Synthesis of N-Substituted 2-Fluoromethylbenzimidazoles via Bis(trifluoroacetoxy)iodobenzene-Mediated Intramolecular Cyclization of N,N′-Disubstituted Fluoroethanimidamides

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Abstract: A mild and efficient method for the synthesis of N-substituted 2-fluoromethylbenzimidazoles via [bis(trifluoroacetoxy)-iodo]benzene-mediated intramolecular cyclization of N,N′-disubstituted bromodifluoro (or trifluoro) ethanimidamides was described.

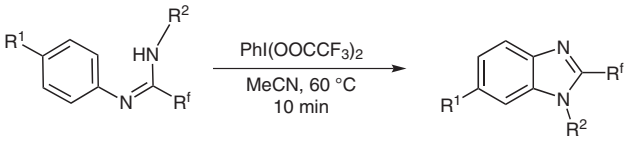
Key words: fluoroethanimidamides, benzimidazoles, BTI, oxidative coupling

Organofluorine compounds, especially fluorinated heterocycles, have received a great deal of attentions in the fields of medicine, agricultural, and material chemistry because of the unique property of the fluorine atom.[1] Among them, 2-fluoroalkylbenzimidazoles are potentially useful as herbicides and insecticides.[2] Recently, we and others have reported syntheses of benzimidazoles from *o*-iodoanilines through the use of copper or palladium catalysts.[3] The main drawbacks of these methods included the limited diversity of the starting anilines and the uses of transition metals as the catalysts. Recently, Uneyama and co-workers demonstrated that electrochemical oxidation of N,N′-disubstituted trifluoroethanimidamides could provide N-substituted 2-trifluoromethylbenzimidazoles in dry acetonitrile.[4] However, in this process symmetric imidamides were needed, as the formation of the benzimidazoles would suffer from low yields when unsymmetrical substrates were used. They also reported another method for the preparation of benzimidazoles by Lewis acid promoted cyclization of the *p*-benzoquninone imine derivatives.[5] Other procedures such as photoinduced and oxidative intramolecular cyclizations by sodium hypochlorite and lead(IV) acetate have been reported.[6] However, the yields and the tolerance were generally not satisfactory.

Hypervalent iodine organic compounds with low toxicity have been used as oxidizing reagents in the transformation of complex organic molecules.[7] Synthesis of benzimidazoles from N-substituted amidines oxidized by (diacetoxyiodo)benzene (DIB) was reported by Ramsden.[8] However, till now there are no reports on the study of the reaction between N,N′-disubstituted imidamides and hypervalent iodine(III) reagents. Herein, we would like to describe a novel method for the synthesis of N-substituted 2-fluoromethylbenzimidazoles **2** by the reaction of [bis(trifluoroacetoxy)iodo]benzene (BTI) with N,N′-disubstituted fluoroethanimidamides **1**.

2-Bromo-2,2-difluoro-*N*,*N*′-diphenylacetimidamide (**1a**), as the initial starting material, was prepared from the reaction of 2-bromo-2,2-difluoro-*N*-phenylacetimidoyl chloride with aniline using potassium carbonate in DMF at 80 °C.[9] This substrate was treated with 1.1 equivalents of BTI in MeCN at room temperature for 12 hours to furnish the desired product, 2-(bromodifluoromethyl)-1-phenyl-1*H*-benzo[*d*]imidazole (**2a**), in only 34% yield. When the reaction time was reduced to 10 minutes at 60 °C, the yield was raised to 62%. To optimize the reaction conditions, other solvents such as THF, CH_2Cl_2, EtOH, toluene, trifluoroethanol, and EtOAc were screened, but they were found to be inferior to MeCN. When DIB and [hydroxy(tosyloxy)iodo]benzene (HTIB) were used as the oxidizing agents, a complex mixture of products were formed under the similar conditions. Thus the optimized

Table 1 Synthesis of *N*-Alkyl-2-fluoromethylbezimidazoles[a]



1b–g **2b–g**

Entry	R^1	R^2	R^f	Yield of **2** (%)[b]
1	H	Bn	CF_3	**2b** 68
2	OMe	Bn	CF_3	**2c** 75
3[c]	Cl	Bn	CF_3	**2d** 58
4	H	Bn	CF_2Br	**2e** 65
5	H	Bu	CF_2Br	**2f** 48
6[c]	CF_3	Bn	CF_2Br	**2g** 45

[a] Conditions: to ethanimidamides **1** (0.5 mmol) in MeCN (10 mL) was added BTI (0.55 mmol) at 60 °C for 10 min.
[b] Isolated yield after silica gel chromatography.
[c] Stirred for 10 h.

