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Synthesis of Tetrasubstituted 4,4′-Biimidazoles

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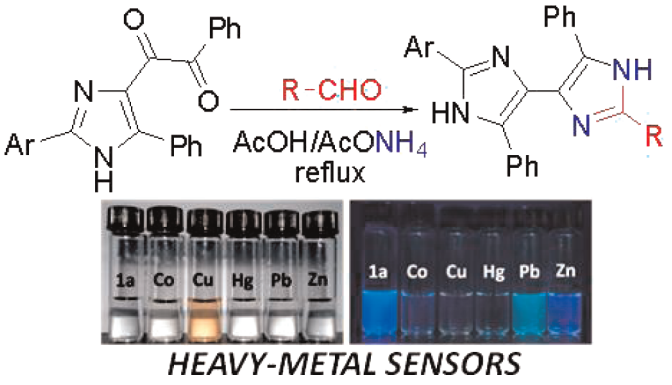
ABSTRACT



Highly substituted 4,4′-biimidazoles were synthesized, in good to excellent yields, through a multicomponent imidazole ring synthesis by using imidazol-4-yl-ethane-1,2-diones as starting materials. The obtained compounds were preliminarily tested as chromogenic and fluorescent sensors for heavy metals.

4,4′-Biimidazoles have received less attention than more studied 2,2′-isomers, and little has been reported about their synthesis and properties.[1] For instance, the parent compound 4,4′-biimidazole was unknown until 1994.[2] Only recently, 4,4′-biimidazole and oligo(imidazole)s with 4,4′-biimidazole moieties have been considered for their potential applications as bidentate ligands capable of multidimensional networks.[3] Assembled metal complexes of 4,4′-biimidazole, exhibiting multidirectional hydrogen bonds, were investigated in Ag, Cu, and Ni complexes,[4] while triple-stranded metallo-helicates of quaterimidazole with Mn(II) or Zn(II) cations gave a prototype of synthetic electron spin qubits, useful in the field of Quantum Computers (QCs).[5] Moreover, charge-transfer salts of protonated cations of 2,2′-disubstituted-4,4′-biimidazoles with tetracyano-quinodimethane (TCNQ) were investigated for their semiconducting behavior.[6]

From a synthetic point of view, to date, obtaining 4,4′-biimidazoles is limited to symmetrically 2,2′-disubstituted compounds and synthetic protocols are based on cross-coupling reactions with the use of metal catalysts.[2,3] Considering the growing interest on these compounds, we

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envisaged the use of imidazol-4-yl-ethane-1,2-diones **2** as synthons for the obtainment of highly substituted 4,4′-biimidazoles **1**, through classical multicomponent imidazole ring synthesis[7] (Figure 1).

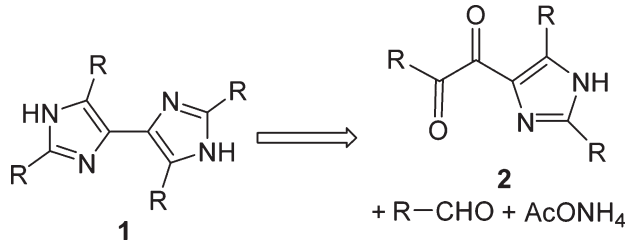
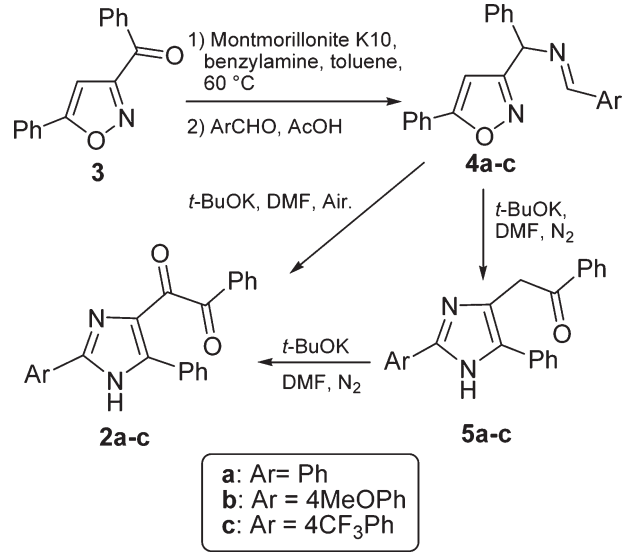


Figure 1. Retrosynthetic analysis for the obtainment of compounds **1**.

