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Copper-Catalyzed Domino Synthesis of Quinazolinones via Ullmann-Type Coupling and Aerobic Oxidative C−H Amidation

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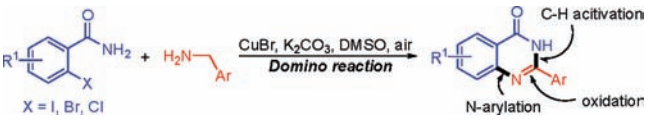
ABSTRACT



An efficient copper-catalyzed approach to quinazolinone derivatives has been developed, and the protocol uses cheap and readily available substituted 2-halobenzamides and (aryl)methanamines as the starting materials as well as economical and environmentally friendly air as the oxidant. This can be the first example of constructing *N*-heterocycles via sequential Ullmann-type coupling under air and aerobic oxidative C−H amidation.

Quinazolinone derivatives widely occur in natural products,[1] and they show a wide range of useful biological and pharmacological activities.[2] The quinazolinone derivatives exhibit many central nervous system (CNS) effects, such as analgesic, antiparkinsonian, CNS depressant, and CNS stimulant activities; they also act as psychotropic, hypnotic, cardiotonic, and antihistamine agents[3] and possess cardiovascular activity (including antihypertensive, antiarrhymic, vasodilatory, and lipid-lowering effects) and antiinflammatory activity (including inhibition of cyclooxygenase activity and leukocyte function).[3,4] They are also potent antibacterial, antifungal, antiviral, antimycobacterial, and antimalarial agents and possess anthelmintic activity.[5] Quinazolinone derivatives are used as inhibitors of various enzymes, and these enzymes include

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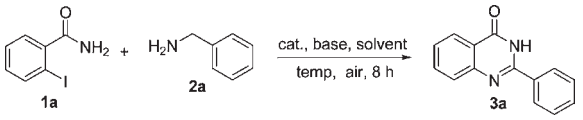
monoamine oxidase, aldose reductase, tumor necrosis factor α, and thymidylate synthase.[5,6] Therefore, they are interesting as structural scaffolds and have been assigned as privileged structures in drug development.[2a] Many methods for syntheses of quinazolinone derivatives[2,7,8] have been developed; however, *ortho*-amino or *ortho*-nitro benzoic acid derivatives are usually used as the starting materials, and they are not readily available or are difficult to prepare. Recently, copper-catalyzed Ullmann *N*-arylations have made great progress,[9] and the *N*-arylation strategy has been used to make *N*-heterocycles.[10] We have also developed some efficient methods for copper-catalyzed cross couplings[11] and synthesis of *N*-heterocycles.[12] However, to the best of our knowledge, there is no example of constructing *N*-heterocycles via sequential Ullmann-type coupling under air together with aerobic oxidative C−H amidation. Herein, we report a simple, practical, and efficient copper-catalyzed strategy for synthesis of quinazolinone derivatives through cascade reactions of substituted 2-halobenzamides and (aryl)methanamines under air without the addition of any ligand or additive.

Initially, 2-iodobenzamide and benzylamine were used as the model substrates to optimize reaction conditions including catalysts, bases, solvents, and reaction temperatures under air (1 atm). As shown in Table 1, five copper catalysts (0.1 equiv) were tested with 3 equiv of K_2CO_3 (relative to amount of 2-iodobenzamide) as the base and DMSO as the solvent at 110 °C (entries 1−5), and CuBr provided the highest yield (entry 2). Other bases, Cs_2CO_3, Na_2CO_3, and K_3PO_4 (entries 6−8), were screened, and

Table 1. Copper-Catalyzed Cascade Coupling of 2-Iodobenzamide with Benzylamine To Form 2-Phenylquinazolin-4(3*H*)-one under Air: Optimization of Conditions[a]



entry	cat.	base	solvent	temp (°C)	yield (%)[b]
1	CuI	K_2CO_3	DMSO	110	61
2	**CuBr**	**K_2CO_3**	**DMSO**	**110**	**75**
3	Cu_2O	K_2CO_3	DMSO	110	56
4	$Cu(OAc)_2$	K_2CO_3	DMSO	110	70
5	CuO	K_2CO_3	DMSO	110	trace
6	CuBr	Cs_2CO_3	DMSO	110	42
7	CuBr	Na_2CO_3	DMSO	110	69
8	CuBr	K_3PO_4	DMSO	110	48
9	CuBr	K_2CO_3	DMF	110	12
10	CuBr	K_2CO_3	ethylene glycol	110	18
11	CuBr	K_2CO_3	dioxane	110	0
12	CuBr	K_2CO_3	toluene	110	0
13	CuBr	K_2CO_3	DMSO	70	0
14	CuBr	K_2CO_3	DMSO	90	42
15	CuBr	K_2CO_3	DMSO	130	70
16	CuBr	K_2CO_3	DMSO	110	11[c]

[a] Reaction conditions: 2-iodobenzamide (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).

