text{-}\boldsymbol{E}/\mathrm{Cu(II)} \xrightleftharpoons[(k_{Z,E})_{Cu}]{(k_{E,Z})_{Cu}} \mathbf{1}\text{-}\boldsymbol{Z}/\mathrm{Cu(II)}$$

Scheme 3. **1-*E***/Cu(II) complexation equilibrium and **1-*E*** ⇄ **1-*Z*** copper assisted isomerization

Moreover, since the formation of chelated adducts can occur in organic systems containing several donor atoms with the correct arrangement,[52–56] we have taken into account this possibility. For both of the isomers, the formation of chelated adducts with a stable five- or six-membered ring [e.g. refer to (**1-*E***/Cu′) and (**1-*Z***/Cu′) in Scheme 4] could be hypothesized, but these species could be considered kinetically 'inactive' versus the isomerization.

In the presence of $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2{\cdot}H_2O$ **1-*Z*** was able also to give the rearrangement (see later). For these salts, with the exception of $CuBr_2$, the isomerization reaction was studied only considering as starting material **1-*E***. Indeed, in the case of **1-*Z***, the rearrangement proceeded too fast to allow the determination of the **1-*E*** isomer concentration, with an acceptable degree of precision and therefore the relevant $(K_Z)_{Cu}$ and $(k_{Z,E})_{Cu}$ constants.

A comparison between data obtained in the presence of $CuCl_2$ or of $CuBr_2$ shows that the latter displays a lower ability to coordinate the substrate $[(K_E)_{CuCl2}/(K_E)_{CuBr2} = 3.2 \pm 0.2]$, but, in contrast, a higher efficiency in catalyzing the **1-*E*** ⇄ **1-*Z*** isomerization $[(k_{E,Z})_{CuCl2}/(k_{E,Z})_{CuBr2} = 0.2 \pm 0.1]$. In line with the qualitative data of Table 1, we observed that the $(K_E)_{CuBr2}$ $(k_{E,Z})_{CuBr2}/(K_E)_{CuCl2}$ $(k_{E,Z})_{CuCl2}$ ratio is higher than 1.

As can be seen from data in Table 2 the adducts stability from **1-*E*** or **1-*Z*** and Cu(II) depends on the present anion. Indeed, for **1-*E*** it increases in the order: $CuBr_2 < CuCl_2 < Cu(ClO_4)_2{\cdot}6H_2O < CuSO_4{\cdot}5H_2O < Cu(OAc)_2{\cdot}H_2O$ and a parallel trend has been observed for **1-*Z***.

This trend is related to the fact that the salts tested individuate two classes of copper Lewis salts: the former with highly coordinating (Cl^- or $CuCl_3^-$; Br^- or $CuBr_3^-$; AcO^-) and the latter with loosely coordinating anions (ClO_4^-, SO_4^{2-}) able, respectively, 'to live in' or 'to live out' the cation sphere.[57–63]

In the first class, $(K_E)_{Cu}$ increases with the anion electronegativity: the high value with $Cu(OAc)_2{\cdot}H_2O$ can also depend on the ability of AcO^- to act as a bidentate ligand.[59] In contrast, in methanol the second class salts would exist as loose ion-pairs. The stability constants concerning **1-*E*** are a little higher than those for **1-*Z***, with a negligible effect of the anions.

Moreover, both SO_4^{2-} and ClO_4^- in the HSAB are hard anion, while Cu(II) is a borderline cation,[64,65] and ClO_4^- was reported to give more loose ion-pairs with respect to SO_4^{2-}. Thus, data in Table 2 show that the more intimate ion-pair gives the more stable complex.

Looking at the rate constants, the $(k_{E,Z})_{Cu}$ smoothly increases in the order: $CuSO_4{\cdot}5H_2O < CuCl_2 < Cu(OAc)_2{\cdot}H_2O < Cu(ClO_4)_2{\cdot}6H_2O < CuBr_2$ [a parallel trend has been observed for $(k_{Z,E})_{Cu}$] showing an opposite trend to that observed for $(K_E)_{Cu}$. Indeed, with the exception of acetate (see above), the reactivity follows an inverse trend with respect to the adduct stability, that is, the reaction proceeds faster when the substrate is more loosely bonded to the cation.

