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FULL PAPER

Diversification of Trifluoromethylthiolation of Aromatic Molecules with Derivatives of Trifluoromethanesulfenamide

Monika Horvat, Marjan Jereb, Jernej Iskra*

Abstract: Trifluoromethylthiolation of aromatic compounds with different electrophilic reagents of $ArNHSCF_3$ type was studied in the presence of triflic acid as an activator. The effect of the reagent structure on the reactivity was studied with three different reagents - $PhNHSCF_3$ (H/SCF_3, **1a**), 4-$ClC_6H_4NHSCF_3$ (Cl/SCF_3, **1b**) and $C_6F_5NHSCF_3$ (F_5/SCF_3, **1c**). *p*-Chloro substituted reagent **1b** was more stable than the unsubstituted one **1a** and the most effective, as it could not react by trifluoromethylthiolation of itself. The later reaction was the most important side reaction in reactions with **1a**. The pentafluoro derivative **1c** was less reactive. Solvent played important role in the transformation and depending on the substrate, DCM, hexane or trifluoroacetic acid gave the best yield of various trifluoromethylthiolated aromatic molecules (63-98%).

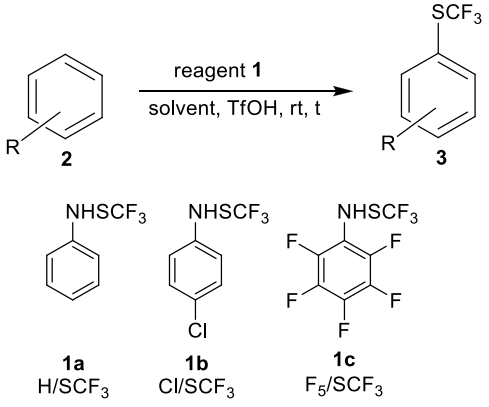
Introduction

In recent years the development of new methods for the introduction of the trifluoromethylsulfanyl group (SCF_3) into organic molecules is highly sought after. Organofluorine compounds have high potential in pharmaceutical industry, agrochemistry, fluoropolymers, material science and in medical chemistry.[1] There are several marketed fluorinated agrochemicals and pharmaceuticals, which possess enhanced stability and biological activity. The trifluoromethylsulfanyl group is of particular interest due to its remarkably high lipophilic parameter (Hansch constant 1.44).[2] The trifluoromethylsulfanyl group is found in several bioactive compounds, such as triflorex, toltrazuril, methionine analogue, adenosine analogue, losartan analogue, cefazaflur.[3]

Several methods were reported for the introduction of the trifluoromethylsulfanyl group into an aromatic ring (Ar-SCF_3) through radical, electrophilic and nucleophilic pathways.[2a, 3-4] Reactions can be divided into a direct introduction of the trifluoromethylsulfanyl group on an unsubstituted position, the replacement of -$B(OH)_2$, -N_2^+ or a halogen substituent and also by catalytic reactions (metals, organocatalysts, photocatalysis).[5] Initially used $Hg(SCF_3)_2$, that is very toxic and corrosive,[4d] was substituted by other nucleophilic reagents $AgSCF_3$, $CuSCF_3$, $[(CF_3S)_2(TDAE)]$[5g, 6] that are of limited reactivity because of their instability. Radical trifluoromethylthiolation reactions have been less studied and used due to toxic and gaseous radical reagents (CF_3SH, CF_3SSCF_3 and CF_3SCl). Recently, this approach become more interesting due to development of new methods, *e.g.* photochemistry.[4e, 5s, 7]

Electrophilic reagents for introduction of the trifluoromethylsulfanyl group into the aromatic ring can be classified into three groups: RSO_2CF_3, N-SCF_3 and O-SCF_3 reagents.[4e, 5a, 5b, 8] Among them, N-SCF_3 reagents are interesting with main reagents based on succinimide, phthalimide and saccharin scaffold.[5c, 5i, 9] Interest in N-SCF_3 reagents increased when Billard and co-workers prepared trifluoromethanesulfenamide reagent ($PhNHSCF_3$, **1a**) and later $PhN(CH_3)SCF_3$, while $PhSO_2N(CH_3)SCF_3$ was the second generation.[10] These reagents are useful for the trifluoromethylthiolation of alkynes, alkenes, indoles, organometallic substrates, tryptamines, allyl silanes, thiols and amines.[4d, 4e, 5b, 11] A strong Lewis (Me_3SiCl, $BF_3{\cdot}Et_2O$, acetyl chloride) or Brønsted (triflic acid, *p*-TsOH) acid is needed for the activation of the reaction.

Derivatives of trifluoromethanesulfenamide reagent were used for direct electrophilic trifluoromethylthiolation of activated aromatic and heteroaromatic molecules[10d, 10e, 12] and recently the second generation of reagent was used for the trifluoromethylthiolation of anilines in super acid media (SbF_5).[13] We were interested in the possibility of selective introduction of the trifluoromethylsulfanyl group on various aromatic compounds. We studied how the structure of the reagent and the solvent could affect the reactivity. The effect of the reagent structure on its activity was studied through modification of phenyl ring and three reagents were prepared - $PhNHSCF_3$ (H/SCF_3, **1a**), 4-$ClC_6H_4NHSCF_3$ (Cl/SCF_3, **1b**) and $C_6F_5NHSCF_3$ (F_5/SCF_3, **1c**).



