Improved Synthesis of Potassium (Trifluoromethyl)trifluoroborate [$K(CF_3BF_3)$]

Gary A. Molander*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

Benjamin P. Hoag

Eastman Kodak Research Laboratories, Rochester, New York 14650

Received April 11, 2003

Summary: An improved synthesis of potassium (trifluoromethyl)trifluoroborate [$K(CF_3BF_3)$] has been developed. Thus Ruppert's reagent, (trifluoromethyl)trimethylsilane, is treated with trimethoxyborane in the presence of potassium fluoride. Aqueous hydrogen fluoride is added to the resulting intermediate, and the title compound can be isolated in 85% overall yield. The process is readily scalable, allowing a viable procedure for the synthesis of this potentially valuable reagent.

Introduction

The trifluoromethyl group has evolved into an indispensable substituent to the pharmaceutical industry because of its unique size, electronic properties, and metabolic stability. Unfortunately, general methods for the introduction of the trifluoromethyl group via transition metal catalyzed reactions have yet to be developed. The instability of trifluoromethyllithium or trifluoromethyl Grignard reagents precludes their use for either nucleophilic substitution or coupling reactions.[1] Trifluoromethylzinc compounds and in particular trifluoromethylcopper have been applied for synthetic purposes but necessitate forcing conditions.[2] A limited number of palladium-catalyzed cross-coupling reactions involving perfluorinated substrates have been reported.[3] The most successful is a Negishi-type coupling reported by Kitazume and Ishikawa two decades ago.[3a,b]

One of the more useful means to incorporate a trifluoromethyl unit into organic electrophiles would be a Suzuki−Miyaura type coupling reaction.[4] This process tolerates a wide variety of functional groups, and the inorganic byproducts are less toxic and easily removed upon workup. Among the available organoboron reagents, potassium trifluoroborates offer many advantages. They are monomeric species, thus eliminating the stoichiometric uncertainty associated with boronic acids that undergo reversible trimerization to boroxines. Organotrifluoroborates are environmentally friendly and exhibit remarkable air and water stability. In fact, most organotrifluoroborates exhibit moderate to high solubility in water, which may minimize or preclude the need for organic solvents in suitable reactions. Finally, the potassium organotrifluoroborates demonstrate greater nucleophilicity than the corresponding organoboranes or boronic acid derivatives and are less susceptible to protodeboronation, thus making them very attractive starting materials. Recent studies have revealed that potassium organotrifluorborates [$K(RBF_3)$], easily prepared from boronic acids or esters,[5] readily undergo palladium-catalyzed cross-coupling as well as other transition metal catalyzed reactions.[6]

Potassium (trifluoromethyl)trifluoroborate (**1**), $K[CF_3BF_3]$, is an air- and water-stable solid first reported in 1960 by Chambers, Clark, and Willis[7] that may be envisioned as a potentially valuable trifluoromethylating agent. Unfortunately, the best reported synthetic procedure of **1** is far from ideal (Scheme 1). It entails a pressurized photochemical reaction of the toxic hexamethylditin with trifluoromethyl iodide to yield (trifluoromethyl)trimethyltin and trimethyltin iodide as a stoichiometric reaction product. The compound $(CH_3)_3SnCF_3$ was then treated with gaseous boron trifluoride

(1) Even at low temperatures, compounds, such as CF_3Li or CF_3MgX, decompose via α-elimination before they may be captured by electrophiles. The complex is presumed to decompose via α-elimination to yield LiF or $Mg(F,X)_2$ and the highly reactive difluorocarbene. For reviews of perfluorinated organometallics see: (a) Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189−275. (b) Burton, D. J.; Lu, L. *Top. Curr. Chem.* **1997**, *193*, 45−89.

(2) (a) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91. (b) Cesnek, M.; Hocek, M.; Holy, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357. (c) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 327. (d) Yang, Z.-Y.; Burton, D. J. *J. Fluorine Chem.* **2000**, *102*, 89. (e) MacNeil, J. G.; Burton, D. J. *J. Fluorine Chem.* **1991**, *55*, 225. (f) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2385. (g) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Chem. Commun.* **1989**, 705. (h) Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. *Tetrahedron Lett.* **1991**, *32*, 7689. (i) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014. (j) Mietchen, R.; Hager, C.; Hein, M. *Synthesis* **1997**, 159. (k) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1981**, 1679. (l) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 1453. (m) Francèse, M.; Tordeux, M.; Wakselman, C. *Tetrahedron Lett.* **1988**, *29*, 1029.

