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Synthesis of aryl 2,2,2-trifluoroethyl sulfides

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ABSTRACT

Aryl 2,2,2-trifluoroethyl sulfides were synthesized by copper(I)-catalyzed nucleophilic aromatic substitution reaction (Goldberg-Ullmann coupling). The method requires aryl iodides and 2,2,2-trifluoroethyl thioacetate as starting materials, benzylamine as solvent and base, and copper(I) bromide as a catalyst. The reaction mixture was stirred at 110 °C for 6 h under inert atmosphere to afford the targeted aryl 2,2,2-trifluoroethyl sulfides in moderate to good yield.

1. Introduction

The unique properties of fluorine [1] have been exploited for the development of novel and effective biochemical tools and therapeutic agents, including active pharmaceutical ingredients (API's) as well. In the past three decades the extraordinary potential of fluorine-containing biologically relevant molecules has been explored in medicinal chemistry [2], chemical biology, pharmacology, drug discovery and development [3], as well as in diagnostic and therapeutic applications. In particular, the fact that a large number of fluorine-containing agents have been approved by the US Food and Drug Administration (FDA) for medical use clearly demonstrates the importance of fluorine in drug discovery and development [4].

Consequently, fluorine is recognized as the second favorite heteroatom in current drug design, after nitrogen. Following this paradigm, e.g. the replacement of a C—H or C—O bond with a C—F bond in biologically active compounds frequently introduce beneficial properties such as higher metabolic stability, increased binding affinity to target proteins, and increased membrane permeability [5]. In practice, for making such fluorinated target molecules either *fluorine containing building-blocks* are used [6], or *selective fluorinating or fluoroalkylation reagents* – allowing late formation of fluorinated functional groups – can be applied in their synthesis strategy [7]. Recently, special attention is called on the potential of the development of sulfur-fluorine overlap pharmaceuticals, where polarity tuning of the target molecule is enabled by the changing the valences of the sulfur fragments (e.g. S, SO, SO_2) in the fluoro-organosulfur compounds [8].

Indeed, fluoroalkylthio groups, such as the trifluoromethylthio (CF_3S-) [9,10], and the 2,2,2-trifluoroethylthio (CF_3CH_2S-) groups [11], are often present in molecules of biologically active ingredients at the *development* or *approved stage* of drugs **1** [12], **2** [13], **3** [14], **4** [15] and agrochemicals **5** [16], **6** [17], **7** [18], **8** [19] (Scheme 1).

Although *fluorine* and *sulfur* substitution could expand the potential for drug discovery, the novel aryl and/or hetaryl trifluoroethyl sulfides (e.g. $ArSCH_2CF_3$) are most frequently prepared by classical sulfide synthesis methods, i.e. including the *S*-trifluoroethylation of the corresponding aryl mercaptanes (ArSH), or by the base-assisted *S*-arylation of trifluoroethane thiolates with an activated halide (ArX); while in the case of unactivated halides the addition of a transition metal catalyst (nickel [20] or palladium [21]) could result in useful S-C(sp^2) coupling procedures (Scheme 2).

The simplest way to synthesize such thioethers (*disconnection type*-i/Scheme 2) is the nucleophilic substitution reaction between the thiophenols and 2,2,2-trifluoroethyl iodide [22], chloride [23], sulfonates [24], or 2,2,2-trifluoro-1-diazoalkanes [25]. It is worthy to note, that CF_3CH_2I reacts by either ionic or radical mechanism. In case of *S*-trifluoroethylation reactions with CF_3CH_2I the UV light induced radical substitution ($S_{RN}1$) afforded better yields than the S_N2 reactions. The disadvantage of such S-C(sp^3) bond forming alkylation reactions is that the starting thiophenols have low tolerance of numerous reaction conditions, thus the 2,2,2-trifluoroethylthio group should be introduced early in the sequence of the synthesis of compounds having various functional groups [17,18].

Recently some electrophilic coupling methods were implemented for the synthesis of aryl trifluoroethyl sulfides (*disconnection type*-ii/Scheme 2). These processes applied trifluoroalkanesulfonyl chloride

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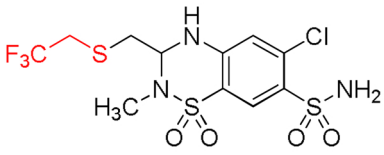
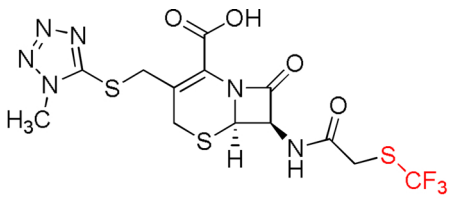
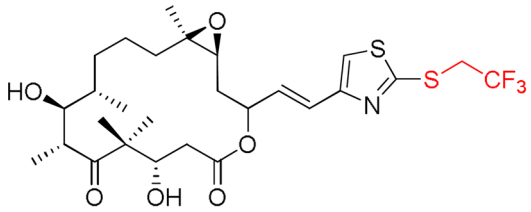


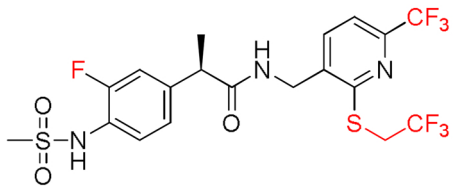
1961_Polythiazide, diuretic (**1**)



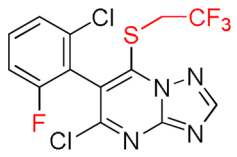
1977_Cefazaflur, antibiotic (**2**)



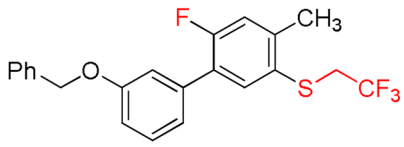
2003_Epothilone B analogue (**3**)



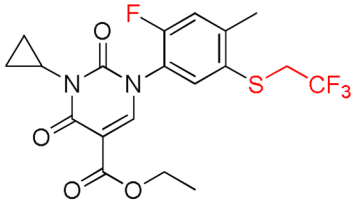
2013_TRPV1 antagonist, analgesic (4)



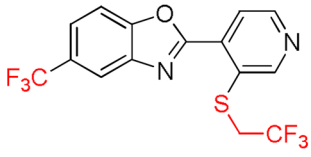
1999_High fungicidal activity agent (**5**)



2013_Low dose pest control agent with safety to crop plants (**6**)



2015_Combatting animal pests: arthropods, insects and acarides (**7**)



2017_Arthropod control composition (**8**) (e.g. combatting mosquito born diseases)

Scheme 1. Selected bioactive molecules featuring fluoroalkylthio groups with their approved and/or potential application fields (cf. Refs [12–19]).