Starting compounds **2** were easily obtained through a novel one-pot tandem Boulton−Katritzky Rearrangement (BKR)−oxidation reaction of isoxazolyl-imine **4** under basic conditions. Alternatively, compounds **2** could be obtained through a two-step procedure, from oxidation with air, under basic conditions, of imidazoles **5**, obtained from the BKR[8] of isoxazoles **4** (Scheme 1).[9]

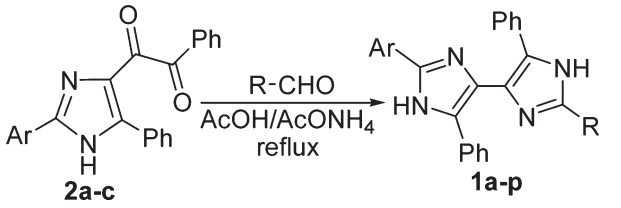
Scheme 1. Synthesis of Imidazoles **2**



In turn, imines **4**[9] were obtained, in two steps, from a clay-catalyzed nonreductive transamination[10] of 5-phenyl-3-benzoyl-isoxazole **3** and condensation of the resulting amine with the appropriate aldehyde in AcOH.

The so-obtained imidazolyl-diones **2** were reacted with different (hetero)aromatic and alphatic aldehydes (2 equiv) in the presence of ammonium acetate (2 equiv) in refluxing acetic acid, giving 2,2′,5,5′-tetrasubtituted 4,4′-bimidazoles **1** in good to excellent yields (Table 1).

Table 1. Results for the Synthesis of 4,4′-Biimidazoles **1**



entry	Ar	R	time (h)	yield (%)[a]
1	Ph	Ph	2	**1a** 94
2	Ph	4-CH_3OPhenyl	4	**1b** 82
3	Ph	4-CH_3Phenyl	4	**1c** 86
4	Ph	4-NO_2Phenyl	1	**1d** 92
5	Ph	4-ClPhenyl	2	**1e** 80
6	Ph	4-CF_3Phenyl	1	**1f** 88
7	Ph	3-CH_3Phenyl	3	**1g** 87
8	Ph	2-CH_3Phenyl	6	**1h** 92
9	Ph	2-Thienyl	5	**1i** 96
10	Ph	2-Furanyl	3	**1j** 65[b]
11	Ph	4-Pyridyl	2	**1k** 96
12	Ph	Et	2	**1l** 75
13	Ph	*n*-Pr	4	**1m** 78
14	Ph	Cyclohexyl	4	**1n** 83
15	4-CH_3OPhenyl	Ph	2	**1b** 89
16	4-CH_3OPhenyl	4-CH_3OPhenyl	5	**1o** 71
17	4-CH_3OPhenyl	4-NO_2Phenyl	1	**1p** 87
18	4-CF_3Phenyl	Ph	2	**1f** 83

[a] Isolated yields. [b] 22% recovered **2a**.

In all cases the reaction proceeded smoothly and allowed, for the first time, the obtainment of asymmetrically 2,2′-disubstituted compounds (see entries 2−15, 17, 18). Interestingly, reaction times were dependent on the electronic demand of the aldehyde substituents. For example, a comparison of entries 1, 2, and 6 confirms the expected higher reactivity of electron-withdrawing substituted aldehydes. This finding is particularly useful for the choice of optimal conditions in the preparation of compounds **1b** and **1f**. The former is obtained, in comparable high yields, through two alternative reagent combinations summarized by entries 2 and 15, the latter of which being more favorable in terms of reaction times.

