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Copper-Catalyzed Tandem *N*-Arylation/Condensation: Synthesis of Quinazolin-4(3*H*)-ones from 2-Halobenzonitrile and Amides

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A novel, straightforward and practical copper-catalyzed domino protocol for synthesis of quinazolin-4(3*H*)-one derivatives from commercially available 2-halobenzonitriles and amides was successfully developed.

The quinazolin-4(3*H*)-one nucleus is a basic structural feature which was found in many biologically active and pharmaceutically relevant natural products and synthetic analogues (Figure 1).[1] Till now, approximately 150 naturally occurring alkaloids comprising the quinazolinone moiety have been isolated from the plant, animals and microorganisms.[1e] In addition, substituted quinazolin-4(3*H*)-ones have been assigned as privileged structures in drug discovery because of the wide range of remarkable pharmacological activities including anticancer,[2] antifungal,[3] antidiabetic,[4] antiinflammatory,[5] antimicrobial,[6] and many others.[7]

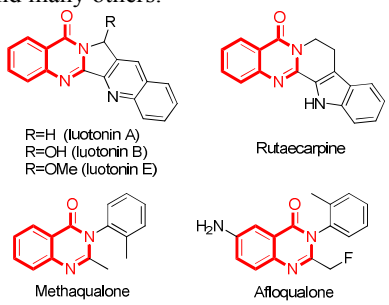
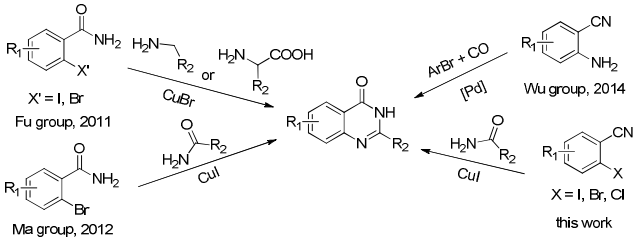


Figure 1. Selected examples of biologically active quinazolinones.

Based on the above-mentioned remarkable importance of quinazolin-4(3*H*)-ones, synthesis of the quinazolin-4(3*H*)-one moieties with diverse substitution patterns has always been one of the top priorities of both synthetic and medicinal chemists. The traditional synthetic routes to quinazolin-4(3*H*)-one compounds utilizing 2-aminobenzoic acid or its derivatives as starting materials suffer from several drawbacks such as tedious multi-step procedures, long reaction time, and harsh refluxing conditions.[1,8] Domino reactions allow the concomitant formation of two or more bonds with a rapid increase in molecular complexity with minimized separation/purification efforts.[9] To overcome above problems and being inspired by significant advantages of domino reactions, several groups have applied metal catalyzed domino reactions for assembling substituted quinazolin-4(3*H*)-ones.[10,11] Copper-catalyzed cross-coupling reactions have made great progress and have been employed for the assembling of important *N*-heterocycles.[12] Typically, using 2-halobenzamides as the starting materials, several copper-catalyzed domino synthesis of quinazolin-4(3*H*)-one derivatives have been developed by Fu and other research groups (scheme 1).[11] The group of Wu has reported a palladium-catalyzed CO insertion for the construction of quinazolin-4(3*H*)-ones *via* *N*-(2-cyanoaryl)benzamides as intermediate.[10b,10i] During our studies on heterocycle synthesis *via* *o*-aminonitriles as strating materials[13], we hypothesized that amides could serve as suitable nucleophiles for coupling reactions with more conveniently available 2-halobenzonitrile, affording *N*-(2-cyanoaryl)amides, which can yield the corresponding quinazolinones through intramolecular cyclocondensation (Scheme 2).



Scheme 1 Methods for the synthesis of quinazolin-4(3*H*)-ones

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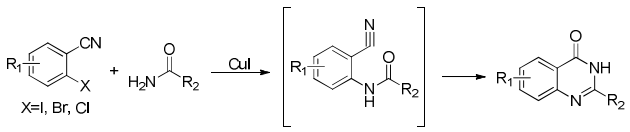
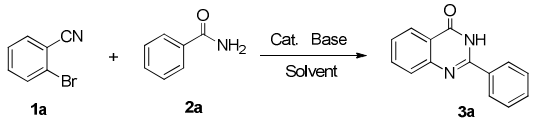


