

Copper-Catalyzed Domino Synthesis of Isoquinolino[2,3-*a*]quinazolinones

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Abstract: A copper-catalyzed domino method for synthesis of isoquinolino[2,3-*a*]quinazolinones has been developed using readily available, substituted methyl 2-(2-haloobenzamido)benzoates and nitriles as the starting materials. The domino process comprises an Ullmann-type C-arylation, intramolecular addition of NH with CN, and nucleophilic attack of amino to ester group. The inexpensive, convenient

and efficient copper-catalyzed method should provide a new and useful strategy for constructing nitrogen heterocycles.

Keywords: copper; domino method; isoquinolino[2,3-*a*]quinazolinones; nitrogen heterocycles; Ullmann-type coupling

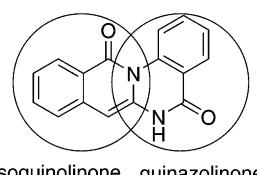
Introduction

Isoquinolinone derivatives widely occur in natural products,^[1] and they are also versatile building blocks for the total synthesis of natural alkaloids.^[2] Some isoquinolinones exhibit various biological and medicinal activities such as antihypertensive activity^[3a,b] and act as NK3 antagonists,^[3c] melatonin MT₁ and MT₂ receptor agonists,^[3d] Rho-kinase inhibitors,^[3e] and JNK inhibitors.^[3f] They also are novel orally active 5-HT3 antagonists,^[4a] thymidylate synthase (TS) inhibitors,^[4b] or find use for the treatment of stomach tumors and diseases of human brain cells.^[1b] Quinazolinone derivatives found in natural products show various biological and pharmacological activities.^[5] For example, they act as psychotropic, hypnotic, cardiotonic and antihistamine agents, and exhibit many central nervous system effects as well as cardiovascular and anti-inflammatory activity.^[5] They are used as potent anti-

bacterial, antifungal, antiviral, antimycobacterial and antimalarial substances.^[6] In addition, they are inhibitors of various enzymes including monoamine oxidase, aldose reductase, tumor necrosis factor α , thymidylate synthase.^[6,7] However, investigations on the hybrid structure of isoquinoline and quinazoline motifs, namely isoquinolino[2,3-*a*]quinazolinone derivatives (Figure 1), are very rare, and only two references were found by Scifinder search in which there are limited and special compounds.^[8] Therefore, the development of a convenient and efficient approach to isoquinolino[2,3-*a*]quinazolinone derivatives will be valuable for the screening of novel biologically active molecules. Recently, there has been great progress in copper-catalyzed Ullmann-type couplings,^[9] and some nitrogen heterocycles were made through such couplings by other groups^[10] and by us^[11] Herein, we report an efficient copper-catalyzed synthesis of isoquinolino[2,3-*a*]quinazolinone derivatives through domino reactions of substituted methyl 2-(2-bromobenzamido)benzoate with nitriles under mild conditions.

Results and Discussion

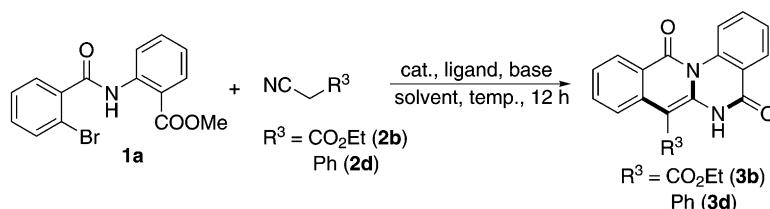
At first, methyl 2-(2-bromobenzamido)benzoate (**1a**) and ethyl 2-cyanoacetate (**2b**) were used as the model substrates to optimize the reaction conditions includ-



isoquinolinone quinazolinone

Figure 1. Isoquinolino[2,3-*a*]quinazolinone as hybrid structure of isoquinoline and quinazolinone motifs.

