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Facile Synthesis of Highly Functionalized Ethyltrifluoroborates

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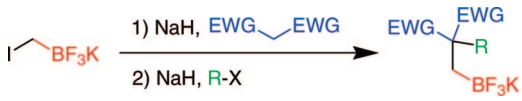


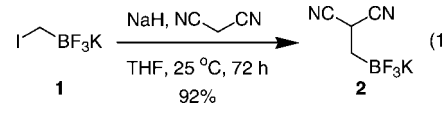
Organotrifluoroborates are generating increased interest because of their ease of preparation and purification and indefinite shelf life. Herein we report the preparation of organotrifluoroborates bearing functional groups that can be manipulated at different stages of the synthetic route, exploiting the inertness of their carbon−boron bonds. The alkylation of 2,2-dicyanoethyltrifluoroborate with a variety of electrophiles and of $(EWG)_2CH_2$ with potassium iodomethyltrifluoroborate resulted in di- and trisubstituted ethyltrifluoroborates in good to excellent yields.

Tricoordinate boronic acids are sensitive to bases, nucleophiles, and oxidants owing to their acidic protons and vacant p-orbital. Consequently, they cannot be carried through synthetic steps involving these reagents. This has limited the preparation of functionalized boronic acids under basic or nucleophilic conditions. The increased stability of boronate esters allows them to survive functionalization under some, but not all, of these conditions.

Organotrifluoroborates have emerged as a versatile alternative to boronic acids and boronate esters. They are tetracoordinate boron salts prepared from the addition of inexpensive KHF_2 to organoboron intermediates.[1] The absence of an empty p-orbital makes them mechanistically inert to many reagents utilized in organic synthesis, allowing their installation early on in a synthetic sequence. Potassium organotrifluoroborates are crystalline solids that are air- and moisture-stable and easy to handle and can be stored indefinitely without special precautions. Although aryl-, vinyl-, and allyltrifluoroborates find use in a variety of applications,[1] alkyltrifluoroborates remain relatively unexplored, with a few notable applications, including their use in the Suzuki−Miyaura cross-coupling,[2] as well as in the preparation of secondary amines[3] and alkyl iodides.[4]

Despite the advantages and increasing applicability of alkyltrifluoroborates, to date they are normally prepared by three general methods: (i) from commercially available boronic acids or boronate esters,[5] (ii) by transmetalation of organolithium or Grignard reagents,[6] and (iii) by hydroboration of alkenes.[7] For that reason, access to more highly elaborated or unique organotrifluoroborates is an area of synthetic interest. Recently, we described a new method for the preparation of a wide range of organotrifluoroborates, including potassium 2,2-dicyanoethyltrifluoroborate (**2**), by direct nucleophilic substitution of potassium iodomethyltrifluoroborate (**1**).[8] Few alkylborons have been elaborated by nucleophilic reactions at ancillary electrophilic functional groups. Herein, we expand the functional diversity of organotrifluoroborates by preparing both di- and trisubstituted ethyltrifluoroborates using just such a strategy.

The gram scale synthesis of the starting potassium 2,2-dicyanoethyltrifluoroborate (**2**) was achieved in 92% yield (eq 1). Malononitrile (3 equiv) was deprotonated with sodium hydride (3 equiv), followed by the addition of potassium iodomethyltrifluoroborate (1 equiv).[8] After completion, the reaction was quenched with potassium hydrogen fluoride to ensure counterion homogeneity, and the product was purified by precipitation from acetone−ether.[9]



With **2** in hand we investigated suitable reaction conditions for its subsequent alkylation. Initially, sodium hydride was used as the base, and the highly reactive iodomethane was utilized as the electrophile. The first solvent tested was THF, which resulted in either no reaction or complex reaction mixtures at longer reaction times. Hexamethylphosphoramide (HMPA) was added to facilitate solubilization of the anion, resulting in a 64% yield of the desired product. To avoid the use of toxic HMPA, more polar solvents (4:1 THF−DMF, DMSO, and DMF) were tested. After reacting for 4 h, all of these protocols resulted in higher yields of the desired product, with the best yields obtained

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(9) Alternatively, **2** can be prepared from pinacol iodomethylboronate (**6**); see Supporting Information for experimental details.

