OL | Organic Letters

pubs.acs.org/OrgLett Letter

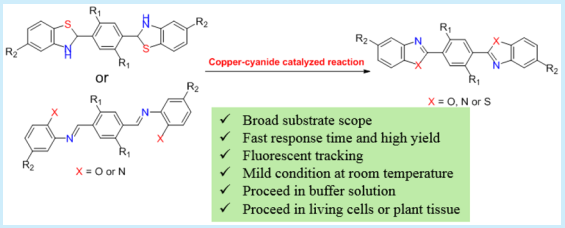
Cyanide Boosting Copper Catalysis: A Mild Approach to Fluorescent Benzazole Derivatives from Nonemissive Schiff Bases in Biological Media

Dejia Wang, Hongjuan Li, Shiguo Sun, and Yongqian Xu*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00784 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An application of nucleophilic cyclization and oxidation of nonemissive Schiff bases via cyanide boosting copper catalysis to synthesize fluorescent benzazole derivatives in high conversion yield is disclosed. This approach is highlighted by broad substrate scope, fast reaction time, and mild conditions and can efficiently proceed in living cells or *Arabidopsis* root tissues. Furthermore, this methodology can be applied for selective detection of Cu^{2+} and CN^-.



Benzazoles that include benzoxazoles, benzothiazoles, and benzimidazoles, based on five-membered compounds with a N, O, and S combined heteroatom, act as a valuable class of functional compounds, which have attracted increasing attention in natural products, pharmaceutical agents, inhibitor drugs, and material science fields such as bioimaging, organic light-emitting diodes (OLEDs), organic solid lasers, fluorescent sensors, information storage, etc.[1−3] 2-(2′-Hydroxy)-benzyl-substituted benzazole derivatives can produce keto tautomer species through the excited state intramolecular proton transfer (ESIPT) process upon excitation, affording dual emission bands with a large Stokes shift. In addition, benzazole derivatives have good photostability and high fluorescence efficiency. Due to the excellent photochemical property, these derivatives have been widely used as a functional optical material and ratiometric fluorescent sensors.[4−6] Although tremendous progress in benzazole synthesis has been achieved, most of them require harsh reaction conditions such as strong acid, high temperature (reflux or more than 80 °C), reaction in organic solvent, and complex catalysts.[2,7,8] The development of convenient, mild, and efficient methods for the synthesis of benzazoles is needed. Importantly, the benzazole-based molecular architecture is found in a variety of natural products,[9,10] so it is very helpful to explore the synthesis methods of benzazoles in the biological environment for studying and understanding the formation of benzoxazole biomolecules in vivo.

Copper catalysis is an effective means to achieve various products.[11] Benzazole syntheses via copper catalysis reactions have been documented.[8b−e] However, these reactions exclusively require high temperature (more than 100 °C) and organic solvents probably due to the weak catalysis capability of copper. Thus, an optimized copper catalyst is in great need.

Cu-cyanide complexes are intensively used in industries such as mining, electroplating, and surface finishing due to the unique properties of cyanide complexing copper.[12] As a result, wastewater coming from these places usually contains large amounts of Cu-cyanide complexes, which are toxic and harmful to living organisms.[13] Therefore, it is essential to selectively detect Cu-cyanide complexes. Fluorescent methods coupled with imaging techniques have been used to detect various ions or molecules in complex media because of their outstanding advantages of high sensitivity, good selectivity, and fine spatiotemporal resolution.[14] A large number of fluorescent sensors have been designed for selective detection of copper cations (Cu^{2+}/Cu^{+}) or cyanide anions.[15−17] Among them, "ON−OFF−ON" sequential detection of Cu^{2+} and CN^- based on the formation of $Cu(CN)_n^{2-n}$ has been reported by one fluorescent molecule.[18] However, there is no single fluorophore, to the best of our knowledge, that has been designed for detection of Cu-cyanide (in the presence of Cu^{2+} and CN^-).

