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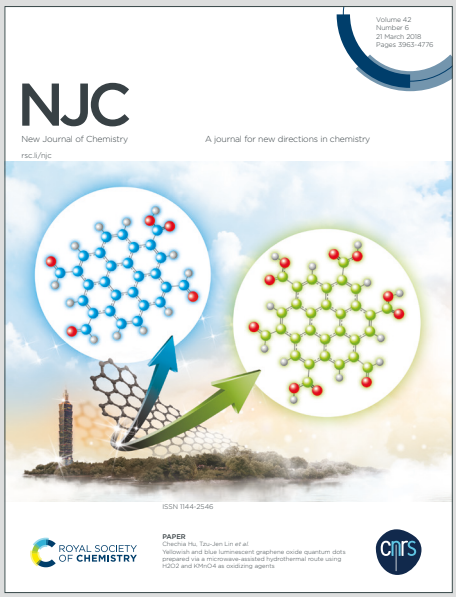

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ARTICLE

Copper-mediated synthesis of quinazolin-4(3*H*)-ones from *N*-(quinolin-8-yl)benzamide and amidine hydrochlorides

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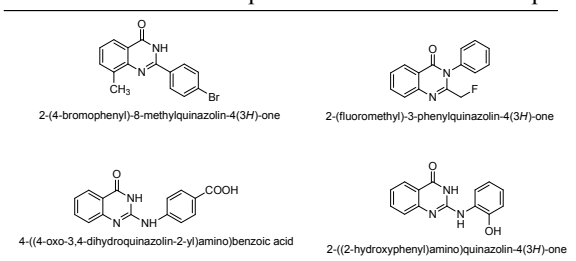
An efficient copper-mediated tandem C(sp²)-H amination to provide quinazolinones from *N*-(quinolin-8-yl)benzamide and amidine hydrochlorides has been developed. It can afford rather complex products in a single synthesis step from easily available starting materials using 8-aminoquinoline as a removable bidentate directing group. The features of this reaction is simple to operate and avoide sensitive and expensive metals, which provides an approach for the construction of polycyclic molecules in the area of organic chemistry.

Quinazolinone is widely found in natural alkaloids and pharmaceuticals.[1] In addition, there are useful biological and medicinal activities to be proved among quinazolinone derivatives, which can be used as antituberculosis,[2] antimalarial,[3] anticancer,[4] antibacterial,[5] anticonvulsants[6] and antihypertensive[7] agents, such as bouchardatine from Bouchardatia neurococca,[8] 2-methyl-4(3*H*)-quinazolinone from Bacillus cereus,[9] 2-(4-hydroxybutyl) quinazolin-4-one from Dichroa febrifuga,[10] and luotonin A from Peganum nigellastrum[11] (Scheme 1). As a result, the quinazolinone skeleton is considered to be a privileged structure.[12] Therapeutic agents containing the quinazolinone core structure have been on the market or used in clinical trials for the treatment of cancer.[13]

The C−N bond of quinazolinone can be formed in a good manner with high regioselectivity and stereoselectivity[14] has attracted considerable attention in the field of chemistry.[15] Great progress has been made toward construction of quinazolinone derivatives. Representative examples of synthesis of quinazolinones include: (i) constructing quinazolinones from easily available 2-arylindoles and amines or ammoniums via Baeyer−Villiger[16] oxidation expansion using O_2 as oxidant, followed by dehydration condensation.[1] (ii) $Cu(OAc)_2$-mediated nucleophilic addition of 2-halobenzamides to nitriles followed by intramolecular SN_{Ar} reaction proceeded under oxidant- and ligand-free conditions.[17] (iii) dehydrogenative coupling of *o*-amino benzamides with benzyl alcohols catalyzed by a square planar Ni(II) complex ([Ni(MeTAA)]) featuring a tetraaza macrocyclic ligand.[18] (iv) reaction between amides and methyl anthranilate mediated by the $Ph_3P{-}I_2$ system.[19] (v) employing copper-catalyzed intramolecular decarboxylative coupling to develop new domino reaction involving isatin and benzamidine hydrochloride.[20] (vi) constructing *N*-heterocycles under ligand-free copper catalysis at room temperature coupling of 2-bromobenzoic acid with acetamidine hydrochloride.[21] (vii) synthesis of 3-(2-aminoethylamino)-propyl-functionalized MCM-41-immobilized copper(I) complex for the homo- and heterocoupling of terminal alkynes and Buchwald *N*-arylation reaction of indoles with aryl halides.[22]

Rencently, our group proposed a copper-mediated tandem-annulation reaction for the synthesis of quinazolin-4(1*H*)-ones from amidines and benzamides[23b] and successfully achieved it. Analogously, synthesis of quinazolin-4(3*H*) ones from *N*-(quinolin-8-yl)benzamide and amidine hydrochlorides is also a convenient access, which is a simple and readily accessible precursors. We displayed a copper-mediated *ortho* C-H amination assisted by a removable 8-aminoquinoline directing group followed by the intramolecular nucleophilic addition toward various quinazolinones. Copper salts are used as transition-metal catalysts for the C−N coupling reaction, and specific base is required for reductive elimination to construct C−N bonds. The combination of cyclization reactions through C−N bond activation has presented an attractive and powerful



Scheme 1 Application of quinazolinones on natural alkaloids.

