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Iodobenzene Catalyzed C−H Amination of *N*-Substituted Amidines Using *m*-Chloroperbenzoic Acid

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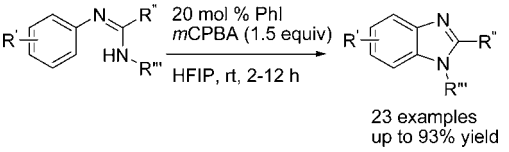
ABSTRACT



The oxidative C−H amination of *N*′-aryl-*N*′-tosyl/*N*′-methylsulfonylamidines and *N*,*N*′-bis(aryl)amidines has been accomplished using iodobenzene as a catalyst to furnish 1,2-disubstituted benzimidazoles in the presence of *m*CPBA as a terminal oxidant at room temperature. The reaction is general, and the target products can be obtained in moderate to high yields.

The benzimidazole moiety has become important over the past decades, as it displays a broad range of biological and therapeutical activities.[1] The accustomed method for the construction of this basic core structure involves condensation followed by oxidative cyclization of benzene-1,2-diamine with carboxylic acids or its equivalent.[2] In addition, C−N bond formation via a cross-coupling reaction and direct aromatic C−H activation, catalyzed by transition metals, have also been reported for the construction of the structural unit.[3] Although these protocols are effective under relatively milder conditions compared to the classical methods, the high cost and toxicity of some of the metal salts restrict their practical utility on a larger scale process. Hence, the development of new routes for the construction of the benzimidazole structural framework under metal-free conditions will be valuable. Ramsden et al. reported the synthesis of benzimidazoles using phenyliodine(III) diacetate (PIDA) in refluxing toluene.[4] More recently, PIDA-promoted cyclization of amidine to benzimidazole has been shown at room temperature.[5a]

The development of the concept of direct functionalization of C−H bonds under metal-free conditions by using hypervalent iodine(III) reagents[6] has proven valuable in the area of organic synthesis, developing effective, safe,

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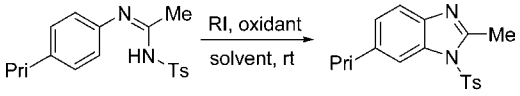
and environmentally benign protocols for carbon−carbon[7] and carbon−heteroatom[8,9] bond formation. These reactions use a hypervalentiodine(III) reagent in a stoichiometric amount and generate undesired iodoarenes in an equimolar amount. To overcome these limitations, in 2005, the Ochiai[10a] and Kita[10b] groups independently reported a catalytic process involving *in situ* oxidation of iodo(I)arenes using *meta*-chloroperbenzoic acid (*m*CPBA). Since then, this concept has been extensively used for the synthesis of a variety of organic molecules.[11] Herein, we report an iodobenzene catalyzed oxidative C−H amination for the preparation of *N*-substituted benzimidazoles from *N*″-aryl-*N*′-tosyl/*N*′-methylsulfonylamidines and *N*,*N*′-bis-(aryl)amidines using *m*CPBA as a terminal oxidant at room temperature.

First, the reaction conditions were optimized using (*Z*)-*N*″-4-isopropylphenyl-*N*′-tosylacetamidine **1c** as a model substrate that can be readily prepared from acetanilide and toluene-4-sulfonamide[12] (Table 1). Treating the substrate **1c** with 20 mol % of iodobenzene and 1.5 equiv of *m*CPBA as an oxidant in 0.5 mL of CH_2Cl_2 as solvent for 12 h at room temperature did not afford the target benzimidazole **2c** (entry 1). Further screening with solvents such as MeOH, DME, DMSO, DMF, and CF_3COOH proved unsuccessful (entries 2−6). However, to our delight, the target benzimidazole was obtained in 76% conversion using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent (entry 7). Employing other substituted iodoarenes gave inferior results (entries 8−9). In addition, oxidants such as *tert*-butyl hydroperoxide (TBHP), H_2O_2, $K_2S_2O_8$, and oxone were not successful (entries 10−13). Lowering the quantity of iodobenzene to 10 mol % led to the product formation in 53% conversion (entry 14). The control experiment confirmed that, without iodobenzene, the formation of the product **2c** was not observed (entry 15). In the presence of 1.0 equiv of PhIO in HFIP, **1c** underwent cyclization to give the benzimidazole **2c** in 62% yield (eq 2).

