ORGANIC LETTERS

2006
Vol. 8, No. 10
2031−2034

Synthesis of Functionalized Organotrifluoroborates via Halomethyltrifluoroborates

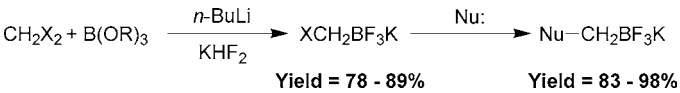
Gary A. Molander* and Jungyeob Ham

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

gmolandr@sas.upenn.edu

Received February 13, 2006

ABSTRACT



Potassium bromo- and iodomethyltrifluoroborates have been prepared via in situ reaction of *n*-BuLi with dibromo- and diiodomethane, respectively, in the presence of trialkyl borates, followed by treatment with KHF_2. Moreover, a new synthetic method for the preparation of potassium organotrifluoroborates through nucleophilic substitution of the halide in these potassium halomethyltrifluoroborates is described.

The Suzuki−Miyaura-type cross-coupling reaction with boronic acids and boronate esters has been widely studied and used as a synthetic method to prepare organic compounds of wide-ranging importance.[1] However, these organoboron derivatives have shown many limitations: (i) Quantitative analysis and stoichiometric reactions using boronic acids are often difficult because of the rapid equilibrium between the boronic acids and the corresponding cyclic, trimeric anhydrides (boroxines). (ii) The diols utilized to generate stable boronate esters such as catechol, pinacol, and diethanolamine add considerable expense to the overall process and must be separated from the final product. Therefore, the use of boronate esters results in a lack of atom economy and an increase in cost. (iii) Boronate esters, as Lewis acids and electrophiles, interact extensively with Lewis bases and nucleophiles. Consequently, elaboration of functionalized boronate esters via nucleophilic reactions may prove challenging.

By contrast, potassium organotrifluoroborates have been shown to overcome these limitations. These reagents are easily prepared by the addition of inexpensive KHF_2 to various organoboron intermediates, and they are stable to air and moisture.[2] Nearly all organotrifluoroborates synthesized to date can be stored indefinitely without special precautions. However, despite the advantages of potassium organotrifluoroborates, to date they are still accessed exclusively from commercially available boronic acids or via transmetalation,[2a,b] hydroboration,[2a,b,3] or C−H activation methods.[4] Access to more highly functionalized or unique potassium organotrifluoroborates would greatly expand their utility. Thus, a simple, efficient synthesis of assorted organotrifluoroborates was sought that would be complementary to the methods described above.

With this in mind, a process analogous to the nucleophilic displacement of α-halo boronic esters and the one-carbon homologation of in situ generated $LiCHX_2$ or $LiCH_2X$ (X = Cl, Br, I) as pioneered and developed extensively by Matteson was attractive for the direct diversification of organoboron compounds (Figure 1).[5] As an example of this approach, Mears and Whiting reported that the iodomethylboronate derivative could be successfully transformed to the corresponding β-boronate carbonyl derivatives with an ester, ketone, or amide enolate in 43−83% yields.[6]

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (d) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (e) Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes*; Aldrich Chemical Co., Inc.: Milwaukee, 2003; Vol. 3.

(2) (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (c) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S. *J. Org. Chem.* **1995**, *60*, 3020. (d) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.

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

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

10.1021/ol060375a CCC: $33.50
Published on Web 04/12/2006

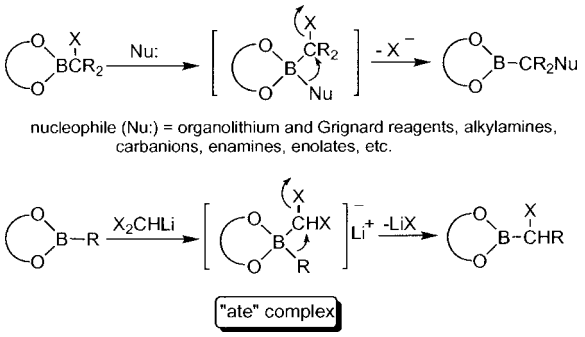
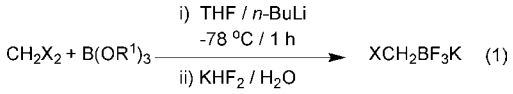
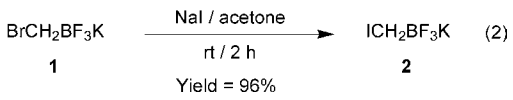


Figure 1. Reaction mechanism of the nucleophilic displacement of α-halo boronate esters with various nucleophiles and the one-carbon homologation of boronate esters with (dihalomethyl)lithium.

