Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles from Triacyloxyborane Intermediates

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Abstract: An efficient one-pot synthesis of 2-substituted benzimidazoles via triacyloxyborane intermediates is reported. The mild protocol is efficient and tolerant of acid-labile functional groups.

Key words: benzimidazoles, borane–THF, carboxylic acids, triacyloxyboranes, diacyloxyboric acids, benzoxazoles

The benzimidazole motif can be found in a number of natural products (represented prominently by vitamin B12) and biological and therapeutic active agents.[1] It has been commonly exploited in many therapeutic areas, such as antiulcers,[1] anticoagulants,[2] antihypertensives,[3] antivirals,[4] antifungals,[4] anticancers,[5] and antihistaminics.[6] Marketed drugs containing benzimidazoles are Nexium, Prevacid, Protonix, Vetmedin, Candesartan, and Telmisartan. Benzimidazoles also have been frequently used as the backbone in dyes[7] and high-temperature polymers.[8]

There is an extensive body of literature documenting the syntheses of bezimidazoles.[9] The most popular approaches generally involve the condensation–dehydration of *o*-aryl diamines with carboxylic acids or their equivalents (esters, nitriles, imidates, etc.),[10] or the condensation of *o*-aryl diamines with aldehydes under oxidative conditions. The use of carboxylic acids or equivalents is usually performed under strongly acidic or harsh dehydrating conditions at elevated temperatures.[9] The aldehyde approach involves an oxidative step for conversion to the corresponding benzimidazole through a benzimidazoline intermediate, which often requires heating in nitrobenzene or DMF at elevated temperatures, as well as the use of metal ions, iodine, organic oxidants, or inorganic sulfites under heating.[11] Condensation of anilines with α-chloroaldoxime *o*-methanesulfonates can also provide benzimidazoles.[12] In addition, transition-metal catalyzed approaches have been developed more recently to synthesize benzimidazoles from anilines or *o*-haloanilines.[13] Despite these advances, many of the processes require harsh reaction conditions and conditions which are incompatible with acid-labile functional groups. Herein, we report a novel protocol for the rapid synthesis of a variety of substituted benzimidazoles under mild reaction conditions using triacyloxyborane intermediates.

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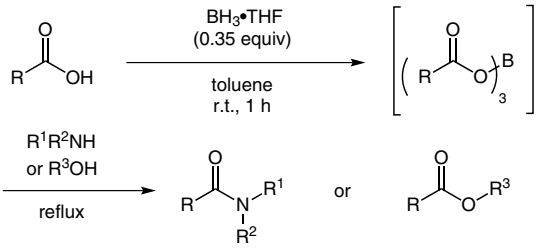
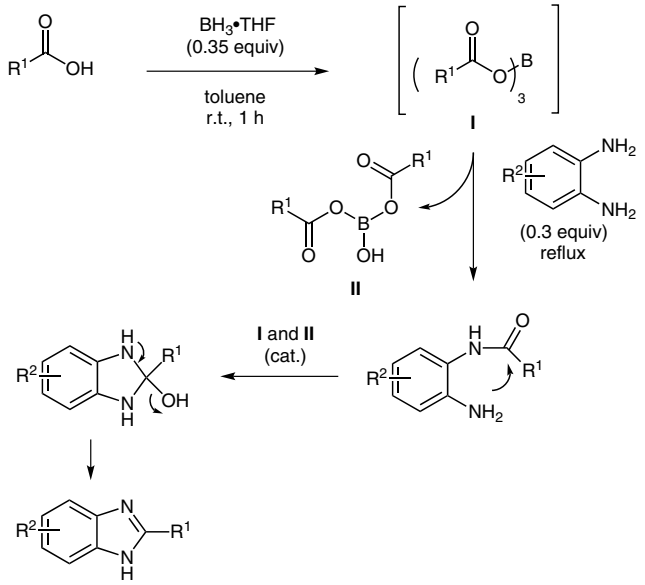
Acyloxyboranes have been used as reactive intermediates to acylate amines to furnish amides for more than forty years.[14] Recently, Huang et al. developed an efficient synthesis of amides and esters using triacyloxyboranes as intermediates (Scheme 1).[14d] The triacyloxyboranes were generated by reacting carboxylic acids with borane–THF or borane–methyl sulfide and effectively react with various nucleophiles including alkylamines, arylamines, hydrazides, alcohols, and phenols.



