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Copper-Catalyzed Domino Synthesis of Benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones Using Cyanamide as a Building Block

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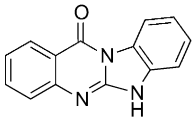
Abstract: A convenient copper-catalyzed domino method for the synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones has been developed *via* reactions of readily available substituted 2-bromo-*N*-(2-halophenyl)benzamides with cyanamide, in which cyanamide acts as a useful building block.

Keywords: benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones; building blocks; copper; cyanamide; domino method

Introduction

Benzimidazoles and quinazolinones are two important subclasses of N-heterocycles that widely occur in biologically active molecules.[1] Benzimidazoles are often used as enzyme inhibitors,[2] drugs,[3] dyes,[4] and polymers.[5] Quinazolinones act as anti-inflammatory,[6] antifungal,[7] hypnotic,[8] sedative,[9] analgesic, anticonvulsant,[10] antibacterial,[11] anticancer agents and AMPA receptor antagonists.[12] The combined structure of benzimidazole and quinazolinone frameworks, the benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one ring system (Figure 1), has attracted much attention for its application in antitumor agents[13] and potential immunosuppressors.[14] To the best of our knowledge, no natural product with the benzimidazoquinazolinone skeleton has been found thus far. Some approaches to benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one derivatives have been developed, such as the thermal rearrangement of 3-oxo-2-phenyl-2,3-dihydro-1*H*-indazolecarbonitrile at 270 °C,[15] the attack of isatoic anhydrides by *o*-phenylenediamine in refluxing acetic acid,[16] and the microwave-mediated heterocyclization of *o*-aryl isothiocyanate esters and *o*-phenylenediamines.[17] Transition metal-catalyzed transformations are useful tools in synthetic organic chemistry.[18] Recently, copper-catalyzed C–N bond formation has received significant attention and has provided a useful strategy for the synthesis of heterocyclic compounds,[19] and various N-heterocycles have been constructed *via* the copper-catalyzed Ullmann couplings by us[20] and other research groups.[21] In 2009, Molina and coworkers reported a practical method for the preparation of benzimidazoquinazoline derivatives *via* the copper-catalyzed intramolecular C–N formation.[22] However, the route involved a multistep process, the starting materials were not readily available, and the total yields were not high. To the best of our knowledge, there is no report on the synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones *via* a one-pot copper-catalyzed domino process. Herein, we report a practical and efficient copper-catalyzed synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-one derivatives under mild conditions.



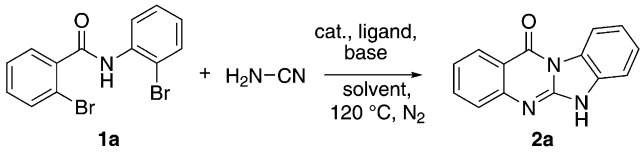
quinazolinone benzimidazole

Figure 1. Structure of benzimidazoquinazolines containing both benzimidazole and quinazolinone frameworks.

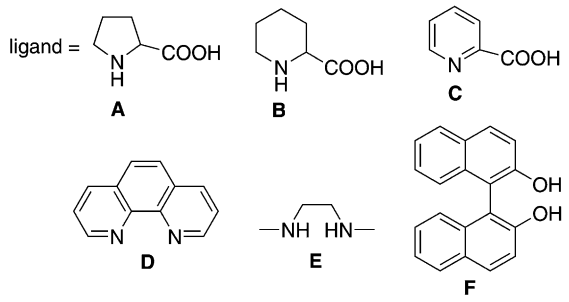
Results and Discussion

As shown in Table 1, 2-bromo-*N*-(2-bromophenyl)-benzamide (**1a**) was used as the partner of cyanamide to optimize reaction conditions including catalysts, li-

Table 1. Copper-catalyzed domino synthesis of benzimidazo-[2,1-*b*]quinazolin-12(6*H*)-one (**2a**) *via* reaction of 2-bromo-*N*-(2-bromophenyl)benzamide (**1a**) with cyanamide: optimization of conditions.[a]



1a **2a**



Entry	Cat.	Ligand	Base	Solvent	Yield [%][b]
1	CuI	A	Cs_2CO_3	DMSO	53
2	CuI	A	K_3PO_3	DMSO	45
3	CuI	A	K_2CO_3	DMSO	51
4	CuI	A	Cs_2CO_3	DMF	64
5	**CuI**	**A**	**K_2CO_3**	**DMF**	**67**
6	**CuI**	**B**	**K_2CO_3**	**DMF**	**67**
7	CuI	C	K_2CO_3	DMF	60
8	CuI	D	K_2CO_3	DMF	65
9	CuI	E	K_2CO_3	DMF	59
10	CuI	F	K_2CO_3	DMF	63
11	CuBr	A	K_2CO_3	DMF	60
12	CuCl	A	K_2CO_3	DMF	63
13	CuI	–	K_2CO_3	DMF	41[c]