Table 1. Copper-catalyzed domino reaction of methyl 2-(2-bromobenzamido)benzoate (**1a**) with ethyl 2-cyanoacetate (**2b**) or 2-phenylacetonitrile (**2d**) leading to isoquinolino[2,3-*a*]quinazolinone **3b** or **3d**: optimization of reaction conditions.^[a]



Entry	R ³	Catalyst	Base	Solvent	Temperature [°C]	Yield [%] ^[b]
1	COOEt	CuI	K₂CO₃	DMF	100	75
2	COOEt	CuCl	K ₂ CO ₃	DMF	100	52
3	COOEt	CuBr	K ₂ CO ₃	DMF	100	72
4	COOEt	Cu ₂ O	K ₂ CO ₃	DMF	100	42
5	COOEt	CuBr ₂	K ₂ CO ₃	DMF	100	30
6	COOEt	Cu(OAc) ₂	K ₂ CO ₃	DMF	100	37
7	COOEt	CuI	Cs ₂ CO ₃	DMF	100	69
8	COOEt	CuI	K ₃ PO ₄	DMF	100	61
9	COOEt	CuI	Na ₂ CO ₃	DMF	100	38
10	COOEt	CuI	K ₂ CO ₃	DMSO	100	44
11	COOEt	CuI	K ₂ CO ₃	dioxane	100	51
12	COOEt	CuI	K ₂ CO ₃	toluene	100	trace
13	COOEt	CuI	K ₂ CO ₃	DMF	110	71
14	COOEt	CuI	K ₂ CO ₃	DMF	90	63
15	Ph	CuI	K ₂ CO ₃	DMF	100	43
16	Ph	CuI	Cs ₂ CO ₃	DMF	100	52
17	Ph	CuI	Cs₂CO₃	DMF	100	71^[c]
18	H	CuI	Cs ₂ CO ₃	DMF	100	0 ^[c]
19	n-C ₅ H ₇	CuI	Cs ₂ CO ₃	DMF	100	0 ^[c]

[a] Reaction conditions: methyl 2-(2-bromobenzamido)benzoate (**1a**) (0.5 mmol), ethyl 2-cyanoacetate (**2b**) or 2-phenylacetonitrile (**2d**) (0.6 mmol), catalyst (0.05 mmol), base (0.75 mmol), solvent (1 mL) under a nitrogen atmosphere.

[b] Isolated yield.

[c] In the presence of L-proline (0.1 mmol).

ing catalysts, ligands, bases, solvents and reaction temperatures under a nitrogen atmosphere. As shown in Table 1, six copper salts were screened in DMF in the presence of 0.1 equiv. of CuI and 1.5 equiv. of K₂CO₃ (relative to amount of **1a**) at 100°C (entries 1–6), and CuI provided the highest yield (entry 1). We tested various bases (compare entries 1, 7–9), and K₂CO₃ showed the best result (entry 1). The effect of solvents was also investigated (compare entries 1, 10–12), and DMF was suitable (entry 1). We attempted different temperatures (compare entries 1, 13 and 14), and 100°C was optimal (entry 1). When 2-phenylacetonitrile (**2d**) was used the partner of **1a**, only 43% yield was afforded (entry 15). The yield rose to 52% when Cs₂CO₃ replaced K₂CO₃ as the base (entry 16). The reaction provided a 71% yield in the presence of L-proline (entry 17). When acetonitrile (entry 18) or butyronitrile (entry 19) was used as the substrate, no reaction was observed. Therefore, the optimized conditions for reactions of substituted methyl 2-(2-halobenzamido)benzoates (**1**) with nitriles (**2**) are as follows: use of 10 mol% of CuI as the catalyst, 1.5 equiv. of

K₂CO₃ as the base (relative to amount of **1**), and DMF as the solvent at 100°C for alkyl 2-cyanoacetates or use of 10 mol% of CuI as the catalyst, 20 mol% L-proline as the ligand, 1.5 equiv. of Cs₂CO₃ as the base (relative to amount of **1**), and DMF as the solvent at 100°C for other nitriles.

We investigated the scope of the copper-catalyzed domino reactions of substituted methyl 2-(2-halobenzamido)benzoates (**1**) with nitriles (**2**) under the optimized conditions. As shown in Table 2, the corresponding isoquinolino[2,3-*a*]quinazolinones (**3**) were obtained in moderate to good yields for various examined substrates at 100°C. For substituted methyl 2-(2-halobenzamido)benzoates, the aryl bromides exhibited higher reactivity than the corresponding chlorides, only aryl chloride containing a nitro group could work. For nitriles (**2**), alkyl 2-cyanoacetates (**2a–c**) showed higher reactivity than substituted 2-phenylacetonitriles and 3-oxo-3-phenylpropanenitrile (**2d–g**), and a ligand (L-proline) and a stronger base (Cs₂CO₃) were required for **2d–g**. The copper-catalyzed domino synthesis of isoquinolino[2,3-*a*]quinazolines showed