K_2CO_3 showed the best activity (compare entries 2, 6−8). The effect of solvents was also investigated, and DMSO was the optimal solvent (compare entries 2 and 9−12). We attempted different reaction temperatures (entries 13−15), and 110 °C was the better choice. A major Ullmann-type *N*-arylation product, 2-(benzylamino)benzamide (**4**), was observed with a small amount of 2-phenylquinazolin-4(3*H*)-one appearing when coupling of 2-iodobenzamide with benzylamine was carried out under a nitrogen atmosphere (extrusion of air) (entry 16).

The scope of copper-catalyzed domino reactions of substituted 2-halobenzamides with (aryl)methanamines was investigated under the optimized conditions [using 10 mol % of CuBr as the catalyst, 3 equiv of K_2CO_3 as the base (relative to the amount of 2-halobenzamides), and DMSO as the solvent]. As shown in Table 2, most of the substrates examined provided good yields at 100−120 °C. For substituted 2-halobenzamides, the aryl iodides showed higher reactivity than the corresponding bromides, and only aryl chloride containing an electron-withdrawing group could perform this domino reaction (entry 25). In general, no significant difference of reactivity was observed for the examined substituted 2-bromobenzamides and (aryl)methanamines with varied electronic properties, including electron-rich, electron-poor, and neutral substrates. The copper-catalyzed domino synthesis of quinazolinones could tolerate various functional groups including ether (entries 14−16), a C−Cl bond (entries 17−20), nitro (entries 21−23, 25) in the substituted 2-halobenzamides, ether

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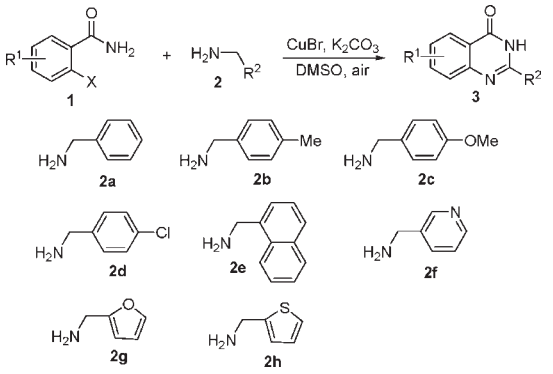
Table 2. Copper-Catalyzed Domino Synthesis of Quinazolinone Derivatives via Ullmann-Type Coupling and Aerobic Oxidative C−H Activation[a]



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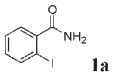
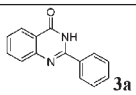
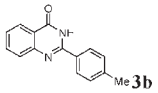
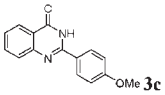
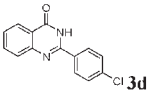
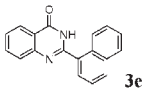
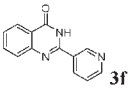
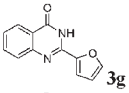
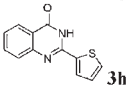
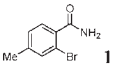
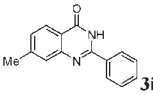
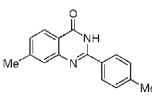
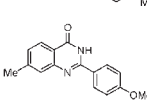
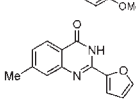
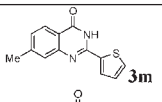
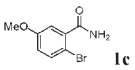
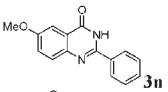
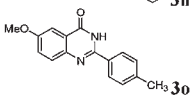
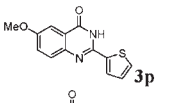
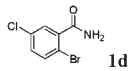
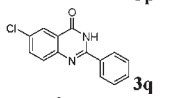
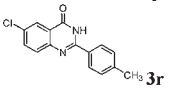
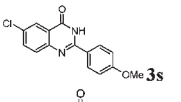
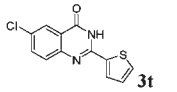
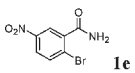
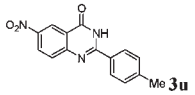
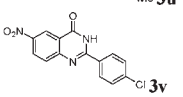
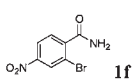
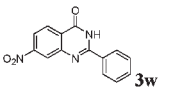
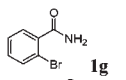
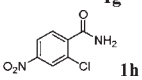
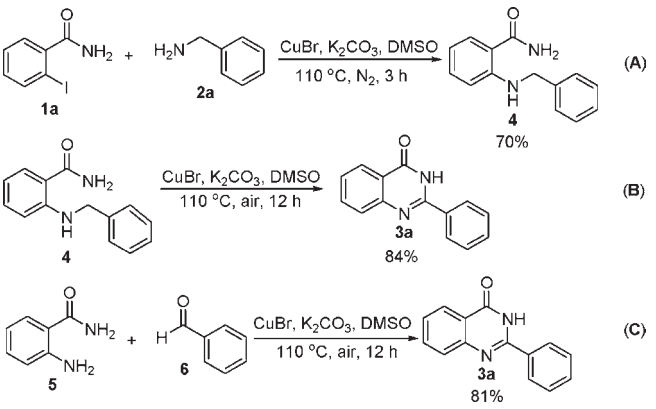
1	 1a	110 /8	 3a	75
2	1a	110 /8	 3b	80
3	1a	110 /8	 3c	84
4	1a	110 /9	 3d	61
5	1a	110 /10	 3e	64
6	1a	110 /9	 3f	73
7	1a	110 /8	 3g	53
8	1a	110 /8	 3h	80
9	 1b	120 /9	 3i	70
10	1b	120 /9	 3j	61
11	1b	120 /9	 3k	84
12	1b	120 /9	 3l	43
13	1b	120 /9	 3m	70
14	 1c	120 /12	 3n	60
15	1c	120 /12	 3o	62
16	1c	120 /12	 3p	82
17	 1d	120 /10	 3q	63
18	1d	120 /10	 3r	59
18	1d	120 /10	 3s	51
20	1d	120 /10	 3t	50
21	 1e	110 /2	 3u	72
22	1e	110 /6	 3v	52
23	 1f	120 /4	 3w	71
24	 1g	110 /8	3a	66
25	 1h	130 /14	3w	46

