New Electrophilic Bromodifluoromethylation and Pentafluoroethylation Reagents

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Abstract: *S*-(fluoroalkyl)diphenylsulfonium salts have been successfully synthesized from the reaction between fluoroalkylsulfinates and triflic anhydride in dichloromethane through a one-pot procedure. These *S*-(fluoroalkyl)diphenylsulfonium salts have been demonstrated to be effective reagents to fluoroalkylate C-nucleophilic substrates. Ionic substitution and radical or halogenophilic mechanism might be all involved in the reactions.

Key words: fluorine, nucleophiles, sulfoxides, *S*-(fluoroalkyl)diphenylsulfonium salts, fluoroalkylation

Compounds containing the fluoroalkyl group have been confirmed to be very important in organic chemistry. The introduction of the fluoroalkyl group into organic molecules often changes their physical, chemical, and physiological properties.[1] Due to the recent progress in these fields, methodologies for the direct introduction of the perfluoroalkyl group are now available through nucleophilic, free radical, and electrophilic approaches.[2] Electrophilic perfluoroalkylation, one of the three fundamental fluoroalkylation methods, has become increasingly important in organic synthesis. However, it is not a trivial task. The formation of the fluoroalkyl cation in these electrophilic fluoroalkylation reagents is quite difficult due to the highest electronegativity of the fluorine atoms.[3] Even so, many reagents have been developed to introduce the fluoroalkyl group into organic molecules. In 1970's, Yagupolskii reported a method for perfluoroalkylation using (perfluoroalkyl)-*p*-tolyl-iodonium salts as the first electrophilic perfluoroalkylation reagent in polar solvent under mild conditions.[4] In 1984, two trifluoromethyl sulfonium salts were prepared as another class of electrophilic perfluoroalkylation reagent, which could react with sodium *p*-nitrothiophenolate in DMF to give *p*-nitrophenyltrifluoromethyl sulfide in high yield.[5] Umemoto further extended these methods to the synthesis of (perfluoroalkyl)phenyliodonium trifluoromethanesulfonates, (perfluoroalkyl)-phenyliodonium hydrogensulfates, and some powerful electrophilic perfluoroalkyl sulfonium agents that could transfer the perfluoroalkyl group to different kinds of organic molecules.[6] In 1998, Shreeve and co-workers developed an alternative route to prepare the analogous trifluoromethyl sulfonium salts from inexpensive reagents and improved their electrophilic power by introducing electron-withdrawing substituents on the benzene rings.[3b] Recently, Prakash reported two new electrophilic fluoromethylating reagents, *S*-(difluoromethyl)diaryl-sulfonium tetrafluoroborate and *S*-(monofluoromethyl)diarylsulfonium tetrafluoroborate, which were shown to be effective for the introduction of difluoromethyl or monofluoromethyl group into C, S, O, N, and P nucleophiles.[7] Although these reagents are very useful, they are always prepared by multistep and laborious synthetic procedures. In 2006, E. Magnier et al. developed a very short and efficient method to synthesize aryl trifluoromethyl sulfonium salts in one pot.[8] Then they extended this method and successfully synthesized some new trifluoromethyl dibenzothiophenium salts such as Umemoto-type reagents.[9] So far, most studies are limited to simple fluoroalkyl sulfonium salts. In order to acquire more information about the electrophilicity of bromodifluoroalkyl and long fluoroalkyl sulfonium salts, we investigated the synthesis and reaction of these fluoroalkyl sulfonium salts.

Based on the previous reports,[3b,8,9] *S*-(fluoroalkyl)diphenylsulfonium salts were synthesized from the simple and inexpensive material in a one-pot procedure (Table 1). Reactivity was tuned successfully via trifluoromethanesulfonylation of fluoroalkylsulfinates with triflic anhydride in dichloromethane. For example, (bromodifluoromethyl)diphenylsulfonium trifluoromethanesulfonate (**1a**) was formed in 44% yield when sodium bromodifluoromethanesulfinate reacted with benzene and triflic anhydride in dichloromethane at 0 °C for 2 hours and then at room temperature for 22 hours (Table 1, entry 1). Its structure was confirmed by single-crystal X-ray diffraction analysis (Figure 1).[10] The reaction became complicated, and the expected sulfonium salts were obtained in a minor amount with longer fluoroalkyl chains. As shown in Table 1, only 20% of (pentafluoroethyl)diphenylsulfonium triflate (**1b**) was formed even after 4 days (entry 2). ^{19}F NMR analysis of the reaction mixture showed that many side reactions occurred. Oxidation of fluoroalkyl sulfinate happened during the reaction. Similar results were obtained in the case of sodium 2-chloro-1,1,2,2-tetrafluoroethanesulfinate (entry 3).

