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Copper-catalyzed one-pot synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones from *ortho*-bromobenzamides and isothiocyanates

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ABSTRACT

Copper-catalyzed tandem reaction of *ortho*-bromobenzamides and isothiocyanates is described, which provides an efficient and practical route for the synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones. The optimal condition involved the following parameters: CuI as precatalyst, Cs_2CO_3 as base, *N*,*N*′-dimethylethane-1,2-diamine as ligand, and toluene as solvent, with reaction temperature at 120 °C.

2-Thioxo-2,3-dihydroquinazolin-4(1*H*)-one is an important subclass of quinazolinones found to possess a variety of bioactivities.[1] For example, altanserin (3-(2-(4-(4-fluorobenzoyl)-l-piperidinyl)-ethyl)-2,3-dihydro-2-thioxo-1*H*-quinazolin-4-one) and nitro altanserin are drugs for 5-HT_{2A} receptor antagonists.[2] R59949, a 2,3-dihydro-2-thioxo-1*H*-quinazolin-4-one derivative, exhibits its DGK (diacylglycerol kinases) inhibitor activity by activating PKC (protein kinase C) by enhancing the levels of the endogenous ligand diacyl glycerol.[3] The 2-thioxo-1*H*-4-quinazolinones are also versatile intermediates for fused heterocycloquinazolinones,[4] such as 2-phenyl-5*H*-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-one, 3-(4-bromophenyl)-2*H*,6*H*-[1,3,4]thiadiazino-[2,3-*b*]quinazolin-6-one, 4-amino-2-phenyl-3a,4-dihydro-2*H*-thiazolo[3,2-*a*]quinazoline-1,5-dione, and 2-phenyl-[1,3,4]thiadiazino[2,3-*b*]quinazoline-3,6(2*H*,4*H*)-dione.[5] General methods for the preparation of these useful structural motifs include condensing the anthranilic acid with isothiocyanates,[6] reaction of aminobenzamide with carbon disulfide,[7] reaction of 2-methoxycarbonyl phenylisothiocyanate with amine,[8] reaction of nitrobenzamide with isothiocyanates,[9] and reaction of isatoic anhydride with isothiocyanates.[10] Although some of these synthetic methods are very useful, most of them are associated with one or the other limitations, such as involving two or more steps, use of toxic chemicals, for example, thiophosgene, employment of harsh reaction conditions, long reaction time, low reaction yields, and the low availability of starting materials. Furthermore, most of the methods provide thioxo-quinazolines with the substituent bonded to the N-3 position[11] while N-1 substituted structures were rarely reported.[12] Consequently, new and efficient methodologies for construction of 1-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones are still desirable.

Metal catalyzed cross-coupling reactions of N-central nucleophiles and aryl halides have been demonstrated to be a powerful tool in the formation of aryl C–N bonds.[13–15] Recently, one-pot strategies for the synthesis of various useful heterocyclic compounds based on the copper-catalyzed C–X (X = N, O, and S) bond formation have been studied.[16–18] For example, benzimidazoles could be efficiently formed via aryl amination/condensative cyclization processes.[16a–c] Also, intermolecular addition/intramolecular C–N, or C–O, or C–S coupling protocols for the formation of indoles,[16h–l] benzofurans,[17b] and benzothiazoles[18d–g] have been disclosed, respectively. To the best of our knowledge, there is no report on the formation of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones via a one-pot copper-catalyzed coupling process. Herein we report an efficient one-pot cascade reaction to synthesize 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones: *ortho*-bromobenzamide would undergo the intermolecular addition/intramolecular C–N coupling process with isothiocyanate in the Cu(I)-ligand-base system. Our proposed approach is summarized in Scheme 1. In the presence of a proper base, the nucleophilic nitrogen of *ortho*-bromobenzamide **1** would attack the carbon atom of NCS on isothiocyanatobenzene **2** and intermediate **4** could be formed (step **a**). In the presence of a proper copper(I) catalyst and ligand, **4** might convert into the product **3** via an intramolecular C–N coupling (step **b**). In the latter step, the nitrogen atom would take priority over sulfur atom in the assaulting action.