Reaction-based detection taking advantage of the chemical reaction to transform nonemissive precursors to fluorescent products is an appealing and efficient design strategy to turn-on detect the metal ions, e.g., copper ions, which are easy to quench fluorescence due to paramagnetic properties, which affords a high signal-to-noise ratio.[19] In this context, an oxidative cyclization reaction-based method for the detection of Cu-cyanide was conducted, in which Cu^{2+} and CN^- catalytically transform nonemissive Schiff bases into highly fluorescent benzazoles. A cyanide boosting copper oxidation

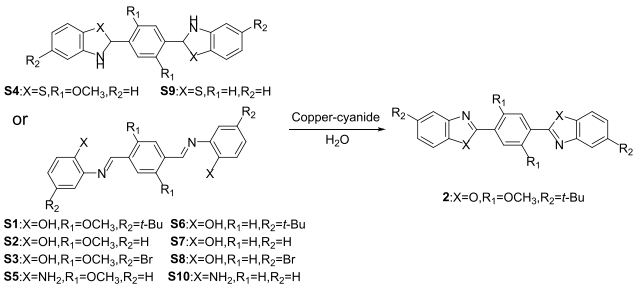
Received: March 1, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00784
Org. Lett. XXXX, XXX, XXX−XXX

catalyst was found. The application range of this kind of reaction can be extended to the synthesis of diverse benzoxazoles, benzothiazoles, and benzimidazole derivatives. Moreover, the de novo reaction can take place in water, and even in living cells and living plant tissue. The fluorescence characteristics of the products provide a convenient way to track the catalytic reaction process without the need for a separation process to determine the conversion rate.

Schiff base compounds **S1**−**S10** (**S4** and **S9** are the spontaneously cyclized intermediates of the Schiff base) (Scheme 1) were obtained through the condensation of

Scheme 1. Molecular Structures of Schiff Bases, Cyclized Intermediates of the Schiff Base, and the Corresponding Benzazole Products



corresponding aldehydes and amines in absolute methanol. The detailed synthesis progress is described in the Supporting Information. In CH_3CN/PBS (v/v = 2:1, 10 mM, pH 7.4) mixed solution, these Schiff base compounds and cyclized intermediates (**S4** and **S9**) show nearly no fluorescence. The fluorescence of these solutions remained unchanged as 20 equiv of cyanide or Cu^{2+} was added alone. In sharp contrast, remarkable fluorescence was observed as the solution was treated with 20 equiv of cyanide and Cu^{2+} (Figure 1). The

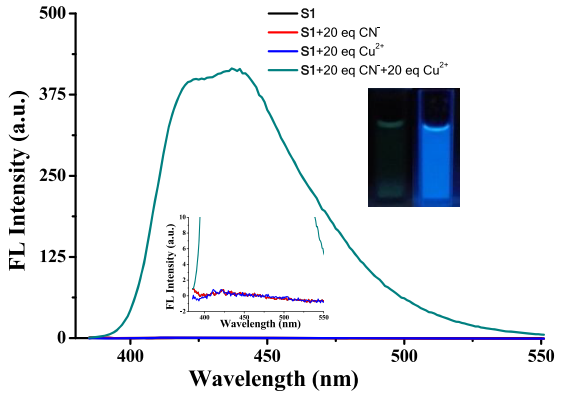


Figure 1. Fluorescence spectra change of **S1** with CN^- and Cu^{2+} in CH_3CN/PBS (v/v = 2:1, 10 mM, pH 7.4) mixtures, λ_{ex} = 375 nm. Inset: photograph of **S1** solution before and after addition of copper-cyanide complex upon excitation at 365 nm.

fluorescence increased and reached saturation within a short time. Compounds **S1** and **S4** have a fast response time of about 5 min, and compounds **S2**, **S3**, **S7**, **S6**, **S8**, and **S9** need 10 min, while compounds **S5** and **S10** require a little longer time (20−50 min). These results implied that the copper-cyanide complex probably catalyzed Schiff bases or cyclized intermediates (**S4** and **S9**) to quickly transform to new compound that are strongly fluorescent.

To verify whether the fluorescent products are benzazoles, we took **S1** as a model sample and synthesized the corresponding benzazole product **2** using the conventional method by condensation of 2,5-dimethoxyterephthalaldehyde with 2-amino-4-(*tert*-butyl)phenol in toluene and subsequent oxidation by 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) in CH_2Cl_2.[20] The product of **S1** treated with the copper-cyanide complex has the same fluorescence spectrum as **2** (Figure S1). In addition, we checked the product by MS spectrum and high-performance liquid chromatography (HPLC). The $[M + 1]^+$ peak (485.28) of the **S1** solution with the copper-cyanide complex corresponds to $[2 + 1]^+$ of 485.24. The retention time of **S1** treated with the copper-cyanide complex is the same as that of **2** in the identical condition of HPLC (Figure S2). It is clear that nonemissive Schiff bases were transformed to fluorescent benzazole derivatives after reaction with the copper-cyanide complex.