In line with the higher stability of **1-*Z*** with respect to **1-*E*** the $(k_{E,Z})_{Cu}$ is higher than the $(k_{Z,E})_{Cu}$, the relevant ratios being only moderately affected by the anion (from 1.7 with $CuBr_2$ up to 3.6 with $CuSO_4{\cdot}5H_2O$).

The 1-Z → T rearrangement

As above reported, copper acetate, bromide and chloride were able to induce the isomerization as well as the MRH. In Fig. 2a–c, the plots of $k_{Z,T}$ as a function of copper salt concentration are reported (details are in Tables 4–6 of Supplementary Material): they point out the occurrence of a 'new' kind of acid-catalysis (Lewis-acid-catalysis, see after) in the MRH.

As can be seen, with copper acetate, the $k_{Z,T}$ follows a hyperbolic trend as a function of salt concentration. In contrast, with copper halides, it follows a parabolic trend suggesting that the 'real' course of the two reactions is different. For this reason, we shall discuss separately the **1-*Z*** → **T** MRH catalyzed by copper acetate from that catalyzed by halides.

Rearrangement in the presence of copper acetate

The trend observed for the MRH of **1-*Z*** in the presence of copper acetate (Fig. 2a) agrees with a reaction following a two steps mechanism (Scheme 5).

The observed rate constant $k_{Z,T}$ can be expressed as

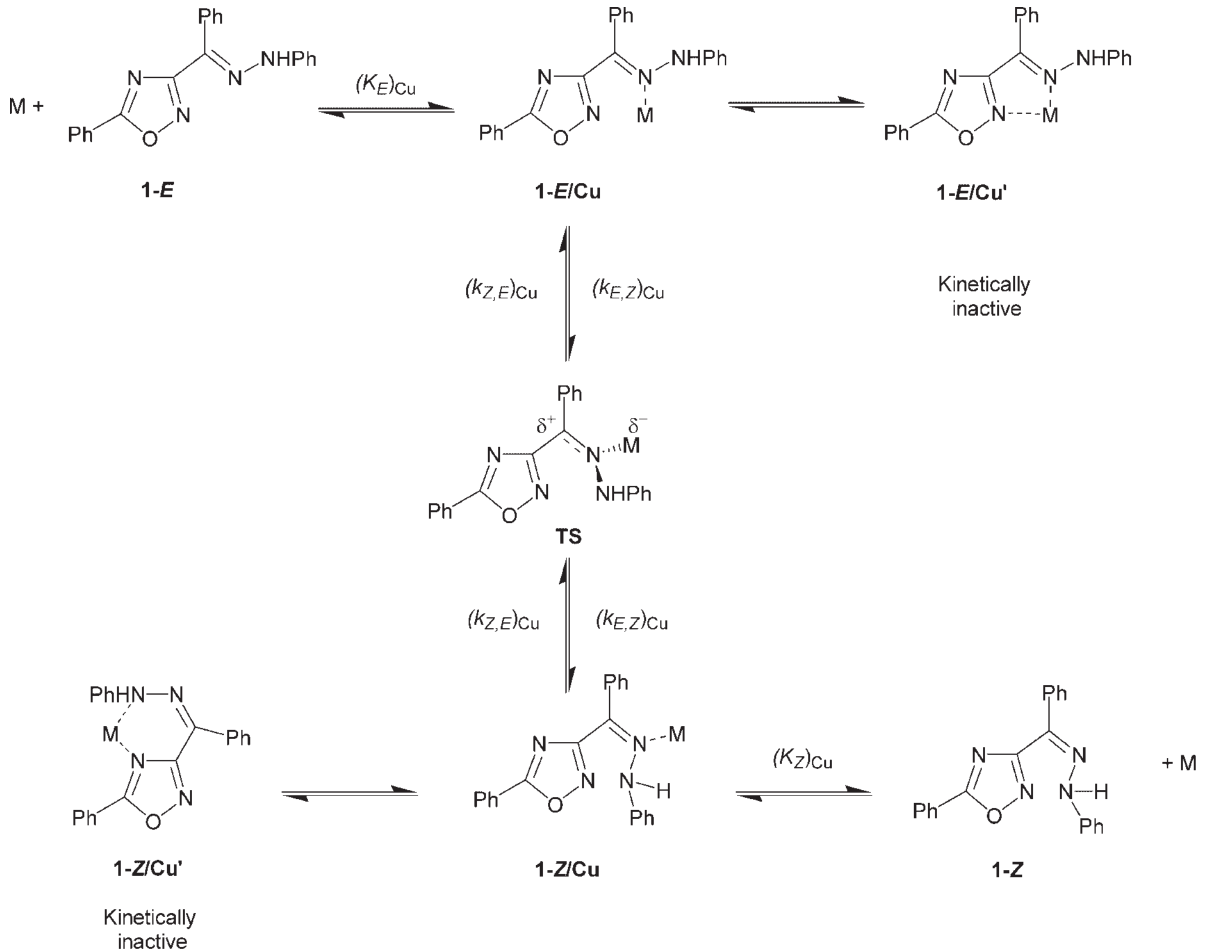
$$k_{Z,T} = \frac{(K_Z)_{Cu}\ (k_{Z,T})_{Cu}[\mathrm{Cu(II)}]}{1 + (K_Z)_{Cu}[\mathrm{Cu(II)}]} \qquad (2)$$

