Fluorinating Reagents

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Direct Electrophilic (Benzenesulfonyl)Difluoromethylthiolation with a Shelf-Stable Reagent

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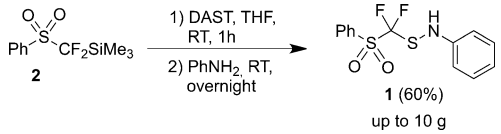
Abstract: *The (benzenesulfonyl)difluoromethylsulfanyl ($PhSO_2CF_2S$) group is a valuable substituent with specific properties which can provide access to new applications of fluoroalkylthiolated compounds. Direct introduction of this moiety can be performed by in an electrophilic manner by using a new shelf-stable reagent, namely a (benzenesulfonyl)-difluoromethanesulfenamide. Furthermore, mild magnesium-mediated reduction of the $PhSO_2CF_2S$ group leads to a facile synthesis of difluoromethylthiolated molecules and their deuterated analogs.*

Fluorinated compounds have received growing interest for a large panel of applications.[1] Accordingly, various fluorinated substituents have been screened to modulate the properties of targeted products. In particular, association of fluorinated groups with a sulfur atom yields very specific properties,[2] as illustrated by the high lipophilicity (Hansch parameter $\pi_R = 1.44$) of the CF_3S group.[3] However, apart from CF_3S,[2,4] HCF_2S[5] and a number of R_FS groups,[6] other substituents, with other modulations, have rarely been described.[7] This can be explained by the lack of efficient synthetic methods.

The phenylsulfonyl ($PhSO_2$) group is characterized by high electronic parameters ($\sigma_m = 0.62$ and $\sigma_p = 0.68$)[8] and a low lipophilicity parameter ($\pi_R = 0.27$) which could be of interest for modulating molecular properties. Accordingly, this substituent is used in various fields such as polymers[9] or life sciences.[10] The association of $PhSO_2$ with a CF_2S moiety could constitute interesting new fluorinated substituents with new properties.

To easily access molecules bearing this substituent, a strategy of direct introduction of the $PhSO_2CF_2S$ group to organic substrates was envisaged. Since we have previously demonstrated that trifluoromethanesulfenamides act as very efficient electrophilic trifluoromethylthiolating reagents,[4b,11] we envisaged the design of a (benzenesulfonyl)difluoromethanesulfenamide (**1**).

Based on the previously described synthesis of trifluoromethanesulfenamides,[12] [(benzenesulfonyl)difluoromethyl]-trimethylsilane (**2**) was synthesized following literature procedures[13] and subsequently reacted in the presence of DAST (diethylaminosulfur trifluoride) and aniline (Scheme 1).



Scheme 1. Synthesis of (benzenesulfonyl)difluoromethanesulfenamide (**1**).

In light of the difference in reactivity between CF_3SiMe_3 and **2**, the original procedure had to be altered. Indeed, with the original reaction conditions (CH_2Cl_2/DIEA/−20 °C) no reaction was observed with DAST. Optimization studies were conducted revealing THF/RT, without DIEA (diisopropylethylamine) as optimal conditions. With these conditions, **1** was produced in 60 % yield from **2** on a 10-gram scale.

With the new reagent **1** in hand, similar reactions to those previously described with the CF_3S reagent were studied.[11a,b] First, electrophilic addition reactions to alkenes were performed (Scheme 2). In contrast to the corresponding trifluoromethanesulfenamide,[14] the best results are obtained with *para*-toluenesulfonic acid (TsOH) as activator rather than $BF_3{\cdot}Et_2O$. These addition reactions give satisfactory results with regioselectivities, stereospecificities and stereoselectivities in accordance with transient sulfenium formation. In the case of (*E*)-oct-4-ene (**3d**), a lower yield for **4d** is observed because the allylic by-product **5d** is also formed. The formation of **5d** can be explained by the steric hindrance of the sulfenium intermediate, which disfavors the attack of tosylate and, consequently, favors deprotonation in α-position of the sulfenium. The elimination product **5d** can be obtained as major product (62 %) when triflic acid (TfOH) is used instead of TsOH.

