Highly efficient copper-catalyzed cascade synthesis of quinazoline and quinazolinone derivatives†

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We have developed a general and highly efficient copper-catalyzed method for synthesis of quinazoline and quinazolinone derivatives, the target products were obtained in good to excellent yields *via* cascade reactions of amidine hydrochlorides with substituted 2-halobenzaldehydes, 2-halophenylketones, or methyl 2-halobenzoates, and the method is of simple, economical and practical advantages.

Quinazoline and quinazolinone derivatives have attracted much attention for their various biological and medicinal properties. For example, quinazoline derivatives act as powerful inhibitors of the epidermal growth factor (EGF) receptors of tyrosine kinase,[1] and some of them show remarkable activity as anticancer,[2] antiviral,[3] and antitubercular agents.[4] They are also used as ligands for benzodiazepine and GABA receptors in the CNS system[5] or as DNA binders.[6] Quinazolinone is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms, such as luotonin **A** from *Peganum nigellastrum*,[7a] 2-methyl-4(3*H*)-quinazolinone from *Bacillus cereus*,[7b] 2-(4-hydroxybutyl)quinazolin-4-one from *Dichroa febrifuga*,[7c] bouchardatine from *Bouchardatia neurococca*.[7d] Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, antitussive, anti-bacterial, anti-diabetic, anti-inflammatory, antitumor.[8,9] Although some methods for the syntheses of quinazoline[10] and quinazolinone derivatives[8,11,12] have been developed, it is highly desirable to search for a more convenient and efficient approach. Recently, copper-catalyzed Ullmann *N*-arylations have made great progress;[13] some research groups,[13] and we,[14] have developed efficient copper catalyst systems to perform aminations of aryl halides, and the *N*-arylation strategy has been used to construct *N*-heterocycles.[15] Herein, we report highly efficient copper-catalyzed cascade reactions of amidines with substituted *o*-carbonylaryl halides to synthesize quinazoline and quinazolinone derivatives.

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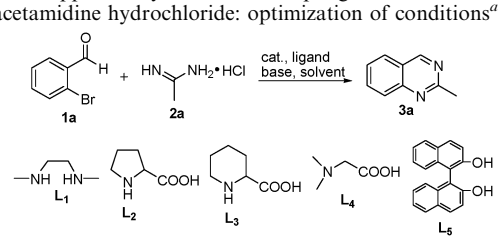
2-Bromobenzaldehyde and acetamidine hydrochloride were firstly chosen as the model substrates to optimize reaction conditions including optimization of the catalysts, ligands, bases and solvents under nitrogen atmosphere. As shown in Table 1, five ligands were tested at 110 °C using 10 mol% CuI as the catalyst and 3 equiv. Cs_2CO_3 as the base (relative to the amount of 2-bromobenzaldehyde) in DMF (entries 1–5), and L-proline showed the best activity (entry 2). No quinazoline **3a** was formed in the absence of ligand (entry 6). When reaction temperature was lowered to 80 °C, only 30% yield was provided (entry 7). CuBr was used as the catalyst in place of CuI, and it showed weaker activity than CuI (entry 8). The effect of solvents was also investigated (compare entries 2, 9–11), and DMF was the best choice (entry 2). Several bases, Cs_2CO_3, Na_2CO_3 and K_3PO_4, were also tested, and Cs_2CO_3 proved to be the most effective base (compare entries 2, 12 and 13).

