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Synthesis of 3-Substituted and 2,3-Disubstituted Quinazolinones via Cu-Catalyzed Aryl Amidation

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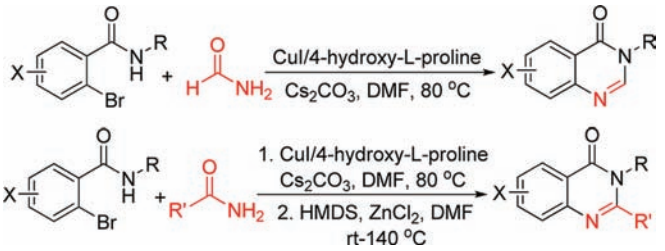
ABSTRACT



CuI/4-hydroxy-L-proline catalyzed coupling of *N*-substituted *o*-bromobenzamides with formamide takes place at 80 °C, affording 3-substituted quinazolinones directly. Under these conditions other amides that were tested only provided simple coupling products, which can be converted into 2,3-disubstituted quinazolinones via HMDS/$ZnCl_2$ mediated condensative cyclization.

Substituted quinazolinones are an important class of fused heterocyclic compounds due to their wide presence in natural products.[1] These include compound **1** (Figure 1) from *Aconitum* plants,[2] dictyoquinazol A **2** from *Dictyophora indusata*,[3] (+)-febrifugine **3** from *Hydrangea chinensis*,[4] and chaetominine **4** from *Adenophora axilliflora*.[5] In addition, many unnatural quinazolinones have shown significant biological activities which include anticancer,[6] antibacterial,[7] antiinflammatory,[8] antihypertensive,[9] antidiabetic,[10] and anticonvulsant[11] properties. For example, KSP ATPase inhibitor **5** displays antimitotic activity and now is in phase II clinical trials as a potential anticancer chemotherapeutic agent, while methaqualone **6** is a clinically used sedative-hypnotic drug.[12]

Although a number of methods have been developed for the synthesis of quinazolinones,[13] these routes mainly rely

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(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650. (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
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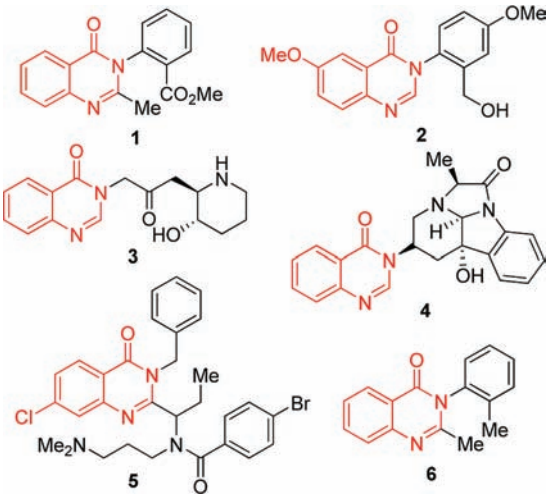

Figure 1. Structures of natural and synthesized biologically important quinazolinones.

on using anthranilic acid[14] or its derivatives[15] as the starting materials and generally suffer from low yields, multistep reactions, or harsh reaction conditions. These problems have stimulated several groups to apply metal-catalyzed reactions to develop new methods for assembling substituted quinazolinones.[16–18] Recently, the Ding and Fu groups independently discovered that copper-catalyzed *N*-arylation of *o*-bromobenzoic acid derivatives with amidines and subsequent intramolecular condensation could afford 2-substituted and 2,3-disubstituted quinazolinones.[17] During our studies on heterocycle synthesis via copper-catalyzed reactions,[19,20] we found that more conveniently available amides could serve as suitable nucleophiles for coupling reactions with *N*-substituted *o*-bromobenzamides, affording 3-substituted and 2,3-disubstituted quinazolinones after condensative cyclization as depicted in Scheme 1. Herein, we wish to disclose our results.