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(8) As recent examples of the Boulton−Katritzky rearrangement, see: (a) Pace, A.; Pibiri, I.; Palumbo Piccionello, A.; Buscemi, S.; Vivona, N.; Barone, G. *J. Org. Chem.* **2007**, *72*, 7656–7666. (b) Palumbo Piccionello, A.; Pace, A.; Buscemi, S.; Vivona, N.; Pani, M. *Tetrahedron* **2008**, *64*, 4004–4010. (c) Pace, A.; Pierro, P. *Org. Biomol. Chem.* **2009**, *7*, 4337–4348. (d) Palumbo Piccionello, A.; Pace, A.; Buscemi, S.; Vivona, N. *Org. Lett.* **2009**, *11*, 4018–4020. (e) D'Anna, F.; Frenna, V.; Zaira Lanza, C.; Macaluso, G.; Marullo, S.; Spinelli, D.; Spisani, R.; Petrillo, G. *Tetrahedron* **2010**, *66*, 5442–5450. (f) D'Anna, F.; Frenna, V.; Ghelfi, F.; Marullo, S.; Spinelli, D. *J. Org. Chem.* **2011**, *76*, 2672–2679.

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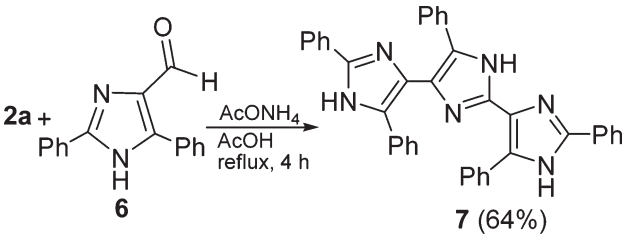
(10) Palumbo Piccionello, A.; Pace, A.; Buscemi, S.; Vivona, N. *Org. Lett.* **2010**, *12*, 3491–3493.

Scheme 2. Synthesis of Terimidazole **7**



Similar considerations pointed out entry 6 as an optimal reagent combination for obtaining **1f**. In order to expand the potential application of compounds **2** to the synthesis of oligo-imidazoles, we also tested the reactivity of representative compound **2a** in the presence of imidazolyl-aldehyde **6**,[9] under the same conditions reported above, allowing the obtainment of the pentaphenyl-substituted 4,4′-2′,4″-terimidazole **7** in good yield (Scheme 2). Considering the great amount of interest in 4,4′-biimidazoles as a ligand for metal complexes,[4,5] we preliminarily studied representative compounds **1a,b,f** and their photophysical behavior in the presence of various metal ions, such as Hg^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, Ca^{2+}, Co^{2+}, Mg^{2+}, Na^{+}, K^{+}, and Ag^{+}, through UV/vis and fluorescence spectroscopy.

The UV/vis spectrum of **1a** recorded in acetonitrile shows a strong absorption band centered at 305 nm (ε = 24 500 M^{-1} cm^{-1}) with a shoulder around 280 nm (Figure 2). From the UV/vis spectra of **1a** (10 μM) in acetonitrile upon addition of 10 equiv of various perchlorate salts of metal ions, such as Hg^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, Ca^{2+}, Co^{2+}, Mg^{2+}, Na^{+}, K^{+}, and Ag^{+}, a metal-dependent behavior was observed (Figure 1, and Supporting Information (SI)). With Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}, and Ag^{+}, no relevant spectral changes were observed (see SI). With other heavy metals a hypochromic shift was observed; particularly, in the presence of Pb^{2+} absorption the maximum was broadened and blue-shifted to 300 nm, while, with Hg^{2+}, Zn^{2+}, and Co^{2+}, absorption spectra were characterized by the presence of two maxima (around 300 and 255 nm) (Figure 2). More interestingly, in the presence of Cu^{2+}, an absorption maximum centered at 293 nm was accompanied by a band in the visible region (λ_{max} = 490 nm), responsible for the pale orange coloration of the solution (Figure 2, lower). The latter feature allows visual detection of Cu^{2+} under ambient light, configuring compound **1a** as a potential sensor for the naked-eye detection of copper ions. Similar results were obtained with compounds **1b,f**, bearing an electron-donating and -withdrawing group on the 2-aryl moiety, respectively (see SI).