(3) (a) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186. (b) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 137. (c) Matsubara, S.; Mitani, M.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 5857. (d) Qing, F.-L.; Zhang, X.; Peng, Y. *J. Fluorine Chem.* **2001**, *111*, 185. (e) Peng, S.; Qing, F.-L.; Hu, C.-M. *J. Org. Chem.* **2000**, *65*, 694.

(4) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Suzuki, A. In *Metal-catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; VCH: Weinheim, 1998; p 49. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (e) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

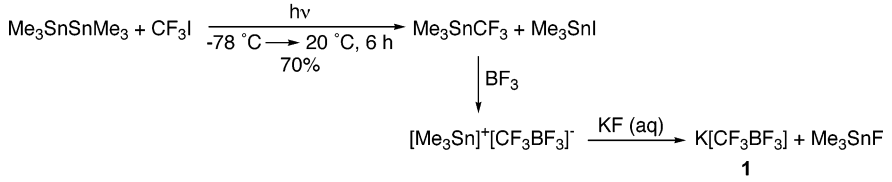
(5) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

(6) (a) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, *1875*, 5. (b) Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045. (c) Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393. (d) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (e) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107. (e) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. (f) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099. For rhodium-catalyzed conjugate additions see: (g) Batey, R. A.; Thadani, A. N. *Org. Lett.* **1999**, *1*, 1683−1686. (h) Pucheautl, M.; Darses, S.; Gênet, J.-P. *Eur. J. Org. Chem.* **2002**, 3552−3557.

(7) Chambers, R. D.; Clark, H. C.; Willis, C. J. *J. Am. Chem. Soc.* **1960**, *82*, 5298.

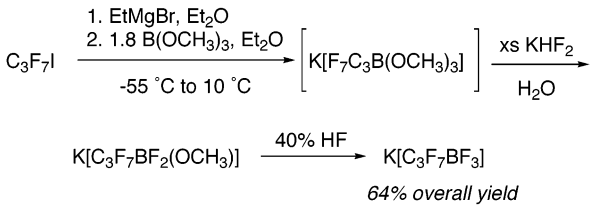
10.1021/om0302645 CCC: $25.00
Publication on Web 06/28/2003

Scheme 1

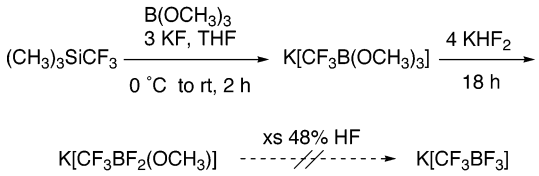


Scheme 2

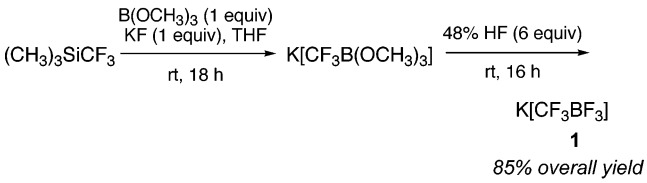
Scheme 3[11b]



Scheme 4



Scheme 5



to give a product described as "$[(CH_3)_3Sn]^+[CF_3BF_3]^-$". Cation exchange in an aqueous solution of potassium fluoride yielded the desired product plus trimethyltin fluoride. To date, this procedure is the most widely accepted for access to $K[CF_3BF_3]$,[8] but it is not conducive to large-scale production. Alternative syntheses to (trifluoromethyl)trialkyltin under milder reaction conditions have been reported that preclude the necessity of a pressurized photochemical reaction,[9] but the generation of large quantities of toxic tin byproducts remains unacceptable. In addition, the use of BF_3 gas is undesirable.

