Journal of Fluorine Chemistry 154 (2013) 43–46

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Nucleophilic fluoroalkylation of (bromomethyl)pinacolborane using silicon reagents

Vitalij V. Levin, Pavel K. Elkin, Marina I. Struchkova, Alexander D. Dilman *

N.D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation

ARTICLE INFO

Article history:
Received 22 May 2013
Received in revised form 14 June 2013
Accepted 17 June 2013
Available online 26 June 2013

Keywords:
Nucleophilic fluoroalkylation
Silanes
Organoboron compounds
Substitution

ABSTRACT

A method for the synthesis of pinacol boronic esters bearing a fluorinated group at the α-carbon atom (R_fCH_2Bpin) from corresponding bromomethyl borane ($BrCH_2Bpin$) and fluorinated silanes (R_fSiMe_3) is described. The fluoroalkylation reaction involves formation of borate anions followed by intramolecular nucleophilic substitution of bromine.

1. Introduction

Fluorinated organoboron compounds have emerged as valuable reagents with broad scope of applications [1–3]. While various structural types of fluoroboron compounds have been synthesized, boranes **1** bearing a methyl group substituted with a fluorinated fragment have been poorly studied (Scheme 1). Indeed, only compounds with pentafluorophenyl [4] of difluorovinyl [5] groups were described, which were prepared by nucleophilic substitution of halogen in halomethylboranes using fluorinated lithium or magnesium reagents [6]. At the same time, boranes **1** containing trifluoromethyl or fluorinated alkyl substituent at the α-carbon have not been reported. Herein we describe the application of fluorinated silanes as equivalents of fluorinated carbanions for the preparation of boranes **1**.

Reactions of fluorinated silanes with sp^2-centered electrophiles, such as C=O, C=N, and electron-deficient C=C bonds [7], as well as substitution of halogen at sp^2-carbon [8], have been studied intensively, whereas reactions with sp^3-centered electrophiles are notably less general. The displacement of halogen at the sp^3-carbon by fluorinated group can be performed by using fluorinated copper species R_fCu generated either from silane [9] or by other means [10]. Alternatively, direct S_N2 type substitution can be realized when silane is activated by Lewis base without transition metal [11], though this process provides reasonable yields mainly with alkyl iodides or benzyl and alkyl bromides.

The major difference of halomethylboranes from conventional alkyl electrophiles is the ability of boron atom to interact with nucleophile to generate tetracoordinate borate salt [12]. Such a behavior was observed in reaction of alkylborates $B(OR)_3$ and esters of boronic acids $RB(OR)_2$ with $TMSCF_3$ [13]. Therefore, it can be expected that the overall substitution of halogen in halomethylboranes can proceed in two steps: by formation of tetracoordinate borate salt followed by intramolecular S_N2 substitution (Scheme 1).

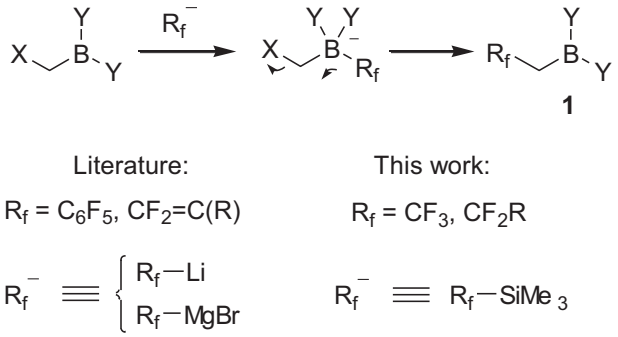
2. Results and discussion

Bromomethyl pinacolborane **2** was reacted with CF_3- and C_2F_5-substituted silanes (**3a** and **3b**, respectively) in the presence of potassium fluoride in DMF at room temperature (Scheme 2). Trifluoromethylated borate salt **4a** was formed cleanly and its structure was supported by ^{19}F and ^{11}B NMR spectroscopy. The yield of salt **4a** was *ca.* 85% determined by ^{19}F NMR spectroscopy with internal standard. To effect intramolecular substitution, the resulting solution of salt **4a** was briefly heated at 70 °C to effect complete conversion. However, the desired product **5a** was isolated in only 45% yield. Analysis of reaction mixture by ^{19}F NMR spectroscopy showed the formation of by-products which we could not identify. The reaction of borane **2** with $TMSC_2F_5$ (**3b**) proceeded similarly generating borate salt **4b**, and its subsequent transformation was carried out at 50 °C affording product **5b** in 80% yield after vacuum distillation.

