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Copper-Catalyzed Sequential Ullmann *N*-Arylation and Aerobic Oxidative C−H Amination: A Convenient Route to Indolo[1,2-*c*]quinazoline Derivatives

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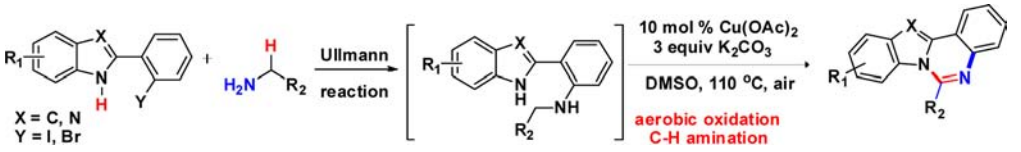
ABSTRACT



An efficient synthesis of indolo[1,2-*c*]quinazoline derivatives has been developed by copper-catalyzed sequential Ullmann N-arylation and aerobic oxidative C−H amination. The protocol uses readily available 2-(2-halophenyl)-1*H*-indoles and (aryl)methanamines as the starting materials to afford indolo[1,2-*c*]quinazolines, which are the core units of hinckdentine A.

Polyheterocycles are frequently found in bioactive natural products and have been intensively studied as drug candidates.[1] Accordingly, substantial attention has been focused on the complementary approach to the synthesis of polyheterocycles over the past decades.[2] In recent years, domino reactions have emerged as powerful tools for the synthesis of polyheterocycles[3] and reaction sequences that involve direct C−H activation are especially attractive since such processes preclude the presence of additional functionalities in the substrate.[4]

The indolo[1,2-*c*]quinazoline is a very important polyheterocycle. It is the core skeleton of the marine alkaloid hinckdentine **A** (Figure 1),[5] and its derivatives have shown interesting biological and pharmacological activities.

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For example, certain derivatives of indolo[1,2-*c*]quinazoline present cataleptogenic activity,[6] and some show excellent antibacterial as well as antifungal properties that make them promising drug candidates for Ampicillin and Ketoconazole.[7]

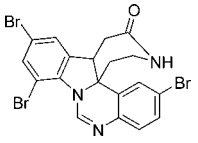

Figure 1. Hinckdentine A.

Currently, indolo[1,2-*c*]quinazolines are synthesized in two steps.[7] First, the condensation between 2-(*o*-aminophenyl)indoles and arylaldehydes affords the corresponding Schiff bases, which were further purified by recrystallization. Second, the prepared Schiff base is subjected to $KMnO_4$ to reflux in acetone to give the indolo-[1,2-*c*]quinazolines. We envisioned that the oxidative C−H amination strategy,[4,8] which was pioneered by Buchwald in 2005,[4f] might be probed in the construction of the pyrimidine cycle in indolo[1,2-*c*]quinazolines. In these transformations, palladium catalysts together with stoichiometric or excess amounts of copper or silver salts have been used predominantly. Herein, we report a copper-catalyzed method for the synthesis of indolo[1,2-*c*]-quinazoline derivatives by the use of readily available 2-(2-halophenyl)-1*H*-indoles via a sequential Ullmann coupling reaction and C−H amination. Notably, this transformation uses air rather than metal salts as the oxidant without the use of any ligands or additives.

Our initial attempt started with the reaction of 2-(2-bromophenyl)-1*H*-indole and benzylamine with 3 equiv of K_2CO_3 (relative to the amount of 2-(2-bromophenyl)-1*H*-indole) as the base and DMSO as the solvent at 110 °C by the use of CuI as the catalyst. To our delight, it afforded fused heterocyclic product **3a** in 36% yield (Table 1, entry 1). Screening of the copper catalysts (Table 1, entries 1−5) revealed that $Cu(OAc)_2$ was optimal to give the product **3a** in 61% yield (Table 1, entry 4). A relatively lower yield was obtained when the reaction was carried out by the use of $CuCO_3 \cdot Cu(OH)_2$ as the catalyst (Table 1, entry 5). No reaction was observed in the absence of the copper catalyst (Table 1, entry 6). It was found that empolying K_2CO_3 as the base showed the best activity (compare entries 4, 7−9), while other bases such as Cs_2CO_3 and K_3PO_4 were less effective (Table 1, entries 7 and 9). A relatively lower yield was obtained when employing Na_2CO_3 as a base (Table 1, entry 8).

