Concise copper-catalyzed one-pot tandem synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives†

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A simple and efficient copper-catalyzed one-pot tandem method has been developed for synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives *via* reactions of substituted 2-halo-*N*-(2-halophenyl)benzamides with alkyl 2-cyanoacetates or malononitrile under mild conditions.

Nitrogen-containing heterocyclic compounds in the form of biologically active drugs or agents play an important role in the pharmaceutical and agrochemical industries.[1] Benzimidazoles have attracted much attention for their wide applications as enzyme inhibitors,[2] drugs,[3] dyes,[4] and polymers.[5] Isoquinolin-1(2*H*)-one derivatives are found in natural products,[6] and they are also versatile building blocks for the total synthesis of natural alkaloids.[7] Isoquinolin-1(2*H*)-ones exhibit various biological and medicinal activities such as antihypertensive activity,[8a,b] as NK3 antagonists,[8c] melatonin MT_1 and MT_2 receptor agonists,[8d] Rho-kinase inhibitors,[8e] and JNK inhibitors.[8f] Some of them are also used as novel orally active 5-HT3 antagonists,[9a] thymidylate synthase (TS) inhibitors,[9b] or for the treatment of stomach tumors and diseases of human brain cells.[6b] The combined molecules of benzimidazole and isoquinolinone frameworks, benzimidazoisoquinolinone derivatives (Fig. 1), are valuable substrates for the synthesis of biologically active compounds with structural features different from those of existing drugs, and some of them are potent anti-*Trypanosoma cruzi* agents.[10] However, the methods for their preparation remain rare, and some starting materials are not readily available or difficult to prepare by the previous routes.[10,11]

Recently, great progress in copper-catalyzed cross couplings has been made,[12] and we have also developed some copper-catalyst systems that were used in the coupling reactions.[13] Some *N*-heterocycles have been constructed *via* the copper-catalyzed

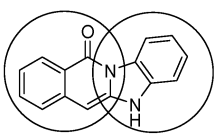

Fig. 1 Structure of benzimidazoisoquinolinone containing benzimidazole and isoquinolinone framework.

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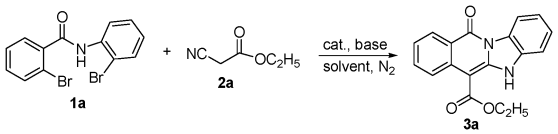
† Electronic supplementary information (ESI) available: General procedure for synthesis of compounds **3a–q**, **5** and **7**, characterization data for compounds **3a–q**, **5** and **7**, and ^1H and ^{13}C NMR spectra of compounds **3a–q**, **5** and **7**. See DOI: 10.1039/c0cc00185f

Table 1 Copper-catalyzed one-pot tandem synthesis of ethyl benzimidazo[1,2-*b*]isoquinolin-11-one-6-carboxylate (**3a**) *via* coupling of 2-bromo-*N*-(2-bromophenyl)benzamide (**1a**) with ethyl 2-cyanoacetate (**2a**): optimization of conditions[a]



Entry	Cat.	Base	Solvent	Yield (%)[b]
1	CuI	K_2CO_3	DMF	65
2	CuI	K_2CO_3	DMSO	70
3	CuI	K_2CO_3	Dioxane	Trace
4	CuBr	K_2CO_3	DMSO	41
5	CuCl	K_2CO_3	DMSO	85
6	Cu_2O	K_2CO_3	DMSO	56
7	—	K_2CO_3	DMSO	0[c]
8	CuCl	Na_2CO_3	DMSO	90
9	CuCl	K_3PO_4	DMSO	82
10	CuCl	Cs_2CO_3	DMSO	84

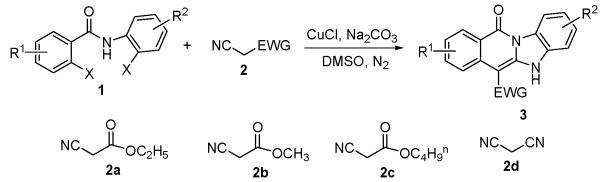
[a] Reaction conditions: 2-bromo-*N*-(2-bromophenyl)benzamide (**1a**) (0.2 mmol), ethyl 2-cyanoacetate (**2a**) (0.24 mmol), catalyst (0.02 mmol), base (0.4 mmol), solvent (2 mL) under nitrogen atmosphere, reaction temperature (60 °C), reaction time (12 h). [b] Isolated yield. [c] No addition of catalyst.

cross couplings by us[14] and other research groups.[15] Herein, we report a concise copper-catalyzed one-pot tandem synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives from reactions of substituted 2-halo-*N*-(2-halophenyl)benzamides with alkyl 2-cyanoacetates or malononitrile under mild conditions.

