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Synthetic Methods

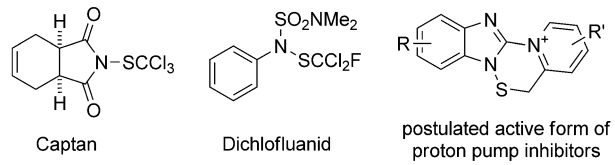
Selective and Scalable Synthesis of Trifluoromethanesulfenamides and Fluorinated Unsymmetrical Disulfides using a Shelf-Stable Electrophilic SCF_3 Reagent

Roman Pluta and Magnus Rueping*[a]

Abstract: The chemoselective trifluoromethylthiolation of nitrogen nucleophiles and thiols using *N*-(trifluoromethylthio)phthalimide under mild, metal-free conditions is described. A series of trifluoromethanesulfenamides and unsymmetrical disulfides is prepared from the corresponding aliphatic and aromatic amines and thiols in good yields. The reactions are operationally simple and tolerate a wide variety of functional groups. Trifluoromethanesulfenamides and disulfides belong to interesting classes of organic molecules which possess remarkable properties for medicinal and agrochemical applications.

Compounds bearing fluoroalkylated groups have attracted increased attention due to their remarkable biological and therapeutic properties.[1] Among the wide range of fluorinated compounds known to date, those containing perfluorinated alkylsulfenyl groups (R_FS-) are valuable for both pharmaceutical and agrochemical industries,[2] as they exhibit unique physical, chemical and biological properties if compared to the non-fluorinated parent compounds.

Sulfenamides are compounds containing an S–N bond (Figure 1). The presence of two reactive centers in these molecules leads to specific properties which can be used in various fields of application. Whereas some simple sulfenamides have found utilization in the rubber vulcanization process and polymer industry, others possess interesting biological activities and have been applied in pharmaceutical and agrochemical industries.[3] They can act as a drug or as a prodrug that is metabolized in cells to provide the active compound.[4,5] In particular the latter activity is of high interest.



Captan | Dichlofluanid | postulated active form of proton pump inhibitors

Figure 1. Examples of bioactive compounds bearing a sulfenamide group.

In this context, fluorine-containing sulfenamides ($R_FS–NR^1R^2$) have also received attention due to the characteristics of the $R_FS–N$ group. The strong electron-withdrawing effect and high lipophilicity increase the ability of such molecules to cross lipid membranes and create opportunities for the modification of known drugs. Measurements showed that the Hansch parameter (lipophilicity values) for the $NSCF_3$ group ($\pi_R = 1.50$) is considerably higher than the value of the CF_3 group ($\pi_R = 0.88$) and SCF_3 group ($\pi_R = 1.44$),[6–7] which is of great interest in the development of new drugs and agrochemicals.

Hence, improved methodologies for the efficient synthesis of complex organic molecules containing these perfluorinated functional groups ($R_FS–NR_1R_2$) are important for both academic and industrial research. Unfortunately, direct access to this important class of compounds is complicated and general, mild, safe, and efficient methods still need to be developed. Whereas several modern methodologies exist for the direct introduction of the trifluoromethanesulfenyl group (SCF_3) into both aromatic and aliphatic compounds,[8–15] resulting in the construction of $C(sp^2)–SCF_3$ and $C(sp^3)–SCF_3$ bonds, the reaction between trifluoromethane-sulfenylating reagents and nitrogen nucleophiles is less explored.

There are only a few known methods for the formation of a trifluoromethanesulfenamide group. One of them consists in the reaction of secondary amines (R^1R^2NH) with either bis(trifluoromethyl) disulfide or trifluoromethanesulfenyl chloride (F_3CSSCF_3, F_3CSCl).[16–18] Both reagents are highly toxic and difficult to handle due to their high volatility. The second approach consists of a thiolation reaction in which secondary amines in combination with strong bases are employed and, as a result, moderate yields are obtained.[19] The third protocol makes use of diethylaminosulfur trifluoride (DAST) and Ruppert–Prakash reagent ($TMSCF_3$).[12a,20]

Given the limitations of these protocols and the increasing interest in these valuable fluorinated compounds, we decided to develop an efficient procedure for the synthesis of trifluoromethylsulfenamides, which, at best, should not use any toxic reagents, metal catalysts, or harsh conditions including strong acids and bases and which could be applied to a wide range of amines.

