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# Direct Electrophilic Monofluoromethylation

**G. K. Surya Prakash,* Istvan Ledneczki, Sujith Chacko, and George A. Olah***

*Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661*

*gprakash@usc.edu; olah@usc.edu*

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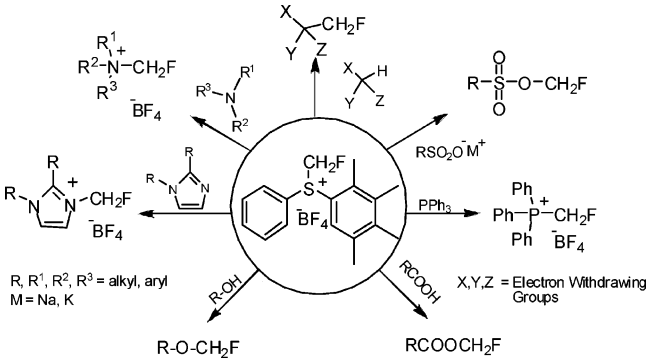
## ABSTRACT




**Monofluoromethyl derivatives of various nucleophiles have been synthesized using a new electrophilic monofluoromethylating reagent developed. The *S*-(monofluoromethyl)diarylsulfonium tetrafluoroborate has been shown to be effective for the introduction of an electrophilic monofluoromethyl group into C, S, O, N, and P nucleophiles. This methodology has been expanded for the synthesis of various biologically important compounds.**

Compounds with monofluoromethyl moiety have a considerable importance in the field of medicinal chemistry. The volatile, monofluorinated anaesthetic Sevoflurane, with one of the fastest onset and offset ability, has attained a great significance in the modern anaesthesiology.[1] Monofluoroacetic acid is known to disrupt the Krebs cycle,[2] and fluoromethylated amino acids were recognized as potent suicide inhibitors of the enzymatic decarboxylation reaction.[3] According to the isostere-based drug design, there are numerous examples[4] of various biologically active monofluoromethylated compounds. In spite of these facts, the number of monofluoromethylation methods is relatively small. Besides the first published direct electrophilic monofluoromethylation using fluoromethanol,[5] only the fluoromethyl halides and triflate[4d,6] (usually $^{18}$[F]-labeled) were used, mainly to synthesize $^{18}$[F]-labeled radiopharmaceuticals. Recently, Hu et al. presented $CH_2ClF$[7] as an indirect electrophilic monofluoromethylating reagent. Nucleophilic monofluoromethylation methods using synthetic equivalent of fluoromethide species such as magnesium benzyl fluo-

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(4) Some examples: (a) Parent, E. E.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **2007**, *72*, 5546. (b) Simeon, F. G.; Brown, A. K.; Zoghbi, S. S.; Patterson, V. M.; Innis, R. B.; Pike, V. W. *J. Med. Chem.* **2007**, *50*, 3256. (c) Silhar, P.; Pohl, R.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2005**, *3*, 3001. (d) Gerus, I. I.; Kolomeitsev, A. A.; Kolycheva, M. I.; Kukhar, V. P. *J. Fluorine Chem.* **2000**, *105*, 31.

(5) Olah, G. A.; Pavlath, A. *Acta Chim. Acad. Sci. Hung.* **1953**, *3*, 425−429.

(6) (a) Zhang, M.-R.; Ogawa, M.; Furutsuka, K.; Yoshida, Y.; Suzuki, K. *J. Fluorine Chem.* **2004**, *125*, 1879. (b) Zheng, L.; Berridge, M. S. *Appl. Radiat. Isotopes* **2000**, *52*, 55. (c) Iwata, R.; Pascali, C.; Bogni, A.; Furumoto, S.; Terasaki, K.; Yanai, K. *Appl. Radiat. Isotopes* **2002**, *57*, 347.