Functionalized silanes **3c–f** were reacted with borane **2** under standard conditions (Table 1). In this case the formation of products **5** did not require heating, and proceeded at a rate

* Corresponding author. Fax: +7 499 1355328.
E-mail addresses: adil25@mail.ru, dilman@ioc.ac.ru (A.D. Dilman).

0022-1139/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2013.06.007

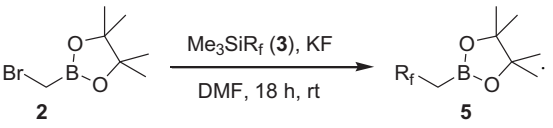


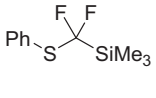
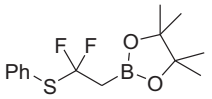
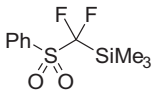
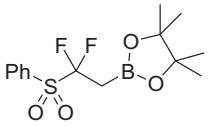
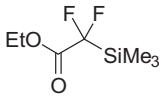
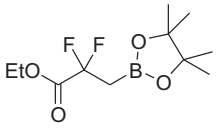
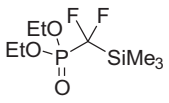
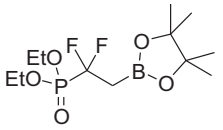
Scheme 1.

comparable to that of the formation of the intermediate borate salts. These observations suggest that the rate of intramolecular S_N2 substitution increases with increasing carbanion stability of migrating group. As a rule, products **5** were formed with the yields exceeding 50%, while their purification was accompanied by product losses.

The general problem for the preparation of 2,2,2-trifluoroethyl and related organometallic reagents is the facile β-elimination of metal fluoride from the fragment RCF_2CH_2M. Rewardingly, boranes **5** are thermally stable compounds showing no tendency for β-elimination under neutral conditions. However, borane **5c** is prone to decomposition in $CDCl_3$ solution, as well as neat upon storage at 5 °C, leading to unidentified mixture despite the fact that it can be distilled under vacuum.

Table 1
Fluoroalkylation of bromomethyl pinacolborane **2**.



Silane		Product		Yield of **5** (%)[a]
	**3c**		**5c**	85
	**3d**		**5d**	55
	**3e**		**5e**	59
	**3f**		**5f**	28 (50)[b]

[a] The yield of purified product.
[b] The yield determined by NMR spectroscopy.

3. Conclusions

In summary, a method for the synthesis of fluorine-substituted pinacolboranes by nucelophilic fluoroalkylation has been described. Taking into account the rich chemistry of organoboron compounds, the obtained boranes may find applications in transition metal catalyzed cross-couplings, as well as in other reactions involving transfer of a partially fluorinated group from boron.

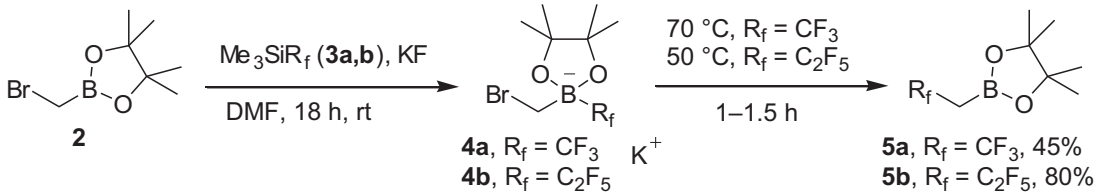
4. Experimental

4.1. General experimental procedures

All reactions were performed under an argon atmosphere. DMF was distilled under vacuum from P_2O_5 and stored over MS 4 Å. NMR spectra were recorded on a Bruker AM-300 instrument. Microanalyses were performed on KarloErba 1106 instrument. Me_3SiCF_3 and $Me_3SiC_2F_5$ were purchased from P&M. Silanes **3c** [14], **3d**,**f** [15] were obtained according to the literature procedures.

4.2. 2-(Bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**) [16]

To a stirred solution of triisopropylborate (32.5 mL, 141 mmol) and dibromomethane (10.8 mL, 154 mmol) in anhydrous THF (150 mL) at −94 °C (acetone/liquid nitrogen), *n*-BuLi (54 mL of 2.4 M solution in hexane, 128 mmol) was added dropwise over 2 min at such a rate that the internal temperature did not rise above −80 °C. The resulting mixture was stirred for 15 min at −78 °C, the cooling bath was removed, and the mixture was stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C (ice/water bath) and a solution of concentrated sulfuric acid (3.8 mL, 70 mmol) in methanol (8.0 mL) was added dropwise over 2 min. The reaction was allowed to reach room temperature and was stirred for 1 h. Pinacol (12.1 g, 128 mmol) was added in one portion, and the mixture was stirred for 1 h at room temperature. The volatiles were removed under vacuum, and the residue was distilled (70 °C/12 Torr) to give 25.5 g (90% yield) of borane **2** as a colorless liquid.