$(K_Z)_{Cu}$ being the binding constant between **1-*Z*** and Cu(II) and $(k_{Z,T})_{Cu}$ the relevant rate constant for its rearrangement. The analysis of experimental data gives: $(K_Z)_{Cu} = 1293 \pm 80\ M^{-1}$; $(k_{Z,T})_{Cu} = (4.77 \pm 0.17)\ 10^{-3}\ s^{-1}$ ($R = 0.999$).

The course of the reaction can be depicted as in Scheme 6 (refer to **1**): the adduct formation makes the hydrazonic hydrogen

Table 2. Binding equilibrium constants and rate constants concerning the **1-*E*** ⇄ **1-*Z*** isomerization in methanol at 313.1 K and in the presence of different copper salts

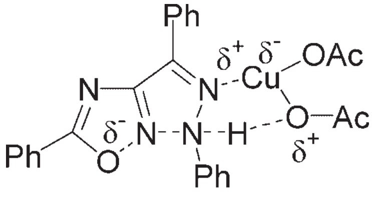
Copper salt	$(K_E)_{Cu}$ (M^{-1})	$(K_Z)_{Cu}$ (M^{-1})	$(k_{E,Z})_{Cu}$ (s^{-1})	$(k_{Z,E})_{Cu}$ (s^{-1})
$CuCl_2$	620 ± 50		$(2.11 \pm 0.06)10^{-3}$	
$CuBr_2$	195 ± 20	140 ± 25	$(1.10 \pm 0.07)10^{-2}$	$(6.44 \pm 0.95)10^{-3}$
$Cu(OAc)_2{\cdot}H_2O$	21100 ± 1170		$(2.47 \pm 0.03)10^{-3}$	
$Cu(ClO_4)_2{\cdot}6H_2O$	1130 ± 110	920 ± 50	$(3.16 \pm 0.08)10^{-3}$	$(7.69 \pm 0.12)10^{-4}$
$CuSO_4{\cdot}5H_2O$	7400 ± 250	5500 ± 280	$(1.12 \pm 0.01)10^{-3}$	$(3.13 \pm 0.04)10^{-4}$



M indicates Cu^{2+} in the instance of $CuSO_4 \bullet 5H_2O$ and $Cu(ClO_4)_2 \bullet 6H_2O$
M indicates CuX_2 in the instance of $CuBr_2$, $CuCl_2$ and $Cu(OAc)_2$

Scheme 4. General scheme for **1-*E*** ⇌ **1-*Z*** isomerization in the presence of copper salts.

more acidic and then prone to interact with feeble bases, such as acetate ion, methanol and so on.



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Indeed, the kinetically active adduct is the one having the imino nitrogen (N_β) coordinated by the cation. The coordination of the imino nitrogen induces an electronic shift causing an acidity increase.[66,67] This kind of coordination has been recently evidenced in substrates bearing also an amino nitrogen.[68] On the other hand, the coordination at the phenylhydrazonic amino nitrogen could give chelated 'inactive' adducts (refer to e.g. **1-*Z*/**Cu' in Scheme 4) unable to evolve into the triazole.

In summary, the kinetically active adduct should show a higher acidity of the of N_α—H proton, favouring the reaction and a lower nucleophilicity of N_α nitrogen, disfavouring the reaction. As a matter of facts, the rearrangement rate is the result of a subtle balance between these effects.[28–35,40]

Also the occurrence of a bifunctional catalysis[69–71] can be supposed as proposed for other nucleophilic substitutions: the Cu(II) acting as a Lewis acid, the relevant anion [in this case, the acetate ion present in the coordination sphere of Cu(II)] acting as a Lewis base.

