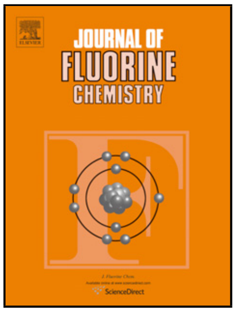

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Metal-free trifluoromethylthiolation of arenediazonium salts with Me_4NSCF_3

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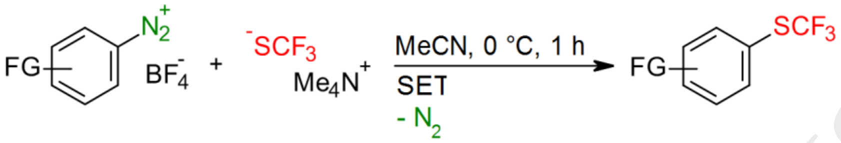


Highlights

- Arenediazonium salts are converted into aryl trifluoromethyl thioethers without the use of any metal mediators.
- The transformation is based on readily available starting materials and tolerates various functional groups.
- Cyclic voltammetry was used to elucidate the reaction mechanism.
- The aryltrifluoromethyl thioether products are interesting for applications in drug discovery.

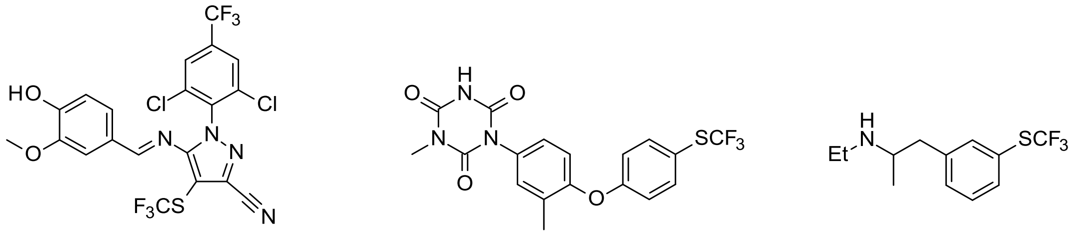
Abstract

A metal-free entry to the pharmaceutically meaningful substrate class of trifluoromethyl thioethers has been developed starting from widely available arenediazonium salts and commercially available $Me_4N^+SCF_3^-$. This reaction proceeds within one hour at 0 °C and is applicable to a wide range of functionalized substrates.

Keywords: trifluoromethylthiolations; arenediazonium salts; trifluoromethyl thioethers; radicals; cyclovoltammetry

1. Introduction

Fluorine-containing molecules are abundant in pharmaceuticals, agrochemicals, material and surface sciences.[1] Their increased lipophilicity compared to the non-fluorinated analogs allows modulating solubility, bioavailability and adhesive properties. Hence, powerful methods for the selective introduction of fluorinated residues into functionalized molecules are constantly sought. In this context, SCF_3 groups, which induce particularly high lipophilicity and membrane permeability[2] have recently received increased attention. Examples of biologically active compounds containing SCF_3 groups include vaniliprole, toltrazuril and tiflorex (Figure 1).



vaniliprole
pesticide

toltrazuril
antiprotozoal agent

tiflorlex
stimulant amphetamine

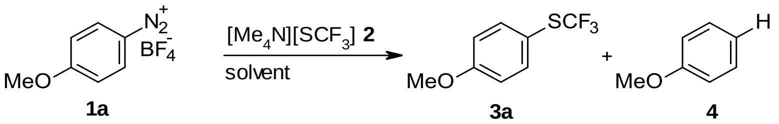
Figure 1: Biologically active trifluoromethyl thioethers.

