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Novel Use of CF_3SO_2Cl for the Metal-Free Electrophilic Trifluoromethylthiolation

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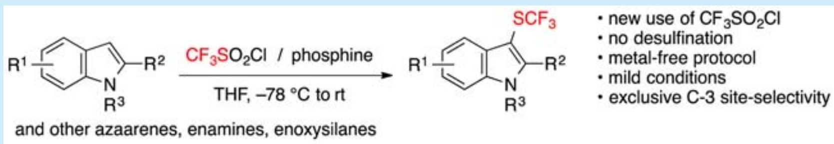
Supporting Information



ABSTRACT: The regioselective trifluoromethylthiolation of indole derivatives was achieved under reductive conditions with trifluoromethanesulfonyl chloride as the readily available source of electrophilic SCF_3 and a phosphine as the reducing agent. It is a straightforward process free from any metal and also applicable for the trifluoromethylthiolation of other azaarenes, enamines, and enoxysilanes.

The fluorine chemotype SCF_3 is virtually absent in marketed drugs even though it has predicted high potential in medicinal chemistry, attributable to the exceptional lipophilicity imparted to SCF_3 molecules.[1] And yet, we are aware of the strong interest in recent years for the chemical positioning of this fluorinated motif in a wide variety of substrates. In the early stage of the direct electrophilic trifluoromethylthiolation, trifluoromethanesulfenyl chloride, CF_3SCl, was the only reagent available, but its gaseous and toxic nature precluded a wider development. Recently, what motivated a revival in the field is the design of a collection of stable and easy to handle reagents to perform efficient trifluoromethylthiolations (Figure 1).[2]

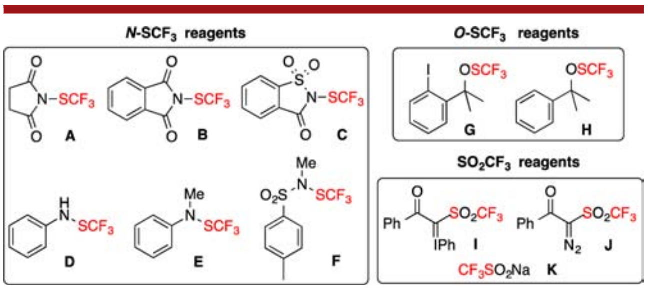
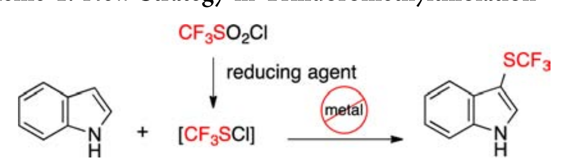


Figure 1. Classes of electrophilic trifluoromethylthiolation reagents.

Although high efficiency was demonstrated in the trifluoromethylthiolation of several substrates,[3] these reagents suffer from a common drawback which is that their preparation requires diverse fluorinated raw materials. Indeed, N-SCF_3 reagents **A**−**C** necessitate a primary source of SCF_3, either CF_3SCl or $AgSCF_3$; trifluoromethanesulfenamides **D**−**F** are prepared using (diethylamino)sulfur trifluoride (DAST) and the Ruppert−Prakash reagent (CF_3SiMe_3); O-SCF_3 reagents **G** and **H** need $AgSCF_3$ directly or through **C**; whereas SO_2CF_3 reagents **I** and **J** ultimately require sodium triflinate (CF_3SO_2Na, **K**). Faced with the increasing level of sophistication of reagents **A**−**J**, it is highly desirable to offer simple solutions suitable for industrial use on a larger scale. In moving toward this goal, Zhang and co-workers reported the use of sodium triflinate for the direct trifluoromethylthiolation of indoles,[4] sodium triflinate being otherwise frequently used as a trifluoromethylation agent[5] with extrusion of SO_2 or, to a lesser extent, as a trifluoromethanesulfonylation agent.[6] Their reaction system consists of a combination of **K** with diethyl phosphite and CuCl in DMSO at 110 °C for the in situ generation of bis(trifluoromethyl) disulfide, CF_3SSCF_3. With the thought in mind to use an alternative readily available raw material at milder temperatures and under metal-free conditions, we selected trifluoromethanesulfonyl chloride, CF_3SO_2Cl, for the synthesis of SCF_3 molecules. The underlying idea was that the highly reactive CF_3SCl could be generated in situ under reductive conditions (Scheme 1).

