

Synthesis of Tetrasubstituted 4,4'-Biimidazoles

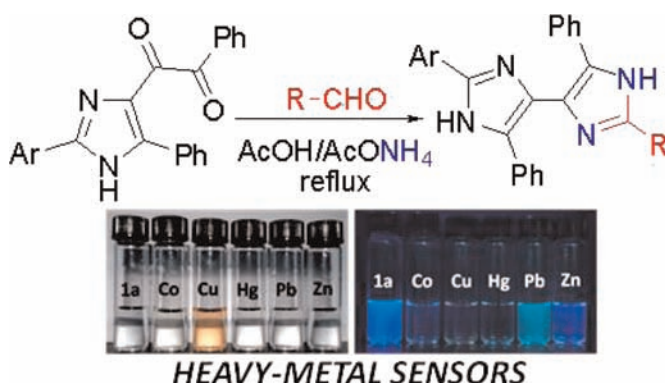
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Received March 15, 2012

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 obtaining of highly substituted 4,4'-biimidazoles **1**, through classical multicomponent imidazole ring synthesis⁷ (Figure 1).

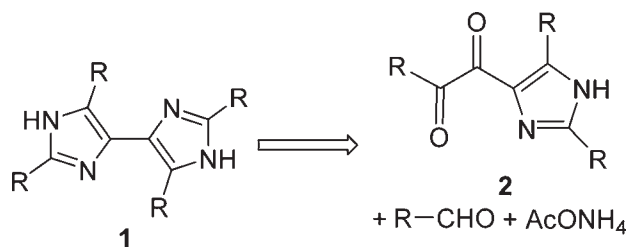
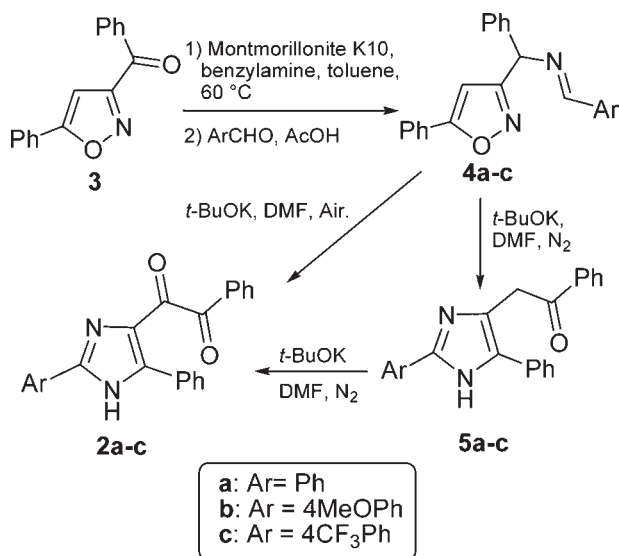


Figure 1. Retrosynthetic analysis for the obtaining of compounds **1**.

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 BKR⁸ of isoxazoles **3** (Scheme 1).⁹

Scheme 1. Synthesis of Imidazoles **2**



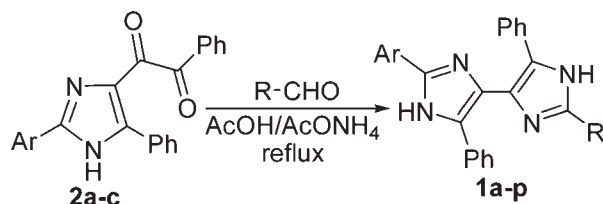
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In turn, imines **4**⁹ were obtained, in two steps, from a clay-catalyzed nonreductive transamination¹⁰ of 5-phenyl-3-benzoyl-isoxazole **3** and condensation of the resulting amine with the appropriate aldehyde in AcOH.

