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Direct Phosphorus-Induced Fluoroalkylthiolation with Fluoroalkylsulfonyl Chlorides

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Abstract: A simple and practical method of fluoroalkylthiolation using fluoroalkylsulfonyl chlorides (R_fSO_2Cl, $R_f = CF_3$, C_4F_9, C_8F_{17}, CF_2H and CH_2CF_3) has been developed. These easy-to-handle reagents are powerful and can be used for electrophilic fluoroalkylthiolation of electron-rich arenes and thiols using diethyl phosphite as reducing agent.

Keywords: electron-rich arenes and thiols; fluoroalkylsulfonyl chlorides; fluoroalkylthiolation; phosphorus-induced reaction

Organofluorine chemistry has experienced a resurgence of interest and consequently a very fast expansion.[1] Due to the unique ability of the fluorine atom and fluorinated groups to modify the biological and physical properties of a molecule, their presence is often crucial for the discovery and design of new pharmaceuticals and agrochemicals.[2] Already today, around 25% of all pharmaceuticals and 30% of the applied agrochemicals contain at least one or even more trifluoromethyl substituents, or a fluorine atom.[3]

In the organofluorine family, the trifluoromethylthio group (SCF_3) has attracted special interest from both academia and the pharmaceutical industry due to its high lipophilicity and high electron-withdrawing character.[4] The SCF_2H group has potential as a lipophilic OH or NH surrogate, and was shown to be uniquely effective in bioactive structures[5] and the SR_f ($R_f = C_4F_9$, C_8F_{17}) moieties with a fluorous chain could stabilize the parent molecules and change their amphiphilic properties as in the study of glycosidase inhibitors.[6] It has been realized that a trifluoroethyl group (SCH_2CF_3) can confer greater activity than other fluoroalkyl groups in many pharmacological studies,[7] which makes the SCH_2CF_3 moiety an interesting group with respect to the design of bioactive molecules. Examples of fluoroalkylthiolated drugs and agrochemicals including Toltrazuril,[8] Cefazaflur,[9] Flomoxef sodium,[10] Pyriprole,[11] Losartan analogues[12] and Polythyazid[13] are shown in Figure 1.

Various approaches for the direct installment of a SCF_3 moiety have been reported and represented more attractive approaches to $RSCF_3$ products.[14] One attractive strategy for the construction of C–SCF_3 bonds is to use an electrophilic trifluoromethylthiolating reagent. The original electrophilic tri-

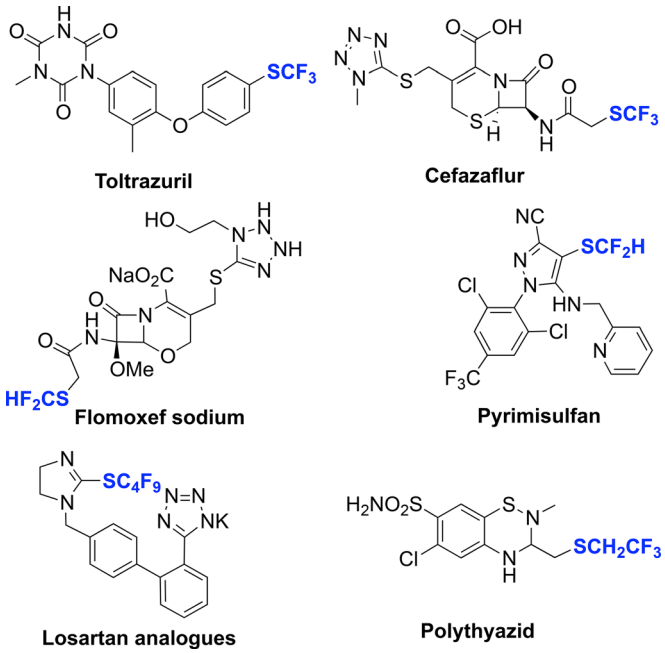


Figure 1. Examples of the R_fS-containing biologically active compounds.

