Iodine(III)-Catalyzed Oxidative Cyclization of Aryl Amines to Construct Benzimidazoles

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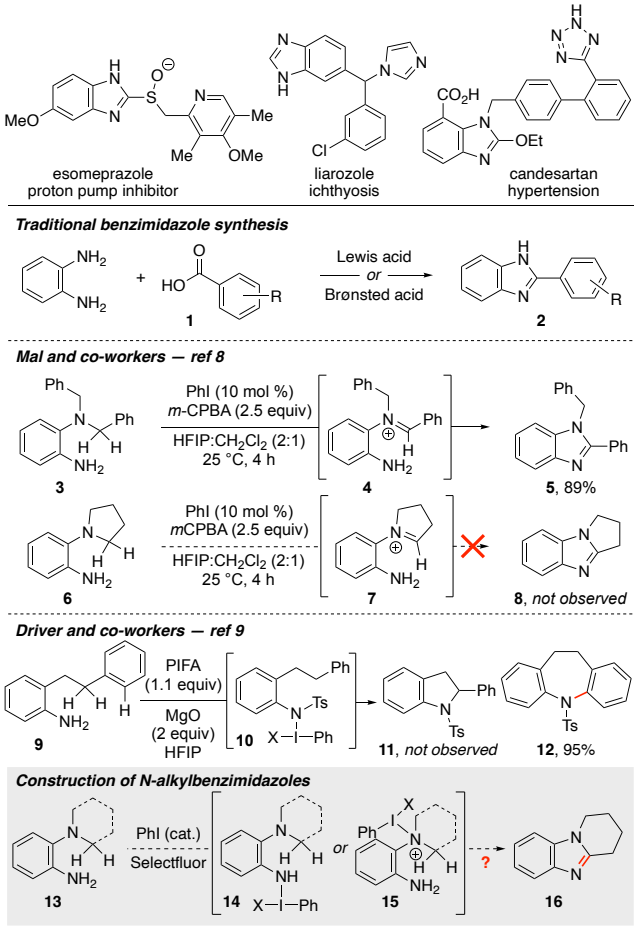
ABSTRACT. An I(III)-catalyzed oxidative cyclization reaction using Selectfluor as the oxidant was developed that converts *ortho*-substituted anilines to benzimidazoles is reported. The mild reaction requires as little as 0.5 mol % of iodobenzene tolerating electron-poor groups on the aniline portion. The size of the ring can be varied to access the pyrrole, azepine, and azocines scaffolds. Preliminary mechanistic investigations suggest that benzimidazole formation occurs via cationic reactive intermediates, and an intramolecular kinetic isotope effect of 1.98±0.01 was measured.

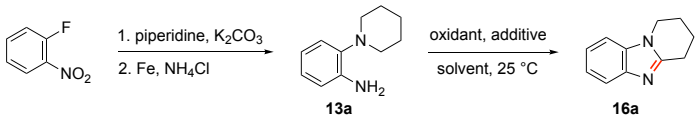
Benzimidazoles are an important class of nitrogen-containing heterocycles, as they possess interesting biological and pharmacological activities.[1] This scaffold is found in the core of pharmaceutical agents, such as esomeprazole[2], liarozole[3], and candesartan[4] which are used to treat heartburn, ichthyosis, and hypertension (Scheme 1). Consequently, the development of synthetic methods for the preparation of functionalized benzimidazoles has gained notable attention. A common reaction mechanism used to access 1,2-disubstituted benzimidazole compounds is through a Lewis acid- or Brønsted-mediated condensation of a 1,2-diaminoarene with a carboxylic acid.[5,6] Recently, the activation of C(sp^3)–H to directly form a new C–N bond has become an attractive method in synthesis due to late stage functionalization and increased structural complexity.[7] In 2019, Mal and co-workers developed an intramolecular C–H amination reaction using 10 mol % PhI and meta-chloroperoxybenzoic acid (*m*-CPBA) to construct the benzimidazole scaffold **5** (Scheme 1).[8] They interpreted their mechanistic data to indicate that C–N bond formation occurred via at the iminium ion **4**. However, the reaction conditions are limited to the amination of activated aminomethylenes; when 2-(pyrrolidin-1-yl)aniline **6** was subjected to their optimal reaction conditions benzimidazole **8** was not observed. We discovered that an electrophilic *N*-aryl iminoiodinane could be generated from I(III)-mediated oxidation of *ortho*-substituted anilines to afford dibenzazepines.[9] Our initial goal was to achieve benzylic C–H bond amination, yet exposure of **9** to the combination of stoichiometric amount of PhI(O_2CCF_3)$_2$ (PIFA) in the presence of magnesium oxide in hexafluoroisopropanol (HFIP) preferentially formed dibenzazepine **12** where 2-phenylindoline **11** was not observed. At the conclusion of our study, we were curious if we could construct *N*-alkylbenzimidazoles from aryl amine **13** by generating a stronger iodine(III) reagent *in situ* using iodobenzene as the catalyst and Selectfluor as the stoichiometric terminal oxidant. If successful, this approach would enable the synthesis of a broader range of benzimidazoles, such as **16**, under mild conditions through the construction of a C–N bond from a C(sp^3)–H bond.