[a] *Reaction conditions:* under a nitrogen atmosphere, 2-bromo-*N*-(2-bromophenyl)benzamide (**1a**) (0.5 mmol), cyanamide (1.0 mmol), catalyst (0.05 mmol), base (2.0 mmol), solvent (2 mL), reaction temperature (120 °C), reaction time (24 h).
[b] Isolated yield.
[c] In the absence of ligand.

gands, bases, and solvents at 120 °C under a nitrogen atmosphere. First, bases were investigated by using 0.1 equivalent of CuI as the catalyst, 0.2 equivalents of L-proline as the ligand, and DMSO as the solvent (entries 1–3), and Cs_2CO_3 and K_2CO_3 gave better yields. When DMF replaced DMSO as the solvent (entries 4 and 5), and K_2CO_3 provided a higher yield (entry 5). The effect of ligands was also investigated (compare entries 5–10), and L-proline and piperidine-2-carboxylic acid gave better results (entries 5 and 6). Here, L-proline was used as the ligand. Other copper salts, CuBr and CuCl, were tested in DMF (entries 11 and 12), and CuI was found to be the most effective catalyst (compare entries 5, 11 and 12). The reaction afforded a 41% yield in the absence of ligand (entry 13).

We investigated the scope of such copper-catalyzed domino coupling reactions of substituted 2-bromo-*N*-(2-bromophenyl)benzamides with cyanamide under the standard condition (10 mol% CuI as the catalyst, 20 mol% L-proline as the ligand, 4 equivalents of K_2CO_3 as the base, DMF as the solvent at 120 °C under a nitrogen atmosphere). As shown in Table 2, most of the examined substrates provided good yields (entries 1–14). For the substituted 2-bromo-*N*-(2-bromophenyl)benzamides, the substrates containing nitro groups gave moderate yields (entries 15–17). We attempted use of a solvent mixture of DMF and DMSO, and the yields were not high (entries 16). One possible reason is that introduction of a nitro group in the *para*-bromo position of the substrates weakened the oxidative addition of copper catalyst. In addition, the substrates containing a C–Cl bond also showed moderate reactivity (entries 18–20). The copper-catalyzed domino reactions could tolerate some functional groups such as amide, ether (entries 5, 6 and 19), ester (entry 4), C–Cl bonds (entries 9–11), C–Br bonds (entries 3, 8, 11–14, 17 and 18), and nitro groups (entries 15–17).

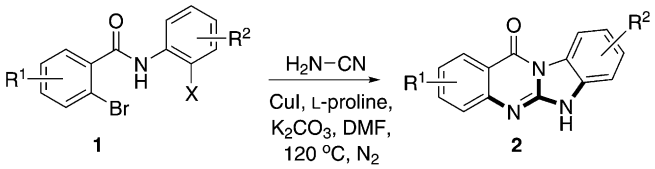
We investigated the reaction mechanism for the synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones. As shown in Scheme 1, four control experiments were performed under the standard conditions. Reactions of 2-bromo-*N*-*p*-tolylbenzamide (**3**) with cyanamide provided 2-amino-3-*p*-tolylquinazolin-4(3*H*)-one (**4**) in 73% yield [(Scheme 1 (A)]. Treatment of *N*-(2-bromophenyl)-4-methylbenzamide (**5**) in the presence of cyanamide produced 2-*p*-tolylbenzo[*d*]oxazole (**6**) [Scheme 1 (B)]. In fact, cyanamide did not participate in the coupling reaction. Coupling of *N*-*p*-tolylbenzamide (**7**) with cyanamide did not work under the standard conditions [Scheme 1 (C)]. We attempted coupling of (2-bromophenyl)acetamide (**9**) with cyanamide, but no cross-coupling product (**10**) and intramolecular cyclization product (**11**) were found [Scheme 1 (D)].

Therefore, a possible mechanism for the synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones is suggested in Scheme 2 according to the above results. First, intermolecular *N*-arylation of cyanamide with **1** provides intermediate **I** under copper catalysis, then intramolecular addition of NH to CN in **I** leads to **II**, and tautomerization of **II** forms **III**. Finally, intramolecular *N*-arylation of **III** gives the target product **2**.