As outlined in Figure 1, the mechanism of the boronate ester reaction is known to involve nucleophilic attack at the boron atom to form an "ate" complex as an intermediate, followed by α-transfer of the nucleophile to the neighboring carbon.[7] Because of the tetracoordinate nature of the boron, this pathway is unavailable to the organotrifluoroborates. The question then became whether the halomethyltrifluoroborates would be robust enough to tolerate direct S_N2 displacement of the halides by a variety of nucleophiles, thus permitting their elaboration while leaving the trifluoroborate group intact. Herein is reported the realization of this novel method, in which the preparation of various potassium organotrifluoroborates can be achieved via the direct nucleophilic substitution of potassium halomethyltrifluoroborates.

As a starting point, syntheses of potassium halomethyltrifluoroborates were developed (eqs 1 and 2). In the first

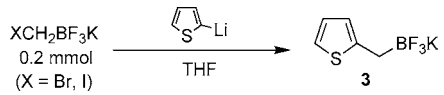




approach (eq 1), potassium bromomethyltrifluoroborate (**1**) was prepared in situ with the use of dibromomethane (25 mmol), triisopropyl borate (0.9 equiv), and *n*-BuLi (0.85 equiv) at −78 °C under a nitrogen atmosphere. After 1 h, the reaction mixture was quenched with a solution of KHF_2 (2.5 equiv)/H_2O (10 mL). After removing the solvent under high vacuum, **1** was isolated in 88% yield by recrystallization. When trimethyl borate was used instead of triisopropyl borate, **1** was accessed in 78% yield. Although potassium iodomethyltrifluoroborate was prepared from diiodomethane in 89% yield through an analogous procedure, this method is less desirable because of the high price and relative instability of commercially available diiodomethane. Therefore, a procedure was developed in which iodide displaced the bromide on potassium bromomethyltrifluoroborate using NaI in acetone, thus obtaining the desired compound **2** in 96% yield (eq 2). Both **1** and **2** are white solids that are stable under atmospheric conditions. The chemical structure of these compounds was confirmed by ^1H, ^{19}F, and ^{11}B NMR analysis.

Subsequently, nucleophilic substitution of the potassium bromo- or iodomethyltrifluoroborates was explored using various nucleophiles such as alkyl- and aryllithiums, Grignard reagents, alkylamines, alkoxides, carbanions, dianions, and lithium arylthiolates. Although the reaction conditions were dependent on the nucleophiles, the reaction could be optimized by varying the amount of nucleophile used. This was necessary because any potassium bromo- or iodomethyltrifluoroborate remaining at the end of the reaction was very difficult to separate from the product. The results of the model reaction are summarized in Table 1.

Table 1. Optimization of Reaction Conditions for the Synthesis of **3**



entry	X	equiv of thienyl Li	temp (°C)	reaction time (h)	conversion (%)[a]
1	I	1.0	−78 to rt	8	37
2	I	2.0	−23 to rt	8	68
3	I	1.0	−23 to rt	8	43
4	I	3.0	−23 to rt	3	100[b]
5	I	3.0	−23 to 0	3	100[c]
6	Br	3.0	−23 to 0	10	14

[a] Percentage conversion was calculated by ^1H NMR. [b] The isolated yield was 82%. However, after recrystallization, unidentified byproducts remained in the final product. [c] The pure product was isolated in 86% yield.

