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Recent Advances in Electrophilic CF_3-Transfer Using Hypervalent Iodine(III) Reagents

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Abstract: The development of new methodologies for an efficient introduction of CF_3 groups into complex molecules constitutes one of the most challenging tasks of modern organic chemistry. Recently, we reported the access to a new class of electrophilic CF_3-transfer reagents based on hypervalent iodine. The versatile application of these reagents to C-centred nucleophiles, such as β-keto esters, silyl enol ethers and α-nitro esters, as well as to thiols and primary and secondary phosphines is described. Experiments with phenols afforded corresponding trifluomethylethers in very low yields.

Keywords: Electrophilic trifluoromethylation · Fluorinated compounds · Hypervalent iodine · Trifluoromethylthio ether · (Trifluoromethyl)phosphine

Introduction

There is a great demand for organofluorine compounds in a wide range of applications. Fluorine modifies the physical and chemical properties of compounds that contain it in a unique manner. The trifluoromethyl unit as drug component affects nearly all physical, adsorption, distribution, metabolism and excretion properties of a lead compound.[1] Therefore the building block approach is commonly used to introduce the CF_3-moiety. To circumvent this building block approach and for economical, ecological and technical feasibility the development of stable, and selective trifluoromethylation agents that allow a direct introduction at a late stage of a multi-step sequence has received considerable attention. Although the radical and nucleophilic methods seem to have been harnessed, electrophilic trifluoromethylation still poses a challenge. The commercial availability of Me_3SiCF_3 (known as Ruppert-Prakash reagent) and its ease of handling turned the anionic trifluoromethylation reaction into one of the most powerful strategies and has led to the development of other nucleophilic trifluoromethylation reagents.[2] On the other hand, only a few reagents are capable of performing electrophilic trifluoromethylation. One class of electrophilic reagents are the trifluoromethylchalcogenium salts (oxonium, sulfonium, selenonium, telluronium) (Fig. 1), devised by Umemoto and co-workers and based on seminal work by Yagupol'skii.[3]

We recently succeeded in preparing a new family of hypervalent iodine compounds showing promising potential for the trifluoromethylation of several types of nucleophiles.[4] Here we highlight two members of this reagent class, their improved scalable syntheses and the advantage of each reagent. Additionally, we summarize the application of these compounds for a mild and selective transfer of a CF_3 group toward selected nucleophiles, such as carbonyl compounds, thiols, phosphines and phenols.

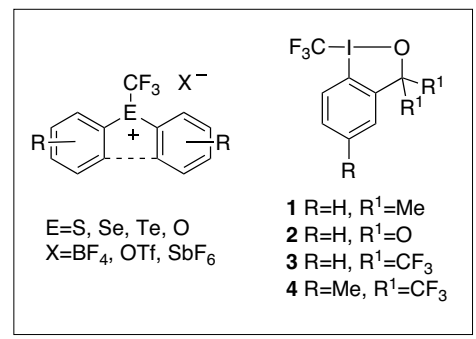

Fig. 1. Reagents for electrophilic trifluoromethylation

Results and Discussion

The I-based trifluoromethylating agents are accessible from cheap commercial chemicals upon oxidation to **5** or **7** (Scheme 1), followed by a consecutive, nucleophilic ligand substitution at the I(III) center using KOAc and Ac_2O, respectively. The subsequent introduction of the CF_3 group corresponds to a formal 'Umpolung' of the CF_3 fragment. This is delivered as a nucleophile using Me_3SiCF_3, but shows

