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Copper-Catalyzed Domino Synthesis of Benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones using Cyanamide as a Building Block

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Abstract: An efficient and practical copper-catalyzed domino synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones has been developed. The protocol uses *N*-(2-halophenyl)-3-alkylpropiolamides and cyanamide as the starting materials, inexpensive copper(I) iodide and pipecolinic acid as the catalyst and ligand, and the corresponding products were obtained in moderate to good yields.

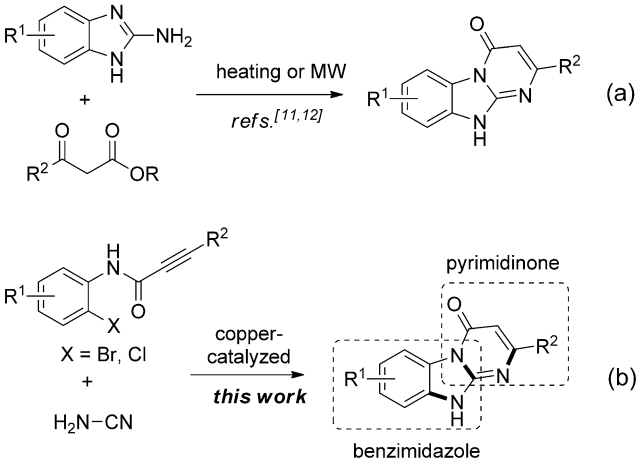
Keywords: benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones; copper; cyanamide; domino reaction; synthetic methods

Introduction

Nitrogen-containing heterocycles widely occur in natural products as well as biologically and pharmaceutically active molecules[1] and they have been assigned as privileged structures in drug development.[2] Benzimidazoles are often found in enzyme inhibitors,[3] drugs,[4] dyes,[5] and polymers.[6] The pyrimidinone unit is a key motif in various fields.[7] For example, they are used as the potent inhibitors of HIV integrase[8] and poly(ADP-ribose) polymerase-1 (PARP-1),[9] and they also exhibit anticancer and antimicrobial activities, inhibition of thymidylate synthase and dihydrofolate reductase.[10] Nitrogen-used molecules with both benzimidazole and pyrimidinone motifs, namely benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones (Scheme 1), are valuable molecules, and they show antimicrobial, antitumor and anticancer activities.[11] However, the methods for their preparation are very limited, and the common route is through the reaction of substituted 5-aminobenzimidazoles with β-keto esters (Scheme 1a).[11,12] Unfortunately, many drawbacks are found such as long reaction times, drastic conditions, tedious experimental procedure and low yields. Therefore, it is necessary to develop an efficient approach to this kind of compounds. Recently, many useful reactions have been developed using copper catalyst systems with low cost and low toxicity,[13] and nitrogen heterocycles were prepared by us and other groups.[14,15] Herein, we report a novel, efficient and practical copper-catalyzed domino method for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones (Scheme 1b).

Results and Discussion

The reaction of *N*-(2-bromophenyl)-3-phenylpropiolamide (**1a**) with cyanamide leading to 2-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-one (**2a**) was applied as the model to optimize conditions including catalysts, ligands, bases, solvents and temperature



Scheme 1. Synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones. (a) The previous common method. (b) Our strategy under copper-catalyzed conditions.