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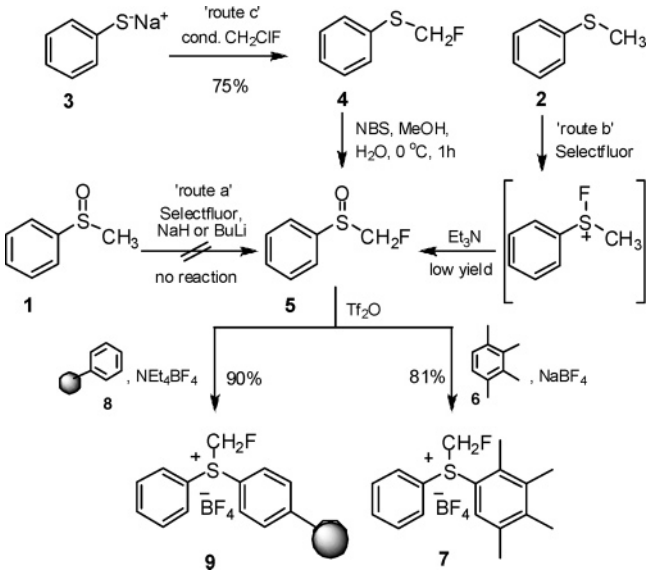
romalonates,[8] fluoromethyl phenyl sulfone,[9] and 1-fluorobis-(phenylsulfonyl)methane[10] were also reported.

Our group has recently developed the first electrophilic difluoromethylating agent (direct "$^{+}CF_2H$" group transfer), which can build difluoromethyl group into several O, N, P nucleophiles.[11] As a continuation of our work, we now disclose the results of the synthesis and use of a new electrophilic monofluoromethylation reagent (for direct "$^{+}CH_2F$" transfer), namely *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**7**).

Our aim was to prepare the tetrafluoroborate salt of the *S*-(monofluoromethyl)diarylsulfonium cation (Scheme 1). At

**Scheme 1.** Preparation of *S*-Monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium Tetrafluoroborate (**7**) and the Solid-Phase Bound *S*-Monofluoromethylsulfonium Tetrafluoroborate Reagent (**9**)




first, we attempted to prepare the monofluoromethyl phenyl sulfoxide (**5**) with the direct fluorination of methyl phenyl sulfoxide (**1**) using Selectfluor and sodium hydride or butyllithium, but our efforts were unsuccessful (Scheme 1, route a). As an alternative, we tried the fluorination of phenyl methyl sulfide (**2**) with Selectfluor followed by oxidation. After separation, the yield was lower than we expected (25%)[12] (Scheme 1, route b). Finally, we chose the nucleophilic substitution ($S_{RN}1$) reaction of the liquefied $CH_2FCl$ with sodium thiophenolate (**3**) for the preparation of monofluoromethyl sulfide (**4**).[13] Having realized the unstable nature of α-fluoro sulfides, without isolation, it was oxidized to the corresponding sulfoxide using *N*-bromosuccinimide. The subsequent Friedel−Crafts type reaction of compound **5** with 1,2,3,4-tetramethylbenzene (**6**) initiated by trifluoromethanesulfonic anhydride and followed by treatment of $BF_4^-$ salt afforded the *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**7**) in good yield (Scheme 1, route c).

In some cases, to overcome the difficulty of the separation of the desired product from the byproduct phenyl tetramethylphenyl sulfide (**13**) by column chromatography, we also prepared the solid-phase bound *S*-monofluoromethylsulfonium tetrafluoroborate salt (**9**), using cross-linked polystyrene resin (**8**).

Since the $CH_2F$ moiety in the reagent contains hydrogens, the most crucial characteristic is its stability toward bases. Comparing the features of our new reagent (**7**) to the di-[11] and trifluoromethyl analogues,[14] we should emphasize that its stability is similar to *S*-(trifluoromethyl)diphenylsulfonium tetrafluoroborate. In contrast with the $CF_2H$ reagent, compound **7** is a solid, non-sensitive to moisture and its preparation does not require an inert atmosphere.

Decomposition of the reagent was not observed and both the triflate and tetrafluoroborate salts are stable. The increased stability is due to the decreased acidity of the hydrogens in the $CH_2F$ group. However, since the $CH_2F$ group contains only one electron-withdrawing fluorine atom, the carbon is less electrophilic and its greater stability enables it to react with more substrates than the difluoromethyl analogue. The new material can be stored in a refrigerator for months without any decrease in activity and it remains stable for days standing in dry $CH_2Cl_2$ and $CH_3CN$ solutions. It reacts with MeOD yielding fluoromethyl methyl ether and decomposes in DMF and THF. With the aim of efficiently synthesizing monofluoromethylated salts of nitrogen and phosphorus nucleophiles, we tested primary, secondary, and tertiary amines, indole, pyridine, and 4-dimethylaminopyridine, several substituted imidazoles and some triarylphosphines as substrates. Burton et al. have reported the synthesis of the monofluoromethyltriphenyl phosphonium salts.[15a] These compounds are very effective reagents to introduce fluoromethyl moiety into a substrate.[15b] A few methods[6a,16] have also been reported on the preparation of the monofluoromethylated quaternary salts of triethylamine. Among the tested nitrogen nucleophiles only the tertiary amines and imidazoles provided the expected monofluoromethylated

