# LETTERS

# Copper-Catalyzed Oxoazidation and Alkoxyazidation of Indoles

Hang Yin,<sup>†</sup> Teng Wang,<sup>†</sup> and Ning Jiao<sup>\*,†,‡</sup>

<sup>†</sup>State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Xue Yuan Road 38, Beijing 100191, China <sup>‡</sup>State Key Laboratory of Elemento-organic Chemistry, Nankai University, 94 Weijin Road, Tianjin 300071, China

**(5)** Supporting Information

**ABSTRACT:** Copper-catalyzed oxoazidation and alkoxyazidation of indoles has been developed. The dearomatization reaction which leads to versatile 3-azido indolenine and oxindole derivatives in moderate to good yields could be used in a further transformation.



The dearomatization<sup>1</sup> of indoles has been an attractive topic in organic synthesis due to the importance of the derivatives of dearomatization products such as indolenines and 2-oxindoles, which are common structural motifs in various natural products and synthetic bioactivity molecules.<sup>2</sup> In the past decades, many efficient approaches have been developed to modify and dearomatize indoles.<sup>3</sup> Among the corresponding products, 3-nitrogen-containing derivatives are very important cores in many useful molecules, including SSR-14945, a vasopressin VIb receptor antagonist, and a gastrin/CCK-B receptor antagonist AG-041R (Figure 1).<sup>4</sup>



Figure 1. Representative 3-nitrogen-containing oxindoles.

As an effective and easy converting unit, azide was widely used in constructing a C–N bond.<sup>5</sup> Our group has been focused on concise and efficient nitrogenation reactions using azides and other N-reagents as the nitrogen source.<sup>6</sup> In the reported methodologies, azides were rarely employed in the dearomatization of indoles, especially the intermolecular reactions with azides and other nucleophiles.<sup>7</sup> In 1976, Ikeda and co-workers reported an interesting azidation and dearomatization of some indoles employing iodine azide reagents.<sup>8</sup> Nevertheless, iodine azides are very unstable and should be prepared on site and used *in situ*. Thus, milder and more efficient approaches are still attractive to accomplish this reaction.

Azidoiodinane<sup>9</sup> (2a), first reported by Zhdankin and coworkers, was used for direct azidation of many organic substrates, which confirmed its stability and efficiency.<sup>10</sup> This solid azide reagent remains active for a very long time. Herein we report an efficient azidation and dearomatization of indoles using azidoiodinane and alcohol.

Our research started with the model reaction with substrates 3-methylindole (1a) and azidoiodinane (2a) under an argon atmosphere, using methanol as the solvent (Table 1). None of the desired product was observed in the absence of any transitional metal catalyst (entry 1). Various transition metal salts such as iron, cobalt, palladium, and manganese were investigated. However, nothing optimal appeared among the results (entries 2-5). To our delight, a 43% yield of 3a was observed when CuBr was employed as the catalyst (entry 6), which indicates that copper salt might benefit the formation of the desired product 3a. It is noteworthy that 3a was obtained highly regioselectively as the sole product. Thus, a broad scope of copper salts was investigated. The dearomatization of 1a in the presence of CuCN or Cu(acac)<sub>2</sub> (10 mol %) proceeded well and afforded 3a in 46% and 50% yield (entries 7 and 11). Since CuCN and Cu(acac)<sub>2</sub> afforded similar yields of product, a rate order experiment was investigated (see Figure S8, Supporting Information), which indicated that both Cu(I)and Cu(II)-catalyzed alkoxyazidation are not a first-order reaction. As the catalyst  $Cu(acac)_2$  was identified, we shortened the reaction time to 1.5 h. Surprisingly, the reaction yield increased to 77% (entry 12). Subsequently, different atmospheres were tested. The results indicate that the presence of air and  $O_2$  could decrease the yield of 3a (entries 14–15). A lower temperature did not improve the yield. Only a 20% yield of 3a was obtained when the reaction was carried out at room temperature (entry 13). In addition, when 2.0 equiv of 2a were employed, the yield of 3a showed not only no improvement but also a slight decrease (entry 16). We also investigated different kinds of  $N_3$  sources, including  $NaN_3$ ,  $TMSN_3$  (azidotrimethylsilane),  $TsN_3$  (p-toluenesulfonyl azide), and DPPA (diphenylphosphoryl azide) with the same amount of PIDA (iodobenzene diacetate). However, only a trace amount of 3a was observed by GC-MS when NaN3 and PIDA were used instead of 2a (entry 17). Other azides did not afford 3a in

