JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

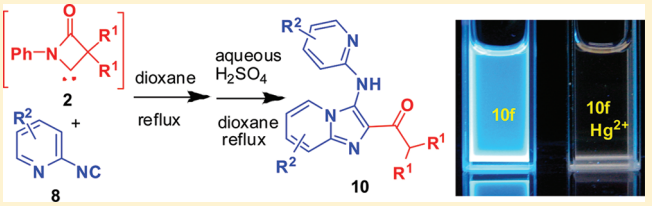
Reaction of β-Lactam Carbenes with 2-Pyridyl Isonitriles: A One-Pot Synthesis of 2-Carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines Useful as Fluorescent Probes for Mercury Ion

Na Shao, Guang-Xian Pang, Cai-Xia Yan, Gao-Feng Shi, and Ying Cheng*

College of Chemistry, Beijing Normal University, Beijing 100875, China

Supporting Information

ABSTRACT: The one-pot reaction of β-lactam carbenes with 2-pyridyl isonitriles followed by an acidic hydrolysis was reported, which produced 2-carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines in moderate to good yields. Among the resulting novel imidazo[1,2-*a*]pyridine derivatives, 1-(6-chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)-2-ethylbutan-1-one was demonstrated to be an efficient fluorescent probe for mercury ion both in acetonitrile and in buffered aqueous solution.



INTRODUCTION

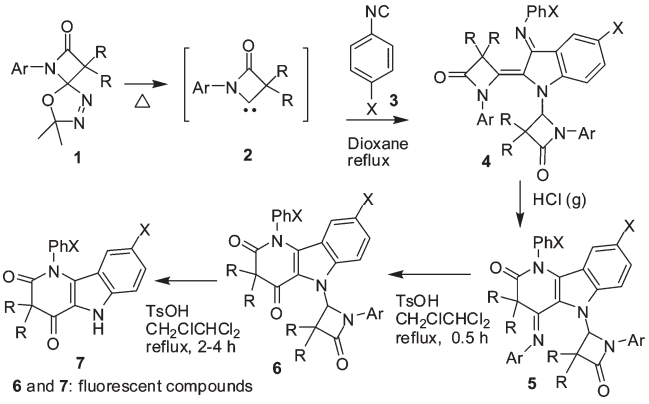
Imidazo[1,2-*a*]pyridines substituted by different functional groups have attracted growing interest from both organic and medicinal chemists owing to their diverse range of biologic and pharmacological activities.[1] For example, a series of imidazo[1,2-*a*]-pyridine derivatives are inhibitors of PIKK, FGFR, Class I PI3 kinase, and protein serine/threonine kinase and therefore have potential applications in the treatment of cancer.[2] Some multi-substituted imidazo[1,2-*a*]pyridines are inhibitors of histone deacetylase,[3] acetylcholinesterase,[4] EphB3 kinase,[5] and geranyl-geranyl transferase,[6] which may be utilized in the treatment of proliferative disorders and Alzheimer's disease, provide neuro-protection and repair of damaged neuronal tissue, and decrease bone resorption by inhibiting farnesyl pyrophosphate synthase in osteoclasts. Imidazo[1,2-*a*]pyridine derivatives also showed antianxiety,[7] antihepatitis C,[8] antibacterium,[9] antiinflammatory,[10] and antiviral activity.[11] Some imidazo[1,2-*a*]pyridine derivatives, such as vasodilator olprinone,[12] and hypnotics zolpidem and alpidem,[13] have been used as clinical medicines. Besides the biologic activities, the optical properties constituted another important feature of imidazo[1,2-*a*]pyridines.[14] Fluorescent imidazo[1,2-*a*]pyridine derivatives have been utilized as fluorescent dopamine D3 receptors ligands[15] or as a fluorescent probe for peripheral benzodiazepine receptors and microglial cell visualization.[16]

The construction of a imidazo[1,2-*a*]pyridine ring was generally based on the cyclocondensations of 2-aminopyridines with α-halo ketones,[17] α-halo acetaldehydes,[11,18] or vinyl ether.[19] The three-component reactions of 2-aminopyridines with aldehydes and isocyanides,[20] or with aldehydes and terminal alkynes,[21] are also efficient methods for the preparation of imidazo[1,2-*a*]-pyridine compounds. Although numerous syntheses of imidazo-[1,2-*a*]pyridine derivatives have been reported because of their remarkable biologic and optical properties, most of them were derived from the structural modification of imidazo[1,2-*a*]-pyridine compounds.[22] The development of simple and efficient methods for the direct construction of multifunctional imidazo-[1,2-*a*]pyridines is still of high importance.

In the 1990s, Warkentin and co-workers investigated the reactions of 2-azetidinone-4-ylidenes, a type of β-lactam carbene derived from thermolysis of spiro[β-lactam-4,2′-oxadiazolines],[23] with both electron-rich and electron-deficient alkenes or alkynes, which formed β-lactam-spiro-cyclopropanes or β-lactam-spiro-cyclopropenes. They demonstrated the β-lactam carbenes to be ambiphilic carbenes but with pronounced electrophilic activity.[24] In recent years, we have been interested in the development of synthetic methods for the construction of novel spiro and fused heterocyclic compounds from the reactions of β-lactam carbenes.[25−27] For example, we found that β-lactam carbenes behaved as nucleophilic carbenes toward aryl isocyanates to form β-lactam-spiro-indole derivatives.[25] On the other hand, the electrophilic reaction of β-lactam carbenes with phenyl isonitriles produced 2-(4-azetidinonylidene)indoles **4** that rearranged into δ-carbolin-2-ones **5** in the presence of an acid. A subsequent acidic hydrolysis controllably converted δ-carbolin-2-ones **5** into two types of fluorescent δ-carboline-2,4-diones **6** and **7** (Scheme 1).[26] We envisioned that, by varying the structures of aryl isonitriles, the reaction between β-lactam carbenes and aryl isonitriles might be developed into a general method for the synthesis of aryl-fused pyrrolo[3,2-*b*]pyridine compounds. To further explore the synthetic utility of β-lactam carbenes, we undertook the current investigation of the reaction of β-lactam carbenes with 2-pyridyl isonitriles. Instead of the formation of the expected

Received: June 16, 2011
Published: August 08, 2011

Scheme 1. Reaction of β-Lactam Carbenes 2 with Phenyl Isonitriles 3.[26]



pyridopyrrolo[3,2-*b*]pyridine derivatives, the reaction produced 2-(4-azetidinonylidene)imidazo[1,2-*a*]pyridines that were further converted into 2-carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines by acidic hydrolysis. The resulting novel imidazo[1,2-*a*]pyridine derivatives can be developed into efficient fluorescent probes for mercury ion. Herein we report our results.