fluoromethylthiolating reagent is CF_3SCl, which was used to react with some nucleophiles but with high toxicity.[15] When it comes to the 20th century, Munavalli utilized *N*-(trifluoromethylthio)-phthalimide (Figure 2, **1a**) as the trifluoromethylthiolating reagent for the preparation of α-SCF_3 carbonyl compounds in 2000.[16] $PhNHSCF_3$ and $PhN(Me)SCF_3$, initially developed by Billard and Langlois, were effective for the trifluoromethylthiolation of alkenes, alkynes, indoles, and Grignard and lithium reagents, but a strong Lewis acid or Brønsted acid was required to activate these reagents.[17] Then in 2013, Lv and Shen reported the trifluoromethylthiolation of β-keto esters using a novel hypervalent iodine reagent **1b**[18a] which was later revised by Buchwald to have the structure of a trifluoromethanesulfenate (**1b′**).[18b] In the same year, the group of Shibata used the hypervalent trifluoromethanesulfonyl iodonium ylide **1c** (R = IPh)[19a] as a CF_3SO_2-based trifluoromethylthiolating reagent and recently they reported another similar reagent (**1c**, R = N_2).[19b,c] In 2014, Shen and his co-workers described a new shelf-stable electrophilic reagent *N*-trifluoromethylthiosaccharin **1d** which was easy to prepare and has a broad scope.[20a] After that Billard reported a trifluoromethanesulfenamide **1e** which could be used for the α-trifluoromethylthiolation of the enolate of acetophenone.[20b] Very recently, Shen and co-workers demonstrated another electrophilic reagent *N*-trifluoromethylthiodibenzenesulfonimide **1f** which was more powerful than **1b′**, **1d** and **1e**.[20c]

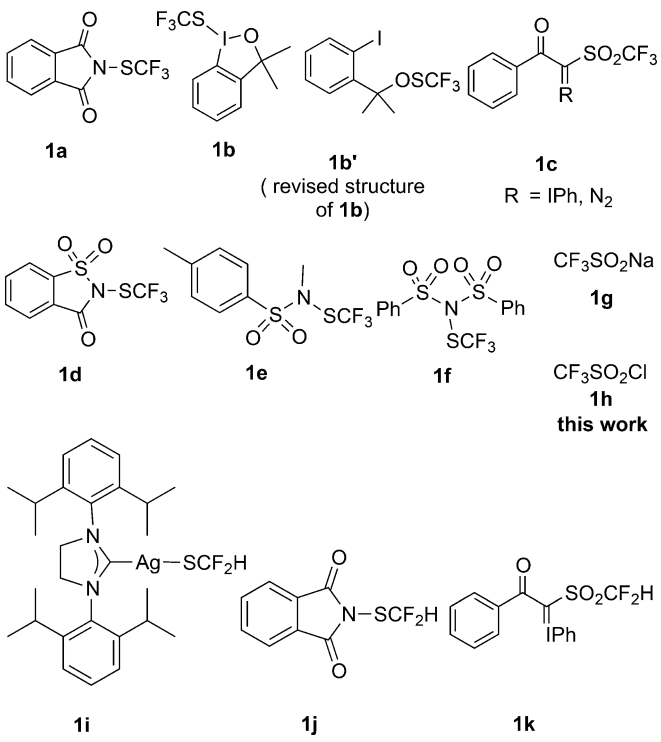


Figure 2. Some user-friendly electrophilic trifluoromethylthiolating and difluoromethylthiolating reagents.

Although there are continuing elegant synthetic works on SCF_3 moieties, methods for the straightforward introduction of SCF_2H, SCH_2CF_3 and SR_f groups are very limited. Recently, Shen and co-workers demonstrated the Sandmeyer-type difluoromethylthiolation of diazonium salts for the formation of electrophilic difluoromethylthiolated arenes and heteroarenes using the N-heterocyclic carbene (NHC) ligated difluoromethylthiolated silver complex [(SIPr)Ag(SCF_2H)] (Figure 2, **1i**).[21] They subsequently reported a new electrophilic reagent *N*-difluoromethylthiophthalimide (**1j**) for the direct difluoromethylthiolation of hydrocarbon derivatives and heteroarenes.[22] The Shibata group reported difluoromethanesulfonyl (SO_2CF_2H) hypervalent iodonium ylides (**1k**) as electrophilic difluoromethylthiolating reagents for a wide range of nucleophiles.[23] As to perfluoroalkylthiolation, our group recently reported a method for the perfluoroalkylthiolation of indoles using $NaSO_2R_f$.[24]

