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Oxidative Condensations To Form Benzimidazole-Substituted Potassium Organotrifluoroborates

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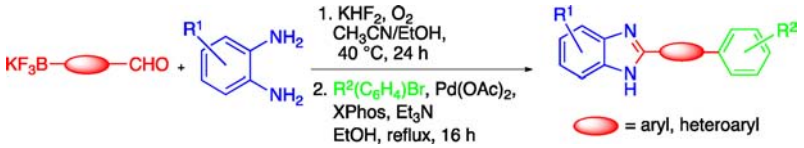
ABSTRACT



A library of benzimidazole-substituted potassium organotrifluoroborates was prepared via the condensation of various potassium formyl-substituted aryl- and heteroaryltrifluoroborates with aromatic 1,2-diamines under oxidative conditions. The efficient Suzuki–Miyaura cross-coupling of products thus formed to various aryl and heteroaryl bromides was achieved in good yields. The method allows the facile preparation of benzimidazole-containing triaromatic products in two steps from simple potassium formyl substituted aryl- or heteroaryltrifluoroborates.

Over the past several decades, organoboron compounds have proven to be supremely useful synthetic intermediates for a wide variety of chemical processes. Boronic acids and esters, in particular, are well suited for the formation of carbon–carbon bonds.[1] However, traditional organoboron compounds suffer from various vulnerabilities that place real limits on their strategic usefulness for the construction of complex molecules.[2] Organotrifluoroborates have emerged as robust boronic acid surrogates that do not suffer from many of those vulnerabilities.[3] We therefore envision organotrifluoroborates continuing to be of service in enabling the synthesis of much more complex organoboron compounds for use in medicinal chemistry, total synthesis, and organic materials discovery.

Heterocycles are among the most important subtypes of organic molecules in the realm of both biomedical and materials science. Benzimidazoles, in particular, have been identified as one of a handful of "privileged scaffolds"[4] found in a variety of natural and pharmaceutical products.[5] Employing privileged scaffolds in combinatorial syntheses would presumably maximize positive screening results for the resulting libraries. We have previously demonstrated the usefulness of the trifluoroborate group for synthesizing substituted triazole[3b] and oxazoline[3e] heterocycles. The robustness of the trifluoroborate group

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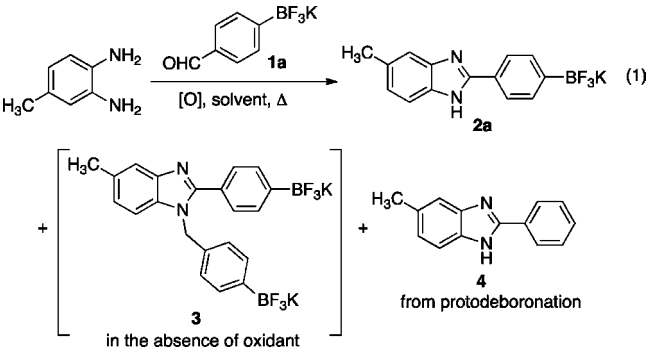
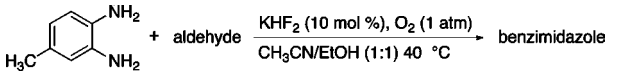
was anticipated to render it suitable for the rapid synthesis of a diverse library of 2-substituted benzimidazoles.

