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Dithiocarbamate-substituted *gem*-difluorinated silicon reagent: generation and addition to aldehydes

Anton S. Maslov [a,b], Vladimir O. Smirnov [a], Marina I. Struchkova [a], Dmitry E. Arkhipov [c], Alexander D. Dilman [a,*]

[a] N. D. Zelinsky Institute of Organic Chemistry, Leninsky Prosp. 47, 119991 Moscow, Russian Federation
[b] Moscow State University, Department of Chemistry, Leninskie Gory 1-3, 119991 Moscow, Russian Federation
[c] A. N. Nesmeyanov Institute of Organoelement Compounds, Vavilov Str. 28, 119991 Moscow, Russian Federation

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ABSTRACT

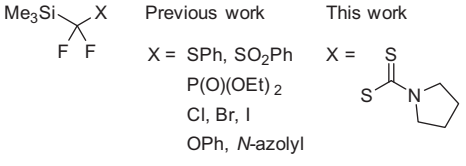
A new *gem*-difluorinated silicon reagent bearing a pyrrolidine dithiocarbamate substituent was prepared by the reaction of (bromodifluoromethyl)trimethylsilane with the corresponding potassium dithiocarbamate. The obtained reagent was employed in the nucleophilic addition to aldehydes and ketones.

Direct introduction of a fluorinated fragment into organic molecules constitutes an important approach in medicinal chemistry and agrochemistry.[1] Among the various methods of synthesizing fluorinated building blocks,[2] nucleophilic fluoroalkylation of carbonyl compounds and related substrates has emerged as a powerful and broadly applicable methodology.[3] Correspondingly, many organometallic derivatives have been evaluated as equivalents of fluorinated carbanions,[4] but only silicon reagents have found widespread use. Indeed, the utility of fluorinated silanes stems from the convenience of handling and mild conditions required to reveal their nucleophilicity.[3a–e]

Besides the most widely used Ruppert–Prakash reagent (Me_3SiCF_3),[5] other silanes bearing a heteroatom substituent instead of one of the fluorine atoms have been prepared and employed for carbonyl addition reactions and related processes[6–9] (Scheme 1). Further extension of the palette of silicon reagents with emphasis on new functional groups would be desirable. Dithiocarbamates have displayed a diverse profile of biological activities, including antifungal, antibacterial, antiviral, and anticancer.[10] Herein, we describe a new fluorinated silane bearing a dithiocarbamate moiety, and demonstrate its utility in fluoroalkylation reactions.[11]

It has recently been noted that (bromodifluoromethyl) trimethylsilane (Me_3SiCF_2Br, **1**) may exchange bromine for chlorine in an equilibrium reaction when exposed to a chloride ion.[12] We proposed that employment of the dithiocarbamate anion would effect a similar bromine substitution. Gratifyingly, when potassium dithiocarbamate **2** (K-dtc), easily obtained from pyrrolidine and carbon disulfide,[13] was added to silane **1**, a substitution reaction occurred rapidly, and product **3** was isolated in 79% yield (Scheme 2). We postulated that the reaction was initiated by attack of the anionic species (X = dtc or Br) at the silicon atom to generate difluorocarbene followed by its trapping by the dithiocarbamate anion and subsequent silylation.

Contrary to typical fluorinated silanes, compound **3** was isolated as a crystalline material, and its structure was proved by single crystal X-ray analysis[14] (Fig. 1). Interestingly, it existed in an eclipsed conformation along the Si–CF_2 bond (see inset). Solid silane **3** could be stored at 0 °C for weeks without visible changes



Scheme 1. Fluorinated silicon reagents.

* Corresponding author.
E-mail address: adil25@mail.ru (A.D. Dilman).

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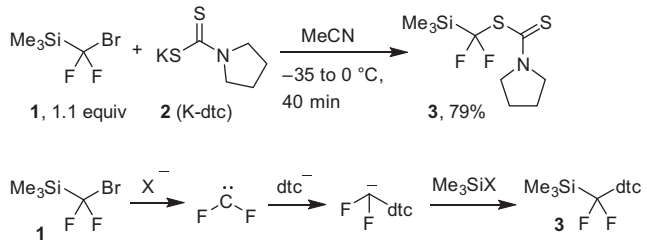


Scheme 2. Synthesis of silane **3**.

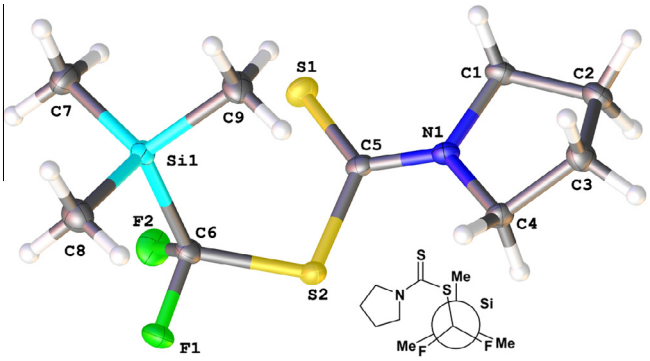
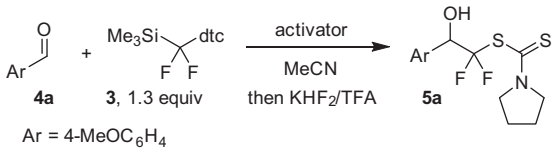


Figure 1. X-ray structure of silane **3**.

and could be conveniently handled in air. However, when the reagent was kept at room temperature it slowly underwent decomposition. Given that silane **3** is rapidly formed from shelf-stable precursors, it is convenient to generate this silicon reagent in situ.