It is worth mentioning that although great progress in direct fluoroalkylthiolation methods was reported in recent years, there are still serious practical limitations in the field, especially in the application for large-scale fluoroalkylthiolation reactions. Most previously reported fluoroalkylthiolating reagents suffer from a common drawback which is that multiple steps are required and the generation of stoichiometric amounts of metal salts decrease the overall synthetic efficiency. Recently, our group reported the reduction of Langlois' reagent (CF_3SO_2Na, **1g**) to CF_3SSCF_3 by using $(EtO)_2P(O)H$, and its application in the electrophilic trifluoromethylthiolation of indoles, pyrroles and enamines. This reagent is cheap and stable compared with the reported reagents and the method has been successfully extended for perfluoroalkylthiolation using R_fSO_2Na.[24a] In the same year, Vivic also reported a method using CF_3SO_2Na to generate $CuSCF_3$ and then reacted it with (hetero)aryl iodides.[24b] Our system was similar to Deng's work, who reported an iodine-catalyzed sulfenylation of indoles with sodium sulfonates (Figure 3).[25] In 2011,You and his co-workers reported the synthesis of di(hetero)aryl sulfides by using arylsulfonyl chlorides, triphenyl-

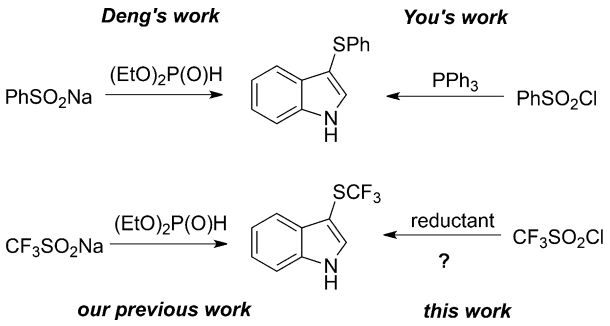
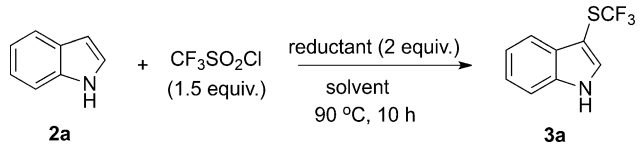


Figure 3. Some related previous work and this work.

phosphine was used as the reductant.[26] As a deduction, we speculated that trifluoromethanesulfonyl chloride (CF_3SO_2Cl) could also conceivably generate reactive SCF_3 species without any additional sulfur sources (Figure 3).[27] Trifluoromethanesulfonyl chloride is an inexpensive and readily available compound. It has been used for more than a century in materials science and medicinal chemistry.[28]

Initial studies were focused on searching for suitable reductants. We first examined the reaction of CF_3SO_2Cl and indole with some phosphine compounds (Table 1, entries 1–3). Reaction of 2 equivalents of PPh_3 and CF_3SO_2Cl at 90 °C gave the trifluoromethylthiolation product **3a** in 35% yield (Table 1, entry 3). Inspired by this result, we screened other reductants. After testing some phosphite esters (Table 1, entries 4 and 5) we were excited to find that the reaction with $(EtO)_2P(O)H$ (2 equiv.) afforded a high yield of **3a**. Optimization of the solvents (Table 1, entries 6 and 7) and temperature (Table 1, entries 8 and 9) revealed that using $(EtO)_2P(O)H$ (2.0 equiv.) in acetonitrile at 90 °C for 10 h could increase the product yield to 91% (Table 1, entry 7).

Table 1. Optimization of trifluoromethylthiolation with CF_3SO_2Cl.[a]



2a 3a

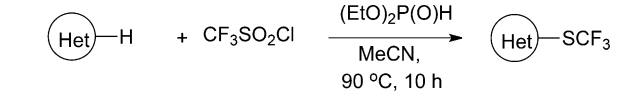
Entry	Reductant	Solvent	Yield [%][b]
1	PPh_3	PhMe	35
2	PPh_2Me	PhMe	23
3	$PPhMe_2$	PhMe	18
4	$(MeO)_2P(O)H$	PhMe	66
5	$(EtO)_2P(O)H$	PhMe	85
6	$(EtO)_2P(O)H$	DCM	81
7	$(EtO)_2P(O)H$	MeCN	91
8	$(EtO)_2P(O)H$	MeCN	trace[c]
9	$(EtO)_2P(O)H$	MeCN	21[d]

