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Dimerization of 2-pyridylisonitriles produces π-extended fused heteroarenes useful as highly selective colorimetric and optical probes for copper ion

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ABSTRACT

A very simple synthesis of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** was achieved from the dimerization of 2-pyridylisonitriles. The optical responses of these π-extended fused heteroarenes to a series of metal ions were investigated by means of UV-visible absorption spectrum in acetonitrile. It was found that most of compounds **2** selectively responded to Cu^{2+}, and the limit of detection was about 3.5×10^{-7} M when using the best probe, 3,9-dimethylpyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine **2d**. Meanwhile some compounds **2** specifically showed a color change from colorless to red or yellow when they are exposed to copper ion in acetonitrile, whereas other transitional, alkali and alkaline earth metal ions could not induce a color change. This work not only established a direct access to π-extended fused heteroarenes, but also supplied novel sensitive and selective colorimetric and optical probes for copper ion.

1. Introduction

Fused polycyclic heteroarenes are the subjects of considerable research interest because their applications are spread over different fields including organic chemistry, analytical chemistry, biochemistry, and material science. For example, benzo[*a*]phenazines,[1] pyrimido[4′,5′:4,5]selenolo[2,3-*b*]quinolines,[2] indolo[2,3-*b*]quinolines,[3] benzo[*f*]pyrido[2,1-*a*]phthalazinium salts,[4] benzo[*f*]quino[2,1-*a*]phthalazinium salts,[4] and pyridazino[1′,6′:1,2]pyrido[4,3-*b*]indolinium salts,[5] behaved as DNA intercalators that might be used as chemotherapeutic agents for cancer treatment. Various fluorescent fused heteroarenes, such as imidazo[1,2-*a*]pyridine,[6] pyrazino[1,2-*a*:4,5-*a*′]diindole,[7] furo[3,2-*h*]quinoline,[8] benzo[*a*]phenoxazinium,[9] benzo[*g*]quinoxaline,[10] benzo[*b*]thiophene derivatives,[11] etc., have potential applications as optical probes for the detection of ions, organic compounds or biomolecules. Highly π-extended fused heteroarenes, on the other hand, have important optoelectronic properties that might be utilized as optoelectronic devices including organic field-effect transistors, light-emitting diodes, and photovoltaic cells.[12] Although numerous studies on the synthesis and optical properties of fused polycyclic heteroarenes have been reported,[13] the potentials of non-functionalized large π-extended fused heteroarenes for optical sensors have been rarely explored.

The design and synthesis of chemosensors for heavy and transition metal ions (HTM) have always been of great importance for medical, environmental, and biological applications.[14] Many kinds of optical sensors[14,15] have been developed for selective recognition of different species on the basis of host-guest interactions, such as hydrogen-bonding, electrostatic force, metal-ligand coordination, hydrophobic, and van de Waals force interactions. In recent years, one of the most attractive approaches focus on the development of novel colorimetric fluorescence sensors, which resulted in a naked eye color change upon metal ion interactions.[16,17] More specifically, sensors directed toward the detection and measurements of divalent copper have attracted particular attention.[17] Copper plays an important role in the areas of biological, environmental, and chemical systems. It is an essential trace element for both plants and animals, including humans.[18] Copper is vital for haemoglobin synthesis, correct nerve functioning and bone development.[19] On the other hand, however, copper is highly toxic to some organisms, such as bacteria and viruses, and it is also harmful to humans at high concentrations.[20] Copper is also associated with neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases.[21] Although various chemsensors for the detection of Cu^{2+} ion have been reported,[17,22] a few of them were based on the colorimetric method.[17a–i] The development of simple, sensitive, and selective sensors for copper ion, especially a colorimetric sensor, is still of great importance.

In the study of the reaction between *N*-heterocyclic carbenes and isonitriles, we occasionally discovered a highly fluorescent product derived from 2-pyridylisonitrile. Herein, we report a extremely

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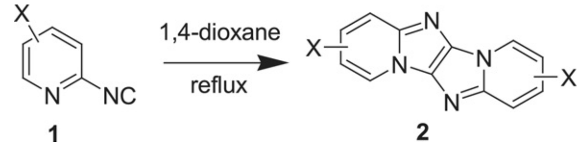
simple synthesis of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines by dimerization of 2-pyridylisonitriles, and their application as sensitive and selective colorimetric and optical probes for copper ion.

