Electrophilic Substitution

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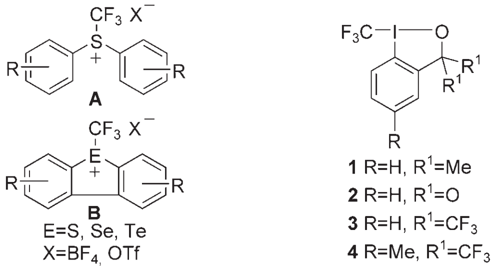
Mild Electrophilic Trifluoromethylation of Carbon- and Sulfur-Centered Nucleophiles by a Hypervalent Iodine(III)–CF_3 Reagent**

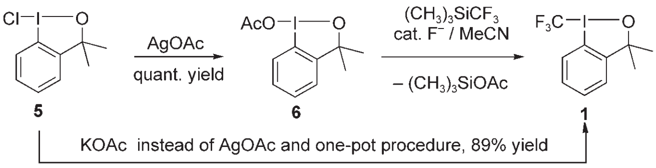
*Iris Kieltsch, Patrick Eisenberger, and Antonio Togni**

Fluorinated and perfluoroalkylated organic compounds constitute important targets in many research fields both in academia and in industry.[1] One of the most challenging synthetic problems is the introduction of a trifluoromethyl group in a mild and selective manner. Thus, trifluoromethylation reactions that could be implemented at a late stage of a multistep synthetic sequence are still highly sought after. These reactions should also be economically and ecologically feasible. In this context, the use of the more environmentally friendly CF_3H instead of CF_3Br as a primary source of the CF_3 synthon was proposed and implemented successfully by Langlois and co-workers for the preparation of new nucleophilic trifluoromethylation reagents.[2] However, the most commonly used nucleophilic CF_3 source is still $(CH_3)_3SiCF_3$, which is usually prepared from CF_3Br.[3] On the other hand, electrophilic trifluoromethylation is much less generally used, partly as a result of the relatively difficult synthetic access to the classical reagents of type **A** and **B** (Scheme 1).[4]

In a search for less expensive and more easily accessible reagents, we succeeded recently in preparing a new family of hypervalent iodine compounds that showed promising reactivity in the trifluoromethylation of carbon-centered nucleophiles (Scheme 1).[5] Herein, we report on the use of one of these reagents, **1**, as a convenient source of electrophilic CF_3 for the mild and selective trifluoromethylation of both active methylene compounds and free thiols. Additionally, we disclose an improved, practical, and scalable synthesis of compound **1**.



Scheme 1. Reagents for electrophilic trifluoromethylation: *S*-trifluoromethyl diaryl sulfonium salts **A**, *S*-(trifluoromethyl)dibenzothiophenium, *Se*-(trifluoromethyl)dibenzoselenophenium, and *Te*-(trifluoromethyl)dibenzotellurophenium salts **B**,[4] and our new hypervalent CF_3–iodine(III) reagents **1**–**4**. Tf = trifluoromethanesulfonyl.[5]



Scheme 2. Improved one-pot synthesis of **1**.

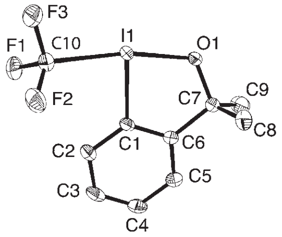


Figure 1. ORTEP drawing of **1** (50% probability for thermal ellipsoids with hydrogen atoms omitted for clarity). Selected bond lengths [Å]: C10–I1 2.267(2), I1–O1 2.1176(14), C1–I1 2.1211(19); bond angles [°]: C10-I1-O1 169.78(7), C1-I1-C10 91.11(8), C1-I1-O1 78.71(6); torsion angles [°]: C6-C1-I1-O1 11.56(15), C2-C1-I1-C10 13.21(18).[8]

For the synthesis of our iodine-based trifluoromethylating agents, we rely on a protocol in which consecutive "ligand-exchange" reactions are carried out at the I^{III} center. Thus, the replacement of the chloride substituent in **5**[6] by an acetoxy group upon treatment with AgOAc was followed by a fluoride-mediated substitution reaction with $(CH_3)_3SiCF_3$ to give the I–CF_3 compound **1** (Scheme 2 and Figure 1). This reaction sequence corresponds to a formal umpolung of the CF_3 group, from being nucleophilic in $(CH_3)_3SiCF_3$ to electrophilic in **1**. We were very pleased to find that the replacement of the light-sensitive AgOAc reagent with inexpensive KOAc did not affect the yield or reaction rate of the transformation.[7] Moreover, this reaction sequence allows the in situ generation of **6** (Scheme 2). Removal of the insoluble salts by filtration and cooling of the reaction mixture to −17 °C, at which temperature the second reaction step is carried out, affords the final product in 89 % yield. This yield compares favorably with the 46 % yield observed when the former two-step process was used. Thus, starting from the