To confirm the importance of the acetate anion, we have carried kinetic measurements at $[Cu(ClO_4)_2{\cdot}6H_2O] = 1 \times 10^{-4}$ M and [NaOAc] variable from 1.8×10^{-4} up to 5×10^{-3} M. Kinetic data have shown that with $Cu(ClO_4)_2$/NaOAc mixtures, differently from what happens in the presence of $Cu(ClO_4)_2$ alone, also **1-*E*** gives the MRH. As can be seen from Fig. 3 (details in Table 9 of Supplementary Material), the $k_{Z,T}$ increases with [NaOAc], furtherly supporting the hypothesis of a bifunctional catalysis.

Rate constants in the presence of mixed salts are lower than those observed in solution of pure $Cu(OAc)_2{\cdot}H_2O$ of similar concentration, well in line with observations[72] that the 'real' concentration of copper acetate deriving from mixtures of Cu(II) [e.g. from a solution of $Cu(ClO_4)_2$] and AcO^- (from a solution of NaOAc) are lower than those from a solution of $Cu(OAc)_2$ of comparable concentration.

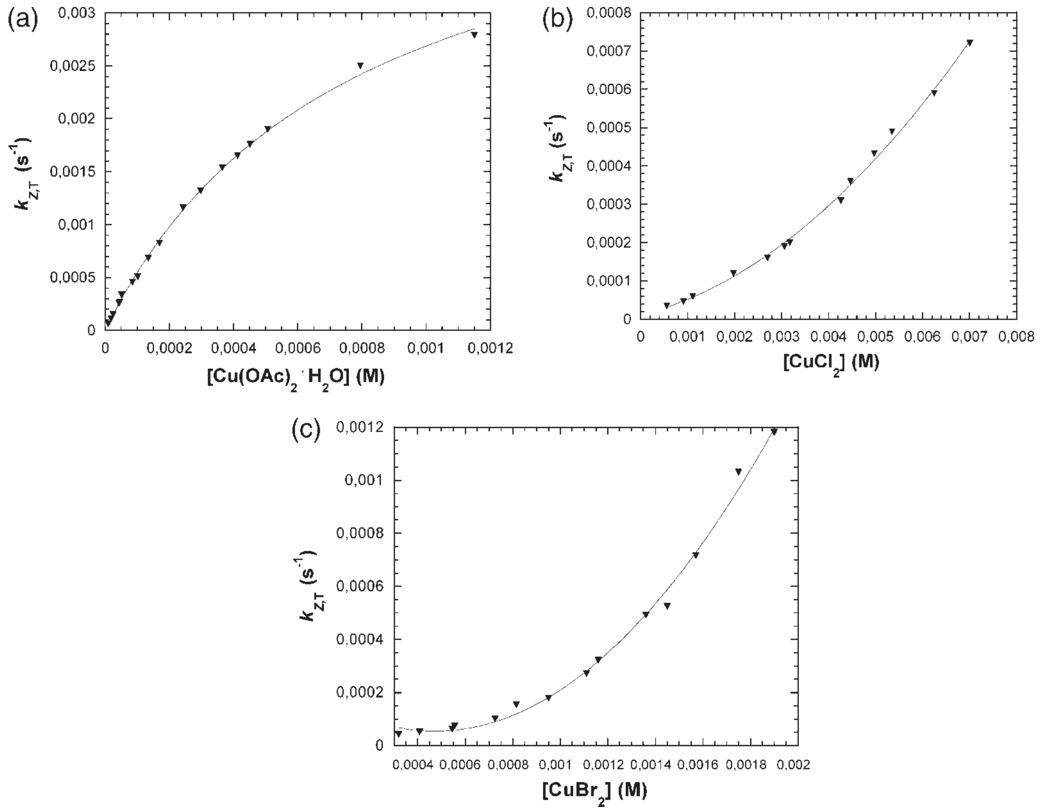


Figure 2. Rate constants ($k_{Z,T}$) versus [Cu(II)] concerning the **1**-Z → **T** rearrangement in methanol at 313.1 K and in the presence of: (a) $Cu(OAc)_2 \cdot H_2O$, (b) $CuCl_2$, (c) $CuBr_2$

Rearrangement in the presence of copper halides

As evidenced in Fig. 2b,c in the presence of copper chloride or bromide, $k_{Z,T}$ as a function of salt concentration shows a parabolic trend. The fit of experimental data agrees with Eqn (3), where k_u and k_{II} represent the first-order and the third-order rate constants concerning the uncatalyzed and trimolecular pathways, respectively.

$$k_{Z,T} = k_u + k_{II}\,[CuX_2]^2 \qquad (3)$$

In Table 3 the relevant results of kinetic data fit are reported.

