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Condensation Reactions To Form Oxazoline-Substituted Potassium Organotrifluoroborates

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ABSTRACT

A library of oxazoline-substituted potassium organotrifluoroborates was prepared via the condensation of various potassium formyl-substituted aryl- and heteroaryltrifluoroborates with tosylmethyl isocyanide under basic conditions. The efficient Suzuki−Miyaura cross-coupling of products thus formed to various aryl bromides was achieved in good yields. The method allows the facile preparation of oxazole-containing triaromatic products in two steps from simple potassium formyl-substituted aryl- or heteroaryltrifluoroborates.

Oxazolines are important intermediates used in the synthesis of bioactive compounds (e.g., β-hydroxy-α-amino acids), amino alcohols, hydroxy amides, imidazoles, and oxazoles, among others.[1] Oxazolines also find applications as chiral ligands in a wide range of asymmetric catalytic processes.[1] 4,5-Disubstituted oxazolines are of interest because they are found in marine alkaloids, such as ulicyclamide (Figure 1), which possess high bioactivity. Relatively few methods have been reported for their preparation.[2,3]

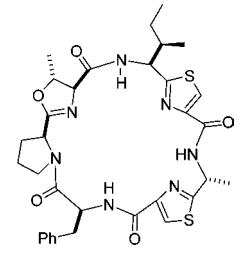

Figure 1. Ulicyclamide.

Potassium organotrifluoroborates are tetracoordinate boron species that are effortlessly prepared by adding inexpensive aqueous KHF_2 to tricoordinate organoboron intermediates. They are crystalline solids that are easily purified by precipitation or crystallization. The lack of an empty *p*-orbital on boron makes them very stable, yet they are effective nucleophiles when used in reactions such as Suzuki−Miyaura cross-couplings. Until recently, the number of potassium organotrifluoroborate structures that contain heterocycles has been limited.[4−6] Currently, the available potassium organ-

(1) Wong, G. S. K.; Wu, W. *2-Oxazolines. In The Chemistry of Heterocyclic Compounds*; Palmer, D. C., Eds.; Oxazoles: Synthesis, Reactions and Spectroscopy, Part B; John Wiley: Hoboken, 2004; Vol. *60*, pp 331−513.

(2) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115–2134.

(3) (a) Hayashi, T.; Uozumi, Y.; Yamazaki, A. *Tetrahedron Lett.* **1991**, *32*, 2799–2802. (b) Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2713–2716. (c) Le Merrer, Y.; Gravier-Pelletier, C.; Gerrouache, M.; Depezay, J.-C. *Tetrahedron Lett.* **1998**, *39*, 385–388. (d) Benito-Garagorri, D.; Bocokiæ, V.; Kirchner, K. *Tetrahedron Lett.* **2006**, *47*, 8641–8644. (e) Shinada, T.; Ikebe, E.; Oe, K.; Namba, K.; Kawasaki, M.; Ohfune, Y. *Org. Lett.* **2007**, *9*, 1765–1767. (f) Gosiewska, S.; Herreras Martínez, S.; Lutz, M.; Spek, A. L.; van Koten, G.; Klein Gebbink, R. J. M. *Eur. J. Inorg. Chem.* **2006**, 4600–4607. (g) Reetz, M. T.; Wünsch, T.; Harms, K. *Tetrahedron Lett.* **1989**, *30*, 3877–3880. (h) Ortuno, J.-C.; Langlois, Y. *Tetrahedron Lett.* **1991**, *32*, 4491–4494.

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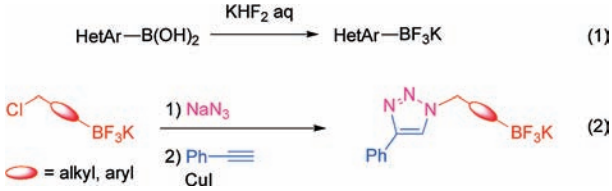
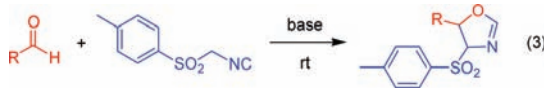
otrifluoroborate-containing heterocycles have been synthesized using two different strategies. The first involves the addition of aqueous KHF_2 to commercially available boronic acids (eq 1).[5] The second strategy allows the assembly of the heterocycles from intermediates that already incorporate the potassium organotrifluoroborate moiety. For example, the synthesis of organo[1,2,3]triazol-1-yltrifluoroborates was achieved from the copper-catalyzed 1,3-dipolar cycloaddition of azidoalkyltrifluoroborates with alkynes (eq 2).[6] The latter approach allows the preparation of complex heterocycles from readily available components.



