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Cascade Coupling/Cyclization Process to N-Substituted 1,3-Dihydrobenzimidazol-2-ones

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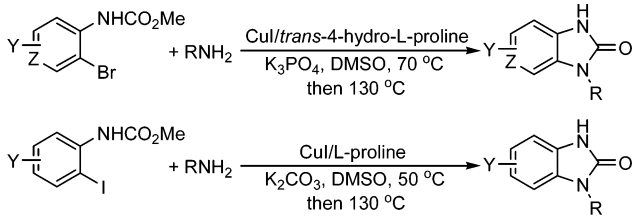
ABSTRACT



Assembly of N-substituted 1,3-dihydrobenzimidazol-2-ones is achieved starting from methyl *o*-haloarylcarbamates via a CuI/amino acid catalyzed coupling with amines and subsequent condensative cyclization. A number of functional groups are tolerated by these reaction conditions, including vinyl, nitro, carboxylate, amide, ester, ketone, and silyl ether groups.

The 1,3-dihydrobenzimidazol-2-one moiety can be found in many pharmaceutically important molecules that possess a wide range of biological activities. Recent examples include RWJ-333966 (**1**), a selective vasopressin 1a receptor antagonist that is a promising candidate for the treatment of anxiety disorders,[1] HIV-1 RT non-nucleoside inhibitor **2**,[2] orally bioavailable sirohydantoin CGRP receptor antagonist **3**,[3] p38 MAP kinase inhibitor **4**,[4] respiratory syncytial virus fusion inhibitor **5**,[5] as well as the progesterone receptor antagonist **6**[6] (Figure 1).

Two typical methods have generally been applied for the elaboration of N-substituted 1,3-dihydrobenzimidazol-2-ones. One is the selective alkylation or arylation of either nitrogen atoms of 1,3-dihydrobenzimidazol-2-ones, which often requires a protection strategy.[3,5,6] Another one involves nucleophilic displacement of 2-fluoronitrobenzenes with amines and subsequent reduction and cyclization with carbonyldiimidazole.[4,7] This route is problematic for the synthesis of diverse products because of the limited source of 2-fluoronitrobenzenes. These drawbacks have prompted Kuethe and co-workers to develop a Pd-catalyzed aryl amination strategy

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(1) Guillaume, M. *Org. Process Res. Dev.* **2006**, *10*, 1227.
(2) Barreca, M. L.; Rao, A.; De Luca, L.; Zappalà, M.; Monforte, A.-M.; Maga, G.; Pannecouque, C.; Balzarini, J.; De Clercq, E.; Chimirri, A.; Monforte, P. *J. Med. Chem.* **2005**, *48*, 3433.
(3) Bell, I. M.; Bednar, R. A.; Fay, J. F.; Gallicchio, S. N.; Hochman, J. h.; McMasters, D. R.; Miller-Stein, C.; Moore, E. L.; Mosser, S. D.; Pudvah, N. T.; Quigley, A. G.; Salvatore, C. A.; Stump, C. A.; Theberge, C. R.; Wong, B. K.; Zartman, C. B.; Zhang, X.-F.; Kane, S. A.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6165.
(4) Hammach, A.; Barbosa, A.; Gaenzler, F. C.; Fadra, T.; Goldberg, D.; Hao, M.-H.; Kroe, R. R.; Liu, P.; Qian, K. C.; Ralph, M.; Sarko, C.; Soleymanzadeh, F.; Moss, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6316.
(5) Yu, K.-L.; Sin, N.; Civiello, R. L.; Wang, X. A.; Combrink, K. D.; Gulgeze, H. B.; Venables, B. L.; Wright, J. J. K.; Dalterio, R. A.; Zadjura, L.; Marino, A.; Dando, S.; D'Arienzo, C.; Kadow, K. F.; Cianci, C. W.; Li, Z.; Cianci, C. W.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Colonno, R. L.; Yang, Z.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 895.
(6) Terefenko, E. A.; Kern, J.; Fensome, A.; Wrobel, J.; Zhu, Y.; Cohen, J.; Winneker, R.; Zhang, Z.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3600.
(7) (a) Li, Q.; Li, T.; Woods, K. W.; Gu, W.-Z.; Cohen, J.; Stoll, V. S.; Galicia, T.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2918. (b) Kawamoto, H.; Nakashima, H.; Kato, T.; Arai, S.; Kamata, K.; Iwasawa, Y. *Tetrahedron* **2001**, *57*, 981.