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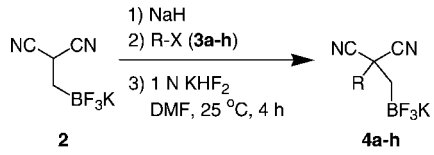
TABLE 1. Alkylation of Potassium 1,2-Dicyanoethyltrifluoroborate (2)[a]



entry	R-X	product	isolated yield (%)
1	ICH_3 **3a**	**4a**	82
2	ICH_2CH_3 **3b**	**4b**	98
3	$ICH(CH_3)_2$ **3c**	**4c**	96
4	$ICH(CH_3)CH_2CH_3$ **3d**	**4d**	95
5	$I(CH_2)_5CH_3$ **3e**	**4e**	97
6[b]	$ICH_2CH{=}CH_2$ **3f**	**4f**	43
7	$BrCH_2C{\equiv}CH$ **3g**	**4g**	83
8	$BrCH_2Ph$ **3h**	**4h**	90

[a] Reaction conditions: substrate (1 equiv), NaH (1.2 equiv), electrophile (3 equiv). [b] Reaction conditions: substrate (1 equiv), NaH (1.1 equiv), electrophile (1.1 equiv).

using DMF. Three equivalents of the electrophile were needed; use of 1 or 2 equiv gave lower yields. This set of conditions gave product **4a** in 82% yield after purification (Table 1), and the method was extended to other electrophiles with the results outlined in Table 1.

All of the products were obtained in good to excellent yields. Of note, we find no evidence for formation of the allenyl product upon using the propargyl bromide (**3g**) as an electrophile in the reaction (entry 7). Some electrophiles were ineffective in the substitution reactions. For example, only **2** was recovered when benzyl bromoacetate, 2-bromoacetophenone, and bromomethyl benzyl ether were used as the electrophiles.

Unfortunately, attempts to substitute **1** directly with nucleophiles derived from substrates such as **5a** under the conditions described in eq 1 were unsuccessful. The use of different bases (KH, NaOH, KOH, K_2CO_3) and solvents (DMSO, CH_3CN) or phase transfer catalysts did not give any product. The reaction conditions described in eq 1 along with a higher temperature (80 °C) and longer reaction time (3 d) in DMF yielded some product along with decomposition of materials as indicated by ^1H NMR. The attenuated electrophilic character of the iodomethyltrifluoroborate represents a challenge when highly enolizable or bulkier nucleophiles were employed.

An alternative route was explored starting from the pinacol iodomethylboronate (**6**),[10] which reacts by an entirely different mechanism than the iodomethyltrifluoroborate. Thus, whereas the organotrifluoroborates appear to react by a direct S_N2 reaction on the halide, the pinacolboronates react by initial complexation of the nucleophile at the boron, generating an intermediate "ate" complex. This is followed by an α-transfer process in which the nucleophile migrates, displacing the halide intramolecularly. Reaction of **6** with various stabilized anions followed by the addition of KHF_2 thus afforded the desired organotrifluoroborates in good yields (Table 2). Only an equimolar amount of base, electrophile, and nucleophile was required to afford the product. A significant advantage of the organotrifluoroborate products over that of the corresponding boronates is the easy purification of the former products via acetone−ether precipitation. In contrast, the boronate esters are usually purified by distillation at high temperatures.[11]

In summary, the high-yielding synthesis of functionalized ethyl trifluoroborates has been described, including the 1 g synthesis of **2**. The scope and limitations in the alkylation of **2** were further described, demonstrating the manipulation and stability advantages of organotrifluoroborates over boronic acids and boronate esters. Studies are underway to optimize the Suzuki−Miyaura cross-coupling reaction conditions for these materials.

Experimental Section

Potassium 2,2-Dicyanoethyltrifluoroborate (2). The title compound was prepared according to the literature procedure[8] from potassium iodomethyltrifluoroborate (**1**) (1.00 g, 4.0 mmol), and the malononitrile anion [generated by treatment of malononitrile (800.6 mg of a 99% purity reagent, 12.0 mmol) with NaH (484.5 mg of a 60% dispersion in oil, 12.0 mmol)], affording 765 mg (92% yield) of the title compound as a pink solid whose spectroscopic data agree with those reported in the literature.[8]

General Experimental Procedure for the Alkylation of Potassium 2,2-Dicyanoethyltrifluoroborate. Preparation of Potassium 2,2-Dicyanobutyltrifluoroborate (4b). To a solution of potassium 2,2-dicyanoethyltrifluoroborate (**2**) (100 mg, 0.53 mmol) in 500 μL of DMF were sequentially added NaH (25 mg of a 60% dispersion in mineral oil, 0.64 mmol) and iodoethane (127 μL, 1.59 mmol). The resulting suspension was stirred at 25 °C until the reaction was complete (4.5 h) as indicated by ^{19}F NMR. The reaction was then quenched with 1 N KHF_2 (0.5 mL). The solvents were removed under high vacuum, the solid was redissolved in HPLC grade acetone (5 mL), and the insoluble salts were filtered off. After concentration, the resulting solid was redissolved in the minimum quantity of HPLC grade acetone (1 mL) and precipitated by adding Et_2O (3 mL). After decantation, the resulting solid was

