Synthesis of 2-fluoroalkylbenzimidazoles *via* copper(I)-catalyzed tandem reactions†

Jiangtao Zhu,[a] Haibo Xie,[a] Zixian Chen,[ab] Shan Li[a] and Yongming Wu*[a]

Received (in Cambridge, UK) 16th January 2009, Accepted 12th February 2009
First published as an Advance Article on the web 9th March 2009
DOI: 10.1039/b900984a

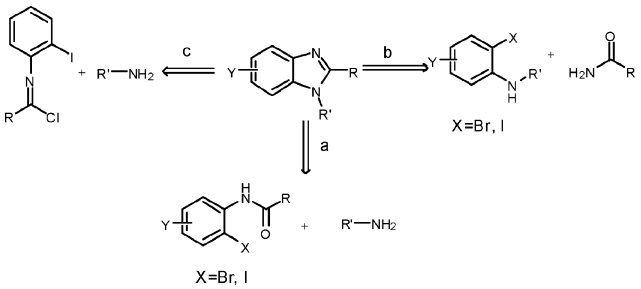
Preparation of 2-fluoroalkylbenzimidazoles from *N*-aryl trifluoroacetimidoyl (or bromodifluoroacetimidoyl) chlorides and primary amines has been achieved *via* copper(I)-catalyzed tandem reactions.

Benzimidazoles are an important class of heterocyclic compounds due to their wide range of biological properties such as antiviral, antifungal, antibacterial, and anti-tumor activities.[1] Benzimidazoles have also served as important synthetic intermediates for the preparation of dyes and high temperature polymers.[2] Among them, 2-fluoroalkyl substituted molecules have already received considerable attention due to their potential bioactivities.[3]

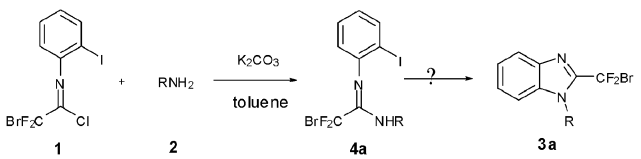
However to date, there are only a few methods reported for the synthesis of 2-fluoroalkylbenzimidazoles compared to non-fluorinated analogues.[4] These compounds are commonly prepared by the following methods: (1) condensation of trifluoroacetic acid with *ortho*-aminoanilines,[5] (2) reductive cyclization of trifluoroacetic acid with *ortho*-nitroanilines,[6] (3) synthesis from perfluoro (or polyfluoro) alkyl aldehydes with *ortho*-aminoanilines,[7] or (4) direct trifluoromethylation of benzimidazoles with trifluoromethyl radicals.[8] The drawbacks of these procedures lie in the limited diversity of the starting materials, harsh reaction conditions and lack of regioselectivity.

Recently, the Ma group reported a new process for the formation of 1,2-disubstituted benzimidazoles from 2-haloanilides and primary amines at low temperature *via* the system of Cu(I) and L-proline (route a, Scheme 1).[9] Buchwald and co-workers also developed a similar method from 2-haloanilines and amides for the regiospecific synthesis of *N*-alkylbenzimidazoles (route b, Scheme 1).[10] Herein, we wish to report a new process for the synthesis of *N*-substituted 2-fluoromethylbenzimidazoles from imidoyl chlorides and amines by a Cu(I)-catalyzed cyclization reaction without any ligands under mild conditions (route c, Scheme 1).

In recent years, trifluoromethyl imidoyl chlorides have been successfully used as building blocks in synthetic organofluorine chemistry by the Uneyama group.[11] To construct new CF_2-containing reactive synthetic intermediates, our group have focused on developing new methods for the synthesis



Scheme 1 A summary of the synthesis of *N*-benzimidazoles *via* Ullmann reactions.



Scheme 2 Strategy for the synthesis of benzimidazoles.

of $BrCF_2$-containing compounds from bromodifluoroacetimidoyl halides.[12] In our previous report, fluorinated amidines could be easily obtained from the reaction of imidoyl chlorides with primary and secondary amines (Scheme 2).[12d] We expected that if there is an iodine at the *ortho* position on the benzene ring, the amidines may undergo Cu(I)-catalyzed cyclization to afforded 1,2-disubstituted benzimidazoles.

