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New Electrophilic Difluoromethylating Reagent

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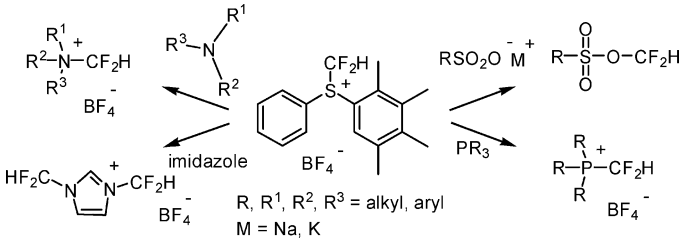
ABSTRACT



A new electrophilic difluoromethylating reagent has been developed. The *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate has been shown to be effective for the introduction of an electrophilic difluoromethyl group into the following nucleophiles: sulfonic acids, tertiary amines, imidazole derivatives, and phosphines. The reagent failed to transfer the difluoromethyl group to phenols, carbon nucleophiles, and primary and secondary amines.

A difluoromethyl group is known to be isosteric and isopolar to a carbinol (CH_2OH) unit and can act as a hydrogen donor through hydrogen bonding.[1] These properties make it a very attractive building block in medicinal chemistry and drug discovery. Because of this unique lipophilic CH_2OH substituent character, methods for the introduction of a CF_2H building block are becoming increasingly important. In spite of this, and in contrast to trifluoromethylation procedures, new methods for the direct introduction of a difluoromethyl group to organic molecules are still relatively sparse.

Although several new methods for the coupling of a difluoromethyl moiety to electrophilic carbon have been reported recently, there are few methods for the synthesis of *O*- and *S*-difluoromethyl ethers, esters, CF_2H-phosphonium salts, and *N*-difluoromethylated heterocyclic compounds. Chlorodifluoromethane,[2] fluorosulfonyl-difluoroacetic acid,[3] and difluoro diazirine[4] have been the most commonly used reagents to introduce a difluoromethyl group to oxygen, sulfur, phosphorus, and nitrogen nucleophiles for a long time. It is worth mentioning that the difluoromethylation power of fluorosulfonyldifluoroacetic acid, difluorodiaziridine, chlorodifluoromethane, and 2-chloro-2,2-difluoroacetophenone is due to a singlet difluorocarbene generated in situ by their decomposition.[5] To the best of our knowledge, an electrophilic reagent for the direct introduction of a "CF_2H^+" building block is yet to be reported. This might be due to the acidity of the proton in the CF_2H group, which can lead to the protonation (deactivation) of the nucleophilic substrate and to the decomposition of the reagent. In our opinion, this phenomenon makes it more difficult to find an appropriate difluoromethylating reagent compared to the trifluoromethylating agents.

In contrast to electrophilic difluoromethylating agents, reagents for the introduction of the trifluoromethyl group are more widely explored. *S*-(Trifluoromethyl)dibenzothiophe-

(1) (a) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882−5886. (b) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Organofluorine Chemistry*; Kodansha and Elsevier Biomedical: Amsterdam, Netherlands, 1983. (c) Computed octanol/water partition coefficient (clogp) of $PhCF_2H$ = 2.3; clogp of $PhCH_2OH$ = 1.1 (CLOGP 4.2/SYBYL 7.3 Tripos In.: St. Louis, MO).

(2) (a) Langlois, B. R.; Rhone-Poulenc, R. C.; Saint-Fosh, S. *J. Fluorine Chem.* **1988**, *41*, 247−261. (b) Lee, H.; Kim, H. S.; Lee, W. K.; Kim, H. *J. Fluorine Chem.* **2001**, 133−136.

(3) Chen, Q.-Y.; Wu, S.-W. *J. Org. Chem.* **1989**, *54*, 3023−3027.

(4) Mitsch, R. A.; Robertson, J. E. *J. Heterocycl. Chem.* **1965**, *2*, 152−156.