Scheme 1

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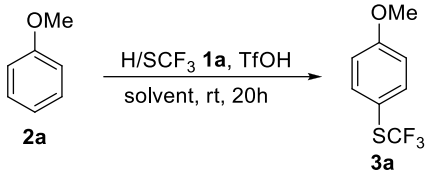
Results and Discussion

Anisole **2a** was chosen as the model substrate for initial study of the reaction conditions for the selective introduction of the trifluoromethylsulfanyl group on the aromatic ring with the basic reagent **1a** (Table 1). A solution of anisole **2a**, reagent H/SCF_3 **1a** and activator TfOH was stirred at room temperature for 20 h. After the work-up procedure, conversion based on the starting material **2a** was determined by ^{1}H NMR on the crude reaction product. Amongst the various tested solvents, the highest conversion was observed in non-polar ones with DCM giving the best results (Table 1, entry 5). Interestingly, reaction did not proceed in polar solvents MeCN and HFIP, although the latter is being known for facilitating the electrophilic processes.[14] Only TFA gave similar yield of **3a** as non-polar solvents. Increasing the amount of TfOH increased the yield. When using 1.3 equiv. of **1a** and TfOH the product **3a** was formed in 93% yield, while further increase of the amount of triflic acid had only small effect on the yield.

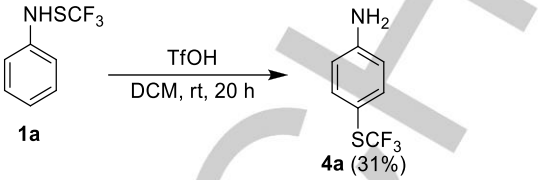
Table 1. Optimization of the reaction conditions for trifluoromethylthiolation of anisole **2a** with **1a**[a]



Entry	**2**:**1a**:TfOH	Solvent	Conv.[b] [%]
1	1:1.0:1.0	DCM	76
2	1:1.0:2.0	DCM	84
3	1:1.3:1.3	TFA	81
4	1:1.3:1.3	hexane	88
5	1:1.3:1.3	DCM	93
6	1:1.3:2.6	DCM	94
7	1:1.5:3.0	DCM	95

[a]Reaction conditions: anisole **2a** (0.1 mmol), reagent H/SCF_3 **1a** (0.1 – 0.15 mmol), TfOH (0.1 – 0.30 mmol), solvent (1 mL), 20h, rt. [b]Conversion to product was determined by ^{1}H NMR.

Since we needed 30% excess of the reagent to get the best yield of trifluoromethylthiolation of anisole, we wondered if some side reaction occurs. We stirred only the reagent **1a** together with TfOH in DCM. Reaction mixture was washed with basic aqueous solution and organic phase was evaporated (Scheme 2). We analyzed the reaction mixture to find that the sink of the reagent was trifluoromethylthiolation of the reagent itself leading to formation of 4-((trifluoromethyl)thio)aniline (**4a**) in 31% yield. Next, we analysed the crude reaction mixture after the reaction of trifluoromethylthiolation (Table 1, entry 5) and found that the same product is formed as a side product in aromatic trifluoromethylthiolation. This side process was observed to a much greater degree in the reaction carried out in polar solvents.



Scheme 2

The result indicates that for less reactive substrates this side reaction will be even more competitive. Hence, we thought of preparing on alternative reagent with less reactive aniline ring and with even higher reactivity. Li and coworkers found linear correlation between the trifluoromethylsulfanyl radical donor ability (Tt·DA) of electrophilic SCF_3 reagents and Brown constant σ_p^+ of the substituent on the aromatic ring of the reagent.[15] According to the data from this theoretical study we chose to study 4-chloro derivative (Cl/SCF_3, **1b**) which had somewhat lower Tt·DA value in DCM (59.9 kcal mol^{-1}) than H/SCF_3 **1a** (60.3 kcal mol^{-1}) and hence more reactive, while it has deactivated aromatic ring for electrophilic substitution. As a comparison, we prepared pentafluoroaniline derivative (F_5/SCF_3, **1c**) that should have more electrophilic character at the sulfur atom due to the electron-withdrawing effect of fluorine atoms.

We have prepared all three reagents under the reported reaction conditions. Pure reagents were analyzed by TGA for their stability. Both substituted reagents Cl/SCF_3 **1b** and F_5/SCF_3 **1c** were found to be more stable than H/SCF_3 **1a** and started to decompose above 50 °C. The classical unsubstituted one **1a** started to decompose already at 40 °C with higher rate of decomposition than **1b** and **1c**.

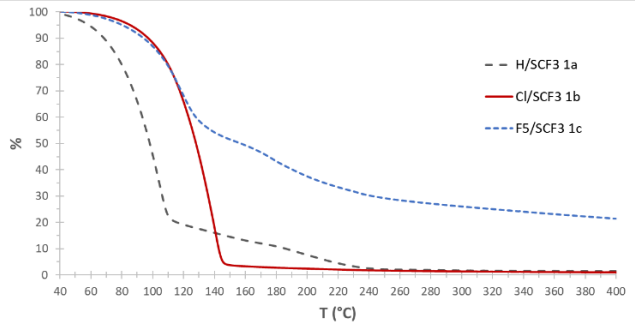
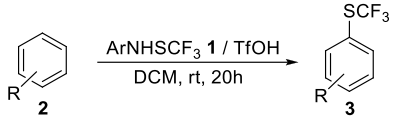


Figure 1. Thermogravimetric analysis of stability of reagents **1**

The effect of the substituent on the reactivity of the reagents **1** was studied in the case of anisole **2a** and two substituted phenols, 4-*tert*-butyl **2b** and 4-bromo **2c** substituted ones. The best reaction conditions from the Table 1 were taken for

trifluoromethylthiolation of anisole **2a** and results confirmed our anticipation that reagent **1b** is more effective than the classical one (Table 2, entry 2). By slow addition of the reagent, quantitative conversion to 4-trifluoromethylthioanisole **3a** was achieved. Surprisingly, F_5/SCF_3 **1c** was less reactive and only 44% of the product was formed under the same reaction conditions. Even using twice the amount of acid, the conversion was only 66%. Since the aromatic ring of the reagent is not active, low reactivity could only arise from the reagent structure. The same trend was even more obvious with activated phenol **2b**. Cl/SCF_3 **1b** was the most active reagent with quantitative conversion to 4-(*tert*-butyl)-2-((trifluoromethyl)thio)phenol **3b** under the slow addition of the reagent. The F_5/SCF_3 **1c** was not active enough and the conversion of 37% was observed using 3.9 equiv. of TfOH. The deactivated 4-bromophenol **2c** was not converted completely to the 4-bromo-2-((trifluoromethyl)thio)phenol **3c** and the highest conversion was achieved by using Cl/SCF_3 **1b** (50% conversion).