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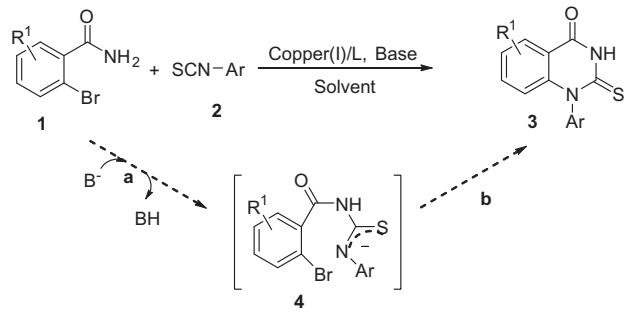
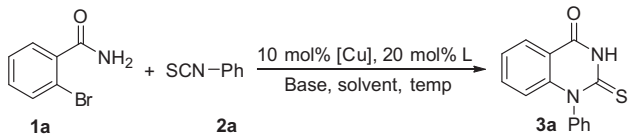


Scheme 1. Proposed one-pot synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones via intermolecular addition/intramolecular C–N coupling.

In our preliminary experiments, *ortho*-bromobenzamide **1a** and isothiocyanate **2a** were chosen as model substrates. The reaction was originally examined in toluene with CuI (10 mol %) as precatalyst, Cs_2CO_3 as base at 120 °C to screen ligand (Table 1). To our delight, among the three ligands examined, *N*,*N*′-dimethylethane-1,2-diamine (DMEDA) **L1** gave an excellent result (entry 1). 1,10-Phenanthroline **L2** and L-proline **L3** also afforded satisfying results (entries 2–3). In the absence of ligand, the reaction can also proceed in 38% yield under the reaction conditions (entry 4). Next, the applicability of other bases and solvents was also evaluated. Clearly, Cs_2CO_3 proved to be superior to ^{t}BuONa, DBU, K_3PO_4, and K_2CO_3 (entry 1, entries 5–8). DABCO and AcONa proved to be inefficient (entries 9–10). The reaction also showed a solvent dependence. Except toluene, other solvents, such as DMF, 1,4-dioxane, and DMSO proved to be appropriate and the product was formed in moderate yield (entries 11–13). The reaction also showed a significant dependence on temperature. When the reaction was treated at 80 °C, the reaction did not proceed (entry 15). When the reaction mixture was warmed to 100 °C, the desired product was formed in 60% yield (entry 14). It is noteworthy that without using CuI, the reaction proceeded in less than 10% yield (entry 16). CuBr also gave product in 69% yield (entry 18).

Table 1
Optimization of the reaction conditions for the formation of **3a**[a]



Entry	[Cat]	Base	Ligand	Solvent	Yield[e] (%)
1	CuI	Cs_2C0_3	L1	Toluene	82
2	CuI	Cs_2C0_3	L2	Toluene	72
3	CuI	Cs_2C0_3	L3	Toluene	65
4	CuI	Cs_2C0_3	—	Toluene	38
5	CuI	^{t}BuONa	L1	Toluene	58
6	CuI	DBU	L1	Toluene	70
7	CuI	K_3P0_4	L1	Toluene	53
8	CuI	K_2C0_3	L1	Toluene	48
9	CuI	DABCO	L1	Toluene	Trace
10	CuI	AcONa	L1	Toluene	NR
11	CuI	Cs_2C0_3	L1	DMF	67
12	CuI	Cs_2C0_3	L1	1,4-Dioxane	74
13	CuI	Cs_2C0_3	L1	DMSO	57
14[b]	CuI	Cs_2C0_3	L1	Toluene	60
15[c]	CuI	Cs_2C0_3	L1	Toluene	NR
16	—	Cs_2C0_3	L1	Toluene	10
17[d]	CuI	Cs_2C0_3	L1	Toluene	62
18	CuBr	Cs_2CQ_3	L1	Toluene	69

[a] Unless otherwise noted, all the reactions were performed in sealed tube with **1a** (0.5 mmol), **2a** (0.75 mmol), cat (10 mol %), ligand (20 mol %), base (1 mmol) in 2 mL solvent for 24 h.
[b] The temperature was 100 °C.
[c] The temperature was 80 °C.
[d] The reaction time was 12 h.
[e] The yields were evaluated by ^{1}H NMR of crude product with CH_2Cl_2 as internal standard.