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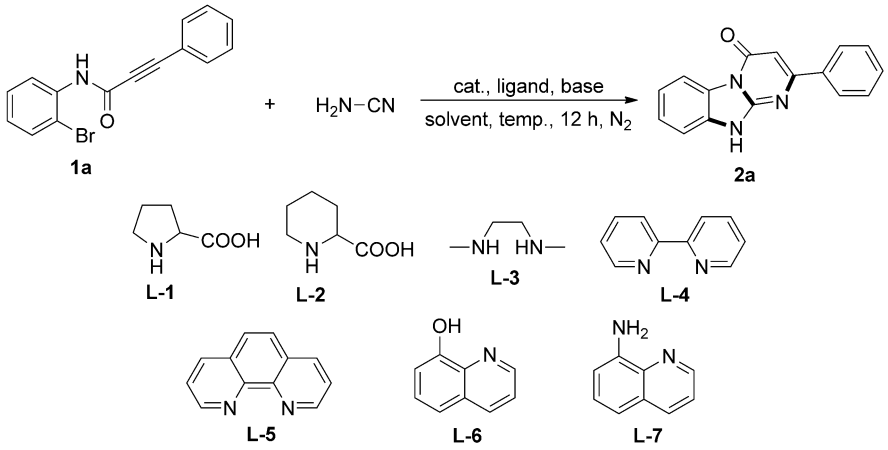
Table 1. Optimization of the conditions for copper-catalyzed synthesis of 2-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-one (**2a**) *via* reaction of *N*-(2-bromophenyl)-3-phenylpropiolamide (**1a**) with cyanamide.[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield [%][b]
1	CuCl	**L-1**	Cs_2CO_3	DMF	71
2	CuBr	**L-1**	Cs_2CO_3	DMF	75
3	CuI	**L-1**	Cs_2CO_3	DMF	77
4	Cu_2O	**L-1**	Cs_2CO_3	DMF	57
5	$CuBr_2$	**L-1**	Cs_2CO_3	DMF	72
6	$Cu(OAc)_2$	**L-1**	Cs_2CO_3	DMF	68
7	$Cu(OTf)_2$	**L-1**	Cs_2CO_3	DMF	76
8	–	**L-1**	Cs_2CO_3	DMF	0
9	**CuI**	**L-2**	**Cs_2CO_3**	**DMF**	**84**
10	CuI	**L-3**	Cs_2CO_3	DMF	72
11	CuI	**L-4**	Cs_2CO_3	DMF	54
12	CuI	**L-5**	Cs_2CO_3	DMF	53
13	CuI	**L-6**	Cs_2CO_3	DMF	50
14	CuI	**L-7**	Cs_2CO_3	DMF	52
15	CuI	**L-2**	K_2CO_3	DMF	54
16	CuI	**L-2**	K_3PO_4	DMF	46
17	CuI	**L-2**	Cs_2CO_3	DMA	80
18	CuI	**L-2**	Cs_2CO_3	DMSO	82
19	CuI	**L-2**	Cs_2CO_3	MeCN	76
20	CuI	**L-2**	Cs_2CO_3	DMF	67[c]

[a] *Reaction conditions:* under nitrogen atmosphere, *N*-(2-bromophenyl)-3-phenylpropiolamide (**1a**) (0.2 mmol), cyanamide (0.4 mmol), catalyst (0.02 mmol), ligand (0.02 mmol), base (0.4 mmol), solvent (3.0 mL), reaction temperature: 120 °C, reaction time: 12 h, in a sealed Schlenk tube.
[b] Isolated yield.
[c] Reaction temperature: 80 °C.

under a nitrogen atmosphere. As shown in Table 1, seven copper catalysts were screened using L-proline as the ligand, Cs_2CO_3 as the base, DMF as the solvent at 120 °C for 12 h (entries 1–7), and they provided 57–76% yields, whereby CuI was the most efficient catalyst (entry 3). No target product was found in the absence of a copper catalyst (entry 8). Other ligands were investigated (entries 9–14), and pipecolinic acid (PA, **L-2**) was found to be a suitable ligand (entry 9). K_2CO_3 and K_3PO_4 were attempted as the bases (entries 15 and 16), and they were inferior to Cs_2CO_3. Effect of solvents was explored (compare entries 9, 17–19), and DMF was a suitable solvent. Yields decreased when the reaction temperature was lowered to 80 °C (entry 20).