The underlying reaction mechanism should involve the following three steps: (1) As a strong nucleophile agent, cyanide ions first attack the carbon nitrogen double bond of the Schiff base to form intermediate **1** (Figure 2).[20] (2) **1**

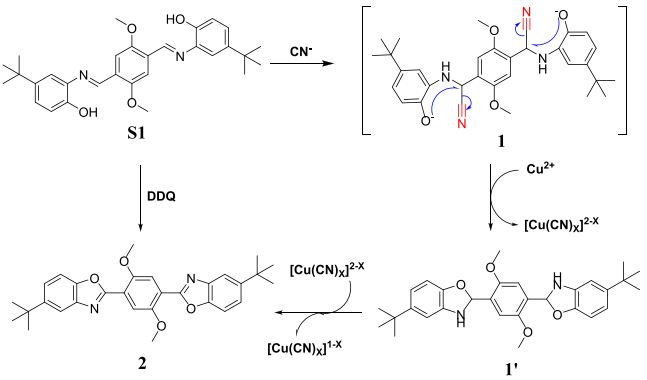


Figure 2. Presumed mechanism that **S1** was catalyzed to form benzazole in the presence of CN^- and Cu^{2+} detection.

spontaneously cyclizes to produce **1′**. (3) **1′** was oxidized to the corresponding benzoxazole derivative in the presence of the copper-cyanide complex and concurrently released $[Cu(CN)_x]^{1-x}$. The first step reaction can be proven through the NMR titration spectra of **S1** upon addition of cyanide. As shown in Figure S3, when a low concentration of cyanide ions is added, the characteristic peak of the Schiff base at about 8.95 ppm disappears. With increasing the concentration of the cyanide ion, new signal peaks at 7.5 and 6.5 ppm occurred, which are assigned to —N*H*— and —C*H*— that derived from the C═N bond, respectively.[21] These results indicated that cyanide ions attack the C═N bond of the Schiff base to induce the addition reaction.

We found that cyclized compounds from **S4** and **S9** (Table S1) cannot be oxidized to corresponding benzothiazole derivatives by copper ions alone, although copper ions are known as good oxidants. The results show that CN^- is indispensable in the third step and probably improves the oxidation capacity of copper in the oxidation process. The redox product Cu^+ in the system can be easily detected by the Cu^+ fluorescent sensor (Figure S4). In addition, the existence of Cu^+ ions in the products of **S1** (1 μM) with 20 equiv of CN^- ions and 20 equiv of Cu^{2+} was proven by XPS spectra of Cu 2p. As shown in Figure S5, the characteristic peaks of

https://dx.doi.org/10.1021/acs.orglett.0c00784
Org. Lett. XXXX, XXX, XXX−XXX

binding energies at 933.1 and 955.0 eV were assigned to Cu $2p_{3/2}$ and Cu $2p_{1/2}$ of Cu^+, respectively.[22,23]

The excitation wavelength and maximum emission wavelength of products, the interaction time, the conversion yield through the HPLC technique, and the fluorescence intensity enhancement of the maximum emission wavelength of **S1**−**S10** after treatment with the copper-cyanide complex are shown in Table S2. Compared with **S6**−**S10**, **S1**−**S5** substituted with *p*-methoxy produce products with a larger Stokes shift. The reason may be that the conjugation of methoxy and the benzene ring increases the π electron cloud density and emission wavelength. In addition, **S1** and **S6** substituted with *tert*-butyl show high conversion efficiency (more than 90%) and fast response time (10 min). The electron-donating property of the *t*-butyl group not only improves the nucleophilic addition cyclization ability of phenolic hydroxyl groups but also facilitates subsequent oxidation. In contrast, the conversion efficiency would be lower as the electron-withdrawing group, e.g., bromine, was introduced, which can easily be found from **S2** and **S7** compounds. Moreover, their fluorescence intensity enhancement is small (less than 30-fold) because of the heavy atom quenching effect of bromine. Compared with **S2**, **S4**, and **S5** which finally form benzoxazole, benzothiazole, and benzimidazole, respectively, the conversion yield to produce benzoxazole is low (about 30%) due to its weak nucleophilic capability of the phenolic hydroxyl group. These experimental results further corroborate the mechanism of cyclization and oxidation.

