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Trifluoromethylthiolation and Trifluoromethylselenolation of α-Diazo Esters Catalyzed by Copper

Christian Matheis, Thilo Krause, Valentina Bragoni and Lukas J. Goossen*[a]

Abstract: α-Diazo esters are smoothly converted into the corresponding trifluoromethyl thio- or selenoethers by reaction with Me_4NSCF_3 or Me_4NSeCF_3, respectively, in the presence of catalytic amounts of copper thiocyanate. This straightforward method gives high yields under neutral conditions at room temperature and is applicable to a wide range of functionalized molecules, including diverse α-amino acid derivatives. It is well-suited for the late-stage introduction of trifluoromethylthio or -seleno groups into drug-like molecules.

Over the past decades, fluorine-containing moieties have become ubiquitous functionalities in modern bioactive molecules. They are present in close to 40% of currently marketed agrochemicals and 25% of pharmaceuticals.[1] Their systematic evaluation, the so-called "fluorine scan", is routinely performed when refining lead structures in drug discovery. Hence, new methods for the late-stage introduction of fluorinated moieties into complex, functionalized molecules are highly sought-after. Originally, research efforts have focused mainly on the development of methods for the introduction of CF_3 groups.[2] Lately, the SCF_3 group has attracted particular attention since it induces an even higher lipophilicity and membrane permeability (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3).[3] Trifluoromethylthio groups are present in an increasing number of bioactive molecules, including the antibiotic Cefazaflur, a trifluoromethylthiolated methionine analog with antimalarial properties, and a ribose derivative with antipneumnonia activity (Figure 1).[4]

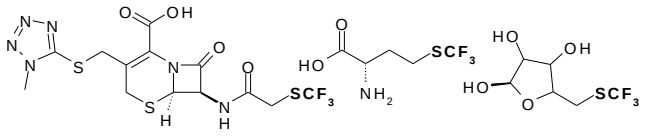

Figure 1. Biologically active trifluoromethyl thioethers.

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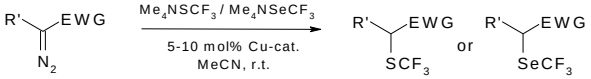
Several efficient strategies for the late-stage trifluoromethylthiolation of organic molecules have recently been devised.[5] These are based on electrophilic,[6] nucleophilic,[7] radical,[8] or oxidative processes,[9] usually starting from arylboronic acids or aryl halides, but also from arenes via C–H activation.[10] Our contribution to this emerging field includes the development of Sandmeyer fluoroalkyl- and fluoroalkylthiolations.[11] In this context, we have demonstrated that (hetero-)aromatic amines can conveniently be converted into aryl trifluoromethylthio ethers by a diazotization / trifluoromethylthiolation sequence using the bench-stable reagent Me_4NSCF_3.[12] This SCF_3-source is readily available from tetramethylammonium fluoride, elemental sulfur and $TMSCF_3$.[13] Following initial reports by Röschenthaler[14] and Yagupolskii,[15] it has successfully been employed in trifluoromethylthiolations of vinyl iodides,[16] boronic acids,[9c] aryl halides,[7b,17] and triflates[18] mediated by Cu, Ni and Pd catalysts.

We envisioned that this stable and easy-to-handle reagent might be the key towards enabling a catalytic trifluoromethylation of α-diazo esters (Scheme 1). These substrates are easily accessible in broad structural diversity from amino acids. Moreover, they can be synthesized from ketones via the Bamford-Stevens reaction or from acetoacetates via a Regitz deprotonation/diazo transfer sequence.[19]



Scheme 1. Catalytic trifluoromethylthiolation / –selenolation of α-diazo esters.

α-Diazo esters have been used as substrates for dediazotative trifluoromethylations, difluoroolefinations,[20] and stoichiometric trifluoromethylthiolations. Wang and Hu have disclosed trifluoromethylthiolation processes based on stoichiometric amounts of $AgSCF_3$ and Cu salts.[21] In an analogous synthesis of trifluoromethyl thioethers, Rueping *et al.* have used preformed $CuSCF_3$.[22] Gouverneur *et al.* have extended this method from α-diazo esters to 1-(diazo-2,2,2-trifluoroethyl)-arenes.[20a] However, in all cases, the stoichiometric use transition metal salts is unavoidable.

