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A Direct Method to Prepare Zwitterionic Organotrifluoroborates: Ammonium and Sulfonium Derivatives

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ABSTRACT

Organotrifluoroborates are an important functional group that is used in synthesis, diagnostics, and, more recently, in theranostics. Here, we present a practical, one-step synthesis of ammonium and sulfonium trifluoroborate zwitterionic derivatives by N- or S- alkylation of bromomethyltrifluoroborate. The reaction proceeds smoothly to produce the desired compounds with good to excellent yields. In particular, the preparation of some sulfonium trifluoroborate derivatives, which avoids the use of expensive or troublesome reagents, their complete spectroscopic characterization, and an example of their application in a click-chemistry reaction are reported.

1 | Introduction

Organotrifluoroborates ($R\text{-}BF_3^-$) are known to be crystalline compounds, easy to handle, and quite stable to moisture and air [1]. Vedejs first described the synthesis of organotrifluoroborates from boronic acids or esters using the convenient and inexpensive reagent KHF_2 [2]. Among them, pinacol esters of organoboronic acid are the main stable and versatile precursors of $R\text{-}BF_3K$ salts. The stability of organo-BF_3 equivalents of organoboronic acids makes these organoboron species resistant to undesirable side reactions with the commonly employed organic reagents, so that they can be considered as a protected form of boronic acids. On the other hand, organotrifluoroborates found application in imaging techniques, where they have recently been used as positron emission tomography (PET) tracers after being labeled with ^{18}F. In this context, as the *in vivo* use of BF_3-containing compounds requires dilution to micromolar levels or less, a sufficient resistance to solvolytic defluorination would be of fundamental importance [3]. Therefore, over the years, some groups have investigated the chemical and metabolic stability of this functional group, highlighting how structural changes can significantly impact their stability [4, 5].

Specifically, electron-withdrawing substituents reduce the rate of solvolysis of aryltrifluoroborates, while electron-donating groups increase it. In particular, it has been observed that a positively charged heteroatom at the β-position significantly enhances the kinetic stability of nonaromatic organotrifluoroborates in water, up to several orders of magnitude. When these zwitterionic species are introduced into molecules capable of targeting malignant cells, it makes them promising agents for PET [6, 7] and, more recently, as radiohybrid theranostics [8] and as theranostics for boron neutron capture therapy [9–11].

Finally, in recent years, trifluoroborate groups (BF_3) have been investigated as probes for ^{19}F magnetic resonance imaging (MRI) using a macrocyclic BF_3-attached ligand [12, 13].

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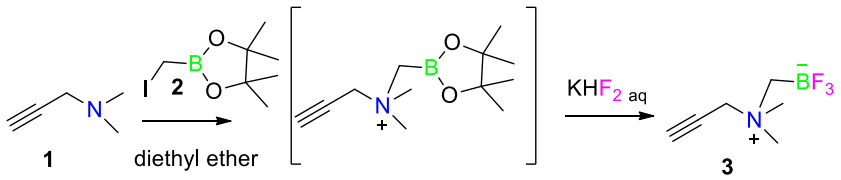
2 | Results and Discussion

Due to its remarkable stability, the most extensively exploited zwitterionic propargyldimethylammonio methyltrifluoroborate ($AMBF_3$) was introduced as a PET tracer linker in 2014 [14]. Its synthesis requires two sequential steps. First is the alkylation of *N*,*N*-dimethylpropargylamine with 2-iodomethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (ICH_2BPin) **2** in diethyl ether. The obtained salt is then treated with 3 M aqueous solution of KHF_2 to exchange the pinacol with the fluorine atoms (Scheme 1). After evaporation of the solvent, the product **3** is recovered with hot acetone, eliminating the insoluble salts. Although the above procedure is commonly used [4, 15] to search for more convenient procedures that allow direct access to both ammonium and sulfonium derivatives, we came across the commercially available potassium (bromomethyl)-trifluoroborate (**4**) and decided to test its suitability on 1,2-dimethylpropargylamine (**1**). Potassium (bromomethyl)-trifluoroborate has been previously exploited for the alkylation of secondary amines. That method has been herein adapted and extended to generate the zwitterionic species using tertiary amine and thioether nucleophiles [16].