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(9) (a) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5882. (b) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693. (c) Liu, J.; Li, Y.; Hu, J. *J. Org. Chem.* **2007**, *72*, 3119.

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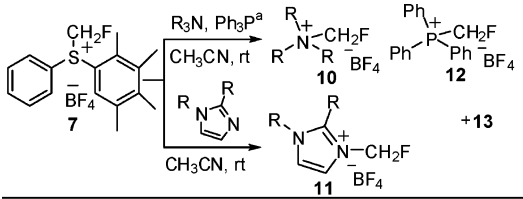
tetrafluoroborate salts (**10**, **11**) in high yield and with high selectivity (Table 1).

**Table 1.** Reaction of Tertiary Amines, Imidazoles, and Triphenylphosphine with **7** Producing the Corresponding Monofluoromethylated Onium Salts[a]




| entry | starting material | product | yield (%) |
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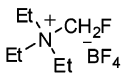
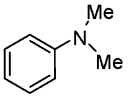
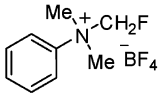
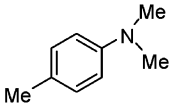
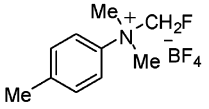
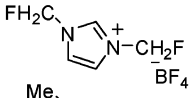
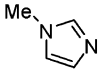
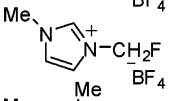
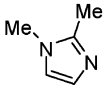
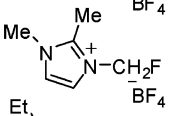
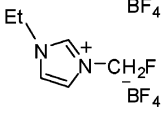
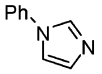
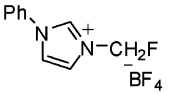
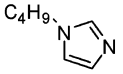
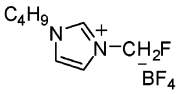
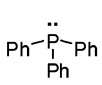
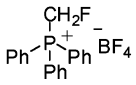
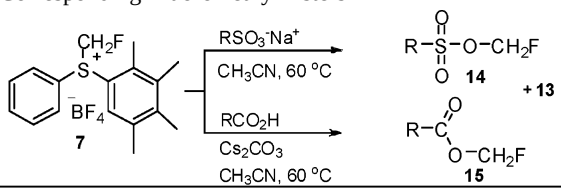
| 1 |  |  | 86 |
| 2 |  |  | 83 |
| 3 |  |  | 81 |
| 4 |  |  | 67 |
| 5 |  |  | 99 |
| 6 |  |  | 85 |
| 7 |  |  | 97 |
| 8 |  |  | 92 |
| 9 |  |  | 95 |
| 10 |  |  | 31[b] |

[a] Values indicate isolated yields. [b] DIAD was used as a co-reagent in $CH_2Cl_2$ as solvent.

Among the tested phosphines only triphenylphosphine gave the corresponding monofluoromethyl tetrafluoroborate salt (**12**) in 31% yield. Modification of different oxygen and sulfur nucleophiles such as methyl ethers, thioethers, and methyl esters of sulfonic and carboxylic acids into the corresponding fluoro analogues is not a straightforward task, and only a few methods are available for the synthesis of such compounds.[1b,6,17] However, there is no method available for the preparation of monofluoromethyl alkanesulfonates.

