



Mononuclear rearrangement of heterocycles in ionic liquids catalyzed by copper(II) salts

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ABSTRACT

The reactivity of *E*- and *Z*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in the presence of CuCl₂ and Cu(ClO₄)₂·6H₂O has been studied in four imidazolium ionic liquids [bmim][X] (X=BF₄⁻, PF₆⁻, SbF₆⁻ and CF₃SO₃⁻). The reaction may follow different mechanistic patterns, depending on the nature of the ionic liquid anion, accounting for both qualitative and kinetic data. In the presence of CuCl₂, two processes take place at the same time, i.e., the *E*↔*Z* isomerization and the rearrangement of *Z*-isomer into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole. In contrast, in the presence of Cu(ClO₄)₂·6H₂O, the rearrangement occurs only in solution of [bmim][BF₄] and [bmim][CF₃SO₃]. Collected data show that the effect of the ionic liquid on the isomerization and the rearrangement is different. In particular, a higher cross-linking degree seems to favour the triazole, but disfavour the *E*↔*Z* isomerization.

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1. Introduction

Ionic liquids have been attracting growing attention during the last decade.¹ Owing to their unusual and intriguing characteristics, new developments have been disclosed in a wide range of research fields, from organic synthesis² to electrochemistry,³ materials science⁴ and so forth. Most of the focus has been put on the so-called room temperature ionic liquids (RTILs), i.e., liquid salts at room temperature. They are generally composed by organic cations and polyatomic fluorinated anions. Ionic liquids (ILs) generally exhibit low melting points (<100 °C), low vapour pressure and flammability.

However, one of the most striking feature is their high structural order degree. In particular, in addition to Coulomb and hydrogen bond interactions, for ILs of aromatic cations, also CH- π , quadrupole- π , and π - π stacking play a significant role in determining the characteristics of ILs.⁵ Dupont showed that imidazolium-based ILs can be considered as supramolecular polymers consisting of a highly extended network of hydrogen bonds linking anions and cations together.⁶ As a result, structural order persists to a significant extent in the liquid and even in the gas phase.

It has been shown that slight modifications in the ILs' cation or anion nature are able to induce radical changes in both rate and selectivity of a particular reaction.⁷ This is the reason why RTILs are

sometimes called 'designer solvents'. Therefore ILs are particularly suitable for transition metal catalysis, providing significant advantages in terms of improved catalyst stability and activity.⁸ For example their ability to dissolve organometallic species allows catalyst immobilization making the use of specifically tailored ligands unnecessary.

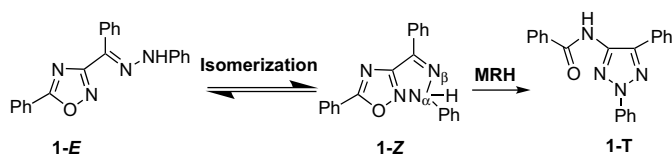
On the other hand, since ILs are poorly miscible with polar organic solvents, catalyst recycling is also facilitated. Moreover a quite recent review has given a detailed picture on the use of chiral imidazolium ILs and on their applications in asymmetric reactions.⁹

A way to gather information about the complex behaviour of these solvents is the study of a reaction whose mechanism in conventional solvents is well defined. In particular, using aromatic ILs, a suitable probe reaction should proceed through a highly ordered transition state, having a different extension of π -conjugation with respect to the reactants. Thus, the mononuclear rearrangement of heterocycles (MRH),¹⁰ which allows azole-to-azole interconversion of suitable heterocyclic compounds, has been recently proven to be a good candidate.

This reaction has been extensively investigated in conventional solvents^{10d} as well as in more complex systems such as micelles¹¹ and cyclodextrins.¹² Investigations carried out recently have shown that the amino-catalyzed rearrangement of the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1-Z**) into the relevant 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (**1-T**) is favoured in IL solution (Scheme 1). The higher reactivity has not been ascribed to a possible higher polarity of these solvent media, but to their organized structure and organizing ability.¹³

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The reactivity of both *E*- and *Z*-phenylhydrazones of the 3-benzoyl-5-phenyl-1,2,4-oxadiazole is also affected by the presence of Lewis acids such as copper(II) salts. Data in methanol collected recently have shown that the outcome of the reaction depends on the nature of the copper salt counteranion.¹⁴ Indeed, in the presence of salts of poorly coordinating anions, such as sulfate or perchlorate, only the **1-E** \rightleftharpoons **1-Z** isomerization has been detected. On the other hand, salts having strongly coordinating anions (able to behave as bases), such as halides or acetate, could promote the rearrangement of **1-Z** into the relevant **1-T**, too.

Both reactions (isomerization and rearrangement) involve the coordination of the metal cation by the imino nitrogen atom (N_{β}) in the side chain. In the presence of strongly coordinating anions, this allows both the rotation around the C–N double bond and the increase in acidity of the hydrogen of the N_{α} –H bond, which favours the following rearrangement.

Thus, bearing in mind the particular sensitivity of these reactions to both the copper salts and the nature of the IL, we supposed that they might be good candidates to test the properties of ILs as solvents for transition metal promoted reactions on heterocyclic compounds. Hence, we undertook a study on the reactivity of **1-E** and **1-Z**, in the presence of CuCl_2 and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in four imidazolium ionic liquids, namely $[\text{bmim}][\text{BF}_4]$, $[\text{bmim}][\text{CF}_3\text{SO}_3]$, $[\text{bmim}][\text{PF}_6]$ and $[\text{bmim}][\text{SbF}_6]$ (bmim = 1-butyl-3-methylimidazolium).

These ionic liquids differ significantly for the coordinating ability and symmetry of the anion and are able to induce a different packing and structural order degree. Furthermore these ILs show different viscosity and β values.¹⁵ In this connection, some literature reports have underlined that changes in these parameters can lead to different reaction outcomes.^{7b}

We chose copper(II) salts differing in the anion nature. In particular, they bear highly (Cl^-) and loosely (ClO_4^-) coordinating anions, respectively, able to 'live in' and 'live out' of the cation coordination sphere, respectively.

Other copper salts, such as CuBr_2 , $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, were not tested because of their low solubility in methanol, the co-solvent used in this work (see Section 4). The reactivity of the title substrates was investigated by means of qualitative tests and kinetic measurements. All of the qualitative tests were carried out at 313 K by treating each substrate with an equimolar amount of copper(II) salt. Since the two substrates (**1-E** and **1-Z**) and the rearrangement product (**1-T**) are active in different regions of the spectrum, the kinetic investigation was carried out at 313 K by means of UV–vis measurements at various copper(II) salt concentrations, ranging from 1.5×10^{-3} M to 1.2×10^{-2} M.