Traditional strategies for the preparation of trifluoromethylthiolated compounds are based on waste-intensive, multistep syntheses involving halogen-fluorine exchange reactions.[3] Trifluoromethylations of sulfur-containing precursors[4] such as thiols,[5] disulfides,[6] or thiocyanates[7] constitute a viable alternative. However, especially for applications in drug discovery, it is advantageous to introduce this subgroup as a whole, starting from easily accessible substrate classes with inexpensive, easily stored and handled reagents. In this context, several processes involving stoichiometric amounts of nucleophilic silver or copper reagents,[8] electrophilic N–SCF_3 reagents,[9] or oxidative cross-couplings[10] have been described. A particularly straightforward approach is the Sandmeyer-type copper-catalyzed trifluoromethylthiolation of arenediazonium salts using tetramethylammonium trifluoromethanethiolate as the SCF_3 source.[11] This reagent was first introduced by Röschenthaler[12] and Yagupolskii,[13]and has meanwhile found numerous applications in the field of trifluoromethylthiolation[14]of vinyl iodides,[15] boronic acids,[16] and aryl halides[17] catalyzed by Cu, Ni and Pd complexes. Lately, it was used by Schönebeck *et al.* for the synthesis of acyl fluorides,[18] thiocyanates[19] and trifluoromethylamines.[20] The Sandmeyer-type reaction is remarkable in that it is one of the few processes in which substoichiometric amounts of copper are sufficient to achieve high yields. Still, for pharmaceutical and agrochemical applications, it would be best if heavy metals could be left out altogether. To the best of our knowledge only one example[21] of synthesis of arene trifluoromethyl thioethers is reported employing the toxic[22] and arduous to prepare $(SCF_3)_2$ as reagent. In the course of the method development leading to the copper-catalyzed trifluoromethylthiolation,[10] we had performed control experiments without copper and in one case surprisingly observed the formation of the desired trifluoromethyl thioethers in appreciable amounts. At that time,[10] we could not reproduce this and attributed the outlying experiment to the presence of copper traces in the apparatus or in the reagents.[23] However, when we later reinvestigated the reaction under highly optimized conditions using new glassware and stirrers as well as analytically pure reagents, we consistently detected trifluoromethylthiolation products even in the absence of copper when treating arenediazonium salts with $Me_4N^+SCF_3^-$. Similar observations were made also for $Me_4N^+SeCF_3^-$.[24] Systematic reaction development led to the discovery of an efficient metal-free trifluoromethylthiolation process that we present herein.

2. Results and discussion

Preliminary investigations had shown that the reaction of 4-methoxybenzenediazonium tetrafluoroborate (**1a**) and $Me_4N^+SCF_3^-$ (**2**) reproducibly afforded 4-methoxyphenyl trifluoromethyl thioether (**3a**), thus this was used as a starting point for reaction optimization (Table 1).

Table 1: Optimization of the reaction conditions[a] .



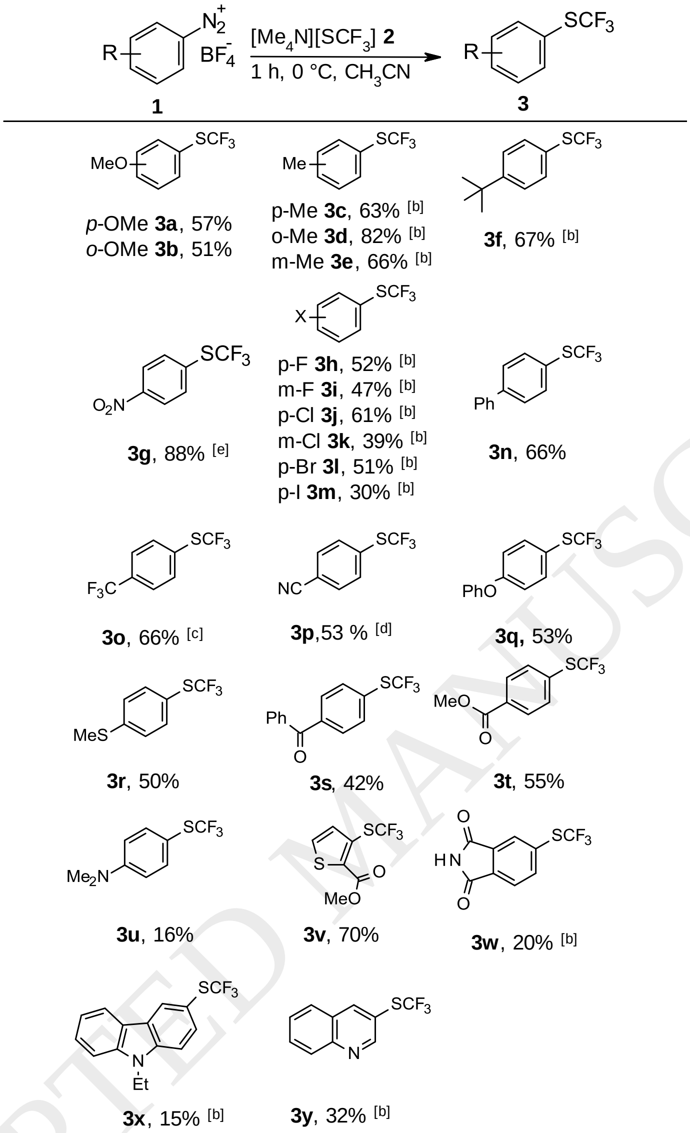
Entry	**Solvent**	**Temperature [°C]**	**2 [equiv.]**	**Yield 3a [%]** [b]	**Yield 4 [%]** [c]
1	CH_3CN	r.t.	1.8	41	18
2 [d]	CH_3CN	r.t.	1.8	40	15
3	acetone	r.t.	1.8	36	20
4	DMF	r.t.	1.8	14	47
5	toluene	r.t.	1.8	-	-
6	CH_3CN	50	1.8	43	16
7	CH_3CN	0	1.8	52	15
8	CH_3CN	0	1.1	48	16
9	CH_3CN	0	3.0	49	16
10 [e]	CH_3CN	0	1.1	55	12
11 [f]	CH_3CN	0	1.1	66	7