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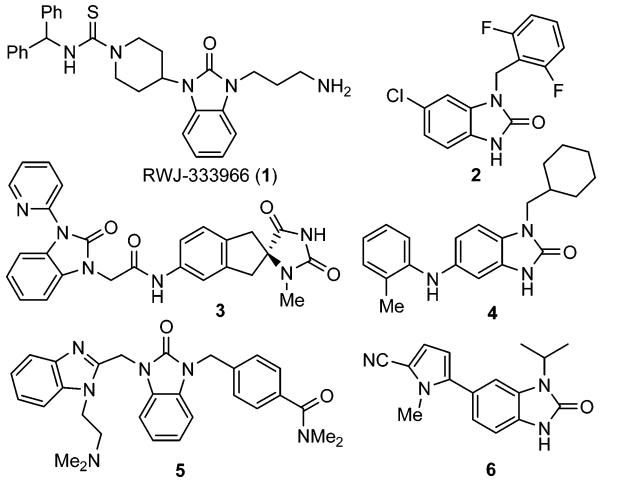


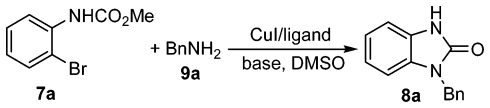
Figure 1. Structures of some biologically important N-substituted 1,3-dihydrobenzimidazol-2-ones.

leading to substituted imidazo[4,5-*b*]pyridin-2-ones.[8] As a part of our continuing effort to assemble heterocycles by Cu-catalyzed cross-coupling reactions,[9,10] we became interested in developing a new protocol for the assembly of N-substituted 1,3-dihydrobenzimidazol-2-ones via CuI/ligand-catalyzed aryl amination[11] of methyl *o*-haloarylcarbamates. The studies thus undertaken are disclosed herein.

The reaction of methyl 2-bromophenylcarbamate **7a** and benzylamine was chosen to screen for suitable reaction conditions (Table 1). Initially, our standard conditions for the amination of aryl bromides were attempted.[11i,l] Accordingly, the reaction was conducted under the action of 20 mol % of CuI, 40 mol % of L-proline, and K_2CO_3 in DMSO at 60 °C. It was found that after 24 h most of the bromide was consumed, and only the cross-coupling product was identified, indicating that the condensative cyclization required higher reaction temperatures. After some trials, we found that the desired cyclization product **8a** could be obtained in moderate yield by heating the reaction mixture at 130 °C for 6 h after the initial cross-coupling step (entry 1). It is noteworthy that the cross-coupling reaction was not complete after heating at 60 °C for 24 h. The lower reactivity displayed by bromide **7a**, compared to the 2-bromoacetanilides reported earlier by our group,[9a] demonstrates that the carbamate does not provide *ortho*-assistance during the coupling reaction. Increasing the temperature of the coupling reaction to 70 °C resulted in an improved yield (entry 2). Switching the base to Cs_2CO_3 provided a similar result (entry 3), while a better yield was observed when K_3PO_4 was employed (entry 4). Further improvement was achieved when *trans*-4-hydroxy-L-proline was used as the ligand[12] (entry 5). The change in solubility of either the ligand or metal complex was tentatively accepted to account for this difference.

We then explored the scope and limits of our newly developed cascade process by varying the bromides and amines. We were pleased to find that functionalized amines such as amino acid **9b**, amino amide **9c**, and allyl amine **9d** delivered the corresponding 1,3-dihydrobenzimidazol-2-ones under our reaction conditions (Table 2). Compound **8b** is obviously a promising intermediate for the assembly of the CGRP receptor antagonist **3**. The electronic nature of the aryl bromides seems to have little influence on the reaction, which is evident from the fact that both electron-rich and electron-deficient aryl bromides gave satisfactory results. For the coupling step, sterically hindered amines generally required longer reaction times (entries 2 and 6), which is consistent with the observations in our previous work.[11l] A wide range of functional groups on the aryl bromides, such as ester, ketone, amide, nitro, and silyl ether groups, survived under these reaction conditions. Heteroaryl bromide **7j**

Table 1. Synthesis of *N*-Benzyl 1,3-Dihydrobenzimidazol-2-one **8a** via Coupling of Bromide **7a** and Benzyl Amine **9a**[a]