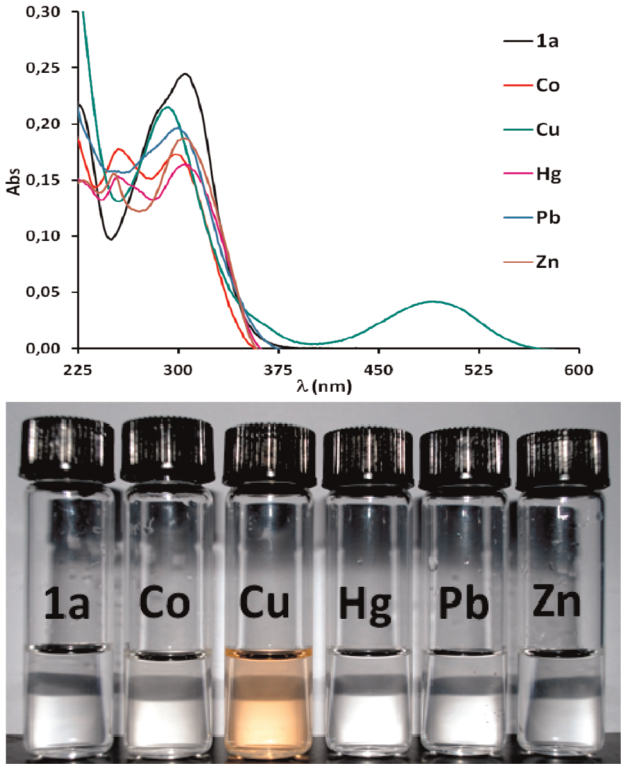


Figure 2. UV/vis absorption spectra of **1a** (10 μM) and upon addition of ClO_4^- salts of Hg^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, and Co^{2+} (10 equiv, each) in CH_3CN (upper). Visual appearance of solutions of **1a** with the above metals, under ambient light (lower).

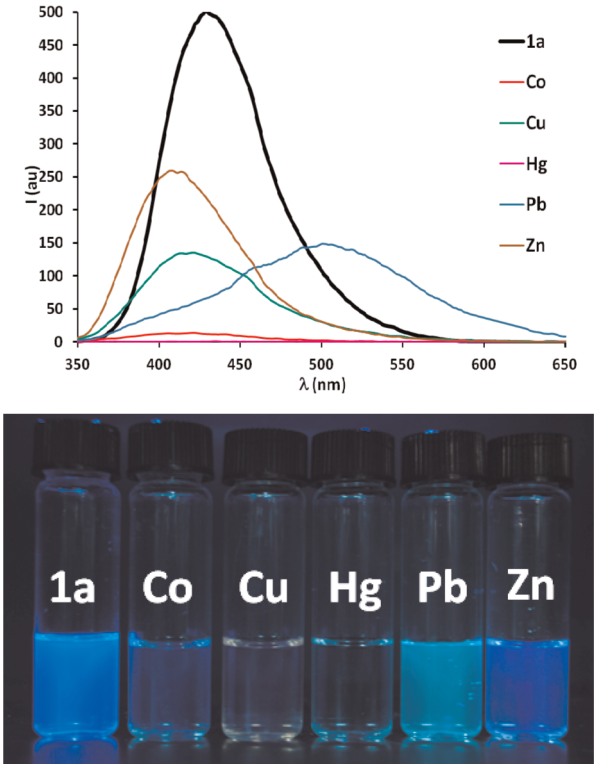


Figure 3. Fluorescence spectra of **1a** (10 μM) and upon addition of ClO_4^- salts of Hg^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, and Co^{2+} (10 equiv, each) in CH_3CN with an excitation at 305 nm (upper). Visual appearance of solutions of **1a** with the above metals, under UV-light (lower).