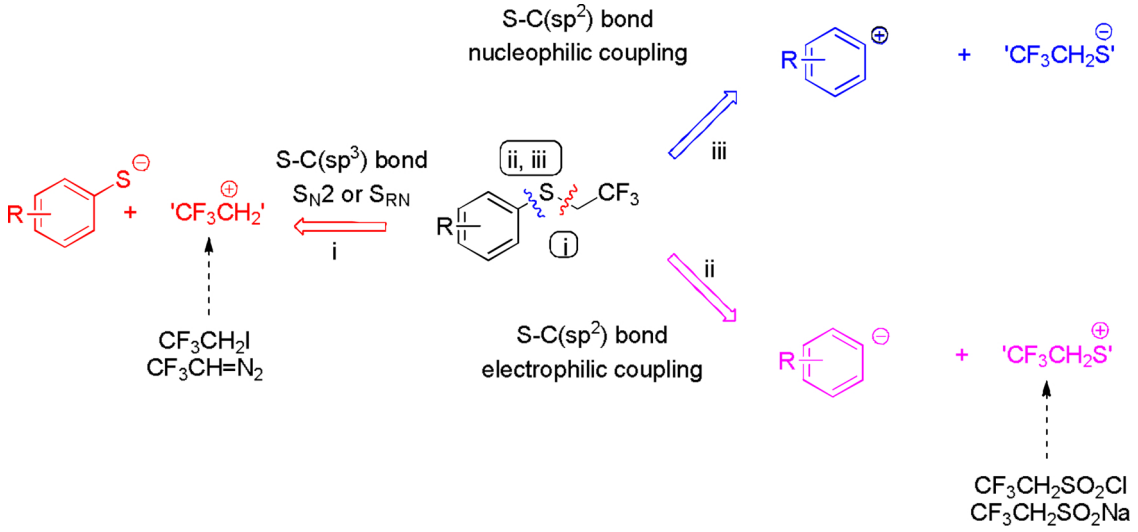
($CF_3CH_2SO_2Cl$) [26], or sodium trifluoroalkanesulfinate ($CF_3CH_2SO_2Na$) [11] along with a reducing agent to introduce the CF_3CH_2S moiety into an aromatic system. However, the latter electrophilic substitution reactions have the disadvantage of the formation of minor amount of positional isomers, and in the case of substrates with multiple aromatic rings the method is not selective enough for the formation of a single product.

However, the title CF_3CH_2SAr sulfides are often made by robust methods at pilot or industrial scale, based on the direct use of *the highly volatile and malodorous* 2,2,2-trifluoroethyl mercaptane (*disconnection type*-iii/Scheme 2) and their reaction with activated aryl (hetaryl) halides as reported in the literature [14,15,27] or disclosed in patents [16,19,28].

Liao and Weng developed the first nucleophilic coupling method for the synthesis of such aryl trifluoroethyl sulfides that is not based on the direct use of aryl and/or trifluoroethyl mercaptanes as the precursor reagents [29]. They have reacted aryl iodides or bromides with trifluoroethyl iodide and elemental sulfur, in the presence of copper(I) iodide with ligands and $NaBH_4$ acting as catalyst and reducing agents, respectively. This strategy is advantageous in the terms of good selectivity (usually not providing positional isomers), and the large tolerance of the starting aryl halides towards functional groups and reaction conditions. Thus, their method can also be applied for late-stage fluorination reactions resulting in good to excellent yields based on the aryl halides used at 0.5 − 10 mmol scales. Furthermore, the *in situ* formation of copper(I) trifluoroethylthiolate and/or copper(I) arenethiolates as key intermediates in the reaction mechanism comprising major and minor pathways, respectively, was experimentally supported.

It is noteworthy to state that the copper-catalyzed coupling of CF_3CH_2SH with aryl halides has not been attempted yet although the efficiency of using copper catalysts for *S*-arylation of appropriate thiols with aryl halides is well known since the pioneering work of Irma Goldberg [30], which has been developed further and later generalized by Buchwald.

In this paper, we present a copper-catalyzed aromatic nucleophilic substitution method (Goldberg-Ullmann coupling) for the synthesis of aryl 2,2,2-trifluoroethyl sulfides at multigram scale using simple reaction conditions (*disconnection type*-iii/Scheme 2).



Scheme 2. Retrosynthetic analysis of aryl 2,2,2-trifluoroethyl sulfides.

2. Results and discussion

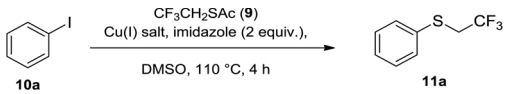
In our new synthesis, the requisite 2,2,2-trifluoroethane thiol (CF_3CH_2SH, bp = 36.5 °C [31]) is generated *in situ* from trifluoroethyl thioacetate (bp = 115 °C [32]; 108 − 110 °C [33]) and reacted with aryl iodides in presence of copper catalyst (CuBr) and benzylamine as a base and solvent (Scheme 3).

Recently, we have reported the synthesis of (fluoroalkyl)methane thiols ($C_nF_{2n+1}CH_2SH$, n = 1–3) from commercially available (fluoroalkyl)methanols *via* the corresponding thioacetates [34]. In the present work, we use 2,2,2-trifluoroethyl thioacetate (**9**) as the thiol source that allows the synthesis of aryl 2,2,2-trifluoroethyl sulfides by copper catalyzed reaction. Compound **9** (d = 1.278, n_D = 1.3940, 25 °C) was prepared in good yield reacting trifluoroethyl benzenesulfonate with an excess of thiolacetic acid in the presence of K_2CO_3. Using vacuum distillation of the crude mixture product isolation was improved relative to that reported in [33]. On cooling the colorless distillate separated into two liquid phases, the lower one enriched in trifluoroethyl thioacetate **9**, while the upper one in DMSO (cf. Experimental).