As shown in Table 1, 2-bromo-*N*-(2-bromophenyl)benzamide (**1a**) and ethyl 2-cyanoacetate (**2a**) were chosen as the model substrates to optimize reaction conditions including catalysts, bases, solvents and temperature under nitrogen atmosphere. First, solvents were investigated by using 0.1 equiv. of CuI as the catalyst and 2 equiv. of K_2CO_3 as the base (relative to amount of **1a**) (entries 1–3), and DMSO provided the highest yield (entry 2). Several copper catalysts were screened (compare entries 2, 4–6), and CuCl was proven to be the most effective catalyst for this tandem reaction (entry 5). No target product was observed in the absence of catalyst (entry 7). Other bases, Na_2CO_3, K_3PO_4, Cs_2CO_3, were tested at 60 °C (entries 8–10), and the results showed that Na_2CO_3 provided the highest yield (entry 8).

The scope of copper-catalyzed one-pot tandem synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives from reactions of substituted 2-halo-*N*-(2-halophenyl)benzamides with alkyl 2-cyanoacetates or malononitrile was investigated under the optimized conditions (10 mol% CuCl as the catalyst, 2 equiv. of Na_2CO_3 as the base, DMSO as the solvent at 60–100 °C

Table 2 Copper-catalyzed one-pot tandem synthesis of benzimidazo-[1,2-*b*]isoquinolin-11-one derivatives[a]



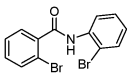
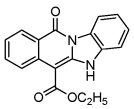
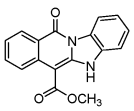
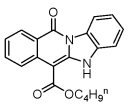
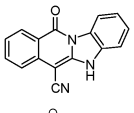
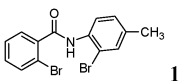
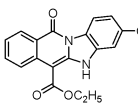
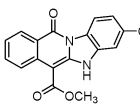
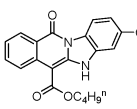
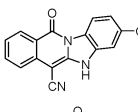
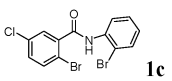
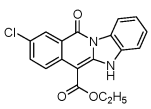
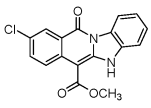
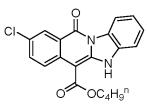
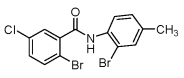
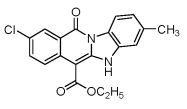
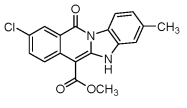
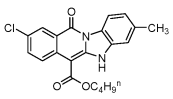
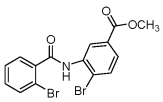
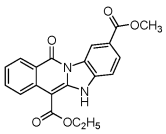
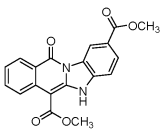
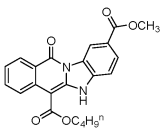
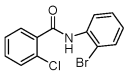
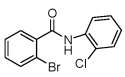
Entry	1	3	Yield (%)[b]
1	 **1a**	 **3a**	90
2	**1a**	 **3b**	87
3	**1a**	 **3c**	87
4	**1a**	 **3d**	85
5	 **1b**	 **3e**	91
6	**1b**	 **3f**	89
7	**1b**	 **3g**	63
8	**1b**	 **3h**	80
9	 **1c**	 **3i**	81
10	**1c**	 **3j**	65
11	**1c**	 **3k**	65
12	 **1d**	 **3l**	78
13	**1d**	 **3m**	83

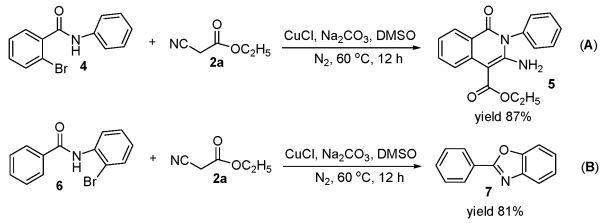
Table 2 (*continued*)