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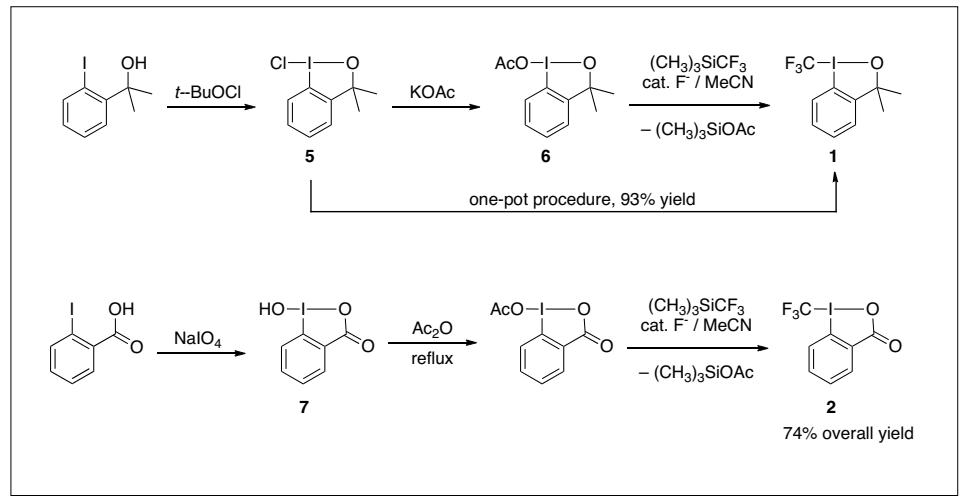
its electrophilic character once bound to iodine. Thus, starting from readily available iodobenzoic acid, **2** is synthesized in 74% overall yield. Compound **1** is also derived from iodobenzoic acid upon an esterification and conversion to the alcohol. Following the one-pot procedure, without isolation of the acetoxy-intermediate, **1** is accessible in an overall four-step-procedure in 62% isolated yield (Scheme 1). Both crystalline reagents can be exposed to and manipulated in moist air for short periods of time without any apparent alteration in the case of **1**. The acid-derived reagent **2** is bench stable for months.[4]

The benefit of trifluoromethylating reagent **1** compared to the previous ones, is the 'dormant' incorporated base. After the CF_3^+ transfer an alkoxide is formed, thus making any additional, stoichiometric amount of base superfluous. However, the less reactive and in this case, more selective acid-derived trifluoromethylating agent **2** requires contingently a base, therefore it excels as the reagent for sensitive substrates such as phosphines. The remaining iodobenzoic acid can be removed easily by filtration or extraction to prevent loss in product purification by column chromatography. Moreover, after the delivery of the CF_3 group to a nucleophile the primary starting material (iodobenzoic acid and alcohol, respectively) is formed as a byproduct in both cases. Therefore, our system allows the recovery of the CF_3-carriers (Scheme 2).

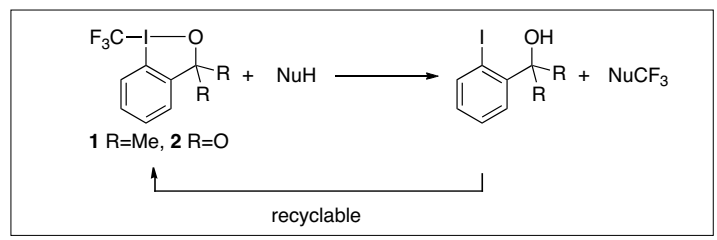
Electrophilic trifluoromethylation of carbonyl compounds, such as β-keto esters, silyl enol ethers, silyl ketene acetals and α-nitro esters, represents a novel example of a C–C bond forming process. Moreover, this method gives a possible access to the enantioselective trifluoromethylation, which Billard branded the new 'grail quest' for chemists.[2b]

Under conditions of phase-transfer catalysis the CF_3-transfer to β-keto esters succeeded to give the products shown in Scheme 3, although the yields do not reach those obtained using the previously reported systems.[5] At elevated temperature, silyl enol ethers and silyl keten acetals exposed to **1** or **2** in MeCN give the corresponding α-CF_3 substituted carbonyl compounds in respectable yields.

