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Copper(I)-Mediated Cascade Reactions: An Efficient Approach to the Synthesis of Functionalized Benzofuro[3,2-*d*]pyrimidines

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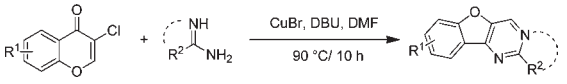
ABSTRACT



A novel cascade reaction was developed for the synthesis of diverse members of a series of benzofuro[3,2-*d*]pyrimidine derivatives. The process utilizes readily prepared 3-chlorochromenones and various commercially available amidines and their analogues as starting materials. This tandem reaction is promoted by using a simple copper(I) reagent and involves a chemoselective Michael addition–heterocyclization–intramolecular cyclization sequence.

Benzofuro[3,2-*d*]pyrimidine is widely found as a core structure in a large variety of substances that exhibit important biological activities. One example of this is found in MP-470 (**1**), which is a multitargeted tyrosine kinase inhibitor that radiosensitizes several GBM cell lines.[1] In addition, the benzofuro[3,2-*d*]pyrimidine derivative **2** has been found to potentiate the CREB (cAMP response element binding) signaling pathway that is associated with the enhancement of long-term memory.[2] Members of a series of benzofuropyrimidine derivatives serve as modulators of the histamine H4 receptor[3] and, in the case of **3**, as histamine H4 receptor inverse agonists (Figure 1). Also, benzofuropyrimidines have been observed to be Hsp90 inhibitors,[4] adenosine receptor (A_{2A}) antagonists,[5] and *E. coli* primase inhibitors.[6]

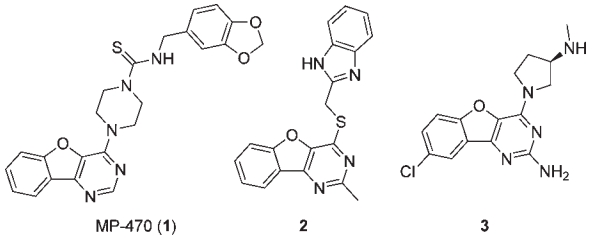


Figure 1. Representative bioactive benzofuro[3,2-*d*]pyrimidines.

A classical synthetic method used earlier to construct the benzofuropyrimidine scaffold (Scheme 1) begins with

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(1) Welsh, J.; Mahadevan, D.; Ellsworth, R.; Cooke, L.; Bearss, D.; Stea, B. *Radiat. Oncol.* **2009**, *4*, 69.

(2) Xia, M.; Huang, R.; Guo, V.; Southall, N.; Cho, M.-H.; Inglese, J.; Austin, C. P.; Nirenberg, M. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 2412.

(3) (a) Chavez, F.; Curtis, M. P.; Edwards, J. P.; Gomez, L.; Grice, C. A.; Kearney, A. M.; Savall, B. M.; Fitzgerald, A. E.; Liu, J.; Mani, N. S.; Curtis, M.; Edwards, J.; Fitzgerald, A.; Grice, C.; Kearney, A.; Mani, N.; Savall, B.; Edweards, J. P.; Lui, J. Patent WO 2008008359, 2008. (b) Cramp, S.; Dyke, H. J.; Higgs, C.; Clark, D. E.; Gill, M.; Savy, P.; Jennings, N.; Price, S.; Lockey, P. M.; Norman, D.; Porres, S.; Wilson, F.; Jones, A.; Ramsden, N.; Mangano, R.; Leggate, D.; Andersson, M.; Hale, R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2516. (c) Savall, B. M.; Gomez, L.; Chavez, F.; Curtis, M.; Meduna, S. P.; Kearney, A.; Dunford, P.; Cowden, J.; Thurmond, R. L.; Grice, C.; Edwards, J. P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6577.

(4) Park, H.; Kim, Y.-J.; Hahn, J.-S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6345.

(5) Matasi, J. J.; Caldwell, J. P.; Hao, J.; Neustadt, B.; Arik, L.; Foster, C. J.; Lachowicz, J.; Tulshian, D. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1333.

