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Copper-Catalyzed Synthesis of Quinazolines in Water Starting from *o*-Bromobenzylbromides and Benzamidines

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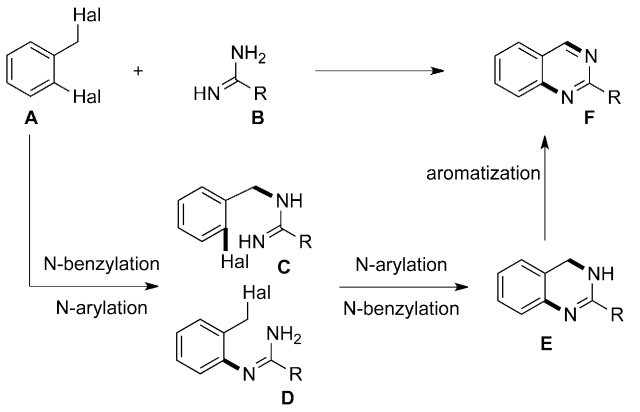
Dedicated to Professor Lutz F. Tietze on the occasion of his 70th birthday

Quinazolines and their derivatives exhibit a wide range of biological and pharmacological activities including anticancer,[1] antiviral,[2] antitubercular,[3] and antimalarial[4] properties. This is why their synthesis receives much attention. Although a number of well-known protocols to synthesize quinazolines are available, there is a strong ongoing interest to develop new and more efficient methods for their preparation.[5,6] More recent approaches to quinazolines include the reaction between 2-aminobenzophenones and benzylic amines by using catalytic amounts of copper-oxide nanoparticles,[6c] the Cu-catalyzed reaction between 2-halobenzaldehydes or 2-halophenylketones with amidines,[6f] the transition-metal-catalyzed intramolecular oxidative C–H functionalization of *N*-phenylbenzamidines[6d] and *N*-(2-iodophenyl)-trifluoroacetimidoyl chlorides,[6b] the Bischler quinazoline synthesis under microwave conditions,[6g] and the oxidative synthesis of 2-aryl quinazolines by reaction of 2-aminobenzophenones with benzylamines.[6a,e] To date, *ortho*-halobenzyl halides have not been employed as substrates for the preparation of quinazolines.

The level of interest in Cu-catalyzed arylations has increased considerably over the last few years.[7] This trend is at least partly due to the fact that Cu reagents are much cheaper than their Pd counterparts, which are usually employed for this type of transformation. Originally, Cu-catalyzed arylations required comparably harsh reaction conditions, but meanwhile protocols that allow for much milder conditions have been developed. Cu-catalyzed arylations are extensively used to synthesize aromatic amines, ethers, and thioethers, but can also be employed for the synthesis of many heterocycles.[7]

Recently, we reported the synthesis of 4*H*-chromenes by Cu-catalyzed reaction between 2-halobenzyl halides and β-ketoesters.[8] In this 4*H*-chromene synthesis one C–C and one C–O bond are formed in a single step, and we have proposed that these transformations proceed as a domino C-benzylation/O-arylation. It is clear that Cu-catalyzed domino reactions with 2-halobenzyl halides can also be employed for the synthesis of other six-membered heterocyclic systems, if they are reacted with suitably 1,3-difunctionalized reaction partners. Considering the synthesis of quinazolines **F**, we assumed that both a domino intermolecular N-benzylation/intramolecular N-arylation (**A**+**B**→**C**→**E**) and a domino intermolecular N-arylation/intramolecular N-benzylation (**A**+**B**→**D**→**E**) between a 2-halobenzyl halide **A** and an amidine **B** followed by aromatization of the resulting 3,4-dihydroquinazoline **E** to the quinazoline **F** could serve this purpose (Scheme 1).



Scheme 1. Proposal for the Cu-catalyzed synthesis of quinazolines.

Herein, we report a new method for the efficient synthesis of quinazolines that is based on the Cu-catalyzed reaction between 2-bromobenzyl bromides and amidines in H_2O. When 1 equivalent of 2-iodobenzyl bromide (**1**) and 2 equivalents of benzamidinium hydrochloride (**3a**) were reacted in the presence of 10 mol% CuI and 2 equivalents of Cs_2CO_3 in DMF at 40°C for 20 h under argon, 2-phenylquinazoline (**4a**) could be isolated in 14% yield (Table 1, entry 1). This result clearly demonstrated that quinazolines can be synthesized by reaction between a 2-halobenzyl halide and an amidine. However, it was obvious that optimization was needed to make this an interesting synthetic method. The yield could not be improved with 4-hydroxy-L-proline as an additive (see the Supporting Information). Further experiments

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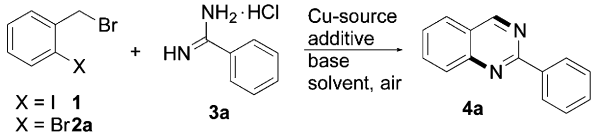
Table 1. Optimization of the Cu-catalyzed reaction of 2-halobenzyl halides **1** and **2a** with benzamidinium hydrochloride (**3a**).



