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Nucleophilic Bromo- and Iododifluoromethylation of Aldehydes

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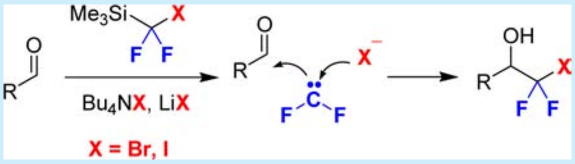
S *Supporting Information*

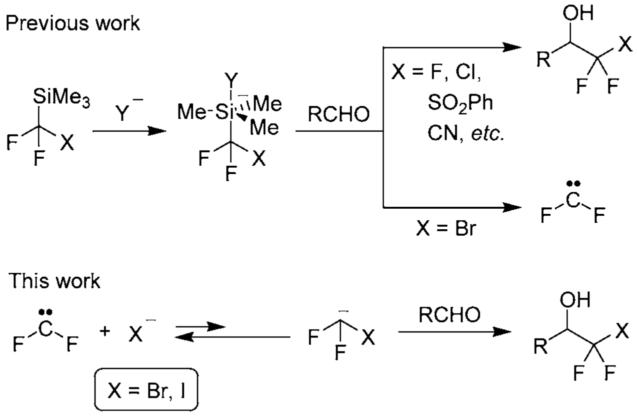
ABSTRACT: A method for bromo- and iododifluoromethylation of aldehydes using bromo- and iodo-substituted difluoromethyl silicon reagents (Me_3SiCF_2X) is described. The reaction is performed in the presence of a combination of tetrabutylammonium and lithium salts Bu_4NX/LiX (X = Br or I) in propionitrile. It is believed that, in this process, a short-lived halodifluoromethyl carbanion serves as nucleophile, which is reversibly generated from difluorocarbene and a halide anion.



Due to the importance of organofluorine compounds in the pharmaceutical and agrochemical industries, as well as in materials science,[1] significant progress has been achieved in the development of a methodology for their synthesis. Among diverse approaches for the introduction of a fluorinated group into organic molecules,[2,3] methods for nucleophilic fluoroalkylation have become most popular.[3] While various organometallics can serve as equivalents of fluorinated carbanions,[4] fluorinated silanes have emerged as the most convenient and widely applicable reagents for nucleophilic fluoroalkylation reactions.[3a−e]

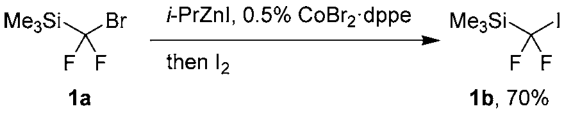
To exhibit nucleophilic reactivity, fluorinated silanes have to be activated by a silaphilic Lewis base (e.g., fluoride anion) through the generation of a pentacoordinate intermediate, which reacts with a suitable electrophile (e.g., aldehyde) (Scheme 1). Reactions of the Ruppert−Prakash reagent (X = F)[3a−e] and chloro-substituted analog (X = Cl),[5] as well as many other functionalized silanes,[6] follow this pathway. However, reactions of a bromo-substituted silane (X = Br) with aldehydes mediated by a fluoride ion have been unsuccessful,[7] presumably owing to facile decomposition of a pentacoordinate intermediate to difluorocarbene.[8] Indeed, silane Me_3SiCF_2Br (**1a**) can generate difluorocarbene even in the presence of weak Lewis bases such as chloride and bromide ions.[9,10] In this work, we describe nucleophilic bromo- and iododifluoromethylation of aldehydes with corresponding silanes in a process, which relies on reverse generation of carbanionic species from difluorocarbene[11] and the halide anion.

Scheme 1. Trapping of Fluorinated Carbanions



While (bromodifluoromethyl)trimethylsilane (**1a**) can be readily obtained from the Ruppert−Prakash reagent,[6h,9a] iodinated silane (**1b**) has not been known. We prepared silane **1b** from silane **1a** in 70% yield by the bromine/zinc exchange[10b] followed by iodination (Scheme 2). Similar to **1a**, the reagent **1b** is a distillable liquid, which can be conveniently handled in air.

Scheme 2. Synthesis of Silane 1b



Benzaldehyde (**2a**) was selected as a model substrate, and its reaction with silane **1a** was investigated (Table 1). The reactions were typically performed in refluxing propionitrile (around 100 °C), and reaction mixtures were analyzed by ^{19}F NMR spectroscopy. Employment of 3 equiv of **1a** along with 5 mol % of tetrabutylammonium bromide for 2 h provided 12% of silylated product **3a** (entry 1). Increasing the amount of bromide salt provided a notable improvement, and finally, using 1.1 equiv of Bu_4NBr lead after desilylative workup to product **4a** in 78% isolated yield (entry 3). Performing the reaction at a lower temperature (refluxing acetonitrile) or with a decreased amount of silane **1a** gave inferior results (entries 4 and 5).