Scheme 2.

4.3. Ethyl difluoro(trimethylsilyl)acetate (**3e**) [17]

Ethyl bromodifluoroacetate (3.2 mL, 25 mmol) was added dropwise to a suspension of magnesium turnings (1.21 mg, 50 mmol) and chlorotrimethylsilane (9.6 mL, 75 mmol) in anhydrous DMF (40 mL) at 0 °C. The reaction mixture was stirred for 90 min at room temperature and quenched with water (40 mL). The aqueous layer was extracted with pentane (3 × 15 mL), the combined organic phase was washed with water, dried over Na_2SO_4. The solvent was evaporated under vacuum, and the residue distilled (110–111 °C/90 Torr) furnishing product **3e** as a pale yellow oil (2.71 g, 55%).

4.4. Borate salt **4a**

KF (145 mg, 2.5 mmol) was added to a solution of borane **2** (550 mg, 2.5 mmol) and silane **3a** (443 μL, 3 mmol) in DMF (2.5 mL), and the resulting suspension was stirred for 18 h at room temperature. The stirring was discontinued, and the aliquot was analyzed by NMR spectroscopy. ^{19}F NMR (282 MHz, DMF), δ: −67.7 (br). ^{11}B NMR (96 MHz, DMF), δ: 1.2 (br).

4.5. Synthesis of boranes **5a**,**b**

KF (291 mg, 5 mmol) was added to a solution of borane **2** (1.10 g, 5 mmol) and silane **3a** or **3b** (6 mmol) in DMF (5 mL), the resulting suspension was stirred for 18 h at room temperature, and then heated on water bath (for **5a**, 1.5 h at 70 °C; for **5b**, 1 h at 50 °C). The mixture was extracted with pentane (2 × 12 mL). More pentane (10 mL) was added to the DMF layer, the two-phase mixture was shaken, water (5 mL) was added, the mixture was again shaken, and the pentane layer was separated. The combined pentane phase was washed with water (3 × 3 mL), dried (Na_2SO_4), and pentane was evaporated at atmospheric pressure. The residue was distilled under vacuum.

4.5.1. 4,4,5,5-Tetramethyl-2-(2,2,2-trifluoroethyl)-1,3,2-dioxaborolane (**5a**)

472 mg, 45% yield. Bp 60–65 °C (bath temp.)/12 Torr. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.27 (s, 12H, 4Me), 1.80 (q, 2H, J = 13.0, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 24.6, 84.3, 127.2 (q, J = 274.1). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −58.1 (t, J = 13.0). Anal. Calcd for $C_8H_{14}BF_3O_2$ (210.00) C, 45.75; H, 6.72. Found: C, 45.64; H, 6.65.

4.5.2. 4,4,5,5-Tetramethyl-2-(2,2,3,3,3-pentafluoropropyl)-1,3,2-dioxaborolane (**5b**)

840 mg, 80% yield. Bp 62–68 °C (bath temp.)/9 Torr. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.27 (s, 12H, 4Me), 1.69 (t, 2H, J = 21.1, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 24.6, 84.4, 116.1 (tq, J = 251.0, 38.6), 119.3 (qt, J = 285.0, 37.4). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −109.2 (t, 2F, J = 21.1), −87.2 (s, 3F). Anal. Calcd for $C_9H_{14}BF_5O_2$ (260.01): C, 41.57; H, 5.43. Found: C, 41.47; H, 5.45.

4.6. 2-[2,2-Difluoro-2-(phenylthio)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5c**)

KF (291 mg, 5 mmol) was added to a solution of borane **2** (1.10 g, 5 mmol) and silane **3c** (1.39 g, 6 mmol) in DMF (5 mL), and the resulting suspension was stirred for 18 h at room temperature. For the work-up, the mixture was extracted with pentane (2 × 12 mL). More pentane (10 mL) was added to the DMF layer, the two-phase mixture was shaken, water (5 mL) was added, the mixture was again shaken, and the pentane layer was separated. The combined pentane phase was washed with water (3 × 3 mL), dried (Na_2SO_4), and concentrated under vacuum. To remove the excess of starting silane **3c**, the crude product was dissolved in DMF (5 mL), treated with MeOH (101 μL, 2.5 mmol) and NaOAc (82 mg, 1 mmol), and the mixture was stirred for 18 h. The work-up with pentane (as described above) gave crude product which was distilled under vacuum. 1.27 g, 85% yield. Bp 115–120 °C (bath temp.)/1 Torr. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.31 (s, 12H, 4Me), 1.92 (t, 2H, J = 17.5), 7.23–7.48 (m, 3H, Ph), 7.60–7.70 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 24.6, 84.0, 127.8 (t, J = 2.1), 128.9, 129.0 (t, J = 277.8) 129.5, 136.0. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −63.7 (t, J = 17.5).