Herein we describe the direct and selective synthesis of trifluoromethanesulfenamides under mild reaction conditions using the shelf-stable *N*-(trifluoromethylthio)phthalimide (**1**) as the SCF_3 source (Scheme 1).

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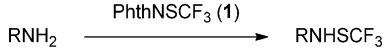


Scheme 1. Preparation of trifluoromethanesulfenamides.

In order to succeed in developing a general protocol and achieving high yields, various reaction parameters were initially evaluated for the reaction of **1** with benzylamine (**2a**; see Table S1 in the Supporting Information). The reaction occurred in most of the common organic solvents (see Table S1, entries 1–13); however, trifluorotoluene was the solvent of choice as it provided the best yield within short reaction time (see Table S1, entries 13–16). No metal catalyst was required and most of the tested additives did not improve the reaction outcome (see Table S1, entries 19–30). The reaction conditions are mild and no effect of moisture or air on the reaction yield was observed.

With the optimized conditions in hand, we decided to investigate the scope and limitations of this method. The reaction worked well for simple aliphatic and benzylic amines **2a**–**e**, **j**, **m**–**o** and gave the desired products **3a**–**e**, **j**, **m**–**o** in good yields (Table 1). Interestingly, **2c** and **2j** reacted selectively at the benzylic amine allowing the use of unprotected anilines and secondary amines under the reaction conditions.

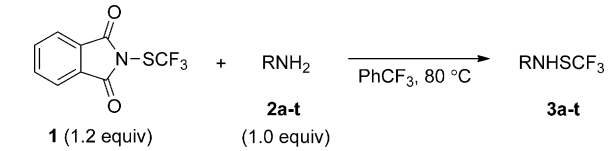
Substituted heterocycles including furan, imidazole, indole or pyridine derivatives also allowed selective formation of the desired products **3f**–**i**, **k**–**l**, **s** (Table 1). The ferrocene derivative **2p** was also compatible with the reaction conditions, affording the product **3p**. When a free hydroxyl group was present in the starting material, the yield of the corresponding product **3q** dropped. However, protection of the alcohol group enabled the reaction, affording the product **3r** in satisfactory yield. Furthermore, amino acids such as histidine and cysteine could be converted into the desired $NHSCF_3$-derivatives **3s** and **3t** (Table 1).

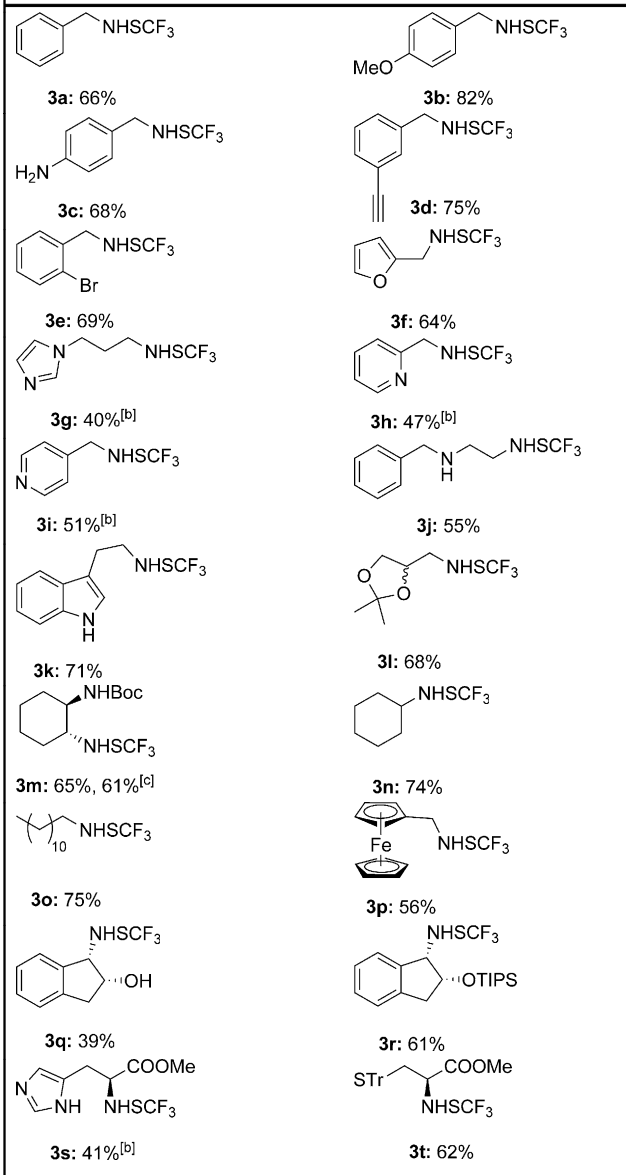
In order to show the potential practical applicability of our method in the preparation of compounds with potent biological activity, we decided to demonstrate the feasibility of this approach in the modification of steroid, carbohydrate, and alkaloid derivatives. When amine derivatives **2u**–**w** were applied as substrates, the corresponding products **3u**–**w** were obtained in good yields (Figure 2).