RESULTS AND DISCUSSION

Study of the Reaction of β-Lactam Carbenes with 2-Pyridyl Isonitriles. In this work, β-lactam carbenes **2** are generated in situ from thermolysis of spiro[β-lactam-4,2′-oxadiazolines] **1**, which were prepared on the bases of Warkentin's method[23] and our previous report.[25] According to Warkentin's reports and our experiences, the optimal temperature for the generation of β-lactam carbenes **2** from spiro-oxadiazolines **1** is around 100−110 °C.[23−26] The reaction of 3,3-dimethyl-1-phenyl-2-azetidinone-4-ylidene **2a** with 1 equiv of 2-pyridyl isonitrile **8a** was initially carried out in refluxing 1,4-dioxane under nitrogen atmosphere. It was found that the reaction of **2a** with **8a** produced a yellow colored product **9a** along with the dimer[28] of 2-pyridyl isonitrile. However, pure **9a** was not obtained, because it partially converted into a fluorescent compound **10a** during chromatography and recrystallization. Because we have known about the reaction of β-lactam carbenes with phenyl isonitriles producing 2-(4-azetidinonylidene)indoles **4** that were converted into δ-carbolinones **5**, **6**, or **7** by treatment with acid (see Scheme 1),[26] we initially guessed that the yellow colored product **9a** and fluorescent compound **10a** derived from carbene **2a** and 2-pyridyl isonitrile **8a**, probably being the aza-analogues of 2-(4-azetidinonylidene)indole **4** and δ-carbolinone **6** or **7**, respectively. However, after the analysis by single crystal X-ray diffraction and spectroscopic methods, the structure of fluorescent compound **10a** was determined to be 2-isobutyroyl-3-(2-pyridylamino)imidazo[1,2-*a*]pyridine. In order to obtain the stable product, the reaction of carbene **2a** with 2-pyridyl isonitrile **8a** followed by an acidic hydrolysis was carried out in a one-pot procedure. Because product imidazo[1,2-*a*]pyridine **10a** contains two pyridine moieties, the reaction of carbene precursor **1a** with 2 equiv of 2-pyridyl isonitrile **8a** was optimized by varying solvents, reaction temperature, and the acids used for the hydrolysis of intermediate **9a**. As shown in Table 1, the mixture of **1a** with **8a** was refluxed in different solvents including 1,4-dioxane, toluene, 1,1,2-trichloroethane, 3-pentanone, and acetonitrile for 7−11 h. After the addition of 10 equiv of aqueous HCl (12 M), the reaction mixture was refluxed for another 8−9 h. From these reactions, product **10a** was isolated in 12−69% yields, among which the best result was obtained from the reaction in dioxane. The reaction was then conducted in refluxing 1,4-dioxane followed by hydrolysis with different acids. To our delight, the yield of **10a** was improved to 84% while using aqueous H_2SO_4 (12 M) to hydrolyze the reaction intermediate.

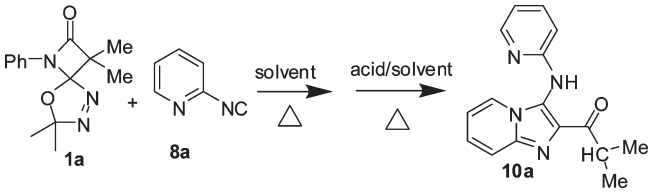
The generality of the reaction was studied in refluxing 1,4-dioxane using spiro[β-lactam-4,2′-oxadiazolines] **1** and 2-pyridyl isonitriles **8**, both bearing different substituents, under optimized conditions. Because we have previously demonstrated that the aryl groups attached to the nitrogen atom of β-lactam carbenes **2** have a negligible effect on the reaction of **2** with phenyl isonitriles,[26] and the products **10** yielded from the current reaction did not contain the *N*-phenyl moiety of the carbenes, we only varied the 3,3-dialkyl groups of carbenes **2** and the substituents attached to the pyridyl of isonitriles **8**. As indicated in Table 2, although all reactions examined produced products **10** in moderate to good yields, the substituents of two reactants did show some effects on the reaction. For example, when different alkyl-substituted β-lactam carbenes, such as dimethyl-**2a**, 3,3-diethyl- **2b**, 3,3-cyclopentyl- **2c** and 3,3-cyclohexyl-β-lactam carbene **2d**, reacted with a isonitrile **8**, 3,3-dimethyl-β-lactam carbene **2a** produced a yield of product higher than that of the others. On the other hand, while different isonitriles including 2-pyridyl **8a**, 2-(5-chloropyridyl) **8b**, and 2-(6-methylpyridyl) isonitrile **8c** reacted with a carbene **2**, the reaction of 2-pyridyl isonitrile **8a** afforded a yield of product higher than that of **8b** or **8c**. The higher efficiency of **2a** compared to **2b**−**d** can be explained by the smaller steric hindrance of methyl compared to other alkyl groups in the reaction, while the lower reactivity of isonitriles **8b** and **8c** compared to **8a** was probably due to the electronic or steric effects of substituents of **8**. Because isonitriles **8** acted as nucleophiles in this reaction, the electron-withdrawing chlorine substituent might deactivate the nucleophilicity of **8b**. The lower efficiency of **8c** compared to **8a** was probably due to the steric hindrance of 6-methyl group of **8c** in the formation of the imidazo[1,2-*a*]pyridine ring (vide infra).

The products **10** were fully characterized by spectroscopic data and microanalysis, which indicated that **10** were the adducts of one β-lactam carbene **2** and two pyridyl isonitrile **8** with the loss of PhN moieties of the carbenes. To identify the products beyond doubt, the structure of **10a** was also determined unambiguously by single crystal X-ray diffraction analysis (see Supporting Information).

To understand the mechanism for the formation of 2-carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines **10** from the interaction of β-lactam carbenes **2** and pyridyl isonitriles **8**, the isolation and characterization of intermediates **9** were very important. It was found that, although compounds **9** were generally unstable during chromatography and recrystallization, the products **9** derived from 3,3-diethyl-β-lactam carbene **2b** were more stable than those yielded from 3,3-dimethyl-β-lactam carbene **2a**. Thus, from the reaction of **2b** with **8c**, a small amount of pure **9j** was obtained, which was identified as 3,3-diethyl-4-(5-methyl-3-(6-methyl-2-pyridylimino)imidazo[1,2-*a*]pyridin-2-ylidene)-1-phenylazetidin-2-one by spectroscopic data. On the basis of the structure of intermediate **9j** and our knowledge of the interaction pathway between β-lactam carbenes and phenyl isonitriles **3** (see Scheme 1),[26] the mechanism for the formation

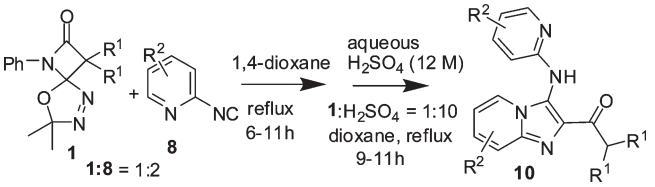
dx.doi.org/10.1021/jo201273p |*J. Org. Chem.* 2011, 76, 7458–7465

Table 1. Optimization of Reaction Conditions for the One-Pot Reaction of 3,3-Dimethyl-1-phenyl-β-lactam-4-ylidene 2a with 2-Pyridyl Isonitrile 8a Followed by an Acidic Hydrolysis



		reaction conditions		
entry	**1a**:**8a**	step 1	step 2	yield of **10a** (%)
1	1:1	1,4-dioxane, reflux, 8 h	HCl (12 M), 1,4-dioxane, reflux, 8 h	39
2	1:2	1,4-dioxane, reflux, 8 h	HCl (12 M), 1,4-dioxane, reflux, 9 h	69
3	1:2	1,1,2-trichloroethane, 110 °C, 7 h	HCl (12 M), 1,1,2-trichloroethane, 110 °C, 9 h	12
4	1:2	toluene, 110 °C, 8 h	HCl (12 M), toluene, 110 °C, 8 h	61
5	1:2	3-pentanone, 110 °C, 10 h	HCl (12M), 3-pentanone, 110 °C, 9 h	46
6	1:2	CH_3CN, reflux, 11 h	HCl (12 M), CH_3CN, reflux, 9 h	31
7	1:2	1,4-dioxane, reflux, 9 h	H_2SO_4 (12 M), 1,4-dioxane, reflux, 9 h	84
8	1:2	1,4-dioxane, reflux, 9 h	TsOH (12 M), 1,4-dioxane, reflux, 9 h	75