Herein, we report the use of the second tactic in the first preparation of oxazoline-containing organotrifluoroborates from the condensation of formyl-substituted aryl- and heteroaryltrifluoroborates with tosylmethyl isocyanide (TosMIC). This approach fulfills a goal of our program to expand the versatility of potassium organotrifluoroborates by incorporating nitrogen-, oxygen-, and sulfur-containing rings in their substructures, taking advantage of the relative resistance of the trifluoroborate moiety to a variety of reaction conditions that are not tolerated by the corresponding boronic acids.

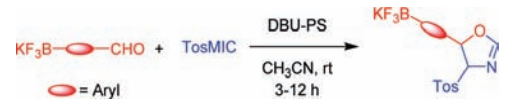
van Leusen et al. were the first to report the one-pot preparation of oxazolines from the condensation between tosylmethyl isocyanide and an aldehyde under basic conditions.[7] In addition, oxazoles were obtained upon elimination of the toluenesulfonyl group under basic conditions at high temperatures. In this report, a series of 4,5-disubstituted trifluoroborato-containing oxazolines were prepared following van Leusen's method (eq 3).

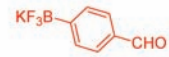
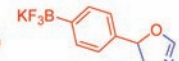
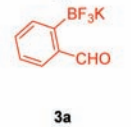
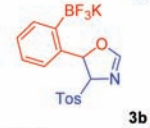
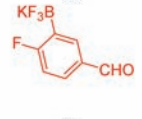
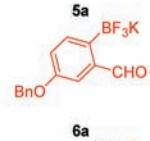
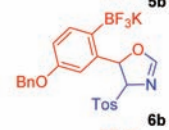
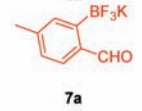
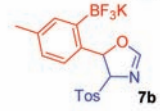
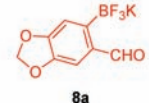
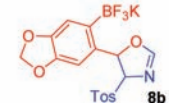


After exploring various reaction conditions, it was determined that the condensation of different formyl-substituted aryl- and heteroaryltrifluoroborates with TosMIC was best achieved in the presence of equimolar amounts of DBU in acetonitrile at rt.[8,9] Commercially available polystyrene-bound DBU (DBU-PS) was used because it could be conveniently removed from the product via filtration and reused indefinitely (>10 times) after washing with methanolic NaOH without lowering the yield.[10] For example, **11b** was prepared in 89% yield with brand new resin and in 82% yield with resin that had been recycled once. Also, **9b** was prepared in 73% yield with brand new resin and in 89% yield with resin that was used and washed approximately five times as described above. The optimal solution concentration was found to be 0.5 M. Lower concentrations required a longer reaction time, while 1 M reactions resulted in a thick slurry that was inefficiently stirred.

With the optimized conditions in hand, we reacted different potassium formyl aryltrifluoroborates (Table 1). The substitu-

Table 1. Aryl-Substituted Oxazolines[a]



entry	aldehyde	oxazoline	reaction time (h)	isolated yield (%)
1	 **1a**	 **1b**	6	84
2	 **2a**	 **2b**	6	97
3	 **3a**	 **3b**	6	83
4	 **4a**	 **4b**	3	94
5	 **5a**	 **5b**	4.5	56
6	 **6a**	 **6b**	3	76
7	 **7a**	 **7b**	4.5	88
8	 **8a**	 **8b**	12	90

[a] Reaction conditions: aldehyde (1 equiv), TosMIC (1 equiv), DBU-PS (1 equiv), CH_3CN (0.5 M), rt.

(4) (a) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288–325. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.

(5) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973–980, and references cited therein.

(6) Molander, G. A.; Ham, J *Org. Lett.* **2006**, *8*, 2767–2770.

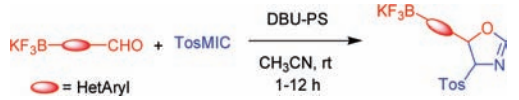
(7) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369–2372.

(8) DBU stands for 1,8-diazabicyclo[5.4.0]undec-7-ene.

(9) Other bases and reagents screened included K_2CO_3, KO*t*-Bu, NEt_3, DIPEA, guanidine, DABCO, and KCN. Other solvents tested were methanol, ethanol, DME, and DMSO, but they resulted in very impure product.

(10) Tomoi, M.; Kato, Y.; Kakiuchi, H. *Makromol. Chem.* **1984**, *185*, 2117–2124.

Table 2. Heteroaryl-Substituted Oxazolines[a]



entry	aldehyde	oxazoline	reaction time (h)	isolated yield (%)
1	9a	9b	12	89
2	10a	10b	12	84
3	11a	11b	1	89
4	12a	12b	12	94
5	13a	13b	12	75
6	14a	14b	12	82
7	15a	15b	12	75

[a] Reaction conditions: aldehyde (1 equiv), TosMIC (1 equiv), DBU-PS (1 equiv), CH_3CN (0.5 M), rt.

tion of the trifluoroborate moiety in the *ortho* (**3a**), *meta* (**2a**) or *para* (**1a**) position of the aryl ring did not significantly affect the product yield. However, the *meta*-substituted substrate gave the best yield (97%). Electron-withdrawing (**4a**) and electron-donating (**5a**) groups *para* to the aldehyde did seem to have an effect, giving higher yields for the former (94%) than the latter (56%). Also, benzyloxy (**6a**), methyl (**7a**), and methylenedioxy (**8a**) substitutions were well tolerated (Table 1).

