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Synthesis of Trifluoromethylated Dithiocarbamates via Photocatalyzed Substitution Reaction: Pentafluoropyridine as Activating Reagent

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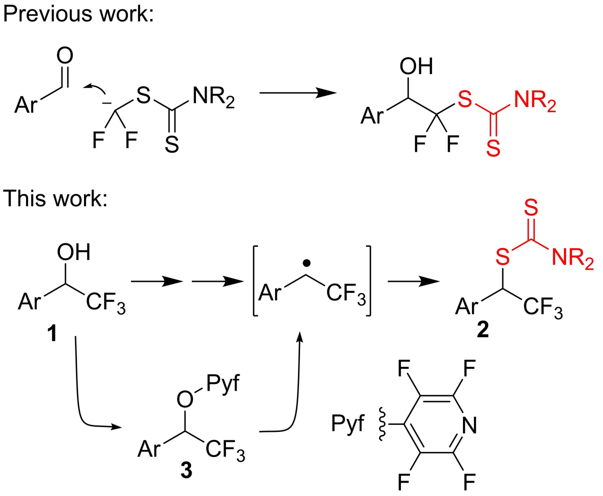
A method for the synthesis of trifluoromethyl-substituted dithiocarbamates from aldehydes is described. The reaction involves nucleophilic trifluoromethylation, derivatization of the silyloxy-group with pentafluoropyridine, and substitution of the fluorinated pyridinyloxy group by dithiocarbamate anion. The substitution step is performed in the presence of 12-phenyl-12*H*-benzo[*b*]phenothiazine and copper cyanide under irradiation of 400 nm LED.

Importance of organofluorine compounds in pharmaceutical and agrochemical areas has stimulated development of methods for their synthesis.[1] Despite significant advances in organofluorine chemistry, synthesis of novel structural motifs based on readily available starting materials constitutes an important problem.[2] In this regard, sulfur compounds bearing a fluorinated fragment have attracted considerable attention.[2b,3]

Dithiocarbamates have demonstrated diverse biological activities,[4] and their fluorinated derivatives could be interesting for medicinal studies. We have previously described direct introduction of a fluorinated dithiocarbamate moiety by using the conventional carbonyl addition reaction[5] (Scheme 1). Herein we report that alcohols **1**, which are readily accessed using the nucleophilic trifluoromethylation chemistry,[6] can be converted into dithiocarbamates **2** using light mediated radical process.

Typically, reactions involving homolytic cleavage of the C–O bond proceed via preliminary derivatization into xanthates[7] or oxalates[8] with the resulting carbon-centered radicals either abstracting a hydrogen atom or being trapped by π-systems.[9,10] Recently, perfluorinated pyridine was used as an activating reagent for the cleavage of C–S[11] and N–O bonds[12] under photocatalytic conditions. In this work we demonstrate that 2,3,5,6-tetrafluoropyridinyl (Pyf) ethers **3** derived from alcohols **1** can undergo light mediated substitution reaction by the dithiocarbamate anion.



Scheme 1. Synthesis of fluorinated thiocarbamates.

Compound **3a** was selected as a model substrate, and it was obtained from alcohol **1a** by heating with pentafluoropyridine and triethylamine at 100 °C for 7 hours (Scheme 2, equation a). However, harsh conditions required for the derivatization of alcohol **1a** prompted us to develop a milder protocol. It is known that alcohols **1** are routinely obtained from aldehydes and the Ruppert–Prakash reagent (Me_3SiCF_3) mediated by fluoride ion.[6] We proposed that silyl ethers, which are the primary products of nucleophilic trifluoromethylation, can be directly converted into Pyf-derivatives **3** by interaction with pentafluoropyridine. Thus, benzaldehyde was reacted with the Ruppert–Prakash reagent in the presence of cesium fluoride (5 mol %) in tetrahydrofuran for one hour. Then, pentafluoropyridine and substoichiometric amount of triethylamine (20 mol %) were added, and after overnight stirring, ether **3a** was cleanly formed (equation b). Though it can be isolated in 95 % yield, the crude product obtained after simple aqueous work-up is of sufficient purity, and this material can be used further without purification. The formation of **3a** is mediated by cesium fluoride, which is present from the trifluoromethylation step, and involves generation of the alkoxide anion followed by aromatic nucleophilic substitution of fluoride.