Table 2. Copper-catalyzed domino synthesis of isoquinolino[2,3-*a*]quinazolinones.^[a]

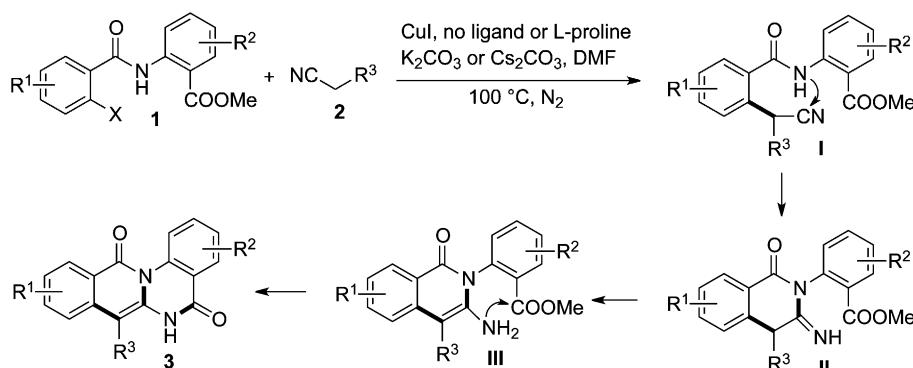
Entry	1	2	Reaction time	3	Yield [%]
1	1a 	2a NC-CH ₂ CO ₂ Me	12 h	3a 	77
2	1a	2b NC-CH ₂ CO ₂ Et	12 h	3b 	75
3	1a	2c NC-CH ₂ CO ₂ Bu- <i>n</i>	12 h	3c 	82
4	1a	2d NC-CH ₂ Ph	12 h	3d 	71
5	1a	2e NC-CH ₂ C ₆ H ₄ Me- <i>p</i>	12 h	3e 	62
6	1a	2f NC-CH ₂ C ₆ H ₄ F- <i>p</i>	12 h	3f 	78
7	1b 	2c	12 h	3g 	54
8	1c 	2c	12 h	3h 	65
9	1d 	2b	12 h	3i 	69

Table 2. (Continued)

Entry	1	2	Reaction time	3	Yield [%]
10	1e 	2c	12 h	3j 	64
11	1f 	2b	12 h	3k 	62
12	1g 	2e	12 h	3l 	59
13	1h 	2b	18 h	3m 	61
14	1h	2c	18 h	3n 	61
15	1h	2d	18 h	3o 	55
16	1h	2g 	18 h	3p 	68
17	1i 	2c	18 h	3q 	52
18	1f 	2c	18 h	3r 	57

[^a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CuI (0.05 mmol), K₂CO₃ (0.75 mmol), Cs₂CO₃ (0.75 mmol), DMF (1 mL) under a nitrogen atmosphere. K₂CO₃ as the base and no addition of ligand for substrates **2a–c**; Cs₂CO₃ as the base and L-proline as the ligand for substrates **2d–g**.

[^b] Isolated yield.

**Scheme 1.** Possible mechanism for copper-catalyzed synthesis of isoquinolino[2,3-*a*]quinazolinones.

good tolerance of the functional groups in the substrates including esters (entries 1–3, 7–14, 17 and 18), ethers (7, 12 and 17), amides (entries 1–18), C–F bond (entry 6), C–Cl bond (entry 12), C–Br bond (entry 18) and nitro group (entries 13–18).

A possible mechanism for the copper-catalyzed domino synthesis of isoquinolino[2,3-*a*]quinazolinones (**3**) is suggested in Scheme 1. The Hurtley-type coupling¹² (*C*-arylation of α -C–H in nitrile) of substituted methyl 2-(2-halobenzamido)benzoates (**1**) with nitriles (**2**) first provides **I**, and then intramolecular addition of NH with CN in **I** leads to **II**. Isomerization of the C=NH double bond forms **III**, and intramolecular nucleophilic attack of NH₂ to the ester group yields the target product **3**.

Conclusions

We have developed a simple and efficient copper-catalyzed domino method for the synthesis of isoquinolino[2,3-*a*]quinazolinones. The protocol uses cheap and readily available CuI as the catalyst and substituted methyl 2-(2-halobenzamido)benzoates and nitriles as the starting materials, and the corresponding isoquinolino[2,3-*a*]quinazolinones were obtained in moderate to good yields under mild conditions. The inexpensive, convenient and efficient copper-catalyzed method should provide a new and useful strategy for the construction of nitrogen-containing heterocycles.