After the optimization process for catalysts, ligands, solvents and bases, the various quinazoline derivatives were synthesized under our standard conditions: 10 mol% CuI as the catalyst, 20 mol% L-proline as the ligand, 3 equiv. of Cs_2CO_3 as the base (relative to 2-bromobenzaldehydes or

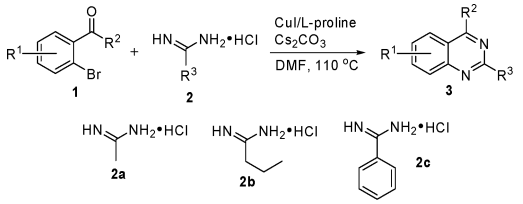
Table 1 Copper-catalyzed cascade coupling of 2-bromobenzaldehyde with acetamidine hydrochloride: optimization of conditions[a]

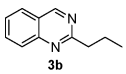
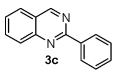
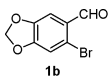
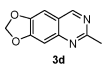
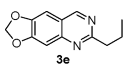
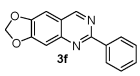
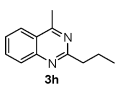
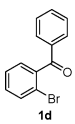
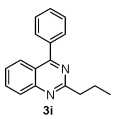
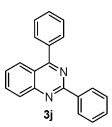


Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	L_1	Cs_2CO_3	DMF	68
2	**CuI**	**L_2**	**Cs_2CO_3**	**DMF**	**75**
3	CuI	L_3	Cs_2CO_3	DMF	50
4	CuI	L_4	Cs_2CO_3	DMF	65
5	CuI	L_5	Cs_2CO_3	DMF	30
6	CuI	—	Cs_2CO_3	DMF	0
7	CuI	L_2	Cs_2CO_3	DMF	30
8	CuBr	L_2	Cs_2CO_3	DMF	50
9	CuI	L_2	Cs_2CO_3	Toluene	0
10	CuI	L_2	Cs_2CO_3	Dioxane	55
11	CuI	L_2	Cs_2CO_3	THF	40
12	CuI	L_2	Na_2CO_3	DMF	72
13	CuI	L_2	K_3PO_4	DMF	69

[a] Reaction conditions: under nitrogen atmosphere, reaction temperature (80 °C for for entry 7, reflux in THF for entry 11, 110 °C for others), time (16 h for entry 12, 24 h for others). 2-bromobenzaldehyde (1 mmol), acetamidine hydrochloride (1.1 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (3 mmol), solvent (10 mL). [b] Isolated yield.

Table 2 Copper-catalyzed synthesis of quinazoline derivatives[a]

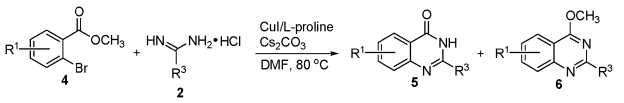


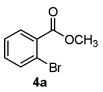
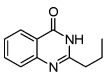
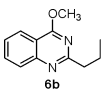
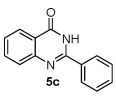
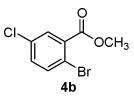
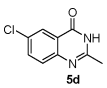
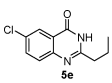
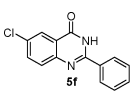
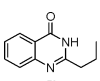
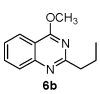
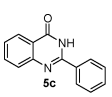
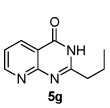
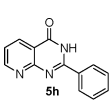
Entry	1	Time/h	Product	Yield (%)[b]
1		24		75
2	**1a**	24		82
3	**1a**	24		55
4		20		92
5	**1b**	20		95
6	**1b**	20		89
7		20		84
8	**1c**	20		86
9		24		81
10	**1d**	24		61[c]

[a] Reaction conditions: under nitrogen atmosphere, **1**(1 mmol), **2** (1.1 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (3 mmol), DMF (10 mL). [b] Isolated yield. [c] CuI (0.2 mmol), L-proline (0.4 mmol).

