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Copper-catalyzed cascade synthesis of benzimidazoquinazoline derivatives under mild condition†

Shan Xu, Juyou Lu and Hua Fu*

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A convenient and efficient copper-catalyzed cascade method has been developed for the synthesis of benzimidazoquinazoline derivatives *via* reactions of readily available substituted 2-(2-halophenyl)benzoimidazoles with amidines or guanidine under mild conditions (*even at room temperature*).

Nitrogen-containing heterocycles widely occur in natural products and biologically active molecules.[1] For example, benzimidazoles are often used as enzyme inhibitors[2] and drugs.[3] Quinazolines also show various biological and medicinal properties, they act as potent tyrosine kinase and cellular phosphorylation inhibitors,[4] ligands for benzodiazepine and GABA receptors in the central nervous system[5] or as DNA binders,[6] and some of them show remarkable activity as anticancer,[7] antiviral,[8] and antitubercular agents.[9] The combined molecules of benzimidazole and quinazoline frameworks, benzimidazoquinazoline derivatives (Fig. 1), are valuable substrates with various biological activities, and they exhibit a wide range of therapeutic activities, such as anticancer,[10] antiviral,[11,12] antimicrobial,[13] anti-inflammatory,[11,14] and anticonvulsants.[15] However, the methods for preparation of benzimidazoquinazoline derivatives remain rare. In previous routes,[16] 2-(2-aminophenyl)benzoimidazoles and their precursors, 2-(2-nitrophenyl)benzoimidazoles, are often used as the starting materials, and toxic isothiocyanates are required for synthesis of benzimidazo[1,2-*c*]quinazolin-5-amines.[16c,d] These methods show limited substrate scopes because the used starting materials are not readily available or difficult to prepare, which greatly impedes discovery of more potent biologically active molecules.

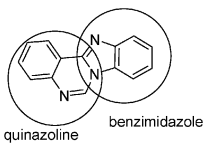

Fig. 1 Structure of benzimidazoquinazoline containing quinazoline and benzoimidazole framework.

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China. E-mail: fuhua@mail.tsinghua.edu.cn; Fax: 86 10 62781695; Tel: 86 10 62797186

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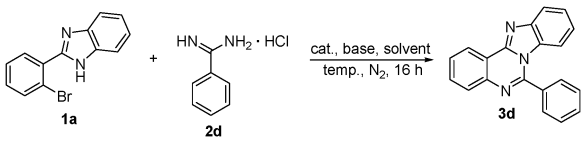
Recently, there has been great progress in copper-catalyzed cross couplings,[17] and some *N*-heterocycles have been constructed *via* copper-catalyzed cross couplings by other research groups[18] and us.[19] Herein, we report a convenient and efficient copper-catalyzed cascade synthesis of benzimidazoquinazoline derivatives under mild conditions.

As shown in Table 1, 2-(2-bromophenyl)benzoimidazole (**1a**) and benzamidine hydrochloride (**2d**) were used as the model substrates to optimize reaction conditions including catalysts, bases, solvents and temperature under nitrogen

Table 1 Copper-catalyzed cascade synthesis of 6-phenylbenzo-[4,5]imidazo[1,2-*c*]quinazoline (**3d**) *via* reaction of 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**1a**) with benzamidine hydrochloride (**2d**): optimization of conditions[a]



Entry	Catalyst	Base	Solvent	Temperature/ °C	Yield[b]/ %
1	CuI	Cs_2CO_3	DMF	60	54
2	CuI	K_2CO_3	DMF	60	64
3	CuI	K_3PO_4	DMF	60	71
4	CuI	K_3PO_4	DMSO	60	81
5	CuI	K_3PO_4	DMSO	40	84
6	CuI	K_3PO_4	DMSO	25	68
7	CuI	K_3PO_4	DMSO : CH_2Cl_2 = 2 : 1	25	83
8	**CuI**	**K_3PO_4**	**DMSO : CH_2Cl_2 = 3 : 1**	**25**	**86**
9	CuBr	K_3PO_4	DMSO : CH_2Cl_2 = 3 : 1	25	42
10	Cu_2O	K_3PO_4	DMSO : CH_2Cl_2 = 3 : 1	25	13
11	$Cu(OAc)_2$	K_3PO_4	DMSO : CH_2Cl_2 = 3 : 1	25	54
12	Cu	K_3PO_4	DMSO : CH_2Cl_2 = 3 : 1	25	65
13	—	K_3PO_4	DMSO : CH_2Cl_2 = 3 : 1	25	0[c]