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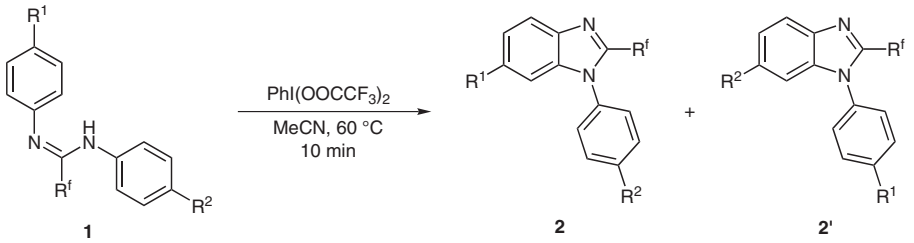
conditions were treating the substrate with BTI (1.1 equiv) in MeCN at 60 °C for 10 minutes.

Having established the optimal conditions, we probed the scope and limitation of this transformation. A series of *N*-aryl-*N*′-alkylfluoroethanimidamides were firstly tested, and fluoromethylbenzimidazoles **2b**–**g** were obtained in moderate yields (Table 1). It was found that the reaction of the substrate with an electron-donating group (4-OMe) on the aromatic ring (**2c**, Table 1, entry 2) was faster than that of the substrates with some electron-withdrawing groups such as 4-Cl (**2d**) and 4-CF_3 (**2g**, Table 1, entries 3 and 6). In the later circumstance the acetanilide was formed as a byproduct.

Next, symmetrical or unsymmetrical *N*,*N*′-diarylfluoroethanimidamides were employed, and the results were summarized in Table 2. All imidamides led to the corresponding benzimidazoles in good yields except for the case when both aromatic rings possessed a NO_2 group (Table 2, entry 4). Theoretically, two possible products could be formed when an unsymmetrical *N*,*N*′-diarylfluoroethamidaimade was used as the reactant (Table 2, entries 6–13). As shown in Table 2, this reaction showed good regioselectivity, the cyclization reaction took place preferentially on the electron-rich benzene ring (Table 2, entry 6). On the other hand, when a strong electron-withdrawing (NO_2, COOEt, CN, CF_3, Ac) group was present at the *para* position of one benzene ring, the cyclization

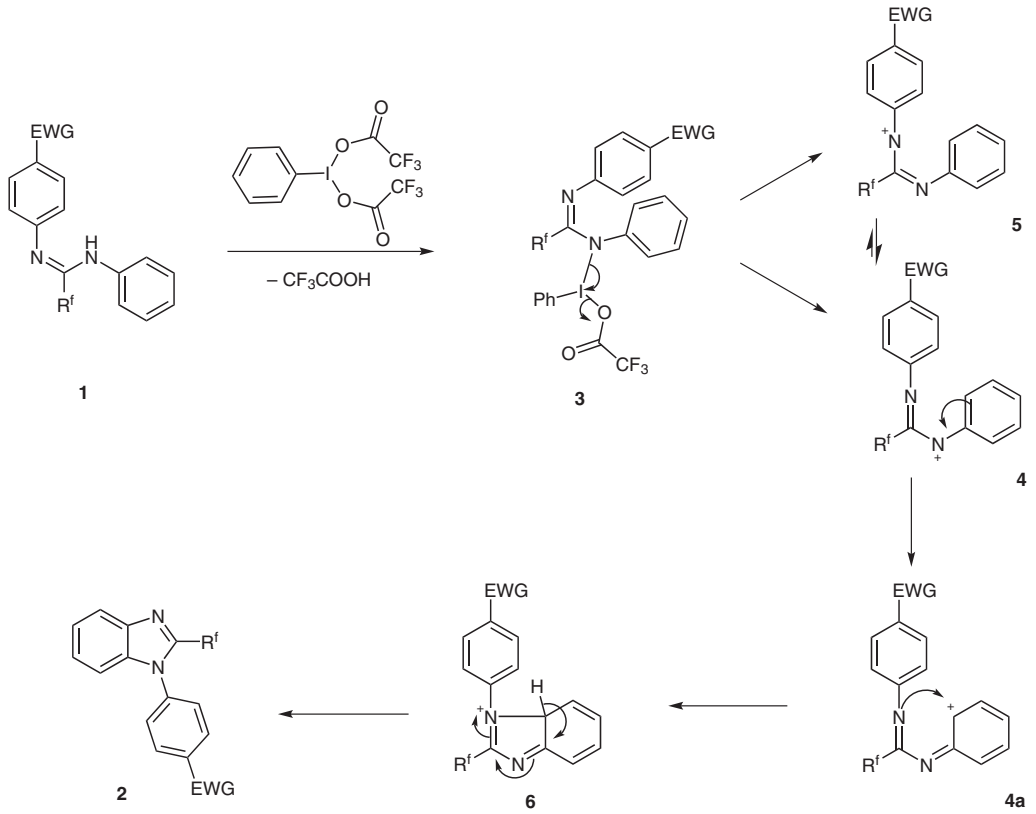
Table 2 Synthesis of *N*-Aryl-2-fluorobenzimidazoles[a]