2. Results and discussion

2.1. Qualitative approach

Firstly, we checked behaviour of the substrates, in IL solution, in the absence of copper salts. According to previous literature results,¹³ **1-Z** and **1-E** stay unchanged at 313 K in solution of $[\text{bmim}][\text{BF}_4]$, $[\text{bmim}][\text{PF}_6]$ and $[\text{bmim}][\text{SbF}_6]$. A remarkably different result was obtained in solution of $[\text{bmim}][\text{CF}_3\text{SO}_3]$, where **1-Z** rearranged into the relevant **1-T**. This was confirmed by the UV–vis spectra of **1-Z** recorded as a function of time in $[\text{bmim}][\text{CF}_3\text{SO}_3]$:

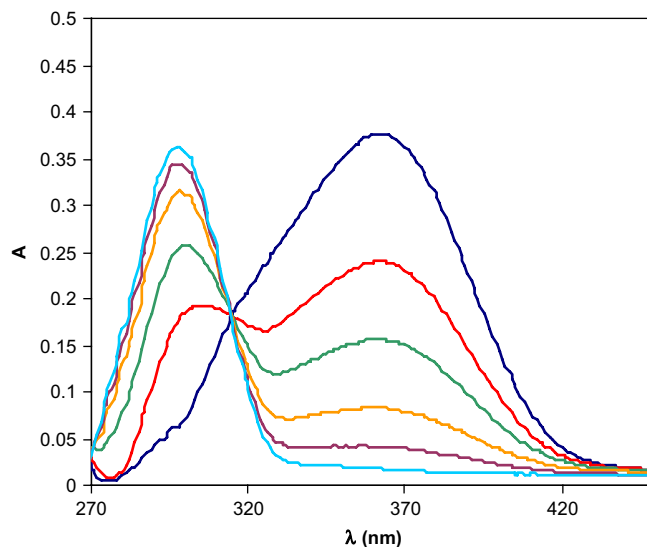


Figure 1. UV–vis spectra of **1-Z** (0.0002 M) in $[\text{bmim}][\text{CF}_3\text{SO}_3]$ recorded at 313 K as a function of time (time range = 105 min).

they showed a decrease of **1-Z** (λ_{max} at 365 nm) and an increase of **1-T** (λ_{max} at 295 nm) concentrations (Fig. 1).

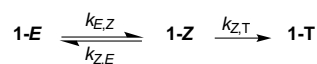
The presence of a sharp isosbestic point agreed with the rearrangement of **1-Z** into the relevant **1-T** in which the trifluoromethanesulfonate anion, an extremely weak base in conventional solvents and having a low hydrogen bond basicity,¹⁶ acts as a general base and promotes the reaction.

Subsequently, we verified, from a qualitative point of view, that the presence of copper salts did not induce any change in the outcome of the reaction. To this end, we carried out the reactions in the presence of equimolar amounts of CuCl_2 and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ at 313 K. All reactions were monitored for 4 h (see Section 4). The obtained results are reported in Table 5 of Supplementary data.

The data collected show that **1-E** \rightleftharpoons **1-Z** always occurs irrespective on the IL or Cu(II) salt used. In contrast, **1-Z** \rightarrow **1-T** rearrangement does not take place when solutions of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in $[\text{bmim}][\text{SbF}_6]$ or $[\text{bmim}][\text{PF}_6]$ are used. Furthermore, the comparison with data previously collected in methanol¹⁴ shows that the latter reaction proceeds faster in IL. Indeed, higher yields were obtained in the half of the time (**1-T** yield in MeOH: 18.0–27.0% in 8 h). Finally, no significant amount of by-products was observed.

2.2. Kinetic study

In order to understand the above results we studied the reactivity in ILs as a function of copper salt concentration. As previously pointed out, hydrazones **1-E** and **1-Z** and the relevant triazole **1-T** are active in different regions of the UV–vis spectrum. The kinetic investigation was carried out at 313 K by means of UV–vis measurements, recording the absorbance values at nine wavelengths ranging from 335 nm to 375 nm as a function of the time. The overall reactivity of hydrazones **1** is summarized in Scheme 2 where $k_{E,Z}$ and $k_{Z,E}$ are the rate constants related to the reversible isomerization reaction and $k_{Z,T}$ is the rate constant for the rearrangement, respectively. Details concerning the reaction mixture analysis and the determination of the rate constants are reported in Supplementary data.



Scheme 2. **1-E** \rightleftharpoons **1-Z** isomerization and **1-Z** \rightarrow **1-T** rearrangement.

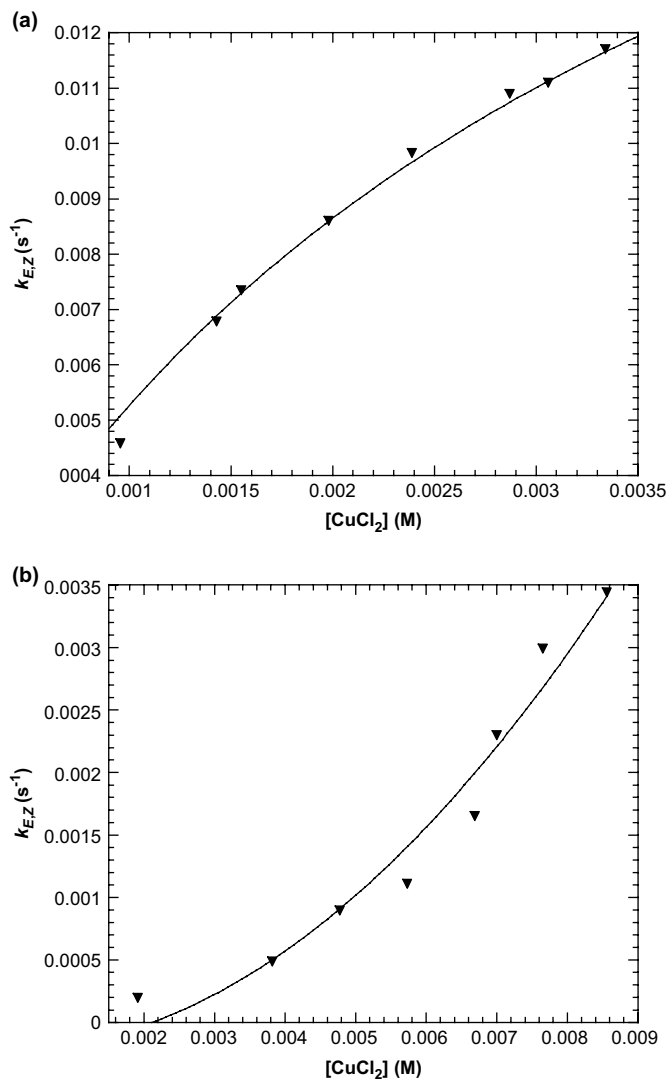


Figure 2. Plots of observed kinetic constants concerning **1-E**→**1-Z** isomerization in the presence of CuCl_2 in: (a) $[\text{bmim}][\text{PF}_6]$ and (b) $[\text{bmim}][\text{BF}_4]$ at 313 K.