After defining the optimized conditions, the scope of this copper-catalyzed synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones (**2**) was investigated. As shown in Table 2, the examined substrates provided moderate to good yields. For the substituent R^1, the substrates (**1**) with neutral and electron-donating groups provided higher yields than those with electron-withdrawing groups (see entries 1, 3 and 6). For the substituent R^2, the substrates (**1**) with aryl groups gave the better results than those with alkyl groups (see entries 18–20). For halogen X, aryl bromides

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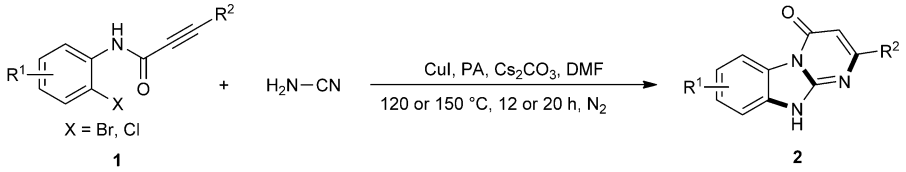
Table 2. Copper-catalyzed synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones (**2**).[a]



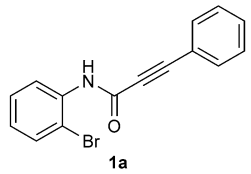
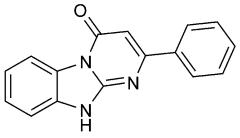
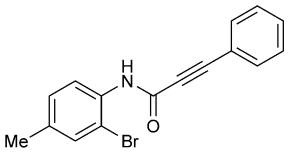
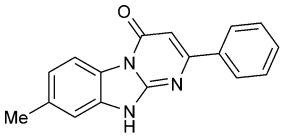
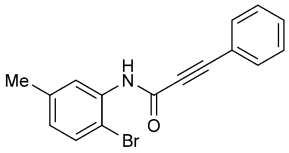
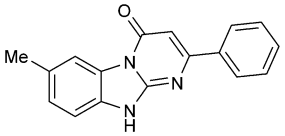
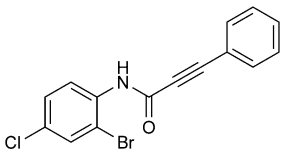
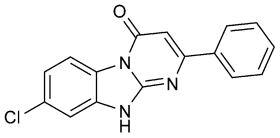
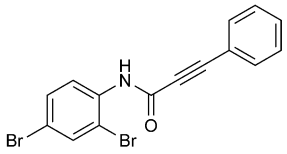
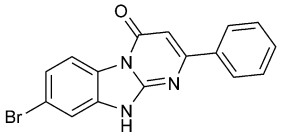
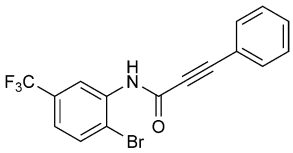
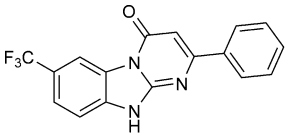
Entry	1	Temperature, Time	2 (Yield[b])
1	 **1a**	120 °C, 12 h	 **2a** (84%)
2	 **1b**	120 °C, 12 h	 **2b** (87%)
3	 **1c**	120 °C, 12 h	 **2c** (90%)
4	 **1d**	120 °C, 12 h	 **2d** (73%)
5	 **1e**	120 °C, 12 h	 **2e** (61%)
6	 **1f**	120 °C, 12 h	 **2f** (60%)

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Table 2. (Continued)

