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DOI: 10.1039/C9OB00020H

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COMMUNICATION

Synthesis of Quinazolin-4(1*H*)-ones via Amination and Annulation of Amidines and Benzamides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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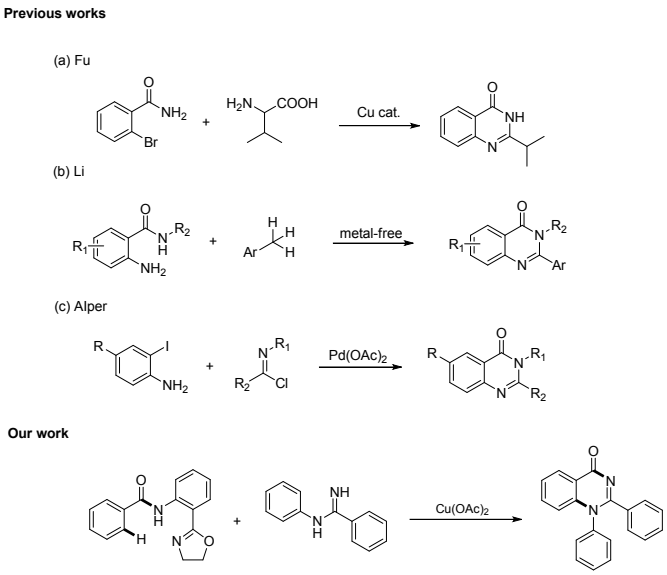
Quinazolinones have board applications in biological, pharmaceutical and material fields. Studies on the synthesis of these compounds are therefore widely conducted. Herein, a novel and highly efficient copper-mediated tandem C(sp²)-H amination and annulation of benzamides and amidines for the synthesis of quinazolin-4(1*H*)-ones is proposed. This synthetic route can be useful for the construction of quinazolin-4(1*H*)-ones frameworks.

Quinazolinone skeletons are widely prevalent in natural products, biologically active compounds and other materials.[1] Owing to their ubiquitous nature and their importance as a pharmacophore in modern medicinal chemistry,[2] these heterocycles have been widely synthesized by various methods.[3, 14b-c, 15c] Among these methods, the acid/base-mediated condensation reaction of carboxylic acid derivatives with 2-aminobenzoic acid and its derivatives, and the cascade condensation reaction of aldehydes with *o*-aminobenzamides, which is followed by oxidation of aminal intermediate, have attracted considerable attention because of their extensive potential applications.[4] However, these methods suffer from some unignorable drawbacks. For example, they have limited scope due to their multi-step reactions, harsh reaction conditions, and unsatisfactory yields, in addition to other ineluctable disadvantages.[5] As a result, development of an efficient, environmentally benign catalyst system for the preparation of heterocycle quinazolines is highly desirable.

Over the last few decades, several alternative strategies have been established to synthesize quinazolinones. For example, in 2014, Fu employed a copper-catalyzed domino method to synthesize quinazolin-4(3*H*)-ones using readily available α-amino acids as the substrates (Scheme 1, path a).[6] Wang also investigated a novel cascade method, α-MnO_2-catalyzed oxidative cyclization, using anthranilamides or



Scheme 1. Comparison of synthetic route to quinazolinones in previous works (paths a-c) and that in our work.

aminobenzylamines and alcohols as the starting materials.[7] Li and colleagues also developed a novel metal-free oxidative synthesis of quinazolinones via dual amination of sp^3 C–H bonds (Scheme 1, path b).[8] Alper found that quinazolinones can be prepared by palladium-catalyzed cyclocarbonylation of *o*-iodoanilines, imidoyl chlorides and carbon monoxide (Scheme 1, path c).[9] Recently, Liu described a new strategy, a copper-mediated tandem reaction of benzamides with 2-aminopyridines, to produce 11*H*-pyrido[2,1-*b*]quinazolin-11-ones.[10]

