# New Solid-Phase Bound Electrophilic Difluoromethylating Reagent

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Fluorine-containing compounds have played a key role in pharmaceutical, agrochemical, and materials science.[1] It is estimated that about 20–25% of drug candidates in the pharmaceutical pipelines contain at least one fluorine atom.[2] This high frequency may be related to the well-known fact that the incorporation of fluorine into organic molecules often drastically changes the chemical, physical, and biological properties of the parent compound. The discussion of such fluorine effects is the subject of many recent books and reviews.[3] In spite of the increasing understanding of the fluorine effects and the recent development of computer-aided drug discovery, prediction of the influence of fluorine substitution on the pharmacological parameters of a drug candidate remains basically a trial and error process. A large number of organofluorine compounds have to be synthesized and tested to identify a fluorine-containing hit or lead compound or a drug candidate. The rare natural occurrence of organofluorine compounds makes new methods for introduction of fluorine-containing building blocks more important.

Compound libraries have an important role in the drug discovery process. While large member diverse libraries became crucial in the hit identification phase, focused small libraries are widely used in the hit-to-lead and lead optimization stages. In 2005, 110 small libraries disclosing biological activities were published.[4] Fluorine-containing hit and lead compounds have been identified too (Figure 1).[5] In the same year, there were 104 candidates from HTS (high-throughput screening) based on the response to a survey.[6]

Solid-phase bound reagents are important tools in compound library synthesis as they enable automation. Nevertheless, to the best of our knowledge, only one solid-phase bound reagent for introduction of a fluorine-containing building block has been published before. Umemoto synthesized a solid-phase bound (perfluoroalkyl)phenyliodonium trifluoromethanesulfonate and used it to transfer perfluoroalkyl groups to aromatic and heteroaromatic compounds.[7] Now, we wish to disclose a convenient, simple synthesis of a new solid-phase bound reagent and its application for the direct introduction of the difluoromethyl building block into certain oxygen and nitrogen nucleophiles.

The significance of the difluoromethyl group in medicinal chemistry can be demonstrated by the fact that until 2005, 39 difluoromethyl derivatives have been registered to be in different developmental phases of the drug discovery process (including compounds in the preclinical phase, the clinical phase, and on the market; Figure 2).[8]

Difluoromethylation methods are discussed in several books[9] and also shortly reviewed in our recent paper. In our paper,[10] the development and the use of a new electrophilic difluoromethylating reagent has been described. It has been demonstrated that it can be used for the synthesis of difluoromethyl sulfonates, *N*-difluoromethyl ammonium, imidazolium, and *P*-difluoromethyl phosphonium salts (Scheme 1).

The key step in the synthesis of the *S*-difluoromethyl diaryl sulfonium salt is the reaction of difluoromethyl phenyl sulfoxide with 1,2,3,4-tetramethylbenzene in the presence of triflic anhydride. Although our reagent is featured by a convenient three-step synthesis and it can be used under mild reaction conditions, there was one drawback. In the case of apolar reaction products, column chromatography is necessary to separate the difluoromethylated product from the phenyl 1,2,3,4-tetramethylphenyl sulfide side product. In order to avoid the time-consuming chromatographic step and to make use of our reagent more efficiently, in terms of easy adaptation to automation and library construction, a solid-phase approach was explored.

Having in mind that difluoromethyl phenyl sulfoxide reacted readily not only with tetramethylbenzene but with benzene as well, the idea of using cross-linked polystyrene instead of tetramethylbenzene seemed to be a reasonable approach. The reaction was conducted under an argon atmosphere in dichloromethane at 0–5 °C by dropwise addition of 1 equiv of triflic anhydride. The detection of difluoromethyl trifluoromethanesulfonate in the solution, similarly to the previous experiments, warned us that the expected difluoromethyl sulfonium compound was not only forming, but it was reacting in situ with the simultaneously formed triflate anion. To eliminate this undesired side reaction, the triflate salt was converted at once into tetrafluoroborate by washing the resin repeatedly with dichloromethane containing an excess amount of tetraethylammonium tetrafluoroborate (Scheme 2).