	Substrate	Cu source [mol%]	Additive [mol%]	Base [equiv]	Solvent	T [°C]	t [h]	Yield [%]
1	**1**	CuI; 10	–	Cs_2CO_3; 2	DMF	40	20	14[a]
2	**2a**	CuI; 10	DMEDA; 20	Cs_2CO_3; 4	DMF	50	24	29[a]
3	**2a**	CuI; 10	DMEDA; 20	Cs_2CO_3; 4	DMF	50	24	30
4	**2a**	Cu_2O; 10	DMEDA; 20	Cs_2CO_3; 4	DMF	100	24	39
5	**2a**	Cu_2O; 10	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	24	45
6	**2a**	Cu_2O; 10	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	40	61
7	**2a**	Cu_2O; 10	–	Cs_2CO_3; 4	H_2O	100	40	traces
8	**2a**	Cu_2O; 10	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	40	40[a]
9	**2a**	CuI; 10	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	40	36
10	**2a**	CuBr; 10	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	40	14
11	**2a**	CuCl; 10	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	40	9
12	**2a**	–	DMEDA; 20	Cs_2CO_3; 4	H_2O	100	40	–
13	**2a**	Cu_2O; 10	DMEDA; 20	K_2CO_3; 4	H_2O	100	40	40
14	**2a**	Cu_2O; 10	DMEDA; 20	Cs_2CO_3; 3	H_2O	100	40	49

[a] The reaction was performed under Ar.

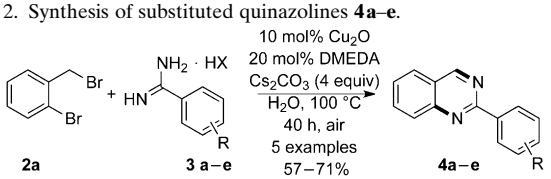
with 2-bromobenzyl bromide (**2a**) revealed that *N*,*N*′-dimethylethylenediamine (DMEDA) was a more suitable additive. The yield of **4a** could be doubled to 29%, when 20 mol% DMEDA was added, and the amount of Cs_2CO_3 was increased to 4 equivalents. (Table 1, entry 2). Unexpectedly, the yield could not be improved further by running the reaction under air (Table 1, entry 3).

Experiments with different Cu sources in DMF at 100°C revealed that the yield of **4a** could be increased to 39% with Cu_2O as the catalyst (Table 1, entry 4). Further improvements were achieved by replacing DMF with H_2O as the solvent (Table 1, entry 5) and by extending the reaction time from 24 h to 40 h (Table 1, entry 6). Finally, **4a** could be isolated with 61% when the reaction was performed with 10 mol% Cu_2O, 20 mol% DMEDA, and 4 equivalents of Cs_2CO_3 in H_2O at 100°C for 40 h in a sealed vial under air (Table 1, entry 6). A control experiment revealed the importance of DMEDA as an additive: without any DMEDA, only traces of **4a** were formed (Table 1, entry 7). Another control showed that the yield of **4a** was higher in the presence of aerial O_2 than in its absence (Table 1, entry 8).

Further studies established that also in H_2O as the solvent, Cu_2O is a more efficient catalyst than CuI, CuBr, and CuCl (Table 1, entries 9–11). When the amount of Cu_2O was decreased, the yield of **4a** dropped considerably (see the Supporting Information). In the absence of any Cu source, not even traces of **4a** were formed (Table 1, entry 12). This result underlines the decisive role of the Cu catalyst for this reaction. Then we focused on the base. When Cs_2CO_3 was replaced with other bases, such as K_2CO_3, the yield dropped to 40% (Table 1, entry 13). Reduction of the amount of Cs_2CO_3 to 3 equivalents also resulted in substantial loss in yield (Table 1, entry 14).

Finally, the influence of different solvents on the outcome of the reaction between **2a** and **3a** was studied. Alcohols, such as *i*PrOH and ethylene glycol, as well as polar aprotic solvents, such as DMF, DMSO, and MeCN, and the nonpolar *meta*-xylene, were found to be less effective than H_2O (see the Supporting Information). To summarize, the highest yield of 2-phenyl quinazoline (**4a**) was obtained when the reaction between 1 equivalent of **2a** and 2 equivalents of **3a**

Table 2. Synthesis of substituted quinazolines **4a–e**.