In order to bring about the trifluoromethanesulfenylation of the less reactive secondary amines and anilines (R^1R^2NH, $ArNH_2$, ArRNH) with reagent **1**, an alternative protocol needed to be applied. Here, the reaction with secondary amines and anilines was performed by simply employing their Li salts. The reactions were performed in THF for 2 h and provided the desired products **4a**–**d** in good yields (65–85%, Table 2).

Finally, the stability of the trifluoromethanesulfenamide group was investigated with model compound **3a**. Studies showed that this functional group possesses stability similar to non-fluorinated sulfenamides. The group is stable under moderate acidic and basic conditions. Strong protic acids, such as triflic acid or mesylic acid, resulted in protonation of the nitrogen and gave moderately stable salts. Milder acids, such as trifluoroacetic acid, did not decompose the sulfenamide group for several hours at room temperature and weaker acids did not affect this group at all. Similar behavior was observed under basic conditions. Strong bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,1,3,3-tetramethylguanidine (TMG), slowly decomposed the sulfenamide group but weaker bases, such as triethylamine (TEA), and other tertiary amines, did not have any effect. Oxidizing agents such as *meta*-chloroperbenzoic acid (*m*-CPBA) first form trifluoromethanesulfin-

Table 1. Reaction scope of trifluoromethanesulfenamides.[a]





[a] Reaction conditions: Amine **2** (0.3 mmol) and **1** (0.36 mmol) in $PhCF_3$ (4 mL) were heated at 80 °C for 0.25–6 h. Yields of the isolated products after column chromatography; [b] reaction performed with 2.0 equivalents of **1**; [c] reaction performed on 3 mmol scale.

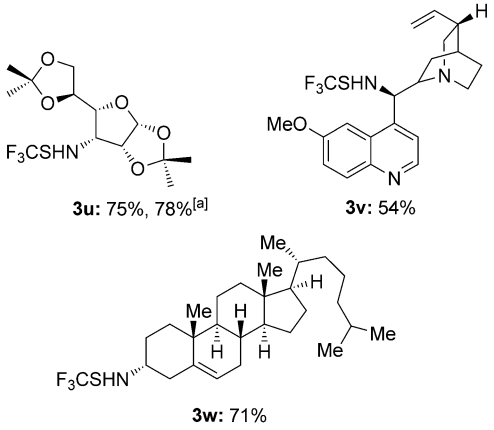
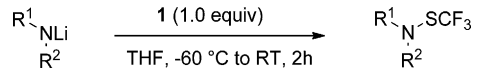
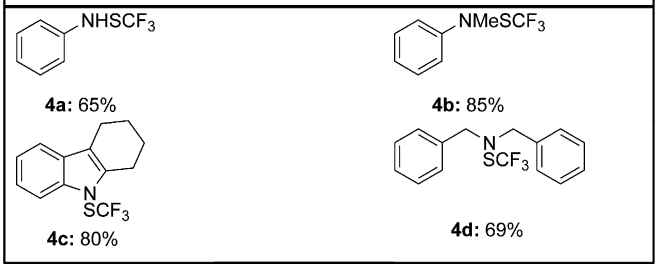


Figure 2. Natural product derivatives **3u**–**w**. [a] Reaction performed on 3 mmol scale.

Table 2. Reaction of lithium amides with reagent **1**.



