EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201400108

Copper-Catalyzed Domino Reaction Involving C–C Bond Cleavage To Construct 2-Aryl Quinazolinones

Li-Xia Wang,[a] Jun-Feng Xiang,[a] and Ya-Lin Tang*[a]

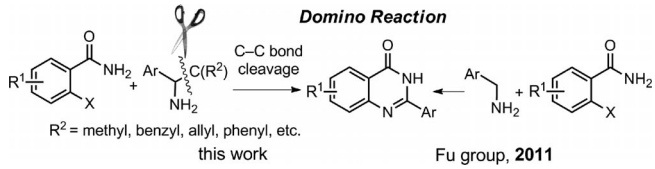
Keywords: Synthetic methods / Domino reactions / Cleavage reactions / Nitrogen heterocycles / Copper

A copper-catalyzed approach for the synthesis of 2-aryl-quinazolinones through a domino reaction involving C–C bond cleavage is described. This protocol involves intramolecular C–C bond cleavage to construct 2-aryl-quinazolinones, which may offer an alternative method to prepare medically important quinazolinone derivatives and a new strategy for C–C bond cleavage. Besides C–C bond cleavage, this domino reaction includes *N*-arylation and benzylic C–H amidation.

Introduction

The quinazolinone skeleton is an important pharmacophore, and it has been assigned as a privileged structure in drug development, because of the diverse range of pharmacological activities and biological properties displayed by compounds consisting of this structural motif.[1] In view of the importance of quinazolinones and their derivatives, many classical synthesis methods have been reported.[2] The main synthetic routes to quinazolinone compounds utilize 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-methoxycarbonylphenyl isocyanate, *N*-arylnitrilium salts, and 4*H*-3,1-benzoxazinones as suitable precursors. Recently, Fu et al. used substituted 2-halobenzamides and (aryl)methanamines as starting materials for CuBr-catalyzed cascade Ullmann-type coupling and aerobic oxidative C–H amidation reactions in air to give 2-substituted quinazolinones in good yields (Scheme 1).[3] In our research, by using α-substituted arylmethanamines as starting materials, we obtained 2-aryl-quinazolinones as the major products, which were surprisingly related to C–C bond cleavage. To the best of our knowledge, no examples of the construction of N-heterocycles through domino reactions involving C–C bond cleavage have been previously reported.

Selective C–C bond cleavage by transition-metal complexes has recently emerged as an active research topic in organic chemistry, along with C–H bond cleavage.[4] In comparison, C–C bond cleavage is more challenging owing to the inertness of this bond. As is known, C–C bond cleavage can be achieved by noble metals, but only a limited number of strategies have been reported with the use of cheap metals such as Cu and Fe.[5] Herein, we describe a copper-catalyzed approach for the synthesis of 2-aryl-quinazolinones through a domino reaction involving C–C bond cleavage.



Scheme 1. Methods for the synthesis of 2-aryl-substituted quinazolinone derivatives.

Results and Discussion

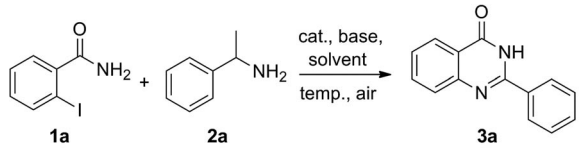
Our initial studies focused on identifying the optimal conditions (Table 1). 2-Iodobenzamide (**1a**) and α-methylbenzylamine (**2a**) were smoothly converted into 2-phenylquinazolin-4(3*H*)-one (**3a**) in 72% yield with CuBr (10 mol-%) as the catalyst, K_2CO_3 (3 equiv.) as the base, and dimethyl sulfoxide (DMSO) as the solvent under an air atmosphere at 120 °C over 24 h (Table 1, entry 1). Performing the reaction under an argon atmosphere led only to a small amount of **3a** in 24 h (Table 1, entry 2), but the yield could be increased to 38% in 72 h (Table 1, entry 3), which suggested the absence of air could decelerate the transformation. Thus, we began to screen other catalysts in air (Table 1, entries 4–6), and we found that CuBr provided the highest yield. The base had a significant effect on the yield; bases such as Cs_2CO_3 (Table 1, entry 7) and Na_2CO_3 (Table 1, entry 8) were tested, and neither of them gave a better result. Using other solvents such as DMF (Table 1, entry 9) and dimethylacetamide (DMA; Table 1, entry 10) instead of DMSO gave the products in lower yields. The