Our aim was to develop a 2,2,2-trifluoroethylthiolation method for aromatic compounds with broad functional group tolerance and substrate scope. Thus thiolester **9** was tested as a thiol precursor in a copper-catalyzed nucleophilic aromatic substitution reaction of unactivated aryl halides, such as iodobenzene (**10a**). During the optimization process we used iodobenzene **10a** as substrate, and tested the effect of the copper source, ligand, solvent, temperature and reaction time on the isolated yield of phenyl trifluoroethyl sulfide (**11a**). First copper(I) iodide, -bromide and -oxide were selected as the copper source.

The test reaction of **10a** with **9** was carried out in DMSO at 110 °C, employing 2 equivalents of imidazole acting as a nucleophile for cleavage of **9** [cf. 32] and as a base to remove the formed hydrogen iodide. The best yield of **11a** was achieved by using stoichiometric amount of copper(I) oxide or catalytic amount of copper(I) halides and adding 2 mol of tetramethylethylenediamine (TMEDA) for 1 mol of copper catalyst to the mixture (Table 1). Thus, we choose CuBr as a copper source for further reactions.

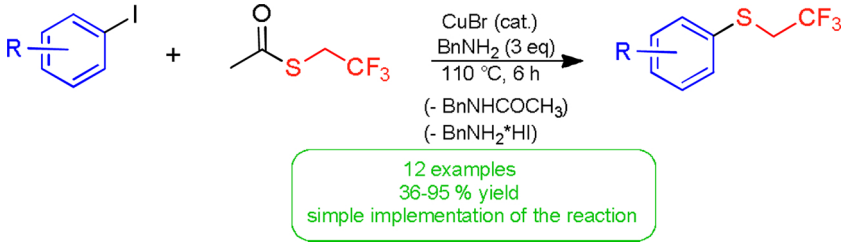
Table 1
The role of copper source in the DMSO-imidazole system.



Entry	Catalyst	mol% Cu	Yield (%)[a]
1	Cu_2O	100	88
2	CuI	20	27
3	CuBr	20	29
4	CuBr	20	61[b]
5	none	0	0

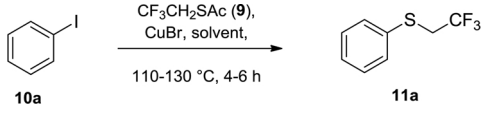
[a] **10a** (1 mmol), **9** (1 mmol), imidazole (2 mmol) and catalyst, 110 °C, 4h.
[b] **10a** (1 mmol), **9** (1 mmol), imidazole (2 mmol), catalyst, and 60 µl TMEDA, 110 °C, 4h.

In the second optimization stage we used amine type solvents, which can also react as ligand enhancing the efficiency of the substitution reactions. Amines and nitrogen-containing heteroaromatic compounds are good ligands for solubilizing copper(I) species. Although these molecules can also act as nucleophiles, in our case the thiol/thiolate soft S-species present in the reaction mixture are much stronger nucleophiles than these amines with relatively hard nucleophilic character [30f], thus the reaction proceeds *via* the formation of the expected sulfide (**11a**). Here we tested benzylamine, dibenzylamine, pyridine and 2-aminoethanol serving as both solvents and bases. Although pyridine is often used as solvent and ligand for Ullmann-type coupling reactions, the reaction of **9** with **10a** did not take place in



Scheme 3. New synthesis of aryl 2,2,2-trifluoroethyl sulfides by a Goldberg-Ullmann coupling reaction.

Table 2
Effect of solvent and temperature on sulfide **11a** formation.



10a **11a**

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	benzylamine	110	4	87
2	dibenzylamine	110	4	86
3	2-aminoethanol	110	4	21
4	benzylamine	110	6	90
5	2-aminoethanol	110	6	69
6	benzylamine	130	6	75
7	2-aminoethanol	130	6	68
8	pyridine	110	4	0

[a] **10a** (5 mmol), **9** (6 mmol), CuBr (0.25 mmol), solvent (15 mmol).

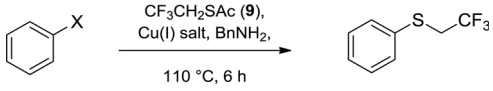
pyridine, thus the starting materials were recovered (Table 2, Entry 8). This latter observation is in accord with the proposed reaction pathway, where the thiolation reagent is the *in situ* formed CF_3CH_2SH (Scheme 4). All solvents except pyridine in Table 2 provide the requisite 1° or 2° amines for the aminolysis reaction of trifluoroethyl thioacetate (**9**). This view is in line with the successful transformations effected by imidazole dissolved in DMSO (cf. [32]) as demonstrated by the yields listed in Table 1 (Scheme 4).

Yields (Table 2, Entries 1, 2 and 4) show that the best results were achieved by the procedures employing benzylamine and dibenzylamine that simultaneously serve as solvent and ligand. Although 2-aminoethanol, also capable of coordinating to metal center through hydroxyl group, gave smaller yield. This figure (Table 2, Entry 3) seems to correlate with the preference of the latter solvent to form intramolecular hydrogen bonding thus it might have a decreased ability to assist thiol deprotonation step *via* intermolecular hydrogen bonding opposed to the benzyl amines.

To further optimize the reaction conditions temperature and the reaction time were also varied in the experiments performed in amine type solvents (Table 2). In all cases longer reaction times improved the yield at 110 °C. On heating the reaction mixture up to 130 °C slight decrease in the yield was observed. Based on the above results the optimal conditions are selected as follows: starting materials were stirred with CuBr catalyst in benzylamine solvent for 6 h at 110 °C. Unfortunately these reaction conditions were not successful when bromobenzene was used as substrate (Table 3, Entry 2).