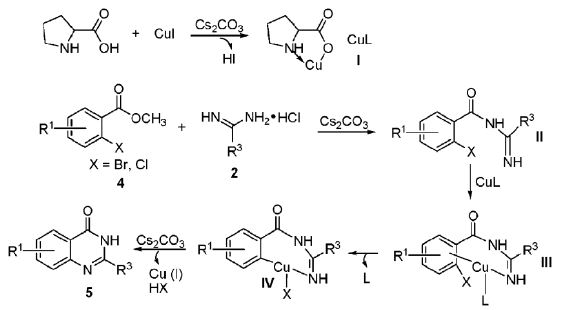
2-bromophenylketones) and DMF as the solvent at 110 °C. As shown in Table 2, all the substrates examined provided good to excellent yields. In general, 2-bromobenzaldehydes showed higher reactivity than 2-bromophenylketones, 6-bromo-1,3-benzodioxole-5-carboxaldehyde (**1b**) was more effective than 2-bromobenzaldehyde (**1a**), and 2′-bromoacetophenone (**1c**) gave higher yields than 2-bromobenzophenone (**1d**). Reactive activity of aliphatic amidines were better than aromatic ones, their order is butyramidine > acetamidine > benzamidine.

Table 3 Copper-catalyzed synthesis of quinazolinone derivatives[a]



Entry	4	Time/h	Product	Yield (%)[b]
1		16		91
2	**4a**	16		74
				22
3	**4a**	16		89
4		16		87
5	**4b**	16		95
6	**4b**	16		86
7		20		90
8	**4c**	20		77
				18
9	**4c**	20		86
10		20		82
11	**4d**	20		76

[a] Reaction conditions: under nitrogen atmosphere, **4** (1 mmol), **2** (1.1 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (3 mmol), DMF (10 mL). [b] Isolated yield.



Scheme 1 Plausible formation mechanism of quinazolinones.

We also attempted cascade reactions of substituted methyl 2-halobenzoates with amidine hydrochlorides to synthesize various quinazolinone derivatives under our standard catalytic conditions. As shown in Table 3, all the examined substrates gave the corresponding quinazolines in good to excellent yields. Interestingly, methyl 2-chlorobenzoate (**4c**) and methyl 2-bromobenzoate (**4a**) almost provided the same yields (compare entries 1–3, 7–9), and methyl 2-chloronicotinate (**4d**) also afforded the corresponding target products (**5g,h**) in good yields (entries 10 and 11). In fact, aryl chlorides are weak substrates in the previous copper-catalyzed *N*-arylations,[13,14] and the results above could show an *ortho*-effect during *N*-arylations (see reaction mechanism). Further, *N*-arylation selectively occurred at the *ortho*-site of the ester group in methyl 2-bromo-5-chlorobenzoate (**4b**) (entries 4–6). It is worthwhile to note that reaction of electron-rich butyramidine with methyl 2-bromobenzoate (**4a**) or methyl 2-chlorobenzoate (**4c**) gave a minor quinozoline (**6b**) besides the major quinazolinone (**5b**) (entries 2 and 8). In addition, reactive activity of amidines also showed similar results to Table 2.

Since the suitable *ortho*-substituents could promote Ullmann-type couplings,[16] a plausible formation mechanism of quinazolinones was proposed in Scheme 1 according to the results in Table 3. Coordination of L-proline with CuI in the presence of base (Cs_2CO_3) first forms **I** (CuL). Substitution reaction of methyl 2-halobenzoate with amidine hydrochloride yields amide **II** in the presence of Cs_2CO_3, and treatment of **II** with CuL (**I**) gives complex **III**, in which one nitrogen of the amidine group may coordinate with the copper center to provide additional stabilization. Oxidation addition of **III** provides coordinate **IV**, and reduction elimination of **IV** affords the target product **5** releasing the copper catalyst.

In summary, we have developed a general and highly efficient method for synthesis of quinazoline and quinazolinone derivatives *via* copper-catalyzed cascade couplings of amidine hydrochlorides with substituted 2-halobenzaldehydes, 2-halophenylketones and methyl 2-halobenzoates under mild conditions. The present method shows simple, economical and practical advantages over the previous methods, so it can provide diverse molecules for organic chemistry and medicinal chemistry.

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