(6) Agarwal, A.; Louise-May, S.; Thanassi, J. A.; Podos, S. D.; Cheng, J.; Thoma, C.; Liu, C.; Wiles, J. A.; Nelson, D. M.; Phadke, A. S.; Bradbury, B. J.; Deshpande, M. S.; Pucci, M. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2807.

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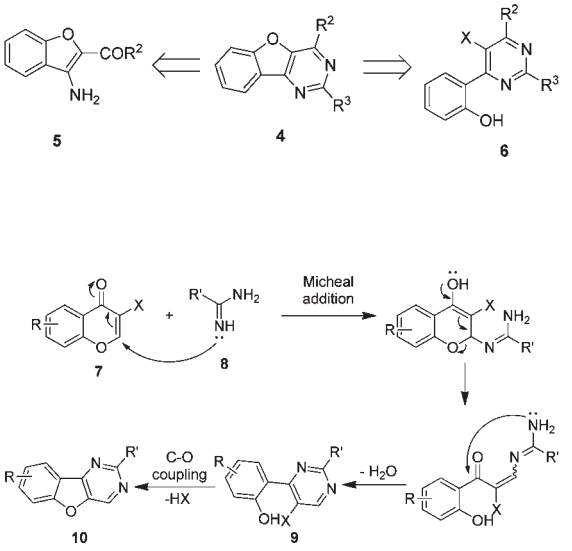
2-carbonyl-3-aminobenzofurans **5** and their equivalents that are transformed to benzofurans **4**, which serve as precursors to pyrimidines **6**.[3,7] Recently, a new route for construction of this scaffold was described, in which Suzuki coupling between 2-chloropyrimidine and 2-methoxyphenyl boronic acid is followed by demethylation and intramolecular C−O bond formation.[3a,b,8] However, both of the approaches described above involve multistep routes and reactions that require reasonably harsh conditions (e.g., high temperatures for cyclization, toxic demethylation reagents and mositure sensitive processes). In the studies described below, we have developed a straightforword method to generate members of a diverse series of benzofuro[3,2-*d*]pyrimidines, starting with 3-chlorochromenones and involving a chemoselective cascacde process.

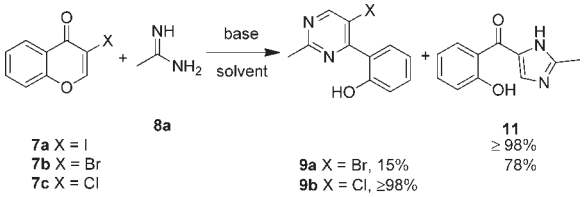
Scheme 1. (Top) Retrosynthetic Plan Serving as Basis of the Classical Synthetic Approach to Benzofuro[3,2-*d*]pyrimidines. (Bottom) Outline of the New Strategy for the Synthesis of Benzofuro[3,2-*d*]pyrimidines Starting with Halogenated Chromones



Recent studies in our group have focussed on the development of new synthetic pathways for the preparation of heterocyclic scaffolds, which rely on the use of cascade or one-pot reactions starting with substituted chromones.[9] As part of this effort, we envisioned 3-halogenated chromones **7** would participate with amidines **8** in Michael addition−elimination−double intramolecular cyclization sequences that result in the formation of biaryl phenols **9** (Scheme 1). If operable, this sequence would generate phenols that should undergo C−O bond-forming cyclization to produce benzofuro[3,2-*d*]pyrimidine derivatives **10**.

In order to explore this proposal, 3-iodochromone **7a** was treated with acetamidine hydrochloride in the presence of a variety of bases and solvents. Under all conditions, the undesired (imidazolyl)(phenyl)methanone derivative **11** was produced as the sole product through a route involving Michael addition−elimination−substitution.[9d,10] These results indicate that the presence of the iodo leaving group in **7a** causes a substitution pathway, which forms the five-membered heterocyclic product, to be more affective than condensation. In contrast, reaction of 3-bromochromone **7b** with acetamidine hydrochloride in the presence of 2 equiv of DBU in DMF at room temperature results in generation of the pyrimidine-phenol **9a** albeit in a 15% yield. This finding suggests that the chemoselectivity of the process can be controlled by decreasing the leaving group ability of the halide. In accord with this expectation, 3-chlorochromone **7c**, easily synthesized from chromone[11] or enaminoketone,[12] was found to react with acetamidine hydrochloride (2 equiv DBU, DMF, rt) to produce **9b** as the predominant product (Scheme 2).