[a] Beijing National Laboratory for Molecular Sciences (BNLMS), Center for Molecular Sciences, State Key Laboratory for Structural Chemistry of Unstable and Stable Species, Institute of Chemistry, Chinese Academy of Sciences,
Beijing 100190, P. R. China
E-mail: tangyl@iccas.ac.cn
www.iccas.ac.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201400108.

effect of temperatures was also investigated, and 120 °C was the best choice (Table 1, compare entries 1, 11, 12).

Table 1. Optimization of the conditions for the copper-catalyzed domino reaction of 2-iodobenzamide with α-methylbenzylamine to form 2-phenylquinazolin-4(3*H*)-one in air.[a]

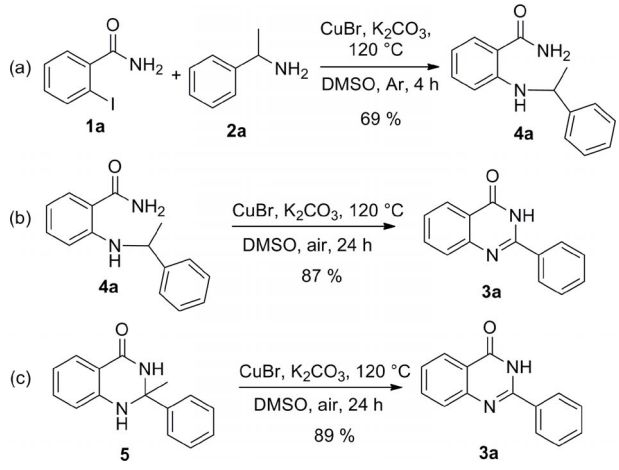


Entry	Cat.	Base	Solvent	*t* [h]	*T* [°C]	Yield[b] [%]
1	CuBr	K_2CO_3	DMSO	24	120	72
2	CuBr	K_2CO_3	DMSO	24	120	13[c]
3	CuBr	K_2CO_3	DMSO	72	120	38[c]
4	$CuBr_2$	K_2CO_3	DMSO	24	120	48
5	$CuCl_2$	K_2CO_3	DMSO	24	120	70
6	CuI	K_2CO_3	DMSO	24	120	23
7	CuBr	Cs_2CO_3	DMSO	24	120	16
8	CuBr	Na_2CO_3	DMSO	24	120	trace
9	CuBr	K_2CO_3	DMF	24	120	58
10	CuBr	K_2CO_3	DMA	24	120	63
11	CuBr	K_2CO_3	DMSO	24	140	61
12	CuBr	K_2CO_3	DMSO	24	100	52

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (0.05 mmol), base (1.5 mmol), and solvent (5 mL) under an air atmosphere. [b] Yield of isolated product. [c] Under an argon atmosphere.