Reaction of tetrafluoropyridinyl ether **3a** with potassium pyrrolidine-derived dithiocarbamate was evaluated under photocatalytic conditions (Table 1). Among various photocatalysts, 12-phenyl-12*H*-benzo[*b*]phenothiazine[13] (3 mol %) irradiated with 400 nm LED provided the best results. Copper additives

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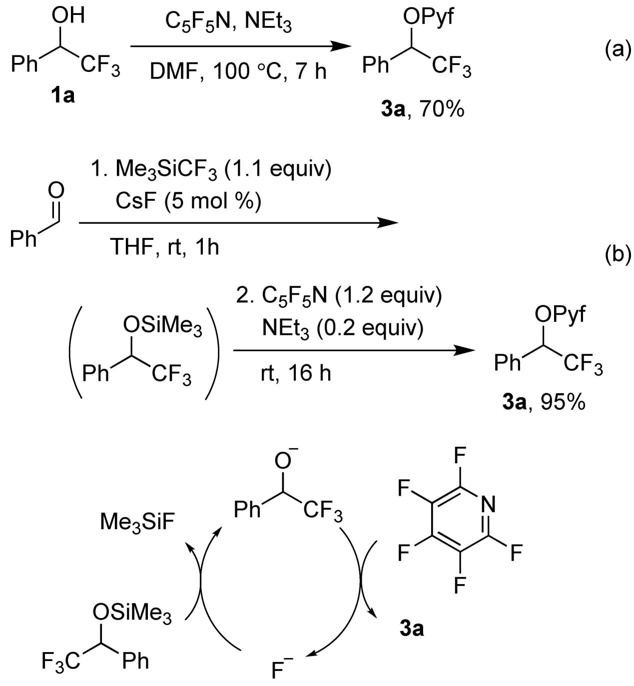
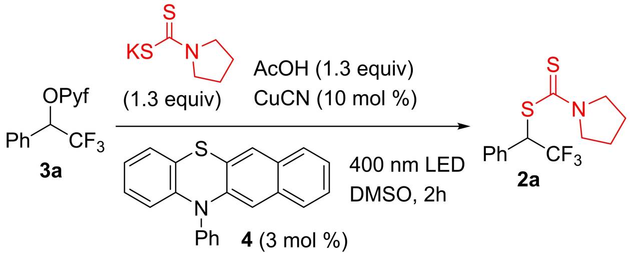


Scheme 2. Synthesis of compound **3a**.

Table 1. Optimization studies.



#	Deviation from standard conditions	Y. of **2a** [%][a]
1	none	80
2	no AcOH	73
3	no CuCN	33[b]
4	no photocatalyst	<5[c]
5	no light	–
6	Ir(ppy)$_3$ (0.25 %) instead of **4**	55[b]
7	[Ir(dtbbpy)(ppy)$_2$]PF$_6$ (0.25 %) instead of **4**	15[b]
8	4CzIPN (1 %) instead of **4**	9[b]
9	3DPA2FBN (1 %) instead of **4**	–
10	CH$_3$CN instead of DMSO	23[b]
11	CH$_2$Cl$_2$ instead of DMSO	20[b]

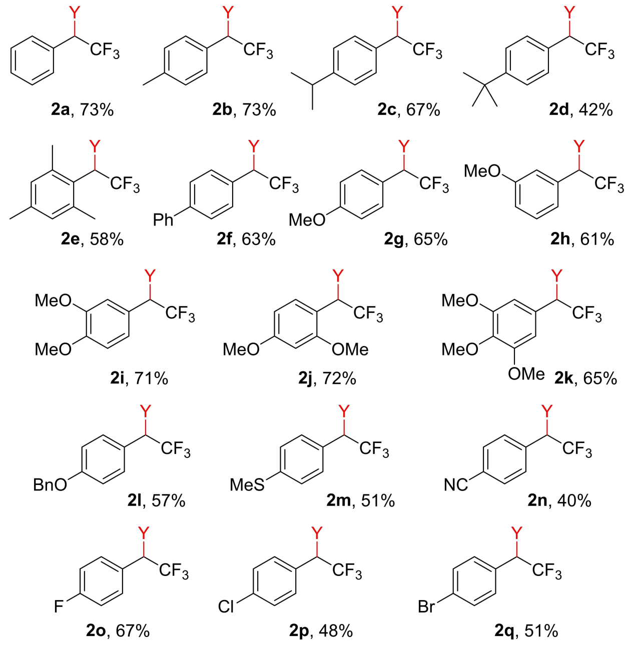
[a] Isolated yield. [b] Determined by ^{19}F NMR with PhCF$_3$ as internal standard. [c] According to GC-MS analysis.