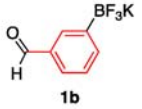
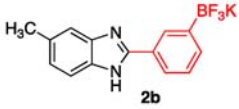
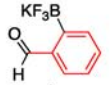
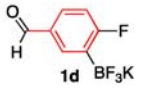
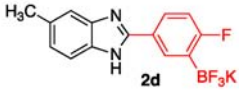
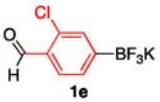
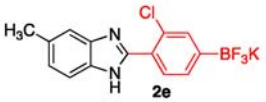
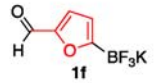
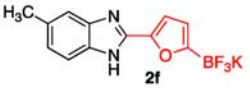
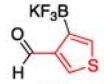
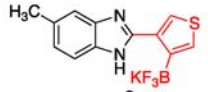
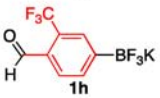
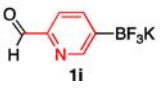
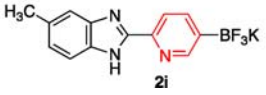
Though many modern methods exist for the synthesis of benzimidazoles,[6] we elected to initiate these studies with a method that allows maximal availability and variability in the starting materials. Benzimidazoles substituted at the 2-position are typically constructed by condensation of aryl 1,2-diamines with either aldehydes in the presence of an oxidant (eq 1) or carboxylic acids in the presence of an acid. We elected to use aldehydes as our starting materials because of the greater variety of commercially available derivatives. A mechanistic study showed that the oxidant is essential for an efficient reaction; in the absence of oxidant, a competing redox process results in the formation of 1,2-disubstituted derivatives.[7] Furthermore, for our particular study, the formation of 1,2-disubstituted benzimidazole **3** would prevent isolation of the desired 1*H*-benzimidazole **2a**, as organotrifluoroborates are not easily separated from one another (eq 1). Therefore, it was imperative to find an effective oxidant for the process that would tolerate the trifluoroborate group.



Toward that end, we began our investigation by surveying the literature for oxidants known to promote the desired condensation. All of the commonly utilized oxidants, including I_2,[8a] CAN,[8b] 1,4-benzoquinone,[8c] $PhI(OAc)_2$,[8d] and $FeCl_3$,[8e] failed to yield any of the desired trifluoroborate **2a**, with the protodeboronated benzimidazole **4** being the major product. Use of bisulfite reagents[9] gave a low yield of the desired product after prolonged heating. We eventually found that the best results came with the use of molecular oxygen as an oxidant. Catalysis with aqueous KHF_2 allowed the reaction to be completed at a reduced temperature, which seemed to be necessary for preservation of the C–B bond. The choice of solvent turned out to be crucial for success; a 1:1 EtOH/CH_3CN solvent mixture provided the optimal environment. An increase in the solvent ratio caused an unacceptable increase in the rate of protodeboronation, while a decrease in the ratio greatly retarded the reaction, necessitating higher temperatures and reducing the yield.

Table 1. Oxidative Condensation of Formyl-Substituted Potassium Aryl and Heteroaryltrifluoroborates with 3,4-Toluenediamine



entry	aldehyde	benzimidazole	reaction time (h)	% isolated yield
1	 **1b**	 **2b**	10	92
2	 **1c**	 **2c**	10	63
3	 **1d**	 **2d**	12	71
4	 **1e**	 **2e**	12	83
5	 **1f**	 **2f**	18	71
6	 **1g**	 **2g**	18	74
7	 **1h**	 **2h**	12	62
8	 **1i**	 **2i**	18	76

(6) Modern benzimidazole syntheses: (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934. (b) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330–9333. (c) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367–3370. (d) Sharghi, H.; Aberi, M.; Doroodmand, M. M. *Adv. Synth. Catal.* **2008**, *350*, 2380–2390. (e) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039–2042. (f) Yamamoto, Y.; Mizuno, H.; Tsuritani, T.; Mase, T. *J. Org. Chem.* **2009**, *74*, 1394–1396. (g) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742–5745. (h) Diao, X.; Wang, Y.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2009**, *74*, 7974–7977. (i) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem.—Eur. J.* **2009**, *15*, 7292–7296. (j) Shiraishi, Y.; Sugano, Y.; Tanaka, S.; Hirai, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1656–1660. (k) Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. *J. Org. Chem.* **2011**, *76*, 9577–9583. (l) Fu, S.; Jiang, H.; Deng, Y.; Zeng, W. *Adv. Synth. Catal.* **2011**, *353*, 2795–2804.

