Synthesis of C2,3-vicinal diaminoindoles via a copper-iodine co-catalytic strategy

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August 16, 2023

Abstract

A one-pot synthesis of vicinal diamines using indoles, pyrazoles, and phenothiazines in a tandem multi-component reaction is developed. The utilization of a copper-iodine co-catalytic system enables the generation of a diverse range of vicinal diaminoindoles with good selectivity and moderate to good yields. An attractive aspect of this method is that it can be conducted under mild and environmentally friendly conditions, showcasing its potential as an alternative approach for synthesizing vicinal diamines. Moreover, the use of a multicomponent tandem reaction highlights the power and versatility of such strategies in synthetic chemistry.

Cite this paper: *Chin. J. Chem.* **2023** , *41* , XXX—XXX. **DOI: 10.1002/cjoc.202300XXX**

Synthesis of C2,3-vicinal diaminoindoles *via* a copper-iodine co-catalytic strategy

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Keywords

Indoles | C-H bonds diamination | Vicinal diamines | Copper-iodine co-catalysis | Multi-component reaction

Comprehensive Summary

A one-pot synthesis of vicinal diamines using indoles, pyrazoles, and phenothiazines in a tandem multi-component reaction

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Background and Originality Content

Vicinal diamines are highly important structural motifs found in a broad range of biologically active compounds, natural products, pharmaceuticals, and materials science.[1] They also serve as privileged ligands in organic and transition metal catalysis, highlighting their significance.[2]Therefore, extensive research efforts have been dedicated to developing synthetic strategies and functionalizing these distinctive scaffolds.[3] Moreover, vicinal diamine-containing compounds, exemplified in Figure 1, have demonstrated remarkable effects on biological activities.[4] For instance, compound (A) exhibits exceptional antiemetic properties, while compounds (B) and (C) possess potent inhibitory effects with respect to anti-arrhythmic and antidepressant applications, respectively.

Figure 1 Representative bioactive vicinal diamines.

Efficient synthetic methods for tandem C-N bond formation have been extensively studied due to the widespread importance of compounds containing such bonds. Traditional strategies involve nucleophilic substitution reactions and metal-catalyzed C-N cross-coupling reactions such as Buchwald-Hartwig, Ullmann-Goldberg, and Chan-Lam reactions.[5] However, these methods typically require pre-functionalization of aromatic substrates into aryl halides or aryl boric acids as coupling reagents. Catalytic diamination of carbon-carbon double bonds has emerged as one of the most efficient and straightforward approaches for synthesizing vicinal diamines, making it a popular topic in synthetic organic chemistry.[6]Despite significant progress in developing catalytic diamination methods, there are still notable challenges and limitations that need to be addressed. Firstly, many of these methods rely on the use of stoichiometric amounts of oxidants and metal reagents, which can lead to cost, environmental, and safety concerns.[7]Additionally, most reported diamination strategies are limited to symmetrical diamination reactions, where two identical diamination reagents are incorporated into the same molecule. Alternatively, specific diamination reagents must be presynthesized in some cases.[8] While there have been advancements in asymmetric diamination reactions of alkenes, achieving regioselective diamination with two readily available and different diamination reagents is still a highly desirable goal.

In 2021, Zhao and colleagues reported a novel method for the regioselective C-N bond formation between anilines and 1,2-diols (as a mixture of diastereomers), enabling the efficient and diastereoselective synthesis of vicinal diamines. This was accomplished through cooperative ruthenium/Lewis acid catalysis or an effective chiral iridium/phosphoric acid co-catalyzed process.[9] Glorius' group later presented a metal-free, photosensitized bifunctional diamination reagent that exhibited excellent regio- and diastereoselectivity in the synthesis of a range of previously inaccessible vicinal diamines (Scheme 1a).[10] Additionally, a novel class of bifunctional nitrogen-free radical precursors was developed, which generated two *N* -centered radicals with different reactivities via an energy transfer process. However, intermolecular regioselective diamination reactions of indole carbon-carbon double bonds have yet to be explored.