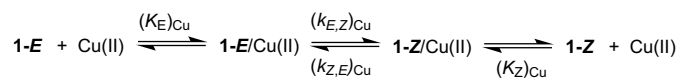
2.2.1. **1-E**⇌**1-Z** Isomerization

The plots of the observed rate constants ($k_{E,Z}$ and $k_{Z,E}$) versus $\text{Cu}(\text{II})$ concentration showed different trends as a function of the IL used. In general, either parabolic trends (for $[\text{bmim}][\text{BF}_4]$ and $[\text{bmim}][\text{CF}_3\text{SO}_3]$ solutions) or hyperbolic trends (for $[\text{bmim}][\text{PF}_6]$ and $[\text{bmim}][\text{SbF}_6]$ solutions) were obtained, suggesting that the 'actual' course of the reaction is different.

As a consequence of this, experimental data will be discussed as a function of the used IL. In Figure 2, $k_{E,Z}$ as a function of CuCl_2 concentration in $[\text{bmim}][\text{BF}_4]$ and in $[\text{bmim}][\text{PF}_6]$ solution are shown.

Data at variable concentration of copper salt, in different ionic liquids, are reported in Supplementary data (Tables 6–11).

2.2.1.1. Kinetic measurements in $[\text{bmim}][\text{PF}_6]$ and $[\text{bmim}][\text{SbF}_6]$. The hyperbolic trend obtained for $k_{E,Z}$ or $k_{Z,E}$ in $[\text{bmim}][\text{PF}_6]$ and in $[\text{bmim}][\text{SbF}_6]$ accounts for a mechanism in which the kinetically



Scheme 3. **1-E**/ $\text{Cu}(\text{II})$ complexation equilibrium and **1-E**⇌**1-Z** copper-assisted isomerization.

active complex, formed in a fast step, has a 1:1 stoichiometry (substrate: copper salt) (Scheme 3). If the **1-E** isomer is the starting material, the above equilibria can be considered.

According to this mechanistic hypothesis, experimental data have been fitted by means of Eq. 1:

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

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

where $(K_E)_{\text{Cu}}$ and $(K_Z)_{\text{Cu}}$ are, respectively, the binding equilibrium constants for the formation of the adducts between **1-E** or **1-Z** and $\text{Cu}(\text{II})$, while $(k_{E,Z})_{\text{Cu}}$ and $(k_{Z,E})_{\text{Cu}}$ represent the isomerization rate constants. In Table 1 the relevant results of kinetic data fit are reported.

Our experimental data, as shown in Table 1, allowed to determine, in the presence of all copper salts, rate constant values relevant to the **1-E**→**1-Z** isomerization. On the other hand, rate constant values concerning the **1-Z**→**1-E** isomerization were determined only in the presence of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. In the presence of CuCl_2 the **1-Z** isomer fastly rearranges into the corresponding **1-T** (see later), preventing the formation of a significant concentration of **1-E**.

According to data previously collected in methanol solution, for both isomers two parallel pathways can be depicted as shown in Scheme 4.

A deeper analysis of the data reported in Table 1 shows that in the same IL **1-E** isomerizes faster in the presence of CuCl_2 than in the presence of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and that the rates of **1-E**→**1-Z** isomerization are also affected by the nature of the IL used. Indeed, for the same copper salt, slightly higher $(k_{E,Z})_{\text{Cu}}$ values were detected in $[\text{bmim}][\text{SbF}_6]$ than in $[\text{bmim}][\text{PF}_6]$. This trend could be a result of the hydrogen bond acceptor ability of the IL anion. Indeed, the decrease in isomerization rate constants parallels the increase in β values of the ILs ($\beta=0.146$ and 0.207 for $[\text{bmim}][\text{SbF}_6]$ and $[\text{bmim}][\text{PF}_6]$, respectively).¹⁵

Probably, an IL such as $[\text{bmim}][\text{PF}_6]$ with a higher β value and a larger cross-linking degree shows a more organized structure, where the rotation around the imino double bond and the relevant isomerization are more difficult. A similar result was previously reported by Asano et al. on studying the thermal *Z* to *E* isomerization of azobenzenes in IL.¹⁷ It is noteworthy that the isomerization can also proceed through a mechanism with inversion at nitrogen.¹⁸ Nevertheless, in our opinion this mechanistic pattern is not operative because of the binding with the copper cation.

The comparison between reactivity data in methanol¹⁴ and in ILs allows us to draw an interesting conclusion: indeed, the relative rate constants of the **1-E**⇌**1-Z** isomerization increase along the series: $\text{MeOH} < [\text{bmim}][\text{PF}_6] < [\text{bmim}][\text{SbF}_6]$.¹⁹

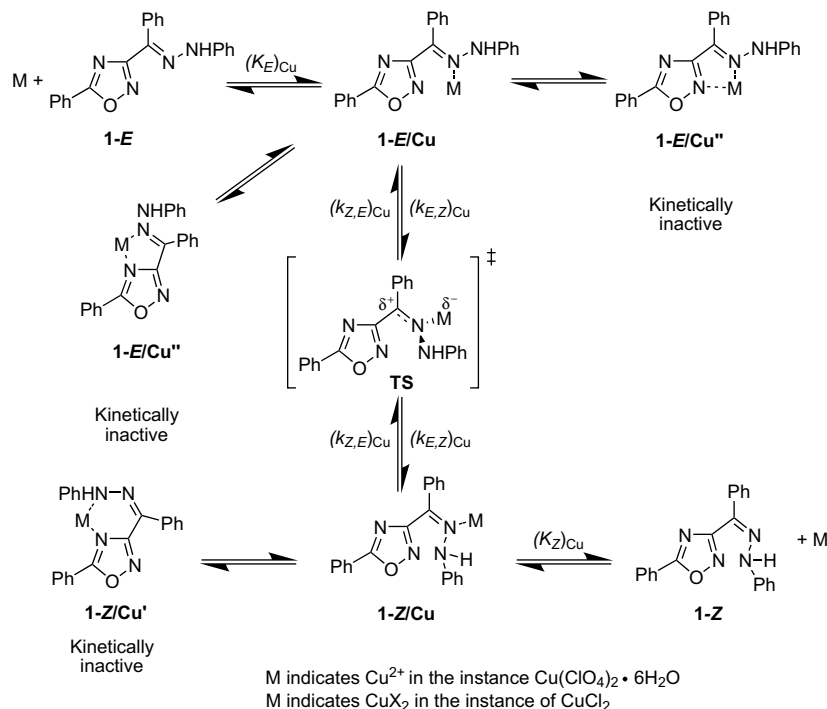
In general, the reaction proceeds faster in ILs than in methanol, but the differences detected are not as high as one would expect on the grounds of the very different characteristics of the involved solvents. In order to understand these results, opposite effects compensating each other should be considered. Indeed, ILs favour the reaction as a consequence of a weaker reagent solvation, allowing the transition state to be reached more easily. However, with respect to methanol, they disfavour the isomerization on the basis of the strong solvent–solvent interactions that, according to previous literature report,²⁰ agree for slow response of the solvent to change in the solute.