Given our interest in Suzuki−Miyaura cross-couplings of organotrifluoroborates and our desire to extend this and other transition metal catalyzed reactions to the important trifluoromethyl derivative, we embarked on an effort to develop an improved synthesis of potassium (trifluoromethyl)trifluoroborate. An ideal synthesis would use inexpensive, nontoxic reagents and afford large amounts of pure product in nearly quantitative yield with a minimal number of byproducts and purification procedures. Herein we report our efforts in this endeavor.

Results and Discussion

Ruppert's reagent,[10] $(CH_3)_3SiCF_3$, is an effective trifluoromethylating agent of ketones, esters, and related electrophiles under fluoride catalysis. It may also be used to transfer the trifluoromethyl group to a boron electrophile, such as trimethoxyborane, forming the "ate" complex (Scheme 2). It was envisioned that this "ate" complex might be converted directly to the desired (trifluoromethyl)trifluoroborate salt by treatment with KHF_2 following known procedures.[5,6,11] Utilizing this protocol, formation of the initial "ate" complex proceeded as expected, but it was determined that the subsequent fluorination with KHF_2 was incomplete.

Recently, Frohn and Bardin published a series of papers on perfluorinated (alkyl/alkenyl/aryl)trifluoroborates.[11] As in our case, they observed that treatment of perfluorinated alkyltrimethoxyborates with KHF_2 even in the presence of aqueous HF did not result in complete transformation to the desired perfluoroalkyltrifluoroborates. Their solution to this was to isolate the partially converted species via extraction and react this with aqueous hydrofluoric acid to complete fluorination (Scheme 3).

We subsequently set out to apply this protocol to the synthesis of potassium (trifluoromethyl)trifluoroborate (Scheme 4). However, the (difluoro)methoxy(trifluoromethyl)borate could not be readily isolated because it possessed solubility characteristics similar to those of the salt byproducts. Additionally, this product was determined to be unstable to mildly basic conditions, making purification that much more difficult. The crude compound was thus treated directly with a 20+ fold excess of aqueous HF after treatment with KHF_2 to complete fluorination. Unfortunately, spectroscopic evaluation of the reaction mixture indicated that the initially formed intermediate had not been converted to the desired product.

An alternative strategy was thus adopted utilizing aqueous hydrofluoric acid as the exclusive fluoride source (Scheme 5). The first step again utilized (trifluoromethyl)trimethylsilane as the trifluoromethylating agent. However, in this instance exactly 1 equiv of

(8) (a) Brauer, D. J.; Bürger, H.; Pawelke, G. *Inorg. Chem.* **1977**, *16*, 2305. (b) Pawelke, G.; Heyder, F.; Bürger, H. *J. Organomet. Chem.* **1979**, *178*, 1. (c) Roschenthaler, G.-V.; Bissky, G.; Kuhner, A.; Schmidt, M.; Franz, K.-D.; Kadyrov, A.; Kolomeitsev Ger. Patent DE 101 03 189 A 1, 2000.

(9) Prakash, G. K. S.; Yudin, A. K.; Deffieux, D.; Olah, G. A. *Synlett* **1996**, 151.

(10) For recent reviews on the use of $(CH_3)_3SiCF_3$ see: (a) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (c) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(11) (a) Frohn, H.-J.; Franke, H.; Fritzen, P.; Bardin, V. V. *J. Organomet. Chem.* **2000**, *598*, 127. (b) Frohn, H.-J.; Bardin, V. V. *Z. Anorg. Allg. Chem.* **2001**, *627*, 15. (c) Frohn, H.-J.; Bardin, V. V. *Z. Anorg. Allg. Chem.* **2001**, *627*, 2499. (d) Frohn, H.-J.; Bardin, V. V. *J. Organomet. Chem.* **2001**, *631*, 54. (e) Frohn, H.-J.; Bardin, V. V. *Z. Anorg. Allg. Chem.* **2002**, *628*, 883. (f) Frohn, H.-J.; Bardin, V. V. *Z. Anorg. Allg. Chem.* **2002**, *628*, 1853.

trimethoxyborane, 1 equiv of potassium fluoride,[12] and a slight excess of (trifluoromethyl)trimethylsilane (1.1 equiv) were used. After all of the trimethoxyborane had been converted to the "ate" complex as determined by ^{11}B NMR spectroscopy, all volatile components [excess (trifluoromethyl)trimethylsilane, trimethylsilyl fluoride, and THF] were removed by slow evaporation under a stream of nitrogen, and the residue was subsequently treated with 48% aqueous HF. Heat was evolved immediately, and the solution was stirred for 16 h at ambient temperature. After neutralization and workup, potassium (trifluoromethyl)trifluoroborate (**1**) was isolated in pure form in 85% overall yield.