Table 2. The effect of reagent structure on the reactivity[a]

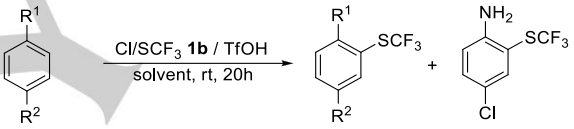


Entry	2	1	2:1:TfOH	Conv.[b] [%]
1	anisole **2a**	**1a**	1:1.3:1.3	93
2	anisole **2a**	**1b**	1:1.3:1.3	95
3	anisole **2a**	**1b**[c]	1:1.3:1.3	100
4	anisole **2a**	**1c**	1:1.3:1.3	44
5	anisole **2a**	**1c**	1:1.3:2.6	61
6	4-*tert*-butylphenol **2b**	**1a**	1:1.3:1.3	75
7	4-*tert*-butylphenol **2b**	**1b**	1:1.3:1.3	96
8	4-*tert*-butylphenol **2b**	**1b**[c]	1:1.3:1.3	100
9	4-*tert*-butylphenol **2b**	**1c**	1:1.3:1.3	0
10	4-*tert*-butylphenol **2b**	**1c**	1:1.3:2.6	5
11	4-*tert*-butylphenol **2b**	**1c**	1:1.3:3.9	37
12	4-bromophenol **2c**	**1a**	1:1.3:1.3	35
13	4-bromophenol **2c**	**1b**	1:1.3:1.3	50
14	4-bromophenol **2c**	**1c**	1:1.3:1.3	0

[a]Reaction conditions: reactant **2** (0.5 mmol), reagent **1** (0.65 mmol), TfOH (0.65 mmol), DCM (5 mL), 20h, rt. [b]Conversion to product **3** was determined by ^{1}H NMR. [c]Stepwise addition of reagent **1**.

We studied the effect of the solvent on the trifluoromethylthiolation with Cl/SCF_3 **1b** to improve its reactivity. We tested this approach on wider substrate scope and besides 4-bromophenol **2c** we included also less reactive substrates 4-*tert*-butyltoluene **2d** and 4-bromoanisole **2e** (Table 3). Reactions were performed on a 0.1 mmol scale and when the reaction was complete, the reaction mixture was washed with saturated solution of $NaHCO_3$ and water; organic phase was evaporated and the crude reaction mixture analyzed by ^{1}H NMR spectroscopy. This work-up procedure kept the reagent's product **4b** in the organic phase so that we could determine the amount of SCF_3 group that was incorporated into the aromatic ring of the reagent. Anisole **2a** was trifluoromethylthiolated by **1b** in all three solvents (DCM, Hex, TFA) and no formation of **4b** occurred (Table 3). Trifluoromethylthiolation in DCM was quantitative with *o*-/*p*- ratio of **3a** 6/94. Reaction in hexane and TFA was less effective (71% and 60% conversion, respectively) and slightly higher amount of *ortho* product was formed in TFA (*o*-/*p*- ratio of **3a** 9/91). Reaction of 4-bromophenol **2c** showed similar trend and reaction occurred in all three solvents with conversion in TFA being the lowest. We also observed the reaction on the reagent leading to the formation of **4b** in small amount. On contrary, 4-*tert*-butyltoluene **2d** and 4-bromoanisole **2e** showed the best conversion in TFA and besides **3d** and **3e**, **4b** was also formed.

Table 3. The effect of solvent on the reaction of Cl/SCF_3 **1b** with less reactive arenes[a]



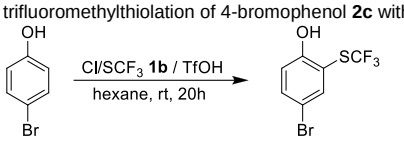
2c: R^1= OH, R^2= Br
2d: R^1= Me, R^2= tBu
2e: R^1= OMe, R^2= Br

Entry	2	Solvent	2	3[b]	4b[c]
1	anisole **2a**	DCM	5	95	0
2	anisole **2a**	hexane	29	71	0
3	anisole **2a**	TFA	40	60	0
4	4-bromophenol **2c**	DCM	55	45	10
5	4-bromophenol **2c**	hexane	48	52	11
6	4-bromophenol **2c**	TFA	85	15	13
7	4-*tert*-butyltoluene **2d**	DCM	37	63	41
8	4-*tert*-butyltoluene **2d**	hexane	11	89	16
9	4-*tert*-butyltoluene **2d**	TFA	9	91	17
10	4-bromoanisole **2e**	DCM	100	0	0
11	4-bromoanisole **2e**	hexane	87	13	19
12	4-bromoanisole **2e**	TFA	59	41	28

[a]Reaction conditions substrate **2** (0.1 mmol), reagent **1b** (0.13 mmol), TfOH (0.13 mmol), solvent (1 mL), 20h, rt. [b]Formation of **3** determined relative to the initial amount of starting compound (**2**+**3** = 100%). [c]The amount of **4b** relative to the initial amount of starting compound.