Scheme 1. New Strategy in Trifluoromethylthiolation



CF_3SO_2Cl is typically employed in the formation of sulfonamides and sulfonic esters[7] but also in electrophilic chlorination,[8] radical desulfinative trifluoromethylation,[9] or trifluoromethylchlorosulfonylation with retention of the SO_2 moiety.[10] Herein, we present a new utilization of CF_3SO_2Cl that retains the C−S bond in transferring the whole SCF_3 motif.

We selected indole **1a** as substrate to evaluate our working hypothesis because indole is a structural unit found in many

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biologically active compounds and is frequently functionalized at the C-3 position by electrophiles including the SCF_3 group.[3,4] As a reducing agent, we first evaluated a trimethylphosphine solution 1.0 M in toluene for the deoxygenation of trifluoromethylsulfonyl chloride to produce in situ the active CF_3SCl. The higher nucleophilicity of alkyl- versus arylphosphines and the water solubility of alkylphosphine oxide byproducts were essential elements in choosing a reducing agent. A combination of indole/CF_3SO_2Cl/PMe_3 in a ratio 1:1.5:3 was placed at low temperature and slowly warmed to ambient temperature in order to deliver progressively the reactive CF_3SCl species. This way, the trifluoromethylthiolation is regioselective at C-3 producing the 3-(trifluoromethylthio) indole **2a** in up to 70% yield (Table 1, runs 1−3). Two side products were identified:

Table 1. Optimization of the Reaction Parameters

run	reducing agent[a]	solvent	temp (°C)	yield[b] (%)
Variation of the Temperature				
1	PMe_3 (1:1.5:3)	toluene	−78 to rt	70
2	PMe_3 (1:1.5:3)	toluene	−4 to rt	62
3	PMe_3 (1:1.5:3)	toluene	−20 to rt	40
Variation of the Amount of CF_3SO_2Cl and of the Ratio CF_3SO_2Cl/Reducing Agent				
4	PMe_3 (1:1.5:1.5)	toluene	−78 to rt	41
5	PMe_3 (1:1.5:3)	toluene	−78 to rt	70
6	PMe_3 (1:1.5:3.75)	toluene	−78 to rt	77
7	PMe_3 (1:1.8:3.6)	toluene	−78 to rt	78
8	PMe_3 (1:1.8:4.5)	toluene	−78 to rt	73
Screening of the Reducing Agent and Solvent				
9	PMe_3 (1:1.8:3.6)	THF	−78 to rt	89
10	PPh_3 (1:1.5:3)	toluene	−78 to rt	35
11	PPh_3 (1:1.5:3)	DCM	−78 to rt	51
12	PPh_3 (1:1.5:3)	$CHCl_3$	−78 to rt	21
13	$P(OMe)_3$ (1:1.8:3.6)	toluene	−78 to rt	21
14	$P(OMe)_3$ (1:1.8:3.6)	DCM	−78 to rt	46
15	$(EtO)_2P(O)H$	toluene	−78 to rt	0
16	TMSCl + NaI	toluene	−78 to rt	0
17	Me_2S	toluene	−78 to rt	0

[a]Ratio indole/CF_3SO_2Cl/reducing agent. [b]Yields were determined by ^{19}F NMR using trifluorotoluene as an internal standard.

3-(trifluoromethyl sulfoxide)indole and bis(trifluoromethyl) disulfide, CF_3SSCF_3; the former results from an incomplete deoxygenation of CF_3SO_2Cl, whereas the latter results from the disproportionation of CF_3SCl. In order to maximize the yield of the desired SCF_3 indole by suppressing the side reactions, we studied variations of the amount of CF_3SO_2Cl and of the ratio CF_3SO_2Cl/PMe_3 (Table 1, runs 4−8). It was found that a ratio of indole/CF_3SO_2Cl/PMe_3 1:1.8:3.6 led to an improved yield of 78% and even up to 89% when toluene was replaced by THF (Table 1, run 9). Next, we screened other reducing agents: triphenylphosphine and trimethyl phosphite led to the desired SCF_3 indole **2a** although in lower yields than with trimethylphosphine (Table 1, runs 10−14), whereas diethyl phosphite (Zhang's best reductant of **K**),[4] trimethylsilyl chloride/sodium iodide, and dimethyl sulfide appeared to be unsuitable for this transformation (Table 1, runs 15−17). We next sought to examine the substrate scope, providing some adjustments to the reaction conditions. Fourteen variously decorated indole derivatives **1a−n** were submitted to our trifluoromethylthiolation protocol (Scheme 2).