Since in the presence of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ the isomerization is the only reaction observed, the $K_{E,Z}$ constant value, corresponding to the **1-E**⇌**1-Z** equilibrium can be calculated. A comparison between data in methanol¹⁴ and in ILs shows that the $K_{E,Z}$ values

Table 1
Binding equilibrium constants and rate constants concerning the **1-E** ⇌ **1-Z** isomerization in the presence of CuCl₂ and Cu(ClO₄)₂·6H₂O in [bmim][PF₆] and [bmim][SbF₆] at 313 K

Salt	IL	(K _E) _{Cu} (M ⁻¹)	10 ³ (k _{E,Z}) _{Cu} (s ⁻¹)	R ^a	(K _Z) _{Cu} (M ⁻¹)	10 ³ (k _{Z,E}) _{Cu} (s ⁻¹)	R ^a
CuCl ₂	[bmim][PF ₆]	280±30	24±2	0.997			
CuCl ₂	[bmim][SbF ₆]	150±20	31±2	0.997			
Cu(ClO ₄) ₂ ·6H ₂ O	[bmim][PF ₆]	990±50	6.3±0.1	0.997	280±30	1.03±0.06	0.994
Cu(ClO ₄) ₂ ·6H ₂ O	[bmim][SbF ₆]	900±100	9.7±0.3	0.997	920±110	0.94±0.03	0.993

^a Correlation coefficient.



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

increase from methanol to [bmim][SbF₆] along the series: MeOH (4.1) < [bmim][PF₆] (6.1) < [bmim][SbF₆] (10.0).

Generally speaking ILs stabilize the **Z** isomer with respect to the **E** isomer to a greater extent than methanol. The highest thermodynamic stability of **1-Z** arises from the intramolecular hydrogen bonds between the hydrazonic hydrogen atom of the side chain and nitrogen atoms of the heterocyclic ring. This effect should be enhanced by the weakest solvating ILs. Accordingly, $K_{E/Z}$ reaches the maximum value in [bmim][SbF₆], which is characterized by the lowest Kamlet–Taft β value,¹⁵ and therefore by the lowest ability to accept hydrogen bonds from the solute molecule.

2.2.1.2. Kinetic measurements in [bmim][BF₄] and [bmim][CF₃SO₃]. In [bmim][BF₄] and in [bmim][CF₃SO₃] the fit of experimental data

agrees with Eq. 2, where k_u and $(k_{E,Z}^{II})_{Cu}$ or $(k_{Z,E}^{II})_{Cu}$ represent the first-order and the third-order rate constants concerning the spontaneous and the trimolecular pathway, respectively.

$$k_{obs} = k_u + (k_{E,Z}^{II})_{Cu} [Cu(II)]^2 \quad (2)$$

In Table 2 the results of the kinetic data fit are reported. In three out of five instances the calculated k_u values are meaningless (negative values), while in the other two their contribution to the overall isomerization process appears negligible ($k^I/k_u \geq 10^5$ M⁻²).

Also in this case a two-step mechanism should be hypothesized. Obviously, considering this hypothesis we are aware of the fact that rate constant values reported in Table 2 are conditioned by binding equilibrium constants, and that our experimental data do not allow to determine them.

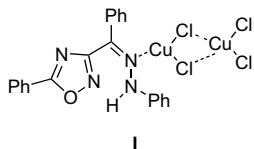
Table 2
Rate constants concerning the **1-E** ⇌ **1-Z** isomerization in the presence of CuCl₂ and Cu(ClO₄)₂·6H₂O in [bmim][BF₄] and [bmim][CF₃SO₃] solution at 313 K

Salt	IL	10 ³ k _u (s ⁻¹)	(k ^{II} _{E,Z}) _{Cu} (s ⁻¹ M ⁻²)	(k ^{II} _{Z,E}) _{Cu} (s ⁻¹ M ⁻²)	R ^a
CuCl ₂	[bmim][BF ₄]	-0.2±0.2	49±4		0.981
CuCl ₂	[bmim][BF ₄]	-0.04±0.02		6.5±0.4	0.987
CuCl ₂	[bmim][CF ₃ SO ₃]	0.02±0.02	10±0.4		0.994
Cu(ClO ₄) ₂ ·6H ₂ O	[bmim][BF ₄]	-0.34±0.06		14±1	0.984
Cu(ClO ₄) ₂ ·6H ₂ O	[bmim][CF ₃ SO ₃]	0.06±0.01	5.5±0.4		0.986

^a Correlation coefficient.

As can be seen from data reported in Table 2, in the presence of CuCl_2 , in $[\text{bmim}][\text{CF}_3\text{SO}_3]$ the $\mathbf{1-Z} \rightarrow \mathbf{1-E}$ isomerization was not detected. Probably in this case $\mathbf{1-Z}$ isomer quickly rearranges into the relevant $\mathbf{1-T}$, preventing the formation of a significant concentration of $\mathbf{1-E}$.

The main course of the reaction seems to be determined by a species involving two CuX_2 units. The structure of kinetically active species can be depicted in the instance of CuCl_2 . Indeed, considering the high coordinating ability of chloride anion and taking in mind the literature reports about the formation of binuclear complexes with CuHal_2 ,²¹ it should be a halo-bridge copper complex such as **I**.



In order to get information concerning the structure of the kinetically active species in the presence of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, we recorded the UV–vis spectrum of this copper salt both in methanol and $[\text{bmim}][\text{BF}_4]$ (Fig. 3a and b). The spectrum recorded in $[\text{bmim}][\text{BF}_4]$ reveals the presence of a weak absorption band centred at 600 nm. This latter band is absent in the spectrum recorded in methanol and does not belong to the ionic liquid.²²

This absorption band should be the result of some weak interactions in the ILs that should allow a tighter association between the perchlorate anion and the copper cation.²³ Alternatively, it should be due to the coordination of the tetrafluoroborate anion, which in the reaction mixture is in overwhelming excess with respect to the copper cation.