Next, we extended the developed conditions to potassium formyl-substituted heteroaryltrifluoroborates (Table 2). The reaction time increased significantly for most cases when compared to the aryltrifluoroborates. The 3-, 4-, and 5-formylfuran-2-trifluoroborates (**10a**, **9a**, **11a**), 5- and 4-formyl-2-thiophenetrifluoroborates (**12a**, **15a**), 4-formyl-3-thiophenetrifluoroborate (**13a**), and 5-formyl-3-methylthiophene-2-trifluoroborate (**14a**) were efficiently reacted in good to excellent yields.

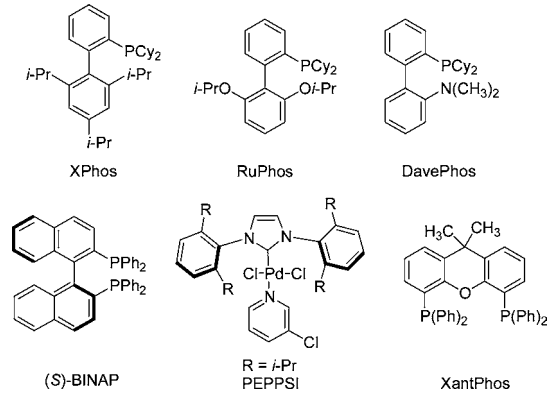


Figure 2. Ligands used in the optimization of the Suzuki−Miyaura coupling.

There have been few reports concerning direct incorporation of boron into oxazolines and oxazoles. To the best of our knowledge, only one oxazoleboronic acid has been prepared and cross-coupled.[11] The lack of oxazoline and oxazole substructures possessing boron-based functional groups might be attributed to the fact that these heterocycles may not be able to withstand the conditions that are used to install the boronic acid group.[1] Furthermore, oxazoleboronic acids may be unstable to protodeboronation, as are other heteroarylboronic acids.[5,11,12] The method described herein serves as a means to prepare oxazolines from components that already incorporate the more robust potassium organotrifluoroborate, circumventing the harsh conditions normally used to install the boronic acid.

A few Suzuki−Miyaura cross-couplings involving oxazoles have been reported. In the vast majority of cases, the oxazole is used as the electrophile. In one example, an oxazole boronate ester was employed, and in a second example an oxazoleboronic acid was utilized as a nucleophilic partner.[11,13,14]

In attempts to carry out the Suzuki−Miyaura cross-coupling of the synthesized oxazoline-incorporated organotrifluoroborates described herein, a variety of catalyst/ligand combinations (Figure 2), solvents, and bases were screened to maximize the yields.[15] None of the conditions tried maintained the integrity of the sulfonyl group. The use of a base and high temperatures typically required for the reaction generated oxazoles instead. We successfully achieved the Suzuki−Miyaura cross-coupling of the oxazolinyl-substituted aryltrifluoroborates to various electrophiles using 1 mol % of $Pd(OAc)_2$/2 mol % of DavePhos

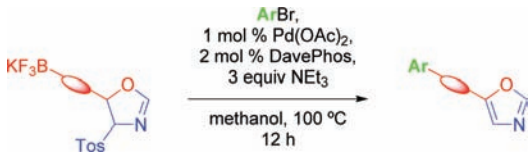
(11) (a) Ferrer Flegeau, E.; Popkin, M. E.; Greaney, M. F. *J. Org. Chem.* **2008**, *73*, 3303–3306. (b) Araki, H.; Katoh, T.; Inoue, M. *Tetrahedron Lett.* **2007**, *48*, 3713–3717. (c) Inoue, M. *Mini-Rev. Org. Chem* **2008**, *5*, 77–84, and references cited therein.