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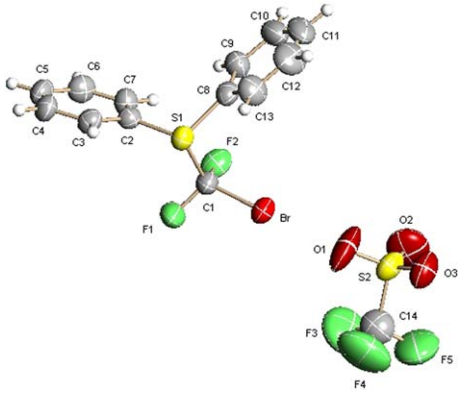
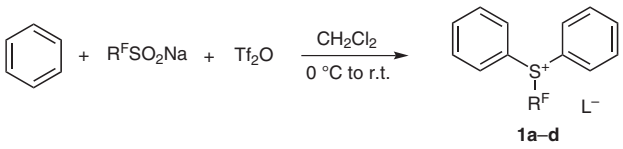


Figure 1 X-ray Crystallographic Structure of **1a**

Table 1 One-Pot Synthesis of *S*-(Fluoroalkyl)diphenylsulfonium Salts[11]



1a–d

Entry	$\mathbf{R^F}$	$\mathbf{R^FSO_2Na}$/ Tf_2O	Time (d)[a]	L	Yield (%)[b]
1	$BrCF_2$	1:2.4	1	CF_3SO_3	**1a** 44
2	CF_3CF_2	1:2.4	4	CF_3SO_3	**1b** 20
3	$Cl(CF_2)_2$	1:2.4	4	$Cl(CF_2)_2SO_3$, CF_3SO_3	**1c** 8
4	$Cl(CF_2)_4$	1:2.4	5	$Cl(CF_2)_4SO_3$	**1d** 4.5

[a] Reacted first at 0 °C for 2 h and then at r.t.
[b] Isolated yield.

Trifluoromethanesulfonate and 2-chloro-1,1,2,2-tetrafluoroethanesulfonate anions were both involved in the sulfonium salts **1c**. Efforts to isolate the two salts failed. In addition, when sodium 4-chloro-1,1,2,2,3,3,4,4-octafluorobutanesulfinate reacted with benzene and triflic anhydride in dichloromethane, (4-chloro-1,1,2,2,3,3,4,4-octafluorobutyl)diphenylsulfonium salt (**1d**) with only one anion was obtained, but the yield was extremely poor (entry 4). Oxidation of 4-chloro-1,1,2,2,3,3,4,4-octafluorobutanesulfinate to the corresponding sulfonate also happened. Triflic anhydride has been known for its oxidative properties,[12] yet there is no explanation proposed. Trifluoromethanesulfonate anions existing in sulfonium salts became easier to be replaced by the oxidized sulfonate with increasing length of the fluoroalkyl chain. The purity of the sodium fluoroalkylsulfinate is an essential factor for the success of this reaction, just as the literature reported.[9] Lower purity of the sodium 2-chloro-1,1,2,2-tetrafluoroethanesulfinate always resulted in the failure of preparation of the desired sulfonium salts. The temperature also has an influence on the yield of the reaction. At the beginning of the reaction, lower reaction temperature had to be employed to assure the mild transformation of fluoroalkylsulfinates. Otherwise, only trace amount of the product was obtained.

With these new *S*-(fluoroalkyl)diphenylsulfonium salts in hand, we investigated their potential to act as electrophiles in alkylation reactions. Sulfonium salts **1a** and **1b** were taken as examples. Bromodifluoromethylation of (2-phenylethynyl)lithium with **1a** proceeded smoothly (Table 2, entry 1). (2-Phenylethynyl)lithium was prepared in situ before **1a** was added in this reaction. Arylethynyl lithium with electron-donating or electron-withdrawing substituent at *para* position of the phenyl ring was bromodifluoromethylated equally well under this reaction condition (entries 2 and 3). Both **2b** and **2c** were formed in moderate yield. Similar result was obtained while treating **1a** with hept-1-ynyllithium (entry 4). Other C-nucleophiles were also successfully bromodifluoromethylated with **1a**. Compound **2e** was satisfactorily produced when **1a** reacted with ethyl 2-methyl-3-oxobutanoate in DMF at –50 °C to room temperature (entry 5).