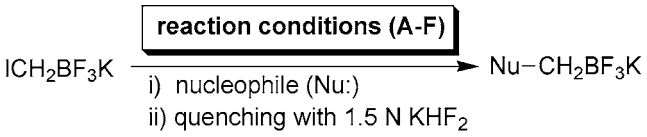
When 1.0 and 2.0 equiv of 2-thienyllithium were used as the nucleophile, the reactions did not completely generate the pure target compound **3** (Table 1, entries 1 and 2). On the other hand, when the initial reaction temperature was

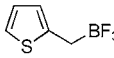
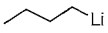
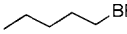
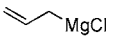
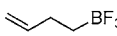
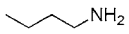
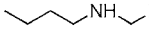
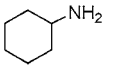
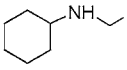
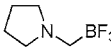
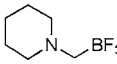
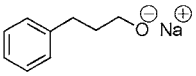
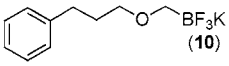
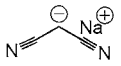
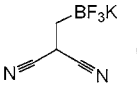
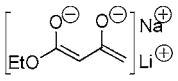
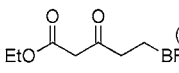
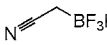
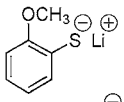
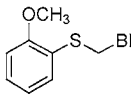
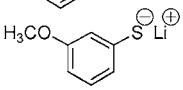
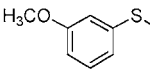
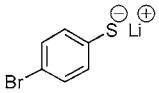
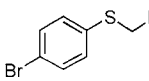
(5) (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (b) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (c) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795. (d) Brown, H. C.; Phadke, A. S.; Rangaishenvi, M. V. *J. Am. Chem. Soc.* **1988**, *110*, 6263. (e) Michnik, T. J.; Matteson, D. S. *Synlett* **1991**, 631. (f) Wallace, R. H.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941. (g) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957. (h) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150. (i) Brown, H. C.; Singh, S. M. *Organometallics* **1986**, *5*, 994. (j) Singh, R. P.; Matteson, D. S. *J. Org. Chem.* **2000**, *65*, 6650. (k) Matteson, D. S.; Soundararajan, R.; Ho, O. C.; Gatzweiler, W. *Organometallics* **1996**, *15*, 152. (l) Kumar, S. K.; Hager, E.; Pettit, C.; Gurulingappa, H.; Davidson, N. E.; Khan, S. R. *J. Med. Chem.* **2003**, *46*, 2813. (m) Davoli, P.; Fava, R.; Morandi, S.; Spaggiari, A.; Prati, F. *Tetrahedron* **2005**, *61*, 4427.

(6) Mears, R. J.; Whiting, A. *Tetrahedron* **1993**, *49*, 177.

(7) (a) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 818. (b) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599. (c) Brown, H. C.; De Lue, N. R.; Yamamoto, Y.; Maruyama, K.; Kasahara, T.; Murahashi, S.; Sonoda, A. *J. Org. Chem.* **1977**, *42*, 4088.

Table 2. Preparation of Various Potassium Alkyltrifluoroborates



entry	nucleophile	reaction condition[a]	time (h)	product	yield (%)[b]
1		A	3	 (**3**)	86
2[c]		A	4	 (**4**)	83
3		A	3	 (**5**)	85
4[d]		B	0.5	 (**6**)	88
5[d]		B	0.5	 (**7**)	98
6[d]		B	0.5	 (**8**)	92
7[d]		B	0.5	 (**9**)	95
8		C	8	 (**10**)	86
9		C	8	 (**11**)	91
10		D	3	 (**12**)	88
11[d]	KCN	E	10	 (**13**)	98
12		F	5	 (**14**)	90
13		F	5	 (**15**)	92
14		F	5	 (**16**)	94