Scheme 1. Methods to access benzimidazole scaffold.

To determine if benzimidazoles could be constructed from *ortho*-substituted anilines, the reactivity of **13a** was investigated towards a series of oxidants (Table 1). The substrate for our study was synthesized first by a S_NAr reaction using 1-fluoro-2-nitrobenzene and piperidine followed by a reduction using iron powder and ammonium chloride (NH_4Cl). The optimization process began by submitting **13a** to iodosobenzene (PhIO) in HFIP with 4 Å molecular sieves as an additive to remove the water biproduct because we found this combination of solvent and oxidant as an efficient method in facilitating iodine(III)oxidative cyclizations.[9-10] In contrast to our previous work, a moderate yield of **16a** was observed (entry 1). Doubling the amount of oxidant successfully gave a quantitative yield and reduced the reaction time to 1 h (entry 2). Other hypervalent iodine reagents screened (e.g. PIFA, [hydroxy(tosyloxy)iodo]benzene (HTIB), and PhI(O_2CCH_3 (PIDA)) gave close to quantitative yields of benzimidazole (entries 3 – 5). To investigate if catalysis of an oxidative cyclization reaction could be achieved, the reactivity of **13a** toward a substoichiometric amount of iodobenzene and a terminal oxidant was examined. Based on our previous investigations,[11] the use of Selectfluor in the presence of substoichiometric amounts of iodobenzene (PhI) was effective in promoting organoiodine-catalyzed oxidative cyclization-migration reactions. The yield was improved to 97% when the time was doubled (entry 7), however if the reaction time was increased to 16 h, the catalyst loading could be lowered to as little as 0.5 mol % and still produce quantitative amount of benzimidazole (entry 8). The yield remained 98% when the reaction was scaled to 1.00 mmol (entry 8). Considering the environmental factors and expense associated with HFIP, other cheaper and greener solvents were explored. A survey of different solvents revealed that a poor reaction outcome was obtained with ethereal and non-polar aprotic solvents.[12] While using polar aprotic solvents, such as DMF and DMSO, provided **16a**, acetonitrile produced benzimidazole in a quantitative yield (entries 9 – 11).

Table 1. Development of optimal conditions.



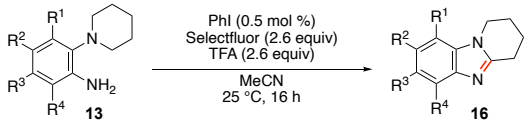
13a 16a

entry	oxidant (equiv)	additive (equiv)	PhI (mol %)	solvent	time	**16a** yield, %[a]
1	PhIO (1.1)	4 Å MS (100 wt %)	-	HFIP	16 h	59
2	PhIO (2.2)	4 Å MS (100 wt %)	-	HFIP	1 h	99
3	$PhI(O_2CCF_3)_2$ (2.2)	MgO (2.0)	-	HFIP	5 min	90
4	$PhI(O_2CCH_3)_2$ (2.2)	MgO (2.0)	-	HFIP	5 min	99
5	HTIB (2.2)	MgO (2.0)	-	HFIP	5 min	92
6	Selectfluor (2.6)	TFA (2.6)	10	HFIP/H_2O (10:1)	2 h	66
7	Selectfluor (2.6)	TFA (2.6)	10	HFIP/H_2O (10:1)	4 h	97
8	Selectfluor (2.6)	TFA (2.6)	0.5	HFIP/H_2O (10:1)	16 h	98[b]
9	Selectfluor (2.6)	TFA (2.6)	0.5	DMF	16 h	18
10	Selectfluor (2.6)	TFA (2.6)	0.5	DMSO	16 h	51
11	Selectfluor (2.6)	TFA (2.6)	0.5	MeCN	16 h	98[b,c]