Conclusions

We have developed a practical and efficient, copper-catalyzed method for the synthesis of benzimidazo-[2,1-*b*]quinazolin-12(6*H*)-ones. The protocol uses in-

Table 2. Copper-catalyzed domino synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones.[a]



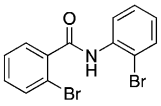
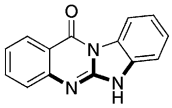
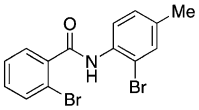
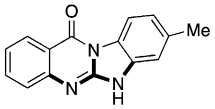
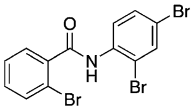
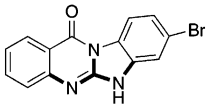
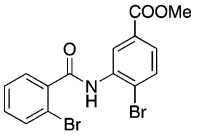
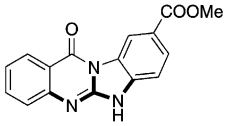
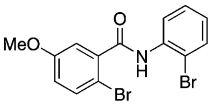
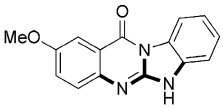
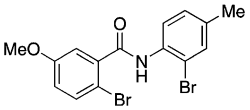
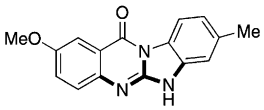
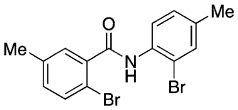
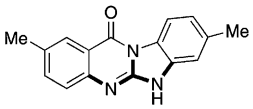
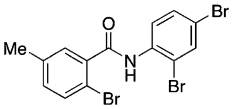
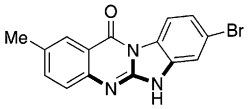
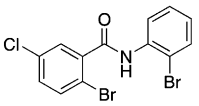
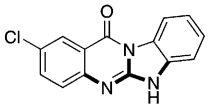
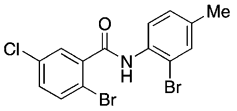
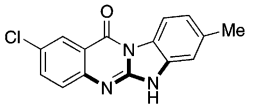
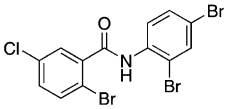
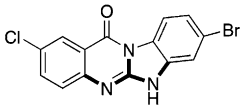
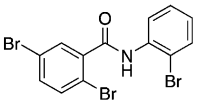
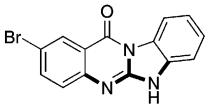
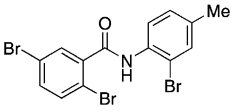
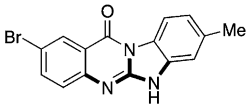
Entry	1		2		Yield [%][b]
1	**1a**		**2a**		67
2	**1b**		**2b**		64
3	**1c**		**2c**		72
4	**1d**		**2d**		76
5	**1e**		**2e**		82
6	**1f**		**2f**		66
7	**1g**		**2g**		61
8	**1h**		**2h**		71
9	**1i**		**2i**		62
10	**1j**		**2j**		59
11	**1k**		**2k**		70
12	**1l**		**2l**		75
13	**1m**		**2m**		55

Table 2. (Continued)

