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Synthesis of Functionalized Organotrifluoroborates via the 1,3-Dipolar Cycloaddition of Azides

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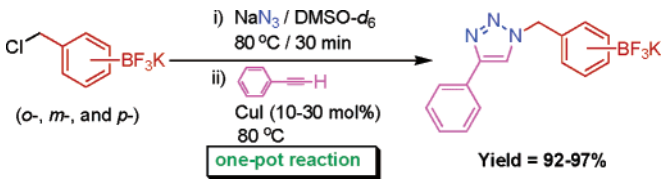
ABSTRACT



We have successfully prepared potassium azidoalkyltrifluoroborates from the corresponding halogen compounds in 94–98% yields through a nucleophilic substitution reaction with NaN_3. In the presence of various alkynes and Cu(I) as a catalyst, these azidotrifluoroborates easily formed 1,4-disubstituted organo-[1,2,3]-triazol-1-yl-trifluoroborates in 85–98% yields. This method was then developed into a facile one-pot synthesis for the preparation of various organo-[1,2,3]-triazol-1-yl-trifluoroborates using haloalkyltrifluoroborates as the starting materials.

Organotrifluoroborates[1] have recently attracted considerable interest as synthetic intermediates for Suzuki−Miyaura-type cross-coupling reactions,[1a,2] rhodium-catalyzed 1,4-addition reactions,[3] and allylations of aldehydes[4] and *N*-toluenesulfonylimines.[5] Moreover, potassium organotrifluoroborate salts are easily prepared by the addition of inexpensive KHF_2 to various organoboron intermediates.[6] These substrates are air- and moisture-stable crystalline solids that are readily isolated.[1,6] However, despite the advantages and potential applications of potassium organotrifluoroborates, to date they are still prepared from commercially available boronic acids or via transmetalation,[1] hydroboration,[1,7] or C−H activation.[8] Therefore, new methods to prepare highly functionalized potassium organotrifluoroborates are of great synthetic interest.

As part of a study to prepare functionalized potassium organotrifluoroborates through nucleophilic substitution reactions of potassium halomethyltrifluoroborates (XCH_2BF_3K),[9] we were pleased to discover that azide-containing potassium organotrifluoroborates are readily obtained in good yield from the treatment of bromo- or iodomethyltrifluoroborate with NaN_3. In the presence of various alkynes and a Cu(I) catalyst, azide-containing potassium organotrifluoroborates

(1) For reviews of organotrifluoroborate salts, see: (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49−56. (b) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313−4327.

(2) (a) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950−3956. (b) Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75−78. (c) Cella, R.; Cunha, R. L. O. R.; Reis, A. E. S.; Pimenta, D. C.; Klitzke, C. F.; Stefani, H. A. *J. Org. Chem.* **2006**, *71*, 244−250. (d) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563−1568. (e) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493−2498.

(3) (a) Batey, R. A.; Thadani, A. N. *Org. Lett.* **1999**, *1*, 1683−1686. (b) Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155−6157. (c) Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2002**, 3552−3557. (d) Navarre, L.; Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **2005**, *46*, 4247−4250.

(4) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289−4292. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Synthesis* **2000**, 990−998. (c) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827−3830. (d) Thadani, A. N.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 8051−8055.

(5) (a) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, *12*, 1382−1383. (b) Solin, N.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2005**, *7*, 685−688.

(6) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027. (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460−2470.

(7) Clay, J. M.; Vedejs, E. *J. Am. Chem. Soc.* **2005**, *127*, 5766−5767.

(8) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 15334−15335.

(9) Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2031−2034.

