Homogeneous Catalysis

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A Simple and Efficient Approach to Quinazolinones under Mild Copper-Catalyzed Conditions**

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Quinazolinone (**Q**) is a key core structure that occurs in natural products such as luotonin A from *Peganum nigellastrum*,[1a] 2-methyl-4(3*H*)-quinazolinone from *Bacillus cereus*,[1b] 2-(4-hydroxybutyl)quinazolin-4-one from *Dichroa febrifuga*,[1c] and bouchardatine from *Bouchardatia neurococca* (Figure 1).[1d] Quinazolinone derivatives are now known to have useful biological and medicinal activities; they can be used as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, antidiabetic, anti-inflammatory, and antitumor agents.[2,3] Additionally, some therapeutic agents containing this core structure have been on the market or are in clinical trials for the treatment of cancer.[4]

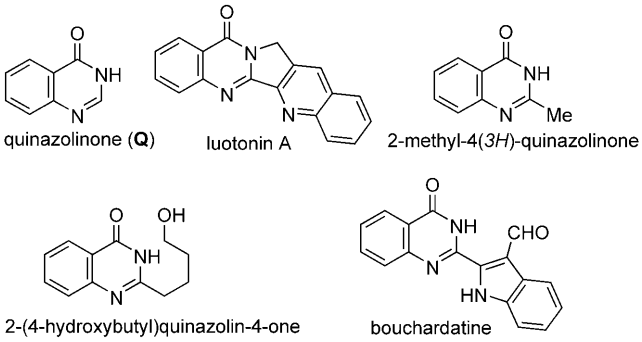
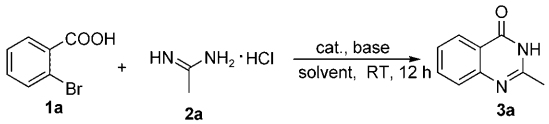


Figure 1. Quinazolinone (**Q**) and examples of related natural products.

Although some methods for the synthesis of quinazolinone derivatives[2,5,6] have been developed, they depend on the availability of the requisite *ortho*-amino- or -nitrobenzoic acid derivatives. Some of the starting materials are also sometimes difficult to prepare. Recently, progress has been made on the copper-catalyzed Ullmann N-arylations,[7] and they have been used to make N-heterocycles.[8] Unfortunately, these methods are not useful for constructing some quinazolinone molecules because the reaction temperatures are too high. Therefore, it is desirable to develop milder copper-catalyzed coupling methods. Recently, Shafir and Buchwald[9] and ourselves[10] have developed copper-catalyzed N-arylations at room temperature, and the results showed that the efficiency of the copper-catalyzed coupling reactions was highly dependent on the involvement of suitable ligands. To the best of our knowledge, there is no example of constructing N-heterocycles under ligand-free copper catalysis at room temperature. Herein, we report a simple, practical, and efficient strategy for the synthesis of quinazolinone derivatives by using mild copper-catalyzed conditions in the absence of ligands or additives.

2-Bromobenzoic acid (**1a**) and acetamidine hydrochloride (**2a**) were chosen as the model substrates for the optimization of the reaction conditions, which include the catalyst, base, and solvent. As shown in Table 1, four copper catalysts were tested at room temperature by using two equivalents of Cs_2CO_3 as the base (relative to amount of **1a**) in DMF

Table 1: Copper-catalyzed coupling of 2-bromobenzoic acid with acetamidine hydrochloride: Optimization of the reaction conditions.[a]



Entry	Catalyst	Base	Solvent	Yield [%][b]
1	Cu	Cs_2CO_3	DMF	19
2	$CuSO_4$	Cs_2CO_3	DMF	23
3	CuBr	Cs_2CO_3	DMF	75
4	CuI	Cs_2CO_3	DMF	81
5	CuI	Cs_2CO_3	DMF	57[c]
6	CuI	K_2CO_3	DMF	74
7	CuI	K_3PO_4	DMF	69
8	CuI	Cs_2CO_3	toluene	trace
9	CuI	Cs_2CO_3	dioxane	62
10	CuI	Cs_2CO_3	DMSO	59
11	–	Cs_2CO_3	DMF	trace[d]
12	CuI	Cs_2CO_3	DMF	trace[e]

[a] Reaction conditions: 2-bromobenzoic acid (0.5 mmol), acetamidine hydrochloride (0.75 mmol), catalyst (0.1 mmol), base (1 mmol), solvent (3 mL) at room temperature (ca. 25 °C) under a nitrogen atmosphere. [b] Yield of isolated product. [c] Base (0.5 mmol). [d] No addition of catalyst. [e] Without nitrogen atmosphere. DMSO = dimethylsulfoxide; DMF = *N*,*N*-dimethylformamide.