In synthetic organic chemistry transition-metal-catalyzed C-N/C-H bonds formation have emerged as a powerful method for the synthesis of nitrogen-containing compounds.[11-12] In the past few decades, rhodium-, palladium- and ruthenium-based catalysts have been used mainly in the construction of C-C or C-Het (Het = heteroatom) bond.[13-14] Due to its low cost, high reactivity and environmental friendliness, copper has recently received tremendous attention.[15-16] Meanwhile, the

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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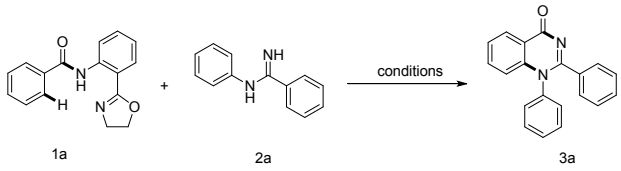
Table 1. Screening of reaction conditions.[a)]



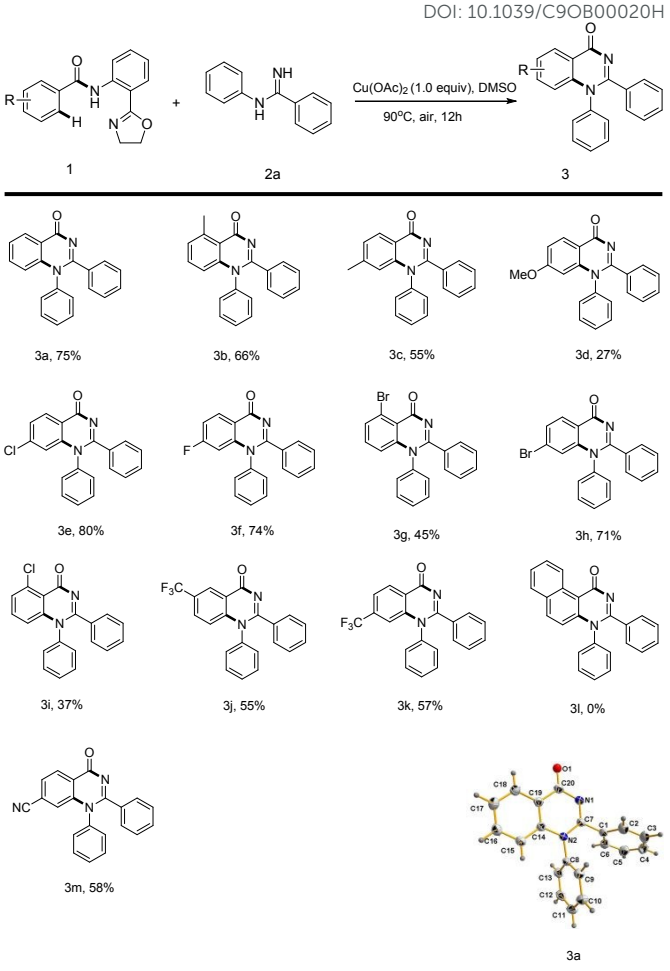
Entry	Cu salt	Oxidant	Solvent	T [℃]	Yield [b)] [%]
1	$Cu(OAc)_2$	-	DMSO	50	44
2	$Cu(OAc)_2$	-	DMSO	70	71
3	$Cu(OAc)_2$	-	DMSO	110	72
4	$Cu(OAc)_2$	-	DMSO	90	75
5	$Cu(OAc)_2$	-	DMF	90	Trace
6	$Cu(OAc)_2$	-	1,4-Dioxane	90	19
7	$Cu(OAc)_2$	-	CH_3CN	90	26
8	$Cu(OAc)_2$	-	Toluene	90	20
9	$Cu(OAc)_2$	-	DCE	90	9
10	$Cu(OAc)_2{\cdot}H_2O$	-	DMSO	90	69
11	$Cu(OTf)_2$	-	DMSO	90	47
12	CuI	-	DMSO	90	60
13	CuBr	-	DMSO	90	Trace
14	-	-	DMSO	90	0
15	$Cu(OAc)_2$	O_2	DMSO	90	25
16	$Cu(OAc)_2$	$K_2S_2O_8$	DMSO	90	23
17	$Cu(OAc)_2$	BQ	DMSO	90	Trace
18	$Cu(OAc)_2$	BPO	DMSO	90	60