2. Results and discussion

In this work, 2-pyridylisonitriles **1** were prepared from 2-pyridinamines in two steps on the basis of a literature method.[23] After the solution of 2-pyridylisonitrile **1a** (X=H) in 1,4-dioxane was refluxed for 20 h, a fluorescent product **2a** was isolated in 63% yield. The spectroscopic data and single crystal X-ray diffraction analysis determined **2a** to be pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridine (see Fig. S1 in Supplementary data). Under the similar conditions, 2-pyridylisonitriles **2** substituted by methyl, methoxy, and halogen groups were heated in 1,4-dioxane for a period of time. As illustrated in Table 1, the reactions produced pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2a**–**h** in 31–77% yields. It was found that, 5-methyl and 5-methoxy 2-pyridylisonitriles **1c** and **1f** produced higher yields of products than the 5-halogen substituted isonitriles **1g** and **1h**, while 3-methyl-2-pyridylisonitrile **1e** afforded lower yield of product than the 4-, 5-, and 6-methyl-2-pyridylisonitriles **1b**–**d** (Table 1). These results can be explained by the electronic and steric effects of substituents of pyridyl isonitriles. Since the electron-donated methoxy and methyl groups can enrich the electron density of the isonitriles functional group, **1c** and **1f** should be more reactive than the halogen substituted isonitriles **1g** and **1h**. On the other hand, the 3-methyl-2-pyridylisonitrile is less reactive than the 4-, 5-, and 6-substituted analogous probably due to the steric hindrance caused by the *ortho* substituent of isonitrile.

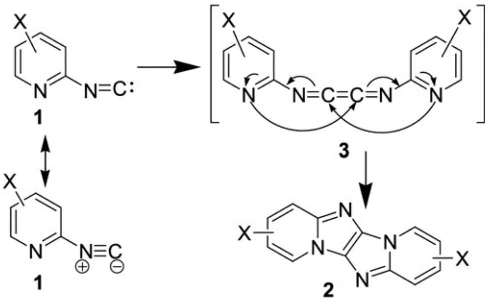
Table 1
Preparation of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** from dimerization of 2-pyridylisonitriles **1** in refluxing 1,4-dioxane



Entry	**1**	X	Time (h)	Yield of **2**[a] (%)
1	**1a**	H	20	**2a**: 63
2	**1b**	6-Me	27	**2b**: 61
3	**1c**	5-Me	24	**2c**: 64
4	**1d**	4-Me	20	**2d**: 56
5	**1e**	3-Me	37	**2e**: 31
6	**1f**	5-OMe	37	**2f**: 77
7	**1g**	5-Cl	21	**2g**: 53
8	**1h**	5-Br	34	**2h**: 44

[a] Isolated yields.

The structures of all products were fully characterized by spectroscopic data and microanalysis. Meanwhile, to identify the products beyond doubt, the structure of **2a** was also confirmed by single crystal X-ray diffraction analysis (see Fig. S1 in Supplementary data). The structures of compounds **2** indicated that they are a kind of dimers of 2-pyridylisonitriles **1**. Thus, the formation of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** can be explained by the coupling of two molecules of isonitriles **1** to form the heterocumulene intermediates **3**. Intramolecular cyclization of **3** produced the pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** (Scheme 1).



Scheme 1. The proposed mechanism for the formation of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2**.

Both isonitrile and carbene are the formal divalent species, and isonitriles are well known to undergo coupling reactions with carbenes to form ketenimines (a kind of heterocumulenes).[24] However, very few of self coupling or dimerization of isonitriles was reported. For example, dimerization of *t*-BuNC catalyzed by BF$_3$ produced BuC(CN)=NBu.[25] A number of alkyl isonitriles were found to dimerize in the presence of LiSiPhMe$_2$ to give, after quenching with RSiMe$_2$Cl, PhSiMe$_2$NRC≡CNRSiMe$_2$R.[26] In the current work, a novel dimerization reaction of isonitriles in the absence of a catalyst was discovered.

In 1986, Leonard and co-workers reported the preparation of non-substituted pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridine **2a** (it was also named as dipyrido[1,2-*a*:1′,2′-*e*]-1,3,4,6-tetraazapentalene) from the reaction of 2-pyridinamine with glyoxal trimer, followed by oxidative cyclization of 3-(2-pyridinylamino)imidazo[1,2-*a*]pyridine intermediate under photochemical conditions.[27] The single crystal structure, spectroscopic, photophysical, and photochemical properties of **2a** including absorption and fluorescence spectra, and photooxidation were also studied.[27,28] With a series of substituted pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** in hand, we envisioned that these π-extended heteroarenes might be developed into a new type of optical probes for metal ions. Thus, the optical responses of **2** toward a number of metal cations including Cu^{2+}, Zn^{2+}, Pb^{2+}, Ni^{2+}, Mn^{2+}, Mg^{2+}, Hg^{2+}, Fe^{2+}, Co^{2+}, Ca^{2+}, Cd^{2+}, Ag^{+}, and Li^{+} were investigated.

