Published in final edited form as:

Org Lett. 2012 August 17; 14(16): 4242–4245. doi:10.1021/ol301956p.

Oxidative Condensations to Form Benzimidazole-Substituted Potassium Organotrifluoroborates

Gary A. Molander* and Kehinde Ajayi

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

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 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),

gmolandr@sas.upenn.edu.

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

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 1H-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.

(1)

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 reagents⁹ 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.

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 $-20^\circ C$. 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 1H 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 hours (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 bezimidazole 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 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 Et₂O to remove most of the organic byproducts. The cross-coupling was then effected directly on the crude organotrifluoroborate by the addition of the aryl halide and catalyst system. In this way, 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 (1H)-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge Lauren Kennedy (University of Pennsylvania) for the preparation of some starting materials. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for obtaining HRMS data. We thank Frontier Scientific for providing the boronic acids that were utilized to prepare the organotrifluoroborates, and we are grateful to Johnson-Matthey for providing the palladium catalysts. This work was supported by the NIH (R01 GM081376), to whom we are also grateful.

References

1. Recent reviews: Suzuki A. *Angew Chem Int Ed.* 2011; 50:6722–6737.(b) Wu, X-F., Anbarasan, P., Neumann, H., Beller, M.
2. Hall, DG. *Boronic Acids*. Hall, DG., editor. Vol. Chapter 1. Wiley-VCH Verlag GmbH & Co, KGaA; Weinheim, Baden-Württemberg: 2005. p. 1-85.
3. (a) Molander GA, Ham J. *Org Lett.* 2006; 8:2767–2770. [PubMed: 16774252] (b) Molander GA, Ellis N. *Acc Chem Res.* 2007; 40:275–286. [PubMed: 17256882] (c) Molander GA, Cooper DJ. *J Org Chem.* 2007; 72:3558–3560. [PubMed: 17408287] (d) Molander GA, Cooper DJ. *J Org Chem.* 2008; 73:3885–3891. [PubMed: 18412389] (e) Molander GA, Febo-Ayala W, Jean-Gerard L. *Org Lett.* 2009; 11:3830–3833. [PubMed: 19708697] (f) Kim DS, Ham J. *Org Lett.* 2010; 12:1092–1095. [PubMed: 20148521] (g) Bolla K, Kim T, Song JH, Lee S, Ham J. *Tetrahedron.* 2011; 67:5556–5563.
4. (a) Welsch ME, Snyder SA, Stockwell BR. *Curr Opin Chem Biol.* 2010; 14:1–15. [PubMed: 20022288] (b) DeSimone RW, Currie KS, Mitchell SA, Darrow JW, Pippin DA. *Comb Chem High T Scr.* 2004; 7:473–493.
5. Biologically active 2-aryl-(1H)-benzimidazoles: Wang P, Zheng G-j, Wang Y-p, Wei H-g, Xiang W-s. *Tetrahedron.* 2012; 68:2509–2512. Dasari M, Lee S, Sy J, Kim D, Lee S, Brown M, Davis M, Murthy N. *Org Lett.* 2010; 12:3300–3303. [PubMed: 20597468] Simard JR, Grutter C, Pawar V, Aust B, Wolf A, Rabiller M, Wulfert S, Robubi A, Kluter S, Ottmann C, Rauh D. *J Am Chem Soc.* 2009; 131:18478–18488. [PubMed: 19950957] Rodriguez-Rodriguez C, Sanchez de Groot N, Rimola A, Alvarez-Larena A, Lloveras V, Vidal-Gancedo J, Ventura S, Vendrell J, Sodupe M, Gonzalez-Duarte P. *J Am Chem Soc.* 2009; 131:1436–1451. [PubMed: 19133767] Charton J, Girault-Mizzi S, Debreu-Fontaine M-A, Foulfelle F, Hainault I, Bizot-Espiard J-G, Caignard D-H, Sergheraert C. *Bioorg Med Chem.* 2006; 14:4490–4518. [PubMed: 16513356] Ismail MA, Batista-Parra A, Miao Y, Wilson WD, Wenzler T, Brun R, Boykin DW. *Bioorg Med Chem.* 2005; 13:6718–6726. [PubMed: 16099661] Goker H, Boykin DW, Yildiz S. *Bioorg Med Chem.* 2005; 13:1707–1714. [PubMed: 15698788] Katz BA, Spencer JR, Elrod K, Luong C, Mackman RL, Rice M, Sprengeler PA, Allen D, Janc J. *J Am Chem Soc.* 2002; 124:11657–11668. [PubMed: 12296731]
6. Modern benzimidazole syntheses: Brasche G, Buchwald SL. *Angew Chem Int Ed.* 2008; 47:1932–1934. Chen YX, Qian LF, Zhang W, Han B. *Angew Chem Int Ed.* 2008; 47:9330–9333. Shen M, Driver TG. *Org Lett.* 2008; 10:3367–3370. [PubMed: 18597473] Sharghi H, Aberi M, Doroodmand MM. *Adv Synth Catal.* 2008; 350:2380–2390. Blacker AJ, Farah MM, Hall MI, Marsden SP, Saidi O, Williams MJ. *Org Lett.* 2009; 11:2039–2042. [PubMed: 19354284] Yamamoto Y, Mizuno H, Tsuritani T, Mase T. *J Org Chem.* 2009; 74:1394–1396. [PubMed: 19178358] Deng X, McAllister H, Mani NS. *J Org Chem.* 2009; 74:5742–5745. [PubMed: 19527012] Diao X, Wang Y, Jiang Y, Ma D. *J Org Chem.* 2009; 74:7974–7977. [PubMed: 19775088] Xiao Q, Wang WH, Liu G, Meng FK, Chen JH, Yang Z, Shi ZJ. *Chem Eur J.* 2009; 15:7292–7296. [PubMed: 19551776] Shiraishi Y, Sugano Y, Tanaka S, Hirai T. *Angew Chem Int Ed.* 2010; 49:1656–1660. Kim Y, Kumar MR, Park N, Heo Y, Lee S. *J Org Chem.* 2011; 76:9577–9583. [PubMed: 22034860] Fu S, Jiang H, Deng Y, Zeng W. *Adv Synth Catal.* 2011; 353:2795–2804.
7. Smith JG, Ho I. *Tetrahedron Lett.* 1971; 12:3541–3544.
8. (a) Lin C, Lai PT, Liao SKS, Hung WT, Yang WB, Fang JM. *J Org Chem.* 2008; 73:3848–3853. [PubMed: 18422361] (b) Bahrami K, Khodaei MM, Naali F. *J Org Chem.* 2008; 73:6835–6837. [PubMed: 18652508] (c) Henary MM, Wu Y, Cody J, Sumalekshmy S, Li J, Mandal S, Fahrni CJ. *J Org Chem.* 2007; 72:4784–4797. [PubMed: 17523666] (d) Aakeroy CB, Fasulo M, Schultheiss N, Desper J, Moore C. *J Am Chem Soc.* 2007; 129:13772–13773. [PubMed: 17956090] (e) Singh MP, Sasmal S, Lu W, Chatterjee MN. *Synthesis.* 2000:1380–1390.
9. (a) Ridley HF, Spickett RGW, Timmis GM. *J Heterocyclic Chem.* 1965; 2:453–456. (b) Arienti KL, Brumark A, Axe FU, McClure K, Lee A, Blevitt J, Neff DK, Huang L, Crawford S, Pandit CR, Karlsson L, Breitenbucher JG. *J Med Chem.* 2005; 48:1873–1885. [PubMed: 15771432]
10. Blatch AJ, Chetina OV, Howard JAK, Patrick LGF, Smethurst CA, Whiting A. *Org Biomol Chem.* 2006; 4:3297–3302. [PubMed: 17036118]
11. Wu CH, Chien CH, Hsu FM, Shih PI, Shu CF. *J Mater Chem.* 2009; 19:1464–1470.