To confirm the structure of the product, colorless single crystals of **3a** suitable for X-ray diffraction analysis were obtained by recrystallization in dichloromethane/*n*-hexane (5/1) at room temperature. The structure of **3a** in Figure 1 clearly shows the formation of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one skeleton, in which the nitrogen ring was formed.

On the basis of these results, the optimal condition involved the following parameters: CuI as precatalyst, Cs_2CO_3 as base, *N*,*N*′-dimethylethane-1,2-diamine as ligand, and toluene as solvent, with reaction temperature at 120 °C. Under these optimized conditions, a study on the substrate scope was carried out and the results are summarized in Table 2.

In order to investigate the scope and the generality of this method, we varied the isothiocyanates, in which several kinds of substituent are linked to the benzene ring. To our delight, the reaction could proceed mostly under the optimized conditions (entries 1–5). When isothiocyanatocyclohexane **2f** was treated with *ortho*-bromobenzamide **1a** under the similar conditions, the desired product was not observed rather 1,3-dicyclohexylthiourea **5a** was obtained (entry 6). This may be attributed to self-condensation under the condition.[19] The reaction of *ortho*-bromobenzamide with *p*-methyl substituent **1b** could perform successfully (entries 7–8). When 4-F-*ortho*-bromobenzamide **1c** was used as the substrate, the yield of product was excellent regardless of electron-donating or electron-withdrawing group linked to the isothiocyanates (entries 10–13). It might be attributed to the strong electron-withdrawing effect of fluoro atom, which greatly enhanced the acidity of the amide proton. It is noteworthy that the reaction of 4,5-dimehoxyl-*ortho*-bromobenzamide **1d** with isothiocyanate **2a** did not afford the desired product, only the corresponding thiourea derivative **6a** and **6b** were found (entries 14–15). Furthermore, the reaction of 5-methoxyl *ortho*-bromobenzamide **1e** and 4-methoxyl *ortho*-bromobenzamide **1f** with isothiocyanate **2a** did not afford the desired product, respectively, only the corresponding thiourea derivative **6a** was found (entries 16–17). It may be that the strong electron-donating group blocked the reaction.

In summary, we have developed a novel, concise, and efficient one-pot synthetic method to synthesize 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one using CuI as precatalyst. Various 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones, which might be potentially applicable in the pharmaceutical and biochemical area, were conveniently synthesized in moderate to excellent yields.