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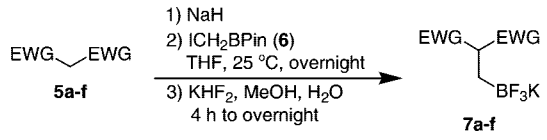
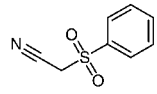
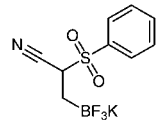
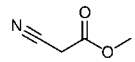
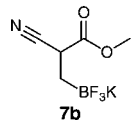
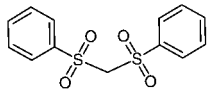
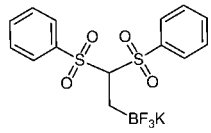
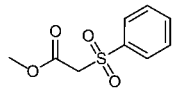
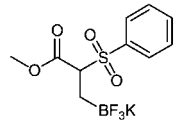
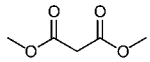
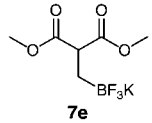
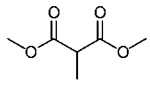
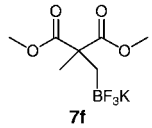
TABLE 2. Preparation of Di- and Trisubstituted Ethyltrifluoroborates[a]



entry	nucleophile	product	isolated yield (%)
1	 **5a**	 **7a**	62
2	 **5b**	 **7b**	76
3	 **5c**	 **7c**	70
4	 **5d**	 **7d**	75
5	 **5e**	 **7e**	64
6	 **5f**	 **7f**	72

[a] Reaction conditions: nucleophile (1 equiv), NaH (1 equiv), electrophile (1 equiv).

pulverized using a mortar and pestle and washed with Et_2O (3 mL) to give a white solid (111 mg, 98% yield). Mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.94 (q, J = 7.3 Hz, 2H), 1.07 (t, J = 7.3 Hz, 3H), 0.76 (br s, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 118.5 (2C), 31.6, 9.9. ^{19}F NMR (470.8 MHz, DMSO-d_6) δ: −135.2. ^{11}B NMR (128.4 MHz, DMSO-d_6) δ: 1.91 (q, J = 52.5 Hz). IR (neat): 2937, 2250, 1683, 1463, 1269, 1024, 926, 770, 483 cm^{-1}. HRMS (*m*/*z*): calcd for $C_6H_7BF_3N_2$, 175.0654 [M − K]$^+$, found 175.0654.

General Experimental Procedure for the Alkylation with Pinacol Iodomethylboronate. Preparation of Potassium Methyl 2-Cyano-3-(trifluoroborato) Propanoate (7b). A flame-dried round-bottom flask with a stir bar was charged with 95% NaH dispersion in mineral oil (14 mg, 0.54 mmol) followed by anhydrous THF (1.7 mL). The flask was cooled to 0 °C, and methyl cyanoacetate (53.4 mg, 0.54 mmol) was added dropwise via syringe. The reaction was slowly warmed to 25 °C and stirred under N_2 for 2 h. Next, the pinacol iodomethylboronate (141.8 mg, 0.53 mmol) was added dropwise and stirred at 25 °C until the reaction was complete as indicated by ^{11}B NMR (12 h). The reaction was quenched with ∼1 mL of H_2O and extracted using Et_2O (∼3 mL). The organic layer was washed with H_2O (2 × 2 mL) and brine (1 × 2 mL). The product was dried ($MgSO_4$), filtered, and concentrated. (Note: in one instance the aqueous workup was not performed, and the yield of the product was unaffected.) The crude product was redissolved in 5.25:1 MeOH−H_2O (1.35 mL) followed by the addition of KHF_2 (124.2 mg, 1.59 mmol). The reaction was stirred at 25 °C until completion as indicated by ^{11}B NMR (4 h). The solvent was then removed under high vacuum and the material redissolved in HPLC grade acetone (10 mL). The insoluble salts were filtered off, and the filtrate was concentrated. The crude product was redissolved in the minimum amount of HPLC grade acetone (2 mL) necessary and precipitated by adding Et_2O (6 mL). The solid was collected via decantation to give a light yellow solid (88.4 mg, 76% yield). Mp = 100−105 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ: 3.69 (s, 3H), 3.44 (t, J = 7.5 Hz, 1H), 0.77 (d, J = 34.5 Hz, 2H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ: 171.1, 120.7, 53.1, 34.9. ^{19}F NMR (470.8 MHz, acetone-d_6) δ: −142.32 (s). ^{11}B NMR (128.4 MHz, acetone-d_6) δ: 4.35 (s). IR (neat): 2958, 2254, 1740, 1439, 1259, 1036 cm^{-1}. HRMS (*m*/*z*): calcd for $C_5H_6BF_3NO_2$, 180.0444 [M − K$^+$], found 180.0422.

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

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