[a] Reaction condition: 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**1a**) (0.5 mmol), benzamidine hydrochloride (**2d**) (0.75 mmol), catalyst (0.05 mmol), base (1.5 mmol), solvent (2 mL) under nitrogen atmosphere, reaction time (16 h). [b] Isolated yield. [c] No addition of catalyst.

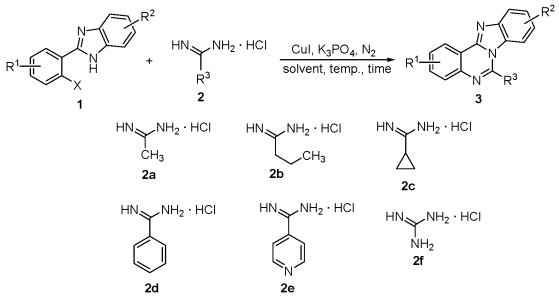
atmosphere. First, bases (3 equiv) were investigated by using 0.1 equiv of CuI as the catalyst (relative to amount of **1a**), and DMF as the solvent at 60 °C (Table 1 entries 1–3), and K_3PO_4 produced the highest yield (Table 1 entry 3). A higher yield (81%) was afforded when DMSO replaced DMF as the solvent (Table 1 entry 4). The yield rose when temperature decreased to 40 °C from 60 °C (Table 1 entry 5). However, a 68% yield was produced at room temperature (~25 °C) (Table 1 entry 6), we observed that part of product **3d** was not dissolved in DMSO at this temperature, so small amount of CH_2Cl_2 was added in order to improve dissolving power of the product (Table 1 entries 7 and 8). We were pleased to find that yields remarkably increased (compare Table 1 entries 6–8). Other copper catalysts were screened (Table 1 entries 9–12), and CuI was proven to be the most effective catalyst for this cascade reaction (compare Table 1 entries 8–12). No target product was observed in the absence of copper-catalyst (Table 1 entry 13).

The scope of copper-catalyzed cascade synthesis of benzimidazoquinazoline derivatives from reactions of substituted 2-(2-halophenyl)benzoimidazoles with amidines or guanidine was investigated under the optimized conditions (10 mol% CuI as the catalyst, 3 equiv of K_3PO_4 as the base under nitrogen atmosphere). As shown in Table 2, most of the tested substrates afforded good to excellent yields. For the substituted 2-(2-halophenyl)benzoimidazoles, their relative reactivity was in the order of aryl bromides > aryl chlorides (compare Table 2 entries 1–17 and 18–22). Substituted 2-(2-bromophenyl)benzoimidazoles worked very well *at room temperature* (Table 2 entries 1–17), and 2-(2-chlorophenyl)-benzoimidazole also provided moderate to good yields when the reaction temperature was raised to 100 °C (Table 2 entries 18–23), which showed *ortho*-substituent effect of benzoimidazole group during *N*-arylation (see Scheme 1) because aryl chlorides were weak substrates in the previous copper-catalyzed coupling reactions.[17] The reactions above did not need aid of any ligand or additive, and the result also showed *ortho*-substituent effect of benzoimidazole group. For amidines and guanidine, amidines exhibited better reactivity than guanidine, and guanidine afforded benzimidazo[1,2-*c*]quinazolin-5-amine derivatives in good yields when the temperature rose (Table 2 entries 23–25). The method for synthesis of benzimidazo[1,2-*c*]quinazolin-5-amine derivatives avoided use of the toxic isothiocyanates used in previous routes.[16c,d] The reactions above did not show an obvious difference for the electronic effect in the substrates.