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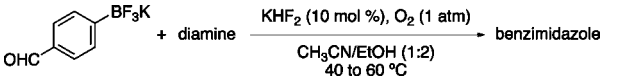
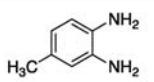
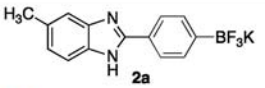
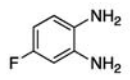
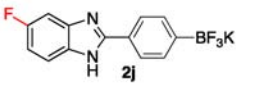
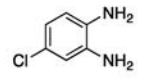
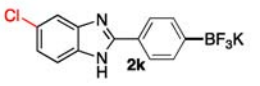
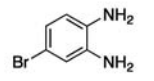
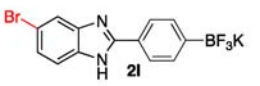
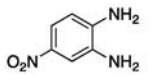
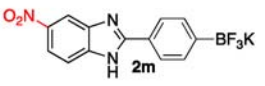
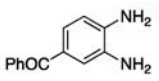
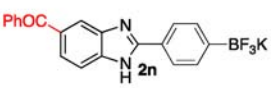
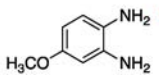
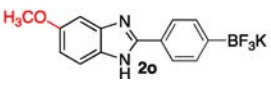
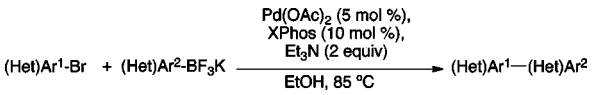
Table 2. Oxidative Condensation of Potassium 4-Formyl Phenyltrifluoroborate with Functionalized 1,2-Diaminobenzenes

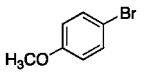
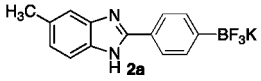
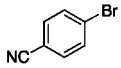
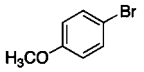
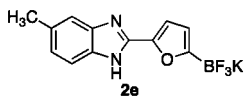
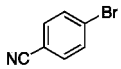


entry	diamine	benzimidazole	reaction time (h)	% isolated yield
1		 **2a**	10	95
2		 **2j**	24	56
3		 **2k**	24	65
4		 **2l**	24	68
5		 **2m**	96	16[a]
6		 **2n**	36	49
7		 **2o**	7	44

[a] Yield determined by ^{1}H NMR.

Table 3. Cross-Couplings of Aryl and Heteroaryl Bromides with Benzimidazole-Substituted Aryl and Heteroaryltrifluoroborates



entry	(Het)Ar^1-Br	(Het)Ar^2-BF$_3$K	% isolated yield
1		 **2a**	80
2		**2a**	88
3		**2a**	63
4		 **2e**	58
5		**2e**	71
6		**2e**	66

With the development of optimal conditions for oxidative condensation, we then examined the effect of substitutions on the aldehyde moiety. The results of those studies are shown in Table 1. Electron-neutral (entries 1 and 2) and electron-poor (entries 3, 4, and 7) benzaldehyde derivatives performed well under the reaction conditions, as well as some heterocyclic aldehydes (entries 5 and 6). On the other hand, electron-rich aldehydes proved too reactive under the reaction conditions to prevent formation of 1,2-disubstituted benzimidazoles, even at temperatures as low as −20 °C. In addition, the reaction is somewhat sensitive to the amount of oxygen introduced; too much oxygen oxidizes the trifluoroborate group to an alcohol under the reaction conditions, often giving phenolic side products in up to 15% yields by ^{1}H NMR. The phenol derivatives, when formed, could not be separated from the desired benzimidazoles in most cases, presumably because of the unexpectedly high degree of similarity in physical properties. A protocol that involves bubbling O_2 into the reaction mixture for 20 s before stirring under positive O_2 pressure gave the optimal results.

We then examined the effect of substitutions on the aromatic diamine moiety (Table 2). Electron-poor diamines successfully couple to aldehydes, though the reaction times are increased in all such cases relative to 3,4-diaminotoluene (entry 1). Mildly deactivated diamines, such as those with halide substituents, react fully within 24 h (entries 2, 3, and 4), while the phenylcarbonyl-substituted diamine completely reacts only after 36 h at 60 °C (entry 6). The nitro-substituted diamine does not react fully under the reaction conditions, even after 96 h (entry 5). The reaction with 4-methoxy-1,2-diaminobenzene goes to completion after 7 h, but oxidative side reactions with the diamine lowered the yield considerably (entry 7).