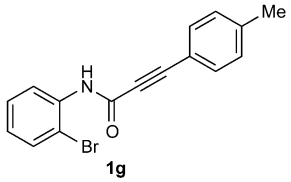
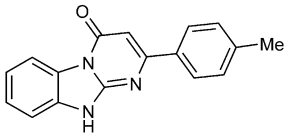
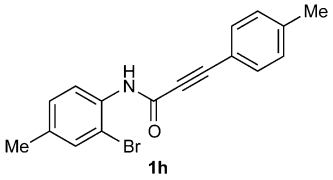
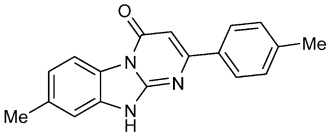
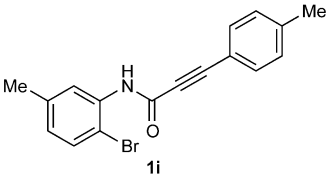
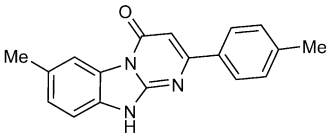
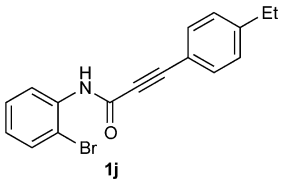
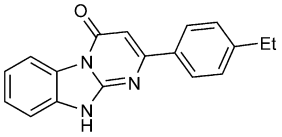
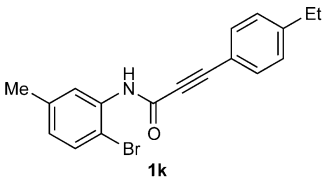
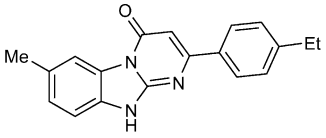
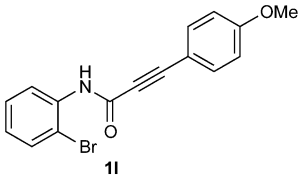
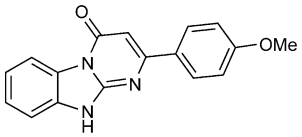
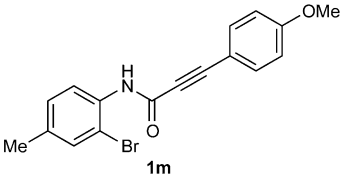
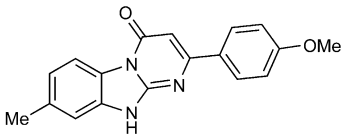
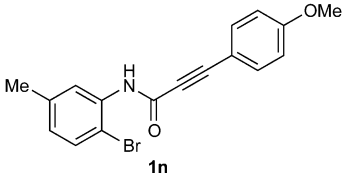
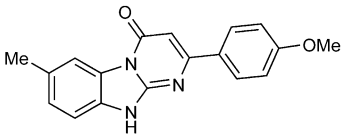
Entry	1	Temperature, Time	2 (Yield[b])
7	 **1g**	120 °C, 12 h	 **2g** (88%)
8	 **1h**	120 °C, 12 h	 **2h** (86%)
9	 **1i**	120 °C, 12 h	 **2i** (83%)
10	 **1j**	120 °C, 12 h	 **2j** (84%)
11	 **1k**	120 °C, 12 h	 **2k** (74%)
12	 **1l**	120 °C, 12 h	 **2l** (65%)
13	 **1m**	120 °C, 12 h	 **2m** (71%)
14	 **1n**	120 °C, 12 h	 **2n** (75%)

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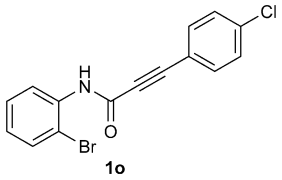
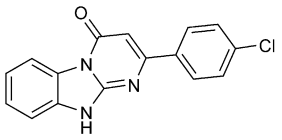
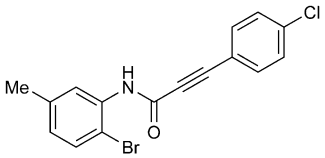
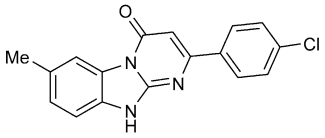
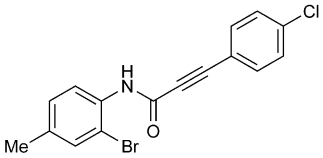
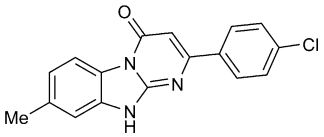
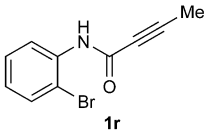
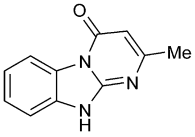
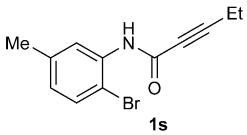
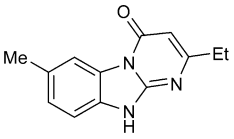
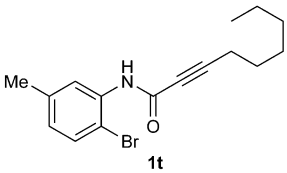
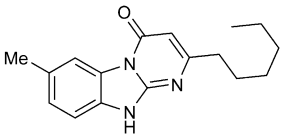
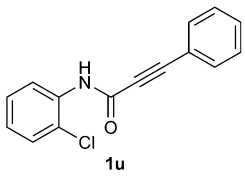
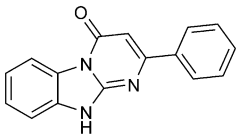
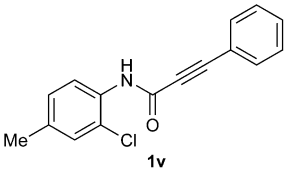
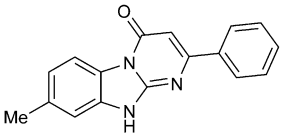
Table 2. (Continued)