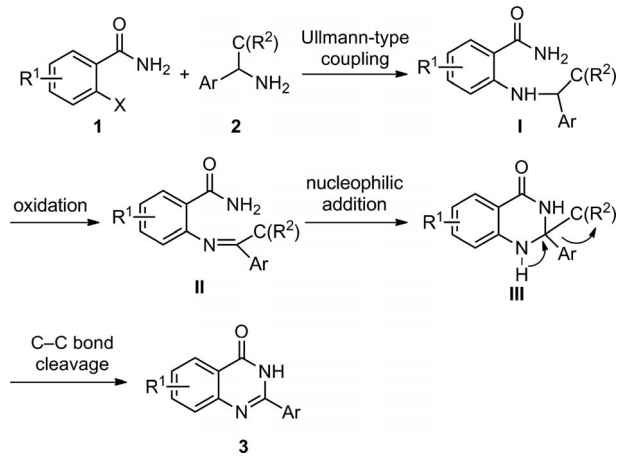
Under the established conditions [CuBr (10 mol-%) as the catalyst, K_2CO_3 (3 equiv.) as the base (relative to the amount of **1a**)], the domino reactions between substituted 2-halobenzamides **1** and α-substituted arylmethanamines **2** were performed. As shown in Table 2, most of the substrates examined provided the corresponding products in 21–73% yield. For substituted 2-halobenzamides, the aryl iodide showed higher reactivity than the corresponding bromide and chloride (Table 2, entries 1, 10, 11), and 2-bromo-5-methoxybenzamide gave a better result than 2-chloro-4-nitrobenzamide (Table 2, entries 12–15, 16). For the starting α-substituted arylmethanamines, if the R^2 group was a methyl (Table 2, entry 1), allyl (Table 2, entry 2), benzyl (Table 2, entry 3), or phenyl group (Table 2, entry 4) and the Ar group was a phenyl group, product **3a** was obtained in all cases in 62–73% yield. The reaction also tolerated Ar groups with varied electronic properties, including electron-neutral (e.g., phenyl: Table 2, entries 1 and 12), electron-rich (e.g., *p*-methylphenyl: Table 2, entries 5 and 13; *p*-methoxyphenyl: Table 2, entries 6 and 14), and electron-poor (e.g., *p*-chlorophenyl: Table 2, entries 7 and 15), in addition to a pyridine ring (Table 2, entry 8) and a naphthalene ring (Table 2, entry 9), all of which gave corresponding products **3a**–**k** in 49–73% yield.

To explore the reaction mechanism, we chose α-methylbenzylamine (**2a**) as the model substrate and launched the control experiments shown in Scheme 2. If 2-iodobenzamide (**1a**) was treated with **2a** under an argon atmosphere (1 atm, with extrusion of air) for 4 h, Ullmann-coupling product **4a** was obtained in 69% yield (see Scheme 2, a). *N*-Arylation product **4a** was placed under the above-optimized conditions and further converted into final product 2-phenylquinazolin-4(3*H*)-one (**3a**) in 87% yield (see Scheme 2, b). We purposely prepared **5** according to the reported method,[6] and it was transformed into final product **3a** efficiently under the established conditions (see Scheme 2, c). Without the involvement of CuBr, the transformation from **5** into **3a** was also realized, but it took 3 days, and the yield of the isolated product was 81%, which revealed the important role of CuBr as the catalyst (see the Supporting Information).



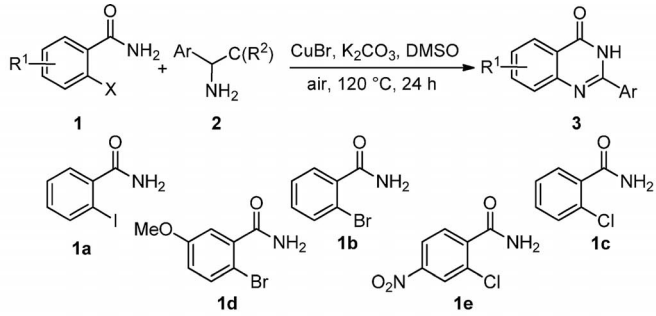
Scheme 2. CuBr-catalyzed (a) Ullmann-type coupling of **1a** with **2a** under an argon atmosphere, (b) domino reaction of **4a** in air, and (c) transformation from **5** into **3a** in air.