Since pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** are insoluble in water, their optical properties were measured in organic solvents. In CH$_3$CN, DMSO or CHCl$_3$, the absorption bands of **2** ranged from 325 to 425 nm, and the maximum absorption wavelengths are summarized in Table S1 of Supplementary data. In these solvents, compounds **2** bearing different substituents have similar emission maxima ranging from 436 to 467 nm, however, both substituent and solvent have a large effect on fluorescent quantum yields (Φ_F) of **2**. For example, compounds **2** generally have much higher quantum yields in DMSO than in CHCl$_3$. On the other hand, in contrast to the high fluorescence of **2a**–**g** (Φ_F 0.50–0.88), the bromine substituted **2h** has the lowest quantum yields (Φ_F 0.03–0.06) in all solvents examined (see Table S1 in Supplementary data).

The optical responses of compound **2a** in acetonitrile to a series of individual metal ions were investigated by UV-visible absorption spectra (see Fig. S2 in Supplementary data). According to the spectroscopic results, the tested cations can be classified into three types. For the first type cations, such as Zn^{2+}, Cd^{2+}, Pb^{2+}, Li^{+}, Ag^{+}, Co^{2+}, Mn^{2+}, Ni^{2+}, Ca^{2+}, and Mg^{2+}, the spectral changes of **2a** were negligible after addition of these cations. The second type cations including Hg^{2+} and Fe^{2+} induced slightly blue-shifted absorption of **2a** with nearly no change in molar absorption coefficient. The third one is Cu^{2+}, which caused about 100 nm red-shifted with increasing intensity of absorption spectrum of **2a**. The UV-visible absorption responses of compounds **2b**–**h** to different metal ions were also conducted (Fig. S2 in Supplementary data). For comparison, the absorbance changes of compounds **2** at their maximum absorption wavelengths upon addition of different metal cations into the acetonitrile solution of **2** are charted in Figure 1, in which $A_{1\ 0}$ and A_1 are the absorbance of **2** in the absence and presence of metal ions. The distinct optical responses of **2** to Cu^{2+} indicate that compounds **2** might have a unique interaction with Cu^{2+} distinguished from other cations.

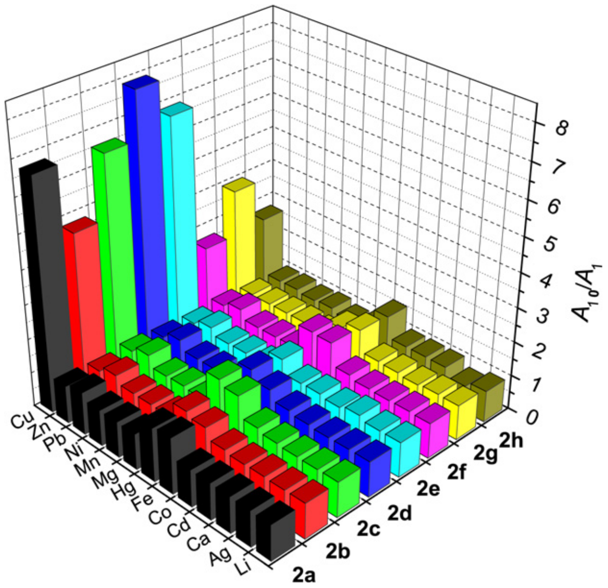


Figure 1. Absorbance changes of **2** (1.0×10^{-5} M) at their corresponding maximum absorption wavelength in CH_3CN upon addition of different metal cations of perchlorate salts (1.1×10^{-4} M).

To optimize the solvents for spectroscopic responses, the UV-visible absorption responses of compounds **2** to Cu^{2+} were recorded in EtOH, DMSO, $CHCl_3$, and CH_3CN, respectively. The responses characteristic of **2** toward copper ion can be described as the changes $A_{1\ 0}/A_1$ at their corresponding maximum absorption wavelength that were around 385 nm. As shown in Figure 2, the obvious responses were obtained in acetonitrile, in which most of compounds **2** gave the highest $A_{1\ 0}/A_1$. The medium responses were found in $CHCl_3$, while negligible responses were recorded in EtOH and DMSO. For example, the $A_{1\ 0}/A_1$ value of **2a** was 6.72 in CH_3CN, but was only 1.08, 1.08, and 2.92, respectively, in EtOH, DMSO, and $CHCl_3$ in the presence of same concentration of Cu^{2+}. These results indicated that acetonitrile is the best medium for the ligation of Cu^{2+} with **2** among the solvents examined.