Table 1. Optimization of the Reaction Conditions[a]



1c **2c**

entry	R	oxidant	solvent	conversion (%)[b]
1	C_6H_5	*m*CPBA	CH_2Cl_2	0
2	C_6H_5	*m*CPBA	MeOH	0
3	C_6H_5	*m*CPBA	DME	0
4	C_6H_5	*m*CPBA	DMSO	0
5	C_6H_5	*m*CPBA	DMF	0
6	C_6H_5	*m*CPBA	CF_3COOH	5
7	C_6H_5	*m*CPBA	HFIP	76
8	4-OMe-C_6H_4	*m*CPBA	HFIP	33
9	4-Me-C_6H_4	*m*CPBA	HFIP	55
10	C_6H_5	TBHP	HFIP	5
11	C_6H_5	H_2O_2	HFIP	3
12	C_6H_5	$K_2S_2O_8$	HFIP	0
13	C_6H_5	Oxone	HFIP	0
14[c]	C_6H_5	*m*CPBA	HFIP	53
15	–	*m*CPBA	HFIP	0

[a] **1c** (0.5 mmol), aryl iodide (20 mol %), oxidant (1.5 equiv), solvent (1 mL), rt, 12 h. [b] Determined by ^{1}H NMR. [c] Iodobenzene (10 mol %) used.

With the optimized conditions in hand, the scope of the procedure was studied for the reaction of a series of substituted acetamidines (Scheme 1). (*Z*)-*N*″-Phenyl-*N*′-tosylacetamidine **1a** reacted to give 2-methyl-1-tosyl-1*H*-

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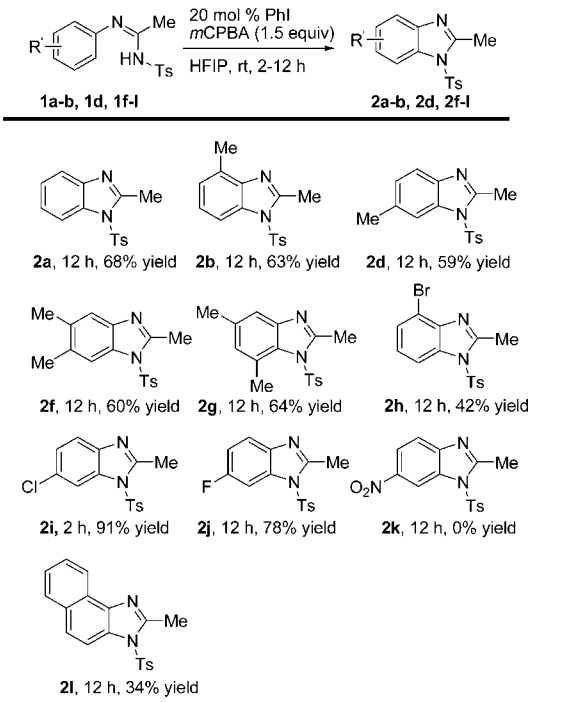
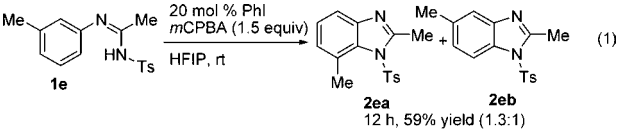
Scheme 1. Reaction of *N*′-Aryl Substituted Acetamidines[a]



[a] Substrates **1a**–**b**, **1d**, and **1f**–**l** (0.5 mmol), iodobenzene (20 mol %), *m*CPBA (1.5 equiv), HFIP (1 mL), rt. **2b**, **2h**: Iodobenzene (40 mol %) used. Isolated yield.