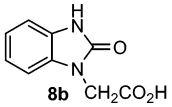
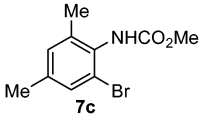
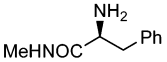
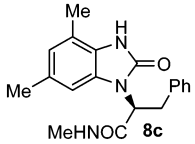
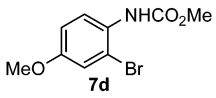
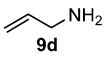
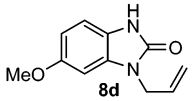
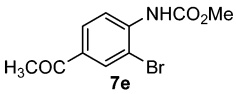
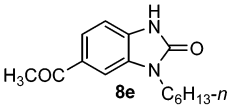
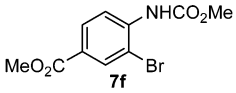
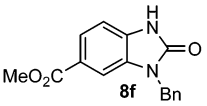
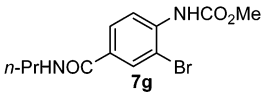
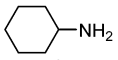
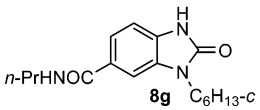
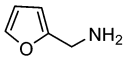
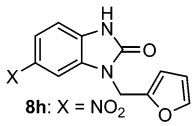
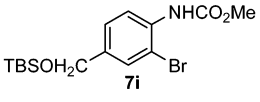
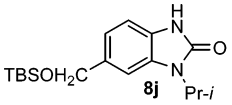
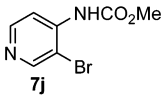
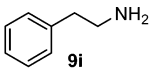
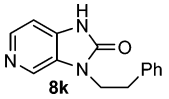
entry	ligand	base	temp (°C)	yield (%)[b]
1	L-proline	K_2CO_3	60−130	52
2	L-proline	K_2CO_3	70−130	58
3	L-proline	Cs_2CO_3	70−130	55
4	L-proline	K_3PO_4	70−130	65
5	*trans*-4-hydroxy-L-proline	K_3PO_4	70−130	77

[a] Reaction conditions: **7a** (0.5 mmol), **9a** (0.5 mmol), CuI (0.1 mmol), ligand (0.2 mmol), base (1.0 mmol), DMSO (1 mL), 60 °C, 24 h (for entry 1), or 70 °C, 4 h (for entries 2−5), then 130 °C, 6 h. [b] Isolated yield.

(8) Kuethe, J. T.; Wong, A.; Davies, I. W. *J. Org. Chem.* **2004**, *69*, 7752.
(9) (a) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598. (b) Lu, B.; Ma, D. *Org. Lett.* **2006**, *8*, 6115.

(10) For recent studies on the synthesis of N-heterocycles through Ullmann-type couplings from other groups, see: (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (c) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (d) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (e) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (f) Martin, R.; Rodríguez, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (g) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (h) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510.
(11) For selected references, see: (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670. (c) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583. (d) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (e) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (f) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (g) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (h) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (i) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (j) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.−Eur. J.* **2004**, *10*, 5607. (k) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496. (l) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (m) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (n) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435. (o) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.−Eur. J.* **2006**, *12*, 3636. (p) Lange, B.; Lambers-Verstappen, M. H.; Vondervoort, L. S.; Sereinig, N.; Rijk, R.; Vries, A. H. M.; Vries, J. G. *Synlett* **2006**, 3105.
(12) This ligand was found to be more effective than L-proline in our previous work on CuI-catalyzed C−C bond formation. See: Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050.

Table 2. Synthesis of Substituted 1,3-Dihydrobenzimidazol-2-ones via a Cascade Coupling/Cyclization Process from Aryl Bromides[a]

entry	bromide	amine	time (h) coupling/cyclization	product	yield (%)[b]
1	**7a**	$NH_2CH_2CO_2H$ **9b**	5/4	 **8b**	73[c]
2	 **7c**	 **9c**	22/24	 **8c**	76
3	 **7d**	 **9d**	11/8	 **8d**	62
4	 **7e**	n-$C_6H_{13}NH_2$ **9e**	10/9	 **8e**	70
5	 **7f**	**9a**	12/12	 **8f**	74
6	 **7g**	 **9f**	21/12	 **8g**	66
7	 **7h**	 **9g**	4/10	 **8h**: X = NO_2	82
8	**7g**		5/4	**8i**: X = CONHPr-*n*	82
9	 **7i**	 **9h**	11/14	 **8j**	75
10	 **7j**	 **9i**	10/12	 **8k**	62

[a] Reaction conditions: bromide **7** (0.5 mmol), amine **9** (0.5 mmol), CuI (0.1 mmol), *trans*-4-hydroxy-L-proline (0.2 mmol), K_3PO_4 (1.0 mmol), DMSO (1 mL), 70 °C, then 130 °C. [b] Isolated yield. [c] 2.0 mmol of base was added.