In order to choose between these hypotheses, we recorded the UV–vis spectrum of $\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ in $[\text{bmim}][\text{BF}_4]$ (Fig. 3c). As can be seen, it shows the same absorption band present in the spectrum of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in $[\text{bmim}][\text{BF}_4]$, confirming the in situ formation of this copper salt. Hence, the kinetically active species should have a dinuclear copper complex structure.²⁴

A further analysis of the data reported in Table 2 shows that the isomerization is affected both by the IL and the copper salt used. In particular, for the same copper salt, the reaction proceeds faster in $[\text{bmim}][\text{BF}_4]$ than in $[\text{bmim}][\text{CF}_3\text{SO}_3]$ (4.9 and 1.8 times for CuCl_2 and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, respectively). On the other hand, for the same IL ($[\text{bmim}][\text{BF}_4]$), $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ seems to be more efficient (2.1 times) with respect to CuCl_2 in catalyzing the $\mathbf{1-Z} \rightarrow \mathbf{1-E}$ isomerization.

2.2.2. $\mathbf{1-Z} \rightarrow \mathbf{1-T}$ Rearrangement

Kinetic data for $\mathbf{1-Z} \rightarrow \mathbf{1-T}$ rearrangement were collected in $\text{CuCl}_2/[\text{bmim}][\text{X}]$ ($\text{X}^- = \text{SbF}_6^-$, PF_6^- and BF_4^-). The rearrangement induced by $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was studied in $[\text{bmim}][\text{BF}_4]$. The $[\text{bmim}][\text{CF}_3\text{SO}_3]$ was not used since the rearrangement proceeded spontaneously in this IL. Hyperbolic (for $[\text{bmim}][\text{PF}_6^-]$ and $[\text{bmim}][\text{SbF}_6^-]$) and parabolic (for $[\text{bmim}][\text{BF}_4^-]$) trends, as a function of copper salt concentration, were detected. In Figure 4, $k_{z,T}$ values as a function of CuCl_2 concentration collected in $[\text{bmim}][\text{PF}_6^-]$ and in $[\text{bmim}][\text{BF}_4^-]$ solution are reported.

It is noteworthy that, as a consequence of $\text{Cu}(\text{BF}_4)_2$ formation (see above), in $[\text{bmim}][\text{BF}_4]$ the rearrangement took place also in the presence of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. Because different behaviours were detected as a function of IL used, for the sake of clarity, experimental data will be discussed separately (data collected as a function of copper salt concentration, in different ILs solutions, are reported in Tables 6–11 of Supplementary data).

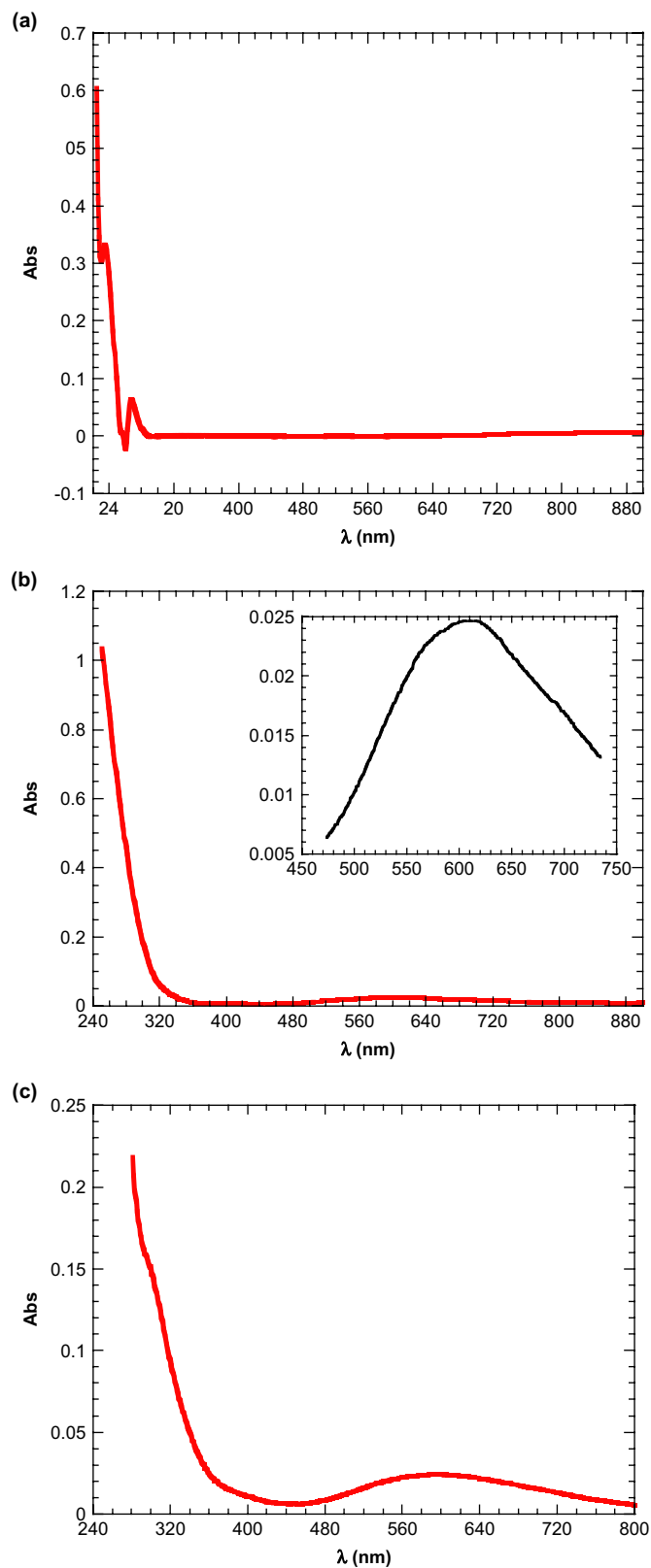


Figure 3. (a) UV–vis spectrum of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 1.98×10^{-3} M in methanol. (b) UV–vis spectrum of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 1.98×10^{-3} M in $[\text{bmim}][\text{BF}_4]$. (c) UV–vis spectrum of $\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ 2.49×10^{-3} M in $[\text{bmim}][\text{BF}_4]$.