As part of our continuous efforts to develop innovative methods for the synthesis and functionalization of indoles,[11] we present our unexpected findings on a one-step, three-component intermolecular C-H diamination reaction for the highly regioselective synthesis of C2,3-diaminoindole. This reaction utilizes a copper-iodine co-catalytic system (Scheme 1b). Notable features of this method include:

1. The mild diamination reaction employs an inexpensive and readily available copper catalyst, making it highly practical for broader applications.

2. The approach exhibits excellent compatibility with various indoles and demonstrates exceptional regioselectivity based on the different reactivity of the utilized amines.

Scheme 1 Previous work and our new observation.

Results and Discussion

Table 1 Screening for optimal reaction conditions.^{a}

Entry	Catalyst	Solvent	Additive	**4aaa**, Yield (%)^b
1	CuI	DMF		10
2	$CuCl_2$	DMF		0
3	$Cu(OAc)_2$	DMF		trace

Entry	Catalyst	Solvent	Additive	**4aaa**, Yield (%)^b
4	$Fe(OTf)_3$	DMF		trace
5	$Cu(OTf)_2$	DMF		52
6	$Cu(OTf)_2$	DMSO		26
7	$Cu(OTf)_2$	PhCl		30
8	$Cu(OTf)_2$	DMA		34
9	$Cu(OTf)_2$	1,4-dioxane		0
10	$Cu(OTf)_2$	p-xylene		15
11	$Cu(OTf)_2$	DMF		(38, 48)^c
12	$Cu(OTf)_2$	DMF		(43, 58)^d
13	$Cu(OTf)_2$	DMF	$AlCl_3$	0
14	$Cu(OTf)_2$	DMF	$Zn(OTf)_2$	41
15	$Cu(OTf)_2$	DMF	NaOTf	62
16	**$Cu(OTf)_2$**	**DMF/TFE**	**NaOTf**	(57, **73**, 12)^e
17	$Cu(OTf)_2$	DMF/1,4-dioxane	NaOTf	57
18	$Cu(OTf)_2$	DMF/HFIP	NaOTf	60

^{a} Reaction conditions, unless specified otherwise: **1a** (0.25 mmol), **2a** (0.375 mmol),**3a** (0.375 mmol), catalyst (30 mol%), I_2 (20 mol%), additive (60 mol%) and solvent (2.0 mL) were stirred at 130 °C under O_2 for 24 h. ^{b} Isolated yield. ^{c} 10 mol% and 30 mol% of I_2 were used respectively. ^{d} 20 mol% and 60 mol% of $Cu(OTf)_2$ were used respectively.^{e} The mixed solutions of DMF and TFE (v/v = 4:1, 3:1, 1:1).

Expanding upon our previous investigations, we embarked on an exploration of the model substrates 1-methyl-1*H* -indole (**1a**), pyrazole (**2a**), and 10*H* -phenothiazine-2-carbonitrile (**3a**) to investigate various reaction parameters (Table 1). In our initial screening, several catalysts were evaluated in the presence of *N,N* -dimethylformamide (DMF) as the solvent, with the reaction exposed to O_2 at 130 °C for 24 hours. However, all the tested catalysts demonstrated inferior performance compared to $Cu(OTf)_2$, which furnished a yield of 52% (entries 1-5). Consequently, we selected a combination of $Cu(OTf)_2$ and I_2 as our preferred catalyst system to examine the influence of different solvents (entries 6-10). Our screening endeavors revealed DMF to be the optimal solvent among the options explored. Furthermore, additional screening experiments indicated that altering the amount of I_2 had no beneficial effects on the reaction outcome (entry 11). Although the use of 60 mol% $Cu(OTf)_2$ slightly enhanced the isolated yield to 58% (entry 12), this effect was not statistically significant. Encouragingly, the inclusion of 60 mol% NaOTf as an additive resulted in an improved yield of 62% (entries 13-15). Further screening experiments involving mixed solvents unveiled that a combination of DMF and trifluoroethanol (v/v = 3:1) yielded a significant enhancement in the overall yield, with a remarkable 73% achieved (entries 16-18). Finally, we established the optimal conditions for maximizing the yield. The identified standard conditions are as follows: **1** (0.25 mmol), **2** (0.375 mmol), **3** (0.375 mmol), $Cu(OTf)_2$ (30 mol%), I_2 (20 mol%), NaOTf (60 mol%), DMF (1.5 mL), and TFE (0.5 mL) were stirred at 130 °C under O_2 for 24 h (entry 16).