Scheme 2. Chemoselectivity of 3-Halogenated Chromone



Because copper salts are broadly used in tandem processes to induce intramolecular C−O bond forming reactions[13] and to serve as Lewis acids to accellerate Michael additions,[14] we believed that the proposed sequence for generation of benzofuro[3,2-*d*]pyrimidines would take place when copper reagents are employed as promoters. In fact, inclusion of CuI in a mixture contaning **7c** and acetamidine hydrochloride caused reaction to occur

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(8) Liu, J.; Fitzgerald, A. E.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2951.

(9) (a) Xie, F.; Cheng, G.; Hu, Y. *J. Comb. Chem.* **2006**, *8*, 286. (b) Xie, F.; Li, S.; Bai, D.; Lou, L.; Hu, Y. *J. Comb. Chem.* **2007**, *9*, 12. (c) Cheng, G.; Li, S.; Li, J.; Hu, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1177. (d) Li, D.; Duan, S.; Hu, Y. *J. Comb. Chem.* **2010**, *12*, 895.

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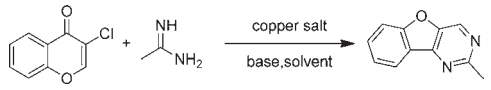
(11) Kim, K. M.; Chung, K. H.; Kim, J. N.; Ryu, E. K. *Synthesis* **1993**, *1993*, 283.

(12) Yokoe, I.; Maruyama, K.; Sugita, Y.; Harashida, T.; Shirataki, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1697.

(13) (a) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (b) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (c) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955. (d) Schuh, K.; Glorius, F. *Synthesis* **2007**, *2007*, 2297. (e) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452. (f) Bhadra, S.; Adak, L.; Samanta, S.; Maidul Islam, A. K. M.; Mukherjee, M.; Ranu, B. C. *J. Org. Chem.* **2010**, *75*, 8533. (g) Liu, Y.; Bao, W. *Org. Biomol. Chem.* **2010**, *8*, 2700. (h) Ye, S.; Liu, G.; Pu, S.; Wu, J. *Org. Lett.* **2012**, *14*, 70. (i) Xia, Z.; Wang, K.; Zheng, J.; Ma, Z.; Jiang, Z.; Wang, X.; Lv, X. *Org. Biomol. Chem.* **2012**, *10*, 1602.

Table 1. Optimization of Reaction Conditions for Formation of Benzofuropyrimidine **10a**[a]



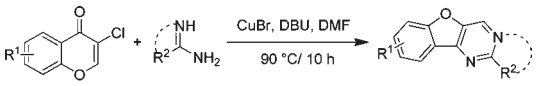
7c **8a** **10a**

entry	copper promoters	base	solvent	yield (%)
1		DBU	DMF	0
2	CuI	DBU	DMF	62
3	**CuBr**	**DBU**	**DMF**	**76**
4	CuCl	DBU	DMF	41
5	Cu	DBU	DMF	26
6	$CuBr_2$	DBU	DMF	0
7	CuBr (0.1 equiv)	DBU	DMF	27
8	CuBr (0.2 equiv)	DBU	DMF	50
9	CuBr (0.5 equiv)	DBU	DMF	65
10	CuBr	Cs_2CO_3	DMF	20
11	CuBr	K_2CO_3	DMF	18
12	CuBr	Et_3N	DMF	0
13	CuBr	*t*-BuONa	DMF	0
14	CuBr	DBU	dioxane	trace
15	CuBr	DBU	tolunene	trace
16	CuBr	DBU	DME	trace
17	CuBr	DBU	CH_3CN	trace
18	CuBr	DBU	DMSO	34
19[b]	CuBr(0.2 equiv)	DBU	DMF	49
20[c]	CuBr(0.2 equiv)	DBU	DMF	72
21[d]	CuBr(0.2 equiv)	DBU	DMF	9
22[e]	CuBr(0.2 equiv)	DBU	DMF	53
23[f]	CuBr(0.2 equiv)	DBU	DMF	35