Finally, the most activating reaction conditions were sought for conversion of less reactive arenes. We used 4-bromophenol **1c** as the model compound, hexane as solvent and changed the amount of reagent **1b** and TfOH. By using 2 equiv. of **1b** and 3 equiv. of TfOH in hexane and with slow addition of reagents, complete conversion of **2c** was observed. (Table 4, entry 5).

Table 4. Optimization of the reaction conditions for trifluoromethylthiolation of 4-bromophenol **2c** with **1b**[a]

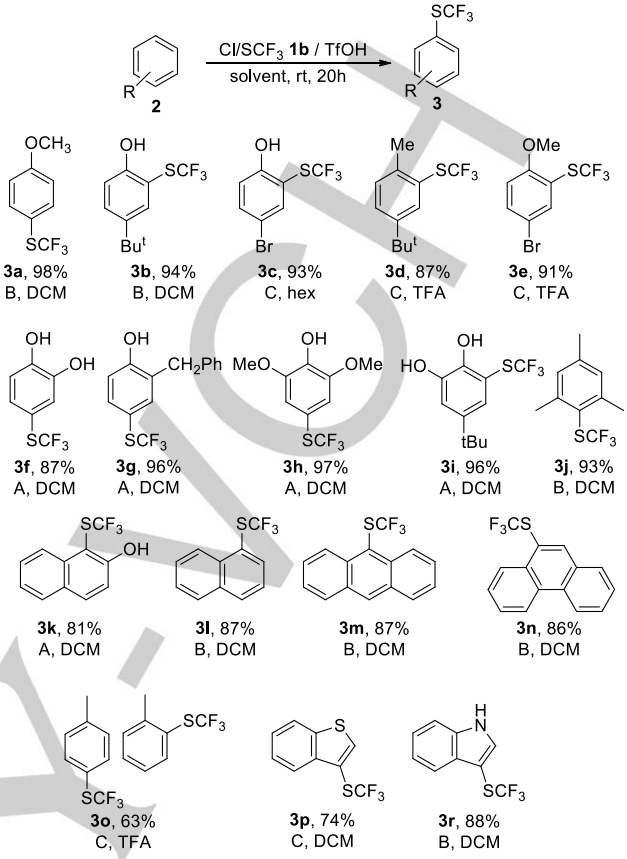


2c **3c**

Entry	**1b** (eq.)	TfOH (eq.)	Conv.[b] [%]
1	1.3	1.3	52
2	1.3	2.6	83
3	1.5	2.6	87
4	2	3	88
5	2[c]	3[c]	100

[a]Reaction conditions: 4-bromophenol **2c** (0.5 mmol), reagent **1b** (0.65 – 1.0 mmol), TfOH (0.13 – 1.5 mmol), hexane (5 mL), 20h, rt. [b]Conversion to product was determined by ^{1}H NMR. [c]Stepwise addition of reagent **1** and TfOH.

With all the knowledge about the trifluoromethylthiolation of arenes that we obtained, we studied the trifluoromethylthiolation of various aromatic and heteroaromatic molecules. In all cases quantitative transformation to **3** was observed with complete selectivity for the mono-substitution and the isolated yields are presented in Scheme 3. Only in the case of **2a** and **2g** a small amount of the *ortho* isomer was formed as was determined by GC-MS. Depending on the reactivity of arene three reaction conditions were used. Typical reaction conditions (method A) were **2**:**1b**:TfOH =1:1.3:1.3 and DCM was used as solvent (rt, 20 °C). For less reactive substrates reagent **1b** was added stepwise to the reaction mixture (method B) to achieve complete conversion of **2**. The most activated conditions were used for even less reactive substrates, where higher amount of TfOH (3 equiv.) and **1b** (2 equiv.) had to be used and added slowly to the reaction mixture, while solvent had to be hexane or TFA. Toluene **2o** reacted with the $TsNMeSCF_3$ in only 8% conversion.[10d] With the reagent Cl/SCF_3 **1b** toluene was completely transformed into a mixture of *ortho* and *para* substituted products **3o** in ratio 45/55 as determined from the ^{1}H NMR spectra. TFA had to be used as a solvent. Benzothiophene **2p** and indole **2r** were more reactive and complete conversion was obtained in DCM.



Scheme 3. Isolated yields of the trifluoromethylated products **3** (Method A: **2**:**1b**:TfOH =1:1.3:1.3; Method B: **2**:**1b**:TfOH =1:1.3:1.3, stepwise addition of **1b**; Method C: **2**:**1b**:TfOH =1:2:3, stepwise addition of **1b** and TFOH).

Conclusions

We have studied the effect of the structure of the trifluoromethanesulfenamide reagent and reaction conditions on trifluoromethyllthiolation of arenes and found that by introducing a chlorine atom to the aniline ring of the reagent, a more reactive and stable reagent **1b** was obtained relative to classical one **1a**. On the other hand, pentafluoro substituted derivative **1c** was less reactive. The reagent **1b** is able to quantitatively trifluoromethylthylthiolate a wide range of aromatic compounds under mild conditions with no formation of disubstituted products. The reaction is limited by the reactivity of the 4-chloroanilinium cation as the reagent decomposes through formation of trifluoromethylthiolated aniline **4**. Reactivity of **1** depends and the amount of reagent and activator (triflic acid), while the solvent plays a crucial role and DCM, hexane or TFA are the solvents of choice depending on the reactivity of the arene.