Scheme 2. Synthetic route to 2-substituted quinazolin-4(3*H*)-ones

Initially, 2-bromobenzonitrile (**1a**) and benzamide (**2a**) as model substrates was performed. As expected, the desired 2-phenylquinazolin-4(3*H*)-one (**3a**) was isolated in 75% yield by treating 2‑bromobenzonitrile (**1a**) (1.0 mmol) with benzamide (**2a**) (1.0 mmol) in the presence of CuI (5 mol%), NaOH (1.2 eq, relative to amount of **1a**) in DMSO (5 mL) at 120 ℃ for 12 h (Table 1, entry 2). Encouraged by this result, we further optimized the reaction conditions by changing solvent, and NMP was found to be the optimal solvent (Table 1, compared entries 1, 2 and 8-11), the yield of **3a** increased to 84% (Table 1, entry 2). Other solvents, such as dioxane and DMF, gave lower product yields (Table 1, entries 8 and 9). No desired **3a** could be detected when the reaction was carried out in toluene or H_2O (Table 1, entries 10 and 11). Compared with CuI, other catalysts, such as Cu_2O, $Cu(OAc)_2$, showed less catalytic activity. Among the examined bases, NaOH showed the best activity (Table 1, compared entries 3-8). No significant improvements in the yields were observed (Table 1, entries 7-9) when increasing the amount of CuI or extending the reaction time. On the other hand, 120 ℃ was a better reaction temperature compared to the others. (Table 1, entries 12-15).

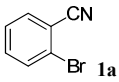
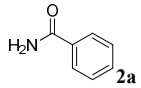
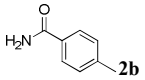
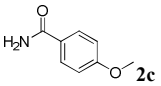
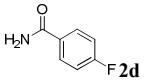
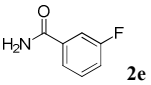
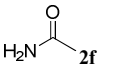
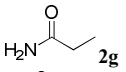
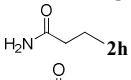
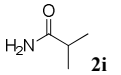
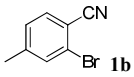
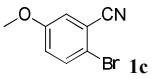
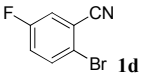
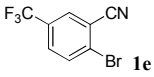
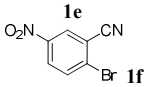
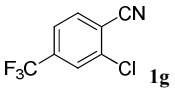
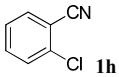
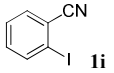
Table 1 Optimization of reaction conditions [a]



Entry	Cat.	Base	Solvent	Temp (℃)	Yield [b] (%)
1	CuI	NaOH	DMSO	120	75 (68[c], 78[d])
2	CuI	NaOH	NMP	120	84 (72[c], 87[d])
3	Cu_2O	NaOH	NMP	120	57
4	$Cu(OAc)_2$	NaOH	NMP	120	23
5	CuI	K_2CO_3	NMP	120	0
6	CuI	DBU	NMP	120	35
7	CuI	Cs_2CO_3	NMP	120	0
8	CuI	NaOH	Dioxane	120	73 (62[c], 76[d])
9	CuI	NaOH	DMF	120	42 (30[c], 45[d])
10	CuI	NaOH	Toluene	110	0
11	CuI	NaOH	H_2O	reflux	0
12	CuI	NaOH	NMP	120	84[e], 85[f]
13	CuI	NaOH	NMP	100	82
14	CuI	NaOH	NMP	80	63
15	CuI	NaOH	NMP	140	83

[a] Reaction conditions: **1a** (1.0 mmol), **2e** (1.0 mmol), catalyst (0.05 mmol), base (1.2 mmol), solvent (5.0 ml), 120 ℃, 12 h, under an air atmosphere. [b] Isolated yield. [c] Time: 8 h. [d] Time: 24 h. [e] 0.1 mmol. [f] 0.2 mmol.

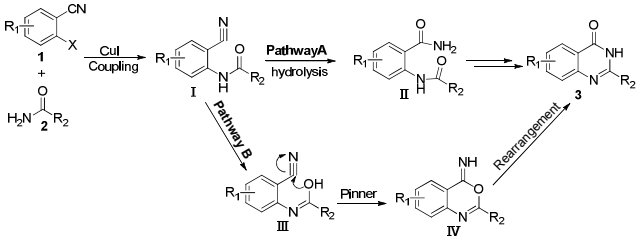
Table 2 Substrate scope for the copper-catalyzed domino synthesis of quinazolin-4(3*H*)-ones [a]