[a)]Reaction conditions: amide **1a** (0.1 mmol), **2a** (0.16 mmol), Cu salt (0.1 mmol), solvent (1.0 mL), 90 ℃ under air for 12 h. [b)] Isolation yield.

precedents in which successive C-H activation/removal of directing group have been reported.[17, 10] Herein, we developed a copper-mediated tandem-annulation reaction for the synthesis of quinazolin-4(1*H*)-ones from amidines and benzamides.

In our initial studies, *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide **1a** (0.1 mmol) and *N*-phenylbenzimidamide **2a** (0.16 mmol) were chosen as model substrates in the presence of $Cu(OAc)_2$ (0.1 mmol) in DMSO (1.0 mL) at 50 °C for 12 h. To our delight, the desired product, 1,2-diphenylquinazolin-4(1*H*)-one **3a**, was obtained with 44% yield (Table 1, entry 1). Encouragingly, the yield was improved to 75% when the temperature was increased to 90 °C (Table 1, entry 4). We found that, DMSO was the most efficient solvent among all solvents that were screened, Other non-polar solvents, (such as DCE and toluene), and polar solvents, (such as DMF, 1,4-dioxane and CH_3CN), were poor solvents (Table 1, entries 4-9). Furthermore, several copper salts were screened, and $Cu(OAc)_2$ was found to give the highest product yield (entries 9-13). The screening of oxidants showed that they only slightly improved the yields (entries 15-18). It is worth noting that, in the absence of copper salts, the reaction could not proceed. This indicates that the copper catalyst is necessary for the reaction (entry 14).

Table 2. Substrate scope of benzamides.[a)]



[a)]Reaction conditions: amide **1** (0.1 mmol), **2a** (0.16 mmol), Cu salt (0.1 mmol), solvent (1.0 mL), 90 ℃ under air for 12 h.

Using the optimal reaction conditions (Table 1, entry 4), we subsequently investigated a wide range of amides substrates, and the results are summarized in Table 2. The amides bearing electron-donating groups (-Me, -OMe) and electron-withdrawing groups (-F, -Cl, -Br, $-CF_3$ and -CN) were moderately compatible, thereby could afford the desired products with moderate to good yield (**3b–3k**, **3m**). For example, the electron-rich methyl-substituted amides could afford the desired quinazolinone derivatives **3b** and **3c** with 66% and 55% yields, respectively. Additionally, the methoxy-substituted amide gave the corresponding product **3d** with 27% yield. On the other hand, the electron-deficient amides bearing halogen and trifluoromethyl groups resulted in the desired products in moderate to good yields (**3e-3k**; 37-80% yield). Interestingly, *o*-amides bearing bromide or chloride atom gave the corresponding products **3g** and **3i** with 45% and 37% yields; this could be attributed to steric hindrance effect. However, the desired product **3l** was not observed when 1-naphthylamide was used as a substrate under the optimal conditions.

We further investigated the reactions of *N*-aryl ring (R^1) substituted amidines (**3aa**-**3ai**). As shown in Table 3, various