1 2 2′

Entry	R^1	R^2	R^f	Yield of **2** (%)[b]	**2**/**2**′[c]
1	Me	Me	CF_3	**2h** 82	
2	H	H	CF_3	**2i** 83	
3	Cl	Cl	CF_3	**2j** 90	
4	NO_2	NO_2	CF_3	–	
5	H	H	CF_2Br	**2a** 62	
6[d]	H	OMe	CF_2Br	**2k** 54	<1:99
7	H	Me	CF_2Br	**2l** 73	1:6.7
8	H	F	CF_2Br	**2m** 65	1:3.3
9	H	Cl	CF_2Br	**2n** 69	1.44:1
10	H	Br	CF_2Br	**2o** 63	1.27:1
11	H	I	CF_2Br	**2p** 83	1:1.2
12	H	COOEt	CF_2Br	**2q** 83	>99:1
13	H	CN	CF_2Br	**2r** 77	>99:1
14	H	CF_3	CF_2Br	**2s** 81	>99:1
15	H	NO_2	CF_2Br	**2t** 87	>99:1
16	H	Ac	CF_2Br	**2u** 78	>99:1
17	H	*t*-Bu	CF_2Br	**2v** 70	1:6.7
19	OMe	OMe	CF_2Br	**2w** 71	
20	*t*-Bu	*t*-Bu	CF_2Br	**2x** 71	

[a] Conditions: to ethanimidamides **1** (0.5 mmol) in MeCN (10 mL) was added BTI (0.55 mmol).
[b] Isolated yield after silica gel chromatography.
[c] Obtained by ^{19}F NMR.
[d] Stirred for 1 h at r.t.



Scheme 1 The proposed mechanism of this transformation

occurred exclusively at the other benzene ring (Table 2, entries 12–16). However, for the substrates with moderate electron-withdrawing or electron-donating groups (F, Cl, Br, I, Me, *t*-Bu), both isomers **2** and **2′** were formed (Table 2, entries 7–11, 17).

To the best of our knowledge, there are two possible mechanisms for this transformation. The first mechanism features the oxidation of **1** by BTI to generate a nitrenium ion intermediate which would act as an electrophile to attack the benzene ring and to afford the benzimidazoles.[10]Another mechanism involves radical intermediate which demonstrated by Zhao's synthesis of indoles via BTI-mediated intramolecular cyclization.[11] In our reaction, the radical mechanism could be ruled out as addition of *p*-dinitrobenzene did not effect the rate of the reaction and the yields of the products. On the other hand, according to the results of this study and related literature,[4b] a nitrenium ion mechanism was most likely in this transformation. Therefore, we proposed a plausible mechanism as shown in Scheme 1. It is assumed that the intermediate **3** heterolytically cleaves to give two nitrenium ions **4** and **5** (**4** is more stable than **5** due to the electron-withdrawing groups on the benzene ring). Next, the nitrogen attacks the benzene cation to afford intermediate **6**. Finally, abstraction of a proton generates the product **2**.

In summary, we have developed a novel and mild process for the synthesis of *N*-aryl or *N*-alkyl 2-fluoro-methylbenzimidazoles from the corresponding N,N′-disubstituted ethanimidamides by oxidative cyclization with BTI. Compared to the existing methods, our strategy can be carried out more easily since the imidamide substrates need not be halogenated at the *ortho* position of the benzene ring. Further investigations of this reaction are ongoing in our laboratories.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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