benzo[*d*]imidaozle **2a** in 68% yield. Similarly, (*Z*)-*N*″-aryl-*N*′-tosylacetamidines **1b**, **1d**, and **1f**–**g** with R′ having 2-methyl, 4-methyl, 3,4-dimethyl, and 3,5-dimethyl substituents reacted to give the corresponding substituted benzimidazoles **2b**, **2d**, and **2f**–**g** in 59–64% yields, while the substrates **1h**–**j** bearing halogen substituents such as 2-bromo, 4-chloro, and 4-fluoro gave the target products **2h**–**j** in 42–91% yields. In contrast, the substrate **1k** with R′ having a 4-nitro substituent showed no reaction and the starting material was recovered intact. However, (*Z*)-*N*″-(naphthalen-4-yl)-*N*′-tosylacetamidine proceeded to cyclize to give the target heterocycle **2l** in 34% yield. In case of the substrate **1e**, a 1.3:1 mixture of regioisomers **2ea** and **2eb** was obtained in 59% yield (eq 1). Crystallization of 6-chloro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole **2i** in CH_2Cl_2 gave a crystal whose structure was confirmed by X-ray analysis (Figure 1).

The reaction of the amidines with R″ having alkyl, aryl, and vinyl substituents was studied next (Scheme 2). The procedure was general, and the reaction proceeded to give the target heterocycles in moderate to high yields. The substrates **1m**–**o** having R″ with alkyl groups, ethyl, *n*-pentyl, and *tert*-butyl, exhibited greater reactivity compared to that bearing phenyl and styryl substituents **1p**–**q** affording the corresponding heterocyles **2m**–**q** in 58–90% yields.



(1)

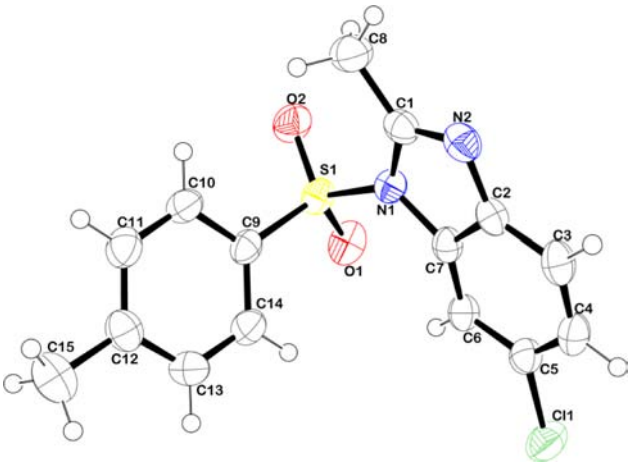
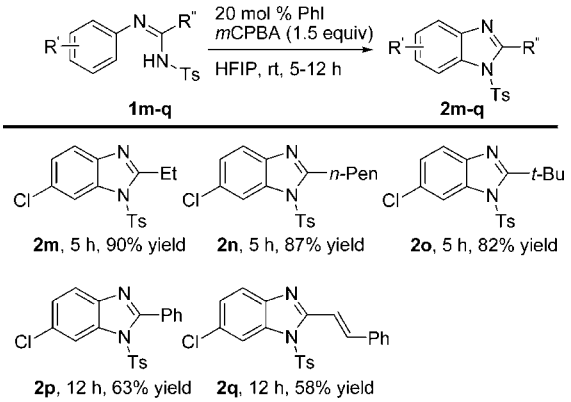


Figure 1. ORTEP diagram of 6-chloro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole **2i**.[13] H-Atoms are omitted for clarity.

Scheme 2. Reaction of 2-Substituted *N*″-(4-Chlorophenyl)-*N*′-tosylamidines[a]

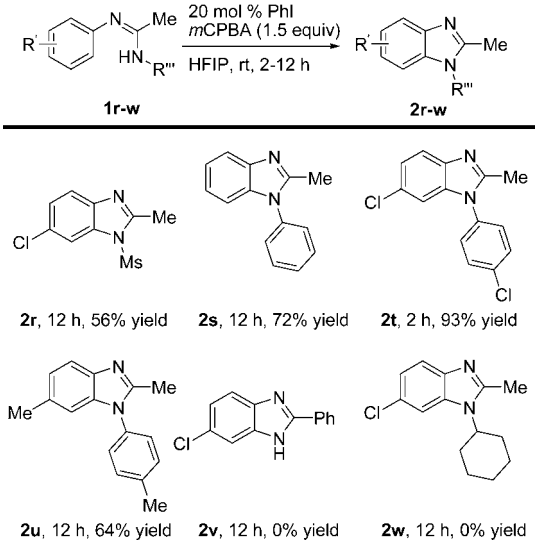


[a] Substrates **1m**–**q** (0.5 mmol), iodobenzene (20 mol %), *m*CPBA (1.5 equiv), HFIP (1 mL), rt. Isolated yield.