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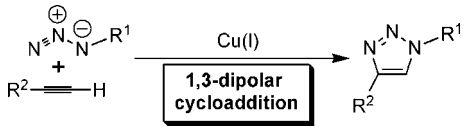
could be used to generate the corresponding triazole products through a 1,3-dipolar cycloaddition reaction ("click reaction").[10]

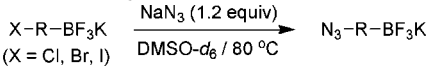


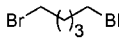
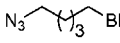
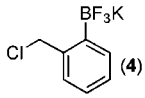
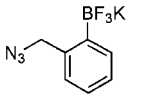
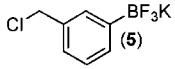
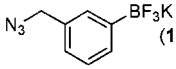
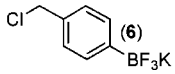
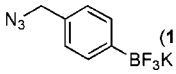
Thus, the 1,3-dipolar cycloaddition reaction of azides would produce a variety of [1,2,3]-triazole-containing potassium organotrifluoroborates which could be employed in organic synthesis, medicinal chemistry, and materials science.[11]

Herein, we report a novel and convenient preparation of potassium azidoalkyltrifluoroborates in good yields via the direct nucleophilic substitution of the corresponding haloalkyltrifluoroborates with NaN_3, followed by a facile and regioselective synthesis of potassium organo-[1,2,3]-triazol-1-yl-trifluoroborates with various alkynes using Cu(I) as a catalyst under mild reaction conditions.

It was first necessary to determine the reactivity of potassium haloalkyltrifluoroborates with NaN_3, as well as the stability of the resulting azide compounds under the reaction and purification conditions prior to development of a one-pot cycloaddition sequence (Table 1).

Table 1. Preparation of Potassium Azidoalkyltrifluoroborates from Potassium Haloalkyltrifluoroborates[a]



entry	X−R−BF_3K	reaction time (h)	product	yield (%)[b]
1	$BrCH_2BF_3K$ (**1**)	8	$N_3CH_2BF_3K$ (**7**)	95
2	ICH_2BF_3K (**2**)	5	$N_3CH_2BF_3K$	94
3	 (**3**)	1	 (**8**)	96
4	 (**4**)	0.5	 (**9**)	96
5	 (**5**)	0.5	 (**10**)	96
6	 (**6**)	0.5	 (**11**)	98

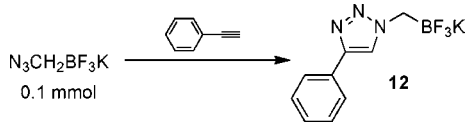
[a] All reactions were performed on a 0.1 mmol scale in 500 μL of DMSO-d_6. [b] Yields are given for isolated products.

Potassium azidoalkyltrifluoroborates were readily prepared from the corresponding halogen compounds and NaN_3 at 80 °C. To determine the exact reaction time, all reactions were performed in an NMR tube using DMSO-d_6 (500 μL) as the solvent. After the reaction was complete, the solvent was removed under high vacuum at 60−70 °C. The pure azides were obtained in 94−98% yields by recrystallization.

Interestingly, 5-bromopentyltrifluoroborate, as well as 1-, 2-, and 3-(chloromethyl)phenyltrifluoroborates (Table 1, entries 3−6), had shorter reaction times than bromo- or iodomethyltrifluoroborate (Table 1, entries 1 and 2) under the same conditions.

Using the potassium azidoalkyltrifluoroborates generated according to the method illustrated in Table 1, we next attempted the click reaction of phenylacetylene and potassium azidomethyltrifluoroborate (Table 2).

Table 2. Optimization of Reaction Conditions for the Synthesis of **12**



entry	catalyst (10 mol %)	solvent[a]	temp (°C)	reaction time (h)	conversion (%)[b]
1	Cu powder	DMSO-d_6	80	48	67
2	CuCN	DMSO-d_6	80	3	100 (84)[c]
3	CuBr	DMSO-d_6	80	1.5	100 (88)[c]
4	Cu(I)	DMSO-d_6	80	1	100 (90)[c]
5	Cu(I)	DMSO-d_6	rt	48	82
6[d]	Cu(I)	DMSO-d_6	80	3	100 (87)[c]
7	Cu(I)	D_2O	80	24	trace
8	Cu(I)	CD_3CN	75	24	trace
9[e]	Cu(I)	CD_3CN	75	2	trace
10	Cu(I)	THF-d_8	65	2	no reaction
11	Cu(I)	CD_3OD	65	2	no reaction

[a] All reactions were performed in 500 μL of solvent. [b] Percentage conversion was calculated by ^{1}H NMR. [c] Isolated yields. [d] 5 mol % of Cu(I) was used. [e] Pyridine-d_5 (10 mol %) was added as a nitrogen-containing ligand to solubilize Cu(I).