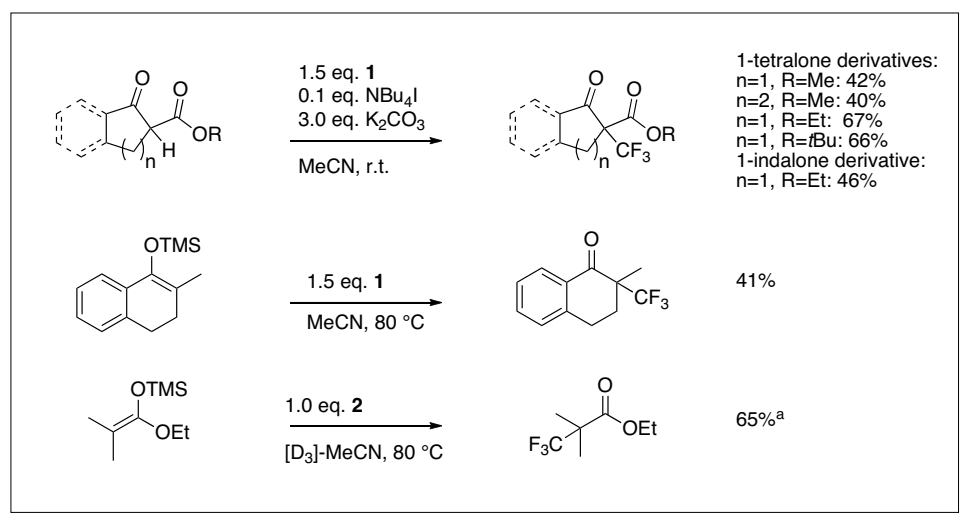
On the other hand, one of the cleanest trifluoromethylation reactions we were able to perform so far involves α-nitro esters as substrates (Scheme 4). In the presence of catalytic amounts of Cu(I) or Cu(II) salts (15 mol%) the reaction proceeds smoothly at room temperature with high conversion in CH_2Cl_2. The products are obvious precursors of the corresponding α-trifluoromethyl-α-amino acids,[6] which can be obtained upon selective reduction of the nitro group (Scheme 5). Promising results for an asymmetric catalytic synthesis



Scheme 1. Improved synthesis of trifluoromethylation reagents **1** and **2**



Scheme 2. General straightforward stoichiometry for electrophilic trifluoromethylations using **1** and **2**, respectively

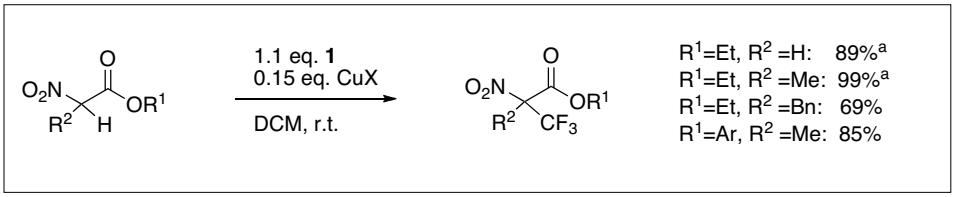


Scheme 3. Electrophilic α-trifluoromethylation of β-keto esters, silyl enol ether and silyl ketene acetals; [a]yields determined by ^{19}F NMR spectroscopy.

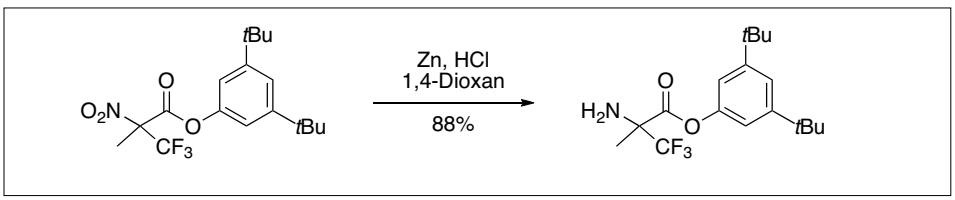
of unnatural α-amino acid precursors were obtained using enantiopure chiral copper complexes; optimization of the enantioselectivity is the subject of active research.