(5) Kirsch, P. *Modern Fluoroorganic Chemistry*; Viley-VCH Verlag GMBH & Co KGaA: Weinheim, Germany, 2004; Chapter 2.3.

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nium (**1**) and *S*-(trifluoromethyl)diphenylsulfonium salts (**2**) constitute an important subset of these reagents (Figure 1).

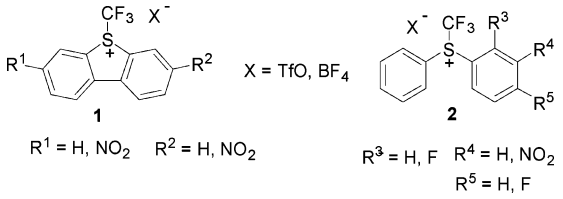


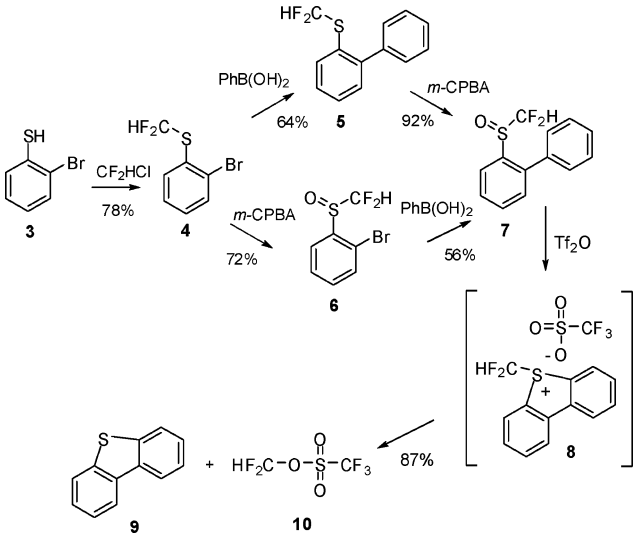
Figure 1. Electrophilic trifluoromethylating agents.

They are known to be powerful electrophilic trifluoromethylation agents, which are successfully used for the trifluoromethylation of a wide range of substrates differing in reactivity.[6] However, neither *S*-(difluoromethyl)dibenzothiophenium nor *S*-(difluoromethyl)diphenylsulfonium salts have been previously reported. Our aim was to explore the chemistry of these compounds and ascertain their use as electrophilic difluoromethylating reagents. Herein, we wish to report the results of our studies toward the synthesis of *S*-(difluoromethyl)dibenzothiophenium triflate and *S*-(difluoromethyl)diphenylsulfonium tetrafluoroborate and demonstrate the effectiveness of these reagents in electrophilic difluoromethylation reactions.

Our first target was the preparation of *S*-(difluoromethyl)-dibenzothiophenium triflate (**8**) (Scheme 1). 2-[(Difluoromethyl)sulfanyl]biphenyl (**5**) was prepared by reacting 2-bromothiophenol (**3**) with difluorochloromethane followed by Suzuki coupling of the resulting sulfide (**4**)[7] with phenylboronic acid. 2-[Difluoromethyl(sulfinyl)]biphenyl (**7**) was obtained from the oxidation of the sulfide with *m*-chloroperbenzoic acid. An alternative reaction pathway consisting of oxidation of 2-(difluoromethylsulfanyl)bromobenzene (**4**) followed by Suzuki reaction also proved to be successful. However, in the latter case, the overall yield was lower.

Cyclization of the sulfoxide (**7**) was carried out by addition of triflic anhydride to the solution in dichloromethane at 0 °C.[6b] The reaction mixture was allowed to warm to room temperature, and after 2 h of stirring, it was analyzed by ^{19}F NMR. Surprisingly, in spite of the fact that only a trace amount of sulfoxide (**7**) was detected, difluoromethyl trifluoromethanesulfonate (**10**) was identified as a major product instead of the expected sulfonium compound (**8**). Formation of the difluoromethyl ester of triflic acid can be explained by the in situ difluoromethylation of the trifluoromethylsulfonyl anion by the *S*-(difluoromethyl)dibenzothiophenium

