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Hydrotrifluoromethylthiolation of α-diazo esters – synthesis of α-SCF_3 substituted esters†

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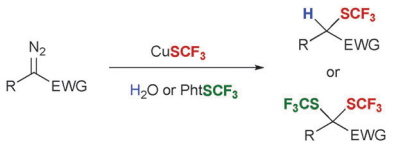
A practical protocol for hydrotrifluoromethylthiolation of diazo compounds has been developed. A range of diazo compounds in combination with a nucleophilic SCF_3 source provided access to valuable trifluoromethylthiolated compounds. Furthermore, a methodology for the first double trifluoromethylthiolation was developed.

Fluorine-containing molecules have been of increasing interest in the last few years. In particular, perfluoroalkyl groups as well as perfluoroalkyl esters or thioesters have attracted significant attention due to their unique properties.[1] For instance, high lipophilicity and stability to metabolic processes are of high value in the field of drug discovery and agrochemistry.[2]

Diazo compounds are readily available from ketones *via* the Bamford–Stevens reaction or can be more conveniently obtained from acetoacetate or ester derivatives in a one-pot α-deprotonation–diazo transfer sequence. The functionalization of diazo compounds has been extensively studied for decades, and rhodium and copper-catalyzed X–H insertions (X = heteroatom) into the resulting carbenoid have emerged as a highly atom-efficient way for creating carbon–heteroatom bonds.[3] In contrast to the large number of reports on the use of oxygen and nitrogen nucleophiles which dominate the recent literature, comparatively less reports address the hydrothiolation of diazo compounds.[4]

In this regard the development of methods for R_F–H insertions (R_F = a fluorine-containing group) would provide straightforward access to valuable fluorinated drug candidates. However, to date only two reports on the fluorination[5] and trifluoromethylation[6] of stabilized carbenoids are known. Interestingly, the hydrotrifluoromethylthiolation of diazo groups has attracted our attention as it would provide fast and mild access to valuable SCF_3 containing products.[9l,m]

Since the pioneering work in the late eighties,[7] numerous methods for the generation of aryl–SCF_3 bonds have been developed.[8]



Scheme 1 Hydrotrifluoromethylthiolation and double trifluoromethylthiolation of α-diazo compounds.

However, the creation of an alkyl–SCF_3 bond in a mild fashion using easy-to-handle reagents is still a challenge.[9] Herein, we present a convenient method for hydrotrifluoromethylthiolation of diazo-compounds, using cheap, stable, and easy to handle copper trifluoromethylthiolate ($CuSCF_3$). Furthermore, we describe for the first time the complementary use of nucleophilic and electrophilic SCF_3-transfering reagents to achieve mild and safe double trifluoromethylthiolation of diazo compounds (Scheme 1).

Initial studies focused on the stability and solubility of $CuSCF_3$ in various organic solvents and its application in the hydrotrifluoromethylthiolation of diazo compound **1a**. We were delighted to see that the reaction proceeded in acetonitrile and product **2a** was indeed formed (Table 1). Lowering the temperature and the amount of copper salt was beneficial (Table 1, entries 2–5), and the desired hydrotrifluoromethylthiolated product **2a** could be obtained in 70% yield. As observed by quantitative NMR studies, prolonged reaction times, with or in the absence of water (Table 1, entries 6, 7 and 9) or use of DMF (Table 1, entry 8) led to complex reaction mixtures. In order to gain insight into the mechanism of this reaction, we performed a control experiment with $AgSCF_3$ (Table 1, entry 10) instead of its copper counterpart. Even though many side-products were identified, product **2a** was observed in 25% NMR yield. Subsequently we carried out the reaction in the presence of an olefin, an aldehyde[11a] and diisopropyl azodicarboxylate (DIAD) (Table 1, entries 11–13). Interestingly, in the first two cases, the reaction proceeded cleanly toward the hydrotrifluoromethylthiolated product **2a**. In the case of DIAD, mostly methyl phenylglyoxylate was formed.