The tertiary amine was dissolved in dry tetrahydrofuran (THF) (over molecular sieves 3 Å), and potassium (bromomethyl)trifluoroborate (1.1 eq) was added (entry 1). The mixture was refluxed for 6 h, and the reaction's progress was monitored by thin layer chromatography (TLC). The solvent was evaporated, and the zwitterionic species was recovered using hot acetone, filtering off the insoluble salts (see SI for details). Purification through a short chromatography column gave the final compound in excellent yield. To determine the optimal conditions, various solvents were tested, and to our pleasure, we observed similar results under nearly all conditions (Table 1).

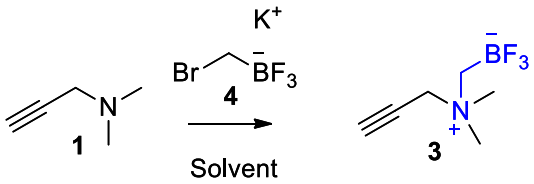
Polar aprotic solvents such as THF, acetonitrile (ACN), methyl-THF, acetone, dichloromethane, and ethyl acetate work well (entries 1–5, 8), as well as protic solvents such as ethanol (entry 6) and apolar solvents such as toluene (entry 7). Dry solvents (molecular sieves 3 Å) performed better (entries 1–8) compared to non-dried counterparts (entry 9). Performing the reaction at room temperature required longer times and resulted in a drastic decrease in yield. (entry 10). Pleased with these preliminary results, we prepared several zwitterionic derivatives, as reported in Figure 1, starting from commercially available tertiary amines to demonstrate the versatility of the reaction on several amines containing heteroatoms (**7**) and other potential reactive functionalities (**5**, **6**, **9**), as well as monoalkylation for compound **8**.

The reactions were carried out either in dry acetonitrile or in dry THF using a slight excess of **4** (see SI). Alkylation



SCHEME 1 | Typical procedure for the preparation of organotrifluoroborate ammonium salt.

TABLE 1 | Optimization of the Reaction Conditions.



Entry[a]	Solvent[b]	T°C	Time (hours)	Isolated yield[c]
1	THF	Reflux	6	90%
2	ACN	Reflux	5	87%
3	Methyl-THF	Reflux	5	75%
4	Acetone	Reflux	5	77%
5	Ethyl acetate	Reflux	5	86%
6	Ethanol	Reflux	5	87%
7	Toluene	Reflux	4.5	87%
8	DCM	Reflux	5.5	81%
9	Ethyl acetate[d]	Reflux	6.5	80%
10	Ethyl acetate[d]	rt	96	40%

[a]The reaction was performed using 1 mmol of **4** and 0.9 mmol of **1** in 1 mL of the corresponding solvent.
[b]Solvents were dried over molecular sieves (3 Å).
[c]Isolated yield after chromatographic purification.
[d]The solvent was used as supplied.