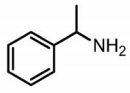
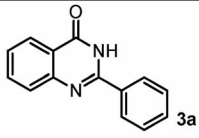
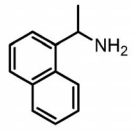
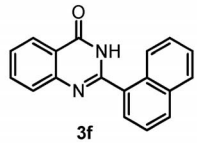
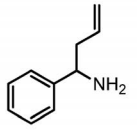
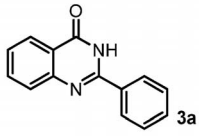
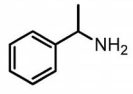
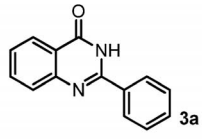
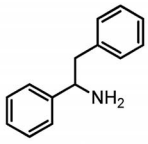
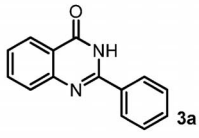
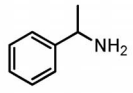
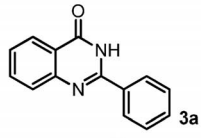
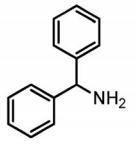
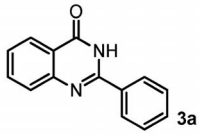
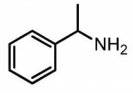
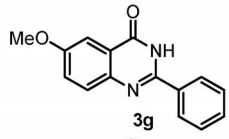
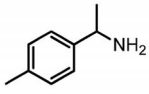
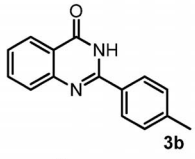
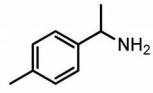
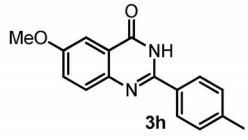
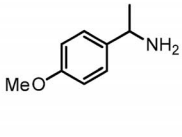
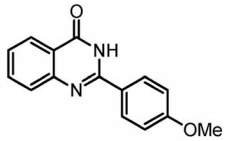
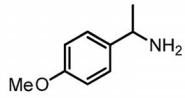
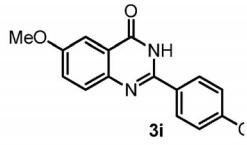
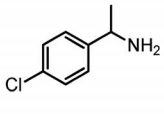
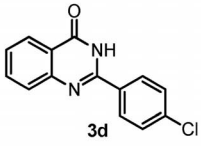
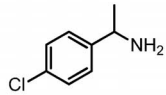
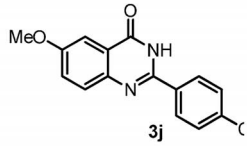
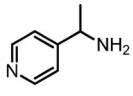
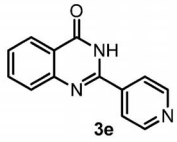
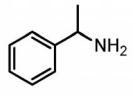
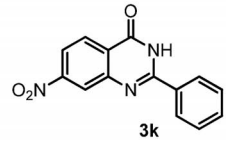
On the basis of the above results, we proposed a possible mechanism, as shown in Scheme 3. Ullmann-type coupling product **I** is first prepared starting from a substituted 2-halobenzamide and an α-substituted arylmethanamine, and the results showed an *ortho*-substituent effect of the amide group in **I** during *N*-arylation.[7] Then, *N*-arylation product **I** is transformed into imine **II**, which was verified indirectly from the isolation of the ketone as a byproduct (see the Supporting Information). Then, intramolecular nucleo-



Scheme 3. Possible mechanism for the CuBr-catalyzed domino synthesis of 2-aryl-substituted quinazolinones in air.