With these optimized conditions we examined the scope of the reaction. As starting materials, a variety of aryl/hetaryl iodides were chosen (Fig. 1). Iodobenzene derivatives with methyl-(**10d**, **10f**), methoxy-(**10b**, **10c**), trifluoromethyl-(**10e**), and chloro-(**10g**) substituents gave high isolated yields, while the reaction of nitro-derivatives (**10h**, **10i**) resulted in lower yields because of losses during their

Table 3
Effect of Cu/CuBr catalyst and of substrate halogen (C_6H_5I/C_6H_5Br).



Entry	Ar halide, X	Catalyst	Equiv. 9	Yield[a]
1	I	Cu	1.2	83
2	Br	CuBr	1.2	0
3	I	CuBr	2	86

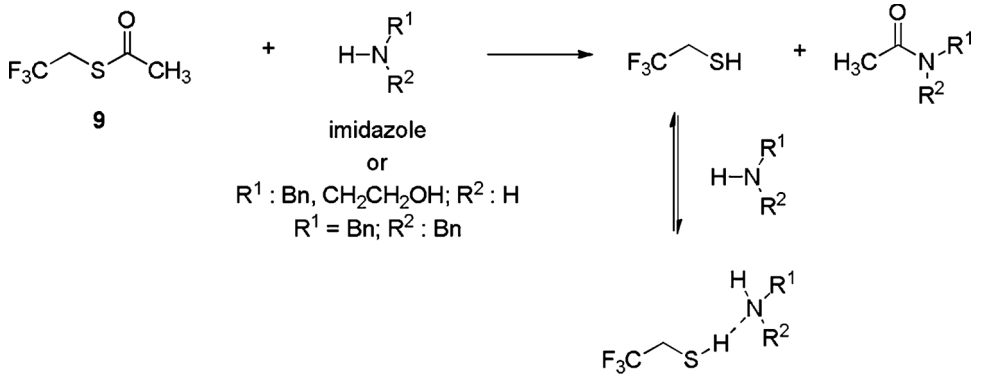
[a] Aryl halide (5 mmol), catalyst (0.25 mmol) in $BnNH_2$ (1.64 ml = 15 mmol) at 110 °C, 6 h.

chromatographic purification. However, under same conditions 2-iodothiophene (**10k**) and 2-iodopyridine (**10j**) gave medium to good isolated yield.

Finally, the reaction of a sterically hindered and electron-rich aryl iodide (**10l**) was tested. Pleasingly, slight modification of the experimental conditions applied to the 5 mmol scale experiments allowed the safe preparation of the corresponding 2,6-dimethyl-6-*tert*-butylphenyl trifluoroethyl sulfide (**11l**) at 15 times larger – multigram – scale in 78 % yield (Fig. 1).

In addition, the work-up of the latter reaction mixture resulted in the isolation of *N*-benzyl acetamide (92 %) as the co-product of **11l** and the recovery of inorganic iodides in the form of copper(I) iodide in about 80 % yields. In the double blank experiment, conducted without CuBr and aryl iodide, the mixing of trifluoroethyl thioacetate **9** and benzyl amine initiated an exothermic reaction, leading to the isolation of CF_3CH_2SH formed as a colorless liquid in 58 % yield with bp = 38 °C (cf. Experimental).

A preliminary mechanistic consideration of the reaction pathway can be drawn based on the analysis of the above larger scale reaction (**10l→11l**) and the relevant literature data [29,30]. The experimental fact, that the isolation of trifluoroethane thiol by atmospheric distillation from the benzylamine media was possible, indicates that no thiolate salt formation occurred there, thus this solvent acts only as a hydrogen-bond base [35] assisting CF_3CH_2SH in the copper(I)-catalyzed (Goldberg-Ullmann coupling) sequence, which involves oxidative addition of aryl iodides to the amine solvent coordinated copper(I) trifluoroethyl thiolate species. In addition, the high efficiency (Table 1, Entry 1) of using one equivalent of Cu_2O in the DMSO-imidazole system can probably be attributed to the high initial concentration of a solvent coordinated $CuSCH_2CF_3$ complex in the course of its stoichiometric coupling reaction with iodobenzene. At this point we do not have sufficient data to prove all details of the suggested reaction pathway presented in Scheme 5.



Scheme 4. Generation of hydrogen bonded mercaptane-amine complexes.