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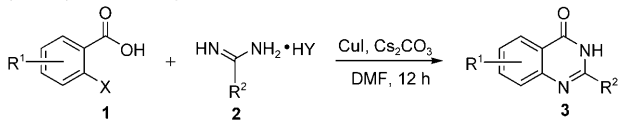
(Table 1, entries 1–4). CuI showed the best activity (Table 1, entry 4) and the coupling yield decreased as the amount of base was reduced (Table 1, entry 4 versus 5). Several bases such as Cs_2CO_3, K_2CO_3, and K_3PO_4 were screened and Cs_2CO_3 proved to be the most effective base (Table 1, entries 4 and 6 versus 7). The effect of the solvent was also investigated (Table 1, entries 4, and 8–10), and DMF was found to be the best choice (Table 1, entry 4). Only trace amounts of quinazoline **3a** were observed when the reaction was run either in the absence of the catalyst (Table 1, entry 11) or the nitrogen atmosphere (Table 1, entry 12).

The scope of copper-catalyzed cascade reactions of the substituted 2-halobenzoic acids with amidines was investigated under the optimized conditions. As shown in Table 2, most of the substrates examined provided good to excellent yields at room temperature. For the substituted 2-halobenzoic acids, their relative reactivity was in the order of aryl iodides > aryl bromides > aryl chlorides. The reactions of 2-iodo- and 2-bromobenzoic acids with amidines produced quinazolinones in good to excellent yields at room temperature, and 2-chlorobenzoic acid gave lower yields under the same reaction conditions. Notably, the yields of the target products were greatly improved as the reaction temperature was increased; for example, 2-chlorobenzoic acid provided the target products in more than 80% yield at 80 °C (Table 2, entries 20 and 21). In fact, aryl chlorides are weak substrates in

Table 2: Copper-catalyzed synthesis of quinazolinone derivatives.[a]



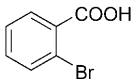
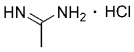
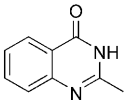
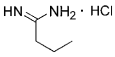
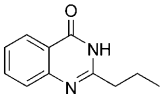
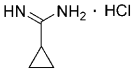
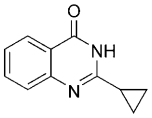
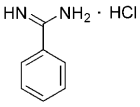
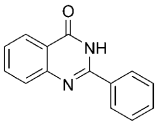
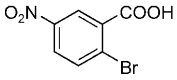
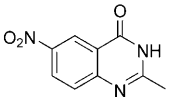
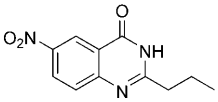
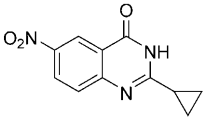
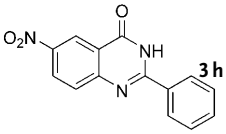
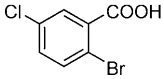
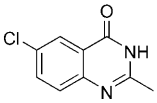
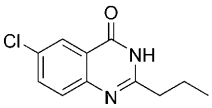
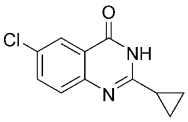
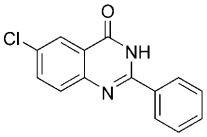
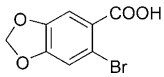
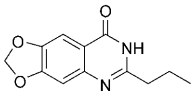
Entry	1		2		Product		Yield [%][b]
1		**1a**		**2a**		**3a**	81
2		**1a**		**2b**		**3b**	79
3		**1a**		**2c**		**3c**	84
4		**1a**		**2d**		**3d**	85
5		**1b**		**2a**		**3e**	69
6		**1b**		**2b**		**3f**	65 (89[c])
7		**1b**		**2c**		**3g**	68
8		**1b**		**2d**		**3h**	79
9		**1c**		**2a**		**3i**	83
10		**1c**		**2b**		**3j**	87
11		**1c**		**2c**		**3k**	75
12		**1c**		**2d**		**3l**	66
13		**1d**		**2b**		**3m**	40[c] (49[d])