The catalytic use of copper in combination with a stable trifluoromethylthiolation reagent would vastly improve the sustainability and practicability of this reaction concept. Making the decisive transition from stoichiometric reactions based on preformed transition metal-SCF_3 complexes to a catalytic trifluoromethylthiolation process would require (a) identifying a copper precursor that reacts with Me_4NSCF_3 to form a Cu-SCF_3 complex capable of transferring the SCF_3 moiety to the substrate, and (b) sufficiently stabilizing the Cu species liberated during

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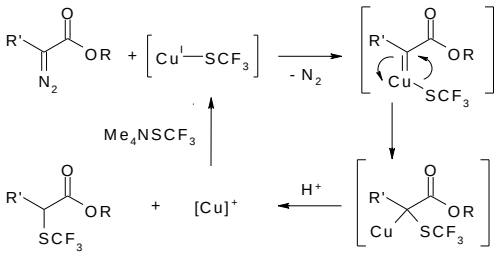
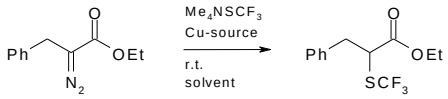
product formation to allow regeneration of the initial Cu-SCF_3 complex (Scheme 2).



Scheme 2. Proposed mechanism for the Cu-catalyzed trifluoromethylthiolation of α-diazo esters.

In order to probe the feasibility of our approach, we investigated the reaction of phenylalanine α-diazo ester **1a** with Me_4NSCF_3 in the presence of a range of copper salts under various conditions (Table 1).

Table 1. Optimization of the reaction conditions.[a]



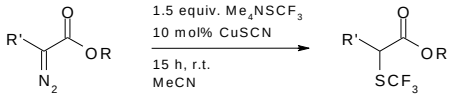
1a **2a**

Entry	Solvent	Cu-source	Me_4NSCF_3 [equiv.]	Yield **2a** [%]
1	MeCN	1 equiv. CuSCN	1.1	86
2	NMP	"	"	37
3	DMF	"	"	63
4	MeCN	1 equiv. Cu	"	6
5	"	1 equiv. CuI	"	24
6	"	1 equiv. CuSCN	1.5	99
7	"	50 mol% CuSCN	"	99
8	"	10 mol% CuSCN	"	99
9	"	5 mol% CuSCN	"	53
10	"	-	"	0
11[b]	"	10 mol% CuSCN	"	64
12[c]		"	"	91
13[d]	"	"	"	85
14	"	"	"	87[e]

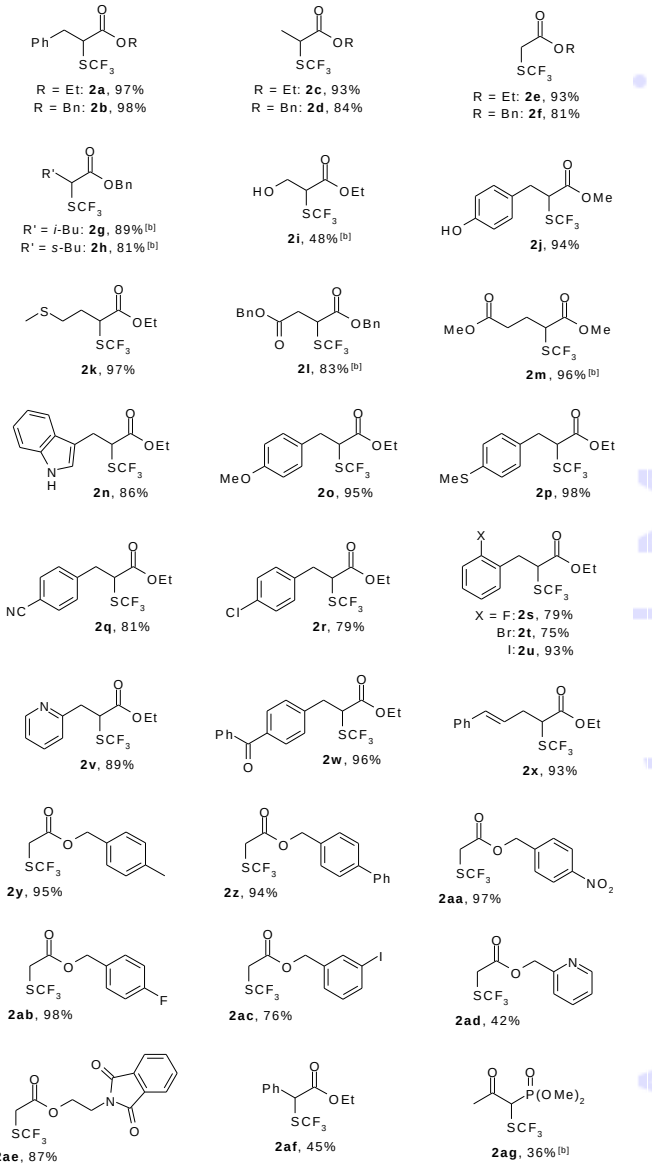
[a] Reaction conditions: 0.5 mmol **1a** in 1 mL solvent was added to Me_4NSCF_3 and the Cu-source in 1 mL solvent, and the mixture stirred for 15 h at room temperature. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard; [b] 6 h reaction time [c] under air; [d] standard-grade MeCN; [e] isolated yield on 10 mmol scale.