Both electron-withdrawing and electron-donating substituents were well tolerated in positions 4, 5, 6, and 7 of the benzo-fused ring (products **2a−h**). The use of a phosphine in this reaction is compatible with other reducible functional groups such as halogens, nitro groups, and esters. 2-Methyl- and 2-phenyl-substituted indoles were converted into the expected products **2i,j**; however, 2-carbethoxyindole **1k** failed to react, probably because of the duality of functions enamine/conjugated ester. Importantly, no protecting group at the nitrogen atom was required; nevertheless, *N*-methylindole derivatives reacted very well, providing better yields for the desired SCF_3 products **2l,m**. When 3-methylindole **1n** was subjected to the trifluoromethylthiolation, only a trace amount of C-2 SCF_3 product was observed.

The reaction mechanism of this reductive deoxygenation−trifluoromethylthiolation starts with the heterolytic cleavage of the S−Cl covalent bonds triggered by the halogen bond between the positive electrostatic potential on the outer side of the chlorine atom in CF_3SO_2Cl and the lone pair of phosphorus atom in the phosphine. The resulting chlorophosphonium sulfinate is converted into the *O*-sulfinatophosphonium chloride, which undergo Arbuzov collapse to trimethylphosphine oxide, confirmed by ^{31}P NMR of the reaction mixture, and trifluoromethanesulfinyl chloride, CF_3SOCl. A second similar sequence affords the trifluoromethanesulfenyl chloride, CF_3SCl, as the desired reactive electrophilic species (Scheme 3). In two recent papers on the use of sodium triflinate as SCF_3 donor, the authors demonstrated that CF_3SSCF_3 is an intermediate reacting with CuCl to generate either an electrophilic[4] or a nucleophilic SCF_3 species.[11] Because CF_3SSCF_3 was identified when our reaction was monitored by ^{19}F NMR spectroscopy, we wondered if this disulfide plays a role in the trifluoromethylthiolation. Accordingly, we performed a reaction in the absence of indole and observed the reductive coupling of CF_3SO_2Cl yielding the symmetrical disulfide (Scheme 4). The disulfide was collected and engaged in the reaction with indole **1a** under our reaction conditions in the presence or not of trimethylphosphine. Product **2a** was not obtained, attesting that in the absence of metal salt CF_3SSCF_3 does not act as an electrophilic trifluoromethylthiolation agent,[12] and therefore, CF_3SCl is the metal-free generated reactive species in our experimental conditions. Compared with the combination CF_3SO_2Na/diethyl phosphite/CuCl described by Zhang that generates CF_3SSCF_3 as a reactive intermediate,[4] our method presents a clear mechanistic difference. In addition, we conducted a similar reaction with methanesulfonyl chloride $MeSO_2Cl$ in order to highlight the specific effect of fluorine.[13] Indeed, $MeSO_2Cl$ failed in the sulfenylation of indole because its deoxygenation by phosphine does not occur. The surface electrostatic potential of the chlorine atom is no longer positive to allow the halogen bonding interaction with the phosphine.

The invention of a route to in situ formation of CF_3SCl prompted us to examine the reaction with other azaarenes that include the synthesis of trifluoromethylthiolated pyrroles **3** and **4**, imidazo[1,2-*a*]pyridine **5**, methyl indolizine-1-carboxylate **6**, and pyrazolone **7** (Scheme 5). Interestingly, pyrroles **4** are potent insecticidal and fungicidal agents that were initially prepared by means of CF_3SCl.[14] Under the same reaction conditions as for indoles, these azaarenes afforded the expected SCF_3 products in moderate to good yields. In addition, we found that enamines and enoxysilanes were suitable substrates