In reactions of alkynes (**6a–c**) the $BF_3{\cdot}Et_2O$/TsONa system gives better results as compared to TsOH, albeit at slightly higher temperature (80 °C vs. 50 °C). Again, single regio- and stereoisomers (**7a–c**) were obtained in satisfactory yields (Scheme 2).

It is noteworthy that these electrophilic addition reactions lead to lower yields than with the corresponding trifluoromethanesulfenamide[11a,14] which can be ascribed to the higher steric hindrance of **1**.

With the aromatic alkene **3e**, cyclization was observed when triflic acid was used instead of TsOH, thus providing 2-(benzenesulfonyl)difluoromethylthiotetrahydronaphthalene **8** (Scheme 3). It can be reasoned that the generated triflate

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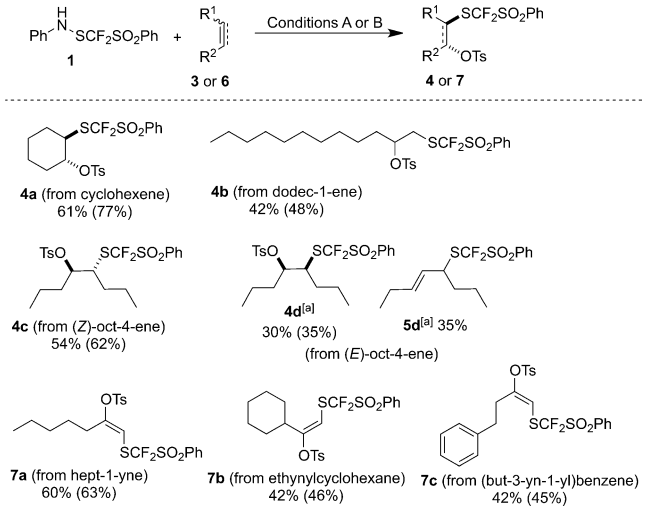
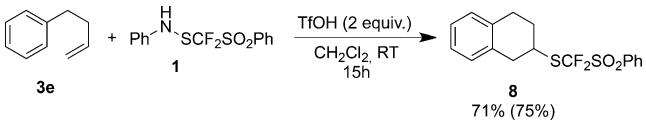


Scheme 2. Electrophilic addition of **1** to alkenes and alkynes. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. Conditions A: TsOH (2.5 equiv), CH_2Cl_2, 50 °C, 15 h. Conditions B: $BF_3{\cdot}Et_2O$ (5 equiv), TsONa (1.5 equiv), $ClCH_2CH_2Cl$, 80 °C, 24 h. [a] A mixture of **4d** and **5d** was obtained.



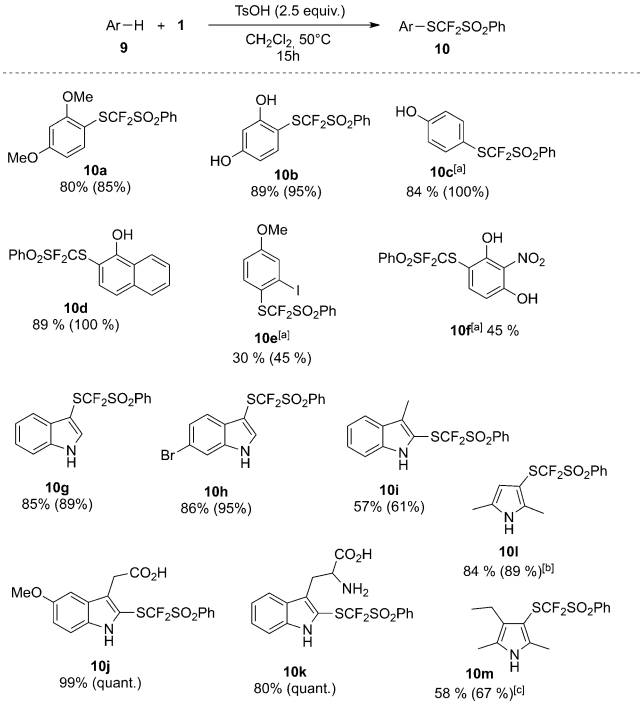
Scheme 3. Cyclization reaction with **3e**. Yield shown is of isolated product; value in parentheses is yield as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

anion is not nucleophilic enough to open the sulfenium species which, hence, reacts with the aromatic core.