Scheme 1. Preparation of *S*-(Difluoromethyl)dibenzothiophenium Trifluoromethanesulfonate



cation. This is supported by the fact that after the solvent was removed a quantitative amount of dibenzothiophene (**9**) was recovered. To support the formation of the *S*-(difluoromethyl)dibenzothiophenium cation, the cyclization reaction was repeated at −80 °C and the reaction mixture was monitored by low-temperature ^{19}F NMR. Under these circumstances, no trace of difluoromethyl trifluoromethanesulfonate was detected. However, a doublet observed at −101.7 ppm in the ^{19}F NMR having $J = 56.8$ Hz as the coupling constant indicates the formation of an *S*-(difluoromethyl)dibenzothiophenium cation. In 2 h at − 80 °C, the conversion was 15% relative to the sulfoxide. Apart from the doublet and the starting material's signals, no other signals were observed in the ^{19}F NMR spectrum.

To compare the reactivity of the *S*-difluoromethyl(dibenzothiophenium) cation to that of the *S*-trifluoromethyl-(dibenzothiophenium) cation, any report of the reaction of the latter with a triflate anion was checked in the literature. It was found that in the case of *S*-(trifluoromethyl)dibenzothiophenium triflate a high temperature of 200 °C is required to transfer the trifluoromethyl group to the triflate anion.[6b]

Having established the instability of *S*-(difluoromethyl)-dibenzothiophenium triflate at room temperature (the cation is too reactive towards the anion), a different approach was pursued.[6f] Considering the fact that in the case of *S*-trifluoromethyl sulfonium cations the *S*-(trifluoromethyl)-diphenylthiophenium salts (**2**) are less reactive than the appropriate *S*-(trifluoromethyl)dibenzothiophenium ones (**1**), we decided to prepare an *S*-(difluoromethyl)diphenylsulfonium derivative.

2-[(Difluoromethyl)sulfinyl]bromobenzene (**6**) was reacted in benzene with triflic anhydride at 0−5 °C. Aside from the unreacted sulfoxide, a significant amount of difluoromethyl trifluoromethanesulfonate was identified by ^{19}F NMR, after 2 h of stirring. A multiplet at −98 ppm having a pattern

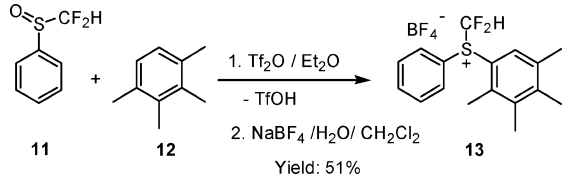
(6) (a) Yagupol'skii, L. M.; Kondratenko, N. Y.; Timofeeva, G. N. *Zh. Org. Khim.* **1984**, *20*, 115−118. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156−2164. (c) Umemoto, T.; Ishihara, S.; Adachi, K. *J. Fluorine Chem.* **1995**, *74*, 77−82. (d) Umemoto, T.; Ishihara, S. *J. Fluorine Chem.* **1999**, *98*, 75−81. (e) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692−5699. (f) Yang, J. J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1998**, *63*, 2656−2660. (g) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726−8729.

(7) Endel'man, E. S.; Danilenko, V. S.; Trinus, F. P.; Yufa, P. A.; Fadeicheva, A. G.; Muravov, I. I.; Fialkov, Y. A.; Yagupol'skii, L. M. *Khim.-Farm. Zh.* **1973**, *7*, 15−19.

matching the expected (difluoromethyl)sulfonium cation was also observed in the reaction mixture. We concluded that similar to the dibenzothiophene derivative, under the conditions needed for the formation of the sulfonium cation, the cation reacts with the triflate anion. To increase the stability of the desired (difluoromethyl)diphenylsulfonium cation, introducing electron-donating substituents onto the phenyl ring seemed a reasonable approach.