[a] Reaction conditions: 0.5 mmol diazonium salt **1a** and Me_4NSCF_3 **2** (0.9 mmol) in 2 mL solvent, 1 h.[b] Yields were determined by ^{19}F NMR analysis using trifluorotoluene as internal standard [c] Yields were determined by GC analysis using *n*-tetradecane as internal standard.[d] 16 h reaction time.[e] 1.3 mL CH_3CN.[f] 0.5 mL CH_3CN.

Indeed, when simply stirring a mixture of **1a** and an excess of **2** in acetonitrile at room temperature, a promising yield of 41% was obtained (Table1, entry 1). The main side product was anisole (**4**), resulting from protodediazotization.[25]The starting material was consumed already within 1 h, and the yield of **3a** was equal when increasing the reaction time to 16 h (Table 1, entry 2). Among the solvents tested, acetonitrile was most effective. In more polar solvents, such as DMF, the amount of protodediazotization product increased and in nonpolar solvents such as toluene, there was no conversion, likely due to solubility issues (Table 1, entries 3–5). The key parameter affecting yield and selectivity was the reaction temperature. Whereas the yield remained unchanged when increasing the temperature to 50 °C, it increased to 52% at 0 °C (Table 1, entries 6-7). The excess of **2** could be reduced to 1.1 equivalents (Table 1, entry 8-9). At increased concentrations, higher yields were obtained and the protodediazotization was suppressed (Table 1, entries 10-11). Under optimal conditions, the product was obtained in 66% yield along with 7% anisole and small amounts of other byproducts including aryl trifluoromethyl disulfide, diaryl sulfide and several biaryls (see SI). Having thus identified an effective and reliable metal-free protocol for the trifluoromethylthiolation of arenediazonium salts, we next investigated its scope (Table

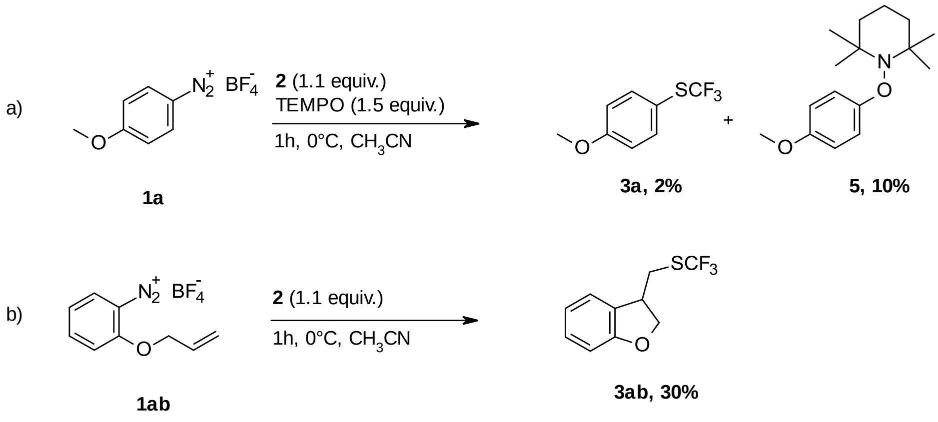
2).