are frequently used to mediate formation of carbon-heteroatom bonds via reductive elimination of Cu(III) species.[14] Here, the presence of copper cyanide was important to achieve high product yield of 80 %, as without the copper salt the yield dropped to 33 % with significant amounts of by-products arising from dimerization of the 1-phenyl-2,2,2-trifluoroethyl radical being detected by GC-MS analysis (entry 3). DMSO also turned out to be the best solvent, which may be associated with good solubility of potassium dithiocarbamate and its generated copper salts. Acetic acid as additive exhibited a beneficial effect, presumably, due to its ability to decrease the nucleophilicity of the dithiocarbamate anion. Indeed, it was shown by a blank experiment that in the presence of the dithiocarbamate salt, a slow nucleophilic substitution of fluoride in the pyridine ring of staring substrate **3a** occurs. Without the photocatalyst, trace amounts of the product were formed, but without light the reaction did not proceed at all (entries 4 and 5). In ^{19}F NMR spectra of the reaction mixtures, a set of signals of tetrafluorinated pyridine fragment is observed, which is ascribed to fluorinated 4-hydroxypyridine (PyfOH) or its anion.

Under the optimized conditions, a series of aldehydes were converted to dithiocarbamates **2** (Table 2). The reaction works with aldehydes bearing electron donating and electron withdrawing groups. Unfortunately, the reaction was unsuccessful with hydrocinnamic aldehyde and acetophenone, since in these cases photocatalytic substitution was problematic with low conversions being observed. With cinnamic aldehyde, the corresponding allylic ether **3** was formed, but its radical reaction gave a complex mixture.

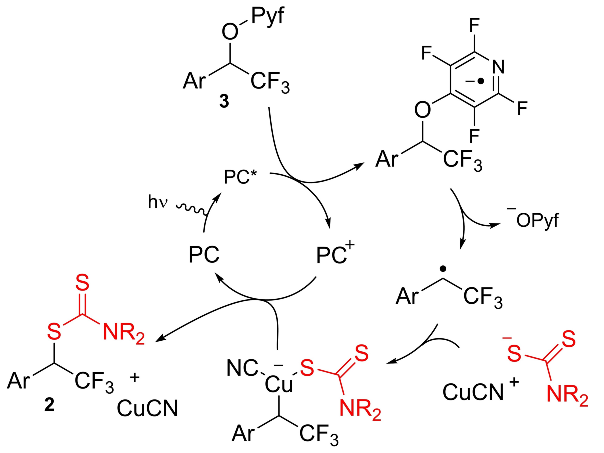
The proposed mechanism is shown in Scheme 3. The light activated catalyst reduces substrate **3** to generate radical anion, which eliminates the stabilized alkoxide anion to give the CF$_3$-substituted benzyl radical.[15] The radical is trapped by a copper species formed between copper cyanide and dithiocarbamate anion, and the copper(II) intermediate is oxidized by cationic

Table 2. Synthesis of dithiocarbamates **3** from aldehydes.[a]



2a, 73%
2b, 73%
2c, 67%
2d, 42%
2e, 58%
2f, 63%
2g, 65%
2h, 61%
2i, 71%
2j, 72%
2k, 65%
2l, 57%
2m, 51%
2n, 40%
2o, 67%
2p, 48%
2q, 51%

[a] Yield of **2** calculated on the corresponding aldehyde.

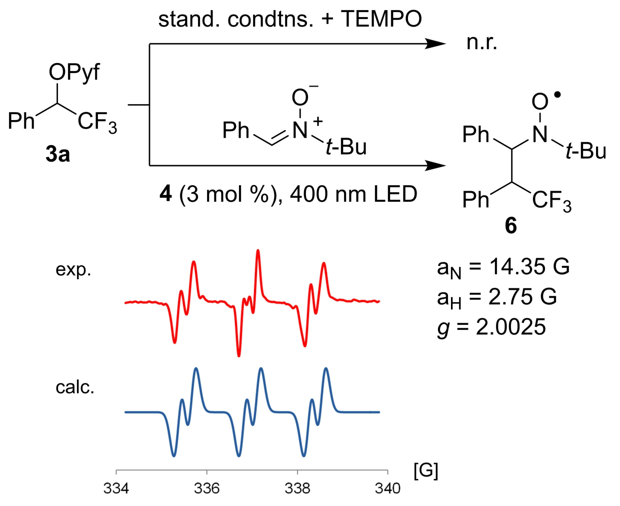


Scheme 3. Proposed mechanism.