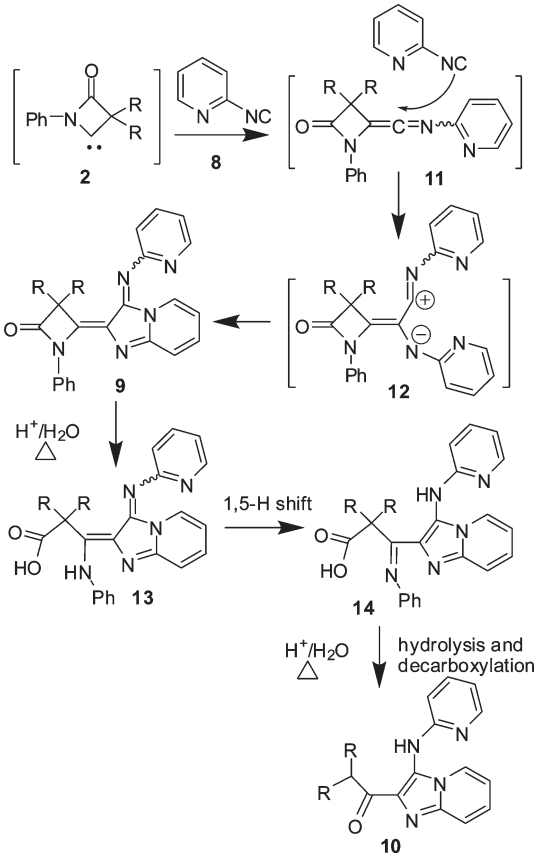
Table 2. Reaction of Spiro[β-lactam-4,2′-oxadiazolines] 1 and 2-Pyridyl Isonitriles 8 under Optimized Conditions



entry	**1**	R^1, R^1	**8**	R^2	yield of **10** (%)
1	**1a**	Me, Me	**8a**	H	**10a**: 84
2	**1b**	Et, Et	**8a**	H	**10b**: 71
3	**1c**	$(CH_2)_4$	**8a**	H	**10c**: 61
4	**1d**	$(CH_2)_5$	**8a**	H	**10d**: 76
5	**1a**	Me, Me	**8b**	5-Cl	**10e**: 63
6	**1b**	Et, Et	**8b**	5-Cl	**10f**: 54
7	**1c**	$(CH_2)_4$	**8b**	5-Cl	**10g**: 41
8	**1d**	$(CH_2)_5$	**8b**	5-Cl	**10h**: 46
9	**1a**	Me, Me	**8c**	6-Me	**10i**: 66
10	**1b**	Et, Et	**8c**	6-Me	**10j**: 62
11	**1c**	$(CH_2)_4$	**8c**	6-Me	**10k**: 58
12	**1d**	$(CH_2)_5$	**8c**	6-Me	**10l**: 63

of 2-carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines **10** from the reaction of carbenes **2** with isonitriles **8** followed by acidic hydrolysis was proposed in Scheme 2. The reaction was initiated by coupling of the carbene with isonitrile to form a ketenimine intermediate **11**. Nucleophilic addition of the second isonitrile to **11** gave a dipolar intermediate **12**. Intramolecular aromatic electrophilic cyclization of imine cation of **12** to the nitrogen atom of pyridine ring led to the formation of imidazo[1,2-*a*]-pyridine derivative **9**. Hydrolysis of the β-lactam moiety of **9** formed an acid intermediate **13**. Aromatization of the dihydroimidazole ring of **13** by 1,5-H shift produced an imino-substituted acid **14**. The hydrolysis and decarboxylation of acid **14** in strong acidic aqueous solution under heating afforded products **10**.

Scheme 2. Proposed Mechanism for the Formation of Imidazo[1,2-*a*]pyridines 10 from the Reaction of Carbenes 2 with Isonitriles 8 Followed by Acidic Hydrolysis



dx.doi.org/10.1021/jo201273p |*J. Org. Chem.* 2011, 76, 7458–7465

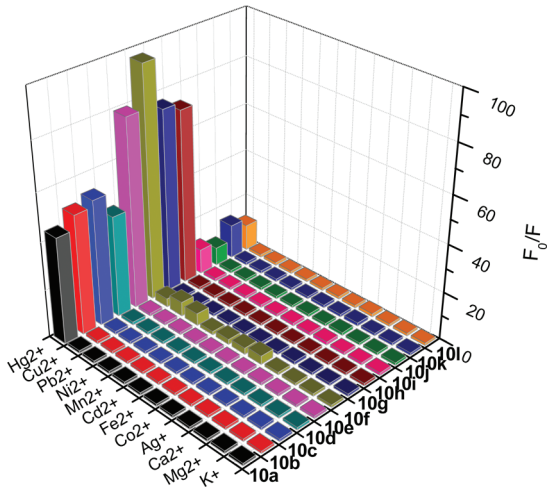


Figure 1. Fluorescent responses of **10a**−**l** (2.5×10^{-5} M) to different metal ions in acetonitrile solution. The excitation was at the maximum absorption wavelength of each compound, and the emission was recorded at the maximum emission wavelength. F_0 and F are the fluorescence intensity of relevant compound in the absence and presence of metal ions, respectively. The concentration of metal ions are all 3.6×10^{-5} M.

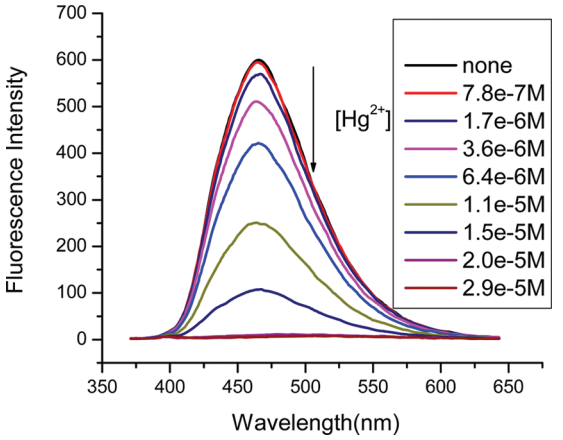


Figure 2. Changes in fluorescence emission spectra (λ_{ex} = 351 nm) of 2.5×10^{-5} mol/L **10f** upon additions of different concentrations of Hg^{2+} in acetonitrile solution. The arrows indicate the signal changes as the Hg^{2+}concentrations are increased.

Study of the Fluorescent Responses of 2-Carbonyl-3-(pyridylamino)imidazo[1,2-*a*]pyridines 10 toward Metal Ions. Because imidazo[1,2-*a*]pyridines **10** are fluorescent multifunctional compounds that contain five heteroatoms in one molecule, we envisioned that compounds **10** might be useful ligands for certain metals and be utilized as fluorescent probes for metal ions. Thus, the spectroscopic properties of **10** and their fluorescent responses toward metal ions were investigated.

First, the UV−visible and fluorescent spectroscopic properties of imidazo[1,2-*a*]-pyridine derivatives **10a**−**l** were studied in acetonitrile and water, and the basic parameters are shown in Table S1 in Supporting Information. The UV−visible absorption, fluorescence excitation, and emission spectroscopy of compounds **10** in acetonitrile are also shown in Figure S1 (see Supporting Information). These compounds show maximum absorption around 340 nm, and all of them are fluorescent, displaying maximal emission wavelength ranging 410−490 nm in the solvents studied. The quantum yields for compounds **10** are listed in Table S2 (see Supporting Information). It was found that the quantum yields of **10** are in the range of 1−3% in acetonitrile and 0.1−0.5% in aqueous solution. All compounds **10** have higher quantum yields in acetonitrile than in water, and **10f** has the highest quantum yield among these 12 compounds in both solvents.

To explore the application of compounds **10** in the molecular recognition, fluorescent responses of **10a**−**l** to different metal ions were examined, and the perchloric salts of Ag^+, K^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, and Pb^{2+} ions were used. Considering the solubility of organic compounds **10** and inorganic metal ions, the titration experiments were first conducted in acetonitrile solution. Figure 1 shows the fluorescent quenching responses (F_0/F) of **10a**−**l** (2.5×10^{-5} mol/L) in acetonitrile solution to different metal ions (3.6×10^{-5} mol/L), where F_0 and F are the fluorescence intensity of the fluorophore at the maximal emission wavelength in the absence and presence of metal ions. It can be seen clearly that each probe has a distinct fluorescence quenching response to Hg^{2+} than to other metal ions. Particularly, the fluorescence quenching value of **10f** is much larger than that of any other probes in the presence of Hg^{2+} (Figure 1).