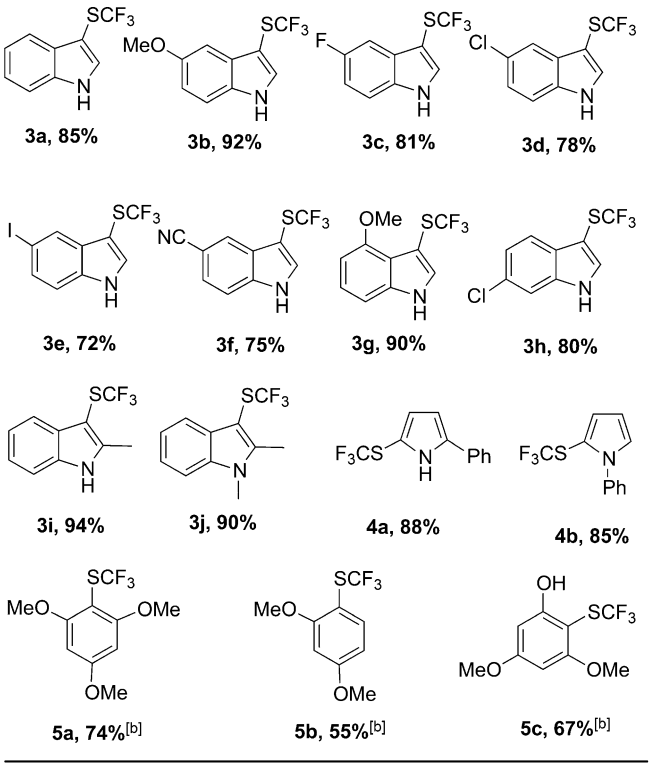
[a] *Conditions:* **2a** (0.2 mmol), solvent (1 mL), 90 °C.
[b] Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[c] At room temperature.
[d] At 50 °C.

Reactions of a variety of indoles with electron-donating or electron-withdrawing groups were conducted under the optimized condition and proceeded in good to excellent yields (Table 2). 5-Substituted indoles with functional groups such as fluoride (**3c**), chloride (**3d**), iodide (**3e**), and cyano (**3f**) groups reacted to generate the corresponding trifluoromethylthiolated indoles in high yields. Other indole derivatives including 4-methoxy (**3g**), 6-chloro (**3h**), 2-methyl (**3i**) and 1,2-dimethyl (**3j**) groups were also submitted to our trifluoromethylthiolation protocol. Indoles with an electron-donating group gave better results than those with an electron-withdrawing group such as for **3b** and **3f**. Similarly, reaction of pyrroles with different substituted groups occurred to give the corresponding trifluoromethylthiolated pyrroles in good yield (**4a**, **4b**). Besides indoles and pyrroles, activated benzenes such as 1,3,5-trimethoxybenzene (**5a**), 1,3-dimethoxybenzene (**5b**) and 3,5-dimethoxyphenol (**5c**) reacted with CF_3SO_2Cl in the presence of iron(III) chloride (3 equiv.) occurred to give the corresponding trifluoromethylthiolated heteroarenes in moderate yields (55–74%, **5a**–**5c**), less active than indoles and pyrroles.

Due to the importance of the SCF_2H group, our examination of the scope of substrates used in reactions with CF_2HSO_2Cl was more extensive. It was found that under the conditions that were optimal for CF_3SO_2Cl, CF_2HSO_2Cl also yielded the desired product (Table 3). Substituents such as ester (**6c**), and

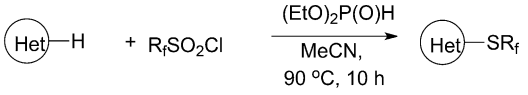
Table 2. Scope of the trifluoromethylthiolation of indole derivatives and other electron-rich heterocycles.[a]