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Table 1. Optimization of the Methoxyazidation of 3-Methyl Indole 1a to Indolenines  $3a^a$ 

ĺ	Me +	N <sub>3</sub> Source Ar, te	0 mol %) eOH mp, time		Me N <sub>3</sub> OMe
	1a <sup>H</sup>			3a	•
entry	cat.	N <sub>3</sub> source (equiv)	temp (°C)	time (h)	yield of 3a <sup>b</sup> (%)
1	_	<b>2a</b> (1.5)	60	10	N.R.
2	$FeCl_2$	<b>2a</b> (1.5)	60	10	N.R.
3	$Co(OAc)_2$	<b>2a</b> (1.5)	60	10	N.R.
4	PdCl <sub>2</sub>	<b>2a</b> (1.5)	60	10	N.R.
5	$Mn(OAc)_2$	<b>2a</b> (1.5)	60	10	N.R.
6	CuBr	<b>2a</b> (1.5)	60	10	43
7	CuCN	<b>2a</b> (1.5)	60	10	46
8	CuI	<b>2a</b> (1.5)	60	10	10
9	CuOAc	<b>2a</b> (1.5)	60	10	29
10	$CuF_2$	<b>2a</b> (1.5)	60	10	26
11	$Cu(acac)_2$	<b>2a</b> (1.5)	60	10	50
12	$Cu(acac)_2$	2a (1.5)	60	1.5	77
13	$Cu(acac)_2$	<b>2a</b> (1.5)	rt	1.5	20
14 <sup>c</sup>	$Cu(acac)_2$	<b>2a</b> (1.5)	60	1.5	61
$15^d$	$Cu(acac)_2$	<b>2a</b> (1.5)	60	1.5	12
16	$Cu(acac)_2$	<b>2a</b> (2.0)	60	1.5	75
$17^e$	$Cu(acac)_2$	NaN <sub>3</sub> (1.5)	60	1.5	trace
$18^e$	$Cu(acac)_2$	$TMSN_3$ (1.5)	60	1.5	N.R.
19 <sup>e</sup>	$Cu(acac)_2$	$TsN_{3}$ (1.5)	60	1.5	N.R.
$20^e$	$Cu(acac)_2$	DPPA (1.5)	60	1.5	N.R.

<sup>*a*</sup>Reaction conditions: **1a** (0.3 mmol), catalyst (10 mol %), and  $N_3$  source in dry MeOH (1.0 mL), stirred under Ar for corresponding time. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>The reaction was carried out under air. <sup>*d*</sup>The reaction was carried out under  $A_2$ . <sup>*c*</sup>I.5 equiv of PIDA was added.

their cases (entries 18-20), which indicate the particularity of the azidoiodinane 2a.

The structure of 3a shows that another nucleophile methanol is involved in this transformation, which demonstrates the potential with various other nucleophiles. Interestingly, methanol highly regioselectively attacked the 2-position of indole followed by the formation of C–N bond at the 3position. No other substitutions were observed in this reaction.

Under the optimal reaction conditions (Table 1, entry 12), dearomatization of different substituted indoles with different kinds of alcohols was investigated (Figure 2). 3-Methylindoles with 5-Me and 5-OMe substituted offered good yields with the methanol nucleophile (3b and 3c), respectively. Although 3arylindoles did not work under these conditions, 3-alkylindoles such 3-ethyl-indole, 3-propyl-indole, and 3-butyl-indole worked well producing the desired products 3d, 3e, and 3f in moderated yields, respectively. Ethanol also worked well with the substrate 1a affording 3g. When different alcohols were used, moderate yields of corresponding products were obtained. Isopropanol and n-propanol gave the same 56% yield of 3h and 3i, respectively, which indicated that the steric effects of the alcohols might not affect the reaction too much. Phenethyl alcohol also afforded the corresponding product 3k but in a lower yield. To our delight, water could participate this reaction well and afforded 2-oxindole 3j in 81% yield. The structure of 3j was further confirmed by single-crystal X-ray analysis. Other nucleophiles such as CH<sub>3</sub>NO<sub>2</sub>, TsNH<sub>2</sub> (ptoluenesulfon amide) have also been investigated. However, no desired corresponding products were obtained. The iodocar-