Scheme 1 Synthesis of amides and esters

On the basis of this work, we envisioned an application toward the synthesis of substituted benzimidazoles. We hypothesized that a key triacyloxyborane intermediate could undergo condensation with an aryldiamine to afford an amide, followed by intramolecular nucleophilic addition and subsequent elimination to yield a benzimidazole (Scheme 2).

We started our exploration of the benzimidazole synthesis by treating glacial acetic acid in toluene with one third equivalent of borane in THF at ambient temperature. The resulting triacyloxyborane was heated at reflux with 1.0 equivalent of benzene-1,2-diamine. After 12 hours, 2-methylbenzimidazole was formed in only 32% yield while 60% of benzene-1,2-diamine remained unreacted. It was thought that benzene-1,2-diamine could only be acylated by the more reactive triacyloxyborane; the less active mono- or diacyloxyboric acid resulting from the triacyloxyborane was unreactive toward benzene-1,2-diamine under these conditions. By reducing the reaction stoichiometry, from 1.0 equivalent to 0.33 equivalents of benzenediamine, we found that benzimidazole was formed cleanly and in excellent yield (88%); no benzene-1,2-diamine was observed after the reaction was complete (Table 1, entry 1). With the initial success of the reaction, we set out to determine the variability and scope of the one-pot procedure. Using the standard conditions,[17] we selected six different substituted benzenediamines and a

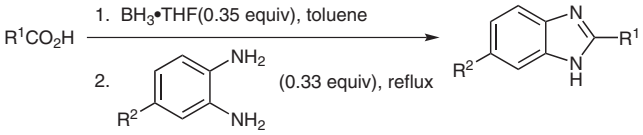


Scheme 2 Synthesis of benzimidazoles from benzene-1,2-diamines and acids

variety of aliphatic or aromatic acids. As shown in Table 1, this method can be applied to numerous substrates, and the benzimidazole products were obtained in moderate to excellent yields.

Among our 16 examples, electron-donating (methyl and methoxy) and weak electron-withdrawing (chloro and bromo) functional groups on the *o*-phenylenediamines have little impact on the reaction yields. However, a strong electron-withdrawing nitro group on the *o*-phenylenediamine led to a very low conversion under the standard conditions and only 15% isolated yield even with extended reaction time (Table 1, entry 15). Both aliphatic carboxylic acids and aromatic carboxylic acids were able to afford benzimidazoles in excellent yields. Aromatic carboxylic acids with electron-donating and electron-withdrawing functional groups on the phenyl ring gave similar reaction yields (Table 1, entries 4–7 and 9–11). In a very recent paper describing the synthesis of benzimidazoles via boric acid catalysis,[16c] aromatic carboxylic acids were found much less reactive than aliphatic carboxylic acids and required more than three days in refluxing toluene or xylene with the azeotropic removal of water for complete conversion. In comparison, the protocol we reported here requires much shorter reaction time for aromatic carboxylic acids to furnish benzimidazoles and no azeotropic removal of water ist needed. It is noteworthy that the acid-sensitive Boc group in entries 12 and 13 (Table 1) survived under the standard reaction conditions and afforded their corresponding benzimidazoles in 74% and 56% yield, respectively. Furthermore, cinnamic acid, a Michael acceptor, was converted to benzimidazole in 60% yield without affecting the styrene at the β-position of the acid (Table 1, entry 8).