The high lipophilicity and the electronic properties of the trifluoromethanethioether group make it a useful unit for pharmaceuticals and agrochemicals. The introduction of an SCF_3 substituent into organic molecules has been previously achieved either by using harsh functional group interconversion reactions, by direct transfer of the SCF_3 moiety, or by the delivery of a CF_3 fragment to the sulfur atom in a nucleophilic, or primarily radical fashion.[7] Electrophilic S-trifluoromethylation using Umemoto' reagents requires preformed sodium thiolates to obtain product formation along with a considerable amount of the corresponding disulfide byproduct.[3,8]

We found that both aromatic and aliphatic thiols will selectively and smoothly undergo S-trifluoromethylation in the presence of 1.1 equivalents of the reagent **1** affording the products in good to excellent yields, as shown in Fig. 2.



Scheme 4. Electrophilic α-trifluoromethylation of α-nitro esters; [a]reaction performed in CD_2Cl_2; yields determined by ^1H NMR spectroscopy



Scheme 5. Reduction of α-trifluoromethylated α-nitro esters

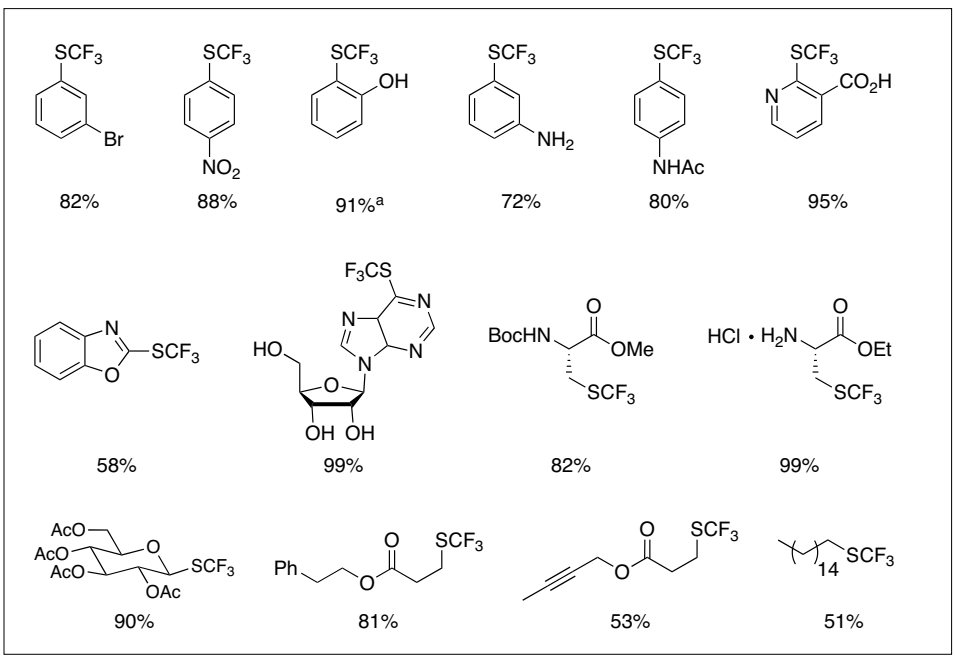


Fig. 2. Products of the S-trifluoromethylation of free thiols; [a]yields determined by ^1H NMR spectroscopy

Table. Electrophilic trifluoromethylation of phosphines

Entry	Substrate	Conditions	Product	Yield[a]
1	Cy_2PH	**1**, –78 °C → r.t.	$Cy_2P(S)(CF_3)$	52%[b]
2	Ph_2PH	**2**, r.t.	$Ph_2P(CF_3)$	78%
3	$(o\text{-Tol})_2PH$	**1**, –78 °C → r.t.	$(o\text{-Tol})_2P(CF_3)$	50%
4	$(p\text{-Tol})_2PH$	**2**, r.t.	$(p\text{-Tol})_2P(CF_3)$	78%
5	$(\beta\text{-Np})_2PH$	**2**, 0 °C → r.t.	$(\beta\text{-Np})_2P(CF_3)$	58%
6	$(p\text{-OMePh})_2PH$	**1**, –78 °C → r.t.	$(p\text{-OMePh})_2P(CF_3)$	58%
7	*rac*-(*o*-anisole)PhPH	**1**, –78 °C → r.t.	*rac*-(*o*-anisole)PhP(CF_3)	63%
8	$PhPH_2$	**1**, r.t.	$PhPH(CF_3)$	84%[c]