Considering the high conversion efficiency, fast response time, and large fluorescence intensity enhancement (400-fold) of **S1**, we take **S1** as the model molecule to study fluorescent detection of the copper-cyanide complex. In the CH_3CN/PBS (v/v = 2:1, 10 mM, pH 7.4) buffer system containing 20 equiv of CN^-, **S1** is nonfluorescent upon excitation at 375 nm. As Cu^{2+} was added, the fluorescence intensity at 439 nm gradually increased. After adding 8 equiv of copper ions, a 400-fold fluorescence enhancement was found. The fluorescence intensity showed a good linear relationship to the concentration of Cu^{2+} in the range 1−6 μM (Figure S7), and the detection limit for Cu^{2+} is 1.53 nM. The selective and competitive experiments of other cations for the detection of copper ions were performed. As shown in Figure S8, the fluorescence intensity at 439 nm increased after addition of Cu^{2+}, while no fluorescence was observed as other cations were added. The fluorescence intensity increased significantly upon addition of 5 equiv of Cu^{2+} in the presence of 10 equiv of competitive cations. These results indicate that **S1** in the presence of CN^- can act as a fluorescent sensor to selectively detect Cu^{2+} without any interference from other analytes.

In the presence of 8 equiv of Cu^{2+}, the fluorescence of **S1** solution gradually increased as 1−30 equiv of CN^- was added. There is an obvious linear relationship between fluorescence intensity and CN^- concentration (Figure S10), demonstrating that **S1** can quantitatively detect cyanide ions. As shown in Figure 3, **S1** coupled with Cu^{2+} can selectively detect CN^- over other competitive anions. The effect of biological glutathione (GSH) on the reaction was checked, as shown in Figure S11; the reaction can proceed in the presence of a low concentration of GSH, but the conversion yield is inferior to that in the absence of GSH, suggesting the existing of GSH interference. It is presumed that the more Cu(I) produced by GSH would decrease the oxidation capability of the cyanide-copper complex. The effect can be screened to some extent by subsequent addition of biological reductant ascorbic acid or H_2O_2 that can transfer Cu(I) to Cu(II), despite the fact that the condition still needed to be optimized.

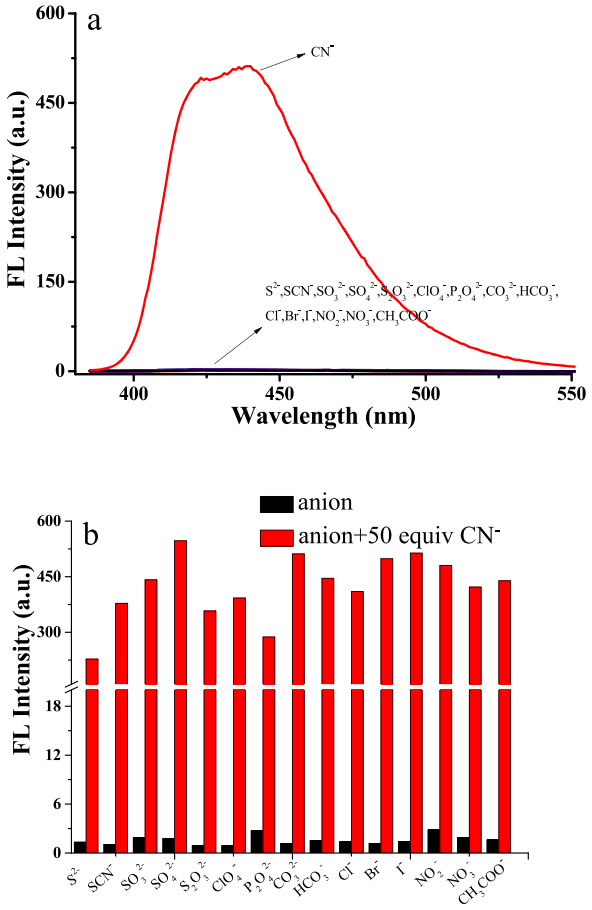


Figure 3. (a) Fluorescence spectra of **S1** (1 μM) in CH_3CN/PBS buffer (v/v = 2:1, 10 mM, pH 7.4) mixtures containing 8 equiv of Cu^{2+} upon addition of CN^- and other anions. (b) Fluorescence intensity value of **S1** upon addition of 50 equiv of various anions (black bars). Red bars represent the changes after the subsequent addition of 50 equiv of CN^-.