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Table 2: (Continued)

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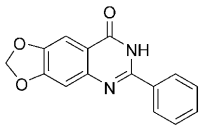
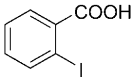
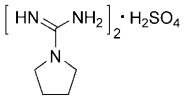
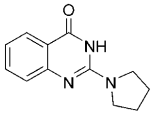
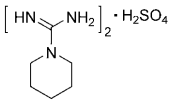
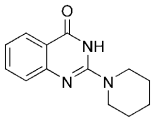
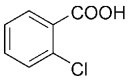
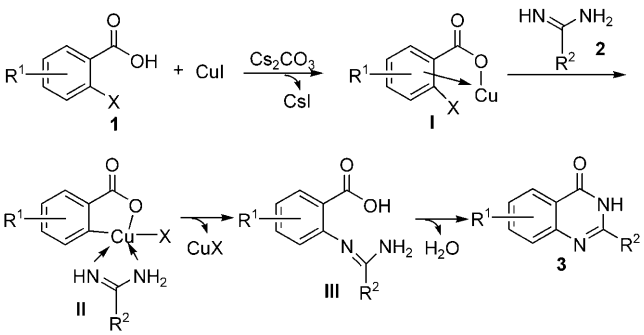
14	1d	2d	 3n	61
15	 1e	2a	3a	89
16	1e	2b	3b	90
17	1e	2d	3d	97
18	1e	 2e	 3o	59[c] (72[d])
19	1e	 2f	 3p	45[c] (70[d])
20	 1f	2b	3b	40[c] (81[d])
21	1f	2d	3d	43[c] (85[d])

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), CuI (0.1 mmol), Cs_2CO_3 (1 mmol), DMF (3 mL) at room temperature (ca. 25 °C) under nitrogen atmosphere. [b] Yield of isolated product. [c] Reaction temperature of 40 °C. [d] Reaction temperature of 80 °C.

the previously reported copper-catalyzed N-arylations,[7–11] and the result above demonstrates that an *ortho*-substituent effect is present during the N-arylation and is derived from the coordination of the carboxyl group (Scheme 1). The reaction of 2-bromo-5-chlorobenzoic acid (**1c**) with amidines took place at the C–Br bond *ortho* to the carboxyl group and not at the C–Cl bond, again demonstrating an the presence of an *ortho*-substituent effect. The substituted 2-halobenzoic acids containing electron-rich groups showed slightly weaker reactivity than those containing electron-neutral or electron-deficient groups; for example, 6-bromo-1,3-benzodioxole-5-carboxylic acid (**1d**) provided lower yields (Table 2, entries 13 and 14). In general, amidines are good substrates, but the couplings of guanidines with 2-halobenzoic acids did not perform well at room temperature. The corresponding quinazolinones were obtained in good yields when temperature was raised to 80 °C (Table 2, entries 18 and19).

Quinazolinones can be readily transformed into the corresponding quinazolines, which have various biological and medicinal activities,[11] so the present method provides a novel strategy for synthesis of a diverse array of quinazolinone and quinazoline derivatives.

Given that suitable *ortho* substituents promote Ullmann-type couplings,[12] a mechanism for the formation of quinazolinones is proposed in Scheme 1. This proposal is based on the results discussed herein and on the other experimental evidence (see the Supporting Information for details). The coordination of substituted 2-halobenzoic acid to CuI forms **I** in the presence of the base (Cs_2CO_3). Oxidative addition of **I** and complexation of copper with the amidine provides **II**, which then undergoes reductive elimination to give the N-arylation product **III** and releases the copper catalyst. The coupling of the carboxyl and amino groups in **III** affords target product **3**.[13]



Scheme 1. Proposed mechanism for the copper-catalyzed formation of quinazolinones.

In summary, we have developed a simple and highly efficient method for the synthesis of quinazolinone derivatives. The coupling reactions of 2-bromo- and iodobenzoic acid derivatives with amidines performed well at room temperature without the addition of a ligand or an additive. The target products were also obtained in higher yields from the nonactive substrates, such as 2-chlorobenzoic acid (**1f**) or guanidines, when the reaction temperature was raised to 80 °C. The present method is economical and practical, and the starting materials are readily available. These advantages, relative to previous methods, provide an opportunity for the construction of diverse and useful molecules within organic and medicinal chemistry.

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Keywords: copper · cyclization · guanidines · heterocycles · quinazolinone

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