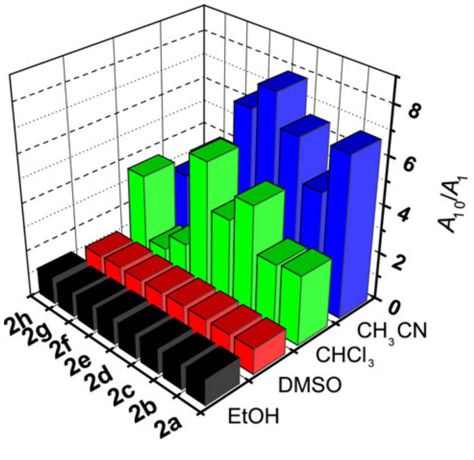


Figure 2. Absorption responses of compounds **2** (1×10^{-5} M) to Cu^{2+} (1.8×10^{-5} M) in different media. $A_{1\ 0}$ and A_1 are the absorbance of **2** at each maximum absorption wavelength in the absence and presence of copper ion, respectively.

To clarify the interactions between **2** and Cu^{2+}, UV-visible absorption spectral variation of **2** (1.0×10^{-5} M) in acetonitrile was titrated with different concentration of Cu^{2+}. Taking **2a**, for example, when the copper ion concentration was ranging from 0 to 1.8×10^{-5} M, the maximum absorbance at 386 nm gradually decreased, and concomitantly a new rising absorption band that peaked at 486 nm appeared (Fig. 3). An isosbestic point was clearly observed at 415 nm. When the concentration of Cu^{2+} was further increased, the absorbance at 486 nm began to decline, along with a small absorption peak at 525 nm appearing. The absorption responses of other probes (**2b**–**h**) to Cu^{2+} were also examined and similar results were obtained. The absorbance of probes **2** at short wavelength decreased with new red-shifted absorption peaks as concomitant when addition of increasing concentrations of Cu^{2+} (see Fig. S3 in Supplementary data).

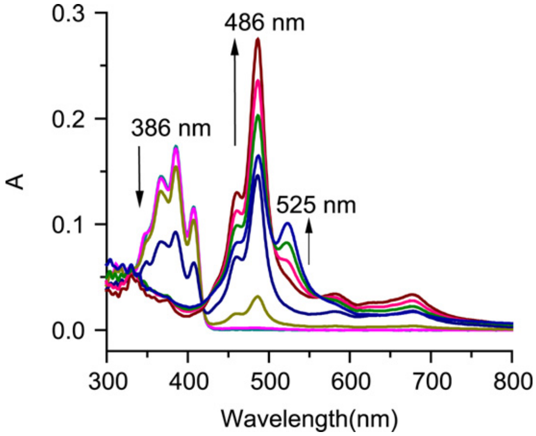


Figure 3. Absorption titration curves of chemosensor **2a** (1.0×10^{-5} M) in acetonitrile upon addition of Cu^{2+} at 0, 7.8×10^{-7}, 1.8×10^{-6}, 3.6×10^{-6}, 8.2×10^{-6}, 1.8×10^{-5}, 3.6×10^{-5}, 8.2×10^{-5} and 1.8×10^{-4} M.

The absorbance changes (A_2–$A_{2\ 0}$) at corresponding maximum absorption wavelength of the copper complexes of **2** were then plotted as the concentration of Cu^{2+} increasing from 0 to 1.7×10^{-4} M. As shown in Figure 4, except **2f** that gave little change in the presence of Cu^{2+}, the absorbance of compounds **2** enhanced obviously while the concentration of Cu^{2+} increased, and the maximum changes were observed when the concentration of Cu^{2+} was around 1.8×10^{-5} M. When the concentration of

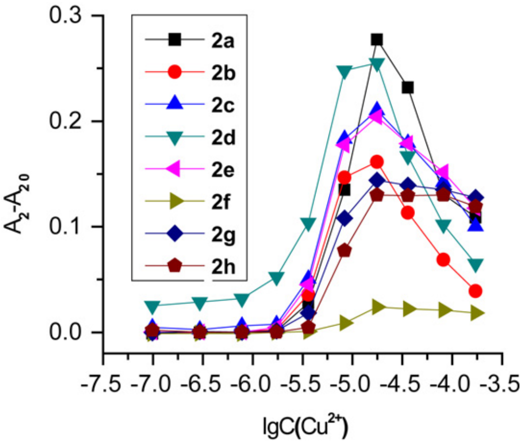


Figure 4. Absorbance changes (A_2–$A_{2\ 0}$) of chemosensor **2** (1.0×10^{-5} M) at corresponding maximum absorption wavelengths of their copper complexes in acetonitrile upon addition of different concentrations of Cu^{2+}. $A_{2\ 0}$ and A_2 are the absorbance of **2** in the absence and presence of Cu^{2+}, respectively.