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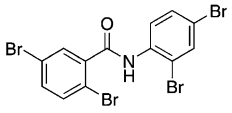
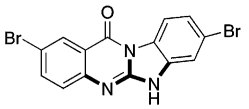
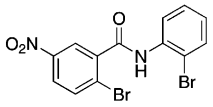
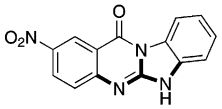
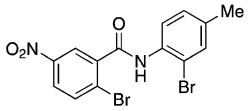
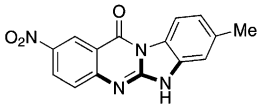
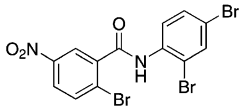
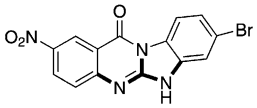
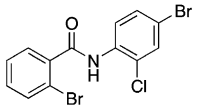
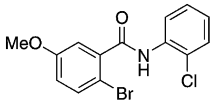
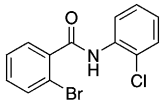
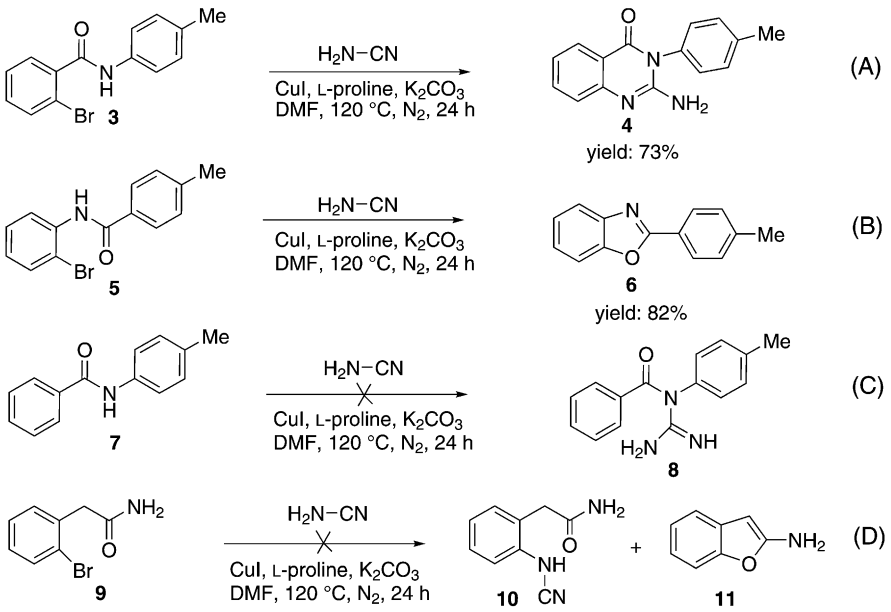
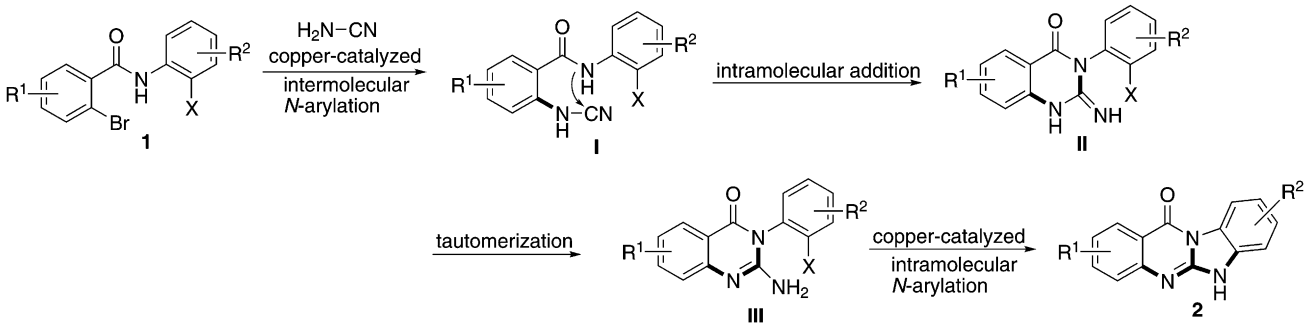
14	**1n**		**2n**		54
15	**1o**		**2o**		39
16	**1p**		**2p**		45; 43;[d] 37[e]
17	**1q**		**2q**		52
18	**1r**		**2c**		47
19	**1s**		**2e**		61
20	**1t**		**2a**		33[c]

[a] *Reaction conditions:* under a nitrogen atmosphere, 2-bromo-*N*-(2-bromophenyl)benzamide (**1**) (0.5 mmol), cyanamide (1.0 mmol), CuI (0.05 mmol), L-proline (0.1 mmol), K_2CO_3 (2.0 mmol), DMF (2 mL), reaction temperature (120 °C), reaction time (24 h).
[b] Isolated yield.
[c] At 130 °C for 48 h.
[d] DMF/DMSO (v/v 5:1).
[e] DMF/DMSO (v/v 3:1).



Scheme 1. Copper-catalyzed treatment of 2-bromo-*N*-*p*-tolylbenzamide (**3**) (A), *N*-(2-*b*romophenyl)-4-methylbenzamide (**5**) (B), *N*-*p*-tolylbenzamide (**7**) (C) or (2-bromophenyl)acetamide (**9**) (D) with cyanamide under the standard conditions.



Scheme 2. Possible mechanism for the copper-catalyzed domino synthesis of benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones.

expensive CuI/L-proline as the catalyst/ligand system, and readily available substituted 2-bromo-*N*-(2-halophenyl)benzamides and cyanamide as the starting materials, and the corresponding benzimidazoquinazoline derivatives were obtained in moderate to good yields. The method is tolerant towards functional groups in the substrates, and it should attract much attention in organic chemistry and medicinal chemistry.

Experimental Section

General Procedure for Copper-Catalyzed Synthesis of Benzimidazo[2,1-*b*]quinazolin-12(6*H*)-ones

An oven-dried Schlenk tube containing a stir bar was charged with CuI (0.05 mmol, 10 mg), 2-bromo-*N*-(2-bromophenyl)benzamide (0.5 mmol), cyanamide (1 mmol, 42 mg), L-proline (0.1 mmol, 12 mg), K_2CO_3 (2 mmol, 276 mg), and DMSO (2 mL). The Schlenk tube was capped with a Teflon screw cap and then evacuated and backfilled with nitrogen (3 cycles). The Schlenk tube was sealed and put into a preheated oil bath at 120 °C or 130 °C. After stirring for 24 h, the reaction mixture was allowed to cool to room temperature, DMSO was removed under rotary evaporation and the residue was purified by column chromatography on silica gel to provide the desired product.

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