Scheme 2 Scope of indoles

^{a} Reaction conditions: **1** (0.25 mmol),**2a** (0.375 mmol), **3a** (0.375 mmol), $Cu(OTf)_2$ (30 mol%), I_2 (20 mol%), NaOTf (60 mol%), DMF (1.5 mL) and TFE (0.5 mL) were stirred at 130 °C under O_2 for 24 h.

With the optimized conditions established, the scope and limitations of the synthetic protocol were carefully examined. Initially, pyrazole**2a** and 10*H* -phenothiazine-2-carbonitrile **3a** were tested in conjunction with various indoles **1** . As depicted in Scheme 2, the majority of the reactions proceeded smoothly, affording the desired C2,3-diaminoindoles in moderate yields upon isolation (**4aaa-4oaa**). Notably, diverse functional groups (-Me, -Et, cyclopropylmethyl, alkyl, -Bn, -OMe, -Bpin, -F, -Cl, and -Br) on the N1 pyrrolyl ring as well as on the C4-7 aryl ring were well tolerated. However, the presence of bulky substituents and the electronic properties of these substituents exerted some influence on the product yield. Specifically, indoles bearing electron-donating groups exhibited relatively high yields (**4aaa-4caa** , **4faa-4jaa**). In the case of halogen substituents (-F, -Cl, and -Br) on the aryl ring, the corresponding products were obtained in acceptable to good yields (**4kaa-4maa** , 31-60%), thereby showcasing the potential for further chemical transformations and the introduction of molecular complexity. Remarkably, despite the significant steric hindrance imposed by the -Bpin group at the C4 position of indole, the corresponding product **4naa** was obtained in a yield of 40%. Furthermore, 1-methyl-1*H* -pyrrolo[2,3-*b*]pyridine **1o** was subjected to the reaction conditions, affording the cross-coupling product **4oaa** in a yield of 43%. Regrettably, indoles with strong electron-withdrawing groups (e.g., -CN, -NO_2) on the aryl ring did not successfully yield the desired products (not depicted in Scheme 2), presumably due to the comparatively lower reactivity of these electron-deficient indole substrates towards the intermolecular amination process. It is noteworthy that our experimental findings indicated the N1 unprotected indole to be unsuitable as a starting material for the synthesis of the target compound, as decomposition was observed under the reaction conditions (not shown in Scheme 2).

Scheme 3 Scope of azoles and phenothiazines

^{a} Reaction conditions: **1a** (0.25 mmol),**2** (0.375 mmol), **3** (0.375 mmol), $Cu(OTf)_2$ (30 mol%), I_2 (20 mol%), NaOTf (60 mol%), DMF (1.5 mL) and TFE (0.5 mL) were stirred at 130 degC under O_2 for 24 h. ^{b} deviation: at 80 degC.

In the subsequent investigations, we explored the reactions between 1-methyl-1*H* -indole **1a** and a diverse array of azoles**2** and phenothiazines **3** . As illustrated in Scheme 3, azoles **2** possessing electron-donating groups or halogen substituents demonstrated favorable reactivity, resulting in the formation of **4aba-4aea** in yields ranging from 51% to 79%. Conversely, lower yields were obtained when electron-withdrawing groups and halogens were present on the azoles (**4afa-4aia** , 39-47%), suggesting a notable influence of the electronic effect on the reaction outcome. Consistent with expectations, the reactions involving other phenothiazines proceeded smoothly, furnishing the desired products in acceptable yields (**4aab-4aaf** , 18-43%). Furthermore, the structure of 4aab was confidently determined *via* X-ray diffraction analysis (CCDC: 2283366).