A number of different Cu catalysts were screened for their effectiveness in promoting the cycloaddition reaction (Table 2, entries 1−4). Although all of the catalysts generated the target compound **12** under the standard reaction conditions, Cu(I) provided the fastest reaction time and the highest isolated yield. By decreasing the catalyst loading from 10 mol % to 5 mol % (Table 2, entries 4 and 6), reaction times were slightly increased. Changes in reaction temperature had a much greater impact on reaction rates. When the reaction

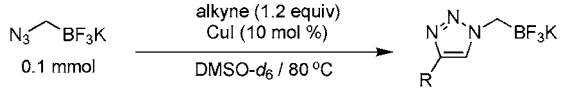
(10) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 1, pp 1−176. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 1069−1109. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−910. (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (e) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (f) Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064.

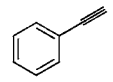
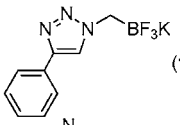
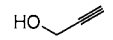
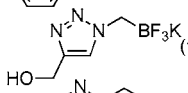
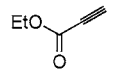
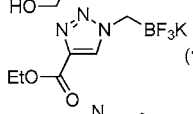
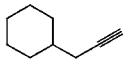
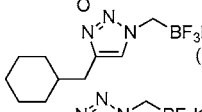
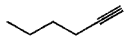
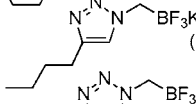
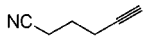
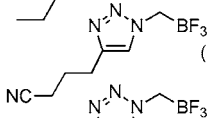
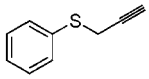
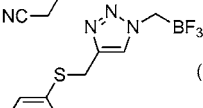
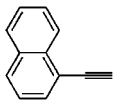
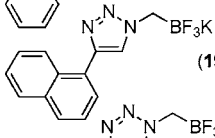
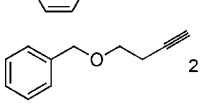
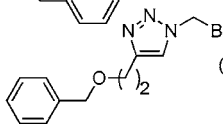
(11) Recent examples: (a) Li, H.; Cheng, F.; Duft, A. M.; Adronov, A. *J. Am. Chem. Soc.* **2005**, *127*, 14518−14524. (b) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc.* **2006**, *128*, 1398−1399. (c) Beryozkina, T.; Appukkuttan, P.; Mont, N.; Van der Eycken, E. *Org. Lett.* **2006**, *8*, 487−490. (d) Srinivasan, R.; Uttamchandani, M.; Yao, S. Q. *Org. Lett.* **2006**, *8*, 713−716.

temperature was decreased from 80 °C to room temperature, the reaction time increased from 1 to 48 h (Table 2, entries 4 and 5). In addition, it was observed that D_2O, CD_3CN, THF-d_8, and CD_3OD were inferior solvents, leading to very low conversion by NMR. This is most likely due to poor solubility of the reactants and catalysts (Table 2, entries 7−11). On the other hand, when pyridine-d_5 (10 mol %) was added as a ligand to solubilize the Cu(I) under the same reaction conditions, no improvement of the reaction was observed after 2 h (Table 2, entry 9).

Using the optimized conditions of **12** as a model reaction, we were able to perform the 1,3-dipolar cycloaddition reaction of potassium azidomethyltrifluoroborate using various alkynes. The results are summarized in Table 3.