[a] Reaction condition **A**: Nucleophile (3.0 equiv), THF, −78 °C to 0 °C. **B**: Alkylamine (solvent), 80 °C. **C**: Substrate (3.0 equiv), NaH (3.0 equiv), THF or DMF, 0 °C, 1 h, and reacted at room temperature. **D**: Ethyl acetoacetate (3.0 equiv), NaH (3.0 equiv), THF, *n*-BuLi (3.0 equiv), 0 °C, 1 h and then reacted at −23 °C. **E**: Potassium cyanide (3.0 equiv), DMSO, 80 °C. **F**: Aryl bromide (3.0 equiv), *t*-BuLi (6.0 equiv), THF, sulfur powder (3.0 equiv), −78 °C and reacted at room temperature (ref 8). [b] Yields were given for isolated products. [c] When 1.0 equiv of *n*-BuLi was used, the reaction time was 10 h (81% yield). [d] $BrCH_2BF_3K$ was used as the starting material.

changed from −78 °C to −23 °C, the conversion calculated by ^{1}H NMR was slightly improved during the same reaction times (Table 1, entries 1 and 3).

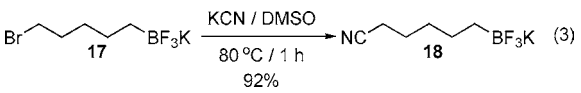
Under the conditions of entry 4, using 3.0 equiv of nucleophile, the starting material was completely reacted; however, the product **3** was contaminated with some inseparable byproducts. The best result was achieved with a combination of 3.0 equiv of nucleophile at −23 to 0 °C for 3 h. Concerning the reactivity of halides as the starting materials (Table 1, entries 5 and 6), as expected, iodide **2** showed better yields and shorter reaction times than those of bromide **1** under the same conditions.

On the basis of the model reaction, we were able to perform the nucleophilic substitution reaction with various nucleophiles (Table 2).

The reactions of aromatic and aliphatic lithium reagents, as well as Grignard reagent nucleophiles, resulted in good yields (Table 2, entries 1−3). Interestingly, primary and secondary alkylamines gave the desired salts in 88−98% yields in short reaction times employing solvent-free reaction of the amines at 80 °C (entries 4−7). Alkoxides, stabilized carbanions, and cyanide anions proceeded slowly even at room temperature. However, the production and purity of the target salts were satisfactory (entries 8−11). The dianion in entry 10 reacted with potassium iodomethyltrifluoroborate to produce the corresponding γ-alkylated product. The formation of compound **13** was accomplished in very good yield only when using potassium bromomethyltrifluoroborate (**1**) instead of iodo compound **2**.

Next, we proceeded to examine the substitution reaction of lithium arylthiolates, which were prepared via one-pot syntheses from the readily available aryl halides (Table 2, entries 12−14).[8] Thus, metal−halogen exchange of the aryl bromides provided the aryllithiums, and subsequent treatment with sulfur powder generated the arylthiolates in situ. Substitution of potassium iodomethyltrifluoroborate with the arylthiolates provided *ortho*-, *meta*-, and *para*-substituted trifluoroborate salts in excellent overall yields.

On the basis of these results, it is evident that the direct nucleophilic displacement of halides in halomethyltrifluoroborates is feasible, and the normal α-transfer process via a borate complex is unnecessary. Further evidence supporting the viability and utility of a direct S_N2 reaction is provided by the observation that the reaction of potassium 5-bromopentyltrifluoroborate **17** with 1.0 equiv of potassium cyanide produced the corresponding nitrile product **18**[9] (eq 3).



In summary, we have successfully prepared the potassium bromo- and iodomethyltrifluoroborates as useful starting materials in 78−89% yields via in situ reaction of *n*-BuLi with dibromo- and diiodomethane in the presence of a trialkyl borate, followed by the treatment with KHF_2. Moreover, we have developed a new synthetic method for making novel, functionalized potassium alkyltrifluoroborates through nucleophilic substitution of the halide in potassium halomethyltrifluoroborates with various nucleophiles in 83−98% yields. Given the tetracoordinate nature of the organotrifluoroborates and the model reaction of 5-bromopentyltrifluoroborate with KCN, the reaction mechanism is consistent

(8) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236.
(9) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.

with a direct nucleophilic substitution. Other nucleophilic substitution reactions using diverse halo-substituted potassium organotrifluoroborates are currently under investigation, as well as coupling reactions of the unusual organoboron reagents derived therefrom.

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 ^{1}H, ^{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.

OL060375A