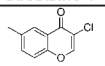
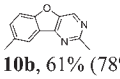
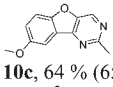
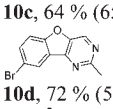
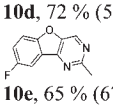
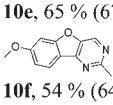
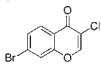
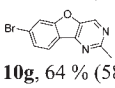
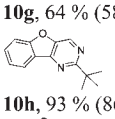
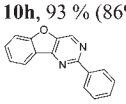
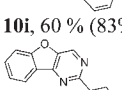
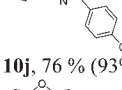
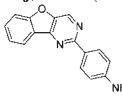
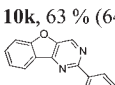
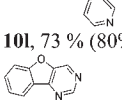
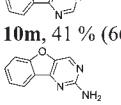
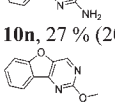
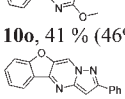
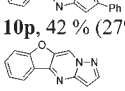
[a] Reaction conditions: mixtures of substrate **7c** (0.55 mmol), acetamidine hydrochloride **8a** (0.61 mmol), copper promoters (0.55 mmol), and bases (1.2 mmol) in solvents (3 mL) were heated at 90 °C for 10 h. [b] *N*,*N*-Dimethylglycine (0.6 equiv) was added. [c] 1,10-Phen (0.6 equiv) was added. [d] DMEDA (0.6 equiv) was added. [e] TMHD (0.6 equiv) was added. [f] Bipy (0.6 equiv) was added.

that forms benzofuropyrimidine **10a** in 62% yield (Table 1, entry 2). The results of an exploration of different copper reagents demonstrated that only copper(I) salts bring about generation of **10a** (Table 1, entries 2−6), and Cu(II) salt did not promote the final C−O bond-forming step to give the intermediate **9b** only (Table 1, entry 6). Probing the use of different amounts of CuBr for this process (Table 1, entries 7−9) led to the observation that a stoichiometric amount of this salt is optimal. When changing to inorganic bases such as Cs_2CO_3 and K_2CO_3, the desired product **10a**

Table 2. Scope of the Cascade Reaction of **7** with **8**[a,b]



7 **8** **10b-10r**

entry	substrate **7**	substrate **8**	product and yield[b]
1	 **7d**	**8a**	 **10b**, 61% (78%)
2	 **7e**	**8a**	 **10c**, 64 % (65%)
3	 **7f**	**8a**	 **10d**, 72 % (52%)
4	 **7g**	**8a**	 **10e**, 65 % (67%)
5	 **7h**	**8a**	 **10f**, 54 % (64%)
6	 **7i**	**8a**	 **10g**, 64 % (58%)
7	 **7c**	 **8b**	 **10h**, 93 % (86%)
8	**7c**	 **8c**	 **10i**, 60 % (83%)
9	**7c**	 **8d**	 **10j**, 76 % (93%)
10[c]	**7c**	 **8e**	 **10k**, 63 % (64%)
11	**7c**	 **8f**	 **10l**, 73 % (80%)
12	**7c**	 **8g**	 **10m**, 41 % (66%)
13[d]	**7c**	 **8h**	 **10n**, 27 % (20%)
14[d]	**7c**	 **8i**	 **10o**, 41 % (46%)
15	**7c**	 **8j**	 **10p**, 42 % (27%)
16	**7c**	 **8k**	 **10q**, 36 % (21%)
17[d]	**7c**	 **8l**	 **10r**, 23 % (0%)

[a] Reaction conditions: mixtures of **7c** (0.55 mmol), **8** (0.61 mmol), CuBr (0.55 mmol), and DBU (1.2 mmol) in DMF (3 mL) were heated at 90 °C for 10 h. [b] Yields by catalyzed CuBr (0.11 mmol) with 1,10-Phen (0.33 mmol) are given in parentheses. [c] DBU (1.8 mmol) was used. [d] **8h**, **8i**, or **8l** (0.30 mmol) was used, respectively.