Table 2. Substrate scope for the CuBr-catalyzed domino synthesis of 2-aryl-substituted quinazolinones.[a]



Entry	1	2	3	Yield[b] [%]	Entry	1	2	3	Yield[b] [%]
1	1a		 3a	72	9	1a		 3f	49
2	1a		 3a	64	10	1b		 3a	58
3	1a		 3a	73	11	1c		 3a	31
4	1a		 3a	62	12	1d		 3g	57
5	1a		 3b	73	13	1d		 3h	59
6	1a		 OMe	69	14	1d		 3i	56
7	1a		 3d Cl	71	15	1d		 3j	61
8	1a		 3e	61	16	1e		 3k	21

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), CuBr (0.05 mmol), K_2CO_3 (1.5 mmol), and DMSO (5 mL) under an air atmosphere. [b] Yield of isolated product.

philic addition of the amide to the C=N bond provides benzylic C–H amidation product **III**.[8] In the end, target 2-aryl-quinazolinone **3** is formed through carbon–carbon bond cleavage. A thorough mechanistic study of the C–C

bond cleavage reaction is needed to unravel the mechanistic intricacies of this process.

Conclusions

In summary, we demonstrated a copper-catalyzed approach for the construction of 2-aryl-quinazolinones through a domino reaction involving C–C bond cleavage by using air as the accelerant. Besides C–C bond cleavage, the domino reactions also included *N*-arylation and benzylic C–H amidation. This reaction not only provides an efficient method for constructing medically important quinazolinones but also offers a new strategy for C–C bond cleavage.

Experimental Section

General Information: Reactions were monitored by analytical thin-layer chromatography (TLC) by using ultraviolet light. Purification of the products was accomplished by flash chromatography on silica gel (100–200 mesh), and the purified compounds showed a single spot by analytical TLC. Chemical shifts are in ppm versus tetramethylsilane with either tetramethylsilane or the residual solvent resonance used as the internal standard. Melting points are uncorrected.

General Procedure for Synthesis of Quinazolinone Derivatives 3a–k: A mixture of substituted 2-halobenzamide **1** (0.5 mmol), α-substituted benzylamine **2** (1.0 mmol), K_2CO_3 (1.5 mmol, 207 mg), and CuBr (0.05 mmol, 7.1 mg) in DMSO (5 mL) was allowed to stir at 120 °C for 24 h. Upon completion of the reaction, the resulting solution was cooled to room temperature and filtered, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to provide desired product **3**.

Supporting Information (see footnote on the first page of this article): Detailed description of the experimental procedures and analytical data for all compounds.

Acknowledgments

The authors wish to thank the National Natural Science Foundation of China (NSFC) (grant numbers 21302188, 81072576, 91027033) and the Chinese Academy of Sciences (grant numbers KJCX2-EW-N06-01 and XDA09030307) for financial support.

[1] a) C. Larksarp, H. Alper, *J. Org. Chem.* **2000**, *65*, 2773; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893; c) S. B. Mhaske, N. P. Argade, *Tetrahedron* **2006**, *62*, 9787, and references cited therein; d) S. R. Padala, P. R. Padi, V. Thipireddy, *Heterocycles* **2003**, *60*, 183; e) F.-R. Zhang, S. Bhat, S. B. Gabelli, X.-C. Chen, M. S. Miller, B. A. Nacev, Y.-L. Cheng, D. J. Meyers, K. Tenney, J. S. Shim, P. Crews, L. M. Amzel, D.-W. Ma, J.-O. Liu, *J. Med. Chem.* **2013**, *56*, 3996.