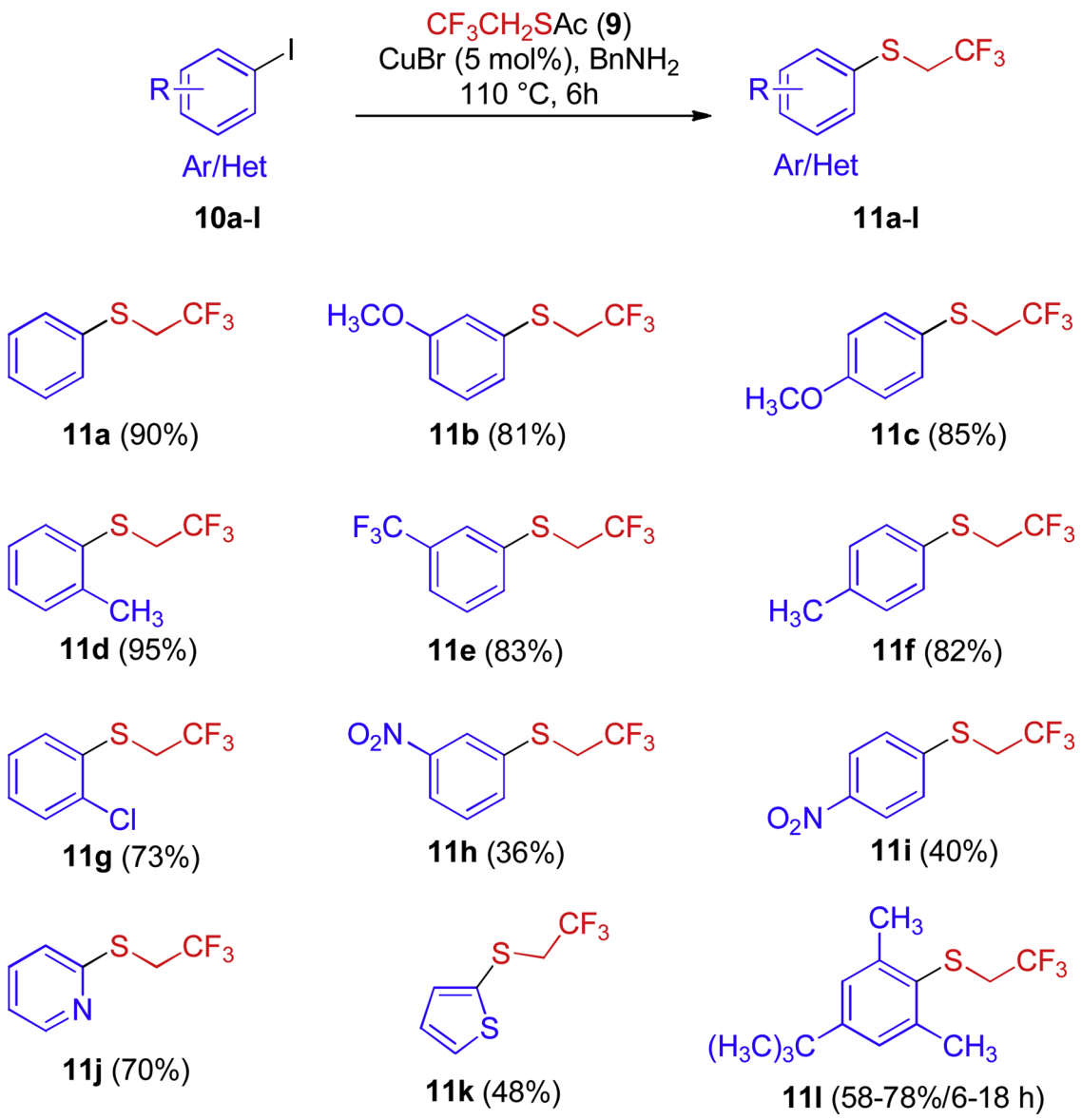
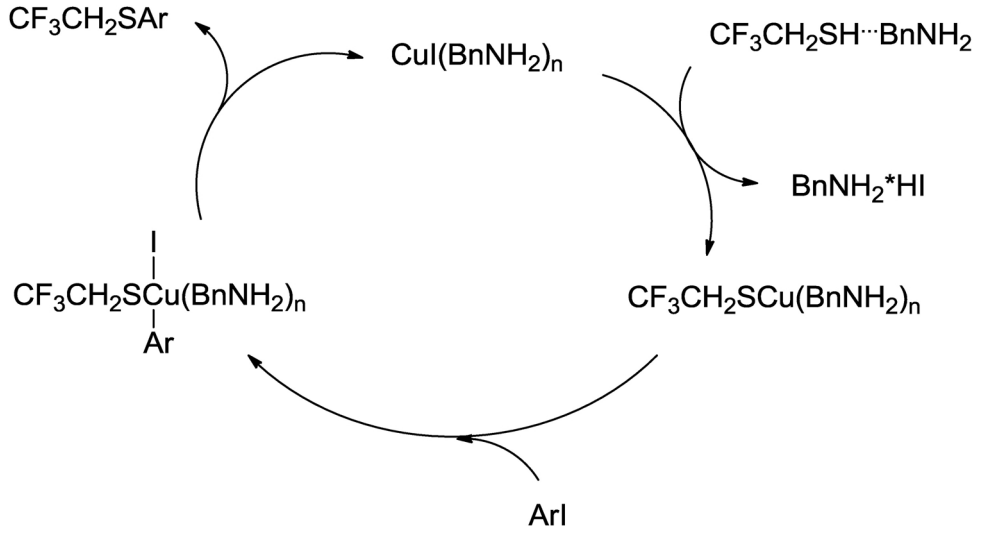


Fig. 1. Substrate scope of the reaction of **9** with aryl/hetaryl iodides.



Scheme 5. Proposed pathway of sulfide formation *via* copper-catalyzed S-arylation reaction.

3. Conclusion

A method was developed for the introduction of trifluoroethylthio group into aromatic compounds by a copper catalyzed aromatic nucleophilic substitution reaction. A systematic optimization of the reaction conditions regarding the choice of the copper source, the applied ligand and solvent, along with the temperature and the reaction time led to the identification of an efficient protocol prescribing the reaction of aryl iodides with 1.2 equivalent of thioacetate **9** in presence of copper(I) bromide catalyst in benzylamine at 110 °C for 6 h. Since benzylamine acted as a solvent, ligand, and base without other additives, the product isolation and purification was simple and efficient. This trifluoroethylthiolation method could easily be adopted for the introduction of trifluoroethylthio group into target molecules of pharmaceutical or agrochemical relevance in discovery laboratories at multigram scale.

4. Experimental section

4.1. General description of methods and materials

The precursor iodides **10a-k** and benzyl amine were purchased from Fluorochem, while the other reagents and the solvents from Sigma-Aldrich. Sterically hindered aryl iodide **10l** was prepared as reported [36]. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker Avance 250 and DRX500 spectrometers using 5 mm inverse ^{1}H/^{13}C/^{31}P/^{19}F and ^{1}H/^{13}C/^{15}N probeheads at room temperature, respectively. Data were expressed as chemical shifts in ppm relative to residual chloroform (^{1}H δ = 7.27), $CDCl_3$ (^{13}C δ = 77.0) or an external standard for ^{19}F ($CFCl_3$, δ = 0) on the δ scale. Exact mass measurements were performed on a high resolution QExactive Focus hybrid quadrupole-orbitrap mass spectrometer (Thermo Scientific, Bremen, Germany), equipped with heated electrospray ionization (HESI) source. Samples were dissolved in methanol-water solvent mixture (1:1, V/V) containing 0.1 % formic acid. Mass spectra were recorded in positive ionization mode using direct sample infusion with a syringe pump (10 μL/min flow rate). Resolution was set to 70.000.