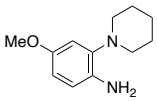
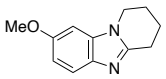
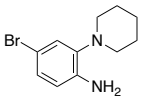
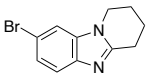
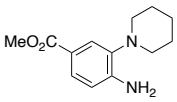
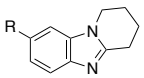
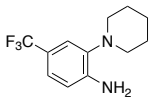
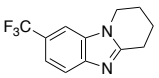
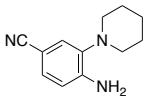
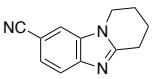
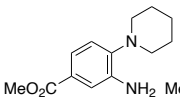
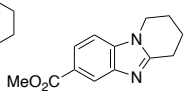
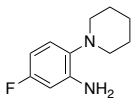
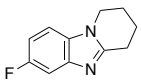
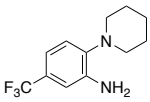
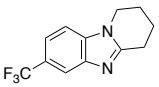
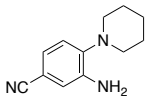
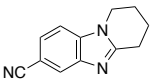
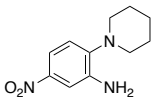
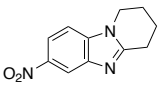
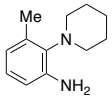
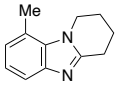
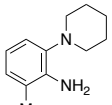
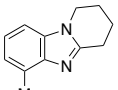
[a] As determined using ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] Isolated yield. [c] Reaction performed using 1.00 mmol scale of **13a**.

Using the optimal conditions, the effect of changing the substituents on the aniline portion **13a** was investigated (Table 2). The impact of changing the electronic nature of the aryl amine was assayed by changing the identity of the R^2- or R^3- substituent. While a moderate yield was obtained with an electron-donating methoxy R^2-group, the yield of benzimidazole **16** increased as R^2 became more electron-withdrawing. Anilines with stronger electron-withdrawing groups (**13f**, **13g**, **13j**, and **13k**) resulted in diminished yields of **16**. However, changing the solvent from acetonitrile to a 10:1 mixture of HFIP:H_2O rescued the reaction to produce benzimidazoles (**16f**, **16g**, **16j**, and **16k**) in good yield. Increasing the steric environment around the nitrogen by adding an R^4-methyl to **13** did not negatively affect the reaction outcome to provide **16l** and **16m** in 88% and 87%.

Table 2. Effect of changing the electronic nature of the aryl amine.

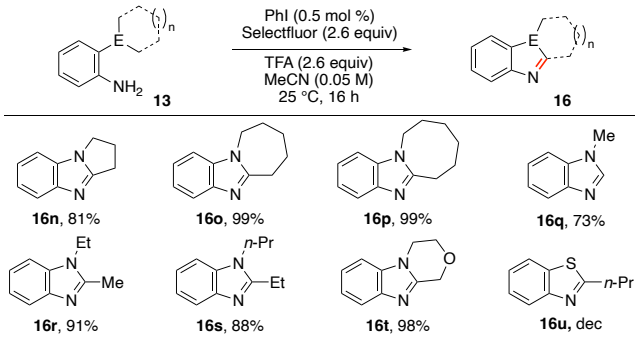


13 **16**

entry[a]	**13**	Aniline	Benzimidazole	**16** yield, %[b]
1	b			65
2	c			98
3	d			82
4	e			76
5	f			24 (93)[c]
6	g			68 (99)[c]
7	h			73
8	i			99
9	j			38 (79)[c]
10	k			16 (76)[c]
11	l			87
12	m			88

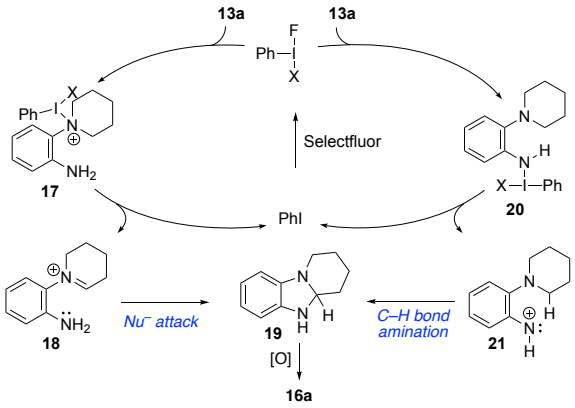
[a] conditions: 0.2 mmol of **13**, 0.001 mmol of PhI, 0.52 mmol of Selectfluor, 0.52 mmol of TFA, 4 mL of MeCN. [b] Isolated after silica gel chromatography. [c] 4 mL of HFIP and 0.4 mL of H_2O.