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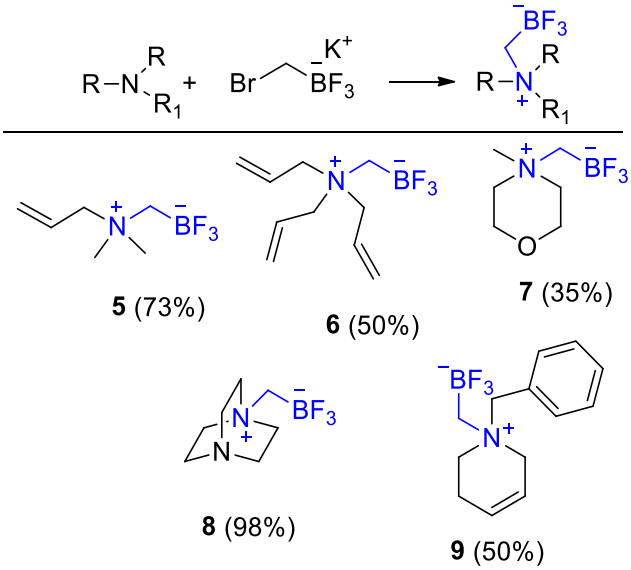
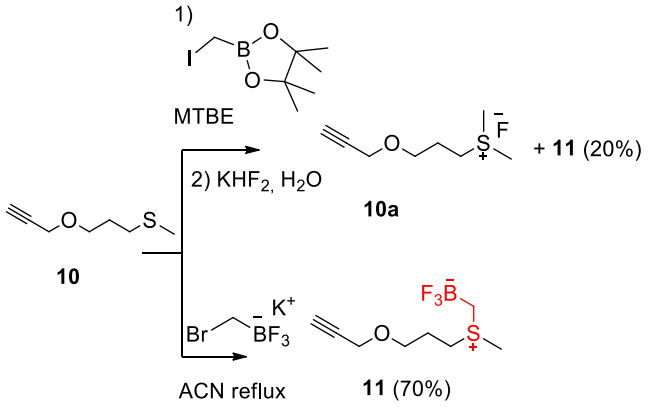


FIGURE 1 | Scope of the method for the synthesis of ammonium trifluoroborates.

of *N*,*N*-dimethylallylamine, triallylamine, and 1-benzyl-1,2,3,6-tetrahydropyridine led to compounds **5**, **6**, and **9**, respectively, in satisfactory yields. For **7** and **8**, a stoichiometric amount of the alkylating agent was used. The lower yield for compound **7** likely stems from the reduced reactivity of *N*-methylmorpholine.

The preparation of alkyl sulfonio trifluoroborates has been demonstrated to be more challenging. To the best of our knowledge, in literature only one sulfonium trifluoroborate is described, namely, the *S*-methylphenylsulfoniomethyltrilfuoroborate **15**. Its preparation involves the use of harmful silver perchlorate and a large excess of thioanisole in the alkylation step. It is quite surprising that no other derivatives of this family have been prepared, as the trialkylsulfonium group stabilizes the trifluoroborate moiety in an aqueous solution at physiological pH for months [4]. Intrigued by their properties, we decided to explore the conditions for the preparation of sulfonium methyltrifluoroborates on the model compound **10** (see SI for its preparation). We began by testing the two-step procedure, namely alkylation of sulfur with ICH_2Bpin **2** in methyl tert-butyl ether followed by the treatment with aqueous 3 M KHF_2 (Scheme 2) to avoid noxious reagent silver perchlorates, but we encountered an unexpected scenario: the TLC showed an intense spot at the bottom, with respect to the spot of the expected product when using a solvent system able to move zwitterionic organotrifluoroborates (SiO_2, 95:5 DCM:MeOH). To gain insight, the mixture was partitioned between chloroform and water, the aqueous phase was evaporated, and the residue was analysed by NMR spectroscopy (see SI), where we could detect only the deboronated compound **10a** (a yield cannot be given due to the presence of residual salts). Only a small amount (20%) of compound **11** was detected in the organic phase. The outcome of the reaction may be related to protodeboronation of boronic esters already described in the presence of fluorine ions and water [17].

When we performed the alkylation procedure with the bromomethyl trifluoroborate (**4**) in acetonitrile at reflux (Scheme 2), we were pleased to observe a clear spot in TLC corresponding to the desired product **11**. The solvent was evaporated, and the zwitterionic species was recovered using hot acetone, filtered,



SCHEME 2 | Synthesis of sulfonium methyltrifluoroborate **11**.

washed with acetone, and concentrated under reduced pressure. The product was purified by chromatography column, obtaining the alkyl sulfonium ion **11** in satisfactory yield. Pleased with this encouraging result, we extended the procedure to other thioethers, obtaining final compounds in good to excellent yields as reported in Figure 2.