4.2. Synthesis of 2,2,2-trifuoroethyl thioacetate *9*

To the stirred suspension of 2,2,2-trifluoroethyl benzenesulfonate (150 g; 0.625 mol) and K_2CO_3 (128 g; 0.925 mol) in DMSO (750 ml) thiolacetic acid (133 ml, 1.875 mol) was added dropwise during 1.5 h. The mixture was stirred and heated at 45 °C internal temperature for 24 h. Then the volatile components were distilled out from the mixture at water pump vacuum using and heating it with a 150–160 °C temperature oil bath. On cooling the colorless distillate was separated into two liquid phases, of which the lower one is enriched in trifluoroethyl thioacetate, while the upper one in DMSO. Ice (100 g) and ether (100 ml) were added and the lower organic phase was separated and dried (Na_2SO_4). The solvent was removed by distillation at ambient pressure. Then the crude product was purified by distillation. Yield: 67.0 g (68 %) colorless liquid, bp 107–110 °C; d = 1.278 (25 °C), n_D = 1.3940 (25 °C).

At smaller scale using 0.25 mol of trifluoroethyl benzenesulfonate 64 % yield of **9** was obtained. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.58 (q, $^{3}J_{HF}$ = 9.9 Hz, 2H, CF_3CH_2S), 2.42 (s, 3H, $SC(O)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.6 (s, **C**(O)CH_3), 124.7 (q, $^{1}J_{CF}$ = 276 Hz, **C**F_3CH_2S), 30.6 (q, $^{2}J_{CF}$ = 34 Hz, CF_3**C**H_2S), 29.8 (s, C(O)**C**H_3); ^{19}F NMR (235 MHz, $CDCl_3$): δ − 67.05 (t, $^{3}J_{HF}$ = 9.9 Hz). IR (neat): ν = 1711, 1309, 1271, 1241, 1121, 1082, 957, 847 cm^{-1}.

4.3. General procedure (GP) for the synthesis of aryl 2,2,2-trifluoroethyl sulfides

Aryl iodide (5.00 mmol) was dissolved in benzylamine (1.64 ml) and CuBr (0.036 g, 0.25 mmol) was added to the mixture. After purging with argon 2,2,2-trifluoroethylthioacetate (**9**, 0.948 g, 6 mmol) was added to the suspension and the vial was sealed under argon. The mixture was stirred at 110 °C bath temperature for 6 h. After cooling to room temperature, hexane (15 ml) was added to the mixture and the resulted suspension was stirred for 2 min then filtered through a Celite pad. The filtrate was washed with 1 M HCl (2 × 10 ml) and water (10 ml), then dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel/hexane).

4.3.1. Phenyl 2,2,2-trifluoroethyl sulfide (*11a*)

Iodobenzene **10a** (1.02 g, 5.00 mmol) was reacted according to GP to afford 0.96 g (87 %) of **11a** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H, Ar), 7.36 – 7.27 (m, 3H, Ar), 3.44 (q, $^{3}J_{HF}$ = 9.7 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5 (Ar), 131.8 (Ar), 129.3 (Ar), 128.0 (Ar), 125.4 (q, $^{1}J_{CF}$ = 276 Hz, CF_3), 38.2 (q, $^{2}J_{CF}$ = 33 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.81 (t, $^{3}J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z*: calcd. for $C_8H_7F_3S$ 192.02206; found 192.02196. Mass error: -0.5 ppm. Characterization data matched that reported in the literature [22,23,24a,25b,37].

4.3.2. 3-Methoxyphenyl 2,2,2-trifluoroethyl sulfide (*11b*)

3-Methoxy-iodobenzene **10b** (1.17 g, 5.00 mmol) was reacted according to GP to afford 0.90 g (81 %) of **11b** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, $^{3}J_{HH}$ = 8.0 Hz, 1H, Ar), 7.07 – 7.01 (m, 1H, Ar), 7.01 – 6.98 (m, 1H, Ar), 6.81 (ddd, $^{3}J_{HH}$ = 8.3 Hz, $^{3}J_{HH}$ = 2.5 Hz, $^{3}J_{HH}$ = 0.8 Hz, 1H, Ar), 3.78 (s, 3H, CH_3), 3.43 (q, $^{3}J_{HF}$ = 9.7 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0 (Ar), 134.9 (Ar), 130.1 (Ar), 125.3 (q, $^{1}J_{CF}$ = 277 Hz, CF_3), 123.6 (Ar), 116.9 (Ar), 113.8 (Ar), 55.3 (CH_3), 37.9 (q, $^{2}J_{CF}$ = 33 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.77 (t, $^{3}J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z*:calcd. for $C_9H_9F_3OS$ 222.03262; found 222.03216. Mass error: -2.0 ppm. Characterization data matched that reported in the literature [29].

4.3.3. 4-Methoxyphenyl 2,2,2-trifluoroethyl sulfide (*11c*)

4-Methoxy-iodobenzene **10c** (1.17 g, 5.00 mmol) was reacted according to GP to afford 0.95 g (85 %) of **11c** as colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, Ar), 6.84 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H, Ar), 3.78 (s, 3H, CH_3), 3.29 (q, $^{3}J_{HF}$ = 9.8 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2 (Ar), 135.4 (Ar), 125.5 (q, $^{1}J_{CF}$ = 277 Hz, CF_3), 124.0 (Ar), 114.8 (Ar), 55.3 (CH_3), 39.6 (q, $^{2}J_{CF}$ = 32 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.77 (t, $^{3}J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z*: calcd. for $C_9H_9F_3OS$ 222.03262; found 222.03229. Mass error: -1.5 ppm. Characterization data matched that reported in the literature [29].