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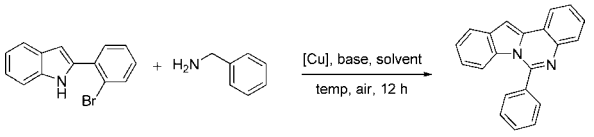
The effect of solvents was also investigated, and DMSO was the optimal solvent (compare entries 4 and 10−13). Other solvents such as DMF, ethylene glycol, dioxane, and toluene furnished the product in poor yields (Table 1, entries 10−13). We attempted different reaction temperatures, and 110 °C was optimal (Table 1, entries 14−15). Under a nitrogen atmosphere, only a small amount of **3a** was obtained.

Table 1. Optimization of Reaction Conditions[a]



1b **2a** **3a**

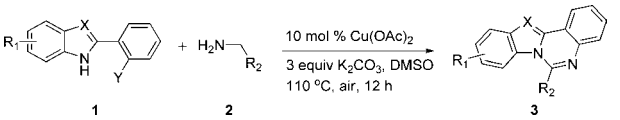
entry	cat.	base	solvent	temp (°C)	yield (%)[b]
1	CuI	K_2CO_3	DMSO	110	36
2	CuBr	K_2CO_3	DMSO	110	46
3	CuCl	K_2CO_3	DMSO	110	34
4	**$Cu(OAc)_2$**	**K_2CO_3**	**DMSO**	**110**	**61**
5	$CuCO_3 \cdot Cu(OH)_2$	K_2CO_3	DMSO	110	53
6	–	K_2CO_3	DMSO	110	0
7	$Cu(OAc)_2$	Cs_2CO_3	DMSO	110	18
8	$Cu(OAc)_2$	Na_2CO_3	DMSO	110	54
9	$Cu(OAc)_2$	K_3PO_4	DMSO	110	22
10	$Cu(OAc)_2$	K_2CO_3	DMF	110	34
11	$Cu(OAc)_2$	K_2CO_3	ethylene glycol	110	18
12	$Cu(OAc)_2$	K_2CO_3	dioxane	110	0
13	$Cu(OAc)_2$	K_2CO_3	toluene	110	12
14	$Cu(OAc)_2$	K_2CO_3	DMSO	90	49
15	$Cu(OAc)_2$	K_2CO_3	DMSO	130	56
16	$Cu(OAc)_2$	K_2CO_3	DMSO	110	9[c]

[a] Reaction conditions: 2-(2-bromophenyl)-1*H*-indole (0.2 mmol), benzylamine (0.4 mmol), catalyst (0.02 mmol), base (0.6 mmol), solvent (2 mL) under air. [b] Isolated yield. [c] Under nitrogen atmosphere (extrusion of air).