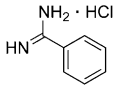
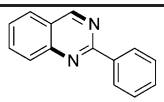
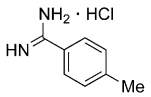
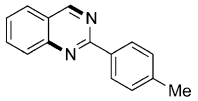
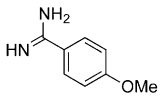
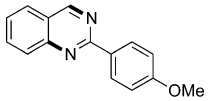
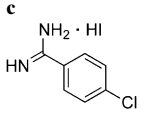
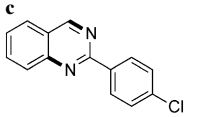
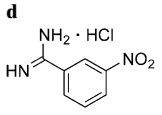
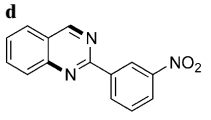
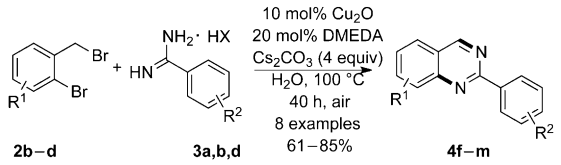
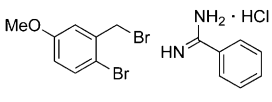
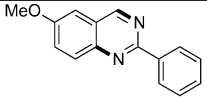
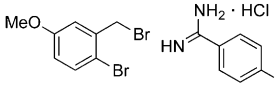
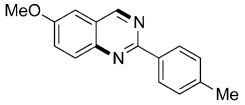
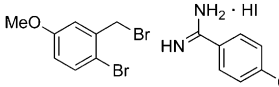
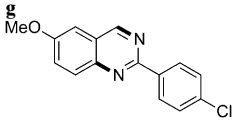
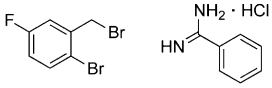
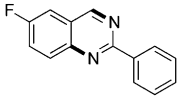
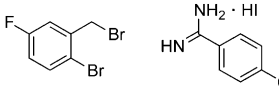
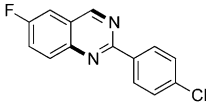
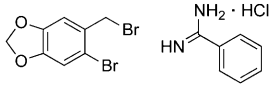
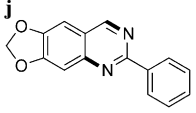
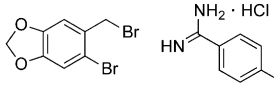
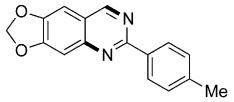
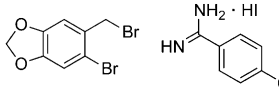
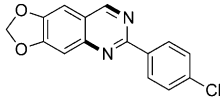
	3	**4**	Yield [%]
1			61
2	**a** 	**a** 	71
3	**b** 	**b** 	57
4	**c** 	**c** 	69
5	**d** 	**d** 	66
	e	**e**	

Table 3. Synthesis of substituted quinazolines **4f–m**.



	2	3	4	Yield [%]
1				81
2	**b** 	**a**	**f** 	83
3	**b** 	**b**	**g** 	79
4	**b** 	**d**	**h** 	69
5	**c** 	**a**	**i** 	80
6	**c** 	**d**	**j** 	83
7	**d** 	**a**	**k** 	61
8	**d** 	**b**	**l** 	85
	d	**d**	**m**	

was performed with 10 mol% Cu_2O, 20 mol% DMEDA, and 4 equivalents of Cs_2CO_3 in H_2O at 100 °C for 40 h in a sealed vial under air (Table 1, entry 6). It should be noted that the quinazoline synthesis presented here is one of the first examples of a Cu-catalyzed synthesis of heterocycles in water.[9]

With optimized reaction conditions at hand, the substrate scope of the new method was examined. It was found that in addition to **3a**, also substituted derivatives **3b–e** could be reacted with **2a** to yield the corresponding quinazolines **4b–e** with yields ranging from 57 to 71% as the sole products (Table 2).

It was also demonstrated that substituted 2-bromobenzyl bromides **2b–d** are tolerated as substrates for the new quinazoline synthesis as well (Table 3). They were reacted under standard conditions with the unsubstituted **3a** as well as with the substituted derivatives **3b,d** to give the quinazolines **4f–m** with yields ranging from 61 to 85%. These results suggest that the newly developed quinazoline synthesis will find a broad range of application.

In conclusion, a simple to execute and efficient one-pot synthesis of substituted quinazolines from easily accessible *ortho*-bromobenzyl bromides and benzamidines as starting materials has been developed. The new Cu_2O-catalyzed reaction delivered the products selectively and with yields ranging from 57 to 85% by using water as the solvent under mild reaction conditions.