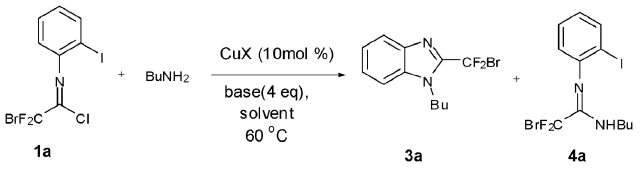
At the beginning, iodoamidine **4a** was used as the starting material to investigate this reaction. It was found that when CuI was used as the catalyst, DMF as the solvent and K_2CO_3 as the base, the cyclization product, benzimidazole **3a**, could be obtained in 79% yield after the mixture was stirred at 60 °C for 3 h.

Because amidines **4** could be easily prepared from the reaction of the corresponding fluorinated acetimidoyl halides **1** and amines **2**, we presumed that in the presence of CuI, benzimidazole **3a** may be formed directly from fluorinated acetimidoyl halides **1** and amines **2**. Then we designed a tandem reaction sequence using imidoyl chlorides and amines as the starting materials to test this hypothesis. The reaction of 2-bromo-2,2-difluoro-*N*-(2-iodophenyl)acetimidoyl chloride **1a** with butylamine was used as a model system to study this transformation. When CuI was used as the catalyst in DMF at 60 °C, benzimidazole **3a** was formed as the exclusive product in 76% yield after 3 h. Then the effects of solvents, bases and copper catalysts were investigated (Table 1). It was found that in toluene or dioxane, amidine **4a** was formed as the sole product and it did not cyclize at all (entries 1, 2, Table 1). In

[a] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 LingLing Road, Shanghai 200032, P. R. China. E-mail: ymwu@mail.sioc.ac.cn; Fax: (+86) 21-54925192*
[b] *Department of Chemistry, Huazhong University of Science and Technology, Wuhan, Hubei 430074, China*

† Electronic supplementary information (ESI) available: General procedures for benzimidazole synthesis; characterization data and NMR spectra for compounds **3a**–**3u**. See DOI: 10.1039/b900984a

Table 1 Optimization of the reaction conditions

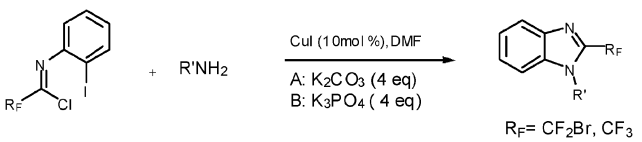


1a 3a 4a

Entry	CuX	Base	Solvent	**3a** (%)[a]	**4a** (%)[a]
1	CuI	K_2CO_3	Toluene	—	85
2	CuI	K_2CO_3	Dioxane	—	82
3	CuI	K_2CO_3	DMF	76	—
4[b]	CuI		DMF	—	83
5		K_2CO_3	DMF	—	87
6	CuI	K_2CO_3	DMSO	77	—
7	CuI	K_3PO_4	DMF	78	—
8	CuI	NaH	DMF	50	Trace
9	CuI	Et_3N	DMF	—	83
10	CuBr	K_2CO_3	DMF	67	—
11	CuCN	K_2CO_3	DMF	67	—
12	CuCl	K_2CO_3	DMF	57	—
13[c]	CuI	K_2CO_3	DMF	40	60

[a] Isolated yield. [b] 2 equiv. *n*-butylamine. [c] Addition of ligand L-proline.

Table 2 Synthesis of *N*-substituted 2-fluoromethylbenzimidazoles[a]