[a]isolated yields; [b]S_8 as oxidant; [c]conversion calculated based on ^{19}F NMR spectroscopy with $PhCF_3$ as an internal reference

The transformation shows a remarkably high functional group tolerance. Therefore it allows a diversified application in synthesis at late stages of a given sequence. In fact, amines, amides, carboxylic acids, thioacetals, alcohols, and alkynes do not interfere with the formation of the SCF_3 group. Moreover, the reactivity of compound **1** does not appear to be particularly solvent dependent, such that solvent choice is mainly dictated by the solubility of the thiol. In fact, the reaction seems to be very robust. The two most important factors appear to be the control of the temperature (–78 °C) to suppress disulfide formation and the solubility of the starting material at this temperature.[4b]

Electrophilic trifluoromethylation of triphenylphosphine to obtain P-trifluoromethyl triphenylphosphonium salts was already carried out by Umemoto and coworkers using S-trifluoromethyldibenzothiophenium salts (Fig. 1).[8] However, the same approach has never been applied to the synthesis of neutral phosphine compounds from secondary, or primary phosphines. However, P-trifluoromethyl phosphines are of interest as ligands in transition metal chemistry because of their altered electronic characteristics, in particular the weak σ-donating and strong π-accepting properties. Therefore, these phosphines can serve as more stable surrogates of CO, NO, or PF_3 from an electronic perspective at the cost of an increased steric demand.[9]

Adaptation of the previous reaction conditions for the reaction of secondary phosphines with 1 equiv. of reagent **1** or **2** in degassed, dry CH_2Cl_2 at ambient or low temperatures produced the desired tertiary trifluoromethylated phosphines (Table, entries 1 to 7). Diaryl(trifluoromethyl) phosphines were found to be fairly stable toward oxidation, whereas the more basic dicyclohexyl(trifluoromethyl)phosphine was susceptible to oxidation and therefore isolated as the corresponding sulfide (entry 1). Interestingly, applying reagent **2** to primary phosphines provides solely the corresponding monotrifluoromethylated phosphines (entry 8).[10]

The trifluoromethylated phosphorus compounds were found to serve as suited ligands for transition metals in several oxidation states and form stable, crystalline complexes with appropriate Pd(II),[11] Ru(II), Rh(I) and Ir(III) precursors. Nevertheless, this is a valuable preparative method for the synthesis of dialkyl- or diaryl-substituted trifluoromethyl phosphines since it does not require the synthesis of elaborate starting materials such as P-cyanophosphines[12] or P-fluorophosphines.[13] These are not commercially available and have to be accessed in multistep procedures.

At this point in time, it is not possible to deduce a mechanistic framework un-

equivocally for these trifluoromethylation reactions. However, it seems to be substrate dependent. Nevertheless, the mechanism most likely involves SET processes. In fact, the best results for a CF_3-transfer using reagent **1** and **2** were achieved with soft nucleophiles such as thiols.

Unfortunately, applying standard S_N2 conditions for the reaction of hard oxygen nucleophiles such as phenols with **2** gives only traces (and 15% yield when the *ortho* and *para* positions are blocked) of the desired O-trifluoromethylated product.[14] Bearing these results in mind we endorse the conclusion drawn by Cahard concerning the 'real' carriers of the electrophilic CF_3^+ species.[2a] Further studies to find a thermally stable and easily accessible solution for the challenges in O-trifluoromethylation are under investigation in our laboratory.

In conclusion, we have shown recent advances in electrophilic trifluoromethylation using our mild and readily accessible reagents **1** and **2**. We demonstrated the advantages of these reagents and their versatile application in C-, S- and P-trifluoromethylation as well as their temporary limitations.

Acknowledgments

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