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protocol to generate quinazolinone derivatives, which involves the departure of large groups and the the formation of C-N bonds.

Initially, *N*-(quinolin-8-yl)benzamide (**1a**) with benzamidine hydrochloride (**2a**) was chosen as a model reaction to examine the reaction, conditions that containing base, catalyst, reaction temperature and reaction time. The results were disclosed in Table 1. Firstly, we selected $Cu(OAc)_2$ as the catalyst and K_2CO_3 as the base for the blank control experiment, and found that both the catalyst and the base were indispensable. Next we concentrated attention on the effect of base in rank. It is obvious that excellent yields were obtained when Na_2CO_3, K_2CO_3 ,Cs_2CO_3 ,NaOH and *t*-BuOK were used as the base and K_2CO_3 was the most effective (Table 1, entries 1-5) base. In the presence of DMAP, the desired product 3a could not be detected (Table 1, entry 6), so K_2CO_3 was finally selected as the base for the reaction. Moreover**,** the effect of the catalyst on the model reaction was also investigated (Table 1, entries 7-12). The yield increased significantly when CuI**,** CuCl**,** $Cu(OTf)_2$ and Cu_2O were used as the reaction media whereas $Cu(acac)_2$ and $CuBr_2$ afforded low yields. As shown in Table 1, $Cu(OAc)_2$ still gave the highest yield . Among the solvents examined, DMSO was found to be the best choice (Table 1, entries 13-16), EtOH also afforded good yield (Table 1, entry 1**6).** While other solvents such as DCE, 1, 4-dioxane and DMF were substantially less effective (Table 1, entries 13-15). The temperature influence was also examined by using K_2CO_3 (2.0 *equiv.*) as the base in DMSO (Table 1, entries 17-18). The reaction at 110 °C gave the best result and other temperatures were distinctly less effective. In the end, the yield of 3a decreased with the reaction time increasing or decreasing (Table 1, entries 19-20) .The results revealed that 2-phenylquinazolin-4(3*H*)-one(**3a**) was obtained as a main product in 91% yield in DMSO at 110 °C when $Cu(OAc)_2$ (20 mol %) was used as catalyst and K_2CO_3 (2 *equiv.*) was used as base .

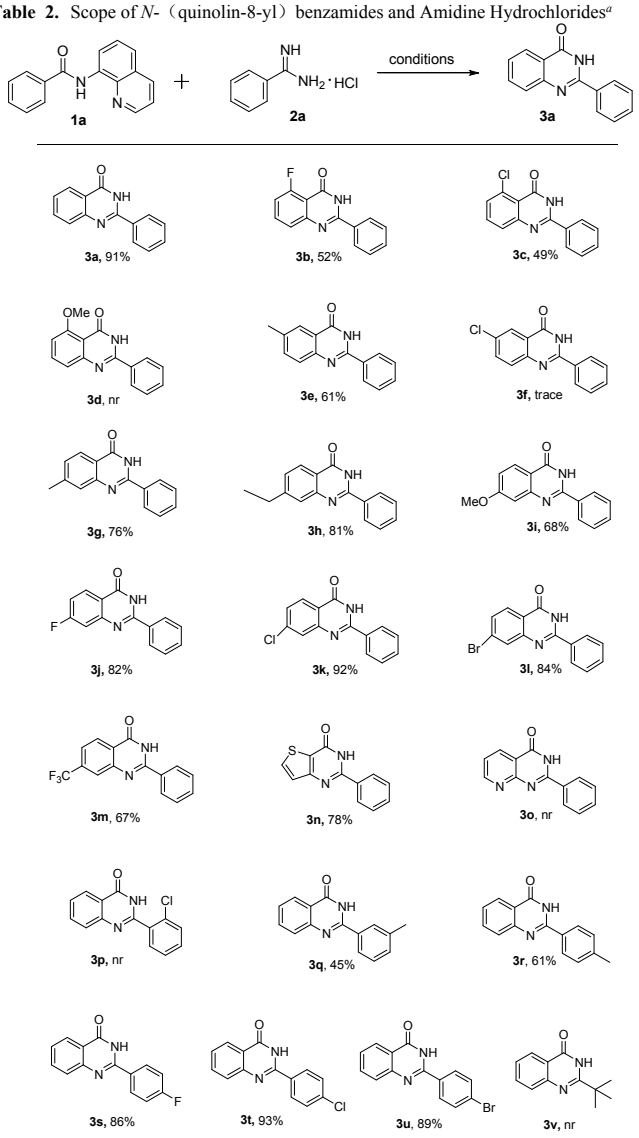
Table 1. Optimization of the reaction conditions[a]