To prepare benzimidazole derivatives for Suzuki–Miyaura cross-couplings, boronates are usually incorporated by electrophilic borylation with a trialkyl borate,[10] or by metal-catalyzed borylation with a diboron reagent.[11] Both methods suffer from functional group tolerance issues, limiting the complexity that can be incorporated. The method shown herein is unique in that it obviates the need for such subsequent functionalization, allowing a more convergent synthesis.

The benzimidazole-containing trifluoroborates so obtained were then subjected to cross-coupling conditions. Using a modified version of the conditions that were previously developed for the cross-coupling of

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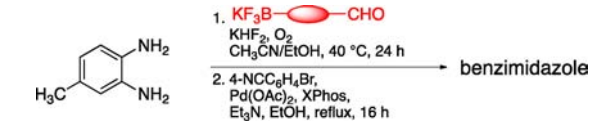
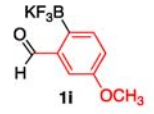
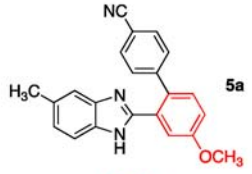
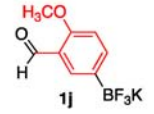
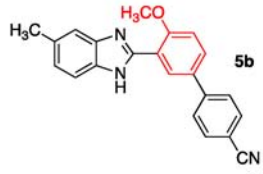
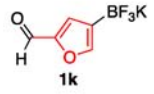
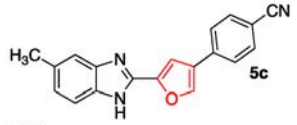
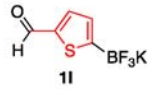
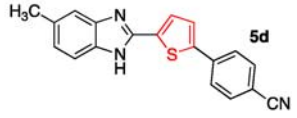
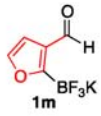
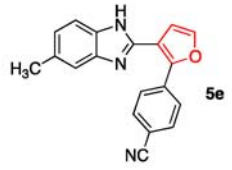
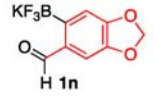
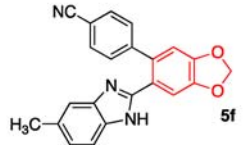
Table 4. Sequential Oxidative Condensation/Cross-Coupling of Formyl-Substituted Potassium Aryl- and Heteroaryltrifluoroborates



entry	aldehyde	benzimidazole	% overall yield
1			41
2			52
3			69
4			66
5			55
6			44

heteroaryltrifluoroborates with heteroaryl halides,[12] we were able to couple unprotected benzimidazole derivatives with organic halides (Table 3). Electron-rich aryl (entries 1 and 3), electron-poor aryl (entries 2 and 4), and heteroaryl halides (entries 3 and 6) underwent cross-coupling in good to excellent yields.

Finally, we thought it would be advantageous to be able to carry out the oxidative condensation and the cross-coupling reactions without having to isolate any intermediates, especially in cases where an analytically pure intermediate is difficult to obtain. The described sequence is shown in Table 4. Operationally, after the oxidative condensation was carried out to generate the benzimidazole, the crude reaction mixture was concentrated and triturated with Et_2O to remove most of the organic by-products. The cross-coupling was then effected directly on the crude organotrifluoroborate by the addition of the aryl halide and catalyst system. In this manner, one can quickly obtain pharmaceutically relevant,[5] elaborated benzimidazoles from electron-rich aromatic aldehydes (entries 1, 2, and 6) and heteroaryl aldehydes (entries 3–6) in good overall yields.

In conclusion, a series of 2-substituted potassium (1*H*)-benzimidazoletrifluoroborates were prepared by condensation of the corresponding aldehyde with aromatic 1,2-diamines under oxidative conditions. When followed with functionalization methods such as Suzuki–Miyaura coupling, the power of the trifluoroborate group in enabling the synthesis of libraries of complex molecules is particularly evident.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.