The loading of the resin referred to the *S*-difluoromethyl sulfonium tetrafluoroborate salt and the disulfide formed by decomposition of the salt was determined based on microanalysis (sulfur and fluorine content) and was found that a 1.02–1.16 mmol/g loading of polymer bound sulfonium

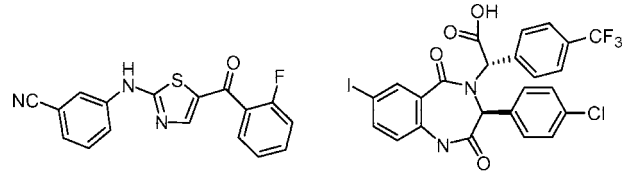


**Figure 1.** Fluorine-containing lead compounds identified by screening compound libraries.

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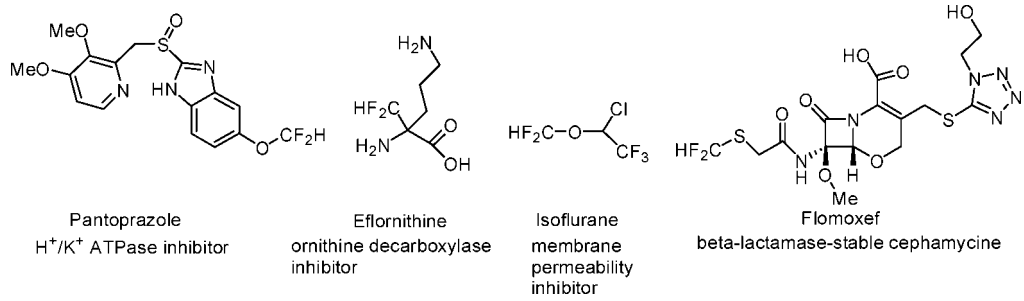
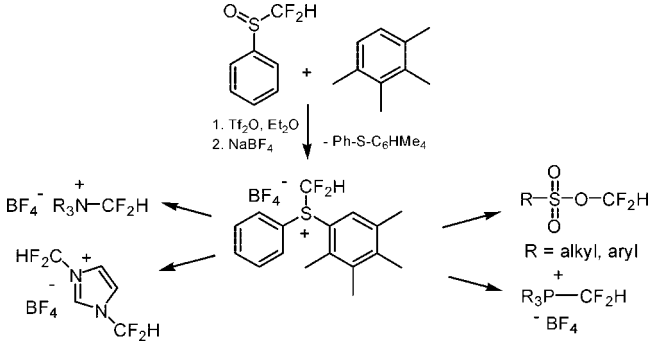



**Figure 2.** Difluoromethyl-group-containing drugs on the market.

**Scheme 1.** Solution-Phase Difluoromethylation of *O*-, *N*-, and *P*-Nucleophiles with the New *S*-Difluoromethyl Sulfonium Reagent




salt was achieved. Similar to the solution-phase approach, dichloromethane and acetonitrile were found to be the best solvents for the solid-phase difluoromethylation reactions. No significant loss in reactivity of the reagent was observed after being stored for weeks under an argon atmosphere in a refrigerator.

Reactions with aryl and alkyl sulfonic acid salts afforded the desired difluoromethyl sulfonates in good yield under reaction conditions similar to the ones used in case of solution-phase chemistry (Scheme 1 and Table 1). Although we could not achieve 100% conversion in all cases, filtration of the reaction mixture followed by diluting the filtrate with dichloromethane and extracting it with sodium carbonate solution in water afforded the pure products.

Since imidazole derivatives were found to be easily difluoromethylated on both nitrogen atoms in solution phase, our newly developed solid-phase bound reagent was also tested and was found to be effective with imidazoles. However, the use of 1.4 equiv of difluoromethylating agent with a solid-supported tertiary amine was necessary to achieve 100% conversion. We surmise that the solid-supported base enhances the reaction by selectively deprotonating the salts of imidazoles without deprotonating the reagent and thus prevents its decomposition (Table 2).

Reaction with triethylamine resulted in the decomposition of the reagent and afforded triethyl ammonium tetrafluoroborate as a major product. Although the expected (difluoromethyl)triethylammonium tetrafluoroborate was also detected by $^{1}H$ and $^{19}F$ NMR, it was evident that this reaction is not suitable for preparing the desired compounds without the extra purification step. Similar results were obtained with triphenylphosphine. Although the reagent reacted readily with triphenylphosphine in the presence of DIAD (azodicarboxylic acid diisopropylester) even at room temperature, the concomitant decomposition of the reagent led to the protonation and thus deactivation of the DIAD. On the other hand, the use of solid supported tertiary amine resulted in the partial deprotonation of the (difluoromethyl)triphenylphosphonium cation affording a mixture of (difluoromethyl)phosphonium salt and (difluoromethyl)phosphonium ylide.