4.7. 2-[2,2-Difluoro-2-(phenylsulfonyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5d**)

KF (291 mg, 5 mmol) was added to a solution of borane **2** (1.10 g, 5 mmol) and silane **3d** (1.58 g, 6 mmol) in DMF (5 mL), and the resulting suspension was stirred for 18 h at room temperature. The mixture was extracted with hexane (2 × 12 mL). More hexane (10 mL) was added to the DMF layer, the two-phase mixture was shaken, water (5 mL) was added, the mixture was again shaken, and the hexane layer was separated. The combined hexane phase was washed with water (3 × 3 mL), dried (Na_2SO_4), and concentrated under vacuum. The crude product was recrystallized from methanol. 913 mg, 55% yield. Mp 94–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.26 (s, 12H, 4Me), 1.98 (t, 2H, J = 21.5, CH_2), 7.54–7.62 (m, 2H, Ph), 7.72 (t, 1H, J = 7.3, Ph), 7.96 (d, 2H, J = 8.0, Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 24.6, 84.4, 125.2 (t, J = 284.5), 129.2, 130.8, 132.4, 135.1. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −95.9 (t, J = 21.5). Anal. Calcd for $C_{14}H_{19}BF_2O_4S$ (332.17): C, 50.62; H, 5.77. Found: C, 50.60; H, 5.86.

4.8. Synthesis of boranes **5e**,**f**

KF (291 mg, 5 mmol) was added to a solution of borane **2** (1.10 g, 5 mmol) and silane **3e** or **3f** (6 mmol) in DMF (5 mL), and the resulting suspension was stirred for 18 h at room temperature. The mixture was extracted with hexane (2 × 12 mL). More hexane (10 mL) was added to the DMF layer, the two-phase mixture was shaken, water (5 mL) was added, the mixture was again shaken, and the hexane layer was separated. The combined hexane phase was washed with water (3 × 3 mL), dried (Na_2SO_4), concentrated under vacuum, and the residue was distilled under vacuum.

4.8.1. Ethyl 2,2-difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (**5e**)

Bp 109–111 °C/1.9 Torr. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.26 (s, 12H, 4Me), 1.36 (t, 3H, J = 7.2, Me), 1.80 (t, 2H, J = 18.4, CF_2CH_2), 4.33 (q, 2H, J = 7.2, OCH_2). ^{13}C (75 MHz, $CDCl_3$), δ: 13.9, 24.6, 62.5, 84.1, 116.5 (t, J = 249.0), 164.3 (t, J = 33.4). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −95.9 (t, J = 18.4). Anal. Calcd for $C_{11}H_{19}BF_2O_4$ (264.07): C, 50.03; H, 7.25. Found: C, 50.25; H, 7.51.

4.8.2. Diethyl 1,1-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylphosphonate (**5f**)

The product contains *ca.* 10% of $CHF_2PO(OEt)_2$. Bp 135–137 °C/1.5 Torr. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.25 (s, 12H, 4Me), 1.33 (t, 6H, J = 7.0, 2Me), 1.72 (td, 2H, J = 23.7, 6.6), 4.23 (qd, 4H, J = 7.2, 7.2, $2OCH_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 16.3 (d, J = 5.2), 24.6, 64.2 (d, J = 6.3), 83.9, 120.9 (td, J = 258.8, 220.0). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −102.5 (dt, J = 112.8, 23.3). ^{31}P (121 MHz, $CDCl_3$), δ: 7.57 (t, J = 112.8). HRMS (ESI) Calcd for $C_{12}H_{25}BF_2O_5P$ (M+H): 329.1497. Found: 329.1499.

Acknowledgments

This work was supported by Russian Foundation for Basic Research (Project 11-03-00362) and the Ministry of Science (Project MD-4750.2013.3).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.06.007.

References

[1] For reviews on C_6F_5-substituted boranes, see:
(a) W.E. Piers, T. Chivers, Chem. Soc. Rev. 26 (1997) 345–354;
(b) W.E. Piers, Adv. Organomet. Chem., Elsevier Academic Press Inc., San Diego, 2005, pp. 1–76;
(c) D.W. Stephan, G. Erker, Angew. Chem. Int. Ed. 49 (2010) 46–76.