4.3.4. 2-Methylphenyl 2,2,2-trifluoroethyl sulfide (*11d*)

2-Methyl-iodobenzene **10d** (1.09 g 5.00 mmol) was reacted according to GP to afford 0.98 g (95 %) of **11d** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.45 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, Ar), 7.25 – 7.13 (m, 3H, Ar), 3.37 (q, $^{3}J_{HF}$ = 9.7 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1 (Ar), 132.8 (Ar), 132.4 (Ar), 130.6 (Ar), 128.3 (Ar), 126.8 (Ar), 125.4 (q, $^{1}J_{CF}$ = 277 Hz, CF_3), 37.9 (q, $^{2}J_{CF}$ = 33 Hz, CH_2), 20.6 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.77 (t, $^{3}J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z*: calcd. for $C_9H_9F_3S$ 206.03771; found 206.03739. Mass error: -0.3 ppm. For an alternative preparation and ^{1}H NMR spectrum, cf. [38].

4.3.5. 2,2,2-Trifluoroethyl 3-(trifluoromethyl)phenyl sulfide (*11e; n. c.*)

3-Trifluoromethyl-iodobenzene **10e** (1.36 g, 5.00 mmol) was reacted according to GP to afford 1.08 g (83 %) of **11e** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H, Ar), 7.64 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, Ar), 7.53 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H, Ar), 7.44 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H, Ar), 3.45 (q, $^{3}J_{HF}$ = 9.5 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1 (Ar), 134.6 (Ar), 131.8 (q, $^{2}J_{CF}$ = 33 Hz, Ar), 129.7 (Ar), 128.1

(q, $^3J_{CF}$ = 4 Hz, Ar), 125.1 (q, $^1J_{CF}$ = 275 Hz, CF_3), 124.8 (q, $^2J_{CF}$ = 33 Hz, Ar), 123.5 (q, $^1J_{CF}$ = 273 Hz, CF_3), 37.7 (q, $^2J_{CF}$ = 33 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -63.43 (s, 3 F, CF_3Ar), -66.84 (t, $^3J_{HF}$ = 9.5 Hz, 3 F, CH_2CF_3). HRMS (ESI), *m/z*: calcd. for $C_9H_6F_6S$ 260.00944; found 260.00911. Mass error: -1.3 ppm.

4.3.6. 4-Methylphenyl 2,2,2-trifluoroethyl sulfide (11f)

4-Methyl-iodobenzene **10f** (1.09 g, 5.00 mmol) was reacted according to GP to afford 0.85 g (82 %) of **11f** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar), 7.12 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar), 3.36 (q, $^3J_{HF}$ = 9.7 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4 (Ar), 132.5 (Ar), 131.2 (Ar), 130.0 (Ar), 125.5 (q, $^1J_{CF}$ = 276 Hz, CF_3), 38.7 (q, $^2J_{CF}$ = 32.5 Hz, CH_2), 21.1 (CH_3); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.84 (t, $^3J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z*: calcd. for $C_9H_9F_3S$ 206.03771; found 206.03732. Mas error: -0.4 ppm. Characterization data matched that reported in the literature [20,23,29].

4.3.7. 2-Chlorophenyl 2,2,2-trifluoroethyl sulfide (11g; n. c.)

2-Chloro-iodobenzene **10g** (1.19 g, 5.00 mmol) was reacted according to GP to afford 0.83 g (73 %) **11g** as colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 1H, Ar), 7.45 – 7.37 (m, 1H, Ar), 7.28 – 7.17 (m, 2H, Ar), 3.46 (q, $^3J_{HF}$ = 9.6 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5 (Ar), 133.5 (Ar), 132.1 (Ar), 130.2 (Ar), 129.5 (Ar), 127.4 (Ar), 125.3 (q, $^1J_{CF}$ = 277 Hz, CF_3), 36.4 (q, $^2J_{CF}$ = 33 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.37 (t, $^3J_{HF}$ = 9.6 Hz). HRMS (ESI), *m/z*: calcd. for $C_8H_6ClF_3S$ 225.98308; found 225.98265. Mass error: -1.9 ppm.

4.3.8. 3-Nitrophenyl 2,2,2-trifluoroethyl sulfide (11h)

3-Nitro-iodobenzene **10h** (1.25 g, 5.00 mmol) was reacted according to GP to afford 0.43 g (36 %) **11h** as yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.32 – 7.53 (m, 4 H), 3.54 (q, $^3J_{HF}$ = 9.7 Hz, 2 H); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.63 (t, $^3J_{HF}$ = 9.7 Hz). Characterization data matched that reported in the literature [29].

4.3.9. 4-Nitrophenyl 2,2,2-trifluoroethyl sulfide (11i)

4-Nitro-iodobenzene **10i** (1.25 g, 5.00 mmol) was reacted according to GP to afford 0.48 g (40 %) **11i** as pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar), 7.49 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar), 3.57 (q, $^3J_{HF}$ = 9.4 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (Ar), 143.1 (Ar), 128.9 (Ar), 124.9 (q, $^1J_{CF}$ = 276 Hz, CF_3), 124.2 (Ar), 35.9 (q, $^2J_{CF}$ = 34 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.53 (t, $^3J_{HF}$ = 9.4 Hz). Characterization data matched that reported in the literature [29].

4.3.10. 2-Pyridyl 2,2,2-trifluoroethyl sulfide (11j)

2-Iodopyridine **10j** (1.03 g, 5.00 mmol) was reacted according to GP to afford 0.68 g (70 %) of **11j** as colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (ddd, $^3J_{HH}$ = 4.9 Hz, $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 0.9 Hz, 1 H), 7.50 (ddd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 1.9 Hz, 1 H), 7.20 (dt, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 1.0 Hz, 1 H), 7.02 (ddd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 4.9 Hz, $^3J_{HH}$ =1.0 Hz, 1 H), 4.02 (q, $^3J_{HF}$ = 10.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7 (Ar), 149.4 (Ar), 136.5 (Ar), 125.4 (q, $^1J_{CF}$ = 274 Hz), 122.4 (Ar), 120.5 (Ar), 31.0 (q, $^2J_{CF}$ = 34 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.71 (t, $^3J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z*: calcd. for $C_7H_6F_3NS$ 193.01730; found 193.01694. Mass error: -0.8 ppm. Characterization data matched that reported in the literature [23,39].