Table 1 Synthesis of Benzimidazoles from Benzene-1,2-diamine Derivatives and Carboxylic Acids[17]



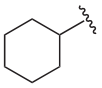
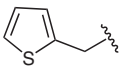
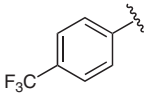
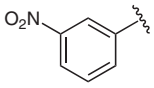
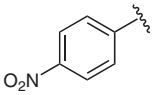
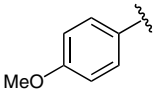
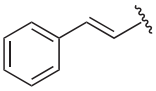
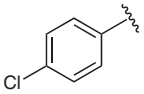
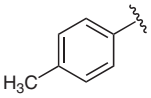
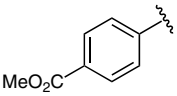
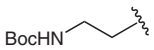
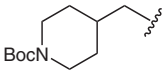
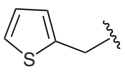
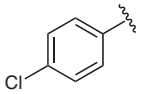
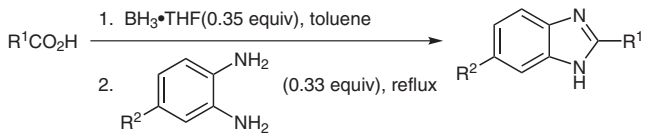
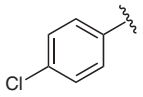
Entry	R^1	R^2	Yield (%)[a]
1		H	88[10e]
2		H	69[15a]
3		H	81[15b]
4		H	50[15c]
5		H	73[11c]
6		H	78[15d]
7		H	82[15d]
8		H	60[15e]
9		Me	87[11d]
10		Me	85[11c]
11		Me	81[17]
12		Me	74[17]
13		Cl	56[17]
14		Br	95[17]
15		NO_2	15[b,17]

Table 1 Synthesis of Benzimidazoles from Benzene-1,2-diamine Derivatives and Carboxylic Acids[17] (continued)

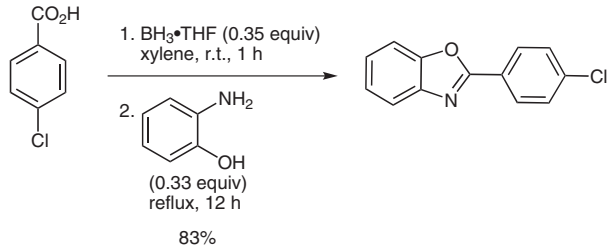


Entry	R^1	R^2	Yield (%)[a]
16		OMe	72[17]

[a] Isolated yield based on benzene-1,2-diamine precursors. All compounds produced satisfactory HPLC, ^{1}H NMR, and MS data.
[b] Isolated yield after refluxing for 36 h.

The reaction is thought to undergo a stepwise process involving the formation of an *N*-acylphenylenediamine intermediate, which is the rate-limiting step, followed by cyclization and dehydration to yield the desired benzimidazoles (Scheme 2). It is known that the cyclization–dehydration of the *N*-monoacyl intermediates to benzimidazoles could occur upon heating, even in the absence of a catalyst,[16b] and could be greatly accelerated as well by acid/base catalysis.[16] The diacyloxyboric acid side product (**II**, Scheme 2) and the triacyloxyborane itself (**I**, Scheme 2) as mild Lewis acids might help to catalyze the dehydrating step. Potential *N*,*N*′-diacylphenylenediamine intermediates were not observed, suggesting that either the *N*-acylphenylenediamine intermediates (less nucleophilic than *o*-phenylenediamine) do not further react with the triacyloxyboranes, or the subsequent cyclization–dehydration was much faster as compared to the acylation step.

To extend the substrate scope, the reaction was carried out using 2-aminophenol and *p*-chlorobenzoic acid (Scheme 3). In this case, however, the initial protocol failed to yield the desired benzoxazole product. We were pleased to find that switching the solvent from toluene to xylenes in order to increase the reaction temperature to 140 °C in the second step gave a very good yield of the benzoxazole (83%).