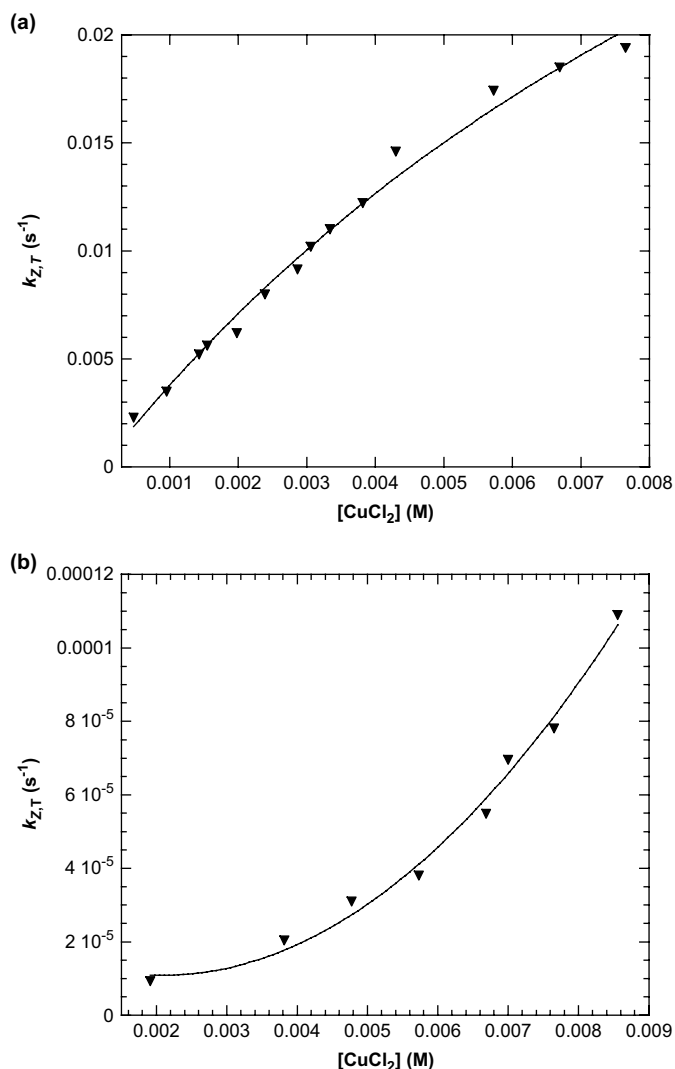
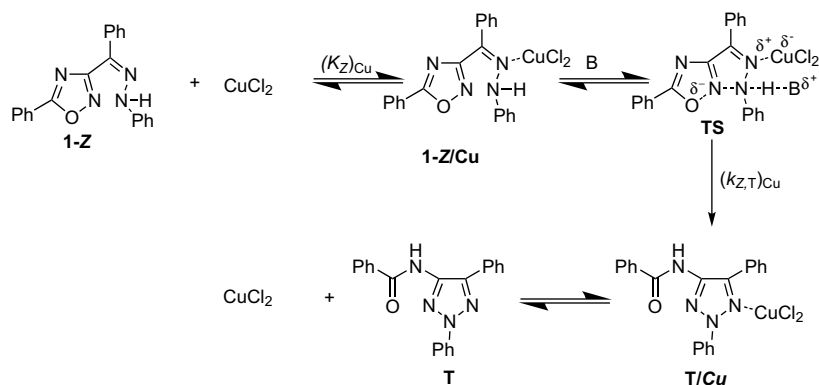
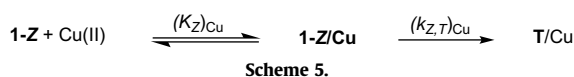


Figure 4. Plots of observed kinetic constants concerning **1-Z**→**1-T** rearrangement in the presence of CuCl_2 in (a) $[\text{bmim}][\text{PF}_6]$ and (b) $[\text{bmim}][\text{BF}_4]$ at 313 K.

2.2.2.1. Kinetic measurements in $[\text{bmim}][\text{PF}_6]$ and in $[\text{bmim}][\text{SbF}_6]$. The kinetic trends of $k_{Z,T}$ versus $[\text{CuCl}_2]$ concentration account for a two-step mechanism (Scheme 5).



Scheme 6. Details on the **1-Z**/ CuCl_2 complexation equilibrium and the relevant **1-Z**→**1-T** rearrangement.

Table 3

Binding equilibrium constants and rate constants concerning the **1-Z**→**1-T** rearrangement in the presence of CuCl_2 in $[\text{bmim}][\text{PF}_6]$ and $[\text{bmim}][\text{SbF}_6]$ solution at 313 K

Salt	IL	$(K_Z)_{\text{Cu}}$ (M^{-1})	$10^3 (k_{Z,T})_{\text{Cu}}$ (s^{-1})	R^a
CuCl_2	$[\text{bmim}][\text{PF}_6]$	70 ± 12	59 ± 7	0.995
CuCl_2	$[\text{bmim}][\text{SbF}_6]$	180 ± 17	24 ± 1	0.998

^a Correlation coefficient.

According to this mechanistic hypothesis, experimental data have been fitted by means of Eq. 3

$$k_{\text{obs}} = \frac{(k_{Z,T})_{\text{Cu}}(K_Z)_{\text{Cu}}[\text{Cu(II)}]}{1 + (K_Z)_{\text{Cu}}[\text{Cu(II)}]} \quad (3)$$

where $(k_{Z,T})_{\text{Cu}}$ is the rate constant for the rearrangement and $(K_Z)_{\text{Cu}}$ is the binding equilibrium constant for the formation of the adduct between **1-Z** and CuCl_2 . In Table 3 the relevant results of kinetic data fit are reported.

Also in this case according to data previously collected in methanol, the overall course of the reaction can be depicted as in Scheme 6.

Analysis of the data reported in Table 3 evidences that the **1-Z**/**Cu** adduct, different from the **1-E**/**Cu** one, is more stable in $[\text{bmim}][\text{SbF}_6]$ than in $[\text{bmim}][\text{PF}_6]$. However, according to data previously discussed about the **1-E**↔**1-Z** isomerization, the rate of the rearrangement increases when the **1-Z**/**Cu** adduct stability decreases. The triazole formation is also affected by the nature of the IL anion. In particular, the reaction is faster in $[\text{bmim}][\text{PF}_6]$ than in $[\text{bmim}][\text{SbF}_6]$.

Furthermore, with respect to the isomerization, in this case the IL anion influence seems to be a little more (twice) significant. The collected data show that the structural order degree of the ILs exert an opposite effect on the isomerization and the rearrangement reactions. In particular, the latter one is favoured by ILs having a higher organization degree. This result agrees with data previously reported by us about the effect of the organized structure and the organizing ability of imidazolium ILs, which is able to favour the rearrangement stabilizing the transition state by means of electrostatic and π - π interactions as well.¹³

An interesting point to be analyzed is the nature of the base that, in this case, favours the hydrazonic proton transfer and consequently the triazole formation. According to data previously reported in methanol,¹⁴ the coordination of the imino nitrogen by Cu(II) induces an electronic shift and causes an acidity increase. Under such a condition, the occurrence of a bifunctional catalysis can be supposed, as well as proposed for other nucleophilic

substitution.²⁵ The Cu(II) acts as a Lewis acid and the relevant anion present in the metal coordination sphere acts as a Lewis base.