Experimental Section

A vial (10 mL) was charged with Cu_2O (0.05 mmol), DMEDA (0.1 mmol), Cs_2CO_3 2.0 mmol), the 2-bromobenzyl bromide **2** (0.5 mmol), and the amidinium salt **3** (1 mmol). The vial was sealed under air, and H_2O (2 mL) was added by syringe. The reaction mixture was heated in an oil bath at 100 °C for 40 h. After cooling to RT, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue thus obtained was purified by flash-column chromatography over silica gel (petrol ether (PE)/EtOAc 20:1).

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Keywords: N-arylation · copper · domino reactions · heterocycles · water chemistry

[1] a) L. Austin Doyle, D. D. Ross, *Oncogene* **2003**, *22*, 7340–7358; b) E. A. Henderson, V. Bavetsias, D. S. Theti, S. C. Wilson, R. Clauss, A. L. Jackman, *Bioorg. Med. Chem.* **2006**, *14*, 5020–5042.

[2] a) T.-C. Chien, C.-S. Chen, F.-H. Yu, J.-W. Chern, *Chem. Pharm. Bull.* **2004**, *52*, 1422–1426; b) T. Herget, M. Freitag, M. Morbitzer, R. Kupfer, T. Stamminger, M. Marschall, *Antimicrob. Agents Chemother.* **2004**, *48*, 4154–4162.

[3] a) K. Waisser, J. Gregor, H. Dostal, J. Kunes, L. Kubicova, V. Klimesova, J. Kaustova, *Farmaco* **2001**, *56*, 803–807; b) J. Kuneš, J. Bažant, M. Pour, K. Waisser, M. Šlosárek, J. Janota, *Farmaco* **2000**, *55*, 725–729.

[4] S. Madapa, Z. Tusi, A. Mishra, K. Srivastava, S. K. Pandey, R. Tripathi, S. K. Puri, S. Batra, *Bioorg. Med. Chem.* **2009**, *17*, 222–234.

[5] For a review, see: D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron* **2005**, *61*, 10153–10202.

[6] a) B. Han, C. Wang, R.-F. Han, W. Yu, X.-Y. Duan, R. Fang, X.-L. Yang, *Chem. Commun.* **2011**, *47*, 7818–7820; b) J. Zhu, H. Xie, Z. Chen, S. Li, Y. Wu, *Chem. Commun.* **2011**, *47*, 1512–1514; c) J. Zhang, C. Yu, S. Yang, C. Wan, Z. Wang, *Chem. Commun.* **2010**, *46*, 5244–5246; d) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2010**, *12*, 3963–3965; e) J. Zhang, D. Zhu, C. Yu, C. Wan, Z. Wang, *Org. Lett.* **2010**, *12*, 2841–2843; f) C. Huang, Y. Fu, H. Fu, Y.

Jiang, Y. Zhao, *Chem. Commun.* **2008**, 6333–6335; g) S. Ferrini, F. Ponticelli, M. Taddei, *Org. Lett.* **2007**, *9*, 69–72; h) D. S. Yoon, Y. Han, T. M. Stark, J. C. Haber, B. T. Gregg, S. B. Stankovich, *Org. Lett.* **2004**, *6*, 4775–4778; i) Y. Bathini, I. Sidhu, R. Singh, R. G. Micetich, P. L. Toogood, *Tetrahedron Lett.* **2002**, *43*, 3295–3296.

[7] For recent reviews, see: a) Y. Liu, J.-P. Wan, *Org. Biomol. Chem.* **2011**, *9*, 6873–6894; b) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641–652; c) J. E. R. Sadig, M. C. Willis, *Synthesis* **2011**, 1–22; d) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088–7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; e) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; f) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460.

[8] C. C. Malakar, D. Schmidt, J. Conrad, U. Beifuss, *Org. Lett.* **2011**, *13*, 1972–1975.

[9] a) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68–82; b) M. Carril, R. SanMartin, E. Domínguez, *Chem. Soc. Rev.* **2008**, *37*, 639–647.

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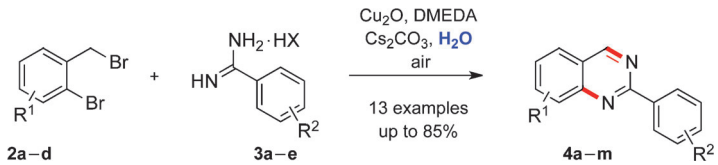

Water makes it possible: The Cu_2O-catalyzed reaction between easily available *o*-bromobenzylbromides and benzamidines by using Cs_2CO_3 as the base and *N*,*N*′-dimethylethylenediamine (DMEDA) as the additive in water as the solvent gives access to substituted quinazolines in a single step with yields ranging from 57 to 85% (see scheme).

Domino Reactions