The fluorescence emission spectrum of compound **1a** in CH_3CN (λ_{ex} = 305 nm) showed an unstructured band centered at 429 nm (Figure 3). On the other hand, by measuring the fluorescence emission spectra of **1a** (10 μM in CH_3CN, λ_{ex} = 305 nm) in the presence of 10 equiv of tested metal salts, again metal-dependent behavior was observed (Figure 3, and SI). As previously observed from UV/vis experiments, with Ca^{2+}, Mg^{2+}, Na^{+}, K^{+}, and Ag^{+}, no relevant spectral changes were observed (see SI). With other heavy metals, fluorescence was quenched in all the cases with respect to **1a**; in particular, fluorescence quenching was partial, with emission maxima slightly blue-shifted, in the presence of Zn^{2+} (λ_{em} = 407 nm), Cu^{2+} (λ_{em} = 421 nm), and Co^{2+} (λ_{em} = 421 nm), while with Hg^{2+} complete fluorescence quenching was reached under these conditions (Figure 3). More interestingly, in the presence of Pb^{2+}, fluorescence emission was broadened and red-shifted with respect to **1a** (λ_{em} = 501 nm), giving the solution a greenish coloration detectable under UV-light (Figure 3, lower). This fluorescence change allows naked-eye detection of Pb^{2+}, configuring compound **1a** as a potential fluorescent sensor for lead cations. Similar results were obtained with compounds **1b,f** (see SI). Moreover, in order to evaluate the practical applicability of the sensor in aqueous media, the sensing ability of compound **1a** was tested in H_2O/CH_3CN mixtures (20%v/v), in the presence of Cu^{2+} and Pb^{2+}, at pH = 7 and 13. Under neutral conditions, the sensing ability was lost, particularly for the UV/vis detection of copper ions (see SI). In contrast, under basic conditions, compound **1a** continues to show a band in the visible region (λ_{max} = 440 nm), maintaining the ability to detect Cu^{2+} ions (Figure 4, upper). More interestingly, emission spectra under basic conditions evidenced a red shift of the emission of compound **1a** (λ_{em} = 514 nm). The fluorescence was quenched in the presence of lead cations and unexpectedly enhanced in the presence of copper ions (Figure 4, lower). In general, the observed metal-dependent behavior, from UV and fluorescence experiments, suggests the use of compounds **1** as multimodal sensors for the discrimination of different heavy metals.

In conclusion, a new method for the synthesis of 4,4′-biimidazoles **1** was achieved by using classical multicomponent imidazole ring synthesis. The proposed methodology allowed obtaining, for the first time, tetrasubstituted substrates and the linkage of different moieties at the 2,2′-positions, producing asymmetrically substituted compounds. This synthetic strategy opens the way to obtaining new compounds with potential use in the material science field. In particular, from preliminary experiments with compound **1a**, the potential application of 4,4′-biimidazoles as multimodal sensors for heavy metal cations has been envisaged.

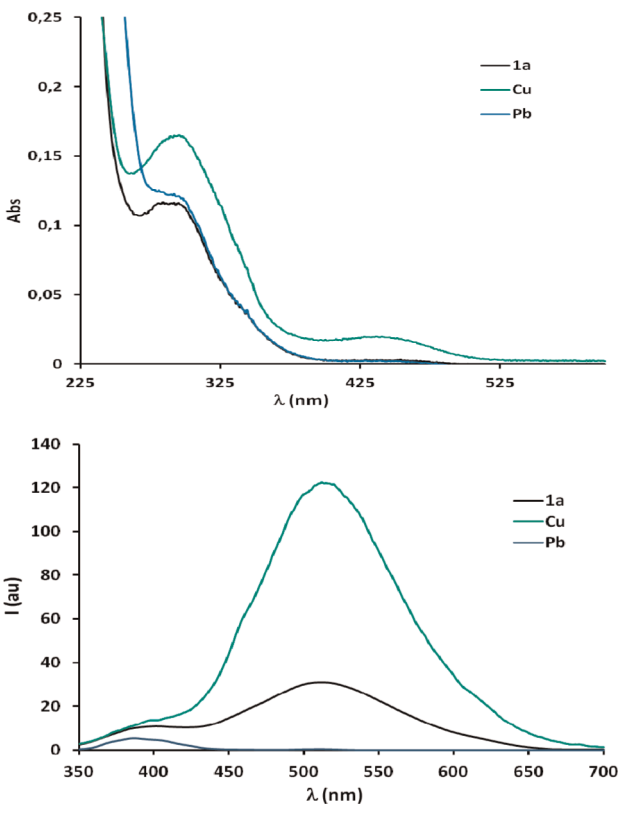


Figure 4. UV/vis absorption spectra (upper) and fluorescence spectra (lower) of **1a** (10 μM) and upon addition of ClO_4^- salts of Pb^{2+} and Cu^{2+} (10 equiv, each) in H_2O/CH_3CN (20% v/v, pH = 13).

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Supporting Information Available. Synthetic details, characterization data, $^{1}H-^{13}C$ NMR spectra of new compounds, UV/vis and fluorescence spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.