Fluoromethyl esters **14** and **15** were prepared under two different reaction conditions; either the corresponding carboxylic acids were reacted in the presence of $Cs_2CO_3$ as a base or the sodium salts of the sulfonic acids were reacted without using a base (Table 2). Unlike the difluoromethyl

**Table 2.** Reaction of Sulfonic and Carboxylic Acids with **7** to the Corresponding Fluoromethyl Esters[a]




| entry | starting material | product | yield (%) |
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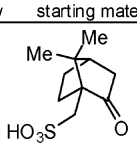
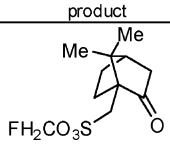
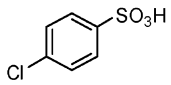
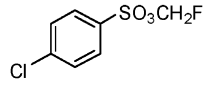
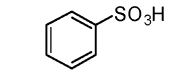
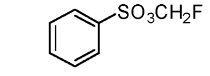
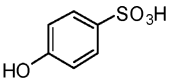
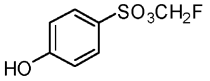
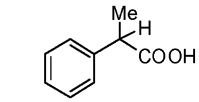
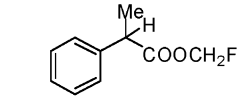
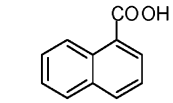
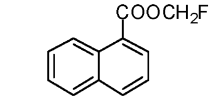
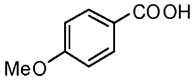
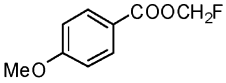
| 1 |  |  | 93<br>70[b] |
| 2 |  |  | 38 |
| 3 |  |  | 79 |
| 4 |  |  | 62 |
| 5 |  |  | 88 |
| 6 |  |  | 63 |
| 7 |  |  | 87 |

[a] Values indicate isolated yields. [b] With solid reagent **9**.

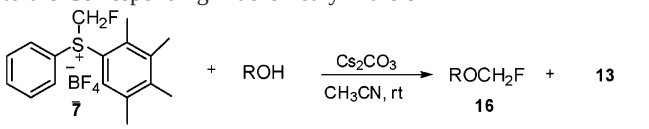
analogues, the monofluoromethyl esters of carboxylic acids (**15**) were reasonably stable and were isolated in good yields.

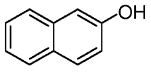
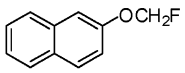
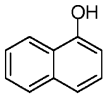
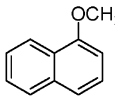
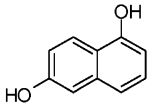
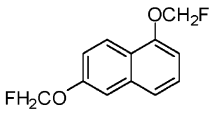
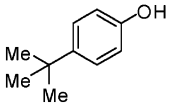
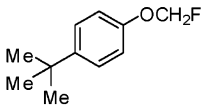
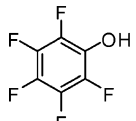
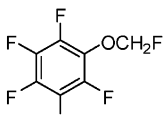
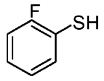
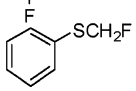
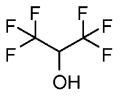
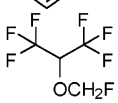
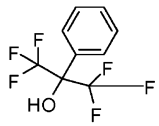
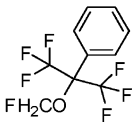
One of the convenient new feature of the reagent **7** is that it reacts with naphthols, phenols, perfluorophenol, thiophenol, and fluorinated alcohols providing the corresponding monofluoromethyl ethers (**16**) in high yield and with high selectivity (Table 3). In these cases, we tested various alkali carbonates such as sodium, potassium, and cesium carbonates[18] with the latter being the base of the choice probably due to its better solubility in $CH_3CN$. Considering the corresponding acid dissociation constants of simple alcohols ($pK_a$ ~15), perfluorinated alcohols ($pK_a$ ~10), phenols ($pK_a$ ~10), carboxylic acids ($pK_a$ ~5), sulfonic acids ($pK_a$ ~0), it is not surprising that we were unable to perform the monofluoromethylation of simple alcohols. Although the

(17) (a) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1993**, *34*, 4355. (b) Ringone, R.; Benneche, T. *J. Fluorine Chem.* **1999**, *95*, 121. (c) Schlosser, M.; Limat, D. *Tetrahedron* **1995**, *51*, 5807.

(18) (a) Flessner, T.; Doyle, S. *J. Prakt. Chem.* **1999**, *341*, 186. (b) Cella, J. A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122. (c) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476.