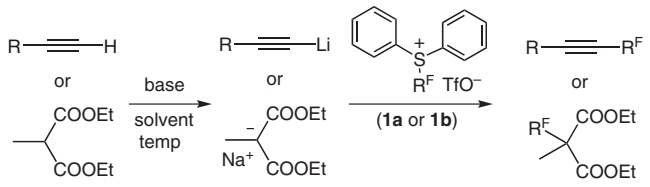
A comparison of these results with the previous reports led us to think that an electrophilic mechanism might be involved in this bromodifluoromethylation reaction.[3b,6c] However, when ethyl 2-methyl-3-oxo-butanoate was replaced by 2-methylcyclopentane-1,3-dione in this reaction, 3-(difluoromethoxy)-2-methyl-cyclopent-2-enone (**2f**) was obtained in 50% yield (entry 6). Trace of bromodifluorinated product could be detected by ^{19}F NMR but not isolated due to its low yield. This indicated that the radical or halogenophilic mechanism could not be excluded in this reaction system.[6c] These mechanisms might coexist and compete with each other. The predominant pathway might depend on the nucleophiles and the reaction conditions.

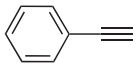
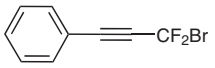
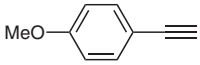
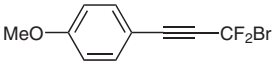
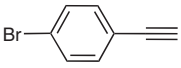
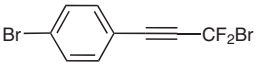
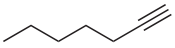
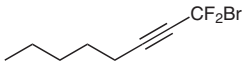
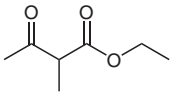
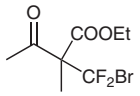
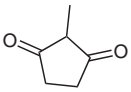
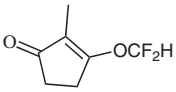
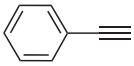
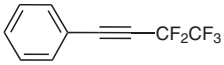
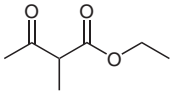
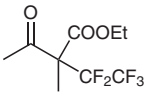
Pentafluoroethylated product was similarly formed in the reaction of sulfonium salt **1b** with phenylacetylene or ethyl 2-methyl-3-oxobutanoate (entries 7 and 8). ^{19}F NMR measurement of the reaction course (entries 7 and 8) showed the simultaneous formation of undesired 1*H*-pentafluoroethanes (CF_3CF_2H). This might be another evidence for the coexistence of the radical and ionic substitution mechanism in these reactions.

In summary, we have successfully synthesized *S*-(bromodifluoromethyl)- and *S*-(pentafluoroethyl)diphenylsulfonium salts by using a slightly modified Magnier's approach. Because of the strong electronegativity of the fluorine atoms, sulfonium salts with long fluoroalkyl chain are very difficult to synthesize. The purity of the sodium fluoroalkylsulfinate as well as the temperature used at the beginning of the reaction has great influence on the reaction. These *S*-(fluoroalkyl)-diphenyl-sulfonium salts have been demonstrated to be effective electrophilic fluoroalkylating agents of C-nucleophilic substrates. Ionic substitution and radical or halogenophilic mechanism might be all involved in these fluoroalkylation reactions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 Electrophilic Fluoroalkylation of Sulfonium Salts[13,14]



Entry	Substrates	Conditions (base, temp, solvent)[a]	Products	Yield (%)[b]
1		BuLi, –78 °C, **1a**, then r.t., THF		**2a** 47
2		BuLi, –78 °C, **1a**, then r.t., THF		**2b** 52
3		BuLi, –78 °C, **1a**, then r.t., THF		**2c** 57
4		BuLi, –78 °C, **1a**, then r.t., THF		**2d** 45
5		NaH, –50 °C, **1a**, then r.t., DMF		**2e** 55
6		NaH, –50 °C, **1a**, then r.t., DMF		**2f** 50
7		BuLi, –78 °C, **1b**, then r.t., THF		**2g** 25
8		NaH, –50 °C, **1b**, then r.t., DMF		**2h** 33

[a] Anions was first generated in the reaction with BuLi or NaH at –78 or –50 °C. Then the fluoroalkylating agents were added. The cooling bath was removed, and the reaction system was warmed to r.t.
[b] Isolated yield.