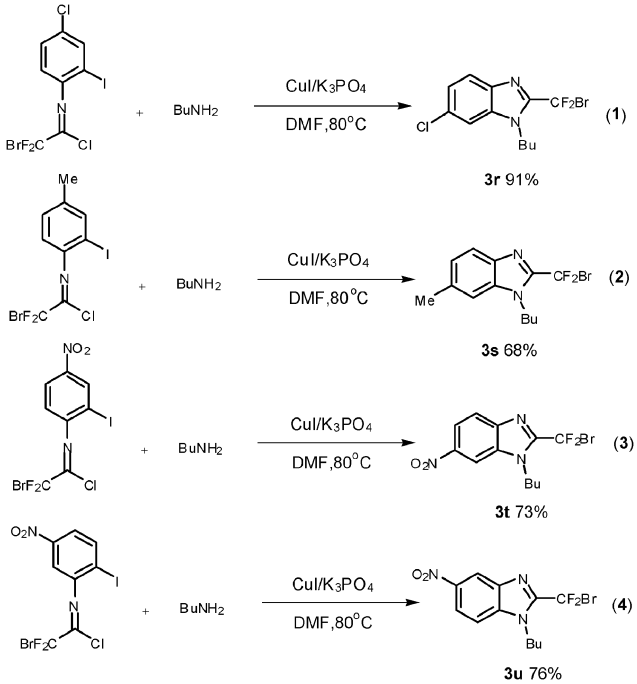


1 2 3a-3n

Entry	R_F	R′	Product/yield (%)[b]/ method/*T* (°C)
1	CF_2Br**1a**	*n*-Bu	**3a**/76/A/60
2		Allyl	**3b**/68/B/60
3		$HO(CH_2)_2$	**3c**/68/A/60
4		Cyclohexyl	**3d**/76/B/60
5		Bn	**3e**/82/B/60
6		*p*-Me-C_6H_4	**3f**/74/A/60
7		*p*-Cl-C_6H_4	**3g**/31/A/80
8		*p*-MeO-C_6H_4	**3h**/67/A/60
9		*p*-NO_2-C_6H_4	**3i**/58/A/80
10	CF_3**1b**	*n*-Bu	**3j**/78/A/rt
11		Allyl	**3k**/70/A/60
12		$HO(CH_2)_2$	**3l**/87/A/40
13		Cyclohexyl	**3m**/69/A/40
14		*p*-Me-C_6H_4	**3n**/93/A/60
15		*p*-MeO-C_6H_4	**3o**/91/A/60
16		*p*-Cl-C_6H_4	**3p**/62/A/80
17		*p*-NO_2-C_6H_4	**3q**/41/A/80

[a] Reaction conditions: imidoyl chloride **1** (0.4 mmol), amine **2** (0.5 mmol), CuI (0.04 mmol), K_2CO_3 (1.6 mmol, method A) or K_3PO_4 (1.6 mmol, method B), DMF (2 ml). [b] Yields of isolated products.

contrast, when DMF or DMSO was employed as the solvent, benzimidazole **3a** could be obtained in good yields (entries 3, 6, Table 1). Use of K_2CO_3 or K_3PO_4 (4 equiv.) was critical for this reaction, other bases (such as NaH or Et_3N) could not effect the complete reaction sequence (entries 8, 9, Table 1). For example, in triethylamine, only the amidine **4a** could be obtained (entry 9, Table 1). Testing different Cu(I) salts



Scheme 3 Synthesis of fluorinated benzimidazoles.

indicated that CuI was superior to CuBr, CuCN and CuCl in this reaction (entries 3, 10–12, Table 1). Addition of ligands such as L-proline was ineffective in improving the yields, under this condition both the products, amidine **4a** and benzimidazole **3a**, were formed while amidine **4a** was the major product (entry 13, Table 1).

On the basis of the above studies, we reached the optimized conditions for this reaction: CuI as the catalyst, DMF as the solvent, and 4 equiv. of K_2CO_3 or K_3PO_4 as the base. The scope of the reaction was then explored with different primary amines and imidoyl chlorides and the results are listed in Table 2.

As summarized in Table 2, both aliphatic amines and aryl amines could provide benzimidazoles **3** in good yields. This reaction was compatible with a hydroxyl group (entries 3, 12, Table 2). The yields of the reaction with 2,2,2-trifluoro-*N*-(2-iodophenyl)acetimidoyl chloride **1b** were higher than that with 2-bromo-2,2-difluoro-*N*-(2-iodophenyl)acetimidoyl chloride **1a**. When 2,2,2-trifluoro-*N*-(2-iodophenyl)acetimidoyl chloride **1b** and butylamine were used as the two starting materials, this transformation could go to completion at room temperature (entry 10, Table 2).

Next, imidoyl chlorides with an extra substituent on the phenyl ring were investigated. We were pleased to observe that substrates with either an electron-donating (Me) or an electron-withdrawing (Cl, NO_2) group in the *para* or *meta* position to the iodo all worked well under the optimized conditions. Especially a pair of regioisomeric benzimidazoles bearing a nitro group were obtained in good yields by applying the conditions described above without the need for further optimization (Scheme 3, eqn (3) and (4)).

In conclusion, we have demonstrated a convenient method for the synthesis of 2-trifluoromethyl (or 2-bromodifluoromethyl) benzimidazoles *via* the reaction of fluorinated imidoyl

chlorides with primary amines catalyzed by CuI in pure form. Compared to the existing methods, our strategy can be easily carried out at low temperatures without ligands. Further investigations on this reaction are ongoing in this laboratory.