Anisaldehyde **4a** was selected as a model substrate and its reaction with silane **3** in acetonitrile was evaluated (Table 1). No reaction occurred in the absence of a Lewis basic activator. Use of K-dtc (0.1 equiv) as an activator gave after desilylative work-up (with KHF_2/TFA), alcohol **5a** in 70% yield within 1 h at 0 °C (entry 2). Increasing the reaction time to 2 h, and generating silane **3** in situ from 1.3 equiv of Me_3SiCF_2Br and 1.4 equiv of K-dtc provided product **5a** in 81% yield (entry 5). It is worth noting that although the reaction could be initiated by the poorly Lewis basic bromide ion, the reaction proceeded at a decreased rate (entry 6).

Table 1
Optimization studies

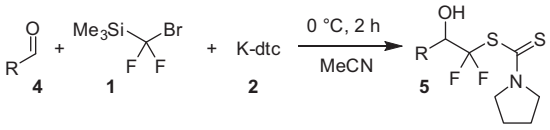


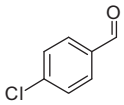
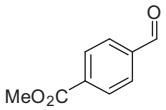
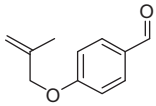
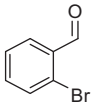
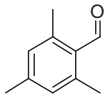
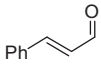
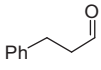
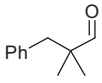
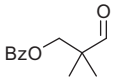
Entry	Activator (equiv)	Temp	Time (h)	Yield of **5a**[a] (%)
1	—	rt	2	—
2	K-dtc (0.1)	0 °C	1	70
3	K-dtc (0.1)	0 °C	2	80
4	K-dtc (0.1)	rt	1	75
5[b]	K-dtc (0.1)	0 °C	2	81
6	Bu_4NBr (1.0)	rt	3	17[c]

[a] Isolated yield.
[b] Silane **3** generated in situ from **1** and K-dtc.
[c] Yield determined by ^{19}F NMR.

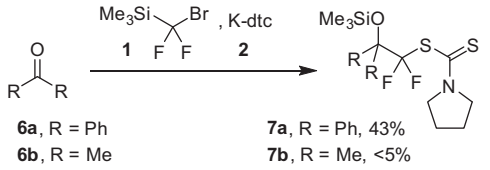
Under the optimized conditions, a series of aldehydes **4** were examined in the dithiocarbamate initiated fluoroalkylation reaction (Table 2). Aromatic, heteroaromatic, and α,β-unsaturated aldehydes gave alcohols **6** in high yields. Addition to an aldehyde bearing an electron withdrawing ester group proceeded rapidly and was complete with 5 min (entry 3). Notably, in the reaction of an aldehyde bearing a methallyl group, no products of double bond difluorocyclopropanation were observed[15] (entry 4). An enolizable aldehyde, hydrocinnamaldehyde, also gave the addition product in high yield (entry 9). However, branched aliphatic aldehydes reacted sluggishly, and an increased loading of reagents **1** (3.0 equiv) and **2** (3.3 equiv) was required (entries 10–12).

Table 2
Addition to aldehydes[a]

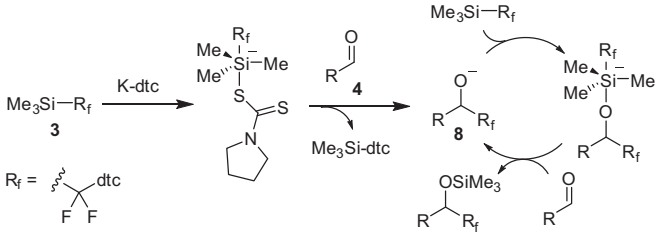


No.	Aldehyde	5	Yield of **5**[b] (%)
1		**5b**	80
2		**5c**	84
3[c]		**5d**	81
4		**5e**	68
5		**5f**	76
6		**5g**	64
7		**5h**	81
8		**5i**	79
9		**5j**	73
10[d]		**5k**	74
11[d]		**5l**	80
12[d]		**5m**	82

[a] Standard conditions: **1** (1.3 equiv), **2** (1.4 equiv).
[b] Isolated yield.
[c] Reaction time 5 min.
[d] Reagents: **1** (3.0 equiv), **2** (3.3 equiv).



Scheme 3. Reactions of ketones.



Scheme 4. Proposed mechanism.

The reactions of ketones were also evaluated (Scheme 3). Using a three-fold excess of reagents **1** and **2**, benzophenone gave the expected product **7a**, albeit in moderate yield. At the same time, in the reaction of acetone, no addition product was observed by ^{19}F NMR, while GC MS analysis suggested the formation of acetone self-condensation products.

Concerning the mechanism, the reaction likely proceeds through the Lewis base initiated generation of alkoxide **8** which subsequently drives the chain process typical of fluorinated silicon reagents (Scheme 4).[3a]

Finally, we attempted to investigate the reactivity of the obtained products. However, Swern oxidation of alcohol **5a** under the conditions suitable for trifluoromethylated alcohols,[16] was unsuccessful. When compound **5a** was subjected to the typical Zard's free-radical atom transfer chemistry[17] (e.g., reaction with *N*-allylphthalimide and dilauroyl peroxide), complex mixtures were formed.

In summary, we have synthesised a novel silicon reagent bearing a dithiocarbamate fragment and demonstrated its utility for the nucleophilic fluoroalkylation of carbonyl compounds. The opportunity for in situ generation of the silane from readily available and shelf-stable precursors makes this a convenient procedure for synthetic applications.

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Supplementary data

Supplementary data (experimental procedures, product characterization, NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.018.

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