However, also the IL anion could play an important role. Indeed, the increase in hydrazonic proton acidity could be so significant to allow proton transfer also by means of a very weak base such as the IL anion. This hypothesis is supported by the literature reports about acid dissociation in IL solution of methylene active

compounds²⁶ or of 2,4-dinitrophenol²⁷ also in the absence of an added base.

It is noteworthy that in [bmim][PF₆] and in [bmim][SbF₆], as well as in methanol, the **1-Z** isomer shows a dichotomic behaviour. Indeed, the **1-Z** → **1-T** rearrangement is promoted by CuCl₂ and not by Cu(ClO₄)₂·6H₂O. This behaviour in methanol was ascribed to the different ability of copper salt anion to 'live in' or 'live out' of the metal coordination sphere.¹⁴

In order to verify whether a similar behaviour could take place also in ILs, we carried out kinetic tests to evaluate the effect of added chloride ion. Thus, variable amounts of [bmim][Cl] have been added to a fixed concentration of Cu(ClO₄)₂·6H₂O in [bmim][SbF₆] to examine how the substrate reactivity was affected. Collected data show that in the binary mixture [bmim][SbF₆]/[bmim][Cl] and in the presence of Cu(ClO₄)₂·6H₂O also the **1-Z** → **1-T** rearrangement occurs (Fig. 5a). (Data collected at different [bmim][Cl] concentrations are reported in Table 14 of Supplementary data.)

Probably, the addition of [bmim][Cl] causes the in situ formation of CuCl₂. Nevertheless, as long as chloride concentration increases, the rate of the rearrangement reaction decreases. A similar effect was detected for the **1-E** → **1-Z** isomerization (Fig. 5b).

In conventional organic solvents, UV–vis spectra show that the addition of chloride ion to a CuCl₂ solution favours the formation of chlorocuprates complexes such as CuCl₃⁻ and CuCl₄²⁻.^{2,28} These, in general, should have a lower ability to interact with substrates, as a consequence of the saturation of the metal coordination sphere. This hypothesis seems to be effective also in IL. Indeed, the UV–vis spectrum of Cu(ClO₄)₂·6H₂O recorded in the binary mixture [bmim][SbF₆]/[bmim][Cl] perfectly accounts for the presence of tetrachlorocuprate anion (Fig. 5c).

2.2.2.2. Kinetic measurements in [bmim][BF₄]. As previously said, in [bmim][BF₄], the **1-Z** → **1-T** rearrangement took place both in the presence of CuCl₂ and Cu(ClO₄)₂·6H₂O. In both cases a parabolic trend of $k_{Z,T}$ versus Cu(II) concentration was detected. Experimental data were fitted according to Eq. (4).

$$k_{\text{obs}} = k_u + (k_{Z,T}^{\text{III}})_{\text{Cu}}[\text{Cu(II)}]^2 \quad (4)$$

where k_u and $(k_{Z,T}^{\text{III}})_{\text{Cu}}$ represent the first-order and the third-order rate constants concerning the spontaneous and the trimolecular pathway, respectively. The relevant results of kinetic data fit are reported in Table 4 (entries 1 and 2). In every case the calculated k_u values are meaningless (negative values).

Once more, k^{III} values underline that the only real pathway involves a substrate–copper complex having a 1:2 stoichiometry. The kinetically active complex should have a dinuclear copper structure (see above). In general, in [bmim][BF₄] the **1-Z** → **1-T** rearrangement proceeds faster in the presence of Cu(ClO₄)₂·6H₂O than in the presence of CuCl₂ and the occurrence of the reaction in the presence of the former salt seems to be the major mechanistic change with respect to what detected in methanol.¹⁴

Probably, as it occurs for isomerization, the kinetically active catalyst is the Cu(BF₄)₂ salt formed in situ. This hypothesis was confirmed by kinetic measurements carried out in [bmim][BF₄] in the presence of increasing amounts of Cu(BF₄)₂·xH₂O (data