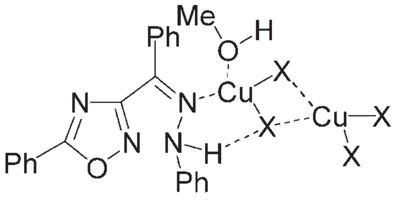
Looking at data in Table 3 the following considerations can be done. The rearrangement (refer also to data of Table 1) proceeds faster in the presence of $CuBr_2$ than in the presence of $CuCl_2$. Rate constants of Table 3 depend also on the stability constants that our experimental data do not allow to determine being included in the calculated rate constants. The higher reactivity in the presence of $CuBr_2$ than in the presence of $CuCl_2$ can be confirmed by comparing the various $k_{Z,T}$ values determined at the same concentration of the two copper salts (e.g. at $[CuX_2] = 1.11 \times 10^{-3}$ M the calculated rate ratio is 4.5. Refer to Supplementary Material, Tables 4–5).

$$\mathbf{1\text{-}Z} + \mathrm{Cu(II)} \xrightleftharpoons{(K_Z)_{Cu}} \mathbf{1\text{-}Z}/\mathrm{Cu}$$

$$\mathbf{1\text{-}Z}/\mathrm{Cu} \xrightarrow{(k_{Z,T})_{Cu}} \mathbf{T}/\mathrm{Cu}$$

Scheme 5. **1-Z**/Cu(II) complexation equilibrium and **1-Z** → **1-T** rearrangement

Furthermore, the main course of the reaction can be determined by a species having two CuX_2 'units'. The kinetically active species could be a halo-bridge dinuclear copper complex such as **2**.

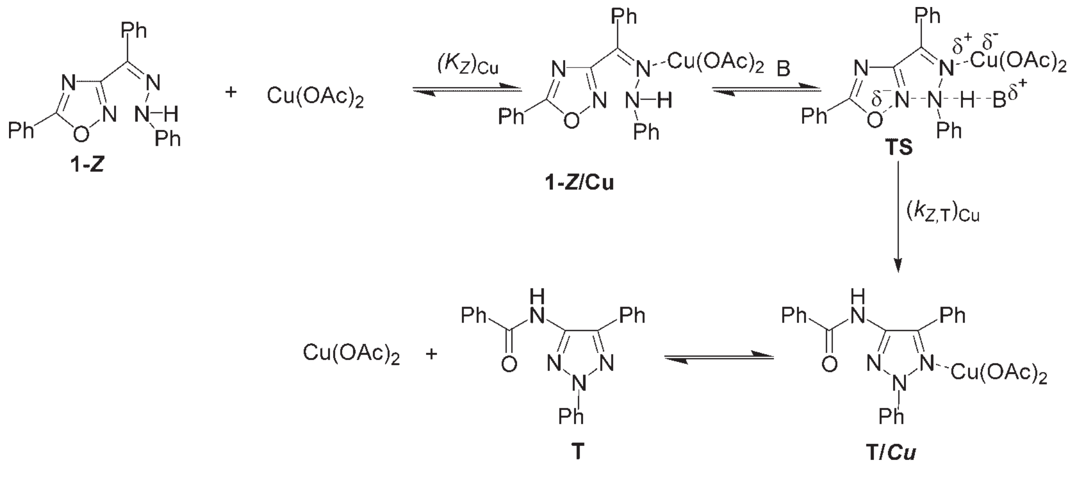


2

The formation of binuclear complexes with $CuHalg_2$ has been well documented.[19,20] Their higher efficiency in catalyzing the MRH, respect to mononuclear complex, can indicate a higher ability of Cu_2X_4 complex to induce the electronic shift from hydrazonic moiety to metal centre or can be related to the occurrence of a bifunctional catalysis.