Experimental Section

General information

TLC was performed on Merck-60-F_{254} plates using mixtures of petroleum ether:dichloromethane (10:1) or dichloromethane. The crude products were purified by column chromatography on silica gel (63-200 μm, 70-230 mesh ASTM; Fluka). The melting points were determined on OptiMelt MPA100. Products were characterized using ^{1}H, ^{13}C and ^{19}F NMR spectra, HRMS, elemental CHN analysis and melting points of solids. ^{1}H spectra were recorded on Bruker Avance 300 DPX, ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker Avance III 500 instruments, C, H, N analysis were recorded on Analizator Perkin-Elmer 2400 II, LC MS analysis were recorded on system Shimadzu LCMS-IT-TOF. Dynamic thermogravimetric measurements were performed on a Mettler Toledo TGA/DSC 1 Instrument in temperature range from 25 to 400 °C under a dynamic argon flow (100 $mLmin^{-1}$). Heating rate was 5 $Kmin^{-1}$. Initial masses of the samples were from 6,0 to 8,7 mg; 150 μL platinum crucibles were used. A baseline was subtracted in all measurements. GC-MS was recorded on GC/MS Hewlett Packard 6890 (HP-1 MS column, initial temperature - 80 °C, 20 °C/min, final temperature - 270 °C; except for **1c**, **5a** and **5b**, where initial temperature was 130 °C).

Synthesis of reagent 1

Reagents (**1a**, **1b**, **1c**) were prepared using the literature procedure of Billard and coworkers using aniline, 4-chloroaniline and 2,3,4,5,6-pentafluoroaniline, respectively.[16] The yield of reagents were: **1a** 61 %; **1b** 58 % and **1c** 49 %. Structure of reagents **1a** and **1b** was determined by comparison of literature data. Reagent **1c** was determined by ^{1}H and ^{19}F NMR spectra and GC-MS, where only one signal was obtained, while there was no ionization in LCMS.

N-(perfluorophenyl)-S-(trifluoromethyl)thiohydroxylamine (F_5/SCF_3, **1c**). 69 mg (49%). Yellow-brown liquid. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ –53.1 (t, J = 3 Hz, 3F), –153.5 (d, J = 22 Hz, 2F), –161.6 (t, J = 22 Hz, 1F), –162.7 (m, 2F). GC-MS: 283 (M, 100%), 214 (50%), 182 (82%), 155 (80%), 69 (33%).

Decomposition of reagent 1

To a solution of 1.0 mmol of reagent **1** in dichloromethane (5 mL) was the TfOH (140 μL, 1.5 mmol) added. The mixture was stirred at room temperature for 20 h. After the reaction was complete, the reaction mixture was washed first with aqueous $NaHCO_3$ (5 mL) and then with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude reaction was subjected to column chromatography (SiO_2, CH_2Cl_2). Solvent was evaporated in vacuo to provide the product **4**.

4-((trifluoromethyl)thio)aniline (4a).[17] Yellow viscous liquid. 41 mg (43%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.41 (d, J = 8.5 Hz, 1H, ArH), 6.65 (d, J = 8.6 Hz, 1H, ArH) ppm. 13C NMR (126 MHz, CDCl3, 25°C): δ = 149.1, 138.3, 129.8 (q, J = 308 Hz), 115.4, 111.2 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –44.9 (s, 3 F) ppm. GC-MS: 193 (M, 76%), 124 (100%), 80 (31%).

4-chloro-2-((trifluoromethyl)thio)aniline (4b). Orange viscous liquid. 44 mg (39%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.48 (s, 1 H, ArH), 7.25 (d, *J* = 8.7 Hz, 1 H, ArH), 6.73 (d, *J* = 8.7 Hz, 1 H, ArH), 4.48 (s, 2 H, NH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 148.9, 137.9, 133.2, 129.3 (d, *J* = 310 Hz), 129.2, 122.5, 116.6 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –43.0 ppm. ESI-HRMS: m/z calcd for $C_7H_5ClF_3NS$ $(M+H)^+$ 227.9856, found 227.9860. GC-MS: 227 (M, 91%), 188 (10%), 158 (100%), 114 (36%), 95 (10%), 69 (15%).

The effect of solvent on the trifluoromethylation of 2c-e and determination of the amount of side products 4

To a solution of aromatic compound **2** (0.1 mmol) in 1 mL of solvent was added reagent Cl/SCF_3 **1b** (0.13 mmol) and TfOH (0.13 mmol). The reaction mixture was stirred at room temperature for 20 h. Conversion was followed by GC-MS. After reaction was complete, the reaction mixture was washed first with water (1 × 3 mL) and with aqueous $NaHCO_3$ (1 × 3 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The isolated reaction mixture was analysed by NMR spectroscopy and GC-MS. Results are presented in the *Table 3*.

General procedure

To a solution of aromatic compound **2** (0.5 mmol) in 5 mL of solvent was added reagent Cl/SCF_3 **1b** (0.65-1.0 mmol, 1.3-2 equiv.) and TfOH (0.65 – 1.5 mmol, 1.3 – 3 equiv.). The reagent and TfOH were added in one portion or slowly in 6 portions every 1 h. The reaction mixture was stirred at room temperature for 2-20 h. Conversion was followed by GC-MS. After reaction was complete, the reaction mixture was washed first with water (1 × 5 mL), then with aqueous HCl (1 × 5 mL), with water (1 × 5 mL) and with aqueous $NaHCO_3$ (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was analyzed by NMR spectroscopy and the product purified by column chromatography on silica gel. Structure was determined by spectroscopic data and comparison with literature data. The structure of **3d** was determined after its oxidation to the corresponding sulfoxide **3d'** with MCPBA by the literature method.[18] Structure of ortho isomers of **3a** and **3g** was confirmed by the GC-MS analysis of the by-product and comparison of literature data.[19] Results are presented in the *Tables 1, 2* and *4* and the *Scheme 3*.