The fluorescence spectra of **10f** in the presence of different concentrations of Hg^{2+} are shown in Figure 2. When 7.8×10^{-7} mol/L Hg^{2+} was added into 2.5×10^{-5} mol/L **10f** in acetonitrile medium, a slight decrease of the initial fluorescence could be observed. In the concentration range from 1.7×10^{-6} mol/L to 2.0×10^{-5} mol/L, an obvious fluorescence decrease is observed. At a higher Hg^{2+} concentration, more than 2.9×10^{-5} M, a total quenching of the fluorescence emission is observed, which reaches a plateau at about 0.94% of its initial intensity. The limit of detection (LOD), defined as three times the standard deviation of the blank solution, is calculated to be 8.0×10^{-8} mol/L (α = 0.99). When titrated down to the clearly obvious change of the probe fluorescence, the limit of detection for Hg^{2+} is determined to be 1.7×10^{-6} mol/L.

The absorption spectroscopic responses of **10f** to different concentrations of Hg^{2+} were also conducted in acetonitrile. While the concentration of Hg^{2+} ranged from 4.95×10^{-7} to 1.75×10^{-4} M, the absorbance of probe **10f** at 358 nm gradually decreased and concomitantly a new rising absorption band appeared at the range of 287−341 nm with an isosbestic point at 341 nm (Figure 3).

It is important that a practical sensor can function in aqueous medium. Because compounds **10** are organic bases, and the interaction of **10** with mercury ion in aqueous solution might be influenced by the acidity of the medium. The dependence of the fluorescence changes of **10f** on the pH in the absence and presence of Hg^{2+} was examined. Titration experiments were carried out by adding standard NaOH or HNO_3 solution to an aqueous solution of **10f** (1.0×10^{-4} mol/L), or **10f** and Hg^{2+}. As indicated in Figure 4, the fluorescence signal of **10f** in the absence of mercury ion is independent of pH in the range 4.5−9.5 (Figure 4, curve a). Curves b and c show the dependence of the **10f** fluorescence response on pH to 2.0×10^{-6} and 2.0×10^{-5} mol/L mercury ion, respectively. The efficient pH range for mercury ion detection is 5.0−9.0. At a pH value below 5.0, **10f** converted to its protonated form that reduces its ligation with mercury ion. At higher pH, mercury ion may be complexed with OH^-, which in turn reduces its complexation with probe **10f**.

dx.doi.org/10.1021/jo201273p |*J. Org. Chem.* 2011, 76, 7458–7465

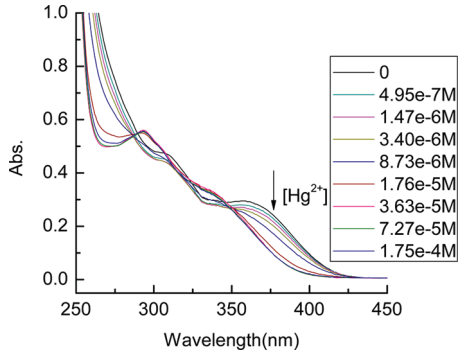


Figure 3. Changes in absorption spectra of 5×10^{-5} mol/L **10f** upon additions of different concentrations of Hg^{2+} in acetonitrile solution. The arrows indicate the signal changes as the Hg^{2+} concentrations are increased.

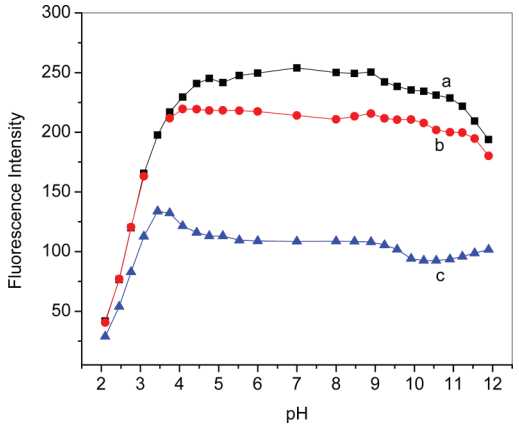


Figure 4. Fluorescence intensity−pH profiles for titrations of **10f** (2.5×10^{-5} mol/L) in 10% ethanol−water solution: (a) in the absence of Hg^{2+}, (b) in the presence of 2.0×10^{-6} mol/L Hg^{2+}, (c) in the presence of 2.0×10^{-5} mol/L Hg^{2+}. The excitation was at 351 nm, and emission was recorded at 476 nm.

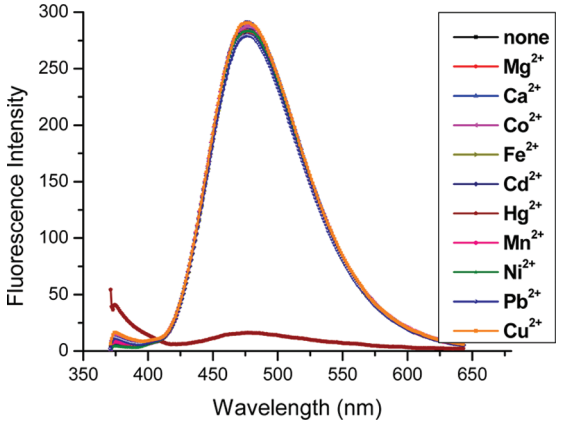


Figure 5. Changes in fluorescence emission spectra (λ_{ex} = 350 nm) of 1.0×10^{-4} mol/L **10f** in Na_2HPO_4−NaH_2PO_4 buffered aqueous solution upon additions of various divalent metal ions at 1.0×10^{-4} mol/L.

Thus, Na_2HPO_4−NaH_2PO_4 buffer was then selected as the aqueous medium for the detection of mercury ion, and the pH was set at 7.0.

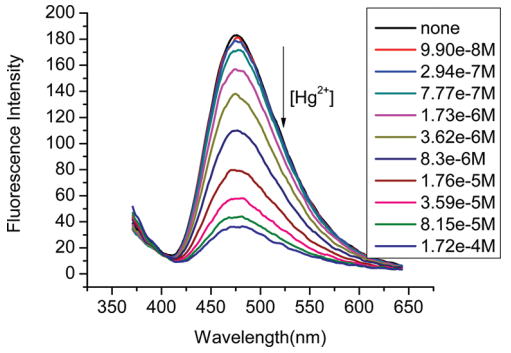


Figure 6. Changes in fluorescence emission spectra (λ_{ex} = 350 nm) of 1.0×10^{-4} mol/L **10f** upon additions of different concentrations of Hg^{2+} in Na_2HPO_4−NaH_2PO_4 buffered aqueous solution. The arrows indicate the signal changes as the Hg^{2+} concentration is increased.

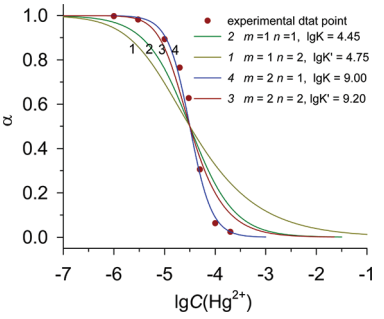


Figure 7. Response parameter value (α) is plotted as a function of the logarithm of the Hg^{2+} concentration with different stoichiometric ratios and association constants, and the experimental data (●) is fitted to them. Fluorescence intensity was recorded at 476 nm with an excitation wavelength of 351 nm in acetonitrile solution.