Cu^{2+} increased further, the absorbance changes began to decline. It was found that compounds **2a** and **2d** are the more sensitive probes to Cu^{2+} compared to other compounds **2**, and **2d** was a little better than **2a** to the lower concentration of Cu^{2+}. Thus, the absorption responses of **2d** to copper ion were examined in detail. The UV-visible absorption spectral changes of **2d** to lower and higher concentration of Cu^{2+} are displayed in Figure 5a and Figure 5b, respectively. The plot of optical density changes ($A_{1\,0}$–A_1) at 385 nm against concentrations of Cu^{2+} shows that the limit of detection is about 3.5×10^{-7} M (Fig. S4 in Supplementary data), which is much lower than most known UV-visible absorption methods.

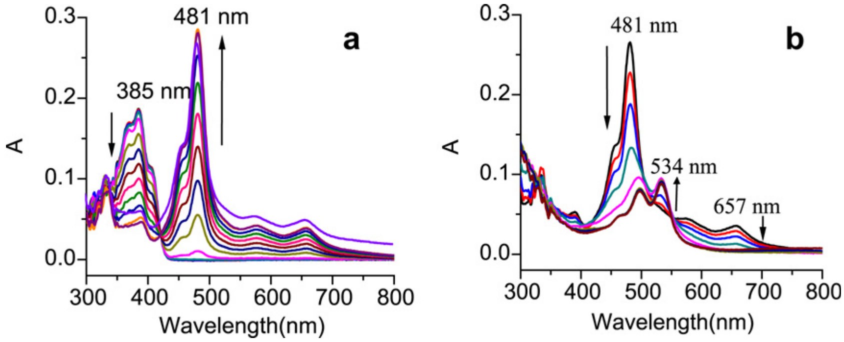


Figure 5. Absorption responses of **2d** (1.0×10^{-5} M) to different concentration of Cu^{2+}. (a): The concentration of Cu^{2+} are 2.9×10^{-7}, 7.8×10^{-7}, 1.7×10^{-6}, 3.6×10^{-6}, 5.5×10^{-6}, 7.3×10^{-6}, 9.1×10^{-6}, 1.1×10^{-5}, 1.3×10^{-5}, 1.4×10^{-5}, 1.6×10^{-5} and 1.8×10^{-5} M, respectively. (b): The concentration of Cu^{2+} are 2.0×10^{-5}, 2.5×10^{-5}, 3.5×10^{-5}, 5.4×10^{-5}, 1.0×10^{-4}, 2.0×10^{-4} and 3.2×10^{-4} M, respectively. The arrows indicate the signal changes as increasing the Cu^{2+} concentration.

To determine the stoichiometry of the copper ligand complex, Job's method for the absorbance was applied, keeping the sum of the initial concentration of copper ion and **2d** at 2.0×10^{-5} M, and the molar ratio of copper ion changing from 0 to 1.[29,30] The 481 nm absorbances of **2d** in the absence ($A_{2\,0}$) and presence (A_2) of copper ion were determined, respectively. A plot of $A_{2\,0}$–A_0 versus the molar fraction of copper ion is provided in Figure 6. It shows that the $A_{2\,0}$–A_0 value goes through a maximum at a molar fraction of 0.5, indicating a 1:1 stoichiometry of the Cu^{2+} to **2** in the complex. And the combination constant was estimated by Benesi-Hildebrand method[31] to be 2.56×10^4 M^{-1} (Fig. S5 in Supplementary data). The stoichiometric ratio was also corroborated by TOF-ESI mass spectroscopy. A peak of M=299.1766 for $[(\mathbf{2d})+Cu]^+$ (calcd 299.0347) was found when **2d** (1.0×10^{-5} M) was mixed with 5.5×10^{-5} M of Cu^{2+} (Fig. S6 in Supplementary data). The mass data supports the formation of a 1:1 complex between **2d** and Cu^{2+}.

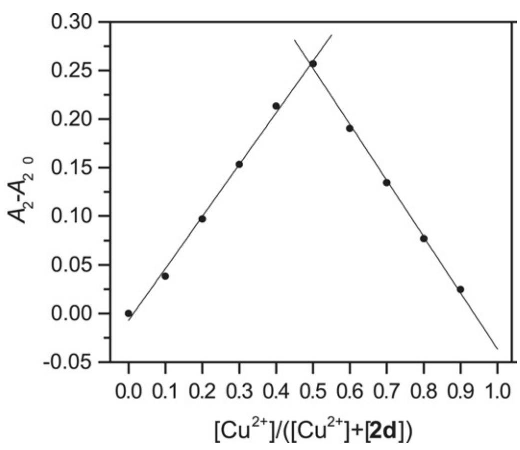
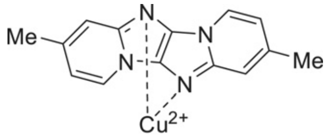


Figure 6. Job plot for determining the stoichiometry of **2d** and Cu^{2+}. The total concentration of **2** and copper was 2.0×10^{-5} M. Molar fraction was given by $[Cu^{2+}]/([Cu^{2+}]+[\mathbf{2d}])$.