Entry	1	Temperature, Time	2 (Yield[b])
15	 **1o**	120 °C, 12 h	 **2o** (68%)
16	 **1p**	120 °C, 12 h	 **2p** (65%)
17	 **1q**	120 °C, 12 h	 **2q** (67%)
18	 **1r**	120 °C, 12 h	 **2r** (67%)
19	 **1s**	120 °C, 12 h	 **2s** (61%)
20	 **1t**	120 °C, 12 h	 **2t** (47%)
21	 **1u**	150 °C, 20 h	 **2a** (54%)
22	 **1v**	150 °C, 20 h	 **2b** (60%)

[a] *Reaction conditions:* under nitrogen atmosphere, substituted *N*-(2-halophenyl)-3-alkylpropiolamide (**1**) (0.2 mmol), cyanamide (0.4 mmol), CuI (0.02 mmol), pipecolinic acid (PA) (0.02 mmol), Cs_2CO_3 (0.4 mmol), DMF (3.0 mL), reaction temperature: 120 or 150 °C, reaction time: 12 or 20 h, in a sealed Schlenk tube.

[b] Isolated yield.

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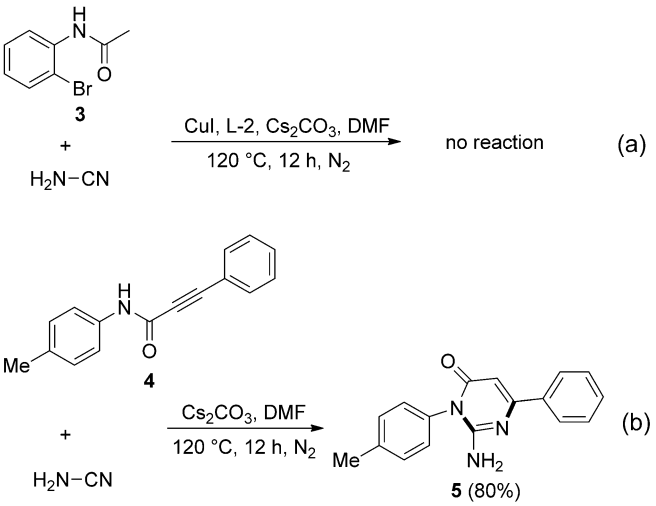
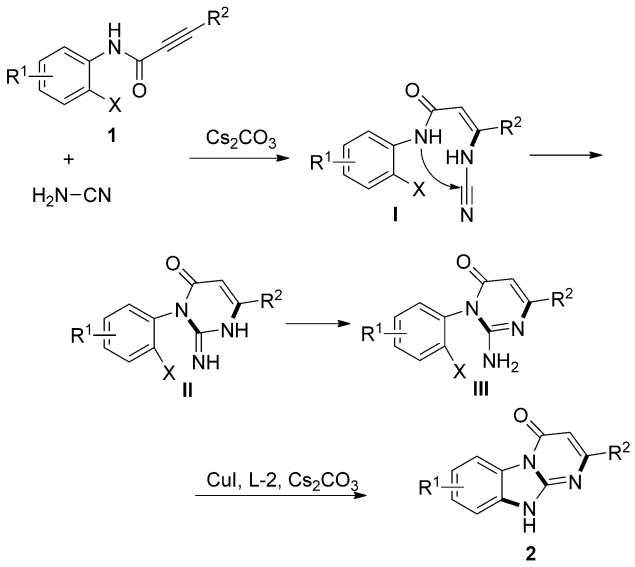