The spectroscopic response of **10f** to different metal ions in Na_2HPO_4−NaH_2PO_4 buffer solution is shown in Figure 5. In buffered aqueous solution, the fluorescence response of **10f** to Hg^{2+} presents excellent selectivity in comparison with other heavy metal ions. Cu^{2+}, Co^{2+}, Mg^{2+}, Ca^{2+}, Fe^{2+}, Mn^{2+}, Pb^{2+}, and Ni^{2+} could hardly induce any change in the fluorescence spectra of **10f** even at a high concentration of 1.0×10^{-4} M, while Hg^{2+} could nearly quench the fluorescence of 1.0×10^{-4} mol/L **10f** completely. The fluorescence spectra of **10f** in the presence of different concentrations of Hg^{2+} are shown in Figure 6. The addition of 9.90×10^{-8} mol/L Hg^{2+} to the buffered aqueous solution of 1.0×10^{-4} mol/L **10f** slightly induced the change of the initial signal. The fluorescence intensity decreased gradually upon addition of 2.94×10^{-7} to 1.72×10^{-4} mol/L Hg^{2+} to **10f** in buffered aqueous solution. In the concentration range from 2.94×10^{-7} mol/L to 8.30×10^{-6} mol/L, the changes in fluorescence intensity are linear in relation to the concentration of Hg^{2+}. The limit of detection defined as three times the standard deviation of the blank solution is calculated to be 1.0×10^{-7} mol/L (α = 0.99). When titrated down to the obvious change in probe fluorescence, the limit of detection for Hg^{2+} is determined to be 2.94×10^{-7} mol/L, which is comparable with common Hg^{2+} fluorescent probes.[29]

To obtain more information about the binding interaction of the probe with Hg^{2+}, we performed fluorescent titrations in acetonitrile, where the evolution of the fluorescence spectra of

dx.doi.org/10.1021/jo201273p |J. Org. Chem. 2011, 76, 7458–7465

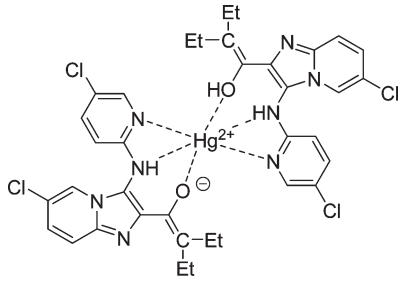


Figure 8. The proposed structure of a 2:1 complex of **10f** with Hg^{2+}.

10f was monitored as a function of the different amounts of Hg^{2+}. Supposing that the probe fluorescence quenching is the result of the formation of a probe-to-Hg^{+2} complex in the ratio of *m*:*n*, detailed examination of the fluorescence intensity changes at 476 nm as a function of Hg^{2+} concentration can determine the stoichiometry *m*:*n* and the association constant *K* using a curve fitting method.[30,31] In Figure 7, the relative fluorescence intensity value α, defined as the concentration of metal-complexed form of **10f** to the initial concentration of the ligand, is given as a function of the logarithm of Hg^{2+} concentration, lg $C(Hg^{2+})$. The experimental data points best fit the curve for a 2:1 probe–Hg^{2+} complex formation. The reasonable equilibrium constants are lg $K = 9.00$ M^2.

In addition, the mixture of **10f** (2.5×10^{-5} mol/L) and Hg^{2+} (5.0×10^{-5} mol/L) in acetonitrile showed a peak of M = 953.1249 in the ESI mass spectrum, which was assigned to [2(**10f**) + Hg^{2+} − H^+] (calcd 953.1332), corroborating the combination of the ligand with the metal ion (see Figure S3 in Supporting Information). A possible structure of **10f**–Hg^{2+} complex is shown in Figure 8. The good correlation of the measured data with the theoretical prediction confirms the validity of the proposed method. We believe that the fluorescence intensity quenching of the probes by Hg^{2+} is contributed by the proximity of the metal ion to the unpaired electrons of the nitrogen atom of the ligand and subsequently results in the intermolecular charge transfer (ICT) from the electron-rich nitrogen atom to the electron-deficient metal center.[32] The ICT affords a dramatically reduced fluorescence as a function of the Hg^{2+} concentration.

CONCLUSION

In summary, we have studied the reaction of β-lactam carbenes **2** with 2-pyridyl isonitriles **8**. Being different from the reaction of β-lactam carbenes with phenyl isonitriles that produced tricyclic δ-carbolinones in the presence of acidic catalyst,[26] the reaction of β-lactam carbenes with 2-pyridyl isonitriles followed by an acidic hydrolysis afforded bicyclic imidazo[1,2-*a*]-pyridine derivatives in moderate to good yields. The resulting novel imidazo[1,2-*a*]pyridine derivatives **10** have shown fluorescent responses to mercury ion. Among the different substituted imidazo[1,2-*a*]pyridines **10** obtained in this work, 1-(6-chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)-2-ethylbutan-1-one **10f** has the most sensitive and selective response to mercury. This work not only provided a simple and efficient one-pot reaction for the construction of multifunctional imidazo[1,2-*a*]pyridines that are not easy accessible by other approaches but also demonstrated their application.

EXPERIMENTAL SECTION

General Procedure for the Reaction of β-Lactam Carbenes with 2-Pyridyl Isonitriles. Under nitrogen atmosphere, a mixture of spiro[β-lactam-4,2′-oxadiazolines] **1** (1 mmol) and 2-pyridyl isonitriles **8** (2 mmol) in 1,4-dioxane (80 mL) was refluxed for 6–11 h. After the reaction mixture was cooled, an aqueous solution of H_2SO_4 (12 M, 0.84 mL) was added, and then the mixture was refluxed for another 9–11 h. The reaction mixture was basified to pH ∼ 8–9, and the solvents were removed under vacuum. The products **10** was isolated by chromatography on a silica gel column, eluting with a mixture of petroleum ether, ethyl acetate, and triethylamine from 20:2:1 to 10:2:1.

2-Methyl-1-(3-(pyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)propan-1-one 10a. 84%, mp 216–218 °C, IR ν (cm^{-1}) 3220, 3166, 1678, 1605, 1560; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24 (s, 1H), 8.14 (dd, J = 5.0, 1.0 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.56–7.62 (m, 2H), 7.22 (ddd, J = 9.2, 6.6, 1.2 Hz, 1H), 6.84 (ddd, J = 7.1, 5.0, 0.6 Hz, 1H), 6.74–6.78 (m, 2H), 3.90–3.97 (m, 1H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.2, 156.0, 147.5, 140.5, 137.8, 131.9, 126.2, 126.0, 124.9, 118.1, 115.1, 112.9, 109.7, 18.5; MS (EI): 237 (100), 280 (M^+, 15%). Anal. Calcd for $C_{16}H_{16}N_4O$: C 68.55, H 5.75, N 19.99; Found: C 68.44, H 5.62, N 19.82.

2-Ethyl-1-(3-(pyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)butan-1-one 10b. 71%, mp 128–130 °C, IR ν (cm^{-1}) 3231, 1668, 1604, 1558; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (br s, 1H), 8.14 (dq, J = 5.0, 1.0 Hz, 1H), 8.14 (dt, J = 7.0, 1.2 Hz, 1H), 8.14 (dt, J = 9.3, 1.0 Hz, 1H), 7.50 (ddd, J = 8.3, 7.3, 1.9 Hz, 1H), 7.14 (ddd, J = 9.2, 6.6, 1.2 Hz, 1H), 6.76 (ddd, J = 7.2, 5.0, 0.8 Hz, 1H), 6.68 (dt, J = 6.8, 1.2 Hz, 2H), 3.65–3.72 (m, 1H), 1.70–1.77 (m, 2H), 1.53–1.60 (m, 2H), 0.81 (t, J = 7.4, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.6, 154.9, 147.9, 140.9, 138.1, 131.0, 128.6, 126.1, 125.3, 119.0, 116.5, 112.1, 110.9, 49.6, 24.2, 11.6; MS (EI): 209 (100), 237 (90), 308 (M^+, 80%). Anal. Calcd for $C_{18}H_{20}N_4O$: C 70.11, H 6.54, N 18.17; Found: C 69.89, H 6.74, N 17.87.

Cyclopentyl(3-(pyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)methanone 10c. 61%, mp 169–171 °C, IR ν (cm^{-1}) 3267, 1674, 1603, 1558; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 (br s, 1H), 8.06 (dd, J = 5.0, 1.0 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.53 (d, J = 9.3 Hz, 1H), 7.49 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H), 7.14 (ddd, J = 9.2, 6.6, 1.1 Hz, 1H), 6.76 (dd, J = 7.2, 5.1 Hz, 1H), 6.66–6.70 (m, 2H), 4.01–4.09 (m, 1H), 1.93–1.98 (m, 2H), 1.78–1.83 (m, 2H), 1.59–1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.4, 154.9, 148.1, 141.0, 138.1, 130.5, 128.7, 126.1, 125.3, 118.9, 116.6, 112.1, 110.9, 47.2, 29.9, 26.3; MS (EI): 209 (80), 237 (100), 306 (M^+, 40%). Anal. Calcd for $C_{18}H_{18}N_4O$: C 70.57, H 5.92, N 18.29; Found: C 70.57, H 6.15, N 18.13.