The so-obtained imidazolyl-diones **2** were reacted with different (hetero)aromatic and aliphatic aldehydes (2 equiv) in the presence of ammonium acetate (2 equiv) in refluxing acetic acid, giving 2,2',5,5'-tetrasubstituted 4,4'-biimidazoles **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 ₃ OPhenyl	4	1b 82
3	Ph	4-CH ₃ Phenyl	4	1c 86
4	Ph	4-NO ₂ Phenyl	1	1d 92
5	Ph	4-ClPhenyl	2	1e 80
6	Ph	4-CF ₃ Phenyl	1	1f 88
7	Ph	3-CH ₃ Phenyl	3	1g 87
8	Ph	2-CH ₃ Phenyl	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	<i>n</i> -Pr	4	1m 78
14	Ph	Cyclohexyl	4	1n 83
15	4-CH ₃ OPhenyl	Ph	2	1o 89
16	4-CH ₃ OPhenyl	4-CH ₃ OPhenyl	5	1o 71
17	4-CH ₃ OPhenyl	4-NO ₂ Phenyl	1	1p 87
18	4-CF ₃ Phenyl	Ph	2	1f 83

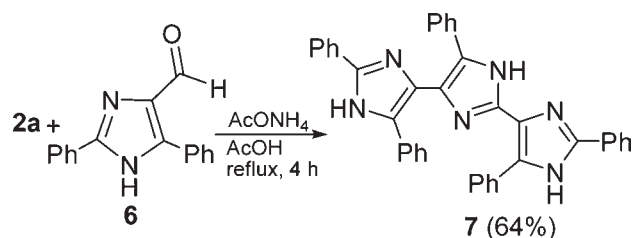
^a Isolated yields. ^b 22% recovered **2a**.

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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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 Hg²⁺, Pb²⁺, Cu²⁺, Zn²⁺, Ca²⁺, Co²⁺, Mg²⁺, 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 ($\epsilon = 24\,500\text{ M}^{-1}\text{ cm}^{-1}$) 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 Hg²⁺, Pb²⁺, Cu²⁺, Zn²⁺, Ca²⁺, Co²⁺, Mg²⁺, Na⁺, K⁺, and Ag⁺, a metal-dependent behavior was observed (Figure 1, and Supporting Information (SI)). With Ca²⁺, Mg²⁺, 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 Pb²⁺ absorption the maximum was broadened and blue-shifted to 300 nm, while, with Hg²⁺, Zn²⁺, and Co²⁺, absorption spectra were characterized by the presence of two maxima (around 300 and 255 nm) (Figure 2). More interestingly, in the presence of Cu²⁺, an absorption maximum centered at 293 nm was accompanied by a band in the visible region ($\lambda_{\text{max}} = 490\text{ nm}$), responsible for the pale orange coloration of the solution (Figure 2, lower). The latter feature allows visual detection of Cu²⁺ 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).

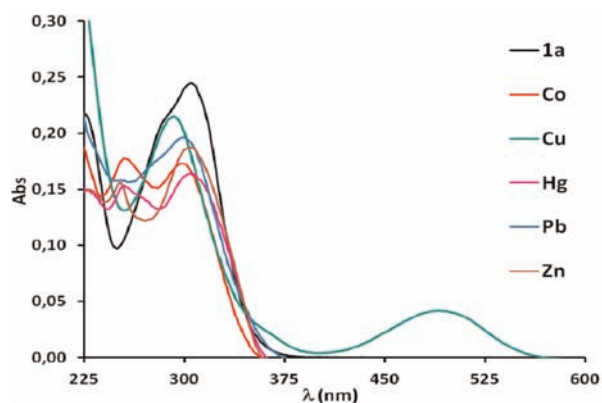


Figure 2. UV/vis absorption spectra of **1a** (10 μM) and upon addition of ClO₄⁻ salts of Hg²⁺, Pb²⁺, Cu²⁺, Zn²⁺, and Co²⁺ (10 equiv, each) in CH₃CN (upper). Visual appearance of solutions of **1a** with the above metals, under ambient light (lower).

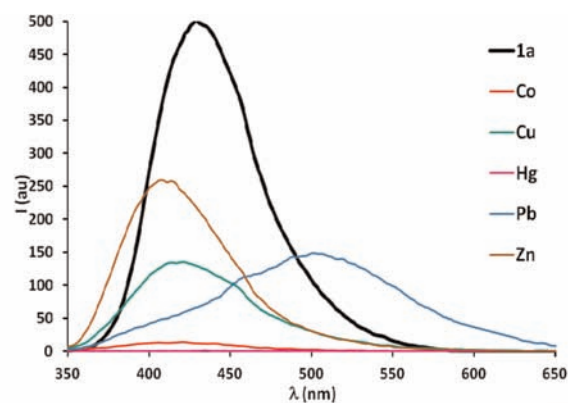


Figure 3. Fluorescence spectra of **1a** (10 μM) and upon addition of ClO₄⁻ salts of Hg²⁺, Pb²⁺, Cu²⁺, Zn²⁺, and Co²⁺ (10 equiv, each) in CH₃CN with an excitation at 305 nm (upper). Visual appearance of solutions of **1a** with the above metals, under UV-light (lower).