Finally, the cyclization of different *N*′-substituted acetamidines was studied (Scheme 3). As in the above-mentioned cases, the substrates having *N*′-methylsulfonyl acetamidine **1r** and *N*′-aryl acetamidines **1s**–**u** underwent reaction to give the benzimidazoles **2r**–**u** in 56–93% yields. The substrate with electron-withdrawing substituent **1t** exhibited enhanced reactivity compared to that bearing electron-donating group **1u**. In contrast, *N*′-unsubstituted and *N*′-cyclohexyl acetamidines **1v**–**w** showed no reaction and the starting materials

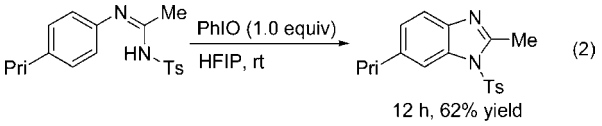
(13) Recrystallization of 6-chloro-2-methyl-1-tosyl-1*H*-benzo[*d*]-imidazole in CH_2Cl_2 afforded single crystals whose X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo Kα radiation in the scan range 1.42° to 24.99°. $C_{15}H_{13}ClN_2O_2S$, M_w = 320.78, monoclinic; space group *P*2(1)/*c*, *a* = 14.7051 (5) Å, *b* = 12.7004 (4) Å, *c* = 7.9795 (2) Å; α = 90°, *β* = 102.019°, *γ* = 90°, *V* = 1457.59(8) Å^3, *Z* = 4, D_{calcd} = 1.462 Mg/m^3, *T* = 296(2) K, crystal dimension 0.30 × 0.18 × 0.12 mm^3; 2420 reflections; $I > 2\sigma(I)$; R_1 = 0.0397, wR_2 = 0.1152, GOF (on F^2) = 0.891.

Scheme 3. Reaction of *N*′-Substituted Acetamides[a]



[a] Substrates **1r**−**w** (0.5 mmol), iodobenzene (20 mol %), *m*CPBA (1.5 equiv), HFIP (1 mL), rt. Isolated yield.

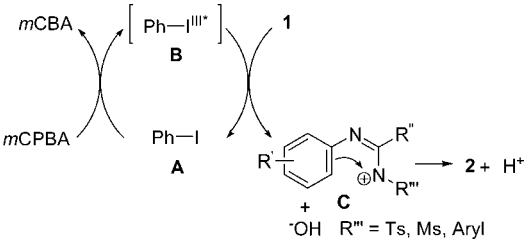
were recovered intact. These results suggest that the nature of the *N*′-substituent is crucial for the cyclization process.



(2)

A putative reaction mechanism is shown in Scheme 4. The oxidation of iodobenzene **A** using *m*CPBA may give the active hypervalent iodine(III) species[11a] that could react with **1** to generate nitrenium ion **C**.[9f,11h] The nucleophilic

Scheme 4. Proposed Catalytic Cycle



arene attacks to the nitrenium ion may lead to the formation of the target benzimidazoles, accompanied by the liberation of iodobenzene **A**, which could be reoxidized to **B** by *m*CPBA.

In summary, we have developed a new protocol for the synthesis of 2-substituted *N*-sulfonyl benzimidazoles and *N*-aryl benzimidazoles using iodobenzene as the catalyst in the presence of *m*CPBA as a terminal oxidant at room temperature. The reaction is simple and general to afford the target products in moderate to good yields.

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Supporting Information Available. Experimental procedure, characterization data, and scan of NMR spectra (^{1}H and ^{13}C) of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.