Scheme 3 Synthesis of benzoxazole using xylenes as solvent

In summary, we described a mild one-pot protocol for the synthesis of 2-substituted benzimidazoles using triacyloxyboranes generated from carboxylic acids and borane–THF requiring no azeotropic removal of water. We also successfully showcased the extension of this methodology toward the synthesis of a benzoxazole. The reaction conditions are mild and are fully compatible with acid-labile functional groups. Studies aimed at generating an extended scope of benzoxazoles are ongoing.

Acknowledgment

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(17) **General Procedure for the Formation of Benzimidazoles**

To a carboxylic acid (2 mmol) in toluene (10 mL) in an ice-water bath was added dropwise a solution of borane–THF (1 M, 0.70 mmol) in THF. The mixture was stirred at r.t. for 30 min. Benzene-1,2-diamine (0.66 mmol) was added, and the mixture was heated at reflux with stirring for 12 h. After cooling, the mixture was concentrated in vacuo, and the residue was purified by flash chromatography. The physical data of the products in Table 1, entries 1–11, 15, and 16 are consistent with those of reported literatures,[10e,11c,d,15] or those of authentic samples. The new compound characterizations are provided below.

***tert*-Butyl 2-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-ethylcarbamate (Table 1, Entry 12)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.1 Hz, 1 H), 7.32 (s, 1 H), 7.04 (d, *J* = 8.1 Hz, 1 H), 5.40 (br, 1 H), 3.68–3.61 (m, 2 H), 3.12–3.18 (m, 2 H), 2.45 (s, 3 H), 1.40 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 152.2, 132.0, 123.7, 114.3, 114.0, 79.9, 38.4, 30.2, 28.4, 21.6. ESI-HRMS: *m/z* calcd for $C_{15}H_{21}N_3O_2 + H^+$: 276.1712; found 2761723.

***tert*-Butyl 4-[(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)-methyl]piperidine-1-carboxylate (Table 1, Entry 13)**

^{1}H NMR (500 MHz, CD_3OD): δ = 7.53 (d, *J* = 1.9 Hz, 1 H), 7.47 (d, *J* = 8.7 Hz, 1 H), 7.20 (dd, *J* = 1.5, 8.6 Hz, 1 H), 4.15 (d, *J* = 13.2 Hz, 2 H), 2.83 (d, *J* = 7.3 Hz, 2 H), 2.76 (br, 2 H), 2.10–2.02 (m, 1 H), 1.66 (d, *J* = 12.2 Hz, 2 H), 1.44 (s, 9 H), 1.36–1.28 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 156.6, 156.5, 140.4, 137.8, 129.0, 123.8, 116.3, 115.4, 81.0, 44.6, 37.0, 36.4, 33.0, 28.7. ESI-HRMS: *m/z* calcd for $C_{18}H_{24}ClN_3O_2 + H^+$: 350.1635; found: 350.1642.

5-Bromo-2-(thiophen-2-ylmethyl)-1*H*-benzo[*d*]-imidazole (Table 1, Entry 14)

^{1}H NMR (500 MHz, CD_3OD): δ = 7.72 (d, *J* = 1.5 Hz, 1 H), 7.47 (d, *J* = 8.5 Hz, 1 H), 7.41 (dd, *J* = 1.5, 8.5 Hz, 1 H), 7.32 (dd, *J* = 1.5, 5.5 Hz, 1 H), 7.04–7.03 (m, 1 H), 6.99 (dd, *J* = 3.5, 5.0 Hz, 1 H), 4.52 (s, 2 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 155.8, 141.1, 139.4, 138.4, 128.1, 127.6, 126.6, 126.1, 118.7, 117.0, 116.3, 30.3. ESI-HRMS: *m/z* calcd for $C_{12}H_9BrN_2S + H^+$: 292.9748; found: 292.9768.