Comparing the reactivity of the reagent described in this article with the difluoromethylating power of the previously described *S*-(difluoromethyl)-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate, we conclude, that the acidity of the difluoromethyl derivative and the basicity of the nucleophilic substrate are critical parameters. We think that by tuning the acidity of the (difluoromethyl)sulfonium

**Scheme 2.** Preparation of Solid-Phase Bound *S*-Difluoromethyl Sulfonium Reagent

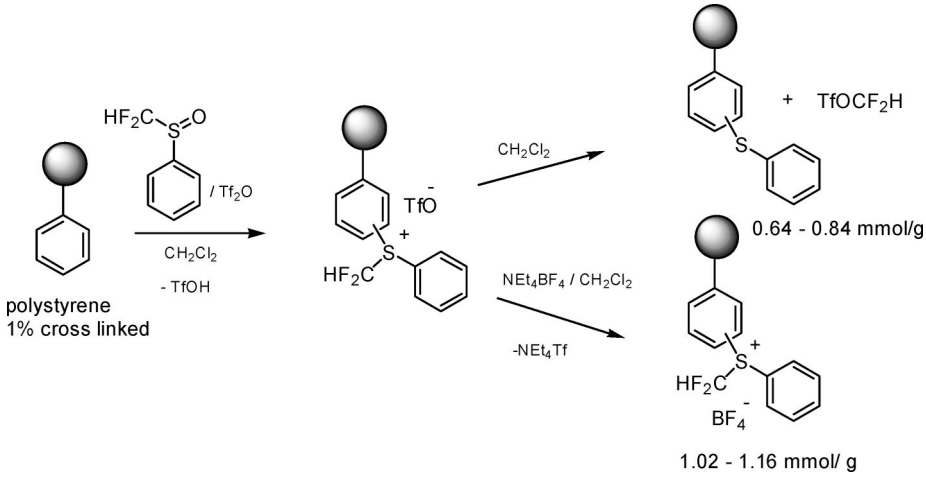
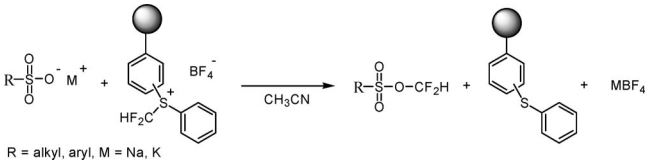


**Table 1.** Difluoromethylation of Sulfonic Acids Using a Solid-Phase Bound Difluoromethylating Reagent




| entry | starting material | product | conditions | yield(%)[a] |
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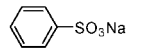
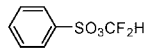
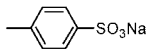
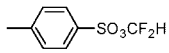
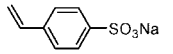
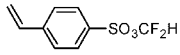
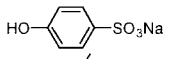
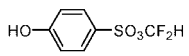
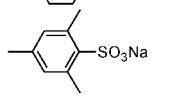
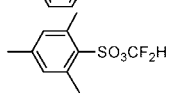
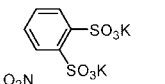
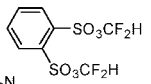
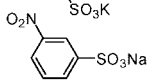
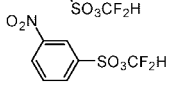
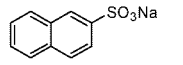
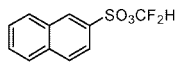
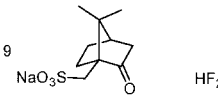
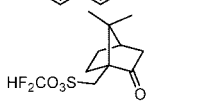
| 1 |  |  | 60°C/1 day | 61 |
| 2 |  |  | 60°C/3 days | 96 |
| 3 |  |  | rt/3 days | 85 |
| 4 |  |  | rt/3 days | 61 |
| 5 |  |  | rt/3 days | 79 |
| 6 |  |  | rt/1 day | 97 |
| 7 |  |  | 60°C/3 days | 81 |
| 8 |  |  | rt/3 days | 60 |
| 9 |  |  | rt/2 days | 95 |