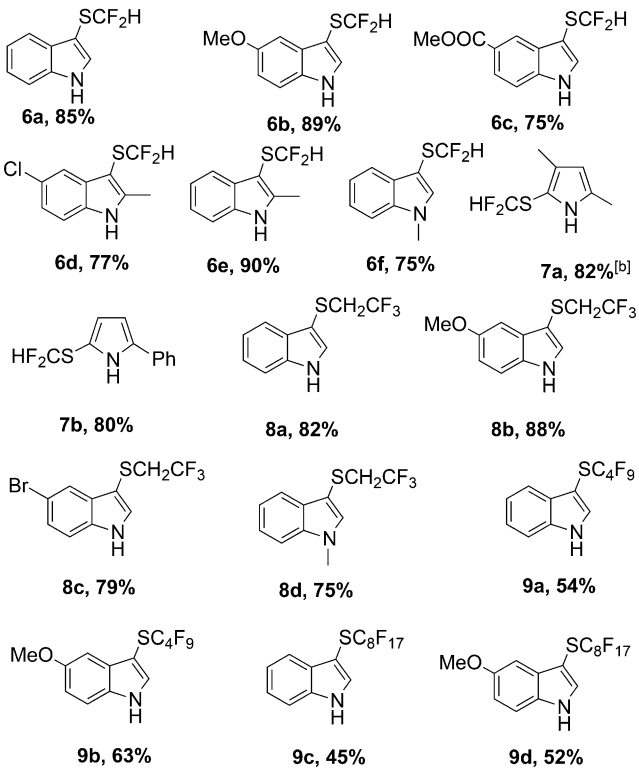


[a] *Conditions:* indole, pyrrole or activated benzene (0.2 mmol), **1h** (0.3 mmol), $(EtO)_2P(O)H$ (0.4 mmol), in MeCN (1 mL) at 90 °C for 10 h; isolated yields.
[b] 3 equiv. $FeCl_3$ were used.

Table 3. Fluoroalkylthiolation with R_fSO_2Cl of indole and pyrrole derivatives.[a]



R_f = CF_2H, CH_2CF_3, C_4F_9, C_8F_{17}



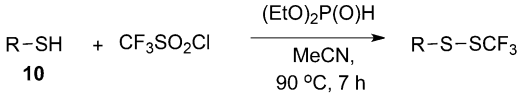
[a] *Conditions:* indole or pyrrole (0.2 mmol), R_fSO_2Cl (0.3 mmol), $(EtO)_2P(O)H$ (0.4 mmol) in MeCN (1 mL) at 90 °C for 10 h; isolated yields.

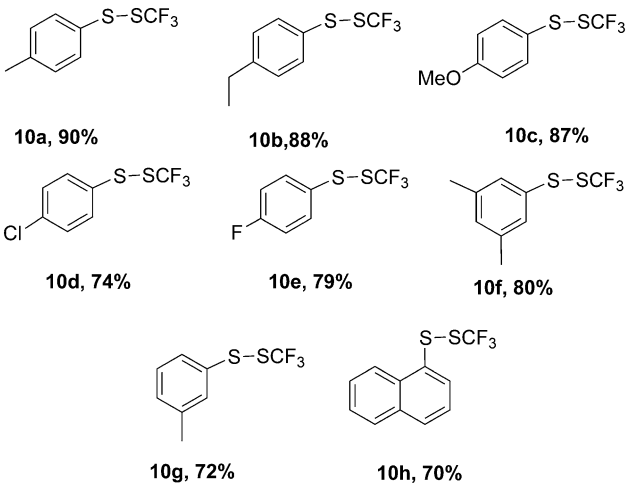
[b] Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

chloride (**6d**) on indoles were well-tolerated in these reactions. Reactions with 2,4-dimethyl- and 2-phenylpyrroles were identified to solely afford 2-SCF_2H products in good yields (**7a**, **7b**). Other fluoroalkylsulfonyl chlorides such as $CF_3CH_2SO_2Cl$, $C_4F_9SO_2Cl$ and $C_8F_{17}SO_2Cl$ were also tested with indole derivatives, the results with $CF_3CH_2SO_2Cl$ were similar to those with CF_3SO_2Cl and CF_2HSO_2Cl (**8a**–**8d**). However, results with $C_4F_9SO_2Cl$ and $C_8F_{17}SO_2Cl$ were more negative than those with CF_3SO_2Cl, CF_2HSO_2Cl and $CF_3CH_2SO_2Cl$, even when the iodole was activated by a methoxy group (**9b, 9d**), the yields were obviously lower.

Trifluoromethyl disulfides are important as precursors of biologically active trifluoromethyl thiosulfonates,[29] thus we futher studied the reaction of thiols with reagent **1h**. To our delight, reactions of **1h** with a variety of aryl thiols under similar conditions occurred in excellent yields (Table 4). Common functional groups such as chloride (**10d**) and fluoride (**10e**) were well tolerated. Thiols with 4-substituted groups gave better results than those with 3-substituted groups such as for **10a** and **10g**. Naphthalene-1-thiol also reacted with **1h** to provide the desired product in 70% yield (**8a**). Although other methods for the syhtnesis of trifluoromethyl-substituted disulfides have been already described,[20c,30] this method provided a alternative route with easy-to-handle reagents under simple conditions.