In a next step we studied aromatic electrophilic substitutions with **1**. Based on previous work with trifluoromethanesulfenamide, where the reactivity was limited to electron-rich substrates, a rapid screening of conditions was performed with indole (Table S1 in the Supporting Information).[11a,15]

Similar as in the addition reactions with alkenes and alkynes, protic acids or Lewis acids are able to activate **1** for this reaction. With TsOH, excess of the acid (2.5 equiv) at 50 °C is required to obtain good results (89 %). With the strong protic acid TfOH lower quantities of the acid are required (1 equiv) to obtain good yields (80 %). A catalytic amount can be even sufficient to obtain satisfactory results (61 %) at 80 °C. The soft Lewis acid $ClSiMe_3$ gave also good yields (83 %) when used in a stoichiometric amount at 80 °C.

With the optimal conditions in hands, various arenes and heteraoarenes were converted with good yields (Scheme 4). As previously demonstrated for the CF_3S series,[15] the reactivity was limited to electron-rich compounds. With less electron-rich arenes (**10c**, **e**, **f**) the stronger acid TfOH is required that increases the electrophilicity of **1** through better activation. Among the heteroarene substrates, the most reactive indoles and pyrroles give good to excellent yields. Interestingly, protection of the free NH group of the indole or pyrrole substrates is not required. The reaction is compatible



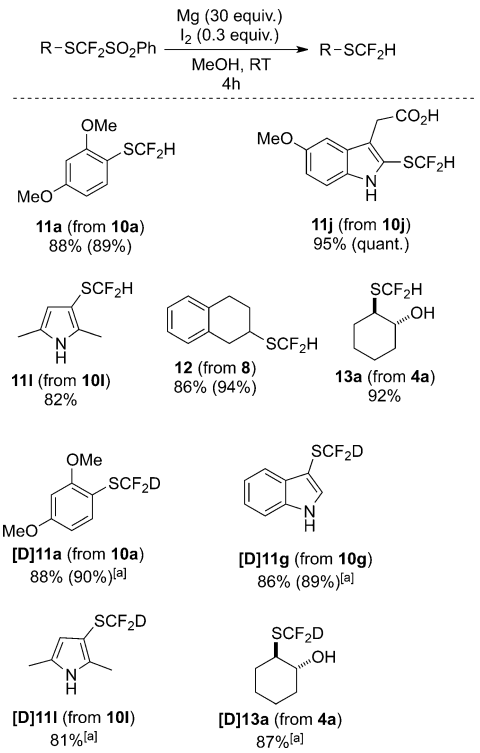
Scheme 4. Electrophilic aromatic substitution of electron-rich arenes with **1**. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [a] TfOH (1 equiv). [b] $ClSiMe_3$ (1 equiv), 80 °C, CH_3CN. [c] $ClSiMe_3$ (1 equiv), RT, CH_3CN.

with free amino and carboxylic functions. For example, the tryptophane derivative **10k** can be synthesized with excellent yield. For more sensitive pyrroles, milder conditions using Lewis acids should be preferable along with temperature control.

These results confirm **1** as a valuable, shelf-stable reagent for facile introduction of the SCF_2SO_2Ph moiety in organic molecules. Cross-coupling reactions with boronic acids were envisaged to extend the panel of aromatic compounds, however, as previously demonstrated with CF_3S reagents,[16] no reaction was observed.