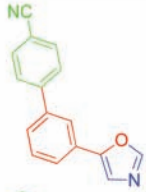
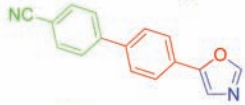
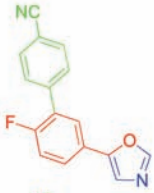
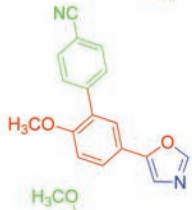
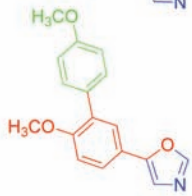
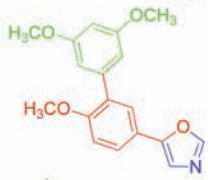
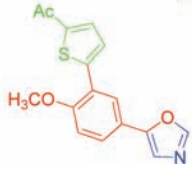
(12) (a) Tyrell, E.; Brookes, P. *Synthesis* **2003**, 469–483. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

(13) For Suzuki−Miyaura cross-couplings of 4,5-disubstituted oxazoles see: (a) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905–2907. (b) Vachal, P.; Toth, L. M. *Tetrahedron Lett.* **2004**, *45*, 7157–7161. (c) Ferrer Flegeau, E.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495–2498. (d) Li, B.; Buzon, R. A.; Zhang, Z. *Org. Proc. Res. Dev.* **2007**, *11*, 951–955, and references cited therein.

(14) Araki, H.; Katoh, T.; Inoue, M. *Synlett* **2006**, *4*, 555–558.

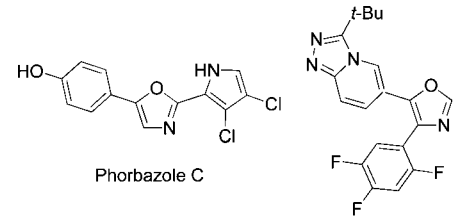
Table 3. Cross-Coupling of Various Potassium Organotrifluoroborates with Various Electrophiles[a]



entry	RBF_3K	Product		isolated yield (%)
1	**2b**		**16**	73[b]
2	**1b**		**17**	68
3	**4b**		**18**	55
4	**5b**		**19**	51
5	**5b**		**20**	51
6	**5b**		**21**	47
7	**5b**		**22**	44

[a] All reactions, unless specified, were carried out using 0.25 mmol of ArBr and 0.28 mmol of RBF_3K. [b] Reaction performed on a 1.0 mmol scale.

and triethylamine as the base in refluxing methanol. Aromatic-containing trifluoroborates cross-coupled in satisfactory yields with electron-poor and electron-rich aryl bromides, and a heteroaryl bromide could be utilized in the process as well (Table 3). Difficulties were encountered with the cross-coupling



3-*tert*-Butyl-6-(4-(2,4,5-trifluorophenyl)oxazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine

Figure 3. Medicinal chemistry targets.

of heteroaryl-containing trifluoroborates, and further optimization may be needed to obtain the desired cross-coupled product in acceptable yields.

Oxazole-containing biaryl structures are well-represented in natural products. Furthermore, oxazoles with substitution at the C-4 and C-5 positions are becoming increasingly important in pharmaceuticals for their therapeutic potential in inflammation, cancer, and asthma.[13d] The one-pot Suzuki−Miyaura cross-coupling/elimination process described herein could be used as an efficient synthetic approach toward the preparation of pharmaceutical targets (Figure 3).[13d,16]

In summary, a series of 4,5-disubstituted potassium oxazolinetrifluoroborates were prepared via the condensation of the corresponding aldehydes with TosMIC under basic conditions. The Suzuki−Miyaura cross-coupling of the oxazolines was successfully achieved in good yields under the optimized conditions. The method presented here allows the facile preparation of oxazole-containing biaryl products in two steps from simple potassium formyl-substituted aryl- or heteroaryltrifluoroborates.

Acknowledgment. We thank Dr. Ángel I. Morales-Ramos (Vitae Pharmaceuticals, Fort Washington, PA) for valuable scientific discussions. Dr. Ruth Figueroa, Jason E. Melvin, and Dr. David Cooper (University of Pennsylvania) are acknowledged for the preparation of some starting materials. Frontier Scientific is acknowledged for their kind donation of boronic acids. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for obtaining HRMS data. This work was supported by the NIH (GM086209, GM035249), to whom we are grateful.

Supporting Information Available: Experimental procedures, compound characterization data, and NMR spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901395C

(15) The variables optimized included: catalyst/ligands [$Pd(OAc)_2$, $Pd(OAc)_2$/SPhos, $Pd(OAc)_2$/XPhos, $Pd(OAc)_2$/RuPhos, $Pd(OAc)_2$/DavePhos, $Pd(OAc)_2$/(*S*)-BINAP/PEPPSI, $Pd(OAc)_2$/XantPhos, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(dppf)Cl_2$], catalyst/ligand mol % [0.5/1, 1/2, 2/4, 3/6, 5/10], solvents [MeOH, dioxane/H_2O, EtOH, toluene/H_2O, DMF/H_2O, 2-MeTHF/H_2O], and bases [K_2CO_3, Cs_2CO_3, NEt_3, DIPEA, DABCO, Na_2CO_3].

(16) Rudi, A.; Stein, Z.; Green, S.; Goldberg, I.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *Tetrahedron Lett.* **1994**, *35*, 2589–2592.