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(10) CCDC 759656 contains the supplementary crystallographic data for the compound **1a**. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
(11) **Typical Procedure for the Preparation of 1a–d**
Under nitrogen atmosphere, benzene (7.5 mL, 84.0 mmol) and trifluoromethanesulfonic anhydride (6.0 mL, 35.5 mmol) were added into a suspension of sodium pentafluoroethanesulfinate[15] (3.18 g, 15.4 mmol) in CH_2Cl_2 (5 mL), which was well cooled by ice bath. After vigorously stirring at 0 °C for 2 h, the reaction mixture was warmed to r.t. and continued to react for 4 d. Then the reaction mixture was

diluted with CH_2Cl_2 (60 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using CH_2Cl_2–MeCN (4:1) as the eluent. After recrystallization from pentane–EtOAc, 1.40 g of **1b** (20%) was obtained as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (t, *J* = 7.7 Hz, 2 H), 7.95 (t, *J* = 8.2 Hz, 1 H), 8.34 (d, *J* = 8.2 Hz, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –94.5 (s, 2 F), –75.7 (s, 3 F), –76.8 (s, 3 F). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 133.9, 132.3, 120.7 (q, *J* = 318.5 Hz, CF_3), 117.0. ESI-MS: *m/z* = 305.0 [M$^+$]. IR (KBr): 3067, 1477, 1455, 1331, 1288, 1254, 1234, 1160, 1128, 1031, 938, 757, 639, 517, 504 cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_8O_3S_2$: C, 39.65, H, 2.22. Found: C, 39.64, H, 2.51.

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(13) **Typical Procedure for the Fluoroalkylation of 2a–d,g**
To a 25 mL round-bottomed flask, 1-ethynylbenzene (50 mg, 0.49 mmol) and anhyd THF (4 mL) were added and maintained under a N_2 atmosphere at –78 °C. *n*-BuLi (0.22 mL of a 2.5 mol L^{-1} solution in hexane, 0.55 mmol) was added, and the reaction mixture was stirred at –78 °C for 30 min. Then **1b** (226 mg in 2 mL of anhyd THF, 0.50 mmol) was added. After 1 h, the cooling bath was removed, and the reaction was warmed naturally to r.t. Then the reaction mixture was poured into H_2O (30 mL), extracted with Et_2O (30 mL), washed with brine (3 × 20 mL), and dried over anhyd Na_2SO_4. Et_2O was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel using pentane as the eluent; 28 mg of **2g** (25%) was obtained as a colorless liquid. ^{1}H NMR: δ = 7.57 (d, *J* = 7.7 Hz, 2 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 7.7 Hz, 2 H). ^{19}F NMR: δ = –101.2 (q, *J* = 4.2 Hz, 2 F), –85.3 (t, *J* = 4.2 Hz, 3 F).

(14) **Typical Procedure for the Fluoroalkylation of 2e–f,h**
To a 25 mL round-bottomed flask, ethyl 2-methyl-3-oxobutanoate (70 mg, 0.49 mmol) was dissolved in anhyd DMF (4 mL). NaH (24 mg, 56%, 0.56 mmol) was added under a N_2 atmosphere. The reaction mixture was stirred at r.t. for 30 min then cooled to –50 °C. Compound **1b** (226 mg in 2 mL of anhyd DMF, 0.50 mmol) was added, and the cooling bath was removed. After warming naturally to r.t., the reaction mixture was poured into H_2O (30 mL), extracted with Et_2O (30 mL), washed with brine (3 × 20 mL), and dried over anhyd Na_2SO_4. The ether layer was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using PE–EtOAc (10:1) as the eluent; 42 mg of **2h** (33%) was obtained as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 (q, *J* = 7.3 Hz, 2 H), 2.34 (s, 3 H), 1.61 (s, 3 H), 1.30 (t, *J* = 7.3 Hz, 3 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.5 (dd, AB, $^2J_{FF}$ = 282.5 Hz, 2 F), –78.8 (s, 3 F). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.1, 166.1, 63.3 (t, *J* = 19.5 Hz), 62.8, 27.9, 15.6, 13.7. MS (EI): *m/z* = 43 (100), 44 (5.3), 73 (3.0), 77 (2.9), 105 (7.3), 123 (6.1), 192 (3.4), 220 (7.3). IR (KBr): 2988, 2942, 1734, 1466, 1389, 1365, 1338, 1260, 1209, 1107, 1004, 745 cm^{-1}. HRMS: *m/z* calcd for $C_9H_{11}O_3F_5$: 262.0628; found: 262.0625.

(15) For the preparation of sodium fluoroalkylsulfinates, see: (a) Huang, W.-Y.; Zhang, H.-Z. *Chin. J. Chem.* **1992**, *10*, 274. (b) Hu, L.-Q.; DesMarteau, D. D. *Inorg. Chem.* **1993**, *32*, 5007. (c) Huang, W.-Y.; Huang, B.-N.; Wang, W. *Huaxue Xuebao* **1985**, 663.