The proposed structure of complex of **2d** with Cu^{2+} was shown in Figure 7. Since the non-bonding electrons of fused nitrogen atom of pyridine have delocalized in the whole π-orbital of **2d**, only the lone-pair electrons of nitrogen atom of imidazole is capable of engaging the copper ion. Thus, we proposed that the copper ion was bonded with two nitrogen atoms of imidazoles of compound **2d**.



(**2d**) + Cu^{2+}

Figure 7. The proposed binding mechanism of Cu^{2+} with **2d**.

The selectivity of **2d** to Cu^{2+} was further demonstrated in the presence of other cations. Absorption intensity changes of chemosensor **2d** (1.0×10^{-5} M) to Cu^{2+} (1.0×10^{-5} M) in the presence of interference ions (3.5×10^{-6} M) were recorded. As shown in Figure 8, the absorbance of the complex of **2d** with Cu^{2+} at 481 nm enhancement over the initial absorbance of **2d** (A_2–$A_{2\,0}$) at this wavelength was nearly affected by cations Li^+, Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Pb^{2+}, Ni^{2+} or Zn^{2+}.

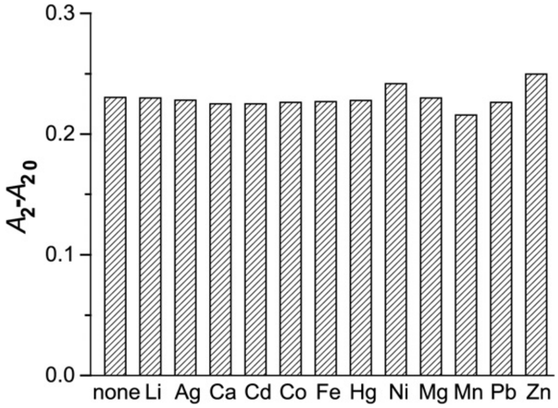


Figure 8. Absorption intensity changes of chemosensor **2d** (1.0×10^{-5} M) to Cu^{2+} (1.0×10^{-5} M) in the presence of selected substrates, and the interference ion concentration is 3.5×10^{-6} M in each case. Bars represent the newly formed 481 nm absorption enhancement over the initial absorbance at this wavelength.

The interactions of compounds **2** with various metal ions were also studied by visual examining the metal-induced color changes of **2** in acetonitrile. It was found that probes **2a**–**e** have colorimetric responses to Cu^{2+} (see Fig. S7 in Supplementary data). Figure 9 shows the photograph of **2d** (2×10^{-5} M) upon additions of different metal ions (5×10^{-4} M). The acetonitrile solution of free **2d** is colorless. No color change was observed upon addition of Ag^+, Li^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Hg^{2+}, Ni^{2+}, Mg^{2+}, Mn^{2+}, Pb^{2+} or Zn^{2+}, separately, to the acetonitrile solution of **2d**. However, the solution of **2d** changed immediately into red or yellow color upon addition of different concentration of Cu^{2+} (Figs. 9 and 10). Thus compound **2d** can be used as colorimetric probes for detecting Cu^{2+}.

Figure 9. Photograph of the acetonitrile solution of **2d** (2.0×10^{-5} M) in the presence of different metal ions (5×10^{-4} M). The metal ions are None, Ag^+, Li^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+} and Cu^{2+}, respectively, from left to right.

Figure 10. Photograph of the acetonitrile solution of **2d** (2.0×10^{-5} M) in the presence of different concentration of Cu^{2+}. The concentrations of Cu^{2+} are 0, 5.0×10^{-5}, 1.0×10^{-4}, 5.0×10^{-4} M from left to right.

We initially also studied the fluorescence responses of compounds **2** to different metal ions due to compounds **2** having strong fluorescence (see Table S1 in Supplementary data). For example, the fluorescence spectroscopy of **2a** in the presence of Cu^{2+}, Hg^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+}, Cd^{2+}, Pb^{2+}, Ag^+, Ca^{2+} or Mg^{2+} was measured, respectively, in acetonitrile. It was found that the fluorescence of **2a** quenched markedly with the gradual addition of Cu^{2+} or Hg^{2+}, but was hardly or slightly influenced by other metal ions (see Fig. 11).

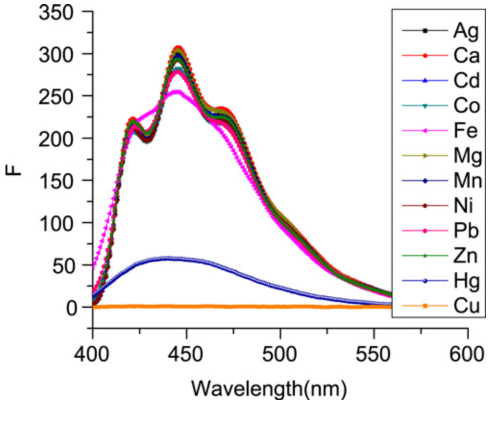


Figure 11. Fluorescence emission spectra of compound **2a** (5.0×10^{-6} M) in the absence and presence of different metal ions (1.1×10^{-4} M) in acetonitrile. λ_{ex}=381 nm.