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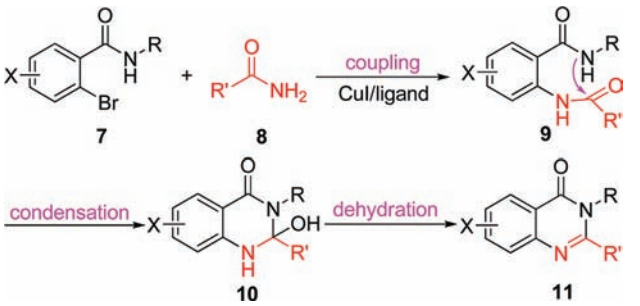
(15) (a) Kotsuki, H.; Sakai, H.; Morimoto, H.; Suenaga, H. *Synlett* **1999**, 1993. (b) Witt, A.; Bergman, J. *Tetrahedron* **2000**, *56*, 7245. (c) Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 6941. (d) Roy, A. D.; Subramanian, A.; Roy, R. *J. Org. Chem.* **2006**, *71*, 382. (e) Zhou, J.; Fang, J. *J. Org. Chem.* **2011**, *76*, 7730.

(16) (a) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 829. (b) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 3642. (c) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* **2011**, *76*, 6362.

(17) (a) Zhou, J.; Fu, L.; Lv, M.; Liu, J.; Pei, D.; Ding, K. *Synthesis* **2008**, *15*, 3974. (b) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem.* **2009**, *121*, 354.

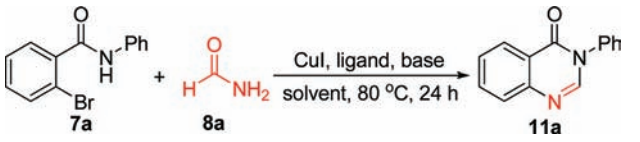
(18) (a) Xu, W.; Fu, H. *J. Org. Chem.* **2011**, *76*, 3846. (b) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274.

Scheme 1



As indicated in Table 1, we selected the reaction of 2-bromo-*N*-phenylbenzamide **7a** with formamide **8a** as a model to explore the optimized conditions. It was found that, under the catalysis of CuI and 4-hydroxy-L-proline, **7a** was consumed completely after 24 h at 80 °C, delivering **11a** in 84% yield (entry 1). Using K_3PO_4 as a base gave a similar result (entry 2). However, the best yield was observed with Cs_2CO_3 as the base (entry 3). Replacement of 4-hydroxy-L-proline with L-proline, glycine, *N*,*N*-dimethylglycine, or 1,10-phenanthroline gave slightly low yields (entries 4–7). Changing solvent from DMF to DMSO, dioxane, or toluene also decreased the reaction yields (entries 8–10). Based on these results, we concluded that, with CuI/4-hydroxy-L-proline as the catalyst, Cs_2CO_3 as the base, and DMF as the solvent, this was the optimized set of conditions for this transformation.

Table 1. Coupling of 2-Bromo-*N*-phenylbenzamide with Formamide under Different Conditions[a]