An interesting aspect of the SCF_2SO_2Ph group is the "chameleon"-like character of the benzenesulfonyl part.[17] In particular, reduction reactions could provide easy access to difluoromethylated compounds which are interesting for biological applications.[18] Whereas reduction with hydride ($LiAlH_4$)[19] leads to a moderate yield (50 %), magnesium gives good results (Scheme S1 in the Supporting Information).[20] By using this mild reduction reaction, a range of difluoromethylthiolated compounds were prepared (Scheme 5).

The reaction conditions are compatible with a free carboxylic acid group (**11j**). In the case of tosylate **4a**, the tosylate part is reduced to furnish the α-CF_3S alcohol **13a**. However, with compounds **7**, degradation is observed because the initially formed enols collapse under the reaction conditions. Such a strategy could provide a valuable alternative to many recently published strategies[5] although it requires two steps as compared to recent direct methods.[5k,l]

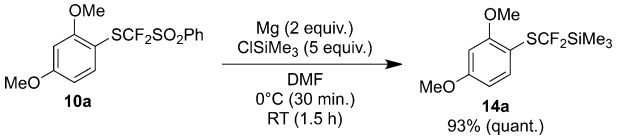


Scheme 5. Reduction of sulfone. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [a] With CD_3OD instead of MeOH as solvent.

Because of the higher metabolic stability of the C–D bond, deuterated molecules find a number of applications in drug design.[21] Molecules bearing a SCF_2D group could open new opportunities in medicinal chemistry. To the best of our knowledge, with the exception of two kinetic isotope exchange studies,[22] such compounds have not been described and no efficient synthetic methods have been proposed to date.

By replacing MeOH by CD_3OD in the reduction reaction described above, deuterium-labeled compounds are obtained in good yields (Scheme 5). This constitutes the first efficient synthesis of SCF_2D-substituted molecules by using an easy two-step procedure.

Finally, to gain access to potential post-transformations of the sulfone moiety, the benzenesulfonyl part was converted to a trimethylsilyl group by using a slightly adapted reduction procedure (Scheme 6). Compound **14a** could be of interest for further fluoroalkylthiolation reactions.[23]



Scheme 6. Synthesis of silylated compound **14a** from **10a**. Yield shown is of isolated product; value in parentheses is yield as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

To conclude, the fluorinated sulfenamide reagent **1** enables the synthesis of various (benzenesulfonyl)difluoromethylthiolated compounds, thus providing an invaluable tool for modulation of the properties of designed molecules. Given the versality of the benzenesulfonyl group further post-transformations can be envisaged. Furthermore, it is the first method for the preparation of SCF_2D-substituted molecules. This new reagent **1** confirms that fluoroalkylsulfenamides constitute a valuable and important family of reagents for the fluoroalkylthiolation of organic substrates.

Experimental Section

Synthesis of **10a**: To a solution of **1** (158 mg, 0.5 mmol, 1 equiv) in dry CH_2Cl_2 (1M), *m*-dimethoxybenzene (**9a**) was added (65.5 µL, 0.5 mmol, 1 equiv). To the resulting mixture *p*-TsOH (237.5 mg, 1.25 mmol, 2.5 equiv) was added and the reaction mixture was heated at 50 °C for 15 h. The reaction mixture was extracted with EtOAc (10 mL × 2) and the organic phase was dried over Na_2SO_4. After removal of the solvent under vacuum the compounds were purified via silica gel column chromatography. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.99–7.97$(m, 2H), 7.75–7.71 (m, 1H), 7.61–7.54 (m, 3H), 6.51–6.46 (m, 2H), 3.83 ppm (d, $J = 2.8$ Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 164.2, 162.9, 140.9, 135.4, 133.0, 130.9, 129.3, 128.1$ (t, $J =$ 325.4 Hz), 105.7, 102.3, 99.3, 56.1, 55.66 ppm. ^{19}F NMR (471 MHz, $CDCl_3$) $\delta = -79.61$ ppm (s, 2F).

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