In order to further study the possibility of the synthesis of benzazoles from Schiff bases and the detection of the copper-cyanide complex in a biological environment, we carried out fluorescence imaging experiments in HepG2 cells. HepG2 cells were first incubated with compound **S1** (1 μM) in the culture media at 37 °C for 30 min. As shown in Figure 4, the cells showed no obvious fluorescence signal. The control groups were further incubated with 20 μM CN^- or 20 μM Cu^{2+} alone for 30 min. It was found that these cells had no fluorescence intensity change. In sharp contrast, strong blue fluorescence in the cells was observed as these cells were treated with the copper-cyanide complex for 20 min. The results showed that compound **S1** had good cell membrane permeability and could in situ form fluorescent benzazoles for detection of CN^- and Cu^{2+} in living cells. It should be noted that this copper-cyanide catalyzed reaction can proceed even in the presence of biological GSH probably due to the fact that there is a complex redox balance in the biological system. We further performed colocalization experiments using commercial mitochondrial tracker Rhodamine 123, endoplasmic reticulum ER-tracker red, and lysotracker green DND-26, respectively (Figure S12).

https://dx.doi.org/10.1021/acs.orglett.0c00784
Org. Lett. XXXX, XXX, XXX−XXX

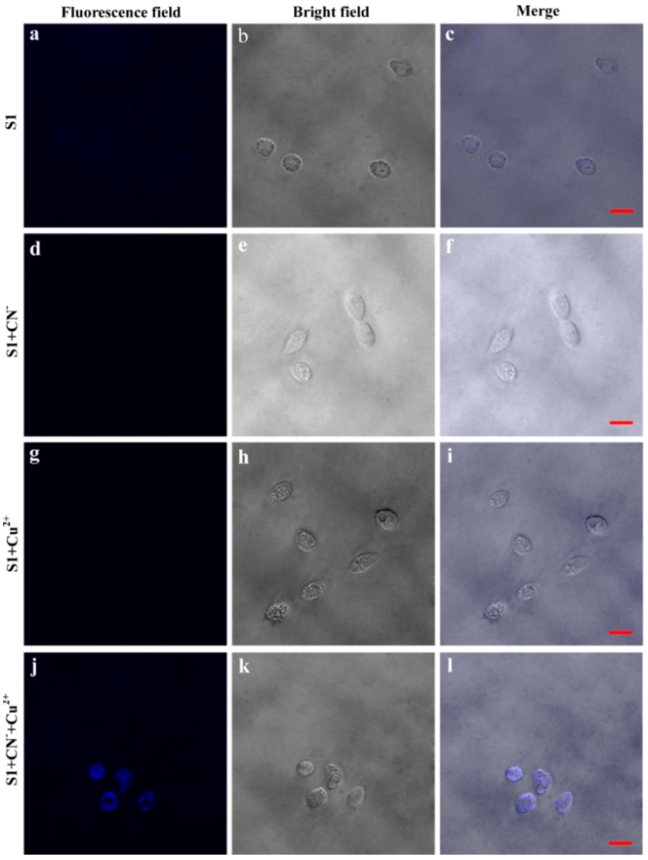


Figure 4. Confocal fluorescence images of liver cancer cells (HepG2 cells). (a–c) Images of HepG2 cells incubated with **S1** (1 μM) for 30 min. (d–f) Images of HepG2 cells pretreated with **S1** for 30 min and subsequent treatment with CN^- (20 μM) for 30 min. (g–i) Images of HepG2 cells pretreated with **S1** for 30 min and subsequent treatment with Cu^{2+} (20 μM) for 30 min. (j–l) Images of HepG2 cells pretreated with **S1** (1 μM) for 20 min and subsequent treatment with CN^- (20 μM) for 20 min, followed by treatment with Cu^{2+} (20 μM). λ_{ex} = 405 nm. Scale bar: 20 μm.

The overlap coefficients were calculated by image-J software. As shown in Figure S11, the Pearson correlation coefficients in mitochondria, endoplasmic reticulum, and lysosome were 0.39, 0.61, and 0.93, respectively, revealing that compound **S1**, which interacts with CN^- and Cu^{2+} in cells, can be well localized in lysosomes. The cytotoxicity of compound **S1** is tested by an MTT assay. As shown in Figure S13, the survival rate of cells cultured with 5 μM **S1** for 24 h is over 80%, showing very low cytotoxicity for biological application.

In order to study whether this synthesis works in biological tissue, we selected the root of *Arabidopsis thaliana* for imaging. As shown in Figure 5, the plant root tissue showed no fluorescence after incubation with **S1** at 37 °C for 1 h. No fluorescence was found after sequential addition of Cu^{2+} or CN^-. However, we found strong blue fluorescence in root tissue as it was treated with the copper-cyanide complex. It is suggested that compound **S1** can enter plant root tissue well and successfully generate emissive benzazoles in complex biological tissue, which can be further applied for detection of CN^- and Cu^{2+} in this environment.