(4-methoxyphenyl)(trifluoromethyl)sulfane (3a).[5s] Orange, viscous liquid. 102 mg (98%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.57 (d, *J* = 8.8 Hz, 2 H, ArH), 6.93 (d, *J* = 8.9 Hz, 2 H, ArH), 3.91 (s, 0.2 H_{ortho}, CH_3), 3.83 (s, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 161.9, 138.3, 129.6 (q, *J* = 308 Hz), 121.2, 115.0, 55.4 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.9 (s, 0.18 F_{ortho}), –44.5 (s, 3 F) ppm. GC-MS (t=6.44): 208 (M, 100%), 139 (18%), 111 (36%), 95 (16%), 69 (21%), 45 (18%). GC-MS (t=6.38): 208 (M, 67%), 139 (100%), 124 (12%), 96 (14%), 69 (17%).

4-(*tert*-butyl)-2-((trifluoromethyl)thio)phenol (3b).[12] Yellow, viscous liquid. 118 mg (94%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.54 (d, *J* = 2.5 Hz, 1 H, ArH), 7.46 (dd, *J* = 8.6, 2.5 Hz, 1 H, ArH), 7.00 (d, *J* = 8.6 Hz, 1 H, ArH), 6.18 (s, 1 H, OH), 1.30 (s, 9 H, $C(CH_3)_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 155.8, 144.5, 134.8, 131.6, 128.8 (q, *J* = 310 Hz), 115.7, 107.6, 34.2, 31.3 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.9 (s, 3 F) ppm. ESI-HRMS: m/z calcd for $C_{11}H_{13}F_3OS$ $(M-H)^-$ 249.0557, found 249.0560. GC-MS: 250 (M, 27%), 235 (100%), 215 (28%), 187 (44%).

4-bromo-2-((trifluoromethyl)thio)phenol (3c).[10d] Orange liquid. 127 mg (93%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.71 (d, *J* = 2.4 Hz, 1 H, ArH), 7.54 (dd, *J* = 8.8, 2.4 Hz, 1 H, ArH), 6.98 (d, *J* = 8.8 Hz, 1 H, ArH), 6.29 (brs, 1 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 157.3, 139.9, 137.3, 128.5 (q, *J* = 311 Hz), 118.0, 112.6, 110.1 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –43.0 (s, 3 F) ppm. ESI-HRMS: m/z calcd for $C_7H_3BrF_3OS$ $(M-H)^-$ 270.9046, found 270.9044. GC-MS: 274 (M+2,

64%), 272 (M, 64%), 254 (100%), 205 (21%), 188 (57%), 175 (33%), 124 (12%), 96 (53%), 69 (41%), 45 (17%).

(5-(*tert*-butyl)-2-methylphenyl)(trifluoromethyl)sulfane (3d). Yellow, viscous liquid. 108 mg (87 %). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.66 (d, *J* = 1.8 Hz, 1 H, ArH), 7.40 (dd, *J* = 8.0, 2.1 Hz, 1 H, ArH), 7.24 (s, 1 H, ArH), 2.50 (s, 3 H, CH_3), 1.31 (s, 9 H, $C(CH_3)_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 150.1, 140.9, 135.4, 130.7, 130.0 (q, *J* = 308 Hz), 128.5, 123.3, 34.4, 31.2, 20.6 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –43.0 (s, 3 F) ppm. GC-MS: 248 (M, 29%), 233 (100%), 205 (15%).

4-(*tert*-butyl)-1-methyl-2-((trifluoromethyl)sulfinyl)benzene (3d').[20] Colorless liquid. 54 % (14.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 8.02 (d, *J* = 1.3 Hz, 1 H, ArH), 7.54 (dd, *J* = 8.0, 2.1 Hz, 1 H, ArH), 7.24 (d, *J* = 8.0 Hz, 1 H, ArH), 2.43 (s, 3 H, CH_3), 1.35 (s, 9 H, $C(CH_3)_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 150.8, 134.9, 133.4, 131.1, 130.4, 125.3 (q, *J* = 335 Hz), 122.5, 35.0, 31.1, 17.7 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –74.1 (s, 3 F) ppm. ESI-HRMS: m/z calcd for $C_{12}H_{15}F_3OS$ $(M+H)^+$ 265.0868, found 265.0869. GC-MS: 264 (M, 10%), 195 (100%), 180 (38%), 165 (14%), 115 (15%), 91 (16%), 69 (15%), 57 (54%).

(5-bromo-2-methoxyphenyl)(trifluoromethyl)sulfane (3e). Yellow, viscous oil. 131 mg (91 %).^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.73 (d, *J* = 2.5 Hz, 1 H, ArH), 7.55 (dd, *J* = 8.8, 2.5 Hz, 1 H, ArH), 6.86 (d, *J* = 8.8 Hz, 1 H, ArH), 3.89 (s, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 159.7, 140.2, 135.5, 129.3 (q, *J* = 309 Hz), 114.5, 113.2, 112.6, 56.4 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.6 (s, 3 F) ppm. ESI-HRMS: m/z calcd for $C_8H_6OSF_3Br$ 285.9275, found: 285.9271. GC-MS: 288 (M+2, 100%), 286 (M, 100%), 138 (62%), 108 (25%), 95 (30%), 69 (23%).

4-((trifluoromethyl)thio)benzene-1,2-diol (**3f**).**[12]** Brown, viscous liquid. 91 mg (87%).^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.17 (d, *J* = 2.0 Hz, 1 H, ArH), 7.14 (dd, *J* = 8.2, 2.0 Hz, 1 H, ArH), 6.90 (d, *J* = 8.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 146.5, 143.7, 130.5, 129.6 (q, *J* = 308 Hz), 123.3, 116.0, 115.0 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –44.3 (s, 3 F) ppm. ESI-HRMS (m/z) calcd for $C_7H_4F_3O_2S$ $(M – H)^–$ 208.9890, found 208.9889. GC-MS: 210 (M, 89%), 141 (100%), 123 (10%), 95 (11%), 69 (18%), 45 (10%).