Next, changing the identity of the *ortho*-piperidine was surveyed (Scheme 2). The size of the *ortho*-piperidine ring was varied with **13n**, **13o**, and **13p** to determine if five-, seven- or eight-membered rings could be constructed. Decreasing the ring size to an *ortho*-pyrrolidine produced the benzimidazole **16n** in an 81% yield. Because medium-sized *N*-heterocycles are underrepresented in pharmaceutical libraries,[13] increasing the ring size was of interest. To our delight, **16o** and **16p** were both produced in a 99% yield. This success prompted us to examine substrates with acyclic substituents. Changing the substituents on the piperidine nitrogen to a methyl group decreased the yield to 73%, however increasing the number of carbons in chain to ethyl and *n*-propyl showed an improved yield of 91% and 88% for benzimidazoles **16r** and **16s**. Increasing the electron-withdrawing of the heteroatom of the ring to morpholine produced the benzimidazole product **16t** in 98% yield. With the success of adding an alkyl chain to the nitrogen atom, we were curious to see the effect of changing the heteroatom. Replacing the nitrogen with sulfur lead to the decomposition of the reaction.



Scheme 2. Survey of the effect of changing the *ortho*-substituent on the reaction outcome.

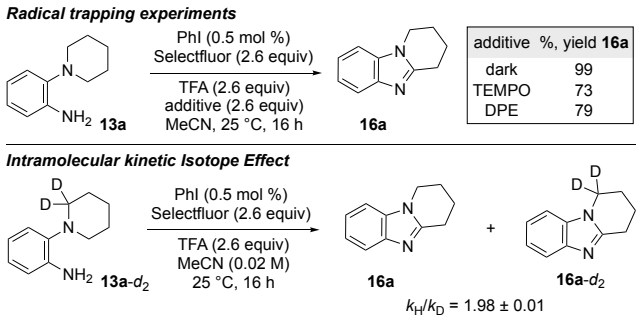
Benzimidazole formation could result from oxidation at either amines (Scheme 3). Attack of the more electron-rich piperidine nitrogen to the iodine(III) oxidant produces **17**, which triggers deprotonation at the aminomethylene position to eliminate PhI and produce iminium ion **18**.[8, 14] Aryl amine attack creates the C–N bond to form **19**, which is oxidized to produce benzimidazole. Alternatively, iodination at the aniline position forms **20** after deprotonation.[10, 15] Elimination of PhI generates nitrenium ion **21**,[14] which reacts with the aminomethylene C–H bond to produce **19**.



Scheme 3. Potential catalytic cycles.

Several experiments were performed to gain more insight into the mechanism of benzimidazole formation (Scheme 3). When ambient light was rigorously excluded, benzimidazole **16a** was produced in a quantitative yield. To examine the potential for trapping putative radical intermediates, TEMPO was added to the reaction mixture, and the yield of **16a** was attenuated to 73%. Because of the nucleophilicity of

TEMPO can lead to inconsistent results,[16] 1,1-diphenylethylene (DPE) was investigated as it has been demonstrated to be a radical trap for nitrogen-centered radical intermediates generated in iodine(III)-mediated reactions.[17,18] Performing the reaction in the presence of DPE resulted in a 79% yield of **16a**. Together these experiments suggest that benzimidazole formation does not occur via a radical intermediate or that the radical intermediate reacts intramolecularly before diffusion occurs.



Scheme 4. Mechanistic experiments.

To provide insight into the mechanism of oxidative cyclization, the reactivity of isotopolog **13a**-d_2 towards the reaction conditions was investigated. We anticipated that the ratio of **16a** and **16a**-d_2 would reveal if the mechanism of oxidation occurred at the piperidine nitrogen (via **17**) where C–H bond was broken through deprotonation or if oxidation occurred at the NH_2 group (via **20**) where the C–H bond cleavage occurs through insertion or H-atom abstraction-radical recombination of the nitrenium ion. An intramolecular competition experiment was performed and the ratio of the two possible products was obtained using ^{1}H NMR spectroscopy. An intramolecular kinetic isotope effect (KIE) of 1.98 ± 0.01 was observed. The magnitude of this isotope effect is significantly smaller than that observed by Murata and co-workers for the reaction of a photochemically generated *N*-aryl nitrene with a proximal benzylic C–H bond (k_H/k_D = 13.6 ± 0.3).[19] While large kinetic isotope effects were measured for E2 elimination reaction in polar protic solvents,[20] significantly smaller values (k_H/k_D ~ 2) have been reported for gas phase E2 reactions.[21] The similar magnitude of the KIE we measured, suggests that the oxidation is occurring at the piperidine nitrogen followed by product-determining E2 elimination of PhI to generate iminium ion **18**.

In conclusion, we discovered an oxidative catalytic process to construct benzimidazoles from activated anilines using the combination of iodobenzene and Selectfluor as the oxidant. Our reaction only requires 0.5 mol % of iodobenzene and tolerates a broad range of functionality due to the mild conditions. Our future studies will build on these results to investigate the oxidation of unactivated anilines using I(III)-catalyzed oxidative reactions.

Acknowledgments

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