**Table 3.** Reaction of Phenols, Naphthols, and Alcohols with **7** to the Corresponding Fluoromethyl Ethers[a]



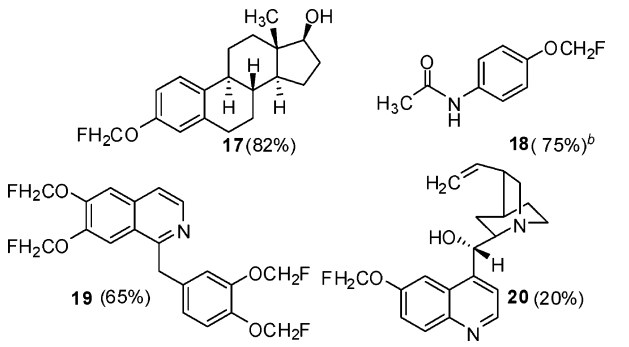

| entry | starting material | product | yield (%) |
|---|---|---|---|
| 1 |  |  | 78 |
| 2 |  |  | 94 |
| 3 |  |  | 82 |
| 4 |  |  | 100[b] |
| 5 |  |  | 88[c] |
| 6 |  |  | 88[c,d] |
| 7 |  |  | 83[c] |
| 8 |  |  | 100[a,b] 62[b] |

[a] Values indicate isolated yields. [b] With solid reagent **9**. [c] Yield based on fluorobenzene as internal standard. [d] Not stable.

sodium salt of the 1,3,5-trimethylbenzyl alcohol was prepared but the conjugate anion being a strong base destroyed the reagent. In contrast, the conjugate base of the hexafluoropropan-2-ol compounds (p$K_a$ ~8−9) are stabilized by the trifluoromethyl groups and possess decreased basicity, and consequently, the expected products could be prepared (Table 3, entries 8 and 9). Considering oxygen nucleophiles, it can be stated that the p$K_a$ of the compound should be at least 10 or less for a successful monofluoromethylation reaction.

Our observations that the reagent is capable of reacting with hydroxy compounds prompted us to prepare the monofluoromethylated derivatives of the major estrogen hormone estradiol (**17**), the analgesic acetaminophene (**18**), the fluorinated analogues of papaverine (**19**), and quinidine alkaloids (**20**) (Scheme 2). In the case of oxygen nucleophiles, we have already discussed the importance of the required acidity of the substrate to avoid the decomposition of the electrophilic reagent. Having considered this fact, we extended the use of our reagent for carbon nucleophiles also.

**Scheme 2.** Synthesis of Biologically and Pharmaceutically Important Monofluoromethyl and Fluorinated Derivatives[a]

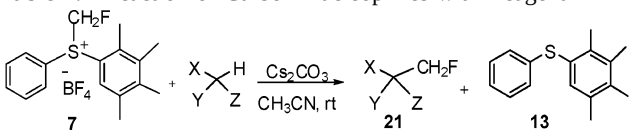


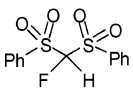
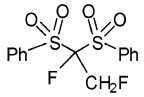
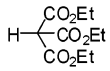
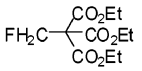
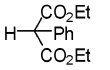
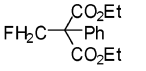
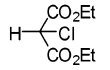
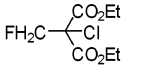

[a] Values indicate isolated yield. [b] With solid reagent **9**.

Of the various carbon nucleophiles containing hydrogen with the proper acidity, only a few proved to be suitable precursors to form C−C bond with reagent **7** (Table 4).

In conclusion, we have developed the first practical electrophilic monofluoromethylating reagent and succesfully transferred the monofluoromethyl group to various nucleophiles including C, N, O, S, and P nucleophiles. We have also applied this methodology for the synthesis of various biologically and pharmaceutically important compounds.

**Table 4.** Reaction of Carbon Nucleophiles with Reagent **7**[a]




| entry | starting material | product | yield (%)[b] |
|---|---|---|---|
| 1 |  |  | 72 |
| 2 |  |  | 75 |
| 3 |  |  | 32[c] |
| 4 |  |  | 71 |

[a] X, Y, Z = electron-withdrawing groups. [b] Values indicate isolated yields. [c] It is not separated from the unreacted starting material, yield based on fluorobenzene as internal standard.

**Acknowledgment.** Support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

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

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