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Fluoride-induced nucleophilic (phenylthio)difluoromethylation of carbonyl compounds with [difluoro(phenylthio)methyl]trimethylsilane (TMS–CF_2SPh)

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Dedicated to Professor Richard D. Chambers on the occasion of his 70th birthday.

Abstract

A fluoride-induced nucleophilic (phenylthio)difluoromethylation method using TMS–CF_2SPh has been achieved. This new methodology efficiently transfers ''$PhSCF_2$'' group into both enolizable and non-enolizable aldehydes and ketones to give corresponding (phenylthio)difluoromethylated alcohols in good to excellent yields. Diphenyldisulfide can also be (phenylthio)difluoromethylated into $PhSCF_2SPh$ in high yield. The reaction with methyl benzoate, however, gives only low yield of (phenylthio)difluoromethyl phenyl ketone. The above-obtained $PhSCF_2$-containing alcohols can be further transformed into difluoromethyl alcohols using an oxidation–desulfonylation procedure. This new type of nucleophilic (phenylthio)difluoromethylation methodology may have other potential applications in the medicinal and agrochemical fields.

Keywords: [Difluoro(phenylthio)methyl]trimethylsilane; (Phenylthio)difluoromethylation; Carbonyl compounds; Fluoride; Autocatalytic reaction

1. Introduction

Recently, the selective introduction of difluoro(arylthio)-methyl or difluoro(heteroarylthio)methyl group ($ArSCF_2$) into organic molecules has been found to be attractive, since these compounds have potential biological applications such as anti-HIV-1 reverse transcriptase inhibitors and other agrochemical intermediates [1,2]. The currently known methods to construct the $ArSCF_2$ moiety are based on the S_RN1 reactions between an aryl- or heteroarylthiolate (ArSNa) and a halodifluoromethyl-containing compound (halo = Br, Cl) [1,2]. To our best knowledge, there is no synthetic method available so far for the direct introduction of a difluoro(arylthio)methyl ($ArSCF_2$) building block into organic molecules.

In 1989, we developed the first general and efficient nucleophilic trifluoromethylation method using (trifluoromethyl)trimethylsilane (TMS–CF_3) [3–5]. With a similar protocol, fluoride-induced nucleophilic chlorodifluoromethylation with TMS–CF_2Cl, (trimethylsilyl)difluoromethylation with $TMSCF_2TMS$, and perfluorovinylation with TMS CF_2CF_2TMS have been developed in our laboratory [6]. Herein, we would like to disclose another nucleophilic fluoroalkylation methodology in this category, using [difluoro(phenylthio)methyl]trimethylsilane (TMS–CF_2SPh) as the nucleophilic (phenylthio)difluoromethylating reagent.

2. Results and discussion

[Difluoro(phenylthio)methyl]trimethylsilane (TMS–CF_2SPh) was prepared for the first time by us as a high-boiling and reasonably stable liquid (b.p. 86–87 °C/4 mmHg), using

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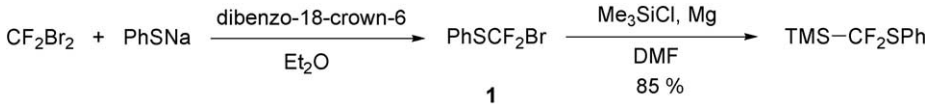


Scheme 1. Preparation of TMS–CF_2SPh.

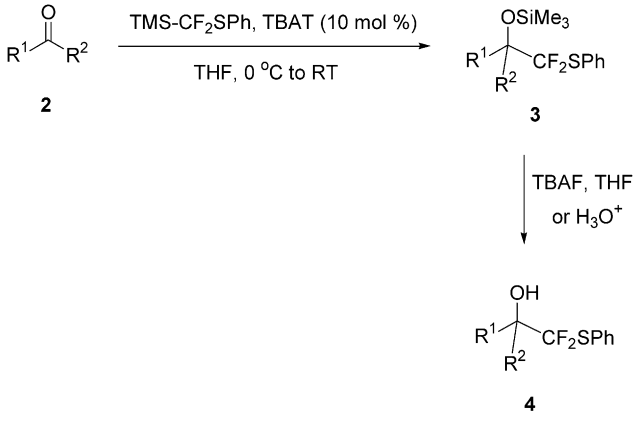
the Barbier coupling reaction of bromodifluoromethyl phenyl sulfide (**1**), magnesium metal and chlorotrimethylsilane (TMSCl) in 85% isolated yield (Scheme 1) [7]. Since compound **1** can be readily prepared from dibromodifluoromethane (Halon 1202) and sodium benzenethiolate [8], TMS–CF_2SPh is an inexpensive chemical and can be widely used.