12. Molander GA, Canturk B, Kennedy LE. J Org Chem. 2009; 74:973–980. [PubMed: 19105735]

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

Table 2

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

$ \begin{array}{c} \text{OHC}-\text{C}_6\text{H}_4-\text{BF}_3\text{K} + \text{diamine} \xrightarrow[\text{CH}_3\text{CN/EtOH (1:2)}]{\text{KHF}_2 (10 \text{ mol } \%), \text{O}_2 (1 \text{ atm})} \text{benzimidazole} \\ \text{40 to 60 } ^\circ\text{C} \end{array} $				
entry	aldehyde	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

^aYield determined by ¹H NMR.

Table 3

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

$\text{(Het)Ar}^1\text{-Br} + \text{(Het)Ar}^2\text{-BF}_3\text{K} \xrightarrow[\text{EtOH, 85 } ^\circ\text{C}]{\text{Pd(OAc)}_2 \text{ (5 mol \%), XPhos (10 mol \%), Et}_3\text{N (2 equiv)}} \text{(Het)Ar}^1\text{—(Het)Ar}^2$			
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

Table 4

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

entry	aldehyde	benzimidazole	% overall yield
1	1i	5a	41
2	1j	5b	52
3	1k	5c	69
4	1l	5d	66
5	1m	5e	55
7	1n	5f	44