However, when we tested *p*-methoxybenzaldehyde (**2b**) under these conditions, product **3b** was formed in 31% yield, with the rest being the unreacted aldehyde (entry 6). Increasing

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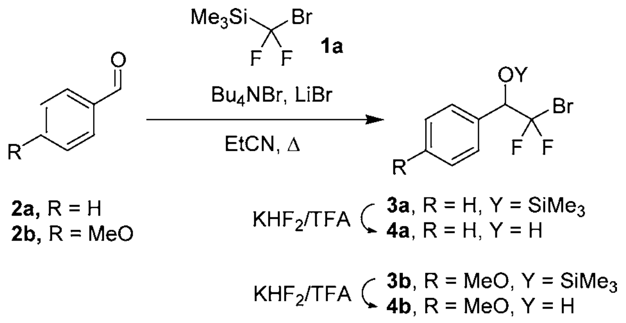
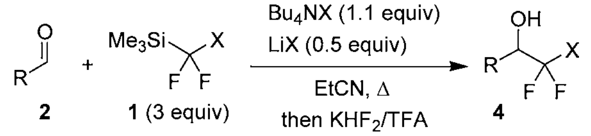
Table 1. Optimization of Bromodifluoromethylation of Aldehydes

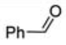
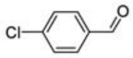
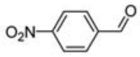
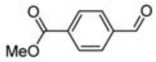
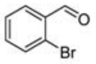
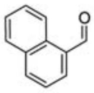
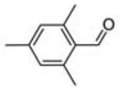
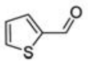
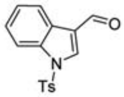
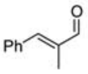
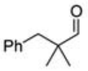
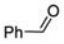
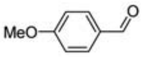
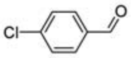
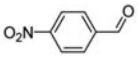
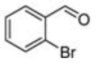


no.	R	**1a**, equiv	Bu_4NBr/LiBr, equiv	time, h	yield of **3**, %[a]
1	H	3	0.05/0	2	12
2		3	0.5/0	2	60
3		3	1.1/0	2	79 (78[b])
4[c]		3	1.1/0	2	51
5		1.5	1.1/0	2	29
6	MeO	3	1.1/0	2	31
7		3	3/0	2	48
8		6	1.1/0	2	83
9		3	1.1/0.5	2	61
10		**3**	**1.1/0.5**	**5**	**92 (92[d])**
11		3	0/1.6	5	76
12[e]		3	0/2	5	88

[a]Determined by ^{19}F NMR using $PhCF_3$ as internal standard. [b]Isolated yield of product **4a**. [c]Reaction performed in refluxing acetonitrile. [d]Isolated yield of product **4b**. [e]Reaction performed in diglyme at 100 °C.

Table 2. Bromo- and Iododifluoromethylation of Aldehydes



no.	aldehyde	X	time	4	yield of **4**, %[a]
1		Br	5	**4a**	96
2		Br	5	**4c**	95
3		Br	2	**4d**	96
4		Br	2	**4e**	90
5		Br	5	**4f**	95
6		Br	5	**4g**	91
7[b]		Br	10	**4h**	84
8		Br	5	**4i**	91
9		Br	5	**4j**	93
10		Br	5	**4k**	89
11[b]		Br	10	**4l**	77
12		I	10	**4m**	92
13		I	10	**4n**	75
14		I	10	**4o**	98
15		I	10	**4p**	78
16		I	10	**4q**	97

[a]Isolated yield. [b]3 equiv of each Bu_4NBr and LiBr were used.

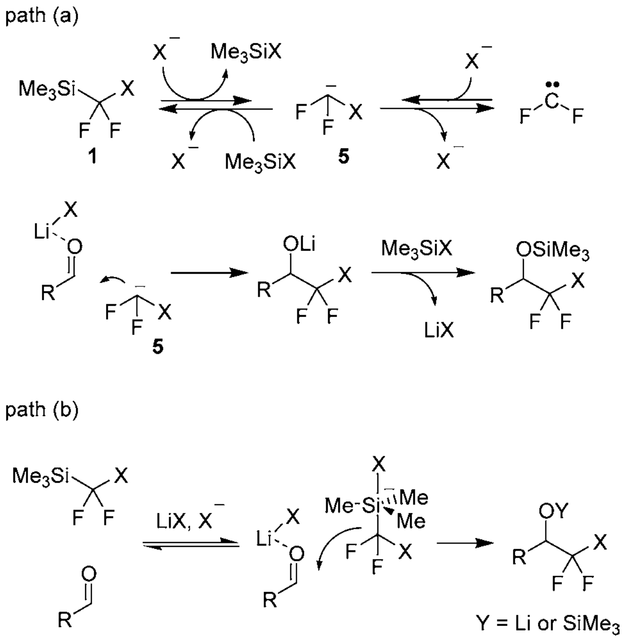
the concentration of Bu_4NBr up to 3 equiv had little effect (entry 7), while use of a huge excess of the silane seemed impractical (entry 8). We reasoned that the reaction rate can be increased by the addition of a metal salt capable of exerting Lewis acidic activation of the carbonyl group. Rewardingly, addition of 0.5 equiv of lithium bromide virtually doubled the product yield (cf. entries 6 and 9). Finally, increasing the reaction time to 5 h allowed isolation of alcohol **4b** in 92% yield (entry 10). The use of lithium bromide without the tetrabutylammonium counterpart gave inferior results (entries 11 and 12).