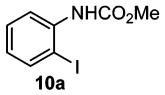
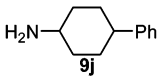
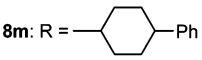
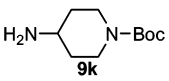
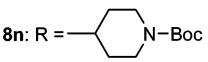
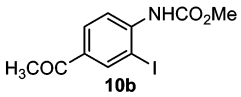
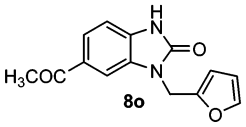
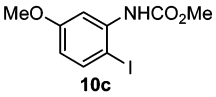
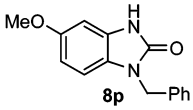
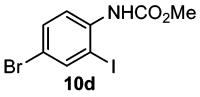
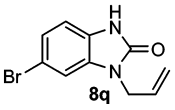
reacted with 2-phenylethylamine **9i** to afford imidazo[4,5-*b*]pyridin-2-one **8k** in 62% yield (entry 10). It is noteworthy that some of its analogues have exhibited potent inhibition activity against respiratory syncytial virus fusion.[5] Our results demonstrate that the present protocol allows diverse synthesis of functionalized 1,3-dihydrobenzimidazol-2-ones.

We next focused our attention on employing methyl *o*-iodoarylcarbamates as the substrates. After screening a number of parameters in the reaction of methyl 2-iodophenylcarbamate **10a** and benzylamine, the use of K_2CO_3 as a base and L-proline as a ligand was found to promote the highest yields (81%, entry 1, Table 3). In these cases, the coupling reaction proceeded at 50 °C even when using 10 mol % of copper catalyst. Under these reaction conditions, a number of aryl iodides and amines were applied, and they all gave the corresponding 1,3-dihydrobenzimidazol-2-ones in good yields, thereby providing an alternative route for the synthesis of these heterocyclic compounds. Some of the products are potential building blocks for the synthesis of known bioactive compounds. For example, **8n** could be used to assemble vasopressin 1a receptor antagonist RWJ-333966[1] and 11b-hydroxysteroid dehydrogenase type I inhibitors.[13] When methyl 2-iodo-4-bromophenylcarbamate **10d** was used, **8q** was isolated exclusively, indicating that selectivity between aryl iodides and aryl bromides can be achieved under the present coupling conditions.

In conclusion, we have developed a novel protocol for the elaboration of N-substituted 1,3-dihydrobenzimidazol-2-ones via a CuI/amino acid catalyzed cascade coupling/

(13) Flyrén, K.; Bergquist, L. O.; Castro, V. M.; Fotsch, C.; Johansson, L.; St. Jean, D. J., Jr.; Sutin, L.; Williams, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3421.

Table 3. Synthesis of Substituted 1,3-Dihydrobenzimidazol-2-ones via a Cascade Coupling/Cyclization Process from Aryl Iodides[a]

entry	bromide	amine	time (h) coupling/cyclization	product	yield (%)[b]
1	 **10a**	**9a**	3/3	 **8a**: R = Bn	81
2		**9d**	4/6	**8l**: R = allyl	82
3		 **9j**	7/3	**8m**: R = 	85
4		 **9k**	7/5	**8n**: R = 	74
5	 **10b**	**9g**	12/12	 **8o**	82
6	 **10c**	**9a**	7/3	 **8p**	80
7	 **10d**	**9d**	7/5	 **8q**	66

[a] Reaction conditions: iodide **10** (0.5 mmol), amine **9** (0.5 mmol), CuI (0.05 mol), L-proline (0.1 mmol), K_2CO_3 (1.0 mmol), DMSO (1 mL), 50 °C, then 130 °C. [b] Isolated yield.

condensative cyclization strategy. This method allows the use of various primary amines and methyl *o*-haloarylcarbamates to assemble versatile heterocycles in a one-pot manner. Thus, it should find extensive applications in the synthesis of biologically active molecules.

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Supporting Information Available: Experimental procedures and copies of ^{1}H NMR 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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