In summary, the copper-cyanide complex can transform nonemissive Schiff bases that are substituted with different groups to corresponding fluorescent benzazole derivatives. The catalyzed reaction experiences the nucleophilic addition of

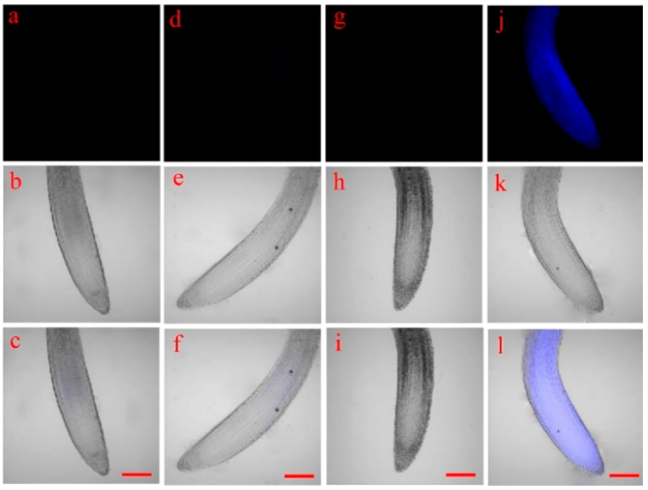


Figure 5. Confocal microscopy images of *Arabidopsis* root tissue (5 days). *Arabidopsis thaliana* incubated with **S1** (2 μM) for 1 h at 37 °C (a–c), followed by the addition of 80 μM CN^- (d–f) or 80 μM Cu^{2+} (g–i) and incubation, respectively, for another 30 min. (j–l) Images of *Arabidopsis thaliana* pretreated with **S1** (2 μM) for 1 h and subsequent treatment with 80 μM CN^- for 30 min and 80 μM Cu^{2+} for 30 min. λ_{ex} = 405 nm. Scare bar: 50 μm.

cyanide to the C=N bond, cyclization addition, and oxidation in the presence of Cu^{2+} and CN^-. The reaction can proceed in buffer solution with high conversion efficiency, fast response time, and large fluorescence enhancement. Moreover, this kind of reaction can take place in living cells and plant tissues and be further applied for selective detection of Cu^{2+} and CN^-. It is envisioned that this reaction would be useful for studying and understanding the formation of benzoxazole-based biomolecules in vivo.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00784.

Detailed experimental procedure, synthesis of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yongqian Xu − *Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy, Northwest A&F University, Yangling, Shaanxi 712100, P. R. China;* orcid.org/0000-0002-3778-7332; Email: xuyq@nwsuaf.edu.cn

Authors

Dejia Wang − *Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy, Northwest A&F University, Yangling, Shaanxi 712100, P. R. China*

Hongjuan Li − *Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy, Northwest A&F University, Yangling, Shaanxi 712100, P. R. China*

Shiguo Sun − *Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Chemistry & Pharmacy,*

https://dx.doi.org/10.1021/acs.orglett.0c00784
Org. Lett. XXXX, XXX, XXX−XXX

Northwest A&F University, Yangling, Shaanxi 712100, P. R. China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00784

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Grant 21676218, 21978241, and 21878249) and Shaanxi Province Science and Technology (2019JM-173 and 2018JM2008).

■ REFERENCES

(1) Cho, Y.-H.; Lee, C.-Y.; Cheon, C.-H. Cyanide as a powerful catalyst for facile synthesis of benzofused heteroaromatic compounds via aerobic oxidation. *Tetrahedron* **2013**, *69*, 6565−6573.

(2) Gu, L.; Wang, W.; Xiong, Y.; Huang, X.; Li, G. Synthesis of 2-Arylbenzoxazoles through Oxidation of C-H Bonds Adjacent to Oxygen Atoms. *Eur. J. Org. Chem.* **2014**, *2*, 319−322.

(3) Sarode, S. A.; Bhojane, J. M.; Nagarkar, J. M. An efficient magnetic copper ferrite nanoparticle: for one pot synthesis of 2-substituted benzoxazole via redox reactions. *Tetrahedron Lett.* **2015**, *56*, 206−210.

(4) (a) Deng, B.; Ren, M.; Kong, X.; Zhou, K.; Lin, W. An ESIPT based fluorescent probe for imaging hydrogen sulfide with a large turn-on fluorescence signal. *RSC Adv.* **2016**, *6*, 62406−62410. (b) Zhang, P.; Fu, C.; Zhang, Q.; Li, S.; Ding, C. Ratiometric Fluorescent Strategy for Localizing Alkaline Phosphatase Activity in Mitochondria Based on the ESIPT Process. *Anal. Chem.* **2019**, *91*, 12377−12383. (C) Goswami, S.; Das, S.; Aich, K.; Pakhira, B.; Panja, S.; Mukherjee, S. K.; Sarkar, S. A. Chemodosimeter for the Ratiometric Detection of Hydrazine Based on Return of ESIPT and Its Application in Live-Cell Imaging. *Org. Lett.* **2013**, *15*, 5412−5415.