After 15 h at room temperature, the trifluoromethyl thioether **2a** was observed in the presence of stoichiometric amounts of CuSCN in acetonitrile, which proves that the first critical step, the generation of a reactive Cu-SCF_3 species, is possible starting from this precursor (Entry 1). Other solvents and copper sources were less effective in these stoichiometric experiments (Entries 2-5). Near-quantitative yields of the desired product were obtained when using 1.5 equiv. of Me_4NSCF_3 in combination with CuSCN (Entry 6). Under these optimized conditions, the copper loading could be reduced to 10 mol% without impacting the yield, and even at 5 mol%, moderate yields were obtained (Entries 6-9). This demonstrates that the reactive $CuSCF_3$ species can indeed be regenerated.

Table 2. Scope of the trifluoromethylthiolation of α-diazo esters.[a]



1 **2**



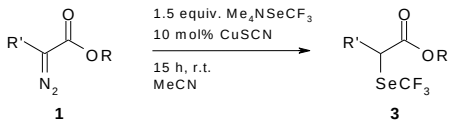
[a] Reaction conditions: 1.0 mmol **1a**-**ag**, 1.5 mmol Me_4NSCF_3 and 0.1 mmol CuSCN, 4 mL MeCN, 15 h, room temperature. Yields of isolated products. [b] Yields determined by ^{19}F NMR using trifluoroethanol as standard.

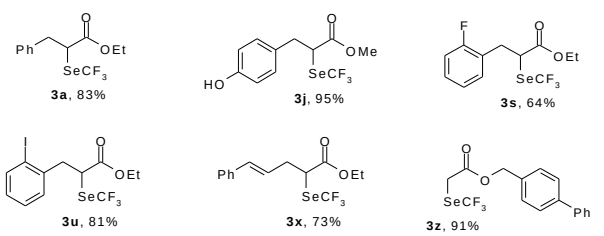
Control experiments confirmed that the reaction does not proceed without copper (Entry 10) and that several hours of reaction time are required (Entry 11). It was found that air and water are tolerated to a certain threshold, so that the reaction can be performed with standard-grade solvents without special precautions (Entries 12-13). This is a great advantage over the stoichiometric reactions reported in the literature, which had to be set up under rigorous exclusion of air or moisture with freshly prepared reagents.[20a,21,22] The scalability of the process was demonstrated by the high-yielding synthesis of **2a** on gram scale (Entry 14).

The scope of this straightforward and convenient method for the trifluoromethylthiolation of α-diazo esters is illustrated by the examples in Table 2. A large number of diversely substituted α-diazo esters were smoothly converted into the corresponding trifluoromethyl thioethers in high yields, with a focus on amino acid-derived starting materials. Moreover, various other common functionalities, such as ether, ester, thio, keto, cyano, nitro, and hydroxy groups, are tolerated. Reactive halide substituents remain unchanged in the process, which opens up opportunities for further derivatization. Even α-diazo esters bearing heterocyclic substituents such as indoles, pyridines, and phthalimides, were successfully converted. Aryl α-diazo esters predominantly underwent homo-coupling to the corresponding olefins under the reaction conditions.[23] Phosphoric acid derivatives were also converted, albeit in somewhat lower yields.