The reaction worked well on different substrates, leading to amino acid derivative **12** and alkyl compounds (**13**, **14**). Alkylation of methyl(phenyl)sulfane and benzyl(methyl)sulfane to obtain respective compounds **15** and **16** proceeded smoothly in acceptable yields.

Since these classes of compounds are not very common, a full characterization was performed, including ^{19}F and ^{11}B NMR spectra. Careful investigation of ^{13}C NMR provided interesting information regarding the spin–spin coupling between carbon atoms and fluorine atoms separated by four single bonds [18]. The interaction is detectable through the identification of some ^{19}F-coupled carbon signals with the expected multiplicity (quartet). In the case of ammonium derivatives, the $^{4}J_{C\text{-}F}$ coupling

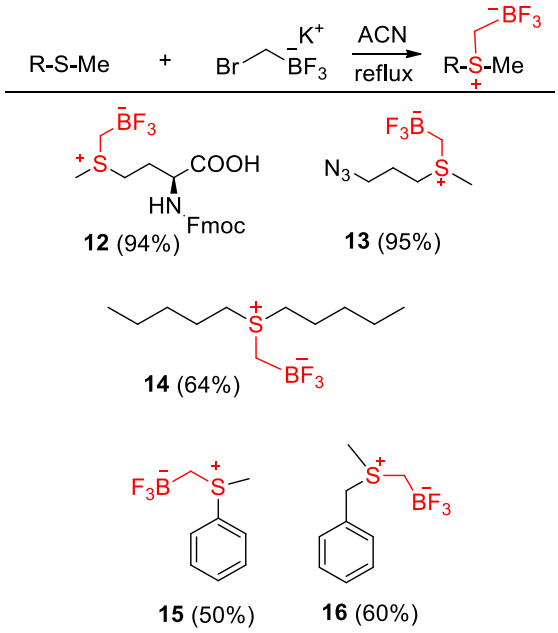


FIGURE 2 | Scope of the method for the synthesis of sulfonium trifluoroborates.

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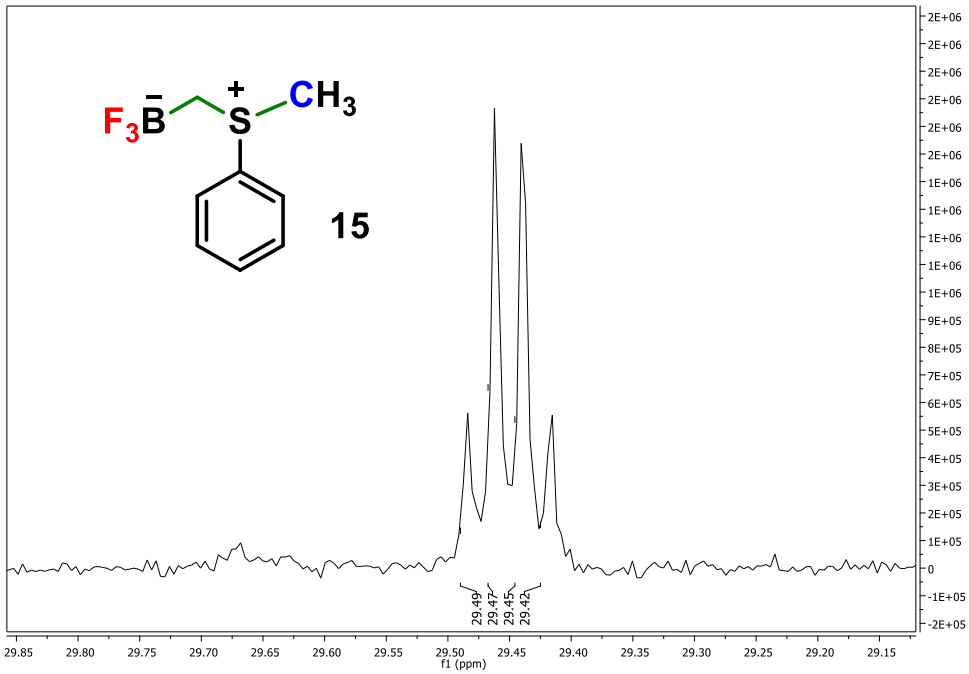