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was obtained in low yields (Table 1, entries 10 and 11). The weak base Et_3N did not promote the reaction well to generate **9b**, with starting material recovered (Table 1, entry 12). The strong base *t*-BuONa afforded the complicated products (Table 1, entry 13). When the reaction was carried out in dioxane, toluent, DME, or CH_3CN, respectively, only a trace amount of **10a** was obtained with **9b** (Table 1, entries 14–17). Also DMSO did not improve the yield (Table 1, entry 18). When addition of the different ligands with catalytic copper(I) bromide such as *N*,*N*-dimethylglycine,[15] 1,10-phenanthroline monohydrate (1,10-phen),[16] *N*,*N*′-dimethylenylene-1,2-*d*iamine (DMEDA),[17] 2,2,6,6-teramethyle-3,5-heptanedione (TMHD),[18] and 2,2′-dipyridine (bipy) (Table 1, entries 19–23) was employed in the reaction, CuBr (0.2 equiv) with 1,10-phen (0.06 equiv) gave the comparable yield.

Reactions of substituted 3-chlorochromones with amidines and their analogues were investigated to probe the scope of this new reaction (Table 2). The results show that 3-chlorochromones, bearing electron-withdrawing and electron-donating groups on the aromatic ring, react under the optimal conditions (see above) to form the corresponding benzofuropyrimidines in moderate to good yields (Table 2, entries 1–6). In contrast, changes in the R^2 amidine substituent were observed to have a profound impact on the efficiencies of the process. Specifically, reactions of amidines with the R^2 substituent being an alkyl group or variously substituted aryl groups (Table 2, entries 7–11) occur in good to excellent yields. However, when R^2 is an electron-donating group, reactions take place in low yields (Table 2, entries 12–14). Interestingly, structurally and functionally complicated polyheterocyclic scaffolds can be constructed by using the new process (Table 2, entries 15–17). Under the catalyzed conditions, reactions gave the similar results except for the formation of **10r**.

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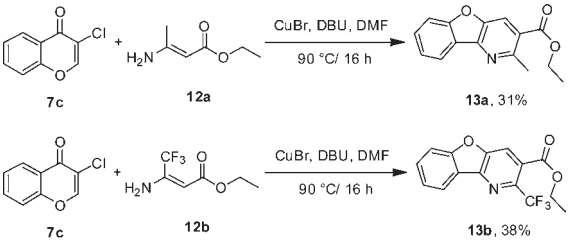
Further investigations revealed that ethyl 3-aminocrotonate (**12a**) and ethyl 3-amino-4,4,4-trifluorocrotonate (**12b**), serving as a C,N bis-nucleophiles, react with 3-chlorochromone to give the corresponding benzofuro[3,2-*b*]pyridines **13a** or **13b** in 31% and 38% respective yields (Scheme 3). However, the catalytic conditions yielded trace amounts of the desired products. These observations show that the new methodology can be applied to substrates other than amidines and used for the construction diverse molecular scaffolds.

Scheme 3. Synthesis of Benzofuro[3,2-*b*]pyridines



In conclusion, the studies described above resulted in the development of a novel cascade reaction in which 3-chlorochromones are transformed to diverse benzofuro[3,2-*d*]-pyrimidines and related polycylic heterocylic scaffolds. The process is promoted by CuBr and takes place *via* a chemoselective Michael addition–elimination–double intramolecular cyclization sequence. Significantly, the conditions utilized for the tandem process are mild and economical. Further applications of the new methodology and biological testing of compounds prepared in this effort are under current investigation.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR spectra for compounds in Table 2 and Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.