Entry	1	2	Product	Yield [b] (%)
1	 **1a**	 **2a**	**3a**	84
2	**1a**	 **2b**	**3b**	72
3	**1a**	 **2c**	**3c**	76
4	**1a**	 **2d**	**3d**	78
5	**1a**	 **2e**	**3e**	75
6	**1a**	 **2f**	**3f**	83
7	**1a**	 **2g**	**3g**	85
8	**1a**	 **2h**	**3h**	74
9	**1a**	 **2i**	**3i**	70
10	 **1b**	**2a**	**3j**	65
11	**1b**	**2h**	**3k**	62
12	 **1c**	**2a**	**3l**	61
13	**1c**	**2g**	**3m**	55
14	 **1d**	**2a**	**3n**	83
15	**1d**	**2h**	**3o**	78
16	 **1e**	**2a**	**3p**	80
17	**1e**	**2g**	**3q**	77
18	 **1f**	**2a**	—	0
19	**1f**	**2g**	—	0
20	 **1g**	**2a**	**3r**	67
21	 **1h**	**2a**	**3a**	62
22	**1h**	**2b**	**3b**	56
23	**1h**	**2f**	**3f**	52
24	**1h**	**2h**	**3h**	56
25	**1h**	**2i**	**3i**	63
26	 **1i**	**2a**	**3a**	86
27	**1i**	**2g**	**3g**	78
28	**1i**	**2i**	**3i**	80

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), CuI (0.05 mmol), NaOH (1.2 mmol), NMP (5.0 ml), 120 ℃, 12 h, under an air atmosphere. [b] Isolated yield

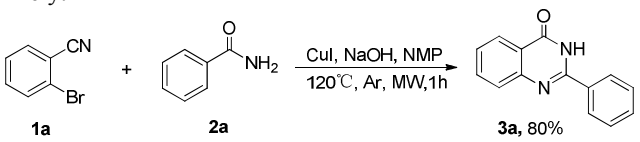
The scope of copper-catalyzed domino reactions of substituted 2-halobenzonitriles with amides was investigated under the optimized conditions (using 5 mol% of CuBr as the catalyst, 1.2 equiv of NaOH as the base, and NMP as the solvent). Initially, 2-bromobenzonitrile was chosen as a model substrate to react with a range of amides. For aromatic amides, in general, no significant difference of reactivity was observed for the examined substituted aryl amides with varied electronic properties, including electron-rich, electron-poor, and neutral substrates. All aliphatic amides tested furnished the corresponding quinazolin-4(3*H*)-ones in good yields (Table 2, entries 4-8). Moreover, the copper-catalyzed domino synthesis of quinazolinones showed good tolerance of the functional groups in the substrates including the methyl, methoxy, a C-F bond and trifluoromethyl in the substituted 2-halobenzonitriles, the 2-bromobenzonitriles containing electron withdrawing groups provided higher yields than the ones containing electron-donating groups, while those with strong electron-withdrawing groups like nitro, no product was observed. Furthermore, *o*-iodobenzonitriles showed higher reactivity than the corresponding 2-bromobenzonitriles and 2-chlomobenzo-nitriles.

A possible mechanism for domino reactions of substituted 2-halobenzonitrile and amides is suggested in Scheme 3. The Ullmann-type coupling of 2-halobenzonitrile (**1**) with amide (**2**) first provides *N*-(2-cyanoaryl)amide **I**. Then, intermediate **I** can undergo two pathways (Scheme 3, pathways A and B). For pathway A, the cyano-group hydration of **I** first occurs to lead to **II**, condensative cyclization and dehydration provides **3**.[11c] For pathway B, enolization of **I** and followed intramolecular Pinner reaction give the benzoxazine **III**, which subsequently rearranges to afford the final product.[14]



Scheme 3 Plausible Mechanism

In order to understand the mechanism of domino reactions of substituted 2-halobenzonitrile and amides, the copper-catalyzed reaction of 2-bromo-benzonitrile (**1a**) and benzamide (**2a**) was investigated, and product (**3a**) was found in 80% yield under microwave irradiation in a sealed argon atmosphere tube and super dry NMP as solvent (Scheme 4). If the cyano-group hydration of **I** occurred, we should observe the existence of the corresponding hydrolysis-product *N*-(2-cyanoaryl)benzamide **II**. However, we did not detect its existence. These results indicated that hydrolysis of intermediate **I** (Pathway A) is less likely.



Scheme 4 Mechanistic studies

In conclusion, we demonstrate for the first time a novel and efficient copper-catalyzed domino protocol for synthesis of quinazolin-4(3*H*)-one derivatives by using commercially available 2-halobenzonitriles and amides as starting materials, inexpensive CuI as the catalyst and cheap inorganic base as a promoter. This methodology does not require any special equipment and protection measures, besides, it also tolerates various functional groups and the corresponding quinazolinones prepared in moderate to good yields without any ligand or additive under air condition. Therefore, the present method provides a complementary strategy for construction of diverse *N*-heterocyclic compounds and will have a wide application in both academic and industrial research.

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