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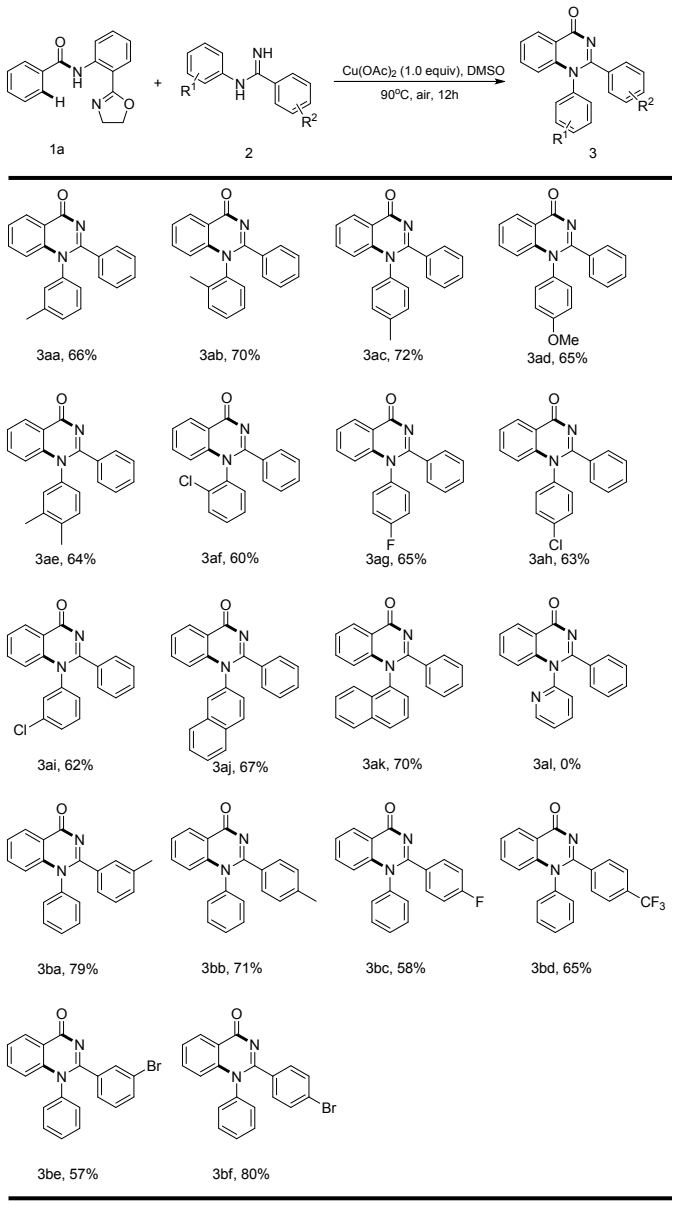
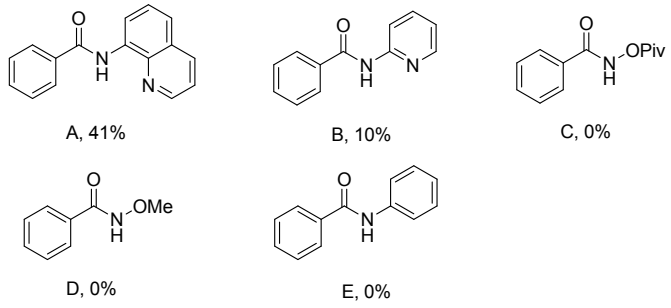
Table 3. Substrate scope of 2-aminopyridines.[a)]

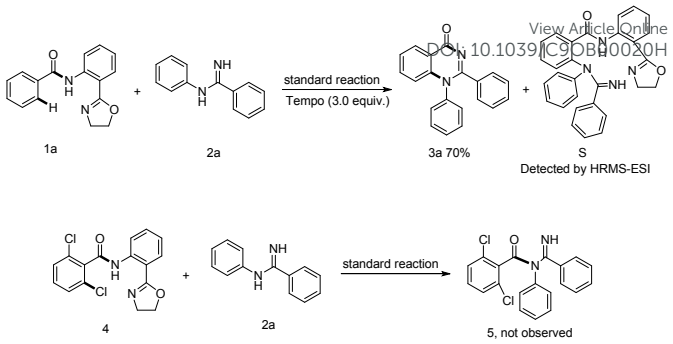


[a)]Reaction conditions: amide **1a** (0.1 mmol), **2** (0.16 mmol), Cu salt (0.1 mmol), solvent (1.0 mL), 90 ℃ under air for 12 h.