The fluorescence titration of **2a** with Cu^{2+} was then carried out in an acetonitrile solution (Fig. 12). The fluorescence intensity of **2a** at 445 nm was obviously reduced when the concentration of Cu^{2+} was increased from 0 to 8.3×10^{-6} M. The fluorescence intensity was quenched more than 99% while the concentration of Cu^{2+} reached about 1.5 equiv of the concentration of **2a**. Although **2a** seems to be a sensitive fluorescent probe for Cu^{2+}, its emission spectra were less selective between Cu^{2+} and Hg^{2+} than the absorption spectra. Thus, we did not make an intensive study of fluorescence responses of **2** to Cu^{2+}.

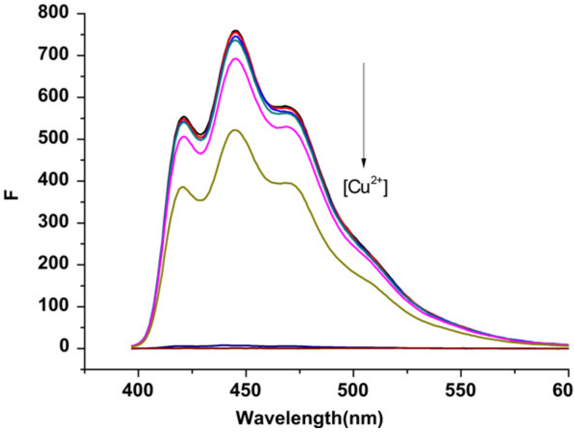


Figure 12. Fluorescent responses of **2a** (5.0×10^{-6} M) to different concentration of Cu^{2+} (9.9×10^{-8}, 2.9×10^{-7}, 7.8×10^{-7}, 1.7×10^{-6}, 3.6×10^{-6} and 8.3×10^{-6} M, respectively). The arrows indicate the signal changes as increasing the Cu^{2+} concentration. λ_{ex}=381 nm.

3. Conclusion

In conclusion, a series of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** were synthesized simply by heating 2-pyridylisonitriles in 1,4-dioxane. The optical responses of these π-extended fused heteroarenes to metal ions including Cu^{2+}, Zn^{2+}, Pb^{2+}, Ni^{2+}, Mn^{2+}, Mg^{2+}, Hg^{2+}, Fe^{2+}, Co^{2+}, Ca^{2+}, Cd^{2+}, Ag^+, and Li^+ were investigated by UV-visible absorption spectrum in acetonitrile. It was found that most of compounds **2** selectively responded to Cu^{2+}, and the limit of detection is about 3.5×10^{-7} M when using the best probe 3,9-dimethylpyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridine **2d**. Meanwhile some compounds **2** specifically communicates a color change from colorless to red or yellow when exposed to copper ion in acetonitrile, whereas other transitional, alkali, and alkaline earth metal ions could not induce such a change. Thus, compounds **2** can be developed into sensitive and selective colorimetric and optical probes for copper ion. This work not only established a extremely simple method for the construction of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines, but also extended the applications of π-extended fused heteroarenes.

4. Experiment section

4.1. General procedure for the preparation of pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines 2

Under nitrogen atmosphere, the solutions of 2-pyridylisonitriles **1**[23] (2 mmol) in dry 1,4-dioxane (50 mL) were refluxed for 20–37 h. After removal of solvent under vacuum, the products pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-*a*]pyridines **2** were isolated in 31–77% yields by chromatography on a neutral Al_2O_3 column eluting with a mixture of petroleum ether (60–90 °C) and ethyl acetate (from 1:1 to pure ethyl acetate) for **2a**–**f**, or chloroform and ethyl acetate (10:1) for the halogen substituted **2g** and **2h**.

4.1.1. Pyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2a***. Yield 63%, mp 292–294 °C. IR ν (cm^{-1}) 1529, 1501; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.48 (d, J=6.8 Hz, 2H), 7.66 (d, J=9.3 Hz, 2H), 7.27 (dd, J=6.8, 1.2 Hz, 1H), 7.24 (dd, J=6.9, 1.2 Hz, 1H), 6.89 (dt, J=6.8, 0.9 Hz, 2H); ^{3}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.8, 134.5, 125.2, 124.0, 118.0, 111.4; MS (EI): 104 (80), 208 (M^+, 90%). Anal. Calcd for $C_{12}H_8N_4$: C 69.22, H 3.87, N 26.91. Found: C 69.25, H 3.96, N 27.27.