Difluoromethyl phenyl sulfoxide[8] (**11**) was prepared from difluoromethyl phenyl sulfide[9] by oxidation with *m*-CPBA. The reaction of the sulfoxide (**11**) with 1,2,3,4-tetramethylbenzene in the presence of triflic anhydride was found to be complete in 2 h by ^{19}F NMR (Scheme 2). As in previous

Scheme 2. Preparation of *S*-Difluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium Tetrafluoroborate (**13**)



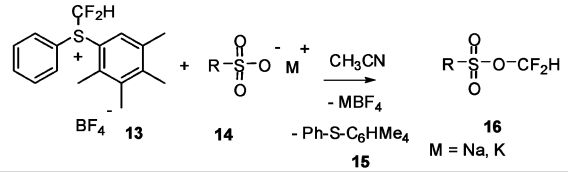
cases, difluoromethyl trifluoromethanesulfonate was also detected in the reaction. To avoid further decomposition of the product, the triflate anion was replaced by tetrafluoroborate having a weaker nucleophilic character. The obtained *S*-(difluoromethyl)diphenylsulfonium tetrafluoroborate (**13**) proved to be stable for several weeks at room temperature and for several months in the refrigerator. Only 13% decomposition was observed after 3 months storage at −20 °C.

In the course of testing the stability of the new reagent (Table 1) in different dry solvents, it was found that it decomposes within several hours in THF, alcohols, and DMF. However, it proved to be quite stable in acetonitrile and dichloromethane. In acetonitrile, only 2% decomposition was observed in 3 days at room temperature. Phenyl 2,3,4,5-tetramethylphenyl sulfide (**15**) was identified as the decomposition product in each case. The first result regarding the CF_2H transfer ability of the reagent was the formation of the expected CD_3OCF_2H in a CD_3OD solution (see Supporting Information). After 40 min, 100% conversion was observed on the basis of ^{1}H and ^{19}F NMR.

The reactivity of the reagent was tested in acetonitrile with the following nucleophiles: alcohols, phenols, thiophenols, carboxylic acids, sulfonic acids, 1-(trimethylsilyloxy)cyclohexene, aniline, imidazole, pyridine, potassium cyanide, and lithium phenylacetilide. In the case of nucleophiles bearing acidic hydrogen, the reactions were attempted with and without alkali carbonates or alkali bicarbonates. Alkali sulfonates, carboxylates, and imidazole were found to be the

(8) Prakash, G. K. S.; Hu, J.; Wang, Y. *Org. Lett.* **2004**, *6*, 4315−4317.
(9) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216−5219.

Table 1. Reaction of **13** with Sulfonic Acid Salts



entry	starting material	product	condn	convn (%)[a,b]	yield(%)[c]
1	SO_3Na	SO_3CF_2H	60°C/12 h	100	77[d]
2	SO_3Na	SO_3CF_2H	45°C/3 days	82	67
3	HO, SO_3Na	HO, SO_3CF_2H	rt/6 days	100	84
4	SO_3Na	SO_3CF_2H	60°C/1 day	88	78
5	SO_3K, SO_3K	SO_3CF_2H, SO_3CF_2H	60°C/1 day	100	89
6	O_2N, SO_3Na	O_2N, SO_3CF_2H	60°C/3 days	92	74[d]
7	SO_3Na	SO_3CF_2H	60°C/1 day	73	54
8	NaO_3S, O	HF_2CO_3S, O	60°C/12 h	100	86[d]

[a] The conversions were determined by ^{19}F NMR on the basis of the internal standard. [b] The conversions refer to the substrates. [c] Isolated yields. Reagent/$-SO_2OM$ group in substrate (molar ratio) = 2.5:1.0. [d] Known compounds. See ref 3.

best substrates. Low yields were obtained using equimolar amounts of alcohols, and we could not detect any product in the case of phenols, thiophenols, and carbon nucleophiles. Because O-nucleophiles with less basic character seemed to work well, we expected that phenols and alcohols with stronger acidic character would react. However, neither pentafluorophenol and 2,4,6-trinitrophenol nor hexafluoroisopropanol reacted under a variety of reaction conditions.