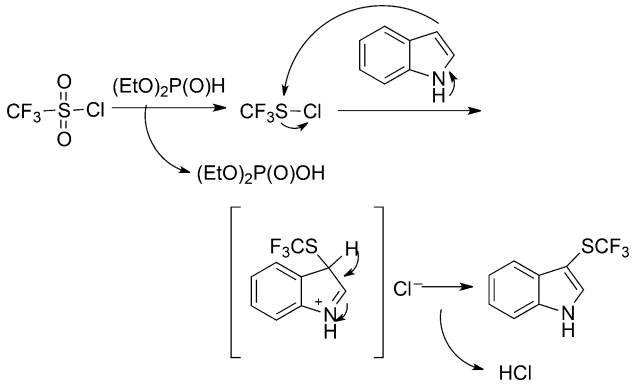
Table 4. Trifluoromethylthiolation of thiols with CF_3SO_2Cl.[a]





[a] *Conditions:* thiols (0.2 mmol), **1h** (0.3 mmol), $(EtO)_2P(O)H$ (0.4 mmol) in MeCN (1 mL) at 90 °C for 7 h; isolated yields.

To understand the mechanism of this phosphorus-reduced reaction, a reaction of indole under the optimized condition was monitored by ^{19}F-NMR. There was only a new peak at $\delta = -78.83$ ppm appeared except for the starting material CF_3SO_2Cl ($\delta = -75.31$) and the trifluoromethylthiolated product **3a** ($\delta = -44.60$). A similar peak of $CF_3S(O)H$ ($\delta = -78.58$) in our previous work was observed,[24] which demonstrated that trifluoromethanesulfinyl chloride (CF_3SOCl, the peak at $\delta = -78.83$) could be firstly formed. A similar reduction of CF_3SOCl afforded trifluoromethanesulfenyl chloride CF_3SCl, which was the real reactive electrophilic species as in Shibata's observation.[27] ^{31}P NMR was also used to monitor the reaction and showed that most of the diethyl phosphite ($\delta = -7.25$) was converted to diethyl phosphate ($\delta = -0.31$). A large amount of diethyl phosphate was also observed from GC-MS. On the basis of these observations, a plausible mechanism consisting of reduction of CF_3SO_2Cl with $(EtO)_2P(O)H$ to CF_3SCl and electrophilic attack of CF_3SCl on indole to give the



Scheme 1. Proposed mechanism for trifluoromethylthiolation with CF_3SO_2Cl.

trifluoromethylthiolated product **3a** is proposed in Scheme 1.

In summary, we have developed a cheap and stable electrophilic trifluoromethylthiolating reagent, CF_3SO_2Cl. This reagent was able to efficiently trifluoromethylthiolate indoles, pyrroles, activated benzenes and thiols. The reaction system is very simple and the method has been successfully extended for other fluoroalkylthiolation reactions using CF_2HSO_2Cl, $CF_3CH_2SO_2Cl$ and R_fSO_2Cl. This user-friendly reagent has a potential for the preparation of more complicated, densely functionalized drug-like molecules. It also has a potential for use on a larger scale, or even in industrial applications.

Experimental Section

General Procedure for Trifluoromethylthiolation of Indoles and Pyrroles (3a–3j, 4a, 4b)

A 10-mL oven-dried reaction vessel was charged with an indole or pyrrole (0.2 mmol), trifluoromethanesulfonyl chloride (**1h**, 50.6 mg, 0.3 mmol) and diethyl phosphite (51.2 μL, 0.4 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at 90 °C for 10 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolation product.

General Procedure for Trifluoromethylthiolation of Activated Benzenes (5a–5c)

A 10-mL oven-dried reaction vessel was charged with the activated benzene (0.2 mmol), trifluoromethanesulfonyl chloride (**1h**, 50.6 mg, 0.3 mmol), diethyl phosphite (51.2 μL, 0.4 mmol), and iron(III) chloride (97.32 mg, 0.6 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at 90 °C for 10 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolation product.

General Procedure for Fluoroalkylthiolation of Indoles and Pyrroles (6a–6f, 7a, 7b, 8a–8d, 9a–9d)

A 10-mL oven-dried reaction vessel was charged with the indole or pyrrole (0.2 mmol), fluoroalkylsulfonyl chlorides (0.3 mmol), and diethyl phosphite (51.2 μL, 0.4 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at 90 °C for 10 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding fluoroalkylthiolation product.

General Procedure for Trifluoromethylthiolation of Thiols (10a–10h)

A 10-mL oven-dried reaction vessel was charged with the thiol (0.2 mmol), trifluoromethansulfonyl chloride (**1h**, 50.6 mg, 0.3 mmol), diethyl phosphite (51.2 μL, 0.4 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at 90 °C for 7 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolation products.

Acknowledgements

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