Cyclohexyl(3-(pyridin-2-ylamino)imidazo[1,2-*a*]pyridin-2-yl)methanone 10d. 76%, mp 154–156 °C, IR ν (cm^{-1}) 3194, 3133, 1673, 1599, 1585, 1562; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24 (br s, 1H), 8.06 (dt, J = 5.0, 0.7 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.50 (ddd, J = 9.1, 7.4, 1.8 Hz, 1H), 7.14 (ddd, J = 9.2, 6.6, 1.1 Hz, 1H), 6.76 (ddd, J = 7.2, 5.1, 0.7 Hz, 1H), 6.66–6.70 (m, 2H), 3.60–3.65 (m, 1H), 1.89–1.97 (m, 2H), 1.64–1.76 (m, 3H), 1.37–1.42 (m, 4H), 1.16–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.0, 154.9, 148.0, 140.9, 138.1, 129.9, 129.0, 126.1, 125.3, 118.9, 116.5, 112.0, 110.9, 46.0, 28.8, 26.1, 25.6; HRMS (TOF-ESI): 321.1804 (M + 1), Anal. Calcd for $C_{19}H_{21}N_4O$: 321.1715 (M + 1).

1-(6-Chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]-pyridin-2-yl)-2-methylpropan-1-one 10e. 63%, mp 166–168 °C, IR ν (cm^{-1}) 3303, 1650, 1594, 1552; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (s, 1H), 8.06 (d, J = 2.2 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.50 (ddd, J = 9.7, 5.2, 2.6 Hz, 1H), 7.14 (dd, J = 9.7, 2.0 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 3.76–3.87 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.5, 153.1, 146.5, 139.2, 138.2, 130.5,

128.7, 127.3, 124.4, 123.7, 120.8, 119.2, 111.9, 36.5, 18.6; MS (EI): 305 (100), 307 (75), 348 (M^+, 55%), 350 (35). Anal. Calcd for $C_{16}H_{14}Cl_2N_4O$: C 55.03, H 4.04, N 16.04; Found: C 55.25, H 4.15, N 15.97.

1-(6-Chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]-pyridin-2-yl)-2-ethylbutan-1-one 10f. 54%, mp 119−121 °C, IR ν (cm^{-1}) 3221, 3152, 1672, 1595, 1551; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (s, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 1.1 Hz, 1H), 7.50 (ddd, J = 8.7, 6.3, 3.8 Hz, 1H), 7.13 (dd, J = 9.7, 2.0 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 3.61−3.67 (m, 1H), 1.67−1.78 (m, 2H), 1.51−1.61 (m, 2H), 0.81 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.6, 153.0, 146.5, 139.2, 138.1, 131.7, 128.5, 127.1, 124.4, 123.7, 120.7, 119.4, 111.9, 49.7, 24.2, 11.6; MS (EI): 305 (100), 307 (70), 376 (M^+, 40%), 377 (45), 378 (35), 379 (30). Anal. Calcd for $C_{18}H_{18}Cl_2N_4O$: C 57.30, H 4.81, N 14.85; Found: C 57.15, H 5.06, N 14.81.

(6-Chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]-pyridin-2-yl)(cyclopentyl)methanone 10g. 41%, mp 159−161 °C, IR ν (cm^{-1}) 3331, 1655, 1586, 1556; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.80 (dd, J = 2.4, 0.7 Hz, 1H), 7.54 (ddd, J = 9.6, 5.5, 0.6 Hz, 1H), 7.17 (dd, J = 9.7, 2.0 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 4.02−4.10 (m, 1H), 1.97−2.05 (m, 2H), 1.80−1.88 (m, 2H), 1.70−1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.3, 153.0, 146.5, 139.3, 138.1, 131.2, 128.5, 127.2, 124.4, 123.7, 120.8, 119.3, 111.9, 47.3, 29.8, 26.3; MS (EI): 112 (100), 278 (65), 306 (60), 374 (M^+, 55%), 376 (50). Anal. Calcd for $C_{18}H_{16}Cl_2N_4O$: C 57.61, H 4.30, N 14.93; Found: C 57.66, H 4.55, N 14.91.

(6-Chloro-3-(5-chloropyridin-2-ylamino)imidazo[1,2-*a*]-pyridin-2-yl)(cyclohexyl)methanone 10h. 46%, mp 171−173 °C, IR ν (cm^{-1}) 3348, 3312, 1649, 1586, 1554; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (s, 1H), 8.02 (d, J = 2.5 Hz, 1H), 7.74 (dd, J = 2.0, 0.8 Hz, 1H), 7.50 (ddd, J = 9.7, 3.6, 0.9 Hz, 2H), 7.11 (dd, J = 9.7, 2.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 3.55−3.62 (m, 1H), 1.90−1.95 (m, 2H), 1.61−1.76 (m, 3H), 1.41−1.45 (m, 4H), 1.32−1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.0, 153.0, 146.5, 139.2, 138.1, 130.7, 128.8, 127.1, 124.4, 123.8, 120.7, 119.3, 111.9, 46.1, 28.8, 26.0, 25.6; MS (EI): 141 (100), 261 (70), 276 (90), 305 (90), 388 (M^+, 75%), 390 (65). Anal. Calcd for $C_{19}H_{18}Cl_2N_4O$: C 58.62, H 4.66, N 14.39; Found: C 58.46, H 5.04, N 14.27.

2-Methyl-1-(5-methyl-3-(6-methylpyridin-2-ylamino)imidazo-[1,2-*a*]pyridin-2-yl)propan-1-one 10i. 66%, mp 170−172 °C, IR ν (cm^{-1}) 3178, 1689, 1590, 1567; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (d, J = 9.1 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.20 (br s, 1H), 7.14 (dd, J = 9.1, 6.8 Hz, 1H), 6.63 (d, J = 7.4 Hz, 1H), 6.51 (dd, J = 6.8, 0.9 Hz, 1H), 6.03 (d, J = 8.2 Hz, 1H), 3.85−3.96 (m, 1H), 2.68 (s, 3H), 2.35 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.3, 158.3, 157.3, 143.1, 138.3, 137.4, 134.2, 127.6, 126.2, 117.0, 115.5, 114.5, 105.3, 36.4, 24.1, 18.8, 18.6; MS (EI): 92 (100), 237 (65), 265 (45), 308 (M^+, 60%). Anal. Calcd for $C_{18}H_{20}N_4O$: C 70.11, H 6.54, N 18.17; Found: C 69.94, H 6.93, N 17.92.

2-Ethyl-1-(5-methyl-3-(6-methylpyridin-2-ylamino)imidazo-[1,2-*a*]pyridin-2-yl)butan-1-one 10j. 62%, mp 143−145 °C, IR ν (cm^{-1}) 3273, 1673, 1597, 1579, 1560; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (d, J = 9.1 Hz, 1H), 7.21(t, J = 7.8 Hz, 1H), 7.04 (br s, 1H), 7.02 (dd, J = 9.2, 6.8 Hz, 1H), 6.51 (d, J = 7.4 Hz, 1H), 6.39 (d, J = 6.8 Hz, 1H), 5.89 (d, J = 8.1 Hz, 1H), 3.58−3.65 (m, 1H), 2.56 (s, 3H), 2.24 (s, 3H), 1.57−1.68 (m, 2H), 1.40−1.50 (m, 2H), 0.70 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.3, 158.4, 157.4, 143.0, 138.2, 137.3, 135.5, 127.4, 126.1, 117.1, 115.4, 114.5, 105.1, 49.7, 24.14, 24.06, 18.9, 11.5; MS (EI): 237 (55), 336 (M^+, 100%), 337 (M + 1, 75). Anal. Calcd for $C_{20}H_{24}N_4O$: C 71.40, H 7.19, N 16.65; Found: C 71.42, H 7.05, N 16.47.