The reaction conditions for the fluoride-induced nucleophilic (phenylthio)difluoromethylation reaction (Scheme 2) is similar to that of trifluoromethylation with TMS–CF_3 [3,4]. Catalytic amount (10 mol.%) of tetrabutylammonium triphenyldifluorosilicate (TBAT) was used as the anhydrous fluoride source. The results are summarized in Table 1.

As shown in Table 1, various aldehydes and ketones were (phenylthio)difluoromethylated in good to excellent yields with this method. Enolizable carbonyl compounds behave similarly as non-enolizable ones, with slightly lower yields (see entries 7 and 8). In the case of an α,β-unsaturated carbonyl compound, only 1,2-addition product was obtained (entry 5).

This new type of (phenylthio)difluoromethylation method was also applied to other systems such as disulfides and esters. For example, when excess potassium *tert*-butoxide was used as the promoter, diphenyl disulfide (**5**) reacted with TMS–CF_2SPh to give product **6** in 85% yield (Scheme 3, Eq. (1)). The reaction between methyl benzoate (**7**) and TMS–CF_2SPh was attempted several times using different solvents at −78 °C to room temperature, and the ketone product **8** was produced in 28–41% conversions (Scheme 3, Eq. (2)).

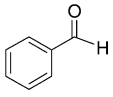
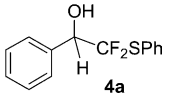
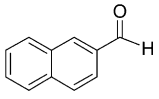
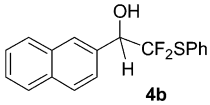
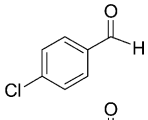
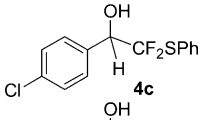
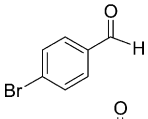
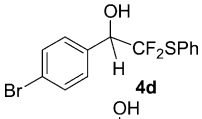
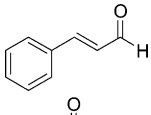
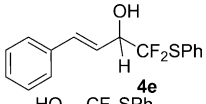
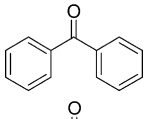
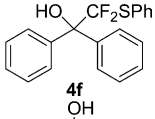
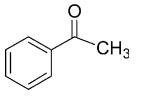
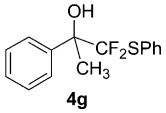
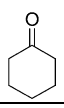
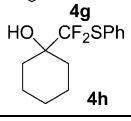
The above-obtained (phenylthio)difluoromethyl carbinols (**4**) can also be further transformed into difluoromethyl carbinols (**10**), using simple oxidation and reductive desulfonylation procedure (Scheme 4). Difluoromethyl alcohols are highly useful compounds for many applications [9].



Scheme 2. Nucleophilic (phenylthio)difluoromethylation with TMS–CF_2SPh.

Concerning the mechanism of this fluoride-induced (phenylthio)difluoromethylation of carbonyl compounds (both aldehydes and ketones), we propose that a pentacovalent silicon anion species **11** is formed from TMS–CF_2SPh and TBAT (Scheme 5). Species **11** acts as a real (phenylthio)difluoromethylating agent, transferring the $PhSCF_2^-$ into the carbonyl compound **2** to give alkoxide **12**. Alkoxide **12** can further act as an initiator for TMS–CF_2SPh to form another pentacovalent silicon species **13** as a (phenylthio)difluoromethylating agent, thus giving the silylated carbinol product **3** from TMS–CF_2SPh and carbonyl compounds **2** in a catalytic cycle (Scheme 5). In principle, the reaction is a fluoride-induced autocatalytic process, and such a mechanism has been previously proposed by us in the case of TMS–CF_3 [3].

Table 1
Nucleophilic (phenylthio)difluoromethylation of carbonyl compounds with TMS–CF_2SPh (after desilylation)

Entry	Carbonyl compounds **2**	Product **4**	Yield (%)[a]
1		 **4a**	85
2		 **4b**	87
3		 **4c**	72
4		 **4d**	81
5		 **4e**	91
6		 **4f**	86
7		 **4g**	82
8		 **4h**	77

[a] Isolated yield.