The fluorescence emission spectrum of compound **1a** in CH₃CN ($\lambda_{\text{ex}} = 305$ 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 CH₃CN, $\lambda_{\text{ex}} = 305$ 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 Ca²⁺, Mg²⁺, 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 Zn²⁺ ($\lambda_{\text{em}} = 407$ nm), Cu²⁺ ($\lambda_{\text{em}} = 421$ nm), and Co²⁺ ($\lambda_{\text{em}} = 421$ nm), while with Hg²⁺ complete fluorescence quenching was reached under these conditions (Figure 3). More interestingly, in the presence of Pb²⁺, fluorescence emission was broadened and red-shifted with respect to **1a** ($\lambda_{\text{em}} = 501$ nm), giving the solution a greenish coloration detectable under UV-light (Figure 3, lower). This fluorescence change allows naked-eye detection of Pb²⁺, 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 H₂O/CH₃CN mixtures (20% v/v), in the presence of Cu²⁺ and Pb²⁺, 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 ($\lambda_{\text{max}} = 440$ nm), maintaining the ability to detect Cu²⁺ ions (Figure 4, upper). More interestingly, emission spectra under basic conditions evidenced a red shift of the emission of compound **1a** ($\lambda_{\text{em}} = 514$ 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

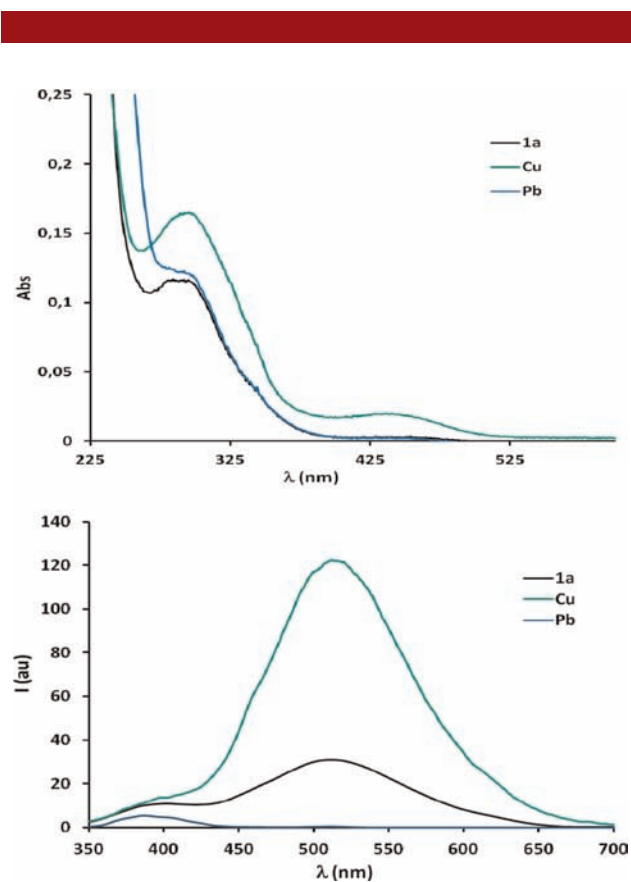


Figure 4. UV/vis absorption spectra (upper) and fluorescence spectra (lower) of **1a** (10 μM) and upon addition of ClO₄⁻ salts of Pb²⁺ and Cu²⁺ (10 equiv, each) in H₂O/CH₃CN (20% v/v, pH = 13).

compound **1a**, the potential application of 4,4'-biimidazoles as multimodal sensors for heavy metal cations has been envisaged.

Acknowledgment. Financial support through the University of Palermo is gratefully acknowledged. 400 MHz NMR experimental data were provided by *Centro Grandi Apparecchiature - UniNetLab - Università di Palermo* funded by *POR Sicilia 2000-2006, Misura 3.15 Quota Regionale*.

Supporting Information Available. Synthetic details, characterization data, ¹H–¹³C 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.