With the optimized conditions in hand, we explored the substrate scope of this reaction. Pleasingly, both electron-withdrawing

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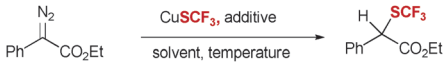
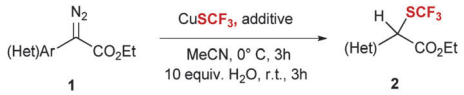
Table 1 Optimization of the hydrotrifluoromethylthiolation of ethyl phenyldiazoacetate



Entry	$CuSCF_3$ (equiv.)	Additive[a]	Temp. [°C]	Time [h]	Yield [%]
1	2.0	H_2O	r.t.	1 + 16	20[b]
2	2.0	H_2O	0	1 + 32	45[b]
3	2.0	H_2O	0 to r.t.	1 + 16	73[b]
4	1.2	H_2O	0 to r.t.	1 + 16	68[b]
5	1.2	H_2O	0 to r.t.	3 + 3	70[b]
6	1.2	H_2O	0 to r.t.	16 + 16	57[c]
7	2.0	H_2O	0 to r.t.	16 + 16	54[c]
8[d]	1.3	H_2O	r.t.	1 + 16	54[c]
9	2.0	—	r.t.	1	45[c,f]
10[e]	1.5	H_2O	r.t.	1	25[c,f]
11	1.2	Styrene[g]/H_2O	0 to r.t.	3 + 16	49[c]
12	1.2	*p*-$NO_2C_6H_4CHO$[g]/H_2O	0 to r.t.	3 + 16	89[c]
13	1.2	DIAD[g]/H_2O	0 to r.t.	3 + 16	—[f]

[a] The additive was added after the time indicated. [b] Yield after column chromatography. [c] NMR yield determined using mesitylene as internal standard. [d] DMF was used as solvent. [e] $AgSCF_3$ was used instead of $CuSCF_3$. [f] A complex mixture was obtained. [g] Two equivalents of the reagent were added directly after the addition of ethyl phenyldiazoacetate.

Table 2 Scope of the reaction using different aryldiazoacetic esters

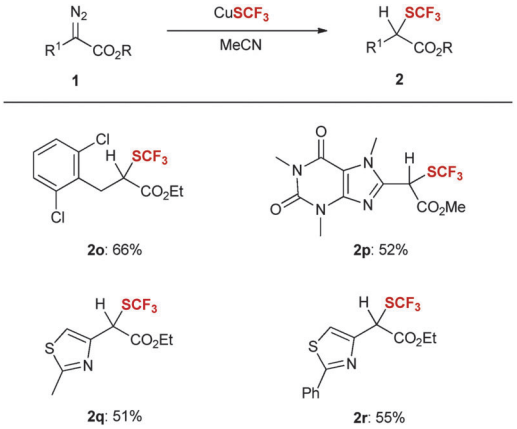


Entry	Ar/HetAr	R	2	Yield[a] [%]
1	C_6H_5	Et	**2a**	70
2	*o*-Br–C_6H_4	Et	**2b**	54
3[b]	1-Np	Me	**2c**	70
4	*m*-MeO–C_6H_4	Et	**2d**	75
5	*m*-Cl–C_6H_4	Et	**2e**	70[c]
6[d]	*p*-F–C_6H_4	Et	**2f**	53
7	*p*-Cl–C_6H_4	Et	**2g**	60
8	*p*-Me–C_6H_4	Et	**2h**	68
9	*p*-MeO–C_6H_4	Me	**2i**	51
10[d]	*p*-AcNH–C_6H_4	Me	**2j**	78
11[d]	*p*-N_3–C_6H_4	Me	**2k**	86
12[d]	*p*-Bpin	Me	**2l**	69
13	*m*,*p*-$(MeO)_2$–C_6H_3	Et	**2m**	61
14	2-Np	Et	**2n**	68

[a] Yield after column chromatography. [b] 20 h reaction time, no water added. [c] Obtained in 90% purity, see ESI for details. [d] Stirred for 20 h after water was added.