This work was supported by the National Science Foundation of China (Nos. 20532040 and 20772145).

Notes and references

1 (*a*) R. Morphy and Z. Rankovic, *J. Med. Chem*., 2005, **48**, 6523; (*b*) R. R. Wexler, W. J. Greenlee, J. D. Irvin, M. R. Goldberg, K. Prendergast, R. P. Smith and P. B. M. W. M. Timmermans, *J. Med. Chem*., 1996, **39**, 625.

2 (*a*) G. Schwartz, K. Fehse, M. Pfeiffer, K. Walzer and K. Leo, *Appl. Phys. Lett*., 2006, **89**, 083509/1; (*b*) J. A. Asensio and P. Gomez-Romero, *Fuel Cells*, 2005, **5**, 336.

3 K. C. Joshi, R. Jain, A. Dandia and K. Sharma, *J. Fluorine Chem*., 1992, **56**, 1.

4 (*a*) M. R. Grimmett, in *Imidazole and Benzimidazole Synthesis, Best Synthetic Methods*, ed. O. Meth-Cohn, Academic, London, 1997; (*b*) D. Yang, D. Fokas, J. Li, L. Yu and C. M. Baldino, *Synthesis*, 2005, 47; (*c*) G. Evindar and R. A. Batey, *Org. Lett*., 2003, **5**, 133; (*d*) G. Evindar and R. A. Batey, *J. Org. Chem*., 2006, **71**, 1802; (*e*) C. T. Brain and S. A. Brunton, *Tetrahedron Lett*., 2002, **43**, 1893; (*f*) C. T. Brain and J. T. Steer, *J. Org. Chem*., 2003, **68**, 6814.

5 (*a*) H. Bishop, A. S. Jones and J. C. Tatlow, *J. Chem. Soc*., 1964, 3076; (*b*) F. Ge, Z. Wang, W. Wan, W. Lu and J. Hao, *Tetrahedron Lett*., 2007, **48**, 3251.

6 D. S. VanVielt, P. Gillespie and J. J. Scicinski, *Tetrahedron Lett*., 2005, **46**, 6741.

7 Q. F. Wang, Y. Y. Mao, Z. S. Zhu and C. M. Hu, *J. Fluorine Chem*., 1999, **95**, 141.

8 (*a*) H. Kimoto, S. Fujii and L. Cohen, *J. Org. Chem*., 1982, **47**, 2867; (*b*) M. Médebielle, J. Pinson and J. M. Saveant, *J. Am. Chem. Soc*., 1991, **113**, 6872; (*c*) J. Pinson and J. M. Saveant, *Tetrahedron Lett*., 1990, **31**, 1279; (*d*) Q. Chen and Z. Qui, *J. Fluorine Chem*., 1987, **35**, 343; (*e*) M. Kobayashi and K. Uneyama, *J. Org. Chem*., 1995, **60**, 6402; (*f*) K. Uneyama and M. Kobayashi, *J. Org. Chem*., 1994, **59**, 3003.

9 B. Zou, Q. Yuan and D. Ma, *Angew. Chem., Int. Ed*., 2007, **46**, 2598.

10 (*a*) N. Zheng, K. W. Anderson, X. Huang, N. Nguyen and S. L. Buchwald, *Angew. Chem., Int. Ed*., 2007, **46**, 7509; (*b*) G. Brasche and S. L Buchwald, *Angew. Chem., Int. Ed*., 2008, **47**, 1932; (*c*) N. Zheng and S. L Buchwald, *Org. Lett*., 2007, **9**, 4749.

11 (*a*) K. Uneyama, *J. Fluorine Chem*., 1999, **97**, 11; (*b*) K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem*., 1993, **58**, 32.

12 (*a*) Y. M. Wu, Y. Li and J. Deng, *J. Fluorine Chem*., 2005, **126**, 791; (*b*) Y. M. Wu, Y. Li and J. Deng, *Tetrahedron Lett*., 2005, **126**, 791; (*c*) Y. M. Wu and Y. Li, *J. Fluorine Chem*., 2006, **127**, 223; (*d*) Y. M. Wu, M. Zhang and Y. Q. Li, *J. Fluorine Chem*., 2006, **127**, 1168.