Table 2: Scope of the metal-free trifluoromethylthiolation^{a}.



[a] Reaction conditions: 0.5 mmol diazonium salt **1** and Me_4NSCF_3 (**2**) (0.55 mmol) in 0.5 mL solvent, 1 h, 0 °C. [b] Yields were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene as internal standard. [c] Yield was determined by ^{19}F NMR analysis using 1,4-difluorobenzene as internal standard. [d] 0.5 mmol diazonium salt **1** and Me_4NSCF_3 (**2**) (0.9 mmol) in 0.5 mL solvent, 1 h, 0 °C. [e] Reaction conditions: 0.5 mmol diazonium salt **1** and Me_4NSCF_3 (**2**) (0.9 mmol) in 2.0 mL solvent, 1 h, 0 °C.

Different arenediazonium salts were converted into the desired products with moderate to high yields. Both electron-withdrawing and electron-donating groups were converted, and common functional groups including ester, ether, keto, and cyano groups were tolerated. Expectedly, the yields were low for arenediazonium salts containing basic amine groups, presumably due to triazene formation.[26] The synthesis of 1-nitro-4-[(trifluoromethyl)thio]benzene (**3g**) was successfully scaled up to 4 mmol yielding 759 mg (85%) of the desired product. 4-fluoro- and 4-iodoarenediazonium salts led to 1,4-disubstituted products, as detected by ^{19}F NMR spectroscopy and/or GC-MS. The presence of these byproducts suggests a radical reaction mechanism. A signal at $\delta = -47.4$ ppm in the ^{19}F NMR spectrum suggests the presence of the dimer $(SCF_3)_2$, which would be expected in the termination step by combination of two SCF_3 radicals.[12]



Scheme 1: *Radical capture experiments.*

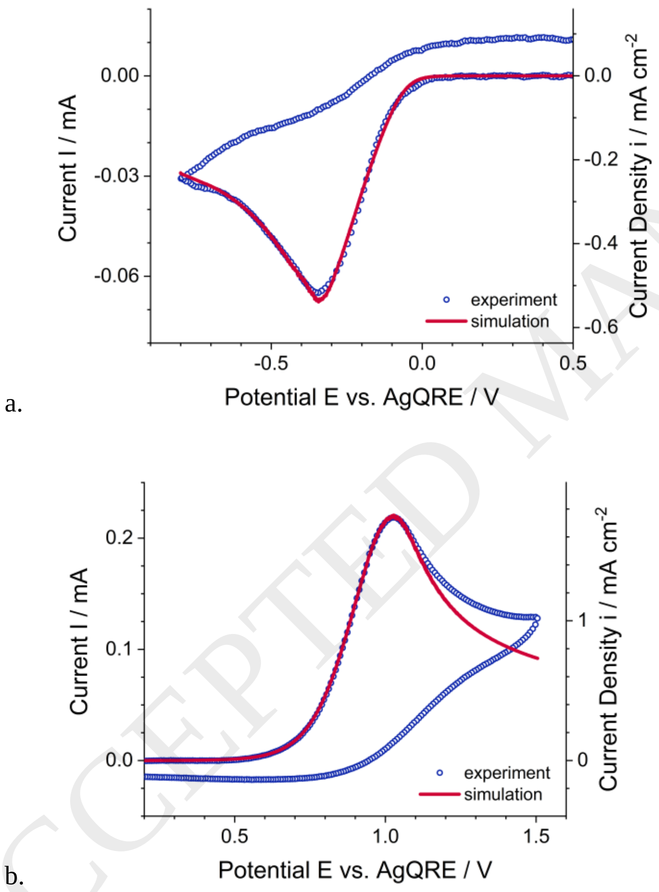
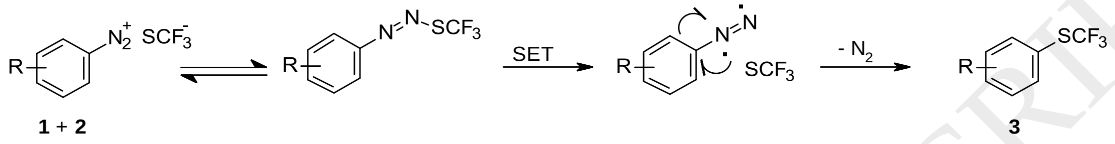