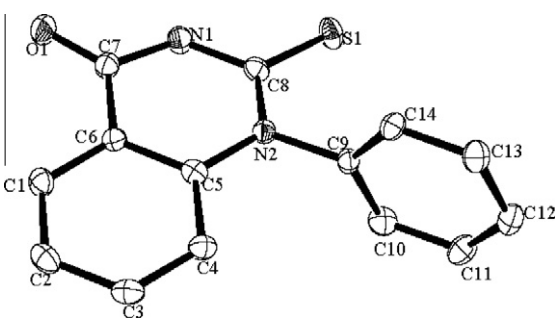
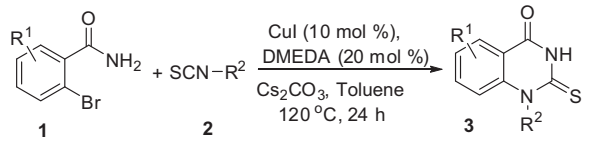
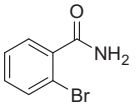
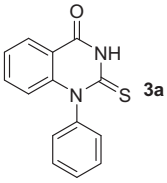
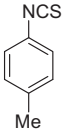
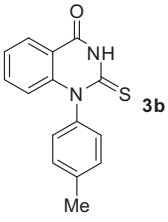
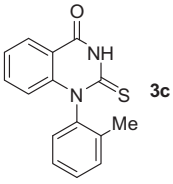
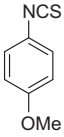
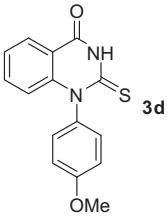
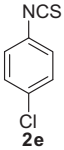
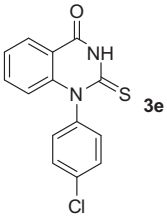
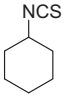
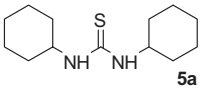
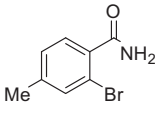
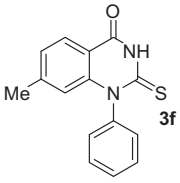
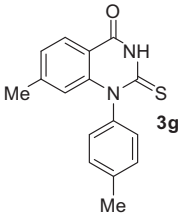


Figure 1. The structure of **3a**.

Table 2
CuI-catalyzed one-pot synthesis of 1-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones[a]

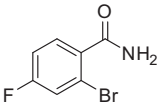
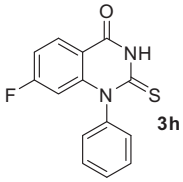
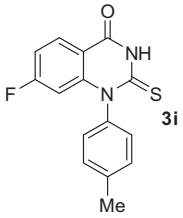
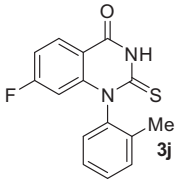
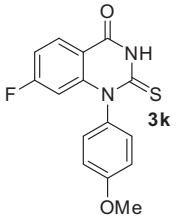
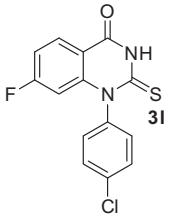
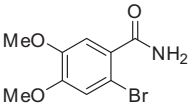
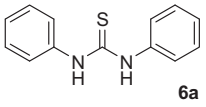
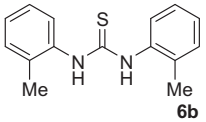
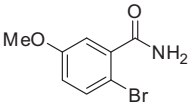
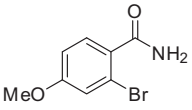


1 2 3

Entry	*ortho*-Bromobenzamide	Isothiocyanate	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	80
2	**1a**	 **2b**	 **3b**	78
3	**1a**	 **2c**	 **3c**	82
4	**1a**	 **2d**	 **3d**	67
5	**1a**	 **2e**	 **3e**	85
6	**1a**	 **2f**	 **5a**	78
7	 **1b**	**2a**	 **3f**	75
8	**1b**	**2b**	 **3g**	72

(*continued on next page*)

Table 2 (*continued*)

Entry	*ortho*-Bromobenzamide	Isothiocyanate	Product	Yield[b] (%)
9	 **1c**	**2a**	 **3h**	85
10	**1c**	**2b**	 **3i**	86
11		**2c**	 **3j**	87
12	**1c**	**2d**	 **3k**	82
13	**1c**	**2e**	 **3l**	90
14	 **1d**	**2a**	 **6a**	84
15	**1d**	**2c**	 **6b**	62
16	 **1e**	**2a**	**6a**	70
17	 **1f**	**2a**	**6a**	65

[a] Unless otherwise noted, all the reactions were performed in sealed tube with **1** (0.5 mmol), **2** (0.75 mmol), CuI (10 mol %), DMEDA (20 mol %), Cs_2CO_3 (1 mmol) in 2 ml toluene for 24 h.

[b] Isolated yields.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data, ^{1}H, ^{13}C NMR spectra and MS data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.010.

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