4.3.11. 2-Thienyl 2,2,2-trifluoroethyl sulfide (11k)

2-Iodothiophene **10k** (1.05 g, 5.00 mmol) was reacted according to GP to afford 0.48 g (48 %) of **11k** as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, $^3J_{HH}$ = 5.4 Hz, $^3J_{HH}$ =1.3 Hz, 1 H), 7.25 (dd, $^3J_{HH}$ = 3.6 Hz, $^3J_{HH}$ = 1.2 Hz, 1 H), 6.97 (dd, $^3J_{HH}$ = 5.4 Hz, $^3J_{HH}$ = 3.6 Hz, 1 H), 3.29 (q, $^3J_{HF}$ = 9.7 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2 (Ar), 131.4 (Ar), 131.1 (Ar), 127.8 (Ar), 125.2 (q, $^1J_{CF}$ = 277 Hz, CF_3), 41.4 (q, $^2J_{CF}$ = 32 Hz, CH_2); ^{19}F NMR (235 MHz, $CDCl_3$) δ -66.71 (t, $^3J_{HF}$ = 9.7 Hz). HRMS (ESI), *m/z:* calcd. for $C_6H_5F_3S_2$ 197.97848; found 197.97829. Mass error: -0.9 ppm. Characterization data matched that reported in the literature [11].

4.3.12. 2,6-Dimethyl-4-tert-butylphenyl 2,2,2-trifluoroethyl sulfide (11l; n. c.)

A glass ampule of 170 mm of length and 50 mm diameter was supplied with an egg-shaped magnetic stirrer bar, charged with benzyl amine (24.6 ml, 24.1 g) and purged with argon. Next CuBr (0.54 g, 3.76 mmol), trifluoroethyl thioacetate (14.2 g, 90 mmol) and the aryl iodide **10l** (21.6 g, 75 mmol) was added. Then it was sealed, next immersed in 40 mm deep into an oil bath of 110 °C temperature and stirred for 18 h. The ampule was cooled, opened and the crude mixture was distilled with steam collecting ~1 L of condensate. The steam volatile oil – mixture of title product and benzyl amine – was extracted with dichloromethane (2 × 150 ml), then the separated organic layer was sequentially washed with 1 M HCl (2 × 100 ml) and water (2 × 30 ml) then dried over Na_2SO_4. The solvent was removed by evaporation (Rotavap) and the residue was distilled in vacuum. The main fraction was collected at 142−143 °C/16 mmHg as a colorless liquid. Yield: 16.12 g (77.8 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 2H, Ar), 3.20 (q, $^3J_{HF}$ = 9.9 Hz, 2H, CH_2), 2.59 (s, 6H, Ar−CH_3), 1.33 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3 (Ar), 142.7 (Ar), 128.4 (Ar), 125.7 (Ar), 125.6 (q, $^1J_{CF}$ = 277 Hz, CF_3), 37.6 (q, $^2J_{CF}$ = 38 Hz, CH_2), 34.4 ($C(CH_3)_3$), 31.2 ($C(CH_3)_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.36 (t, $^3J_{HF}$ = 10.0 Hz, 3 F, CF_3). HRMS (ESI), *m/z*: calcd. for $C_{14}H_{19}F_3S$ 276.11596; found 276.11587. Mass error: -0.3 ppm.

4.3.12.1. Gravimetric determination of the aryl iodide conversion. Using 1/3 amounts of reagents and same conditions as above but heating the reaction mixture only for 6 h at 110 °C resulted in ~80 % conversion of aryl iodide (30 mmol), the limiting reagent. This figure was calculated by gravimetric analysis of the water soluble iodide ions in the form of CuI precipitate. For this reason the steam distillation residue of the boiler flask was first extracted with ether to remove the co-product *N*-benzyl acetamide and the residual free benzyl amine. Next the water layer was filtered to remove the remains of the copper(I) catalyst (5 mol %) used. Note that CuBr was transformed to CuI in the reaction due to its higher stability and lower solubility in the amine solvents and water. The clear filtrate was treated with $CuSO_4 \times 5H_2O$ (35 mmol) and the liberated I_2 was titrated with $NaHSO_3$ solution. The precipitated CuI was filtered, triturated with methanol, filtered again and washed with 20 % HCl and water, and dried to give 4.6 g (24 mmol) of CuI as cream-white powder.

Working up the steam distillate of this experiment as shown in subsection 4.3.12 gave 6.04 g (73 %) **11l** sulfide as a colorless oil of bp 142−143 °C/16 mmHg, containing ~15 mol% unreacted **10l** aryl iodide as determined by ^{1}H NMR analysis. This result suggests that the sulfide **11l** and its precursor iodide **10l** should have similar boiling points, thus they are difficult to separate by distillation. Instead, longer reaction time or the use of a larger excess of the CF_3CH_2SH source could result in the complete conversion of this sterically hindered aryl iodide and will allow simple isolation of the pure product by distillation.

4.3.12.2. Isolation of the N-benzyl acetamide co-product. The ether extract of the experiment in subsection 4.3.12.1 was washed with 5 % HCl and water, then dried (Na_2SO_4). Evaporation of the solvent afforded slightly brown crystalline product, which was identified by ^{1}H and ^{13}C NMR as $CH_3CONHCH_2C_6H_5$. Yield: 4.10 g (27.5 mmol, 92 % referred to the 30 mmol of trifluoroethyl thioacetate **9** used).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 5H, Ar), 6.28 (br s, 1H, NH), 4.38 (d, $^3J_{HH}$ = 5.7 Hz, 2H, CH_2), 1.97 (s, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.6 (CO), 138.6 (Ar), 129.1 (Ar), 128.2 (Ar), 127.9 (Ar), 44.1(CH_3), 23.5 (CH_2).

4.3.12.3. Double blank experiment – isolation of CF_3CH_2SH. A 100 ml volume pearl shaped distillation flask was charged with trifluoroethyl thioacetate **9** (15.8 g, 100 mmol) and mixed with benzylamine (27 ml, 247 mmol). An exothermic reaction started and the distillation of the title compound with bp 36 °C was maintained by heating with an oil bath up to 150 °C. Yield: 6.7 g (58 %) colourless liquid. Characterization data matched that reported in the literature [34].

Declaration of Competing Interest

All authors of this paper have no conflict of interest.

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