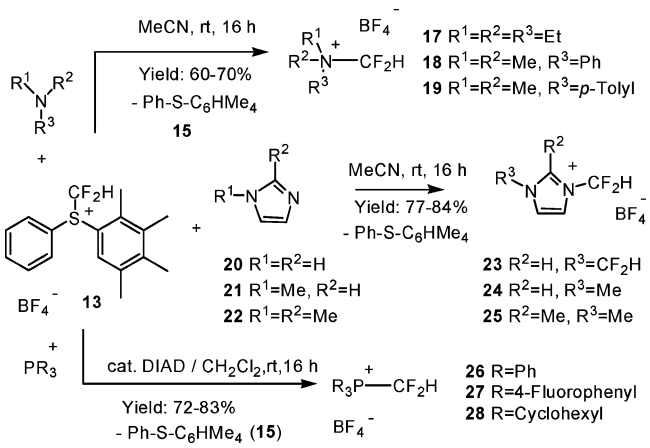
Because sulfonic acids were considered to be one of the most promising substrates, their reactions were studied more thoroughly. Li, Na, and K salts of benzenesulfonic acid were reacted under similar conditions. The highest reactivity was found in the case of K salt, but so was the concomitant decomposition. Considering these two factors and the solubility of the sulfonic acid salts, sodium salts seemed to be the best choice.

We obtained high conversions using aromatic sulfonic acids having both electron-withdrawing and electron-donating substituents. The reaction also proved to be selective in the case of phenolic as well as vinyl phenylsulfonic acid derivatives. Among aliphatic sulfonic acids, 10-camphorsulfonic acid also afforded the desired product in high yield and purity.

Although carboxylic acid sodium salts such as sodium benzoate, acetate, or sodium 4-phenylbutyrate afforded the desired difluoromethyl esters on the basis of ^{19}F NMR, they were not stable enough to be separated by silica gel column chromatography.

In the course of testing some nitrogen nucleophiles it was found that, in the presence of primary and secondary amines, the reagent decomposed without transferring the CF_2H group to the nitrogen atom. However, tertiary amines and certain nitrogen-containing heterocyclic compounds reacted readily even at room temperature to give difluoromethylammonium salts and N-difluoromethylated heterocycles (Scheme 3, **17**−**19**). Imidazole derivatives were found to be one of the most reactive substrates as evident by their exothermic reaction with **13**. It should be noted that the synthesis of *N*-difluoromethyl−ammonium compounds from tertiary and *N*-formyl secondary amines is known.[10] The preparation of *N*-(difluoromethyl)imidazolium derivatives (**23**−**25**) has not yet been reported in the literature. Perfluorinated imidazolium salts are of interest as hydrophobic ionic liquids.[11]

Scheme 3. Reaction of (**13**) with Imidazoles, Phosphines, and Tertiary Amines[a]



[a] Isolated yields. (The conversion referred to the substrate which was found to be 100% in all cases.) Reagent/substrate (molar ratio) = 1.05:1.0. In the case of non-N-alkylated imidazole, 2.1 equiv of reagent was used.

To test the reactivity toward phosphorus nucleophiles, **13** was reacted with phosphines (Scheme 3). In the case of triphenyl phosphine, we observed only 15% conversion after 1 day of stirring at room temperature. However, by repeating the experiment in the presence of at least 15% of diisopropyl azodicarboxylate, 100% conversion was achieved in 16 h. Other phosphines worked equally well under similar conditions. Although (difluoromethyl)triphenylphosphonium tetrafluoroborate is a new compound, other related salts were already known: for example, the tetrachlorobismutate salt was synthesized by reacting triphenylphosphine with $Bi(CF_3)_3$.[12]

In conclusion, the first member of the *S*-(difluoromethyl)-diphenylsulfonium ion derivative family has been synthesized. It has been shown that it is a useful electrophilic difluoromethylating reagent for varied oxygen, nitrogen, and phosphorus nucleophiles.

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Supporting Information Available: General experimental procedure and spectroscopic data of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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