(5) (a) Chen, W.-H.; Xing, Y.; Pang, Y. A Highly Selective Pyrophosphate Sensor Based on ESIPT Turn-On in Water. *Org. Lett.* **2011**, *13*, 1362−1365. (b) Tang, L.; Shi, J.; Huang, Z.; Yan, X.; Zhang, Q.; Zhong, K.; Hou, S.; Bian, Y. An ESIPT-based fluorescent probe for selective detection of homocysteine and its application in live-cell imaging. *Tetrahedron Lett.* **2016**, *57*, 5227−5231. (c) Wu, F.; Wang, L.; Tang, H.; Cao, D. Excited State Intramolecular Proton Transfer Plus Aggregation-Induced Emission-Based Diketopyrrolopyrrole Luminogen: Photophysical Properties and Simultaneously Discriminative Detection of Trace Water in Three Organic Solvents. *Anal. Chem.* **2019**, *91*, 5261−5269.

(6) Zhang, D.; Yang, Z.; Li, H.; Pei, Z.; Sun, S.; Xu, Y. A simple excited-state intramolecular proton transfer probe based on a new strategy of thiol-azide reaction for the selective sensing of cysteine and glutathione. *Chem. Commun.* **2016**, *52*, 749−752.

(7) (a) Shi, X.; Guo, J.; Liu, J.; Ye, M.; Xu, Q. Unexpectedly Simple Synthesis of Benzazoles by t-BuONa-Catalyzed Direct Aerobic Oxidative Cyclocondensation of o-Thio/Hydroxy/Aminoanilines with Alcohols under Air. *Chem. - Eur. J.* **2015**, *21*, 9988−9993. (b) Varma, R. S.; Kumar, D. Manganese triacetate oxidation of phenolic Schiff bases: synthesis of 2-arylbenzoxazoles. *J. Heterocycl. Chem.* **1998**, *35*, 1539−1540.

(8) (a) Xing, R.-G.; Li, Y.-N.; Liu, Q.; Meng, Q.-Y.; Li, J.; Shen, X.-X.; Liu, Z.; Zhou, B.; Yao, X.; Liu, Z.-L. Facile and Efficient Synthesis of Benzoxazoles and Benzimidazoles: the Application of Hantzsch Ester 1,4-Dihydropyridines in Reductive Cyclization Reactions. *Eur. J. Org. Chem.* **2010**, *34*, 6627−6632. (b) Kidwai, M.; Bansal, V.; Saxena, A.; Aerry, S.; Mozumdar, S. Cu-Nanoparticles: efficient catalysts for the oxidative cyclization of Schiffs' bases. *Tetrahedron Lett.* **2006**, *47*, 8049−8053. (c) Viirre, R. D.; Evindar, G.; Batey, R. Copper-Catalyzed Domino Annulation Approaches to the Synthesis of Benzoxazoles under Microwave-Accelerated and Conventional Thermal Conditions. *J. Org. Chem.* **2008**, *73*, 3452−3459. (d) Riadi, Y.; Mamouni, R.; Azzalou, R.; El Haddad, M.; Routier, S.; Guillaumet, G.; Lazar, S. An efficient and reusable heterogeneous catalyst Animal Bone Meal for facile synthesis of benzimidazoles, benzoxazoles, and benzothiazoles. *Tetrahedron Lett.* **2011**, *52*, 3492−3495. (e) Wu, X.-F.; Neumann, H.; Neumann, S.; Beller, M. Sequential one-pot synthesis of benzoxazoles from aryl bromides: successive palladium- and copper-catalyzed reactions. *Tetrahedron Lett.* **2013**, *54*, 3040−3042.

(9) Don, M.-J.; Shen, C.-C.; Lin, Y.-L.; Syu, W.-J.; Ding, Y.-H.; Sun, C.-M. Nitrogen-Containing Compounds from Salvia miltiorrhiza. *J. Nat. Prod.* **2005**, *68*, 1066−1070.

(10) McKee, M. L.; Kerwin, S. M. Synthesis, metal ion binding, and biological evaluation of new anticancer 2-(2'-hydroxyphenyl)-benzoxazole analogs of UK-1. *Bioorg. Med. Chem.* **2008**, *16*, 1775−1783.