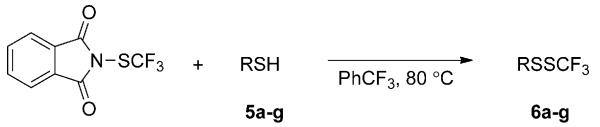


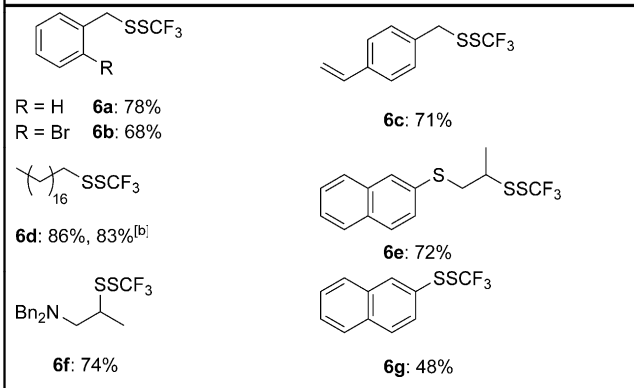
amides, which are oxidized further to trifluoromethanesulfonamides. In the presence of fluoride and iodide ions, decomposition was not observed. Additionally, we did not observe decomposition of **3a** in the presence of tributyltin hydride (toluene, 100 °C, 20 min) and sodium borohydride (methanol, 25 °C, 1 h). These experiments show the generally high stability of trifluoromethanesulfenamides and together with the high lipophilicity demonstrate their value for use as bioactive compounds.

Many drugs with different applications contain free thio groups, which are essential for the pharmacological effect due to their high reactivity.[21] Protection of these groups in prodrugs is of particular interest as it leads to improved pharmacokinetic properties, as well as stability of molecules. Methods for protection of the thiol moiety include acylation, alkylation, and preparation of mixed disulfides. Preparation of unsymmetrical fluorinated disulfides is an interesting challenge in synthetic organic chemistry. To date, disulfides bearing an SCF_3 group were prepared exclusively from CF_3SCl or CF_3SSCF_3[22] and thus research and potential applications were strongly limited. Simultaneously to our research, Shen described the preparation of such disulfides in a similar approach.[20]

Under the same reaction conditions as for the amines, unsymmetrical disulfides could be prepared in good yields

Table 3. Reaction of thiols with reagent **1**.[a]





[a] Reaction conditions: Thiol **5** (0.3 mmol) and **1** (0.36 mmol) in $PhCF_3$ (4 mL) were heated at 80 °C for 0.25–1 h. Yields of the isolated products after column chromatography; [b] reaction performed on 3 mmol scale.

(Table 3). However, unlike in the case of amines, oxygen had to be excluded, as formation of significant amounts of symmetrical disulfides was observed due to oxidation with molecular oxygen. The reaction conditions allowed the preparation of various aliphatic disulfides with good yields. Aromatic thiol **5g** works also under these reaction conditions however with lower yield and even higher loadings of reagent **1** could not improve it.

In addition, to show the efficiency and practicability of our approach, we performed the reactions with amines **2m** and **2u** and thiol **5d** on a 3 mmol scale. The corresponding products were obtained without a significant change in the yield.

To summarize, we have developed a practical method for the synthesis of trifluoromethanesulfenamides and mixed trifluoromethyl-containing disulfides. The electrophilic and shelf-stable *N*-(trifluoromethylthio)phthalimide was efficiently applied for the selective synthesis of trifluoromethanesulfenamides starting from primary and secondary aliphatic and aromatic amines. Similarly, both aliphatic and aromatic thiols were converted into the corresponding disulfides. Sulfenamides and disulfides belong to promising classes of organic molecules and as such the corresponding trifluoromethylated analogs will be of interest for medicinal, agrochemical, and materials chemistry.

Keywords: fluorine · S–N bond formation · sulfenamides · synthetic methods · trifluoromethanesulfenylation

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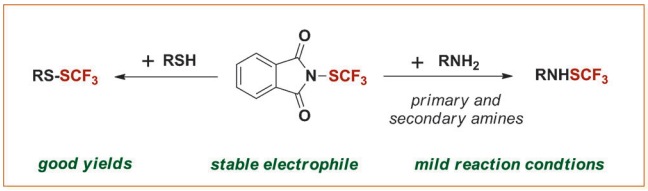

S–N-tial: The selective trifluoromethylthiolation of nitrogen nucleophiles and thiols using *N*-(trifluoromethylthio)phthalimide under mild, metal-free conditions is described. A series of aliphatic and aromatic amines and thiols was transformed into the corresponding trifluoromethanesulfenamides and disulfides. The reactions are operationally simple and tolerate a wide variety of functional groups.

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