[2] For reviews on CF_3-substituted boranes, see:
(a) G. Pawelke, H. Bürger, Appl. Organomet. Chem. 10 (1996) 147–174;
(b) M. Finze, E. Bernhardt, H. Willner, Angew. Chem. Int. Ed. 46 (2007) 9180–9196.

[3] For a general review of polyfluorinated organic compounds of boron, see:
Yu.N. Adonin, V.V. Bardin, Russ. Chem. Rev. 79 (2010) 757–785.

[4] (a) R.P. Singh, B. Twamley, L. Fabry-Asztalos, D.S. Matteson, J.M. Shreeve, J. Org. Chem. 65 (2000) 8123–8125;
(b) P.V. Ramachandran, M.P. Jennings, J. Fluorine Chem. 128 (2007) 827–831.

[5] (a) P.V. Ramachandran, A. Chatterjee, Org. Lett. 10 (2008) 1195–1198;
(b) P.V. Ramachandran, A. Chatterjee, J. Fluorine Chem. 130 (2009) 144–150;
(c) P.V. Ramachandran, A. Tafelska-Kaczmarek, A. Chatterjee, J. Org. Chem. 77 (2012) 9329–9333;
(d) P.V. Ramachandran, A. Tafelska-Kaczmarek, K. Sakavuyi, Org. Lett. 13 (2011) 4044–4047.

[6] Different approach for the preparation of a borane bearing $C_6F_5CH_2$ group was demonstrated based on iridium catalyzed C–H borylation of $C_6F_5CH_3$; see
(a) T.A. Boebel, J.F. Hartwig, Organometallics 27 (2008) 6013–6019;
For alternative approach toward difluorovinyl-type borane based on copper catalyzed boration/elimination sequence, see
(b) R. Corberán, N.W. Mszar, A.H. Hoveyda, Angew. Chem. Int. Ed. 50 (2011) 7079–7082.

[7] (a) G.K.S. Prakash, A.K. Yudin, Chem. Rev. 97 (1997) 757–786;
(b) R.P. Singh, J.M. Shreeve, Tetrahedron 56 (2000) 7613–7632;
(c) A.D. Dilman, V.V. Levin, Eur. J. Org. Chem. (2011) 831–841.

[8] For a recent review, see:
T. Liu, Q. Shen, Eur. J. Org. Chem. (2012) 6679–6687.

[9] J. Kim, J.M. Shreeve, Org. Biomol. Chem. 2 (2004) 2728–2734.

[10] (a) Q.-Y. Chen, J.-X. Duan, Tetrahedron Lett. 34 (1993) 4241–4244;
(b) H. Kawai, T. Furukawa, Y. Nomura, E. Tokunaga, N. Shibata, Org. Lett. 13 (2011) 3596–3599;
(c) Q.-Y. Chen, S.-W. Wu, J. Chem. Soc. Chem. Commun. (1989) 705–706.

[11] (a) W. Tyrra, D. Naumann, S. Quadt, S. Buslei, Y.L. Yagupolskii, M.M. Kremlev, J. Fluorine Chem. 128 (2007) 813–817;
(b) Y. Li, J. Hu, J. Fluorine Chem. 129 (2008) 382–385;
(c) L. Zhu, Y. Li, Y. Zhao, J. Hu, Tetrahedron Lett. 51 (2010) 6150–6152.

[12] For the chemistry of α-haloboronic esters, see:
D.S. Matteson, Chem. Rev. 89 (1989) 1535–1551.

[13] (a) G.A. Molander, B.P. Hoag, Organometallics 22 (2003) 3313–3315;
(b) A.A. Kolomeitsev, A.A. Kadyrov, J. Szczepkowska-Sztolcman, M. Milewska, H. Koroniak, G. Bissky, J.A. Barten, G.-V. Röschenthaler, Tetrahedron Lett. 44 (2003) 8273–8277;
(c) P.K. Elkin, V.V. Levin, A.D. Dilman, M.I. Struchkova, P.A. Belyakov, D.E. Arkhipov, A.A. Korlyukov, V.A. Tartakovsky, Tetrahedron Lett. 52 (2011) 5259–5263.

[14] F. Toulgoat, B.R. Langlois, M. Medebielle, J.Y. Sanchez, J. Org. Chem. 72 (2007) 9046–9052.

[15] M.D. Kosobokov, A.D. Dilman, M.I. Struchkova, P.A. Belyakov, J. Hu, J. Org. Chem. 77 (2012) 2080–2086.

[16] A.P. Pulis, V.K. Aggarwal, J. Am. Chem. Soc. 134 (2012) 11298.

[17] K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, Org. Lett. 13 (2011) 5560–5563.