Figure 2: Cyclic voltammograms of **1a** (a) and **2** (b) in 1 mM concentration, respectively, with 0.1 M $^{t}Bu_4NPF_6$ in CH_3CN. Blue circles: experimental data, red line: simulated curves.

Further evidence for a radical mechanism was obtained by performing the reaction between **1a** and **2** in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidin-1-yl-N-oxyl (TEMPO). Under these conditions, the TEMPO adduct (**5**) was formed as the major product along with small quantities of **3a** (Scheme 1a). Moreover, a radical capture experiment with 2-(allyloxy)diazonium tetrafluoroborate (**1ab**) resulted in the formation of **3ab** (Scheme 1b). The question to answer was how radical formation leading to a SET mechanism takes place in the absence of metals or radical initiators. The thermodynamics of this transformation was addressed by cyclic voltammetry studies of 4-methoxybenzenediazonium tetrafluoroborate (**1a**) and Me_4NSCF_3 (**2**) in acetonitrile using silver as a quasi-reference electrode.[27] As can be seen in Figure 2, the cyclic voltammetric wave shows a single-electron transfer in both cases. These were fitted to simulated curves using DigiElch® software to extract the formal potentials and the electron transfer rates (k). The formal potential of arenediazonium salt **1a** was determined as -0.147 V, with k = 0.0025 cm/s, that of Me_4NSCF_3 (**2**) as 0.153 V, with $k = 1.0 \cdot 10^{-6}$ cm/s (see the SI). One can thus conclude that the electron transfer from **2** to **1a** under the conditions used is endergonic by ΔG roughly estimated as $-z \cdot F \cdot E = 28.9$ kJ/mol and relatively slow. However, under typical experimental conditions, such a small activation barrier can easily be crossed. It is thus conceivable that the formation of radicals takes place even in the absence of radical initiators or metal mediators. Once these active species have been formed, the rest of the reaction can be expected to be energetically downhill. Based on these findings, we propose a mechanism that consists of reduction of the diazonium ion by the SCF_3^- ion, followed by dediazotization and subsequent recombination of the two radical species (Scheme 2), in analogy to reports by Studer et al.[28]



Scheme 2: Proposed radical mechanism of the trifluoromethylthiolation.

3. Conclusions

Overall, this study demonstrates that it is possible to perform trifluoromethylthiolations of arene nucleophiles in the absence of heavy metal mediators. The reaction times are short, and the conditions mild. This protocol is beneficial especially for applications in which even ppm quantities of metals need to be avoided. However, it is also evident from the results that the copper-mediated reaction variants remain of great use whenever near-quantitative yields are required, or whenever product separation is an issue.

4. Experimental

An oven-dried 20 mL crimp-cap vessel with magnetic stirrer was charged with tetramethylammonium trifluoromethanethiolate (**2**, 1.10 mmol) and the aryl diazonium tetrafluoroborate (**1**, 1.00 mmol). Cold (0 °C), degassed acetonitrile (1 mL) was added and the reaction mixture was stirred at 0 °C for 1 h. After the reaction, the mixture was diluted with diethyl ether (20 mL), and aq. sat. $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with diethyl ether (2 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was purified by flash chromatography (SiO_2, *n*-pentane/dichloromethane gradient). The solvent was removed by slow evaporation through a Vigreux column at ambient pressure, yielding the aryl trifluoromethyl thioethers. The yields of particularly volatile compounds and of those that could only be obtained in low yields were determined by ^{19}F NMR, and their identity was confirmed by MS.

Acknowledgments

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