Experimental Section

General Procedure for Domino Reactions of Substituted 2-Halobenzamides with Nitriles leading to Isoquinolino[2,3-*a*]quinazolinones

A 25-mL Schlenk tube equipped with a magnetic stirring bar was charged with CuI (0.05 mmol, 9 mg), substituted methyl 2-(2-halobenzamido)benzoate (**1**) (0.5 mmol), nitrile

(**2**) (0.6 mmol), K₂CO₃ (0.75 mmol, 104 mg) (without ligand) for substrates **2a–c** or Cs₂CO₃ (0.75 mmol, 245 mg) and L-proline (0.01 mmol, 12 mg) for substrates **2d–g**. The tube was evacuated twice and backfilled with nitrogen, and DMF (1 mL) was added to the tube under a nitrogen atmosphere. The tube was sealed and then the mixture was allowed to stir under a nitrogen atmosphere at 100°C for 12 or 18 h. After completion of the reaction, the resulting solution was cooled to room temperature, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using chloroform/methyl alcohol (10:1) as eluent to provide the desired product (**3**). Three representative examples are shown as follows:

Methyl 6,12-dihydro-5,12-dioxo-5*H*-isoquinolino[2,3-*a*]-quinazoline-7-carboxylate (3a): Eluent: chloroform/methyl alcohol (10:1); yield: 123 mg (77%); yellow solid; mp 195–197°C. ¹H NMR (DMSO-*d*₆, 300 MHz): δ =8.60 (s, 1H), 8.07–8.16 (m, 3H), 7.67–7.78 (m, 2H), 7.37–7.53 (m, 2H), 3.90 (s, 3H); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ =169.1, 161.8, 158.0, 146.1, 137.9, 134.4, 134.3, 133.9, 128.6, 127.6, 127.0, 125.7, 125.7, 122.7, 122.4, 119.7, 86.9, 53.0; HR-MS (ESI): *m/z*=321.0877, calcd. for C₁₈H₁₃N₂O₄ [M+H]⁺: 321.0875.

7-Phenyl-6*H*-isoquinolino[2,3-*a*]quinazoline-5,12-dione (3d): Eluent: chloroform/methyl alcohol (10:1); yield: 120 mg (71%); yellow solid; mp 243–245°C. ¹H NMR (DMSO-*d*₆, 300 MHz): δ =9.41 (s, 1H), 9.05 (d, *J*=4.5 Hz, 1H), 8.32 (d, *J*=3.9 Hz, 1H), 8.08 (d, *J*=4.6 Hz, 1H), 7.78 (m, 1H), 7.37–7.60 (m, 8H), 6.90 (m, 1H); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ =162.2, 157.9, 138.4, 137.2, 133.9, 133.9, 133.8, 133.0, 132.3, 130.3, 129.1, 128.6, 127.6, 127.0, 125.4, 124.1, 122.6, 121.8, 119.6, 100.5; HR-MS (ESI) *m/z*=361.0955, calcd. for C₂₂H₁₄N₂NaO₂ [M+Na]⁺: 361.0953.

Butyl 10-chloro-6,12-dihydro-2,3-dimethoxy-5,12-dioxo-5*H*-isoquinolino[2,3-*a*]quinazoline-7-carboxylate (3l): Eluent: chloroform/methyl alcohol (6:1); yield: 135 mg (59%); yellow solid; mp 197–199°C. ¹H NMR (DMSO-*d*₆, 300 MHz): δ =8.37 (m, 1H), 8.29 (m, 1H), 8.14 (m, 1H), 7.74 (m, 1H), 7.45 (m, 1H), 4.36 (m, 2H), 3.87 (b, 6H), 1.73 (m, 2H), 1.41 (m, 2H), 0.91 (t, *J*=7.2 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 75 MHz): δ =168.5, 160.8, 157.3, 153.5, 148.7, 145.6, 133.9, 132.7, 132.5, 129.9, 128.1, 128.0, 127.7, 123.5, 112.9, 107.9, 106.5, 86.4, 66.0, 56.6, 30.6, 19.4, 14.0; HRMS (ESI) *m/z*=479.0989, calcd. for C₂₃H₂₁ClN₂NaO₆ [M+Na]⁺: 479.0986.

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