[2] For selected examples, see: a) A. Witt, J. Bergman, *Curr. Org. Chem.* **2003**, *7*, 659, and references cited therein; b) D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron* **2005**, *61*, 10153; c) L. Wang, J. Xia, F. Qin, C. Qian, J. Sun, *Synthesis* **2003**, 1241; d) B. B. Snider, H. Zeng, *Heterocycles* **2003**, *61*, 173; e) M. Dabiri, P. Salehi, M. S. Khajavi, A. A. Mohammadi, *Heterocycles* **2004**, *63*, 1417; f) R. J. Abdel-Jalil, W. Voelter, M. Saeed, *Tetrahedron Lett.* **2004**, *45*, 3475; g) B. A. Bhat, D. P. Sahu, *Synth. Commun.* **2004**, *34*, 2169; h) A. Kamal, K. S. Reddy, B. R. Prasad, A. H. Babu, A. V. Ramana, *Tetrahedron Lett.* **2004**, *45*, 6517; i) J.-F. Liu, J. Lee, A. M. Dalton, G. Bi, L. Yu, C. M. Baldino, E. McElory, M. Brown, *Tetrahedron Lett.* **2005**, *46*, 1241; j) T. M. Potewar, R. N. Nadaf, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *Synth. Commun.* **2005**, *35*, 231; k) M. Dabiri, P. Salehi, A. A. Mohammadi, M. Baghbanzadeh, *Synth. Commun.* **2005**, *35*, 279.

[3] W. Xu, H.-X. Liu, Y.-Y. Jiang, H. Fu, *Org. Lett.* **2011**, *13*, 1274.

[4] For reviews on C–C bond cleavage, see: a) K. C. Bishop III, *Chem. Rev.* **1976**, *76*, 461; b) R. H. Crabtree, *Chem. Rev.* **1985**, *85*, 245; c) B. Rybtchinski, D. Milstein, *Angew. Chem. Int. Ed.* **1999**, *38*, 870; *Angew. Chem.* **1999**, *111*, 918; d) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610; e) C.-H. Jun, J.-W. Park, *Top. Organomet. Chem.* **2007**, *24*, 117; f) Y.-J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222; g) C. Nájera, J. W. Sansano, *Angew. Chem. Int. Ed.* **2009**, *48*, 2452; *Angew. Chem.* **2009**, *121*, 2488.

[5] W. Zhou, Y.-Q. Yang, Y. Liu, G.-J. Deng, *Green Chem.* **2013**, *15*, 76 and references cited therein.

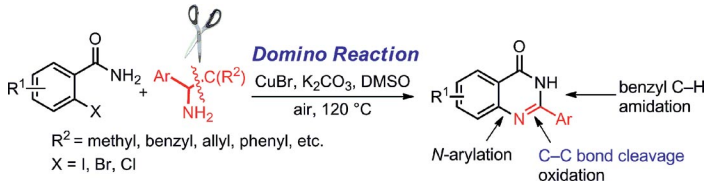
[6] T. P. Natin, G. Pediredla, S. Vipender, *Eur. J. Org. Chem.* **2010**, 4719.

[7] a) K. C. Nicolaou, C. N. C. Boddy, S. Natarajar, T.-Y. Yue, H. Li, J. M. Ramanjulu, *J. Am. Chem. Soc.* **1997**, *119*, 3421; b) Q. Cai, B. Zou, D. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 1276; *Angew. Chem.* **2006**, *118*, 1298; c) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; d) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954; *Angew. Chem.* **2009**, *121*, 7088; e) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; f) X. Liu, H. Fu, Y. Jiang, Y. Zhao, *Angew. Chem. Int. Ed.* **2009**, *48*, 348; *Angew. Chem.* **2009**, *121*, 354; g) C. Huang, Y. Fu, H. Fu, Y. Jiang, Y. Zhao, *Chem. Commun.* **2008**, 6333; h) D. Yang, H. Fu, L. Hu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 7841; i) D. Yang, H. Liu, H. Yang, H. Fu, L. Hu, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 1999; j) F. Wang, H. Liu, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2009**, *11*, 2469.

[8] a) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.* **2012**, *77*, 7046; b) Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2007**, *9*, 3813.

Received: January 22, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry



A copper-catalyzed approach for the synthesis of 2-aryl-quinazolinones through a domino reaction involving C–C bond cleavage is described. This transformation offers an alternative method to prepare medically important quinazolinone derivatives and a new strategy for C–C bond cleavage.

Keywords: Synthetic methods / Domino reactions / Cleavage reactions / Nitrogen heterocycles / Copper