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[*] I. Kieltsch, P. Eisenberger, Prof. A. Togni
Department of Chemistry and Applied Biosciences
Swiss Federal Institute of Technology
ETH Zurich
8093 Zürich (Switzerland)
Fax: (+41) 44-632-1310
E-mail: togni@inorg.chem.ethz.ch

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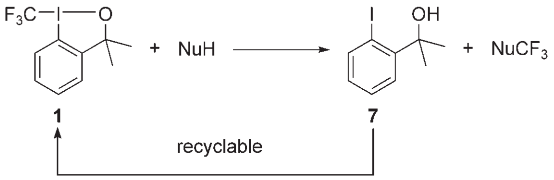
readily available 2-iodobenzoic acid, the crystalline[8] reagent **1** is accessible in an overall four-step procedure, requiring only two distillations and one recrystallization. This method therefore facilitates a scale-up to multigram quantities. Compound **1** can be exposed to and manipulated in moist air at least for short periods of time without any apparent alteration. However, it is important to note that exothermic decomposition occurs when the compound is heated beyond its melting temperature of 76–79 °C, as shown by DSC (differential scanning calorimetry) and TGA (thermogravimetric analysis) measurements. Despite this behavior, **1** does not qualify as explosive under ambient conditions; however, it certainly should not be heated as a solid material.

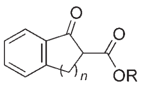
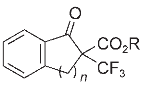
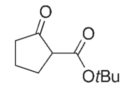
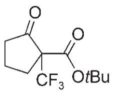
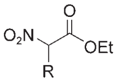
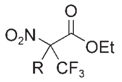
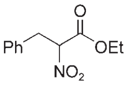
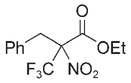
With this convenient synthesis in hand, we were able to explore the reactivity of **1** with a series of nucleophiles in closer detail. One of the benefits of our trifluoromethylation reagent **1**, as compared to the classical types **A** and **B**, is the incorporated base. Indeed, an alkoxide is formed upon formal CF_3^+ transfer, thus making any additional, stoichiometric amount of a base superfluous. Moreover, it is possible to isolate the alcohol **7** formed as a by-product. Alcohol **7** is the starting material for the preparation of intermediate **5** by oxidation and is, therefore, formally the recyclable CF_3 carrier (Scheme 3).



Scheme 3. General straightforward stoichiometry for electrophilic trifluoromethylation reactions with **1**.

Carbonyl compounds, such as β-keto esters and α-nitro esters, react with **1** to give the corresponding α-trifluoromethylated derivatives. Under conditions of phase-transfer catalysis the β-keto esters in Table 1 (entries 1–5) derived from 1-indanone, 1-tetralone, or pentanone give the products **C1**–**C5**, although the yields are not as high as those observed with the previously reported systems.[9] Under identical conditions, the less reactive, open-chain β-keto esters show no product formation at all. On the other hand, one of the cleanest trifluoromethylation reactions that we have been able to carry out so far with **1** is the trifluoromethylation of α-nitro ester substrates (Table 1, entries 6–8). The very encouraging aspect is that in the presence of a catalytic amount of CuCl (20 mol%) the reaction proceeds smoothly in CH_2Cl_2 at room temperature with high conversion. However, some difficulties have been encountered in the isolation of the products in pure form in high yield, probably also as result of their high volatility. Compound **C7**, for example, was detected by NMR spectroscopy as the only product, but could only be isolated in a modest yield of 31%. Nevertheless, to the best of our knowledge this is the first direct trifluoromethylation of α-nitro esters. The products are obvious precursors of the corresponding α-trifluoromethyl-α-amino acids,[10] which could be obtained by selective reduction of the nitro group and hydrolysis of the ester group.

Table 1: Electrophilic α trifluoromethylation of β-keto esters and α-nitro esters.

Entry	Substrate	Product		Yield [%]
1			**C1** $n=1$, R=Me	42
2			**C2** $n=1$, R=Et[5]	67
3			**C3** $n=1$, R=tBu	66
4			**C4** $n=2$, R=Me	40
5			**C5**	46[a]
6			**C6** R=H	89[a]
7			**C7** R=Me	99[a]
8			**C8**	59

[a] Yield was determined by ^1H and ^{19}F NMR spectroscopy.

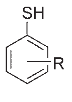
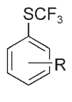
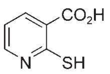
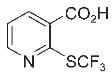
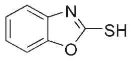
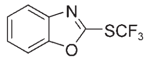
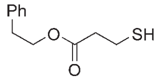
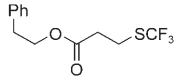
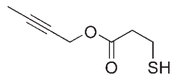
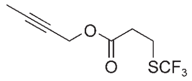
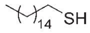
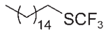
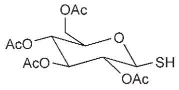
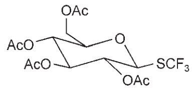
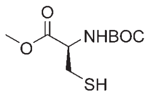
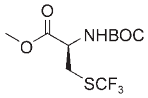
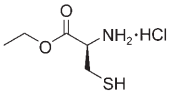
Previously, an SCF_3 substituent was introduced into organic molecules by harsh functional-group-interconversion reactions,[11] by direct transfer of the SCF_3 moiety,[12] or by the delivery of a CF_3 fragment to an appropriate sulfur atom by a nucleophilic, or, more often, a radical reaction.[13] The less common electrophilic S trifluoromethylation with the reagents **B** developed by Umemoto and Ishihara requires preformed sodium thiolates, and the desired product is accompanied by a considerable amount of the corresponding disulfide by-product.[4,14]