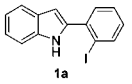
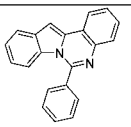
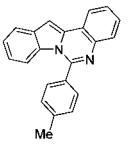
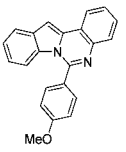
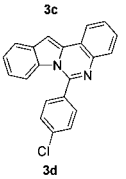
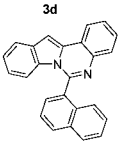
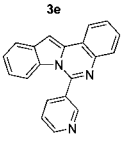
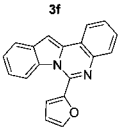
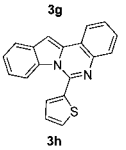
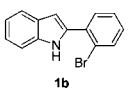
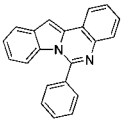
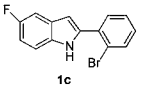
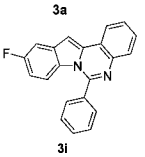
We next studied the generality of this copper-catalyzed domino reaction under the optimized conditions [using 10 mol % of $Cu(OAc)_2$ as the catalyst, 3 equiv of K_2CO_3 as the base, and DMSO as the solvent]. As shown in Table 2, most of the substrates examined provided moderate to good yields. For substituted 2-(2-halophenyl)-1*H*-indoles, the aryl iodides showed higher reactivity than the corresponding bromides (Table 2, entries 1−19). The electronic properties of the substituents in the indole ring exerted a very limited influence over the reactivity (Table 2, entries 10−19). Functional groups, including methyl, flouride, and chloride, could be tolerated in this domino transformation. The selective amination in the presence of a chloride functionality provided a useful handle for further cross-coupling reactions (Table 2, entries 15 and 16).

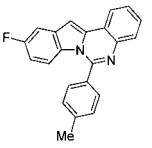
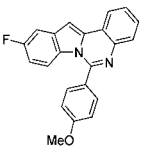
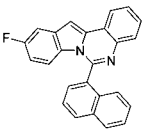
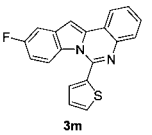
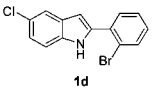
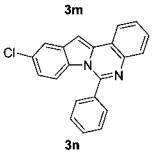
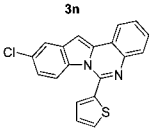
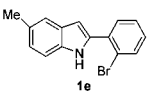
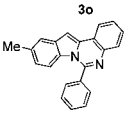
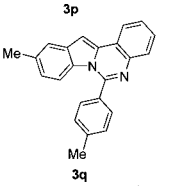
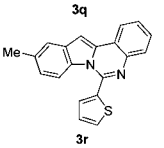
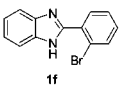
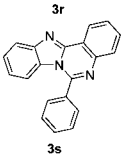
The scope of arylmethanamines was also examined as shown in Table 2. Both electron-rich and -deficient arylmethanamines participated in the reaction smoothly to afford the desired products (Table 2, entries 1−4, 11−18).

Table 2. Scope of the Indolo[1,2-*c*]quinazolines Synthesis[a]



1 2 3

entry	1	3	yield (%)[b]
1	 1a	 3a	66 (61)[c]
2	**1a**	 3b	58 (52)[c]
3	**1a**	 3c	72 (66)[c]
4	**1a**	 3d	84 (78)[c]
5	**1a**	 3e	61 (54)[c]
6	**1a**	 3f	52 (49)[c]
7	**1a**	 3g	47 (43)[c]
8	**1a**	 3h	68 (61)[c]
9	 1b	 3a	61
10	 1c	 3i	73

entry	1	3	yield (%)[b]
11	**1c**	 3j	55
12	**1c**	 3k	63[d]
13	**1c**	 3l	59
14	**1c**	 3m	51[d]
15	 1d	 3n	68
16	**1d**	 3o	40
17	 1e	 3p	61
18	**1e**	 3q	59
19	**1e**	 3r	43
20	 1f	 3s	54[d]