Under the optimized conditions, a series of aldehydes were reacted with silane **1a** (Table 2, entries 1–11). Aromatic aldehydes bearing donating and withdrawing substituents, heterocyclic aldehydes, unsaturated, and nonenolizable aliphatic aldehydes afforded products **4a–l** in high yields. Electron-withdrawing nitro and ester groups accelerated the nucleophilic addition, and the reactions were complete within 2 h (entries 3 and 4). For sterically hindered aldehydes a longer reation time and 3 equiv of both ammonium and lithium salts were needed (entries 7 and 11). Fortunately, α-methylcinnamaldehyde gave addition product **4k** in 89% yield, while ^{19}F NMR analysis or crude material indicated only small amounts (ca. 5%) of difluorocyclopropane byproducts. However, hydrocinnamaldehyde gave a complex mixture, presumably, owing to its propensity to aldolization. The reaction of acetophenone was also unsuccessful with the product being formed in less than 10% yield. The ester group is tolerated (for an aromatic substrate, see entry 4, whereas, in the reaction of an aliphatic ester, methyl 4-phenylbutanoate, no product was detected).

Reactions of aldehydes with iodo-substituted silane **1b** were performed using the Bu_4NI/LiI system under similar conditions. Typically, the reactions proceeded slower compared to those with silane **1a**. Nevertheless, good yields of iododifluoroalkylation products were achieved after heating for 10 h (entries 12–16).

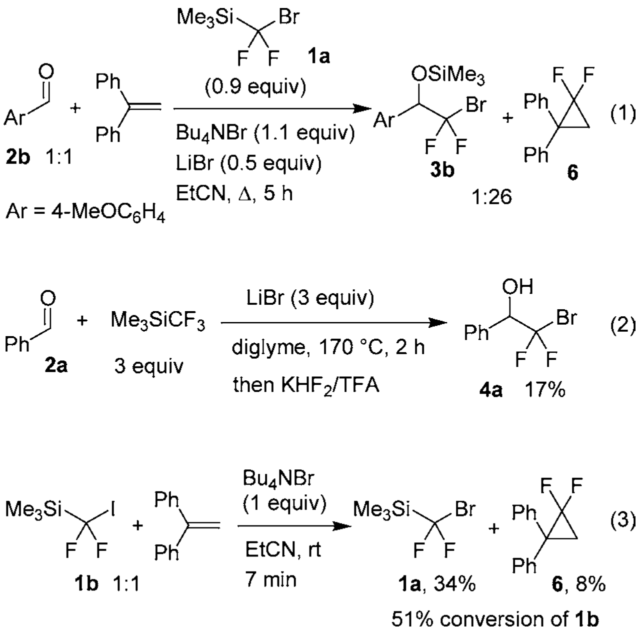
Concerning the reaction mechanism, two pathways can be considered (Scheme 3). In path (a), the halide anion reversibly generates a difluorocarbene through the intermediacy of halodifluoromethyl carbanion **5**. While the latter species is believed to be very short-lived, it can be trapped with the appropriate electrophile. A lithium salt can activate the carbonyl group though some association of the lithium cation with

Scheme 3. Reaction Mechanism



carbanionic species **5** cannot be excluded. In an alternative mechanism, path (b), the halodifluoromethyl group can be transferred in a concerted fashion from a pentacoordinate siliconate intermediate.

Scheme 4. Mechanistic Studies



To gain some mechanistic information, several experiments were carried out (Scheme 4). Thus, when the reaction of aldehyde **2b** was performed in the presence of 1,1-diphenylethylene employing a deficient amount of silane **1a**, difluorocyclopropane **6** was formed preferentially (eq 1). This fact suggests the intermediacy of difluorocarbene[11,12] which is generated faster than the aldehyde addition product is formed. Furthermore, use of the Ruppert−Prakash reagent as a source of difluorocarbene[13] afforded bromodifluoromethylated alcohol **4a** as a sole product in 17% yield (eq 2). To probe the reversible generation of difluorocarbene, iodo-substituted silane **1b** was combined with tetrabutylammonium bromide in the presence of 1,1-diphenylethylene (eq 3). The halogen exchange proceeded rapidly even at room temperature, and in 7 min silane **1a** and cyclopropane **6** were detected.[14] Taken together, these observations support path (a), in which the nucleophilic species **5** is generated from the interaction of difluorocarbene with a halide anion.

In summary, a convenient method for nucleophilic bromo- and iododifluoromethylation of aldehydes by means of corresponding silicon reagents is described. The use of a stoichiometric amount of a halide anion is important to achieve good yields of products. The role of the halide is believed to trap difluorocarbene generating a transient halodifluoromethyl carbanion.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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