Table 3. Preparation of Potassium Organo-[1,2,3]-triazol-1-yl-trifluoroborates from Various Alkynes and Potassium Azidomethyltrifluoroborate



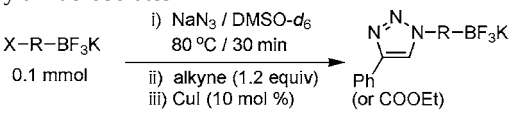
entry	alkyne	reaction time (h)	product	yield (%)[a]
1		1	 (**12**)	90
2		1	 (**13**)	85
3		1	 (**14**)	98
4		2	 (**15**)	94
5		3	 (**16**)	91
6		2	 (**17**)	97
7		1	 (**18**)	93
8[b]		7	 (**19**)	93
9		2	 (**20**)	89

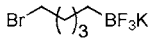
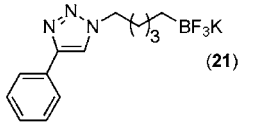
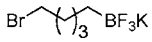
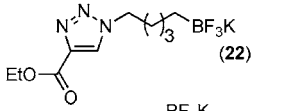
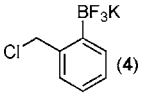
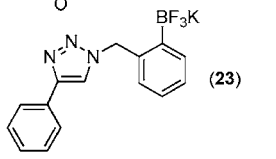
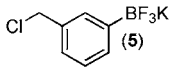
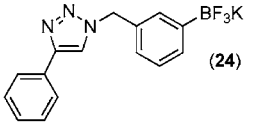
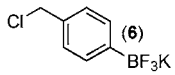
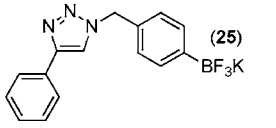
[a] Yields are given for isolated products. [b] Reaction was performed with 30 mol % of Cu(I).

All reactions were carried out in DMSO-d_6 with potassium azidomethyltrifluoroborate (0.1 mmol), 1.2 equiv of alkyne, and 10 mol % of Cu(I) at 80 °C in an NMR tube. After removing the solvent under high vacuum at 60−70 °C, the salt products were purified by recrystallization. The 1,4-disubstituted organo-[1,2,3]-triazol-1-yl-trifluoroborates were obtained in 85−98% yields. Interestingly, increasing the carbon chain length or steric hindrance of the alkyne resulted in prolonged reaction times (Table 3, entries 4−6, 8, and 9). When 1-ethynylnaphthalene (Table 3, entry 8) was used, the reaction proceeded slowly despite the use of 30 mol % of Cu(I).

Next, we turned our attention to the one-pot, multicomponent preparation of potassium organo-[1,2,3]-triazol-1-yl-trifluoroborates from the corresponding halogen salts (Table 4).

Table 4. One-Pot Synthesis of Potassium Organo-[1,2,3]-triazol-1-yl-trifluoroborates from Potassium Haloalkyltrifluoroborates



entry	X−R−BF_3K	reaction time (h)	product	yield (%)[a]
1	 (**3**)	4	 (**21**)	95
2		3	 (**22**)	93
3[b]	 (**4**)	6	 (**23**)	97
4	 (**5**)	4	 (**24**)	96[c]
5	 (**6**)	4	 (**25**)	92

[a] Yields are given for isolated products. [b] Reaction was performed with 30 mol % of Cu(I). [c] Product was obtained as a 9:1 mixture of regioisomers.

As previously shown, 5-bromopentyltrifluoroborate and 2-, 3-, and 4-(chloromethyl)phenyltrifluoroborates reacted efficiently when treated with NaN_3 in DMSO-d_6 at 80 °C. The resulting azido intermediates were smoothly transformed to the triazole products even though the 1,3-dipolar cycloaddition of these azide salts were slightly slower than that of azidomethyltrifluoroborate. The overall conversion of haloalkyltrifluoroborates to [1,2,3]-triazol-1-yl-trifluoroborates

was accomplished as a one-pot method by simply adding the Cu(I) catalyst and the alkyne substrate to the DMSO-d_6 solution once the S_N2 displacement of haloalkyltrifluoroborate with NaN_3 had reached completion as indicated by ^1H NMR.