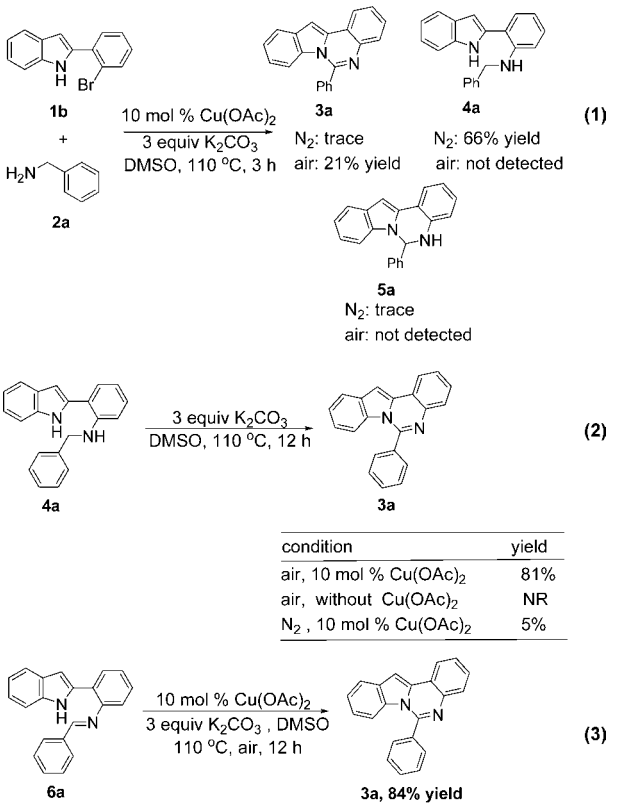
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (0.02 mmol), K_2CO_3 (0.6 mmol), DMSO (2 mL) under air. [b] Isolated yield. [c] Y = Br. [d] 24 h reaction time.

The naphthyl-substituted methanamines were tolerated in this process to provide the corresponding indolo[1,2-*c*]-quinazoline derivatives **3e** and **3l**. Importantly, various heteroaromatic methanamines are compatible with this domino reaction to give the desired products. It was found that the reactivity of thiophen-2-ylmethanamine showed a better reactivity than furan-2-ylmethanamine and pyridin-3-ylmethanamine (**3f**–**3h**).

Notably, 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole participated in the reaction easily with benzylamine to afford the benzimidazoquinazoline derivative **3s** in moderate yield (Table 2, entry 20). Benzimidazoquinazoline derivatives are valuable substrates with various biological activities and exhibit a wide range of therapeutic activities, such as anticancer,[9] antiviral,[10,11] antimicrobial,[12] anti-inflammatory,[10,13] and anticonvulsants.[14] Thus, we also provided an alternative approach for the benzimidazoquinazoline derivatives.

Control experiments for the mechanism studies were carried out as shown in Scheme 1. We found that this copper-catalyzed domino reaction was partially inhabited under a nitrogen atmosphere to afford mainly *N*-benzyl-2-(1*H*-indol-2-yl)aniline **4a** (eq 1). Only a trace of cyclization products **3a** and **5a** was detected by HRMS (eq 1 and Supporting Information). These results reveal that the copper-catalyzed domino reaction may first undergo an Ullmann-type coupling between 2-(2-halophenyl)-1*H*-indoles and (aryl)methanamines. In contrast, under air atmosphere, **3a** was obtained, and **4a** or **5a** was not detected (eq 1), indicating that the subsequent cyclization and aromatization require oxygen as the oxidant. We treated **4a** under standard conditions, and **3a** was afforded in 81% yield (eq 2). No reaction was observed in the absence of the copper catalyst (eq 2). Again, under a nitrogen atmosphere, only a small amount of **3a** was obtained (eq 2). We treated **6a** under standard conditions, and **3a** was afforded in 84% yield (eq 3). Further studies to elucidate the detailed reaction mechanism are ongoing in our laboratory.

Scheme 1. Control Experiments



In summary, we have developed a simple and efficient copper-catalyzed method for the synthesis of indolo[1,2-*c*]-quinazoline derivatives. The protocol uses environmentally friendly air as the oxidant, cheap $Cu(OAc)_2$ as the catalyst, and readily available 2-(2-halophenyl)-1*H*-indoles and (aryl)methanamines as the starting materials without the use of ligands. The accessibility and generality of this process make it highly valuable in view of the medicinal importance of these polyheterocycles.

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Supporting Information Available. The experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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