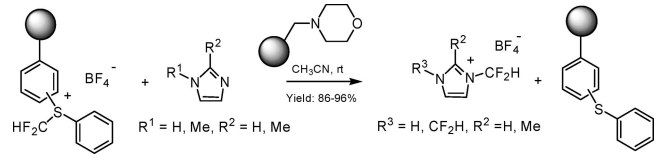
[a] isolated yields

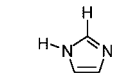
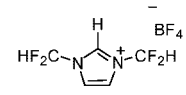
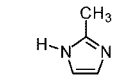
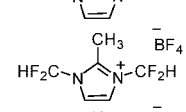
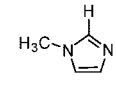
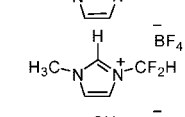
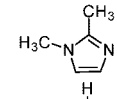
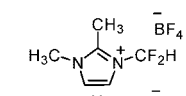
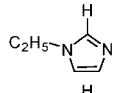
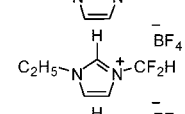
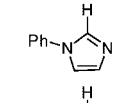
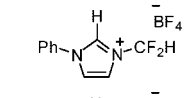
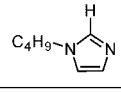
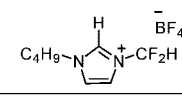
cation, the scope of the reagent can be widened and difluoromethylation of varied nucleophiles can be achieved.

Once we established that our solid-phase bound regent is suitable for difluoromethylation of certain *O*- and *N*-nucleophiles, we decided to investigate whether our newly developed solid-phase approach could be used in the case of *S*-trifluoromethyl sulfonium type trifluoromethylation reagents, which are known to be widely used in solution-phase reactions.[11]

Trifluoromethyl phenyl sulfoxide was prepared and reacted with polystyrene under conditions similar to that which were used in the case of the difluoromethyl analogue (Scheme 3). Here, 1.67 mmol/g loading was achieved based on microanalysis of the resin (fluorine content). It is known that the trifluoromethylation power of *S*-trifluoromethyl diaryl sulfonium compounds not containing electron-withdrawing groups on the aryl rings is limited. Moderate yield was reported with thiophenol, and only trace amount of C-trifluoromethylated product was detected with aniline. In light of these results, it was not unreasonable that 2 equiv of solid-phase bound reagent had to be used to achieve moderate yield in the case of thiophenol and that only poor conversion was obtained with aniline. Although the trifluoromethylation power of the solid-phase bound *S*-trifluoromethyl sulfonium compound was found to be limited, we think, that these preliminary results suggest that the solid-phase approach presented above is applicable in trifluoromethylation chemistry as well.

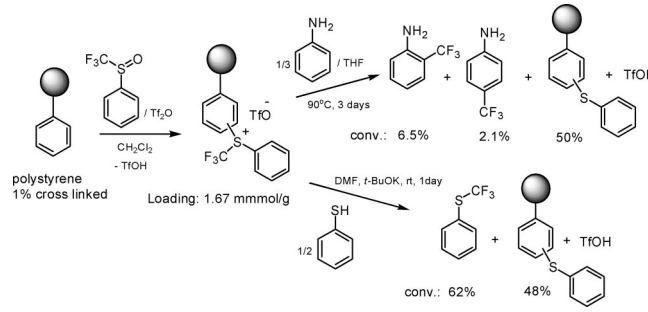
**Table 2.** Difluoromethylation of Imidazoles Using a Solid-Phase Bound Difluoromethyl Sulfonium Reagent




| entry | starting material | product | yield(%)[a] |
|---|---|---|---|
| 1 |  |  | 93 |
| 2 |  |  | 96 |
| 3 |  |  | 90 |
| 4 |  |  | 86 |
| 5 |  |  | 89 |
| 6 |  |  | 90 |
| 7 |  |  | 86 |

[a] isolated yields

**Scheme 3.** Preparation and Reactivity of Solid-Phase Bound *S*-Trifluoromethyl Sulfonium Reagent[a]




[a] The conversions are based on the parent compounds.

In conclusion, an efficient, short, two-step synthetic route from commercially available reagents, for the first solid-phase bound electrophilic difluoromethylating agent, has been developed. It has been shown that the reagent can be used for *O*-difluoromethylation of sulfonic acids and *N*-difluoromethylation of imidazoles affording pure product without further purification. The use of this reagent for target and/or diversity oriented manual or automated library synthesis should provide a valuable collection of molecules for pharmacological and materials screening.

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

**Supporting Information Available.** Synthesis detail, $^{1}H$ NMR, $^{13}C$ NMR, $^{19}F$ NMR, and HRMS data of the new compounds. This material is available free of charge via the internet at http://pubs.acs.org.

## References and Notes


(1) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004;Chapter 4, pp 203–278.
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