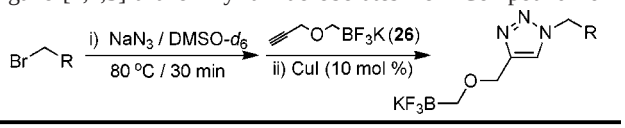
When ethyl propiolate was used, the reaction proceeded slightly faster than with phenylacetylene, and its product (**22**) was isolated in 93% yield (Table 4, entry 2). In the reaction of 2-, 3-, and 4-(chloromethyl)phenyltrifluoroborates, the use of 30 mol % of Cu(I) was required for obtaining good yields (Table 4, entry 3). Moreover, compound **24** was obtained as a 9:1 mixture of regioisomers (major isomer shown).

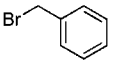
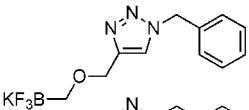
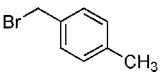
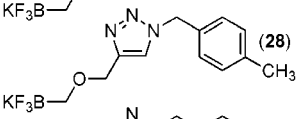
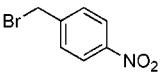
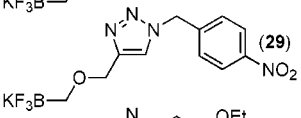
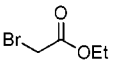
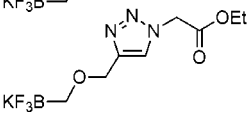
Finally, we investigated the one-pot reaction using potassium prop-2-ynyloxymethyltrifluoroborate (**26**) that was prepared from the nucleophilic substitution reaction with the corresponding sodium alkoxide and bromomethyltrifluoroborate (Table 5).[9]

As expected, all of the alkyl azides were quickly prepared from the corresponding bromides when treated with NaN_3 in DMSO-d_6 at 80 °C. Benzyl bromide and electron-poor 4-nitrobenzyl bromide reacted quickly with accompanying high yields (Table 5, entries 1 and 3). However, ethyl bromoacetate and electron-rich 4-methylbenzyl bromide required longer reaction times or 30 mol % of Cu(I) for the completion of these reactions (Table 5, entries 2 and 4). Unfortunately, when subjected to standard reaction conditions, the products (**28** and **30**) were obtained as a mixture containing approximately 10% of the 1,5-disubstituted triazole compound. Therefore, long reaction times in the 1,3-dipolar cycloaddition step appear to result in lower regioselectivity of the desired 1,4-disubstituted triazoles.

In summary, we have successfully prepared potassium azidoalkyltrifluoroborates from the corresponding halogen compounds in 94−98% yields through a nucleophilic substitution reaction with NaN_3. In the presence of various alkynes and Cu(I) as a catalyst, these azidotrifluoroborates easily formed 1,4-disubstituted organo-[1,2,3]-triazol-1-yltrifluoroborates in good yields. Moreover, we developed a facile synthetic method for the preparation of novel, functionalized potassium organo-[1,2,3]-triazol-1-yl- and organo-[1,2,3]-triazol-4-yl-trifluoroborates through a one-pot reaction using 5-bromopentyltrifluoroborate (**3**), 2-, 3-, and 4-(chloromethyl)phenyltrifluoroborates (**4**−**6**), and prop-2-ynyloxymethyltrifluoroborate (**26**) as the starting materials. These organotrifluoroborates would appear to be very useful precursors for the Suzuki−Miyaura-type cross-coupling reaction. Further applications using these compounds are currently in progress and will be reported in due course.

Table 5. One-Pot Synthesis of Potassium Organo-[1,2,3]-triazol-4-yl-trifluoroborates from Compound **26**



entry	XCH_2R	reaction time (h)	product	yield (%)[a]
1		2	 (**27**)	93
2[b]		8	 (**28**)	91[c]
3		3	 (**29**)	87
4[b]		18	 (**30**)	94[c]

[a] Yields are given for isolated products. [b] Reaction was performed with 30 mol % of Cu(I). [c] Products were obtained as a 9:1 mixture of regioisomers.

Acknowledgment. This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005−214-C00170). We thank the National Institutes of Health (GM35249), Merck Research Laboratories, and Amgen for their generous support.

Supporting Information Available: Experimental procedures, spectral characterization, and copies of ^1H, ^{13}C, ^{19}F, and ^{11}B NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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