2-benzyl-4-((trifluoromethyl)thio)phenol (3g).[12] Brown, viscous liquid. 137 mg (96%).^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.43 – 7.39 (m, 2 H, ArH), 7.31 – 7.29 (m, 2 H, ArH), 7.24 –7.20 (m, 3 H, ArH), 6.78 (d, 1 H, ArH), 4.03 (s, 0.18 H_{ortho}, CH_2), 3.98 (s, 2 H, CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 156.3, 139.4, 138.8, 136.6, 135.1, 129.7 (q, *J* = 296 Hz), 128.8, 128.6, 128.5, 128.4, 126.7, 116.8, 115.1, 36.2 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –43.2 (s, 3 F), –43.4 (s, 0.20 F_{ortho}) ppm. ESI-HRMS: m/z calcd for $C_{14}H_{10}F_3OS$ $(M – H)^–$ 283.0410, found 283.0409. GC-MS (t=10.43): 284 (M, 100%), 263 (10%), 206 (64%), 181 (43%), 165 (30%), 152 (29%), 137 (18%), 109 (15%), 91 (18%), 77 (12%), 65 (11%), 51 (10%). GC-MS (t=11.29): 284 (M, 100%), 206 (63%), 183 (38%), 165 (19%), 152 (20%), 137 (22%), 109 (23%), 91 (16%), 69 (10%).

2,6-dimethoxy-3-((trifluoromethyl)thio)phenol (3h).[12] Brown solid. mp 46.4-48.6 °C (lit. 44.7-46.5 °C). 123 mg (97%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.17 (d, *J* = 8.7 Hz, 1 H, ArH), 6.69 (d, *J* = 8.7 Hz, 1 H, ArH), 3.98 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 150.5, 149.0, 139.2, 129.1, 129.4 (q, *J* = 309 Hz), 109.5 (d, *J* = 2.0 Hz), 106.7, 61.3, 56.3 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –43.6 (s, 3 F) ppm. ESI-HRMS: m/z calcd for $C_9H_{10}F_3O_3S$ $(M + H)^+$ 255.0297, found 255.0297. GC-MS: 254 (M, 100%), 185 (11%), 139 (52%), 111 (10%), 69 (12%).

5-(*tert*-butyl)-3-((trifluoromethyl)thio)benzene-1,2-diol (3i). Brown, viscous liquid. 128 mg (96%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 7.19 (s, 1 H, ArH), 7.04 (s, 1 H, ArH), 1.45 (s, 9 H, $C(CH_3)_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 148.2, 145.3, 140.9, 129.5 (q, *J* = 309 Hz), 126.2, 117.2, 115.1, 36.2, 31.4 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.9 (s, 3 F) ppm. ESI-HRMS: m/z calcd for $C_{11}H_{12}F_3O_2S$ $(M – H)^–$ 256.0516, found 256.0516. GC-MS: 266 (M, 53%), 251 (44%), 182 (100%), 167 (33%), 57 (10%).

Mesityl(trifluoromethyl)sulfane (3j).[21] Colorless liquid. 102 mg (93%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 6.99 (s, 2 H, ArH), 2.52 (s, 6 H, CH_3), 2.29 (s, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 145.3, 141.4, 130.2 (q, *J* = 309 Hz), 129.6, 120.1, 22.1, 21.2 ppm. ^{19}F (500 MHZ, $CDCl_3$, 25°C): δ = –42.5 (s, 3 F) ppm. GC-MS: 220 (M, 85%), 151 (100%), 107 (25%), 91 (15%), 45 (16%).

1-((trifluoromethyl)thio)naphthalen-2-ol (3k).[9f] Orange liquid. 99 mg (81%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 8.33 (d, *J* = 8.5 Hz, 1 H, ArH), 7.95 (d, *J* = 9.0 Hz, 1 H, ArH), 7.81 (d, *J* = 8.1 Hz, 1 H, ArH), 7.63 (m, 1 H, ArH), 7.43 (m, 1 H, ArH), 7.30 (d, *J* = 9.0 Hz, 1 H, ArH), 6.92 (s, 1 H, OH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 158.4, 135.8, 134.9, 129.4, 128.8 (d, *J* = 313 Hz), 128.6, 128.4, 124.4, 124.3, 117.1, 100.8 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.3 (s) ppm. ESI-HRMS: m/z calcd for $C_{11}H_6F_3OS$ $(M – H)^–$ 243.0097, found 243.0098. GC-MS: 244 (M, 73%), 224 (19%), 175 (66%), 158 (10%), 147 (100%), 102 (11%), 69 (20%).

Naphthalen-1-yl(trifluoromethyl)sulfane (3l).[6a] Brown, viscous oil. 99 mg (87%).^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 8.53 (d, *J* = 8.5 Hz, 1 H, ArH), 7.98 (d, *J* = 8.5 Hz, 1 H, ArH), 7.95 (d, *J* = 7.2 Hz, 1 H, ArH), 7.87 (d, *J* = 8.2 Hz, 1 H, ArH), 7.63 (m, 1 H, ArH), 7.55 (m, 1 H, ArH), 7.48 (dd, *J* = 8.2, 7.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 137.8, 135.4, 134.3, 132.4, 129.7 (q, *J* = 309.2 Hz), 128.6, 127.7, 126.8, 125.8, 125.6, 121.6 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.7 (s, 3 F). GC-MS: 228 (M, 100%), 159 (88%), 115 (86%).