Scheme 2. (a) Reaction of *N*-(2-bromophenyl)acetamide (**3**) with cyanamide under the standard conditions. (b) Reaction of 3-phenyl-*N*-*p*-tolylpropiolamide (**4**) with cyanamide in the presence of base.

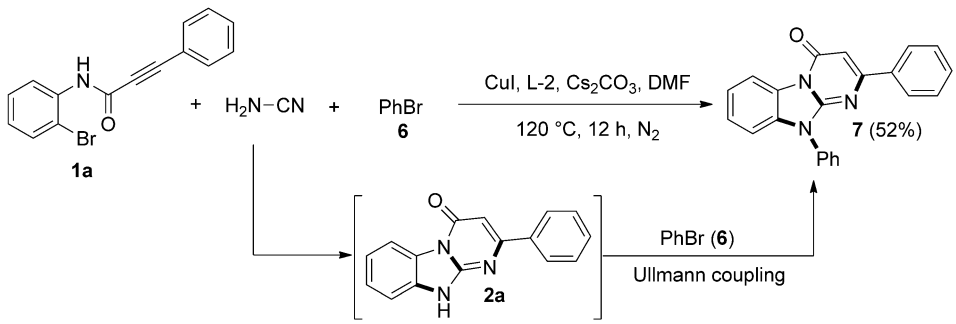


Scheme 3. Possible mechanism for the copper-catalyzed synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-one derivatives.

showed higher reactivity than aryl chlorides, but aryl chlorides also afforded the reasonable yields when the reaction temperature was raised and time was extended (see entries 21 and 22). The copper-catalyzed synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones (**2**) could tolerate some functional groups including C–Cl bond (entries 4, 15–17), C–Br bond (entry 5), CF_3 (entry 6), and ether (entries 12–14).

In order to explore the reaction mechanism, two control experiments were performed (Scheme 2). As shown in Scheme 2a, reaction of *N*-(2-bromophenyl)-acetamide (**3**) with cyanamide did not work under the standard conditions. Treatment of 3-phenyl-*N*-*p*-tolylpropiolamide (**4**) with cyanamide in the presence of base (Cs_2CO_3) provided 2-amino-6-phenyl-3-*p*-tolylpyrimidin-4(3*H*)-one (**5**) in 80% yield (Scheme 2b), and the result showed that the copper-catalyzed synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones (**2**) initiated from Michael addition of cyanamide to propiolamide in **1**. Therefore, a possible mechanism is suggested in Scheme 3 according to the results above. First, Michael addition of cyanamide to **1** in the presence of base (Cs_2CO_3) gives **I**, then nucleophilic attack of NH to the cyano group in **I** produces **II**, and isomerization of **II** leads to **III**. Finally, a copper-catalyzed intramolecular Ullmann-type coupling furnishes the target product (**2**) in the presence of pipecolinic acid (**L-2**) as the ligand.[16]

We have extended the applications of the present method. As shown in Scheme 4, a three-component reaction of *N*-(2-bromophenyl)-3-phenylpropiolamide (**1a**), cyanamide and bromobenzene (**6**) was carried out under the standard conditions. Interestingly, product **7** was obtained in 52% yield, and the reaction underwent sequential base-mediated and copper-catalyzed formation of **2a** from treatment of **1a** with cyanamide, and copper-catalyzed Ullmann-typed coupling of **2a** with **6**. Therefore, the three-component method can provide diverse dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones.