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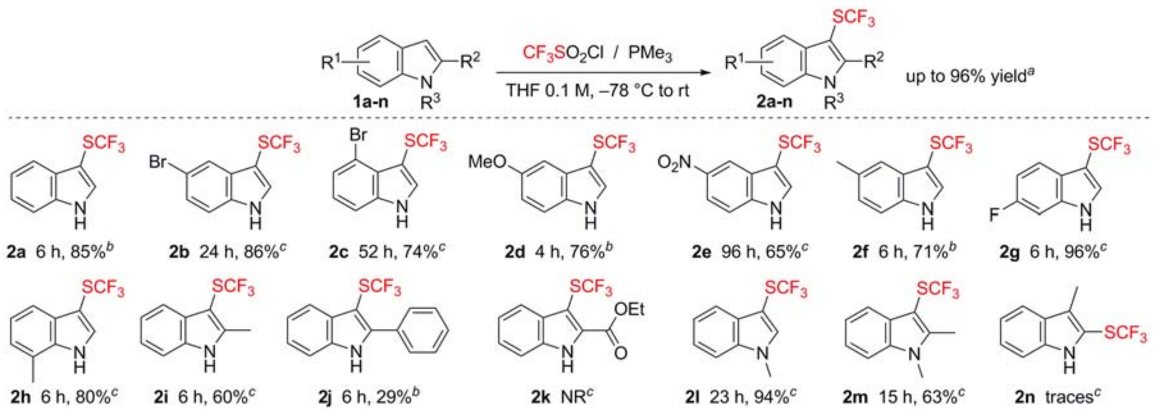
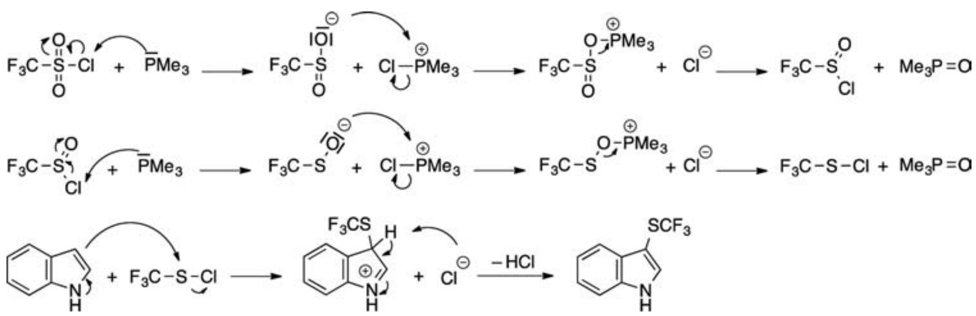
Scheme 2. Scope of Trifluoromethylthiolation of Indole Derivatives

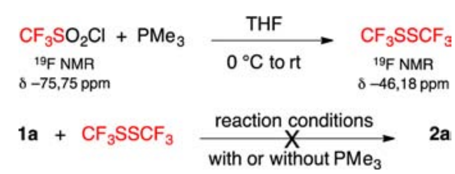


[a]Yields of isolated pure products. [b]Ratio indole/CF_3SO_2Cl/PMe_3 1:1.8:3.6. [c]Ratio indole/CF_3SO_2Cl/PMe_3 1:2.2:4.4. N.R.: no reaction.

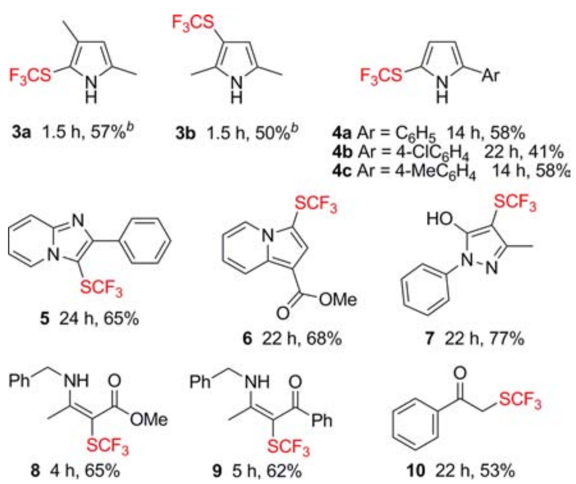
Scheme 3. Proposed Deoxygenative Sulfenylation Mechanism



Scheme 4. Insights into the Active Species



Scheme 5. Scope of Trifluoromethylthiolation[a]



[a]Ratio indole/CF_3SO_2Cl/PMe_3 1:1.8:3.6 for **3**–**4**, **9** and 1:2.2:4.4 for **5**–**8**, **10**. Yields of isolated pure products. [b]Yields were determined by ^{19}F NMR.

for further development of our methodology, affording SCF_3 products **8**–**10** in 53–65% yields (Scheme 5).

In conclusion, we have tamed the transient existence of trifluoromethylsufenyl chloride in a novel phosphine-mediated reductive deoxygenation–trifluoromethylthiolation reaction of indoles, other azaarenes, enamines, and enoxysilanes with trifluoromethanesulfonyl chloride. The metal-free mild protocol is simple to implement with readily available reagents bypassing sophisticated SCF_3 reagents which are difficult to use on a larger scale. The invention offers an alternative access to SCF_3 compounds and unveils a novel application of trifluoromethanesulfonyl chloride that is otherwise frequently used in organic chemistry. Our approach also allows a convenient preparation of CF_3SSCF_3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01026.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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