electron-donating and electron-withdrawing groups substituted *N*-aryl ring gave the 1,2-diphenylquinazolin-4(1*H*)-ones in moderate to good yields (60-72%). While 1-naphthyl and 2-naphthyl amidines gave products **3ak** (70% yield) and **3aj** (67% yield) with remarkable yields, the desired product **3al** was not obtained. The desired products (**3ba**-**3bf**) were obtained in moderate to excellent yields (57-80%) when another aryl ring (R^2) was added.

Table 4. Other directing groups



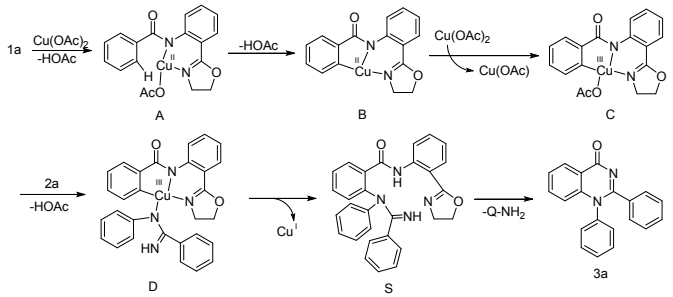


Scheme 2. Reactions carried out in control experiments.

Effects of other directing groups were also examined. The monodentate coordinated benzamides (Table 4, **C**-**E**) failed to produce the corresponding product **3a**, while other representative bidentate coordinated benzamides (Table 4, **A** and **B**) gave the corresponding product **3a** in 41% and 10% yields, respectively.

To gain insights into the reaction mechanism, a series of control experiments were carried out, as shown in Scheme 2. First, a stoichiometric amount of the radical inhibitor 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was used under the optimal reaction conditions, and the desired product **3a** was obtained with 70% yield, which is a slight decrease compared with the yield obtained from the optimal reaction conditions. This indicates that a free radical pathway is not involved in the reaction. Fortunately, the potential intermediate **S** was detected by HRMS-ESI (m/z = 461) (see the Supporting Information). However, the *ortho*-blocked amide **4** failed to give the intermediate **5**. These control experiments prompted us to interpret that the tandem reaction is likely initiated with C(sp^2)-H amination of benzamides and amidines. Amide carbonyl group then induce intramolecular nucleophilic substitution, which in turn gives quinazolin-4(1*H*)-ones.

Based on these results and the literature data,[15c, 10, 18] we propose a plausible mechanism for the tandem reaction of *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamides and amidines in the synthesis of 1,2-diphenylquinazolin-4(1*H*)-one (Scheme 3).



Scheme 3. Plausible mechanistic pathway.

In the presence of $Cu(OAc)_2$, the intermediate **A** is initially generated by ligand exchange coordination of *N*,*N*-bidentate substrate **1a** with $Cu(OAc)_2$, which undergoes intramolecular C-H cupration to give the species **B**. $Cu(OAc)_2$-promoted oxidation of **B** subsequently leads to the formation of copper(III) species **C**,[10, 18b] which then reacts with amidines to produce copper intermediate **D**.[10, 18a] This intermediate **D** then undergoes a reductive elimination to produce the key intermediate **S** (as detected by HRMS-ESI). Finally, the target product **3a** is produced by intramolecular nucleophilic substitution of **S**.

We designed and developed a convenient, operationally simple, and highly efficient protocol for the synthesis of quinazolinone derivatives. Notably, one feature of this new protocol is that it can used novel starting material *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamides as bidentate-directing groups. The reaction uses copper as the catalyst, thus the use of expensive noble metals can be avoided. Unfortunately, we cannot find the possible directing group after the reaction. Currently, the application of this protocol in the synthesis of other products is under investigation in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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