To further investigate the reaction mechanism, several control experiments were conducted (Scheme 4). Firstly, in order to observe the reaction sequence, a reaction between the C2-aminated product**1a-1** and phenothiazine **3b** was performed under the standard conditions, yielding the desired C3-aminated product**4aab** in 80% yield (eq. (1)). However, when the C3-aminated product **1a-2** was reacted with pyrazole **2a** under the standard conditions, only 15% yield of **4aab** was obtained (eq. (2)). This observation suggests a preference for amination at the C2 position over the C3 position. Additionally, a radical trapping experiment was performed. When a stoichiometric amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the model reaction, complete suppression of the diamination reaction was observed (eq. (3)), indicating the occurrence of a free radical process during the reaction.

Scheme 4 Control experiments

Scheme 5 Plausible reaction mechanisms

Based on the observed results and in consideration of previous relevant studies,[12]a plausible mechanism is proposed, as illustrated in Scheme 5. The reaction begins with the nucleophilic addition of **1a** to I_2, resulting in the formation of iodonium species**I** . Subsequently, nucleophilic attack by **2a** at the C2 position of I gives rise to intermediate **II** , which undergoes elimination of HI to afford the 2-azolated product **1a-1** . In the presence of the $Cu(OTf)_2$, the 2-azolated product**1a-1** undergoes single-electron-transfer (SET), yielding a radical cation. Deprotonation by NaOTf yields the radical intermediate**III** . Likewise, an analogous process occurs with phenothiazine**3** , generating intermediate **IV** . Finally, a dual-radical cross-coupling between the C-centered radical intermediate III and the N-centered radical intermediate **IV** occurs, leading to the formation of the target molecule **4aaa** .

Conclusions

In summary, our research has led to the development of a novel and efficient strategy for the regioselective synthesis of vicinal diamines using indoles, pyrazoles, and phenothiazides in a three-component tandem reaction. This methodology offers a straightforward route to 2,3-diaminoindoles and presents several notable advantages, which include excellent tolerance towards functional groups, high chemo-selectivity, outstanding step- and atom-economy, and the elimination of the need for pre-installed specific coupling agents. The results of our study not only provide an alternative approach for the synthesis of vicinal diamines but also contribute to the further advancement of multicomponent tandem reactions.

Experimental

All the obtained products were characterized by melting points (m.p.),^{1}H-NMR, ^{13}C-NMR,^{19}F-NMR, high resolution mass spectra (HRMS). Melting points were measured on an Electrothemal SGW-X4 microscopy digital melting point apparatus and are uncorrected; ^{1}H-NMR,^{13}C-NMR, ^{19}F-NMR spectra were obtained on Bruker-600. All the new compounds were further characterized by high resolution mass spectra (HRMS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m); TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm; All the reagents were purchased from commercial sources, and used without further purification.

Typical procedure for the synthesis of 4aaa. The mixture of 1-methylindole **1a** (33.0 mg, 0.25 mmol), **2a** (27.0 mg, 0.375 mmol), **3a** (84.0 mg, 0.375 mmol), and $Cu(OTf)_2$ (30 mol%), I_2 (20 mol%), NaOTf (60 mol%), DMF (1.5 mL) and TFE (0.5 mL) were stirred at 130 °C under O_2 for 24 h. The resulting mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica gel by using petroleum ether/ethyl acetate (v/v = 8:1) as the eluent to give **4aaa** as yellow solid (76.0 mg, 73% yield).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

Acknowledgement

The authors thank the National Natural Science Foundation of China (22201048), the Natural Science Foundation of Guangxi Province (2022GXNSFBA035480), the Specific Research Project of Guangxi for Research Bases and Talents (2022AC21099) and the Start-up Fund of Guangxi University (A3040051013) for financial support.

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Manuscript received: XXXX, 2023 Manuscript revised: XXXX, 2023 Manuscript accepted: XXXX, 2023 Accepted manuscr

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Entry for the Table of Contents

Synthesis of C2,3-vicinal diaminoindoles via a copper-iodine co-catalytic strategy Wenhua Yu,$^{++,a}$ Yingying Zh
A one-pot synthesis of vicinal diamines using indoles, pyrazoles, and phenothiazines in a tandem multi-component reaction