In the cascade reactions above, no ligand or additive were required, and the result showed the *ortho*-substituent effect[20] of benzoimidazole group. Therefore, a possible mechanism for synthesis of benzimidazoquinazoline derivatives is proposed in Scheme 1. Firstly, coordination of substituted 2-(2-halophenyl)-benzoimidazole with CuI gives **I**, and oxidative addition of **I** leads to **II**. *N*-Arylation of **II** with amidine provides intermediate **III** (see Supporting Information for the experimental evidence†), and the intramolecular nucleophilic attack of NH in benzoimidazole group to carbon in amidine or guanidine affords the target product (**3**) releasing NH_3.

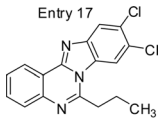
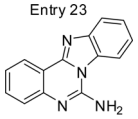
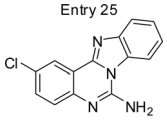
In summary, we have developed an efficient copper-catalyzed cascade method for the synthesis of benzimidazoquinazoline derivatives. The protocol uses inexpensive

Table 2 Copper-catalyzed cascade synthesis of benzimidazoquinazoline derivatives[a]

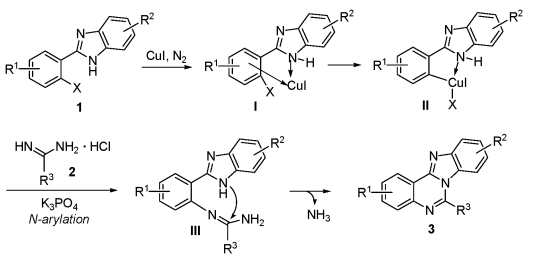


3 (X, Yield[b])	**3** (X, Yield[b])
Entry 1 **3a** (X = Br, 95%)	Entry 2 **3b** (X = Br, 87%)
Entry 3 **3c** (X = Br, 87%)	Entry 4 **3d** (X = Br, 86%)
Entry 5 **3e** (X = Br, 74%)	Entry 6 **3f** (X = Br, 84%)
Entry 7 **3g** (X = Br, 77%)	Entry 8 **3h** (X = Br, 61%)
Entry 9 **3i** (X = Br, 69%)	Entry 10 **3j** (X = Br, 66%)
Entry 11 **3k** (X = Br, 80%)	Entry 12 **3l** (X = Br, 67%)
Entry 13 **3m** (X = Br, 61%)	Entry 14 **3n** (X = Br, 50%)
Entry 15 **3o** (X = Br, 60%)	Entry 16 **3p** (X = Br, 63%)

Table 2 (*continued*)

3 (X, Yield[b])	**3** (X, Yield[b])
Entry 17  **3q** (X = Br, 57%)	Entry 18 **3a** (X = Cl, 80%) Entry 19 **3b** (X = Cl, 76%)
Entry 20 **3c** (X = Cl, 62%)	Entry 21 **3d** (X = Cl, 46%)
Entry 22 **3e** (X = Cl, 53%)	Entry 23  **3r** (X = Cl, 67%)
Entry 24 **3r** (X = Br, 74%)	Entry 25  **3s** (X = Br, 65%)

[a] Reaction condition: under nitrogen atmosphere, **1** (0.5 mmol), **2** (0.75 mmol), CuI (0.05 mmol), K_3PO_4 (1.5 mmol), solvent (1.5 mL of DMSO and 0.5 mL of CH_2Cl_2 for entries 1–17; 2 mL of DMSO for others), reaction temperature (~25 °C for entries 1–17; 100 °C for entries 18–23; 80 °C for entries 24 and 25), reaction time (16 h for entries 1–17; 26 h for entries 18–23; 20 h for entries 24 and 25). [b] Isolated yield.



Scheme 1 Possible copper-catalyzed mechanism for synthesis of benzimidazoquinazoline derivatives.

CuI as the catalyst, readily available substituted 2-(2-halophenyl)-benzoimidazoles (from reactions of substituted benzene-1,2-diamines with 2-haloobenzoic acids in acid medium[21]), amidines and guanidine as the starting materials, reactions of substituted 2-(2-bromophenyl)benzoimidazoles with amidines worked very well *at room temperature*, and 2-(2-chlorophenyl)-benzoimidazole and guanidine were also good substrates at 80 or 100 °C. Benzimidazoquinazoline and benzimidazo[1,2-*c*]-quinazolin-5-amine derivatives were obtained in good to excellent yields.

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