Anthracen-9-yl(trifluoromethyl)sulfane (3m).[6b] Yellow solid. Mp 145.2-147.7 °C. 121 mg (87%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 8.86 (d, *J* = 8.9 Hz, 2 H, ArH), 8.67 (s, 1 H, ArH), 8.05 (d, *J* = 8.4 Hz, 2 H, ArH), 7.71 – 7.65 (m, 2 H, ArH), 7.58 – 7.53 (m, 2 H, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 136.1, 132.5, 131.8, 130.5 (q, *J* = 137 Hz), 128.9, 127.9, 126.5, 125.7, 117.1 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –41.8 (s, 3 F). Anal Calced for $C_{15}H_9SF_3$: C, 64.74; H, 3.26, found: C, 64.47; H, 2.90. GC-MS: 278 (M, 80%), 209 (100%), 165 (68%).

Phenanthren-9-yl(trifluoromethyl)sulfane (3n).[6b] Yellow solid. Mp 96.6–98.2 °C (98.3–99.8 °C). 119 mg (86%). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 8.74–8.62 (m, 3 H, ArH), 8.32 (s, 1 H, ArH), 7.92 (d, *J* = 7.6 Hz, 1 H, ArH), 7.74–7.71 (m, 3 H, ArH), 7.65 (t, *J* = 7.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 140.2, 132.5, 131.8, 131.2, 131.0, 129.7 (q, *J* = 309 Hz), 129.3, 128.9, 127.5, 127.4, 127.3, 126.8, 123.0, 122.8, 120.6 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ –42.6 (s, 3 F). GC-MS: 278 (M, 75%), 209 (38%), 165 (100%).

***p*-tolyl(trifluoromethyl)sulfane** and ***o*-tolyl(trifluoromethyl)sulfane** (**3o**).[21,22] Colourless oil. 61 mg (63%, *o*/*p* 45/55). ^{1}H NMR (300 MHz, CDCl3, 25°C) δ = 7.66 (d, J = 7.7 Hz, 1H, *o*-ArH), 7.54 (d, J = 7.9 Hz, 2.H, *p*-ArH), 7.42 – 7.31 (m, 3H, *o*-ArH), 7.23 (d, J = 7.7 Hz, 2H, *p*-ArH), 2.55 (s, 3H, *o*-CH_3), 2.39 (s, 3H, *p*-CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 144.1, 141.4, 138.3, 136.4, 131.4, 131.1, 130.3, 129.6 (q, *J* = 290 Hz), 129.8 (q, *J* = 288 Hz), 129.2, 126.9, 121.6, 21.4, 21.2 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –42.9 (s, 3 F), –43.7 (s, 3 F) ppm. GC-MS (t=4.730): 192 (100%), 123 (50%), 91 (13%), 77 (14%), 95 (31%). GC-MS (t=4.818): 192 (M, 100%), 123 (60%), 91 (23%), 79 (15%), 45 (11%).

3-((trifluoromethyl)thio)benzo[*b*]thiophene (**3p**).[6a] Orange oil. 87 mg (74%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 8.07 (d, *J* = 8.0 Hz, 1H, ArH), 7.98 (s, 1H, CH), 7.91 (d, *J* = 8.0 Hz, 1H, ArH), 7.50 (dt, *J* = 21.3, 7.0 Hz, 2H, ArH) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 8.07 (d, *J* = 8.0 Hz, 1H, ArH), 7.98 (s, 1H, CH), 7.91 (d, *J* = 8.0 Hz, 1H, ArH), 7.50 (dt, *J* = 21.3, 7.0 Hz, 2H, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 139.4, 139.4, 137.9, 129.0 (q, *J* = 310 Hz), 125.4, 125.3, 122.9, 122.8, 115.2 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –43.1 (s, 3 F) ppm. GC-MS: 234 (M, 75%), 165 (100%), 121 (46%), 69 (11%).

3-((trifluoromethyl)thio)-*1H*-indole (**3r**).[10d] Orange oil. 96 mg (88%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 8.47 (s, 1H, NH), 7.92 – 7.77 (m, 1H, ArH), 7.52 (d, *J* = 2.7 Hz, 1H, ArH), 7.46 – 7.37 (m, 1H, ArH), 7.33 – 7.30 (m, 2H, ArH) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): δ = 136.0, 132.8, 129.4 (q, *J* = 310 Hz), 129.4, 123.4, 121.6, 119.3, 111.7, 95.4 ppm. ^{19}F NMR (471 MHz, $CDCl_3$, 25°C): δ = –45.1 (s, 3 F). GC-MS: 217 (M, 67%), 148 (100%), 121 (12%), 77 (13%).

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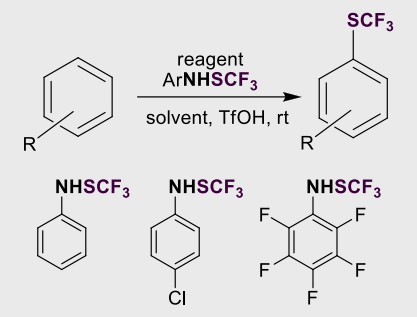
Trifluoromethylthiolation of aromatic compounds with different electrophilic reagents of $ArNHSCF_3$ type was studied in the presence of triflic acid as activator. *p*-Chloro substituted reagent **1b** was more stable than the unsubstituted one **1a** and the most effective for trifluoromethylthiolation of arenes. Reactions in DCM, hexane or trifluoroacetic acid gave various trifluoromethylthiolated aromatic molecules with isolated yields of 81-98%.



Trifluoromethylthiolation of aromatic molecules*

*Monika Horvat, Marjan Jereb, Jernej Iskra**

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Diversification of Trifluoromethylthiolation of Aromatic Molecules with Different Trifluoromethanesulfenamides

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