Cyclopentyl(5-methyl-3-(6-methylpyridin-2-ylamino)imidazo-[1,2-*a*]pyridin-2-yl)methanone 10k. 58%, mp 169−171 °C, IR ν (cm^{-1}) 3179, 1685, 1590, 1559; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43 (d, J = 9.1 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.15 (s, 1H), 7.06 (dd, J = 9.2, 6.8 Hz, 1H), 6.55 (d, J = 7.4 Hz, 1H), 6.44 (d, J = 6.8 Hz, 1H), 5.95 (d, J = 8.2 Hz, 1H), 3.97−4.06 (m, 1H), 2.60 (s, 3H), 2.26 (s, 3H), 1.85−1.93 (m, 2H), 1.70−1.76 (m, 2H), 1.55−1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.0, 158.4, 157.5, 143.1, 138.2, 137.4, 134.8, 127.5, 126.1, 117.0, 115.5, 114.5, 105.2, 47.5, 29.7, 26.3, 24.2, 18.9; MS (EI): 119 (90), 183 (87), 198 (95), 226 (100), 236 (95), 265 (85), 334 (M^+, 84%). Anal. Calcd for $C_{20}H_{22}N_4O$: C 71.83, H 6.63, N 16.75; Found: C 71.57, H 7.01, N 16.71.

Cyclohexyl(5-methyl-3-(6-methylpyridin-2-ylamino)imidazo-[1,2-*a*]pyridin-2-yl)methanone 10l. 63%, mp 165−167 °C, IR ν (cm^{-1}) 3233, 3156, 1668, 1604, 1558; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49 (d, J = 9.1 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.25 (s, 1H), 7.12 (dd, J = 9.2, 6.8 Hz, 1H), 6.61 (d, J = 7.4 Hz, 1H), 6.50 (dd, J = 6.7, 1.8 Hz, 1H), 5.99 (d, J = 8.1 Hz, 1H), 3.63−3.69 (m, 1H), 2.67 (s, 3H), 2.32 (s, 3H), 1.91−1.93 (m, 2H), 1.67−1.78 (m, 3H), 1.33−1.48 (m, 4H), 1.14−1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.7, 158.4, 157.5, 143.0, 138.2, 137.3, 134.5, 127.7, 126.1, 117.0, 115.4, 114.5, 105.2, 46.3, 28.7, 26.0, 25.6, 24.2, 18.9; MS (EI): 237 (70), 241 (80), 348 (M^+, 100%). Anal. Calcd for $C_{21}H_{24}N_4O$: C 72.39, H 6.94, N 16.08; Found: C 72.08, H 7.12, N 15.95.

3,3-Diethyl-4-(5-methyl-3-(6-methylpyridin-2-ylimino)-imidazo[1,2-*a*]pyridin-2(3*H*)-ylidene)-1-phenylazetidin-2-one 9j. 88%, mp 196−198 °C, IR ν (cm^{-1}) 1746, 1633, 1593, 1519, 1496; ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 7.45 (d, J = 6.6 Hz, 2H), 7.14 (t, J = 7.7 Hz, 2H), 6.99 (d, J = 9.0 Hz, 1H), 6.92 (tt, J = 7.4, 1.0 Hz, 1H), 6.86 (dd, J = 9.1, 6.8 Hz, 1H), 6.81 (dd, J = 9.1, 6.4 Hz, 1H), 6.62 (dd, J = 9.1, 1.0 Hz, 1H), 6.41 (dt, J = 6.8, 1.0 Hz, 1H), 5.98 (dd, J = 6.4, 0.6 Hz, 1H), 2.88 (s, 3H), 2.32 (s, 3H), 1.69−1.75 (m, 2H), 1.40−1.46 (m, 1H), 1.32−1.37 (m, 1H), 0.72 (t, J = 7.4 Hz, 3H), 0.43 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm) 171.1, 151.4, 144.4, 144.1, 140.1, 137.9, 133.8, 132.6, 129.8, 126.0, 124.9, 124.4, 121.7, 119.3, 116.3, 114.6, 112.7, 88.0, 76.0, 24.8, 21.6, 19.5, 8.7, 8.0; MS (EI): 92 (100), 339 (50), 394 (60), 437 (M^+, 55%). Anal. Calcd for $C_{27}H_{27}N_5O$: C 74.12, H 6.22, N 16.01; Found: C 73.78, H 6.39, N 15.95.

■ ASSOCIATED CONTENT

Supporting Information. General procedure for the preparation of spiro[β-lactam-4,2′-oxadiazolines] **1**, spectroscopic parameters (maximum absorption wavelength, maximum emission and excitation wavelength) and quantum yields of compounds **10**, mass spectra of 2:1 complex of **10f** with Hg^{2+}, the method for Hg^{2+} detection, copies of ^{1}H NMR and ^{13}C NMR spectra of products **10** and **9j**, as well as single crystal data of **10a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ycheng2@bnu.edu.cn. Fax: +86-10-58805558.

■ ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (nos. 20832006 and 20972017 for Y.C., and no. 20905008 for N.S.), Beijing Municipal Commission of Education, and the Fundamental Research Funds for the Central Universities (2009SC-1).

■ REFERENCES

(1) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888–899.

(2) (a) Bode, C.; Boezio, A.; Cheng, A. C.; Choquette, D.; Coats, J. R.; Copeland, K. W.; Huang, H.; La, D.; Lewis, R.; Liao, H.; Potashman, M.; Stellwagen, J.; Yi, S.; Norman, M.; Stec, M.; Peterson, E. A.; Graceffa, R. Int. Pat. WO 2010132598, 2010; *Chem. Abstr.* **2010**, *153*, 643531. (b) Saxty, G.; Berdini, V.; Freyne, E. J. E.; Papanikos, A.; Benderitter, P.; Embrechts, W. C. J.; Wroblowski, B.; Akkari, R. Int. Pat. WO 2010119284, 2010; *Chem. Abstr.* **2010**, *153*, 530561. (c) Saxty, G.; Berdini, V.; Murray, C. W.; Freyne, E. J. E.; Ligny, Y. A. E.; Bonnet, P. G. A.; Wroblowski, B.; Papanikos, A. Int. Pat. WO 2010119285, **2010**; *Chem. Abstr.* **2010**, *153*, 555185. (d) Kendall, J. D.; Giddens, A. C.; Tsang, K. Y. Int. Pat. WO 2010074586, 2010; *Chem. Abstr.* **2010**, *153*, 145492. (e) Jaramillo, C.; De Diego, J. E.; Hamdouchi, C.; Collins, E.; Keyser, H.; Sanchez-Martinez, C.; Del Prado, M.; Norman, B.; Brooks, H. B.; Watkins, S. A.; Spencer, C. D.; Dempsey, J. A.; Anderson, B. D.; Campbell, R. M.; Leggett, T.; Patel, B.; Schultz, R. M.; Espinosa, J.; Vieth, M.; Zhang, F.; Timm, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6095–6099.

(3) Lee, K. C. L.; Sun, E. T. Int. Pat. WO 2006101455, 2006; *Chem. Abstr.*, 2006, *145*, 377338.

(4) Boppana, S.; Ahmed, F.; Chandra, N. S.J. N.; Rangappa, K. S.; Urooj, A. *J. Pharm. Res.* **2010**, *3*, 645–649.

(5) Qiao, L.; Glicksman, M.; Gainer, T.; Lo, D. C.; Stein, R. L.; Choi, S.; Cuny, G. D. Int. Pat. WO 2010117787, 2010; *Chem. Abstr.* **2010**, *153*, 522303.

(6) McKenna, C. E.; Kashemirov, B. A.; Blazewska, K. M.; Mallard-Favier, I.; Stewart, C. A.; Rojas, J.; Lundy, M. W.; Ebetino, F. H.; Baron, R. A.; Dunford, J. E.; Kirsten, M. L.; Seabra, M. C.; Bala, J. L.; Marma, M. S.; Rogers, M. J.; Coxon, F. P. *J. Med. Chem.* **2010**, *53*, 3454–3464.