(11) (a) Miwa, N.; Tanaka, C.; Ishida, S.; Hirata, G.; Song, J.; Torigoe, T.; Kuninobu, Y.; Nishikata, T. Copper-catalyzed tertiary alkylative cyanation for the synthesis of cyanated peptide building blocks. *J. Am. Chem. Soc.* **2020**, *142*, 1692−1697. (b) Wei, W.-T.; Teng, F.; Li, Y.; Song, R.-J.; Li, J.-H. Oxidative [4 + 2] Cycloaddition of α-(N-Arylamino) Carbonyls with Aryl Alkenes by Multiple C-H Functionalizations and [1,2]-Aryl Shifts. *Org. Lett.* **2019**, *21*, 6285−6288. (c) Liang, Y.; Tan, Z.; Jiang, H.; Zhu, Z.; Zhang, M. Copper-Catalyzed Oxidative Multicomponent Annulation Reaction for Direct Synthesis of Quinazolinones via an Imine-Protection Strategy. *Org. Lett.* **2019**, *21*, 4725−4728.

(12) Irwin, R. J.; Van Mouweric, M.; Stevens, L.; Seese, M. D.; Basham, W. *Environmental Contaminants Encyclopedia: Cyanide*; National Park Service, Water Resources Division: Fort Collins, CO, 1997.

(13) Zhao, X.; Zhang, J.; Qu, J. Photoelectrocatalytic Oxidation of Cu-cyanides and Cu-EDTA at TiO_2 nanotube electrode. *Electrochim. Acta* **2015**, *180*, 129−137.

(14) Wang, F.; Wang, L.; Chen, X.; Yoon, J. Recent progress in the development of fluorometric and colorimetric chemosensors for detection of cyanide ions. *Chem. Soc. Rev.* **2014**, *43*, 4312−4324.

(15) Jo, J.; Lee, D. Turn-On Fluorescence Detection of Cyanide in Water: Activation of Latent Fluorophores Through Remote Hydrogen Bonds that Mimic Peptide β-Turn Motif. *J. Am. Chem. Soc.* **2009**, *131*, 16283−16291.

(16) Xu, Z.; Chen, X.; Kim, H. N.; Yoon, J. Sensors for the optical detection of cyanide ion. *Chem. Soc. Rev.* **2010**, *39*, 127−137.

(17) Jo, J.; Lee, H. Y.; Liu, W.; Olasz, A.; Chen, C.-H.; Lee, D. Reactivity-Based Detection of Copper(II) Ion in Water: Oxidative Cyclization of Azoaromatics as Fluorescence Turn-On Signaling Mechanism. *J. Am. Chem. Soc.* **2012**, *134*, 16000−16007.

(18) Chandra, R.; Ghorai, A.; Patra, G. K. A simple benzildihydrazone derived colorimetric and fluorescent 'on-off-on' sensor for sequential detection of copper(II) and cyanide ions in aqueous solution. *Sens. Actuators, B* **2018**, *255*, 701−711.

(19) Chan, J.; Dodani, S. C.; Chang, C. J. Reaction-based small-molecule fluorescent probes for chemoselective bioimaging. *Nat. Chem.* **2012**, *4*, 973−984.

(20) Xu, Y.; Pang, Y. Zinc binding-induced near-IR emission from excited-state intramolecular proton transfer of a bis(benzoxazole) derivative. *Chem. Commun.* **2010**, *46*, 4070−4072.

(21) Miyagawa, S.; Yoshimura, K.; Yamazaki, Y.; Takamatsu, N.; Kuraishi, T.; Aiba, S.; Tokunaga, Y.; Kawasaki, T. Asymmetric Strecker Reaction Arising from the Molecular Orientation of an Achiral Imine at the Single-Crystal Face: Enantioenriched L- and D-Amino Acids. *Angew. Chem., Int. Ed.* **2017**, *56*, 1055−1058.

(22) Adongo, J. O.; Neubert, T. J.; Sun, G.; Janietz, S.; Lauermann, I.; Rademann, K.; Rappich, J. Fabrication and Characterization of Surfaces Modified with Carboxymethylthio Ligands for Chelate-Assisted Trapping of Copper. *ACS Appl. Mater. Interfaces* **2017**, *9*, 24273−24281.

(23) Chen, F.; Hu, C.; Sun, M.; Liu, H.; Qu, J.; Tao, Z. Enhancing destruction of copper (I) cyanide and subsequent recovery of Cu(I)

by a novel electrochemical system combining activated carbon fiber and stainless steel cathodes. *Chem. Eng. J.* **2017**, *330*, 1187−1194.

https://dx.doi.org/10.1021/acs.orglett.0c00784
Org. Lett. XXXX, XXX, XXX−XXX