A series of experiments was performed to better understand the reaction mechanism (Scheme 2). A signal at -28.0 ppm in the ^{19}F NMR spectrum of a mixture of Me_4NSCF_3 and CuSCN gives evidence for the formation of $CuSCF_3$.[12,14] Based on the findings of Hu and Wang, we excluded a radical pathway.[21] Still, radical quenchers, such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone, suppressed the reaction but did not form adducts, pointing to a deactivation of the SCF_3 species.[24] It is interesting that the reaction, which is formally an ipso addition of H-SCF_3 to a carbene, does not seem to require a proton source. Deuterium labeling experiments indicate that the extra proton in the product originates from the tetramethylammonium ion and/or traces of water in the reaction mixture, but not from the solvent (for details see SI).

Table 3. Scope of the trifluoromethylselenolation of α-diazo esters.[a]





[a] Reaction conditions: 1.0 mmol **1a**-**z**, 1.5 mmol Me_4NSeCF_3 and 0.1 mmol CuSCN, 4 mL MeCN, 15 h, room temperature. Yields of isolated products.

We next probed whether it was possible to extend this reaction concept to trifluoromethylseleno groups. The $SeCF_3$ moiety should impart similarly beneficial properties as the SCF_3 group, but its introduction is less developed,[12,25] and trifluoromethylselenolations of α-diazo esters are unknown to date. We were pleased to find that by simply replacing Me_4NSCF_3 with Me_4NSeCF_3, various trifluoromethyl selenoethers are accessible in high yields from the corresponding α-diazo esters (Table 3). None of the structures have previously been synthesized.

In conclusion, the catalytic trifluoromethylthiolation / trifluoromethylselenolation process reported herein opens up a convenient entry to trifluoromethyl thio- and selenoethers from easily available α-diazo esters. Its key advantages are the operational simplicity, tolerance to air and moisture, use of inexpensive, easy-to-store and handle SCF_3 / $SeCF_3$ sources, mild reaction conditions, and exceptional functional group tolerance. As a result, this method is well-suited for the late-stage derivatization of drug-like molecules.

Experimental Section

An oven-dried 20 mL crimp-cap vessel with stirrer bar was charged with CuSCN (12 mg, 0.10 mmol), Me_4NSCF_3 (262 mg, 1.50 mmol) and MeCN (2 mL). The α-diazo ester **1a-ag** (1 mmol) in MeCN (2 mL) was then added. The reaction mixture was stirred for 15 h at room temperature, then diluted with diethyl ether (20 mL) and washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40°C). The residue was purified by flash chromatography (SiO_2, cyclohexane / ethyl acetate gradient), yielding the trifluoromethyl thioethers **2a-ag**.

Acknowledgements

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Keywords: copper • diazo compounds • fluorine • fluoroalkylthiolation • synthetic methods

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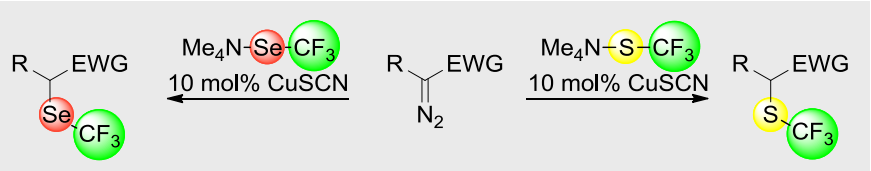

In the presence of catalytic amounts of copper thiocyanate, α-diazo esters are smoothly converted into the corresponding trifluoromethyl thio- or selenoethers by reaction with inexpensive, easy-to-store and handle Me_4NSCF_3 or Me_4NSeCF_3, respectively. This straightforward method gives high yields under neutral conditions at room temperature and is applicable to a wide range of functionalized molecules.

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