4.1.2. 1,7-Dimethylpyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2b***. Yield 61%, mp 291–292 °C. IR ν (cm^{-1}) 1531, 1517; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (d, J=9.2 Hz, 2H), 7.16(dd, J=9.2, 6.9 Hz, 2H), 6.60 (d, J=6.8 Hz, 2H), 3.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 146.2, 136.3, 135.0, 125.5, 114.9, 110.2, 19.3; MS (ESI): 237 (M+1). Anal. Calcd for $C_{14}H_{12}N_4$: C 71.17, H 5.12, N 23.71. Found: C 70.99, H 5.52, N 23.95.

4.1.3. 2,8-Dimethylpyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2c***. Yield 64%, mp 315–317 °C. IR ν (cm^{-1}) 1539, 1498; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.29 (s, 2H), 7.59 (d, J=9.3 Hz, 2H), 7.13 (dd, J=9.4, 1.4 Hz, 2H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.9, 134.5, 128.0, 121.6, 120.7, 117.3, 18.3; MS (ESI): 237 (M+1). Anal. Calcd for $C_{14}H_{12}N_4$: C 71.17, H 5.12, N 23.71. Found: 70.98, H 4.92, N 23.74.

4.1.4. 3,9-Dimethylpyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2d***. Yield 56%, mp 288–289 °C. IR ν (cm^{-1}) 1635, 1503; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.41(d, J=7.0 Hz, 2H), 7.45 (s, 2H), 6.78 (dd, J=7.0, 1.4 Hz, 2H), 2.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.8, 135.9, 134.0, 123.0, 116.2, 113.9, 21.7; MS (ESI): 237 (M+1). Anal. Calcd for $C_{14}H_{12}N_4$: C 71.17, H 5.12, N 23.71. Found: C 71.08, H 5.11, N 23.23.

4.1.5. 4,10-Dimethylpyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2e***. Yield 31%, mp >350 °C. IR ν (cm^{-1}) 1555, 1503, 1469; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.46 (d, J=6.7 Hz, 2H), 7.07 (d, J=6.8 Hz, 2H), 6.81(t, J=6.8 Hz, 2H), 2.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.7, 133.8, 127.5, 124.8, 122.2, 111.6, 17.3; HRMS (TOF-ESI): 237.1145(M+1), $C_{14}H_{13}N_4$ (M+1) required 237.1140.

4.1.6. 2,8-Dimethoxypyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2f***. Yield 77%, mp 309–310 °C. IR ν (cm^{-1}) 1638, 1544, 1519; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (d, J=1.3 Hz, 2H), 7.58 (d, J=9.9 Hz, 2H), 7.10 (dd, J=9.8, 2.0 Hz, 2H), 3.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 148.4, 143.0, 135.7, 120.5, 118.1, 105.6, 56.2; HRMS (TOF-ESI): 269.1040 (M+1), $C_{14}H_{13}N_4O_2$ (M+1) required 269.1039.

4.1.7. 2,8-Dichloropyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2g***. Yield 53%, mp >300 °C. IR ν (cm^{-1}) 1534, 1500; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.70 (s, 2H), 7.77 (d, J=9.8 Hz, 2H), 7.42 (d, J=9.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CF_3CO_2D) δ (ppm): 142.1, 134.7, 126.8, 126.0, 124.2, 115.9; HRMS (TOF-ESI): 277.0039 (M+1), $C_{12}H_7Cl_2N_4$ (M+1) required 277.0048.

4.1.8. 2,8-Dibromopyrido[2″,1″:2′,3′]imidazo[4′,5′:4,5]imidazo[1,2-a]pyridine ***2h***. Yield 44%, mp >350 °C. IR ν (cm^{-1}) 1526, 1457; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.66 (s, 2H), 7.60 (d, J=9.8 Hz, 2H), 7.38 (dd, J=9.7, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CF_3CO_2D) δ (ppm): 142.3, 136.8, 126.4, 126.2, 116.1, 111.9; MS (ESI): 364 (M+1). Anal. Calcd for $C_{12}H_6Br_2N_4$: C 39.38, H 1.65, N 15.31. Found: C 39.13, H 1.98, N 15.12.

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Supplementary data

The maximum absorption, emission wavelength and quantum yields of compounds **2**, the absorption responses of **2** toward different cations, the absorption responses of **2** to different concentration of Cu^{2+}, the limit of detection of Cu^{2+}, the association constant of **2d** and Cu^{2+}, the mass spectra of [(**2d**)+Cu]$^+$ complex, the copies of ^{1}H NMR and ^{13}C NMR spectra of products **2**. The Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.096. These data include MOL files and InChIKeys of the most important compounds described in this article.

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