The contribution of the uncatalyzed pathway that is physically meaningful in the presence of $CuCl_2$, appears in line with some our previous results [$k_u = (1.67 \pm 0.18)\ 10^{-5}$ in methanol].[31]

To confirm the importance of the nature of the anion in the Lewis acids, we have carried out kinetic measurements for the **1-*Z*** → **T** reaction at $[Cu(ClO_4)_2 \cdot 6H_2O] = 3 \times 10^{-3}$ M and [LiCl]



B = acetate ion, methanol, and so on

Scheme 6. Details on the **1-*Z***/copper acetate complexation equilibrium and the relevant **1-*Z*** → **1-T** rearrangement

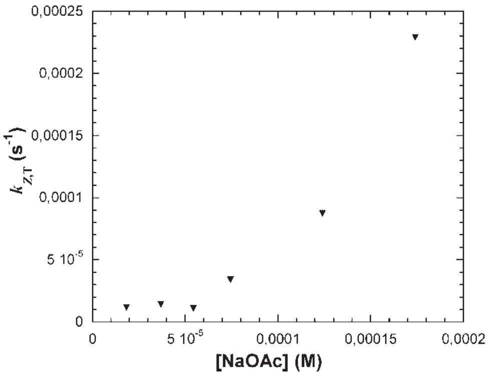


Figure 3. Observed rate constants ($k_{Z,T}$) versus [NaOAc] concerning the **1**-Z → **T** rearrangement in methanol at 313.1 K and in the presence of a fixed concentration of $Cu(ClO_4)_2 \cdot 6H_2O$ (1×10^{-4} M)

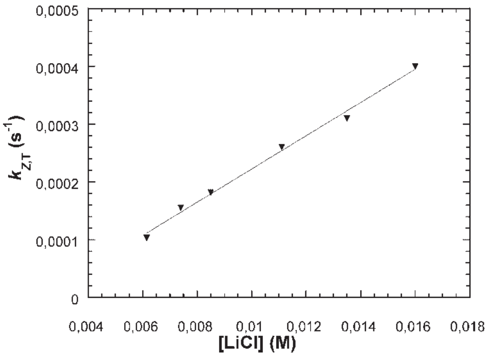


Figure 4. Observed rate constants ($k_{Z,T}$) versus [LiCl] concerning the **1**-Z → **T** rearrangement in methanol at 313.1 K and at a fixed concentration of $Cu(ClO_4)_2 \cdot 6H_2O$ (3×10^{-3} M)

variable from 6×10^{-3} M up to 16×10^{-3} M. As can be seen from Fig. 4 (details in Table 10 of Supplementary Material), unlike what happens in the presence of the only $Cu(ClO_4)_2 \cdot 6H_2O$, also the **1-*Z*** → **T** occurs, confirming the role of particular anions in the MRH.

In such a kind of conditions the formation of various complexes ($CuCl^+$, $CuCl_2$, $CuCl_3^-$, $CuCl_4^{2-}$ etc.) can occur:[57] thus, it can be necessary the presence of salts with anions able to furnish a bifunctional catalysis or else, a base-assistance on proton abstraction from the N_α—H bond (e.g. by AcO^-, $CuHalg_3^-$ and so on). As a matter of fact the $(k_{Z,T})_{Cu}$ increases linearly [$i = (6.55 \pm 1.24) \times 10^{-5}$, $s = (2.87 \pm 0.11) \times 10^{-2}$, $r = 0.997$] with [LiCl] (refer to Fig. 4).

Table 3. Rate constants concerning the **1-Z** → **T** rearrangement in methanol at 313.1 K and in the presence of copper halides according to Eqn (3)

Copper salt	k_u (s⁻¹)	k_{II} (s⁻¹ M⁻²)	*R*
$CuCl_2$[a]	$(5.41 \pm 0.84)\ 10^{-5}$	14.15 ± 0.38	0.996
$CuBr_2$	$(-6.22 \pm 2.64)\ 10^{-5}$	326 ± 15	0.987

[a] In an attempt to correlate kinetic data by using three-parametric equation we found a k_I value about 500 times lower than k_{II} value ($k_I = 0.0301$ M⁻¹ s⁻¹ and $k_{II} = 14.15$ M⁻¹ s⁻¹).