Entry	1	3	Yield (%)[b]
14	**1d**	 **3n**	69
15	 **1e**	 **3o**	72
16	**1e**	 **3p**	81
17	**1e**	 **3q**	70
18	 **1f**	**3a**	82
19	**1f**	**3d**	71
20	 **1g**	**3a**	75
21	**1g**	**3d**	70

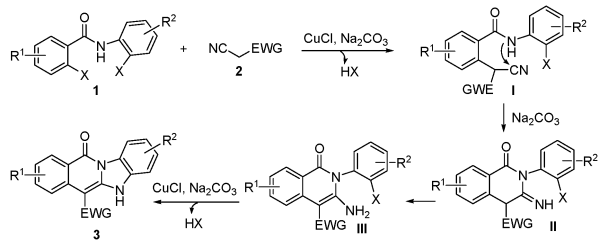
[a] Reaction conditions: under nitrogen atmosphere, **1** (0.2 mmol), **2** (0.24 mmol), CuCl (0.02 mmol), Na_2CO_3 (0.4 mmol), DMSO (2 mL), reaction temperature (60 °C for entries 1–8, 80 °C for entries 9–17; 100 °C for entries 18–21), reaction time (12 h). [b] Isolated yield.

under nitrogen atmosphere). As shown in Table 2, most of the substrates examined provided good yields. For the substituted 2-halo-*N*-(2-halophenyl)benzamides, aryl bromides showed higher reactivity than aryl chlorides (compare entries 1–4, 18–21). For *N*-(2-bromophenyl)-2-chlorobenzamide and 2-bromo-*N*-(2-chlorophenyl)benzamide, the target products were also provided in good yields when reaction temperature was raised to 100 °C (entries 18–21). In fact, the aryl chlorides are weak substrates in the previous copper-catalyzed coupling reactions,[12] and the result above showed an *ortho*-substituent effect of the amide group during *C*-arylations and *N*-arylations. The reactions above did not need addition of any ligand or additive, and the result also showed an *ortho*-substituent effect of the amide group. In addition, the copper-catalyzed one-pot tandem reactions could tolerate functional groups such as ester, non-*ortho*-site C–Cl bond of the amides (entries 9–14).

In order to explore the copper-catalyzed one-pot tandem synthetic mechanism of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives, the following control experiments were performed under our standard conditions as shown in Scheme 1. Reaction of 2-bromo-*N*-phenylbenzamide (**4**) with ethyl 2-cyanoacetate (**2a**) provided product **5** in 87% yield (Scheme 1A). However, treatment of *N*-(2-bromophenyl)benzamide (**6**) with 2-cyanoacetate (**2a**) gave 2-phenylbenz[*d*]oxazole (**7**) in 81% yield (Scheme 1B), and 2-cyanoacetate was not involved in the coupling reaction. The result showed that the couplings of substituted 2-halo-*N*-(2-halophenyl)benzamides with alkyl



Scheme 1 Reactions of ethyl 2-cyanoacetate with 2-bromo-*N*-phenylbenzamide (A) or *N*-(2-bromophenyl)benzamide (B) under our standard conditions.



Scheme 2 Possible copper-catalyzed formation mechanism of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives.

2-cyanoacetates or malononitrile were initiated from the C–X bond at the *ortho*-site of carbonyl of amide in **1**. Therefore, a possible formation mechanism of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives is proposed in Scheme 2 according to the *ortho*-substituent effect of the Ullmann coupling reaction.[14b–e,16] Firstly, copper-catalyzed Ullmann-type coupling of substituted 2-halo-*N*-(2-halophenyl)benzamide with alkyl 2-cyanoacetate (*C*-arylation of alkyl 2-cyanoacetate) provides **I** in the presence of base (Na_2CO_3), base-promoted nucleophilic attack of the nitrogen in the amide of **I** yields **II**, and transfer of double bond in **II** affords **III**. Finally, copper-catalyzed intramolecular *N*-arylation of **III** provides the target products **3**.

In summary, we have developed a simple and efficient copper-catalyzed one-pot tandem method for synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives. The couplings of substituted 2-halo-*N*-(2-halophenyl)benzamides with alkyl 2-cyanoacetates or malononitrile were performed well under mild conditions without addition of any ligand or additive. The present method shows economical, practical and starting material readily available advantages over the previous methods, so it will provide a new strategy for construction of diverse and useful nitrogen-containing heterocyclic compounds for organic chemistry and medicinal chemistry.

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