(7) Lopez-Martinez, M.; Salgado-Zamora, H.; Ramirez, S.-J., E.; Zamudio, S.; Picazo, O.; Campos, M. E.; Naranjo-Rodriguez, E. B. *Drug Dev. Res.* **2010**, *71*, 371–381.

(8) Baskaran, S.; Maung, J.; Neitzel, M. L.; Rai, R.; Slododov, I.; Tai, V. W.-F. U.S. Pat. 20100204265, 2010; *Chem. Abstr.* **2010**, *153*, 286997.

(9) Starr, J. T.; Sciotti, R. J.; Hanna, D. L.; Huband, M. D.; Mullins, L. M.; Cai, H.; Gage, J. W.; Lockard, M.; Rauckhorst, M. R.; Owen, R. M.; Lall, M. S.; Tomilo, M.; Chen, H.; McCurdy, S. P.; Barbachyn, M. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5302–5306.

(10) Lacerda, R. B.; de Lima, C. K. F.; da Silva, L. L.; Romeiro, N. C.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Med. Chem. Lett.* **2009**, *17*, 74–84.

(11) (a) Gueiffier, A.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J.-C.; Kerbal, A.; Essassi, M. E.; Debouzy, J.-C.; Witvrouw, M.; Blache, Y.; Balzarini, J.; Clercq, D. E.; Chapat, J.-P. *J. Med. Chem.* **1996**, *39*, 2856–2859. (b) Gueiffier, A.; Mavel, S.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J.-C.; Witvrouw, M.; Balzarini, J.; Clercq, E. D.; Chapat, J.-P. *J. Med. Chem.* **1998**, *41*, 5108–5112.

(12) Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H. *Cardiovasc. Drug Rev.* **2002**, *20*, 163–174.

(13) Mereu, G.; Carcangiu, G.; Concas, A.; Passino, N.; Biggio, G. *Eur. J. Pharmacol.* **1990**, *179*, 339–345.

(14) (a) Mutai, T.; Tomoda, H.; Ohkawa, T.; Yabe, Y.; Araki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9522–9524. (b) Tomoda, H.; Hirano, T.; Saito, S.; Mutai, T.; Araki, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1327–1334. (c) Knoelker, H. J.; Boese, R.; Hitzemann, R. *Chem. Ber.* **1990**, *123*, 327–39. (d) Rackham, D. M. *Appl. Spectrosc.* **1979**, *33*, 561–563. (e) Tanaka, K.; Takeyama, T.; Yukawa, R.; Iwata, S.; Kurushima, T. *Supramol. Chem.* **2010**, *22*, 186–193. (f) Niziol, J.; Baran, W.; Gondek, E.; Kityk, I. V.; Mendys, A.; Zylewski, M.; Reshak, A. H. *Chem. Eng. Commun.* **2009**, *196*, 1466–1474.

(15) Leopoldo, M.; Lacivita, E.; Passafiume, E.; Contino, M.; Colabufo, N. A.; Berardi, F.; Perrone, R. *J. Med. Chem.* **2007**, *50*, 5043–5047.

(16) Laquintana, V.; Denora, N.; Lopedota, A.; Suzuki, H.; Sawada, M.; Serra, M.; Biggio, G.; Latrofa, A.; Trapani, G.; Liso, G. *Bioconjugate Chem.* **2007**, *18*, 1397–1407.

(17) (a) Chezal, J.-M.; Paeshuyse, J.; Gaumet, V.; Canitrot, D.; Maisonial, A.; Lartigue, C.; Gueiffier, A.; Moreau, E.; Teulade, J.-C.; Chavignon, O.; Neyts, J. *Eur. J. Med. Chem.* **2010**, *45*, 2044–2047. (b) Zhu, D.-J.; Chen, J.-X.; Liu, M.-C.; Ding, J.-C.; Wu, H.-Y. *J. Braz. Chem. Soc.* **2009**, *20*, 482–487.

(18) (a) Starr, J. T.; Sciotti, R. J.; Hanna, D. L.; Huband, M. D.; Mullins, L. M.; Cai, H.; Gage, J. W.; Lockard, M.; Rauckhorst, M. R.; Owen, R. M.; Lall, M. S.; Tomilo, M.; Chen, H.; McCurdy, S. P.; Barbachyn, M. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5302–5306. (b) Rees, C. W.; Smith, D. I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1159–1163. (c) Lombardino, J. G. *J. Org. Chem.* **1965**, *30*, 2403–2407.

(19) Collins, M. R.; Huang, Q.; Ornelas, M. A.; Scales, S. A. *Tetrahedron Lett.* **2010**, *51*, 3528–3530.

(20) (a) Guchhait, S. K.; Madaan, C. *Org. Biomol. Chem.* **2010**, *8*, 3631–3634. (b) Pirrung, M. C.; Ghorai, S.; Ibarra-Rivera, T. R. *J. Org. Chem.* **2009**, *74*, 4110–4117.

(21) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743–2746.

(22) See examples: (a) Mjalli, A. M. M.; Hari, A.; Gaddam, B.; Gohimukkula, D. R.; Polisetti, D. R.; El Abdellaoui, H.; Rao, M.; Andrews, R. C.; Xie, R.; Ren, T. Int. Pat. WO 2010126745, 2010; *Chem. Abstr.*, 2010, *153*, 600782. (b) Allen, S.; Marmsater, F. P.; Robinson, J. E.; Schlachter, S. T.; Lyssikatos, J. P. Int. Pat. WO 2010039825, 2010; *Chem. Abstr.*, **2010**, *152*, 429711. (c) Katsifis, A.; Fookes, C. J. R.; Pham, T. Q.; Greguric, I. D.; Mattner, M. F. P. S. Int. Pat. WO 2008022396, 2008; *Chem. Abstr.*, **2008**, *148*, 308345.

(23) Zoghbi, M.; Warkentin, J. *J. Org. Chem.* **1991**, *56*, 3214. (b) Zoghbi, M.; Warkentin, J. *Can. J. Chem.* **1993**, *71*, 912.

(24) (a) Zoghbi, M.; Warkentin, J. *Can. J. Chem.* **1992**, *70*, 2967. (b) Zoghbi, M.; Horne, S. E.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 4090.

(25) Cheng, Y.; Wang, B.; Cheng, L.-Q. *J. Org. Chem.* **2006**, *71*, 4418–4427.

(26) Cheng, Y.; Cheng, L.-Q. *J. Org. Chem.* **2007**, *72*, 2625–2630.

(27) Xing, J.; Wang, X.-R.; Yan, C.-X.; Cheng, Y. *J. Org. Chem.* **2011**, *76*, 4746–4752.

(28) Shao, N.; Pang, G.-X.; Wang, X.-R.; Wu, R.-J.; Cheng, Y. *Tetrahedron* **2010**, *66*, 7302–7308.

(29) (a) Lippard, S. J.; Nolan, E. M. *J. Am. Chem. Soc.* **2007**, *129*, 5910–5918. (b) Varma, R. L.; Praveen, L.; Ganga, V. B.; Thirumalai, R.; Sreeja, T.; Reddy, M. L. P. *Inorg. Chem.* **2007**, *46*, 6277–6282. (c) Yang, R. H.; Wang, H.; Wang, Y. X.; Jin, J. Y. *Anal. Chem.* **2008**, *80*, 9021–9028.

(30) Yang, R. H.; Li, K. A.; Wang, K. M.; Zhao, F. L.; Li, N.; Liu, F. *Anal. Chem.* **2003**, *75*, 612–621.

(31) Yang, R. H.; Chan, W. H.; Lee, A. W. M.; Xia, P. F.; Zhang, H. K.; Li, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 2884–2885.

(32) Shunmugam, R.; Gabriel, G. J.; Smith, C. E.; Aamer, K. A.; Tew, G. N. *Chem.—Eur. J.* **2008**, *14*, 3904–3907.