(Table 2, entries 2, 5–7, 10 and 11) and electron-donating substituents (Table 2, entries 9 and 13) were tolerated. However, nitro groups were not compatible with our developed reaction conditions. Valuable fluorine-containing building blocks such as **2j–n** (Table 2, entries 10–14) could also be obtained, demonstrating the applicability of our method for the preparation of trifluoromethylthio-containing synthetically useful molecules.

After examining the preliminary scope of this transformation we decided to expand the synthetic utility of our method to other more functionalized diazo-containing molecules **1o–1r** and the results are summarized in Scheme 2.



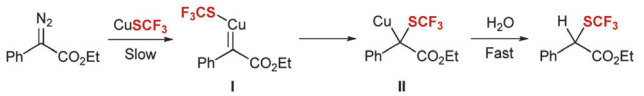
Scheme 2 Scope of the reaction using different aryldiazoacetic esters.[10]

Based on our observations, we propose the following mechanism (Scheme 3): insertion of copper into the diazo compound occurs, followed by migratory insertion, and rapid hydrolysis of the enolate-type intermediate. The absence of cyclopropanation observed when styrene was added to the reaction mixture could be explained by the strong coordination of SCF_3 to the copper-carbenoid of intermediate **I**. The excess of water efficiently hydrolyses intermediate **II**, preventing addition of electrophiles as benzaldehyde derivatives.

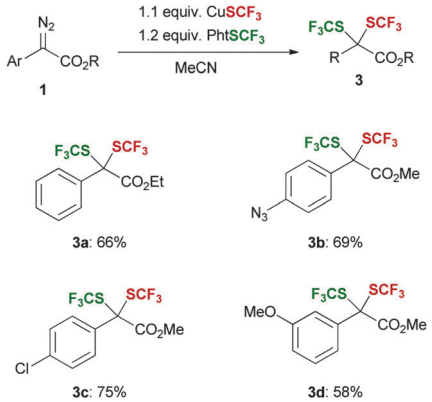
Thus, we became interested in exploring the full potential of diazo compounds by trapping the intermediate enol or ylide with an electrophile. Although this has been demonstrated for rhodium-catalyzed addition of alcohols onto diazo compounds,[11] no sequential trapping with an S-electrophile has been reported to date. Intrigued by this lack of data and by the possibility to introduce two SCF_3 groups we added an electrophilic SCF_3 source, *N*-trifluoromethylthiophthalimide[9k] ($PhtSCF_3$), to the reaction mixture in the absence of water. To our delight, the reaction proceeded and we were for the first time able to isolate the dithiolated products **3** (Scheme 4). Interestingly, even the *p*-azidophenyldi(trifluoromethylthio)acetate **3b** a valuable "clickable" fluorine-containing synthon could be prepared with good yield.[12,13]

In order to understand the mechanism of this dithiolation procedure, we studied the interactions of the reaction components by NMR. Interestingly, the addition of $PhtSCF_3$ to a solution of $CuSCF_3$ in acetonitrile induces the formation of the disulfide $(CF_3S)_2$ which itself is a potent electrophilic SCF_3 source. Remarkably, this species is stable in solution, and reacts readily to give the ditrifluoromethylthiolated products **3** (for a detailed study, see the ESI†).

In summary, we have developed a convenient method for the hydrotrifluoromethylthiolation of various diazo compounds. The reaction tolerates most of the common functional groups, and the use of readily available and easy to handle $CuSCF_3$ under mild conditions ensures potential for applications in



Scheme 3 Plausible mechanism of the hydrotrifluoromethylthiolation of aryldiazoacetic esters (for a preliminary mechanistic study by NMR, see the ESI†).



Scheme 4 Double trifluoromethylthiolation of diazo esters.[10]

post-functionalization of complex drug-like molecules. Furthermore, we were able to expand the methodology to the first double trifluoromethylthiolation providing novel fluorinated products in good yield.

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