Entry	Catalyst	Base	Solvent	Yield(%)[b]
1	$Cu(OAc)_2$	Na_2CO_3	DMSO	59
2	**$Cu(OAc)_2$**	**K_2CO_3**	**DMSO**	**91**
3	$Cu(OAc)_2$	Cs_2CO_3	DMSO	72
4	$Cu(OAc)_2$	NaOH	DMSO	63
5	$Cu(OAc)_2$	*t*-BuOK	DMSO	50
6	$Cu(OAc)_2$	DMAP	DMSO	nr
7	CuI	K_2CO_3	DMSO	59
8	CuCl	K_2CO_3	DMSO	86
9	$Cu(OTf)_2$	K_2CO_3	DMSO	54
10	$Cu(acac)_2$	K_2CO_3	DMSO	23
11	$CuBr_2$	K_2CO_3	DMSO	23
12	Cu_2O	K_2CO_3	DMSO	72
13	$Cu(OAc)_2$	K_2CO_3	DCE	14
14	$Cu(OAc)_2$	K_2CO_3	DMF	nr
15	$Cu(OAc)_2$	K_2CO_3	1,4-dioxane	14
16	$Cu(OAc)_2$	K_2CO_3	EtOH	54
17[d]	$Cu(OAc)_2$	K_2CO_3	DMSO	41
18[e]	$Cu(OAc)_2$	K_2CO_3	DMSO	59
19[f]	$Cu(OAc)_2$	K_2CO_3	DMSO	65
20[g]	$Cu(OAc)_2$	K_2CO_3	DMSO	86

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (20 mol %), base (0.2 mmol) in solvent (2.0 mL) at 110 °C for 16 h. [b]Isolated yield. [c]nr=no reaction. [d] 100 °C. [e]120 °C. [f]12 h. [g]20 h.

Using the optimized reaction conditions, the scope of the substrates were investigated (Table 2), excellent yields were obtained for (**1a**) with different electronic properties effectively and benzamidine hydrochloride (**2a**) with its derivatives to provide the corresponding products in moderate to good yields (45−93%, **3a−v**). In addition, *N*-(quinolin-8-yl)benzamide with electron-withdrawing groups (fluoro- and chloro-) reacted well and furnished the desired products **3b**, **3c** in 52% and 49% yield, respectively. However, *o*-substituted substrates bearing electron-donating groups proceeded badly and we failed to find the target product (**3d**). Meanwhile, *m*-substituted substrates reacted smoothly and resulted in the desired quinazolinones in moderate yields (**3e**, **3f**). The greater reactivity of the substrates containing both electron-withdrawing groups and electron-donating groups at the 4-position of the aryl ring could lead to formation of the corresponding quinazolin-4(3*H*)-ones in higher yields (**3g-3m**). We were pleased to find that the *N*-(quinolin-8-yl） benzamide, 4-methyl, 4-ethyl, 4-methoxyl, 4-fluoro, 4-chloro , 4-bromo and 4-trifluoromethyl groups worked well and provided

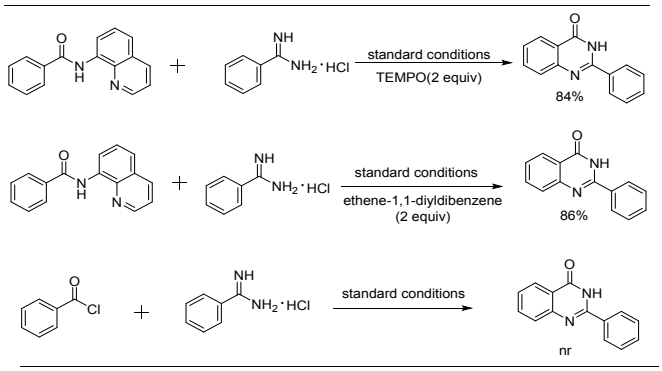
Table 2. Scope of *N*-（quinolin-8-yl）benzamides and Amidine Hydrochlorides[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (20 mol %), base (0.2mmol) in solvent (2.0 mL). [b]Isolated yield. [c]nr=no reaction.