**Figure 2.** Cu-catalyzed dearomatization of 3-methylindoles **1** to indolenines and 2-oxindoles **3**. Reaction conditions unless specified otherwise: **1** (0.3 mmol), **2a** (0.45 mmol), Cu(acac)<sub>2</sub> (0.03 mmol) in corresponding R<sub>2</sub>OH (1.0 mL) at 60 °C under Ar, 1.5 h. Isolated yields. Conditions for **3j**: **1a** (0.3 mmol), **2a** (0.45 mmol), Cu(acac)<sub>2</sub> (0.03 mmol), PEG 6000 (74.0 mg) in H<sub>2</sub>O (0.5 mL), and ethyl acetate (0.5 mL) at 60 °C under Ar, 10 h. Isolated yield.

boxylic acid decomposed by 2a did not participate in the reaction (see eqs S1-2 and Figure S5, Supporting Information).

Intramolecular reactions of substituted tryptophols were also investigated in DMSO (Figure 3). The desired tricyclic dearomatization products were obtained in moderate to good yields. The substituted tryptophols bearing either an electronwithdrawing group (5-F) or an electron-donating group (5-Me) were tolerant in this transformation. A longer chain of 3-



**Figure 3.** Substrate scope for Cu-catalyzed dearomatization of indoles. Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), Cu(acac)<sub>2</sub> (0.03 mmol) in DMSO (2.0 mL) at 60 °C under Ar, 1.5 h. All isolated yield.

## **Organic Letters**

substituted tryptophols and a large steric group such as 2-Ph also afforded the corresponding six-membered ring product and 2-phenyl substituted product in moderate yields, respectively (**3o**, **3p**).

The obtained 3-azido oxindole 3j could be converted into various derivatives. Reacting with phenyl acetylene (4) afforded a 95% yield of the triazole product 5 (eq 1). In addition, the 3-azido group could be easily converted into an amino group in 76% yield (eq 2), which indicates further transformations of this product.<sup>11</sup>



To investigate the mechanism, a series of reactions were investigated. In order to trap the possible radical intermediates, 1.5 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) were respectively added as the radical scavenger in the reaction of **1a** (eqs 3



and 4). Neither of the reactions afforded the corresponding product **3a**. Although 3-methylindolin-2-one (7) afforded **3j** in a 76% yield under the optimal conditions (eq 5),<sup>10i</sup> 7 was not detected by <sup>1</sup>H NMR in the reaction of **1a** under similar conditions but in the absence of azido reagent **2a** (see eqs S3–4, Supporting Information). These results may suggest that the attack of alcohols may be the second step after the azidation step.

On the basis of the above results, a plausible mechanism of this intramolecular transformation is proposed (Scheme 1). Initially, copper is oxidized by 2a to afford a higher valence copper with the generation of the N<sub>3</sub> radical.<sup>10,12</sup> Subsequently, the N<sub>3</sub> radical is trapped by 1l at the more nucleophilic 3-position to produce the intermediate **B**. Then the copper assists single electron oxidation<sup>13</sup> of intermediate **B** leading to the corresponding cation **C** and its resonance cation **D**. Finally, the intramolecular nucleophilic attack proceeds with cation **D** to generate the desired product **3**l. For the intermolecular transformation, **2a** may also participate in the reaction in the last step to afford a further oxidative product.

Scheme 1. Proposed Mechanism of the Direct Intramolecular Transformation



In summary, we have developed a novel and efficient Cucatalyzed dearomatization of 3-substituted indoles. 3-Azido indolenine and oxindole derivatives are easily constructed which could be used for further transformation by this oxoazidation and alkoxyazidation. An intramolecular reaction also performs well in this transformation to afford azido tricyclic molecules. Further mechanistic study and applications of this reaction are ongoing in our group.

# ASSOCIATED CONTENT

## Supporting Information

Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

#### AUTHOR INFORMATION

# **Corresponding Author**

\*E-mail: jiaoning@bjmu.edu.cn.

# Notes

The authors declare no competing financial interest.

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