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), CuBr (0.02 mmol), K_2CO_3 (0.6 mmol), DMSO (2 mL) under air. [b] Isolated yield.

(entries 3, 11, and 18), a C−Cl bond (entries 4 and 22), a naphthalene ring (entry 5), and heterocycles containing nitrogen, oxygen, or sulfur (entries 6−8, 12, 13, 16, and 20) in the arylmethanamines.

Scheme 1. (A) Copper-Catalyzed Ullmann-Type Coupling of **1a** with **2a** under N_2; (B) Copper-Catalyzed Aerobic Oxidative Domino Reaction of **4**; (C) Copper-Catalyzed Aerobic Oxidative Cascade Coupling of **5** with **6**

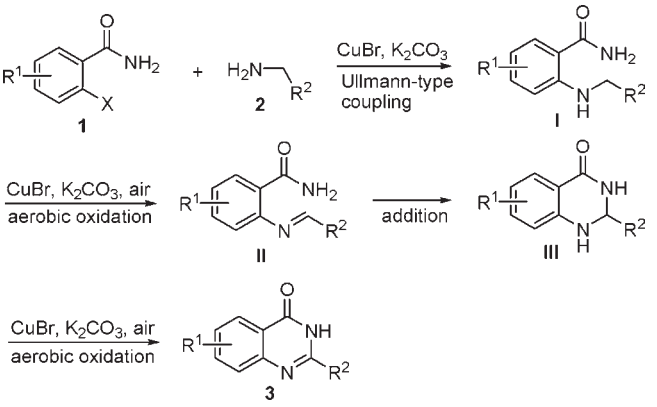


In order to explore the reaction mechanism for synthesis of quinazoline derivatives, the following control experiments were performed as shown in Scheme 1. Copper-catalyzed coupling of 2-iodobenzamide (**1a**) with benzylamine (**2a**) provided 2-(benzylamino)-benzamide (**4**) in 70% yield under a nitrogen atmosphere (extrusion of air), and only a small amount of quinazoline was observed (see Scheme 1A and entry 16 in Table 1). **4** transformed into 2-phenylquinazolin-4(3*H*)-one (**3a**) in 84% yield under our standard conditions (see Scheme 1B). Copper-catalyzed cascade coupling of 2-aminobenzamide (**5**) with benzaldehyde (**6**) provided **3a** in 81% yield (see Scheme 1C).

A possible mechanism for synthesis of quinazolinone derivatives is proposed in Scheme 2 according to the results above. Copper-catalyzed Ullmann-type coupling of substituted 2-halobenzamide with (aryl)methanamine first provides a *N*-arylation product (**I**). Interestingly, no ligand or additive was required in the reaction system, and the result showed an *ortho*-substituent effect[12,13] of the amide group in **1** during *N*-arylation. Copper-catalyzed aerobic oxidation of **I** affords intermediate **II** containing a C=N bond, and intramolecular nucleophilic addition of the amide to the C=N bond in **II** gives **III**.

(13) (a) Nicolaou, K. C.; Boddy, C. N. C.; Natarajar, S.; Yue, T.-Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421. (b) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276.

Scheme 2. Possible Mechanism for Copper-Catalyzed Aerobic Oxidative Domino Synthesis of Quinazolinones



Finally, further aerobic oxidation of **III** provides the target product **3a**.

In summary, we have developed a simple and efficient copper-catalyzed method for the synthesis of quinazolinone derivatives. The protocol uses cheap and readily available CuBr as the catalyst, substituted 2-halobenzamides and (aryl)methanamines as the starting materials, and economical and environmentally friendly air as the oxidant; the domino reactions underwent sequential copper-catalyzed Ullmann-type coupling, aerobic oxidation, and an intramolecular nucleophilic addition process without the addition of any ligand and additive, and the corresponding quinazolinone derivatives were obtained in good yields. This can be the first example of constructing *N*-heterocycles via sequential Ullmann-type coupling and aerobic oxidative C−H amidation under air. The method is of high tolerance toward various functional groups in the substrates, and it will attract much attention in academic and industrial research.

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Supporting Information Available. Synthetic procedures, characterization data, and ^1H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.