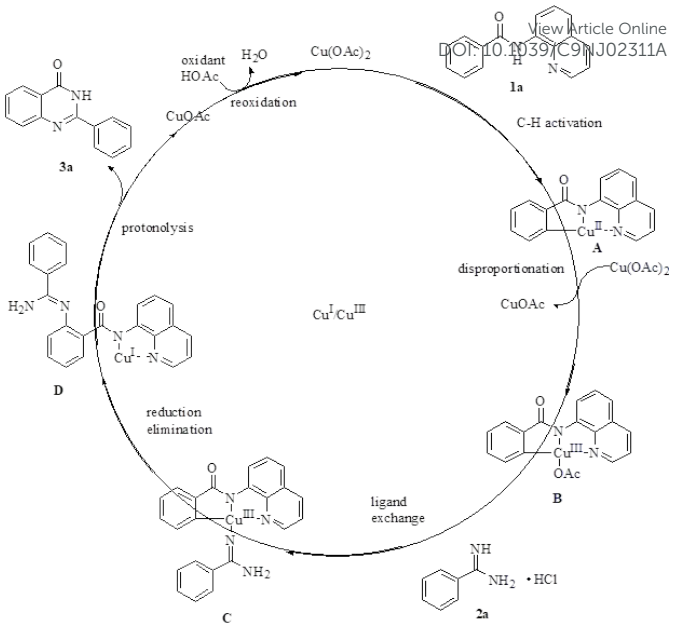
quinazolin-4(3*H*)-one derivatives in 67%–92% yields. Interestingly, thiophene ring (**3n**) could be a suitable substrate. Nevertheless, pyridine ring (**3o**) was examined no target product. Notably, the quinazoline scaffolds which formed with a diverse range of halogen atoms, providing enormous possibilities for further modification. The reactions were also attempted with a range of amidine hydrochlorides under the optimal conditions. It was found that the reaction conditions were suitable for both electron-rich (4- methyl and 3-methyl) and halogenic (4-F, Cl, Br) substituents on the phenyl rings of the benzamidine hydrochloride, which obtained the corresponding products in good yields (45−93%, **3q**−**3u**). However, alkyl and 2-chloro (**3v**, **3p**) substituents were not found to be compatible with this transformation. Steric hindrance had an obvious effect on this transformation, indicating that at the para-position was easily available target in this reaction.

A series of control experiments were conducted to gain more insight into the reaction mechanism of this tandem reaction. First, when a stoichiometric amount of a radical inhibitor 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was employed in the standard reaction, the yield of the desired product **3a** was only slightly decreased, which indicated that a free radical pathway might be ruled out in this transformation. So the ethene-1,1-diyldibenzene was reacted as a radical inhibitor. Meanwhile, we used benzoyl chloride instead of *N*-(quinolin-8-yl)benzamide to participate in the reaction, with the results of no target **3a** (Scheme 2) appeared. Based on the experiments and other supporting information, a mechanism[23] for the formation of quinazolinones has been proposed in Scheme 3.



Scheme 2 Control Experiments

The distinct catalytic cycle of C−H coupling with aryl nitrogen proceeding through a transmetalation step supported the formation of an aryl cupperate intermediate. First, intermediate **A** was generated via coordination of *N, N*-bidentate substrate **1a** with $Cu(OAc)_2$ followed by ligand exchange, which underwent intramolecular C-H activation. Next, the disproportionation gave CuOAc (Cu Ⅰ) and **B** (Cu Ⅲ). Benzamidine hydrochloride (**2a**) then interacted with intermediate **B**, which subsequently led to the formation of intermediate **C**. The intermediate **C** then experienced a reductive elimination and produced the important intermediate **D**. Finally, the target product **3a** was generated by protonolysis reaction.



Scheme 3. Plausible mechanistic pathway.

In summary, a method for copper-catalyzed reaction of *N*-(quinolin-8-yl)benzamide and amidine hydrochlorides has been developed for assembling quinazolinone framework ,which provided an approach for the construction of polycyclic molecules in organic synthesis. The wide availability of the starting materials, and the simplicity of the procedure enabled a convenient access to diverse quinazolin-4(3*H*)-ones from simple and readily accessible materials. Moreover, we used cheap copper catalysts, avoiding sensitive and expensive metals. It is worthwhile to explore experiments on the formation of quinazolinones.

Conflicts of interest

There are no conflicts to declare.

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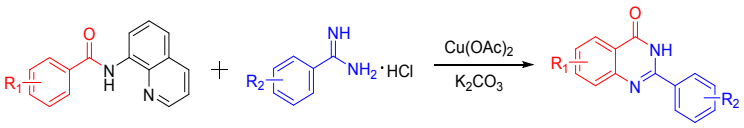

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