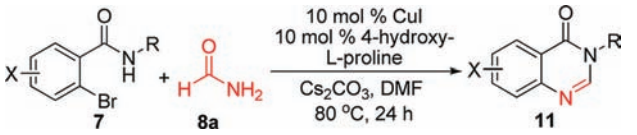


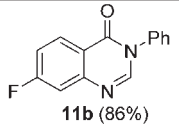
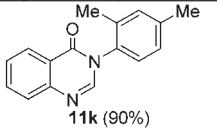
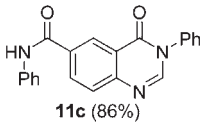
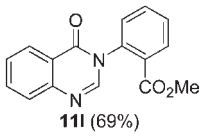
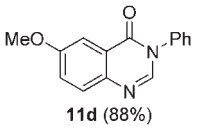
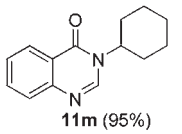
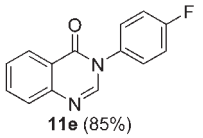
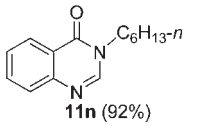
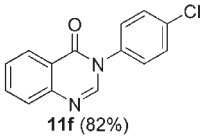
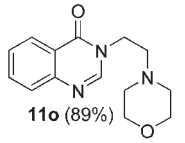
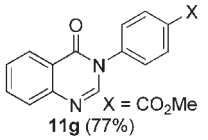
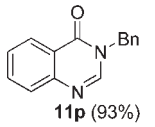
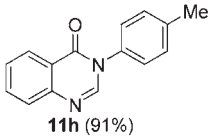
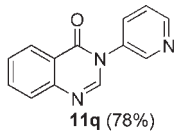
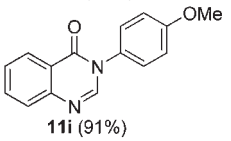
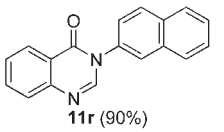
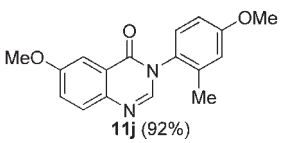
entry	ligand[b]	base	solvent	yield (%)[c]
1	A	K_2CO_3	DMF	84
2	A	K_3PO_4	DMF	83
3	*A*	*Cs_2CO_3*	*DMF*	*95*
4	B	Cs_2CO_3	DMF	72
5	C	Cs_2CO_3	DMF	75
6	D	Cs_2CO_3	DMF	68
7	E	Cs_2CO_3	DMF	40
8	A	Cs_2CO_3	DMSO	51
9	A	Cs_2CO_3	dioxane	67
10	A	Cs_2CO_3	toluene	40

[a] Reaction conditions: **7a** (0.25 mmol), **8a** (0.5 mmol), CuI (0.025 mmol), ligand (0.025 mmol), base (0.5 mmol), solvent (1 mL), 80 °C, 24 h. [b] A: 4-hydroxy-L-proline. B: L-proline. C: glycine. D: *N*,*N*-dimethylglycine. E: 1,10-phenanthroline. [c] Isolated yield.

With these conditions identified, we next investigated a series of 2-bromobenzamides to examine the scope and the limitations of this process. As shown in Table 2, our

Table 2. Synthesis of 3-Substituted Quinazolinones from 2-Bromobenzamides and Formamide[a]

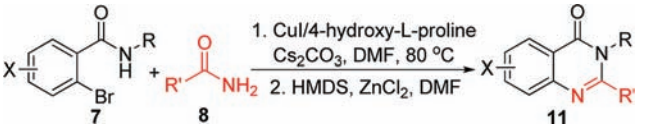


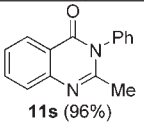
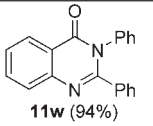
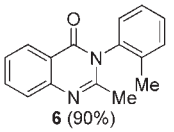
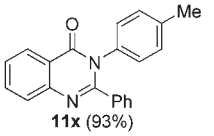
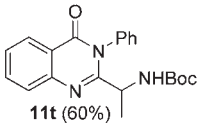
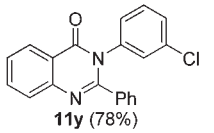
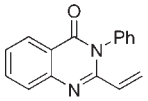
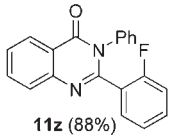
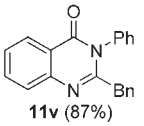
entry	product (yield)[b]	entry	product (yield)[b]
1	 **11b** (86%)	10	 **11k** (90%)
2	 **11c** (86%)	11[c]	 **11l** (69%)
3	 **11d** (88%)	12	 **11m** (95%)
4	 **11e** (85%)	13	 **11n** (92%)
5	 **11f** (82%)	14	 **11o** (89%)
6	 **11g** (77%)	15	 **11p** (93%)
7	 **11h** (91%)	16	 **11q** (78%)
8	 **11i** (91%)	17	 **11r** (90%)
9	 **11j** (92%)		

[a] Reaction conditions: **7** (0.25 mmol), **8a** (0.5 mmol), CuI (0.025 mmol), 4-hydroxy-L-proline (0.025 mmol), Cs_2CO_3 (0.5 mmol), DMF (1 mL), 80 °C, 24 h. [b] Isolated yield. [c] The reaction was carried out at 90 °C.