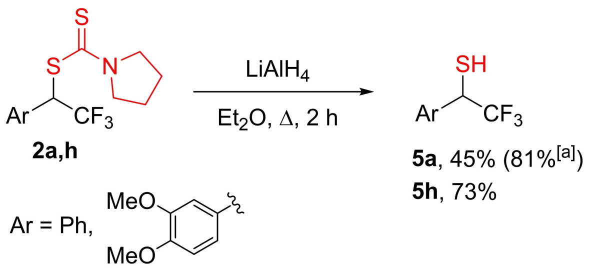
form of the photocatalyst leading to a copper(III) species with subsequent reductive elimination.

To support the radical character of the substitution reaction, several experiments were performed (Scheme 4). Thus, the desired reaction of ether **3 a** with potassium dithiocarbamate was completely inhibited by TEMPO (2 equiv). When ether **3 a** was irradiated in the presence of a nitrone, nitroxyl radical **6** was detected by EPR spectroscopy.

Compounds **2** can be considered as precursors of fluorinated thiols, if it would be possible to remove the thiocarbamoyl group. It should be noted that methods for the synthesis of the CF_3-susbtituted thiols are rare.[16] Indeed, it was shown in the literature that a conventional oxygen/sulfur exchange using Lowesson reagent, which could be anticipated to convert alcohols **1** to the corresponding thiols, is inefficient.[17] Starting from compounds **2**, initial experiments involving base mediated hydrolytic cleavage of the thiocarbamoyl fragment were unsuccessful. After considerable experimentation we found that treatment of compounds **2** with lithium aluminum hydride in refluxing ether effects the desired transformation (Scheme 5).



Scheme 4. Mechanistic experiments.



Scheme 5. Synthesis of thiols **5**. [a] Determined by ^{19}F NMR with $PhCF_3$ as internal standard.

Thiols **5 a,h** were formed in reasonable yields, though high volatility of thiol **5 a** led to decreased yield upon isolation.

In summary, a method for the synthesis of trifluoromethylated dithiocarbamates from aldehydes is described. The reaction involves intermediate formation of tetarfluoropyridinyl ethers, which undergo photocatalytic substitution of the pyridinyloxy-group by dithiocarbamate anion. In the dithiocarbamate products, the carbamoyl group can be removed affording trifluoromethylated thiols.

Experimental Section

Synthesis of 2 a–q (General Procedure 1).

Aldehyde (0.5 mmol) was added to a stirred suspension of dry cesium fluoride (4 mg, 0.025 mmol) in THF (1 mL). The reaction vessel was immersed in a water bath and then (trifluoromethyl) trimethylsilane (89 μL, 0.6 mmol) was added dropwise. The reaction was stirred for 1 hour at room temperature, then NEt_3 (14 μL, 0.1 mmol) and pentafluoropyridine (82 μL, 0.75 mmol) were added. The resulting mixture was stirred overnight at room temperature, diluted with water (5 mL) and extracted with methyl *tert*-butyl ether (3×3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under the pressure of 400 Torr. The residue was dissolved in a small amount of methyl *tert*-butyl ether, transferred into a tube, and the solvent was evaporated under vacuum, and dissolved in DMSO (1 mL). Then, CuCN (5 mg, 0.05 mmol), 12-phenyl-12*H*-benzo[*b*]phenothiazine (4 mg, 0.015 mmol), AcOH (37 μL, 0.65 mmol) and potassium pyrrolidine-1-carbodithioate (120 mg, 0.65 mmol) were added successively. The tube was briefly evacuated (7 Torr), and backfilled with argon. The tube was sealed with a screw cap, irradiated by 400 nm LED matrix (80 W) for 2 hours with stirring; during irradiation, the tube was cooled with water (18 °C). The reaction was quenched with water (5 mL) and extracted with methyl *tert*-butyl ether (3×3 mL). The combined organic phases were filtered through a small pad of Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography.

Synthesis of 5 a, h (General Procedure 2).

A solution of dithiocarbamate **2** (0.3 mmol) in diethyl ether (1.0 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (23 mg, 0.6 mmol) in diethyl ether (1.0 mL), and the mixture was refluxed for 2 hours. The reaction was carefully quenched with water (2 mL) and aqueous hydrochloric acid (3 mL, 1.0 M). In case of highly volatile thiol **5 a**, the mixture was extracted with pentane (3×3 mL), concentrated under atmospheric pressure, and the residue purified by flash chromatography in pentane. In case of thiol **5 h**, the mixture was extracted with hexane (3×3 mL), the combined organic phases were concentrated under reduced pressure, and the residue was purified by column chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Dithiocarbamates · Fluorine · Photocatalysis · Radical reactions · Trifluoromethylation

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