We found that both aromatic and aliphatic thiols undergo S trifluoromethylation selectively and smoothly in the presence of 1.1 equivalent of the reagent **1** to afford the products in good to excellent yields, as shown in Table 2.

Disulfide formation is essentially completely suppressed because the reactions are run at low temperature (−78 °C). The transformation shows a remarkably high functional-group tolerance: amines, amides, carboxylic acids, thioacetals, alcohols, and alkynes do not interfere with the formation of the trifluoromethylsulfenyl group. Moreover, given the simplicity of handling and the efficiency of this method, we anticipate that the assembly of the SCF_3 functional group should be possible at a very late stage of a synthesis, even of a highly functionalized molecule, provided a thiol group is present. Thus, this approach represents a real alternative to the more common building-block strategy. Furthermore, the reactivity of compound **1** does not appear to be particularly solvent dependent, so that solvent choice is mainly dictated by the solubility of the thiol. MeOH is required in the case of substrates that display poor solubility in less polar solvents (Table 2, entries 7 and 14). The products are usually separated by chromatography, but in some cases by simple filtration (Table 2, entries 8 and 14).

Fluorinated non-natural amino acids and carbohydrates are important targets in medicinal and bioorganic chemis-

Table 2: Electrophilic trifluoromethylation of thiols.

Entry	Substrate	Product		Yield [%]
1			**S1**[a] R = *m*-Br	82
2			**S2**[a] R = *p*-NO_2	88
3			**S3**[a] R = *o*-NH_2	82
4			**S4**[a] R = *m*-NH_2	72
5			**S5**[a] R = *p*-NHAc	80
6			**S6**[a] R = *o*-OH	91[b]
7			**S7**[c]	95
8			**S8**[a]	58
9			**S9**[a]	81
10			**S10**[a]	53
11			**S11**[a,d]	51
12			**S12**[a]	90
13			**S13**[a]	82
14			**S14**[c]	99

[a] The reaction was carried out in CH_2Cl_2. [b] Yield was determined by ^1H NMR spectroscopy. [c] The reaction was carried out in MeOH. [d] The disulfide by-product was isolated in 41 % yield.

try.[15] Trifluoromethylthio-substituted sugars are rare compounds. We are aware of only very few pyranose derivatives bearing a SCF_3 moiety that are comparable to product **S12**.[16] Previous methods for the direct preparation of *S*-trifluoromethyl-L-cysteine derivatives required reaction conditions involving *t*BuOOH[17] or liquid ammonia.[18] However, with compound **1** the S trifluoromethylation of simple cysteine esters in either the N-protected or the unprotected form can be carried out in high yield under very mild conditions. We anticipate that the trifluoromethylation of cysteine residues in higher peptides should also be possible by this method.

In conclusion, we have shown the very promising potential of the mild, relatively cheap, and readily accessible reagent **1** in the C and S trifluoromethylation of a variety of substrates. Further studies with an emphasis on catalytic and enantioselective reactions with reagents of type **1** are ongoing in our laboratory and shall be reported in due course.

Experimental Section

Improved synthesis of **1**:[4] All manipulations were conducted under an inert atmosphere. Dry KOAc (6.66 g, 67.9 mmol, 1.68 equiv) and intermediate **5**[6] (11.94 g, 40.3 mmol) were stirred in dry MeCN (100 mL) for 1 h at ambient temperature. Filtration and washing of the remaining white solid with MeCN gave a clear, almost colorless solution to which further MeCN (100 mL) was added. The solution was cooled to −17 °C, and Me_3SiCF_3 (9.16 mL, 61.97 mmol, 1.54 equiv) was added, followed by dropwise addition of a solution of tetrabutylammonium triphenyldifluorosilicate (TBAT; 0.065 g, 0.120 mmol, 0.3 mol % based on **5**) in MeCN (2 mL). The reaction mixture was stirred for 16 h at −17 °C, then warmed to −12 °C, at which temperature further Me_3SiCF_3 (1.31 mL, 8.9 mmol, 0.22 equiv) was added. The reaction mixture was warmed to room temperature over 3 h and then stirred at room temperature for a further 3 h. After the volatile components of the mixture had been removed, the residue was dried in vacuo. Dry pentane (150 mL) was added to the remaining brown solid, and the resulting mixture was filtered through a pad of dry alox. The clear, colorless solution obtained was evaporated to dryness, and the residue was dried in vacuo to yield **1** (11.823 g, 35.8 mmol, 89 %) as a white solid.

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