catalytic system worked well for a wide range of aryl bromides. Substrates derived from functionalized 2-bromobenzoic acids and substituted anilines with either electron-donating or -withdrawing groups engaged in this process to generate the corresponding products in good to excellent yields (entries 1–10). The results indicated that electronic variations on the benzene rings have a minor impact on the yields. But electronic effects in association with steric hindrance seem to diminish the product yield significantly. In the case of the 2,4-dimethylaniline-derived substrate, the yield of product **11k** was up to 90% (entry 10). In contrast, when a substrate derived from methyl 2-aminobenzoate was used, the reaction became sluggish even at 90 °C and only a 69% yield of **11l** was obtained (entry 11). The catalytic system could also tolerate a variety of nonaromatic N-substituents, including cyclic and acyclic alkyl, benzyl groups and functionalized carbon chains (entries 12–15). Pyridinyl and naphthyl groups as *N*-substituents also afforded the corresponding products **11q** and **11r** in 78% and 90% yields, respectively (entries 16 and 17). Noteworthy is that product **11j** could be easily converted to dictyoquinazol A **2** according to a known procedure,[21] indicating that the utility of our method in natural product synthesis is promising.

Table 3. Stepwise Synthesis of 2,3-Disubstituted Quinazolinones from 2-Bromobenzamides and Amides[a]



entry	product (yield)[b]	entry	product (yield)[b]
1	 **11s** (96%)	6[c]	 **11w** (94%)
2	 **6** (90%)	7[c]	 **11x** (93%)
3	 **11t** (60%)	8[c]	 **11y** (78%)
4	 **11u** (86%)	9[d]	 **11z** (88%)
5	 **11v** (87%)		

[a] Reaction conditions: Step 1: **7** (0.25 mmol), **8** (0.5 mmol), CuI (0.025 mmol), 4-hydroxy-L-proline (0.025 mmol), Cs_2CO_3 (0.5 mmol), DMF (1 mL), 80 °C, 24 h. Step 2: HMDS (0.75 mmol), $ZnCl_2$ (0.125 mmol), DMF (1 mL), rt. [b] Isolated yield. [c] The cyclization reaction was carried out at 120 °C. [d] The cyclization reaction was carried out at 140 °C.

After success in the elaboration of 3-substituted quinazolinones, we moved our attention to investigate a variety of aliphatic and aromatic amides as coupling partners. Our first attempt to employ ethyl amide met with limited success, with only the simple coupling product being obtained under the current reaction conditions. Hence we had to isolate this product and then conduct the cyclization step with HMDS/$ZnCl_2$ at room temperature.[22] Using this two-step procedure, a number of aliphatic amides were surveyed and the corresponding quinazolinones were isolated in yields ranging from 60% to 96% (Table 3, entries 1−5). Noteworthy is that, by using this method, methaqualone **6** was obtained directly in 90% yield. Interestingly, when aromatic amides were used, the corresponding coupling products could not be converted into quinazolinones at room temperature via HMDS/$ZnCl_2$ treatment. After some experimentation, we were pleased to find that this problem could be solved by increasing the reaction temperatures to 120−140 °C (entries 6−9).

In conclusion, we have developed a facile and efficient approach for assembling substituted quinazolinones, which relies on a copper-catalyzed aryl amidation reaction of *N*-substituted *o*-bromobenzamides with amides and subsequent spontaneous or HMDS/$ZnCl_2$ mediated condensative cyclization. The protocol could tolerate a variety of functional groups, providing a wide range of 3-substituted and 2,3-disubstituted quinazolinones in good to excellent yields. Its usage has been demonstrated by formal synthesis of dictyoquinazol A **2** and facile preparation of methaqualone **6**. The relatively mild coupling conditions used here are remarkable and may result from the *ortho*-substitution effect displayed by *N*-alkyl and *N*-aryl aminocarbonyl groups.[23] Investigations on the detailed mechanism of this coupling reaction are actively being pursued, and these results will be disclosed in due course.

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Supporting Information Available. Experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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