Scheme 4. Three-component reaction of *N*-(2-bromophenyl)-3-phenylpropiolamide (**1a**), cyanamide and bromobenzene (**6**).

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Conclusions

We have developed a simple, efficient and practical copper-catalyzed domino synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4-ones, and the corresponding target products were prepared in moderate to good yields. The protocol uses *N*-(2-halophenyl)-3-alkylpropiolamides and cyanamide as the starting materials, inexpensive CuI and pipecolinic acid as the catalyst system, and the domino reactions underwent the sequential base-mediated Michael addition, nucleophilic attack of NH to cyano and copper-catalyzed Ullmann-type coupling. The method exhibited some tolerance of functional groups, and the three-component reaction extended the diversity of benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-ones. Therefore, the present method provides a novel strategy for synthesis of nitrogen heterocycles.

Experimental Section

General Procedure

A Schlenk tube was charged with the mixture of CuI (0.02 mmol, 3.8 mg), pipecolinic acid (0.04 mmol, 5.2 mg), Cs_2CO_3 (0.4 mmol, 130 mg) and *N*-(2-halophenyl)-3-phenylpropiolamide derivatives **1** (0.2 mmol), cyanamide (0.4 mmol, 16.8 mg). The tube was evacuated and recharged with N_2 for three times. After DMF (3.0 mL) was added, and the tube was sealed, and the mixture was allowed to stir at 120 or 150 °C for 12 or 20 h. After completion, the mixture was cooled to room temperature, 5 mL of water were added to the tube. The solution was extracted with EtOAc (3×5 mL), and the combined organic phase was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was isolated by silica gel CC (DCM/PE/MeOH = 5:5:1) to provide the target product (**2**).

Three representative examples are shown below.

8-Methyl-2-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-one (2b): Eluent: DCM/PE/MeOH (5:5:1); isolated yield: 87% (47.8 mg) for X = Br in substrate **1**; 60% (33 mg) for X = Cl in substrate **1**; yellow solid; mp 297–299 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32 (d, J = 8.2 Hz, 1H), 8.10 (dd, J = 6.6, 3.1 Hz, 2H), 7.53–7.47 (m, 3H), 7.31 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.60 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.7, 160.1, 150.0, 137.5, 136.4, 130.9, 130.6, 129.1 (2×CH), 127.4 (2×CH), 124.1, 123.2, 115.7, 111.5, 97.3, 21.7; ESI-MS: m/z = 276.1, $C_{17}H_{14}N_3O$ $[M+H]^+$.

2-(*p*-Tolyl)benzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-one (2g): Eluent: DCM/PE/MeOH (5:5:1); isolated yield: 88% (48.4 mg); yellow solid; mp 292–293 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.42 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.44 (s, 2H), 7.27 (dd, J = 12.4, 5.5 Hz, 3H), 6.53 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.6, 159.8, 149.5, 140.1, 134.2, 130.7, 129.3 (2×CH), 127.0 (2×CH), 126.1, 125.8, 121.8, 115.7, 111.1, 96.5, 20.9; ESI-MS: m/z = 276.1, $C_{17}H_{14}N_3O$ $[M+H]^+$.

2-(4-Chlorophenyl)-8-methylbenzo[4,5]imidazo[1,2-*a*]pyrimidin-4(10*H*)-one (2q): Eluent: DCM/PE/MeOH (5:5:1); isolated yield: 67% (41.5 mg); yellow solid; mp 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.31 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.32–7.27 (m, 3H), 7.14 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (76 MHz, DMSO-d_6): δ = 161.1, 160.2, 150.0, 146.7, 136.5, 135.1, 131.3, 128.6 (2×CH), 127.5 (2×CH), 124.3, 123.3, 115.8, 111.5, 97.1, 21.9. ESI-MS: m/z = 310.1, $C_{17}H_{13}ClN_3O$ $[M+H]^+$.

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