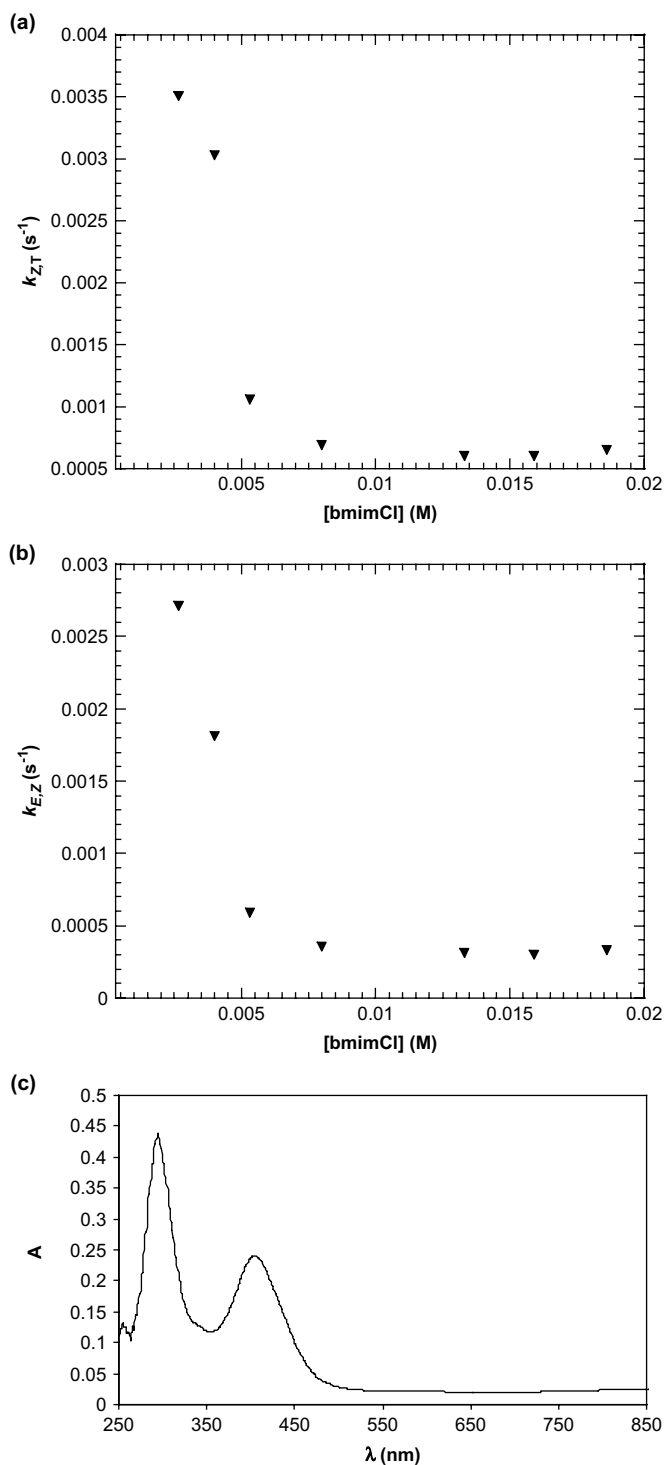


Figure 5. Plots of observed kinetic constants concerning: (a) the **1-E** → **1-Z** isomerization and (b) the **1-Z** → **1-T** rearrangement at 313 K in the presence of fixed concentration of Cu(ClO₄)₂·6H₂O (0.001 M) and variable amounts of [bmim][Cl] in [bmim][SbF₆] solution. (c) UV–vis spectrum of Cu(ClO₄)₂·6H₂O (0.001 M) and [bmim][Cl] (0.0186 M) in [bmim][SbF₆].

Table 4

Rate constants concerning the **1-Z** → **1-T** rearrangement in the presence of Cu(ClO₄)₂·6H₂O, CuCl₂ and Cu(BF₄)₂·xH₂O in [bmim][BF₄] at 313 K

Entry	Salt	10 ⁵ k_u (s ⁻¹)	$k_{Z,T}^{\text{III}}$ (s ⁻¹ M ⁻²)	$k_{Z,E}^{\text{III}}$ (s ⁻¹ M ⁻²)	R ^a
1	CuCl ₂	-0.1 ± 0.4	1.4 ± 0.1		0.988
2	Cu(ClO ₄) ₂ ·6H ₂ O	-2.8 ± 0.5	10 ± 1		0.984
3	Cu(BF ₄) ₂ ·xH ₂ O	-8 ± 2		5.9 ± 0.3	0.993
4	Cu(BF ₄) ₂ ·xH ₂ O	-8 ± 1	3.8 ± 0.2		0.988

^a Correlation coefficient.

collected at different $\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ concentrations are reported in Table 15 of Supplementary data). Experimental results show that this copper salt is able to promote the isomerization and the rearrangement as well. Also in this case parabolic trends for observed rate constant values versus $\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ concentrations were obtained. Fit of experimental data gave results reported in Table 4 (entries 3 and 4).

Analysis of data reported in the table shows that this copper salt in [bmim][BF₄] is less efficient than $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in catalyzing the rearrangement, but anyway more efficient than CuCl_2 .

3. Conclusions

The collected data show that the reactivity of both *E*- and *Z*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in ILs is affected by the presence of CuCl_2 or $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. In particular, different mechanistic patterns arise, depending on the nature of the copper salt anion, with the isomerization promoted by both copper salts and the rearrangement preferably promoted by CuCl_2 .

Comparison with data previously collected in MeOH^{14} shows that the studied reactions proceed faster in IL than in MeOH . However, these reactions are differently affected by the nature of the anion of ILs. In particular, according to data previously reported,¹³ a high structural order degree favours the rearrangement, stabilizing the transition state by means of electrostatic and π - π interactions. On the other hand, the same factor disfavours the isomerization on the grounds of a slower response of the solvent to structural changes in the solute, arising from the rotation around the imino double bond.

Once more, collected results seem to indicate that ILs are solvent systems having peculiar features, whose effects can be rationalized only starting from their nature of polymeric supramolecular fluids and considering the effects that, other things being equal, the different anions can exert.

4. Experimental section

4.1. Materials

Commercial methanol was distilled before use. Commercial CuCl_2 and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ were dried in a muffle over phosphorous pentoxide. Then they were stored in a drier over CaCl_2 . Commercial $\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ was used without any purification. Commercial [bmim][BF₄], [bmim][PF₆] and [bmim][CF₃SO₃] were dried on a vacuum line at 60 °C at least for 2 h and kept in a desiccator under argon and over calcium chloride. [bmim][SbF₆] was prepared by anion metathesis from [bmim][Cl] and NaSbF_6 according to a reported procedure.²⁹

$\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ solutions were prepared by appropriate dilution of stock solutions in methanol, which were standardized by means of redox iodometric titrations.³⁰ **1-Z**, **1-E** and **1-T** were prepared according to procedure previously reported.³¹

4.2. General procedure for qualitative studies

Each experiment was carried out at 313 K suspending 0.1 g of substrate in 1 ml of IL and 400 μl of anhydrous methanol and adding the copper salt. The composition of the reaction mixture was examined by TLC time by time and the reaction was monitored for 4 h. Then each mixture was extracted several times with ethyl ether. After removing the solvent, the resulting residues were separated by flash chromatography on silica gel.

4.3. Kinetic measurements

UV-vis spectra for kinetic measurements were carried out by using a spectrophotometer equipped with a Peltier temperature controller, in order to keep the temperature constant within 0.1 K. The sample for a typical kinetic run was prepared by mixing into a quartz cuvette (light path 0.2 cm) 500 μl of ionic liquid, 50 μl of a substrate solution in methanol and then 25 μl of a concentrated solution of copper salt in methanol, previously thermostated. A mixture with the same composition of the one undergoing measurements, containing all components but the substrate, was used as a blank. The initial concentration of substrate was fixed to 1.0×10^{-4} M. The copper salts concentration ranged from 1.5×10^{-3} M to 1.2×10^{-2} M. All of kinetic data were analyzed by means of Kaleidagraph 3.0 software.

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Supplementary data

Qualitative, kinetic data and calculation method are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.055.

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19. $(\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}) : (\text{K}_{E,Z})\text{Cu} : \text{MeOH} : (\text{K}_{E,Z})\text{Cu} : [\text{bmim}][\text{PF}_6] : (\text{K}_{E,Z})\text{Cu} : [\text{bmim}][\text{SbF}_6] = 1 : 2.0 : 3.1$
 $(\text{K}_{Z,E})\text{Cu} : \text{MeOH} : (\text{K}_{Z,E})\text{Cu} : [\text{bmim}][\text{PF}_6] : (\text{K}_{Z,E})\text{Cu} : [\text{bmim}][\text{SbF}_6] = 1 : 1.3 : 1.2$. $\text{CuCl}_2 : (\text{K}_{E,Z})\text{Cu} : \text{MeOH} : (\text{K}_{E,Z})\text{Cu} : [\text{bmim}][\text{PF}_6] : (\text{K}_{E,Z})\text{Cu} : [\text{bmim}][\text{SbF}_6] = 1 : 11.4 : 14.7$.
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