FIGURE 3 | Expansion of the ^{13}C methyl signal of compound **15** ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5 (q, $J = 2.2$ Hz).

TABLE 2 | $^4J_{C\text{-}F}$ from selected ^{13}C NMR data for sulfonium trifluoroborates.

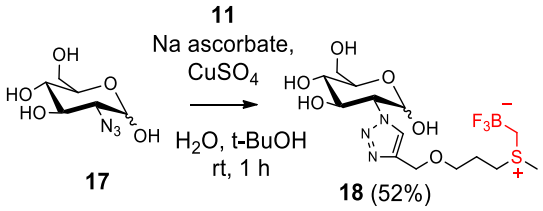
Compound	Solvent	ppm[a]	Signal (q)	$^4J_{C\text{-}F}$ (Hz)
11	CD_3OD	25.1	SCH_3	2.1
13	CD_3OD	23.8	SCH_3	1.7
14	CD_3OD	40.4	CH_2CH_2S	1.5
15	$CDCl_3$	29.5	SCH_3	2.2
16	CD_3OD	22.8	SCH_3	1.7

[a]Identification signal at ^{13}C.

was detected only for compound **9** (δ 65.7, q, $J = 2.9$ Hz, benzylic CH_2, visible only after resolution enhancement), while for the other ammonium derivatives (**3**, **5**, **6**, **7**, **8**), the coupling resulted into a broad ^{13}C signals, probably due to the presence of the quadrupolar nitrogen nucleus. In sulfonium derivatives, we were able to detect the multiplicity of signals more clearly. Figure 3 shows the expansion of the -SCH_3 signal in ^{13}C NMR spectrum of compound **15**, where a clear quartet is detected, as evidence of the $^4J_{C\text{-}F}$ coupling. On the other hand, the coupling constant between fluorine and the CH_2 group between boron and sulfur cannot be measured as the signal is very broad due to the coupling with fluorine and to the quadrupolar effect of ^{11}B [19].

$^4J_{C\text{-}F}$ values have been measured for compounds reported in Table 2, showing a range between 1.5 and 2.2 Hz, depending on substrate.

Having in hand several potential linkers, we decided to test the applicability on a model compound. As the stability and reactivity of alkyne **3** are well documented [15, 20–23], we chose to explore the click reaction of the new alkyne **11** with the sugar derivative **17** [24] in a water and t–BuOH mixture with sodium ascorbate and copper sulfate (Scheme 3). With our pleasure, the reaction



SCHEME 3 | Synthesis of **18**.

proceeded quickly in only 60 min, and the solvent was then evaporated, allowing the compound **18** to be easily purified via chromatography column (yield 52%). This confirmed the stability of the moiety when exposed to silica gel, unlike previous studies, where the facile hydrolysis of other trifluoroborates has been observed [25].

3 | Conclusion

In summary, an efficient synthesis of stable trifluoroborate ammonium and sulfonium salts was achieved, exploiting potassium (bromomethyl)trifluoroborate as a key reagent. The zwitterionic compounds were found to be stable under chromatographic conditions. The compounds were carefully characterized, and, for the sulfonium derivatives, $^4J_{C\text{-}F}$ were observed, and their values were determined. The novel moieties suitable for application in bioconjugation will be explored for theranostic and imaging purposes.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. The Supporting Information is available free of charge on the ACS Publications website and reports: Experimental procedures, full spectroscopic data for all new compounds, and copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{11}B NMR spectra.

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