CONCLUSIONS

The results of a thermodynamic and kinetic study of the behaviour in methanol of **1-*E*** and of **1-*Z*** in the presence of different copper salts [$CuSO_4 \cdot 5H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2 \cdot H_2O$] have been discussed, giving a role to both copper cation and present anions on the occurring processes. In fact $CuSO_4 \cdot 5H_2O$ and $Cu(ClO_4)_2 \cdot 6H_2O$ are able to cause only the **1-*E*** ⇄ **1-*Z*** isomerization. In contrast $Cu(OAc)_2 \cdot H_2O$, $CuBr_2$ and $CuCl_2$ are also able to determine the subsequent **1-*Z*** → **T** MRH, as well as the global **1-*E*** ⇄ **1-*Z*** → **T** process.

The different course of the rearrangement in the presence of copper acetate or of copper halides has been examined.

To confirm the role of the anion we have studied the reaction in the presence of mixed salts [such as $Cu(ClO_4)_2 \cdot 6H_2O + NaOAc$, or $+$ LiCl], observing in such conditions also the **1-*Z*** → **T** rearrangement.

The whole of the obtained results has evidenced the occurrence of a 'new' kind of Lewis-acid-catalysis in MRH, completely different from that recently discovered in the case of the (*Z*)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole in the presence of protic acids.[41–43] In that case the basic centre protonated by the added acids was the N-4 of the 1,2,4-oxadiazole ring.

In contrast, in the instance now examined the basic centre appears to be the imino nitrogen of the phenylhydrazone moiety able to interact with Lewis acids giving the relevant adducts. The weakening of the $>C{=}N{-}$ bond makes possible the **1-*E*** ⇄ **1-*Z*** isomerization and in case the **1-*Z*** → **T** MRH (increasing the acidity of the $N_\alpha{-}\underline{H}$ proton). As a matter of fact this acidity increase makes the proton able to interact with bases (AcO^-, $CuBr_3^-$, methanol and so on). This fact causes the occurrence of a sort of bifunctional catalysis,[69–71] whose course can be easily realized looking at the structure of the intermediates **1** and **2**.

In the whole the present study has enlightened a new aspect of the possible reactivity of 1,2,4-oxadiazole derivatives in MRH showing how azoles, particularly 1,2,4-oxadiazoles characterized by a very low heteroaromaticity,[73–76] can offer new and new kinds of reactivity.

EXPERIMENTAL

Materials

Commercial methanol was distilled before use. Commercial $CuSO_4 \cdot 5H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2 \cdot H_2O$ were dried in a muffle at 60°C over phosphorous pentoxide. Then they were stored in a dryer over $CaCl_2$. **1-*Z***, **1-*E*** and (**T**) were prepared according to procedure previously reported.[77,78]

General procedure for qualitative studies

Each experiment was carried out at 313 K suspending 0.1 g of substrate in 40 ml of anhydrous methanol and adding the copper salt dissolved in 10 ml of solvent. Different behaviours were observed depending on the isomer used as starting material: thus, with **1**-***E***, a clear solution was immediately obtained; while with **1**-***Z*** [excluding the reaction in the presence of $Cu(OAc)_2 \cdot H_2O$] a suspension was observed, which became clear in the time (ca. 3 h).

The composition of the reaction mixture was examined by TLC time by time and the reaction was monitored for 8 h. Then the solvent was eliminated at reduced pressure and the obtained residue was extracted several times with ethyl ether. After the ethyl ether elimination the residues were separated by flash chromatography on silica gel. In the presence of copper perchlorate, in order to avoid the decomposition of the reaction products during the solvent elimination, the reaction mixture was poured in water and then extracted with ethyl ether.

Kinetic measurements

UV–Vis spectra for kinetic measurements were carried out by using a spectrophotometer equipped with a Peltier temperature controller, to keep the temperature constant within 0.1 K. The sample for a typical kinetic run was prepared by mixing in a quartz cuvette (light path 1 cm) 2 ml of a solution of the substrate in methanol with 1 ml of the appropriate copper salt solution. Both the solutions were thermostated at 313.1 K. The concentration of the substrates was 5×10^{-5} M. The copper salt concentration ranged from 2×10^{-4} up to 8×10^{-3} M. All kinetic data were analysed by means of Kaleidagraph 3.0.1 software.

Supplementary Material associated with this article can be found in the online version.

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