Conclusion

An efficient, high-yielding route to potassium (trifluoromethyl)trifluoroborate **1** has been demonstrated. This synthetic strategy for $K[CF_3BF_3]$ meets many of the criteria necessary for a successful synthesis. All of the reagents are very inexpensive with the exception of (trifluoromethyl)trimethylsilane, which may be synthesized according to a literature procedure.[13] In fact, one of the initial reagents, potassium fluoride, is generated upon neutralization in the final step and may be used in subsequent production of $K[CF_3BF_3]$. Purification is straightforward, and the entire process is very high yielding (85% overall) and scalable.[14] Research is under way to determine the conditions under which this reagent can be utilized as a trifluoromethylating agent in selective organic synthesis.

Experimental Section

General Procedures. Potassium fluoride (spray-dried) was used without any purification. Trimethoxyborane was distilled from sodium prior to use. THF was passed through A-2 alumina prior to use. All reactions were run in air unless specified otherwise.

Potassium (Trifluoromethyl)trifluoroborate ($K[CF_3BF_3]$). To a 40 oz Nalgene (HDPE) bottle were added potassium fluoride (3.57 g, 61.5 mmol), THF (60 mL), trimethoxyborane (6.89 mL, 61.5 mmol), and (trifluoromethyl)trimethylsilane (10.0 mL, 67.7 mmol). The reaction mixture was stirred at ambient temperature for 18 h. ^{11}B NMR spectroscopy indicated the complete consumption of the $B(OCH_3)_3$. The volatile components were removed via evaporation under a stream of nitrogen to afford a white solid. A 48% aqueous solution of hydrogen fluoride (20 mL) was added to the Nalgene bottle. Heat was evolved, and the resulting solution was stirred at ambient temperature for 12 h. Potassium hydroxide (21.0 g, 375 mmol, diluted in 75−100 mL of distilled/deionized water) was added slowly to the reaction mixture, which remained slightly acidic. Potassium bicarbonate was added portionwise as a solid until CO_2 evolution ceased, and the reaction mixture had a pH greater than 7. Water was removed with a rotary evaporator to afford a white solid. (Note: it is necessary to remove as much water as possible.) The white solid was ground into a fine powder with a mortar and pestle, and the material was dried further by gently heating the outside of the flask with a Bunsen burner while swirling the powder inside in vacuo. The powder was transferred into a 1 L Erlenmeyer flask stirred in boiling acetonitrile (250 mL) and filtered while still hot. The acetonitrile of the filtrate was removed with a rotary evaporator to afford the product as a white powder (9.19 g, 85.0%). The powder may be recrystallized from a 2:1 mixture of ethanol/2-propanol. ^{19}F NMR (D_2O, 470 MHz): δ (ppm) −155.2 (q, J = 40.7 Hz), −76.7 (q, J = 33.1 Hz).[15] ^{11}B NMR (D_2O, 64.2 MHz): δ (ppm) 0.8 (qq (appears like a septet), J = 40.7, 33.1 Hz).

Acknowledgment. We thank Johnson & Johnson, Merck Research Laboratories, Aldrich Chemical Co., Array BioPharma, and Johnson Matthey for their generous support.

OM0302645

(12) It is important to use *only 1 equiv of potassium fluoride* in the first step. If more than 1 equiv of KF is used, potassium fluoride will be present upon addition of aqueous HF, will generate KHF_2, and will deter the complete fluorination of the "ate" complex.

(13) Paweleke, G. *J. Fluorine Chem.* **1989**, *42*, 429. The reaction is high yielding but necessitates high-pressure equipment in order to be economical in bulk scale. Costs to industrial companies must be considerably lower than retail prices.

(14) The reaction times have not been optimized, especially the fluorination step, which is likely complete within a few hours.

(15) Brauer, D. J.; Bürger, H.; Chebude, Y.; Pawelke, G. *Inorg. Chem.* **1999**, *38*, 3972.